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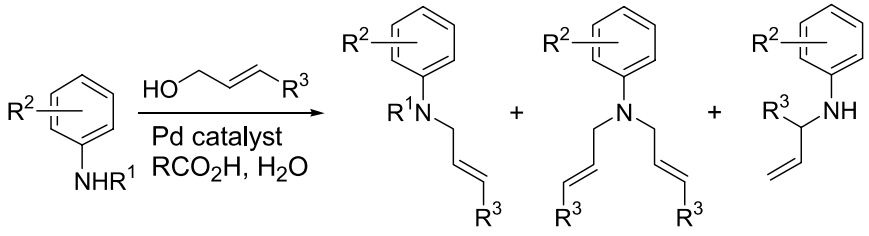
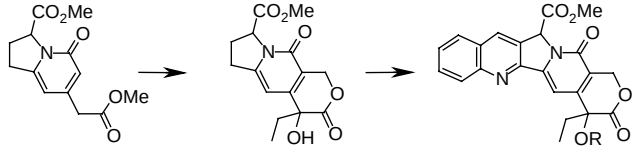
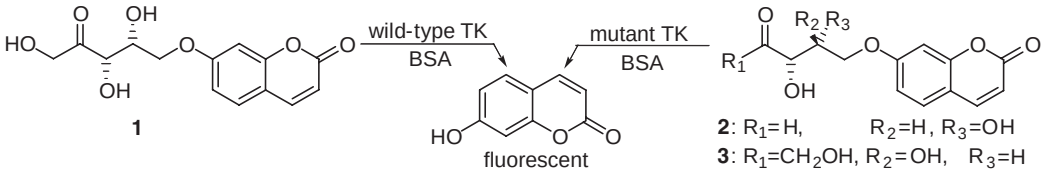
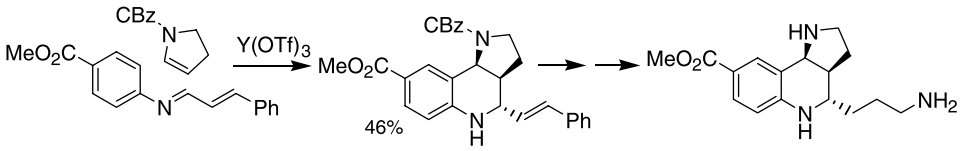


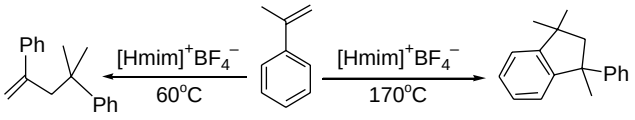


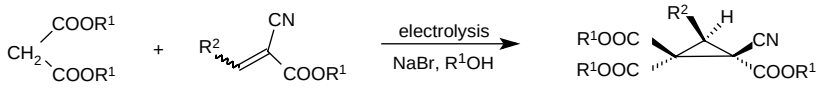
The synthesis of two camptothecin analogs substituted by a carbonyl function on position 5 of cycle C was realized.

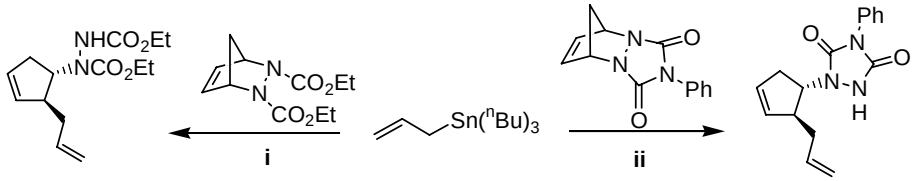




Povarov reaction of an aromatic imine derived from cinnamaldehyde with a cyclic enamide gave a key intermediate for the synthesis of martinellic acid in 46% isolated yield with complete regiocontrol. This intermediate was converted to the titled compound in five additional steps.

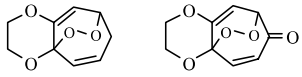




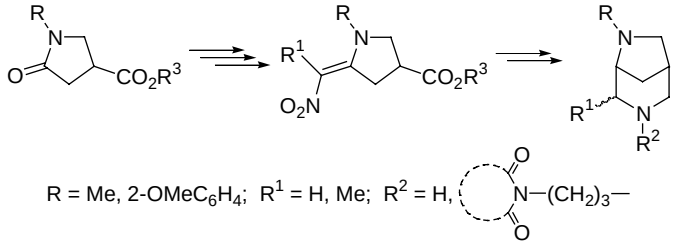


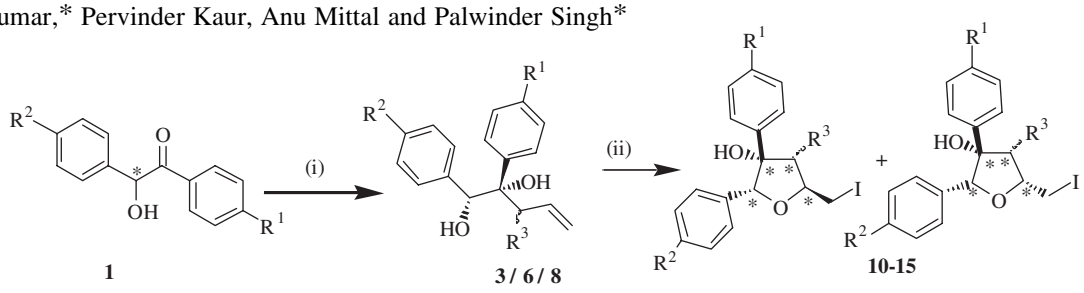
i =[Pd(allyl)Cl]$_2$ (5 mol %), dppe (10 mol %), Sc(OTf)$_3$ (2 mol %), [bmim]PF$_6$, R.T., 1 h, 90%.

ii =[Pd(allyl)Cl]$_2$ (5 mol %), dppe (10 mol %), Sc(OTf)$_3$ (2 mol %), [bmim]PF$_6$, 60 °C, 8 h, 89%.

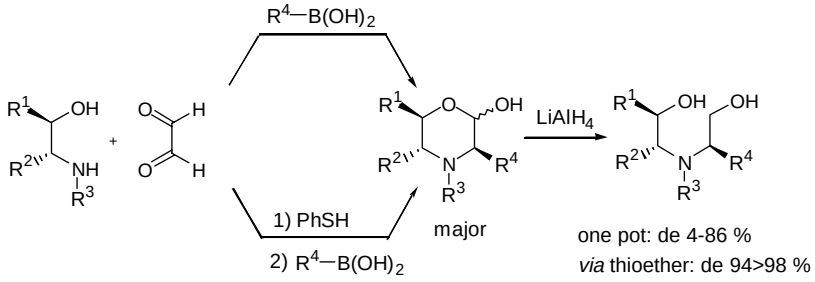


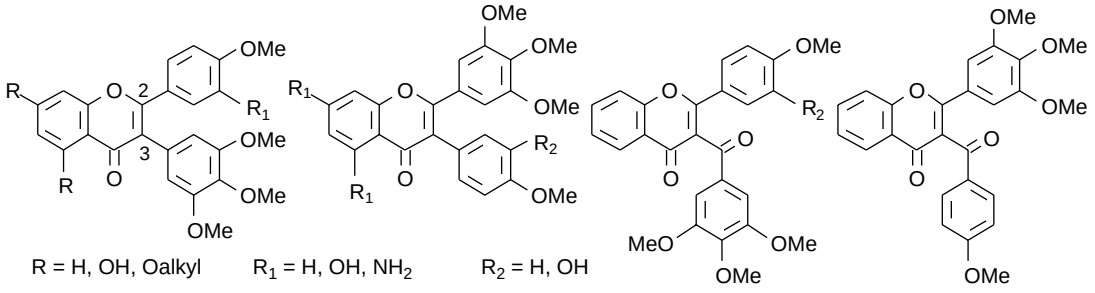
The chemistry of two bicyclic endoperoxides, obtained by photooxygenation of the corresponding cycloheptatriene derivatives was investigated with the aim of synthesizing the respective tropolone derivatives.

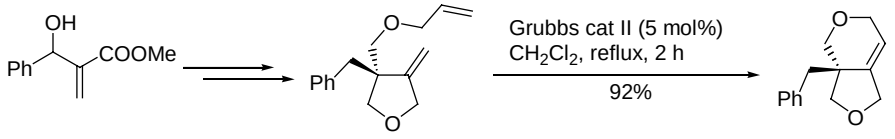


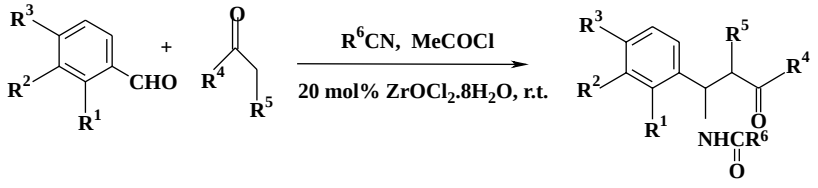


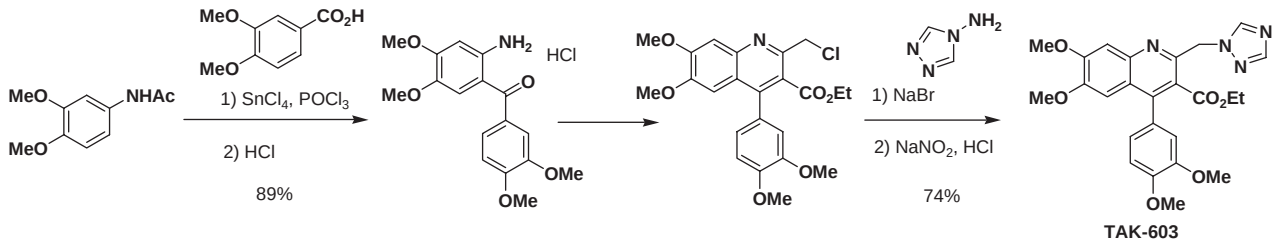
(i) In, R^3-CH=CHCH$_2$Br, THF : H_2O (2:1); (ii) I_2, $NaHCO_3$, CH_3CN / DMF

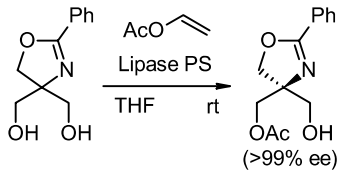




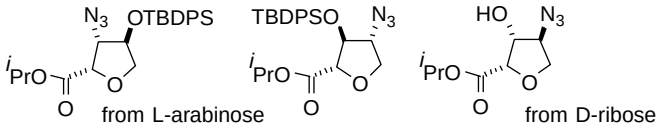




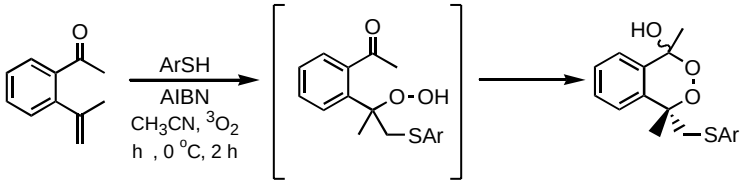


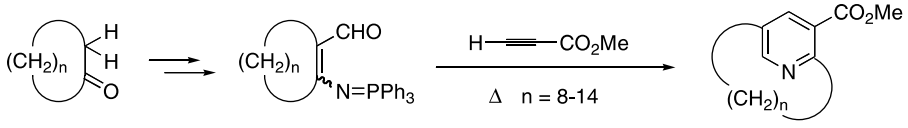


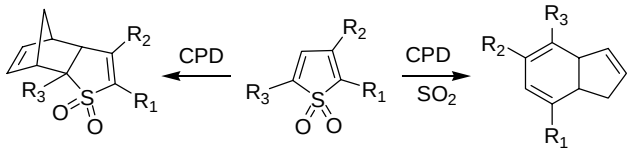
(*R*)-4-Hydroxymethyl-2-phenyl-4,5-dihydrooxazol-4-ylmethyl acetate was efficiently obtained by lipase-catalyzed asymmetrization of the prochiral diol.

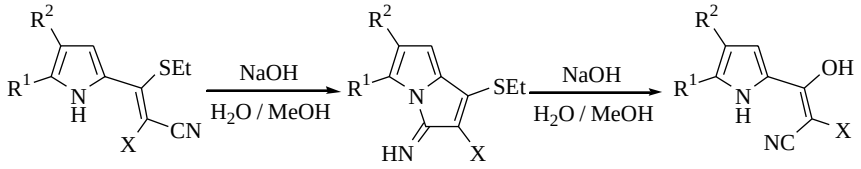


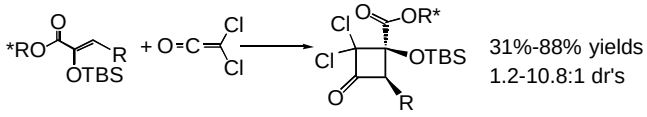
The efficient synthesis of cyclically rigidified β- and γ-amino acids from carbohydrate starting materials.

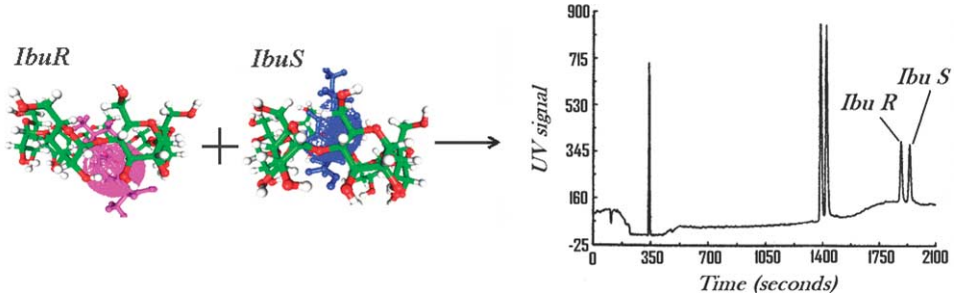


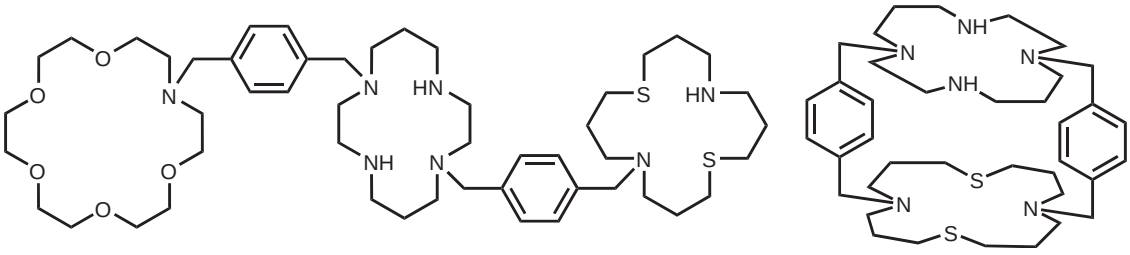


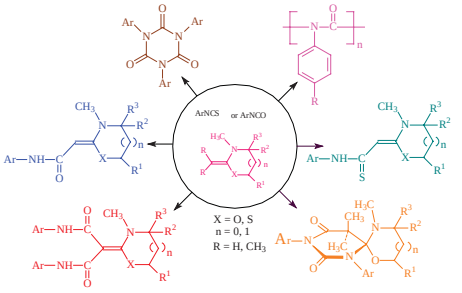


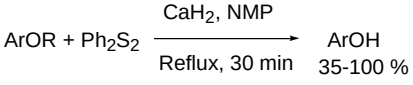


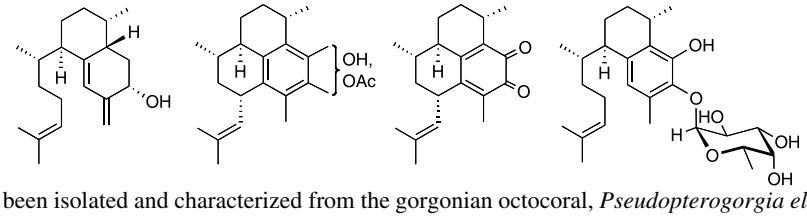




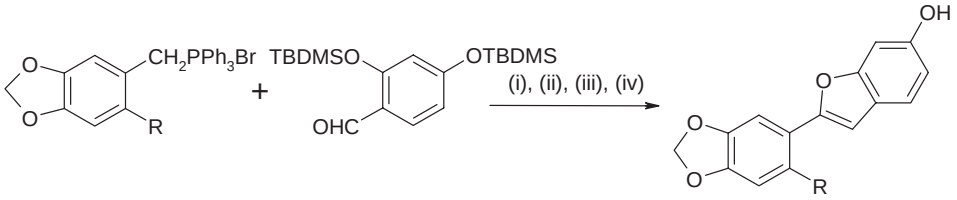




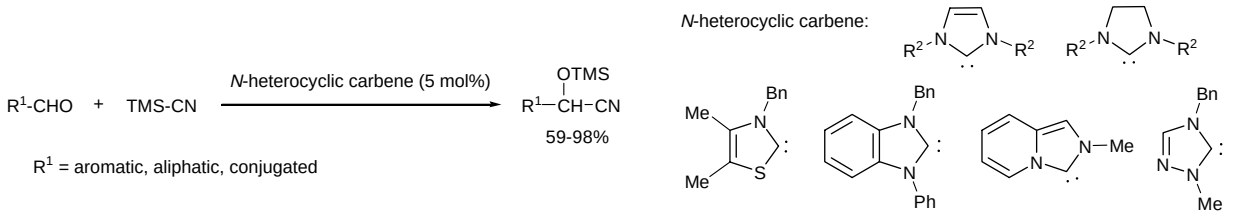


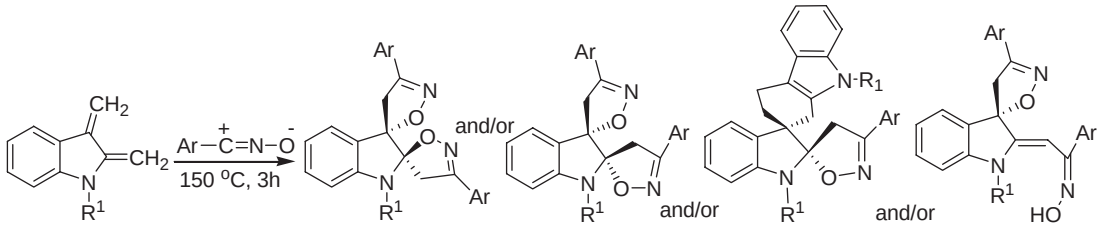


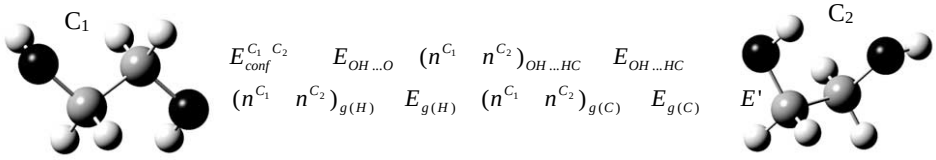
Four new diterpenes have been isolated and characterized from the gorgonian octocoral, *Pseudopterogorgia elisabethae*, collected in San Andrés and Providencia islands, Colombian Caribbean.

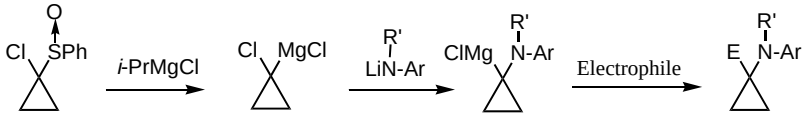


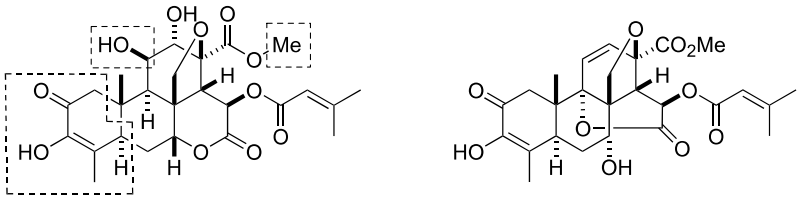
(i) NaHMDS, THF; (ii) 3-CPBA, DCM; (iii) $CuCl_2$, acetone, water; (iv) pTSA, $CHCl_3$
A novel method is described for the synthesis of oxygenated benzofurans by epoxidation and cyclisation of 2'-hydroxystilbenes











OTHER CONTENTS

*Corresponding author
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Direct palladium/carboxylic acid-catalyzed allylation of anilines with allylic alcohols in water

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Abstract—The direct activation of C–O bonds in allylic alcohols in water as a suspension medium by palladium complexes has been accelerated by carrying out the reactions in the presence of a carboxylic acid. The palladium-catalyzed allylation of anilines using allylic alcohols directly gave allylic anilines in good yields.

1. Introduction

A principal goal of organometallic chemistry is the catalytic synthesis of organic compounds by using the chemistry of organic ligands covalently bound to transition metals. Most organometallic chemistry has focused on complexes with covalent metal–carbon or metal–hydrogen bonds. Transition metals, in particular palladium and rhodium, have been workhorse elements in many commercialized catalytic processes that include hydrogenations, hydroformylations, acetic acid production, and other C–C and C–H bond forming processes.[1] Although carbon–oxygen, carbon–nitrogen, or carbon–sulfur bonds are found in the majority of important organic molecules, catalytic organometallic reaction chemistry that leads to the formation of carbon-heteroatom bonds is less common than that forming carbon–carbon and carbon–hydrogen bonds. Transition metal η^3-allyl complexes, as well as transition metal σ-alkyl complexes, play important roles as active species and key intermediates in many reactions catalyzed by transition metal complexes.[2] The palladium-catalyzed allylation is a powerful tool for C–C, C–N, and C–O bond formation, which has been widely applied to organic chemistry.[3] The processes have been shown to proceed by attack of nucleophiles on intermediate η^3-allylpalladium(II) complexes generated by oxidative addition of allylic compounds including halides,[4] esters,[5] carbonates,[6] carbamates,[7] phosphates,[8] and related derivatives[9] to a Pd(0) complex. Because these substrates are synthesized from the corresponding allylic alcohols, palladium-catalyzed conversion of allylic alcohols directly into allylation products are highly desirable, especially from the viewpoint of the atom economy.[10] For achieving the palladium-catalyzed C–O bond cleavage of allylic alcohols, various other processes to facilitate the bond cleavage have been reported.[11] These processes include conversion of allylic alcohols into the esters of inorganic acids (e.g., As_2O_3,[12] B_2O_3,[13] CO_2[3b]) or employment of a Lewis acid (e.g., BEt_3,[14] BF_3,[15] BPh_3,[16] $SnCl_2$[17]). However, there have been only limited and sporadic reports dealing with the direct cleavage of the C–O bond in allylic alcohols on interaction with a transition metal complex.[18] Successful applications using allylic alcohols directly in catalytic processes are even more limited. This apparently stems from the poor capability of a nonactivated hydroxyl to serve as a leaving group.[16] Ozawa reported that (π-allyl)palladium complexes bearing diphosphinidenecyclobutene ligands effectively catalyze the direct conversion of allylic alcohols in the absence of activating agents.[19] Manabe[20] in 2003 and Patil[21] in 2004 disclosed the direct palladium-catalyzed allylic substitution of allylic alcohols by carbon nucleophiles. We have recently reported our attempts and some successful applications of a process involving the C–O bond cleavage with direct use of allylic alcohols catalyzed by palladium complexes in the presence of $Ti(OPr^i)_4$ in benzene.[22] However, reactions in water have recently attracted much attention, not only because unique reactivity is often observed in water but also because water is a safe and economical solvent.[23] Thus, development of atom-economical reactions in water is one of the most important goals of synthetic chemistry. Due to our continuing interest in the palladium-catalyzed allylation of anilines, we disclose a new catalytic system for palladium-catalyzed allylation of anilines with allylic alcohols in water as a suspension

Keywords: Palladium-catalyzed; Allylation; Water; Anilines; Allylic alcohols.
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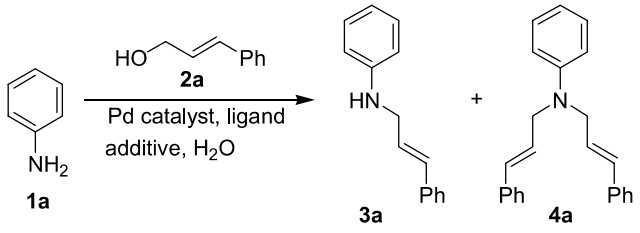
medium.[24] This is, to our knowledge, the first example of palladium/carboxylic acid-catalyzed allylation of anilines by the direct use of allylic alcohols in water.

2. Results and discussion

To evaluate the scope and limitations of the N-allylation of anilines with allylic alcohols, we treated a mixture of aniline (**1a**, 1 mmol) and cinnamyl alcohol (**2a**, 0.8 mmol) in the presence of $Pd(acac)_2$ (0.02 mmol), PPh_3 (0.08 mmol), and 1-adamantanecarboxylic acid (1-$AdCO_2H$) (0.1 mmol) in water at 50 °C for 30 min. The mixtures of *N*-cinnamylaniline (**3a**) and *N*,*N*-dicinnamylaniline (**4a**) were formed in 35 and 7%, respectively (entry 1 in Table 1). The reaction, under reflux, increased the yields of products **3a** and **4a** to 54 and 42%, respectively (entry 2). It was confirmed that the yield was decreased in the absence of PPh_3 (entry 3). The reaction did not occur in the absence of the palladium species as a catalyst or without water solvent (entries 4 and 5). The effect of water may activate allyl alcohol via hydration of the hydroxyl group for the smooth generation of the π-allylpalladium intermediate.[25] The absence of a carboxylic acid gave only a 10% yield of **3a** (entry 6). The effect of addition of 1-$AdCO_2H$ to promote the palladium-catalyzed allyl–OH bond cleavage remarkably enhanced both the reaction rate and yield. Other carboxylic acids such as $PhSCH_2CO_2H$ (entry 7), $PhOCH_2CO_2H$ (entry 8), and lauric acid (entry 9) were also effective for the allylation. (*S*)-(−)-2-bromopropionic acid (entry 10) and $PhCO_2H$ (entry 11) gave moderate yields of products. CH_3CO_2H (entry 12), 4-octylbenzoic acid (entry 13), and Ph_2CHCO_2H (entry 14) retarded the allylation. Strong acids such as C_6F_5OH (entry 15) and dodecylbenzenesulfonic acid (DBSA) (entry 16) also enhanced the substitution reaction.

Table 1. Allylation of aniline (**1a**) with cinnamyl alcohol (**2a**): temperature and acid effects[a]



Entry	Additive	Yield (%) (**3a**+**4a**)[b]	Yield (%) of **3a**[b]	Yield (%) of **4a**[b]
1[c]	1-$AdCO_2H$	42	35	7
2	1-$AdCO_2H$	96	54	42
3[d]	1-$AdCO_2H$	6	6	
4[e]	1-$AdCO_2H$	0		
5[f]	1-$AdCO_2H$	0		
6[g]	—	10	10	
7	$PhSCH_2CO_2H$	91	55	36
8	$PhOCH_2CO_2H$	86	49	37
9	$CH_3(CH_2)_{10}CO_2H$	84	50	34
10	$CH_3CH(Br)CO_2H$	59	21	38
11	$PhCO_2H$	56	41	15
12	CH_3CO_2H	14	9	5
13	4-Oct$C_6H_4CO_2H$	11	11	
14	Ph_2CHCO_2H	11	11	
15	C_6F_5OH	80	62	18
16	DBSA	78	55	23

[a] Reaction conditions: **1a** (1 mmol), **2a** (0.8 mmol), $Pd(acac)_2$ (0.02 mmol), PPh_3 (0.08 mmol), and additive (0.1 mmol) in water (5 mL) were refluxed for 30 min.
[b] Isolated yield was based on **2a**.
[c] Stirred at 50 °C for 30 min.
[d] Without PPh_3.
[e] Without $Pd(acac)_2$.
[f] Without water.
[g] Without acid.

A comparative study of different palladium catalysts and phosphine ligands in water was reported (Table 2). Among the palladium catalysts including $Pd(acac)_2$ (entry 1), $PdCl_2$(1,10-phen) (entry 2), $Pd(OAc)_2$ (entry 3), $Pd(OCOCF_3)_2$ (entry 4), $PdCl_2(MeCN)_2$ (entry 5), $PdCl_2(PhCN)_2$ (entry 6), $PdCl_2$ (entry 7), Pd(propionate)$_2$ (entry 8), Pd(hfacac)$_2$ (entry 9), $Pd_2(dba)_3$ (entries 10 and 11), and $Pd(PPh_3)_4$ (entries 12 and 13) were used. $Pd(acac)_2$, $PdCl_2$(1,10-phen), $PdCl_2$, $Pd(PPh_3)_4$, and Pd(propionate)$_2$ were found to be superior. However, using $Pd_2(dba)_3$ or $Pd(PPh_3)_4$ with extra PPh_3 as catalyst increased the yield of products (entries 11 and 13). The catalytic reactivity of the phosphine ligands is likely due to improved catalyst stability. In the presence of various monodentate ligands including PPh_3, Bu_3P, $(PhO)_3P$, $(2\text{-}MeC_6H_4)_3P$, $(2\text{-furyl})_3P$, $(2\text{-pyridyl})Ph_2P$, $(3\text{-}MeC_6H_4)_3P$, $(4\text{-}MeC_6H_4)_3P$, $(4\text{-}MeOC_6H_4)_3P$, $(4\text{-}FC_6H_4)_3P$, $(4\text{-}ClC_6H_4)_3P$, and $[2,4,6\text{-}(MeO)_3C_6H_2]_3P$ (entries 1 and 14–24) showed that PPh_3 (entry 1), $(PhO)_3P$ (entry 15), $(3\text{-}MeC_6H_4)_3P$ (entry 19), and $(4\text{-}MeOC_6H_4)_3P$ (entry 21) were the most effective ligands. The bidentate ligand dppp, dppb, and dpph gave moderate yields of products (entries 25–29). (±)-BINAP afforded high yields of products (entry 30).

We also studied the influence of the substituent on aniline on the reactivity of the amination of cinnamyl alcohol (**2a**) using $Pd(acac)_2$, PPh_3, and 1-$AdCO_2H$. Allylation of 4-substituted anilines containing both electron-withdrawing and electron-donating groups **1b–g** worked well with cinnamyl alcohol (**2a**) under reflux giving the corresponding *N*-allylanilines and *N*,*N*-diallylanilines in overall yields ranging from 65 to 96% (entries 1–6 in Table 3). These differences in reactivity could be related to the nucleophilicity of the corresponding aniline. 4-Nitroaniline (**1g**) gave 65% yield; the lower yield observed may arise from the nature of the nitro group. The more acidic nitroaniline is probably less reactive in attack on the π-allyl complex than the methoxyaniline, for example. The sterically more demanding 2-substituted anilines **1h–n** gave lower yields (entries 7–13). The reaction of 2-nitroaniline (**1i**), because of its strong electron-withdrawing and sterically group, gave only 27% yields. Conversely, anilines having groups on the 3-position, such as 3-OCH_2Ph (**1o**), 3-NO_2 (**1p**), and 3,5-di-OMe (**1q**), also gave the products in the high yields of 81, 92 and 77%, respectively (entries 14–16). Secondary aromatic amine, such as diphenylamine (**1r**) and phenothiazine (**1s**), also reacted to give the *N*-allylamine in excellent yields (entries 17 and 18).

Results for amination of both aromatic and aliphatic allylic alcohols **2b–j** with aniline (**1a**) using $Pd(acac)_2$, PPh_3, and 1-$AdCO_2H$ are summarized in Table 4. In addition to the parent cinnamyl alcohol (**2a**), *trans*-1,3-diphenyl-2-propen-1-ol (**2b**) reacted to give the allylating product **5** in excellent yields (entry 1). In contrast to the previous systems for

Table 2. Allylation of aniline (**1a**) with cinnamyl alcohol (**2a**): palladium and phosphine ligand effects[a]

Entry	Palladium	Ligand	Yield (%) (**3a**+**4a**)[b]	Yield (%) of **3a**[b]	Yield (%) of **4a**[b]
1	$Pd(acac)_2$	PPh_3	96	54	42
2	$PdCl_2$(1,10-phen)	PPh_3	99	43	56
3	$Pd(OAc)_2$	PPh_3	70	34	36
4	$Pd(OCOCF_3)_2$	PPh_3	86	63	23
5	$PdCl_2(MeCN)_2$	PPh_3	78	41	37
6	$PdCl_2(PhCN)_2$	PPh_3	66	41	25
7	$PdCl_2$	PPh_3	95	44	51
8	Pd(propionate)$_2$	PPh_3	91	56	35
9	Pd(hfacac)$_2$[c]	PPh_3	37	34	3
10	$Pd_2(dba)_3$	—	22	22	
11	$Pd_2(dba)_3$	PPh_3	69	42	27
12	$Pd(PPh_3)_4$	—	75	49	26
13	$Pd(PPh_3)_4$	PPh_3	98	59	39
14	$Pd(acac)_2$	Bu_3P	67	34	33
15	$Pd(acac)_2$	$(PhO)_3P$	89	51	38
16	$Pd(acac)_2$	$(2\text{-}MeC_6H_4)_3P$	39	26	13
17	$Pd(acac)_2$	$(2\text{-Furyl})_3P$	55	29	26
18	$Pd(acac)_2$	$(2\text{-Pyridyl})Ph_2P$	39	21	18
19	$Pd(acac)_2$	$(3\text{-}MeC_6H_4)_3P$	89	51	38
20	$Pd(acac)_2$	$(4\text{-}MeC_6H_4)_3P$	63	38	25
21	$Pd(acac)_2$	$(4\text{-}MeOC_6H_4)_3P$	86	37	49
22	$Pd(acac)_2$	$(4\text{-}FC_6H_4)_3P$	54	31	23
23	$Pd(acac)_2$	$(4\text{-}ClC_6H_4)_3P$	37	25	12
24	$Pd(acac)_2$	$[2,4,6\text{-}(MeO)_3C_6H_2]_3P$	28	28	
25	$Pd(acac)_2$	Dppm[d]	2	2	
26	$Pd(acac)_2$	Dppe[e]	1	1	
27	$Pd(acac)_2$	Dppp[f]	41	34	7
28	$Pd(acac)_2$	Dppb[g]	59	43	16
29	$Pd(acac)_2$	Dpph[h]	45	35	12
30	$Pd(acac)_2$	(±)-BINAP[i]	92	46	46

[a] Reaction conditions: **1a** (1 mmol), **2a** (0.8 mmol), Pd catalyst (0.02 mmol), ligand (0.08 mmol), and 1-AdCO_2H (0.1 mmol) in water (5 mL) were refluxed for 30 min.
[b] Isolated yield was based on **2a**.
[c] Palladium hexafluoroacetylacetonate.
[d] Bis(diphenylphosphino)methane.
[e] 1,2-Bis(diphenylphosphino)ethane.
[f] 1,3-Bis(diphenylphosphino)propane.
[g] 1,4-Bis(diphenylphosphino)butane.
[h] 1,6-Bis(diphenylphosphino)hexane.
[i] (±)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl.

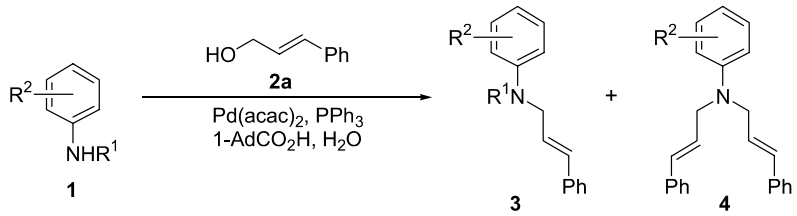
allylic substitution, reactions of aliphatic allylic alcohols occurred only moderate yields (entries 2–9). Allylation of aniline with allyl alcohol (**2c**) and methallyl alcohol (**2d**), the corresponding monoallylated and diallylated products were formed in overall 45 and 62% yields, respectively (entries 2 and 3). Using 2-chloro-2-propen-1-ol (**2e**) as allylating reagent gave only monoallylated product *N*-(2-chloroallyl)aniline (**10**) in 40% yield (entry 4). The sterically more demanding secondary alcohol **2f** gave lower yields (entry 5). Treatment of aniline (**1a**) with crotyl alcohol (**2g**) gave mixtures of stereo- and regioisomeric anilines **12** and **13** in the yield of 41 and 9%, respectively (entry 6). These products may all be derived from the same π-allyl intermediate, which can be attacked at either the C-1 or C-3 position. The 80:20 *E*/*Z* ratio of **12** was determined by GC. The product *E* alkene arising from the more thermodynamically stable *syn* π-allyl complex. Since both regioisomeric alcohols **2g** and **2h** gave identical mixtures of the anilines **12** and **13** in similar ratios, the reaction is considered to proceed via π-allylpalladium intermediates (entry 7). The loss of the stereochemistry of the starting alcohol **2g** is due to a rapid $\sigma \rightleftarrows \eta^3 \rightleftarrows \sigma$ interconversion of the π-allyl intermediate compared to the rate of amination of this intermediate. With the unsymmetrical allylic alcohols **2**, the major products were obtained from approach of **1** at the less sterically hindered primary site. Similarly, both regioisomeric alcohols **2i** and **2j** reacted with aniline to give identical mixtures of **14** and regioisomeric aniline **15**, as expected from attack of the aniline on the two allylic termini of the π-allylpalladium species, in similar ratios (entries 8 and 9).

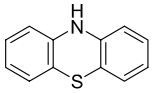
A possible mechanism for the formation of *N*-allylanilines from **1** and **2** is illustrated in Scheme 1, in which the substituent on allylic alcohol is omitted. Oxidative addition of alcohol **2** or protonated alcohol, formed by the acid, to Pd(0) species affords the π-allylpalladium intermediate (**16**). The formation of the π-allylpalladium may be accelerated by the acid, possibly by protonation to increase the leaving group ability of the OH group of the allyl alcohol.[26] Formation of a π-allylpalladium with the carboxylic acid could be the key for the rate enhancement by the acid.[27] Intermolecular nucleophilic substitution of the amino group of **1** takes place at the π-allyl system to give intermediate **17**, followed by reductive elimination gives *N*-allylaniline. In the presence of anilines, which may be relatively reactive toward the palladium center, **16** should be predominantly transformed to **17** to afford aryl amine.

3. Conclusions

In summary, we have developed a catalytic system that enables reactions of aromatic amines with allylic alcohols as

Table 3. Allylic amination of cinnamyl alcohol (**2a**) with anilines (**1b–s**)[a]



Entry	1	R^1	R^2	Yield (%) (3+4)[b]	Yield of 3[b]	Yield of 4[b]
1	**1b**	H	4-Me	81	**3b** 41%	**4b** 40%
2	**1c**	H	4-Cl	78	**3c** 63%	**4c** 15%
3	**1d**	H	4-OMe	96	**3d** 69%	**4d** 27%
4	**1e**	H	4-CO_2Et	91	**3e** 81%	**4e** 10%
5	**1f**	H	4-CN	87	**3f** 70%	**4f** 17%
6	**1g**	H	4-NO_2	65	**3g** 51%	**4g** 14%
7	**1h**	H	2-Br	30	**3h** 30%	
8	**1i**	H	2-CN	78	**3i** 78%	
9	**1j**	H	2-NO_2	27	**3j** 27%	
10	**1k**	H	2,4-Di-Me	60	**3k** 55%	**4k** 5%
11	**1l**	H	2-Cl, 4-Me	73	**3l** 73%	
12	**1m**	H	2-Me, 4-OMe	65	**3m** 59%	**4m** 6%
13	**1n**	H	2-OMe, 4-NO_2	73	**3n** 73%	
14	**1o**	H	3-OCH_2Ph	81	**3o** 65%	**4o** 16%
15	**1p**	H	3-NO_2	92	**3p** 76%	**4p** 16%
16	**1q**	H	3,5-Di-OMe	77	**3q** 56%	**4q** 21%
17	**1r**	Ph	H	92	**3r** 92%	
18	**1s**			95	**3s** 95%	

[a] Reaction conditions: **1** (1 mmol), **2a** (0.8 mmol), $Pd(acac)_2$ (0.02 mmol), PPh_3 (0.08 mmol), and 1-$AdCO_2H$ (0.1 mmol) in water (5 mL) were refluxed for 30 min.
[b] Isolated yield was based on **2a**.

Table 4. Reaction of aniline (**1a**) with allylic alcohols (**2b–j**)[a]

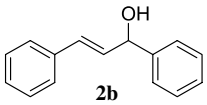
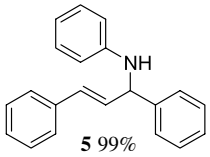
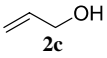
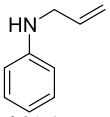
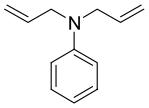
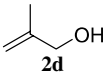
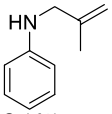
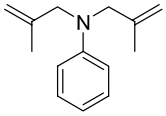
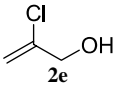
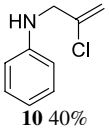
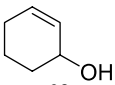
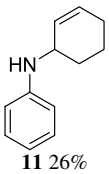
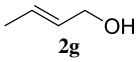
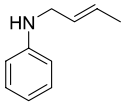
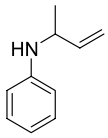
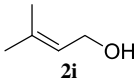
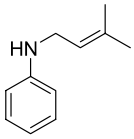
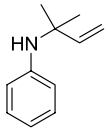
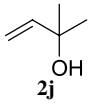
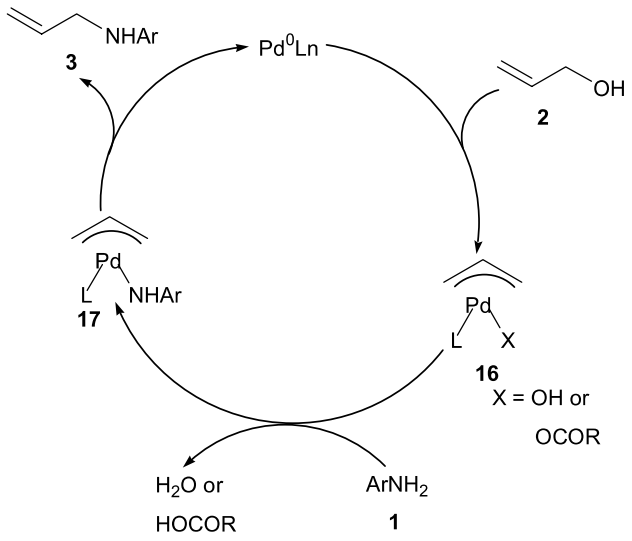
Entry	2	Yields[b]		
1	 **2b**	 **5** 99%		
2	 **2c**	 **6** 31%	 **7** 14%	
3	 **2d**	 **8** 46%	 **9** 16%	
4	 **2e**	 **10** 40%		
5	 **2f**	 **11** 26%		

Table 4 (*continued*)

Entry	2	Yields[b]	
6	 **2g**	 **12** 41% (*E*/*Z*=80/20)[c]	 **13** 9%
7	 **2h**	**12** 40% (*E*/*Z*=78/22)[c]	**13** 11%
8	 **2i**	 **14** 35%	 **15** 8%
9	 **2j**	**14** 38%	**15** 7%

[a] Reaction conditions: **1a** (1 mmol), **2** (0.8 mmol), $Pd(acac)_2$ (0.02 mmol), PPh_3 (0.08 mmol), 1-$AdCO_2H$ (0.1 mmol) and water (5 mL) were refluxed for 30 min.
[b] Isolated yield was based on **2**.
[c] Determined by GC.



Scheme 1.

allylating agents in water. This is a simple and efficient route for C–N bond formation. The effect of addition of a carboxylic acid to promote the palladium-catalyzed allyl–OH bond cleavage remarkably enhanced both the reaction rate and yield. The amination of aromatic and aliphatic allylic alcohol worked well with anilines, giving generally good to high yields of the corresponding allylic anilines. Anilines with steric constraints gave lower chemical yields.

4. Experimental

4.1. General considerations. General method

All melting points were uncorrected. IR absorption spectra were recorded on a Perkin-Elmer System 2000 FT-IR spectrophotometer. Proton and carbon-13 NMR were measured with a Unity-400 or Mercury Plus-400 spectrometer. Carbon multiplicities were obtained from DEPT experiments. Chemical shifts (δ) and coupling constants (Hz) were measured with respect to TMS or chloroform-d_1. MS and high-resolution mass spectra (HRMS) were taken on a Thermo-Finnigan trace GC or Finnigan MAT-95XL instrument, with a direct inlet system. Elemental analyses were carried out on a Heraeus CHN-O-Rapid elemental analyzer. All the following chemicals were commercially available and used without further purification. $Pd(acac)_2$ (acac=acetylacetonate), $Pd_2(dba)_3$ (dba=dibenzylideneacetone), $(2\text{-}MeC_6H_4)_3P$, $(2\text{-furyl})_3P$, $(4\text{-}MeOC_6H_4)_3P$, $(4\text{-}FC_6H_4)_3P$, dppm, 1-adamantanecarboxylic acid, C_6F_5OH, 3,5-dimethoxyaniline, and diphenylamine were purchased from Lancaster. $PdCl_2$(1,10-phen) (phen=phenanthroline), $Pd(OCOCF_3)_2$, $PdCl_2(MeCN)_2$, $PdCl_2(PhCN)_2$, Pd(propionate)$_2$, Pd(hfacac)$_2$, (2-pyridyl)Ph_2P, $(3\text{-}MeC_6H_4)_3P$, $(4\text{-}MeC_6H_4)_3P$, $[2,4,6\text{-}(MeO)_3C_6H_2]_3P$, dppp, dppb, dpph, phenoxyacetic acid, diphenylacetic acid, 2-chloro-4-methylaniline, 4-methoxy-2-methylaniline, 3-benzyloxyaniline, and 2-chloro-2-propen-1-ol were purchased from Aldrich. $Pd(OAc)_2$, PPh_3, $(PhO)_3P$, and allyl alcohol were purchased from Riedel-de Haen. $PdCl_2$, $(4\text{-}ClC_6H_4)_3P$, (±)BINAP, lauric acid, 4-octylbenzoic acid, 4-chloroaniline, 2-cyanoaniline, 2-nitroaniline, and phenothiazine were purchased from Acros Organics. $Pd(PPh_3)_4$, Bu_3P, dppe, (phenylthio)acetic acid, (*S*)-(−)-2-bromopropionic acid, sodium dodecylbenzenesulfonate, aniline, *p*-tolulidine, *p*-anisidine, 4-aminobenzoic acid ethyl ester, 4-cyanoaniline, 4-nitroaniline, 2-bromoaniline, 2,4-dimethylaniline, 2-methoxy-4-nitroaniline, 3-nitroaniline, cinnamyl alcohol, 2-buten-1-ol, 3-buten-2-ol, 2-cyclohexen-1-ol, methallyl alcohol, 2-methyl-3-buten-2-ol, 3-methyl-2-buten-1-ol, and 2-methyl-3-buten-2-ol were purchased from TCI. *trans*-1,3-Diphenyl-2-propen-1-ol was purchased from Fluka. Benzoic acid and acetic acid were purchased from Showa.

4.2. General procedure for the palladium-catalyzed allylation of anilines. Reaction with aniline (1a)

Cinnamyl alcohol (**2a**) (107 mg, 0.8 mmol) and 1-adamantanecarboxylic acid (18 mg, 0.1 mmol) were suspended in water (5 mL) at rt, and then $Pd(acac)_2$ (6 mg, 0.02 mmol), PPh_3 (21 mg, 0.08 mmol) and aniline (93 mg, 1 mmol) were added. The whole was heated under reflux conditions for 30 min. After the mixture was cooled to rt, water and brine were added. The organic materials were extracted with dichloromethane, dried over magnesium sulfate, and concentrated under vacuum. Column chromatography (chloroform/*n*-hexane 1:2) of the residue afforded **3a** and **4a** in 54 and 42% yields, respectively.

Products **3f**,[22e] **4f**,[22e] **3g**,[22e] **4g**,[22e] **3j**,[22e] **3p**,[22e] **4p**,[22e] **3r**,[22e] **3s**,[22e] **6**,[22a] **7**,[22a] **12**,[22b] and **13**,[22b] are known.

4.2.1. *N*-Cinnamylaniline (3a).[28] Light brown oil. IR (KBr) ν: 3421 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.58 (br s, 1H, NH), 3.89 (dd, $J=1.6$, 5.6 Hz, 2H, CH_2), 6.29 (dt, $J=5.6$, 16.0 Hz, 1H, vinyl H), 6.59 (dt, $J=1.6$, 16.0 Hz, 1H, vinyl H), 6.63–6.66 (m, 2H, ArH), 6.72 (ddt, $J=0.8$, 1.2, 7.2 Hz, 1H, ArH), 7.17–7.23 (m, 3H, ArH), 7.28 (dd, $J=7.6$, 7.6 Hz, 2H, ArH), 7.34 (dd, $J=1.6$, 8.0 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ: 46.1 (CH_2), 113.0 (CH), 117.6 (CH), 126.3 (CH), 126.9 (CH), 127.5 (CH), 128.5 (CH), 129.2 (CH), 131.4 (CH), 136.8 (C), 147.9 (C). EI-MS *m/z*: 209 (M^+), 132, 117, 115, 91. HR-MS calcd for $C_{15}H_{15}N$ 209.1204, found 209.1204.

4.2.2. *N,N*-Dicinnamylaniline (4a).[29] Light yellow crystals. Mp 81–83 °C (chloroform/hexane). ^1H NMR ($CDCl_3$) δ: 4.13 (d, $J=5.2$ Hz, 4H, $CH_2\times2$), 6.28 (dt, $J=5.2$, 16.0 Hz, 2H, vinyl H), 6.54 (d, $J=16.0$ Hz, 2H, vinyl H), 6.72 (dd, $J=6.8$, 7.2 Hz, 1H, ArH), 6.82 (d, $J=8.0$ Hz, 2H, ArH), 7.19–7.25 (m, 4H, ArH), 7.29 (dd, $J=7.2$, 8.0 Hz, 4H, ArH), 7.36 (dd, $J=1.2$, 7.2 Hz, 4H, ArH). ^{13}C NMR ($CDCl_3$) δ: 52.2 (CH_2), 112.6 (CH), 116.6 (CH), 125.8 (CH), 126.3 (CH), 127.4 (CH), 128.5 (CH), 129.2 (CH), 131.2 (CH), 136.8 (C), 148.8 (C). EI-MS *m/z*: 325 (M^+), 234, 220, 206, 144, 117, 115, 91, 77. HR-MS calcd for $C_{24}H_{23}N$ 325.1830, found 325.1832. Anal. Calcd for $C_{24}H_{23}N$: C, 88.57; H, 7.12; N, 4.30. Found: C, 88.18; H, 7.16; N, 4.19.

4.2.3. *N*-Cinnamyl-4-methylaniline (3b). Deep yellow oil. IR (KBr) ν: 3406 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.23 (s, 3H, CH_3), 3.43 (br s, 1H, NH), 3.87 (dd, $J=1.6$, 6.0 Hz, 2H, CH_2), 6.30 (dt, $J=6.0$, 16.0 Hz, 1H, vinyl H), 6.58 (dt, $J=1.6$, 16.0 Hz, 1H, vinyl H), 6.58 (d, $J=8.4$ Hz, 2H, ArH), 6.99 (d, $J=8.0$ Hz, 2H, ArH), 7.18–7.22 (m, 1H, ArH), 7.28 (dd, $J=7.2$, 7.6 Hz, 2H, ArH), 7.34 (dd, $J=1.6$, 8.0 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ: 20.4 (CH_3), 46.5 (CH_2), 113.2 (CH), 126.3 (CH), 126.8 (C), 127.2 (CH), 127.4 (CH), 128.5 (CH), 129.7 (CH), 131.3 (CH), 136.8 (C), 145.7 (C). EI-MS *m/z*: 223 (M^+), 208, 196, 181, 165, 146, 131, 117, 115, 91, 77. HR-MS calcd for $C_{16}H_{17}N$ 223.1361, found 223.1361.

4.2.4. *N,N*-Dicinnamyl-4-methylaniline (4b). Light yellow crystals. Mp 66–68 °C (chloroform/hexane). ^1H NMR ($CDCl_3$) δ: 2.24 (s, 3H, CH_3), 4.07 (dd, $J=1.6$, 5.2 Hz, 4H, $CH_2\times2$), 6.25 (dt, $J=5.2$, 16.0 Hz, 2H, vinyl H), 6.51 (d, $J=16.0$ Hz, 2H, vinyl H), 6.74 (d, $J=8.8$ Hz, 2H, ArH), 7.03 (d, $J=8.0$ Hz, 2H, ArH), 7.17–7.21 (m, 2H, ArH), 7.27 (dd, $J=7.2$, 7.6 Hz, 4H, ArH), 7.33 (dd, $J=1.6$, 8.0 Hz, 4H, ArH). ^{13}C NMR ($CDCl_3$) δ: 20.2 (CH_3), 52.4 (CH_2), 112.9 (CH), 125.8 (C), 126.1 (CH), 126.3 (CH), 127.3 (CH), 128.5 (CH), 129.7 (CH), 131.1 (CH), 136.9 (C), 146.7 (C). EI-MS *m/z*: 339 (M^+), 327, 320, 299, 281, 267, 250, 234, 207, 171, 158, 128, 115, 91, 73. HR-MS calcd for $C_{25}H_{25}N$ 339.1987, found 339.1988. Anal. Calcd for $C_{25}H_{25}N$: C, 88.45; H, 7.42; N, 4.13. Found: C, 88.44; H, 7.64; N, 3.98.

4.2.5. *N*-Cinnamyl-4-chloroaniline (3c). White crystals. Mp 77–79 °C (chloroform/hexane). IR (KBr) ν: 3421 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.71 (br s, 1H, NH), 3.86 (dd, $J=1.6$, 6.0 Hz, 2H, CH_2), 6.26 (dt, $J=6.0$, 16.0 Hz, 1H, vinyl H), 6.55 (d, $J=8.8$ Hz, 2H, ArH), 6.58 (d, $J=16.0$ Hz, 1H, vinyl H), 7.11 (d, $J=8.8$ Hz, 2H, ArH), 7.19–7.24 (m, 1H, ArH), 7.29 (dd, $J=7.2$, 8.0 Hz, 2H, ArH), 7.34 (dd, $J=1.6$, 7.2 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ: 46.2 (CH_2), 114.1 (CH), 122.1 (C), 126.2 (CH), 126.3 (CH), 127.6 (CH), 128.5 (CH), 129.0 (CH), 131.7 (CH), 136.6 (C), 146.4 (C). EI-MS *m/z*: 245 ($M^+ + 2$), 243 (M^+), 226, 208, 191, 166, 140, 130, 117, 115, 91, 77. HR-MS calcd for $C_{15}H_{14}ClN$ 243.0814, found 243.0815. Anal. Calcd for $C_{15}H_{14}ClN$: C, 73.92; H, 5.79; N, 5.75. Found: C, 73.95; H, 5.80; N, 5.75.

4.2.6. *N,N*-Dicinnamyl-4-chloroaniline (4c). Light yellow crystals. Mp 79–81 °C (chloroform/hexane). ^1H NMR ($CDCl_3$) δ: 4.11 (dd, $J=1.6$, 5.2 Hz, 4H, $CH_2\times2$), 6.24 (dt, $J=5.2$, 16.0 Hz, 2H, vinyl H), 6.51 (d, $J=16.0$ Hz, 2H, vinyl H), 6.72 (d, $J=8.4$ Hz, 2H, ArH), 7.16 (d, $J=9.2$ Hz, 2H, ArH), 7.20–7.25 (m, 2H, ArH), 7.30 (dd, $J=7.2$, 7.6 Hz, 4H, ArH), 7.35 (dd, $J=1.6$, 7.2 Hz, 4H, ArH). ^{13}C NMR ($CDCl_3$) δ: 52.4 (CH_2), 113.7 (CH), 121.3 (C), 125.2 (CH), 126.3 (CH), 127.6 (CH), 128.6 (CH), 129.0 (CH), 131.4 (CH), 136.7 (C), 147.3 (C). EI-MS *m/z*: 361 ($M^+ + 2$), 359 (M^+), 327, 299, 281, 268, 254, 240, 225, 217, 207, 204, 192, 190, 178, 166, 154, 142, 140, 127, 125, 115, 111, 91, 77. HR-MS calcd for $C_{24}H_{22}ClN$ 359.1440, found 359.1441. Anal. Calcd for $C_{24}H_{22}ClN$: C, 80.10; H, 6.16; N, 3.89. Found: C, 79.96; H, 6.19; N, 3.77.

4.2.7. *N*-Cinnamyl-4-methoxyaniline (3d). Light yellow crystals. Mp 63–64 °C (chloroform/hexane). IR (KBr) ν: 3400 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.42 (br s, 1H, NH), 3.72 (s, 3H, OCH_3), 3.85 (dd, $J=1.6$, 6.0 Hz, 2H, CH_2), 6.31 (dt, $J=6.0$, 16.0 Hz, 1H, vinyl H), 6.59 (d, $J=16.0$ Hz, 1H, vinyl H), 6.62 (d, $J=8.8$ Hz, 2H, ArH), 6.78 (d, $J=8.8$ Hz, 2H, ArH), 7.18–7.22 (m, 1H, ArH), 7.29 (dd, $J=7.2$, 8.0 Hz, 2H, ArH), 7.35 (dd, $J=1.2$, 7.2 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ: 47.1 (CH_2), 55.6 (CH_3), 114.3 (CH), 114.8 (CH), 126.2 (CH), 127.3 (CH), 127.4 (CH), 128.5 (CH), 131.3 (CH), 136.8 (C), 142.1 (C), 152.2 (C). EI-MS *m/z*: 239 (M^+), 222, 208, 197, 162, 147, 122, 117, 115, 91, 77. HR-MS calcd for $C_{16}H_{17}NO$ 239.1310, found 239.1312. Anal. Calcd for $C_{16}H_{17}NO$: C, 80.32; H, 7.16; N, 5.85. Found: C, 80.29; H, 7.17; N, 5.79.

4.2.8. *N,N*-Dicinnamyl-4-methoxyaniline (4d). Light brown oil. ^1H NMR ($CDCl_3$) δ: 3.75 (s, 3H, OCH_3), 4.06 (dd, $J=1.6$, 5.6 Hz, 4H, $CH_2\times2$), 6.26 (dt, $J=5.6$, 16.0 Hz, 2H, vinyl H), 6.53 (d, $J=16.0$ Hz, 2H, vinyl H), 6.76–6.84 (m, 4H, ArH), 7.18–7.23 (m, 2H, ArH), 7.29 (dd, $J=7.2$,

8.0 Hz, 4H, ArH), 7.35 (dd, J=1.2, 7.2 Hz, 4H, ArH). ^{13}C NMR ($CDCl_3$) δ: 53.2 (CH_2), 55.7 (CH_3), 114.7 (CH), 115.0 (CH), 126.2 (CH), 126.3 (CH), 127.4 (CH), 128.5 (CH), 131.4 (CH), 136.9 (C), 143.4 (C), 151.9 (C). EI-MS *m/z*: 355 (M^+), 327, 315, 281, 264, 250, 238, 221, 207, 174, 160, 149, 134, 121, 117, 115, 91, 77. HR-MS calcd for $C_{25}H_{25}NO$ 355.1936, found 355.1937.

4.2.9. Ethyl 4-(cinnamylamino)benzoate (3e). White crystals. Mp 132–133 °C (chloroform/hexane). IR (KBr) ν: 3429 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.34 (t, J=7.2 Hz, 3H, CH_3), 3.96 (dd, J=1.6, 5.6 Hz, 2H, CH_2), 4.30 (dd, J=7.2, 7.2 Hz, 2H, CH_2), 4.49 (br s, 1H, NH), 6.26 (dt, J=5.6, 15.6 Hz, 1H, vinyl H), 6.59 (dt, J=1.2, 16.0 Hz, 1H, vinyl H), 7.20–7.25 (m, 1H, ArH), 7.30 (dd, J=7.2, 7.6 Hz, 2H, ArH), 7.35 (dd, J=1.6, 7.2 Hz, 2H, ArH), 7.88 (d, J=9.2 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ: 14.4 (CH_3), 45.5 (CH_2), 60.2(CH_2), 111.7 (CH), 119.0 (C), 125.6 (CH), 126.3 (CH), 127.7 (CH), 128.5 (CH), 131.4 (CH), 132.0 (CH), 136.5 (C), 151.5 (C), 166.8 (C). EI-MS *m/z*: 281 (M^+), 252, 236, 208, 191, 150, 130, 117, 115, 91. HR-MS calcd for $C_{18}H_{19}NO_2$ 281.1416, found 281.1415. Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.77; H, 6.81; N, 4.90.

4.2.10. Ethyl 4-(dicinnamylamino)benzoate (4e). White crystals. Mp 120–122 °C (chloroform/hexane). ^{1}H NMR ($CDCl_3$) δ: 1.35 (t, J=7.2 Hz, 3H, CH_3), 4.20 (dd, J=1.2, 5.2 Hz, 2H, $CH_2\times2$), 4.32 (dd, J=7.2 Hz, 2H, CH_2), 6.25 (dt, J=5.2, 16.0 Hz, 2H, vinyl H), 6.51 (d, J=16.0 Hz, 2H, vinyl H), 6.79 (d, J=9.2 Hz, 2H, ArH), 7.21–7.25 (m, 2H, ArH), 7.30 (dd, J=7.2, 7.6 Hz, 4H, ArH), 7.35 (dd, J=1.6, 7.2 Hz, 4H, ArH), 7.92 (d, J=8.8 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ: 14.4 (CH_3), 52.2 (CH_2), 60.1 (CH_2), 108.1 (C), 111.3 (CH), 124.2 (CH), 126.3 (CH), 127.6 (CH), 128.5 (CH), 131.3 (CH), 131.7 (CH), 136.4 (C), 151.7 (C), 166.7 (C). EI-MS *m/z*: 397 (M^+), 368, 352, 341, 327, 319, 306, 292, 281, 267, 253, 230, 207, 192, 178, 163, 150, 135, 117, 91, 77. HR-MS calcd for $C_{27}H_{27}NO_2$ 397.2041, found 397.2043. Anal. Calcd for $C_{27}H_{27}NO_2$: C, 81.58; H, 6.85; N, 3.52. Found: C, 81.75; H, 6.90; N, 3.45.

4.2.11. *N*-Cinnamyl-2-bromoaniline (3h). Light brown oil. IR (KBr) ν: 3422 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 3.99 (dd, J=1.6, 5.6 Hz, 2H, CH_2), 4.68 (br s, 1H, NH), 6.31 (dt, J=5.6, 16.0 Hz, 1H, vinyl H), 6.59 (ddd, J=1.2, 7.2, 7.6 Hz, 1H, ArH), 6.62 (dd, J=1.6, 16.0 Hz, 1H, vinyl H), 6.70 (dd, J=1.6, 8.4 Hz, 1H, ArH), 7.17 (ddd, J=1.6, 7.2, 7.6 Hz, 1H, ArH), 7.20–7.25 (m, 1H, ArH), 7.28–7.33 (m, 2H, ArH), 7.35–7.39 (m, 2H, ArH), 7.44 (dd, J=1.6, 8.0 Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ: 46.0 (CH_2), 109.8 (C), 117.8 (CH), 118.1 (CH), 126.1 (CH), 126.4 (CH), 127.6 (CH), 128.5 (CH), 128.6 (CH), 131.8 (CH), 132.4 (CH), 136.6 (C), 144.6 (C). EI-MS *m/z*: 290 (M^++2), 288 (M^+), 208, 191, 130, 117, 115, 91. HR-MS calcd for $C_{15}H_{14}BrN$ 287.0310, found 287.0309.

4.2.12. *N*-Cinnamyl-2-cyanoaniline (3i). Colorless crystals. Mp 70–72 °C (chloroform/hexane). IR (KBr) ν: 3431, 2212 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 4.00 (dd, J=1.6, 5.6 Hz, 2H, CH_2), 4.85 (br s, 1H, NH), 6.24 (dt, J=5.6, 16.0 Hz, 1H, vinyl H), 6.60 (dt, J=1.6, 16.0 Hz, 1H, vinyl H), 6.67 (ddd, J=0.8, 7.2, 7.6 Hz, 1H, ArH), 6.69 (d, J=8.4 Hz, 1H, ArH), 7.21–7.25 (m, 1H, ArH), 7.31 (dd, J=7.2, 7.6 Hz, 2H, ArH), 7.33–7.40 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$) δ: 45.1 (CH_2), 95.7 (C), 110.8 (CH), 116.5 (CH), 117.8 (C), 125.1 (CH), 126.2 (CH), 127.6 (CH), 128.4 (CH), 131.9 (CH), 132.6 (CH), 134.1 (CH), 136.2 (C), 149.9 (C). EI-MS *m/z*: 234 (M^+), 217, 207, 155, 131, 117, 115, 102, 91. HR-MS calcd for $C_{16}H_{14}N_2$ 234.1157, found 234.1159. Anal. Calcd for $C_{15}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 82.18; H, 6.00; N, 11.94.

4.2.13. *N*-Cinnamyl-2,4-dimethylaniline (3k). Brown oil. IR (KBr) ν: 3431 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.12 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 3.40 (br s, 1H, NH), 3.90 (dd, J=1.6, 6.0 Hz, 2H, CH_2), 6.33 (dt, J=6.0, 16.0 Hz, 1H, vinyl H), 6.57 (d, J=8.0 Hz, 1H, ArH), 6.59 (dt, J=1.6, 16.0 Hz, 1H, vinyl H), 6.89 (s, 1H, ArH), 6.92 (dd, J=1.6, 8.0 Hz, 1H, ArH), 7.17–7.23 (m, 1H, ArH), 7.27 (dd, J=7.2, 7.6 Hz, 2H, ArH), 7.34 (dd, J=1.6, 7.2 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ: 17.4 (CH_3), 20.3 (CH_3), 46.4 (CH_2), 110.3 (CH), 122.2 (C), 126.2 (CH), 127.1 (C), 127.2 (CH), 127.3 (CH), 127.4 (CH), 128.5 (CH), 130.9 (CH), 131.2 (C), 131.4 (CH), 136.8 (C). EI-MS *m/z*: 237 (M^+), 144, 132, 117, 115, 91. HR-MS calcd for $C_{17}H_{19}N$ 237.1518, found 237.1517.

4.2.14. *N,N*-Dicinnamyl-2,4-dimethylaniline (4k). Light brown oil. ^{1}H NMR ($CDCl_3$) δ: 2.27 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 3.74 (d, J=6.4 Hz, 4H, $CH_2\times2$), 6.21 (dt, J=6.4, 16.0 Hz, 2H, vinyl H), 6.51 (d, J=16.0 Hz, 2H, vinyl H), 6.93–7.01 (m, 3H, ArH), 7.18–7.25 (m, 2H, ArH), 7.28 (dd, J=7.2, 7.6 Hz, 4H, ArH), 7.34 (d, J=7.2 Hz, 4H, ArH). ^{13}C NMR ($CDCl_3$) δ: 18.3 (CH_3), 20.7 (CH_3), 55.3 (CH_2), 121.9 (CH), 126.3 (CH), 126.6 (CH), 127.3 (CH), 128.1 (CH), 128.5 (CH), 131.8 (CH), 132.1 (CH), 132.6 (C), 133.7 (C), 137.2 (C), 147.5 (C). EI-MS *m/z*: 353 (M^+), 262, 248, 237, 220, 172, 158, 147, 132, 117, 115, 103, 91, 77. HR-MS calcd for $C_{26}H_{27}N$ 353.2144, found 353.2144.

4.2.15. *N*-Cinnamyl-2-chloro-4-methylaniline (3l). Yellow oil. IR (KBr) ν: 3418 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.20 (s, 3H, CH_3), 3.93 (dd, J=1.6, 5.6 Hz, 2H, CH_2), 4.36 (br s, 1H, NH), 6.29 (dt, J=5.6, 16.0 Hz, 1H, vinyl H), 6.59 (d, J=15.6 Hz, 1H, vinyl H), 6.60 (d, J=8.4 Hz, 1H, ArH), 6.92 (dd, J=2.0, 8.4 Hz, 1H, ArH), 7.09 (d, J=2.0 Hz, 1H, ArH), 7.18–7.23 (m, 1H, ArH), 7.30 (dd, J=7.2, 7.6 Hz, 2H, ArH), 7.35 (dd, J=1.2, 7.2 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ: 20.1 (CH_3), 46.0 (CH_2), 111.6 (CH), 119.0 (C), 126.3 (CH), 126.5 (CH), 127.5 (CH), 128.3 (CH), 128.5 (CH), 129.5 (CH), 131.5 (CH), 136.7 (C), 141.5 (C). EI-MS *m/z*: 259 (M^++2), 257 (M^+), 222, 205, 178, 154, 144, 117, 115, 91, 77. HR-MS calcd for $C_{16}H_{16}ClN$ 257.0971, found 257.0970.

4.2.16. *N*-Cinnamyl-4-methoxy-2-methylaniline (3m). Deep brown oil. IR (KBr) ν: 3422 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.14 (s, 3H, CH_3), 3.20 (br s, 1H, NH), 3.71 (s, 3H, OCH_3), 3.89 (dd, J=1.2, 5.6 Hz, 2H, CH_2), 6.34 (dt, J=6.0, 16.0 Hz, 1H, vinyl H), 6.59 (d, J=16.0 Hz, 1H, vinyl H), 6.60 (d, J=8.4 Hz, 1H, ArH), 6.67–6.71 (m, 2H, ArH), 7.18–7.22 (m, 1H, ArH), 7.28 (dd, J=7.2, 7.6 Hz, 2H, ArH), 7.35 (dd, J=1.6, 7.2 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ: 17.7 (CH_3), 46.9 (CH_2), 55.6 (CH_3), 111.2 (CH), 111.4 (CH), 116.9 (CH), 123.9 (C), 126.2 (CH), 127.3 (CH), 127.4 (CH), 128.5 (CH), 131.4 (CH), 136.8 (C), 140.1 (C),

151.7 (C). EI-MS *m/z*: 253 (M^+), 136, 117, 115, 93, 91. HR-MS calcd for $C_{17}H_{19}NO$ 253.1467, found 253.1468.

4.2.17. *N*,*N*-Dicinnamyl-4-methoxy-2-methylaniline (4m). Yellow oil. ^1H NMR ($CDCl_3$) δ: 2.37 (s, 3H, CH_3), 3.70 (d, $J=6.4$ Hz, 4H, $CH_2\times2$), 3.74 (s, 3H, OCH_3), 6.20 (dt, $J=6.4$, 16.0 Hz, 2H, vinyl H), 6.49 (d, $J=16.0$ Hz, 2H, vinyl H), 6.68 (dd, $J=2.8$, 8.8 Hz, 1H, ArH), 6.75 (d, $J=2.8$ Hz, 1H, ArH), 7.02 (d, $J=8.8$ Hz, 1H, ArH), 7.19–7.23 (m, 2H, ArH), 7.29 (dd, $J=7.2$, 7.6 Hz, 4H, ArH), 7.32 (dd, $J=1.6$, 7.6 Hz, 4H, ArH). ^{13}C NMR ($CDCl_3$) δ: 18.4 (CH_3), 55.2 (CH_3), 55.9 (CH_2), 111.0 (CH), 116.2 (CH), 123.3 (CH), 126.2 (CH), 127.2 (CH), 127.3 (CH), 128.4 (CH), 132.1 (CH), 135.8 (C), 137.2 (C), 143.2 (C), 155.6 (C). EI-MS *m/z*: 369 (M^+), 278, 264, 252, 207, 188, 148, 135, 133, 117, 115, 91. HR-MS calcd for $C_{26}H_{27}NO$ 369.2093, found 369.2089.

4.2.18. *N*-Cinnamyl-2-methoxy-4-nitroaniline (3n). Light yellow crystals. Mp 129–131 °C (chloroform/hexane). IR (KBr) ν: 3429 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.91 (s, 3H, OCH_3), 4.04 (dd, $J=1.6$, 5.6 Hz, 2H, CH_2), 5.28 (br s, 1H, NH), 6.26 (dt, $J=5.6$, 15.6 Hz, 1H, vinyl H), 6.52 (d, $J=8.8$ Hz, 1H, ArH), 6.60 (d, $J=15.6$ Hz, 1H, vinyl H), 7.21–7.26 (m, 1H, ArH), 7.31 (dd, $J=7.2$, 7.6 Hz, 2H, ArH), 7.36 (dd, $J=1.6$, 7.2 Hz, 2H, ArH), 7.61 (d, $J=2.4$ Hz, 1H, ArH), 7.88 (dd, $J=2.4$, 8.8 Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ: 44.9 (CH_2), 55.8 (CH_3), 104.6 (CH), 106.9 (CH), 119.7 (CH), 124.7 (CH), 126.3 (CH), 127.8 (CH), 128.5 (CH), 132.4 (CH), 136.2 (C), 137.2 (C), 143.9 (C), 145.1 (C). EI-MS *m/z*: 284 (M^+), 253, 237, 207, 193, 165, 147, 117, 115, 91. HR-MS calcd for $C_{16}H_{16}N_2O_3$ 284.1161, found 284.1162. Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.56; H, 5.64; N, 9.72.

4.2.19. *N*-Cinnamyl-3-benzyloxyaniline (3o). Brown oil. IR (KBr) ν: 3411 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.75 (br s, 1H, NH), 3.82 (dd, $J=1.2$, 6.0 Hz, 2H, CH_2), 4.97 (s, 2H, CH_2), 6.24 (dt, $J=6.0$, 15.6 Hz, 1H, vinyl H), 6.24–6.28 (m, 2H, ArH), 6.34 (ddd, $J=0.8$, 2.4, 8.0 Hz, 1H, ArH), 6.54 (d, $J=16.0$ Hz, 1H, vinyl H), 7.06 (t, $J=8.0$ Hz, 1H, ArH), 7.17–7.21 (m, 1H, ArH), 7.27 (d, $J=7.2$ Hz, 2H, ArH), 7.28–7.35 (m, 5H, ArH), 7.38 (dd, $J=1.6$, 6.8 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ: 46.0 (CH_2), 69.7 (CH_2), 99.8 (CH), 103.5 (CH), 106.4 (CH), 126.2 (CH), 126.8 (CH), 127.4 (CH), 127.4 (CH), 127.7 (CH), 128.4 (CH), 128.5 (CH), 129.9 (CH), 131.4 (CH), 136.7 (C), 137.2 (C), 149.3 (C), 160.0 (C). EI-MS *m/z*: 315 (M^+), 288, 271, 239, 224, 207, 196, 182, 146, 117, 115, 91, 77. HR-MS calcd for $C_{22}H_{21}NO$ 315.1623, found 315.1625.

4.2.20. *N*,*N*-Dicinnamyl-3-benzyloxyaniline (4o). Brown crystals. Mp 73–74 °C (chloroform/hexane). ^1H NMR ($CDCl_3$) δ: 4.10 (dd, $J=1.2$, 5.6 Hz, 4H, $CH_2\times2$), 5.03 (s, 2H, CH_2), 6.25 (dt, $J=5.6$, 16.0 Hz, 2H, vinyl H), 6.37 (d, $J=8.0$ Hz, 1H, ArH), 6.42–6.49 (m, 2H, ArH), 6.52 (d, $J=16.0$ Hz, 2H, vinyl H), 7.11–7.24 (m, 4H, ArH), 7.28–7.33 (m, 2H, ArH), 7.29 (dd, $J=6.8$, 8.0 Hz, 4H, ArH), 7.35 (dd, $J=1.6$, 7.2 Hz, 4H, ArH), 7.41 (dd, $J=1.6$, 6.8 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ: 52.2 (CH_2), 69.9 (CH_2), 100.0 (CH), 102.4 (CH), 105.9 (CH), 125.7 (CH), 126.4 (CH), 127.4 (CH), 127.5 (CH), 127.8 (CH), 128.3 (CH), 128.5 (CH), 129.9 (CH), 131.3 (CH), 136.8 (C), 137.3 (C), 150.2 (C), 160.1 (C). EI-MS *m/z*: 431 (M^+), 401, 355, 340, 327, 281, 250, 207, 179, 166, 150, 131, 117, 91. HR-MS calcd for $C_{31}H_{29}NO$ 431.2249, found 431.2250. Anal. Calcd for $C_{31}H_{29}NO$: C, 86.27; H, 6.77; N, 3.25. Found: C, 86.16; H, 6.83; N, 3.20.

4.2.21. *N*-Cinnamyl-3,5-dimethoxyaniline (3q). Light green oil. IR (KBr) ν: 3408 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.70 (s, 6H, $CH_3\times2$), 3.82 (br s, 1H, NH), 3.83 (dd, $J=1.6$, 5.6 Hz, 2H, CH_2), 5.83 (d, $J=2.4$ Hz, 2H, ArH), 5.89 (dd, $J=2.0$, 2.4 Hz, 1H, ArH), 6.25 (dt, $J=5.6$, 16.0 Hz, 1H, vinyl H), 6.55 (d, $J=16.0$ Hz, 1H, vinyl H), 7.16–7.21 (m, 1H, ArH), 7.27 (dd, $J=7.6$, 7.6 Hz, 2H, ArH), 7.33 (dd, $J=1.6$, 7.2 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ: 46.0 (CH_2), 54.9 (CH_3), 54.9 (CH_3), 89.7 (CH), 91.7 (CH), 126.2 (CH), 126.7 (CH), 127.4 (CH), 128.4 (CH), 131.3 (CH), 136.7 (C), 149.9 (C), 161.6 (C). EI-MS *m/z*: 269 (M^+), 252, 238, 223, 190, 178, 166, 147, 117, 115, 91. HR-MS calcd for $C_{17}H_{19}NO_2$ 269.1416, found 269.1416.

4.2.22. *N*,*N*-Dicinnamyl-3,5-dimethoxyaniline (4q). Brown oil. ^1H NMR ($CDCl_3$) δ: 3.75 (s, 6H, $OCH_3\times2$), 4.10 (dd, $J=1.2$, 5.2 Hz, 4H, $CH_2\times2$), 5.92 (dd, $J=2.0$, 2.0 Hz, 1H, ArH), 6.01 (d, $J=2.0$ Hz, 2H, ArH), 6.26 (dt, $J=5.2$, 16.0 Hz, 2H, vinyl H), 6.53 (d, $J=16.0$ Hz, 2H, vinyl H), 7.19–7.23 (m, 2H, ArH), 7.29 (dd, $J=7.2$, 7.6 Hz, 4H, ArH), 7.35 (dd, $J=1.6$, 7.2 Hz, 4H, ArH). ^{13}C NMR ($CDCl_3$) δ: 52.3 (CH_2), 55.1 (CH_3), 88.6 (CH), 91.9 (CH), 125.7 (CH), 126.3 (CH), 127.4 (CH), 128.5 (CH), 131.2 (CH), 136.8 (C), 150.7 (C), 161.7 (C). EI-MS *m/z*: 385 (M^+), 356, 318, 307, 294, 268, 253, 238, 222, 210, 190, 177, 166, 153, 117, 115, 91. HR-MS calcd for $C_{26}H_{27}NO_2$ 385.2041, found 385.2038.

4.2.23. (1,3-Diphenylallyl)phenylamine (5). Brown oil. IR (KBr) ν: 3414 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.08 (br s, 1H, NH), 5.04 (d, $J=6.0$ Hz, 1H, CH), 6.34 (dd, $J=6.0$, 15.6 Hz, 1H, CH), 6.58 (d, $J=15.6$ Hz, 1H, ArH), 6.59 (dd, $J=0.8$, 8.8 Hz, 2H, CH, ArH), 6.67 (ddt, $J=0.8$, 1.2, 7.2 Hz, 1H, ArH), 7.07–7.40 (m, 12H, ArH). ^{13}C NMR ($CDCl_3$) δ: 60.5 (CH), 113.5 (CH), 117.6 (CH), 126.4 (CH), 127.1 (CH), 127.4 (CH), 127.6 (CH), 128.5 (CH), 128.7 (CH), 129.1 (CH), 130.6 (CH), 131.0 (CH), 136.6 (C), 142.0 (C), 147.1 (C). EI-MS *m/z*: 285 (M^+), 270, 206, 193, 178, 165, 152, 115, 91, 77, 65. HR-MS calcd for $C_{21}H_{19}N$ 285.1517, found 285.1514.

4.2.24. *N*-(2-Methylprop-2-enyl)aniline (8).[30] Deep brown oil. IR (KBr) ν: 3419 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.77 (s, 3H, CH_3), 3.66 (s, 2H, CH_2), 3.80 (br s, 1H, NH), 4.86–4.89 (m, 1H, vinyl H), 4.95–4.98 (m, 1H, vinyl H), 6.60 (d, $J=8.0$ Hz, 2H, ArH), 6.69 (t, $J=7.2$ Hz, 1H, ArH), 7.16 (dd, $J=7.2$, 8.0 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ: 20.4 (CH_3), 49.9 (CH_2), 110.9 (CH_2), 112.8 (CH), 117.3 (CH), 129.1 (CH), 142.7 (C), 148.2 (C). EI-MS *m/z*: 147 (M^+), 132, 118, 106, 91, 77. HR-MS calcd for $C_{10}H_{13}N$ 147.1048, found 147.1045.

4.2.25. *N*,*N*-Bis(2-methylprop-2-enyl)aniline (9). Deep blue oil. ^1H NMR ($CDCl_3$) δ: 1.74 (s, 6H, $CH_3\times2$), 3.80 (s, 4H, $CH_2\times2$), 4.81 (d, $J=24.8$ Hz, 4H, $CH_2\times2$), 6.62 (d, $J=8.8$ Hz, 2H, ArH), 6.66 (d, $J=7.2$ Hz, 1H, ArH), 7.17 (dd, $J=7.6$, 8.0 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ: 20.0 (CH_3), 56.3 (CH_2), 110.2 (CH_2), 111.9 (CH), 115.9 (CH), 128.8 (CH), 140.5 (C), 148.7 (C). EI-MS *m/z*: 201 (M^+),

186, 160, 145, 130, 118, 104, 91, 77. HR-MS calcd for $C_{14}H_{19}N$ 201.1518, found 201.1517.

4.2.26. *N*-(2-Chloroallyl)aniline (10). Deep brown oil. IR (KBr) ν: 3418 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.88 (dd, $J=1.2$, 1.2 Hz, 2H, CH_2), 4.03 (br s, 1H, NH), 5.29 (dt, $J=1.2$, 2.8 Hz, 1H, vinyl H), 5.39 (dt, $J=1.6$, 2.8 Hz, 1H, vinyl H), 6.58 (dd, $J=0.8$, 8.4 Hz, 2H, ArH), 6.73 (ddt, $J=0.8$, 1.2, 7.6 Hz, 1H, ArH), 7.17 (dd, $J=7.6$, 8.4 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ: 50.0 (CH_2), 112.4 (CH_2), 112.9 (CH), 118.1 (CH), 129.2 (CH), 139.2 (C), 146.7 (C). EI-MS *m/z*: 169 ($M^+ +2$), 167 (M^+), 132, 118, 106, 92, 77. HR-MS calcd for $C_9H_{10}ClN$ 167.0502, found 167.0503.

4.2.27. *N*-(2-Cyclohexenyl)aniline (11). Light brown oil. IR (KBr) ν: 3407 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.57–1.74 (m, 3H, CH_2), 1.86–1.92 (m, 1H, CH_2), 1.99–2.05 (m, 2H, CH_2), 3.57 (br s, 1H, NH), 3.94–4.01 (m, 1H, CH), 5.74 (ddt, $J=2.4$, 2.4, 10.0 Hz, 1H, vinyl H), 5.83 (ddt, $J=1.6$, 3.6, 10.0 Hz, 1H, vinyl H), 6.60 (d, $J=8.4$ Hz, 2H, ArH), 6.67 (dt, $J=0.8$, 7.2 Hz, 1H, ArH), 7.12–7.18 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ: 19.6 (CH_2), 25.1 (CH_2), 28.8 (CH_2), 47.8 (CH), 113.2 (CH), 117.1 (CH), 128.5 (CH), 129.2 (CH), 130.0 (CH), 147.1 (C). EI-MS *m/z*: 173 (M^+), 145, 144, 130, 96. HR-MS calcd for $C_{12}H_{15}N$ 173.1205, found 173.1203.

4.2.28. *N*-(3-Methylbut-2-enyl)aniline (14). Brown oil. IR (KBr) ν: 3408 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.71 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 3.60 (br s, 1H, NH), 3.68 (d, $J=$ 6.8 Hz, 2H, CH_2), 5.30–5.35 (m, 1H, vinyl H), 6.61 (dd, $J=$ 1.2, 8.4 Hz, 2H, ArH), 6.70 (ddd, $J=0.8$, 1.2, 7.2 Hz, 1H, ArH), 7.17 (dd, $J=7.2$, 8.4 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ: 17.9 (CH_3), 25.7 (CH_3), 42.0 (CH_2), 112.9 (CH), 117.3 (CH), 121.6 (C), 129.1 (C), 135.6 (C), 148.4 (C). EI-MS *m/z*: 161 (M^+), 146, 144, 130, 118, 106, 93, 77. HR-MS calcd for $C_{11}H_{15}N$ 161.1205, found 161.1204.

4.2.29. *N*-(1,1-Dimethylprop-2-enyl)aniline (15). Brown oil. IR (KBr) ν: 3421 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.38 (s, 6H, $CH_3\times2$), 3.52 (br s, 1H, NH), 5.10 (dd, $J=1.2$, 10.8 Hz, 1H, vinyl H), 5.18 (dd, $J=1.2$, 17.6 Hz, 1H, vinyl H), 6.01 (dd, $J=10.8$, 17.6 Hz, 1H, vinylH), 6.66–6.70 (m, 1H, ArH), 6.69 (dd, $J=1.2$, 7.6 Hz, 2H, ArH), 7.10 (dd, $J=$ 7.6, 8.4 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ: 28.3 (CH_3), 54.6 (CH), 112.7 (CH_2), 115.7 (CH), 117.4 (CH), 128.7 (CH), 146.1 (CH), 146.6 (C). EI-MS *m/z*: 161 (M^+), 146, 131, 130, 120, 118, 103, 93, 91, 77. HR-MS calcd For $C_{11}H_{15}N$ 161.1205, found 161.1207.

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Towards new camptothecins. Part 3: Synthesis of 5-methoxycarbonyl camptothecin☆

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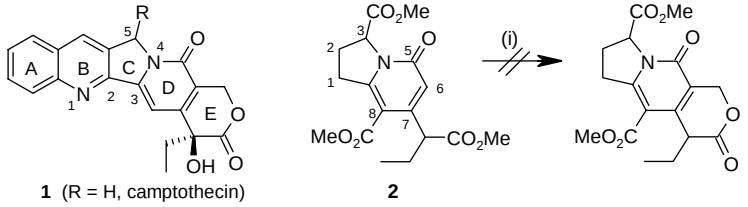
Abstract—The synthesis of two camptothecin analogs substituted by a carbonyl function on position 5 of cycle C was realized. New conditions were studied to obtain the E-lactone ring of these heterocycles. These compounds were obtained from the reaction of Bredereck's reagent with indolizines derived from pyroglutamic acid. This yielded dimethylaminovinyl groups whose oxidation by $NaIO_4$ yielded ketones. The indolizinones obtained were reacted in Friedlander condition, to give the scaffold of the desired camptothecins.

1. Introduction

In the context of the synthesis of new camptothecins **1** substituted in position 5, we chose to use the general method of Danishefsky.[1] In previous paper in this series,[2a] we solved the problem of the introduction of a ketone function in position 1 of indolizines **2** derived from pyroglutamic acid. The next crucial point now was the formation of the E ring. We have already shown[2b] that this lactone ring cannot be obtained by reacting formaldehyde with indolizines **2** under Danishefsky conditions (Scheme 1). Herein, we report on attempts to obtain the lactone ring E by using an intramolecular cyclization of intermediates **3** or **4**, then a successful Mannich reaction of pyridone **2**, in conditions different from the previous ones (Scheme 2). Transformation of the compound thus obtained led to a camptothecin analog, although in low yields.

2. The intramolecular approach

Considering the poor yields of the classical Mannich condensation,[2b] we thought that an intramolecular reaction could allow the synthesis of the cycle E. This can be obtained by cyclizing sulfonium **3a** (Pummerer reaction)[3] or oxonium **3b** (Mannich reaction)[4] salts, or by attack of the pyridone ring on a methyl ester substituted by a chloride or sulfinate leaving group (Scheme 2). In order to obtain these intermediates, it was necessary to differentiate the three appended carbonyl groups located on the pyrrolo–pyridone scaffold **2**. Because saponification of heterocycle **2** (R=H, Et) (Scheme 1) was not selective and led to hydrolysis of the two aliphatic esters groups, we used the carboxamides **5** and **6** (Scheme 3) as the starting compounds.



1 (R = H, camptothecin) **2**

Scheme 1. Reaction conditions: (i) CH_2O, dioxane, H_2O, H_2SO_4.

☆ Part 2 in this series: see Ref. 2a.

Keywords: Camptothecins; Mannich reaction; Bredereck's reagent.
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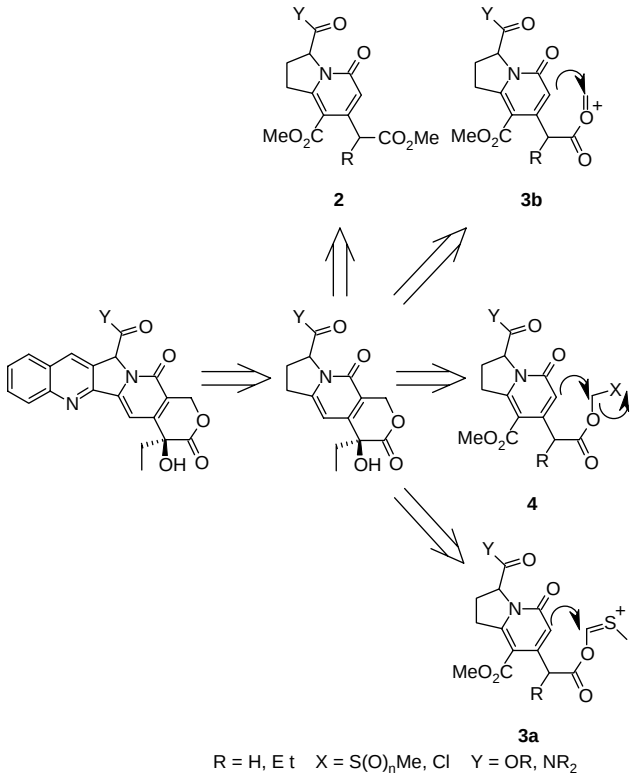
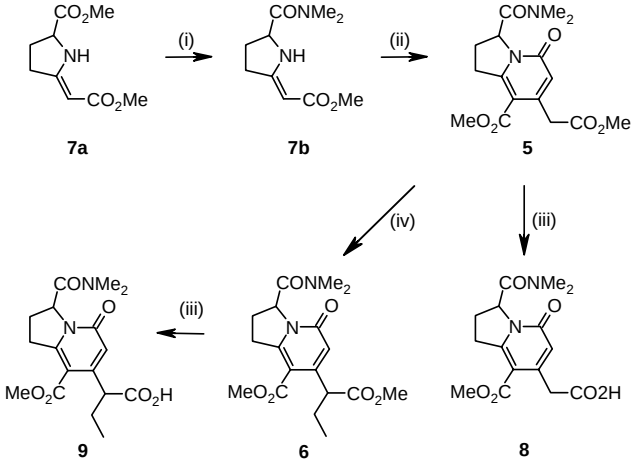


Scheme 2. Retrosynthetic approach towards modified camptothecins.



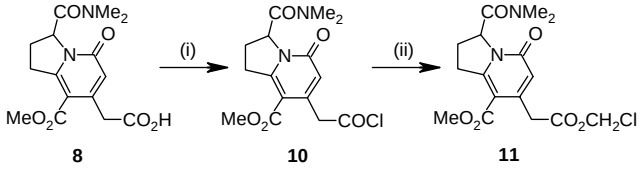
Scheme 3. Reaction conditions: (i) Me_2NH, MeOH (77%);[2a] (ii) dimethyl 3-chloroglutaconate, Et_3N, MeOH (95%);[2a] (iii) NaOH, 20 °C, 30 min (**8** 89%, **9** 78%); (iv) EtI, NaH, THF (78%).[2a]

2.1. Synthesis of acids 8 and 9

Amides **5** and **6** were obtained from enaminoesters **7a**,**b** as already described.[2a] The aliphatic ester group of these heterocycles was selectively saponified at room temperature by a dilute sodium hydroxide solution. Afterward, acidification gave very good yields in acids **8** and **9** (Scheme 3). It is worthy to note that the reaction of ester **5** with potassium trimethylsilanolate[5] reaches also the aromatic ester group to give a mixture of mono and diacids.

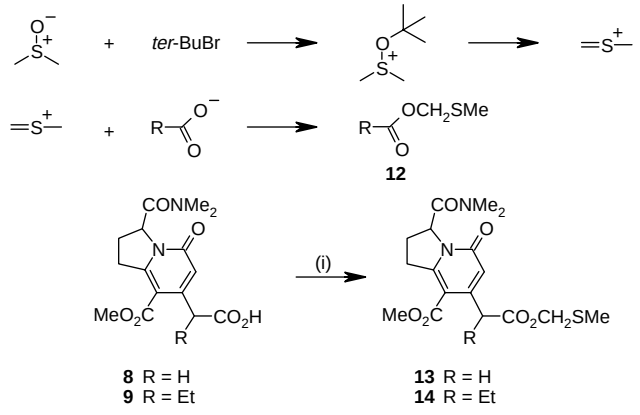
2.2. Synthesis of functionalized esters

It is well known that acid chlorides react with formaldehyde, in the presence of a Lewis acid, giving chloromethyl esters.[6] Thus, acid **8** was reacted with oxalyl chloride to give compound **10** in quantitative yield. Reaction of chloride **10** with formaldehyde and $AlCl_3$ as catalyst led to chloromethyl ester **11** in an unoptimized yield of 20% (Scheme 4). This reaction did not succeed when zinc chloride or boron trifluoride etherate was used as catalyst.



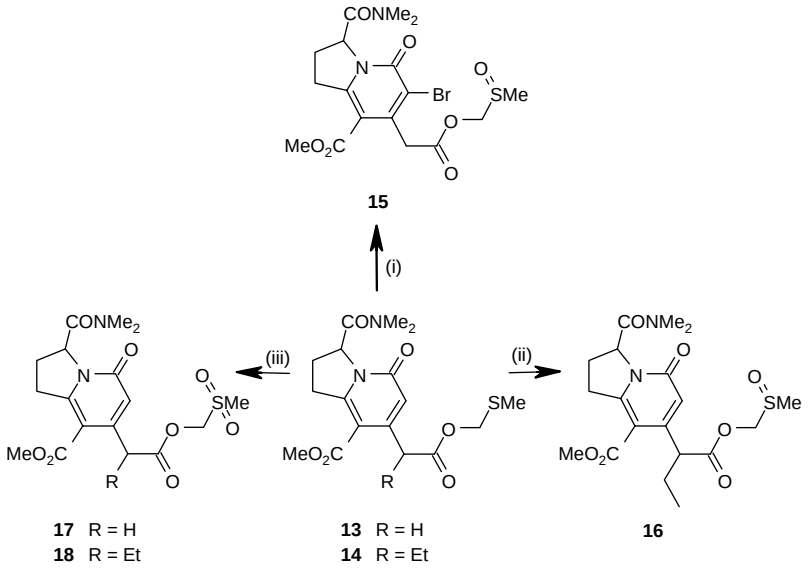
Scheme 4. Reaction conditions: (i) $(ClCO)_2$, $CHCl_3$, DMF cat., 20 °C, 30 min (100%); (ii) CH_2O, $AlCl_3$, PhCl, reflux, 24 h (20%).

Reaction of DMSO with *tert*-BuBr in the presence of a base yields a methylenesulfonium cation that can be trapped by a carboxylate ion to give methylsulfanylmethyl esters **12** (Scheme 5).[7] Following this method, esters **13** and **14** were easily obtained in 77–84% yields starting from acids **8** and **9**. Though the reaction can be performed at room temperature in pure DMSO,[7] the use of DMSO diluted in another solvent (CH_2Cl_2) improved the yield in the extraction step. It was then necessary to proceed under reflux conditions.



Scheme 5. Reaction conditions: (i) DMSO, *tert*-BuBr, $NaHCO_3$, (**13**: 20 °C, 24 h, 84%, **14**: 12 h, reflux, 77%).

Taking into account that sulfoxide function could generate a thionium in acid medium (Pummerer reaction), the sulfoxidation of substrates **13** and **14** was investigated. Thus, oxidation of a sulfur atom can be obtained with bromine,[8] but the ring bromination of pyridone also occurred, and ester **13** then gave bromopyridone **15** (because of the acidity if the $ArCH_2CO$ group, treatment of this compound with a base was not attempted). Sodium periodate and magnesium monoperoxyphtalate (MMPP) are more selective reagents, providing, respectively, very good yields in sulfoxide **16** or sulfones **17** and **18** (Scheme 6).



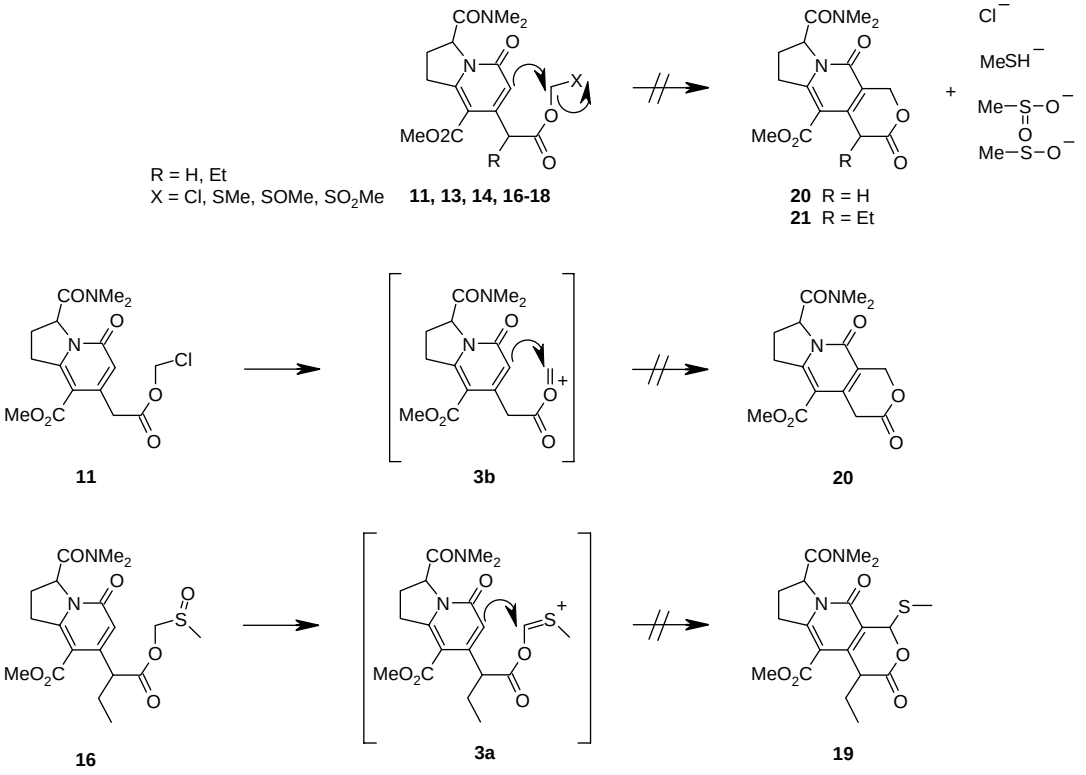
Scheme 6. Reaction conditions: (i) Br_2, $KHCO_3$, H_2O, CH_2Cl_2, 20 °C, 15 h (92%); (ii) $NaIO_4$, H_2O, MeOH, 20 °C, 12 h (86%); (iii) MMPP, MeOH, 20 °C, 12 h (**17**: 98%, **18**: 92%).

2.3. Attempts for the formation of cycle E

Formation of the wanted lactone ring E from previous functionalized esters can be envisaged by a direct attack of the pyridone ring on a C-leaving group, with loss of chloride, methanethiolate, methanesulfenate or methane–sulfinate ion. In another reaction mechanism, treatment of chloromethyl ester **11** with a Lewis acid[6] or sulfoxide **16** with TFAA or Ac_2O and PTSA,[9] could lead to a sulfonium **3a** or oxonium **3b** cation, to give lactones **19** or **20** (Scheme 7). All our attempts to carry out these processes only led to mixtures of many unidentified products.

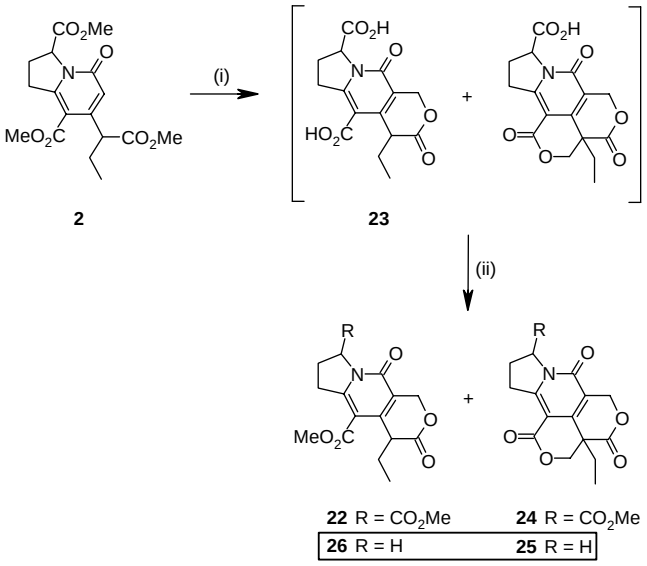
3. The bimolecular approach

At the beginning of this work, it was though necessary to introduce the 5-carboxamide group at the start of the reaction sequence, in order to differentiate the two aliphatic carboxyl functions. In a bimolecular approach it was not



Scheme 7. Attempted formation of the lactone ring E.

necessary to distinguish these groups, and the starting material was now indolizine **2** (Scheme 8).



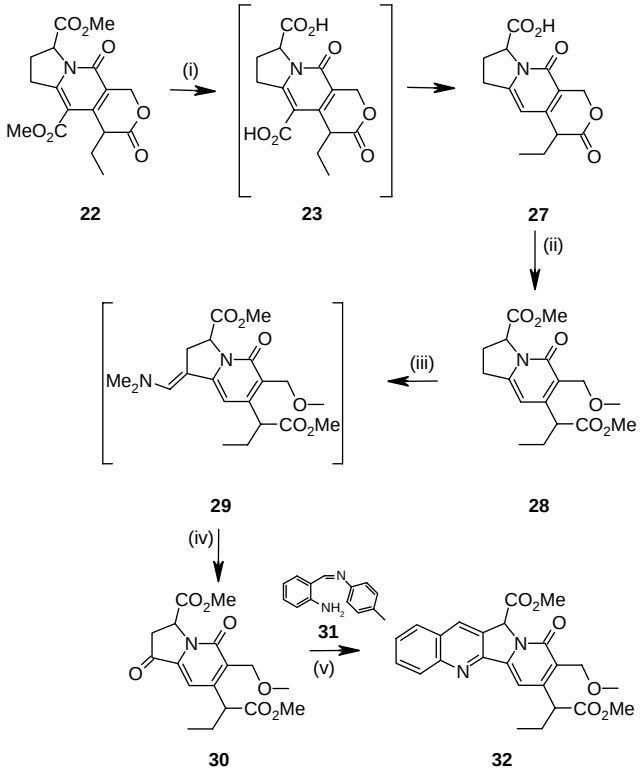
Scheme 8. Reaction conditions: (i) CH_2O, AcOH, 34% HCl, 80 °C, 24 h; (ii) MeOH, $CHCl_3$, H^+, reflux, 24 h (**22**: 84% from **2**, **24**: 0–6% from **2**).

3.1. Mannich reaction of indolizinone 4

We have already described how reaction of formaldehyde with a diastereoisomer mixture of tetrahydroindolizinone **2**[2] in the general conditions of Danishefsky[1,10] (CH_2O, H_2SO_4, dioxane, H_2O, reflux 24 h) does not give lactone **22**.[2b] We now tried other general conditions for Mannich reactions that use aqueous formaldehyde in a mixture of AcOH and concentrated HCl.[11] In that case, a hydroxymethyl group was indeed introduced in the pyridone ring, but a great part of the mixture of products obtained was hydrolyzed, mainly leading to hydroxyacids. To decrease the water content of the reaction mixture, aqueous formaldehyde was replaced by polyoxymethylene. Under these conditions, lactone **23** was formed in very good yield. Due to the difficulties encountered during its purification, it was transformed into the corresponding methyl esters **22**. The esterification was realized in 84% reproducible yield with MeOH under the ternary Azeotropic conditions (H_2O/MeOH/$CHCl_3$).[2a,12] gave a lactone **22**. It should be noted that this product was often accompanied by a small amount of di-lactone **24**, analog to compound **25** (R=H) that was obtained[2b] in attempts to reproduce the synthesis of heterocycle **26** described earlier (Scheme 8).[1]

3.2. Synthesis of 5-methoxycarbonyl camptothecin analog 32

Reflux of diester **22** in 48% HBr[1] led to the hydrolysis of the ester functions followed by a decarboxylation of the aromatic acid as in **23** (Scheme 9). Lactone **27** was thus obtained in 92% yield. It was necessary to esterify again the free acid group before performing the next step.[13] When the esterification was performed in our usual conditions (MeOH, $CHCl_3$, H^+),[2a,12] opening of the lactone ring occurred and 64% of ether **28** was isolated. Ether **28** was an

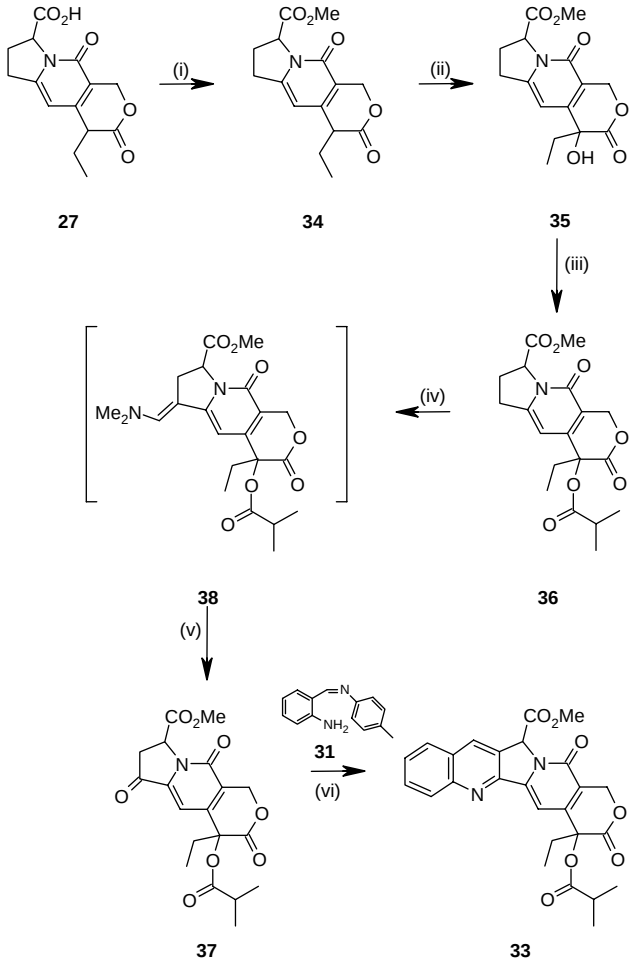


Scheme 9. Reaction conditions: (i) 48% HBr, reflux, 5 h (92%); (ii) MeOH, $CHCl_3$, CH_3SO_3H cat., reflux, 48 h (64%); (iii) *tert*-BuOCH$(NMe_2)_2$, 110 °C, 2 h; (iv) $NaIO_4$, THF, 20 °C, 30 min (80% from **28**); (v) AcOH, reflux, 1 h (70%).

important product because it allowed to test again our synthesis of a ketone group in such indolizines,[1b] and it can also increase the knowledge of the 'crucial' necessity[14] of the E lactone ring of camptothecin analogs. For that reason and following the method developed previously,[2a] reaction of pyridone **28** with Bredereck's reagent {*tert*-BuOCH$(NMe_2)_2$},[15] then $NaIO_4$ oxidation[16] of the intermediate enamide **29** were completed, resulting in 80% yield of ketone **30**. Friedlander reaction[1,17,18] of imine **31**[19,20] with heterocycle **30** in AcOH[1,2a] gave ultimately deoxycamptothecin analog **32** in 70% yield, thus validating this part of the reaction scheme (Scheme 9).

3.3. Formation of 5-methoxycarbonyl camptothecin analog 33

With this sequential protocol in hand, camptothecin analog **33** was now synthesized from the same pyridone **27**. Reaction of this acid, first with oxalyl chloride, then with MeOH, furnished 71% yield of ester **34**. Introduction of the important ternary alcohol group[14a,21] was performed following the method of Wall,[18] by bubbling oxygen in a methanol solution of ethyl lactone **34**, in the presence of potassium carbonate as a base. This led to 95% of lactone **35**. This alcohol was then esterified with isobutyric anhydride in pyridine, giving 73% yield of ester **36**. Formation of this ester was realized not only to protect the hydroxyl group during the next steps, but also to decrease the opening of the lactone ring of camptothecin **33** during the biological screening[22] (Scheme 10).



Scheme 10. Reaction conditions: (i) $(COCl)_2$, CH_2Cl_2, 20 °C, 3 h then MeOH, 20 °C, 3 h (71%); (ii) O_2, K_2CO_3, MeOH, 20 °C, 24 h (95%); (iii) $(i\text{-PrCO})_2O$, Py, 85 °C, 5 h (73%); (iv) *tert*-$BuOCH(NMe_2)_2$, 110 °C, 2 h; (v) $NaIO_4$, THF, 20 °C, 30 min (42% from **36**); (vi) AcOH, reflux, 1 h 67%.

Formation of ketone **37** was obtained following the same method as for pyridone **30**, by reacting the mixture of diastereoisomers of diester **36** first with Bredereck's reagent to give **38**, then with $NaIO_4$. Ketone **37** was thus obtained in 42% crude yield. That compound proved to be rather unstable; after purification by chromatography on a silica gel column, a very low amount of **37** was treated with imine **31** in AcOH, to give the camptothecin analog **33** in 67% yield. Due to the very low amount of **33** isolated, identification of this compound was performed only through NMR and mass spectrometry (Scheme 10).

4. Conclusion

The new camptothecin analog **33** (as a mixture of diastereoisomers) was isolated in low yield of (11%) from pyridone **2**, but the yield from **2** to **32** was of 27%. This justifies that the new methodologies reported herein can be utilized in the camptothecin field, at least when intermediates ketones are stable enough. To be noted in these syntheses are the new conditions for Mannich reaction that lead to high yields, and a new method for the introduction of a keto group in tetrahydroindolizinones. The use of these reaction sequences for the synthesis of other camptothecin analogs, whose biological properties will be tested, will be reported in due course.

5. Experimental

5.1. Materials

Melting points were determined using an Electrothermal apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were obtained on a Varian Gemini 2000 at 200 and 50 MHz, respectively. IR spectra were obtained in ATR mode on a FTIR Bruker Tensor 27. Thin-layer chromatographies were performed on precoated Kieselgel $60F_{254}$ plates. Microanalyses were performed by the 'Service de Microanalyses' of LSEO, Université de Bourgogne, Dijon, France or by the 'Service Central de Microanalyses' of CNRS in Vernaison, France. Methyl pyroglutamate used was racemic.

5.1.1. [3-[(Dimethylamino)carbonyl]-8-(methoxycarbonyl)-5-oxo-1,2,3,5-tetrahydro-7-indolizinyl]acetic acid (8). A stirred mixture of ester **5** (5 g, 0.015 mol) and sodium hydroxide (0.71 g, 0.018 mol) in water (20 mL) was stirred for 30 min. Upon acidification (concd HCl) acid **8** was obtained as a white powder in 89% yield, mp (H_2O): 155–156 °C; TLC R_f (CH_2Cl_2/MeOH, 90:10): 0.20; IR: ν cm^{-1} 3541, 3430, 1753, 1709, 1639, 1608, 1540, 1128; ^1H NMR (D_2O): δ ppm 2.17–2.32 (m, 1H, CH_2CH), 2.53–2.73 (m, 1H, CH_2CH), 2.98 (s, 3H, NCH_3), 3.23 (s, 3H, NCH_3), 3.35–3.67 (m, 2H, CH_2CH_2), 3.83 (s, 3H, CO_2CH_3), 3.91 (s, 2H, CH_2CO), 5.65 (dd, J=9.3, 2.3 Hz, 1H, C*H*CO), 6.42 (s, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ ppm 24.9 (CH_2), 30.2 (CH_2), 35.7 (CH_3), 36.8 (CH_3), 41 (CH_2), 48.7 (CH_3), 60.7 (CH), 116.0 (CH), 118.8 (C), 150.1 (C), 151.2 (C), 151.7 (C), 170.8 (C), 173.1 (C), 177.9 (C). Anal. Calcd for $C_{15}H_{18}N_2O_6$, H_2O: C, 52.94; H, 5.92; N, 8.23. Found: C, 53.16; H, 6.15; N, 8.17.

5.1.2. 2-[3-[(Dimethylamino)carbonyl]-8-(methoxycarbonyl)-5-oxo-1,2,3,5-tetrahydro-7-indolizinyl]-butanoic acid (9). A mixture of diester **6** (2 g, 5.5 mmol) and NaOH (0.24 g, 6.1 mmol) in water (20 mL) was stirred at room temperature for 30 min. The solution was acidified until pH 4 with HCl then the solution was extracted six times with dichloromethane (6×50 mL). The combined organic phases were dried (Na_2SO_4) then evaporated, giving the mixture of diastereoisomers **9** as a white powder (78%), mp (acetone): 157–159 °C; TLC R_f (CH_2Cl_2/MeOH, 80:20): 0.27; IR: ν cm^{-1} 3430, 1728, 1656, 1640, 1567, 1523, 1441, 1209; ^1H NMR ($CDCl_3$): δ ppm 0.96 and 0.97 (2t, J= 7.4 Hz, 3H, CH_2CH_3), 1.59–1.87 (m, 1H, CH_2CH$_3$), 1.98–2.28 (m, 2H, CH_2CH$_2$, CH_2CH$_3$), 2.28–2.52 (m, 1H, CH_2CH$_2$), 2.99 and 3.00 (2s, 3H, NCH_3), 3.21 (s, 3H, NCH_3), 3.33–3.75 (m, 2H, CH_2CH$_2$), 3.84 and 3.87 (2s, 3H, CO_2CH_3), 3.90 and 4.09 (dd, J=7.6, 6.6 Hz and dd, J=8.0, 6.0 Hz, 1H, C*H*CH$_2$), 5.49 and 5.54 (dd, J=5.9, 2.3 Hz and dd, J=5.9, 2.2 Hz, 1H, C*H*CH$_2$), 6.48 and 6.49 (2s, 1H, Ar*CH*); ^{13}C NMR ($CDCl_3$): δ ppm 12.4 (CH_3), 25.5 ($2CH_2$), 33.7 (CH_3), 36.0 (CH_2), 37.2 (CH_3), 50.0 (CH), 51.7 (CH_3), 59.5 (CH), 107.3 (C), 117.1 (CH), 152.8 (C), 157.0 (C), 160.8 (C), 166.1 (C), 168.8 (C), 175.0 (C). Anal. Calcd for $C_{17}H_{22}N_2O_6$, $0.5H_2O$: C, 56.82; H, 6.45; N, 7.79. Found: C, 56.45; H, 6.73; N, 7.41.

5.1.3. Methyl 7-[2-(chloromethoxy)-2-oxoethyl]-3-[(dimethylamino)carbonyl]-5-oxo-1,2,3,5-tetrahydro-8-indolizinecarboxylate (11). Oxalyl chloride (0.2 mL, 0.29 g, 2.29 mmol) was added with a syringe to a stirred mixture of acid **8** (0.5 g, 1.55 mmol) and DMF (3 drops) in chloroform (10 mL). The solution was stirred for 30 min then evaporated. Chlorobenzene (10 mL), paraformaldehyde (0.1 g, 3.67 mmol) then $AlCl_3$ (1.2 g, 8.8 mmol) were added to the solution. After reflux for 24 h, dichloromethane (100 mL) and water (10 mL) were added. The organic phase was dried (Na_2SO_4) then evaporated leading to compound **11** (~20%) as an impure oil, which was used directly in the next step; ^{1}H NMR ($CDCl_3$): δ ppm 1.84–2.20 (m, 1H, CH_2CH$_2$), 2.30–2.58 (m, 1H, CH_2CH$_2$), 3.00 (s, 3H, NCH_3), 3.23 (s, 3H, NCH_3), 3.52–3.69 (m, 2H, CH_2CH$_2$), 3.70 (d, J=16.5 Hz, 1H, CH_2CO), 3.79 (s, 3H, CO$_2$CH_3), 4.02 (d, J=16.5 Hz, 1H, CH_2CO), 5.31 (dd, J=9.6, 2.2 Hz, 1H, CHCO), 5.73 (s, 2H, CH_2Cl), 6.28 (s, 1H, ArCH); ^{13}C NMR ($CDCl_3$): δ ppm 25.4 (CH_2), 34.1 (CH_2), 36.0 (CH_3), 37.2 (CH_3), 41.3 (CH_2), 51.7 (CH_3), 59.6 (CH), 77.05 (CH_2), 106.0 (C), 120.5 (CH), 146.7 (C), 158.7 (C), 160.3 (C), 165.5 (C), 168.4 (C), 168.8 (C).

5.1.4. Methyl 3-[(dimethylamino)carbonyl]-7-{2-[(methylsulfanyl)methoxy]-2-oxoethyl}-5-oxo-1,2,3,5-tetrahydro-8-indolizinecarboxylate (13). *tert*-Butyl bromide (7 mL, 62 mmol) in dimethyl sulfoxide (200 mL) was added to a stirred suspension of acid **8** (2 g, 6.2 mmol) and sodium hydrogencarbonate (5.2 g, 62 mmol). The mixture was stirred at room temperature for 24 h then water (100 mL) was added. The aqueous phase was extracted with dichloromethane (2×150 mL). The combined organic phases were washed with brine (3×100 mL), then dried (Na_2SO_4) and evaporated. The oil obtained crystallized from ethyl acetate, giving amide **13** as a white powder (84%), mp (EtOAc): 72–74 °C; TLC R_f (MeOH/CH_2Cl_2, 5:95): 0.42; IR: ν cm^{-1} 1745, 1710, 1660, 1590, 1515, 1440, 1150; ^{1}H NMR ($CDCl_3$): δ ppm 2.13–2.29 (m, 1H, CH_2CH$_2$), 2.24 (s, 3H, SCH_3), 2.30–2.51 (m, 1H, CH_2CH$_2$), 3.00 (s, 3H, NCH_3), 3.23 (s, 3H, NCH_3), 3.55–3.69 (m, 2H, CH_2CH$_2$), 3.67 (d, J=16.9 Hz, 1H, CH_2CO), 3.80 (s, 3H, CO$_2$CH_3), 4.01 (d, J=16.9 Hz, 1H, CH_2CO), 5.17 (s, 2H, OCH_2S), 5.52 (dd, J=9.5, 2.3 Hz, 1H, CHCO), 6.33 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$): δ ppm 15.3 (CH_3), 25.3 (CH_2), 33.9 (CH_2), 35.8 (CH_3), 37.0 (CH_3), 41.4 (CH_2), 51.4 (CH_3), 59.4 (CH), 68.5 (CH_2), 106.2 (C), 120.0 (CH), 147.4 (C), 158.2 (C), 160.2 (C), 165.5 (C), 168.7 (C), 169.8 (C). Anal. Calcd for $C_{17}H_{22}N_2O_6S$: C, 53.39; H, 5.80; N, 7.32; S, 8.38. Found: C, 53.31; H, 6.13; N, 7.63; S, 8.04.

5.1.5. Methyl 3-[(dimethylamino)carbonyl]-7-(1-{[(methylsulfanyl)methoxy]carbonyl}propyl)-5-oxo-1,2,3,5-tetrahydro-8-indolizinecarboxylate (14). *tert*-Butyl bromide (6.4 mL, 57 mmol) in dimethyl sulfoxide (10 mL, 11 g, 141 mmol) was added to a stirred suspension of acid **9** (2 g, 5.7 mmol) and sodium hydrogencarbonate (4.8 g, 57 mmol) in dichloromethane (30 mL). The mixture was refluxed for 12 h, cooled at room temperature then water (50 mL) was added. The aqueous phase was extracted with dichloromethane (5×100 mL). The combined organic phases were washed with brine (3×100 mL) then dried (Na_2SO_4) and evaporated. The oil obtained crystallized from ethyl acetate, giving amide **14** as a white powder (77%), mp (EtOAc): 83–85 °C; TLC ($C_{18}SiO_2$) R_f (MeOH/H_2O, 60:40): 0.4; IR: ν cm^{-1} 1746, 1712, 1659, 1589, 1519, 1439, 1152; ^{1}H NMR ($CDCl_3$): δ ppm 0.97 (t, J=7.3 Hz, 3H, CH$_2$CH_3), 1.65–1.86 (m, 1H, CH_2CH$_3$), 1.98–2.31 (m, 2H, CH_2CH$_3$, CH_2CH$_2$), 2.18 (s, 3H, SCH_3), 2.31–2.53 (m, 1H, CH_2CH), 3.00 (s, 3H, NCH_3), 3.23 (s, 3H, NCH_3), 3.34–3.73 (m, 2H, CH_2CH$_2$), 3.83 (s, 3H, CO$_2$CH_3), 4.08 (t, J=7.0 Hz, 1H, CHCO$_2$), 5.06 (d, J=11.8 Hz, 1H, OCH_2S), 5.18 (d, J=11.8 Hz, 1H, OCH_2S), 5.49 (dd, J=9.3, 2.2 Hz, 1H, CHCON), 6.38 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$): δ ppm 12.4 (CH_3), 15.3 (CH_3), 25.5 (CH_2), 33.9 (CH_2), 36.0 (CH_3, CH_2), 37.2 (CH_3), 50.1 (CH_3), 51.6 (CH), 59.4 (CH), 66.6 (CH_2), 106.6 (C), 117.4 (CH), 152.0 (C), 157.3 (C), 160.4 (C), 165.8 (C), 168.8 (C), 171.9 (C). Anal. Calcd for $C_{19}H_{26}N_2O_6S$: C, 55.59; H, 6.38; N, 6.82; S, 7.81. Found: C, 55.75; H, 6.51; N, 6.93; S, 7.35.

5.1.6. Methyl 6-bromo-3-[(dimethylamino)carbonyl]-7-{2-[(methylsulfinyl)methoxy]-2-oxoethyl}-5-oxo-1,2,3,5-tetrahydro-8-indolizinecarboxylate (15). Bromine (0.017 g, 0.20 mmol) in dichloromethane (2.2 mL) was added to amide **13** (0.050 g, 0.11 mmol) and potassium hydrogenocarbonate (0.040 g, 0.40 mmol) in methylene dichloride (2 mL) and water (2 mL). The mixture was stirred for 15 h, methylene dichloride (10 mL) was added, and the aqueous layer was extracted with methylene dichloride (10 mL). The combined organic phases were dried (Na_2SO_4), then evaporated giving 92% of **15** as a mixture of two isomers (purity estimated by NMR ~95%); this compound was only checked by NMR. ^{1}H NMR ($CDCl_3$): δ ppm 2.13–2.33 (m, 1H, CH_2CH$_2$), 2.33–2.51 (m, 1H, CH_2CH$_2$), 2.66 and 2.67 (2s, 3H, SCH_3), 3.00 (s, 3H, NCH_3), 3.26 (s, 3H, NCH_3), 3.38–3.78 (m, 2H, CH_2CH$_2$), 3.82 and 3.83 (2s, 3H, CO$_2$CH_3), 4.30 (s) and 4.31 (d, J=1.0 Hz) (2H, CH_2CO), 5.02 and 5.03 (2d, J=10.4 Hz, 1H, OCH_2S), 5.10 and 5.12 (2d, J=10.4 Hz, 1H, OCH_2S), 5.57 (dd, J=9.6 Hz, 1H, CHCO); ^{13}C NMR ($CDCl_3$): δ ppm 25.5 (CH_2), 34.3 (CH_2), 36.0 (CH_3), 36.1 (CH_3), 37.3 (CH_3), 40.9 (CH_2), 52.1 (CH_3), 60.7 (CH), 78.6 (CH_2), 107.0 and 107.1 (C), 118.4 (C), 145.2 and 145.3 (C), 156.2 and 156.9 (2C), 165.2 and 165.3 (C), 168.1 (C), 168.7 and 169.8 (C).

5.1.7. Methyl 3-[(dimethylamino)carbonyl]-7-(1-{[(methylsulfanyl)methoxy]carbonyl}propyl)-5-oxo-1,2,3,5-tetrahydro-8-indolizinecarboxylate (16). Sodium periodate (1.25 g, 5.84 mmol) was added to a stirred solution of amide **14** (2 g, 4.87 mmol) in a mixture of methanol (30 mL) and water (30 mL). After stirring at room temperature for 12 h solvents were evaporated and the residue was dissolved in dichloromethane (100 mL). The solution was washed with water (50 mL), the aqueous phase was extracted with dichloromethane (3×50 mL), the combined organic phases were dried (Na_2SO_4) then evaporated. The residue crystallized from ethyl acetate, giving a mixture of three isomers of **16** as a white powder (86%), mp (EtOAc): 142–144 °C; TLC ($C_{18}SiO_2$) R_f (MeOH/H_2O, 60:40): 0.51; IR: ν cm^{-1} 1746, 1716, 1644, 1591, 1523, 1436, 1187, 1016; ^{1}H NMR ($CDCl_3$): δ ppm 0.96 and 0.97 (t, J=7.4 Hz, 3H, CH_3CH$_2$), 1.65–1.91 (m, 1H, CH$_3$CH_2), 2.01–2.28 (m, 2H, CH$_3$CH_2, CH$_2$CH_2), 2.28–2.49 (m, 1H, CH$_2$CH_2), 2.56, 2.58 and 2.60 (3s, 3H, SCH_3), 3.00 and 3.01 (2s, 3H, NCH_3), 3.23 (s, 3H, NCH_3), 3.36–3.74 (m, 2H, CH_2CH$_2$), 3.81, 3.82 and 3.83 (3s, 3H,

CO_2CH_3), 4.14 and 4.17 (2t, $J=6.8$ Hz, 1H, $CHCO_2$), 4.87, 4.98, 5.03, 5.06 (4d, $J=10.3$ Hz, 2H, OCH_2S), 5.50 (dd, $J=$ 9.4, 2.2 Hz, 1H, CHCON), 6.33, 6.34 and 6.36 (3s, 1H, ArH); ^{13}C NMR ($CDCl_3$): δ ppm 12.2 and 12.3 (CH_3), 24.9 and 25.3 and 25.4 (CH_2), 34.0 (CH_2), 35.9 ($2CH_3$, CH_2), 37.1 (CH_3), 49.6 (CH), 50.5 and 51.7 (CH_3), 59.5 (CH), 78.3 and 78.7 (CH_2), 105.8 and 106.1 (C), 117.5 and 118.1 (CH), 151.1 and 151.3 (C), 157.7 and 157.8 (C), 160.2 (C), 165.7 (C), 168.6 (C), 171.0 and 171.2 (C). Anal. Calcd for $C_{19}H_{26}N_2O_7S$: C, 53.51; H, 6.14; N, 6.57; S, 7.52. Found: C, 53.14; H, 6.40; N, 6.21; S, 7.15.

5.1.8. Methyl 3-[(dimethylamino)carbonyl]-7-{2-[(methylsulfonyl)methoxy]-2-oxoethyl}-5-oxo-1,2,3,5-tetrahydro-8-indolizinecarboxylate (17). The synthesis of this compound was performed from compound **13**, using the same method as for **18**. The product crystallized from ethyl acetate, giving sulfone **17** as a white powder (95%), mp (EtOAc): 136–138 °C; TLC ($C_{18}SiO_2$) R_f (MeOH/H_2O, 60:40): 0.5; IR: ν cm^{-1} 1770, 1710, 1675, 1645, 1595, 1525, 1445, 1100; ^{1}H RMN ($CDCl_3$): δ ppm 2.12–2.29 (m, 1H, CH_2CH_2), 2.29–2.55 (m, 1H, CH_2CH_2), 2.98 (s, 3H, SCH_3), 3.00 (s, 3H, NCH_3), 3.20 (s, 3H, NCH_3), 3.52–3.67 (m, 2H, CH_2CH_2), 3.77 (d, $J=17.3$ Hz, 1H, CH_2CO), 3.79 (s, 3H, CO_2CH_3), 4.09 (d, $J=17.3$ Hz, 1H, CH_2CO), 5.03 (d, $J=12.6$ Hz, 1H, OCH_2S), 5.12 (d, $J=12.6$ Hz, 1H, OCH_2S), 5.52 (dd, $J=9.6$, 2.1 Hz, 1H, CHCO), 6.28 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$): δ ppm 24.4 (CH_2), 33.4 (CH_2), 35.0 (CH_{32}), 36.2 (CH_3), 38.6 (CH_3), 39.9 (CH_3), 50.8 (CH_3), 58.8 (CH), 74.4 (CH_2), 104.6 (C), 119.5 (CH), 145.8 (C), 157.9 (C), 159.2 (C), 164.8 (C), 167.8 (C), 168.0 (C). Anal. Calcd for $C_{17}H_{22}N_2O_8S$, $3/2H_2O$: C, 46.25; H, 5.71; N, 6.35; S, 7.26. Found: C, 46.67; H, 5.37; N, 6.36; S, 7.69.

5.1.9. Methyl 3-[(dimethylamino)carbonyl]-7-(1-{[(methylsulfonyl)methoxy]carbonyl}propyl)-5-oxo-1,2,3,5-tetrahydro-8-indolizinecarboxylate (18). Magnesium monoperoxyphtalate (1.27 g, 2.58 mmol) was added to a stirred solution of amide **14** (1 g, 2.35 mmol) in methanol (15 mL). After stirring at room temperature for 12 h solvent was evaporated, and the residue was dissolved in dichloromethane (100 mL). The solution was washed with water (50 mL), the aqueous phase was extracted with dichloromethane (3×50 mL) and the combined organic phases were dried (Na_2SO_4) then evaporated. The residue crystallized from ethyl acetate, giving sulfone **18** as a white powder (92%), mp (EtOAc): 161–163 °C; TLC ($C_{18}SiO_2$) R_f (MeOH/H_2O, 60:40): 0.54; IR: ν cm^{-1} 1746, 1717, 1644, 1590, 1523, 1436, 1277, 1186; ^{1}H RMN ($CDCl_3$): δ ppm 0.96 and 0.97 (2t, $J=7.4$ Hz, 3H, CH_3CH_2), 1.70–1.94 (m, 1H, CH_3CH_2), 2.05–2.30 (m, 2H, CH_3CH_2, CH_2CH_2), 2.30–2.56 (m, 1H, CH_2CH_2), 2.90 and 2.93 (2s, 3H, SCH_3), 3.00 (s, 3H, NCH_3), 3.23 and 3.26 (2s, 3H, NCH_3), 3.39–3.72 (m, 2H, CH_2CH_2), 3.80 and 3.82 (2s, 3H, CO_2CH_3), 4.12 and 4.14 (2t, $J=7.3$ Hz, 1H, $CHCO_2$), 5.02 and 5.03 (2s, 2H, OCH_2S), 5.51 and 5.57 (2dd, $J=9.5$, 2.0 Hz, 1H, CHCON), 6.35 and 6.38 (2s, 1H, ArH); ^{13}C NMR ($CDCl_3$): δ ppm 12.2 (CH_3), 24.8 and 25.3 (CH_2), 34.1 (CH_2), 35.9 ($2CH_3$), 37.1 (CH_2), 39.6 (CH_3), 50.1 (CH), 51.7 (CH_3), 59.6 (CH), 75.3 (CH_2), 105.8 (C), 118.0 (CH), 150.9 (C), 158.0 (C), 160.2 (C), 165.8 (C), 168.6 (C), 170.3 (C). Anal. Calcd for $C_{19}H_{26}N_2O_8S$: C, 51.57; H, 5.92; N, 6.33; S, 7.25. Found: C, 51.65; H, 6.04; N, 6.75; S, 7.10.

5.1.10. Dimethyl 4-ethyl-3,10-dioxo-3,4,6,7,8,10-hexahydro-1*H*-pyrano[3,4-*f*]indolizine-5,8-dicarboxylate (22) and methyl 3a-ethyl-1,4,7-trioxo-3a,4,7,8,9,10-hexahydro-1*H*,3*H*,6*H*-2,5-dioxa-7a-azacyclopenta[*a*]phenalene-8-carboxylate (24). A stirred mixture of triester **2** (5 g, 14.2 mmol), acetic acid (15 mL), 34% HCl (5 mL) and paraformaldehyde (1.28 g, 42.6 mmol) was heated at 80 °C for 24 h then the solution was evaporated giving crude acid **23**. The residue was dissolved in methanol (300 mL) and chloroform (200 mL). Methane sulfonic acid (2 drops) was added and the solution was refluxed for 24 h while drying the distillate by condensing it in a soxhlet-type apparatus containing 3 Å molecular sieves (50 g). Dichloromethane (200 mL) was added to the residue obtained upon evaporation, and the solution was washed with a $NaHCO_3$ solution. The organic phase was dried then evaporated. The residue was dissolved in hot ethyl acetate and crystallization gave lactone **22** as a white mixture of diastereoisomers (84%), mp (EtOAc): 145–147 °C; TLC R_f (EtOAc): 0.7; IR: ν cm^{-1} 1745, 1715, 165, 1595, 1545, 1440, 1205; ^{1}H NMR ($CDCl_3$): ppm 1.10 and 1.11 (2t, $J=7.4$ Hz, 3H, CH_3CH_2), 1.73–2.05 (m, 2H, CH_3CH_2), 2.25–2.44 (m, 1H, CH_2CH_2), 2.44–2.65 (m, 1H, CH_2CH_2), 3.41–3.64 (m, 2H, CH_2CH_2), 3.81 and 3.82 (2s, 3H, $CHCO_2CH_3$), 3.87 (s, 3H, $ArCO_2CH_3$), 4.34 and 4.42 (2dd, $J=9.3$, 4.9 Hz, 1H, $ArCHCH_2$), 5.07–5.24 (m, 2H, $ArCH_2O$, $CHCO_2$), 5.45 and 5.49 (2d, $J=15.9$ Hz, 1H, $ArCH_2O$); ^{13}C NMR ($CDCl_3$): δ ppm 11.7 (CH_3), 24.9 and 25.0 (CH_2), 25.2 and 25.4 (CH_2), 33.4 (CH_2), 44.0 and 44.2 (CH), 51.8 (CH_3), 52.8 (CH_3), 61.7 (CH), 64.4 (CH_2), 104.8 (C), 118.7 (C), 147.9 and 148.0 (C), 156.6 (C), 156.9 and 157.2 (C), 164.6 (C), 169.5 and 169.8 (C), 170.8 and 170.9 (C). Anal. Calcd for $C_{17}H_{19}NO_7$: C, 58.45; H, 5.48; N, 4.01. Found: C, 58.49; H, 5.68; N, 4.29.

The ethyl acetate solution remaining after crystallization of lactone **22** was purified by chromatography on SiO_2 column (EtOAc), giving dilactone **24** as a white mixture of diastereoisomers (up to 6%), mp (EtOAc): 162–164 °C; TLC R_f (EtOAc): 0.63; IR: ν cm^{-1} 1745, 1725, 1655, 1565, 1525, 1435, 1205; this compound was not submitted to elemental analysis; ^{1}H NMR ($CDCl_3$): δ ppm 1.10 and 1.12 (2t, $J=7.6$ Hz, 3H, CH_2CH_3), 1.78–2.17 (m, 2H, CH_2CH_3), 2.29–2.51 (m, 1H, CH_2CH_2), 2.51–2.74 (m, 1H, CH_2CH_2), 3.15–4.04 (m, 2H, CH_2CH_2), 3.83 (s, 3H, CO_2CH_3), 4.35 and 4.42 (2dd, $J=11.9$, 0.6 Hz, 1H, OCH_2), 4.72 and 4.73 (2d, $J=11.9$ Hz, 1H, OCH_2), 5.12–5.24 (m, 1H, $CHCO_2$), 5.22 and 5.25 (2dt, $J=16.0$, 1.2 Hz, 1H, $ArCH_2$), 5.46 and 5.49 (2d, $J=16.0$ Hz, 1H, $ArCH_2$); ^{13}C NMR ($CDCl_3$): δ ppm 9.1 and 11.6 (CH_3), 25.6 and 25.7 (CH_2), 26.8 and 27.3 (CH_2), 32.4 and 32.7 (CH_2), 42.4 and 42.5 (C), 53.0 and 53.2 (CH_3), 61.9 and 62.1 (CH), 65.7 (CH_2), 68.6 (CH_2), 98.5 and 98.6 (C), 115.6 (C), 146.7 and 146.8 (C), 156.9 and 157.3 (C), 160.7 and 161.7 (C), 168.5 and 168.7 (C), 169.6 and 169.7 (C), 170.1 (C).

5.1.11. 4-Ethyl-3,10-dioxo-3,4,6,7,8,10-hexahydro-1*H*-pyrano[3,4-*f*]indolizine-8-carboxylic acid (27). A stirred solution of lactone **22** (5 g, 14.2 mmol) in 48% hydrobromic acid (30 mL) was heated at 135 °C for 5 h then evaporated. The residue crystallized from acetone, giving 92% of acid **27** as white crystals, mp (acetone): 203–205 °C; TLC R_f (CH_3OH): 0.6; IR: ν cm^{-1} 1745, 1740, 1645, 1575, 1545, 1470, 1445, 1205; ^{1}H NMR (DMSO-d_6): δ ppm 0.96 and

0.98 (2t, $J=7.3$ Hz, 3H, CH_2CH_3), 1.93 (quint, $J=7.2$ Hz, 2H, CH_2CH_3), 2.14–2.31 (m, 2H, CH_2CH_2), 3.14 (dd, $J=9.1$, 6.1 Hz, 2H, CH_2CH_2), 3.60 (t, $J=6.6$ Hz, 1H, $CHCH_2$), 4.97 and 4.99 (2dd, $J=9.7$, 3.0 Hz, 1H, $CHCO_2$), 5.16 (d, $J=15.3$ Hz, 1H, CH_2O), 5.31 (d, $J=15.3$ Hz, 1H, CH_2O), 6.28 (s, 1H, Ar*H*); ^{13}C NMR (DMSO-d_6): δ ppm 11.1 and 11.3 (CH_3), 23.2 (CH_2), 25.7 (CH_2), 30.2 (CH_2), 44.7 (CH), 61.2 (CH), 64.9 (CH_2), 99.4 (CH), 116.5 and 116.6 (C), 147.4 (C), 151.3 (C), 157.2 (C), 171.0 (C), 171.3 (C). Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.65; H, 5.45; N, 5.05. Found: C, 60.27; H, 5.62; N, 5.04.

5.1.12. Methyl 7-[1-(methoxycarbonyl)propyl]-6-(methoxymethyl)-5-oxo-1,2,3,5-tetrahydro-3-indolizinecarboxylate (28). A stirred solution of acid **27** (3 g, 10.8 mmol) and methanesulfonic acid (0.44 g, 0.3 mL, 4.6 mmol) in methanol (300 mL) and chloroform (200 mL) was refluxed for 48 h while drying the solvent by condensing it in a soxhlet-type apparatus containing 3 Å molecular sieves (50 g). Dichloromethane (200 mL) was added to the residue obtained upon evaporation, and the solution was washed with a $NaHCO_3$ solution. The organic phase was dried then evaporated. The residue was purified by chromatography on SiO_2 column (EtOAc), giving the diester **28** as a colorless oil (64%); TLC R_f (EtOAc): 0.63; IR: ν cm^{-1} 1740, 1655, 1600, 1545, 1435, 1205; ^{1}H NMR ($CDCl_3$): 0.91 and 0.93 (2t, $J=7.5$ Hz, 3H, CH_3CH_2), 1.55–1.83 (m, 1H, CH_3CH_2), 1.91–2.16 (m, 1H, CH_3CH_2), 2.16–2.37 (m, 1H, CH_2CH_2), 2.37–2.63 (m, 1H, CH_2CH_2), 3.06 (ddd, $J=16.6$, 8.2, 4.3 Hz, 1H, CH_2CH_2), 3.18 (dd, $J=16.6$, 8.2 Hz, 1H, CH_2CH_2), 3.33 and 3.34 (2s, 3H, OCH_3), 3.67 and 3.68 (2s, 3H, $ArCHOCH_3$), 3.78 (s, 3H, CH_2CHOCH_3), 3.91 and 3.92 (2t, $J=7.6$ Hz, 1H, ArC*H*), 4.48 and 4.49 (2d, $J=11.0$ Hz, 1H, $ArCH_2$), 4.56 and 4.59 (2d, $J=11.0$ Hz, 1H, $ArCH_2$), 5.05 and 5.06 (2dd, $J=9.3$, 3.6 Hz, 1H, NC*H*), 6.22 and 6.24 (2s, 1H, ArC*H*); ^{13}C NMR ($CDCl_3$): δ ppm 11.6 and 11.7 (CH_3), 25.2 and 25.4 (CH_2), 25.7 (CH_2), 30.1 (CH_2), 47.9 (CH), 51.6 and 51.7 (CH_3), 52.2 (CH_3), 57.3 and 57.4 (CH_3), 61.1 (CH), 64.2 (CH_2), 99.7 (CH), 122.8 and 122.9 (C), 149.0 (C), 151.9 and 152.0 (C), 160.9 (C), 170.2 (C), 172.9 and 173.0 (C). Anal. Calcd for $C_{17}H_{23}NO_6$, $0.5H_2O$: C, 58.95; H, 6.98; N, 4.04. Found: C, 58.80; H, 6.61; N, 4.06.

5.1.13. Methyl 7-[1-(methoxycarbonyl)propyl]-6-(methoxymethyl)-1,5-dioxo-1,2,3,5-tetrahydro-3-indolizinecarboxylate (30). A stirred mixture of diester **28** (1 g, 5.9 mmol) and Bredereck's reagent (1.44 g, 8.3 mmol) was heated to 110 °C for 2 h (N_2), giving formation of enamine **29**. After cooling at room temperature, tetrahydrofuran (10 mL) and water (10 mL) were added. When a homogenous solution was obtained, sodium metaperiodate (3.8 g, 17.7 mmol) was added and the mixture was stirred for 30 min. The solid was filtered then washed with dichloromethane. The filtrate was extracted with dichloromethane, the combined organic phases were dried (Na_2SO_4) then evaporated. The residue was purified by chromatography on SiO_2 column (EtOAc), giving ketone **30** as an orange oil in a crude yield of 80%; TLC R_f (EtOAc): 0.57; due to its low stability this compound was analyzed only by NMR; ^{1}H NMR ($CDCl_3$): 0.91 and 0.95 (2t, $J=7.3$ Hz, 3H, CH_2CH_3), 1.60–1.96 (m, 1H, CH_2CH_3), 1.99–2.22 (m, 1H, CH_2CH_3), 2.84 (dd, $J=19.5$, 3.7 Hz, 1H, $COCH_2$), 3.19 and 3.20 (2dd, $J=19.5$, 9.3 Hz, 1H, $COCH_2$), 3.36 and 3.38 (2s, 3H, OCH_3), 3.68 and 3.70 (2s, 3H, $ArCHCO_2CH_3$), 3.83 and 3.84 (2s, 3H, $NCHCO_2CH_3$), 4.01 and 4.03 (2t, $J=7.6$ Hz, 1H, ArC*H*), 4.55 and 4.56 (2d, $J=11.3$ Hz, 1H, CH_2O), 4.63 and 4.65 (2d, $J=11.3$ Hz, 1H, CH_2O), 5.18 and 5.19 (2dd, $J=9.3$, 3.7 Hz, 1H, NC*H*), 7.00 and 7.02 (2s, 1H, Ar*H*).

5.1.14. Methyl 7-[1-(methoxycarbonyl)propyl]-8-(methoxymethyl)-9-oxo-9,11-dihydroindolizino[1,2-*b*]-quinoline-11-carboxylate (32). A stirred solution of ketone **30** (1 g, 2.85 mmol) and imine **31** (0.72 g, 3.42 mmol) in acetic acid (10 mL) was refluxed for 1 h (N_2). After cooling at room temperature, water (50 mL) was added then the solution was extracted with methylene dichloride. The organic phase was washed with brine then with a solution of $NaHCO_3$. After drying (Na_2SO_4), the solution was evaporated and the residue was purified by chromatography on SiO_2 column (EtOAc), giving the diester **32** as a white powder (70%), mp (EtOAc): 221–222 °C; TLC R_f (EtOAc): 0.56; IR: ν cm^{-1} 1735, 1660, 1615, 1535, 1435, 1205; ^{1}H NMR ($CDCl_3$): δ ppm 0.97 and 1.02 (2t, $J=7.3$ Hz, 3H, CH_2CH_3), 1.79–2.03 (m, 1H, CH_2CH_3), 2.12–2.36 (m, 1H, CH_2CH_3), 3.41 and 3.42 (2s, 3H, CH_2OCH_3), 3.71 and 3.74 (2s, 3H, CO_2CH_3), 3.84 and 3.85 (2s, 3H, $ArCO_2CH_3$), 4.09 and 4.10 (2t, $J=7.4$ Hz, 1H, CH_2CH), 4.65 and 4.66 (2d, $J=11.0$ Hz, 1H, OCH_2), 4.73 and 4.74 (2d, $J=11.0$ Hz, 1H, OCH_2), 6.06 and 6.07 (2d, $J=1.2$ Hz, 1H, NC*H*), 7.39 and 7.41 (2s, 1H, CHAr*H*), 7.65 (td, $J=6.9$, 1.3 Hz, 1H, Ar*H*), 7.83 (td, $J=6.9$, 1.6 Hz, 1H, Ar*H*), 7.93 (dd, $J=8.2$, 1.2 Hz, 1H, Ar*H*), 8.22 (br d, $J=8.6$ Hz, 1H, Ar*H*), 8.42 (br s, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ ppm 11.9 and 12.1 (CH_3), 25.5 and 25.7 (CH_2), 48.7 (CH), 52.1 and 52.2 (CH_3), 53.3 (CH_3), 57.9 and 58.0 (CH_3), 62.6 (CH), 64.6 and 64.7 (CH_2), 100.4 (CH), 127.5 (C), 127.6 (C), 127.8 (CH), 128.2 (CH), 129.7 (CH), 130.8 (CH), 130.9 (CH), 144.2 (2C), 149.3 (C), 152.6 (2C), 160.6 (C), 166.5 (C), 172.8 (C). Anal. Calcd for $C_{24}H_{24}N_2O_6$, $0.5H_2O$: C, 64.71; H, 5.66; N, 6.29. Found: C, 64.45; H, 5.43; N, 6.21.

5.1.15. Methyl 4-ethyl-4-(isobutyryloxy)-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-12-carboxylate (33). A stirred solution of ketone **37** (0.1 g, 0.25 mmol) and imine **31** (0.065 g, 0.3 mmol) in acetic acid (1 mL) was refluxed for 1 h (N_2). After cooling at room temperature, water (5 mL) was added then the solution was extracted with dichloromethane. The organic phases were washed with brine then with a solution of $NaHCO_3$. After drying (Na_2SO_4) the solution was evaporated and the residue purified by chromatography on SiO_2 column (EtOAc) giving the diester **32** as a orange oil at 67% yield of crude compound; identification of **32** was obtained through NMR and mass spectra; TLC R_f (EtOAc): 0.53; MS (CI): $m/z=477$ [$M^+ + 1$]; ^{1}H RMN ($CDCl_3$): δ ppm 1.01 and 1.05 (2t, $J=7.4$ Hz, 3H, CH_2CH_3), 1.28 and 1.30 (2d, $J=6.8$ Hz, 6H, $C(CH_3)_2$), 2.20–2.30 (m, 2H, CH_2CH_3), 3.05–3.22 (m, 1H, $CH(CH_3)_2$), 3.80 and 3.83 (2s, 3H, CO_2CH_3), 5.37 and 5.41 (2d, $J=17.5$ Hz, 1H, CH_2O), 5.65 and 5.68 (2d, $J=17.5$ Hz, 1H, CH_2O), 6.07 and 6.09 (2d, $J=1.3$ Hz, 1H, CHCO), 7.17 and 7.18 (2s, 1H, CHAr*H*), 7.69 (td, $J=7$, 1.3 Hz, 1H, Ar*H*), 7.86 (td, $J=6.7$, 1.8 Hz, 1H, Ar*H*), 7.95 (br d, $J=8.0$ Hz, 1H, Ar*H*), 8.22 (br d, $J=8.4$ Hz, 1H, Ar*H*), 8.46 (br s, 1H, Ar*H*).

5.1.16. Methyl 4-ethyl-3,10-dioxo-3,4,6,7,8,10-hexahydro-1*H*-pyrano[3,4-*f*]indolizine-8-carboxylate (34). Oxalyl chloride (2.3 mL, 27 mmol) was dropped at room temperature into a stirred suspension of acid **27** (5 g, 18 mmol) in dichloromethane (20 mL) then the mixture was stirred for 3 h. Toluene (50 mL) was added and the solution was evaporated. Dichloromethane (30 mL) was added, then methanol (5 mL) in dichloromethane (20 mL) was dropped into the solution. After stirring for 3 h the solution was evaporated and dichloromethane (50 mL) was added. The solution was washed with a solution of $NaHCO_3$. The organic phase was dried then evaporated. The residue crystallized from toluene, giving lactone **34** as a white powder (71%), mp (toluene): 143–145 °C; TLC R_f (EtOAc): 0.34; IR: ν cm^{-1} 1745, 1660, 1600, 1570, 1435, 1210; ^1H NMR ($CDCl_3$): 1.02 and 1.05 (t, $J=7.3$ Hz, 3H, CH_2CH_3), 1.85–2.05 (m, 2H, CH_2CH_3), 2.25–2.43 (m, 1H, CH_2CH_2), 2.43–2.67 (m, 1H, CH_2CH_2), 3.00–3.31 (m, 2H, CH_2CH_2), 3.38 and 3.41 (t, $J=7.3$ Hz, 1H, ArCH), 3.81 and 3.82 (2s, 3H, CO_2CH_3), 5.11 and 5.14 (2dd, $J=9.3$, 3.4 Hz, 1H, NCH), 5.23 and 5.24 (2d, $J=15.7$ Hz, 1H, CH_2O), 5.39 and 5.40 (2d, $J=15.7$ Hz, 1H, CH_2O, ArH), 6.03 (br s, 1H); ^{13}C NMR ($CDCl_3$): 11.2 and 11.4 (CH_3), 24.8 and 24.9 (CH_2), 26.2 and 26.3 (CH_2), 30.4 (CH_2), 45.6 and 46.0 (CH), 52.9 (CH_3), 61.1 (CH), 65.7 (CH_2), 100.2 and 100.4 (CH), 117.5 and 117.7 (C), 147.4 and 147.6 (C), 150.3 (C), 157.9 (C), 170.2 and 170.3 (C), 171.0 and 171.1 (C). Anal. Calcd for $C_{15}H_{17}NO_5$, $0.5H_2O$: C, 59.99; H, 6.04; N, 4.66. Found: C, 60.28; H, 6.43; N, 4.31.

5.1.17. Methyl 4-ethyl-4-hydroxy-3,10-dioxo-3,4,6,7,8,10-hexahydro-1*H*-pyrano[3,4-*f*]indolizine-8-carboxylate (35). Potassium carbonate (0.95 g, 6.8 mmol) was added to a stirred solution of lactone **34** (2 g, 6.8 mmol) in methanol (20 mL) then oxygen was slowly bubbled into the mixture for 24 h. Neutralization was obtained by adding 1 N HCl and the resulting solution was extracted with dichloromethane. The organic phase was dried (Na_2SO_4) then evaporated. The residue crystallized from ethyl acetate, giving alcohol **35** as a white powder (95%), mp (EtOAc): 146–148 °C; TLC R_f (EtOAc/MeOH, 90:10): 0.48; IR: ν cm^{-1} 3385, 1745, 1655, 1565, 1435, 1210; ^1H NMR ($CDCl_3$): δ ppm 0.97 and 0.99 (2t, $J=7.3$ Hz, 3H, CH_2CH_3), 1.79 and 1.80 (2b quint, $J=7.3$ Hz, 2H, CH_2CH_3), 2.25–2.43 (m, 1H, CH_2CH_2), 2.43–2.69 (m, 1H, CH_2CH_2), 3.02–3.39 (m, 2H, CH_2CH_2), 3.69 (s, 1H, OH, deuterium oxide exchangeable), 3.80 and 3.82 (2s, 3H, CO_2CH_3), 5.12 and 5.16 (2dd, $J=9.4$, 3.4 Hz, 1H, NCH), 5.16 (d, $J=16$ Hz, 1H, CH_2O), 5.54 and 5.57 (2d, $J=16$ Hz, 1H, CH_2O), 6.51 (br s, 1H, ArH); ^{13}C NMR ($CDCl_3$): δ ppm 7.7 (CH_3), 26.2 and 26.4 (CH_2), 30.6 (CH_2), 31.1 and 31.3 (CH_2), 52.8 (CH_3), 61.3 (CH), 66.0 (CH_2), 72.6 (C), 98.1 and 98.2 (CH), 115.8 and 115.9 (C), 150.3 (C), 150.8 and 150.9 (C), 157.7 (C), 170.0 and 170.3 (C), 173.8 and 173.9 (C). Anal. Calcd for $C_{15}H_{17}NO_6$, $0.5H_2O$: C, 56.96; H, 5.74; N, 4.43. Found: C, 56.87; H, 5.48; N, 4.43.

5.1.18. Methyl 4-ethyl-4-(isobutyryloxy)-3,10-dioxo-3,4,6,7,8,10-hexahydro-1*H*-pyrano[3,4-*f*]indolizine-8-carboxylate (36). A mixture of isobutyric anhydride (4 mL, 3.8 g, 24.1 mmol) and pyridine (4 mL) was stirred for 10 min then alcohol **35** (1 g, 3.2 mmol) was added and the solution was heated at 85 °C for 5 h. After cooling at room temperature, the mixture was neutralized with $NaHCO_3$ solution then extracted with dichloromethane. The organic phase was dried (Na_2SO_4) then evaporated. The residue crystallized from diethyl ether, giving **36** as a white powder (73%), mp 152–154 °C; TLC R_f (EtOAc) 0.55; IR: ν cm^{-1} 1760, 1740, 1665, 1600, 1570, 1470, 1215; ^1H NMR ($CDCl_3$): δ ppm 0.91 and 0.98 (2t, $J=7.3$ Hz, 3H, CH_2CH_3), 1.19 and 1.22 (2d, $J=7.0$ Hz, 3H, $C(CH_3)_2$), 1.23 and 1.24 (2d, $J=7.0$ Hz, 3H, $C(CH_3)_2$), 1.86–2.07 (m, 1H, CH_2CH_3), 2.07–2.24 (m, 1H, CH_2CH_3), 2.24–2.44 (m, 1H, CH_2CH_2), 2.44–2.62 (m, 1H, CH_2CH_2), 2.62–2.76 (m, 1H, $CH(CH_3)_2$), 2.96–3.14 (m, 1H, CH_2CH_2), 3.14–3.32 (m, 1H, CH_2CH_2), 3.80 and 3.82 (2s, 3H, CO_2CH_3), 5.07 and 5.08 (2dd, $J=9.2$, 3.7 Hz, 1H, NCH), 5.20 and 5.22 (2dt, $J=16.7$, 1.2 Hz, 1H, CH_2O), 5.49 and 5.51 (2d, $J=16.7$ Hz, 1H, CH_2O), 5.99 (t, $J=1.2$ Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$): δ ppm 7.4 and 7.5 (CH_3), 18.4 (CH_3), 18.5 (CH_3), 26.1 and 26.3 (CH_2), 30.6 (CH_2), 31.3 and 31.6 (CH_2), 33.5 (CH), 52.8 (CH_3), 61.1 and 61.2 (CH), 66.5 and 66.6 (CH_2), 75.2 and 75.4 (C), 95.9 and 96.0 (CH), 117.5 (C), 146.1 (C), 150.0 and 150.2 (C), 157.5 (C), 167.4 (C), 169.7 (C), 175.0 (C). Anal. Calcd for $C_{19}H_{23}NO_7$: C, 60.47; H, 6.14; N, 3.71. Found: C, 60.19; H, 6.41; N, 3.62.

5.1.19. Methyl 4-ethyl-4-(isobutyryloxy)-3,6,10-trioxo-3,4,6,7,8,10-hexahydro-1*H*-pyrano[3,4-*f*]indolizine-8-carboxylate (37). A stirred mixture of diester **36** (1 g, 2.6 mmol) and Bredereck's reagent (0.65 g, 3.7 mmol) was heated at 110 °C for 2 h (N_2), giving enamine **38**. After cooling at room temperature, tetrahydrofuran (10 mL) and water (10 mL) were added. When a homogenous solution was obtained, sodium metaperiodate (0.65 g, 3.7 mmol) was added and the mixture was stirred for 30 min. The solid was filtered then washed with methylene dichloride. The aqueous phase was extracted with methylene dichloride, and the combined organic phases were dried (Na_2SO_4) then evaporated. The residue was purified by chromatography on SiO_2 column (EtOAc), giving ketone **37** as a brown oil (42%); TLC R_f (EtOAc): 0.51; because of its low stability, this compound was characterized only by NMR ^1H NMR ($CDCl_3$): δ ppm 0.95 and 0.97 (2t, $J=7.3$ Hz, 3H, CH_3CH_2), 1.29 and 1.31 (2d, $J=6.9$ Hz, 3H, $C(CH_3)_2$), 1.35 and 1.37 (2d, $J=6.9$ Hz, 3H, $C(CH_3)_2$), 1.82–2.04 (m, 2H, CH_3CH_2), 2.57–2.71 (m, 1H, $CH(CH_3)_2$), 3.33–3.90 (m, 2H, $COCH_2$), 3.81 and 3.83 (2s, 3H, CO_2CH_3), 5.09 and 5.10 (2dd, $J=9.3$, 3.3 Hz, 1H, NCH), 5.40–5.70 (m, 2H, CH_2O), 6.80 (s, 1H, ArH).

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Synthesis of stereochemical probes for new fluorogenic assays for yeast transketolase variants

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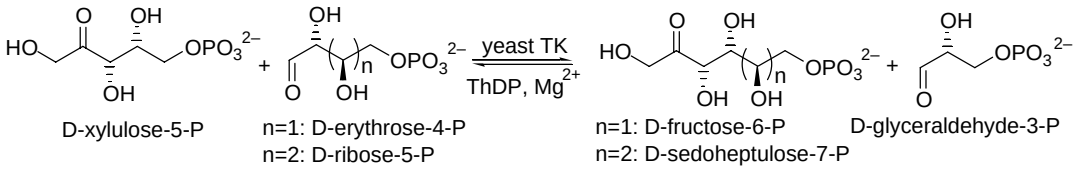
Abstract—For the screening of yeast transketolase (TK) variants with improved or new properties acquired by random mutagenesis, we report on the stereoselective synthesis of fluorogenic substrates as probes for measuring TK activity. Compound **1** (7-(2′,3′,5′-trihydroxy-4′-oxo-pentyl)oxycoumarine), prepared as previously described, [*Tetrahedron Lett.* **2003**, *44*, 827–830] enabled us to evaluate wild type TK velocity in a simple, specific and reproducible way. To select TK mutants able to produce D-*threo* aldoses, we prepared compound **2** (dihydroxy-4-O-(2′-oxo-benzopyran-7′-yl-D-threose) from dimethyl tartrate. Starting from D-ribose, we successfully obtained compound **3** (7′-(2,3,5-trihydroxy-4-oxo-pentyl)oxycoumarine) as a probe for TK mutants able to produce L-*erythro* ketoses.

1. Introduction

The discovery of new biocatalysts that mediate selective transformations is a growing field of research in organic chemistry. Diversity is either generated artificially by random mutagenesis from the gene that encodes an existing enzyme or collected directly from a natural reservoir.[1] Such libraries must be screened to identify suitable enzymes with desired properties. Recently, new sensitive detection methods for the evaluation of large numbers of catalysts have been reported. Efficient high throughput screening assays have been achieved using solid phase bound tests related to immunoassays[2] and a variety of spectroscopic methods, such as IR thermography[3] or mass spectrometry.[4] One of the most popular methods consists in using chromogenic or fluorogenic substrates as product formation sensors.[5] In this area, Reymond developed a simple stereospecific assay consisting of a fluorescence release based on the secondary release of umbelliferone by β-elimination catalysed by bovine serum albumin (BSA) from a primary or secondary carbonyl reaction product. The prototypical example of this technique was an enantioselective assay for alcohol dehydrogenase.[6] This approach was extended to the use of acylases, lipases, epoxide hydrolases, phophatases,[7] aldolase catalytic antibodies[8] and more recently for the transaldolase[9] enzyme catalysing C–C bond formation. In the latter case, the assay was based on microscopic reversibility, assuming that if transaldolase was able to cleave a C–C bond by retroaldolisation, it would be able to catalyse its formation by aldolisation. Our interest in this assay stemmed from our ongoing investigation of TK enzyme catalysing a stereocontrolled C–C bond formation, according to a similar natural reversible reaction (Scheme 1). Here we report on the stereoselective synthesis



Scheme 1. Natural reaction catalysed by transketolase.

Keywords: Enzyme evolution; Transketolase; Fluorogenic assays; C–C bond formation; High throughput screening.
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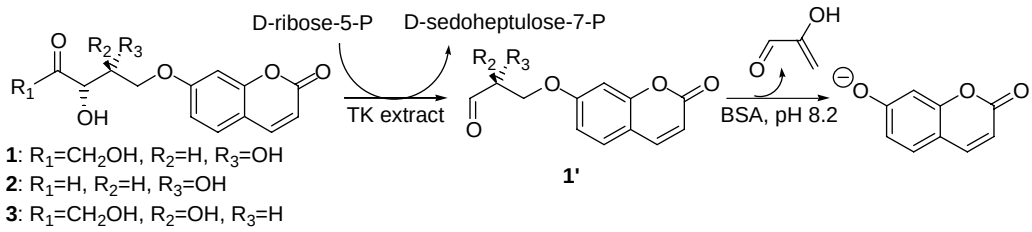
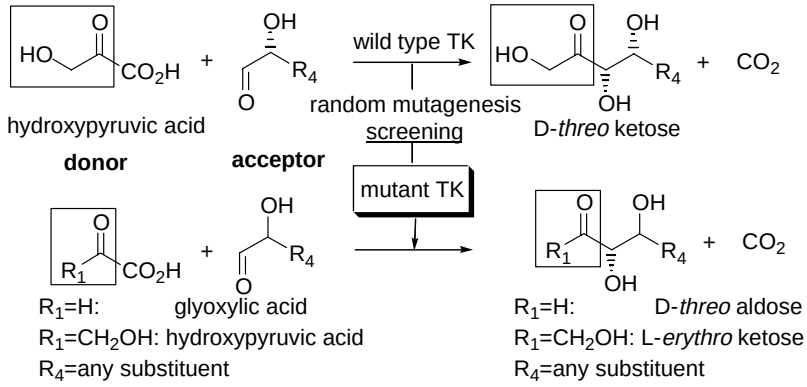


Scheme 2. Fluorescence assay based on umbelliferone release.



Scheme 3. Access to new D-*threo*-aldoses or L-*erythro*-ketoses by TK engineering.

of fluorogenic substrates as probes for measuring wild type or altered TK activity from variants with improved or new properties acquired by random mutagenesis.

2. Results and discussion

TK is a useful catalyst for ketoses syntheses. For this purpose, β-hydroxypyruvic acid was used as a donor substrate because it rendered the reaction irreversible. In this case, TK catalysed the irreversible transfer of a ketol unit from this donor substrate to various phosphorylated or non-phosphorylated aldehydes to generate D-*threo* (3*S*,4*R*) ketoses. TK isolated from spinach leaves,[10] baker's yeast,[11] *Escherichia coli*,[12] were investigated. Morerecently, we used *Saccharomyces cerevisiae* recombinant TK.[13]

2.1. Substrate design

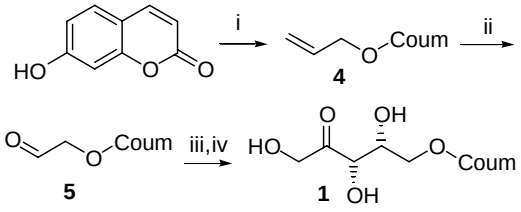
We have shown the possibility of measuring wild type TK activity from *S. cerevisiae* using the suitable stereoselective fluorogenic substrate **1**.[14] This compound (Scheme 2) was used as a donor substrate of the enzyme in the presence of D-ribose-5-phosphate as an acceptor substrate. TK cleaved the C_2–C_3 bond of **1** and generated **1′**. A fluorescent signal appeared because **1′** underwent a rapid β-elimination catalysed by bovine serum albumin (BSA) to release umbelliferone, a highly fluorescent compound. Our goal is to use this assay in the evaluation of TK mutants generated by random mutagenesis with fluorogenic substrates containing a sugar moiety depending on the enzymatic property desired.

We would like to modify the substrate specificity of TK to extend its synthetic potential to the L-*erythro* ketoses and D-*threo* aldoses series (Scheme 3). In the latter case, variants of TK would be able to accept glyoxylic acid as the donor substrate yielding D-*threo* aldoses while in the former case, variants would be able to accept (*S*)-hydroxyaldehydes as acceptor substrates yielding L-*erythro* ketoses.

Here we report the stereoselective syntheses of the fluorogenic compounds **1**, **2** and **3** as stereochemical probes for de novo TK activities. Compound **2** should be suitable for evaluating altered selectivity for the donor substrate, while compound **3** should be suitable for evaluating altered stereoselectivity for the acceptor substrate.

2.2. Synthesis

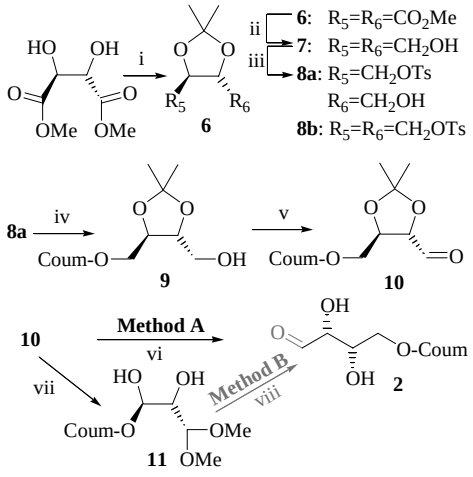
As previously described,[14] the fluorogenic compound **1** was prepared by a chemoenzymatic route from the known umbelliferone (Scheme 4). Olefin **4** was obtained in 96% yield after allylation in refluxing acetone.[15] As reported in the literature,[16] aldehyde **5** was obtained by a two-step procedure using OsO_4/NMMO to give the diol followed by overoxidation by $NaIO_4$. To carry out the reaction in a single step, we performed an ozonolysis of crude **4** at −30 °C in methylene chloride with 10% DMF. Reduction of the ozonide intermediate with dimethyl sulfide gave the aldehyde **5** in 62% yield with high selectivity for the exocyclic double bond versus the conjugated lactone double bond.



Scheme 4. Synthesis of **1**: (i) CH_2=CH–CH_2Br, K_2CO_3, (**4**, 96%); (ii) O_3, Me_2S, (**5**, 62%); (iii) RAMA, DHAP, mCD; (iv) acid phosphatase, (**1**, 35% overall for the last two steps).

Our strategy was to introduce both chiral centers (3*S*,4*R*) of the sugar moiety of the fluorogenic substrate **1** at once, by using fructose-1,6-bisphosphate aldolase from rabbit muscle (RAMA; E.C.4.1.2.13). The utility of this enzyme is well-documented[17] for the synthesis of D-*threo* ketoses by C–C bond formation in a highly stereoselective manner. Aldehyde **5** thus underwent aldol addition using RAMA with dihydroxyacetone phosphate (DHAP) as the donor substrate (DHAP was prepared and assayed according to Charmantray et al.[18]). Because of the high hydrophobicity of the coumarin part of the molecule, we added a modified cyclodextrin (mCD) to make the aldehyde water-soluble. In these conditions, the reaction proceeded smoothly giving higher yields than using co-solvents such as DMSO or MeOH. After dephosphorylation catalysed by acid phophatase (E.C.3.1.3.2) at pH 4.8, compound **1** was obtained in 35% overall yield for the two enzymatic steps.

To obtain compound **2**, we investigated the use of commercially available D-dimethyl tartrate (2*S*,3*S*) as a building block to set the chirality on C_2 and C_3 at an early stage (Scheme 5).



Scheme 5. Synthesis of **2**: (i) $(CH_3)_2C(OCH_3)_2$ (**6**, 85%); (ii) $NaBH_4$ (**7**, 73%); (iii) TsCl, NaOH (**8**, 83%); (iv) Coum-OH, NaH (**9**, 71%); (v) Dess–Martin periodinane (**10**, 49%); (vi) Dowex H^+ resin (**2**, 25%); (vii) Dowex H^+ resin (**11**, 43%); (viii) Dowex H^+ resin (**2**, 28%).

Compound **8a** was easily obtained from D-dimethyl tartrate (2*S*,3*S*) in a three-step sequence. Intermediate **6** was synthesised by transacetalisation in dimethoxypropane in 85% yield as described in the literature.[19a] Subsequent reduction of the diester was achieved using 1.5 equiv of $NaBH_4$ in ethanol instead of 2.0 equiv in methanol.[19b] In this way, the yield of compound **7** was increased from 30 to 73% without significant transesterification.

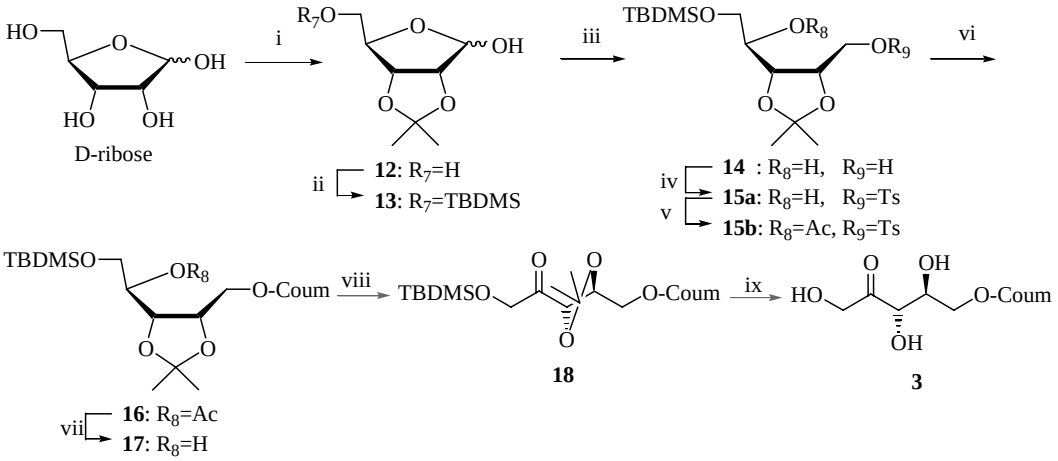
Monotosylation of compound **7** was described earlier in 89% yield.[20] Following this procedure, we failed to obtain **7** in more than 57% yield. Both increasing reaction time at room temperature to 5 h from 45 min and introducing strictly 1 equiv of tosyl chloride as the tosylating agent, we succesfully obtained compound **8a** in 83% yield along with 10% of the corresponding bistosylated compound **8b**, which were separable by column chromatography.

At this stage, it was necessary to convert the primary alcohol function from **8a** into a coumarinyl ether. We chose the sodium salt of umbelliferone as the nucleophile to substitute the tosylate **8a**, as described by Gonzalez-Garcia et al.[9] for the synthesis of 6-*O*-coumarinyl D-fructose from protected D-fructose furanoside. The new compound **9** was recovered in 71% yield after purification. None of our attempts to increase the yield by either modifying the reaction temperature (60, 70 and 90 °C) or changing the counter-ion (from sodium to *tert*-butyl ammonium)[21] was successful.

Oxidation of alcohol **9** was carried out using various oxidising reagents. Neither CrO_3/Pyr nor PCC/NaOAc gave any desired product, whereas Dess–Martin periodinane or Pyr-SO_3/DMSO/NEt_3 gave compound **10** with similar yields (50%). In these latter conditions, reaction monitoring by TLC showed that the starting material was fully converted to the aldehyde **10** but the moderate yield may be explained by the instability of compound **10** on silica gel during purification by chromatography. Finally, this step was achieved using the easily handled periodinane reagent.

The final step dealt with the deprotection of the diol **10**. We tried several usual acidic conditions such as AcOH, TFA, HCl, and Dowex H^+ resin to hydrolyse the acetonide. We noted that when using AcOH, TFA, and HCl in water, compound **10** was fully dissolved, whereas when Dowex H^+ resin was used in water, it was necessary to add a minimum amount of co-solvent to obtain a clear solution. The co-solvents used were DMSO, THF, MeOH and acetone. Only the combination of Dowex H^+ resin in acetone/H_2O at room temperature gave compound **2** in 25% yield (method A). It is noteworthy that when the reaction was carried out in the same conditions but in MeOH/H_2O as the solvent mixture, we characterised compound **11** as a single product resulting from the deprotection of the diol with concomitant acetalisation of the aldehyde **2**. We tried to increase the yield of compound **11** by using larger amounts of MeOH to favour the acetal formation. The highest yield of **11** (43%) was obtained with Dowex H^+ resin in MeOH/H_2O 99:1 as the solvent mixture. We thus investigated the deprotection of **11** as an alternative route to compound **2** (method B). For that purpose, we followed the same conditions as described for the reaction of **10** to **2**. Starting from **11**, we obtained compound **2** in 28% yield. Due to its propensity to oligomerise because of the presence of a hydroxy group alpha to a carbonyl, compound **2** was recovered in moderate yields whatever the route followed. It was characterised by NMR and HRMS. The presence of the aldehyde function was confirmed by derivatisation to the corresponding diphenylhydrazone **2′** according to the protocol described by Friestad et al.[22]

The synthesis of substrate **3** started from inexpensive D-ribose, useful for setting both C_3 and C_4 chirality in the final product[9] (Scheme 6). The first steps required prior protection of the two secondary alcohols in acetonide **12** followed by protection of the primary one in a silylated derivative according to the literature.[23–26] Compound **13** thus obtained was converted into **14** after ring opening by reduction over sodium borohydride in ethanol.[27]



Scheme 6. Synthesis of **3**: (i) acetone, PTSA, (**12**, 63%); (ii) TBDMSCl, imidazole, (**13**, 71%); (iii) $NaBH_4$, (**14**, 80%); (iv) TsCl, NEt_3, DMAP, (**15a**, not isolated) then (v) Ac_2O, NEt_3, (**15b**, 53% overall); (vi) $n$$Bu_4NBr$, umbelliferone, NaOH, (**16**, 60%); (vii) K_2CO_3, (**17**, 90%); (viii) Dess–Martin reagent, (**18**, 74%); (ix) I_2, MeOH, (**3**, 56%).

At this stage, it was necessary to activate selectively the primary alcohol function of **14** into a tosyl group. In our case, neither the use of NaOH[28] nor NEt_3/DMAP[29] as bases gave satisfactory yields. The tosylated compound **15a** was obtained in the reaction mixture but was sensitive to intramolecular cyclisation by nucleophilic attack of the free secondary alcohol on the tosyl group, leading to a furan type compound. As this side reaction occurred mainly during workup, this unwanted reaction was prevented by protecting the free secondary alcohol as an acetyl group directly in the reaction medium, just after formation of the tosyl derivative. Compound **15b** was then obtained in satisfactory yield (53% overall).

The tosyl displacement by umbelliferone was first attempted using the protocol described by Gonzalez-Garcia et al.,[10] that is, using NaH as base. Unfortunately, in our case, these conditions suffered from appearance of many byproducts resulting of a loss of silylated protecting group.

Finally, we chose to make the tetrabutylammonium salt of umbelliferone beforehand following the procedure described by Vasela et al.[21] to carry out the intermolecular nucleophilic substitution in neutral conditions at a lower reaction temperature. This gave the desired product **16** in 60% yield. A single alkaline hydrolysis of the acetyl group followed by an oxidation using the smooth Dess–Martin reagent[30] then gave **18** in 67% overall yield. Usual acidic hydrolysis of all the remaining protective groups using acidic resin, TFA or HCl in various co-solvents to solubilise the starting material (MeOH, acetone, DMF) at different reaction temperatures ranging from room temperature to 65 °C (the degradation threshold temperature) failed to give product **3**. The ether bond proved to be easily cleaved causing umbelliferone release. The highest yield (56%) was obtained using iodine in methanol,[31] an alternative method for the cleavage of acetals into carbohydrate derivatives, leading to the final L-*erythro* ketose **3**.

2.3. Yeast TK fluorogenic assays

Assay conditions were optimised with wild type TK[14] and fluorogenic compound **1**, bearing the glycosyl moiety of D-*threo* ketose configuration as the donor substrate. The reaction proceeded in the presence of D-ribose-5-phosphate as acceptor substrate, thiamine pyrophosphate and Mg^{2+} as cofactors and BSA as catalyst for umbelliferone β-elimination in Tris buffer (pH 8.2). We observed a fluorescent signal proportional to both TK quantity and compound **1** concentration.[14] Under the same conditions, fluorogenic compounds **2** and **3** bearing, respectively, D-*threo* aldose and L-*erythro* ketose moieties did not lead to a significant fluorescence signal in the presence of wild type TK. This experiment showed that wild type TK was able to discriminate between the natural (D-*threo*) configuration of compound **1** and the non-natural (L-*erythro*) configuration of compound **3**. Moreover, TK was able to discriminate between the natural hydroxyacetyl moiety of **1**, mimicking the natural substrate, and the non-natural formyl moiety of **2**.

3. Conclusion

In conclusion, three stereochemical fluorogenic probes for transketolase have been prepared. The fluorogenic compound **1** with natural D-*threo* ketose configuration enabled us to design a highly sensitive fluorogenic assay for wild type TK, in the presence of BSA as auxiliary protein. Our interest was to modify the substrate specificity of TK by random mutagenesis. In this field, the principle of this stereospecific fluorogenic assay could be used to screen TK variants able to recognize the D-*threo* aldose (compound **2**) and L-*erythro* ketose (compound **3**) moieties. Some experiments in this field are currently under investigation.

4. Experimental

4.1. General information

Chemicals and solvents were purchased from Aldrich and Acros and were reagent grade. Rabbit muscle aldolase (E.C.4.1.2.13), acid phosphatase (E.C.3.1.3.2) from wheat germ and BSA were purchased from Sigma. Transketolase from *S. cerevisiae* was produced and purified by us as

previously described.[32] Merck 60 F254 silica gel TLC plates and Merck 60/230–400 and 60/40–63 mesh silica gel for column chromatography were used. ^{1}H, and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$, D_2O, CD_3OD and CD_3COCD_3, δ values are given in parts per million and J values in Hertz. MS and HRMS were recorded on a Micromass Q-Tof spectrometer equipped with an electrospray ionisation source. Optical rotations were determined on a Jasco DIP-370 polarimeter using a 10 cm cell. Melting points are uncorrected and were measured on a Reichert apparatus.

4.1.1. 7-(2-Oxoethoxy) coumarine (5). Eight hundred and sixty milligrams of compound **4** (4.57 mmol) was dissolved in 2 mL of DMF and 20 mL of dichloromethane at room temperature, and then cooled to −40 °C and treated with a stream of ozone. When the reaction was complete as seen by TLC using cyclohexane/ethyl acetate 2:8, ozone was removed by flushing with an argon stream for 1 h. 1 mL of dimethylsulfide (13.4 mmol, 3 equiv) was added dropwise at −40 °C. The reaction mixture was then warmed to room temperature overnight and evaporated under vacuum. The crude material was dissolved in 50 mL of ethyl acetate and washed five times with 50 mL of water. After evaporation under vacuum, the product was chromatographed on silica gel using cyclohexane/ethyl acetate 1:1 as eluent. 560 mg of compound **5** was obtained as a white solid in 64% yield. The analytical data for characterisation are similar to those already reported in the literature.[16]

4.1.2. 7-(2′,3′,5′-Trihydroxy-4′oxo-pentyl)oxycoumarine (1). 0.878 g of (2-Hydroxypropyl)-β-cyclodextrin (0.63 mmol) and 100 mg (0.53 mmol, 1.2 equiv) of 7-(2-oxoethoxy)coumarin **5** were dissolved in 3.9 mL of methanol and stirred for 15 min. 2.6 mL of water were added and the methanol was evaporated. 1.3 mL of a DHAP solution (400 mM, 0.53 mmol, 1 equiv, pH 7.8) were then poured in (to give a 200 mM final substrate concentration) followed by 150 U of commercially available RAMA. The mixture was stirred for 48 h at room temperature. The reaction was followed by TLC with 1-propanol/ethylacetate/water/ethanol/pyridine/acetic acid 35:15:25:15:10:10 as eluent until complete disappearance of the starting aldehyde. The pH was adjusted to 4.8 and 150 U of acid phosphatase was added. The mixture was then stirred overnight. Three volumes of methanol were added to precipitate proteins, the mixture was centrifuged at 8000 rpm and the subsequent supernatant was evaporated to dryness under vacuum. Two flash chromatographies (methylene chloride/methanol 9:1) gave 56 mg of compound **1** as a white solid (35% yield).

^{1}H NMR (CD_3COCD_3, 400 MHz) δ (ppm): 4.15 (1H, dd, $J_{1'-2'}=6.2$ Hz, $J_{1'-1''}=9.8$ Hz, $H_{1'}$), 4.26 (1H, dd, $J_{1''-2}=6.2$ Hz, $J_{1''-1'}=9.8$ Hz, $H_{1''}$), 4.40 (1H, td, $J_{2'-3'}=2.4$ Hz, $J_{2'-1'}=6.2$ Hz, $J_{2'-1''}=6.2$ Hz, $H_{2'}$), 4.45 (1H, d, $J_{5'-5''}=19.6$ Hz, $H_{5'}$), 4.50 (1H, d, $J_{3'-2'}=2.4$ Hz, $H_{3'}$), 4.55 (1H, d, $J_{5''-5'}=19.6$ Hz, $H_{5''}$), 6.20 (1H, d, $J_{3-4}=9.2$ Hz, H_3), 6.8 (1H, s, H_8), 6.9 (1H, d, $J_{6-5}=8.5$ Hz, H_6), 7.54 (1H, d, $J_{5-6}=8.5$ Hz, H_5), 7.87 (1H, d, $J_{4-3}=9.2$ Hz, H_4). ^{13}C NMR (CD_3COCD_3, 100 MHz) δ (ppm): 66.8 ($C_{5'}$), 68.9 ($C_{1'}$), 70.1 ($C_{2'}$), 75.7 ($C_{3'}$), 101.3 (C_6), 112.5 (C_8), 112.7 (C_9), 112.8 (C_3), 129.3 (C_5), 143.7 (C_4), 155.8 (C_{10}), 160.1 (C_7), 161.9 (C_2), 211.9 ($C_{4'}$). HRMS (ESI+) calculated for $C_{14}H_{15}O_7$: $[M+H]^+$ 295.0818, found 295.0823.

4.1.3. 2,3-*O*-Isopropylidene-1-tosyl-D-threitol (8b). This compound was synthesised according to the method of Valverde et al.[20] Starting from 2.77 g (17.1 mmol) of compound **7**, we recovered compound **8a**, isolated in 83% yield as a colourless oil (4.48 g, 14.2 mmol) after column chromatography. Bistosylated compound **8b** was also isolated from the crude product in 10% yield.

4.1.4. 2,3-Isopropyliden-1-*O*-(2′-oxo-benzopyran-7′-yl)-D (9). To a solution of 1.25 g of umbelliferone (7.73 mmol, 1.5 equiv) in 30 mL of DMF under nitrogen was dissolved 0.31 g of sodium hydride (60% oil dispersion, 7.73 mmol, 1.5 equiv). The mixture was stirred at room temperature for 1 h. A mixture of compound **8b** (1.63 g, 5.15 mmol, 1 equiv) in DMF (12 mL) was then added. The reaction mixture was then heated under stirring at 80 °C and was followed by TLC (cyclohexane/AcOEt 4:6) until complete disappearance of the starting material (18 h). After extraction with ethyl acetate, the collected organic phases were washed with brine and evaporated under reduced pressure. The title compound **9** was purified from the crude product by column chromatography on silica gel, eluted in cyclohexane/AcOEt 6:4, 5:5, 4:6 gradient. Compound **9** was recovered as white needles (1.12 g, 3.65 mmol) in 71% yield.

TLC: R_f (cyclohexane/AcOEt 4:6)=0.30. $[\alpha]_D^{22}$ 24.3 (c 1.01, acetone). Mp 79–83 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.45 (6H, 2s, $2H_6$), 2.31 (1H, s, 1OH), 3.75 (1H, dd, $J_{4-3}=4$ Hz, $J_{4-4'}=12$ Hz, H_4), 3.88 (1H, dd, $J_{4'-3}=4$ Hz, $J_{4'-4}=12$ Hz, $H_{4'}$), 4.10 (1H, ddd, $J_{3-4}=4$ Hz, $J_{3-4'}=4$ Hz, $J_{3-2}=8$ Hz, H_3), 4.14 (1H, dd, $J_{1-2}=5$ Hz, $J_{1-1'}=10$ Hz, H_1), 4.18 (1H, dd, $J_{1'-2}=5$ Hz, $J_{1'-1}=10$ Hz, $H_{1'}$), 4.31 (1H, ddd, $J_{2-1}=5$ Hz, $J_{2-1'}=5$ Hz, $J_{2-3}=8$ Hz, H_2), 6.24 (1H, d, $J_{3'-4'}=10$ Hz, $H_{3'}$), 6.81 (1H, s, $H_{8'}$), 6.85 (1H, d, $J_{6'-5'}=8$ Hz, $H_{6'}$), 7.35 (1H, d, $J_{5'-6'}=8$ Hz, $H_{5'}$), 7.62 (1H, d, $J_{4'-3'}=10$ Hz, $H_{4'}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.0 ($2C_6$), 62.2 (C_4), 68.9 (C_1), 75.5 (C_3), 78.6 (C_2), 101.7 ($C_{6'}$), 110.7 (C_5), 112.9 ($C_{8'}$), 113.0 ($C_{9'}$), 113.5 ($C_{3'}$), 128.9 ($C_{5'}$), 143.5 ($C_{4'}$), 155.8 ($C_{10'}$), 161.2 ($C_{7'}$), 161.7 ($C_{2'}$). HRMS (ESI^+) m/z: $[M+H^+]$: calculated for $C_{16}H_{19}O_6$ 307.1182, found 307.1195.

4.1.5. 2,3-Isopropyliden-4-*O*-(2′-oxo-benzopyran-7′-yl)-D-threose (10). A cold (4 °C) 15% solution of Dess–Martin periodinane in CH_2Cl_2 (800 μL, 1.2 equiv) was added to a solution of compound **9** (97 mg, 0.32 mmol, 1 equiv) in dichloromethane (6.3 mL) at 5 °C. The reaction mixture was kept at 5 °C with stirring for 2 h, and then poured into an ice–0.1 N $NaHCO_3$ mixture (20 mL). After 3 extractions with ethyl acetate, the organic layer was successively washed with 0.1 N $NaHCO_3$ and brine. It was then dried on $MgSO_4$. After evaporation under reduced pressure the crude residue was purified by flash chromatography on silica gel (cyclohexane/AcOEt 1:1). Compound **10** (43 mg, 0.14 mmol) was isolated as white needles in 50% yield.

TLC: R_f (cyclohexane/AcOEt 4:6)=0.30. Mp 67–69 °C. $[\alpha]_D^{25}$ 4.95 (c 1.07, chloroform). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.50 (6H, 2s, $2H_6$), 4.19 (1H, dd, $J_{4a-3}=5$ Hz,

$J_{4a-4b}=10$ Hz, H_{4a}), 4.26 (1H, dd, $J_{4b-3}=4$ Hz, $J_{4b-4}=10$ Hz, $H_{4'}$), 4.36 (1H, d, $J_{2-3}=7$ Hz, H_2), 4.47 (1H, m, H_3), 6.27 (1H, d, $J_{3'-4'}=10$ Hz, $H_{3'}$), 6.84 (1H, s, $H_{8'}$), 6.87 (1H, d, $J_{6'-5'}=9$ Hz, $H_{6'}$), 7.38 (1H, d, $J_{5'-6'}=9$ Hz, $H_{5'}$), 7.63 (1H, d, $J_{4'-3'}=10$ Hz, $H_{4'}$), 9.85 (1H, s, H_1). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.4, 26.7 ($2C_6$), 68.2 (C_4), 75.3 (C_3), 81.5 (C_2), 101.8 ($C_{6'}$), 112.2 (C_5), 112.8 ($C_{8'}$), 113.5 ($C_{9'}$), 113.6 ($C_{3'}$), 128.9 ($C_{5'}$), 143.3 ($C_{4'}$), 155.7 ($C_{10'}$), 161.0 ($C_{7'}$), 161.4 ($C_{2'}$), 200.8 (C_1). HRMS (ESI^+) *m/z*: [M+H^+]: calculated for $C_{16}H_{17}O_6$ 305.1025, found 305.1035.

4.1.6. 2,3-Dihydroxy-1,1-dimethylacetal-4-*O*-(2′-oxo-benzopyran-7′-yl)-D-threose (11). Fifty four milligrams (0.18 mmol, 1 equiv) of the starting compound was solubilised in 2 mL of methanol and 20 μL of water. 1.5 mL of Dowex H^+ resin (50WX8-400) was then added and the reaction mixture allowed to stir for 2 days. The reaction was monitored by TLC using CH_2Cl_2/MeOH 9:1 as eluent. After completion of the reaction, the resin was removed by filtration and the mixture evaporated under vacuum. The white residue thus obtained was purified by flash chromatography on silica gel using CH_2Cl_2/MeOH 95:5 as eluent. Compound **11** was isolated in 43% yield as white crystals.

TLC: R_f (DCM/MeOH 9:1)=0.75. Mp 112–114 °C. $[\alpha]_D^{25}$ −7.8 (*c* 0.92, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.75 (1H, s, OH), 2.92 (1H, s, OH), 3.5 (6H, 2s, $2H_5$), 3.72 (1H, dd, $J_{2-3}=2$ Hz, $J_{2-1}=6$ Hz, H_2), 4.11 (2H, d, $J_{4a-3}=6$ Hz, $H_{4a}+H_{4b}$), 4.23 (1H, td, $J_{3-2}=2$ Hz, $J_{3-4a}=6$ Hz, $J_{3-4b}=6$ Hz, H_3), 4.50 (1H, d, $J_{1-2}=6$ Hz, H_1), 6.23 (1H, d, $J=10$ Hz, $H_{3'}$), 6.82 (1H, s, $H_{8'}$), 6.85 (1H, d, $J_{6'-5'}=9$ Hz, $H_{6'}$), 7.34 (1H, d, $J_{5'-6'}=9$ Hz, $H_{5'}$), 7.61 (1H, d, $J_{4'-3'}=10$ Hz, $H_{4'}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 53.3, 56.7 ($2C_5$), 68.5 (C_3), 69.6 (C_4), 70.2 (C_2), 101.9 ($C_{6'}$), 105.4 (C_1), 112.9 ($C_{8'}+C_{9'}$), 113.3 ($C_{3'}$), 128.9 ($C_{5'}$), 143.5 ($C_{4'}$), 155.8 ($C_{10'}$), 161.3 ($C_{7'}$), 161.9 ($C_{2'}$). HRMS (ESI^+) *m/z*: [M+H^+]: calculated for $C_{15}H_{19}O_7$ 311.1131, found 311.1139.

4.1.7. 2,3 Dihydroxy-4-*O*-(2′-oxo-benzopyran-7′-yl)-D-threose (2). General method for acidic hydrolysis of acetals.

Acetal was dissolved in binary system (water/acetone 3:1). Dowex H^+ resin (50WX8-400) was added and the reaction suspension stirred. The suspension was refluxed for 1 h with stirring under reflux until completion (reaction monitored by TLC). After cooling to room temperature, the reaction mixture was filtered and washed with 1 mL of acetone–water mixture (1/2). Acetone was removed under reduced pressure and the pH of the water layer was adjusted to 7 with an Amberlite resin (IRA-93). After lyophilisation, the crude material was flash chromatographed on silica gel using CH_2Cl_2–MeOH (97/3) as the eluent. The final compound **2** was obtained as a colourless oil.

When compound **10** was used as the starting acetal, title compound **2** was recovered in 25% yield whereas conversion of compound **11** afforded compound **2** in 28% yield.

TLC: R_f (CH_2Cl_2/MeOH 9:1)=0.33. $[\alpha]_D^{25}$ 1.84 (*c* 3.3, chloroform). ^{1}H NMR (400 MHz, CD_3OD) δ: 3.25–3.52 (1H, m, H_2), 3.54–4.13 (3H, m, H_3+2H_4), 4.71 (1H, d, $J_{1-2}=6$ Hz, H_1), 6.14 (1H, d, $J_{3'-4'}=9.6$ Hz, $H_{3'}$), 6.83 (1H, s, $H_{8'}$), 6.88 (1H, d, $J_{6'-5'}=8.4$ Hz, $H_{6'}$), 7.45 (1H, d, $J_{5'-6'}=8.4$ Hz, $H_{5'}$), 7.77 (1H, d, $J_{4'-3'}=9.6$ Hz, $H_{4'}$). ^{13}C NMR (100 MHz, CD_3OD) δ: 68.7 (C_2), 69.7 (C_4), 73.3 (C_3), 89.6 (C_1, hydrate form), 101.4 ($C_{6'}$), 112.7 ($C_{8'}$), 113.4 ($C_{9'}$), 113.8 ($C_{3'}$), 129.6 ($C_{5'}$), 145.9 ($C_{4'}$), 154.9 ($C_{10'}$), 163.9 ($C_{2'}+C_{7'}$). HRMS (ESI^+) *m/z*: [M+H^+]: calculated for $C_{13}H_{13}O_6$ 265.0712, found 265.0708.

4.1.8. Derivatisation of compound 2 into the corresponding *N,N*-diphenylhydrazone 2′. To a solution of compound **2** (56 mg, 0.21 mmol, 1 equiv) in 4 mL of toluene were successively added *N,N*-diphenylhydrazine hydrochloride (94 mg; 0.42 mmol; 2 equiv) and sodium sulphate Na_2SO_4 (1.26 g; 10.2 mmol) at room temperature. The reaction mixture was kept at room temperature under stirring for 24 h. After filtration, the crude mixture was concentrated under vacuum, and purified by flash chromatography on silica gel (cyclohexane/AcOEt 6:4). Hydrazone **2′** was recovered as a bright yellow oil in 36% yield.

TLC: R_f (cyclohexane/AcOEt 6:4)=0.13. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.63 (1H, d, $J=5$ Hz, OH), 3.35 (1H, d, $J=5$ Hz, OH), 4.04 (3H, m, H_4), 4.43 (1H, ddd, $J_{2-3}=10$ Hz, $J_{2-1}=4$ Hz, $J_{2-1'}=4$ Hz, H_2), 6.20 (1H, d, $J_{3'-4'}=9.6$ Hz, $H_{3'}$), 6.56 (1H, d, $J=3$ Hz, H_1), 6.74 (1H, s, $H_{8'}$), 6.77 (1H, d, $J_{6'-5'}=8.4$ Hz, $H_{6'}$), 7.11 (4H, m), 7.19 (2H, m), 7.33 (1H, d, $J_{5'-6'}=8.4$ Hz, $H_{5'}$), 7.35 (4H, m), 7.54 (1H, d, $J_{4'-3'}=9.6$ Hz, $H_{4'}$). ^{13}C NMR (100 MHz, CD_3COCD_3) δ: 70.6 (C_4), 72.4 (C_2), 72.9 (C_3), 102.3 ($C_{6'}$), 113.5 ($C_{8'}$), 113.7 ($C_{3'}$), 123.1 ($C_{2''}$), 125.2 ($C_{4''}$), 130.1 ($C_{5'}$), 130.6 ($C_{3''}$), 138.9 (C_1), 144.5 ($C_{4'}$), 144.7 ($C_{1''}$).

4.1.9. 4-*O*-Acetyl-2,3-*O*-isopropylidene-5-*O*-terbutyldimethylsilyl-1-*O*-tosyl-D-ribitol (15b). In 16 mL of anhydrous dichloromethane were dissolved 400 mg (1.3 mmol) of compound **14**, 273 mg (1.43 mmol, 1.1 equiv) of tosyl chloride, 192 μL (1.43 mmol, 1.1 equiv) of anhydrous triethylamine and 160 mg (1.3 mmol, 1 equiv) of DMAP. The reaction mixture was stirred for 30 min at room temperature and was monitored by TLC using cyclohexane/ethyl acetate 7:3 as eluent. 615 mg (6.5 mmol, 5 equiv) of acetic anhydride was then added followed by 364 μL (2.8 mmol, 2.2 equiv) of anhydrous triethylamine. The mixture was evaporated under vacuum. The crude product was dissolved in ethyl acetate and the organic phase was washed three times with water. After drying on $MgSO_4$, rotary evaporation and flash chromatography on silica gel (cyclohexane/ethyl acetate 8:2), 346 mg (53%) of product **15b** was obtained as a colourless oil.

TLC: R_f (cyclohexane/AcOEt 7:3)=0.65. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.02 (6H, s, $2H_8$), 0.87 (9H, s, $9H_{10}$), 1.30–1.31 (6H, 2s, $2H_7$), 2.04 (3H, s, H_{17}), 2.44 (3H, s, H_{15}), 3.74 (1H, dd, $J_{5-4}=4$ Hz, $J_{5-5'}=12$ Hz, H_5), 3.87 (1H, dd, $J_{5'-4}=2$ Hz, $J_{5'-5}=12$ Hz, $H_{5'}$), 3.92 (1H, dd, $J_{1-2}=7$ Hz, $J_{1-1'}=10$ Hz, H_1), 4.08 (1H, dd, $J_{1'-2}=6$ Hz, $J_{1'-1}=10$ Hz, $H_{1'}$), 4.38 (2H, m, H_2+H_3), 4.78 (1H, ddd, $J_{4-5'}=2$ Hz, $J_{4-5}=4$ Hz, $J_{4-3}=9$ Hz, H_4), 7.33 (2H, d, $J_{13-12}=8$ Hz, $2H_{13}$), 7.80 (2H, d, $J_{12-13}=8$ Hz, $2H_{12}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −5.4 ($2C_8$), 18.4 (C_9), 21.1,

21.8 ($2C_7$), 25.9 ($3C_{10}$), 27.0 (C_{15}), 27.9 (C_{17}), 62.0 (C_5), 68.2 (C_1), 71.6 (C_4), 73. 8 (C_3), 75.0 (C_2), 109.3 (C_6), 128.2, 130.0 ($C_{12}+C_{13}$), 132.8 (C_{14}), 145.0 (C_{11}), 170.0 (C_{16}). HRMS (ESI^+) *m/z*: $[M+H^+]$: calculated for $C_{23}H_{39}O_8SiS$ 503.2135, found 503.2141.

4.1.10. 4-*O*-Acetyl-2,3-*O*-isopropylidene-1-*O*-(2′-oxo-benzopyran-7′-yl)-5-*O*-terbutyldimethylsilyl-D (16). The tetrabutylammonium salt of umbelliferone was obtained by mixing 616 mg (3.8 mmol, 1 equiv) of umbelliferone with 1.22 g (3.8 mmol, 1 equiv) of tetrabutylammonium bromide in 10 mL of a NaOH solution (228 mg, 5.7 mmol, 1.5 equiv). After stirring for few minutes, the salt was extracted with chloroform and the organic phase was dried on $MgSO_4$ and evaporated under vacuum. Thus 1.5 g of crude salt was obtained and used without further purification. The salt previously obtained was transferred to a flask containing 200 mg of **15b** (0.38 mmol, 1 equiv) dissolved in 20 mL of anhydrous DMF. The mixture was then stirred for 96 h at 50 °C under argon. The reaction was monitored by TLC using cyclohexane/ethyl acetate 6:4 as eluent. After disappearance of the starting compound, 50 mL of water was added followed by 50 mL of ethyl acetate, and the aqueous phase was extracted twice with 2×50 mL of ethyl acetate. The organic phase was dried on $MgSO_4$ and evaporated under vacuum. The crude product was purified by column chromatography on silica gel using cyclohexane/ethyl acetate 6:4 as eluent. Compound **16** was isolated in 60% yield as a white solid.

TLC: R_f (cyclohexane/AcOEt 6:4)=0.42. Mp 95–96 °C. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.03 (6H, s, $2H_8$), 0.87 (9H, s, $3H_{10}$), 1.39, 1.47 (6H, 2s, $2H_7$), 2.03 (3H, s, H_{12}), 3.81 (1H, dd, $J_{5a-4}=4$ Hz, $J_{5a-5b}=12$ Hz, H_{5a}), 3.92 (1H, dd, $J_{5b-4}=2$ Hz, $J_{5b-5a}=12$ Hz, H_{5b}), 4.09 (1H, dd, $J_{1a-2}=6$ Hz, $J_{1a-1b}=10$ Hz, H_{1a}), 4.15 (1H, dd, $J_{1b-2}=5$ Hz, $J_{1b-1a}=10$ Hz, H_{1b}), 4.48 (1H, dd, $J_{3-2}=6$ Hz, $J_{3-4}=8$ Hz, H_3), 4.56 (1H, m, H_2), 5.02 (1H, ddd, $J_{4-5b}=2$ Hz, $J_{4-5a}=4$ Hz, $J_{4-3}=8$ Hz, H_4), 6.24 (1H, d, $J_{3'-4'}=10$ Hz, $H_{3'}$), 6.78 (1H, s, $H_{8'}$), 6.82 (1H, d, $J_{6'-5'}=9$ Hz, $H_{6'}$), 7.36 (1H, d, $J_{5'-6'}=9$ Hz, $H_{5'}$), 7.62 (1H, d, $J_{4'-3'}=10$ Hz, $H_{4'}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −5.4 ($2C_8$), 18.4 (C_9), 21.3 (C_{12}), 25.5 ($2C_7$), 25.9 ($3C_{10}$), 62.3 (C_5), 67.3 (C_1), 72.0 (C_2), 74.2 (C_4), 75.4 (C_3), 101.8 ($C_{6'}$), 109.2 (C_6), 112.8 ($C_{8'}$), 113.0 ($C_{9'}$), 113.5 ($C_{3'}$), 129.0 ($C_{5'}$), 143.4 ($C_{4'}$), 155.9 ($C_{10'}$), 161.2 ($C_{7'}$), 161.8 ($C_{2'}$), 170.0 (C_{11}). HRMS (ESI^+) *m/z*: $[M+H^+]$: calculated for $C_{25}H_{37}O_8Si$ 493.2258, found 493.2267.

4.1.11. 2,3-*O*-Isopropylidene-1-*O*-(2′-oxo-benzopyran-7′-yl)-5-*O*-terbutyl-dimethylsilyl-D (17). To a solution of 191 mg (0.39 mmol) of compound **16** in 9 mL of methanol were added 107 mg (0.77 mmol, 2 equiv) of potassium carbonate. The mixture was stirred at room temperature for 4 h. After disappearance of the starting compound (cyclohexane/ethyl acetate 4:6), a mixture of ethyl acetate and water (v/v 1:1) was added and the solution was extracted. The organic phase was dried under $MgSO_4$ and evaporated under vacuum to give 141 mg (90%) of compound **17** as a colourless oil, used without further purification.

TLC: R_f (cyclohexane/AcOEt 4:6)=0.65. $[\alpha]_D^{24}$ −22.75 (*c* 0.4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 0.102 (6H, s, $2H_8$), 0.92 (9H, s, $3H_{10}$), 1.39, 1.47 (6H, 2s, $2H_7$), 3.70 (2H, m, H_4+H_{5a}), 3.85 (1H, dd, $J_{5b-4}=5$ Hz, $J_{5b-5a}=12$ Hz, H_{5b}), 4.12 (1H, dd, $J_{1a-2}=6$ Hz, $J_{1a-1b}=10$ Hz, H_{1a}), 4.19 (1H, dd, $J_{1b-2}=8$ Hz, $J_{1b-1a}=10$ Hz, $H_{1'}$), 4.48 (1H, dd, $J_{3-2}=3$ Hz, $J_{3-4}=10$ Hz, H_3), 4.60 (1H, ddd, $J_{2-3}=3$ Hz, $J_{2-1a}=6$ Hz, $J_{2-1b}=8$ Hz, H_2), 6.25 (1H, d, $J_{3'-4'}=9$ Hz, $H_{3'}$), 6.89 (1H, s, $H_{8'}$), 6.92 (1H, d, $J_{6'-5'}=8$ Hz, $H_{6'}$), 7.36 (1H, d, $J_{5'-6'}=8$ Hz, $H_{5'}$), 7.63 (1H, d, $J_{4'-3'}=9$ Hz, $H_{4'}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −5.2 ($2C_8$), 18.5 (C_9), 25.7 ($2C_7$), 26.0 ($3C_{10}$), 64.4 (C_1), 68.1 (C_5), 69.5 (C_4), 76.1 (C_2+C_3), 101.9 ($C_{6'}$), 109.6 (C_6), 112.7 ($C_{8'}$), 112.8 ($C_{9'}$), 113.3 ($C_{3'}$), 128.8 ($C_{5'}$), 143.5 ($C_{4'}$), 155.8 ($C_{10'}$), 161.3 ($C_{7'}$), 162.2 ($C_{2'}$). MS *m/z* 473 ($M+Na^+$). HRMS *m/z*: $[M+Na^+]$: calculated for $C_{23}H_{34}NaO_7Si$ 473.1971, found 473.1965.

4.1.12. 2,3-*O*-Isopropylidene-4-oxo-5-*O*-terbutyl-dimethylsilyl-7′-(2,3,5-trihydroxy-4-oxo-pentyl)oxy-coumarine (18). Four hundred and ten milligrams (0.96 mmol, 1.4 equiv) of Dess–Martin reagent were dissolved in 6 mL of anhydrous dichloromethane. 310 mg (0.69 mmol, 1 equiv) of compound **17** dissolved in 4 mL of anhydrous dichloromethane were then added and the mixture was stirred for 5 h at room temperature. 30 mL of diethyl ether were poured in followed by 12 mL of a 1.3 M NaOH solution. The mixture was stirred for 10 min and the organic layer was washed with 20 mL of water, dried on $MgSO_4$ and evaporated under reduced pressure to yield 230 mg (74%) of yellow oil, used in the next step without further purification.

TLC: R_f (cyclohexane/AcOEt 4:6)=0.69. $[\alpha]_D^{24}$ −52.2 (*c* 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 0.06 (9H, s, $2H_8$), 0.88 (9H, s, $3H_{10}$), 1.40, 1.58 (6H, 2s, $2H_7$), 4.00 (1H, dd, $J_{1-2}=4$ Hz, $J_{1-1'}=10$ Hz, H_1), 4.15 (1H, dd, $J_{1'-2}=4$ Hz, $J_{1'-1}=10$ Hz, $H_{1'}$), 4.52 (2H, 2s, $J_{5a-5b}=19$ Hz, $2H_5$), 4.77 (1H, ddd, $J_{2-1}=4$ Hz, $J_{2-1'}=4$ Hz, $J_{2-3}=8$ Hz, H_2), 4.87 (1H, d, $J_{3-2}=8$ Hz, H_3), 6.24 (1H, d, $J_{3'-4'}=9$ Hz, $H_{3'}$), 6.77 (1H, s, $H_{8'}$), 6.79 (1H, d, $J_{6'-5'}=8$ Hz, $H_{6'}$), 7.33 (1H, d, $J_{5'-6'}=8$ Hz, $H_{5'}$), 7.61 (1H, d, $J_{4'-3'}=9$ Hz, $H_{4'}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −5.3 ($2C_8$), 18.4 (C_9), 24.9 ($2C_7$), 26.0 ($3C_{10}$), 66.5 (C_1), 68.5 (C_5), 76.0 (C_2), 76.5 (C_3), 102.2 ($C_{6'}$), 110.5 (C_6), 112.7 ($C_{8'}$), 113.2 ($C_{9'}$), 113.6 ($C_{3'}$), 128.9 ($C_{5'}$), 143.3 ($C_{4'}$), 154.8 ($C_{10'}$), 161.2 ($C_{2'}+C_{7'}$), 206.5 (C_4). HRMS *m/z* $[M+H^+]$: calculated for $C_{23}H_{33}O_7Si$ 449.1996, found 449.2002.

4.1.13. 7′-(2,3,5-Trihydroxy-4-oxo-pentyl)oxycoumarine (3). Eighty six milligrams (0.19 mmol) of compound **18** and 48 mg (0.19 mmol, 1 equiv) of iodine were dissolved in 8 mL of methanol. The mixture was stirred and refluxed for 2 h. After disappearance of the starting compound (dichloromethane/methanol 9:1), the reaction mixture was cooled in an ice bath and 30 mg (1.9 mmol, 10 equiv) of Na_2SO_3 was added under stirring. After evaporation of methanol under vacuum and flash chromatography on silica gel (dichloromethane/methanol 95:5), 32 mg of the final compound **3** was obtained (56%) as a colourless oil.

TLC: R_f (CH_2Cl_2/MeOH 9:1)=0.62. $[\alpha]_D^{24}$ −16.4 (*c* 1, MeOH). ^1H NMR (400 MHz, CD_3COCD_3) δ: 4.12 (1H, dd, $J_{1a-2}=6$ Hz, $J_{1a-1b}=10$ Hz, H_{1a}), 4.21 (2H, m, $H_{1b}+H_2$), 4.35 (1H, d, $J_{3-2}=5$ Hz, H_3), 4.52 (2H, 2 d, $J_{5a-5b}=19$ Hz, $2H_5$), 5.37 (1H, d, $J_{3'-4'}=10$ Hz, H3′), 6.05 (1H, s, $H_{8'}$),

6.07 (1H, d, $J_{6'-5'}=8$ Hz, $H_{6'}$), 6.66 (1H, d, $J_{5'-6'}=8$ Hz, $H_{5'}$), 7.00 (1H, d, $J_{4'-3'}=10$ Hz, $H_{4'}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 67.9 (C_5), 69.7 (C_1), 72.3 (C_2), 77.2 (C_3), 102.5 ($C_{6'}$), 113.4 ($C_{8'}$), 113.6 ($C_{9'}$), 114.0 ($C_{3'}$), 130.5 ($C_{5'}$), 145.7 ($C_{4'}$), 156.8 ($C_{10'}$), 161.1 ($C_{7'}$), 162.8 ($C_{2'}$), 212.4 (C_4). HRMS *m/z*: $[M+Na^+]$: calculated for $C_{14}H_{14}NaO_7$ 317.0637, found 317.0627.

4.2. Yeast TK fluorogenic assays

TK enzyme (0–0.02 mg mL^{-1}) was incubated for 30 min in a reaction mixture containing 2 mM ThDP, 3 mM $MgCl_2$, 1 mM D-ribose-5-phosphate, 100 μM of fluorogenic substrate (**1**, **2** or **3**) and 2 mg mL^{-1} BSA in a 50 mM aq Tris buffer, pH 8.2. The reaction progress was followed by fluorescence detection at $\lambda_{em}=412$ nm ($\lambda_{ex}=390$ nm). Fluorescence was correlated with umbelliferone concentration by means of a calibration curve.

Acknowledgements

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Synthesis of the heterocyclic core of martinelline and martinellic acid

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Abstract—A Povarov reaction, between an aromatic imine derived from cinnamaldehyde and a cyclic enamide, was employed to rapidly construct the tricyclic core of the alkaloids martinelline and martinellic acid. The cycloaddition was completely regioselective though the *exo*/*endo* selectivity was poor. The diastereoisomers were readily separated by flash chromatography and the relative stereochemistry of the *exo*-isomer confirmed by single crystal X-ray crystallography. This intermediate was converted to the central core of the aforementioned alkaloids in five additional synthetic operations.

1. Introduction

There is currently much interest in identifying non-peptide bradykinin inhibitors as potential therapeutic agents.[1–7] Bioassay guided fractionation of an extract from the medicinal plant *Martinella iquitosensis* led to the isolation of the first natural product bradykinin receptor inhibitors, martinellic acid and martinelline **1a**,**b**, respectively, Figure 1.[8] These alkaloids are unique in that they contain the unusual hexahydropyrroloquinoline moiety. The biological activity, coupled with the unusual heterocyclic motif, has made these alkaloids very attractive synthetic targets. This has prompted new methods for forming hexahydropyrroloquinolines,[9–26] culminating in four syntheses[27–30] and three formal syntheses of these alkaloids,[31–33] and the subject has been recently reviewed.[34]

The major challenges in this synthesis are control of the regiochemistry on the trisubstituted aromatic ring, the stereochemistry at the three contiguous chiral centres and coping with the labile heteroatom at C9b. On the last point, it is well known that heteroatoms on the 4-position of a tetrahydroquinoline are prone to eliminate, ultimately giving quinolines. Therefore, methods for producing the hexahydropyrroloquinoline must be mild and it is prudent not to do too much additional chemistry once the hexahydropyrroloquinoline is in place. We previously communicated the first approach to the heterocyclic core of martinelline **17**, using a Povarov reaction of imines derived from aromatic amines with cyclic enamides as the key step and now report full details on this study. Triamine **17** was the key intermediate in all subsequent syntheses of martinellic acid.

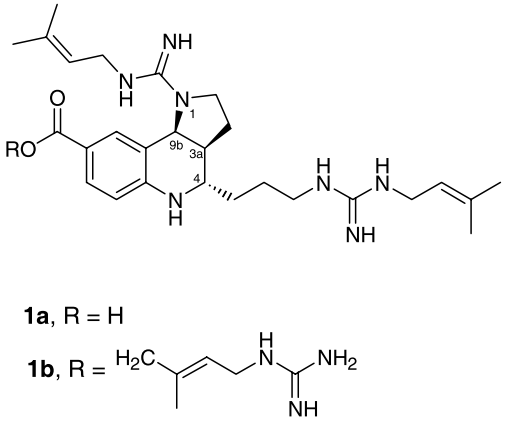

Figure 1. Structure of martinelline and martinellic acid.

2. Results and discussion

Our initial strategy, Scheme 1, focussed on using a Povarov reaction to construct the hexahydropyrroloquinoline with all

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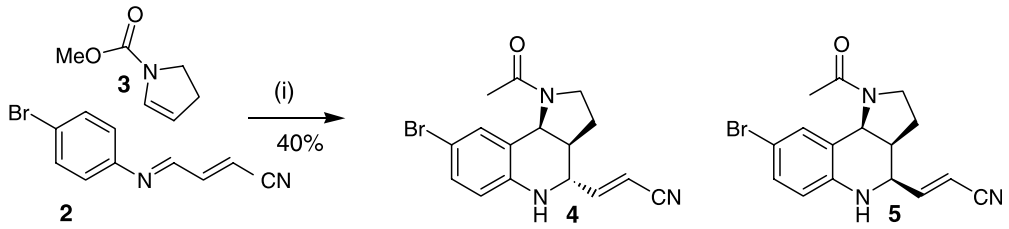
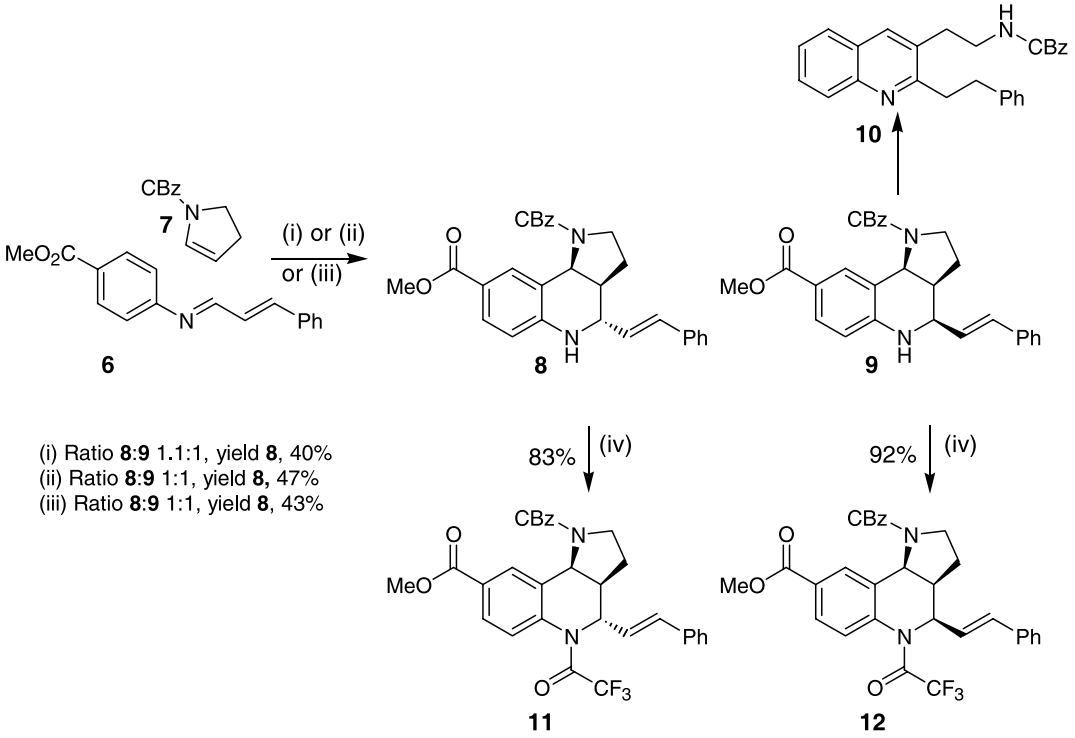


Scheme 1. Reagents and conditions: (i) indium trichloride 20%, acetonitrile 30 min 25 °C.

the carbons, bar the 8-carboxy, and nitrogens in place, though not at the correct oxidation level for martinellic acid. The main advantages of this approach were its convergence, its complete regioselectivity, and the symmetry was such that *p*-substituted benzenes ensured the correct regiochemistry of the tri-substituted aromatic ring on cycloaddition. The regioselectivity from this ionic stepwise pathway was governed by the stability of the acyliminium ion intermediate. Unfortunately, this chemistry failed with aliphatic aldehydes and with α,β-unsaturated aldehydes with hydrogens on the γ-position, making it difficult to introduce the required 4-substituent. However, this problem was overcome by using (*E*)-3-oxo-1-propenyl cyanide[35] as the aldehyde component.

We previously reported that 3-cyanoacrolein condensed with *p*-bromaniline to give an unstable imine **2**, which underwent Povarov reaction with cyclic enamide **3** to give a 1:3 mixture of *exo*/*endo* hexahydropyrroloquinolines **4** and **5** in 40% combined yield. Although this chemistry elegantly gave the gross structure of a key martinelline intermediate in one step, the low yield and *endo*-selectivity was unacceptable. Furthermore, attempts to reduce the alkene and nitrile using hydrogen and palladium led to a complex mixture of products, suggesting that N5 may need protecting prior to reduction of the nitrile and that the 8-bromo substituent was also labile under these conditions. Enamide **3** was initially chosen as the NMR spectra of the cycloadducts derived from this were reasonably sharp and easy to interpret. However, with compound **4**, attempted removal of the carbomethoxy group with trimethylsilyl iodide[36] led to intractable material. It was clear from this initial study that we would have to improve the yield and *exo*-selectivity of the cycloaddition, use an enamide in which the group on N1 was more easily removed than a carbomethoxy, protect N5 before reduction of the nitrile, and have the 8-carboxy group present before the key cycloaddition. Incorporation of all these design features led to the successful synthesis of the martinelline core, **17** Scheme 2, though some convergence was inevitably lost.

Imine **6**, derived from cinnamaldehyde and methyl 4-aminobenzoate, was a yellow crystalline compound, which was stable to storage at room temperature. Enamide **7**, made by the literature procedure,[37,38] was chosen as the coupling partner because it was envisaged that in the later



Scheme 2. Reagents and conditions: (i) 12 mol% $InCl_3$, CH_3CN, 25 °C, 12 h; (ii) 1 mol% $Y(OTf)_3$, CH_3CN 25 °C, 2 h; (iii) 100 mol% $LiBF_4$, CH_3CN, 12 h; (iv) trifluoroacetic anhydride, DMAP, toluene 108 °C, 24 h.

stages it could be removed simultaneously with the alkene or nitrile under reducing conditions. The main disadvantage of using enamide **7** was that the proton NMR spectra of the products were fairly broad and difficult to interpret due to hindered rotation at the carbamate.

Initially, reaction of imine **6** with enamide **7** using 12 mol% indium trichloride as catalyst gave a 1.1:1 mixture of *exo*/*endo* stereoisomers **8** and **9**, respectively, from which the desired *exo*-isomer **8** was easily separated in 40% yield. In our hands, indium trichloride lost its catalytic activity on storage once the bottle was opened. Yttrium triflate proved to be a much more reliable and robust catalyst. It did not deteriorate on storage, much lower loadings (1%) could be employed, and the isolated yield of the desired *exo*-hexahydropyrroloquinoline **8** rose to 46%. The relative stereochemistry of the desired *exo*-isomer **8** was established by X-ray crystallography, and this is shown in Figure 2. Interestingly, the molecule adopts a conformation, which puts the groups at C3a and C4 *trans*-diaxial in the solid state. This conformation is also the preferred one in solution and was confirmed by NOE studies. Hence, saturation of H4 led to a NOE of 5.5% onto H3a and no enhancement onto H9b indicating that H4 was indeed equatorial. Unfortunately, the peaks for H4 and H3a in the proton NMR spectrum were too broad, due to hindered rotation, to extract *J* values, but in similar compounds devoid of the CBz protecting group this coupling constant is of the order of 2 Hz for the *exo*-isomer confirming the solution conformation.

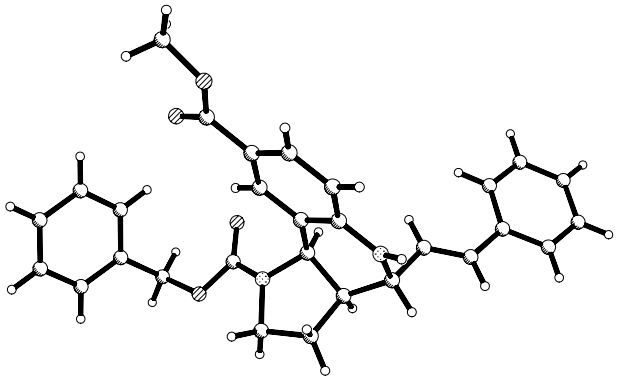


Figure 2. X-ray structure of *exo*-cycloadduct **8** depicting relative configuration and unusual conformation.

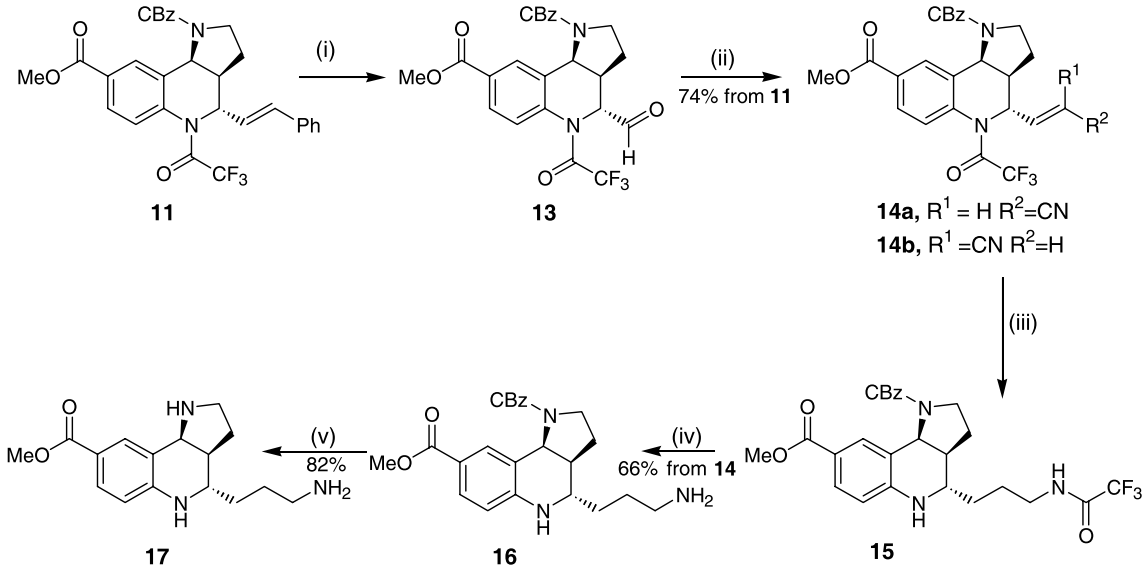
In an attempt to improve the diastereoselectivity of the cycloaddition a range of catalysts were screened. The reaction failed completely with aluminium[39] and chromium catalysts.[40] With copper chloride and triflate the reaction proceeded smoothly but with no improvement in diastereoselectivity. In order to increase the steric bulk around the metal, chiral bisoxazole complexes were employed.[41] Again, although the reaction proceeded smoothly to completion, no increase in the diastereoselectivity was observed. Unfortunately, conditions could not be found to separate the enantiomers on an analytical chiral HPLC column, but the very low optical rotation of the *exo*-isomer **8**, strongly suggested that within the error of the measurement it was racemic. High *exo*-selectivity has previously been observed in Povarov reactions of cyclic enol ethers, catalysed by lithium tetrafluoroborate[42] prompting an investigation of this catalyst in our system. Initial results seemed promising and only the *exo*-hexahydropyrroloquinoline **8** was formed, though the isolated yield, 43%, was disappointingly low with the mass balance comprising of quinoline **10**. When this reaction was repeated, and the solvent removed, proton NMR analysis of the crude mixture revealed it was a 1:1 mixture of *exo*/*endo* isomers. Clearly this reaction is not showing any *exo*-selectivity and the quinoline appears to be selectively derived from the *endo*-isomer during the aqueous work up. Presumably the mechanism for this reaction involves isomerisation of the alkene into the hexahydropyrroloquinoline six-membered ring, followed by elimination of the nitrogen from C9b to give the quinoline **10**. It is not clear why the *endo*-isomer participates in this isomerisation whilst the *exo*-isomer does not.

Finally, an attempt was made to recycle the unwanted *endo*-isomer. We have previously shown in 1-propionyl-4-phenyl substituted hexahydropyrroloquinolines, the Povarov reaction is reversible and after 20 days at room temperature in *d*-3-acetonitrile containing a crystal of yttrium triflate, the *endo*-isomer equilibrates to a 10:7 mixture of *endo*/*exo* isomers. As suspected the *endo*-isomer is slightly more thermodynamically stable than the *exo*-isomer. Unfortunately, the same study on the more complex tetrahydropyrroloquinoline **9** was thwarted as the initial reaction was irreversible even at 60 °C for 7 days. It is presently not clear if it is the carbamate protecting group, the 8-carbomethoxy group, or the more complex C4 substituent, which is rendering this cycloaddition irreversible.

Although it was disappointing that the *exo*/*endo* selectivity could not be improved further for the key reaction, the fact that the starting materials were so readily available and that the *exo*/*endo* isomers were easy to separate still made this an attractive synthetic procedure. With **8** at hand all that remained was elaboration of the C4 side chain.

The aromatic amine N5 was incredibly unreactive due to conjugation to the 8-carbomethoxy group. However, forcing conditions of refluxing toluene containing trifluoroacetic anhydride and a catalytic quantity of 4-dimethylaminopyridine for 24 h gave the trifluoroacetamides **11** and **12** in 83 and 92% yield, respectively. Ozonolysis of adduct **11** followed by a reductive work up gave aldehyde **13**, which was trapped at −78 °C with the nitrile stabilised ylide (triphenylphosphoranylidene)acetonitrile prior to work up, Scheme 3 Proton NMR analysis of the crude mixture showed a 2:1 mixture of *Z*–*E* α,β-unsaturated nitriles **14a** and **14b**, respectively. However, on flash chromatography this ratio changed to 1:5 and gave the alkenes in a combined overall yield of 74% from **11**. These alkene isomers could be separated by preparative TLC for characterisation, but for synthetic purposes the mixture was used.

At this stage, an attempt was made to incorporate the redundant *endo*-isomer into the synthesis by epimerising C4. Ma[30] has recently reported that in hexahydropyrroloquinolines with aldehyde functionality at C4 and an amide at N5, an *exo*/*endo* mixture isomerises to give the *exo* aldehyde. The reason for this facile isomerisation is fairly obvious. For six-membered ring cyclic amides with



Scheme 3. Reagents and conditions: (i) CH_2Cl_2, O_3 −78 °C then Me_2S; (ii) $Ph_3P{=}CHCN$; (iii) PtO_2, EtOH, $CHCl_3$, 70 °C, 45 psi, 144 h; (iv) MeOH, NH_3, 25 °C, 24 h; (v) $Pd(OH)_2$, CH_3OH, 60 °C, 45 psi, 24 h.

a 2-substituent, the thermodynamically more stable conformer is the one in which the 2-substituent is axial as this minimises pseudo allylic 1,3-strain.[43] For N5 amides derived from hexahydropyrroloquinolines then the *exo*-isomer would undoubtedly be more stable that the *endo*-isomer, as this can accommodate the adjacent axial substituent. The alkene **12** was ozonolised followed by the addition of dimethyl sulphide and then allowed to warm to room temperature. Proton NMR analysis of the crude reaction mixture revealed three aldehyde peaks at δ 10.03, 9.66 and 9.46 corresponding to benzaldehyde, *exo*-aldehyde and *endo*-aldehyde, respectively, in the ratio 1:0.53:0.47. A fresh aliquot was removed after 24 h and proton NMR analysis revealed the ratio of the three aldehydes was 1:0.72:0.15. It was clear that the amount of *exo*-aldehyde was not increasing as fast as the *endo*-aldehyde was decreasing indicating decomposition. Finally after 48 h proton NMR analysis showed no *endo*-aldehyde remaining but the amount of *exo*-isomer had dropped to 30% relative to benzaldehyde, indicating extensive decomposition. This was supported by the observation of quinoline peaks in the aromatic region of the proton NMR spectra. Due to the instability of the hexahydropyrroloquinoline aldehydes this isomerisation was not pursued further as a means of recycling the *endo*-isomer.

Catalytic reduction of the nitrile **14a**,**b** proved to be the most challenging reaction in the entire sequence. Initial studies focused on an Rh/C catalyst under a hydrogen pressure of 15–45 psi but this only resulted in hydrogenation of the alkene. Platinum oxide was next investigated as the catalyst. Secrist reported that in reduction of nitriles using platinum oxide as catalyst, addition of chloroform improves the efficiency of the process and minimises formation of secondary amines.[44] Using platinum oxide as the catalyst under Secrist's conditions the alkene in **14a**,**b** was selectively hydrogenated but the nitrile remained intact. To get reduction of both the alkene and nitrile it was necessary to increase the temperature to 70 °C for 6 days. Analysis of the proton NMR spectrum of the crude reduction product revealed an 85:15 mixture of two compounds, from which the major product **15** could be isolated by flash chromatography. The aromatic proton in the major product H6 had changed its chemical shift from δ 7.57 in the starting material to 6.41 ppm in the product strongly indicating that the trifluoroacetyl on N5 was no longer present. However, accurate mass data and ^{19}F NMR spectra revealed that the compound still contained a trifluoroacetyl group. The most likely explanation is that the trifluoroacetyl group has migrated from the aromatic secondary amine to the aliphatic primary amine and that the minor component is the compound that was initially expected. There is good literature precedent for migrations of this type.[45] Removal of the trifluoroacetyl group on the crude mixture was accomplished with ammonia in methanol, to give **16** in 66% for the two steps. Finally, the carbobenzyloxo group was reductively removed using palladium hydroxide as catalyst to give **17** in 82% yield completing the synthesis of the tricyclic core of martinellic acid. The triamine **17** was very polar, difficult to purify by chromatography, did not give mass spectral data and decomposed on storage at 0 °C. However, the ^{13}C NMR spectrum of the crude material was clean and was in reasonable agreement with the published spectra,[28] maximum deviation 2.6 ppm average deviation 0.9 ppm, which can be attributed to these spectra being recorded in *d*-chloroform and *d*-4-methanol, respectively.

3. Conclusion

In conclusion, we have demonstrated that the Povarov reaction can be employed to give rapid entry to hexahydropyrroloquinolines with a carbomethoxy group at the 8-position and useful alkene functionality at C-4. Although the diastereoselectivity is poor, the regioselectivity and high convergence of this approach makes it very attractive. The alkene functionality can be readily converted to the required 3-aminopropyl group. The overall yield for the synthesis of

the central core of martinellic acid was 22% from methyl 4-aminobenzoate.

4. Experimental

4.1. General

Melting points were recorded using a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 983G instrument coupled to a Perkin-Elmer 3700 Data Station as potassium bromide (KBr) disks, or films (liquids). ^{1}H nuclear magnetic resonance (NMR) spectra were recorded at 300 MHz using Bruker DPX 300 and at 500 MHz using a Bruker DRX500 NMR spectrometers. Chemical shifts are given in parts per million (δ down field from tetramethylsilane as internal standard and coupling constants are given in Hertz). Unless otherwise stated, deuteriochloroform was used as solvent. Spectra splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were recorded using Double Focusing Triple Sector VG Auto Spec and accurate molecular masses were determined by the peak matching method using perfluorokerosene as standard reference and were accurate to within +/− 0.006 amu. Analytical TLC was carried out on Merck Kielselgel 60_{254} plates and the spots visualised using a Hanovia Chromatolite UV lamp. Flash chromatography was affected using Merck Kielselgel 60 (230–400 mesh).

4.1.1. 4-(3-Phenyl-allylideneamino)-benzoic acid methyl ester 6. *trans*-Cinnamaldehyde (0.81 g, 6.13 mmol) and methyl 4-aminobenzoate (0.92 g, 59.5 mmol) were dissolved in dry methylene chloride (30 ml). Activated, 4 Å molecular sieves were then added and the reaction vessel was flushed with nitrogen for 5 min and the mixture was stirred for 6 h. The molecular sieves were removed by filtration and the methylene chloride was removed under reduced pressure and the residue was crystallised from hexane/ethyl ethanoate 9:1 to yield the titled product (1.45 g, 90%) as yellow needles. Mp 134–135 °C. HRMS (EI): $C_{17}H_{15}NO_2$ requires M^+ 265.1103, found M^+ 265.1090; υ_{max} (KBr)/cm^{-1} 1716, 1628, 1279, 735, 696; ^{1}H NMR (500.1 MHz, $CDCl_3$) δ (ppm) 3.92 (s, 3H), 7.11 (dd, J=16.0, 8.8 Hz, 1H), 7.18 (d, J=8.7 Hz, 2H), 7.21 (d, J=16.0 Hz, 1H), 7.38–7.44 (overlapping m, 3H), 7.55 (d, J=8.3 Hz, 2H), 8.06 (d, J=8.8 Hz, 2H), 8.25 (d, J=8.7 Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ (ppm) 52.1, 120.8 (2C), 127.5, 127.7 (2C), 128.3, 129.0 (2C), 130.0, 130.9 (2C), 135.4, 145.4, 155.9, 163.0, 166.8; MS (EI), *m/z* (%), 265 (M^+, 38), 264 (100), 129 (3), 103 (15), 77 (26).

4.1.2. *exo*-4-Styryl-2,3,3a,4,5,9b-hexahydro-pyrrolo[3,2-*c*]quinoline-1,8-dicarboxylic acid 1-benzyl ester 8-methyl ester 8. Imine **6** (0.45 g, 1.70 mmol) and ene–carbamate **7** (0.34 g, 1.66 mmol) were dissolved in dry acetonitrile (30 ml) and a catalytic amount of yttrium triflate (0.01 g, 1 mol%) was added and the reaction stirred for 2 h under nitrogen. The solvent was removed under reduced pressure and the residue was dissolved in methylene chloride (40 ml), washed with saturated aqueous sodium bicarbonate (20 ml), water (20 ml), dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash chromatography (eluent; hexane/diethyl ether 1:1, R_f: 0.17) afforded the titled compound (0.36 g, 46%) as a white solid. Mp 144.5–146.0 °C. HRMS (EI): $C_{29}H_{28}N_2O_4$ requires M^+ 468.2049, found M^+ 468.2049; υ_{max} (KBr)/cm^{-1} 3354, 1702, 1107, 966, 769, 695; ^{1}H NMR (500.1 MHz, $CDCl_3$) δ (ppm) (mixture of rotamers at 25 °C) 2.05 (m, 2H), 2.51 (br, 1H), 3.41 (m, 1H), 3.59 (br, 1H), 3.82 (s, 3H), 4.00 (m, 1H), 4.50 (s, 1H), 5.23 (overlapping m, 3H) 6.23 (dd, J=15.8, 6.9 Hz, 1H), 6.47 (d, J=15.8 Hz, 1H), 6.51 (d, J=8.5 Hz, 1H), 7.21–7.36 (m, 10H), 7.73 (dd, J=8.5, 2.0 Hz, 1H), 8.20 (br, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ (ppm) (mixture of rotamers at 25 °C) 27.2 (br), 41.5 (br), 44.8, 51.6, 53.0, 54.0, 67.3 (br), 113.7, 119.5, 120.0 (br), 126.5 (2C), 127.9 (2C), 128.0, 128.1, 128.5 (2C), 128.6 (2C), 130.26, 130.3, 130.8, 132.5, 136.1, 136.8 (br), 145.7, 156.0 (br), 167.2; MS (EI), *m/z* (%), 468 (M^+, 23), 377 (11), 333 (14), 290 (71), 91 (47), 56 (100).

An isomeric product was also isolated (eluent; hexane/diethyl ether 1:1, R_f: 0.31) (0.36 g, 46%) as a white solid. Mp 164–165 °C. HRMS (FAB): $C_{29}H_{28}N_2O_4$ requires M^+ 468.2049, found M^+ 468.2070; υ_{max} (KBr)/cm^{-1} 3348, 1701, 1280, 1098, 772; ^{1}H NMR (500.1 MHz, $CDCl_3$) δ (ppm) (mixture of rotamers at 25 °C) 1.96–2.06 (m, 2H), 2.50 (m, 1H), 3.40 (m, 1/2H), 3.41 (m, 1/2H), 3.49 (q, J=9.6 Hz, 1/2H), 3.58 (q, J=9.7 Hz, 1/2H), 3.80 (s, 3H), 4.23 (br s, 1H), 4.27 (br, 1H), 5.29–5.34 (overlapping m, 3H), 6.19 (dd, J=15.9, 7.6 Hz, 1H), 6.50 (d, J=8.5 Hz, 1H), 6.66 (dd, J=15.9, 4.4 Hz, 1H), 7.26–7.39 (overlapping m, 9H), 7.50 (d, J=7.3 Hz, 1H), 7.72 (d, J=8.3 Hz, 1H), 8.19 and 8.30 (br, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ (ppm) (mixture of rotamers at 25 °C) 22.1 and 23.1, 41.8 and 42.4, 44.8 and 44.9, 52.0, 54.3, 55.7 and 55.9, 67.0 and 67.5, 113.9, 119.9, 120.2 and 120.9, 126.4 (2C), 127.7, 127.8, 128.0 and 128.1, 128.2 and 128.3, 128.4 and 128.5, 128.6 (2C) 130.0, 132.1 and 132.4, 132.3 and 132.5, 136.1, 136.5 and 136.9, 147.0, 155.5 and 156.5, 167.1; MS (FAB), *m/z* (%), 469 (M^++1, 36), 468 (M^+, 35), 437 (22), 377 (10), 333 (23), 290 (12), 154 (100), 136 (75); Anal. calcd for $C_{29}H_{28}N_2O_4$: C 74.3, H 6.0, N 5.9. Found: C 74.0, H 5.8, N 6.0.

4.1.3. 3-(2-Benzyloxycarbonylamino-ethyl)-2-phenethyl-quinoline-6-carboxylic acid methyl ester 10. Imine **6** (69 mg, 0.26 mmol) and ene–carbamate **7** (51 mg, 0.25 mmol) were dissolved in dry acetonitrile (10 ml) under a nitrogen atmosphere, lithium tetrafluoroborate (24 mg, 0.26 mmol) was then added and the mixture stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the residue was dissolved in methylene chloride (30 ml) and washed with aqueous saturated sodium bicarbonate (20 ml) and water (20 ml). The organic phase was dried over magnesium sulfate and concentrated under reduced pressure. Purification by preparative TLC (eluent; ethyl ethanoate/hexane 3:7, R_f: 0.30) afforded the titled product (48 mg, 41%) as a yellow oil. HRMS (FAB): $C_{29}H_{29}N_2O_4$ requires $M^+(+1)$ 469.2127, found $M^+(+1)$ 469.2106; υ_{max} (KBr)/cm^{-1} 3359, 1717, 1262, 1099, 750, 699; ^{1}H NMR (500.1 MHz, $CDCl_3$) δ (ppm) 2.93 (t, J=6.7 Hz, 2H), 3.20 (t, J=8.2 Hz, 2H), 3.30 (t, J=8.2 Hz, 2H), 3.43 (q, J=6.4 Hz, 2H), 3.98 (s, 3H), 4.82 (br, 1H), 5.08 (s, 2H), 7.17–7.33 (overlapping

m, 10H), 7.89 (s, 1H), 8.07 (d, $J=8.8$ Hz, 1H), 8.23 (dd, $J=8.8$, 1.9 Hz, 1H), 8.46 (s, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ (ppm) 32.9, 35.5, 37.8, 41.3, 52.7, 67.2, 126.5, 127.9, 128.5 (2C), 128.6, 128.83, 128.89 (2C), 128.9 (2C), 129.0 (2C), 129.1, 129.3, 130.7, 131.7, 136.8, 137.2, 142.0, 149.1, 156.7, 163.7, 167.2; MS (FAB), *m/z* (%), 469 (M^{+1}, 100), 468 (M^+, 15), 377 (11), 318 (10), 304 (11), 147 (41), 105 (43).

4.1.4. *exo*-4-Styryl-5-(2,2,2-trifluoro)-2,3,3a,4,5,9b-hexahydro-pyrrolo[3,2-*c*]quinoline-1,8-dicarboxylic acid 1-benzyl ester 8-methyl ester 11. Anhydrous pyridine (0.17 ml, 2.10 mmol), 4-dimethylaminopyridine (8 mg, 17 mol%), and trifluoroacetic anhydride (0.11 ml, 0.79 mmol) were added sequentially to a stirred solution of amine **8** (181 mg, 0.39 mmol) in anhydrous toluene (15 ml) under a nitrogen atmosphere. The reaction was then refluxed for 24 h and the solvent was removed under reduced pressure. The residue was dissolved in methylene chloride (30 ml) and washed with 9% aqueous HCl (15 ml), saturated sodium bicarbonate (15 ml) and water (15 ml). The organic phase was dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash chromatography (eluent; hexane/diethyl ether 35:65, R_f: 0.45) afforded the titled compound (182 mg, 83%) as a cream foam. HRMS (EI): $C_{31}H_{27}F_3N_2O_5$ requires M^+ 564.1872, found M^+ 564.1873; υ_{max} (KBr)/cm^{-1} 2954, 1708, 1699, 1409, 1277, 1196, 770, 736, 696; ^{19}F NMR (282.3 MHz, $CDCl_3$) δ (ppm) -67.6 (s, 3F); ^{1}H NMR (500.1 MHz, $CDCl_3$) δ (ppm) (mixture of rotamers at 25 °C) 1.92 (dq, $J=12.7$, 8.9 Hz, 1H), 2.23 (br, 1H), 2.89 (dtd, $J=9.6$, 7.4, 2.4 Hz, 1H), 3.46 (br, 1H), 3.62 and 3.75 (br, 1H), 3.89 (br s, 3H), 5.18 (overlapping, 3H), 5.33 (br, 1H), 5.95 (br, 1H), 6.56 (d, $J=15.9$ Hz, 1H), 7.19–7.26 (overlapping m, 5H), 7.30–7.36 (overlapping m, 5H), 7.67 (br, 1H), 7.96 (d, $J=8.4$ Hz, 1H), 8.38 and 8.64 (br, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ (ppm) (mixture of rotamers at 25 °C) 27.9 (br), 42.8 (br), 45.4, 52.3, 54.7, 58.6 (br), 67.4 (br), 110.8–122.3 (q, $J=288.8$ Hz), 124.3, 124.7, 126.6 (2C), 127.9, 128.1, 128.5 (2C), 128.7 (2C), 128.9, 129.4, 130.8, 132.7, 132.9, 133.9, 135.3, 136.5 (br), 137.3 (br), 156.4, 156.8 (q, $J=36.7$ Hz), 166.1; MS (EI), *m/z* (%), 564 (M^+, 1.5), 533 (1), 473 (5), 429 (8), 279 (29), 149 (100), 91 (74), 57 (42).

4.1.5. *endo*-4-Styryl-5-(2,2,2-trifluoro)-2,3,3a,4,5,9b-hexahydro-pyrrolo[3,2-*c*]-quinoline-1,8-dicarboxylic acid 1-benzyl ester 8-methyl ester 12. Anhydrous pyridine (0.16 ml, 1.98 mmol), dimethyl aminopyridine (7.7 mg, 17 mol%) and trifluoroacetic anhydride (0.11 ml, 0.76 mmol) were added to a stirred solution of *endo*-4-styryl-2,3,3a,4,5,9b-hexahydro-pyrrolo[3,2-*c*]quinoline-1,8-dicarboxylic acid 1-benzyl ester 8-methyl ester **9** (174 mg, 0.37 mmol) in dry toluene (40 ml) and the resulting solution was refluxed for 24 h. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (40 ml), washed with 9% aqueous hydrochloric acid (20 ml), saturated sodium bicarbonate solution (20 ml) and water (20 ml). The organic phase was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Purification by flash chromatography (6:4 hexane/ethyl acetate), afforded **12** as a light brown powder (193 mg, 92%). Mp 69–70 °C. R_f: 0.66 (6:4 hexane/ethyl acetate); ($C_{31}H_{27}F_3N_2O_5$ requires M^+ 564.1872, found M^+ 564.1870); υ_{max} (KBr)/cm^{-1} 2952, 1699, 1410, 1271, 1207, 767, 737, 696; δ_H (500 MHz, $CDCl_3$) (mixture of rotamers, 25 °C) 1.52 (br m, 1H), 1.89 (dq, $J=5.7$, 15.9 Hz, 1H), 3.40 (br, 1H), 3.50 (br, 1H), 3.61 (br, 1H), 3.92 (s, 3H), 4.97 (br, 1H), 5.25 (overlapping m, 3H), 5.64 (br, 1H), 6.65 (d, $J=15.6$ Hz, 1H), 7.18–7.27 (m, 5H), 7.31–7.37 (m, 5H), 7.39 (br, 1H), 7.67 (d, $J=8.6$ Hz, 1H), 8.04–8.14 (br m, 1H); δ_C (125 MHz, $CDCl_3$) (mixture of rotamers at 25 °C) 27.1 (br), 43.6 (br), 44.6 (br), 46.4, 52.2, 55.9 (br), 67.3, 114.9, 117.2, 119.6, 122.5, 125.4 (br), 126.3 (2C), 127.8, 128.2 (br), 128.4 (2C), 128.5 (2C), 128.6–129.1 (q), 129.6, 130.7, 133.6, 134.5, 135.2, 136.2 (br), 137.4, 155.2 (q, $J=38.1$ Hz), 165.9; ^{19}F (282 MHz, $CDCl_3$) -67.5 (3F, s, C=OCF_3); MS (EI), *m/z* (%), 564 (M^+, 36), 489 (100), 473 (51), 466 (25), 369 (12), 152 (28), 91 (100), 57 (30).

4.1.6. *exo*-4-(2-Cyano-vinyl)-5-(2,2,2-trifluoro)2,3,3-a,4,5,9b-hexahydro-pyrrolo[3,2-*c*]quinoline-1,8-dicarboxylic acid 1-benzyl ester 8-methyl ester 14. Alkene **11** (1.26 g, 2.23 mmol) was dissolved in anhydrous methylene chloride (60 ml) and the solution was cooled to -78 °C under a nitrogen atmosphere. Ozone was then bubbled through the system at a rate of 1 l/min for 30 min. The reaction solution changed from colourless to a deep blue hue during the course of the reaction. While maintaining the system at -78 °C, the residual ozone was removed by slowly bubbling nitrogen gas through the reaction mixture. Dimethyl sulphide (1.8 ml, 24 mmol) was added dropwise and the solution was stirred for another hour at -78 °C. (Triphenylphosphoranylidene)acetonitrile (1.90 g, 6.31 mmol) in methylene chloride (3 ml) was introduced and the solution maintained at -78 °C for a further 2 h, after which it was allowed to warm to room temperature overnight. The methylene chloride solution was washed with saturated aqueous sodium bicarbonate (15 ml), water (15 ml), dried over magnesium sulfate and concentrated under reduced pressure. The titled compound was obtained as a mixture of cis and trans isomers by flash chromatography (eluent; diethyl ether/hexane 8:2) as a white powder (0.85 g, 74%). A small sample was separated by preparative TLC R_f: 0.37 (diethyl ether/hexane 8:2) and crystallised from methanol to give the trans product **14b** as prisms. Mp 69–72 °C. HRMS (EI): $C_{26}H_{22}F_3N_3O_5$ requires M^+ 513.1512, found M^+ 513.1518; υ_{max} (KBr)/cm^{-1} 2211, 1703, 1411, 1292, 1198; ^{19}F NMR (282.3 MHz, $CDCl_3$) δ (ppm) -67.69 (s, 3F); ^{1}H NMR (500.1 MHz, $CDCl_3$) δ (ppm) (mixture of rotamers at 25 °C) 1.90 (dq, $J=12.7$, 8.2 Hz, 1H), 2.24 (td, $J=12.5$, 7.5 Hz, 1H), 2.83 (ddd, $J=16.4$, 7.2, 2.1 Hz, 1H), 3.43 (br, 1H), 3.65 (br, 1H), 3.91 (br s, 3H), 5.20 (overlapping m, 4H), 5.45 (d, $J=15.1$ Hz, 1H), 6.46 (br, 1H), 7.27–7.36 (m, 5H), 7.57 (br, 1H), 8.00 (d, $J=7.8$ Hz, 1H), 8.32 and 8.61 (br, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ (ppm) (mixture of rotamers at 25 °C) 27.3 (br), 40.9 (br), 44.3 (br), 51.4, 53.6 (br), 56.8 (br), 66.5 and 67.0 (br), 102.9, 111.7–118.6 (q, $J=288.8$ Hz), 114.4, 123.4, 126.9, 127.2 (2C overlapping), 127.5 (2C), 128.6 (br), 128.9 (2C), 129.3 (br), 132.2 (br), 135.3 (br), 147.5, 155.1 (br), 155.9 (q, $J=37.2$ Hz), 164.7; MS (EI), *m/z* (%), 513 (M^+, 1.1), 482 (1.6), 407 (1.4), 378 (15), 277 (30), 148 (6), 91 (100), 77 (18).

cis Product **14a**. R_f: 0.29 (diethyl ether/hexane 8:2) crystallised from methanol as prisms. Mp 66–69 °C. HRMS (EI): $C_{26}H_{22}F_3N_3O_5$ requires M^+ 513.1512, found M^+ 513.1527; υ_{max} (KBr)/cm^{-1} 2955, 2275, 2224, 1698, 1409, 1197, 770, 732, 698; ^{19}F NMR (282.3 MHz, $CDCl_3$) δ (ppm) −67.69 (s, 3F); ^{1}H NMR (500.1 MHz, $CDCl_3$) δ (ppm) (mixture of rotamers at 25 °C) 2.03 (br m, 1H), 2.33 (td, J=12.5, 7.3 Hz, 1H), 2.89 (ddd, J=14.2, 9.1, 2.4 Hz, 1H), 3.46 (br, 1H), 3.66 (br, 1H), 3.91 (br s, 3H), 5.13–5.25 (overlapping m, 4H), 5.48 (br, 1H), 6.26 (br, 1H), 7.30–7.36 (m, 5H), 7.64 (br, 1H), 7.99 (d, J=7.9 Hz, 1H), 8.38 and 8.61 (s, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ (ppm) (mixture of rotamers at 25 °C) 27.4 (br), 42.5 and 43.4 (br), 44.3 (br), 51.4, 53.7 (br), 56.3 (br), 66.5 (br), 101.8, 111.8–118.5 (q, J=288.5 Hz), 113.1, 123.9 (br), 126.9, 127.2, 127.5 (2C), 128.7 (2C), 129.7, 129.8 (br), 132.0 (br), 132.0 (br), 135.3 (br), 147.3, 155.2 (br), 155.6 (q, J=36.5 Hz), 164.8 (br); MS (EI), *m/z* (%), 513 (M^+, 0.4), 482 (0.3), 378 (2), 277 (65), 122 (75), 105 (100).

4.1.7. *exo*-4-[3-(2,2,2-Trifluoro-acetylamino)-propyl]-2,3,3a,4,5,9b-hexahydro-pyrrolo[3,2]quinoline-1,8-dicarboxylic acid 1-benzyl ester 8-methyl ester 15. Platinum oxide (4.5 mg, 10 mol%) was added to a solution of alkenes **14a**,**b** (100 mg, 0.19 mmol) in methanol (10 ml). Three drops of chloroform were then added and the reaction mixture was hydrogenated (50 psi) at the elevated temperature of 70 °C for 144 h. The mixture was filtered through Hyflo-Supercel and the solvent was removed in vacuo. The residue was dissolved in methylene chloride (30 ml) and washed with 2 M sodium hydroxide (15 ml), water (15 ml), dried over magnesium sulfate and concentrated under reduced pressure. An analytical sample was purified by flash chromatography (eluent; chloroform/methanol 95:5, R_f: 0.49) afforded the titled compound as a clear oil. HRMS (FAB): $C_{26}H_{29}F_3N_3O_5$ requires M^{+1} 520.2059, found M^{+1} 520.2068; υ_{max} (KBr)/cm^{-1} 3367, 2949, 1701, 1609, 1436, 1280, 1187, 769; ^{19}F NMR (282.3 MHz, $CDCl_3$) δ (ppm) −76.2 (s, 3F); ^{1}H NMR (500.1 MHz, $CDCl_3$) δ (ppm) (mixture of rotamers at 25 °C) 1.47 (m, 1H), 1.55 (m, 1H), 1.67 (m, 2H), 1.95 (br m, 2H), 2.32 (m, 1H), 3.31 (overlapping m, 4H), 3.51 (br, 1H), 3.80 (s, 3H), 4.75 (br, 1H), 5.12 (br, 1H), 5.29 (s, 2H), 6.41 (d, J=8.5 Hz, 1H), 6.98 and 7.15 (br, 1H), 7.26–7.40 (overlapping m, 5H), 7.66 (dd, J=8.5, 2.0 Hz, 1H), 8.18 (br, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ (ppm) (mixture of rotamers at 25 °C) 25.7, 26.8 and 27.7 (br), 32.9 (br), 39.6, 40.4 and 41.1 (br), 44.7, 51.0, 51.6, 52.9 (br), 67.1 and 67.7, 112.4–119.3 (q, J=287.8 Hz), 113.7, 118.9, 119.6 (br), 127.7, 128.0 (2C), 128.5 (2C), 130.2, 132.4 (br), 136.8 (br), 145.4, 156.7, 157.5 (q, J=36.9 Hz), 167.4; MS (FAB), *m/z* (%), 520 (M^+, 15), 461 (11), 341 (29), 281 (76).

4.1.8. *exo*-4-(3-Amino-propyl)-2,3,3a,4,5,9b-hexahydro-pyrrolo[3,2-*c*]quinoline-1,8-dicarboxylic acid 1-benzyl ester 8-methyl ester 16. Trifluoroacetamide **15** (103 mg, 0.20 mmol, crude from previous step) was added to a saturated solution of ammonia in methanol (6 ml) and the reaction was stirred for 3 days at room temperature. The solvent was removed under reduced pressure and the residue dissolved in methylene chloride (20 ml) and washed with 2 M sodium hydroxide (10 ml), water (10 ml), dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash chromatography (eluent; methylene chloride/methanol 95:5, R_f: 0.43) afforded the titled product (53 mg, 66% from **14**) as a clear oil. HRMS (FAB): $C_{24}H_{29}N_3O_4$ requires M^+ 423.2158, found M^+ 423.2146; υ_{max} (KBr)/cm^{-1} 3354, 2948, 1698, 770, 736, 698; ^{1}H NMR (500.1 MHz, $CDCl_3$) δ (ppm) (mixture of rotamers at 25 °C) 1.53 (overlappping m, 4H), 1.96 (br m, 2H), 2.36 (dtd, J=9.2, 8.3, 2.1 Hz, 1H), 2.69 (m, 2H), 3.25 (m, 1H), 3.38 (m, 1H), 3.53 (br, 1H), 3.80 (s, 3H), 5.04 and 5.12 (br, 1H), 5.24 (s, 2H), 6.44 (d, J=8.5 Hz, 1H), 7.24–7.50 (overlapping m, 5H), 7.68 (dd, J=8.5, 2.0 Hz, 1H), 8.19 (br, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ (ppm) (mixture of rotamers at 25 °C) 26.9 and 27.8 (br), 30.0, 33.6 (br), 40.6 and 41.4 (br), 41.7, 44.7, 51.5, 51.6, 53.0, 67.0 and 67.5, 113.7, 118.9 (br), 127.7, 128.0 (2C), 128.5 (2C), 130.2, 132.4 (br), 137.0, 137.2, 145.6, 156.7, 167.2; MS (FAB), *m/z* (%), 424 (M^{+1}, 100), 423 (M^+, 26), 393 (21), 365 (46), 275 (32), 257 (18).

4.1.9. *exo*-4-(3-Amino-propyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-8-carboxylic acid methyl ester 17. Tricycle **16** (11 mg, 0.02 mmol) was dissolved in methanol (5 ml) in a glass Parr hydrogenation flask. A catalytic quantity of 20% w/w palladium hydroxide on carbon (5 mg, 20 mol%) was suspended in methanol (1 ml) and then added to the hydrogenation flask. The system was hydrogenated (45 psi 60 °C) for 24 h. The reaction solution was filtered through Hyflo-Supercel and the solvent was removed under reduced pressure. The residue was dissolved in methylene chloride (20 ml) and washed with 2 M sodium hydroxide (10 ml), water (10 ml), dried over magnesium sulfate and concentrated under reduced pressure to give the titled compound (6.2 mg, 82%) as a clear oil. Due to the high polarity of **17** further purification was not attempted. υ_{max} (KBr)/cm^{-1} 1770, 1470, 1192, 866, 769, 644; ^{1}H NMR (500.1 MHz, $CDCl_3$) δ (ppm) 1.44–1.63 (5H overlap), 1.89 (m, 1H), 1.99 (m, 1H), 2.60–2.74 (overlapping m, 3H), 2.80 (m, 1H), 3.01 (m, 1H), 3.70 (s, 3H), 3.77 (d, J=6.5 Hz, 1H), 6.41 (d, J=8.5 Hz, 1H), 7.58 (dd, J=8.5, 2.1 Hz, 1H), 7.85 (d, J=2.0 Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ (ppm) 29.5, 29.7, 31.0, 41.0, 42.0, 44.7, 51.5, 52.2, 57.7, 113.6, 118.6, 121.0, 129.9, 132.6, 148.8, 167.3. Mass spectral data were not secured due to the high polarity and presumably involatility of the sample. The sample also proved to be very unstable and decomposed after days on storage at 0 °C.

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Temperature-controlled highly selective dimerization of α-methylstyrene catalyzed by Brönsted acidic ionic liquid under solvent-free conditions

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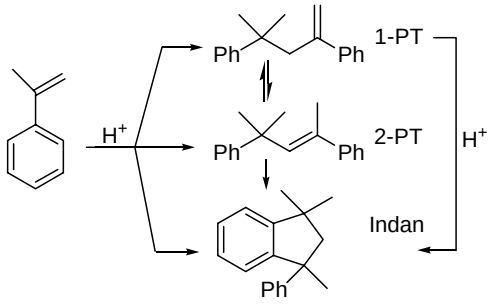
Abstract—A temperature-controlled highly selective dimerization of α-methylstyrene to produce 2,4-diphenyl-4-methyl-1-pentene and 1,1,3-trimethyl-3-phenylindan was catalyzed by Brönsted acidic ionic liquid $[Hmim]^+BF_4^-$. At 60 °C, 2,4-diphenyl-4-methyl-1-pentene was formed in 93% selectivity with >92% conversion under a solvent-free condition while 1,1,3-trimethyl-3-phenylindan could be obtained in 100% selectivity when the reaction temperature was increased to 170 °C. The ionic liquid $[Hmim]^+BF_4^-$ could be reused with almost no loss of activity.

1. Introduction

Brönsted acid-catalyzed dimerization of α-methylstyrene (AMS) generally produces a mixture of three isomers: 2,4-diphenyl-4-methyl-1-pentene (1-PT), 2,4-diphenyl-4-methyl-2-pentene (2-PT) and the saturated cyclic isomer, 1,1,3-trimethyl-3-phenylindan (Indan) (Scheme 1).[1]



Scheme 1. Brönsted acid-catalyzed dimerization of α-methylstyrene.

Among the dimers, 2,4-diphenyl-4-methyl-1-pentene (1-PT) is a versatile molecular weight regulator that is odorless and has few effects on the color and stability of resulting polymers, thus widely used in polymerization producing polystyrene, ABS resin and the likes.[1] The saturated cyclic isomer, 1,1,3-trimethyl-3-phenylindan (Indan), also has wide applications in polymers, for example, as a photo and thermo stabilizer,[2] plasticizer[3] as well as mobility and viscosity modifier[4] in the production of polystyrene or ABS resin. The Brönsted acid-catalyzed dimerization of AMS is the straightest way to produce these useful chemicals.[1] However, due to the interconvertion and the difficulties of separation of these isomers, highly selective dimerization of AMS is the precondition for practical process for production of the desired isomers, especially for the production of 1-PT. The acidity of Brönsted acid catalysts and reaction temperature have proved to be crucial to the selectivity in the dimerization of AMS.

Ionic liquids, featuring low volatility as well as high thermal and chemical stability, have attracted much attention as environmentally friendly replacement for traditional volatile organic solvents in catalysis and organic transformations.[5] Brönsted acidic ionic liquids have been recently reported to serve as both reaction medium and catalysts in many organic transformations.[6] A sulfonic acid based Brönsted acidic ionic liquid, *N*-alkyl-*N*′-(4-sulfonic butyl) imidazolium triflate, was reported to catalyze dimerization of AMS under solvent-free conditions.[7] However, a mixture of 1-PT, 2-PT and Indan was generated with poor selectivity. We have recently described a highly selective dimerization of α-methylstyrene for 1-PT in a Brönsted acidic ionic liquid, $[Hmim]^+BF_4^-$, where $[Hmim]^+BF_4^-$ severed as both catalyst and reaction medium.[8] Herein, we further report a temperature-controlled dimerization of

Keywords: Brönsted acidic ionic liquid; α-Methylstyrene; Dimerization.
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AMS for highly selective production of 1-PT and Indan catalyzed by $[Hmim]^+BF_4^-$ under solvent-free conditions.

2. Results and discussion

2.1. Effects of the loading of $[Hmim]^+BF_4^-$ on the dimerization

Although $[Hmim]^+BF_4^-$ represents the simplest and the most readily prepared ionic liquid, it would be attractive, especially in practical respect, to use the ammonium in minimum amount in the dimerization of AMS, for example, as catalyst, if the high selectivity for 1-PT could be maintained. To our delight, when $[Hmim]^+BF_4^-$ previously used as solvent was reduced to 50 mol% of AMS the selectivity for 1-PT and rate of the dimerization of AMS just slightly decreased within experimental errors at 60 °C. Further investigations showed the selectivity in the dimerization of AMS was not sensitive to the loading of the Brönsted acidic ionic liquids (Table 1). For example, when the molar ratio of $[Hmim]^+BF_4^-$ to AMS was reduced from 4/1, 1/1 to 1/2, the selectivity for 1-PT decreased from 93.5, 91.2 to 90.3% and with conversion of AMS reaching 96.4, 93.1 and 93.5%, respectively, in 10 h (Table 1, entries 1, 3 and 6). In fact, further reducing the loading of $[Hmim]^+BF_4^-$ to 25 mol% of AMS slightly increased the selectivity of 1-PT (92.8%) while the rate of dimerization decreased sharply and only 23.9% AMS was converted after 10 h. Interestingly, the selectivity of 1-PT, 2-PT and Indan remained almost unchanged at low conversion of AMS (Table 1, entries 8–10).

Table 1. $[Hmim]^+BF_4^-$ promoted dimerization of AMS at 60 °C

Entry	IL/AMS	Time (h)	Conv. (%)	Distribution of dimers (%)[a]		
				Indan	1-PT	2-PT
1	4/1	10	96.4	0.5	93.5	6.0
2	1/1	5	90.0	2.7	91.5	5.8
3	1/1	10	93.1	2.9	91.2	5.9
4	1/1	24	98.1	4.0	89.1	6.9
5	1/2	5	69.5	3.0	91.5	5.5
6	1/2	10	93.5	3.4	90.3	6.3
7	1/2	24	94.7	3.5	90.1	6.4
8	1/4	5	13.8	1.6	93.0	5.4
9	1/4	10	23.9	1.8	92.8	5.4
10	1/4	24	49.2	2.1	92.2	5.7

[a] Determined by GC.

2.2. Recycling of the ionic liquid $[Hmim]^+BF_4^-$

Separation of $[Hmim]^+BF_4^-$ from the organics is very simple. Organic layer was readily separated from the ionic liquid by decanting and the residue was washed by hexane and dried in vacuum to recycle the ionic liquid $[Hmim]^+BF_4^-$. Due to the gel-like property, about 5–10% weight of $[Hmim]^+BF_4^-$ was lost for each cycle. Thus for each reuse, some (5–10% weight) fresh $[Hmim]^+BF_4^-$ was added to keep the constant weight of the ionic liquid for each experiment. Since the dimerization was very slow at low loading of $[Hmim]^+BF_4^-$ it reasonable to omit the influence of the newly added ionic liquid on the dimerization. The reuse of catalytic system was investigated with $[Hmim]^+BF_4^-$/AMS = 1:2 (mol/mol) at 60 °C and results were collected in Table 2. As revealed in Table 2, the dimerization showed almost no change with respect to conversion and selectivity.

Table 2. Recycling $[Hmim]^+BF_4^-$ in the dimerization of AMS[a]

Recycle	Conv. (%)[b]	Indan	1-PT	2-PT
1	95	3.5	90.1	6.4
2	96	4.5	89.5	6.1
3	95	4.4	90.3	5.3
4	93	3.9	90.2	5.9
5	96	4.1	90.5	5.4
6	95	4.3	89.6	6.1

[a] Reaction was carried out at 60 °C for 24 h with $[Hmim]^+BF_4^-$/AMS = 1:2 (mol/mol).
[b] Determined by GC.

2.3. Effects of temperature on the dimerization

The reaction temperature showed a great effect on both the selectivity and the rate of dimerization of AMS catalyzed by 25 mol% $[Hmim]^+BF_4^-$ (Table 3). The conversion of AMS decreased from 92.5 to 78.4% for 48 h as reaction temperature being lowered from 60 to 40 °C (Table 3, entries 1 and 2). Further elongating the reaction time did not increase the AMS conversion remarkably at 60 °C, implying that the reaction could be very slow at low concentration of AMS. However, when the reaction was conducted at 80 °C the conversion reached 92.7% in 24 h, just half of that at 60 °C (Table 1, entry 10), but the 1-PT selectivity decreased to 86.9% (Table 3, entry 6). No AMS was detected by GC after 10 and 5 h when the reaction was carried out at 120 and 150 °C, respectively (Table 3, entries 8 and 9). However, the selectivity of the dimerization was poor and cyclic isomer, Indan, became the major product in the later case (Table 3, entries 9 and 10).

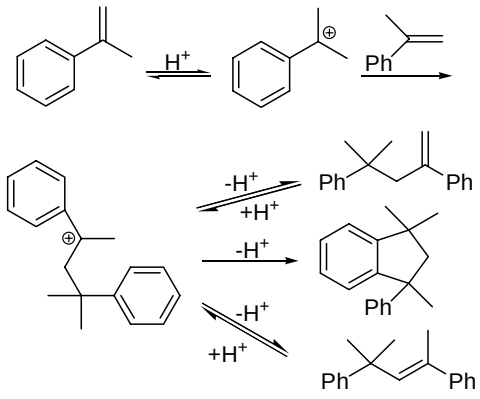
Table 3. Temperature effects on the $[Hmim]^+BF_4^-$ catalyzed dimerization of AMS[a]

Entry	T (°C)	Time (h)	Conv. (%)	Distribution of dimers (%)[b]		
				Indan	1-PT	2-PT
1	40	48	78.4	1.8	93.4	4.8
2	60	48	92.5	2.2	92.6	5.2
3	60	90	92.7	2.5	92.1	5.4
4	80	5	44.8	4.2	89.1	6.7
5	80	10	64.4	4.4	88.4	7.2
6	80	24	92.7	5.8	86.9	7.3
7	120	5	98.0	37.0	48.5	14.5
8	120	10	100	43.5	39.5	17.0
9	150	5	100	62.0	24.5	13.5
10	150	10	100	76.5	9.5	13.0

[a] Reaction was carried out with $[Hmim]^+BF_4^-$/AMS = 1:4 (mol/mol).
[b] Determined by GC.

According to the mechanism of acid-catalyzed dimerization of AMS, Indan was formed from ionic dimeric intermediate, which could be formed not only from dimerization of AMS but also from 1-PT and 2-PT under acidic conditions (Scheme 2).

Therefore, we anticipated, using the same catalyst system, it should be possible to convert the chain isomers 1-PT and 2-PT into cyclic isomer Indan, for which most acid-catalyzed



Scheme 2. A general mechanism for acid-catalyzed dimerization of AMS.

procedure required use of organic solvents to form a homogenous catalysis. Recently, Shan et al. reported a solvent-free procedure for preparation of Indan from AMS. However, an extremely moisture-sensitive Lewis acidic ionic liquid Et_3NHCl–$AlCl_3$ was used as catalyst.[3] Reaction temperature was screened for conversion of chain isomers into Indan with $[Hmim]^+BF_4^-$/AMS = 1:2 (mol/mol). The results were compiled in Table 4. From Table 4, it looked like that conversion of both 1-PT and 2-PT into Indan was slow at reaction temperature ranging from 120–150 °C. For example, at 120 and 150 °C, Indan, among the dimers, just increased from 41 and 76% to 54 and 88%, respectively, when the reaction time was prolonged from 8 to 48 h (Table 4, entries 1–4). The similar trend was also observed even at higher temperature 170 °C. For example, no AMS remained in the system within 4 h and distribution of dimers was 89% Indan, 5% 1-PT and 6% 2-PT. Under this condition, both 1-PT and 2-PT were slowly converted into Indan and disappeared after 18 and 30 h, respectively, (Table 4, entries 5–10). It is clear that, at higher reaction temperature, the dimerization produces Indan as the major product and the minor isomers 1-PT and 2-PT could be converted into Indan ultimately. Compared with the recently reported dimerization of AMS catalyzed by Brönsted and Lewis acid ionic liquids, advantages of our procedure are obvious: the ionic liquid $[Hmim]^+BF_4^-$ was readily available and air and moisture stable, and more importantly, both of two useful products could be obtained in high selectivity.

Table 4. Cyclolization of AMS catalyzed by $[Hmim]^+BF_4^-$[a]

Entry	T (°C)	Time (h)	Conv. (%)	Distribution of dimers (%)[b]		
				Indan	1-PT	2-PT
1	120	8	100	41	43	16
2	120	48	100	54	25	21
3	150	8	100	76	13	11
4	150	48	100	88	2	10
5	170	4	100	89	5	6
6	170	8	100	91	2	7
7	170	12	100	93	1	6
8	170	18	100	97	—	3
9	170	24	100	98	—	2
10	170	30	100	100	—	—

[a] Reaction was carried out with $[Hmim]^+BF_4^-$/AMS = 1:2 (mol/mol).
[b] Determined by GC.

3. Conclusion

In conclusion, we described a Brönsted acidic ionic liquid catalyzed and temperature-controlled highly selective dimerization of α-methylstyrene to produce widely used chemicals in polymers: 2,4-diphenyl-4-methyl-1-pentene and the saturated cyclic isomer, 1,1,3-trimethyl-3-phenylindan. At low reaction temperature, such as 60 °C, 2,4-diphenyl-4-methyl-1-pentene was formed in 93% selectivity with >92% conversion using 25 mol% $[Hmim]^+BF_4^-$ under a solvent-free condition while Indan could be obtained in 100% selectivity when the reaction temperature was increased to 170 °C. The ionic liquid $[Hmim]^+BF_4^-$ was recycled six times showing no decrease of activity after the mention of quantity loss of the ionic liquid during work-up procedure.

4. Experimental

All commercial chemicals were used without further purification. Ionic liquid $[Hmim]^+BF_4^-$ was prepared according to the reported procedure.[6c] GC and GC-Mass analyses were performed on a HP-Agilent 6890 with a 30 m Hp-5MS column. ^1H NMR spectra were acquired on a Bruker Avance 500 spectrometer in $CDCl_3$ using TMS as internal standard.

4.1. General procedure for the dimerization of α-methylstyrene (AMS)

To a 25 mL flask charged with a magnetic stirrer and a reflux condenser was added 1.7 g (10 mmol) $[Hmim]^+BF_4^-$ and 2.4 g (20 mmol) α-methylstyrene. The resulting biphasic mixture was heated in oil bath at designed temperature under N_2. After being cooled to room temperature, the organic layer was separated from the ionic liquid by decanting. Composition of products was analyzed by GC and compared with authentic samples. Mass balances (>95%) were obtained in all cases and only traces of organics (substrate AMS and products) were found remained in ionic liquid phase, which was removed by wash with hexane in the recycling of the ionic liquid.

4.1.1. 2,4-Diphenyl-4-methyl-1-pentene. ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.30 (s, 6H, CH_3), 2.91 (s, 2H, CH_2), 4.89 (d, J=1.8 Hz, 1H, =CH_2), 5.22 (d, J=1.8 Hz, 1H, =CH_2), 7.19–7.30 (m, 10H, Ph); MS (EI) m/z: 236 $[M]^+$, 221 $[M-CH_3]^+$, 119, 91, 77.

4.1.2. 1,1,3-Trimethyl-3-phenylindan. ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.03 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 2.19 (d, J=13 Hz, 1H, CH_{2a}), 2.42 (d, J=13 Hz, 1H, CH_{2b}), 7.10–7.27 (m, 9H, Ph). MS (EI) m/z: 236 $[M]^+$, 221 $[M-CH_3]^+$, 143, 128, 91, 77.

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Stereoselective electrocatalytic transformation of malonate and alkylidenecyanoacetates into (*E*)-3-substituted 2-cyanocyclopropane-1,1,2-tricarboxylates

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Abstract—Electrolysis of malonate and alkylidenecyanoacetates in alcohols in an undivided cell in the presence of NaBr results in stereoselective formation of (*E*)-3-substituted 2-cyanocyclopropane-1,1,2-tricarboxylates in 75–90% yields.

1. Introduction

Functionalized cyclopropanes possess a wide spectrum of physiological activities[1] and belong to an important class of compounds used in the synthesis of natural biologically active substances.[1–3] Cyclopropanecarboxylic acid derivatives are successfully used in medicine and agriculture. Naturally occurring and synthetic pyrethroids have found wide application as insecticides.[1,4]

Due to extensive research into electrochemistry of organic compounds conducted over the past three decades, electrosynthesis has become a competitive method of modern organic chemistry.[5] Electrochemical synthesis is assuming increasing importance because of its great and, in some cases, unique possibilities for performing various transformations of organic compounds.[6]

The use of mediators and mediator systems for electroreduction and electrooxidation of organic compounds was an important stage in the development of electrosynthesis. Among numerous mediators, a halide anion—halogen system is one of the most promising mediator systems for application in organic synthesis.[7]

The present study continues investigations on electrochemical transformations of CH-acids, such as malononitrile, cyanoacetic ester, and malonic ester, into functionalized cyclopropanes in the presence of mediators, viz., alkali metal halides. In our earlier studies of electrocatalytic oxidation of organic compounds in the presence of mediators, we have performed electrochemical cyclotrimerization of malonic[8] and cyanoacetic esters,[9] transformations of aldehydes and cyanoacetic ester[10] into functionalized cyclopropanes, and ketones and malononitrile into 3,3-disubstituted tetracyanocyclopropanes.[11]

The latter process is an electrochemical variant of the Wideqvist reaction, i.e., the reaction of bromomalononitrile with ketones in the presence of stoichiometric amounts of sodium iodide.[12]

The electrochemical modification of this reaction is performed with the use of malononitrile instead of bromomalononitrile and catalytic amounts of sodium bromide, which is completely regenerated during the reaction.[13]

Several years ago, we developed a new procedure for the synthesis of functionalized cyclopropanes based on simultaneous electrolysis of CH-acids and activated olefins[14,15] (Scheme 1).

Recently, we have performed the 'one-pot' electrocatalytic transformation of malonic ester and alkylidenemalononitriles into 3-substituted 2,2-dicyanocyclopropane-1,1-

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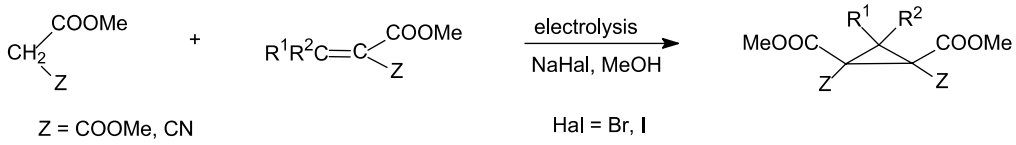
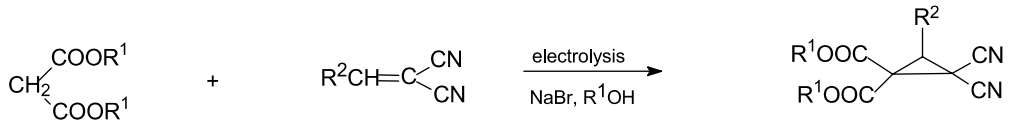
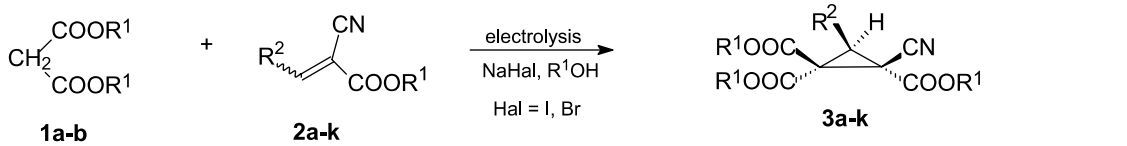


Scheme 1.



Scheme 2.



Scheme 3.

dicarboxylic acid esters. This process was carried out in alcohols in an undivided cell with the use of NaBr as mediator (Scheme 2).[16]

In the present paper, we describe our results on investigation of the stereoselective 'one-pot' electrocatalytic transformation of malonic ester and alkylidenecyanoacetic esters into (*E*) isomers of trialkyl esters 3-substituted 2-cyanocyclopropane-1,1,2-tricarboxylic acids (**3a**–**k**). This reaction was carried out in alcohols (methanol or ethanol) in an undivided cell with the use of NaBr or NaI as a mediator (Scheme 3, Table 1); for a preliminary communication, see Ref. 17.

2. Results and discussion

Electrolysis of methyl malonate **1a** or ethyl malonate **1b** in the presence of alkylidenecyanoacetic esters **2a**–**k** in methanol or ethanol, respectively, was carried out under constant current mode in an undivided cell equipped with a graphite anode and an iron cathode until complete conversion of malonic and alkylidenecyanoacetic esters was achieved.

The optimum temperature for simultaneous electrolysis of malonic ester and alkylidenecyanoacetic esters, as in

Table 1. Electrocatalytic transformation of malonic esters **1a**,**b** and alkylidenecyanoacetic esters **2a**–**k** into cyclopropanes **3a**–**k**[a]

Malonic ester	R^1	Alkylidenecyanoacetic ester	R^2	Temperature (°C)	Mediator	Cyclopropane	Yield (%)[b]
1a	Me	**2a**	Ph	20	NaBr	**3a**	(35)[c]
1a	Me	**2a**	Ph	10	NaBr	**3a**	(61)[c]
1a	Me	**2a**	Ph	0	NaBr	**3a**	81 (92)[c]
1b	Et	**2b**	Ph	0	NaBr	**3b**	82
1a	Me	**2a**	Ph	0	NaI	**3a**	67
1a	Me	**2c**	4-MeC_6H_4	0	NaBr	**3c**	83
1a	Me	**2d**	4-$MeOC_6H_4$	0	NaBr	**3d**	87
1a	Me	**2e**	2-ClC_6H_4	0	NaBr	**3e**	81
1a	Me	**2f**	4-ClC_6H_4	0	NaBr	**3f**	87
1b	Et	**2g**	4-ClC_6H_4	0	NaBr	**3g**	83
1a	Me	**2h**	3-BrC_6H_4	0	NaBr	**3h**	93
1a	Me	**2i**	Me	0	NaBr	**3i**	88
1a	Me	**2i**	Me	0	NaI	**3i**	71
1a	Me	**2j**	Et	0	NaBr	**3j**	79
1a	Me	**2k**	*n*-Pr	0	NaBr	**3k**	75

[a] Malonic ester (10 mmol), alkylidenecyanoacetic ester (10 mmol), mediator (5 mmol), alcohol (20 ml), Fe cathode, C anode, current density 100 mA/cm^2, 3.0 F/mol of electricity was passed.
[b] Based on the isolated cyclopropane.
[c] The yields given in parentheses were determined from ^{1}H NMR spectroscopic and GLC data.

the case of co-electrolysis of malonic ester and alkylidenemalononitrile, is 0 °C. An increase in the temperature up to +10 or +20 °C (at +20 °C, electrolysis of malonic ester in the presence of alkylidenemalonates was performed)[14] leads to a substantial decrease in the yield of cyclopropanes **3a–k**, and the reaction gives a considerable amount of oligomeric compounds, which hinders isolation of cyclopropanes **3a–k**.

As in the analogous reactions of malonic ester with alkylidenemalonates[14] or alkylidenemalononitriles,[16] reactions of cyanoacetic ester with alkylidenecyanoacetic esters,[15] and reactions of malononitrile with alkylidenemalononitriles,[18] sodium bromide is a more efficient as mediator than NaI for the electrocatalytic process studied. Thus, with the use of NaBr as a mediator the cyclopropanes **3a–k** were obtained in higher yields.

In co-electrolysis of ester **1a** and benzylidenecyanoacetic ester **2a** when a quantity of electricity was less than the optimum value of 3 F/mol (0.5 and 1.0 F/mol), trimethyl 3-cyanopropane-2-phenyl-1,1,3-tricarboxylate (**4**) (57 and 36% yields, respectively) was detected by ^{1}H NMR spectroscopy along with cyclopropane **3a** (16 and 37% yields, respectively).

The formation of only one of two possible isomers of cyclopropanes **3a–k** was established by the ^{1}H and ^{13}C NMR spectroscopic data. The structures of **3a** and **3i** were established by X-ray diffraction.[17] Taking into account the factor of the minimum steric hindrance in the cyclopropane ring formation, all cyclopropanes **3** should have a structure containing the cyano group and R^2-substituent in cis arrangement (Fig. 1).

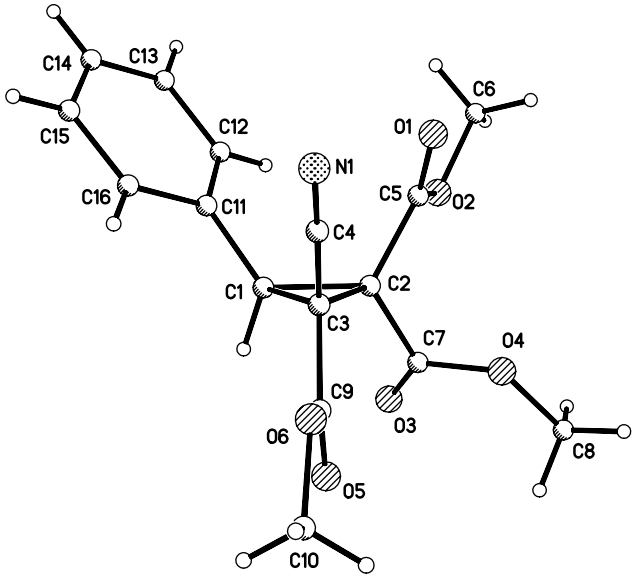
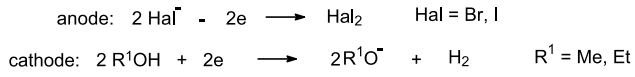


Figure 1. Molecule structure of **3a**.

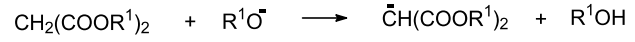
Based on our results and the data on the electrochemical transformation of malonic ester and alkylidenemalonic esters[14] or alkylidenemalononitriles[16] into functionalized cyclopropanes, we suggest the following mechanism for the stereoselective electrocatalytic transformation of malonic ester and alkylidenecyanoacetic esters into (*E*)-3-substituted 2-cyanocyclopropane-1,1,2-tricarboxylic acid esters.

Reactions at electrodes are usual for the mediator system consisting of the halide anion and molecular halogen in alcohols. These reactions involve the formation of halogen at the anode and liberation of hydrogen at the cathode resulting in the generation of alkoxide ions (Scheme 4):



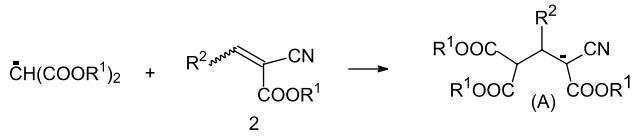
Scheme 4.

Then malonate anions appear in solution as a result of the reaction of the electrogenerated alkoxide ions with malonic ester (Scheme 5):



Scheme 5.

The reaction of the malonate anion with activated olefin **2** yields the anion (**A**) (Scheme 6):



Scheme 6.

Subsequent halogenation of the anion **A** and cyclization under the action of alkoxide ions could afford functionalized cyclopropane **3** (Scheme 7).

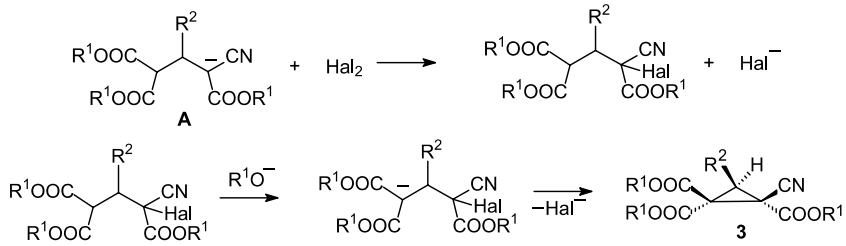
However, this mechanism could provide the observed stereoselectivity of the cyclopropane **3** formation only if halogenation of the anion **A** occurred stereoselectively.

The more probable is the existence of another process involving the initial halogen transfer by the Hal_T^+ transfer mechanism[19] giving rise to an anion (**B**) followed by thermodynamically controlled cyclization (Scheme 8).

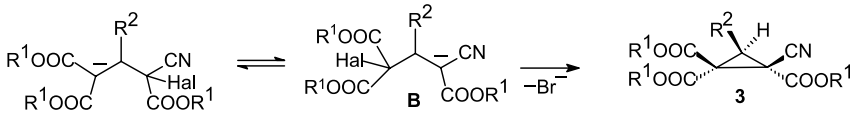
Stereoselective thermodynamically controlled cyclization was also observed in electrocatalytic cyclotrimerization of cyanoacetic ester into *trans*-1,2,3-tricyanocyclopropane-1,2,3-tricarboxylic acid ester.[9]

Earlier, NaI was shown to be a more efficient mediator for electrocatalytic cyclization of 2-substituted propane-1,1,3,3-tetracarboxylic acid esters than NaBr.[20] This fact is associated with the higher selectivity of iodine as an oxidant of the 2-substituted propane-1,1,3,3-tetracarboxylic acid esters anion in the presence of alkoxide ions compared to bromine.

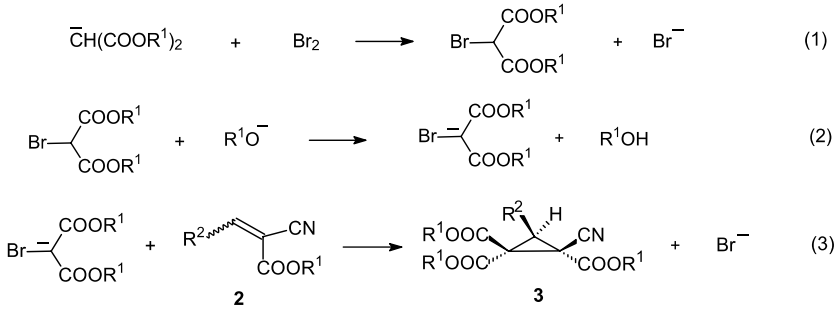
In the electrocatalytic process under consideration, NaBr is a more efficient mediator for the stereoselective transformation of malonic ester and alkylidenecyanoacetic esters into (*E*)-3-substituted 2-cyanocyclopropane-1,1,2-tricarboxylic acid esters **3a–k** compared to NaI.



Scheme 7.



Scheme 8.



Scheme 9.

Most likely, this result is attributed to the presence of another way of the electrocatalytic process (Scheme 9).

The fact that electrolysis of malonic ester in alcohols in the presence of NaBr in an undivided cell produces the bromomalonate anion has been established previously.[21]

The high efficiency of NaBr as a mediator for the reaction pathway shown in Scheme 9 is associated with the fact that bromomalonic ester is a stronger CH-acid compared to iodomalonic ester due to which the step (2) involving the proton abstraction by the alkoxide ion occurs more rapidly in bromomalonic ester than in iodomalonic ester. Besides, it is also probable that the addition of the bromomalonate anion to activated olefin **2** occurs more rapidly in the step (3).

The formation of 3-substituted-2-cyanocyclopropane-1,1,2-tricarboxylic acid esters **3a**,**j** was also investigated by performing the alternative electrolysis of cyanoacetic ester and alkylidenemalonic esters **5** (Table 2, Scheme 10).

However, as it follows from the data of Table 2, in this case the synthesis of cyclopropanes **3** requires that the electrolysis was performed at lower temperature (at −20 °C rather than at 0 °C, see Tables 1 and 2).

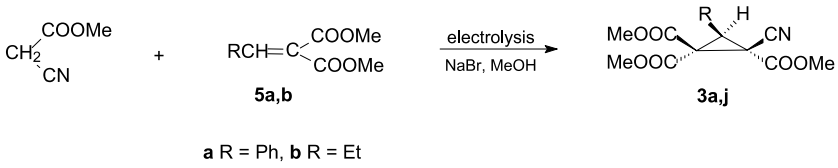
It should also be noted that the reaction performed according to Scheme 10, even at −20 °C, produces cyclic esters **3a**,**j** (Table 2) in 30–50% lower yields than those obtained as described above (Table 1) by simultaneous electrolysis of malonic ester and alkylidenecyanoacetic esters at 0 °C.

Table 2. Stereoselective electrocatalytic transformation of methyl cyanoacete and alkylidenemalonic esters **5a**,**b** into cyclopropanes **3a**,**j**[a]

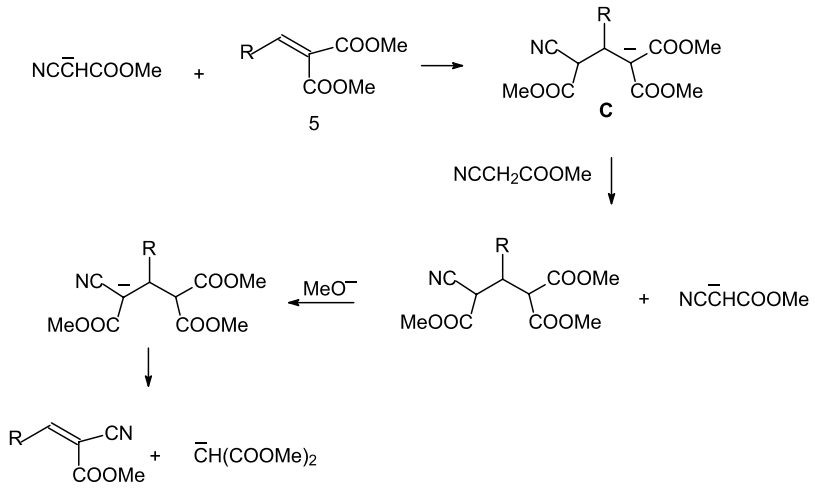
Alkylide-nemalonic ester	R	Temperature (°C)	Mediator	Cyclopropane	Yield (%)[b]
5a	Ph	0	NaBr	**3a**	26
5a	Ph	−10	NaBr	**3a**	35
5a	Ph	−20	NaBr	**3a**	43
5a	Ph	−20	NaI	**3a**	34
5b	Et	0	NaBr	**3j**	33
5b	Et	−10	NaBr	**3j**	45
5b	Et	−20	NaBr	**3j**	51
5b	Et	−20	NaI	**3j**	43

[a] Methyl cyanoacete (10 mmol), **5a** or **5b** (10 mmol), a mediator (5 mmol), MeOH (20 ml), Fe cathode, C anode, the current density 100 mA/cm^2, 3.0 F/mol of electricity was passed.
[b] The ^{1}H NMR spectroscopic and GLC data.

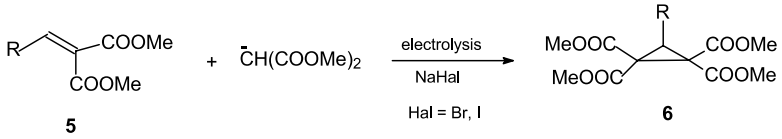
The lower yields of cyclopropanes **3** prepared according to the second approach (Table 2) are, apparently, attributable to the following facts: (1) alkylidenemalonic esters are more prone to reductive dimerization[22] compared to the competitive addition of cyanoacetate or halocyanoacetate anions; (2) the oligomerization of cyanoacetic ester in the presence of bases,[9,23] unlike malonic ester, which is stable under these conditions; (3) the reaction proceeds through the intermediate formation of the anion (**C**), which can undergo the transformation and decomposition giving rise to the malonate anion according to the Scheme 11.



Scheme 10.



Scheme 11.



Scheme 12.

Transformations analogous to those presented in Scheme 11 have been described earlier for the reactions of substituted benzylidenemalononitriles with the cyanoacetate anion.[24]

Electrolysis of malonate anions thus generated and alkylidenemalonic ester produces cyclic ester **6** (Scheme 12).

Electrolysis of methyl cyanoacetate and benzylidenemalonic ester **5a** at 0, −10, and −20 °C afforded a mixture, in which cyclic ester **3a** (26, 35, and 43% yields, respectively), ester **6** (R=Ph) (23, 17, and 7%, respectively), and tetramethyl 2,3-diphenylbutane-1,1,4,4-tetracarboxylate (**7**) (18, 13, and 6%, respectively) were detected by ^{1}H NMR spectroscopy and GLC analysis.

3. Conclusion

To summarize, we have performed simultaneous electrolysis of malonic ester and alkylidenecyanoacetic esters in an undivided cell in the presence of a sodium halide as mediator. With this method was realized the 'one-pot' stereoselective synthesis of (*E*)-3-substituted 2-cyanocyclopropane-1,1,2-tricarboxylic acid esters in 75–90% yields. These compounds can be synthesized according to conventional methods of organic chemistry in two steps: (1) halogenation of malonic ester and (2) the addition of halomalonic ester to the double bond of alkylidenecyanoacetic ester followed by cyclization.[25]

Thus, we developed a convenient and simple electrocatalytic procedure for the stereoselective transformation of malonic ester and alkylidenecyanoacetic esters into (*E*)-3-substituted 2-cyanocyclopropane-1,1,2-tricarboxylic acid esters. This method requires the use of standard and commercially available reagents, inexpensive apparatus, and an undivided cell. The techniques for electrolysis and isolation of the reaction products are simple and convenient to use both under laboratory conditions and in large-scale apparatus.

4. Experimental

All melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. GLC analyses were carried out on a LKhM-80 chromatograph with a flame-ionisation detector, 3 m×3 mm glass columns packed with 5% OV-17 on Inerton (0.16–0.20 mm) or 10% FFAP on Chromaton N-Super (0.13–0.16 mm), respectively. ^{1}H and ^{13}C NMR spectra were recorded on Bruker WM-250, Bruker AM-300 and Varian Unity 500-PLUS spectrometer instruments operating at 250, 300 and 500 MHz, respectively. The chemical shifts were measured on the δ scale

relative to Me_4Si. Mass-spectra (70 eV) were determined directly using Finningan MAT INCOS 50 spectrometer.

X-ray diffraction experiments were carried out on CAD4 Siemens P3/PC (**3a**) and Enraf-Nonius (**3i**) difractometers (T 293 K, graphite monochromated Mo K_α radiation, $\theta_{max}=25°$) The structures **3a** and **3i** were solved by direct methods and refined by the full-matrix least-squares technique on F^2_{hkl} in the anisotropic approximation. H atoms were located from the difference Fourier synthesis and then refined isotropically. The final values of R factors were as follows: $R_1=0.039$ (912 observed reflections), $wR_2=0.2348$ (for all 1547 reflections) for **3a**, and $R_1=0.0580$ (1704 observed reflections), $wR_2=0.1278$ (for all 2226 reflections used in refinement) for **3i**. All calculations were carried out with the complex of programs SHELXTL.

PLUS 5 [Sheldrick, G. M. *SHELXTL Software Reference Manual*, Version 5, Siemens Industrial Automation, Inc.: Madison, 1994].

Crystallographic data for **3a** and **3i** (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 284947 and CCDC 284948. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

Malonic and cyanoacetic esters were purchased from Aldrich. Alkylidenecyanoacetic esters **2a**–**k** and benzylidene- and propylidenemalonic esters **5a**,**b** were prepared by Knoevenagel condensation[26] of the corresponding aldehydes and cyanoacetic or malonic esters (Merck and Aldrich).

4.1. General procedure for simultaneous electrolysis of malonic ester and alkylidenecyanoacetic esters

A solution of malonic ester **1a**,**b** (10 mmol), alkylidenecyanoacetic ester **2a**–**k** (10 mmol), and a mediator (5 mmol) in MeOH or EtOH (20 ml) was electrolyzed in an undivided cell equipped with C-anode and Fe-cathode (the electrode surface area was 5 cm^2) thermometer, external cooling and magnetic stirring at a constant current density of 100 mA/cm^2 by passing 3.0 F/mol of electricity. At the end of electrolysis, the solution was additionally cooled to −10 °C. The precipitate of cyclopropane **3** that formed was filtered off and washed with cooled to 5 °C alcohol. An additional amount of cyclopropane **3** was isolated as follows. The reaction mixture was concentrated, extracted with chloroform, washed with water, and dried over Na_2SO_4. The chloroform was distilled off. The residue was crystallised from an acetone–hexane or diethyl ether–hexane mixture, and cyclopropane **3** was isolated. After evaporation of the reaction mixture, cyclopropanes **3b**,**c**,**g** were isolated by flash chromatography (eluent chloroform/hexane 1:1) and cyclopropanes **3j**,**k** were isolated by vacuum distillation.

4.1.1. (*E*)-Trimethyl 2-cyanocyclopropane-3-phenyl-1,1,2-tricarboxylate (3a). Yield 2.57 g (81%), white solid, mp 140–142 °C. ^{1}H NMR (CD_3CN), δ: 3.70 (s, 3H, CH_3O), 3.79 (s, 3H, CH_3O), 3.88 (s, 3H, CH_3O), 3.96 (s, 1H, CH), 7.38 (m, 5H, C_6H_5). ^{13}C NMR ($CDCl_3$), δ: 30.6 (C), 39.6 (CH), 47.7 (C), 53.5 (CH_3O), 53.7 (CH_3O), 54.5 (CH_3O), 112.4 (CN), 128.5, 128.7, 128.8, 129.3 (Ph), 162.7 (OC=O), 164.27 (OC=O), 164.8 (OC=O). MS (70 eV): m/z (relative intensity %): 317 (M^+, 8), 286 (9), 258 (100), 198 (71), 121 (52), 59 (72). IR (KBr): ν_{max} 2252, 1772, 1756, 1436, 1232. Anal. Calcd for $C_{16}H_{15}NO_6$: C, 60.57; H, 4.76; N, 4.41. Found: C, 60.39; H, 4.61; N, 4.25.

Crystal data for **3a**: $C_{16}H_{15}NO_6$, $M=317.29$, rhombic, space group $P2_12_12_1$, $a=9.715(5)$ Å, $b=10.693(5)$ Å, $c=15.013(8)$ Å, $V=1559.9(14)$ Å^3, $Z=4$, $D_c=1.351$ g cm^{-3}.

4.1.2. (*E*)-Triethyl 2-cyanocyclopropane-3-phenyl-1,1,2-tricarboxylate (3b). Yield 3.05 g (85%), colourless oil. ^{1}H NMR ($CDCl_3$), δ: 1.12 (t, CH_3, $J=7.1$ Hz), 1.29 (t, CH_3, $J=7.1$ Hz), 1.38 (t, CH_3, $J=7.1$ Hz), 3.93 (s, 1H, CH), 4.12 (q, 2H, CH_2O, $J=7.1$ Hz), 4.20–4.45 (m, 4H, CH_2O), 7.25–7.51 (m, 5H, C_6H_5). ^{13}C NMR ($CDCl_3$), δ: 13.4 (CH_3), 13.6 (CH_3), 13.8 (CH_3), 30.6 (C), 39.0 (CH), 47.7 (C), 62.7 (CH_2O), 62.8 (CH_2O), 64.0 (CH_2O), 112.5 (CN), 128.5, 128.6, 128.9, 129.6 (Ph), 162.3 (OC=O), 163.7 (OC=O), 164.2 (OC=O). MS (70 eV): m/z (relative intensity %): 359 (M^+, 3), 314 (5), 286 (100), 258 (32), 212 (23), 140 (32), 105 (17). IR (KBr): ν_{max} 2256, 1752, 1448, 1264, 1232. Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.32; H, 5.93; N, 3.81.

4.1.3. (*E*)-Trimethyl 2-cyanocyclopropane-3-(4-methylphenyl)-1,1,2-tricarboxylate (3c). Yield 2.75 g (83%), white solid, mp 72–74 °C. ^{1}H NMR ($CDCl_3$), δ: 2.34 (s, 3H, CH_3), 3.72 (s, 3H, CH_3O), 3.83 (s, 3H, CH_3O), 3.89 (s, 1H, CH), 3.91 (s, 3H, OCH_3), 7.18 (d, 2H, $J=8.3$ Hz), 7.25 (d, 2H, $J=8.3$ Hz). ^{13}C NMR ($CDCl_3$), δ: 21.0 (CH_3), 30.5 (C), 39.4 (CH), 47.6 (C), 53.4 (CH_3O), 53.6 (CH_3O), 54.4 (CH_3O), 112.4 (CN), 127.0, 128.2, 129.4, 138.5 (Ar), 162.6 (OC=O), 164.2 (OC=O), 164.8 (OC=O). MS (70 eV): m/z (relative intensity %): 331 (M^+, 13), 300 (7), 272 (68), 212 (100), 135 (52), 59 (76). IR (KBr): ν_{max} 2252, 1756, 1748, 1436, 1232. Anal. Calcd for $C_{17}H_{17}NO_6$: C, 61.63; H, 5.17; N, 4.23. Found: C, 61.44; H, 4.98; N, 4.14.

4.1.4. (*E*)-Trimethyl 2-cyanocyclopropane-3-(4-methoxyphenyl)-1,1,2-tricarboxylate (3d). Yield 3.01 g (87%), white solid, mp 110–112 °C. ^{1}H NMR ($CDCl_3$), δ: 3.72 (s, 3H, CH_3O), 3.80 (s, 3H, CH_3O), 3.82 (s, 3H, CH_3O), 3.87 (s, 1H, CH), 3.91 (s, 3H, CH_3O), 6.88 (d, 2H, Ar, $J=8.2$ Hz), 7.29 (d, 2H, Ar, $J=8.2$ Hz). ^{13}C NMR ($CDCl_3$), δ: 30.7 (C), 39.3 (CH), 47.8 (C), 53.5 (CH_3O), 53.7 (CH_3O), 54.5 (CH_3O), 55.2 (CH_3O), 112.5 (CN), 114.2, 124.2, 129.7, 159.7 (Ar), 162.7 (OC=O), 164.3 (OC=O), 164.8 (OC=O). MS (70 eV): m/z (relative intensity %): 347 (M^+, 57), 316 (3), 288 (13), 228 (100), 170 (39), 151 (38), 59 (82). IR (KBr): ν_{max} 2252, 1756, 1752, 1440, 1240. Anal. Calcd for $C_{17}H_{17}NO_7$: C, 58.79; H, 4.93; N, 4.03. Found: C, 58.61; H, 4.84; N, 3.92.

4.1.5. (*E*)-Trimethyl 3-(2-chlorophenyl)-2-cyanocyclopropane-1,1,2-tricarboxylate (3e). Yield 2.85 g (81%), white solid, mp 97–99 °C. ^{1}H NMR ($CDCl_3$), δ: 3.78 (s, 3H, CH_3O), 3.83 (s, 3H, CH_3O), 3.88 (s, 1H, CH), 3.94 (s, 3H, CH_3O), 7.25–7.48 (m, 4H, Ar). ^{13}C NMR ($CDCl_3$), δ: 31.4

(C), 38.6 (CH), 47.4 (C), 53.6 (CH_3O), 53.7 (CH_3O), 54.7 (CH_3O), 112.2 (CN), 127.1, 127.5, 129.9, 130.1, 134.9 (Ar), 162.9 (OC=O), 164.2 (OC=O), 164.8 (OC=O). MS (70 eV): *m/z* (relative intensity %): 351 (M^+, 8), 320 (7), 292 (100), 232 (36), 155 (33), 59 (89). IR (KBr): ν_{max} 2256, 1760, 1748, 1440, 1236. Anal. Calcd for $C_{16}H_{14}ClNO_6$: C, 54.64; H, 4.01; Cl, 10.08; N, 3.98. Found: C, 54.43; H, 3.95; Cl, 9.87; N, 3.84.

4.1.6. (*E*)-Trimethyl 3-(4-chlorophenyl)-2-cyanocyclopropane-1,1,2-tricarboxylate (3f). Yield 3.06 g (87%), white solid, mp 73–75 °C. ^{1}H NMR ($CDCl_3$), δ: 3.76 (s, 3H, CH_3O), 3.84 (s, 3H, CH_3O), 3.87 (s, 1H, CH), 3.93 (s, 3H, CH_3O), 7.23–7.45 (m, 4H, Ar). ^{13}C NMR ($CDCl_3$), δ: 30.5 (C), 38.6 (CH), 47.5 (C), 53.5 (CH_3O), 53.6 (CH_3O), 54.6 (CH_3O), 112.1 (CN), 127.7, 129.0, 129.8, 134.8 (Ar), 162.4 (OC=O), 164.0 (OC=O), 164.5 (OC=O). MS (70 eV): *m/z* (relative intensity %): 351 (M^+, 8), 320 (6), 292 (72), 232 (51), 174 (21), 155 (36), 59 (100). IR (KBr): ν_{max} 2256, 1756, 1744, 1440, 1232. Anal. Calcd for $C_{16}H_{14}ClNO_6$: C, 54.64; H, 4.01; Cl, 10.08; N, 3.98. Found: C, 54.71; H, 4.09; Cl, 10.15; N, 3.75.

4.1.7. (*E*)-Triethyl 3-(4-chlorophenyl)-2-cyanocyclopropane-1,1,2-tricarboxylate (3g). Yield 3.27 g (83%), colourless oil. ^{1}H NMR ($CDCl_3$), δ: 1.08 (t, CH_3, J=7.1 Hz), 1.24 (t, CH_3, J=7.1 Hz), 1.35 (t, CH_3, J=7.1 Hz), 3.91 (s, 1H, CH), 4.15–4.45 (m, 6H, CH_2O), 7.20–7.45 (m, 4H, Ar). ^{13}C NMR ($CDCl_3$), δ: 13.47 (CH_3), 13.53 (CH_3), 13.8 (CH_3), 33.1 (C), 38.2 (CH), 46.7 (C), 62.8 (CH_2O), 62.9 (CH_2O), 64.1 (CH_2O), 112.4 (CN), 128.9, 129.4, 129.9, 133.8 (Ar), 163.4 (OC=O), 166.1 (OC=O), 167.5 (OC=O). MS (70 eV): *m/z* (relative intensity %): 393 (M^+, 6), 348 (7), 320 (100), 246 (98), 202 (91), 174 (78), 169 (78). IR (KBr): ν_{max} 2252, 1752, 1736, 1440, 1260. Anal. Calcd for $C_{19}H_{20}ClNO_6$: (%): C, 57.95; H, 5.12; Cl, 9.00; N, 3.56. Found: C, 57.74; H, 5.15; Cl, 8.91; N, 3.43.

4.1.8. (*E*)-Trimethyl 3-(3-bromophenyl)-2-cyanocyclopropane-1,1,2-tricarboxylate (3h). Yield 3.88 g (98%), yellow solid, mp 89–91 °C. ^{1}H NMR ($CDCl_3$), δ: 3.73 (s, 3H, CH_3O), 3.80 (s, 3H, CH_3O), 3.87 (s, 1H, CH), 3.89 (s, 3H, CH_3O), 7.20–7.33 (m, 2H, Ar), 7.40–7.50 (m, 2H, Ar). ^{13}C NMR ($CDCl_3$), δ: 30.4 (C), 38.4 (CH), 47.3 (C), 53.6 (CH_3O), 53.7 (CH_3O), 54.6 (CH_3O), 111.9 (CN), 122.4, 128.1, 130.3, 131.46, 131.53, 131.7 (Ar), 162.4 (OC=O), 163.8 (OC=O), 164.4 (OC=O). MS (70 eV): *m/z* (relative intensity %): 397 (M^+, 15), 395 (M^+, 14), 364 (3), 366 (2), 338 (61), 336 (78), 278 (28), 276 (34), 201 (25), 199 (27), 59 (100). IR (KBr): ν_{max} 2268, 1756, 1746, 1440, 1232. Anal. Calcd for $C_{16}H_{14}BrNO_6$: C, 48.51; H, 3.56; Br, 20.17; N, 3.54. Found: C, 48.35; H, 3.47, Br, 19.93; N, 3.29.

4.1.9. (*E*)-Trimethyl 2-cyanocyclopropane-3-methyl-1,1,2-tricarboxylate (3i). Yield 2.24 g (88%), white solid, mp 87–89 °C. ^{1}H NMR ($CDCl_3$), δ: 1.45 (d, 3H, CH_3, J=6.7 Hz), 2.67 (q, 1H, CH, J=6.7 Hz), 3.70 (s, 3H, CH_3O), 3.79 (s, 6H, CH_3O). ^{13}C NMR ($CDCl_3$), δ: 9.6 (CH_3), 31.0 (C), 31.8 (CH), 47.0 (C), 53.61 (CH_3O), 53.8 (CH_3O), 54.4 (CH_3O), 112.6 (CN), 163.2 (OC=O), 164.4 (OC=O), 164.9 (OC=O). MS (70 eV): *m/z* (relative intensity %): 255 (M^+, 2), 224 (8), 196 (51), 164 (32), 137 (7), 92 (11), 59 (100). IR (KBr): ν_{max} 2256, 1756, 1744, 1444, 1240. Anal. Calcd for $C_{11}H_{13}NO_6$: C, 51.77; H, 5.13; N, 5.49. Found: C, 51.55; H, 4.98; N, 5.38.

Crystal data for **3i**: $C_1H_{13}NO_6$, M=255.22, monoclinic, space group $P2_1/n$, a=8.972(3) Å, b=15.159(7) Å, c=9.732(4) Å, β=106.89(3)°, V=1266.5(9) Å^3, Z=4, D_c=1.339 g cm^{-3}.

4.1.10. (*E*)-Trimethyl 2-cyano-3-ethylcyclopropane-1,1,2-tricarboxylate (3j). Yield 2.13 g (79%), colourless oil, bp 131–143 °C (0.10 Torr). ^{1}H NMR ($CDCl_3$), δ: 1.03 (t, 3H, CH_3, J=7.3 Hz), 1.68–1.84 (m, 2H, CH_2), 2.61 (t, 1H, CH, J=7.3 Hz), 3.72 (s, 3H, CH_3O), 3.81 (s, 6H, CH_3O). ^{13}C NMR ($CDCl_3$), δ: 12.2 (CH_3), 18.0 (CH_2), 30.4 (C), 38.2 (CH), 46.8 (C), 53.5 (CH_3O), 53.7 (CH_3O), 54.3 (CH_3O), 112.5 (CN), 163.25 (OC=O), 164.4 (OC=O), 164.8 (OC=O). MS (70 eV): *m/z* (relative intensity %): 269 (M^+, 5), 238 (12), 210 (63), 178 (57), 146 (29), 133 (37), 59 (100). IR (KBr): ν_{max} 2252, 1755, 1748, 1436, 1238. Anal. Calcd for $C_{12}H_{15}NO_6$: C, 53.53; H, 5.62; N, 5.20. Found: C, 53.35; H, 5.48; N, 5.31.

4.1.11. (*E*)-Trimethyl 2-cyanocyclopropane-3-propyl-1,1,2-tricarboxylate (3k). Yield 2.18 g (77%), colourless oil, bp 140–142 °C (0.08 Torr). ^{1}H NMR ($CDCl_3$), δ: 0.98 (t, 3H, CH_3, J=7.3 Hz), 1.46–1.58 (m, 2H, CH_2), 1.73–1.83 (m, 2H, CH_2), 2.62 (t, 1H, CH, J=7.3 Hz), 3.73 (s, 3H, CH_3O), 3.82 (s, 6H, CH_3O). ^{13}C NMR ($CDCl_3$), δ: 13.3 (CH_3), 21.2 (CH_2), 26.2 (CH_2), 30.4 (C), 36.7 (CH), 46.6 (C), 53.4 (CH_3O), 53.5 (CH_3O), 54.2 (CH_3O), 112.6 (CN), 163.3 (OC=O), 164.4 (OC=O), 164.9 (OC=O). MS (70 eV): *m/z* (relative intensity %): 283 (M^+, 2), 252 (17), 224 (71), 192 (65), 160 (28), 132 (88), 59 (100). IR (KBr): ν_{max} 2252, 1748, 1742, 1436, 1236. Anal. Calcd for $C_{13}H_{17}NO_6$: (%): C, 55.12; H, 6.05; N, 4.94. Found: C, 54.93; H, 6.11; N, 4.71.

4.1.12. Trimethyl 2-phenyl-3-cyanopropane-1,1,3-tricarboxylate (4). The solution of Na (1 mmol) in 5 ml of methanol was added to solution of dimethyl malonate (10 mmol) and methyl benzylidenecyanoacetate (10 mmol) at room temperature. After 30 min the resulting solid was filtered off. The solvent was evaporated, the residue was extracted with 30 ml of chloroform, washed with water and dried over Na_2SO_4. Chloroform was removed under reduced pressure and the residue together with the first solid part were crystallised from methanol. After crystallization **4** was obtained as a mixture of two diastereomers (ratio 10:1), 2.55 g, 85% yield, white solid, mp 87–89 °C. Main diastereomer ^{1}H NMR ($CDCl_3$), δ: 3.52 (s, 3H, OCH_3), 3.77 (s, 3H, CH_3O), 3.82 (s, 3H, CH_3O), 4.16 (dd, 1H, CH, J_1=5 Hz, J_2=11 Hz), 4.25 (d, 1H, CH, J=5 Hz), 4.38 (d, 1H, CH, J=11 Hz), 7.30–7.40 (m, 5H, Ph). Minor diastereomer ^{1}H NMR ($CDCl_3$), δ: 3.47 (s, 3H, OCH_3), 3.63 (s, 3H, CH_3O), 3.86 (s, 3H, CH_3O), 4.14 (dd, 1H, CH, J_1=5 Hz, J_2=11 Hz), 4.18 (d, 1H, CH, J=11 Hz), 4.54 (d, 1H, CH, J=5 Hz), 7.30–7.40 (m, 5H, Ph). Main diastereomer ^{13}C NMR ($CDCl_3$), δ: 41.86 (CH), 44.81 (CH), 52.68, 53.10, 53.49, 54.17 (3OCH_3 and CH), 115.07 (CN), 128.02, 128.75, 128.93, 136.20 (Ph), 165.20 (OC=O), 167.12 (OC=O), 168.00 (OC=O). Minor diastereomer ^{13}C NMR ($CDCl_3$), δ: 41.89 (CH), 43.97 (CH), 53.08, 53.25, 53.33, 53.75 (3OCH_3 and CH), 114.85 (CN), 128.48,

128.66, 128.71, 134.68 (Ph), 164.86 (OC═O), 166.85 (OC═O), 167.97 (OC═O). IR (KBr): ν_{max} 2260, 1732, 1456, 1252, 1228. Anal. Calcd for $C_{16}H_{17}NO_6$: (%): C, 60.18; H, 5.37; N, 4.39. Found: C, 60.25; H, 5.26; N, 4.28.

4.1.13. Tetramethyl 3-phenylcyclopropane-1,1,2,2-tetracarboxylate (6). The title compound was prepared according to a known procedure,[14] mp 85–86 °C (cf. lit. data:[27] mp 87 °C). ^{1}H NMR ($CDCl_3$), δ: 3.66 (s, 6H, CH_3O), 3.78 (s, 1H, CH), 7.20–7.35 (m, 5H, Ph).

4.1.14. Tetramethyl 2,3-diphenylbutane-1,1,4,4-tetracarboxylate (7). The title compound was prepared according to a known procedure[22] in 58% yield as a mixture of *meso* and D,L isomers in a ratio of 2:1. The *meso* form was isolated by crystallization from methanol. The D,L form was isolated by column chromatography of the residue obtained after crystallization; a 2:1 diethyl ether/hexane mixture was used as the eluent. The *meso* form **7** was also isolated by crystallization from the reaction mixture, which was obtained by simultaneous electrolysis of methyl cyanoacetate and benzylidenemalonic ester **5a** at 0 °C (Table 2), in 9% yield. The physicochemical and spectroscopic characteristics of the *meso*- and D,L-**7** forms were analogous to those described earlier.[22]

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A facile synthesis of 3-allyl-4-hydrazinocyclopentenes by the palladium/Lewis acid mediated ring opening of bicyclic hydrazines with allyltributyltin and allyltrimethylsilane

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Abstract—A facile method for the synthesis of 3-allyl-4-hydrazinocyclopentenes from bicyclic hydrazines by the Pd/Lewis acid catalyzed reaction of allyltributyltin and allyltrimethylsilane is described. The role of ionic liquid [bmim]PF_6 as a solvent as well as a promoter is also demonstrated by carrying out the reactions in ionic liquid without Lewis acid.

1. Introduction

Disubstituted cyclopentanes are versatile synthons for the construction of numerous biologically active molecules.[1] They are well utilized for the preparation of glycosidase inhibitors, antiviral and antitumor carbonucleosides and in prostaglandin research.[2] Among the disubstituted cyclopentenes, hydrazinocyclopentenes are of great importance because they have been extensively utilized for the preparation of carbocyclic ribavirin, which is supposed to have greater metabolic stability to the phosphorylase enzymes.[3] Substituted cyclopentenyl hydroxamic acid derived inhibitors of metal containing enzymes like 5-lipoxygenase are used for the treatment of many diseases like rheumatoid arthritis, asthma, inflammatory bowel disease, psoriasis and allergy.[4] Some of the bioactive cyclopentane derivatives are shown in Figure 1.

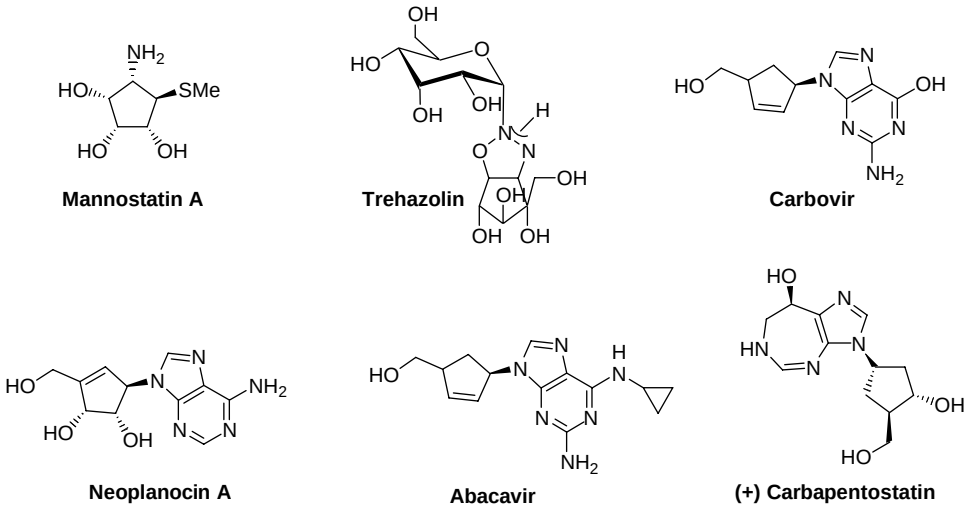

Figure 1.

Keywords: Bicyclic hydrazines; Disubstituted cyclopentanes; [bmim]PF_6; Allyltri-*n*-butyltin; Lewis acids; Palladium catalyst.
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Various methods are known in the literature for the preparation of disubstituted cyclopentene derivatives.[5] Trost has utilized π-allyl palladium chemistry for introducing a variety of substituents to the cyclopentenic core.[6] Miller and co-workers achieved the synthesis of disubstituted cyclopentenes by using acyl nitroso-hetero Diels–Alder cycloadducts.[7] Desymmetrization of the bicyclic hydrazines is another tool for the synthesis of disubstituted cyclopentenes and it has been well utilized by Kaufmann[8] and Micouin.[9] But all of the reported methods lead to the formation of 3,5-disubstituted cyclopentenes. In some of the above cases, 3,4-disubstituted cyclopentenes were observed as minor products.[7,8,10]

2. Results and discussion

2.1. Pd/Lewis acid mediated ring opening

Owing to our interest in the cascade carbopalladation of bicyclic alkenes, we undertook an investigation of the domino Heck–Stille coupling of bicyclic hydrazines. The Stille protocol have been employed by Kosugi and co-workers[11] for the synthesis of 2,3-disubstituted norbornanes from organic halide, organostannane and norbornene. Bicyclic hydrazines are suitable candidates for the preparation of disubstituted cyclopentenes due to their good reactivity and an internal point of fracture, the C–N bond. Moreover, they are easily accessible. The bicyclic hydrazines selected for our studies are given in Figure 2.

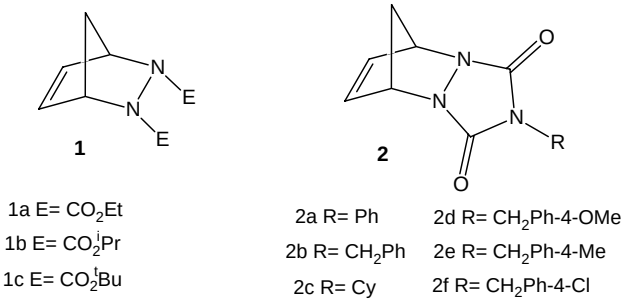
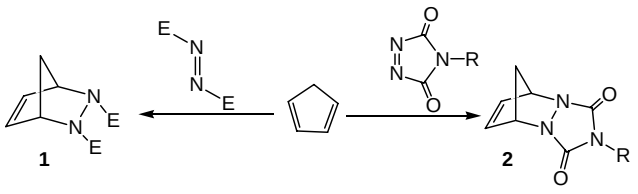


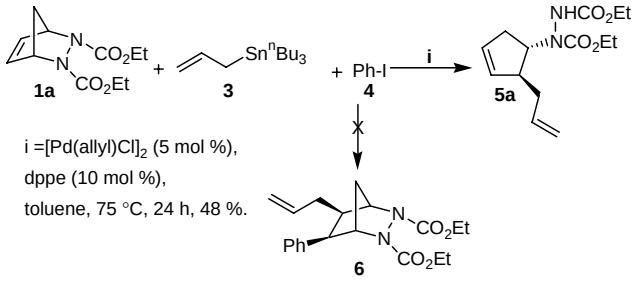
Figure 2.

Bicyclic hydrazines, the starting materials for our investigations were prepared by the Diels–Alder cycloaddition reaction between cyclopentadiene and the corresponding dialkylazodicarboxylate[12] or 1,2,4,-triazoline-3,5-dione (Scheme 1).[13]



Scheme 1.

Our experiments started with the reaction of 2,3-diazabicyclo[2.2.1]heptene with aryl iodide and allyltributyl tin in the presence of $[Pd(allyl)Cl]_2$ and dppe in dry toluene. Contrary to the expected addition product, the reaction afforded allylated hydrazinocyclopentene (Scheme 2).



Scheme 2.

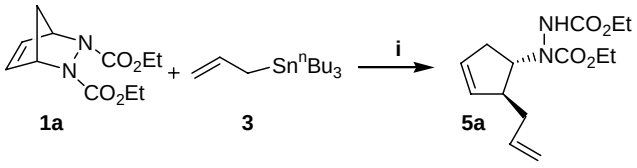
The reaction was optimized under different conditions. Details of the optimization studies are shown in Table 1.

Table 1

Catalyst	Ligand	Solvent	Time/ temperature	Yield
$Pd_2(dba)_3 \cdot CHCl_3$	dppm	Toluene	20 h, 70 °C	Complicated reaction
$Pd_2(dba)_3 \cdot CHCl_3$	dppe	Toluene	20 h, 70 °C	Complicated reaction
$PdCl_2(PPh_3)_2$	—	Toluene	24 h, 100 °C	20%
$PdCl_2(PhCN)_2$	—	Toluene	24 h, 60 °C	No reaction
$Pd(OAc)_2$	—	THF	24 h, 60 °C	Complicated reaction
$[Pd(allyl)Cl]_2$	—	Toluene	36 h, 75 °C	30%
$[Pd(allyl)Cl]_2$	dppe	Toluene	24 h, 75 °C	48%
$[Pd(allyl)Cl]_2$	PPh_3	Toluene	24 h, 75 °C	15%
$[Pd(allyl)Cl]_2$	dppm	Toluene	24 h, 75 °C	Complicated reaction

After a series of experiments, 5 mol% $[Pd(allyl)Cl]_2$ along with 10 mol% dppe as ligand was found to be the best catalyst system with toluene as the solvent.

It was interesting to note that aryl iodide was recovered almost completely and no reaction could be observed in the absence of aryl iodide. The question remained as to the role of aryl iodide in the reaction. We suspected that the trace amount of iodine present in the aryl iodide or aryl iodide itself may be acting as a nucleophile facilitating the C–N bond cleavage. Molecular iodine is known to bring about various organic transformations with high selectivity under convenient conditions.[14] The possibility of iodine acting as a promoter for various reactions, has been a topic of discussion for organic chemists in recent years. The role of iodine as a promoter, facilitating the formation of **5a** was proved by carrying out the reaction with catalytic amount of iodine instead of aryl iodide. The reaction afforded **5a** in 85% yield (Scheme 3).[15]



Scheme 3. i=$[Pd(allyl)Cl]_2$ (5 mol%), dppe (10 mol%), I_2 (2 mol%), toluene, 75 °C, 24 h, 85%.

This prompted us to investigate the effect of other Lewis acids and the reaction was found to be general with a number of Lewis acids. Scandium triflate was found to be the best, the reaction was complete in 5 h at rt and our observations are given in Table 2.

Table 2. Effect of different Lewis acids

No.	Lewis acid	Time (h)	Temperature	Yield (%)
1	I_2	24	75 °C	85
2	$Yb(OTf)_3$	5	rt	80
3	$Sc(OTf)_3$	5	rt	95
4	AgOTf	12	rt	62
5	$Cu(OTf)_2$	12	rt	68
6	$Sn(OTf)_2$	24	50 °C	60

Amount of Lewis acid=2 mol%.

The structure of the compound **5a** was assigned based on the spectral data. In the IR spectrum the stretching vibrations of NH and CO were observed at 3294 and 1713 cm^{-1}, respectively. In the ^1H NMR spectrum, the NH proton and the carboethoxy protons were seen at δ 6.52, 4.19 and 1.27 ppm, respectively, while the CH proton of the allyl group was observed at δ 5.79 ppm. The carbonyl carbons were discernible at δ 156.7 and 155.9 in the ^{13}C NMR spectrum. The structure was further confirmed by elemental analysis and high resolution mass spectral analysis. The HOMO-COSY and HETERO-COSY analyses were also in agreement with the proposed structure. The stereochemistry of the product was assigned by comparison to the literature data.[8,21]

Due to our continuing interest in this field, we decided to investigate the reactivity of some tricyclic hydrazines derived from triazoline dione. The common solvents like toluene and THF were not suitable for these substrates as the yields were substantially low. In an attempt to optimize the yield of the reaction by changing solvents, we decided to use rt ionic liquid $[bmim]PF_6$ as the solvent.

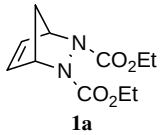
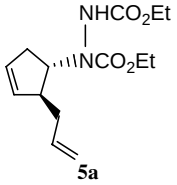
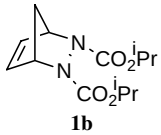
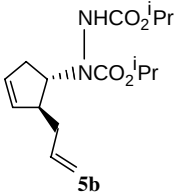
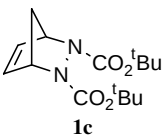
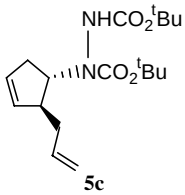
2.2. Reactions in ionic liquid $[bmim]PF_6$

It is well known that the microenvironment generated by a solvent can change the outcome of a reaction in terms of both equilibria and rate. Since ionic liquids have the potential to provide reaction media that are unique at rt, it is possible that they will have dramatic effects on reactions carried out in them.[16] Ionic liquids are composed of anions and cations; either of which may interact with solutes and therefore affect the outcome of the reaction. Some ionic liquids have also been shown to act as catalysts further augmenting their wide spread introduction into general synthetic chemistry. The ionic liquids offer an attractive alternative to conventional organic solvents for clean synthesis, as they are easy to recycle and possess no effective vapor pressure.[17]

When the reaction of bicyclic hydrazine **1** was carried out in ionic liquid instead of toluene, the reaction rate was found to enhance but with similar yield. In addition to this we observed that the reaction occurs in $[bmim]PF_6$ even in the absence of Lewis acid, but with longer reaction time. This demonstrates the ability of ionic liquid to act as a promoter. The results of our investigations are given in Table 3.

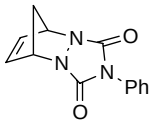
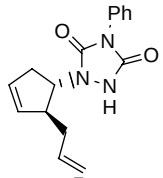
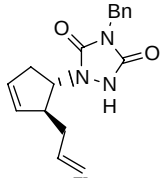
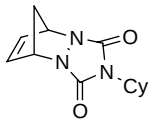
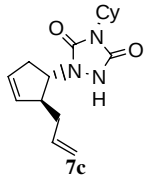
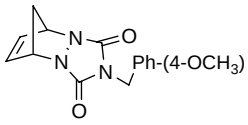
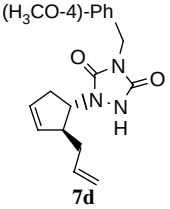
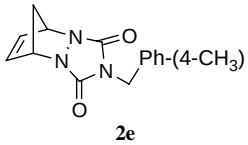
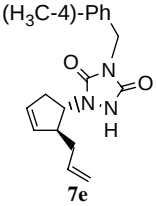
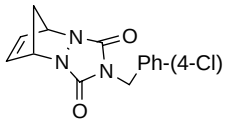
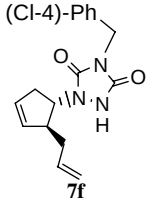
Similar reactivity was observed in the case of azatricyclic olefins. To prove the generality of this strategy we have extended the Pd(0)/Lewis acid catalyzed reaction of allyltributyltin to various tricyclic substrates. Our observations are summarized in Table 4.

Table 3. Palladium-catalyzed reaction of azabicyclic olefins with allyltributyltin

Entry	Substrate	Lewis acid	Time (h)	Solvent/ temperature (°C)	Yield (%)	Product
1	 **1a**	$Sc(OTf)_3$	5	Toluene, rt	95	 **5a**
		$Sc(OTf)_3$	1	$[bmim]PF_6$, rt	90	
		—	12	$[bmim]PF_6$, 60 °C	76	
2	 **1b**	$Sc(OTf)_3$	12	Toluene, 60 °C	75	 **5b**
		$Sc(OTf)_3$	8	$[bmim]PF_6$, 60 °C	80	
		—	24	$[bmim]PF_6$, 60 °C	78	
3	 **1c**	$Sc(OTf)_3$	12	Toluene, 60 °C	77	 **5c**
		$Sc(OTf)_3$	8	$[bmim]PF_6$, 60 °C	72	

Reaction conditions=$[Pd(allyl)Cl]_2$ (5 mol%), dppe (10 mol%), $Sc(OTf)_3$ (2 mol%).

Table 4. Palladium-catalyzed reaction of azatricyclic olefins with allyltributyltin

Entry	Substrate	Lewis acid	Time (h)	Solvent/temperature (°C)	Yield (%)	Product
1	 **2a**	$Sc(OTf)_3$ $Sc(OTf)_3$ —	36 8 24	Toluene, 60 °C [bmim]PF_6, 60 °C [bmim]PF_6, 60 °C	20 89 90	 **7a**
2	 **2b**	$Sc(OTf)_3$ —	8 24	[bmim]PF_6, 60 °C [bmim]PF_6, 60 °C	95 97	 **7b**
3	 **2c**	$Sc(OTf)_3$ —	8 24	[bmim]PF_6, 60 °C [bmim]PF_6, 60 °C	88 85	 **7c**
4	 **2d**	$Sc(OTf)_3$ —	10 24	[bmim]PF_6, 60 °C [bmim]PF_6, 60 °C	85 81	 **7d**
5	 **2e**	$Sc(OTf)_3$ —	10 24	[bmim]PF_6, 60 °C [bmim]PF_6, 60 °C	95 93	 **7e**
6	 **2f**	$Sc(OTf)_3$ —	10 24	[bmim]PF_6, 60 °C [bmim]PF_6, 60 °C	78 76	 **7f**

Reaction conditions = $[Pd(allyl)Cl]_2$ (5 mol%), dppe (10 mol%), $Sc(OTf)_3$ (2 mol%).

2.3. Reactions with allyltrimethylsilane

Organometals containing relatively electronegative metals such as organoboranes and organosilanes are also known to participate in palladium-catalyzed cross-coupling reactions.[18] These reactions are thought to proceed via transmetallation on palladium. The carbon–silicon bond of allyltrimethylsilane, although less polarized, has sufficient nucleophilicity to react with palladium complexes.[19] As expected, the reaction of bicyclic hydrazine **1a** with allyltrimethylsilane in the presence of Pd/Lewis acid catalyst afforded allyl substituted hydrazinocyclopentene as the product, but with low yield. The reaction was found to be general for bicyclic and tricyclic olefins. The results of our investigations with allyltrimethylsilane are summarized in Table 5.

Table 5. Reaction of allyltrimethysilane

Entry	Starting material	Solvent/temperature (°C)	Product	Yield (%)
1	**1a**	Toluene, 60 °C	**5a**	30
2	**2a**	[bmim]PF_6, 60 °C	**7a**	28
3	**2c**	[bmim]PF_6, 60 °C	**7c**	32

Reaction conditions = $[Pd(allyl)Cl]_2$ (5 mol%), dppe (10 mol%), $Sc(OTf)_3$ (2 mol%), 12 h.

3. Conclusions

In conclusion, we have developed a new methodology for the synthesis of 3,4-disubstituted cyclopentenes. The products are suitable for further synthetic transformations. Transformations like dihydroxylation and conversion of

the hydrazine to amine could result in the formation of versatile synthons, which can be used for the synthesis of many biologically active molecules like glycosidase inhibitors,[20] carbocyclic nucleosides, antiviral and anti-tumor agents[22] etc. The role of ionic liquid as a solvent as well as a promoter was also established by carrying out the reactions in ionic liquid without Lewis acid.

4. Experimental

4.1. General

All reactions were carried out in oven-dried glass wares under nitrogen atmosphere. Progress of the reaction was monitored by thin-layer chromatography, which was performed on Merck precoated plates (silica gel 60 F_{254}, 0.25 mm) and was visualized by fluorescence quenching under UV light or by staining with Enholm yellow solution. Column chromatography was done using 100–200 mesh silica gel and appropriate mixture of petroleum ether (60–80 °C) and ethyl acetate for elution. The solvents were removed using Buchi rotary evaporator. The IR spectra were recorded on Nicolet FT-IR spectrometer. NMR spectra were recorded on Bruker FT-NMR spectrometer using $CDCl_3$ or $CDCl_3$–CCl_4 mixture (7/3) as solvent. TMS was used as internal standard and chemical shifts are in δ-scale. High-resolution mass spectra were recorded under EI/HRMS using JEOL JMS 600H mass spectrometer. Abbreviations used in ^{1}H NMR are s-singlet, t-triplet, q-quartet and m-multiplet.

4.2. General procedure for the reaction of bicyclic hydrazines with organostannanes and organosilanes

Method A. The bicyclic hydrazine (1 equiv) and organostannane/organosilane (1 equiv) were taken in a Wheaton reactor and dissolved in dry toluene (4 mL). The ligand dppe (10 mol%) was added, followed by the catalyst $[Pd(allyl)Cl]_2$ (5 mol%). To this $Sc(OTf)_3$ (2 mol%) was added. The reaction mixture was stirred at 60 °C for 12 h. Completion of the reaction was monitored by TLC and the reaction mixture was subjected to column chromatography (silica gel 100–200 mesh, 15% EtOAc–hexane) to afford the product in good yield.

Method B. The bicyclic hydrazine (1 equiv) and the organostannane/organosilane (1 equiv) were taken in a Wheaton reactor and dissolved in ionic liquid [bmim]PF_6 (2 mL). The ligand dppe (10 mol%) was added, followed by the catalyst $[Pd(allyl)Cl]_2$ (5 mol%). To this $Sc(OTf)_3$ (2 mol%) was added. The reaction mixture was stirred at 60 °C for 12 h. Completion of the reaction was monitored by TLC. The reaction mixture was extracted several times with diethyl ether until the ether layer contains no compound. Ether was evaporated off and the crude sample was subjected to column chromatography (silica gel 100–200 mesh, 15% EtOAc–hexane) to afford the product in good yield. The ionic liquid was washed, dried and reused.

4.2.1. Data for compound 5a. Method A. Colorless viscous liquid. Yield=95%. IR (neat) ν_{max}: 3294, 3057, 2979, 2923, 1713, 1517, 1414, 1295, 1239, 1125, 1063, 909, 759, 713 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.52 (s, 1H), 5.72–5.86 (m, 1H), 5.59–5.63 (m, 2H), 4.99–5.09 (m, 2H), 4.55–4.57 (m, 1H), 4.19 (q, 4H), 2.85 (br s, 1H), 2.31–2.53 (m, 3H), 2.10–2.17 (m, 1H), 1.27 (t, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.7, 155.9, 136.4, 132.8, 128.5, 116.3, 63.1, 62.4, 61.9, 47.6, 37.6, 35.2, 14.5, 14.4. MS (LR-FAB): *m/z* calculated for $C_{14}H_{22}N_2O_4$ (M+1): 283.1658. Found: 283.1666 (M+1). Anal. Calc for $C_{14}H_{22}N_2O_4$ C, 59.56; H, 7.85; N, 9.92. Found C, 59.86; H, 7.94; N, 10.23.

4.2.2. Data for compound 5b. Method B. Colorless viscous liquid. Yield=80%. IR (neat) ν_{max}: 3296, 2981, 2934, 1732, 1689, 1468, 1411, 1297, 1109, 956 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.29 (s, 1H), 5.72–5.85 (m, 1H), 5.60–5.62 (m, 2H), 5.08 (s, 1H), 4.98–5.02 (m, 2H), 4.91–4.95 (m, 2H), 2.83 (s, 1H), 2.45–2.48 (m, 2H), 2.30–2.37 (m, 1H), 2.07–2.16 (m, 1H), 1.24–1.26 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.1, 156.6, 136.6, 133.1, 128.7, 116.4, 70.2, 69.8, 63.1, 47.8, 37.8, 37.6, 27.1, 22.3, 22.2, 17.6. HRMS (EI): *m/z* calculated for $C_{16}H_{26}N_2O_4$: 310.1893. Found: (M^+) 310.1895.

4.2.3. Data for compound 5c. Method A. Colorless viscous liquid. Yield=77%. IR (neat) ν_{max}: 3318, 2979, 2931, 1703, 1641, 1478, 1395, 1248, 1170, 950 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.16 (s, 1H), 5.77–5.79 (m, 1H), 5.61 (m, 2H), 4.97–5.07 (m, 2H), 4.45 (br s, 1H), 2.78 (s, 1H), 2.42–2.45 (m, 2H), 2.11 (m, 2H), 1.45 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.3, 156.8, 136.4, 133.2, 128.5, 116.8, 63.3, 62.2, 47.5, 35.9, 28.4, 26.9, 22.5, 22.1. HRMS (EI): *m/z* calculated for $C_{18}H_{30}N_2O_4$: 338. 2206. Found: (M^+) 338.2175.

4.2.4. Data for compound 7a. Method B. Colorless viscous liquid. Yield=90%. IR (neat) ν_{max}: 3433, 3175, 3067, 2954, 2923, 2851, 1769, 1697, 1604, 1506, 1429, 1249, 1130, 914, 770, 708 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.22 (br s, 1H), 7.37–7.75 (m, 5H), 5.73–5.75 (m, 1H), 5.66–5.69 (m, 2H), 5.02–5.11 (m, 2H), 4.58–4.61 (m, 1H), 2.89 –2.90 (m, 1H), 2.69–2.70 (m, 1H), 2.48–2.49 (m, 1H), 2.16–2.26 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.7, 151.6, 135.2, 132.7, 131.3, 128.8, 128.3, 127.9, 125.3, 117.1, 115.9, 59.8, 48.4, 37.6, 35.4. MS (LR-FAB): *m/z* calculated for $C_{16}H_{17}N_3O_2$ (M+1): 284.1399. Found: (M+1) 284.6529.

4.2.5. Data for compound 7b. Method B. Colorless viscous liquid. Yield=97%. IR (neat) ν_{max}: 3435, 3178, 3064, 2956, 2923, 2850, 1767, 1698, 1609, 1508, 1432, 1250, 1140, 916, 767, 718 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.06 (s, 1H), 7.29–7.50 (m, 5H), 5.74–5.79 (m, 1H), 5.65–5.72 (m, 2H), 4.99–5.09 (m, 2H), 4.65 (s, 2H), 4.48–4.55 (m, 1H), 2.82–2.84 (m, 1H), 2.63–2.72 (m, 1H), 2.34–2.42 (m, 1H), 2.09–2.29 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.7, 154.7, 135.3, 132.7, 128.5, 128.3, 128.2, 127.9, 116.9, 76.5, 64.5, 59.9, 48.4, 43.2, 42.7, 37.7, 35.3. MS (LR-FAB): *m/z* calculated for $C_{17}H_{19}N_3O_2$ (M+1): 298.1477. Found: (M+1) 298.20.

4.2.6. Data for compound 7c. Method B. Colorless viscous liquid. Yield=88%. IR (neat) ν_{max}: 3298, 2932, 1767, 1698, 1484, 1092, 956 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59 (s, 1H), 5.79–5.82 (m, 1H), 5.70–5.73 (m, 2H), 5.04–5.07 (m, 2H), 4.48–4.56 (m, 1H), 3.85 (m, 1H), 2.86 (m, 1H), 2.71–2.74 (m, 2H), 2.65–2.68 (m, 2H), 1.66–1.76 (m, 10H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 155.4, 153.7, 135.7, 133.1, 128.7, 117.3, 60.2, 52.2, 48.8, 38.1, 35.6, 29.9, 29.7, 29.6, 26.1, 25.3. HRMS (EI): *m/z* calculated for $C_{16}H_{23}N_3O_2$: 289.1790. Found: (M^+) 289.1796.

4.2.7. Data for compound 7d. Method B. Colorless viscous liquid. Yield=85%. IR (neat) ν_{max}: 3302, 2982, 1728, 1698, 1396, 1180, 948 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.24–7.49 (m, 4H), 5.67 (m, 1H), 5.61 (m, 2H), 4.93–5.03 (m, 2H), 4.51 (s, 2H), 4.38–4.45 (m, 1H), 3.70 (s, 3H), 2.74 (m, 1H), 2.56–2.64 (m, 1H), 2.26–2.32 (m, 1H), 2.07–2.20 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.9, 153.8, 137.5, 135.1, 133.4, 132.6, 129.1, 128.6, 128.2, 118.1, 60.1, 52.3, 48.3, 42.5, 38.0, 35.1. HRMS (EI): *m/z* calculated for $C_{18}H_{21}N_3O_3$: 327.1583. Found: (M^+) 327. 1536.

4.2.8. Data for compound 7e. Method B. Colorless viscous liquid. Yield=95%. IR (neat) ν_{max}: 3297, 2980, 2932, 1767, 1685, 1458 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.01 (s, 1H), 7.21–7.01 (m, 4H), 5.67–5.73 (m, 1H), 5.60–5.65 (m, 2H), 4.93–5.02 (m, 2H), 4.53 (s, 2H), 4.40–4.46 (m, 1H), 2.75–2.76 (m, 1H), 2.56–2.64 (m, 1H), 2.32–2.34 (m, 1H), 2.25 (s, 3H), 2.02–2.16 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.1, 153.2, 137.9, 135.6, 133.0, 132.9, 129.6, 128.9, 128.6, 117.3, 60.1, 48.8, 42.9, 37.9, 35.7, 21.4. MS (FAB): *m/z* calculated for $C_{18}H_{21}N_3O_2$: 312.1634 (M+1). Found: 312. 21.

4.2.9. Data for compound 7f. Method B. Colorless viscous liquid. Yield=78%. IR (neat) ν_{max}: 3295, 3066, 2854, 1767, 1688, 1492, 1355, 1093, 916 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.82 (s, 1H), 7.25–7.34 (m, 4H), 5.74–5.80 (m, 1H), 5.68–5.72 (m, 2H), 5.01–5.10 (m, 2H), 4.60 (s, 2H), 4.47–4.53 (m, 1H), 2.80 (m, 1H), 2.64–2.73 (m, 1H), 2.33–2.39 (m, 1H), 2.12–2.27 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.8, 153.0, 135.5, 134.2, 131.3, 130.3, 130.1, 129.1, 128.7, 117.4, 60.1, 48.9, 42.8, 37.9, 35.7, 24.3, 13.9. HRMS (EI): *m/z* calculated for $C_{17}H_{18}N_3O_2Cl$ (M+2): 333.1088. Found: (M+2) 333.1092.

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Chemistry of dioxine-annelated cycloheptatriene endoperoxides and their conversion into tropolone derivatives: an unusual non-benzenoid singlet oxygen source

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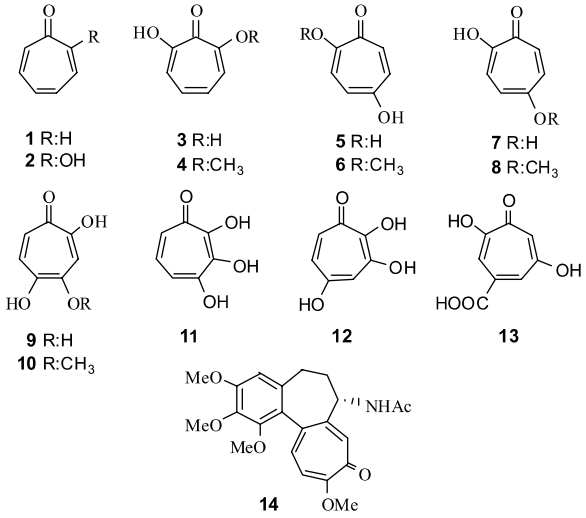
Abstract—The chemistry of two bicyclic endoperoxides, obtained by photooxygenation of 2,3-dihydro-7*H*-cyclohepta[1,4]dioxine and 2,3-dihydro-7*H*-cyclohepta[*b*][1,4]dioxin-7-one was investigated with the aim of synthesizing the respective tropolone derivatives. The reaction of these endoperoxides with base, thiourea and their thermolysis provided the desired tropolone derivatives in high yield. On the other hand, the thermolysis of the endoperoxide derived from 2,3-dihydro-7*H*-cyclohepta[*b*][1,4]dioxin-7-one underwent an unprecedented route and formed parent molecule and singlet oxygen instead of the expected troponoids. The formation mechanisms of all products are discussed.

1. Introduction

Tropone (**1**) and tropolone (**2**) have fascinated organic chemists for well over 50 years. The most significant reason for the interest in ring system tropones is that they represent the key structural element in a wide range of natural products, many of which **3**–**14** display interesting biological activity[1] such as the inhibitor activity of inositol monophosphatase,[2] antibiotic,[3] antitumor,[3a,4] antibacterial activity,[5] and lipoxygenase inhibitor activity.[6]



The synthesis of substituted tropone as well as tropolones continues to be a considerable synthetic challenge. Recently, renewed interest in the ability of colchicine **14** to inhibit tubulin polymerisation has been complemented by special new approaches to tropolone structures.[7] A number of syntheses of tropolone derivatives have been developed.[8] Although the tropones can be oxidized to the tropolones, those approaches suffer from regiochemical control problems when the substituted tropones are used as starting materials. In connection with the development of new synthetic strategies to tropolones, we recently studied the applicability of bicyclic endoperoxides derived by the cycloaddition of singlet oxygen[9] to the appropriate cyclic dienes and subsequently synthesized a new isomer of stipitatic acid **13**[10] and some benzotroponoid systems.[11]

In this paper, we report on the synthesis of new and possible bioactive tropolones via photooxygenation of oxygen-functionalized cycloheptatriene derivatives.

2. Results and discussion

The starting materials **16** and **18** were synthesized as reported in the literature. The thermolysis of tropone

Keywords: Tropone; Tropolone; Endoperoxide; Singlet oxygen; Rearrangement.
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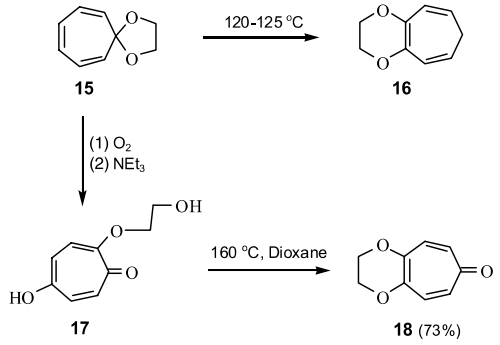
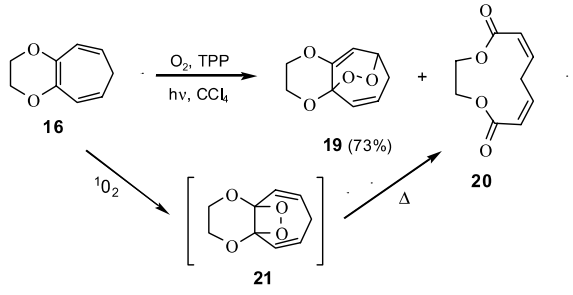
ethylene ketal **15**[12] provided the cycloheptatriene derivative **16**.[13] The photooxygenation of **15**, followed by the reaction of the formed bicyclic endoperoxide with NEt_3 gave the tropolone derivative **17**.[14] The thermolysis of **17** in dioxane resulted in the formation of the starting material **18** (Scheme 1).



Scheme 1.

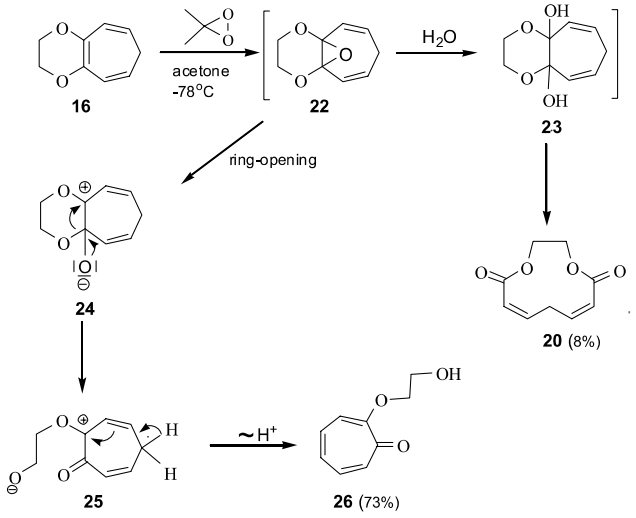
The tetraphenylporphyrin-sensitized photooxygenation of **16** produced the tricyclic endoperoxide **19** in 73% yield (Scheme 2). The sensitized photooxygenation of electron-rich olefins constitutes an effective means of preparing 1,2-dioxetanes through [2+2] cycloaddition.[15] During the photooxygenation reaction of **16** we expected a large amount of dioxetane **21**. Careful inspection of the reaction mixture showed the formation of dilactone **20** in trace amounts, which is a secondary product formed by the cleavage of the initially formed dioxetane **21**. The structural assignments of the products were performed from ^1H and ^{13}C NMR spectra.



Scheme 2.

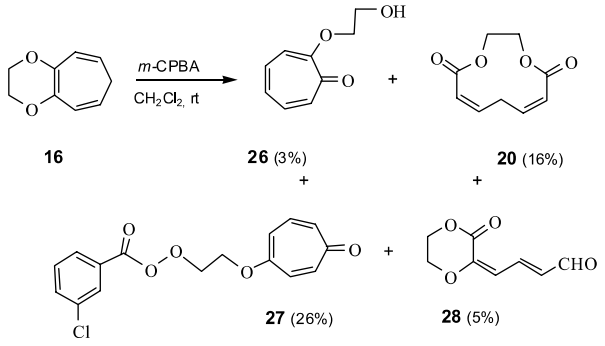
On the other hand, the oxidation of **16** with 3,3-dimethyldioxirane (DMD)[16] in acetone at −78 °C followed by column chromatography gave tropone derivative **26** as the major product as well as dilactone **20** in only 8% yield (Scheme 3). The formation of those products can be rationalized by the following mechanism. The initially formed monoepoxide **22** can undergo two different reactions; (i) forming the diol **23** by the opening of epoxide **22** with water to produce dilactone **20**, and (ii) opening of epoxide **22** to stable oxy-cation **24**, which can be rearranged through the intermediate **25** to the stable tropone **26**[13b] (Scheme 3).

For the further conversion of cycloheptatriene derivative **16** to tropolone derivatives, it was oxidized with *m*-chloroperbenzoic acid (*m*-CPBA). The reaction of **16** with



Scheme 3.

m-CPBA at room temperature in an ultrasonic bath gave four products; two tropolone derivatives **26**[13] and **27**, where *m*-CPBA was incorporated into the molecule, dilactone **20** and an unusual rearranged product **28** in yields of 3, 26, 16 and 5% yields, respectively (Scheme 4). Full characterization of all of the formed products was accomplished by means of detailed NMR analysis.

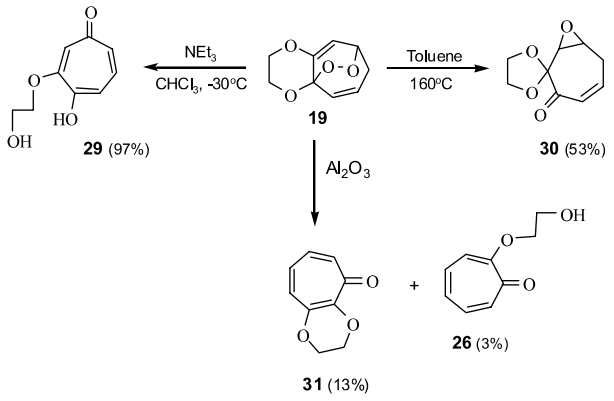


Scheme 4.

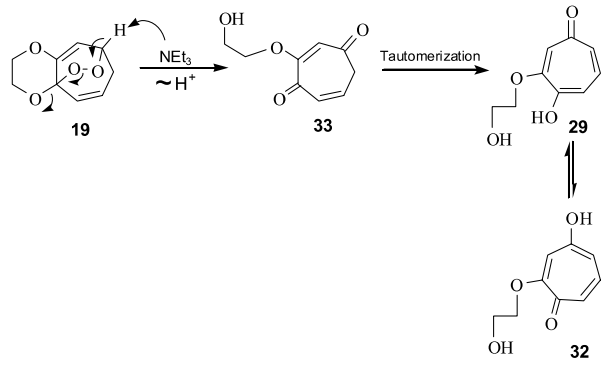
Base-catalyzed decomposition of unsaturated bicyclic peroxides generally results in the formation of hydroxy ketones.[9,17] Application of this reaction to the cycloheptatriene endoperoxides opens up an entry to the synthesis of troponoid compounds.[8g,10,11]

Treatment of endoperoxide **19** with a catalytic amount of triethylamine in dichloromethane at −30 °C provided a new tri-oxygenated tropolone **29** as the sole product in 97% yield (Scheme 5). The unsymmetrical tropolone derivative **29** can be in equilibrium with its tautomer **32** (Scheme 6). In order to determine, which is the most stable tautomer we undertook some AM1 calculations. The results show that the tautomer **29** has 0.48 kcal/mol lower heat of formation than the tautomer **32**. Therefore, the structure was tentatively assigned as **29**.

For the conversion of **19** to **29** we propose the mechanism depicted in Scheme 6. The abstraction of the bridgehead proton in **19** by the amine catalyst with the concomitant



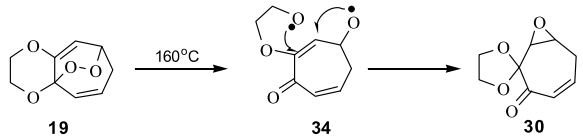
Scheme 5.



Scheme 6.

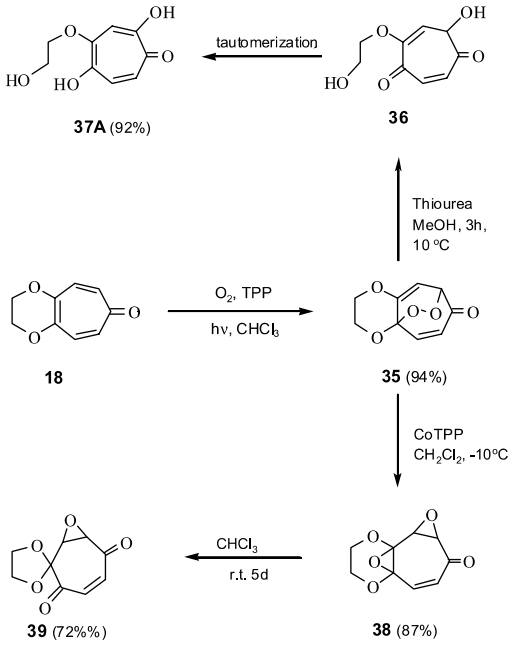
cleavage of O–O bond followed by ring opening can generate the unsaturated alkoxydiketone **33**, which could then afford substituted tropolone **29** by tautomerization (Scheme 6). Furthermore, we noticed that the endoperoxide **19** was partly rearranged during column chromatography on aluminum oxide to give troponoids **31** and **26** in 13 and 3% yields, respectively (Scheme 5).

Thermal decomposition of endoperoxides generally results in the formation of bisepoxides.[9,18] When endoperoxide **19** was heated to 160 °C in toluene in a sealed tube for 6 h, the epoxyketal **30** was isolated after chromatography on a florisil column in 53% yield (Scheme 5). Full characterization of the product was accomplished by means of ^{1}H and ^{13}C NMR spectra. No trace of any bisepoxide was detected. The formation of this product can be rationalized by the following mechanism. An initial cleavage of the peroxide linkage to diradical **34**, followed by rearrangement forms the product **30** (Scheme 7).



Scheme 7.

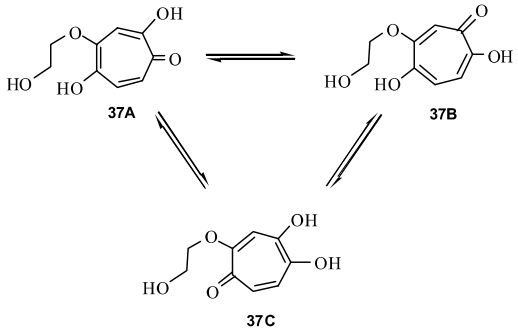
The tetraphenylporphyrin-sensitized photooxygenation of the cycloheptatriene derivative **18** produced only tricyclic endoperoxide **35** in 94% yield (Scheme 8). The expected [2+2] cycloaddition product was unformed, which may be



Scheme 8.

attributed to the reduced electron density caused by the carbonyl group.

It is well established that thiourea reduces the oxygen–oxygen bond to give a diol.[9] Recently, we showed that the substituted cycloheptatriene endoperoxide can easily form troponoid systems upon treatment with thiourea.[10,11a] Therefore, the bicyclic endoperoxide **35** was reacted with thiourea in methanol at 10 °C and the desired tetraoxygenated tropolone **37** was obtained in 94% yield (Scheme 8). The structure of **37** was characterized by its ^{1}H NMR spectrum. Vicinal olefinic protons (H_5 and H_6) of **37** resonate as an AB-system. The A-part of the AB-system appears at δ 7.08 ppm as a doublet ($J=11.3$ Hz) and the B-part at δ 6.95 ppm again as doublet, whereas the olefinic proton H_3 resonates at δ 7.04 ppm as a singlet. Its nine-line ^{13}C NMR spectrum supports the suggested unsymmetrical structure. For this compound, three different tautomers (**37A**, **37B** and **37C**) can be written (Scheme 9).



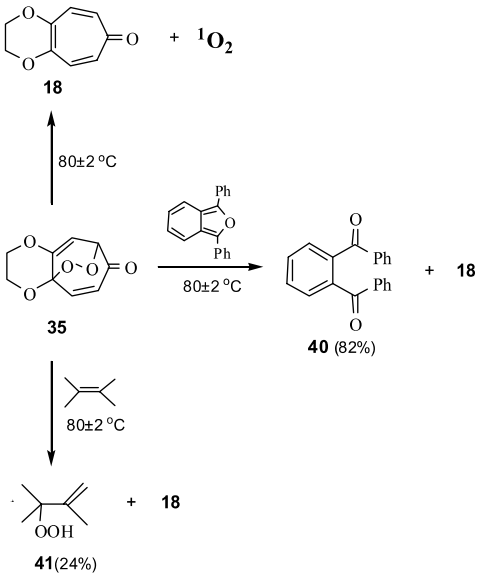
Scheme 9.

In order to find the most stable tautomer we carried out AM1 calculations for the three possible tautomers and found that the isomer **37A** is thermodynamically about 2.76 and 5.96 kcal/mol more stable than the isomers and **37C** and

37B, respectively. Therefore, the structure **37A** was assigned tentatively.

Foote et al.[19] and our group[20] have reported that cobalt *meso*-tetraphenylporphyrin (CoTPP) promotes the rearrangement of the bicyclic endoperoxides to the corresponding bis-epoxide with *syn*-configuration. In addition to this previously observed reaction of CoTPP we further demonstrated that some bicyclic endoperoxides derived from cycloheptatriene can be converted into tropolone derivatives upon treatment with CoTPP.[10] For that reason, endoperoxide **35** was treated with a catalytic amount of CoTPP at a low temperature. The corresponding bisepoxide **38** was isolated in 87% yield (Scheme 8). It was noticed that the bis-epoxide **38** was unstable at room temperature and was rearranged smoothly to epoxyketal **39** by way of standing at room temperature over a period of 5 days.

It is well known that benzenoid aromatic hydrocarbons such as anthracene, rubrene, tetracene, and substituted naphthalanes[21] undergo photosensitized autoxidation to form bicyclic endoperoxides. These peroxides undergo dissociation on heating to regenerate singlet oxygen and the parent aromatic compounds. The ease of oxygen release from these systems depends on the polycyclic aromatic system and the nature of the substituents. During the thermal reaction of endoperoxide **35** we observed that it loses oxygen and forms the parent tropone **18** as the sole product (Scheme 10). In order to test whether the formed oxygen is singlet or molecular oxygen, the thermolysis reaction of endoperoxide **35** was carried out in the presence of the known singlet oxygen acceptors, such as 1,3-diphenylisobenzofuran (DBI)[22] and tetramethylethylene. The decomposition of **35** in the presence of tetramethylethylene gave the ene-product **41**, whereas the DBI formed **40** as the trapping product.



Scheme 10.

3. Conclusions

In conclusion, we synthesized two bicyclic endoperoxides by the photooxygenation reaction of two different dioxine-annelated cycloheptatrienes. The reaction of these endoperoxides with base, thiourea and their thermolysis provided an entry to the synthesis of new tropolone derivatives in high yield. Furthermore, we have studied their oxidation and thermal reactions. The tricyclic endoperoxide **35** obtained by the photooxygenation of **18** showed an unprecedented behavior and produced singlet oxygen and the parent tropone upon thermolysis. To the best of our knowledge it is the first report where a non-benzonoid system generative singlet oxygen. The results described here should lead to the synthesis of new tropon and tropolone derivatives upon photooxygenation of highly oxygenated cycloheptatriene derivatives.

4. Experimental

4.1. General

Melting points are uncorrected. Infrared spectra were obtained from solution in 0.1 mm cells or KBr pellets on a regular instrument. The ^1H and ^{13}C NMR spectra were recorded on 200 (50) MHz spectrometers. Apparent splittings are given in all cases. Column chromatography was performed on silica gel (60-mesh, Merck). TLC was carried out on Merck 0.2 mm silica gel 60 F_{254} analytical aluminum plates. All substances reported in this paper are in their racemic form.

4.1.1. Synthesis of 2,3-dihydro-7*H*-cyclohepta[1,4]-dioxine (16). The tropone ethylene ketal **15**[12] (3.0 g, 0.02 mol) was dissolved in cyclohexane (3 mL) and heated to 123±2 °C for 16 days in a sealed tube. After evaporation of the solvent the residue was distilled to give **16**[13] (2.04 g, 68%, pale yellow liquid). ^1H NMR (200 MHz, $CDCl_3$): δ 5.99 (d, A-part of, AX system, $J_{5,6}=J_{8,9}=9.8$ Hz, 2H, H_5 and H_9), 5.27 (dt, X-part of, AX system, $J_{5,6}=J_{8,9}=9.8$ Hz, $J_{6,7}=J_{8,7}=6.9$ Hz, 2H, H_6 and H_8), 4.16 (s, 4H, OCH_2), 2.33 (t, $J_{6,7}=J_{8,7}=6.9$ Hz, 2H, H_7). ^{13}C NMR (50 MHz, $CDCl_3$): δ 139.1, 123.4, 118.5, 64.4, 28.0.

4.1.2. Synthesis of 2,3-dihydro-cyclohepta[1,4]dioxin-7-one (18). Tropolone **17**[14] (300 mg, 1.65 mmol) was dissolved in dioxane (5 mL) and heated to 160 °C for 48 h in a sealed tube. After evaporation of the solvent the residue was filtered through silica gel column (30 g) eluting with *n*-hexane–ethyl acetate (6/4) to give **18**[14a] (197 mg, 73%, pale yellow crystals), mp 150–151 °C from methylene chloride/*n*-hexane 1:1 (lit. mp 151–152 °C).[14a] ^1H NMR (200 MHz, $CDCl_3$): δ 7.03 (AA′ part of AA′BB′ system, 2H, H_5 and H_9), 6.82 (BB′ part of AA′BB′ system, 2H, H_6 and H_8), 4.24 (s, 4H, OCH_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 187.2, 146.4, 136.1, 135.4, 65.8.

4.1.3. Photooxygenation of 2,3-dihydro-7*H*-cyclohepta[1,4]dioxine (16). The cycloheptatriene derivative **16**[13a] (1.0 g, 6.67 mmol) and tetraphenylporphyrin (10 mg) were dissolved in 200 mL of CCl_4. The solution was then irradiated with a projection lamp (500 W) while a slow stream of dry oxygen was passed through the solution at 10 °C. After 1.5 h, the solvent was evaporated (20 °C). The crystallization of the residue from CH_2Cl_2–ether (1/4) provided endoperoxide **19** as colorless crystals (886 mg,

73%, mp 97–98 °C). *(4aR(S),8S(R))-2,3,7,8-Tetrahydro-4a,8-epidioxycyclohepta[b][1,4]-dioxine* (**19**): ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.95 (ddd, A-part of AB system. $J_{5,6}=12.2$ Hz, $J_{5,7}=3.0$ Hz, $J_{5,7'}=1.8$ Hz, 1H, H_5), 5.65 (bddd, B-part of AB system, $J_{5,6}=12.2$ Hz, $J_{6,7}=4.7$ Hz, $J_{6,7'}=3.8$ Hz, 1H, H_6), 5.39 (d, $J_{8,9}=7.7$ Hz, 1H, H_9), 4.87 (m, 1H, H_8), 4.34–3.79 (m, 4H, OCH_2), 2.89 (br d, A-part of AB system, $J_{7,7'}=19.5$ Hz, 1H, H_7), 2.35 (br d, B-part of AB system, $J_{7,7'}=19.5$ Hz, 1H, $H_{7'}$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 155.3, 133.7, 130.6, 101.0, 99.6, 79.4, 68.3, 63.6, 38.0. MS (EI, 70) *m/z* 182 (M^+, 10), 164 (8), 154 (6), 139 (12), 125 (66), 112 (96), 81 (100), 68 (74). Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.20; H, 5.46.

The ^{1}H NMR spectral studies of the residue obtained after crystallization showed the presence of dilactone **20**, which was formed in about 1–2% (for spectral data see Section 4.1.4).

4.1.4. Oxidation of 16[13a] with 3,3-dimethyl-dioxirane (DMD) To a dioxirane–acetone solution (8.5 mL, 0.08 M) synthesized as described in the literature[16] was added a solution of **16** (100 mg, 0.67 mmol) in acetone (10 mL) over a period of 10 min at −78 °C. The reaction mixture was allowed to come to room temperature during 1 h. After additional stirring for 1 h at room temperature the solvent was evaporated and the residue was chromatographed on a silica gel (30 g) column eluting with *n*-hexane–ethyl acetate (9/1). The first fraction was identified as dilactone **20** (9 mg, 8%). *1,4-Dioxacycloundeca-6,9-diene-5,11-dione* (**20**): ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.15 (dt, A-part of AB system, $J_{6,7}=J_{9,10}=11.7$ Hz, $J_{7,8}=J_{8,9}=8.4$ Hz, 2H, H_7 and H_9), 5.89 (dt, B-part of AB system, $J_{6,7}=J_{9,10}=11.7$ Hz, $J_{6,8}=J_{10,8}=1.1$ Hz, 2H, H_6 and H_{10}), 4.48 (s, 4H, OCH_2), 3.45 (tt, $J_{7,8}=J_{8,9}=8.4$ Hz, $J_{6,8}=J_{10,8}=1.1$ Hz, 2H, Hg). ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.0, 140.6, 125.0, 63.5, 31.4. IR (KBr, cm^{-1}): 3055, 3030, 2979, 2953, 2928, 1728, 1446, 1396, 1294, 1268, 1243, 1217, 1166, 1064, 911, 834. Anal. MS (EI, 70 eV) *m/z* 138 (M^+-CO_2, 6), 122 (8), 94 ($M^+-2\times CO_2$, 100), 82 (9). Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.31; H, 5.72.

The second fraction was identified as **26** (81 mg, 73%), mp 80–81 °C, (lit. mp[13] 83–84 °C). *2-(2-Hydroxyethoxy)-cyclohepta-2,4,6-trien-1-one* (**26**): [13] ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.34–7.05 (m, 5H, H_3, H_4, H_5, H_6 and H_7), 4.90 (m, 1H, OH), 4.15 (A_2-part of A_2B_2 system, 2H, OCH_2), 4.05 (B_2-part of A_2B_2 system, 2H, OCH_2). ^{13}C NMR ($CDCl_3$): δ 182.8, 166.9, 139.1, 139.0, 135.0, 130.6, 116.7, 73.2, 62.4. IR (KBr, cm^{-1}): 3361, 2953, 2876, 1626, 1603, 1568, 1475, 1290, 1279, 1209, 1094, 1024, 781, 723.

4.1.5. Oxidation of 16 with *m*-chloroperbenzoic acid (*m*-CPBA). To a solution of **16** (360 mg, 2.40 mmol) in methylene chloride (20 mL) was added Na_2CO_3 (1.27 g, 12 mmol) and *m*-CPBA (426 mg, 2.47 mmol). The resulting mixture was stirred for 4 h at room temperature in an ultrasound bath. The precipitate was filtered and the solvent evaporated to dryness. The residue was chromatographed on silica gel (100 g) eluting with *n*-hexane–ethyl acetate (8/2). The first fraction was identified as **27** (200 mg, 26%, mp 105–106 °C from methylene chloride–*n*-hexane 1/2). *2-[(5-Oxocyclohepta-1,3,6-trien-1-yl)oxy]ethyl 3-chlorobenzenecarboperoxoate* (**27**): ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.03 (m, 1H, $H_{2'}$), 7.92 (br d, $J_{5'6'}=7.6$ Hz, 1H, $H_{6'}$), 7.55 (br d, $J_{4',5'}=7.6$ Hz, 1H, $H_{4'}$), 7.40 (t, $J_{4',5'}=J_{5',6'}=7.6$ Hz, 1H, $H_{5'}$), 6.48 (bdd, A-part of AB system, $J_{6,7}=12.1$ Hz, $J_{2,7}=4.0$ Hz, 1H, H_7), 6.29 (dd, A-part of AB system, $J_{3,4}=11.4$ Hz, $J_{2,3}=5.1$ Hz, 1H, H_3), 6.04 (br d, B-part of AB system, $J_{3,4}=11.4$ Hz, 1H, H_4), 5.87 (d, B-part of AB system, $J_{6,7}=12.1$ Hz, 1H, H_6), 5.17 (br d, $J_{2,3}=5.1$ Hz, 1H, H_2). 4.52 (A_2-part of A_2B_2 system, 2H, OCH_2), 4.37 (B_2-part of A_2B_2 system, 2H, OCH_2). ^{13}C NMR (APT, 50 MHz, $CDCl_3$): δ 168.7, 164.7, 153.7, 141.3 (−)(C_7), 136.7, 135.8 (−), 132.5, 132.1 (−), 131.9 (−), 130.3 (−), 129.7 (−)(C_4), 128.0 (−)(C_3), 125.5 (−)(C_6), 99.3 (−)(C_2), 69.7 (OCH_2), 65.2 (OCH_2). IR (KBr film, cm^{-1}): 3029, 2978, 1753, 1707, 1429, 1417, 1325, 1255, 1198, 1094, 1059, 1024, 885. MS (EI, 70 eV) *m/z* 320 (M^+, 5), 232 (5), 183 (62), 139 (100), 111 (40), 75 (25%). Anal. Calcd for $C_{16}H_{13}ClO_5$: C, 59.92; H, 4.09. Found: C, 59.80; H, 4.06.

The second fraction was identified as dilactone **20** (70 mg, 16%). The elution of the column was continued with ethyl acetate–methanol (98/2) and as the third fraction; the aldehyde **28** was isolated (20 mg, 5%, imp. 128–129 °C from methylene chloride/*n*-hexane 1:1). *(2E,4E)-4-(3-Oxo-1,4-dioxan-2-ylidene)but-2-enal* (**28**): ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.63 (d, $J_{1,2}=7.8$ Hz, 1H, H_1), 7.44 (dd, $J_{2,3}=15.6$ Hz, $J_{3,4}=11.7$ Hz, 1H, H_3), 6.73 (d, $J_{3,4}=11.7$ Hz, 1H, H_4), 6.33 (dd, $J_{2,3}=15.6$ Hz, $J_{1,2}=7.8$ Hz, 1H), 4.58 (AA'-part of $AA'BB'$ system, 2H, OCH_2), 4.33 (BB'-part of $AA'BB'$, 2H, OCH_2). ^{13}C NMR (APT) (50 MHz, $CDCl_3$): δ 195.1, 160.8, 147.1, 143.8, 136.3, 116.8, 68.6, 66.0. IR (KBr film, cm^{-1}): 3080, 2978, 2953, 2825, 1778, 1753, 1728, 1676, 1472, 1421, 1344, 1319, 1293, 1268, 1242, 1217, 1114, 1089. MS (EI, 70 eV) *m/z* 168 (M^+, 19), 139 (41), 110 (13), 96 (95), 83 (19), 68 (100%). The last fraction was identified as tropolone **26** (12 mg, 3%).

4.1.6. Reaction of the endoperoxide 19 with NEt_3. To a solution of endoperoxide **19** (200 mg, 1.10 mmol) in 10 mL of CH_2Cl_2 at −30 °C, one drop of freshly distilled triethylamine was added. The mixture was then stirred at −30 °C for 3.5 h and to the residue ether (10 mL) was added to precipitate the product. The formed product was separated by filtration and crystallized from hot water to give pure **29** (194 mg, 97%, mp 223–224 °C). *4-Hydroxy-3-(2-hydroxyethoxy)cyclohepta-2,4,6-trien-1-one* (**29**): ^{1}H NMR (200 MHz, CD_3OD) 7.32 (dd, A-part of AB system and A-part of AX system, $J_{5,6}=11.7$ Hz, $J_{6,7}=10.4$ Hz, 1H, H_6), 6.88 (d, $J_{2,7}=2.3$ Hz, 1H, H_2), 6.86 (d, B-part of AB system, $J_{5,6}=11.7$ Hz, 1H, H_5), 6.62 (dd, X-part of AX system, $J_{6,7}=10.4$ Hz, $J_{2,7}=2.3$ Hz, 1H, H_7), 4.09 (A_2-part of A_2B_2 system, 2H, OCH_2), 3.96 (B_2-part of A_2B_2 system, 2H, OCH_2). ^{13}C NMR (CD_3OD): 177.4, 173.4, 166.7, 141.8, 126.5, 119.5, 115.8, 74.2, 62.8. IR (KBr film, cm^{-1}): 3464, 3004, 2979, 2953, 2927, 2570, 1600, 1548, 1523, 1446, 1421, 1191, 1165, 936. MS (EI, 70 eV) *m/z* 182 (M^+, 12), 154 (18), 138 (3), 125 (66), 110 (100), 83 (17). Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.39; H, 5.63.

4.1.7. Reaction of endoperoxide 19 with Al_2O_3. A solution of endoperoxide **19** (200 mg, 1.10 mmol) in 5 mL of $CHCl_3$ was loaded to an aluminum oxide column

(30 g, neutral, activity 3) prepared with hexane, and the top of the column was closed for 30 min. After a total waiting time of 30 min, the top of the column was opened and elution was continued with *n*-hexane–ethyl acetate (4/6) to give **31** as pale yellow crystals (23 mg, 13%, mp 98 °C from methylenechloride–*n*-hexane (1/2). Later, the elution was continued with ethyl acetate and methanol (4:1) to give **26**[13] as pale yellow crystals (6 mg, 3%). *2,3-Dihydro-5H-cyclohepta[b][1,4]dioxin-5-one* (**31**): ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.95–6.84 (m, 3H, H_7, H_8 and H_9 (or H_6)), 6.61 (dd, $J=8.8$, 1.7 Hz, 1H, H_9 (or H_6)), 4.30 (br s, 4H, OCH_2). ^{13}C NMR ($CDCl_3$): δ 186.4, 155.9, 154.7, 139.4, 134.4, 128.3, 118.5, 65.9, 65.7. IR (KBr, cm^{-1}): 3055, 2978, 2927, 1651, 1548, 1472, 1425, 1293, 1217, 1191, 1089, 885, 808. MS (EI, 70 eV) *m/z*) 164 (M^+, 9), 136 (65), 80 (100), 52 (65%). Anal. Calcd for $C_9H_8O_3$: C, 65.85; H, 4.91. Found: C, 66.02; H, 4.95.

4.1.8. Thermolysis of endoperoxide 19. The endoperoxide **19** (160 mg, 0.88 mmol) was dissolved in toluene (5 mL) and heated to 160 °C for 6 h in a sealed tube. After evaporation of the solvent the residue was filtered through florisil column (30 g) eluting with *n*-hexane–ethyl acetate (4/1) to give **30** (85 mg, 53%, pale yellow crystals, mp 94–95 °C from ether/*n*-hexane 1:1). *(7R(S),8R(S))-7,8-Epoxy-1,4-dioxaspiro[4.6]undec-10-en-6-one* (**30**): ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.67 (m, 2H, H_{10} and H_{11}), 4.17–3.95 (m, 4H, OCH_2), 3.74 (d, A-part of AB system, $J_{7,8}=$ 4.8 Hz, 1H, H_7), 3.54 (dd, B-part of AB system, $J_{7,8}=$ 4.8 Hz, $J_{8,9}=4.5$ Hz, 1H, H_8), 3.02 (ddt, A-part of AB system, $J_{9,9'}=19.2$ Hz, $J_{8,9}=J_{9,10}=4.5$ Hz, $J_{9,11}=1.9$ Hz, 1H, H_9), 2.76 (br d, B-part of AB system, $J_{9,9'}=19.2$ Hz, 1H, $H_{9'}$). ^{13}C NMR ($CDCl_3$): δ 200.6, 129.6, 128.4, 107.5, 68.3, 67.4, 59.2, 54.8, 28.7. IR (KBr film): 3029, 2998, 2985, 2896, 2883, 2870, 1727, 1446, 1395, 1217, 1191, 1089, 1012, 961. MS (EI, 70 eV) *m/z* 183 (M^+, 1), 125 (19), 113 (43), 82 (69), 68 (56), 53 (100%). Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.14; H, 5.48.

4.1.9. Photooxygenation of 2,3-dihydro-7*H*-cyclohepta[*b*][1,4]dioxin-7-one (18). The reaction was carried out according to the above mentioned procedure (Section 4.1.2) by using 200 mg (1.22 mmol) of **18**[14] and TPP (10 mg) in 200 mL of chloroform. After 45 min irradiation, the solvent was evaporated and the ^{1}H NMR analysis of residue indicated the formation of the endoperoxide **35** as the sole product. The recrystallization of the residue from CH_2Cl_2–ether (1/3) gave the endoperoxide **35** as colorless crystals (225 mg, 94%, mp 106–107 °C). *(4aR(S),8R(S))-2,3-Dihydro-4a,8-epidioxycyclohepta[b][1,4]-dioxin-7(8H)-one* (**35**): ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.80 (d, A-part of AX system, $J_{5,6}=11.4$ Hz, 1H, H_5), 5.93, (dd, B-part of AX system, $J_{5,6}=11.4$ Hz, $J_{6,8}=1.9$ Hz, 1H, H_6), 5.52 (d, A-part of AX system, $J_{8,9}=8.1$ Hz, 1H, H_9), 5.00 (dd, X-part of AX system, $J_{8,9}=8.1$ Hz, $J_{6,8}=1.9$ Hz, 1H, H_8), 4.41–3.94 (m, 4H, OCH_2). ^{13}C NMR ($CDCl_3$): δ 195.4, 159.0, 147.5, 130.3, 102.6, 97.0, 89.12, 68.3, 64.5. IR (KBr, film): 3080, 3055, 2978, 2953, 2927, 1728, 1702, 1676, 1472, 1395, 1370, 1344, 1293, 1268, 1165, 1013, 859. MS (EI, 70 eV) *m/z* 196 (M^+, 2), 164 (M^+-O_2, 14), 137 (28), 83 (38), 69 (48), 54 (100%). Anal. Calcd for $C_9H_8O_5$: C, 55.11; H, 4.11. Found: C, 55.13; H, 4.18.

4.1.10. Reaction of endoperoxide 35 with thiourea. The endoperoxide **35** (100 mg, 0.51 mmol) was dissolved in CH_3OH (10 mL) at 10 °C. A solution of thiourea (53 mg, 0.69 mmol) in CH_3OH (3 mL) was added dropwise over 1 min, then the solution was stirred 3 h at room temperature. The residue was filtered and the solvent was reduced to half of its volume. After standing in freezer for one night, the formed crystals were characterized as tropolone **37A** (93 mg, 92%, pale yellow crystals, mp 185–186 °C from methanol). *2,5-Dihydroxy-4-(2-hydroxyethoxy)cyclohepta-2,4,6-trien-1-one* (**37**): ^{1}H NMR (200 MHz, CD_3OD): δ 7.08 (d, A-part of AB system. $J_{6,7}=11.3$ Hz, 1H, H_6), 7.04 (s, 1H, H_3), 6.95 (d, B-part of AB system, $J_{6,7}=1.3$ Hz, 1H, H_6), 4.20 (A_2-part of A_2B_2 system, 2H, OCH_2), 3.98 (B_2-part of A_2B_2 system, 2H, 2H, OCH_2). ^{13}C NMR (50 MHz, CD_3OD): 176.7, 162.2, 161.21, 154.3, 119.9, 117.6, 115.7, 74.4, 62.7. IR (KBr, cm^{-1}): 3423, 3269, 2436, 1603, 1549, 1472, 1425, 1263, 1197, 1078, 916, 870. MS (EI, 70 eV) *m/z* 199 (M^+, 5), 154 (10), 127 (52), 96 (16), 70 (24), 64 (100), 53 (39%). Anal. Calcd for $C_9H_{10}O_5$: C, 54.55; H, 5.09. Found: C 54.01 H: 5.60.

4.1.11. CoTPP-catalyzed reaction of endoperoxide (35). To a magnetically stirred solution of endoperoxide **35** (100 mg, 0.51 mmol) in CH_2Cl_2 (10 mL) at −10 °C was added cobalt-*meso*-tetraphenylporphyrin (C0TPP) (20 mg) in portions. The mixture was stirred for 2 min. The solvent was then evaporated. The ^{1}H NMR spectral analysis of the residue indicated the formation of bisepoxide **38** (87 mg, 87%, colorless crystals from methylenechloride/ether 1:1, mp 105–106 °C). *2,3,(7aR(S)),(8aS(R))-Tetra-hydro-7H-(4aR(S)),8b(S(R))-epoxyoxireno[3,4]cyclohepta[1,2-b][1,4]dioxin-7-one* (**38**): ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.38 (d, A-part of AB system, $J_{5,6}=11.5$ Hz, 1H, H_5), 5.89 (dd, B-part of AB system, $J_{5,6}=11.5$ Hz, $J_{7a,6}=1.8$ Hz, 1H, H_6), 3.98 (m, 2H, OCH_2), 3.78 (d, A-part of AB system, $J_{7a,8a}=$ 4.3 Hz, 1H, H_{8a}), 3.74 (m, 2H, OCH_2), 3.68 (dd, B-part of AB system, $J_{7a,8a}=4.3$ Hz, $J_{7a,6}=1.8$ Hz, 1H, H7a). ^{13}C NMR (50 MHz, $CDCl_3$): δ 199.3, 132.1, 129.8, 86.1, 84.6, 64.3, 63.4, 61.6, 56.4. IR (KBr, cm^{-1}): 2961, 2899, 1641, 1449, 1410, 1317, 1171, 1101, 1032, 909. Anal. Calcd for $C_9H_8O_5$: C, 55.11; H, 4.11. Found: C, 55.20; H, 4.01.

4.1.12. The formation of 39 from 38. Bisepoxide **38** (40 mg, 0.20 mmol) was dissolved in 0.5 mL of $CDCl_3$ and its rearrangement was followed by the ^{1}H NMR spectroscopy. After 5 days, the bisepoxide was completely rearranged to epoxy ketal **39** at room temperature. The residue was recrystallized from methylene chloride–ether (2/1) to give pure **39** (29 mg, 72%, colorless crystals mp 97–98 °C). *(7S(R),8R(S))-7,8-Epoxy-1,4-dioxaspiro[4.6]undec-10-ene-6,9-dione* (**39**): ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.25 (d, A-part of AB system, $J_{10,11}=12.9$ Hz, 1H, H_{11}), 6.00 (dd, B-part of AB system, $J_{1,11}=12.9$ Hz, $J_{8,10}=1.8$ Hz, 1H, H_{10}), 4.28–3.98 (m, 4H, OCH_2), 4.01 (d, A-part of AB system, $J_{7,8}=5.0$ Hz, 1H, H_7), 3.88 (dd, B-part of AB system, $J_{7,8}=5.0$ Hz, $J_{8,10}=1.8$ Hz, 1H, H_8). ^{13}C NMR (50 MHz, $CDCl_3$): δ 197.7, 196.8, 140.1, 129.7, 106.3, 69.0, 67.9, 58.8, 58.1. IR (KBr, cm^{-1}): 2976, 2902, 1730, 1702, 1611, 1384, 1173, 1030, 950, 782. MS (EI, 70 eV) *m/z* 196 (M^+, 1), 167 (3), 140 (16), 126 (22), 114 (19), 99 (77), 86 (47), 69 (50), 54 (100%). Anal. Calcd for $C_9H_8O_5$: C, 55.11; H, 4.11. Found: C, 54.95; H, 4.05.

4.1.13. Thermolysis of endoperoxide 35. Endoperoxide **35** (104 mg, 0.53 mmol) was dissolved in toluene (10 mL) and heated to 80±2 °C for 2 days in a sealed tube. After evaporation of the solvent, the ^{1}H NMR spectrum of the residue showed the formation of **18** as the sole product in quantitative yield. (104 mg, 100%).

4.2. Thermolysis of endoperoxide 35 in the presence of DBI. Endoperoxide **35** (200 mg, 1.02 mmol) and 1,3-diphenyl-isobenzofuran (DBI) (551 mg, 2.04 mmol) were dissolved in anhydrous benzene (10 mL) and heated to 80± 2 °C for 2 days in a sealed tube. After evaporation of the solvent the residue was chromatographed on silica gel (20 g) eluting with *n*-hexane–ethyl acetate (9/1). The first fraction was identified as diketone **40** (240 mg, 82%).[21a] Further elution with hexane–ethyl acetate (1/1) gave the tropone **18** (150 mg, 90%) as the second product.

4.3. Thermolysis of endoperoxide in the presence of 2,3-dimethyl-but-2-ene. The endoperoxide **35** (200 mg, 1.02 mmol) and 2,3-dimethyl-but-2-ene (172 mg, 2.04 mmol) in 10 mL of anhydrous benzene was reacted in a sealed tube as described above. The ^{1}H NMR analysis of the residue showed the formation of the hydroperoxide **41**[21a] in 24% yield and tropone **18** in 90% yield.

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A general and efficient synthesis of 3,6-diazabicyclo[3.2.1]octanes

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Abstract—A convenient and efficient synthesis of N^6-substituted 3,6-diazabicyclo[3.2.1]octanes (**6a–c**) has been achieved starting from suitably substituted lactams, which were converted to nitroenamines followed by reductive cyclization to afford 3,6-diazabicyclo[3.2.1]-octane-2-ones in good yields. These bicyclic lactams were then reduced to the corresponding 3,6-diazabicyclo[3.2.1]octanes and converted to the required N^3,N^6-disubstituted 3,6-diazabicyclo[3.2.1]octanes (**7a–h**), which were screened for α_1-adrenoceptors antagonistic activities.

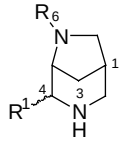
1. Introduction

Lactams have been the subject of much study in this laboratory for creation of molecular diversity, a useful source of leads for potential bioactive agents/intermediates,[1,2] through conversion to reactive intermediates such as lactim ethers, lactim thioethers and lactam acetals, which undergo facile reaction with both nucleophiles and electrophiles and also with bifunctional reagents. In our studies directed to the design of conformationally constrained prototypes incorporating the essential structural features of important pharmacophores,[3] we were interested in the synthesis of 3,6-diazabicyclo[3.2.1]octanes (**6**). A literature survey revealed that 6-methyl-3,6-diazabicyclo[3.2.1]octane **6a** (Fig. 1) has been reported once as a conformationally rigid ethylenediamine systems from 2-azabicyclo[2.2.1]hept-5-ene via ozonolysis of the double bond to a dialdehyde followed by reductive amination using benzylamine.[4] But this method has several limitations: (a) ozonolysis is not a very convenient reaction to carry out, (b) reductive amination was carried out in presence of sodium cyanoborohydride, which during workup generate hydrogen cyanide gas, and (c) poor yields (18–40%). In this paper, we wish to report a convenient and efficient synthesis of 3,6-diazabicyclo[3.2.1]octanes from readily available 5-oxopyrrolidine-3-carboxylic acid methyl ester. This method also provides an easy access to the substitution at the N-3, N-6 and C-4 centre.

2. Results and discussion

A retrosynthetic analysis of compound **6** (Scheme 1) indicated the possibility of constructing 3,6-diazabicyclo[3.2.1]octanes ring through reductive cyclization of a nitroenamine of type II, which could in turn be obtained from lactam I, by activation of the amide group followed by condensation with nitroalkane.

1-Methyl-5-oxopyrrolidine-3-carboxylic acid methyl ester **1a** and 1-(2-methoxyphenyl)-5-oxopyrrolidine-3-carboxylic acid methyl ester **1b**, prepared from itaconic acid following



6a; R = Me, R^1 = H
6b; R = R^1 = Me
6c; R = 2-$OMeC_6H_4$, R^1 = H

Figure 1.

Keywords: 3,6-Diazabicyclo[3.2.1]octanes; Lactams; Itaconic acid; Nitroenamine; Reductive cyclization; RBx 2258.
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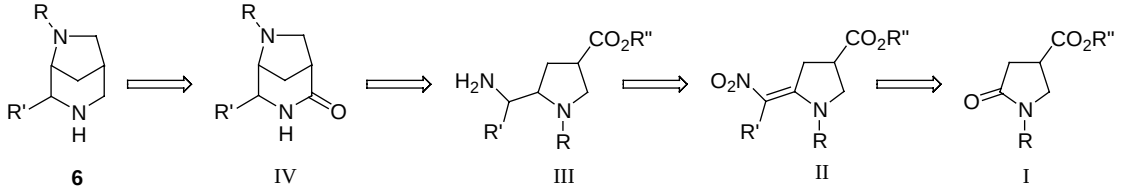
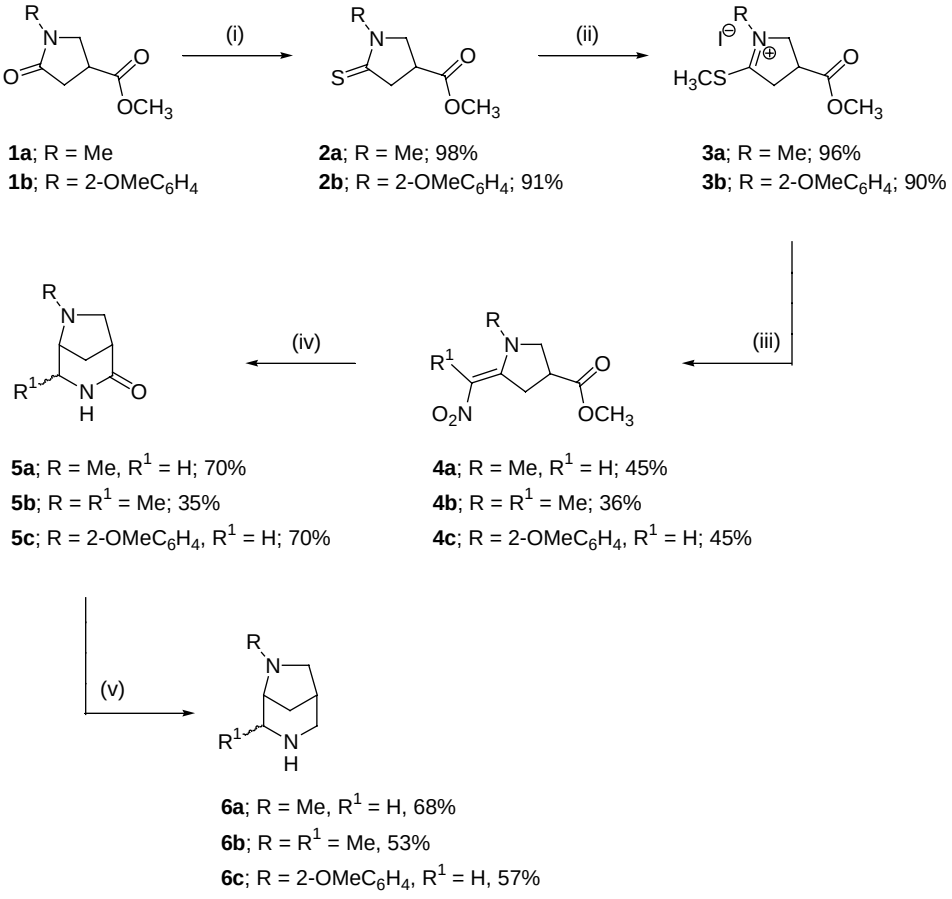


Scheme 1. Retrosynthetic approach to 3,6-diazabicyclo[3.2.1]octanes (**6**).

the procedure described in the literature,[1d,5] were chosen as the starting material for the synthesis of 3,6-diazabicyclo-[3.2.1]octanes (**6**). The lactam **1a** was treated with Lawesson's reagent to give the corresponding thiolactam **2a** in almost quantitative yields. The thiolactam **2a** was converted to methylthioimonium iodide **3a** with excess methyl iodide in 96% yield, which on condensation with nitromethane in DMF and excess of triethylamine yielded the corresponding nitroenamine **4a** in 45% yield (Scheme 2). The nitroenamine **4a** appeared to be thermodynamically stable as the *E*-isomer as shown by NMR studies; irradiation of the olefinic proton resulted in 11% NOE enhancement for the *N*-methyl protons. Catalytic transfer hydrogenation of nitroenamine **4a** over 10% Pd–C in presence of ammonium formate in MeOH at reflux, resulted in reduction of both the double bond and the nitro group followed by in situ cyclization to furnish 6-methyl-3,6-diazabicyclo[3.2.1]-octan-2-one **5a** in 70% yield. Finally, this bicyclic lactam **5a** was subjected to LAH reduction in THF at reflux, which after chromatographic purification afforded 6-methyl-3,6-diazabicyclo[3.2.1]octane (**6a**) in 68% yield (Scheme 2). Analogously, the corresponding 4,6-dimethyl analogue **6b** and 6-(2-methoxyphenyl) analogue **6c** were synthesized in 53 and 57% yield, respectively, by using the appropriate lactams and nitroalkanes. Compound **6b** ($R^1=CH_3$) was isolated as a mixture of diastereoisomers of unassigned relative configuration.

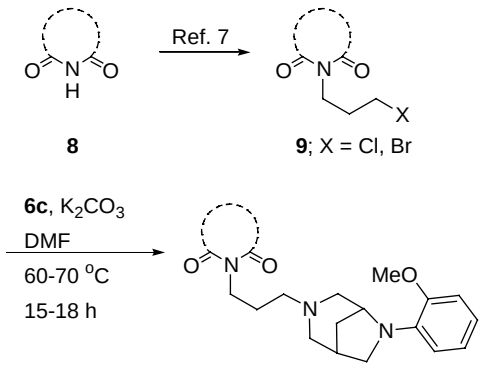
In the light of the likely benefits of restricted flexibility[6] on the pharmacokinetic properties of bioactive agents, various 3-substituted 6-(2-methoxyphenyl)-3,6-diazabicyclo-[3.2.1]octanes (**7a**–**h**) were prepared because of the structural analogy of 6-(2-methoxyphenyl)-3,6-diazabicyclo[3.2.1]octane nucleus (**6c**) with 1-(2-methoxyphenyl)piperazine the structural unit present in RBx 2258 (entry 9, Table 1), the analogue RBx 2258,[7]

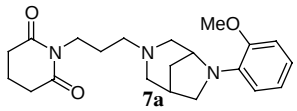
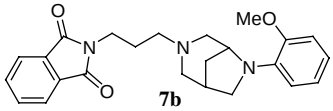
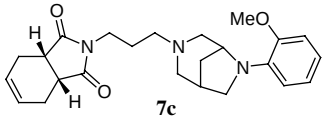
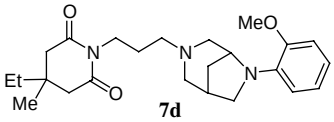
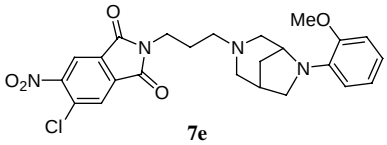
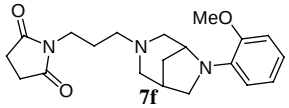
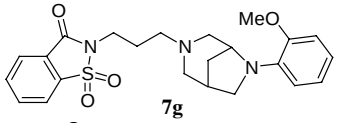
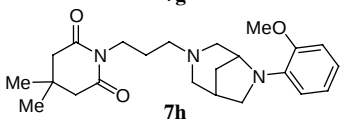
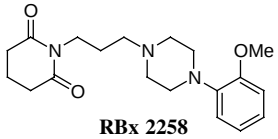


Scheme 2. Reagents and conditions: (i) Lawesson's reagent, THF, rt, 3 h; (ii) CH_3I, PhMe or PhH, rt, 24 h; (iii) $R^1CH_2NO_2$, Et_3N, DMF, rt, 24 h; (iv) $HCOONH_4$, 10% Pd–C, MeOH, reflux, 7–10 h; (v) LAH, THF, reflux, 18 h.

which has shown good α_1-adrenoceptor blocking activity and appear promising for the treatment of benign prostatic hyperplasia (BPH) is in phase II clinical trials.

Table 1. Preparation of 3-substituted 6-(2-methoxyphenyl)-3,6-diazabicyclo[3.2.1]octanes (**7a–h**)



Entry	Product	Yield (%)[a]
1	 **7a**	78
2	 **7b**	70
3	 **7c**	67
4	 **7d**	54
5	 **7e**	71
6	 **7f**	64
7	 **7g**	45
8	 **7h**	46
9	 **RBx 2258**	—

[a] The yields are based on products isolated by column chromatography over silica gel.

The compounds **7a–h** (Table 1) were prepared starting from 1-(3-halopropyl)dicarboximides (**9**), which in turn were prepared by condensing various α,ω-dicarboximides (**8**) and 1-bromo-3-chloropropane according to the procedure described in literature.[7] The compounds **9** were then condensed with 6-(2-methoxyphenyl)-3,6-diazabicyclo[3.2.1]octane (**6c**) in presence of K_2CO_3 in DMF at 60–70 °C to give 1-[6-(2-methoxyphenyl)-3,6-diazabicyclo[3.2.1]octan-3-yl]-3-[*N*-(α,ω-dicarboximido)]propanes **7a–h** in good yields (Table 1). Compounds **6b–c** and **7a–h** are hitherto unknown in the literature and their structures were confirmed on the basis of elemental and spectroscopic analysis.

Receptor binding assays were performed for native α_1-adrenoreceptors. Rat submaxillary and liver membrane preparations were used to assess the affinity for α_{1A} and α_{1B} subtypes, respectively.[8] Aliquots of membrane protein (100–200 μg) were incubated in a final volume of 250 μL assay buffer (50 mM Tris, 0.5 mM EDTA at pH 7.4) with 0.5 nM [^{3}H]prazosin for 60 m at 28 °C. Reaction was stopped by rapid filtration on Millipore filters. Filters were dried and bound radioactivity counted. Non-specific binding was determined in the presence of 0.3 mM prazosin. Protein was assayed according to the method of protein estimation[9] with minor modifications. All the newly synthesized analogues of RBx 2258 were screened for α_{1A} inhibition. However, none of these compounds have shown any remarkable activity.

3. Conclusion

In conclusion, a convenient and new approach for the synthesis of 3,6-diazabicyclo[3.2.1]octanes (**6**) has been accomplished. The key step of the synthesis involves catalytic hydrogenation, accompanied with spontaneous cyclization, of the nitroenamine **4**. These nitroenamine can be conveniently prepared in large quantities from readily available starting materials. In addition, various conformationally constrained analogues of RBx 2258 have been synthesized. However, derivatives of our novel 6-(2-methoxyphenyl)-3,6-diazabicyclo[3.2.1]octane ring systems have not shown any activity against α_1-adrenoreceptors. The lack of activity against α_1-adrenoceptors may be probably due to steric hindrance of the methylene bridge in the ligands–receptor interaction.

4. Experimental

4.1. General

Melting points were recorded on a Büchi B-540 melting point apparatus. Compounds were routinely checked for their purity on silica gel 60 F_{254} TLC plates and their spots were visualized by exposing them to iodine vapor, UV lamp or by spraying the plates with Dragendorff's or $KMnO_4$ reagents. IR spectra (υ_{max} in cm^{-1}) were recorded on Perkin Elmer Paragon-1000PC instrument and NMR (300 MHz) spectra were recorded on Bruker 300-DRX instrument as solutions using TMS as internal standard, and chemical shifts are expressed in δ units. Mass spectra were recorded

on API-3000 LCMS/MS using direct inlet system under positive ion electrospray ionization source. Elemental analyses were carried out with a Perkin Elmer 2400 analyzer and values found were within ±0.4% of theoretical values.

4.2. General method of lactam 1

4.2.1. 1-Methyl-5-oxopyrrolidine-3-carboxylic acid methyl ester (1a). This was prepared according to the literature method[1d,5] starting from itaconic acid in 87% yield as a thick oil; υ_{max} (CH_2Cl_2) 1736, 1689 cm^{-1}; δ_H ($CDCl_3$) 2.67–2.71 (m, 2H), 2.87 (s, 3H), 3.26 (m, 1H), 3.56–3.76 (m, 2H), 3.76 (s, 3H); *m/z* 158 (M+1). Anal. Calcd for $C_7H_{11}NO_3$ (157.17): C, 53.49; H, 7.05; N, 8.91. Found: C, 53.52; H, 6.99; N, 9.05%.

4.2.2. 1-(2-Methoxyphenyl)-5-oxopyrrolidine-3-carboxylic acid methyl ester (1b). To a cooled (−5 °C) solution of MeOH (100 mL), freshly distilled thionyl chloride (13.09 g, 0.11 mmol) was added dropwise over a period of 0.5 h, after addition was completed the resulting mixture stirred at the same temperature for 0.5 h. To this 1-(2-methoxyphenyl)-5-oxopyrrolidine-3-carboxylic acid[5a] (23.5 g, 0.10 mmol) was added portion wise, at the same temperature, stirred for another 0.5 h and then temperature was allowed to rise to 25–30 °C and then stirred for 3 h. MeOH was removed completely under reduced pressure. The residue was dissolved in $CHCl_3$ (200 mL) and washed with 20% aq $NaHCO_3$ (3×50 mL), water (1×50 mL), brine (1×25 mL), dried (Na_2SO_4) and filtered. The filtrate was concentrated under reduced pressure to give **1b** as white powder, yield 23.8 g (96%), mp 82–83 °C; υ_{max} (KBr) 3000, 2960, 1729, 1690, 1593, 1503, 1414 cm^{-1}; δ_H ($CDCl_3$) 2.74–2.94 (m, 2H), 3.35–3.46 (m, 1H), 3.77 (s, 3H), 3.85 (s, 3H), 3.94–3.97 (d, *J*=7.7 Hz, 2H), 6.94–7.00 (m, 2H), 7.24–7.30 (m, 2H); δ_C ($CDCl_3$) 174.4, 170.0, 153.9, 126.5, 125.0, 121.4, 121.0, 114.1, 56.3, 50.6, 42.5, 36.0, 31.1; *m/z* 250 (M+1). Anal. Calcd for $C_{13}H_{15}NO_4$ (249.26): C, 62.64; H, 6.07; N, 5.62. Found: C, 63.00; H, 6.13; N, 5.29%.

4.3. General method of thiolactam 2

4.3.1. 1-Methyl-5-thioxopyrrolidine-3-carboxylic acid methyl ester (2a). This was prepared according to the literature method[1d] starting from **1a** in 98% yield as a thick oil; υ_{max} (CH_2Cl_2) 1736, 1210 cm^{-1}; δ_H ($CDCl_3$) 3.26 (s, 3H), 3.31–3.35 (m, 3H), 3.74 (s, 3H), 3.90–3.97 (m, 1H), 4.04–4.09 (m, 1H); *m/z* 174 (M+1). Anal. Calcd for $C_7H_{11}NO_2S$ (173.23): C, 48.53; H, 6.40; N, 8.09. Found: C, 48.20; H, 6.55; N, 8.00%.

4.3.2. 1-(2-Methoxyphenyl)-5-thioxopyrrolidine-3-carboxylic acid methyl ester (2b). To a solution of lactam **1b** (23.65 g, 95 mmol) in dry THF (100 mL) was added Lawesson's reagent (19.19 g, 47.5 mmol) portion wise under stirring at 25–30 °C and resulting reaction mixture stirred for 4–5 h at same temperature. THF was removed under reduced pressure to obtain a viscous residue, which was dissolved in EtOAc (200 mL), washed with 10% $NaHCO_3$ (5×50 mL), brine (30 mL), dried (Na_2SO_4) and filtered. The filtrate was concentrated under reduced pressure to give the thiolactam **2b** as off white powder, yield 22.91 g (91%), mp 92–93 °C; υ_{max} (CH_2Cl_2) 1738, 1585, 1210 cm^{-1}; δ_H ($CDCl_3$) 3.47–3.50 (m, 3H), 3.78 (s, 3H), 3.84 (s, 3H), 4.17–4.27 (m, 2H), 7.01–7.06 (m, 2H), 7.26–7.39 (m, 2H); δ_C ($CDCl_3$) 197.9, 174.4, 158.9, 126.5, 125.6, 125.0, 121.1, 114.5, 59.5, 56.0, 50.8, 48.5, 36.5; *m/z* 266 (M+1). Anal. Calcd for $C_{13}H_{15}NO_3S$ (265.33): C, 58.85; H, 5.70; N, 5.28. Found: C, 59.03; H, 5.86; N, 5.02%.

4.4. General procedure for compounds 3

4.4.1. 3-Methoxycarbonyl-1-methyl-5-methylthio-3,4-dihydro-2*H*-pyrrolium iodide (3a). A solution of the thiolactam **2a** (17.3 g, 100 mmol) and methyl iodide (70.95 g, 500 mmol) was stirred at 25–30 °C for 2 h, the formation of a yellow precipitate indicates the formation of the methylthioimonium iodide. The excess of methyl iodide was removed under reduced pressure, the residue taken up in dry benzene, stirred for 10 min, the solid, which separated out was filtered, washed well with dry benzene and dry ether and dried under vacuum over P_2O_5 to give **3a** as pale yellow solid, yield 30.24 g (96%), mp 104–106 °C; υ_{max} (KBr) 2363, 2344, 1735, 1617 cm^{-1}; δ_H ($CDCl_3$) 2.94 (s, 3H), 3.45 (s, 3H), 3.68–3.74 (m, 1H), 3.80 (s, 3H), 3.94–4.02 (m, 1H), 4.26 (dd, *J*=10.2 Hz, 1H), 4.45 (dd, *J*=4.5 Hz, 1H), 4.79 (t, *J*=11.1 Hz, 1H); *m/z* 189 (M+1). Anal. Calcd for $C_8H_{14}INO_2S$ (315.17): C, 30.49; H, 4.48; N, 4.44. Found: C, 30.59; H, 4.56; N, 4.50%.

4.4.2. 3-Methoxycarbonyl-1-(2-methoxyphenyl)-5-methylthio-3,4-dihydro-2*H*-pyrrolium iodide (3b). This was obtained in 90% yield as creamish-white powder by reacting methyl iodide with thiolactam **2b** according to the procedure described for compound **3a**; mp 139–141 °C; υ_{max} (KBr) 2951, 1792, 1573, 1497 cm^{-1}; δ_H ($CDCl_3$) 2.84 (s, 3H), 3.66 (m, 1H), 3.82 (s, 3H), 3.90 (s, 3H), 4.28–4.29 (m, 1H), 4.58–4.68 (m, 1H), 4.72–4.80 (m, 2H), 7.04–7.15 (m, 2H), 7.48–7.54 (m, 2H); *m/z* 281 (M+1). Anal. Calcd for $C_{14}H_{18}INO_3S$ (407.27): C, 41.29; H, 4.45; N, 3.44. Found: C, 41.05; H, 4.65; N, 3.03%.

4.5. General procedure for compounds 4

4.5.1. 1-Methyl-5-nitromethylene-pyrrolidine-3-carboxylic acid methyl ester (4a). To a stirred solution of **3a** (7.88 g, 25 mmol) in dry DMF (50 mL), dry Et_3N (2.78 g, 27.5 mmol) and distilled nitromethane (7.63 g, 125 mmol) were added under nitrogen atmosphere. The reaction mixture was stirred at 25–30 °C for 12 h. DMF and excess of nitromethane were removed under reduced pressure to give a crude product, which was purified by column chromatography over silica gel (230–400 mesh) using $CHC1_3$–MeOH (98/2) as eluent to afford nitroenamine **4a** as yellow solid, yield 2.27 g (45%), mp 76–78 °C; υ_{max} (KBr) 1733, 1590, 1359 cm^{-1}; δ_H ($CDCl_3$) 2.87 (s, 3H), 3.23–3.33 (m, 1H), 3.63–3.69 (m, 3H), 3.73 (s, 3H), 3.84–3.89 (m, 1H), 6.63 (s, 1H); δ_C ($CDCl_3$) 174.8, 161.5, 102.1, 57.5, 51.0, 46.1, 35.5, 33.5; *m/z* 201 (M+1). Anal. Calcd for $C_8H_{12}N_2O_4$ (200.19): C, 48.00; H, 6.04; N, 13.99. Found: C, 47.98; H, 6.22; N, 14.10%.

4.5.2. 1-Methyl-5-(1-nitroethylidene)-pyrrolidine-3-carboxylic acid methyl ester (4b). This was obtained in 36% yield as thick oil by reacting nitroethane with **3a**

according to the procedure described for compound **4a**; υ_{max} (CH_2Cl_2) 1738, 1581, 1376 cm^{-1}; δ_H ($CDCl_3$) 2.31 (s, 3H), 3.14 (s, 3H), 3.18–3.28 (m, 1H), 3.57–3.60 (m, 3H), 3.72 (s, 3H), 3.77–3.88 (m, 1H); δ_C ($CDCl_3$) 174.9, 154.1, 111.5, 57.6, 50.6, 46.5, 35.8, 32.9, 10.8; *m/z* 215 (M+1). Anal. Calcd for $C_9H_{14}N_2O_4$ (214.22): C, 50.46; H, 6.59; N, 13.08. Found: C, 50.55; H, 6.51; N, 13.17%.

4.5.3. 1-(2-Methoxyphenyl)-5-nitromethylene-pyrrolidine-3-carboxylic acid methyl ester (4c). This was obtained in 45% yield as thick yellow oil by reacting nitromethane with **3b** according to the procedure described for compound **4a**; υ_{max} (CH_2Cl_2) 2948, 1728, 1570, 1506, 1351 cm^{-1}; δ_H ($CDCl_3$) 3.40–3.50 (m, 1H), 3.79 (s, 3H), 3.84 (s, 3H), 3.85–3.92 (m, 3H), 4.03–4.23 (m, 1H), 6.38 (s, 1H), 6.99–7.04 (m, 2H), 7.35–7.40 (m, 2H); δ_C ($CDCl_3$) 174.6, 153.7, 145.5, 129.1, 117.7, 114.6, 113.5, 103.5, 57.5, 56.1, 50.7, 45.5, 29.9; *m/z* 293 (M+1). Anal. Calcd for $C_{14}H_{16}N_2O_5$ (292.29): C, 57.53; H, 5.52; N, 9.58. Found: C, 57.39; H, 5.65; N, 9.88%.

4.6. General procedure for compounds 5

4.6.1. 6-Methyl-3,6-diazabicyclo[3.2.1]octan-2-one (5a). To a solution of nitroenamine **4a** (3.0 g, 15.0 mmol) and ammonium formate (18.9 g, 300 mmol) in MeOH (80 mL) was added 10% Pd–C (2.25 g, wet) and the resulting reaction mixture was refluxed under stirring for 10 h. After completion of reaction, reaction mixture was cooled to 25–30 °C and filtered through Celite bed, washed with MeOH (2×5 mL) and the combined filtrate was concentrated under reduced pressure to afford crude product, which was dissolved in $CHCl_3$ (10 mL). To this 10% NH_3–$CHCl_3$ (10 mL) was added and stirred for 0.5 h at 25–30 °C, solid separated out was filtered off and filtrate was concentrated under reduced pressure to obtain an oily residue, which was purified by column chromatography over silica gel (100–200 mesh) using $CHCl_3$–MeOH (99.5/0.5)→(98/2) as eluent to afford bicyclic lactam **5a** as thick oil, yield 1.48 g (70%); υ_{max} (CH_2Cl_2) 1682 cm^{-1}; δ_H ($CDCl_3$) 2.03–2.16 (m, 2H), 2.58 (s, 3H), 2.85 (br s, 1H), 3.01–3.11 (m, 2H), 3.36 (br s, 1H), 3.24 (d, *J*=11.5 Hz, 1H), 3.48 (d, *J*=11.2 Hz, 1H), 5.92 (br s, 1H); δ_C ($CDCl_3$) 179.9, 63.6, 51.8, 49.2, 39.5, 35.8, 30.6; *m/z* 141 (M+1). Anal. Calcd for $C_7H_{12}N_2O$ (140.18): C, 59.98; H, 8.63; N, 19.98. Found: C, 59.73; H, 8.56; N, 19.80%.

4.6.2. 4,6-Dimethyl-3,6-diazabicyclo[3.2.1]octan-2-one (5b). This was obtained in 35% yield as thick oil from **4b** according to the procedure described for compound **5a**; υ_{max} (CH_2Cl_2) 1680 cm^{-1}; δ_H ($CDCl_3$) 1.58 (d, *J*=6.3 Hz, 3H), 1.92 (br s, 3H), 2.49 (s, 3H), 2.79 (br s, 2H), 3.28–3.38 (m, 2H), 5.30 (br s, 1H); δ_C ($CDCl_3$) 179.8, 67.5, 52.2, 48.6, 39.5, 36.3, 27.9, 17.1; *m/z* 155 (M+1). Anal. Calcd for $C_8H_{14}N_2O$ (154.21): C, 62.31; H, 9.15; N, 18.17. Found: C, 62.57; H, 8.99; N, 18.06%.

4.6.3. 6-(2-Methoxyphenyl)-3,6-diazabicyclo[3.2.1]octan-2-one (5c). This was obtained in 70% yield as thick oil from **4c** according to the procedure described for compound **5a**; υ_{max} (CH_2Cl_2) 1685 cm^{-1}; δ_H ($CDCl_3$) 2.04–2.11 (m, 2H), 2.97 (br s, 1H), 3.28–3.33 (m, 1H), 3.55–3.72 (m, 3H), 3.83 (s, 3H), 4.62 (br s, 1H), 5.40 (br s, 1H), 6.60–6.69 (m, 4H); δ_C ($CDCl_3$) 179.6, 146.7, 130.3, 121.5, 119.1, 115.0, 114.3, 63.5, 56.1, 51.9, 48.7, 39.0, 30.2; *m/z* 233 (M+1). Anal. Calcd for $C_{13}H_{16}N_2O_2$ (232.28): C, 67.22; H, 6.94; N, 12.06. Found: C, 67.25; H, 6.89; N, 11.96%.

4.7. General procedure for compounds 6

4.7.1. 6-Methyl-3,6-diazabicyclo[3.2.1]octane (6a). To a stirred suspension of pulverized lithium aluminum hydride (2.96 g, 78 mmol) in dry THF (5 mL), a solution of bicyclic lactam **5a** (2.73 g, 19.5 mmol) in dry THF (10 mL) was added under N_2 atmosphere at 25–30 °C and the resulting reaction mixture was refluxed under stirring for 18 h. After completion of reaction, reaction mixture was cooled to −5 °C and cautiously decomposed with water (15 mL). After stirring for 1 h at 25–30 °C, the reaction mass was filtered, washed with THF, the filtrate was collected and dried over Na_2SO_4, and filtered. The solvent was evaporated to yield crude product, which was purified by column chromatography over silica gel (100–120 mesh) using $CHC1_3$–MeOH (95/5) as eluent to afford 1.68 g (68%) of 6-methyl-3,6-diazabicyclo[3.2.1]octane (**6a**) as a pale yellow oil; υ_{max} (CH_2Cl_2) 2908, 2805, 1490 cm^{-1}; δ_H ($CDCl_3$) 1.65–1.78 (m, 2H), 1.85–1.95 (m, 1H), 2.20–2.25 (m, 2H), 2.31 (s, 3H), 2.58–2.70 (m, 1H), 2.75–2.90 (m, 4H); δ_C ($CDCl_3$) 64.5, 54.3, 52.7, 51.5, 37.8, 36.9, 33.1; *m/z* 127 (M+1). Anal. Calcd for $C_7H_{14}N_2$ (126.20): C, 66.62; H, 11.18; N, 22.20. Found: C, 66.75; H, 11.22; N, 21.95%.

4.7.2. 4,6-Dimethyl-3,6-diazabicyclo[3.2.1]octane (6b). This was obtained in 53% yield as thick oil from bicyclic lactam **5b** according to the procedure described for compound **6a**; υ_{max} (CH_2Cl_2) 2890, 2800, 1495 cm^{-1}; δ_H ($CDCl_3$) 1.38 (d, *J*=7.2 Hz, 3H), 1.95 (br s, 3H), 2.18–2.22 (m, 2H), 2.30 (s, 3H), 2.45–2.50 (m, 1H), 2.70–2.85 (m, 2H), 3.22–3.30 (m, 1H); δ_C ($CDCl_3$) 69.2, 54.8, 52.7, 49.2, 38.1, 36.7, 31.4, 18.6; *m/z* 141 (M+1). Anal. Calcd for $C_8H_{16}N_2$ (140.23): C, 68.52; H, 11.50; N, 19.98. Found: C, 68.25; H, 11.38; N, 20.10%.

4.7.3. 6-(2-Methoxyphenyl)-3,6-diazabicyclo[3.2.1]octane (6c). This was obtained in 57% yield as pale yellow oil from bicyclic lactam **5c** according to the procedure described for compound **6a**; υ_{max} (CH_2Cl_2) 2900, 2815, 1498 cm^{-1}; δ_H ($CDCl_3$) 1.78–1.82 (m, 2H), 1.94–1.99 (m, 1H), 2.30 (br s, 1H), 2.62–2.67 (d, *J*=9.6 Hz, 1H), 2.79–2.93 (dd, *J*=9.9 Hz, 2H), 3.29–3.32 (d, *J*=9.6 Hz, 1H), 3.60–3.65 (q, *J*=4.8 Hz, 1H), 3.78 (s, 3H), 4.21–4.24 (t, *J*=5.4 Hz, 1H), 6.67–6.73 (m, 2H), 6.82–6.88 (m, 2H); δ_C ($CDCl_3$) 146.5, 130.3, 121.9, 119.3, 115.6, 114.2, 63.6, 56.2, 53.9, 51.5, 50.0, 35.3, 31.9; *m/z* 219 (M+1). Anal. Calcd for $C_{13}H_{18}N_2O$ (218.29): C, 71.53; H, 8.31; N, 12.83. Found: C, 71.68; H, 8.11; N, 12.80%.

4.8. General procedure for compounds 7

4.8.1. 1-{3-[6-(2-Methoxyphenyl)-3,6-diazabicyclo-[3.2.1]oct-3-yl]propyl}piperidine-2,6-dione (7a). A mixture of 1-(3-chloropropyl)piperidine-2,6-dione (0.834 g, 4.4 mmol), 6-(2-methoxyphenyl)-3,6-diazabicyclo[3.2.1]octane (**6c**, 0.863 g, 3.96 mmol, 0.9 equiv), K_2CO_3 (0.303 g, 2.2 mmol, 0.5 equiv) and KI (0.146 g, 0.88 mmol, 0.2 equiv) in DMF (15 mL) was heated at 60–70 °C under stirring for

18 h. After cooling the reaction mixture to ambient temperature, water (75 mL) was added and extracted with CH_2Cl_2 (2×50 mL). The combined organic phase was washed with water (2×50 mL) and dried (Na_2SO_4), filtered and concentrated under reduced pressure to give crude product, which was purified by column chromatography over silica gel (100–120 mesh) using $CHCl_3$–MeOH (99/1)→(97/3) as eluent to afford **7a** as thick oil, yield 1.15 g (78%); υ_{max} (CH_2Cl_2) 2945, 1771, 1710, 1594, 1503, 1395 cm^{-1}; δ_H ($CDCl_3$) 1.52–1.55 (m, 2H), 1.84–1.96 (m, 4H), 2.00–2.08 (br d, 1H), 2.32–2.41 (br d, 4H), 2.57 (t, J=6.3 Hz, 4H), 2.95 (d, J=9.3 Hz, 2H), 3.45–3.54 (m, 3H), 3.74 (d, J=7.5 Hz, 1H), 3.78 (s, 3H), 4.39 (br s, 1H), 6.61–6.84 (m, 4H); δ_C ($CDCl_3$) 172.6, 146.5, 130.3, 121.6, 119.0, 115.1, 114.4, 61.5, 56.2, 54.7, 53.7, 51.3, 38.9, 33.7, 32.8, 32.0, 28.6, 18.1; *m/z* 372 (M+1). Anal. Calcd for $C_{21}H_{29}N_3O_3$ (371.47): C, 67.90; H, 7.87; N, 11.31. Found: C, 68.03; H, 8.01; N, 11.38%.

4.8.2. 2-{3-[6-(2-Methoxyphenyl)-3,6-diazabicyclo-[3.2.1]oct-3-yl]propyl}isoindole-1,3-dione (7b). This was obtained in 70% yield as thick oil by reacting 2-(3-chloropropyl)isoindole-1,3-dione with **6c** according to the procedure described for compound **7a**; υ_{max} (CH_2Cl_2) 2947, 1777, 1698, 1503, 1450 cm^{-1}; δ_H ($CDCl_3$) 1.67–1.71 (m, 2H), 1.95–1.99 (br d, 2H), 2.15 (d, J=10.2 Hz, 2H), 2.35 (t, J=6.6 Hz, 2H), 2.41 (d, J=3.9 Hz, 1H), 2.88–3.12 (m, 2H), 3.42 (d, J=6.3 Hz, 1H), 3.46 (t, J=5.1 Hz, 2H), 3.68–3.70 (m, 1H), 3.78 (s, 3H), 4.39 (d, J=3.9 Hz, 1H), 6.60–6.75 (m, 1H), 6.78–6.81 (m, 3H), 7.65–7.69 (m, 2H), 7.70–7.80 (m, 2H); δ_C ($CDCl_3$) 167.2, 148.2, 133.4, 133.0, 131.1, 128.4, 122.9, 120.1, 116.2, 115.5, 62.8, 57.6, 57.0, 55.7, 54.9, 52.5, 40.2, 33.9, 33.2, 30.1; *m/z* 406 (M+1). Anal. Calcd for $C_{24}H_{27}N_3O_3$ (405.49): C, 71.09; H, 6.71; N, 10.36. Found: C, 70.94; H, 6.80; N, 10.13%.

4.8.3. 2-{3-[6-(2-Methoxyphenyl)-3,6-diazabicyclo-[3.2.1]oct-3-yl]propyl}-3a,4,7,7a-tetrahydroisoindole-1,3-dione (7c). This was obtained in 67% yield as thick oil by reacting 2-(3-chloropropyl)-3a,4,7,7a-tetrahydroisoindole-1,3-dione with **6c** according to the procedure described for compound **7a**; υ_{max} (CH_2Cl_2) 3976, 3396, 2949, 1722, 1671, 1590, 1505, 1350 cm^{-1}; δ_H ($CDCl_3$) 1.51–1.59 (m, 4H), 1.65–1.70 (m, 2H), 1.94 (d, J=9.9 Hz, 2H), 2.13 (dd, J=10.5 Hz, 2H), 2.26 (t, J=6.6 Hz, 2H), 2.39 (br s, 1H), 2.52–2.57 (m, 1H), 2.92–2.93 (m, 1H), 2.97 (t, J=6.6 Hz, 2H), 3.18–3.25 (m, 2H), 3.45–3.47 (t, J=6.3 Hz, 2H), 3.78 (s, 3H), 4.39 (br s, 1H), 5.83–5.84 (d, J=2.4 Hz, 2H), 6.61–6.84 (m, 4H); δ_C ($CDCl_3$): δ 179.1, 147.8, 132.8, 131.4, 123.0, 120.1, 115.2, 114.9, 63.1, 57.6, 57.1, 55.8, 54.8, 52.5, 44.1, 40.1, 33.2, 33.0, 29.8, 28.0; *m/z* 410 (M+1). Anal. Calcd for $C_{24}H_{31}N_3O_3$ (409.52): C, 70.39; H, 7.63; N, 10.26. Found: C, 70.49; H, 7.68; N, 10.30%.

4.8.4. 4-Ethyl-1-{3-[6-(2-methoxyphenyl)-3,6-diazabicyclo[3.2.1]oct-3-yl]propyl}-4-methyl-piperidine-2,6-dione (7d). This was obtained in 54% yield as thick oil by reacting 1-(3-chloropropyl)-4-ethyl-4-methylpiperidine-2,6-dione with **6c** according to the procedure described for compound **7a**; υ_{max} (CH_2Cl_2) 3970, 3394, 2943, 1724, 1673, 1592, 1510 cm^{-1}; δ_H ($CDCl_3$) 0.83–0.88 (t, J=7.5 Hz, 3H), 0.95 (s, 3H), 1.25–1.33 (m, 2H), 1.52–1.67 (m, 4H), 1.97 (d, J=10.8 Hz, 2H), 2.12 (br s, 1H), 2.30–2.34 (t, J=7.2 Hz, 2H), 2.42 (s, 4H), 2.88–3.12 (m, 2H), 3.46–3.57 (m, 3H), 3.79 (br s, 4H), 4.40 (t, J=4.2 Hz, 1H), 6.61–6.84 (m, 4H); δ_C ($CDCl_3$) 174.2, 148.2, 131.4, 123.3, 120.0, 116.2, 115.5, 63.3, 57.8, 57.1, 56.2, 55.0, 52.3, 45.6, 40.1, 34.0, 33.4, 33.0, 30.1, 25.3, 22.4, 10.5; *m/z* 414 (M+1). Anal. Calcd for $C_{24}H_{35}N_3O_3$ (413.55): C, 69.70; H, 8.53; N, 10.16. Found: C, 70.01; H, 8.68; N, 10.01%.

4.8.5. 5-Chloro-2-{3-[6-(2-methoxyphenyl)-3,6-diazabicyclo[3.2.1]oct-3-yl]propyl}-6-nitro-isoindole-1,3-dione (7e). This was obtained in 71% yield as thick oil by reacting 5-chloro-2-(3-chloropropyl)-6-nitro-isoindole-1,3-dione with **6c** according to the procedure described for compound **7a**; υ_{max} (CH_2Cl_2) 3447, 2944, 1767, 1708, 1627, 1592, 1520 cm^{-1}; δ_H ($CDCl_3$) 1.94 (d, J=10.6 Hz, 1H), 2.06–2.13 (m, 3H), 2.58 (br s, 1H), 2.88–2.95 (m, 1H), 3.11 (d, J=9.3 Hz, 1H), 3.26 (t, J=13.2 Hz, 2H), 3.46–3.60 (m, 4H), 3.77 (t, J=6.6 Hz, 2H), 3.88 (s, 3H), 4.43–4.44 (m, 1H), 6.62–6.64 (m, 1H), 6.73–6.84 (m, 2H), 6.89–6.91 (m, 1H), 7.57 (s, 1H), 8.09 (s, 1H); δ_C ($CDCl_3$) 167.5, 154.3, 148.5, 141.6, 133.4, 132.3, 131.2, 129.7, 125.2, 122.7, 120.0, 116.4, 115.5, 63.1, 57.4, 57.0, 55.7, 54.9, 52.4, 40.5, 33.9, 33.1, 29.9; *m/z* 485 (M+1). Anal. Calcd for $C_{24}H_{25}ClN_4O_5$ (484.93): C, 59.44; H, 5.20; N, 11.55. Found: C, 59.51; H, 5.22; N, 11.50%.

4.8.6. 1-{3-[6-(2-Methoxyphenyl)-3,6-diazabicyclo-[3.2.1]oct-3-yl]propyl}pyrrolidine-2,5-dione hydrochloride (7f). This was obtained by reacting 1-(3-chloropropyl)-pyrrolidine-2,5-dione with **6c** according to the procedure described for compound **7a**, which was converted to corresponding hydrochloride salt by treating with 1 equiv ethanolic-HCl, 64% yield, mp 114–116 °C; υ_{max} (KBr) 3428, 2958, 1769, 1694, 1593, 1502 cm^{-1}; δ_H (D_2O) 1.96–2.07 (m, 2H), 2.77 (s, 4H), 2.83 (br s, 1H), 3.18 (t, J=7.8 Hz, 2H), 3.26 (br d, J=12.0 Hz, 2H), 3.51–3.54 (m, 4H), 3.84 (br s, 4H), 3.90 (s, 3H), 4.30 (br s, 1H), 6.97–7.07 (m, 4H); δ_C (D_2O) 175.5, 148.2, 132.4, 122.7, 120.6, 117.3, 116.1, 63.6, 58.5, 57.9, 55.7, 55.2, 52.3, 40.6, 34.2, 33.6, 30.8, 28.8; *m/z* 358 (M+1). Anal. Calcd for $C_{20}H_{27}N_3O_3 \cdot HCl$ (393.91): C, 60.98; H, 7.16; N, 10.67. Found: C, 60.61; H, 7.52; N, 10.35%.

4.8.7. 2-{3-[6-(2-Methoxyphenyl)-3,6-diazabicyclo-[3.2.1]oct-3-yl]propyl}-1,1-dioxo-1,2-dihydro-1-benzo[*d*]isothiazol-3-one (7g). This was obtained in 45% yield as thick oil by reacting 2-(3-chloropropyl)-1,1-dioxo-1,2-dihydro-1-benzo[*d*]isothiazol-3-one with **6c** according to the procedure described for compound **7a**; υ_{max} ($CHCl_3$) 3417, 2915, 1731, 1594, 1502, 1457, 1332 cm^{-1}; δ_H ($CDCl_3$) 1.94 (br s, 2H), 2.31 (t, J=6.9 Hz, 2H), 2.84 (br s, 1H), 3.08 (d, J=6.6 Hz, 1H), 3.30–3.39 (m, 5H) 3.64–3.68 (m, 2H), 3.75–3.80 (m, 5H), 4.26 (br s, 1H), 6.90–6.95 (m, 4H), 7.84–8.11 (m, 4H); δ_C ($CDCl_3$) 170.2, 148.2, 139.9, 134.5, 132.8, 131.5, 132.1, 129.4, 126.8, 123.5, 121.3, 116.8, 115.6, 63.5, 57.3, 57.0, 55.8, 54.9, 53.0, 38.9, 33.8, 33.0, 30.1; *m/z* 442 (M+1). Anal. Calcd for $C_{23}H_{27}N_3O_4S$ (441.54): C, 62.56; H, 6.16; N, 9.52. Found: C, 62.25; H, 5.99; N, 9.50%.

4.8.8. 1-{3-[6-(2-Methoxyphenyl)-3,6-diazabicyclo-[3.2.1]oct-3-yl]propyl}-4,4-dimethylpiperidine-2,6-dione (7h). This was obtained in 46% yield as thick oil by reacting 1-(3-chloropropyl)-4,4-dimethylpiperidine-2,6-dione with

6c according to the procedure described for compound **7a**; υ_{max} ($CHCl_3$) 2954, 2764, 1723, 1672, 1594, 1503, 1358 cm^{-1}; δ_H ($CDCl_3$) 1.01 (s, 6H), 1.51–1.63 (m, 5H), 1.97 (d, $J=10.2$ Hz, 1H), 2.10 (d, $J=9.9$ Hz, 1H), 2.32 (t, $J=6.9$ Hz, 2H), 2.43 (s, 4H), 2.91–3.01 (m, 2H), 3.52 (t, $J=7.5$ Hz, 2H), 3.73 (d, $J=9.3$ Hz, 2H), 3.78 (s, 3H), 4.39 (br s, 1H), 6.16–6.81 (m, 4H); δ_C ($CDCl_3$) 174.8, 148.2, 131.6, 123.1, 121.5, 116.8, 115.5, 63.3, 57.8, 57.0, 55.7, 55.1, 52.7, 48.0, 39.9, 34.2, 33.6, 30.3, 27.7, 19.8; *m/z* 400 (M+1). Anal. Calcd for $C_{23}H_{33}N_3O_3$ (399.53): C, 69.14; H, 8.33; N, 10.52. Found: C, 69.22; H, 8.50; N, 10.53%.

4.8.9. 1-(3-Halopropyl)dicarboximides (9). These were prepared according to the literature procedure[7] by condensing various commercially available α,ω-dicarboximides (**8**) and 1-bromo-3-chloropropane.

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Regio- and stereochemical aspects in the synthesis of homoallylic alcohols from benzoins and their iodocyclisation to 2,3-diphenyltetrahydrofurans

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Abstract—Indium mediated allylation, crotylation and cinnamylation of benzoins and its substituted derivatives in THF–H_2O (2/1) provide a range of homoallylic alcohols. In general, the benzoins undergo allylation and crotylation in a sluggish manner compared to those observed earlier in the case of α-hydroxy aldehydes and are significantly affected by the electronic features of both the benzoin and indium organometallic reagent. The reactions exhibit higher order of diastereoselectivities than those observed for α-hydroxy aldehydes. The cinnamylation though proceeds in a highly diastereoselective manner but is restricted to only benzoin and 4,4′-dichlorobenzoin. The homoallylic alcohols undergo I_2 mediated intramolecular diastereoselective cyclization to provide 2,3-diphenyltetrahydrofuran derivatives. The relative stereochemistries in tetrahydrofurans and homoallylic alcohols have been assigned by coupling constants, NOE experiments and in one case by X-ray crystallography.

1. Introduction

The allylation of carbonyl compounds with allyl organometallic reagents constitutes a simple approach for the synthesis of homoallylic alcohols, versatile synthons in organic synthesis.[1] The stability of indium metal in water, ease in generation of allyl indium reagents under anhydrous conditions and in situ generation under aqueous Barbier type conditions; the lower basicity and thus the higher stability of allylindium reagents in the presence of water and other proton donor functionalities such as OH, COOH; the applicability even in the presence of NO_2, CN, ester functional groups, have highlighted the superiority of allyl indium reagents[2] over conventional organometallic reagents.[3] The environment friendly reaction conditions and the higher reactivities in these multi-component reactions in aqueous media are added advantages of indium mediated allylation reactions.[4]

The pioneering investigations of Paquette et al.[5] on the stereochemical outcome of allylation of α-hydroxy aldehdyes, in general, show the participation of Cram's chelation model and allylic anions preferably add from the sterically less hindered face to provide *syn* homoallylic alcohols. The presence of water does not inhibit the operation of chelation control. The choice of the solvent, different additives and pH of the reaction medium also affect the diastereoselective outcome of the reaction. However, due to poor reactivities of ketones compared to aldehydes towards nucleophiles, these investigations have been limited to allylation of hydroxycyclohexanones[6] and carbohydrates[7] with only allyl bromide.

The present work is aimed to unravel the regio- and diastereochemical aspects in allylation of benzoins—the acyclic α-hydroxyketones[8] with allyl and substituted allyl bromides. The presence of two aryl rings at adjacent carbons make them attractive synthons for α,β-diaryl heterocycles—an essential structural feature in many bioactive molecules especially COX-2 inhibitors.[9]

The findings show that benzoins, in general, undergo indium mediated allylation and crotylation in a sluggish manner than those observed earlier in the case of α-hydroxy aldehydes. The presence of electron-withdrawing groups on the aryl rings facilitates the allylation and the presence of electron-donating groups retards the allyl transfer. The cinnamylation proceeds in a highly diastereoselective manner (>98:2) with benzoin and 4,4′-dichlorobenzoin. Homoallylic alcohols thus obtained undergo I_2 mediated diastereoselective intramolecular cyclizations to give

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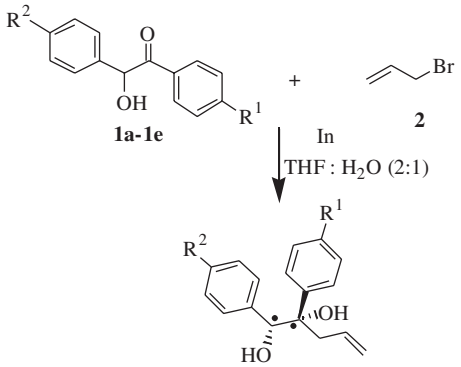
2,3-diaryltetrahydrofurans. The configurations of tetrahydrofurans and homoallylic alcohols have been assigned by NOE experiments and by X-ray crystallography in one case.

2. Results and discussion

2.1. Diastereoselective allylation with allyl bromide: generation of one new chiral center

A solution of **1a**, allyl bromide **2** and indium metal (suspension) (1:1.5:1) in THF–H_2O (2/1) on stirring at 30 ± 2 °C for 6–8 h, after usual work-up and chromatography provided (1*R**,2*S**)-**3a** (92%), mp 95 °C, (lit.[10] mp 96–97 °C (Scheme 1). This procedure offers a convenient alternative to similar allylation performed through tetraallyltin.[10] In order to evaluate the contribution of electronic features on the reactivity and diastereoselectivity of allylation on benzoins, the substituted benzoin derivatives **1b–1e** were subjected to indium mediated allylation under Barbier type conditions. Benzoins **1b–1d** on allylation gave homoallylic alcohols **3b–3d** with diastereoselectivities >99:1 (Scheme 1, Table 1). *N*,*N*-Dimethylbenzoin **1e** did not undergo indium mediated allylation and even on performing the reaction at 50 °C, the starting **1e** (~50%) was recovered.



For 1, 3 (a) $R^1=R^2=H$; (b) $R^1=R^2=Cl$; (c) $R^1=OCH_3$, $R^2=H$; (d) $R^1=R^2=OCH_3$; (e) $R^1=N(CH_3)_2$, $R^2=H$

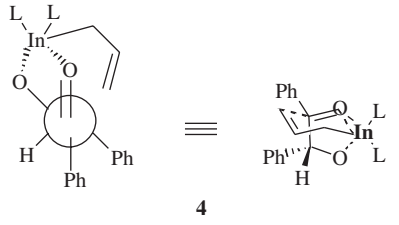
Scheme 1.

Table 1. Diastereoselective allylation of benzoins **1a–1e**

Entry	R^1	R^2	Product	Time (h)	dr	Yield (%)
1	H	H	**3a**	7–8	>99:1	92
2	Cl	Cl	**3b**	4–5	>99:1	45
3	OCH_3	H	**3c**	12–14	>99:1	69
4	OCH_3	OCH_3	**3d**	12–14	>99:1	72
5	$N(CH_3)_2$	H	**3e**	24	No reaction	

The time required for allylation of benzoins **1a–1e** is considerably affected by the nature of the substituent on the aryl ring and is by and large in parallel with the electron-densities available on the carbonyl carbon. 4,4′-Dichlorobenzoin **1b** undergoes allylation faster than benzoin **1a** and in the case of anisoin **1d** and benzanisoin **1c**, possessing electron-donating group (OMe) the allylation takes a longer time (Table 1, entry 1–4). The presence of a strong electron-donating group [$N(CH_3)_2$] leads to complete inhibition of the allyl transfer even at elevated temperature (50 °C). A comparison of reaction times required for allylation of benzoins with those of α-hydroxyaldehydes[5] shows that benzoins (4–14 h) take more time for completion of the reaction than taken by α-hydroxyaldehydes (2–4 h). These results are in agreement with the known higher reactivities of aldehydes compared to ketones towards nucleophilic addition reactions. Interestingly, the lower reactivities of benzoins towards indium mediated allylation than observed for α-hydroxyaldehydes, results in high (>99:1) diastereoselectivities.

In these reactions, the formation of *syn* products can be visualized on the basis of classic Cram's chelation model **4** (Scheme 2). The ability of the indium cation to lock the hydroxy carbonyl substrates conformationally prior to the nucleophilic attack is indicative that co-ordination to the substrate indeed overcomes the solvation forces.

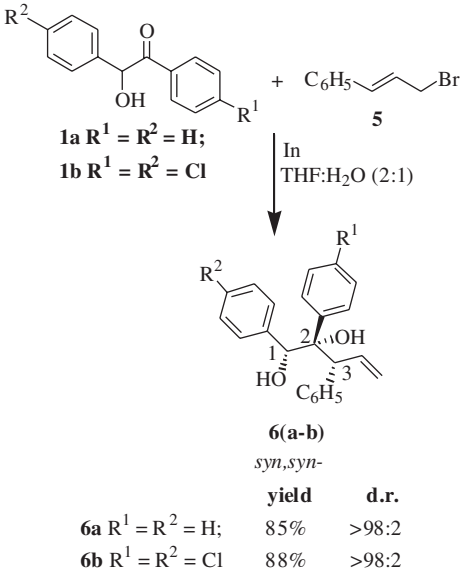


Scheme 2.

2.2. Diastereoselective allylation with substituted allyl bromides: generation of two new chiral centers

The allylic anions generated from substituted allyl bromides are unsymmetrical and the documented preferred carbon–carbon bond formation in the case of aldehydes from the more substituted carbon results in the generation of two new chiral centers.[2] In the case of benzoins, it would lead to formation of homoallylic alcohols with three chiral centers resulting in possible formation of four diastereomers. In order to evaluate the regio- and stereoselective aspects in allylation of benzoins **1a–1d**, indium mediated Barbier type allylations with crotyl bromide, cinnamyl bromide and ethyl 4-bromocrotonate were performed.

Stirring of a solution of benzoin **1a** with cinnamyl bromide (**5**) in THF–H_2O (2/1) at 0 °C containing fine flakes of indium gave a pale yellow liquid (85%), M^+ *m/z* 330 (Scheme 3). It's ^1H NMR spectrum shows a singlet at δ 3.02 (PhC*H*OH), doublet at δ 4.14 (PhC*H*) and multiplet at δ 5.11–5.17 (=CH_2), dt at 6.15 (1H, =CH) and multiplet at 7.02–7.56 (15H, ArH). These spectral data along with the ^{13}C NMR spectrum assigns structure **6a** for this compound. Therefore, cinnamylation of **1a** proceeds in a complete regio- and diastereoselective manner and provides only the γ-addition product. The presence of only one set of signals in the ^1H and ^{13}C NMR spectra of **6a** indicates that only one

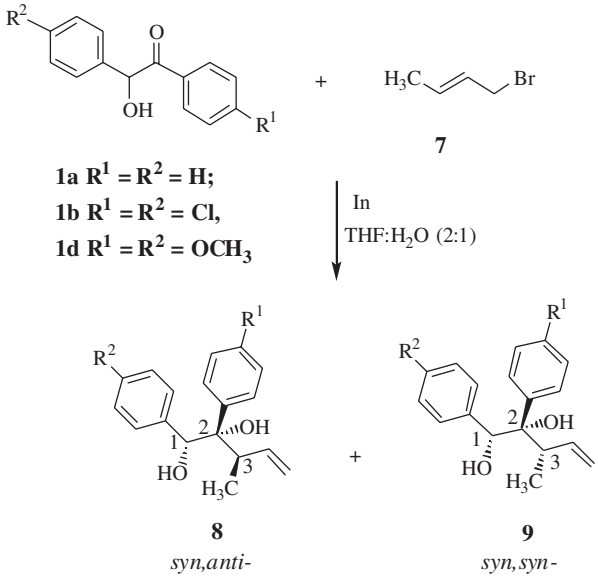


	yield	d.r.
6a $R^1 = R^2 = H$;	85%	>98:2
6b $R^1 = R^2 = Cl$	88%	>98:2

Scheme 3.

diastereomer is formed. On the basis of NOE experiments on its iodocyclized tetrahydrofuran derivatives **14a** and **15a**, it has been assigned as *syn*,*syn*-addition product-(1*R**,2*S**,3*R**)-1,2,3-triphenylpent-4-ene-1,2-diol (**6a**). **1b** also underwent diastreoselective cinnamylation to provide **6b**. However, the electron rich benzoins **1c** and **1d** failed to react with cinnamyl bromide under these conditions.

In the case of crotyl bromide, the minimum steric requirement inherited by the CH_3 group provides a good opportunity to test the diastereoselectivity of the system under investigation. The reaction of benzoin **1a** with crotyl bromide in THF–H_2O (2/1) at 0 °C gave a yellow liquid (78% yield) (Scheme 4). Its ^1H NMR spectrum shows two distinct signals each for CH_3, CH and =CH protons in a 64:36 ratio. The two CH_3 doublets appear at δ 0.93 and 1.06 and could be assigned to CH_3 attached to the sp^3 hybridized carbon. The absence of a signal due to the methyl group between δ 1.5–2.5 shows the non-formation of α-addition product. Therefore, the crotylation too proceeds in a highly regioselective manner to provide only the γ-addition products. Further, out of the possible four diastreomers only two are formed. The two diastereomers could not be separated but relative configurations at the chiral centers have been assigned on the basis of NOE experiments on their iodocyclized products **12a** and **13a**. The major diastereomer has been assigned the configurations (1*R**,2*S**,3*R**)-**8a** and found to be *syn*,*anti*-addition product and minor, which is a *syn*,*syn*-addition product has been assigned configurations (1*R**,2*S**,3*S**)-**9a**. Similarly, **1b** and **1d** on crotylation gave **8b**+**9b** and **8c**+**9c** (Table 2). Amongst these pairs of diastereomers **8a**–**8c** and **9a**–**9c**, the methine vinylic proton (=CH) of *syn*,*anti*-addition products **8** appear downfield at δ 6.07–6.12 in comparison with that of the *syn*,*syn*-addition products **9** (δ 5.78–5.92). These results are in consonance with earlier reported downfield appearance of methine vinylic proton in *anti*-addition product compared to in *syn*-addition product.[11] The allylation of **1a**–**1d** with ethyl 4-bromocrotonate failed to occur even at elevated temperature (50 °C) and only unreacted **1a**–**1d** could be isolated.



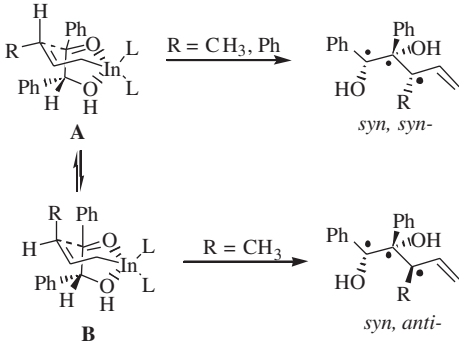
		yield	dr
For 8 and 9	(a) $R^1 = R^2 = H$	78%	64:36
	(b) $R^1 = R^2 = Cl$	74%	64:36
	(c) $R^1 = R^2 = OCH_3$	71%	78:22

Scheme 4.

Table 2. Diastereoselective allylation of benzoins **1** with substituted allyl bromides

Entry	Allyl bromide	Benzoin	Time (h)	Product (*syn*,*syn*:*syn*,*anti*)	Yield (%)
1	5	**1a**	24	**6a** (98:2)	85
2	5	**1b**	4–5	**6b** (98:2)	88
3	7	**1a**	3–4	**8a**+**9a** (64:36)	78
4	7	**1b**	1–2	**8b**+**9b** (64:36)	71
5	7	**1d**	5–6	**8c**+**9c** (78:22)	74

The allylation reactions of **1a** with cinnamyl and crotyl bromide also proceed through Cram's chelation model. The reaction of benzoin **1a** and **1b** with cinnamyl bromide proceed through transition state **A** resulting in the formation of *syn*,*syn*-addition product in which the cinnamyl anion is transferred to the carbonyl carbon from less hindered π-face. However, crotylation of **1a**, **1b** and **1d** preferentially proceeds through transition state **B**, resulting in formation of the *syn*,*anti*- as the major products (Scheme 5).

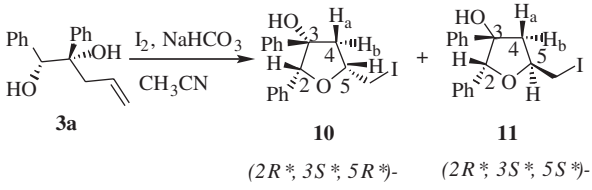


Scheme 5.

The comparison of these results with crotylation of 2-hydroxypropanal shows that whereas in the latter case the mixture of *syn*,*syn*-, *syn*,*anti*- and *anti*,*anti*-addition products is formed,[5d] the crotylations of benzoins provide only *syn*,*syn*- and *syn*,*anti*-addition products.

2.3. Diastereoselective conversion of homoallylic alcohols to 2,3-diphenyltetrahydrofurans 10–15

Stirring a mixture of **3a**, I_2 and $NaHCO_3$ in dry CH_3CN for 72 h after usual work up gave a mixture of two diastereomers in the ratio 80:20 (^{1}H NMR integration) (Scheme 6). The fast moving component (minor 8%) in its ^{1}H NMR spectrum shows two 1H double doublets at δ 2.48 and 2.78 (H-4), a doublet at δ 3.63 (CH_2I), 1H singlet at δ 5.29 (H-2), 1H multiplet at δ 4.57–4.72 (H-5) and 10H multiplet at δ 7.04–7.39. The assignment of the signals has been carried out on the basis of decoupling experiments and ^{1}H–^{13}C COSY spectrum. The relative configurations at C-2 and C-3 carbons are predefined by ^{1}H NMR and X-ray structure of **3a**, and relative configurations at C-2 and C-5 carbons could be assigned on the basis of NOE experiments. The observation of positive NOE at H-4a and H-5 on irradiating H-2 and NOE at H-2, H-5 on irradiating H-4a indicates the presence of H-2, H-4a and H-5 protons on the same side of tetrahydrofuran ring. On the basis of these results the minor component has been assigned the structure (2*R**,3*S**,5*R**)-5-iodomethyl-2,3-diphenyl-tetrahydro-furan-3-ol (**10**) (Fig. 1).



Scheme 6.

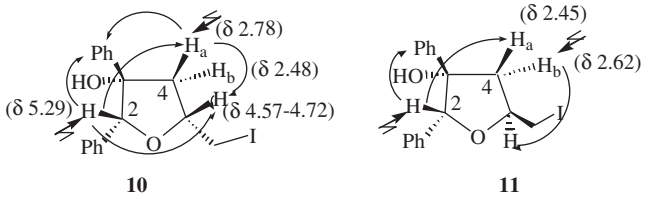


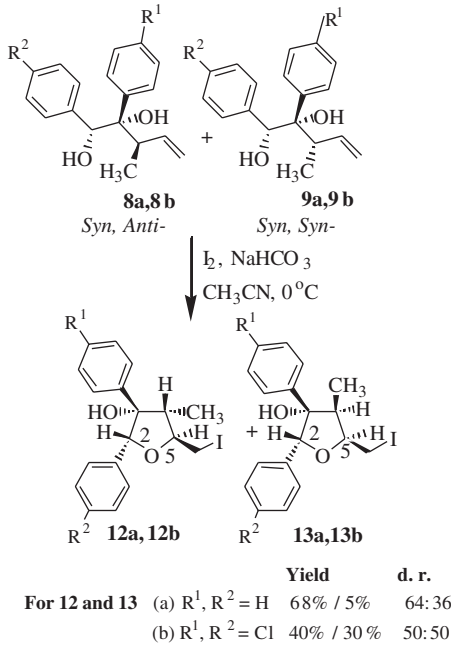
Figure 1. The relative stereochemistries in **10** and **11** from NOE experiments.

The slow moving component (major diastereomer, 32%) in its ^{1}H NMR spectrum shows two 1H double doublets at δ 2.45 and 2.62 (CH_2-4) and two double doublets at δ 3.51 and 3.61 (CH_2I), 1H singlet at δ 5.53 (H-2) and multiplet at δ 4.55–4.60 (H-5) along with aromatic protons. The presence of NOE at H-4a and its absence at H-5 on irradiating H-2 assigns the structure (2*R**,3*S**,5*S**)-5-iodomethyl-2,3-diphenyl-tetrahydro-furan-3-ol (**11**) to this isomer. Therefore, **3a** undergoes regioselective iodocyclisation to provide only tetrahydrofuran derivatives. However, the cyclization proceeds with moderate diastereselectivity to provide two diastereomers in 80:20 ratio. Since, diastereoselectivities in iodocyclisations of **3a** are affected by the temperature and the polarity of the solvent,[12] in order to improve diastereoselectivities, the iodocyclisation was performed at different temperatures using solvents with varied polarities. It was observed that lowering the reaction temperature to 0 °C increased the overall yield to 90% and marginally improved the diastereoselectivity from 80:20 to 86:14. However, on performing iodocyclisation in CH_2Cl_2 diastereoselectivity decreased and in toluene both yield and diastereoselectivity was lowered (Table 3).

Table 3. Effect of solvent and temperature on iodocyclisation of **2a**

S.no.	Solvent	Temperature (°C)	10:11	Yield (%)
1	CH_3CN	30	20:80	40
2	CH_3CN	0	14:86	90
3	CH_2Cl_2	0	25:75	87
4	Toluene	0	20:80	75

Iodocyclisation of a 64:36 mixtures of **8a** and **9a** in CH_3CN at 0 °C provides a 64:36 mixtures of two diastereomers (Scheme 7). The diastereomeric ratio has been calculated on the basis of integration of 1H singlets due to H-2 protons of two diastereomers at δ 5.57 (major) and 5.94 (minor). The formation of only two compounds indicates that **8a** and **9a** underwent highly regio- and stereoselective iodocyclisation to provide one product each, **12a** and **13a**, respectively. Similarly, iodocyclisation of mixture of **8b**+**9b** in CH_3CN at 0 °C gave **12b** and **13b** in 1:1 ratio (Scheme 7). In case of **12a–12b**, $J_{H4,H5}$=9.3 Hz and in **13a–13b** $J_{H4,H5}$=4.5 Hz show that H-4 and H-5 are placed trans to each other in **12** and cis to each other in **13**. The relative stereochemistries at C-2, C-4 and C-5 carbons in **12a–12b** and **13a–13b** have been assigned on the basis of coupling constants, NOE experiments and by X-ray structure in the case of **12b**.



Scheme 7.

The X-ray crystal structure of **12b** (Fig. 2) shows that CH_2I, C(5) Ph and C(12) H are placed on one face of the five member ring whereas C(12) Ph, OH and CH_3 are on the other face of the five member ring. As a result the protons at

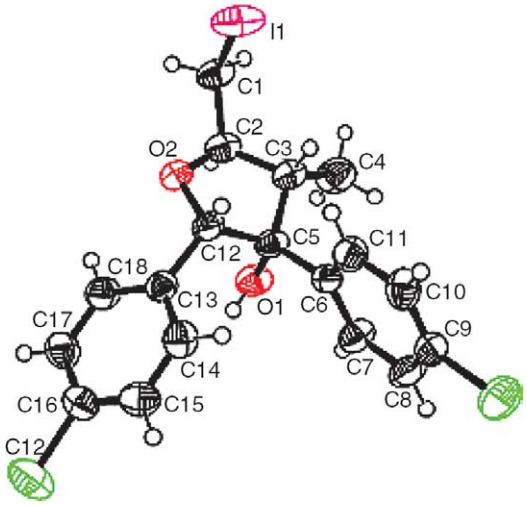
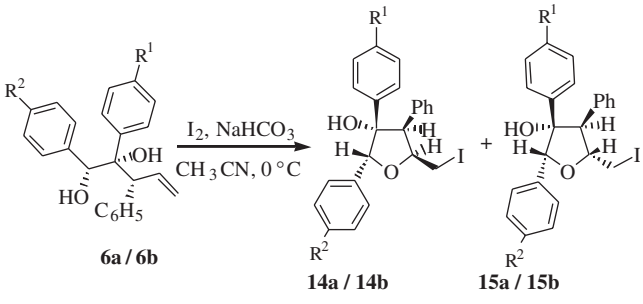


Figure 2. The ORTEP view (50% ellipsoid) of **12b**.

C(2) and C(3) carbons are placed trans to each other. C(12)–O(2)–C(2)–C(3) atoms of the tetrahydrofuran ring are by and large in the same plane and C(5) carbon bearing phenyl and hydroxyl groups moves out of plane making the five member ring as an envelope type structure. All atoms of Cl-Ph rings are in one plane. Cl-Phenyl at the C(5) carbon is almost perpendicular to the plane of five member ring. The results of NOE experiments on **12b** are consistent with the X-ray structure.

Iodocyclisation of **6a** gave a 70:30 mixture of two diastereomers **14a** and **15a** (Scheme 8). ^{1}H NMR of this mixture shows distinct signals for all the protons except aryl protons. The assignment of the signals to specific protons has been made on the basis of 1H decoupling experiments. In the minor component, decoupling of 1H dt at δ 4.87 converts doublets at δ 3.82 and 3.61 into singlets. In the major component, decoupling of H-5 (ddd at δ 5.46) converts H-4 doublet (δ 3.64) into singlet and two double doublets due to CH_2I (δ 3.19 and 3.51) into two doublets. The assignment of relative stereochemisteries at various carbons is made on the basis of NOE experiments. In major diastereomer, irradiation of H-5 (ddd at δ 5.46) shows 14.2% NOE enhancement of H-4 (δ 3.64) and irradiation of H-2 singlet (δ 6.11) shows 9.2% NOE enhancement of 1H of CH_2I (δ 3.51) (Fig. 3). Therefore, H-2 and CH_2I



		yield	d. r.
For **14** and **15**	(a) $R^1 = R^2 = H$	80%	70:30
	(b) $R^1 = R^2 = Cl$	75%	53:47

Scheme 8.

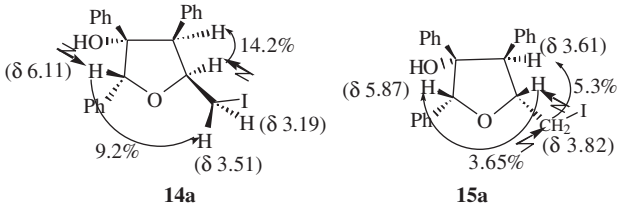


Figure 3. The relative stereochemistries in **14a** and **15a** from NOE experiments.

are on same face and H-4 and H-5 are on the other face of tetrahydrofuran ring and assign structure (2*R**,3*S**,4*S**,5*S**)-**14a** to the major component.

In the case of minor diastereomer, irradiation of H-5 (dt, δ 4.87) shows 3.65% NOE enhancement of H-2 and irradiation of CH_2I (d, δ 3.82) shows 5.34% NOE enhancement of CH-4 (δ 3.61). Therefore, H-5 and H-2 are on same face of the furan ring and CH_2I and H-4 are on the other face of the furan ring (Fig. 3). These spectral data assign structure (2*R**,3*S**,4*S**,5*R**)-**15a** to the minor component. Similarly, **6b** on iodocylisation gave non-separable mixture of **14b** and **15b**.

3. Conclusion

The benzoins in indium mediated allylation reactions follow Cram's chelation model to provide mainly or only *syn*-addition products. The reactions are more sluggish than for α-hydroxy aldehdyes but exhibit higher regio- and diastereoselectivity and are significantly affected by the electron-densities available on the ketone carbon and the reactivity of the allylic anion. The more reactive allylic and crotyl anions add on the benzoins **1a**–**1d**, but cinnamyl anion adds on electron-deficient benzoins **1a** and **1b** only and least reactive ethyl crotonate anion fails to react with all the benzoins. The diastereoselectivities in iodine mediated intramolecular cyclizations are significantly affected by the substituent at C-3 of the homoallylic alcohols. Also the presence or absence of a substituent at C-4 carbon do not affect the preffered relative stereochemistries at C-2 and C-5 carbons and in the case of the only or the major iodocyclized tetrahydrofuran derivatives C2-Ph and C-5 CH_2I are placed on the opposite face.

4. Experimental

4.1. General details

Melting points were determined in capillaries. ^{1}H and ^{13}C NMR spectra were run on JEOL 300 and 75 MHz NMR, respectively, using $CDCl_3$ as solvent. Chemical shifts are given in ppm with TMS as an internal reference. *J* values are given in Hertz. Chromatography was performed with silica 100–200 mesh and the reactions were monitored by thin-layer chromatography (TLC) with silica plates coated with silica gel HF-254.

4.2. General procedure

Procedure A. Barbier type conditions: the carbonyl compound **1** (5 mmol), allyl bromide (7.5 mmol), indium metal (5 mmol) were taken in THF–H_2O (2/1) mixture (10 mL) and the reaction mixture was stirred at 30+2 °C till the indium metal dissolved. The turbid reaction mixture was treated with 4 N HCl and was extracted with $CHCl_3$ (3× 25 mL). The organic phase was dried over Na_2SO_4. The solvent was distilled off and the residue was column chromatographed (silica gel, 60–120 mesh) to isolate pure homoallylic alcohol. The reactions of **1** with cinnamyl and crotyl bromides were performed at 0 °C.

4.2.1. (1*R,2*S**)-1,2-Diphenyl-pent-4-ene-1,2-diol (3a).** Procedure A. 1.17 g, 92%, white solid, mp 95 °C ($CHCl_3$); M^+ *m/z* 237 (M^+-OH); ^1H NMR ($CDCl_3$): δ 2.58 (s, 1H, OH, exchanges with D_2O), 2.59 (s, 1H, exchanges with D_2O, OH), 2.77 (dd, $J_1=14.1$ Hz, $J_2=8.7$ Hz, 1H, 1H of CH_2), 2.93 (dd, $J_1=14.1$ Hz, $J_2=5.7$ Hz, 1H, 1H of CH_2), 4.80 (s, 1H, CH), 5.06–5.26 (m, 2H, $=CH_2$), 5.50–5.63 (m, 1H, =CH), 6.96–7.23 (m, 10H, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 42.4 (CH_2), 78.3 (C), 80.4 (CH), 119.8 (CH_2), 126.5 (CH), 126.9 (CH), 127.4 (CH), 127.6 (CH), 127.7 (CH), 133.2 (CH), 139.2 (C), 141.4 (C); IR ν_{max} (KBr): 3469 (OH), 3552 (OH) cm^{-1}. (Found C 80.1%, H 6.9% $C_{17}H_{18}O_2$ requires C 80.28%, H 7.13%).

4.2.2. (1*R,2*S**)-1,2-Bis(4-chloro-phenyl)-pent-4-ene-1,2-diol (3b).** 726 mg, 45%, white solid, mp 92 °C, FAB mass M^+ *m/z* 323, 325, 327 (100:69:1) (M^+); ^1H NMR ($CDCl_3$): δ 2.61 (br s, 2H, 2×OH), 2.71 (dd, $J_1=14$ Hz, $J_2=8.7$ Hz, 1H, 1H of CH_2), 2.87 (dd, $J_1=14$ Hz, $J_2=5.4$ Hz, 1H, 1H of CH_2), 4.72 (s, 1H, CH), 5.12–5.21 (m, 2H, $=CH_2$), 5.49–5.59 (m, 1H, CH), 6.92–7.26 (m, 8H, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 42.5 (CH_2), 77.9 (C), 79.6 (CH), 120.4 (CH_2), 127.7 (CH), 127.9 (CH), 129.1 (CH), 131.5 (CH), 132.5 (CH), 133.0 (C), 133.5 (C), 137.6 (C) 139.8 (C); IR ν_{max} (KBr): 3348 (OH), 3421 (OH) cm^{-1}. (Found C 63.0%, H 4.7% $C_{17}H_{16}O_2Cl_2$ requires C 63.17%, H 4.99%).

4.2.3. (1*R,2*S**)-1-(4-Methoxy-phenyl)-2-phenyl-pent-4-ene-1,2-diol (3c).** Procedure A. 979 mg, 69%, light yellow liquid, FAB mass M^+ *m/z* 284 (M^+); ^1H NMR ($CDCl_3$): δ 2.53 (br s, 1H, OH, exchanges with D_2O), 2.57 (br s, 1H, OH, exchanges with D_2O), 2.71 (dd, $J_1=14$ Hz, $J_2=8.7$ Hz, 1H, 1H of CH_2), 2.90 (dd, $J_1=14$ Hz, $J_2=5.4$ Hz, 1H, 1H of CH_2), 3.77 (s, 3H, OCH_3), 4.81 (s, 1H, CH), 5.08–5.19 (m, 2H, $=CH_2$), 5.51–5.63 (m, 1H, CH), 6.74 (d, $J=8.7$ Hz, 2H, ArH), 6.99–7.21 (m, 7H, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 42.3 (CH_2), 55.1 (CH_3), 78.1 (C), 80.5 (CH), 112.9 (CH), 119.7 (CH_2), 127.4 (CH), 127.6 (CH), 127.8 (CH), 127.9 (CH), 127.9 (CH), 128.4 (CH), 130.1 (CH), 132.3 (CH), 133.2 (CH), 133.3 (CH), 133.4 (C), 139.3 (C), 158.4 (C); IR ν_{max} ($CHCl_3$): 3390 (OH), 3430 (OH) cm^{-1}. (Found C 76.5%, H 6.90% $C_{18}H_{20}O_3$ requires C 76.03%, H 7.09%).

4.2.4. (1*R,2*S**)-1,2-Bis(4-methoxy-phenyl)-pent-4-ene-1,2-diol (3d).** 1.13 g, 72%, white solid, mp 90 °C ($CHCl_3$); FAB mass M^+ *m/z* 314 (M^+); ^1H NMR ($CDCl_3$): δ 2.59 (br s, 2H, 2×OH, exchanges with D_2O), 2.68 (dd, $J_1=14$ Hz, $J_2=8.7$ Hz, 1H, 1H of CH_2), 2.85 (dd, $J_1=14$ Hz, $J_2=5.4$ Hz, 1H, 1H of CH_2), 3.73 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 4.74 (s, 1H, CH), 5.07–5.18 (m, 2H, $=CH_2$), 5.52–5.63 (m, 1H, CH), 6.67 (d, $J=9$ Hz, 2H, ArH), 6.72 (d, $J=9$ Hz, 2H, ArH), 6.91 (d, $J=9$ Hz, 2H, ArH), 7.03 (d, $J=9$ Hz, 2H, ArH); the decoupling of 2H doublet at δ 6.91 converts doublet at δ 6.67 into singlet and decoupling of doublet at δ 7.03 converts doublet at δ 6.72 into singlet. This indicates that two doublets at δ 7.03 and 6.72 and two doublets at δ 6.67 and 6.91 are due to protons of the same ring. ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 42.4 (CH_2), 55.0 (OCH_3), 55.4 (OCH_3), 78.1 (C), 80.1 (CH), 112.7 (CH), 112.8 (CH), 119.5 (CH_2), 127.8 (CH), 128.9 (CH), 131.5 (C), 133.4 (CH), 133.5 (C), 158.3 (C), 158.9 (C); IR ν_{max} (KBr): 3369 (OH), 3404 (OH) cm^{-1}. (Found C 72.30%, H 6.98% $C_{19}H_{22}O_4$ requires C 72.59%, H 7.05%).

4.2.5. (1*R,2*S**,3*R**)-1,2,3-Triphenyl-pent-4-ene-1,2-diol (6a).** 1.40 g, 85%, pale yellow liquid, FAB mass M^+ *m/z* 330 (M^+); ^1H NMR ($CDCl_3$): δ 3.02 (br s, 2H, 2×OH, exchanges with D_2O), 4.14 (d, $J=8.7$ Hz, 1H, CHPh), 5.11–5.17 (m, 2H, $=CH_2$), 5.22 (s, 1H, CHOH), 6.15 (dt, $J_1=18$ Hz, $J_2=9$ Hz, 1H, =CH), 7.02–7.56 (m, 15H, ArH). The decoupling of dt at δ 6.15 converts doublet at δ 4.14 into singlet and multiplet at δ 5.10–5.16 into broad singlet. ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 58.2 (CH), 76.9 (CH), 80.8 (C), 117.9 (CH_2), 126.9 (CH), 127.1 (CH), 127.4 (CH), 127.5 (CH), 128.4 (CH), 128.6 (CH), 130.0 (CH), 130.3 (CH), 138.2 (CH), 139.6 (C), 139.9 (C), 140.8 (C); IR ν_{max} ($CHCl_3$): 3446 (OH), 3523 (OH) cm^{-1}. (Found C 82.75%, H 6.23% $C_{23}H_{22}O_2$ requires C 83.60%, H 6.71%).

4.2.6. (1*R,2*S**,3*R**)-1,2-Bis(4-chloro-phenyl)-3-phenyl–pent-4-ene-1,2-diol (6b).** 1.76 g, 88%, white solid, mp 72 °C ($CHCl_3$); FAB mass M^+ *m/z* 399 (M^+), 401, 403 (100:69:1) (M^+);^1H NMR ($CDCl_3$): δ 3.01 (br s, 1H, OH, exchanges with D_2O), 4.10 (d, $J=9.3$ Hz, 1H, CHPh), 5.13–5.18 (m, 3H, $=CH_2$, C*H*OH), 5.85 (br s, 1H, exchanges with D_2O), 6.10 (ddd, $J_1=13.8$ Hz, $J_2=9$ Hz, $J_3=6.3$ Hz, 1H, =CH), 6.97–7.41 (m, 13H, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 58.3 (CH), 75.4 (CH), 76.1 (CH), 80.4 (C), 118.5 (CH_2), 127.2 (CH), 130.4 (CH), 131.2 (CH), 134.7 (C), 137.5 (CH), 138.2 (C), 138.9 (C), 139.2 (C), 140.7 (C); IR ν_{max} (KBr): 3421 (OH), 3434 (OH) cm^{-1}. (Found C 68.9%, H 4.9% $C_{23}H_{20}O_2Cl_2$ requires C 69.18%, H 5.05%).

4.2.7. (1*R,2*S**,3*R**)-3-Methyl-1,2-diphenyl-pent-4-ene-1,2 diol (8a)+(1*R**,2*S**,3*S**)-3-methyl-1,2-diphenyl-pent-4-ene-1,2 diol (9a).** 998 mg, 78%, pale yellow liquid, FAB mass M^+ *m/z* 268 (M^+); ^1H NMR ($CDCl_3$): δ 0.90 (d, $J=6.6$ Hz, 3H, $CH_{3\text{-major}}$), 1.02 (d, $J=6.9$ Hz, 3H, $CH_{3\text{-minor}}$), 1.25 (br s, 2H, 2×OH, exchanges with D_2O), 2.92–2.99 (m, 1H, CH_{major}), 3.02–3.09 (m, 1H, CH_{minor}), 5.12–5.34 (m, 3H, 2H of $=CH_2$, 1H of CHOH), 5.86 (ddd, $J_1=18.3$ Hz, $J_2=9.9$ Hz, $J_3=7.8$ Hz, 1H, $=CH_{minor}$), 6.13 (ddd, $J_1=19.2$ Hz, $J_2=9.0$ Hz, $J_3=8.1$ Hz,1H, $=CH_{major}$), 6.98–7.19 (m, 10H, ArH); decoupling of doublet at δ 0.90 due to $CH_{3\text{-major}}$ converts multiplet at δ 2.92–2.99 into doublet while decoupling of d at δ 1.06 converts multiplet at 3.02–3.09 into doublet; ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 14.2 ($CH_{3\text{-minor}}$), 16.2 ($CH_{3\text{-major}}$), 44.6 ($CH_{\text{-minor}}$), 45.2 (CH_{major}), 76.6 (CH), 77.9 (CH), 80.6 ($C_{\text{-minor}}$),

80.8 ($C_{\text{-major}}$), 116.4 ($CH_{2\text{-minor}}$), 116.8 ($CH_{2\text{-major}}$), 126.6 (CH), 126.7 (C), 126.8 (CH), 127.1 (CH), 127.2 (CH), 127.4 (CH), 127.5 (C), 127.5 (CH), 127.6 (CH), 127.8 (CH), 127.9 (CH), 140.3 (CH), 141.1 (CH); IR ν_{max} ($CHCl_3$): 3479 (OH), 3492 (OH) cm^{-1}. (Found C 80.27%, H 7.12% $C_{18}H_{20}O_2$ requires C 80.56%, H 7.51%).

4.2.8. (1*R,2*S**,3*R**)-1,2-Bis(4-chloro-phenyl-3-methyl-pent-4-ene-1,2-diol (8b)+(1*R**,2*S**,3*S**)-3-methyl-1,2-bis(4-chloro-phenyl)-pent-4-ene-1,2-diol (9b).** 1.19 g, 71%, light yellow liquid, FAB mass M^+ *m/z* 337, 339, 341 (100:69:1) (M^+); ^1H NMR ($CDCl_3$): δ 0.86 (d, J=6.9 Hz, 3H, $CH_{3\text{-minor}}$), 0.97 (d, J=6.9 Hz, 3H, $CH_{3\text{-major}}$), 1.93 (br s, 1H, exchanges with D_2O), 2.39–2.41 (m, 1H, CH_{minor}), 2.52–2.58 (m, 1H, CH_{major}), 4.61 (d, J=7.5 Hz, 1H, CHPh), 5.02–5.09 (m, 2H, $=CH_2$), 5.78 (ddd, J_1=17.4 Hz, J_2=10.2 Hz, J_3=7.8 Hz, 1H, $=CH_{major}$), 6.05 (ddd, J_1=17.1 Hz, J_2=10.2 Hz, J_3=9 Hz, 1H, $=CH_{minor}$), 7.22–7.32 (m, 6H, ArH), 7.49 (d, J=8.7 Hz, 1H, ArH), 7.92 (d, J=8.7 Hz, 1H, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): (major component) δ 13.8 ($CH_{3\text{-major}}$), 44.6 (CH_{major}), 76.5 (CH), 77.2 (C), 115.9 ($CH_{2\text{-major}}$), 127.8 (CH_{major}), 128.5 (CH_{major}), 131.3 (CH_{major}), 132.9 (CH_{major}), 132.3 (CH), 139.9 (CH_{major}), 140.2 (C_{major}), 141.8 (C_{major}), 192.4 (C_{major}). Some signals for minor component are at δ 14.1 ($CH_{3\text{-minor}}$), 46.4 (CH_{minor}), 117.3 ($CH_{2\text{-minor}}$), 128.4 (CH_{minor}), 140.2 (CH_{minor}); IR ν_{max} ($CHCl_3$): 3446 (OH) cm^{-1}. (Found C 63.90%, H 5.00% $C_{18}H_{18}Cl_2O_2$ requires C 64.11%, H 5.38%).

4.2.9. (1*R,2*S**,3*R**)-1,2-Bis(4-methoxy-phenyl)-3-methyl-pent-4-ene-1,2 diol (8c)+(1*R**,2*S**,3*S**)-3-methyl-1,2-bis(4-methoxy-phenyl)-pent-4-ene-1,2 diol (9c).** 1.21 g, 74%, light yellow liquid, FAB mass M^+ *m/z* 328 (M^+); ^1H NMR ($CDCl_3$): δ 0.89 (d, J=6.9 Hz, 3H, $CH_{3\text{-major}}$), 1.01 (d, J=6.6 Hz, 3H, $CH_{3\text{-minor}}$), 1.25 (br s, 2H, 2×OH, exchanges with D_2O), 2.83–2.86 (m, 1H, CH_{major}), 2.90–2.95 (m, 1H, CH_{minor}), 3.73 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 5.19–5.29 (m, 3H, $=CH_2$, CHOH), 5.82 (ddd, J_1=17.4 Hz, J_2=13.4 Hz, J_3=10.5 Hz, 1H, $=CH_{minor}$), 6.11 (ddd, J_1=17.1 Hz, J_2=10.2 Hz, J_3=9 Hz, 1H, $=CH_{major}$), 6.64–6.74 (m, 4H, ArH), 6.96–7.08 (m, 4H, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 14.2 ($CH_{3\text{-minor}}$), 16.2 ($CH_{3\text{-major}}$), 44.5 (CH_{minor}), 44.8 (CH_{major}), 55.0 ($OCH_{3\text{-minor}}$), 55.1 ($OCH_{3\text{-major}}$), 76.1 (CH_{minor}), 77.4 (CH_{major}), 80.4 (C_{minor}), 80.6 (C_{major}), 112.4 (CH_{minor}), 112.5 (CH_{major}), 112.8 (CH_{major}), 113.0 (CH_{minor}), 116.2 ($CH_{2\text{-minor}}$), 116.6 ($CH_{2\text{-major}}$), 127.9 (CH_{minor}), 128.1 (CH_{major}), 129.1 (CH_{major}), 129.2 (CH_{minor}), 131.8 (C_{major}), 132.4 (C_{minor}), 132.4 (C_{minor}), 132.5 (CH_{major}), 140.5 (CH_{minor}), 140.1 (CH_{major}), 158.1 (C_{minor}), 158.2 (C_{major}), 158.8 (C_{major}). Signals for major and minor compounds are assigned on the basis of ^1H–^{13}C HETCOR experiment); IR ν_{max} ($CHCl_3$): 3395 (OH), 3440 (OH) cm^{-1}. (Found C 72.85%, H 7.11% $C_{20}H_{24}O_2$ requires C 73.15%, H 7.37%).

4.3. Iodine mediated cyclization of homoallylic alcohols

Procedure B. Sodium hydrogen carbonate (9 mmol) was added to an ice cold solution of homoallylic alcohol (3 mmol) in dry acetonitrile and resulting suspension was stirred for 15 min at 0 °C. Iodine (9 mmol) was added and stirring was continued for 24–72 h at 0 °C in dark (TLC monitoring). The reaction mixture was diluted with water and extracted with $CHCl_3$. The organic layer was washed with saturated aqueous sodium thiosulphate to remove excess of iodine. The organic layer was dried over anhydrous sodium sulphate and was distilled off. The residue was column chromatographed (silica gel 100–200) to isolate substituted tetrahydrofuran derivatives.

4.3.1. (2*R,3*S**,5*R**)-2,3-Diphenyl-3-hydroxy-5-iodomethyl tetrahydrofuran (10).** Procedure B. Higher R_f component: 91 mg, 8%; white solid, mp 98 °C ($CHCl_3$); FAB mass M^+ *m/z* 380; ^1H NMR ($CDCl_3$): δ 1.92 (br s, 1H, exchanges with D_2O), 2.48 (dd, J_1=14.1 Hz, J_2=3.9 Hz, 4-H_b), 2.78 (dd, J_1=14.8 Hz, J_2=9 Hz, 4-H_a), 3.63 (d, J=6.6 Hz, 2H, 5-CH_2I), 4.57–4.72 (m, 1H, 5-H), 5.29 (s, 1H, 2-H), 7.04–7.39 (m, 10H, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 10.7 (CH_2I), 48.4 (CH_2-4), 77.9 (CH-5), 82.2 (C-3), 90.8 (CH-2), 125.2 (CH), 126.5 (CH), 127.2 (CH), 128.2 (CH), 128.2 (CH), 134.7 (C), 141.9 (C). NOE experiments: irradiation of singlet at δ 5.29 (2-H) shows positive NOE with signals at δ 4.57–4.72 (5-H), 2.79 (4-H_a) and 7.05, 7.39 (ArH) and irradiation of multiplet at δ 4.57–4.72 (5-H) shows positive NOE with dd at δ 2.79 and doublet at δ 3.63 shows positive NOE with dd at δ 2.48; IR ν_{max} (KBr): 3421 (OH) cm^{-1}. (Found C 53.4%, H 4.2% $C_{17}H_{17}IO_2$ requires C 53.70%, H 4.51%).

4.3.2. (2*R,3*S**,5*S**)-2,3-Diphenyl-5-iodo methyltetrahydro-furan-3-ol (11).** Procedure B. Lower R_f component: 365 mg, 32%; pale yellow liquid; M^+ *m/z* 380 (M^+); ^1H NMR ($CDCl_3$): δ 1.79 (br s, 1H, exchanges with D_2O), 2.45 (dd, J_1=12.9 Hz, J_2=9.3 Hz, 4-H_a), 2.62 (dd, J_1=10.2 Hz, J_2=6.0 Hz, H-4$_b$), 3.49 (dd, J_1=10.2 Hz, J_2=3.3 Hz, 1H of CH_2I), 3.60 (dd, J_1=10.2 Hz, J_2=6.0 Hz, 1H of CH_2I), 4.50–4.59 (m, 1H, H-5), 5.51 (s, 1H, H-2), 6.98–7.45 (m, 10H, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 12.4 (CH_2I), 49.4 (CH_2-4), 77.1 (CH-5), 83.4 (C-3), 89.9 (CH-2), 125.3 (CH), 126.6 (CH), 127.4 (CH), 128.3 (CH), 128.4 (CH), 135.1 (C), 141.2 (C). NOE experiments: irradiation of singlet at δ 5.51 (2-H) shows NOE for signals at δ 2.45 (4-H_a) and Ph (δ 7.04, 7.45) but does not show NOE for H-5 (δ 4.50–4.59). The dd at δ 2.62 (H_b) shows positive NOE with signal at H-5 (δ 4.50–4.59); IR ν_{max} ($CHCl_3$): 3546 (OH) cm^{-1}. (Found C 53.4%, H 4.2% $C_{17}H_{17}IO_2$ requires C 53.70%, H 4.51%).

4.3.3. (2*R,3*S**,4*R**,5*S**)-2,3-Diphenyl-4-methyl-5-iodomethyl tetrahydro-furan-3-ol (12a).** Procedure B. 804 mg, 68%, white solid, mp 98 °C ($CHCl_3$); FAB mass M^+ *m/z* 394 (M^+); ^1H NMR ($CDCl_3$): δ 0.91 (d, J=6.9 Hz, 3H, CH_3), 1.61 (br s, 1H, exchanges with D_2O), 2.68 (dq, J_1=9.3 Hz, J_2=6.6 Hz, 1H, CH), 3.48 (dd, J_1=10.8 Hz, J_2=3.3 Hz, 1H, 1H of CH_2I), 3.76 (dd, J_1=10.8 Hz, J_2=3.9 Hz, 1H, 1H of CH_2I), 3.90 (dt, J_1=9.3 Hz, J_2=3.6 Hz, 1H, CH-5), 5.56 (s, 1H, CH-2), 7.02–7.30 (m, 2H, ArH), 7.32–7.47 (m, 8H, ArH); decoupling of dq at δ 2.68 converts doublet at δ 0.91 due to CH_3 into singlet while decoupling of double doublet at δ 3.48 converts double doublet at δ 3.76 into doublet and dt at δ 3.90 into double doublet; ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 8.7 (CH_3), 12.3 (CH_2), 52.5 (CH), 82.1 (CH), 83.9 (C), 89.5 (CH), 125.6 (CH), 126.6 (CH), 127.4 (CH), 128.3 (CH), 128.3 (CH), 128.4 (CH),

135.4 (C), 140.7 (C). NOE experiments: the irradiation of H-4 dq at δ 2.68 shows NOE with H-2 (7.06%) and CH_2I (3.77, 2.77%). Irradiation of H-5 (δ 3.88–3.93) shows NOE with CH_3 (10.6%) (d, δ 0.92) and irradiation 1H of CH_2I at δ 3.76 shows 16.1% NOE with H-2 and irradiation of other CH_2I proton at δ 3.48 shows 2.8% NOE with H-2 proton at δ 5.56; IR ν_{max} (KBr): 3550 (OH) cm^{-1}. (Found C 54.6%, H 4.6% $C_{18}H_{19}IO_2$ requires C 54.84%, H 4.86%).

4.3.4. (2*R,3*S**,4*S**,5*S**)-2,3-Diphenyl-4-methyl-5-iodomethyl tetrahydro-furan-3-ol (13a).** Procedure B. 590 mg, 5%; pale yellow liquid; FAB mass M^+ *m/z* 394 (M^+); ^1H NMR ($CDCl_3$): δ 0.78 (d, $J=7.5$ Hz, 3H, CH_3), 1.64 (br s, 1H, OH exchanges with D_2O), 2.52 (dq, $J_1=7.5$ Hz, $J_2=4.5$ Hz, 1H, CH-4), 3.15 (t, $J=9.3$ Hz, 1H, 1H of CH_2I), 3.44 (dd, $J_1=9.3$ Hz, $J_2=6.3$ Hz, 1H, 1H of CH_2I), 5.10 (ddd, $J_1=9.0$ Hz, $J_2=6.0$ Hz, $J_3=4.5$ Hz, 1H, CH-5), 5.93 (s, 1H, CH), 7.02–7.30 (m, 2H, ArH), 7.32–7.47 (m, 8H, ArH); decoupling of dq at δ 2.52 converts doublet at δ 0.78 due to CH_3 into singlet while decoupling of triplet at δ 3.15 converts dd at δ 3.44 into doublet and ddd at δ 5.10 into dd. Decoupling of ddd at δ 5.10 converts dd (δ 3.44) and triplet (3.15) into doublets and dq at δ 2.52 into a quartet; ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 3.8 (CH_2), 10.2 (CH_3), 48.7 (CH), 82.3 (CH), 83.8 (CH), 86.3 (C), 126.9 (CH), 127.2 (CH), 127.7 (CH), 128.1 (CH), 128.2 (CH), 128.4 (CH), 136.8 (C), 140.5 (C). NOE experiments: the irradiation of CH_3 (d, δ 0.78) shows 2.6% NOE enhancement of H-2 (s, δ 5.93) and 2.1% enhancement of 1H of CH_2I (t, δ 3.15). The irradiation of H-4 (dq, δ 2.52) shows 11% NOE enhancement of H-5 (ddd, δ 5.10). Irradiation of H-2 singlet at δ 5.93 shows 2.5% NOE enhancement of 1H of CH_2I (dd, δ 3.44); IR ν_{max} ($CHCl_3$): 3495 (OH) cm^{-1}. (Found C 54.34%, H 4.70% $C_{18}H_{19}IO_2$ requires C 54.84%, H 4.86%).

4.3.5. (2*R,3*S**,4*R**,5*S**)-2,3-Bis(4-chlorophenyl)-4-methyl-5-iodomethyltetrahydrofuran-3-ol (12b).** Procedure B. 930 mg, 68%, white solid, mp 120 °C ($CHCl_3$); FAB mass M^+ *m/z* 463 (M^+); ^1H NMR ($CDCl_3$): δ 0.90 (d, $J=6.9$ Hz, 3H, CH_3), 1.49 (br s, 1H, exchanges with D_2O), 2.63 (dq, $J_1=9$ Hz, $J_2=6.9$, 1H, CH-4), 3.47 (dd, $J_1=10.8$ Hz, $J_2=3.3$ Hz, 1H, 1H of CH_2I), 3.75 (dd, $J_1=10.8$ Hz, $J_2=3.6$ Hz, 1H, 1H of CH_2I), 3.86 (dt, $J_1=9.3$ Hz, $J_2=3.6$ Hz, 1H, CH-5), 5.46 (s, 1H, CH-2), 6.94–6.98 (m, 2H, ArH), 7.20–7.26 (m, 2H, ArH), 7.32–7.38 (m, 8H, ArH); decoupling of dq at δ 2.63 converts doublet at δ 0.90 due to CH_3 into singlet and double triplet at δ 3.86 into singlet while decoupling of dd at δ 3.47 converts double doublet at δ 3.75 into doublet and dt at δ 3.86 into triplet; ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 8.6 (CH_3), 12.0 (CH_2), 52.3 (CH), 81.9 (CH), 83.6 (C), 88.8 (CH), 127.0 (CH), 127.9 (CH), 128.5 (CH), 128.7 (CH), 133.5 (CH), 133.7 (CH), 134.2 (C), 138.9 (C). NOE experiments: the irradiation of H-2 singlet at δ 5.46 shows 6.03% NOE with H-4 (δ 2.63); irradiation of CH_3 doublet at δ 0.90 shows 2.5% NOE with H-5 (δ 3.86) and irradiation of one of CH_2I proton at δ 3.47 shows 4% NOE with H-4; IR ν_{max} (KBr): 3529 (OH) cm^{-1}. (Found C 47.00%, H 3.20% $C_{18}H_{17}Cl_2IO_2$ requires C 46.68%, H 3.70%).

4.3.6. (2*R,3*S**,4*S**,5*S**)-2,3-Bis(4-chlorophenyl)-4-methyl-5-iodomethyltetrahydro-furan-3-ol (13b).** Procedure B. 70 mg, 5%; pale yellow liquid; FAB mass M^+ *m/z* 463 (M^+); ^1H NMR ($CDCl_3$): δ 0.79 (d, $J=7.5$ Hz, 3H, CH_3), 1.64 (br s, 1H, OH exchanges with D_2O), 2.49 (dq, $J_1=7.5$ Hz, $J_2=4.5$ Hz, 1H, CH-4), 3.13 (t, $J=9.3$ Hz, 1H, 1H of CH_2I), 3.42 (dd, $J_1=9.9$ Hz, $J_2=6.3$ Hz, 1H, 1H of CH_2I), 5.07 (ddd, $J_1=9.0$ Hz, $J_2=5.4$ Hz, $J_3=4.5$ Hz, 1H, CH-5), 5.81 (s, 1H, CH), 7.03–7.50 (m, 10H, ArH); decoupling of dq at δ 2.49 converts doublet at δ 0.79 due to CH_3 into singlet and ddd at δ 5.07 into a dd, while decoupling of ddd at δ 5.07 converts dd at δ 3.42 and triplet at δ 3.13 into two doublets and dq at δ 2.49 into quartet; ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 3.4 (CH_2), 10.2 (CH_3), 48.7 (CH), 82.5 (CH), 83.3 (CH), 86.0 (C), 128.3 (CH), 128.4 (CH), 128.6 (CH), 128.7 (CH), 133.9 (C), 134.1 (C), 135.1 (C), 138.8 (C). NOE experiments: the irradiation of CH_3 (d, δ 0.79) shows 3.62% NOE enhancement of H-2 (s, δ 5.81) and 3.36% enhancement of 1H of CH_2I (t, δ 3.13). The irradiation of H-4 (ddd, δ 2.49) shows 13.06% NOE enhancement of H-5 (ddd, δ 5.07); IR ν_{max} ($CHCl_3$): 3436 (OH) cm^{-1}. (Found C 47.05%, H 3.26% $C_{18}H_{17}Cl_2I\ O_2$ requires C 46.68%, H 3.70%).

4.3.7. (2*R,3*S**,4*S**,5*S**)-2,3,4-Triphenyl-5-iodomethyl tetrahydro-furan-3-ol (14a) (2*R**,3*S**,4*S**,5*R**)-2,3,4-triphenyl-5-iodomethyltetrahydro-furan-3-ol (15a).** Procedure B. 1.1 g, (81%), transparent liquid, FAB mass M^+ *m/z* 456 (M^+); ^1H NMR ($CDCl_3$): (major) (**14a**): δ 1.79 (br s, 1H, OH exchanges with D_2O), 3.19 (dd, $J_1=9.6$ Hz, $J_2=8$ Hz, 1H, 1H of CH_2I), 3.51 (dd, $J_1=9.6$ Hz, $J_2=6.9$ Hz, 1H, 1H of CH_2I), 3.64 (d, $J=4.5$ Hz, 1H, H-4), 5.46 (ddd, $J_1=7.2$ Hz, $J_2=6.9$ Hz, $J_3=4.5$ Hz, 1H, H-5), 6.11 (s, 1H, CH-2), 6.95–7.26 (m, 15H, ArH $_{(major+minor)}$). Compound **15a** (minor): δ 1.84 (br s, 1H, OH exchanges with D_2O), 3.61 (d, $J=3.9$ Hz, 1H, H-4), 3.82 (d, $J_1=6.6$ Hz, 2H, CH_2I), 4.87 (dt, $J_1=6.6$ Hz, $J_2=3.9$ Hz, 1H, H-5), 5.87 (s, 1H, CH-2). Decoupling of dt at δ 4.87 due to minor component converts doublet at δ 3.82 and 3.61 into singlet. Decoupling of 1H ddd at δ 5.46 (H-5 major diastereomer) converts H-4 doublet (δ 3.64) into singlet and two dds of CH_2I (δ 3.19 and 3.51) into two doublets; ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): (compound **14a** major) δ 4.2 (CH_2), 63.2 (CH), 83.1 (CH), 85.2 (CH), 86.3 (C), 126.4 −139.8 (CH). Compound **15a** (minor) δ 10.5 (CH_2), 63.7 (CH), 84.3 (CH), 86.6 (CH), 86.8 (C). ^{13}C NMR signals have been assigned on the basis of ^1H–^{13}C HETCOR experiment. NOE experiments: in major diastereomer, irradiation of H-5 (ddd, δ 5.46) shows NOE with H-4 (14.2%, δ 3.63) and irradiation of H-2 (s, δ 6.11) shows NOE with 1H of CH_2I (9.17%, δ 3.51). In minor isomer, irradiation of H-5 (dt, δ 4.87) shows NOE with H-2 (4.76%, δ 5.87) and irradiation of CH_2I (d, δ 3.82) shows NOE with CH-4 (5.34%, δ 3.61). IR_{major} ν_{max} ($CHCl_3$): 3535 (OH) cm^{-1}. (Found C 59.89%, H 4.92% $C_{23}H_{21}IO_2$ requires C 60.54%, H 4.64%).

4.3.8. (2*R,3*S**,4*S**,5*S**)-2,3-Bis(4-chloro-phenyl)-5-iodo methyl-4-phenyl-tetrahydro-furan-3-ol (14b) (2*R**, 3*S**,4*S**,5*R**)-2,3,4-triphenyl-5-iodomethyltetrahydro-furan-3-ol (15b).** Procedure B. 1.05 g, (81%), transparent liquid, FAB mass M^+ *m/z* 525 (M^+); ^1H NMR ($CDCl_3$): (major) (**14b**): δ 1.72 (br s, 1H, OH exchanges with D_2O), 3.18 (dd, $J_1=9.9$ Hz, $J_2=8.4$ Hz, 1H, 1H of CH_2I), 3.49 (dd, $J_1=9.6$ Hz, $J_2=7.2$ Hz, 1H, 1H of CH_2I), 3.60 (t, $J=$

3.9 Hz, 1H, H-4), 5.42 (ddd, $J_1=8.1$ Hz, $J_2=6.6$ Hz, $J_3=4.5$ Hz, 1H, H-5), 5.97 (s, 1H, CH-2), 7.02 (m, 13H, ArH $_{(major+minor)}$). Compound **15** (minor): δ 1.72 (br s, 1H, OH exchanges with D_2O), 3.49 (t, $J=3.9$ Hz, 1H, H-4), 3.77 (d, $J=6.6$ Hz, 2H,CH_2I), 4.84 (ddd, $J_1=6.6$ Hz, $J_2=6.6$ Hz, $J_3=3.3$ Hz, 1H, H-5), 5.73 (s, 1H, CH-2). In minor component, decoupling of ddd at δ 4.84 converts doublet at δ 3.77 into singlet and triplet at δ 3.59 into distorted triplet. While decoupling of 1H ddd at δ 5.42 (H-5 major diastereomer) converts triplet at δ 3.59 (H-4) into singlet and two dds at δ 3.175 and 3.49 (CH_2I) into two doublets; ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): (compound 14 major) δ 3.6 (CH_2), 63.0 (CH), 83.3 (CH), 84.9 (CH), 86.1 (C), 127.3–138.2 (CH, C)$_{major+minor}$ (compound **15b** minor) δ 10.0 (CH_2), 63.6 (CH), 84.3 (CH), 86.0 (CH), 86.5 (C). In major diastereomer, irradiation of H-5 (ddd, δ 5.42) shows 14% NOE enhancement of H-4 (δ 3.59) and irradiation of H-2 (s, δ 5.97) shows 3.86% NOE enhancement with 1H of CH_2I (δ 3.49). In minor diastereomer, irradiation of H-5 (ddd) shows 2.31% NOE enhancement of H-2 (δ 5.73) and irradiation of CH_2I doublet (δ 3.77) shows 5.17% NOE enhancement of CH-4 (δ 3.59). IR$_{major}$ ν_{max} ($CHCl_3$): 3544 (OH) cm^{-1}. (Found C 53.01%, H 3.98% $C_{23}H_{19}Cl_2IO_2$ requires C 52.60%, H 3.65%).

4.4. X-ray crystal data collection for 12b

X-ray crystal data was measured by using θ–2θ scan mode. The structures were solved by using direct method SHELX-97. CCDC 284604, molecular formulae $C_{18}H_{17}IO_2$; triclinic space group P-1, $a=9.0434$ Å, $b=10.3870$ Å, $c=11.0240$ Å, $\alpha=78.543(4)°$, $\beta=84.009(5)°$, $\gamma=66.497(6)°$, $V=930.33(10)$ Å^3, $Z=2$, $D_c=1.653$ mg/m^3, θ range for data collection 1.89–24.97°. The structure solution is based on 3453 reflections, which converged to $R=0.0150$. Refinement method: full-matrix least squares on $F2$, goodness of fit=1.058.

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Stereoselective synthesis of 2-hydroxymorpholines and aminodiols via a three-component boro-Mannich reaction

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Abstract—The three-component coupling of an 1,2-aminoalcohol, a 1,2-dicarbonyl compound and a boronic acid was investigated. The reaction is supposed to proceed through the formation of a heterocyclic iminium species followed by the addition of the organoboron derivative. The diastereoselectivity of this process is discussed. Best results were observed when the probable intermediate was generated from a preformed 3-phenylthiomorpholin-2-ol. Products of this three-component boro-Mannich could be readily converted to the corresponding aminodiols by reduction with lithium aluminium hydride.

1. Introduction

The 2-hydroxymorpholine structural core is found as a basic skeleton in a wide range of biologically active compounds.[1] For example, Aprepitant **1**, an orally active NK_1 receptor antagonist, shows potent and promising activities for the treatment of chemotherapy-induced emesis and depression.[2] (3,5-Difluorophenyl)morpholinol **2** selectively inhibits norepinephrine uptake with antidepressant properties (Fig. 1).[3]

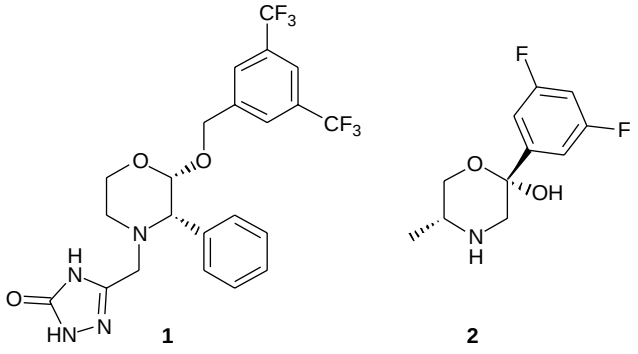

Figure 1.

Based on the NMR structure of the complex between the antibiotic paromomycin and the A-site ribosomal RNA, a set of analogs **3** possessing a morpholino moiety was designed and synthesized.[4] In addition to their antioxidant activities, nitric esters **4** appeared to release NO that can be exploited for the inhibition of artherogenic mechanism (Fig. 2).[5]

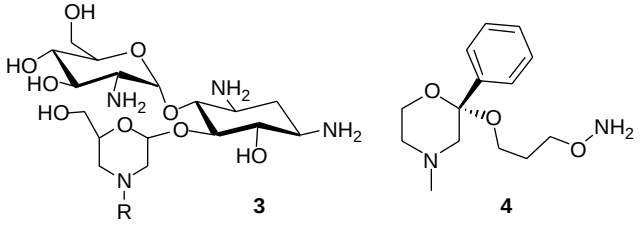

Figure 2.

Besides these remarkable pharmacological properties, 2-hydroxymorpholines are also direct precursors of morpholine-2-ones, their oxidation products. These heterocycles have proven to be versatile intermediates in asymmetric synthesis, as it was amply demonstrated in the stereocontrolled access to α-aminoacids.[6]

Few stereoselective preparations of 2-hydroxymorpholines and derivatives have been hitherto reported. Main procedures include the condensation of an 1,2-aminoalcohol with α-halogeno-ketone,[7] the reaction of an amine with an epoxide [8] and the reduction of morpholin-2-ones.[9] Addition of organometallic reagents to *N*-cyanomethyl-1,3-oxazolidines[10]

Keywords: 2-Hydroxymorpholine; Multicomponent reaction; Boro-Mannich condensation; Boronic acid; Chiral aminodiol.
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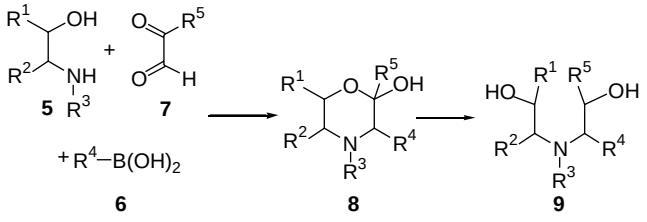
or 2-hydroxy-3-phenylthiomorpholines[11] have been also successfully used in non-racemic series. However, these previous approaches are limited in versatility and restrict the number of accessible structures.

Multicomponent methodologies are still attracting considerable interest due to their high flexibility, selectivity and convergence.[12] Among them, the boro-Mannich reaction, widely developed by Petasis and co-workers, has drawn a lot of attention for the construction of nitrogen-containing systems.[13] With this in mind, we decided to study the three-component condensation of a 1,2-aminoalcool **5**, a boronic acid **6** and a 1,2-dicarbonyl compound **7** (Scheme 1).[14] The use of organoboron compounds is especially valued due to their easily accessibility or commercial availability, their tolerance for a broad range of functional groups, and their air and water stability compared with usual organometallics reagents. We here present a detailed study of the scope and limitations of this reaction, as well as its stereochemical course in the case of chiral *C*-substituted aminoalcohols. Further reduction of the resulting product **8** led to the corresponding aminodiols **9**, some useful ligands in asymmetric catalysis.[15] During the course of our work, Pye and co-workers, from Merck Laboratories, reported an asymmetric version based on the use of a chiral group at the nitrogen atom of the starting aminoalcohol and its application to the synthesis of Aprepitant **1**.[16]



Scheme 1.

2. Results and discussion

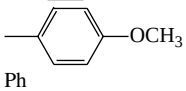
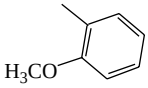
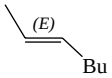
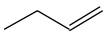
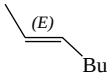
2.1. Synthesis of 2-hydroxymorpholines from achiral 1,2-aminoalcohols

Using *N*-methylaminoethanol ($R^1=R^2=H$, $R^3=Me$), phenylboronic acid ($R^4=Ph$) and glyoxal ($R^5=H$) as models reagents, we first screened several solvents including ethanol, acetonitrile, toluene, tetrahydrofuran and methylene chloride. Of these, ethanol gave best results in terms of yields and reproducibility. The subsequent reactions were therefore carried out by simple mixing equimolar amounts of the aminoalcohol, 1,2-dicarbonyl compound and boronic acid in ethanol for 12 h at room temperature. With aryl and alkenyl boronic acids, the formation of the expected 2-hydroxymorpholines **8** proceeded readily with satisfactory yields and was compatible with the presence of various substituents in different positions of the morpholine core (Table 1). Owing to ring-chain tautomerism, all these compounds were obtained as mixtures of diastereoisomers with a ratio depending on R^3–R^5. In the case of $MeB(OH)_2$, glyoxal and *N*-benzylaminoethanol, the only identified product was the tricyclic compound **10** (see Scheme 3) as previously reported when the reaction was conducted in the absence of the methyl boronic acid.[17] We were also unable to isolate any 2-hydroxy-1,4-oxazepane from *N*-methylaminopropanol instead of *N*-methylaminoethanol.

2.2. Mechanistic hypothesis

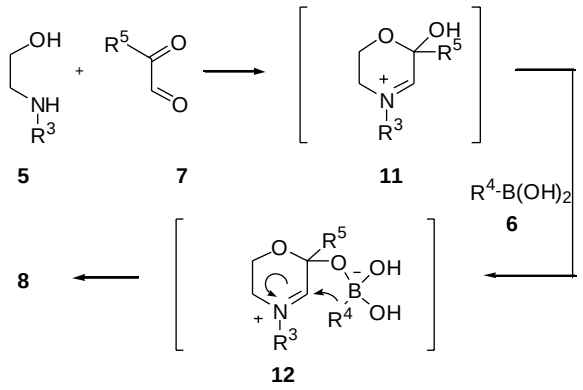
With regard to mechanism, the most plausible hypothesis involves the initial reaction of the amino group of the 1,2-aminoalcohol **5** with the aldehyde function of **7** to give the key intermediate **11**. The coordination between the hydroxyl function of this cyclic iminium species and the boron atom of **6** leads to the formation of a tetracoordinate boron

Table 1. One-pot three-component boro-Mannich reaction with achiral 1,2-aminoalcohols ($R^1=R^2=H$)

Entry	Product	R^3	R^4	R^5	Yield (%)[a]	dr[b]
1	**8a**	Me	Ph	H	62	95/5
2	**8b**	Me		H	65	70/30
3	**8c**	Me		H	80	90/10
4	**8d**	$PhCH_2$	Ph	H	70	85/15
5	**8e**	$PhCH_2$		H	50	80/20
6	**8f**	$PhCH_2$		H	65	75/25
7	**8g**	$PhCH_2$		H	67	60/40
8	**8h**		Ph	H	75	75/25
9	**8i**	$PhCH_2$	Ph	Me	57	85/15
10	**8j**	$PhCH_2$		Me	59	55/45
11	**8k**	$PhCH_2$	Ph	Ph	58	90/10

[a] Yield of isolated product after purification by column chromatography.
[b] Determined by ^1H NMR in $CDCl_3$ solution.

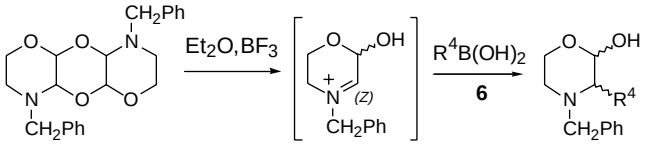
derivative **12** that evolves via an irreversible transfer of the R^4 group to afford the 2-hydroxymorpholine **8** (Scheme 2). Similar intramolecular migrations have been already suggested in the case of 3-hydroxypyrrolidines or salicylaldehyde.[18]



Scheme 2.

2.3. Synthesis of 2-hydroxymorpholines from an activated alkenylboronic ester

No expected 2-hydroxymorpholine was obtained in the one pot procedure from an activated alkenyl boronic acid **5** (R^4=CH=CH–CO_2Me), which may be due to a competitive Michael addition of the amine to the activated double bond. This failure was successfully overcome by using perhydro-4,8-dibenzyl-4,8-diaza-1,5,9,10-tetraoxoanthracene **10** as an iminium precursor in accordance with the suggested mechanism (Scheme 3).[19] By way of comparison with the one pot process, **8d** (R^4=Ph) was obtained from phenylboronic acid in a better yield by this approach.



Compound	R^4	Yd (%)	d.r.
8d	Ph	84	75/25
8l	CO_2Me	76	60/40

Scheme 3.

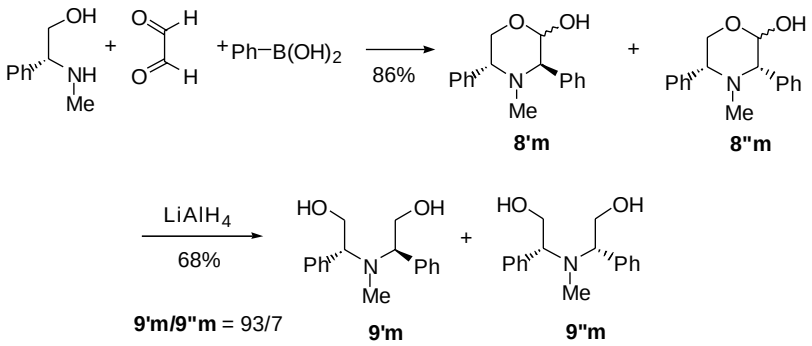
2.4. Synthesis of 2-hydroxymorpholines from chiral 1,2-aminoalcohols

Having developed an efficient method for the preparation of substituted 2-hydroxymorpholines, we then turned our attention to the diastereoselectivity of this process with chiral aminoalcohols. We first chose (1*R*)-*N*-methylphenylglycinol and phenylboronic acid as model reagents. As previously reported, the reaction was carried out in ethanol at room temperature without any special precaution. Compound **8m** was isolated as a mixture of four diastereoisomers (24/69/2/5) in a 86% yield after purification by column chromatography. Stereoselectivity at the new stereocenter C-3 was determined after conversion to the corresponding aminodiols by reduction with $LiAlH_4$. A mixture of two epimers **9′m** and **9″m** was obtained in a 93/7 ratio (Scheme 4).

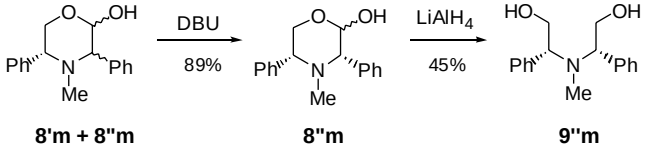
The stereochemistry of the minor isomer **9″m**, and therefore of the major one **9′m**, was determined by treatment of the crude mixture resulting from the boro-Mannich reaction with DBU at 60 °C for 24 h. Under these conditions, epimerisation at C_3 was complete to give the more stable diequatorial compound, that was confirmed after reduction with $LiAlH_4$. Compound **9″m** has indeed an $[\alpha]_D=0$. By comparison, the other epimer **9′m**, which was synthesised from the corresponding thioether **13a** as described further in Scheme 7 (Table 3, entry 1), has an $[\alpha]_D$ +86.5 (*c* 1.35, CH_2Cl_2). (Scheme 5).

To expand the scope and utility of the sequence described in Scheme 4, we envisioned using other boronic acids and 1,2-aminoalcohols. The results of these three-component boro-Mannich reactions followed by the reductive morpholine ring opening are summarized in Table 2 (Scheme 6).

Whatever R^1 and R^2, the control of the configuration at C_3 is definitely more efficient for R^4=Ph than for R^4=alkenyl (entries 1 and 3, 4 and 5, 8 and 9). The replacement of R^2=Ph (entry 1) by R^2=*i*Pr (entry 6) did not induce any significant modification of the diastereoisomeric ratio. Similarly, the same conclusion can be drawn when **5** was substituted at a position α to the oxygen (R^1=Me or Ph, entries 7–9), although it was less significant when the phenyl group is located in α to the oxygen of the starting material. The configuration of the new stereogenic center α to the nitrogen for compounds **9′p**[20] and **9″t**[21] were established from their ^{1}H NMR spectra by comparison



Scheme 4.



Scheme 5.

with literature. For other aminodiols, it was done by analogy with **9′m**, **9′p** or **9′t**. From a stereochemical point of view, the formation of the major compound could be ascribed to a preferred axial attack of the boron derivative that could be favoured by the formation of the tetracoordinate boron complex **12** (Fig. 3).

To improve the stereoselectivity of this reaction, we decided to generate the iminium intermediate from the corresponding 5-phenyl-3-phenylthiomorpholin-2-ols **13**, as previously reported by Agami and co-workers.[19] Compounds **13a** and **13b**, selected as examples, were first prepared by condensation of the aminoalcools **5**, with glyoxal and thiophenol (Scheme 7).

As expected, the addition of a boronic acid in dichloromethane at −78 °C in presence of BF_3–etherate led to the corresponding 2-hydroxymorpholines **8** in good isolated yields (Table 3). Reduction with $LiAlH_4$ in ether gave the corresponding aminoalcohols with good to excellent

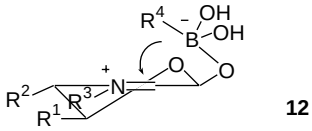
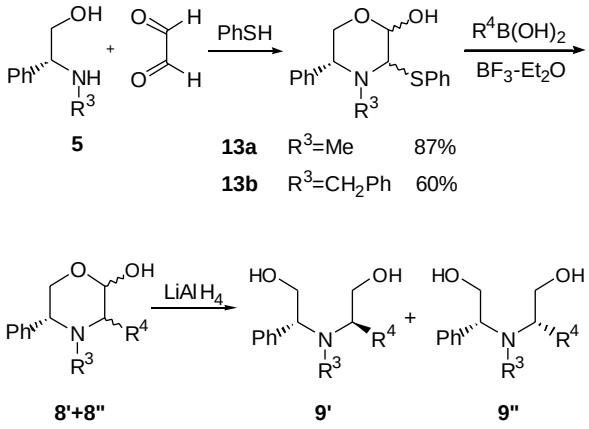
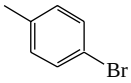
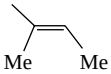


Figure 3.

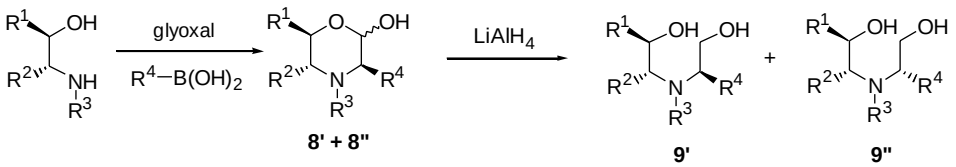


Scheme 7.

Table 2. One-pot three-component boro-Mannich reaction/$LiAlH_4$ reduction

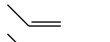
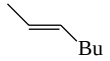
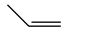
Entry	2-Hydroxy-morpholine	R^1	R^2	R^3	R^4	**8′ + 8″**	**9′ + 9″**	
						Yield (%)[a,b]	Yield (%)[a]	de[c]
1	**8m**	H	Ph	Me	Ph	86	68	86
2	**8n**	H	Ph	Me		47	56	40
3	**8o**	H	Ph	Me		75	78	4
4	**8p**	H	Ph	$PhCH_2$	Ph	76	66	72
5	**8q**	H	Ph	$PhCH_2$		77	63	4
6	**8r**	H	*i*Pr	Me	Ph	74	63	82
7	**8s**	Me	H		Ph	43	76	60
8	**8t**	Ph	H	$PhCH_2$	Ph	66	75	80
9	**8u**	Ph	H	$PhCH_2$		56	72	50
10	**8v**	H	Ph	$PhCH_2$		51	—	—

[a] Yield of isolated product after purification by column chromatography.
[b] All the reactions were performed with optically pure products except **8s**.
[c] Determined by ^1H NMR.



Scheme 6.

Table 3. 2-Hydroxymorpholines **8** and aminodiols **9** from thioethers **13**

Entry	2-Hydroxy-morpholine	R^3	R^4	**8**	**9′+9″**	
				Yield (%)[a]	Yield (%)[a]	de[b]
1	**8m**	Me	Ph	71	96	>98%
2	**8w**	Me		82	92	>98%
3	**8o**	Me		61	72	94
4	**8p**	$PhCH_2$	Ph	65	66	96
5	**8x**	$PhCH_2$		77	72	94

[a] Yield of isolated product after purification by column chromatography.
[b] Determined by ^{1}H NMR.

diastereoisomer excesses from 94 to >98%. This highlights the fact that a modification of the iminium generation can greatly improve the stereoselectivity of the reaction (entries 1, 3 and 4; Tables 2 and 3). The exact origin of this significant amelioration remains unclear for the moment.

3. Conclusion

In conclusion, the preparation of 2-hydroxymorpholines was achieved, either in a one-pot process from aminoalcohol, glyoxal and boronic acid or from a preformed 3-phenylthiomorpholin-2-ol. Better results in term of diastereoselectivity were obtained in the last case. Moreover, the corresponding chiral aminodiols were prepared by reduction with lithium aluminium hydride. Further studies focusing on the use of 2-hydroxymorpholines in the synthesis of more elaborated substrates are underway in our laboratory.

4. Experimental

4.1. General comments

^{1}H NMR spectra (300 MHz) and ^{13}C NMR (75 MHz) were recorded on a Bruker AC 300 spectrometer, ^{1}H NMR spectra (200 MHz) and ^{13}C NMR (50 MHz) on a Bruker ARX 200 spectrometer, in $CDCl_3$ solutions with Me_4Si as internal reference. Chemical shifts are given in parts per million and coupling constants *J* in Hertz. Diethylether and tetrahydrofuran were distilled from Na/benzophenone under N_2, dichloromethane from P_2O_5 under N_2. Elemental analyses were performed by the Microanalytical Laboratory of the Centre National de la Recherche Scientifique, Gif sur Yvette. High-resolution mass (HRMS) data spectrum was recorded on a Varian MAT 311 spectrometer from the Centre Regional de Mesures Physiques de l'Ouest. Analytical thin-layer chromatography was performed on Merck Silica Gel 60 F254 plates. Aminoalcohols **5** and boronic acids **6** are commercially available, except the precursor of **8l**, whose preparation is described further. Thioethers **13a** and **13b** were prepared as described by Agami and co-workers.[19]

4.2. 1-Synthesis of 2-hydroxymorpholines 8a–k from achiral 1,2-aminoalcohols

General procedure. A mixture of 1,2-aminoalcohol **5** (1 mmol), boronic acid **6** (1 mmol) and 1,2-dicarbonyl compound **7** (1 mmol) in ethanol (5 mL) was stirred at room temperature for 12 h. The solvent was removed in vacuo to give crude **8**, which was purified by flash chromatography (silica gel, ethyl acetate/heptane).

4.2.1. 4-Methyl-3-phenylmorpholin-2-ol 8a. Yield 62%, mp 115–17 °C (diisopropylether). Major epimer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.99 (s, 3H), 2.42 (td, J=4.1, 11.6 Hz, 1H), 2.71 (d, J=11.7 Hz, 1H), 2.79 (d, J=7.3 Hz, 1H), 3.80–3.94 (m, 2H), 4.51 (br s, 1H), 4.66 (d, J=7.4 Hz, 1H), 7.27–7.35 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.2, 54.2, 63.9, 74.4, 97.0, 127.7, 128.3, 128.7, 138.3. Minor epimer (characteristic signals): ^{1}H (300 MHz, $CDCl_3$) δ 2.04 (s, 3H), 4.93 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.8, 56.1, 58.7, 72.8, 92.9. Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.39; H, 7.78; N, 7.40.

4.2.2. 3-(2-Furyl)-4-methylmorpholin-2-ol 8b. Yield 65%, mp 130–32 °C (diisopropylether). Major epimer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.18 (s, 3H), 2.41 (ddd, J=3.4, 9.0, 12.0 Hz, 1H), 2.78 (dq, J=3.8, 11.8 Hz, 1H), 3.18 (d, J=5.9 Hz, 1H), 3.77 (br s, 1H), 3.87 (ddd, J=2.9, 9.0, 11.8 Hz, 1H), 4.04 (dt, J=3.8, 11.8 Hz, 1H), 4.99 (d, J=5.9 Hz, 1H), 6.39–6.41 (m, 2H), 7.45 (d, J=0.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.2, 52.8, 63.0, 66.2, 94.4, 109.7, 110.2, 142.3, 150.9. Minor epimer (characteristic signals): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.13 (s, 3H), 2.45 (ddd, J=3.6, 9.5, 12.9 Hz, 1H), 3.58 (d, J=1.3 Hz, 1H), 3.71 (dt, J=3.8, 11.7 Hz, 1H), 4.22 (ddd, J=3.0, 9.5, 12.1 Hz, 1H), 5.03 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.4, 53.1, 60.4, 64.8, 92.4, 110.0, 110.3, 142.5, 150.1. Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.02; H, 7.29; N, 7.62.

4.2.3. 3-(4-Methoxyphenyl)-4-methylmorpholin-2-ol 8c. Yield 80%, mp 168–170 °C (diethylether/pentane). Major epimer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.82 (br s, 1H), 2.07 (s, 3H), 2.45 (dt, J=3.5, 11.5 Hz, 1H), 2.78 (d, J=7.2 Hz, 1H), 2.81 (d, J=11.7 Hz, 1H), 3.83 (s, 3H), 3.94 (dt, J=1.7, 11.3 Hz, 1H), 4.01 (d, J=11.3 Hz, 1H), 4.71 (d, J=7.2 Hz, 1H), 6.92 (d, J=8.6 Hz, 2H), 7.32 (d, J=8.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.3, 54.3, 55.2, 64.2, 73.8, 97.4, 113.9, 129.7, 130.3, 159.3. Minor epimer (characteristic signals): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.13 (s, 3H), 2.51 (dt, J=3.6, 11.8 Hz, 1H), 2.90 (d, J=11.7 Hz, 1H), 3.28 (s, 1H), 3.70 (d, J=8.3 Hz, 1H), 4.32 (dt, J=2.7, 11.7 Hz, 1H), 4.94 (d, J=1.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.1, 55.4, 59.0, 72.0, 93.3, 113.8, 130.0. MS (EI) calcd for $C_{12}H_{17}NO_3$ $[M]^+$: 223.1208. Found: 223.1206.

4.2.4. 4-Benzyl-3-phenylmorpholin-2-ol 8d.[22] Yield 70%, mp 148–150 °C. Major epimer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (td, J=4.0, 10.8 Hz, 1H), 2.76 (dt, J=2.0, 11.8 Hz, 1H), 2.98 (d, J=13.4 Hz, 1H), 3.17 (d, J=7.2 Hz, 1H), 3.40–4.24 (m, 4H), 4.78 (d, J=7.2 Hz, 1H), 7.21–7.60 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 50.4, 58.7, 64.4, 72.8, 97.6, 126.9, 128.2, 128.3, 128.5, 128.7, 128.9, 138.3, 138.7. Minor epimer (characteristic signals): ^{1}H NMR

(300 MHz, $CDCl_3$) δ 2.88 (d, J=11.6 Hz, 1H), 4.16 (t, J=12.6 Hz, 1H), 5.01 (d, J=6.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.7, 59.1, 70.9, 93.3. MS (EI) calcd for $C_{17}H_{19}NO_2$ $[M]^+$: 269.1416. Found: 269.1418.

4.2.5. 4-Benzyl-3-(2-methoxyphenyl)morpholin-2-ol 8e. Yield 50%, mp 159–160 °C (diisopropylether). Major epimer: ^1H NMR (200 MHz, $CDCl_3$) δ 2.35 (td, J=3.8, 11.5 Hz, 1H), 2.79 (dt, J=1.9, 11.8 Hz, 1H), 2.99 (d, J=13.5 Hz, 1H), 3.48 (d, J=8.9 Hz, 1H), 3.78 (s, 1H), 3.83 (d, J=5.6 Hz, 1H), 3.84–4.00 (m, 2H), 3.93 (s, 3H), 4.66 (dd, J=7.4, 8.8 Hz, 1H), 6.98 (d, J=8.2 Hz, 1H), 7.10 (td, J=1.0, 7.5 Hz, 1H), 7.26–7.38 (m, 6H), 7.80 (dd, J=1.7, 7.5 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 50.8, 55.6, 58.5, 63.9, 64.4, 98.6, 110.7, 121.2, 126.8, 127.9, 128.1, 128.4, 128.6, 128.7, 138.4, 158.1. Minor epimer (characteristic signals): ^1H NMR (200 MHz, $CDCl_3$) δ 2.81 (d, J=13.6 Hz, 1H), 4.96 (br s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 52.2, 55.2, 58.9, 91.8, 120.7, 125.3, 157.2. Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.03; H, 7.24; N, 4.43.

4.2.6. 4-Benzyl-3-(2-thienyl)morpholin-2-ol 8f. Yield 65%, mp 100–102 °C (diisopropylether). Major epimer: ^1H NMR (300 MHz, $CDCl_3$) δ 2.25 (td, J=3.5, 11.8 Hz, 1H), 2.67 (ddd, J=1.3, 3.0, 11.9 Hz, 1H), 3.05 (d, J=13.4 Hz, 1H), 3.54 (d, J=5.8 Hz, 1H), 3.64–4.02 (m, 4H), 4.76 (d, J=5.8 Hz, 1H), 6.93–7.29 (m, 8H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 49.2, 58.8, 62.9, 66.4, 96.4, 125.7, 126.5, 127.2, 127.7, 128.3, 128.8, 137.9, 140.2. Minor epimer (characteristic signals): ^1H NMR (300 MHz, $CDCl_3$) δ 3.09 (d, J=13.1 Hz, 1H), 5.06 (br s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 64.9, 93.6, 126.3, 126.8, 128.9. Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22; N, 5.09. Found: C, 65.26; H, 6.26; N, 5.08.

4.2.7. 4-Benzyl-3-[(1*E*)-hex-1-en-1-yl]morpholin-2-ol 8g. Yield 67%, oil. Major epimer: ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, J=6.6 Hz, 3H), 1.28–1.48 (m, 4H), 2.10–2.17 (m, 2H), 2.28 (dt, J=3.5, 8.2 Hz, 1H), 2.67 (dt, J=3.4, 12.3 Hz, 1H), 2.80 (dd, J=4.6, 8.8 Hz, 1H), 3.28 (d, J=13.3 Hz, 1H), 3.63–3.71 (m, 1H), 3.86 (d, J=13.3 Hz, 1H), 3.94–4.02 (m, 1H), 4.70 (d, J=4.6 Hz, 1H), 5.61 (dd, J=8.8, 15.6 Hz, 1H), 5.75 (dt, J=6.5, 15.5 Hz, 1H), 7.29–7.37 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 22.0, 31.1, 32.1, 48.6, 58.4, 62.1, 68.2, 95.0, 125.4, 126.8, 128.0, 128.8, 137.4, 138.2. Minor epimer (characteristic signals): ^1H NMR (300 MHz, $CDCl_3$) 2.73 (dd, J=3.1, 6.5 Hz, 1H), 3.05 (dd, J=2.0, 9.2 Hz, 1H), 3.16 (d, J=13.4 Hz, 1H), 4.86 (d, J=1.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.1, 32.0, 49.7, 58.6, 60.4, 68.2, 93.7, 126.9, 137.3, 137.6. MS (EI) calcd for $C_{17}H_{25}NO_2$ $[M]^+$: 275.1885. Found: 275.1897.

4.2.8. 4-Allyl-3-phenylmorpholin-2-ol 8h. Yield 75%, oil. Major epimer: ^1H NMR (300 MHz, $CDCl_3$) δ 2.38 (dt, J=3.3, 11.6 Hz, 1H), 2.58 (dd, J=8.1, 13.8 Hz, 1H), 2.87 (dt, J=1.8, 11.9 Hz, 1H), 3.09 (d, J=7.1 Hz, 2H), 3.85 (dt, J=2.2, 11.4 Hz, 1H), 3.97 (d, J=11.0 Hz, 1H), 4.41 (br s, 1H), 4.72 (d, J=7.1 Hz, 1H), 5.09 (d, J=11.6 Hz, 1H), 5.14 (d, J=4.4 Hz, 1H), 5.68–5.81 (m, 1H), 7.28–7.58 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 50.2, 57.2, 63.9, 72.0, 97.1, 118.1, 127.6, 128.3, 128.9, 134.0, 138.1. Minor epimer (characteristic signals): ^1H NMR (300 MHz, $CDCl_3$) δ 2.46 (dt, J=3.7, 11.8 Hz, 1H), 2.98 (d, J=11.8 Hz, 1H), 3.13 (d, J=4.8 Hz, 2H), 3.27 (dd, J=5.1, 13.8 Hz, 1H), 3.56 (d, J=1.8 Hz, 1H), 3.64 (dd, J=1.8, 12.0 Hz, 1H), 4.28 (dt, J=2.5, 11.8 Hz, 1H), 5.00 (d, J=1.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.5, 57.5, 58.6, 70.7, 92.7. MS (EI) calcd for $C_{10}H_{12}NO_2$ $[M-C_3H_5]^+$: 178.0868. Found: 178.0852.

4.2.9. 4-Benzyl-2-methyl-3-phenylmorpholin-2-ol 8i. Yield 57%, mp 178–180 °C (diisopropylether). Major epimer: ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (s, 3H), 2.34 (dt, J=4.0, 12.4 Hz, 1H), 2.77–2.83 (m, 1H), 2.84 (d, J=10.1 Hz, 1H), 3.38 (s, 1H), 3.59–3.67 (m, 1H), 3.79 (d, J=13.4 Hz, 1H), 4.08 (dt, J=2.8, 12.4 Hz, 1H), 4.41 (br s, 1H), 7.20–7.56 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1, 52.3, 59.2, 59.5, 75.7, 95.7, 127.0, 127.8, 127.9, 128.2, 128.4, 128.7, 137.5, 138.1. Minor epimer (characteristic signals): ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 3H), 3.19 (d, J=13.6 Hz, 1H), 3.46 (d, J=13.6 Hz, 1H), 5,20 (s, 1H). MS (EI) calcd for $C_{18}H_{21}NO_2$ $[M]^+$: 283.1572. Found: 283.1569.

4.2.10. 4-Benzyl-3-[(1*E*)-hex-1-en-1-yl]-2-methylmorpholin-2-ol 8j. Yield 59%, oil. Major epimer: ^1H NMR (200 MHz, $CDCl_3$) δ 0.96 (t, J=7.0 Hz, 3H), 1.33–1.47 (m, 4H), 1.36 (s, 3H), 2.12–2.24 (m, 2H), 2.81 (d, J=9.4 Hz, 1H), 3.00 (d, J=13.6 Hz, 1H), 3.54 (dd, J=13.1, 22.7 Hz, 2H), 3.93 (dd, J=3.0, 12.1 Hz, 2H), 4.17 (d, J=13.4 Hz, 1H), 4.57 (br s, 1H), 5.41 (ddt, J=1.3, 9.3, 15.4 Hz, 1H), 5.81 (dt, J=5.1, 15.4 Hz, 1H), 7.29–7.41 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.8, 22.2, 24.7, 31.2, 32.1, 51.4, 58.7, 59.7, 73.8, 95.5, 127.0, 128.2, 128.4, 128.8, 137.5, 138.4. Minor epimer (characteristic signals): ^1H NMR (200 MHz, $CDCl_3$) δ 1.25 (s, 3H), 2.45 (dd, J=3.7, 11.8 Hz, 1H), 2.66 (ddd, J=1.2, 3.0, 11.7 Hz, 2H), 2.94 (d, J=10.7 Hz, 1H), 3.72 (dd, J=3.8, 11.8 Hz, 1H), 4.04 (dd, J=3.8, 8.3 Hz, 1H), 4.14 (d, J=11.8 Hz, 1H), 5.22 (s, 1H), 5.61 (dt, J=6.3, 15.5 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.8, 22.1, 24.2, 31.4, 32.3, 45.1, 58.7, 59.9, 67.6, 95.2, 121.1, 127.2, 127.4, 128.3, 137.7, 138.9. MS (EI) calcd for $C_{18}H_{27}NO_2$ $[M]^+$: 289.2042. Found: 289.2040.

4.2.11. 4-Benzyl-2,3-diphenylmorpholin-2-ol 8k. Yield 58%, mp 112–114 °C (diethylether/pentane). Major epimer: ^1H NMR (200 MHz, $CDCl_3$) δ 2.51 (td, J=3.8, 12.2 Hz, 1H), 2.85–2.95 (m, 2H), 3.53 (s, 1H), 3.81 (dd, J=3.7, 12.0 Hz, 1H), 3.88 (d, J=13.4 Hz, 1H), 4.31 (td, J=2.8, 12.3 Hz, 1H), 4.58 (br s, 1H), 7.11–7.19 (m, 15H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 52.4, 59.4, 59.9, 76.8, 97.3, 126.2, 127.1, 127.3, 127.4, 127.5, 127.6, 127.8, 128.3, 128.8, 136.4, 138.0, 141.0. Minor epimer (characteristic signals): ^1H NMR (200 MHz, $CDCl_3$) δ 3.16 (d, J=13.2 Hz, 1H), 4.08 (dd, J=3.7, 11.3 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 52.7, 58.9, 60.2, 70.5, 96.4. Anal. Calcd for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.05. Found: C, 79.82; H, 6.67; N, 4.35.

4.3. 2-Synthesis of 2-hydroxymorpholine 8l starting from the tetraoxoanthracene 10

4.3.1. Perhydro-4,8-dibenzyl-4,8-diaza-1,5,9,10-tetraoxo anthracene 10.[19] To a solution of glyoxal (22 mmol, 40%

in water) in water (3 mL) was added dropwise *N*-benzylethanolamine (20 mmol) at 0 °C. The solution was stirred at room temperature for 3 h and extracted with dichloromethane (3×20 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was washed with diethylether to give **10** as a white solid (yield 70%), mp 190 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.18 (dd, J=1.6, 11.3 Hz, 2H), 2.86 (dt, J=3.6, 11.5 Hz, 2H), 3.71 (dt, J=2.7, 11.45 Hz, 4H), 3.72 (d, J=13.8 Hz, 2H), 3.92 (dd, J=2.8, 11.3 Hz, 4H), 3.95 (d, J=13.8 Hz, 2H), 7.20–7.34 (m, 10H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 42.8, 57.4, 65.2, 79.0, 94.1, 127.2, 128.3, 128.8, 138.2.

4.3.2. [(1*E*)-3-Methoxy-3-oxoprop-1-en-1-yl]boronic acid. At −10 °C, under N_2, borane–methylsulfide complex (6.6 mL, 66 mmol) was added dropwise to a solution of α-pinene (22.6 mL, 141.2 mmol) in dry THF (20 mL). The mixture was kept at 0 °C for 1 h and then allowed to reach room temperature by removing the cold bath (formation of a white suspension of diisopinocampheylborane). After 2 h, the suspension of $(Ipc)_2BH$ was cooled to −30 °C. A solution of methyl propiolate (6.25 mL, 70 mmol) in dry THF (10 mL) was added dropwise. After 1 h at −30 °C, the reaction mixture was allowed to warm to room temperature (limpid solution). Five hours later, the mixture was cooled to 0 °C and freshly distilled acetaldehyde (43.5 mL, 700 mmol, 10 equiv) was added dropwise. The solution was kept at room temperature for 18 h and then 1 h at 40 °C. The excess of acetaldehyde and about half of the solvent were removed by distillation (15 mmHg). A mixture of THF/water (5 mL/5 mL) was added. The mixture was stirred overnight. After removing most of the solvent under reduced pressure, 30 mL of pentane were added give a solid, which was filtered and washed several times with pentane. Yields varied from 30 to 55%. The boronic acid is only soluble in DMSO that gives an ill-resolved NMR spectrum. It was best characterized as its pinacol derivative, obtained by addition of 1 equiv of pinacol in diethylether in the presence of 2 equiv of methanol during one night. *Pinacol derivative*.[23] Eb=80–85 °C/0.1 mmHg (Kugelrohr). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 12H), 3.76 (s, 3H), 6.63 (d, J=18.3 Hz, 1H), 6.76 (d, J=18.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7, 51.6, 84.3, 134.4, 138.2, 166.4.

4.3.3. Methyl-(2*E*)-3-(4-benzyl-2-hydroxymorpholin-3-yl)acrylate 8l. To a solution of perhydro-4,8-dibenzyl-4,8-diaza-1,5,9,10-tetraoxoanthracene **10** (1 mmol) and [(1*E*)-3-methoxy-3-oxoprop-1-en-1-yl]boronic acid (2 mmol) in dry methylene chloride (20 mL) was added dropwise BF_3–etherate (4.5 mmol) at −78 °C. The solution was stirred at −78 °C for 0.5 h, warmed to room temperature and stirred overnight. After addition of a saturated solution of $NaHCO_3$ (15 mL) at −78 °C, the mixture was extracted with methylene chloride (3×30 mL). The organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography using 30% ethyl acetate in heptane afforded **8l** as an oil (yield 76%). Major epimer: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.24 (td, J=3.3, 8.6 Hz, 1H), 2.66 (td, J=1.5, 4.3 Hz, 1H), 2.94 (dd, J=5.3, 8.8 Hz, 1H), 3.20 (br s, 1H), 3.56–4.04 (m, 4H), 3.75 (s, 3H), 4.68 (d, J=5.4 Hz, 1H), 6.16 (d, J=15.9 Hz, 1H), 7.03 (d, J=1.5, 8.8 Hz, 1H), 7.24–7.33 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 48.6, 51.6, 59.2, 62.4, 67.2, 94.3, 125.9, 127.2, 128.3, 128.8, 137.3, 144.6, 166.1. Minor epimer (characteristic signals): ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.72 (td, J=1.2, 4.5 Hz, 1H), 4.90 (d, J=2.3 Hz, 1H), 6.07 (d, J=16.1 Hz, 1H), 7.03 (d, J=1.6, 9.6 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 49.2, 59.3, 60.7, 66.7, 93.3, 125.4, 127.3, 128.9, 137.0, 165.9. MS (EI) calcd for $C_{15}H_{19}NO_4$ $[M]^+$: 277.1314. Found: 277.1317.

4.4. 3-One-pot synthesis of 2-hydroxymorpholines 8m–8v from chiral 1,2-aminoalcohols

4.4.1. (3*R*,5*R*)-4-Methyl-3,5-diphenylmorpholin-2-ol 8′m. From thioether **13a**, yield 71%. Major epimer: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.84 (s, 3H), 3.66–4.12 (m, 5H), 5.19 (d, J=2.6 Hz, 1H), 7.24–7.56 (m, 10H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 39.6, 60.7, 65.7, 67.5, 93.9, 127.9, 128.0, 128.2, 128.3, 128.8, 130.3, 135.4, 138.3. Minor epimer (characteristic signals): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.81 (s, 3H), 5.27 (d, J=3.0 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 39.7, 60.2, 68.0, 71.2, 95.4, 133.6, 138.5. MS (EI) calcd for $C_{17}H_{19}NO_2$ $[M]^+$: 269.1416. Found: 269.1415. $[\alpha]_D^{20}$ +78.5 (*c* 0.9, CH_2Cl_2).

4.4.2. (3*S*,5*R*)-4-Methyl-3,5-diphenylmorpholin-2-ol 8″m. From epimerisation, yield 89%, mp 150–52 °C (diethylether/pentane). Major epimer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.82 (s, 3H), 3.07 (d, J=7.5 Hz, 1H), 3.06 (dd, J=3.0, 10.4 Hz, 1H), 3.45 (br s, 1H), 3.68 (dd, J=10.5, 11.8 Hz, 1H), 3.87 (dd, J=3.3, 11.7 Hz, 1H), 4.79 (d, J=7.5 Hz, 1H), 7.24–7.50 (m, 10H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 40.8, 67.4, 70.8, 74.0, 97.9, 127.8, 127.9, 128.0, 128.4, 128.6, 128.8, 139.1. Minor epimer (characteristic signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.91 (s, 3H), 5.03 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 41.2, 64.6, 69.1, 72.1, 93.3. Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.96; H, 7.05; N, 5.12.

4.4.3. (5*R*)-3-(4-Bromophenyl)-4-methyl-5-phenylmorpholin-2-ol 8′n+8″n. Yield 47%. Major diastereoisomer: RMN ^{1}H (300 MHz, $CDCl_3$) δ 1.78 (s, 3H), 3.56 (dd, J=3.7, 8.5 Hz, 1H), 3.69 (d, J=2.7 Hz, 1H), 3.78 (dd, J=3.9, 11.8 Hz, 1H), 3.85 (br s, 1H), 4.05 (dd, J=8.6, 11.8 Hz, 1H), 5.06 (d, J=2.8 Hz, 1H), 7.21–7.44 (m, 9H). RMN ^{13}C (50 MHz, $CDCl_3$) δ 39.6, 60.6, 65.8, 66.7, 93.9, 122.1, 128.0, 128.3, 128.7, 131.2, 132.0, 133.1, 138.0. Minor diastereoisomer (characteristic signals): RMN ^{1}H (300 MHz, $CDCl_3$) δ 1.76 (s, 3H), 5.24 (d, J=3.0 Hz, 1H). RMN ^{13}C (50 MHz, $CDCl_3$) δ 39.7, 60.1, 67.2, 71.1, 95.3, 122.5, 138.2. MS (EI) calcd for $C_{17}H_{18}NO_2Br$ $[M]^+$: 347.0521. Found: 347.0526.

4.4.4. (3*R*,5*R*)-3-[(1*E*)-Hex-1-en-1-yl]-4-methyl-5-phenylmorpholin-2-ol 8′o. From thioether **13a**, yield 61%. Major epimer: ^{1}H RMN (300 MHz, $CDCl_3$) δ 0.92 (t, J=7 Hz, 3H), 1.36–1.38 (m, 4H), 2.02 (s, 3H), 2.14 (q, J=7.2 Hz, 2H), 3.27 (dd, J=1.3, 9.3 Hz, 1H), 3.55–4.03 (m, 3H), 4.40 (br s, 1H), 4.67 (d, J=7.6 Hz, 1H), 5.73 (dd, J=8.8, 15.5 Hz, 1H), 5.83 (dt, J=8.7, 15.5 Hz, 1H), 7.29–7.36 (m, 5H). RMN ^{13}C (75 MHz, $CDCl_3$) δ 13.8, 22.1, 31.2, 32.5, 39.5, 61.6, 64.5, 67.3, 93.3, 121.8, 128.4, 128.5, 128.6, 138.7, 141.9. Minor epimer (characteristic signals): RMN (300 MHz, $CDCl_3$) δ 2.02 (s, 3H), 2.18 (q, J=7.3 Hz, 2H),

3.33 (dt, J=2.4, 6.8 Hz, 1H), 5.03 (d, J=2.5 Hz, 1H). RMN ^{13}C (75 MHz, $CDCl_3$) δ 22.2, 31.3, 32.3, 39.8, 61.1, 66.6, 71.2, 94.4, 119.4, 138.0, 138.2. MS (EI) calcd for $C_{17}H_{25}NO_2$ $[M]^+$: 275.1885. Found: 275.1883.

4.4.5. (3*S*,5*R*)-3-[(1*E*)-Hex-1-en-1-yl]-4-methyl-5-phenylmorpholin-2-ol 8″o. Major epimer: ^{1}H RMN (200 MHz, $CDCl_3$) δ 0.88 (t, J=6.5 Hz, 3H), 1.29–1.39 (m, 4H), 2.04 (s, 3H), 2.07 (q, J=7.2 Hz, 2H), 3.22 (dd, J=3.7, 10.7 Hz, 1H), 3.52 (dd, J=3.8, 12.1 Hz, 1H), 3.79 (dd, J=3.6, 11.8 Hz, 1H), 3.97–4.23 (m, 2H), 4.69 (d, J=7.6 Hz, 1H), 5.36 (dd, J=9.0, 15.5 Hz, 1H), 5.75 (dt, J=6.7, 15.4 Hz, 1H), 7.25–7.36 (m, 5H). RMN ^{13}C (50 MHz, $CDCl_3$) δ 13.9, 22.2, 31.1, 32.1, 40.2, 64.7, 69.2, 70.7, 93.8, 127.6, 127.7, 128.0, 128.6, 135.9, 138.6. Minor epimer (characteristic signals): RMN (200 MHz, $CDCl_3$) δ 1.99 (s, 3H), 4.94 (d, J=1.8 Hz, 1H). RMN ^{13}C (75 MHz, $CDCl_3$) δ 14.1, 22.7, 31.2, 32.2, 40.5, 67.6, 70.5, 72.5, 96.3, 137.2, 139.0. MS (EI) calcd for $C_{17}H_{25}NO_2$ $[M]^+$: 275.1885. Found: 275.1870.

4.4.6. (3*R*,5*R*)-4-Benzyl-3,5-diphenylmorpholin-2-ol 8′p. From thioether **13b**, yield 65%. Major epimer (characteristic signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.87 (br s, 1H), 3.00 (d, J=14.3 Hz, 1H), 3.59 (d, J=14.3 Hz, 1H), 3.88–4.28 (m, 3H), 5.20 (d, J=2.8 Hz, 1H), 7.28–7.57 (m, 15H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 52.3, 58.7, 63.1, 66.3, 94.6, 127.1, 128.1, 128.3, 128.4, 128.6, 128.7, 128.8, 128.9, 130.5, 138.4, 138.7, 138.9. Minor epimer (characteristic signals): RMN (300 MHz, $CDCl_3$) δ 2.98 (d, J=14.4 Hz, 1H), 5.32 (br s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 52.9, 59.1, 62.8, 71.8, 95.8. $[\alpha]_D^{20}$ −78.2 (*c* 1.1, CH_2Cl_2).

4.4.7. (3*S*,5*R*)-4-Benzyl-3,5-diphenylmorpholin-2-ol 8″p. Major epimer (characteristic signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.78 (d, J=7.5 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 51.7, 60.8, 62.9, 72.5, 98.4. Minor epimer (characteristic signals): RMN (300 MHz, $CDCl_3$) δ 5.06 (d, J=2.6 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 53.7.

4.4.8. (2*E*,5*R*)-4-Benzyl-3-(2-phenylethylenyl)-2-hydroxy-5-phenylmorpholine 8′q+8″q. Yield 77%. Mixture of four diastereoisomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.90–4.11 (m, 6H), 4.69 (d, J=7.35 Hz, 1H) and 4.93 (d, J=1.7 Hz, 1H) and 4.98 (br s, 1H) and 5.01 (d, J=2.2 Hz, 1H), 5.93 (dd, J=9.3, 16.0 Hz, 1H) and 6.02 (dd, J=8.7, 16.0 Hz, 1H) and 6.63–6.76 (m, 1H+1H), 6.40 (d, J=16.0 Hz, 1H) and 6.55 (d, J=16.0 Hz, 1H) and 6.63 (d, J=16.0 Hz, 1H) and 6.72 (d, J=16.1 Hz, 1H), 7.04–7.47 (m, 15H). RMN ^{13}C (50 MHz, $CDCl_3$) δ 52.9 and 53.7 and 54.3 and 55.1, 60.1 and 60.6 and 61.2 and 62.4, 63.1 and 65.9 and 69.0 and 69.4, 65.0 and 70.8 and 72.1 and 73.2, 93.2 and 93.9 and 95.4 and 96.4, 119.6 and 122.3, 126.4–129.6, 132.9 and 134.7 and 136.8 and 139.5, 136.0 and 136.4 and 136.7 and 138.2. MS (EI) calcd for $C_{24}H_{23}N$ $[M-CH_2O_2]^+$: 325.18305. Found: 325.1844.

4.4.9. (5*R*)-2-Hydroxy-5-isopropyl-4-methyl-3-phenylmorpholine 8′r+8″r. Yield 74%. Major diastereoisomer: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.81 (d, J=7.0 Hz, 3H), 0.87 (d, J=6.9 Hz, 3H), 1.82–1.95 (m, 1H), 2.05 (s, 3H), 2.46–2.52 (m, 1H), 3.58–3.66 (m, 2H), 3.92 (t, J=10.3 Hz, 1H), 4.22 (br s, 1H), 5.17 (d, J=3.0 Hz, 1H), 7.16–7.47 (m, 5H). RMN ^{13}C (50 MHz, $CDCl_3$) δ 16.2, 19.8, 25.9, 38.8, 58.6, 59.5, 67.6, 93.0, 127.8, 130.0, 131.5, 135.7. Second diastereoisomer (characteristic signals): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.79 (d, J=6.8 Hz, 3H), 1.98 (s, 3H), 2.46–2.52 (m, 1H), 3.70 (dd, J=3.0, 11.4 Hz, 1H), 5.25 (br s, 1H). RMN ^{13}C (50 MHz, $CDCl_3$) δ 15.0, 19.6, 25.6, 57.2, 64.5, 68.3, 94.9, 133.9. Third diastereoisomer (characteristic signals): ^{1}H RMN (200 MHz, $CDCl_3$) δ 1.00 (d, J=4.1 Hz, 3H), 1.00 (d, J=4.1 Hz, 3H), 1.03 (d, J=4.0 Hz, 3H), 2.01 (s, 3H), 2.21–2.35 (m, 2H), 2.97 (d, J=7.6 Hz, 1H), 3.68 (t, J=11.5 Hz, 1H), 3.97 (dd, J=3.0, 11.6 Hz, 1H), 4.61 (d, J=7.6 Hz, 1H). RMN ^{13}C (50 MHz, $CDCl_3$) δ 15.1, 19.5, 26.2, 38.9, 64.2, 64.9, 74.1, 97.7, 127.6, 128.3, 128.8, 140.2. MS (EI) calcd for $C_{14}H_{21}NO_2$ $[M]^+$: 235.1572. Found: 235.1572.

4.4.10. 4-Allyl-2-hydroxy-6-methyl-3-phenylmorpholine 8′s+8″s. Prepared from racemic 1-(allylamino)propan-2-ol, yield 43%. Major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (d, J=6.5 Hz, 3H), 2.43–2.49 (m, 2H), 2.79 (dd, J=6.2, 13.8 Hz, 1H), 3.02 (dd, J=6.3, 13.9 Hz, 1H), 3.65 (d, J=2.3 Hz, 1H), 4.28–4.38 (m, 1H), 5.15–5.22 (m, 3H), 5.76–5.89 (m, 1H), 7.34–7.56 (m, 5H). RMN ^{13}C (75 MHz, $CDCl_3$) δ 18.5, 51.9, 57.3, 65.7, 66.8, 92.9, 118.0, 127.8, 128.0, 130.2, 135.2, 135.3. Minor diastereoisomer (characteristic signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (d, J=7.3 Hz, 3H), 2.67 (dd, J=6.7, 13.4 Hz, 1H), 3.91 (d, J=3.1 Hz, 1H), 3.96–4.06 (m, 1H). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.00; H, 8.16; N, 6.01.

4.4.11. (6*R*)-4-Benzyl-2-hydroxy-3,6-diphenylmorpholine 8′t+8″t. Yield 66%, mp 157–58 °C (diethylether/pentane). Major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.28 (t, J=11.2 Hz, 1H), 2.83 (d, J=5.2 Hz, 1H), 2.98 (d, J=13.4 Hz, 2H), 3.23 (d, J=7.4 Hz, 1H), 3.82 (d, J=13.4 Hz, 1H), 4.88 (dd, J=1.8, 10.5 Hz, 1H), 5.00 (dd, J=5.3, 7.0 Hz, 1H), 7.24–7.63 (m, 15H). RMN ^{13}C (75 MHz, $CDCl_3$) δ 57.6, 58.6, 72.1, 76.1, 99.1, 126.3, 127.0, 127.9, 127.95, 128.2, 128.3, 128.6, 128.7, 128.9, 138.0, 138.8, 139.0. Second diastereoisomer (characteristic signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.64 (dd, J=2.8, 11.2 Hz, 1H), 3.04 (t, J=11.0 Hz, 1H), 3.79 (d, J=13.4 Hz, 1H), 4.05 (d, J=13.4 Hz, 1H), 4.39 (br s, 1H), 4.72 (dd, J=2.6, 10.6 Hz, 1H), 5.44 (dd, J=2.4, 9.1 Hz, 1H). RMN ^{13}C (75 MHz, $CDCl_3$) δ 59.1, 70.6, 93.6. Third diastereoisomer (characteristic signals): ^{1}H RMN (300 MHz, $CDCl_3$) δ 2.57 (dd, J=9.3, 11.8 Hz, 1H), 3.18 (dd, J=2.7, 11.8 Hz, 1H), 3.39 (d, J=13.5 Hz, 1H), 4.25 (d, J=13.4 Hz, 1H), 5.31 (dd, J=5.7, 8.0 Hz, 1H). Anal. Calcd for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.05. Found: C, 79.97; H, 6.97; N, 4.18.

4.4.12. (6*R*)-4-Benzyl-3-hexen-1-yl-2-hydroxy-6-phenylmorpholine 8′u+8″u. Yield 56%. Major diastereoisomer: ^{1}H RMN (300 MHz, $CDCl_3$) δ 0.87 (t, J=6.3 Hz, 3H), 1.18–1.36 (m, 4H), 1.99–2.15 (m, 3H), 2.57 (d, J=11.0 Hz, 1H), 2.61 (d, J=11.9 Hz, 1H), 3.10 (d, J=9.3 Hz, 1H), 3.44 (d, J=10.7 Hz, 1H), 3.50 (d, J=14.8 Hz, 1H), 4.97 (br s, 1H), 5.07 (dd, J=3.9, 10.7 Hz, 1H), 5.62 (dt, J=6.6, 15.5 Hz, 1H), 5.83 (ddt, J=1.2, 9.3, 15.5 Hz, 1H), 7.17–7.32 (m, 10H). RMN ^{13}C (50 MHz, $CDCl_3$) δ 13.8, 22.2, 31.4, 32.5, 52.2, 58.5, 63.3, 70.1, 93.6, 121.6, 126.3, 128.3, 128.4, 128.6, 128.9, 129.0, 137.6, 138.4, 139.8. Second

diastereoisomer (characteristic signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.20 (dd, J=2.6, 9.0 Hz, 1H), 4.73 (dd, J=3.6, 10.3 Hz, 1H), 4.99 (d, J=2.7 Hz, 1H). RMN ^{13}C (50 MHz, $CDCl_3$) δ 31.5, 32.6, 52.7, 58.7, 64.2, 76.9, 94.8, 118.7, 126.1, 128.1, 128.2, 138.5, 141.9. Third diastereoisomer (characteristic signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.71 (d, J=10.1 Hz, 1H). RMN ^{13}C (50 MHz, $CDCl_3$) δ 31.2, 32.2, 69.1, 94.2, 136.7. Fourth diastereoisomer (characteristic signals): ^{1}H RMN (300 MHz, $CDCl_3$) δ 5.01 (d, J=2.6 Hz, 1H). RMN ^{13}C (50 MHz, $CDCl_3$) δ 75.9, 96.6, 137.9. MS (EI) calcd for $C_{23}H_{29}NO_2$ $[M]^+$: 351.2198. Found: 351.2177.

4.4.13. (3*E*,5*R*)-4-Benzyl-2-hydroxy-3-(1-methylpropen-1-yl)-5-phenylmorpholine 8′v+8″v. Yield 51%. Major diastereoisomer: ^{1}H RMN (300 MHz, $CDCl_3$) δ 1.67 (d, J= 6.7 Hz, 3H), 1.83 (s, 3H), 3.09 (d, J=14.6 Hz, 1H), 3.28 (d, J=5.8 Hz, 1H), 3.52 (br s, 1H), 3.71 (d, J=14.6 Hz, 2H), 3.82 (t, J=3.7 Hz, 1H), 4.07 (dt, J=3.6, 11.6 Hz, 2H), 5.00 (d, J=5.7 Hz, 1H), 5.58 (q, J=6.6 Hz, 1H), 7.25–7.54 (m, 10H). RMN ^{13}C (75 MHz, $CDCl_3$) δ 13.1, 13.2, 52.4, 57.4, 67.7, 68.2, 95.1, 126.6, 127.4, 127.9, 128.1, 128.2, 128.5, 129.7, 132.6, 138.6, 139.2. Second diastereoisomer (characteristic signals): ^{1}H RMN (300 MHz, $CDCl_3$) δ 1.73 (d, J= 7.0 Hz, 3H), 1.97 (s, 3H), 3.36 (d, J=14.1 Hz, 1H), 3.39 (d, J=3.15 Hz, 1H), 3.69 (d, J=14.4 Hz, 1H), 4.11 (dt, J=4.1, 11.5 Hz, 2H), 5.07 (d, J=6.2 Hz, 1H), 5.40 (q, J=6.5 Hz, 1H). RMN ^{13}C (75 MHz, $CDCl_3$) δ 13.2, 17.0, 53.2, 60.0, 65.5, 70.3, 95.1, 126.5, 131.5, 138.8, 139.7. Third diastereoisomer (characteristic signals): ^{1}H RMN (300 MHz, $CDCl_3$) δ 4.76 (d, J=7.5 Hz, 1H), 5.78 (q, J= 5.7 Hz, 1H). RMN ^{13}C (75 MHz, $CDCl_3$) δ 12.6, 13.3, 53.3, 62.2, 70.7, 72.9, 95.2, 133.2, 139.0. MS (EI) calcd for $C_{21}H_{25}NO_2$ $[M]^+$: 323.1885. Found: 323.1872.

4.4.14. 4-Epimerisation of 8. To a solution of **8′m** and **8″m** (0.5 mmol) in toluene (2 mL), was added diaza(1,3)bicyclo-[5.4.0]undecane (1 mmol). The solution was stirred for 24 h at 60 °C. The mixture was concentrated in vacuo. Flash chromatography using 30% ethyl acetate in heptane afforded **8″m** (yield 89%) (see above for the NMR data).

4.5. 5-Synthesis of 2-hydroxymorpholines 8 from thioethers 13a and 13b

To a mixture of **13a** or **13b** (1 mmol) and boronic acid **6** (1 mmol) in dry dichloromethane (15 mL) was added BF_3–etherate (567 μL, 4.5 mmol) at −78 °C. The solution was stirred at −78 °C for 0.5 h, warmed to room temperature and stirred overnight. At −78 °C, the mixture was quenched with saturated solution of $NaHCO_3$ (15 mL). The aqueous layer was extracted with dichloromethane (3×15 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography using 30% ethyl acetate in heptane afforded **8**.

4.5.1. (3*R*,5*R*)-3-Vinyl 4-methyl-5-phenylmorpholin-2-ol 8′w. Yield 82%. Two epimers (56/44): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.08 (s, 3H) and 2.10 (s, 3H), 3.25–4.20 (m, 5H+ 5H), 5.00 (d, J=1.2 Hz, 1H) and 5.05 (d, J=2.6 Hz, 1H), 5.25–5.70 (m, 2H+2H), 6.10–6.41 (m, 1H+1H), 7.21–7.58 (m, 5H+5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 39.7 and 40.1, 61.0 and 61.4, 64.8 and 71.6, 67.5 and 68.3, 93.0 and 94.5, 121.5 and 124.4, 127.9, 128.0, 128.1, 128.2, 128.5, 128.6, 129.2 and 131.2, 138.5. MS (EI) calcd for $C_{13}H_{17}NO_2$ $[M]^+$: 219.1259. Found: 219.1244. $[\alpha]_D^{20}$ +41.9 (*c* 1.01, CH_3OH).

4.5.2. (5*R*)-4-Benzyl-2-hydroxy-5-phenyl-3-vinylmorpholine 8′x. Yield 77%. Two epimers (50/50): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.91 (d, J=11.6 Hz, 1H) and 3.19 (d, J=11.6 Hz, 1H), 3.27 (d, J=13.4 Hz, 1H) and 3.32 (d, J=13.4 Hz, 1H), 3.60–3.74 (m, 2H+2H), 3.96–4.11 (m, 2H+2H), 4.49 (d, J=10.3 Hz, 1H), 4.94 (d, J=9.5 Hz, 1H) and 4.98 (dd, J=2.5, 11.5 Hz, 1H), 5.21 (dd, J=1.7, 17.3 Hz, 1H) and 5.23 (dd, J=1.9, 17.3 Hz, 1H), 5.53 (dd, J=1.8, 10.4 Hz, 1H) and 5.70 (dd, J=7.9, 10.4 Hz, 1H), 6.25–6.40 (m, 1H+1H), 7.26–7.52 (m, 10H+10H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 52.7 and 53.5, 58.8 and 60.0, 60.5 and 61.8, 62.9 and 63.4, 65.0 and 72.1, 93.1 and 94.8, 122.2 and 125.2, 126.9 and 127.2, 128.0, 128.1, 128.2, 128.5, 128.6, 128.65, 128.7, 128.9, 131.0, 137.8 and 138.1, 138.9 and 139.0. MS (EI) calcd for $C_{19}H_{21}NO_2$ $[M]^+$: 295.1572. Found: 295.1567. $[\alpha]_D^{20}$ +37.2 (*c* 1.04, CH_2Cl_2).

4.6. 6-Synthesis of aminodiols 9 from 2-hydroxymorpholines 8

General procedure. A solution of 2-hydroxymorpholine **8** (1 mmol) in dry diethylether (4 mL) was added dropwise to a suspension of $LiAlH_4$ (3.3 mmol) in dry diethylether (4 mL) at 0 °C. The mixture was stirred at room temperature for 5 h, cooled to 0 °C, and quenched by carefully addition of water (2.5 mL) and a solution of 15% NaOH (2.5 mL). Aqueous phase was extracted with diethylether (2×10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated to give crude aminodiol **9**, which was purified by flash chromatography using 5% methanol in dichloromethane.

4.6.1. (1*R*,1′*R*)-2,2′-Dihydroxy-1,1′-diphenyl-*N*-methyldiethanamine 9′m. Yield 96%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.25 (s, 3H), 3.52 (dd, J=5.4, 10.4 Hz, 2H), 3.66 (dd, J=5.4, 6.9 Hz, 2H), 3.77 (dd, J=6.9, 10.4 Hz, 2H), 4.76 (br s, 2H), 7.10–7.30 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.5, 62.4, 65.8, 127.6, 128.3, 128.8, 137.6. MS (EI) calcd for $C_{17}H_{21}NO_2$ $[M]^+$: 271.1572. Found: 271.1584. $[\alpha]_D^{20}$ +86.5 (*c* 1.35, CH_2Cl_2).

4.6.2. (1*S*,1′*R*)-2,2′-Dihydroxy-1,1′-diphenyl-*N*-methyldiethanamine 9″m. Yield 45%.^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 3H), 2.96 (br s, 2H), 3.89 (dd, J=4.7, 10.3 Hz, 2H), 4.03 (dd, J=7.8, 10.3 Hz, 2H), 4.09 (dd, J= 4.7, 7.8 Hz, 2H), 7.23–7.35 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.4, 62.2, 66.5, 127.6, 128.4, 128.5, 138.4. MS (EI) calcd for $C_{16}H_{18}NO$ $[M-CH_2OH]^+$: 240.1388. Found: 240.1376. $[\alpha]_D^{20}$=0 (*c* 1, CH_2Cl_2).

4.6.3. 2-(4-Bromophenyl)-2-[((1*R*)-2-hydroxy-1-phenylethyl)-*N*-methylamino]ethanol 9′n+9″n. Yield 56%. Major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 3H), 0.97 (br s, 2H), 3.57–3.70 (m, 4H), 3.78–3.88 (m, 2H), 7.04 (d, J=8.4 Hz, 1H), 7.13–7.20 (m, 3H), 7.26–7.31 (m, 4H), 7.43 (d, J=8.4 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 32.6, 62.6, 65.6, 121.8, 128.0, 128.6, 128.9, 130.5,

131.6, 136.7, 137.3. Minor diastereoisomer (characteristic signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.22 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 30.9, 62.4, 64.9. MS (EI) calcd for $C_{17}H_{20}NO_2Br$ $[M]^{+\cdot}$: 240.13884. Found: 240.1379.

4.6.4. (2*R*,3*E*)-2-[((1*R*)-2-Hydroxy-1-phenylethyl)-*N*-methylamino]oct-3-en-1-ol 9′o. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78–0.85 (m, 3H), 1.18–1.28 (m, 4H), 2.02 (q, J=6.3 Hz, 2H), 2.25 (s, 3H), 2.35 (br s, 2H), 3.18 (dt, J=5.5, 8.6 Hz, 1H), 3.31 (dd, J=5.5, 10.6 Hz, 1H), 3.50 (dd, J=9.1, 10.6 Hz, 1H), 3.69–3.91 (m, 3H), 5.17 (dd, J=8.4, 15.5 Hz, 1H), 5.39 (dt, J=6.4, 15.5 Hz, 1H), 7.18–7.33 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 22.0, 31.2, 32.2, 32.7, 61.6, 62.4, 62.9, 66.7, 124.4, 127.5, 128.3, 128.6, 136.2, 138.8. MS (EI) calcd for $C_{17}H_{27}NO_2$ $[M]^{+\cdot}$: 277.2042. Found: 277.2041. $[\alpha]_D^{20}$ −80.2 (*c* 1.15, CH_2Cl_2).

4.6.5. (2*S*,3*E*)-2-[((1*R*)-2-Hydroxy-1-phenylethyl)-*N*-methylamino]oct-3-en-1-ol 9″o. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79–0.83 (m, 3H), 1.16–1.25 (m, 4H), 1.91 (dt, J=6.8, 5.8 Hz, 2H), 2.05 (s, 3H), 2.53 (br s, 2H), 3.44–3.52 (m, 3H), 3.74–3.94 (m, 3H), 5.23 (dd, J=15.3, 6.4 Hz, 1H), 5.53 (dt, J=15.5, 6.7 Hz, 1H), 7.20–7.27 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9, 21.1, 30.1, 30.2, 31.3, 60.9, 61.5, 63.5, 67.5, 123.4, 126.8, 127.4, 127.8, 135.1, 138.5.

4.6.6. (1*R*,1′*R*)-*N*-Benzyl-2,2′-dihydroxy-1,1′-diphenyldiethanamine 9′p. Mp 138–39 °C (ethylacetate) [lit.[22] 137.5–39 °C (ethylacetate)]. ^{1}H NMR (300 MHz, CD_3OD) δ 2.07 (br s, 2H), 3.51 (d, J=14.9 Hz, 1H), 3.73 (dd, J=4.1, 10.2 Hz, 2H), 4.02 (d, J=9.1 Hz, 1H), 4.04–4.12 (m, 3H), 4.14 (d, J=15.0 Hz, 1H), 7.07–7.49 (m, 15H). ^{13}C NMR (75 MHz, CD_3OD) δ 50.0, 60.9, 61.6, 124.9, 125.2, 126.2, 126.4, 126.7, 127.0, 138.3, 140.1. MS (EI) calcd for $C_{22}H_{22}NO$ $[M-CH_2OH]^+$: 316.17014. Found: 316.1698. $[\alpha]_D^{20}$ −162 (*c* 1.2, $CHCl_3$) [lit.[22] −165.6 (*c* 1.01, $CHCl_3$)].

4.6.7. (1*S*,1′*R*)-*N*-Benzyl-2,2′-dihydroxy-1,1′-diphenyldiethanamine 9″p. Characteristic signals: ^{1}H NMR (300 MHz, CD_3OD) δ 3.26 (d, J=14.0 Hz, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 48.6, 59.7, 62.6, 138.9.

4.6.8. (3*E*)-2-[Benzyl((1*R*)-2-hydroxy-1-phenylethyl)-amino]-4-phenylbut-3-en-1-ol 9′q+9″q. Yield 63%. Major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.59 (br s, 2H), 3.51 (d, J=7.1 Hz, 1H), 3.63 (d, J=14.3 Hz, 1H), 3.67–3.81 (m, 2H), 3.75 (d, J=15.2 Hz, 1H), 3.89 (d, J=2.4 Hz, 1H), 4.03 (d, J=14.7 Hz, 1H), 4.07–4.15 (m, 1H), 6.24 (dd, J=7.7, 16.1 Hz, 1H), 6.49 (dd, J=0.7, 16.1 Hz, 1H), 7.26–7.39 (m, 15H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 49.8, 50.8, 59.2, 60.8, 65.4, 126.3, 126.9, 127.4, 127.8, 128.4, 128.5, 128.6, 128.7, 128.8, 132.3, 133.1, 138.3, 140.0, 140.4. Minor diastereoisomer (characteristic signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69 (dd, J=6.4, 16.3 Hz, 1H), 6.10 (d, J=16.3 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 61.8, 62.4, 62.5, 63.5, 133.1, 136.2, 139.8. MS (EI) calcd for $C_{24}H_{24}NO$ $[M-CH_2OH]^{+\cdot}$: 342.1858. Found: 342.1854.

4.6.9. 2-[((1*R*)-2-Hydroxy-1-phenylethyl)(methyl)-amino]-3-methylbutan-1-ol 9′r+9″r. Yield 63%. Major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, J=6.5 Hz, 3H), 0.87 (d, J=6.7 Hz, 3H), 1.67–1.75 (m, J=6.7 Hz, 1H), 2.44 (s, 3H), 2.62 (dt, J=4.9, 9.3 Hz, 1H), 3.16 (br s, 2H), 3.46–3.58 (m, 2H), 3.69 (dd, J=8.4, 14.4 Hz, 1H), 3.93–4.01 (m, 2H), 7.25–7.37 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.9, 21.7, 28.4, 33.8, 60.3, 63.5, 66.3, 68.0, 127.3, 128.1, 128.3, 140.5. Minor diastereoisomer (characteristic signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 60.5, 62.6, 69.8, 70.5, 140.3. MS (EI) calcd for $C_{14}H_{23}NO_2$ $[M]^{+\cdot}$: 237.1728. Found: 237.1725.

4.6.10. 1-[Allyl((1*R*)-2-hydroxy-1-phenylethyl)amino]-propan-2-ol 9′s+9″s. Yield 76%. Major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (d, J=6.2 Hz, 3H), 2.21 (dd, J=2.3, 13.3 Hz, 1H), 2.63 (dd, J=10.2, 13.3 Hz, 1H), 2.99 (dd, J=8.1, 14.3 Hz, 1H), 3.31 (ddt, J=2.2, 4.6, 14.3 Hz, 1H), 3.52 (br s, 2H), 3.73 (dd, J=10.0, 16.0 Hz, 1H), 3.85–3.95 (m, 1H), 4.04 (d, J=3.8 Hz, 1H), 4.06 (d, J=2.5 Hz, 1H), 5.19 (d, J=9.3 Hz, 1H), 5.23 (d, J=16.2 Hz, 1H), 5.81–5.94 (m, 1H), 7.19–7.39 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 54.4, 56.3, 61.3, 63.9, 64.4, 117.3, 127.4, 128.1, 128.5, 136.6, 136.7. Minor diastereoisomer (characteristic signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (d, J=9.2 Hz, 1H), 2.50 (d, J=8.6 Hz, 1H), 2.71 (d, J=4.0 Hz, 1H), 5.10 (d, J=3.2 Hz, 1H), 5.12 (d, J=6.7 Hz, 1H). MS (EI) calcd for $C_{13}H_{18}NO$ $[M-CH_2OH]^{+\cdot}$: 204.1388. Found: 204.1386.

4.6.11. (1*R*)-2-[Benzyl(2-hydroxy-1-phenylethyl)amino]-1-phenylethanol 9′t+9″t.[21] Yield 75%. Major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (dd, J=2.6, 13.7 Hz, 1H), 2.95 (dd, J=10.3, 13.7 Hz, 1H), 3.46 (d, J=13.9 Hz, 1H), 3.62 (dd, J=4.4, 10.8 Hz, 1H), 3.85 (d, J=13.9 Hz, 1H), 3.92 (dd, J=4.4, 10.2 Hz, 1H), 4.02 (dd, J=10.5, 21.2 Hz, 1H), 4.59 (dd, J=2.5, 10.3 Hz, 1H), 7.05–7.37 (m, 15H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 56.1, 57.4, 61.7, 64.5, 71.2, 125.8, 127.3, 127.5, 127.8, 128.4, 128.5, 128.6, 128.8, 129.0, 136.5, 139.1, 142.3. Minor diastereoisomer (characteristic signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.78 (dd, J=7.8, 13.6 Hz, 1H), 2.99 (dd, J=5.0, 13.7 Hz, 1H), 3.39 (d, J=13.9 Hz, 1H), 3.48 (dd, J=6.9, 13.7 Hz, 1H), 3.88 (d, J=13.9 Hz, 1H), 4.41 (dd, J=5.2, 7.9 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 55.5, 59.4, 61.4, 66.2, 72.8. MS (EI) calcd for $C_{16}H_{18}NO$ $[M-PhCH_2OH]^{+\cdot}$: 240.1388. Found: 240.1376.

4.6.12. (1*R*,3*E*)-2-[Benzyl(2-hydroxy-2-phenylethyl)-amino]oct-3-en-1-ol 9′u+9″u. Yield 72%. Major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (t, J=7.0 Hz, 3H), 1.21–1.31 (m, 4H), 1.97 (q, J=6.1 Hz, 2H), 2.50 (dd, J=2.7, 13.5 Hz, 1H), 2.70 (dd, J=10.5, 13.5 Hz, 1H), 3.08 (br s, 2H), 3.43 (dd, J=1.6, 7.7 Hz, 1H), 3.53 (d, J=4.0 Hz, 1H), 3.57 (br s, 2H), 3.86 (d, J=13.5 Hz, 1H), 4.57 (dd, J=2.7, 10.3 Hz, 1H), 5.15 (dd, J=9.9, 15.4 Hz, 1H), 5.63 (dt, J=6.7, 15.3 Hz, 1H), 7.17–7.31 (m, 10H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.9, 22.1, 31.4, 32.3, 56.1, 57.3, 62.2, 63.1, 70.9, 122.9, 125.8, 126.0, 127.3, 127.5, 128.4, 128.6, 137.7, 139.2, 142.3. Minor diastereoisomer (characteristic signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.86 (dd, J=5.2, 13.5 Hz, 1H), 3.80 (d, J=13.5 Hz, 1H), 5.28 (dd, J=8.3, 15.4 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 56.0, 63.5, 71.8. MS (EI) calcd for $C_{22}H_{28}NO$ $[M-CH_2OH]^{+\cdot}$: 322.2171. Found: 322.2175.

4.6.13. (2*R*)-2-[[(1*R*)-2-Hydroxy-1-phenylethyl](methyl)-amino]but-3-en-1-ol 9′w. Yield 92%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.66 (br s, 2H), 3.21–4.08 (m, 6H), 5.05 (dt, $J=0.9$, 17.3 Hz, 1H), 5.26 (dd, $J=1.8$, 10.5 Hz, 1H), 5.58–5.79 (m, 1H), 7.27–7.46 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 33.2, 61.8, 63.4, 63.5, 67.3, 119.9, 128.2, 129.0, 129.1, 134.2, 139.1. MS (EI) calcd for $C_{12}H_{16}NO$ $[M-CH_2OH]^{+\cdot}$ 190.12319. Found: 190.1231. $[\alpha]_D^{20}$ −32.1 (*c* 0.76, CH_2Cl_2).

4.6.14. (2*R*)-2-{Benzyl[(1*R*)-2-hydroxy-1-phenylethyl]-amino}but-3-en-1-ol 9′x. Mp 98–100 °C (ether/heptane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.94 (br s, 2H), 3.59 (d, $J=14.5$ Hz, 1H), 3.65–3.73 (m, 4H), 3.93–4.00 (m, 2H), 4.10 (dd, $J=10.1$, 10.7 Hz, 1H), 4.88 (dd, $J=10.3$, 17.6 Hz, 1H), 5.01 (d, $J=10.3$ Hz, 1H), 5.30–5.38 (m, 1H), 7.28–7.48 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 50.7, 59.1, 61.6, 61.7, 62.5, 117.5, 127.2, 127.8, 128.5, 128.6, 128.8, 128.85, 135.0, 138.15, 140.2. Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.80; N, 4.71. Found: C, 76.69; H, 7.79; N, 4.67. $[\alpha]_D^{20}$ −187.8 (*c* 0.74, CH_2Cl_2).

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Synthesis and anti-tubulin evaluation of chromone-based analogues of combretastatins

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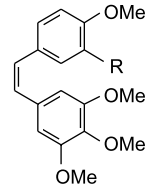
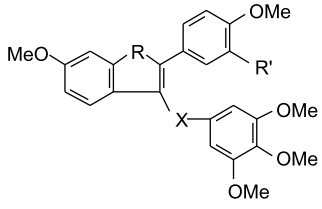
Abstract—Twenty new hybrid compounds with both combretastatin and flavone moieties were synthesized. These derivatives are classified according to the position of the trimethoxyphenyl ring at C-2 or C-3 of the chromone and presence or absence of a carbonyl as a linker between C-3 and the aryl ring. Most of these compounds were prepared from hesperidin or naringin, two natural and abundant *Citrus* flavonoids. Seven of these combretastatin analogues revealed anti-tubulin activity but in a medium range.

1. Introduction

Tubulin is a heterodimeric protein, which can exist as α,β-dimers and microtubules in a dynamic equilibrium. Polymerization into microtubules provides the main constituents of the mitotic spindle, which explains the crucial role of this protein in cellular division. Compounds that interfere with this equilibrium, either by stabilizing the microtubules or inhibiting their formation, are interesting as potential anticancer drugs.[1] So tubulin appears as a major target in this field of drugs discovery. Combretastatin A-4 (CA-4) **1** is a powerful inhibitor of tubulin polymerization (ITP) displaying cytotoxic and antivascular activities by binding at the colchicine site.[2] This natural stilbene, which was isolated from the bark of *Combretum caffrum* Kuntze, a South African bush willow tree, proved to be the most promising compound of the new class of combretastatins and was chosen as the model for the synthesis of hundreds of analogues.[3] Clear structure–activity relationships could be drawn from these synthesis, which display the importance for the bioactivity of: (a) the 3,4,5-trimethoxyphenyl ring (however, replacement by a 3,4,5-trimethylphenyl ring is not prejudicial);[4] (b) a 4′-methoxy substituted phenyl ring with or without a second substituent at C-3′ (removal of the 3′-OH or its substitution by an amino group result in compounds **2**[5] and **3**[6] with similar bioactivities as CA-4); (c) a *cis*-ethene bridge (isomerization of CA-4 and cis combretastatin analogues during storage and administration cause a reduction in both cytotoxicity and anti-tubulin activity).[7] This last point of the SAR studies led to the synthesis of many cis-restricted analogues with an ethene bridge as part of a heterocycle.[7] Although the most fruitful results were found among the substituted monocycle-bridged analogues,[8] compounds with a bicyclic system on the bridge, such as the indole **4**, displayed a strong bioactivity.[9] Furthermore, addition of a one-carbon linker (C═O) between the bicyclic system (indole, benzo[*b*]thiophene, benzo[*b*]furane) and the trimethoxyphenyl ring seemed to be favorable and sometimes essential for cytotoxicity and ITP (**6** active vs **5** inactive).[9,10]



R	
OH	**1**
H	**2**
NH_2	**3**



R	R'	X	
NH	OH	nothing	**4**
O	H	nothing	**5**
O	H	C=O	**6**

Keywords: Flavones; *Citrus* flavonoids; Combretastatins; Tubulin.
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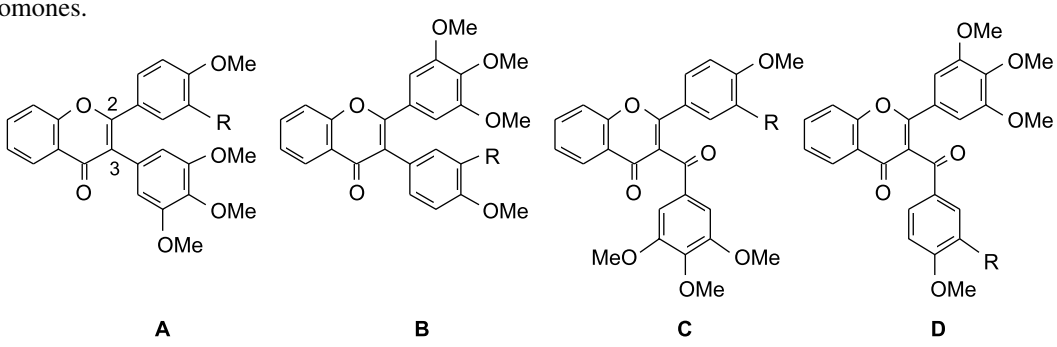
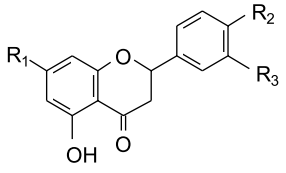
In order to enlarge the SAR studies of these bicyclic-bridged compounds, we have synthesized new analogues of combretastatins with the ethene bridge as part of a chromone. These new derivatives can be regarded as hybrid structures with both combretastatin and flavone moieties. This last point seemed of interest owing to the previously described cytotoxicity and antitubulin activity of some flavones.[11] All the chromone-based analogues related in this paper possess a substructure of combretastatins **1**, **2** or **3** and can be classified into four groups (**A**, **B**, **C**, **D** with R=H, OH or NH_2) according to the position of the trimethoxyphenyl ring at C-2 or C-3 of the chromone and presence or not of a C=O linker at C-3. They can also differ in the substitution pattern (unsubstituted or 5,7-disubstituted) of the chromone moiety. Unsubstituted flavones were prepared by total synthesis, while most of the 5,7-disubstituted ones were obtained by semisynthesis. By starting from some natural abundant flavonoids (vide infra), the second aim of this study was also to display the importance of such raw materials for an easy access to novel possibly interesting 2,3-diaryl chromones.



2. Results and discussion

2.1. Synthesis of analogues of the group A (24–32, 47 and 48)

We began our study by the group **A** because of the easy availability of two *Citrus* flavonoids, hesperidin **7** and naringin **8**, which have been used as starting materials for semisynthesis. **7** and **8** were chosen because of their adequate substitutions at C-3′ and C-4′ allowing access to analogues of combretastatins **1**, **2** and **3**. Compounds **24–31**, **47** and **48** substituted at C-5 and C-7 were prepared from **7** or **8**, while total synthesis provided the last one, **32**, unsubstituted on the chromone ring. For all the compounds, the trimethoxyphenyl ring was fixed at the C-3 carbon of the chromone by a Suzuki reaction between a 3-bromoflavone and 3,4,5-trimethoxybenzeneboronic acid.[12]



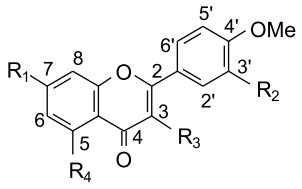
R_1	R_2	R_3	
O-rutinosyl	OMe	OH	**7**
O-neohesperidosyl	OH	H	**8**

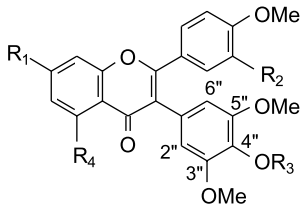
2.1.1. Analogues of combretastatin 1.

The synthesis of **24–29**, analogues of CA-4 **1** is shown in Scheme 1. Hesperidin **7** provided by a well-known process (I_2–pyridine)[13] the corresponding flavone, diosmin **9**, which led in three steps to 3-bromodiosmetin **12** via peracetyldiosmin **10** and its 3-bromo derivative **11**. It is worth noting that the prior peracetylation step is necessary for it allows regiospecific bromination at C-3 by deactivation of C-6 and C-8 (as previously reported, 5-deacetylated analogue of **10** underwent bromination at C-6 and C-8 only).[14] A direct Suzuki coupling with **12** was attempted [with an excess K_2CO_3 (6.2 equiv) because of 5, 7, 3′ free phenol groups], which provided the expected compound **26** under tedious conditions of isolation because of the polar character of 7-hydroxyflavones. Therefore, we thought that **26** would be more conveniently obtained by carrying out the Suzuki coupling from a lipophilic 3-bromodiosmetin protected at the 7-OH group, such as the 7-isopropyl or 7-benzyl ethers **13** and **14**. As expected, **13** and **14** led easily and in good yields (69 and 73%) to the corresponding coupling compounds **27** and **25**. However, we observed that the removal of the isopropyl group of **27** by BCl_3 in CH_2Cl_2 always competed, more or less according to temperature, with demethylation of the 4″-methoxy group (at 0 °C, the 4″-*O*-demethyl **29** was even the sole reaction compound starting from **25** or **27**). In contrast, removal of the benzyl group by hydrogenolysis over Pd–C afforded quantitatively **26** from **25**. In order to study the influence of the substitution at C-5 on bioactivity, the two methyl ethers **24** and **28** were also synthesized. Access to **24** and **28** made use of the known weaker reactivity of the 5-OH towards alkylation (by involvement into chelation with the carbonyl) and the observed slower hydrogenolysis of the 3′benzyl ether group (probably by steric hindrance).

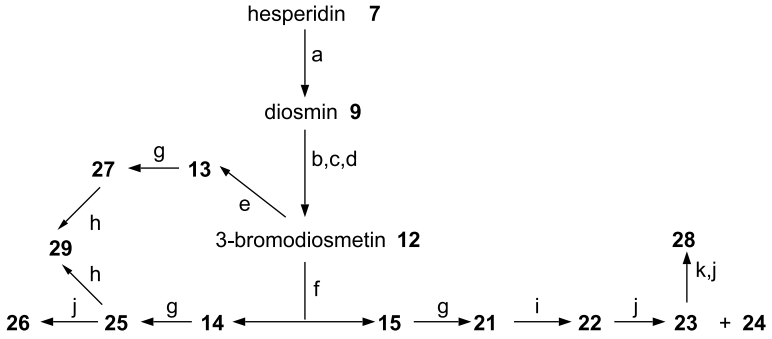
2.1.2. Analogues of combretastatin 2.

Three analogs of deoxy CA-4 **2** were prepared, semisynthetically (**30** and **31**) and by total synthesis (**32**). Access to **30** and **31** was performed from linarin **16**, a natural flavonoid previously obtained in our laboratory by deoxygenation of diosmin.[15] Synthesis of **30** and **31** from **16** via 3-bromoacacetin **17** and 7-benzyl-3-bromoacacetin **18** was similar to the sequence **9**→**12**→**14**→**25**→**26** depicted in Scheme 1. Compound **32**, unsubstituted at C-5 and C-7, was obtained from the commercial (2-hydroxybenzoyl)methylenetriphenylphosphorane **35** by a four-step sequence via the flavones **19**

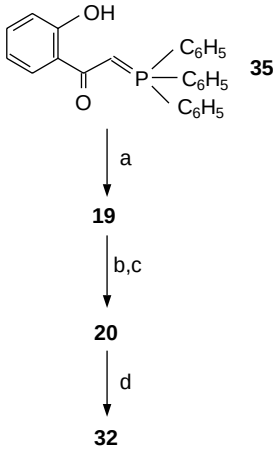




R_1	R_2	R_3	R_4		R_1	R_2	R_3	R_4	
				Analogues of combretastatin **1**					
O-Rutinosyl	OH	H	OH	**9**	OBn	OBn	Me	OH	**21**
O-HAR*	OAc	H	OAc	**10**	OBn	OBn	Me	OMe	**22**
O-HAR	OAc	Br	OAc	**11**	OH	OBn	Me	OMe	**23**
OH	OH	Br	OH	**12**	OH	OH	Me	OMe	**24**
O-Isopropyl	OH	Br	OH	**13**	OBn	OH	Me	OH	**25**
OBn	OH	Br	OH	**14**	OH	OH	Me	OH	**26**
OBn	OBn	Br	OH	**15**	O-Isopropyl	OH	Me	OH	**27**
					OMe	OH	Me	OMe	**28**
* Hexaacetylrutinosyl					OH	OH	H	OH	**29**
				Analogues of combretastatin **2**					
O-Rutinosyl	H	H	OH	**16**	OBn	H	Me	OH	**30**
OH	H	Br	OH	**17**	OH	H	Me	OH	**31**
OBn	H	Br	OH	**18**	H	H	Me	H	**32**
H	H	H	H	**19**					
H	H	Br	H	**20**					



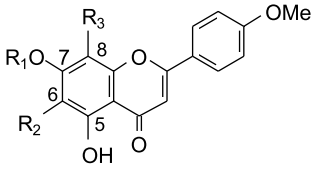
Scheme 1. Reagents and conditions: (a) I_2, pyridine, 90 °C, 16 h, 90%; (b) Ac_2O, pyridine, rt, 72 h, 95%; (c) NBS, CH_2Cl_2/pyridine 4:1, rt, 20 h, 90%; (d) HCl 11 N, 50 °C, 2 h, 75%; (e) 2-bromopropane, K_2CO_3, DMF, 75 °C, 6 h, 54%; (f) benzyl chloride, $KHCO_3$, DMF, 120 °C, 2.5 h, 34% (**14**), 34% (**15**); (g) 3,4,5-trimethoxybenzeneboronic acid, $Pd(PPh_3)_4$, K_2CO_3 2 N, dioxane, reflux, reaction time-yield: 3 h-95% (**21**), 3 h-73% (**25**), 4 h-69% (**27**); (h) BCl_3, CH_2Cl_2, −78 °C 30 min, then 0 °C 15 h, 43% (from **25**); (i) $(CH_3)_2SO_4$, tetrabutylammonium hydrogen sulfate, CH_2Cl_2–NaOH 0.5 N, rt, 22 h 65%; (j) H_2, Pd–C 10%, DMF, rt, reaction time-yield: 72 h-45% (**23**) and 10% (**24**), 3 h-96% (**26**), 5 days after; (k) 39% (**28** from **23**); (l) iodomethane, K_2CO_3, DMF, rt, 20 h.



Scheme 2. Reagents and conditions: (a) 4-methoxybenzoyle chloride, pyridine, toluene, reflux, 5 h (65%); (b) NBS, CH_2Cl_2/MeOH 2:1, rt, 3 h; (c) THF/NaOH N 1:3, rt, 3 h, 42% (**20** from **19**); (d) 3,4,5-trimethoxybenzeneboronic acid, $Pd(PPh_3)_4$, K_2CO_3 2 N, dioxane, reflux, 4 h-42%.

and **20** according to Le Corre[16] for synthesis of **19** and Brown[17] for bromination to **20** (Scheme 2).

2.1.3. Analogues of combretastatin 3. An easy semisynthetic entry to **47** and **48**, two analogues of aminocombretastatin **3**, requires a regiospecific nitration at C-3′. First attempts were undertaken with acacetin **36**, easily available from linarin **16**. Prior deactivation of C-6 and C-8 positions towards nitration seemed necessary and was accomplished by esterification of the 7-OH phenol group as benzylsulfonate. This group, recently described as a valuable protecting and deactivating group in phenol chemistry, is stable under many drastic conditions and easily removed by catalytic hydrogenolysis.[18] Unfortunately, nitration of 7-*O*-benzylsulfonate **37** (HNO_3 1 equiv in TFA, 0 °C, 2 h) provided the mixture (4/3) of 6 and 8-nitro compounds **38** and **39** (68%). Under the same conditions, the more deactivated 5,7-disulfonate led to a mixture with the starting compound still major after 24 h.

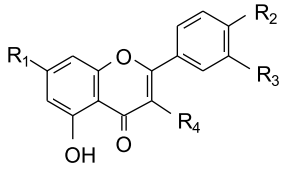


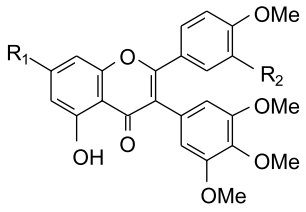
R_1	R_2	R_3	
H	H	H	**36**
$C_6H_5CH_2SO_2$	H	H	**37**
$C_6H_5CH_2SO_2$	NO_2	H	**38**
$C_6H_5CH_2SO_2$	H	NO_2	**39**

These negative results led us to select, as starting material, a 4′-hydroxyflavone with a C-3′ position more activated towards nitration than in acacetin derivatives (Scheme 3). The *Citrus* flavanone naringin **8** provided this 4′-hydroxyflavone, rhoifolin **40**, by the same dehydrogenation procedure (I_2–pyridine) previously described to obtain diosmin. The key nitration step of rhoifolin **40** into 3′-nitrorhoifolin **41** was accomplished very easily by 1 equiv HNO_3 in TFA at 0 °C. The choice of TFA as solvent on the one hand, a strict stoichiometry of HNO_3 on the other hand, prevented **40** from any hydrolysis of glycosidic bonds. It is noteworthy that presence of the sugar moiety at C-7 makes the nitration of the flavone at C-3′ very clean: under the same conditions applied to apigenin (5,7,4′-trihydroxyflavone), significant nitration was also observed at the other benzene ring.[19] A direct hydrolysis of crude **41** gave 3′-nitroapigenin **42** while a prior methylation then acid hydrolysis furnished 3′-nitroacacetin **43**. This compound led by a similar sequence (acetylation, bromination, hydrolysis, alkylation, Suzuki coupling) as described in the 3′ hydroxy series to the nitro products **33** and **34**. A last step of catalytic hydrogenation (Pd–C, rt) gave, respectively, the expected analogues **47** and **48** by reduction of the nitro group and, in the case of **34**, concomitant debenzylation of the ether group.

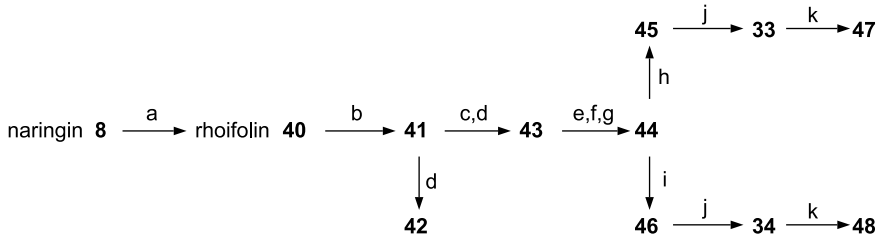
2.2. Synthesis of analogues of the group B (54, 58 and 59)

In order to study a possible influence on the bioactivity, we then synthesized compounds displaying a reverse relative position of the two phenyl rings of the combretastatin moiety on the chromone. Lack of easily available natural flavones with a trimethoxyphenyl ring at C-2 made total synthesis necessary. Three compounds, **54**, **58** and **59**, isomers, respectively, of **32**, **31** and **26** were prepared.

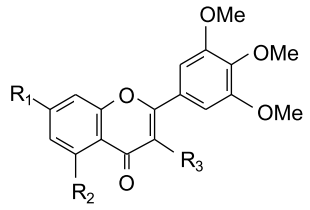




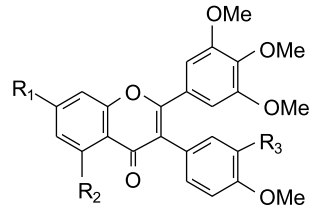
R_1	R_2	R_3	R_4		R_1	R_2	
Analogues of combretastatin **3**							
O-Neohesperidosyl	OH	H	H	**40**	OMe	NO_2	**33**
O-Neohesperidosyl	OH	NO_2	H	**41**	OBn	NO_2	**34**
OH	OH	NO_2	H	**42**	OMe	NH_2	**47**
OH	OMe	NO_2	H	**43**	OH	NH_2	**48**
OH	OMe	NO_2	Br	**44**			
OMe	OMe	NO_2	Br	**45**			
OBn	OMe	NO_2	Br	**46**			



Scheme 3. Reagents and conditions: (a) I_2, pyridine, 90 °C, 16 h, 95%; (b) HNO_3 53%, TFA, 0 °C, 2 h, quantitative yield (crude **41**); (c) iodomethane, K_2CO_3, DMF, rt, 48 h; (d) HCl 11 N, 60 °C, 1 h, 73% (**43** from **41**), 83% (**42**); (e) Ac_2O, pyridine, rt, 72 h, 95%; (f) NBS, CH_2Cl_2/MeOH 2:1, rt, 3 h, 86%; (g) THF/NaOH N 1:1, rt, 4 h, 80%; (h) iodomethane, K_2CO_3, DMF, rt, 20 h, quantitative yield; (i) benzyl chloride, $KHCO_3$, DMF, 120 °C, 2 h, 86%; (j) 3,4,5-trimethoxybenzeneboronic acid, $Pd(PPh_3)_4$, K_2CO_3 2 N, dioxane, reflux, reaction time-yield: 3 h-77% (**33**), 2.5 h-84% (**34**); (k) H_2, Pd–C 10%, DMF, rt, 3 h, quantitative yield (**47** and **48**).



R_1	R_2	R_3	
H	H	H	**49**
H	H	Br	**50**
OH	OH	H	**51**
OH	OH	Br	**52**
OBn	OH	Br	**53**
OBn	OH	H	**57**

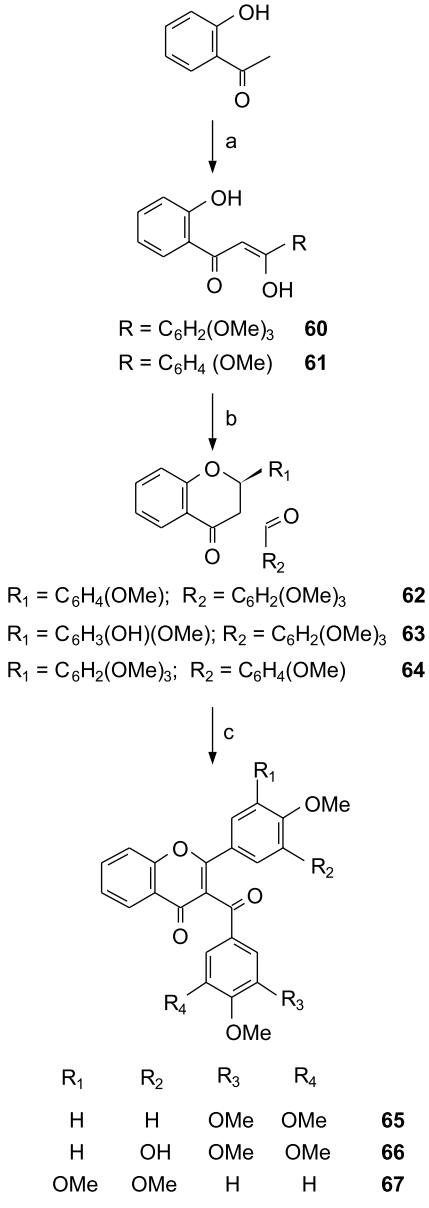


R_1	R_2	R_3	
H	H	H	**54**
OBn	OH	H	**55**
OBn	OH	OBn	**56**
OH	OH	H	**58**
OH	OH	OH	**59**

Synthesis of **54** via 3′,4′,5′-trimethoxyflavone **49** and its 3-bromoderivative **50** followed the procedure described for **32**. However, the Suzuki coupling step between **50** and 4-methoxyphenylboronic acid led to **54** with a poor yield (13%) because of a major debromination of **50** into **49**. This unwanted reaction was proved to be related to the boronic acid, since the same result was observed by coupling 7-benzyl-3-bromodiosmetin **14** with 4-methoxyphenylboronic acid (vs 73% yield between **14** and trimethoxyphenylboronic acid, vide supra). Therefore we turned to another method for this last step by using a iron-catalysed Grignard coupling developed in the laboratory.[20] The cross-coupling reaction of 4-methoxyphenylmagnesium bromide with **50** [THF, −25 °C, $Fe(acac)_3$] again provided a mixture **54/49** but **54** was isolated with a slightly more favourable yield (18%). Preparation of the 5,7-dihydroxylated analogues **58** and **59** started with synthesis of the 5,7-dihydroxy-3′,4′,5′-trimethoxyflavone (=tricetin trimethyl ether) **51** from (2,4,6-trihydroxybenzoyl)methylenetriphenylphosphorane,[21] and proceeded through the 3-bromo derivative **52** and its 7-benzyl ether **53** as already described in the **A** group. The coupling step of **53** at C-3 was then carried out by both methods: Suzuki reaction with commercial 4-methoxyphenylboronic acid produced the expected **55** (21%), while iron-catalysed Grignard coupling with 3-benzyloxy-4-methoxyphenylmagnesium bromide[22] led to **56** (12%). A major debromination reaction into **57** again accounts for low yields of both couplings. Lastly, catalytic hydrogenolysis (Pd–C, rt) of **55** and **56** gave the expected analogues **58** and **59** quantitatively.

2.3. Synthesis of analogues of the groups C (65, 66) and D (67)

Taking into account the positive effect observed in some bicyclic analogues of combretastatins by addition of a C=O linker,[9,10] we synthesized three 3-aroylflavones bearing at C-3 either a 3,4,5-trimethoxyphenyl ring (**65**, **66**) or a 4-methoxyphenyl ring (**67**). First attempts to prepare such compounds from 3-bromoflavones by use of BuLi and the adequate aroyl chloride were unsuccessful so that we turned to classical synthesis of 3-aroylflavones.[23] Starting from 2′-hydroxyacetophenone and 3,4,5-trimethoxy or 4-methoxybenzoyl chlorides, access to **65**–**67** (Scheme 4) proceeded in three steps: (a) one-pot esterification of the phenol group followed by a Baker–Vankataraman rearrangement into **60**



Scheme 4. (a) 3,4,5-Trimethoxybenzoyle chloride or 4-methoxybenzoyle chloride, pyridine, 0 °C, 5 min, then rt, 2.5 h; addition of anhydrous KOH, 100 °C, 3 h, 37% (**60**) and 34% (**61**); (b) *p*-anisaldehyde or isovanillin or 3,4,5-trimethoxybenzaldehyde, piperidine, EtOH, reflux, reaction time: 5 h; (c) SeO_2, dioxane, reflux, 6 h, 36% (**65** from **60**), 40% (**66** from **60**), 54% (**67** from **61**).

and **61** [according to ^{1}H NMR spectra, **61** was the pure keto-enol, while **60** was a mixture of β-diketone (18%) and keto-enol (82%) forms]; (b) Knoevenagel condensation of **60** with *p*-anisaldehyde or isovanillin, and of **61** with 3,4,5-trimethoxybenzaldehyde giving, respectively, crude 3-aroylflavanones **62**, **63** and **64**, which were used in the next step without purification [formation of the trans aroylflavanone form as a major compound was proved in ^{1}H NMR by the presence of H-2 and H-3 signals (2d, $J=12.8$ Hz about 5.0 and 5.8 ppm)]; (c) dehydrogenation of **62**, **63**, **64** by SeO_2 into the desired 3-aroylflavones **65**, **66** and **67**.

2.4. Biological activity

Inhibition of tubulin polymerization (ITP) was determined according to Zavala and Guenard's method.[24] Compounds were tested at 0.1 mg/mL ($\approx 2\times10^{-4}$ M) and estimated inactive when they decreased by less than 30% the maximum assembly rate of tubulin without drug. The IC_{50} was calculated only for the most active compounds and expressed in relation to colchicine in terms of the $IC_{50}/IC_{50\ colchicine}$ ratio. As depicted in Table 1, results were disappointing since only seven of the twenty tested compounds displayed an activity, usually in a medium range. Compound **31**, with a substructure of deoxycombretastatin A4 **2**, was the most active, while all the other 5,7-dioxygenated synthesized analogues, having combretastatin A4 **1** (**24**–**28** and **59**) or aminocombretastatin **3** (**47**, **48**) substructures, were devoid of activity. It is worth noting about analogues of **2** that inversion of substituents at C2 and C3 interfered strongly with activity in one case (**31** vs **58**) but was almost ineffective (**32** vs **54**) in another one. Lastly, insertion of a C=O linker between C3 and the phenyl ring seemed favourable to ITP (**65** vs **32** and, to a lower extent, **67** vs **54**) with, once again, a better activity with the analogue of **2** (**65** vs **66**).

Table 1. ITP activity

Compound	Activity [a]
Analogs of **1**	
24	Inactive [b]
25	Inactive
26	Inactive
27	Inactive
28	Inactive
59	Inactive
Analogs of **2**	
30	Inactive [b]
31	2.4[c]
32	40%[d]
54	54%
55	35%
58	Inactive
Analogs of **3**	
47	Inactive
48	Inactive
Other 3-arylflavones	
29	Inactive
33	Inactive
34	Inactive
3-Aroylflavones	
65	5.4[c]
66	39%
67	66%
Reference	
Colchicine	1

[a] Measurement at 0.1 mg/mL.
[b] Decreasing $<30\%$.
[c] $IC_{50}/IC_{50colchicine}$.
[d] Decreasing of the maximum assembly rate of tubulin without drug.

3. Conclusion

Though failing in its initial goal of access to new combretastatins analogues with strong ITP activity, this study seems to us noteworthy from a chemical point of view for the following reasons: (a) access to 3-phenyl flavones via a cross-coupling reaction from 3-bromo-5,7-dioxygenated flavones led us to achieve a very easy and regiospecific 3-bromination of natural 5,7-dihydroxyflavones and their 7-glycosides (3-bromination of synthetic flavones is well documented,[17,25] but has never been described to the best of our knowledge from natural 5,7-dihydroxyflavones); (b) the C3-aryl bond was usually formed via a Suzuki reaction, but the coupling with a Grignard reagent, easier to prepare than a boronic acid, seemed to be a possible alternative; (c) synthesis of analogues of aminocombretastatin **3** allowed us to develop an original nitration process of a flavone glycoside without prior protection nor hydrolysis of the sugar moiety; (d) lastly, most of this study started from two easily available *Citrus* flavonoids, hesperidin and naringin, which confirms the interest of some natural products as raw materials for organic chemistry.

4. Experimental

4.1. General experimental procedures

Melting points were determined with a micro-Koffler and are uncorrected. ^{1}H NMR spectra were recorded on Bruker AC-200 (200 MHz) or Bruker AM-400; NOESY experiments and the ^{1}H–^{1}H (COSY) and ^{1}H–^{13}C (HMQC and HMBC) were performed with a Bruker AM-400. EIMS were registered on an Automass Thermoquest with EI source (70 eV) and ESIMS on a Navigator Aqa thermoquest with an ES source (MeOH, flow rate: 5 μL/min) (70 eV). MHz spectrometers. Flash chromatography (FC) was performed with silica gel 60 (9385 Merck) or aluminium oxide 90 (1097 Merck), or alumina 90 standard II–III (1097 Merck). Preparative TLC were performed with 60 F 254 silica gel (5715 Merck) or 60 F 254 aluminium oxide (5713 Merck).

4.2. Synthesis of analogues of the group A

4.2.1. Synthesis of 3-bromoflavones, intermediates for 3-arylflavones analogues of 1 and 2.

4.2.1.1. 3-Bromo-octoacetyldiosmin 11. A solution of diosmin **9** (3.04 g, 5 mmol) in Ac_2O/pyridine 1:5 (20 mL) was left at rt for 48 h. The reaction mixture was taken up in iced water, stirred at 0 °C for 2 h then extracted with CH_2Cl_2. Standard work-up of the organic layer provided an amorphous residue of pure octoacetyldiosmin **10** (4.5 g, 95%). A solution of **10** (4.25 g, 4.5 mmol) in CH_2Cl_2/pyridine 5:1 (50 mL) was added with NBS (4.05 g, 22.5 mmol) then kept at rt for 20 h. The reaction mixture was taken up in CH_2Cl_2, washed with water and evaporated to dryness. The dried residue was left at rt for 20 h more

(this step allowed completion of the bromination), then taken up in CH_2Cl_2, and washed with 0.1 M aqueous sodium thiosulphate then water. Standard work-up of the reaction, then purification of the residue by FC (silica gel, CH_2Cl_2/MeOH 98.5:1.5) led to 3-bromo-octoacetyldiosmin **11** (4.15 g, 90%). Yellowish amorphous powder. ^{1}H NMR ($CDCl_3$) δ [aglycone moiety]: 2.33 and 2.44 (6H, 2s, OAc-5 and 3′), 3.91 (3H, s, OMe-4′), 6.69 (1H, d, J=2 Hz, H-6), 6.89 (1H, d, J=2 Hz, H-8), 7.08 (1H, d, J=8.8 Hz, H-5′), 7.58 (1H, d, J=2.2 Hz, H-2′), 7.77 (1H, dd, J=8.8, 2.2 Hz, H-6′); [sugar moiety: inner glucose (″) and terminal rhamnose (‴)] 1.13 (3H, d, J=6.4 Hz, H-6‴), 1.92–2.06 (18H, 6s, 6 sugar acetyles). 3.66 (1H, H-6″), 3.80 (2H, H-6″ and H-5‴), 3.94 (1H, H-5″), 4.67 (1H, s, H-1‴), 4.99 (1H, H-4‴), 5.13–5.28 (5H, H-2″, 3″, 4″, 2‴ and 3‴), 5.27 (1H, H-1″). ^{13}C NMR ($CDCl_3$) δ [aglycone moiety] 56.0 (OMe-4′), 101.4 (C-8), 109.5 and 110.7 (C-3 and C-10), 109.8 (C-6), 111.6 (C-5′), 124.1 (C-2′), 124.5 (C-1′), 128.7 (C-6′), 139.2 (C-3′), 150.8 (C-5), 153.4 (C-4′), 157.6 (C-9), 159.7 and 159.9 (C-2 and C-7), C-4 not detected; [sugar moiety: inner glucose (″) and terminal rhamnose (‴)] 17.2 (C-6‴), 65.9 (C-6″), 66.6 (C-5‴), 68.5, 68.8, 69.1, 70.6, 70.7 and 72.2 (C-2″, C-3″, C-4″, C-2‴, C-3‴ and C-4‴), 73.5 (C-5″), 97.5 (C-1″), 97.9 (C-1‴); 20.5–21 and 168.6–170.6 (8 sugar acetyl groups).

4.2.1.2. 3-Bromodiosmetin 12. 3-Bromo-octoacetyldiosmin **11** (4 g, 3.9 mmol) in aqueous 11 N HCl (75 mL) was stirred at 55 °C for 2 h and left for 2 h at rt. The resulting suspension was filtered, washed several times with water then dried with P_2O_5 under vacuum to yield a crude residue of 3-bromodiosmetin **12**, which was crystallized from MeOH (1.11 g, 75%). Beige-yellowish crystals: mp> 300 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 3.87 (s, 3H, OMe-4′), 6.27 (d, J=1.8 Hz, 1H, H-6), 6.40 (d, J=1.8 Hz, 1H, H-8), 7.09 (d, J=8.2 Hz, 1H, H-5′), 7.31 (d, J=2 Hz, 1H, H-2′), 7.33 (dd, J=8.2, 2 Hz, 1H, H-6′), 9.46 (s, 1H, OH-3′), 11.0 (s, 1H, OH-7), 12.38 (s, 1H, OH-5). ^{13}C NMR (DMSO-d_6) δ 56.1 (OMe-4′), 94.2 (C-8), 99.6 (C-6), 102.9 (C-10), 105.1 (C-3), 111.9 (C-5′), 116.5 (C-2′), 121.8 (C-6′), 124.5 (C-1′), 146.4 (C-3′), 150.7 (C-4′), 157.2 (C-9), 161.2 and 162.3 (C-2 or C-5), 165.0 (C-7), 176.7 (C-4). EIMS m/z (%) 380–378 (M^+, 92–100), 379–377 (54–38).

4.2.1.3. 3-Bromodiosmetin 7-isopropyl ether 13. To a mixture of **12** (152 mg, 0.4 mmol) and K_2CO_3 (55 mg, 0.4 mmol) in DMF (6 mL) was added isopropyl bromide (0.4 mL, 4 mmol) and the mixture stirred under nitrogen for 6 h at 75 °C. The reaction mixture was cooled, filtered, and evaporated to dryness. The dried residue was purified by FC (silica gel, CH_2CH_2/MeOH 99.5:0.5) to provide 3-bromodiosmetin 7-isopropyl ether **13** (90 mg, 54%). Pale-yellow crystals: mp: 182–185 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 1.37 (d, J=6 Hz, 6H, isopropyl), 4.62 (heptuplet, J=6 Hz, 1H, isopropyl), 3.99 (s, 3H, OMe-4′), 6.38 and 6.39 (2d, J= 2 Hz, 2H, H-6 and H-8), 6.97 (d, J=8.4 Hz, 1H, H-5′), 7.44 (d, J=2.1 Hz, 1H, H-2′), 7.46 (dd, J=8.4, 2.1 Hz, 1H, H-6′), 12.36 (s, 1H, OH-5). ^{13}C NMR ($CDCl_3$) δ 21.7 (isopropyl), 55.9 (OMe-4′), 71.0 (isopropyl), 93.2 (C-8), 99.6 (C-6), 103.8 (C-10), 110.0 (C-5′), 115.4 (C-2′), 121.9 (C-6′), 125.4 (C-1′), 145.5 (C-3′), 149.1 (C-4′), 156.9 (C-9), 161.2 (C-2), 162.0 (C-5), 164.1 (C-7); C-3 and C-4 not detected.

4.2.1.4. 3-Bromodiosmetin 7-benzyl ether 14 and 3-bromodiosmetin 7,3′-dibenzyl ether 15. To a mixture of **12** (380 mg, 1 mmol) and $KHCO_3$ (150 mg, 1.5 mmol) in DMF (10 mL) was added benzyl chloride (0.23 mL, 2 mmol) and the mixture stirred under nitrogen for 2.5 h at 120 °C. The reaction mixture was cooled, filtered, and evaporated to dryness. The dried residue was purified by FC (silica gel, CH_2CH_2 then CH_2CH_2/MeOH 99:1) to provide 3-bromodiosmetin 7,3′-dibenzyl ether **15** (190 mg, 34%) then 3-bromodiosmetin 7-benzyl ether **14** (160 mg, 54%). Compound **14**. Pale-yellow crystals: mp: 191–194 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H, OMe-4′), 5.25 (s, 2H, benzyl), 6.57 (d, J=2 Hz, 1H, H-6), 6.80 (d, J= 2 Hz, 1H, H-8), 7.12 (d, J=8.4 Hz, 1H, H-5′), 7.3–7.5 (m, 7H, H-2′, H-6′ and benzyl), 9.50 (s, 1H, OH-3′), 12.40 (s, 1H, OH-5). ^{13}C NMR (DMSO-d_6) δ 56.1 (OMe-4′), 70.5 (benzyl), 93.7 (C-8), 99.4 (C-6), 103.9 (C-10), 105.4 (C-3), 111.9 (C-5′), 116.6 (C-2′), 121.9 (C-6′), 124.4 (C-1′), 128.2, 128.5 and 128.9 (benzyl), 136.3 (benzyl), 146.4 (C-3′), 150.8 (C-4′), 157.1 (C-9), 160.9 (C-5), 162.8 (C-2), 164.9 (C-7), 176.9 (C-4). Compound **15**. Yellow crystals: mp: 165–167 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.98 (s, 3H, OMe-4′), 5.11 and 5.23 (2s, 4H, benzyls), 6.45 and 6.47 (2d, J=2 Hz, 2H, H-6 and H-8), 7.00 (d, J=8.4 Hz, 1H, H-5′), 7.3–7.5 (m, 12H, H-2′, H-6′ and benzyls), 9.50 (s, 1H, OH-3′), 12.40 (s, 1H, OH-5). ^{13}C NMR ($CDCl_3$) δ 56.0 (OMe-4′), 70.5 and 71.3 (benzyls), 93.1 (C-8), 99.2 (C-6), 104.2 (C-10), 105.7 (C-3), 111.0 (C-5′), 115.4 (C-2′), 123.5 (C-6′), 124.3 (C-1′), 127.1, 127.3, 127.4, 128.0, 128.3 and 128.7 (benzyls), 135.5 and 136.3 (benzyls), 147.4 (C-3′), 152.3 (C-4′), 157.0 (C-9), 161.7 (C-2 and C-5), 164.8 (C-7), 177.0 (C-4).

4.2.1.5. 3-Bromoacacetin 17; 3-bromoacacetin 7-benzyl ether 18. 3-Bromoacacetin **17** was prepared from 900 mg (1.5 mmol) linarin **16** as **12** from **9** (60% **17** from **16**), then its benzyl ether **18** as **14** from **12** (1.1 equiv $KHCO_3$, 1.2 equiv BnCl, 77%). Compound **17**. Beige-yellowish crystals: mp: 297–298 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 3.86 (s, 3H, OMe-4′), 6.27 (d, J=2 Hz, 1H, H-6), 6.41 (d, J=2 Hz, 1H, H-8), 7.12 (d, J=8.8 Hz, 2H, H-3′ and H-5′), 7.84 (d, J=8.8 Hz, 2H, H-2′ and H-6′), 11.0 (s, 1H, OH-7), 12.37 (s, 1H, OH-5). ^{13}C NMR (DMSO-d_6) δ 55.9 (OMe-4′), 94.3 (C-8), 99.7 (C-6), 102.9 (C-10), 105.2 (C-3), 114.2 (C-3′ and C-5′), 124.4 (C-1′), 131.6 (C-2′ and C-6′), 157.2 (C-9), 161.2, 161.9 and 162.0 (C-2, C-5 and C-4′), 165.0 (C-7), 176.7 (C-4). ESIMS (+) m/z 387–385 $[M+Na]^+$, 365–363 $[M+H]^+$. Compound **18**. Light-yellow crystals: mp: 134–136 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H, OMe-4′), 5.13 (s, 2H, benzyl), 6.50 (s, 2H, H-6 and H-8), 7.02 (d, J=8.8 Hz, 2H, H-3′ and H-5′), 7.35–7.45 (m, 5H, benzyl), 7.87 (d, J=8.8 Hz, 2H, H-2′ and H-6′), 12.41 (s, 1H, OH-5). ^{13}C NMR ($CDCl_3$) δ 55.5 (OMe-4′), 70.6 (benzyl), 93.2 (C-8), 99.3 (C-6), 104.1 (C-10), 105.6 (C-3), 113.7 (C-3′ and C-5′), 124.4 (C-1′), 127.4, 128.4 and 128.7 (benzyl), 131.2 (C-2′ and C-6′), 135.6 (benzyl), 157.1 (C-9), 161.7, 161.8 and 162.0 (C-2, C-5 and C-4′), 164.9 (C-7), 177.0 (C-4).

4.2.1.6. 4′-Methoxyflavone 19. Flavone **19** (655 mg, 65% from 4 mmol phosphorane) was prepared according to Ref.16 White-yellowish crystals: mp: 159–161 °C (MeOH), lit.[16] 157–158 °C; ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H, OMe-4′),

6.75 (s, 1H, H-3), 7.03 (d, $J=9$ Hz, 2H, H-3′ and H-5′), 7.41 (t, $J=8.1$ Hz, 1H, H-6), 7.55 (dd, $J=7.8$, 1.4 Hz, 1H, H-8), 7.69 (m, 1H, H-7), 7.90 (d, $J=9$ Hz, 2H, H-2′ and H-6′), 8.23 (dd, $J=8.1$, 1.7 Hz, 1H, H-5).

4.2.1.7. 3-Bromo-4′-methoxyflavone 20. Bromination of the flavone **19** was performed from Ref. 17: a solution of **19** (504 mg, 2 mmol) in CH_2Cl_2/MeOH 2:1 (60 mL) was added with NBS (712 mg, 4 mmol) then kept at rt for 3 h. The reaction mixture was taken up in CH_2Cl_2, and washed with 0.1 M aqueous sodium thiosulphate then water. Standard work-up furnished a dried residue, which was dissolved then stirred in the mixture THF/NaOH 0.5 M 1:3 (60 mL) for 3 h at rt. The reaction mixture was adjusted to pH 6 with HCl 11 N then extracted with CH_2Cl_2. Standard work-up of the reaction, then purification of the residue by FC (alumina, CH_2Cl_2) led to 3-bromo-4′-methoxyflavone **20** (276 mg, 42%). **20**. Light-yellow crystals: mp: 137–139 °C (MeOH), lit.[25d] 140–141 °C; ^{1}H NMR ($CDCl_3$) δ 3.91 (s, 3H, OMe-4′), 7.04 (d, $J=8.9$ Hz, 2H, H-3′ and H-5′), 7.40–7.55 (m, 2H, H-6 and H-8), 7.65–7.75 (m, 1H, H-7), 7.88 (d, $J=8.9$ Hz, 2H, H-2′ and H-6′), 8.29 (dd, $J=7.9$, 1.5 Hz, 1H, H-5).

4.2.2. Synthesis of 3-arylflavones analogues of 1 and 2. Typical procedure of the Suzuki cross-coupling reaction: a 3-bromoflavone (0.1 mmol), 3,4,5-trimethoxybenzeneboronic acid (35 mg, 0.16 mmol) and tetrakis(triphenylphosphine)palladium (5 mg, 0.005 mmol) were added in a flask fitted with a reflux condenser. The flask was evacuated and back-filled with nitrogen and then 3 mL of dioxane and 0.16 mL of a 2 M solution of K_2CO_3 were added (with 3-bromo-hydroxyflavones, 0.05 mL 2 M K_2CO_3 more were added per each phenol group). The reaction mixture was stirred at 110 °C until completion of the reaction. After cooling, the mixture was taken up in water, adjusted to pH 6 with 1 N HCl and extracted with CH_2Cl_2. Standard work-up then purification by FC led to the expected 3-arylflavone.

4.2.2.1. 3-(3″,4″,5″-Trimethoxyphenyl)diosmetin 7,3′-dibenzyl ether 21. Prepared by Suzuki cross-coupling from 224 mg (0.4 mmol) **15**; yield 95% (245 mg). Light-yellow crystals: mp: 182–185 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.73 (s, 6H, OMe-3″ and 5″), 3.84 (s, 3H, OMe-4″), 3.87 (s, 3H, OMe-4′), 4.86 (s, 2H, benzyl-3′), 5.17 (s, 2H, benzyl-7), 6.46 (s, 2H, H-2″ and H-6″), 6.46 and 6.49 (2d, $J=2$ Hz, 2H, H-6 and H-8), 6.79 (d, $J=8.5$ Hz, 1H, H-5′), 6.89 (d, $J=2.1$ Hz, 1H, H-2′), 7.11 (dd, $J=8.5$, 2.1 Hz, 1H, H-6′), 7.2–7.5 (m, 10H, benzyls), 12.87 (s, 1H, OH-5). EIMS *m/z* (%) 646 (M^+, 73), 556 (76), 555 (100), 540 (47).

4.2.2.2. 3-(3″,4″,5″-Trimethoxyphenyl)diosmetin 7,3′-dibenzyl-5-methyl ether 22. A solution of **21** (183 mg, 0.28 mmol) in CH_2Cl_2 (30 mL) was stirred for 22 h at rt in the presence of 0.5 M aqueous NaOH (30 mL), dimethyl sulfate (3 mL) and tetrabutylammonium hydrogen sulfate (50 mg) as phase-transfer catalyst. Standard work-up of the organic layer, then purification of the dry residue by FC (silica gel, CH_2Cl_2/MeOH 99:1; alumina, CH_2Cl_2/MeOH 99.5:0.5) provided **22** (121 mg, 65%). Pale-yellow crystals: mp: 163–166 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.71 (s, 6H, OMe-3″ and 5″), 3.84 (s, 3H, OMe-4″), 3.88 (s, 3H, OMe-4′), 3.92 (s, 3H, OMe-5), 4.85 (s, 2H, benzyl-3′), 5.18 (s, 2H, benzyl-7), 6.45 (s, 2H, H-2″ and H-6″), 6.46 (d, $J=1.8$ Hz, 1H, H-6), 6.56 (d, $J=1.8$ Hz, 1H, H-8), 6.80 (d, $J=8.5$ Hz, 1H, H-5′), 6.90 (d, $J=2.1$ Hz, 1H, H-2′), 7.12 (dd, $J=8.5$, 2.1 Hz, 1H, H-6′), 7.2–7.5 (m, 10H, benzyls). ^{13}C NMR ($CDCl_3$) δ 55.8 (CH_3, OMe-4′), 55.9 ($2CH_3$, OMe-3″ and 5″), 56.1 (OMe-5), 60.8 (OMe-4″), 70.2 (benzyl-7), 70.4 (benzyl-3′), 93.0 (C-8), 96.2 (C-6), 108.1 (C-2″ and C-6″), 108.7 (C-10), 110.7 (C-5′), 114.1 (C-2′), 122.1 (C-3), 122.5 (C-6′), 124.9 (C-1′), 126–130 (benzyls), 128.3 (C-1″), 135.5 (C, benzyl-7), 136.1 (benzyl-3′), 137.0 (C-4″), 147.0 (C-3′), 151.0 (C-4′), 152.7 (C-3″ and C-5″), 157.8 (C-2), 158.9 (C-9), 161.1 (C-5), 162.9 (C-7); C-4 not detected. EIMS *m/z* (%) 660 (M^+, 11), 570 (43), 569 (100), 541 (28).

4.2.2.3. 3-(3″,4″,5″-Trimethoxyphenyl)diosmetin 3′-benzyl-5-methyl ether 23 and 3-(3″,4″,5″-trimethoxyphenyl)diosmetin 5-methyl ether 24. A solution of **22** (86 mg, 0.13 mmol) in DMF (3 mL) was hydrogenated under 1 atm pressure hydrogen with 10% Pd–C (8.5 mg) at rt for 72 h. The catalyst was separated and the filtrate concentrated to dryness. Crystallization of the dried residue from CH_2Cl_2–MeOH afforded pure **23** (26 mg, 35%), while TLC (silica gel, CH_2Cl_2/MeOH 94:6) of the mother liquor provided **23** (8 mg, 10%) and **24** (6 mg, 10%). Compound **23**. Pale-yellow crystals: mp: 206–210 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 3.62 (s, 9H, OMe-3″, 4″ and 5″), 3.74 (s, 3H, OMe-4″), 3.78 (s, 3H, OMe-4′), 3.92 (s, 3H, OMe-5), 4.70 (s, 2H, benzyl), 6.38 (d, $J=1.8$ Hz, 1H, H-6), 6.43 (s, 2H, H-2″ and H-6″), 6.46 (d, $J=1.8$ Hz, 1H, H-8), 6.93 (d, $J=8.5$ Hz, 1H, H-5′), 6.97 (d, $J=1.7$ Hz, 1H, H-2′), 7.13 (dd, $J=8.5$, 1.7 Hz, 1H, H-6′), 7.3–7.4 (m, 5H, benzyl groups). HRESIMS *m/z* 593.1818 (calcd for $C_{33}H_{30}O_9Na$, 593.1788). Compound **24**. Pale-yellow crystals: mp: 267–270 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 3.62 (s, 6H, OMe-3″ and 5″), 3.67 (s, 3H, OMe-4″), 3.75 (s, 3H, OMe-4′), 3.78 (s, 3H, OMe-5), 6.38 (d, $J=2$ Hz, 1H, H-6), 6.40 (s, 2H, H-2″ and H-6″), 6.43 (d, $J=2$ Hz, 1H, H-8), 6.78 (dd, $J=8.2$, 1.9 Hz, 1H, H-6′), 6.85 (d, $J=8.2$ Hz, 1H, H-5′), 6.86 (d, $J=1.9$ Hz, 1H, H-2′). ^{13}C NMR (DMSO-d_6) δ 55.6 (OMe-7, 4′, 3″ and 5″), 59.8 (OMe-4″), 94.4 (C-8), 96.6 (C-6), 109.0 (C-2″ and C-6″), 111.1 (C-5′), 115.7 (C-2′), 121.1 (C-6′), 121.8 (C-3), 124.4 (C-1′), 136.4 (C-4″), 145.5 (C-3′), 148.8 (C-4′), 151.8 (C-3″ and C-5″), 160.8 (C-5); C-2, C-4, C-7, C-9, C-10 and C-1″ not detected. HRESIMS *m/z* 503.1345 (calcd for $C_{26}H_{24}O_9Na$, 503.1318), 481.1543 (calcd for $C_{26}H_{25}O_9$, 481.1499).

4.2.2.4. 3-(3″,4″,5″-Trimethoxyphenyl)diosmetin 7-benzyl ether 25. Prepared by Suzuki cross-coupling from 282 mg (0.6 mmol) **14**; yield 73% (244 mg). Light-yellow crystals: mp: 235–238 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.74 (s, 6H, OMe-3″ and 5″), 3.86 (s, 3H, OMe-4″), 3.88 (s, 3H, OMe-4′), 5.15 (s, 2H, benzyl-7), 6.45 (s, 2H, H-2″ and H-6″), 6.46 (d, $J=2.2$ Hz, 1H, H-6), 6.53 (d, $J=2.2$ Hz, 1H, H-8), 6.67 (d, $J=8.5$ Hz, 1H, H-5′), 6.79 (dd, $J=8.5$, 2.1 Hz, 1H, H-6′), 7.14 (d, $J=2.1$ Hz, 1H, H-2′), 7.3–7.5 (m, 5H, benzyl), 12.90 (s, 1H, OH-5). ^{13}C NMR ($CDCl_3$) δ 55.8 (OMe-4′), 55.9 (OMe-3″ and 5″), 60.7 (OMe-4″), 70.1 (benzyl), 92.7 (C-8), 98.3 (C-6), 105.4 (C-10), 107.8 (C-2″ and C-6″), 109.5 (C-5′), 115.0 (C-2′), 120.8 (C-3), 122.7 (C-6′), 125.3 (C-1′), 127–128.5 (benzyl), 127.2 (C-1″), 135.5 (benzyl), 137.1 (C-4″), 145.0 (C-3′), 147.5 (C-4′), 152.9 (C-3″ and C-5″), 157.0 (C-9), 161.8

(C-2), 162.1 (C-5), 164.3 (C-7); C-4 not detected. EIMS *m/z* (%) 556 (M^+, 45), 91 (100).

4.2.2.5. 3-(3″,4″,5″-Trimethoxyphenyl)diosmetin 26. Catalytic hydrogenation of **25** (110 mg, 0.2 mmol) in DMF (Pd–C, rt, 3 h) provided after filtration of the catalyst a dry residue of pure **26** (87 mg, 96%). Pale-beige yellowish crystals: mp: 262–264 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 3.62 (s, 6H, OMe-3″ and 5″), 3.67 (s, 3H, OMe-4″), 3.75 (s, 3H, OMe-4′), 6.21 (d, J=2 Hz, 1H, H-6), 6.40 (d, J=2 Hz, 1H, H-8), 6.49 (s, 2H, H-2″ and H-6″), 6.83 (dd, J=8.5, 2 Hz, 1H, H-6′), 6.87 (d, J=8.5 Hz, 1H, H-5′), 6.90 (d, J=2 Hz, 1H, H-2′), 12.97 (s, 1H, OH-5). ^{13}C NMR (DMSO-d_6) δ 55.9 (OMe-4′), 56.0 (OMe-3″ and 5″), 60.5 (OMe-4″), 93.3 (C-8), 99.0 (C-6), 103.2 (C-10), 108.5 (C-2″ and C-6″), 111.4 (C-5′), 116.1 (C-2′), 119.8 (C-3), 121.6 (C-6′), 124.9 (C-1′), 127.8 (C-1″), 137.1 (C-4″), 146.0 (C-3′), 149.8 (C-4′), 152.5 (C-3″ and C-5″), 157.2 (C-9), 161.9 (C-2), 162.0 (C-5), 164.2 (C-7); C-4 not detected. EIMS *m/z* (%) 466 (M^+, 100), 451 (48).

4.2.2.6. 3-(3″,4″,5″-Trimethoxyphenyl)diosmetin 7-isopropyl ether 27. Prepared by Suzuki cross-coupling from 42 mg (0.1 mmol) **13**; purification by FC (silica gel, CH_2Cl_2/MeOH 98:2); yield 69% (35 mg). Light-yellow crystals: mp: 219–219 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 1.39 (d, J=6 Hz, 6H, isopropyl), 4.64 (heptuplet, J=6 Hz, 1H, isopropyl), 3.74 (s, 6H, OMe-3″ and 5″), 3.86 (s, 3H, OMe-4″), 3.89 (s, 3H, OMe-4′), 6.35 and 6.43 (2d, J=2.2 Hz, 2H, H-6 and H-8), 6.44 (s, 2H, H-2″ and H-6″), 6.68 (d, J=8.5 Hz, 1H, H-5′), 6.79 (dd, J=8.5, 2.1 Hz, 1H, H-6′), 7.15 (d, J=2.1 Hz, 1H, H-2′), 12.86 (s, 1H, OH-5). ^{13}C NMR ($CDCl_3$) δ 21.6 (isopropyl), 55.8 (OMe-4′), 56.0 (OMe-3″ and 5″), 60.6 (OMe-4″), 70.7 (isopropyl), 93.0 (C-8), 98.8 (C-6), 104.1 (C-10), 107.8 (C-2″ and C-6″), 110.0 (C-5′), 115.1 (C-2′), 120.8 (C-3), 122.7 (C-6′), 125.5 (C-1′), 137.0 (C-4″), 145.0 (C-3′), 147.9 (C-4′), 152.9 (C-3″ and C-5″), 157.1 (C-9), 162.2 (C-5); C-2, C-4, C-7 and C-1″ not detected. EIMS *m/z* (%) 508 (M^+, 100), 451 (33), 151 (27).

4.2.2.7. 3-(3″,4″,5″-Trimethoxyphenyl)diosmetin 5,7-dimethyl ether 28. Methylation of **23** (27 mg, 0.047 mmol) in DMF by the system K_2CO_3/MeI, then catalytic hydrogenation (DMF, rt, 5 days), and final purification by TLC (silica gel, CH_2Cl_2/MeOH 95:5) led to **28** (9 mg, 39% from **23**). Light-yellow crystals: mp: 178–180 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 6H, OMe-3″ and 5″), 3.85 (s, 3H, OMe-4″), 3.88 (s, 3H, OMe-4′), 3.91 (s, 3H, OMe-7), 3.93 (s, 3H, OMe-5), 6.38 (d, J=2.2 Hz, 1H, H-6), 6.46 (s, 2H, H-2″ and H-6″), 6.53 (d, J=2.2 Hz, 1H, H-8), 6.66 (d, J=8.5 Hz, 1H, H-5′), 6.77 (dd, J=8.5, 2.1 Hz, 1H, H-6′), 7.19 (d, J=2.1 Hz, 1H, H-2′). ^{13}C NMR ($CDCl_3$) δ 55.7 and 56.3 (OMe-7 and 4′), 55.9 (2OMe-3″ and 5″), 60.9 (OMe-4″), 92.4 (C-8), 96.1 (C-6), 108.7 (C-10), 108.7 (C-2″ and C-6″), 109.8 (C-5′), 114.9 (C-2′), 122.5 (C-3), 122.8 (C-6′), 125.6 (C-1′), 128.1 (C-1″), 137.3 (C-4″), 144.8 (C-3′), 148.3 (C-4′), 153.5 (C-3″ and C-5″), 158.7 (C-2), 159.1 (C-9), 161.1 (C-5), 164.0 (C-7); C-4 not detected. HRESIMS *m/z* 517.1481 (calcd for $C_{27}H_{26}O_9Na$, 517.1475), 495.1635 (calcd for $C_{27}H_{27}O_9$, 495.1635).

4.2.2.8. 3-(3″,5″-Dimethoxy-4″-hydroxyphenyl)-diosmetin 29. To a solution of **25** (40 mg, 0.072 mmol) in anhydrous CH_2CH_2 (5 mL) stirred at −78 °C under nitrogen was added dropwise 1 M boron trichloride in CH_2CH_2 (1 mL). The reaction was stirred for 0.5 h at −78 °C then 16 h at 0 °C. The reaction mixture was taken up in iced water, adjusted at pH 6 with $NaHCO_3$ then extracted with AcOEt. Standard work-up of the organic layer afforded a dry residue (29 mg), which was purified by TLC (silica gel, CH_2CH_2/MeOH 96:4) to give **29** (14 mg, 43%). Light-yellow crystals: mp: 280–283 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 3.61 (s, 6H, OMe-3″ and 5″), 3.76 (s, 3H, OMe-4′), 6.20 (d, J=2 Hz, 1H, H-6), 6.38 (d, J=2 Hz, 1H, H-8), 6.42 (s, 2H, H-2″ and H-6″), 6.79 (dd, J=8.5, 2 Hz, 1H, H-6′), 6.86 (d, J=8.5 Hz, 1H, H-5′), 6.92 (d, J=2 Hz, 1H, H-2′), 13.04 (s, 1H, OH-5). ^{13}C NMR (DMSO-d_6) δ 55.9 (OMe-4′), 56.4 (OMe-3″ and 5″), 93.8 (C-8), 99.1 (C-6), 103.7 (C-10), 109.4 (C-2″ and C-6″), 111.7 (C-5′), 116.5 (C-2′), 120.1 (C-3), 121.8 (C-6′), 122.1 (C-1″), 125.3 (C-1′), 135.7 (C-4″), 146.2 (C-3′), 148.2 (C-3″ and C-5″), 149.8 (C-4′), 157.5 (C-9), 162.0 and 162.1 (C-2 and C-5), 164.7 (C-7), 181.3 (C-4). EIMS *m/z* (%) 452 (M^+, 100), 451 (10).

4.2.2.9. 3-(3″,4″,5″-Trimethoxyphenyl)acacetin 7-benzyl ether 30. Prepared by Suzuki cross-coupling from 136 mg (0.3 mmol) **18**; reaction time 1 h; purification by FC (silica gel, CH_2Cl_2/MeOH 95:5); yield 90% (146 mg). Light-yellow crystals: mp: 184–185 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.74 (s, 6H, OMe-3″ and 5″), 3.80 and 3.85 (2s, 6H, OMe-4′ and 4″), 5.14 (s, 2H, benzyl), 6.45 (s, 2H, H-2″ and H-6″), 6.45 and 6.53 (2d, J=2 Hz, 2H, H-6 and H-8), 6.78 (d, J=8.8 Hz, 2H, H-3′ and H-5′), 7.3–7.45 (m, 7H, H-2′, H-6′ and benzyl), 12.94 (s, 1H, OH-5). ^{13}C NMR ($CDCl_3$) δ 55.2 (OMe-4′), 56.0 (OMe-3″ and 5″), 60.8 (OMe-4″), 70.3 (benzyl), 93.0 (C-8), 98.7 (C-6), 105.2 (C-10), 108.3 (C-2″ and C-6″), 113.5 (C-3′ and C-5′), 120.1 (C-3), 124.6 (C-1′), 127.3, 128.2 and 128.6 (benzyl), 130.9 (C-2′ and C-6′), 135.7 (benzyl), 137.7 (C-4″), 153.3 (C-3″ and C-5″), 157.3 (C-9), 161.1, 161.7 and 162.4 (C-2, C-5 and C-4′), 164.6 (C-7), 181.3 (C-4); C-1″ not detected. HRESIMS *m/z* 541.1883 (calcd for $C_{32}H_{29}O_8$, 541.1862).

4.2.2.10. 3-(3″,4″,5″-Trimethoxyphenyl)acacetin 31. Catalytic hydrogenation of **30** (81 mg, 0.15 mmol) in DMF (Pd–C, rt, 3 h) provided after filtration of the catalyst a dry residue of pure **31** (63 mg, 93%). Pale-yellow crystals: mp: 284–288 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 3.61 (s, 6H, OMe-3″ and 5″), 3.67 (s, 3H, OMe-4″), 3.76 (s, 3H, OMe-4′), 6.23 (d, J=1.8 Hz, 1H, H-6), 6.44 (d, J=1.8 Hz, 1H, H-8), 6.50 (s, 2H, H-2″ and H-6″), 6.91 (d, J=8.8 Hz, 2H, H-3′ and H-5′), 7.38 (d, J=8.8 Hz, 2H, H-2′ and H-6′), 12.97 (s, 1H, OH-5). ^{13}C NMR (DMSO-d_6) δ 55.8 (OMe-4′), 56.0 (OMe-3″ and 5″), 60.5 (OMe-4″), 93.8 (C-8), 98.8 (C-6), 102.8 (C-10), 108.6 (C-2″ and C-6″), 113.8 (C-3′ and C-5′), 119.1 (C-3), 124.5 (C-1′), 131.0 (C-2′ and C-6′), 137.0 (C-4″), 152.8 (C-3″ and C-5″), 157.0 (C-9), 160.9 (C-2), 161.0 (C-4′), 161.9 (C-5); C-4, C-7 and C-1″ not detected. HRESIMS *m/z* 473.1243 (calcd for $C_{25}H_{22}O_8Na$, 473.1212), 451.1406 (calcd for $C_{25}H_{23}O_8$, 451.1393).

4.2.2.11. 4′-Methoxy-3-(3″,4″,5″-trimethoxyphenyl)-flavone 32. Prepared by Suzuki cross-coupling from 100 mg (0.3 mmol) **20**; reaction time 4 h; yield 42% (52 mg). White crystals: mp: 170–172 °C (MeOH); ^{1}H

NMR ($CDCl_3$) δ 3.71 (s, 6H, OMe-3″ and 5″), 3.81 (s, 3H, OMe-4′), 3.86 (s, 3H, OMe-4″), 6.47 (s, 2H, H-2″ and H-6″), 6.80 (d, J=8.7 Hz, 2H, H-3′ and H-5′), 7.39 (d, J=8.7 Hz, 2H, H-2′ and H-6′), 7.42 (t, J=7.8 Hz, 1H, H-6), 7.53 (d, J=7.8 Hz, 1H, H-8), 7.70 (t, J=7.8 Hz, 1H, H-7), 8.28 (d, J=7.8 Hz, 1H, H-5). ^{13}C NMR ($CDCl_3$) δ 54.6 (OMe-4′), 55.9 (OMe-3″ and 5″), 61.0 (OMe-4″), 108.9 (C-2″ and C-6″), 114.0 (C-3′ and C-5′), 117.9 (C-8), 121.4 (C-3), 123.1 (C-10), 124.8 (C-1′), 125.7 (C-6), 126.3 (C-5), 128.3 (C-1″), 132.2 (C-2′ and C-6′), 133.5 (C-7), 137.0 (C-4″), 152.6 (C-3″ and C-5″), 156.0 (C-9), 161.2 (C-4′), 176.8 (C-4); C-2 not detected. ESIMS (+) m/z 441 $[M+Na]^+$, 419 $[M+H]^+$.

4.2.3. Synthesis of 3-bromoflavones, intermediates for 3-arylflavones analogues of 3. (a) From acacetin **36**.

4.2.3.1. 7-Benzylsulfonylacacetin 37; 7-benzylsulfonyl-6-nitroacacetin 38 and 7-benzylsulfonyl-8-nitroacacetin 39. A solution of acacetin **36** (85 mg, 0.3 mmol) in anhydrous THF (10 mL) was added with triethylamine (0.1 mL) and α-toluenesulfonyl chloride (57 mg, 0.3 mmol), then left at rt for 0.5 h. Standard work-up of the reaction provided the sulfonate **37** (123 mg, 94%). To a solution of **37** (44 mg, 0.1 mmol) in TFA (4 mL) at 0 °C was added 1 equiv HNO_3 53%. The reaction was stirred for 2 h at 0 °C, then taken up in iced water and carefully adjusted at pH 6 with 30% aqueous NaOH. Standard work-up of the reaction then purification of the dried residue by FC (silica gel, CH_2Cl_2/MeOH 99.5:0.5) afforded pure isomers **38** (19 mg, 39%) and **39** (14 mg, 29%).

Compound **37**. Beige-yellowish crystals: mp: 170–173 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H, OMe-4′), 4.58 (s, 2H, benzyl), 6.50 (d, J=1.8 Hz, 1H, H-6), 6.62 (s, 1H, H-3), 6.85 (d, J=1.8 Hz, 1H, H-8), 7.02 (d, J=8.8 Hz, 2H, H-3′ and H-5′), 7.48 (m, 5H, benzyl), 7.82 (d, J=8.8 Hz, 2H, H-2′ and H-6′), 12.89 (s, 1H, OH-5). ESIMS (+) m/z 899 $[2M+Na]^+$. Compound **38**. Orange-yellow crystals: mp: 198–202 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H, OMe-4′), 4.69 (s, 2H, benzyl), 6.72 (s, 1H, H-3), 7.05 (d, J=8.8 Hz, 2H, H-3′ and H-5′), 7.07 (s, 1H, H-8), 7.47 (m, 5H, benzyl), 7.85 (d, J=8.8 Hz, 2H, H-2′ and H-6′), 14.05 (s, 1H, OH-5). Compound **39**. Orange-yellow crystals: mp: 193–196 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3H, OMe-4′), 4.69 (s, 2H, benzyl), 6.72 (s, 1H, H-3), 6.78 (s, 1H, H-6), 7.05 (d, J=8.8 Hz, 2H, H-3′ and H-5′), 7.48 (m, 5H, benzyl), 7.85 (d, J=8.8 Hz, 2H, H-2′ and H-6′), 13.48 (s, 1H, OH-5). ESIMS (−) m/z 482 $[M-H]^-$.

(b) From naringin **8**

4.2.3.2. 3′-Nitrorhoifolin 41. Rhoifolin **40** was prepared from naringin by the classical procedure (I_2, pyridine, 90 °C, 16 h, 95%).[13] To a solution of rhoifolin **40** (6.87 g, 11.2 mmol) in TFA (50 mL) at 0 °C was added dropwise 1 equiv HNO_3 53%. The reaction was stirred for 2 h at 0 °C, then carefully evaporated at rt with a vacuum system equipped with a KOH trap, and finally dried in a dessicator to provide crude 3′-nitrorhoifolin **41** (quantitative yield) used as it is in the following steps. Lemon-yellow crystals: mp: 220–230 °C; ^{1}H NMR (DMSO-d_6) δ 1.22 (d, J=6 Hz, 3H, Me-6‴), 5.14 (s, 1H, H-1‴), 5.26 (d, J=7 Hz, 1H, H-1″), 6.39 (d, J=1.6 Hz, 1H, H-6), 6.83 (d, J=1.6 Hz, 1H, H-8), 7.03 (s, 1H, H-3), 7.26 (d, J=8.8 Hz, 1H, H-5′), 8.18 (dd, J=8.8, 2.2 Hz, 1H, H-6′), 8.50 (d, J=2.2 Hz, 1H, H-2′). ^{13}C NMR (DMSO-d_6) δ [aglycone moiety] 94.5 (C-8), 99.5 (C-6), 104.9 (C-3), 105.5 (C-10), 119.6 (C-5′), 121.4 (C-1′), 123.4 (C-2′), 132.3 (C-6′), 137.6 (C-3′), 154.4 (C-4′), 156.9 (C-9), 161.0 (C-5), 161.7 (C-2), 162.6 (C-7), 181.8 (C-4); [sugar moiety]: inner glucose 60.4 (C-6″), 69.5[a] (C-4″), 76.4[b] (C-2″), 76.9[b] (C-3″), 77.0[b] (C-5″), 97.6 (C-1″); terminal rhamnose 17.9 (C-6‴), 68.3 (C-5‴), 70.0[a] (C-2‴), 70.2[a] (C-3‴), 72.0 (C-4‴), 100.4 (C-1‴)[a,b] interchangeable. ESIMS (−) m/z 622 $[M-H]^-$.

4.2.3.3. 3′-Nitroapigenin 42; 3′-nitroacacetin 43. Hydrolysis of crude **41** (311 mg, 0.5 mmol) by 11 N HCl (see above **11**→**12**) provided a dry residue of pure 3′-nitroapigenin **42** (131 mg, 83%). Methylation of crude **41** (1.38 g, 2.25 mmol) was performed in DMF (20 mL, stirring at rt) by successive additions of the couple K_2CO_3/MeI until completion of the reaction (1.1 equiv K_2CO_3/0.45 mL MeI for 10 h, 0.55 equiv/0.2 mL for 16 h, 0.22 equiv/0.1 mL for 20 h). The reaction mixture was then filtered and evaporated to dryness. Dry residue was hydrolyzed in 11 N HCl (see above) and furnished after a final crystallization in MeOH 3′-nitroacacetin **43** (541 mg, 73% from **41**). Compound **42**. Lemon-yellow crystals: mp>300 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 6.19 (d, J=1.4 Hz, 1H, H-6), 6.50 (d, J=1.4 Hz, 1H, H-8), 6.93 (s, 1H, H-3), 7.25 (d, J=8.8 Hz, 1H, H-5′), 8.19 (dd, J=8.8, 1.9 Hz, 1H, H-6′), 8.51 (d, J=1.9 Hz, 1H, H-2′), 12.78 (s, 1H, OH-5). ^{13}C NMR (DMSO-d_6) δ 93.4 (C-8), 98.6 (C-6), 103.5 (C-10), 104.1 (C-3), 119.4 (C-5′), 121.5 (C-1′), 122.8 (C-2′), 131.8 (C-6′), 137.5 (C-3′), 153.9 (C-4′), 157.5 (C-9), 161.3 (C-5), 161.6 (C-2), 164.0 (C-7), 181.9 (C-4). ESIMS (−) m/z 314 $[M-H]^-$. Compound **43**. Dark-yellow crystals: mp: 299–300 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 4.01 (s, 3H, OMe-4′), 6.20 (d, J=1.4 Hz, 1H, H-6), 6.53 (d, J=1.4 Hz, 1H, H-8), 7.02 (s, 1H, H-3), 7.51 (d, J=9 Hz, 1H, H-5′), 8.33 (dd, J=9, 2 Hz, 1H, H-6′), 8.54 (d, J=2 Hz, 1H, H-2′), 10.90 (s, 1H, OH-7), 12.75 (s, 1H, OH-5). ^{13}C NMR (DMSO-d_6) δ 57.0 (OMe-4′), 93.9 (C-8), 98.8 (C-6), 103.3 (C-10), 104.8 (C-3), 114.5 (C-5′), 122.2 (C-1′), 122.5 (C-2′), 131.8 (C-6′), 139.5 (C-3′), 153.8 (C-4′), 156.9 (C-9), 160.9 (C-2), 161.5 (C-5), 164.1 (C-7), 181.5 (C-4). ESIMS (+) m/z 352 $[M+Na]^+$, 330 $[M+H]^+$.

4.2.3.4. 3-Bromo-3′-nitroacacetin 44; 3-bromo-3′-nitroacacetin 7-methyl ether 45; 3-bromo-3′-nitroacacetin 7-benzyl ether 46. Acetylation of **43** (165 mg, 0.5 mmol) then bromination of the dry residue by the two-step sequence (see above **19**→**20**) afforded 3-bromo-3′-nitroacacetin **44** (133 mg, 65% from **43**). Methylation (DMF, 1 equiv K_2CO_3, 10 MeI, rt, 20 h) and benzylation (DMF, 1.05 equiv $KHCO_3$, 3 equiv BnCl, 120 °C, 2 h) of **44** (61 mg, 0.15 mmol for each reaction) provided, respectively, **45** (quantitative yield) and **46** (86%). Compound **44**. Light-yellow crystals: mp: 291–294 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 4.03 (s, 3H, OMe-4′), 6.30 (d, J=1.8 Hz, 1H, H-6), 6.44 (d, J=1.8 Hz, 1H, H-8), 7.57 (d, J=9 Hz, 1H, H-5′), 8.16 (dd, J=9, 2.1 Hz, 1H, H-6′), 8.42 (d, J=2.1 Hz, 1H, H-2′), 11.07 (s, 1H, OH-7), 12.27 (s, 1H, OH-5). ^{13}C NMR (DMSO-d_6) δ 56.8 (OMe-4′), 93.8 (C-8), 99.0 (C-6), 102.3 (C-10), 114.1 (C-5′), 123.6 (C-1′), 126.1 (C-2′), 135.1

(C-6′), 138.5 (C-3′), 153.9 (C-4′), 157.1 (C-9), 159.1 (C-2), 160.9 (C-5), 164.2 (C-7); C-3 and C-4 not detected. ESIMS (−) *m/z* 408–406 $[M-H]^-$. Compound **45**. Light-yellow crystals: mp: 256–259 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H, OMe-7), 4.05 (s, 3H, OMe-4′), 6.43 (s, 2H, H-6 and H-8), 7.23 (d, J=9 Hz, 1H, H-5′), 8.13 (dd, J=9, 2.1 Hz, 1H, H-6′), 8.37 (d, J=2.1 Hz, 1H, H-2′), 12.24 (s, 1H, OH-5). Compound **46**. Amorphous; ^{1}H NMR ($CDCl_3$) δ 4.05 (s, 3H, OMe-4′), 5.10 (s, 2H, benzyl), 6.51 (s, 2H, H-6 and H-8), 7.22 (d, J=9 Hz, 1H, H-5′), 7.3–7.45 (m, 5H, benzyl), 8.11 (dd, J=9, 2.1 Hz, 1H, H-6′), 8.37 (d, J=2.1 Hz, 1H, H-2′), 12.24 (s, 1H, OH-5).

4.2.4. Synthesis of 3-arylflavones analogues of 3.

4.2.4.1. 3′-Nitro-3-(3″,4″,5″-trimethoxyphenyl)acacetin 7-methyl ether 33. Prepared by Suzuki cross-coupling from 55 mg (0.13 mmol) **45**; reaction time 3 h; yield 77% (51 mg). Light-yellow crystals: mp: 245–247 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.76 (s, 6H, OMe-3″ and 5″), 3.88 (s, 3H, OMe-4″), 3.91 (s, 3H, OMe-7), 3.97 (s, 3H, OMe-4′), 6.40 (d, J=2 Hz, 1H, H-6), 6.45 (s, 2H, H-2″ and H-6″), 6.51 (d, J=2 Hz, 1H, H-8), 6.92 (d, J=9 Hz, 1H, H-5′), 7.39 (dd, J=9, 2.1 Hz, 1H, H-6′), 8.17 (d, J=2.1 Hz, 1H, H-2′), 12.70 (s, 1H, OH-5). ^{13}C NMR ($CDCl_3$) δ 56.2 (OMe-7), 56.7 (OMe-3″ and 5″), 57.1 (OMe-4′), 60.6 (OMe-4″), 92.9 (C-8), 98.8 (C-6), 105.5 (C-10), 107.8 (C-2″ and C-6″), 112.3 (C-5′), 121.1 (C-3), 124.9 (C-1′), 126.2 (C-1″), 127.0 (C-2′), 135.7 (C-6′), 138.3 (C-4″), 139.1 (C-3′), 153.8 (C-3″ and C-5″), 154.2 (C-4′), 157.1 (C-9), 158.4 (C-2), 162.7 (C-5), 166.0 (C-7); C-4 not detected. HRESIMS *m/z* 532.1218 (calcd for $C_{26}H_{23}NO_{10}Na$, 532.1220), 510.1406 (calcd for $C_{26}H_{24}NO_{10}$, 510.1400).

4.2.4.2. 3′-Nitro-3-(3″,4″,5″-trimethoxyphenyl)acacetin 7-benzyl ether 34. Prepared by Suzuki cross-coupling from 60 mg (0.3 mmol) **46**; reaction time 2.5 h; yield 84% (59 mg). Pale-yellow crystals: mp: 168–171 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.76 (s, 6H, OMe-3″ and 5″), 3.88 (s, 3H, OMe-4″), 3.96 (s, 3H, OMe-4′), 5.17 (s, 2H, benzyl), 6.45 (s, 2H, H-2″ and H-6″), 6.49 (d, J=2 Hz, 1H, H-6), 6.58 (d, J=2 Hz, 1H, H-8), 6.92 (d, J=9 Hz, 1H, H-5′), 7.35–7.45 (m, 6H, benzyl and H-6′), 8.16 (d, J=2.1 Hz, 1H, H-2′), 12.70 (s, 1H, OH-5). ^{13}C NMR ($CDCl_3$) δ 56.2 (OMe-3″ and 5″), 56.8 (OMe-4′), 60.9 (OMe-4″), 70.5 (benzyl), 93.1 (C-8), 99.2 (C-6), 105.2 (C-10), 108.0 (C-2″ and C-6″), 113.0 (C-5′), 121.4 (C-3), 124.6 (C-1′), 126.5 (C-1″), 127.4 (C-2′), 128.4, 128.7 and 128.9 (5CH, benzyl), 135.2 (C-6′), 135.6 (C, benzyl), 138.3 (C-4″), 139.2 (C-3′), 153.8 (C-3″ and C-5″), 154.1 (C-4′), 157.3 (C-9), 158.4 (C-2), 162.4 (C-5), 165.0 (C-7), 181.2 (C-4). HRESIMS *m/z* 586.1741 (calcd for $C_{32}H_{28}NO_{10}$, 586.1713).

4.2.4.3. 3′-Amino-3-(3″,4″,5″-trimethoxyphenyl)acacetin 7-methyl ether 47; 3′-amino-3-(3″,4″,5″-trimethoxyphenyl)acacetin 48. Catalytic hydrogenation of **33** (31 mg, 0.06 mmol) and **34** (38 mg, 0.065 mmol) in DMF (Pd–C, rt, 3 h) provided, respectively, after filtration of the catalyst dry residues of pure **47** (29 mg) and **48** (29 mg) in quantitative yields. Compound **47**. Dark-yellow crystals: mp: 225–227 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.73 (s, 6H, OMe-3″ and 5″), 3.83, 3.85 and 3.86 (3s, 9H, OMe-7, 4′ and 4″), 6.36 (d, J=2.2 Hz, 1H, H-6), 6.45 (s, 2H, H-2″ and H-6″), 6.45 (d, J=2.2 Hz, 1H, H-8), 6.60 (d, J=8.5 Hz, 1H, H-5′), 6.70 (dd, J=8.5, 2.1 Hz, 1H, H-6′), 6.82 (d, J=2.1 Hz, 1H, H-2′), 12.93 (s, 1H, OH-5). ^{13}C NMR ($CDCl_3$) δ 55.4, 55.6 and 56.0 (OMe-7, 4′, 3″ and 5″), 60.8 (OMe-4″), 92.0 (C-8), 97.9 (C-6), 105.0 (C-10), 108.3 (C-2″ and C-6″), 109.4 (C-5′), 114.9 (C-2′), 120.0 (C-3), 120.7 (C-6′), 124.9 (C-1′), 127.7 (C-1″), 135.8 and 137.7 (C-3′ and C-4″), 148.8 (C-4′), 153.2 (C-3″ and C-5″), 157.4 (C-9), 162.2 and 162.3 (C-2 and C-5), 165.5 (C-7), 181.3 (C-4). HRESIMS *m/z* 502.1491 (calcd for $C_{26}H_{25}NO_8Na$, 502.1478), 480.1655 (calcd for $C_{26}H_{26}NO_8$, 480.1658). Compound **48**. Dark-yellow crystals: mp: 133–135 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 3.63 (s, 6H, OMe-3″ and 5″), 3.68 (s, 3H, OMe-4″), 3.75 (s, 3H, OMe-4′), 6.22 (d, J=1.8 Hz, 1H, H-6), 6.40 (d, J=1.8 Hz, 1H, H-8), 6.51 (s, 2H, H-2″ and H-6″), 6.52 (dd, J=8.2, 2 Hz, 1H, H-6′), 6.71 (d, J=8.2 Hz, 1H, H-5′), 6.88 (d, J=2 Hz, 1H, H-2′), 13.01 (s, 1H, OH-5). ^{13}C NMR (DMSO-d_6) δ 55.2 (OMe-4′), 55.8 (OMe-3″ and 5″), 60.0 (OMe-4″), 93.3 (C-8), 98.7 (C-6), 103.2 (C-10), 108.7 (C-2″ and C-6″), 109.5 (C-5′), 113.5 (C-2′), 118.4 (C-6′), 119.3 (C-3), 124.5 (C-1′), 127.7 (C-1″), 136.9 and 137.2 (C-3′ and C-4″), 147.8 (C-4′), 152.4 (C-3″ and C-5″), 157.0 (C-9), 161.6 and 162.3 (C-2 and C-5), 164.2 (C-7), 180.5 (C-4). HRESIMS *m/z* 488.1309 (calcd for $C_{25}H_{23}NO_8Na$, 488.1321), 466.1548 (calcd for $C_{25}H_{24}NO_8$, 466.1502).

4.3. Synthesis of analogues of the group B

4.3.1. Synthesis of 3-bromoflavones, intermediates for 3-arylflavones analogues of 1 and 2.

4.3.1.1. 3′,4′,5′-Trimethoxyflavone 49; 3-bromo-3′,4′,5′-trimethoxyflavone 50. For the preparation, see compounds **19** and **20**. Compound **49**. (735 mg, 79% from 3 mmol phosphorane). White crystals: mp: 172–174 °C (MeOH), lit.[26] 175 °C; ^{1}H NMR ($CDCl_3$) δ 3.94 (s, 3H, OMe-4′), 3.96 (s, 6H, OMe-3′ and 5′), 6.77 (s, 1H, H-3), 7.14 (s, 2H, H-3′ and H-5′), 7.43 (t, J=7.9 Hz, 1H, H-6), 7.58 (d, J=8 Hz, 1H, H-8), 7.71 (m, 1H, H-7), 8.24 (d, J=7.9 Hz, 1H, H-5). Compound **50**. (348 mg, 44% from 2 mmol **49**). White crystals: mp: 158–159 °C (MeOH), lit.[25b] 155–156 °C; ^{1}H NMR ($CDCl_3$) δ 3.94 (s, 3H, OMe-4′), 3.96 (s, 6H, OMe-3′ and 5′), 7.10 (s, 2H, H-3′ and H-5′), 7.49 (m, 2H, H-6 and H-8), 7.73 (t, J=8.5 Hz, 1H, H-7), 8.30 (d, J=7.8 Hz, 1H, H-5).

4.3.1.2. Tricetin 3′,4′,5′-trimethyl ether 51; 3-bromotricetin 3′,4′,5′-trimethyl ether 52; 3-bromotricetin 7-benzyl-3′,4′,5′-trimethyl ether 53. Flavone **51** was prepared according Ref. 21 for bromination then benzylation to **52** and **53**, see above **43**→**44**→**46**. Compound **51**. (463 mg, 34% from 4 mmol phosphorane). Lemon-yellow crystals: mp: 270–273 °C (MeOH), lit.[27] 277–278 °C; ^{1}H NMR (DMSO-d_6) δ 3.75 (s, 3H, OMe-4′), 3.90 (s, 6H, OMe-3′ and 5′), 6.22 (d, J=2 Hz, 1H, H-6), 6.56 (d, J=2 Hz, 1H, H-8), 7.04 (s, 1H, H-3), 7.32 (s, 2H, H-3′ and H-5′), 10.81 (s, 1H, OH-7), 12.84 (s, 1H, OH-5). Compound **52**. (296 mg, 59% from 1.2 mmol **51**). Lemon-yellow crystals: mp: 244–247 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 3.77 (s, 3H, OMe-4′), 3.84 (s, 6H, OMe-3′ and 5′), 6.30 (d, J=2 Hz, 1H, H-6), 6.46 (d, J=2 Hz, 1H, H-8), 7.17 (s, 2H, H-3′ and H-5′), 11.01 (s, 1H, OH-7), 12.32 (s, 1H, OH-5). Compound **53**. (237 mg, 69% from 0.67 mmol **52**). Pale-yellow crystals: mp: 123–126 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H, OMe-4′), 3.95 (s, 6H, OMe-3′ and

5′), 5.13 (s, 2H, benzyl), 6.51 (s, 2H, H-6 and H-8), 7.07 (s, 2H, H-3′ and H-5′), 7.35–7.45 (m, 5H, benzyl), 12.35 (s, 1H, OH-5).

4.3.2. Synthesis of 3-arylflavones analogues of 1 and 2. Method (a) by Suzuki cross-coupling between a 3-bromoflavone and 4-methoxybenzeneboronic acid according typical procedure.

Method (b) by iron-catalysed Grignard coupling: to a mixture of 3-bromoflavone (0.1 mmol) and $Fe(acac)_3$ (6 mg, 0.015 mmol) in THF (4 mL) between −20 and −30 °C under nitrogen was added arylmagnesium bromide (0.2 mmol). The reaction mixture was stirred at the same temperature for 3 h, then taken up in water and extracted with CH_2Cl_2. Standard work-up then purification by FC and/or TLC led to the expected 3-arylflavone.

4.3.2.1. 3-(4″-Methoxyphenyl)-3′,4′,5′-trimethoxyflavone 54. Preparation by: method (a) (5.5 mg, 13% from 0.1 mmol **50**); method (b) (7.5 mg, 18% from 0.1 mmol **50**); purification by FC (silica gel CH_2Cl_2/MeOH 98.5:1.5) and TLC (alumina CH_2Cl_2/cyclohexane 1:1). Amorphous; ^{1}H NMR ($CDCl_3$) δ 3.65 (s, 6H, OMe-3′ and 5′), 3.80 (s, 3H, OMe-4″), 3.86 (s, 3H, OMe-4′), 6.67 (s, 2H, H-2′ and H-6′), 6.89 (d, J=8.6 Hz, 2H, H-3″ and H-5″), 7.18 (d, J=8.6 Hz, 2H, H-2″ and H-6″), 7.43 (t, J=7.9 Hz, 1H, H-6), 7.55 (d, J=8.4 Hz, 1H, H-8), 7.71 (m, 1H, H-7), 8.29 (d, J=7.9 Hz, 1H, H-5). ^{13}C NMR ($CDCl_3$) δ 55.3 (OMe-4″), 56.0 (OMe-3′ and 5′), 60.9 (OMe-4′), 107.3 (C-2′ and C-6′), 114.1 (C-3″ and C-5″), 117.9 (C-8), 122.2 (C-3), 123.5 (C-10), 125.0 (C-6), 125.5 (C-1″), 126.4 (C-5), 128.2 (C-1′), 132.1 (C-2″ and C-6″), 133.6 (C-7), 139.6 (C-4′), 152.7 (C-3′ and C-5′), 155.9 (C-9), 159.1 (C-4″), 160.7 (C-2), 177.6 (C-4). ESIMS (+) m/z 441 $[M+Na]^+$, 419 $[M+H]^+$.

4.3.2.2. 3-(4″-Methoxyphenyl)tricetin 7-benzyl-3′,4′,5′-trimethyl ether 55. Preparation by method (a); purification by TLC (alumina CH_2Cl_2/MeOH 99:1); (23 mg, 21% from 0.2 mmol **53**). White crystals: mp: 145–148 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.64 (s, 6H, OMe-3′ and 5′), 3.80 (s, 3H, OMe-4″), 3.86 (s, 3H, OMe-4′), 5.16 (s, 2H, benzyl), 6.47 (d, J=2.2 Hz, 1H, H-6), 6.56 (d, J=2.2 Hz, 1H, H-8), 6.64 (s, 2H, H-2′ and H-6′), 6.91 (d, J=8.6 Hz, 2H, H-3″ and H-5″), 7.16 (d, J=8.6 Hz, 2H, H-2″ and H-6″), 7.3–7.45 (m, 5H, benzyl), 12.90 (s, 1H, OH-5). ^{13}C NMR ($CDCl_3$) δ 55.4 (OMe-4″), 56.0 (OMe-3′ and 5′), 60.9 (OMe-4′), 70.4 (benzyl), 93.2 (C-8), 98.8 (C-6), 105.3 (C-10), 107.2 (C-2′ and C-6′), 114.3 (C-3″ and C-5″), 120.6 (C-3), 124.3 (C-1″), 127.5, 128.4 and 128.7 (benzyl), 132.1 (C-2″ and C-6″), 135.8 (benzyl), 139.8 (C-4′), 152.6 (C-3′ and C-5′), 157.4 (C-9), 159.3 (C-4″), 161.1 (C-5), 162.5 (C-2), 164.7 (C-7), 181.7 (C-4); C-1′ not detected. ESIMS (+) m/z 563 $[M+Na]^+$, 541 $[M+H]^+$.

4.3.2.3. 3-(3″-Benzyloxy-4″-methoxyphenyl)tricetin 7-benzyl-3′,4′,5′-trimethyl ether 56. Preparation by method (b); purification by FC (silica gel CH_2Cl_2/MeOH 99:1) and TLC (silica gel cyclohexane/acetone 1:1); (15 mg, 12% from 0.2 mmol **53**). Amorphous; ^{1}H NMR ($CDCl_3$) δ 3.60 (s, 6H, OMe-3′ and 5′), 3.85 and 3.88 (2s, 6H, OMe-4′ and 4″), 5.03 and 5.16 (2s, 4H, benzyls), 6.48 (d, J=2.2 Hz, 1H, H-6), 6.53 (d, J=2.2 Hz, 1H, H-8), 6.57 (s, 2H, H-2′ and H-6′), 6.7–7.0 (m, 3H, H-2″, H-5″ and H-6″), 7.2–7.5 (m, 10H, benzyls), 12.90 (s, 1H, OH-5).

4.3.2.4. Tricetin 7-benzyl-3′,4′,5′-trimethyl ether 57. Pale-yellow crystals: mp: 203–205 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.94 (s, 3H, OMe-4′), 3.95 (s, 6H, OMe-3′ and 5′), 5.15 (s, 2H, benzyl), 6.48 (d, J=2 Hz, 1H, H-6), 6.59 (d, J=2 Hz, 1H, H-8), 6.78 (s, 1H, H-3), 7.09 (s, 2H, H-3′ and H-5′), 7.35–7.45 (m, 5H, benzyl), 12.72 (s, 1H, OH-5).

4.3.2.5. 3-(4″-Methoxyphenyl)tricetin 3′,4′,5′-trimethyl ether 58; 3-(3″-hydroxy-4″-methoxyphenyl)tricetin 3′,4′,5′-trimethyl ether 59. Catalytic hydrogenation of **55** (15 mg, 0.028 mmol) and **56** (15 mg, 0.023 mmol) in THF (Pd–C, rt, 3 h) provided, respectively, after filtration of the catalyst dry residues of pure **58** (12 mg) and **59** (10 mg) in quantitative yields. Compound **58**. Amorphous; ^{1}H NMR (DMSO-d_6) δ 3.56 (s, 6H, OMe-3′ and 5′), 3.66 (s, 3H, OMe-4′), 3.75 (s, 3H, OMe-4″), 6.24 (d, J=2.1 Hz, 1H, H-6), 6.49 (d, J=2.1 Hz, 1H, H-8), 6.69 (s, 2H, H-2′ and H-6′), 6.93 (d, J=8.6 Hz, 2H, H-3″ and H-5″), 7.13 (d, J=8.6 Hz, 2H, H-2″ and H-6″), 10.89 (s, 1H, OH-7), 12.92 (s, 1H, OH-5). ^{13}C NMR (DMSO-d_6) δ 55.1 (OMe-4″), 55.6 (OMe-3′ and 5′), 60.0 (OMe-4′), 93.8 (C-8), 98.8 (C-6), 103.3 (C-10), 107.2 (C-2′ and C-6′), 113.6 (C-3″ and C-5″), 119.8 (C-3), 124.1 (C-1″), 127.2 (C-1′), 132.1 (C-2″ and C-6″), 138.9 (C-4′), 152.1 (C-3′ and C-5′), 157.1 (C-9), 158.7 (C-4″), 160.8 (C-2), 161.5 (C-5), 164.4 (C-7), 180.8 (C-4). ESIMS (+) m/z 473 $[M+Na]^+$, 451 $[M+H]^+$. Compound **59**. Amorphous; ^{1}H NMR (DMSO-d_6) δ 3.58 (s, 6H, OMe-3′ and 5′), 3.66 (s, 3H, OMe-4′), 3.75 (s, 3H, OMe-4″), 6.21 (d, J=2.1 Hz, 1H, H-6), 6.46 (d, J=2.1 Hz, 1H, H-8), 6.58 (dd, J=8.2, 2 Hz, 1H, H-6″), 6.64 (d, J=2 Hz, 1H, H-2″), 6.73 (s, 2H, H-2′ and H-6′), 6.90 (d, J=8.2 Hz, 1H, H-5″), 12.94 (s, 1H, OH-5). ^{13}C NMR (DMSO-d_6) δ 55.5 (OMe-3′, 5′ and 4″), 60.0 (OMe-4′), 93.5 (C-8), 98.3 (C-6), 107.1 (C-2′ and C-6′), 112.3 (C-5″), 118.5 (C-2″), 121.9 (C-6″), 124.8 (C-1″), 127.4 (C-1′), 139.2 (C-4′), 146.4 (C-3″), 147.7 (C-4″), 152.4 (C-3′ and C-5′), 161.0 (C-2); C-3, C-4, C-5, C-7, C-9 and C-10 not detected. ESIMS (+) m/z 489 $[M+Na]^+$, 467 $[M+H]^+$.

4.4. Synthesis of analogues of the groups C and D

4.4.1. One-pot access to keto-enols 60 and 61 by esterification then Baker–Vankataraman rearrangement.

4.4.1.1. 3′,4′,5′-Trimethoxy-2-hydroxy-dibenzoylmethane 60 (mixture of keto-enol and β-diketone tautomers 82/18); 4′-methoxy-2-hydroxy-dibenzoylmethane 61. A solution of 2′-hydroxyacetophenone (1.36 g, 10 mmol) in dry pyridine (10 mL) at 0 °C under nitrogen was added with the adequate aroyl chloride (15 mmol), and the reaction mixture stirred for 2.5 h at rt. Powdered dry KOH (1.68 g, 30 mmol) was added and the reaction heated at 100 °C for 2 h, then same quantity of KOH was added again and the mixture heated for a further 1 h. After cooling, the mixture was poured into water, adjusted to pH 6 with 1 N HCl and extracted by CH_2Cl_2. Standard work-up of the organic layer and crystallization in MeOH provided the intermediates **60** (1.23 g, 37%) and **61** (925 mg, 34%). Compound **60**. Lemon-yellow crystals: mp: 134–136 °C (MeOH), lit.[26] 136 °C; ^{1}H NMR ($CDCl_3$)

characteristic signals at δ 4.70 (s, CH_2) and 12.12 (s, phenol) for the β-diketone form; at 6.84 (s, CH–C═O), 12.20 (s, phenol) and 15.84 (s, enol) for the enol tautomer. Compound **61**. Lemon-yellow crystals: mp: 110–111 °C (MeOH), lit.[26] 114 °C; ^{1}H NMR ($CDCl_3$) δ 3.90 (s, OMe-4′), 6.89 (d, H-3), 6.97 and 7.45 (m, H-4 and H-5), 6.98 (d, H-3′ and 5′), 7.76 (d, H-6), 7.92 (d, H-2′ and 6′), 6.77 (s, CH–C═O), 12.17 (s, phenol), 15.80 (s, enol).

4.4.2. Knoevenagel condensation to crude 3-aroylflavanones then dehydrogenation by SeO_2 to 65, 66 and 67. General procedure: compounds **60** or **61** (0.5 mmol) and adequate aromatic aldehyde (0.55 mmol) were dissolved in EtOH (5 mL) by heating under reflux. Piperidine (12 mg, 0.14 mmol) was then added, and the reaction stirred under reflux for 5 h. The reaction mixture was evaporated to dryness and used as it is in the following step. Fifth of the dried residue and SeO_2 (in equal weight) were stirred in dioxane at reflux for 6 h under nitrogen. Reaction mixture was filtered, and evaporated to dryness. Dry residue was then purified by FC and crystallization.

4.4.2.1. 4′-Methoxy-3-(3″,4″,5″-trimethoxybenzoyl)-flavone 65. Preparation from **60** and *p*-anisaldehyde; purification by FC (silica gel CH_2Cl_2/MeOH 99:1); (16 mg, 36% from **60**). White crystals: mp: 90–92 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 9H, OMe-4′, 3″ and 5″), 3.89 (s, 3H, OMe-4″), 6.89 (d, J=8.9 Hz, 2H, H-3′ and H-5′), 7.20 (s, 2H, H-2″ and H-6″), 7.46 (t, J=8 Hz, 1H, H-6), 7.59 (d, J=8.1 Hz, 1H, H-8), 7.64 (d, J=8.9 Hz, 2H, H-3′ and H-5′), 7.75 (m, 1H, H-7), 8.24 (dd, J=8, 1.4 Hz, 1H, H-5). ^{13}C NMR ($CDCl_3$) δ 55.4 (OMe-4′), 56.3 (OMe-3″ and 5″), 60.9 (OMe-4″), 107.0 (C-2″ and C-6″), 114.3 (C-3′ and C-5′), 118.0 (C-8), 121.3 (C-3), 123.2 (C-10), 123.9 (C-1′), 125.5 (C-6), 126.1 (C-5), 130.2 (C-2′ and C-6′), 132.3 (C-1″), 134.2 (C-7), 143.3 (C-4″), 153.2 (C-3″ and C-5″), 156.0 (C-9), 162.0 and 162.2 (C-2 and C-4′), 176.3 (C-4), 192.8 (C═O). ESIMS (+) *m*/*z* 915 $[2M+Na]^+$, 469 $[M+Na]^+$.

4.4.2.2. 3′-Hydroxy-4′-methoxy-3-(3″,4″,5″-trimethoxybenzoyl)flavone 66. Preparation from **60** and isovanillin; purification by FC (silica gel CH_2Cl_2/MeOH 98.5:1.5); (18 mg, 40% from **60**). Amorphous; ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 6H, OMe-4′, 3″ and 5″), 3.89 (s, 6H, OMe-4′ and 4″), 6.78 (d, J=8.5 Hz, 1H, H-5′), 7.16 (dd, J=8.5, 2.2 Hz, 1H, H-6′), 7.19 (s, 2H, H-2″ and H-6″), 7.33 (d, J=2.2 Hz, 1H, H-2′), 7.45 (m, 1H, H-6), 7.58 (d, J=7.8 Hz, 1H, H-8), 7.75 (m, 1H, H-7), 8.26 (dd, J=7.9, 1.5 Hz, 1H, H-5). ESIMS (+) *m*/*z* 947 $[2M+Na]^+$, 485 $[M+Na]^+$.

4.4.2.3. 3-(4″-Methoxybenzoyl)-3′,4′,5′-trimethoxyflavone 67. Preparation from **61** and 3,4,5-trimethoxybenzaldehyde; purification by FC (silica gel CH_2Cl_2/MeOH 98.5:1.5); (24 mg, 54% from **61**). White crystals: mp: 139–141 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.63 (s, 6H, OMe-3′ and 5′), 3.77 (s, 6H, OMe-4′ and 4″), 6.90 (d, J=8.9 Hz, 2H, H-3″ and H-5″), 6.91 (s, 2H, H-2′ and H-6′), 7.46 (t, J=7.9 Hz, 1H, H-6), 7.60 (d, J=8.1 Hz, 1H, H-8), 7.75 (m, 1H, H-7), 7.94 (d, J=8.9 Hz, 2H, H-3″ and H-5″), 8.24 (dd, J=7.9, 1.5 Hz, 1H, H-5). ^{13}C NMR ($CDCl_3$) δ 55.5 (OMe-4″), 56.1 (OMe-3′ and 5′), 60.9 (OMe-4′), 106.1 (C-2′ and C-6′), 114.1 (C-3″ and C-5″), 118.0 (C-8), 122.6 (C-3), 123.3 (C-10), 125.6 (C-6), 126.1 (C-5), 126.7 (C-1′), 130.4 (C-1″), 131.8 (C-2″ and C-6″), 134.2 (C-7), 140.5 (C-4′), 153.2 (C-3′ and C-5′), 156.0 (C-9), 161.5 (C-2), 164.2 (C-4″), 176.4 (C-4), 192.0 (C═O). ESIMS (+) *m*/*z* 915 $[2M+Na]^+$, 469 $[M+Na]^+$.

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Construction of furo[3,4-*c*]pyran skeleton starting from the Baylis–Hillman adducts via the ring-closing metathesis (RCM) reaction of *exo*-methylene tetrahydrofuran

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Abstract—Construction of furo[3,4-*c*]pyran ring skeleton was achieved starting from the Baylis–Hillman adducts. The synthesis was carried out by the successive introduction of propargyl alcohol, radical cyclization, reduction, allylation, and finally ring-closing metathesis reaction.

1. Introduction

Ring-closing metathesis (RCM) reaction is a powerful tool in modern chemistry due to its wide applicability in synthetic organic chemistry.[1–3] By using the RCM reaction tremendous cyclic compounds have been elegantly constructed including carbocyclic and heterocyclic rings.[1–3]

However, RCM reaction between the *exo*-methylene unit of cyclic compound and double bond of the appropriate tether has not been reported much.[4] Barrett and co-workers have reported the example, which dealt with the synthesis of C-19-functionalized 1α-hydroxyvitamin D2 analogues by the RCM reaction of *exo*-methylene compounds.[4a] In their report, they examined silicon and phosphorous tether in the reaction with methylene cyclohexane moiety. Botta and co-workers have used RCM reaction of methylenecyclohexane moiety in their synthesis of Taxuspine X in 20–25% yield.[4b] Fürstner and colleagues reported the successful RCM reaction of methylenecycloalkane derivatives with ruthenium carbene complexes with *N*,*N*-bis(mesityl)imidazole-2-ylidene ligand.[4c] To the best of our knowledge the RCM reaction of *exo*-methylene moiety with the double bond of oxygen atom-containing tether has not been published.

Although RCM reaction could provide very effective routes for the synthesis of a variety of fused heterocyclic compounds,[1–3] the synthesis of furo[3,4-*c*]pyran skeleton using RCM protocol has not been reported. Various furopyran nucleus has been known to constitute an essential part of many biologically important compounds.[5,6] The reported methods for the synthesis of furo[3,4-*c*]pyran nucleus were much limited and used either tungsten-mediated [3+3] cycloaddition of epoxides with tethered alkynes[5a,b] or intramolecular hetero-Diels–Alder reaction.[5c,d,f]

2. Results and discussion

Recently, we have reported the synthesis of 3,4-disubstituted 2,5-dihydrofuran derivatives from the triple bond-containing Baylis–Hillman adducts via radical cyclization and iodolactonization strategy.[7] Meantime we thought that the intermediate, methylene tetrahydrofuran derivative **2a** could be used for the construction of furo[3,4-*c*]pyran skeleton[5,6] of **5a** by using the RCM reaction as shown in Scheme 1.

exo-Methylene tetrahydrofuran **2a** was prepared as previously reported.[7] Reduction of **2a** with $LiAlH_4$ was conducted successfully to give **3a** in 80% yield. Allylation of **3a** was carried out (*t*-BuOK, THF, allyl bromide) to give the requisite starting material **4a** in 81% yield. The RCM reaction of **4a** in the presence of 5 mol% of Grubbs type II catalyst in CH_2Cl_2 at refluxing temperature afforded the desired furo[3,4-*c*]pyran compound **5a** in 92% yield. Although much steric crowdedness could be arisen at the transition state toward the formation of the corresponding intermediate, metallacyclobutane stage (shown in Fig. 1 in a simplified manner),[3d] the desired compound **5a** was synthesized in good yield.[5] In addition, **5a** could be

Keywords: Furo[3,4-*c*]pyran; Baylis–Hillman adducts; *exo*-Methylene tetrahydrofuran; Ring-closing metathesis.
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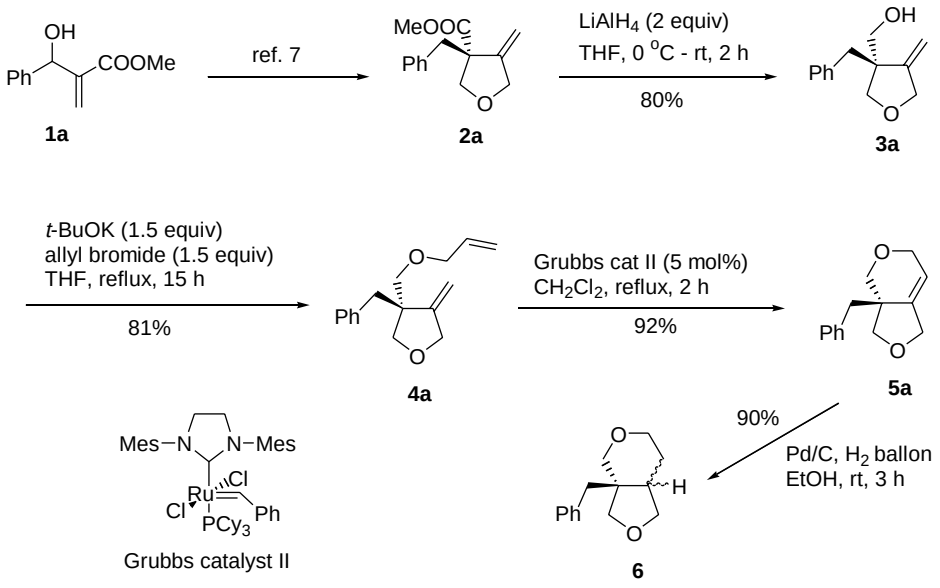


Scheme 1.

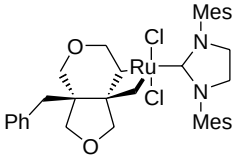
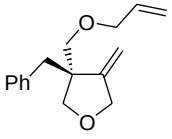
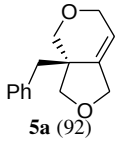
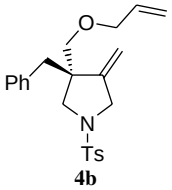
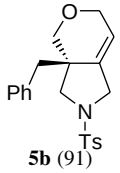
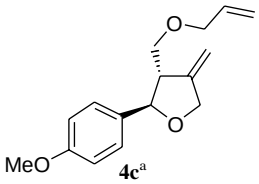
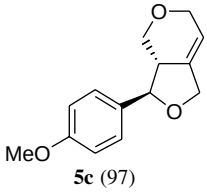
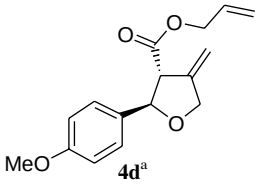
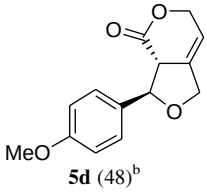


Figure 1. Metallacyclobutane intermediate for **5a**.

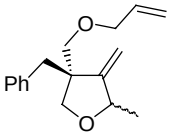
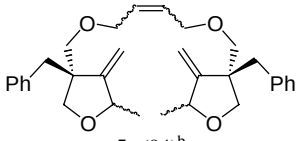
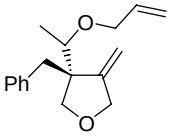
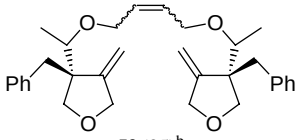
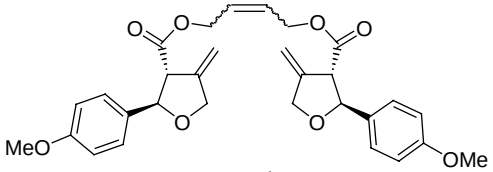
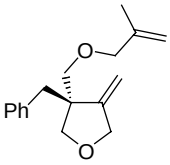
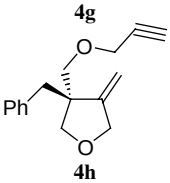
transformed into **6** in 90% yield under catalytic hydrogenation conditions (Pd/C, H_2, EtOH, room temperature, 3 h). We obtained **6** as a single isomer but we did not determine the stereochemistry at this stage. Encouraged by the results we examined the RCM reactions with similar starting materials **4b–h** and the results are summarized in Tables 1 and 2.

Table 1. Successful RCM reaction of *exo*-methylene compounds and Grubbs catalyst

Entry	Substrate	Conditions	Product (%)
1	 **4a**	Cat (5 mol%), 2 h	 **5a** (92)
2	 **4b**	Cat (10 mol%), 80 min	 **5b** (91)
3	 **4c**[a]	Cat (5 mol%), 20 min	 **5c** (97)
4	 **4d**[a]	Cat (5 mol%), 20 min	 **5d** (48)[b]

[a] Pure trans isomer.[9]
[b] Self-metathesis product **5g** was also isolated in 24% yield.

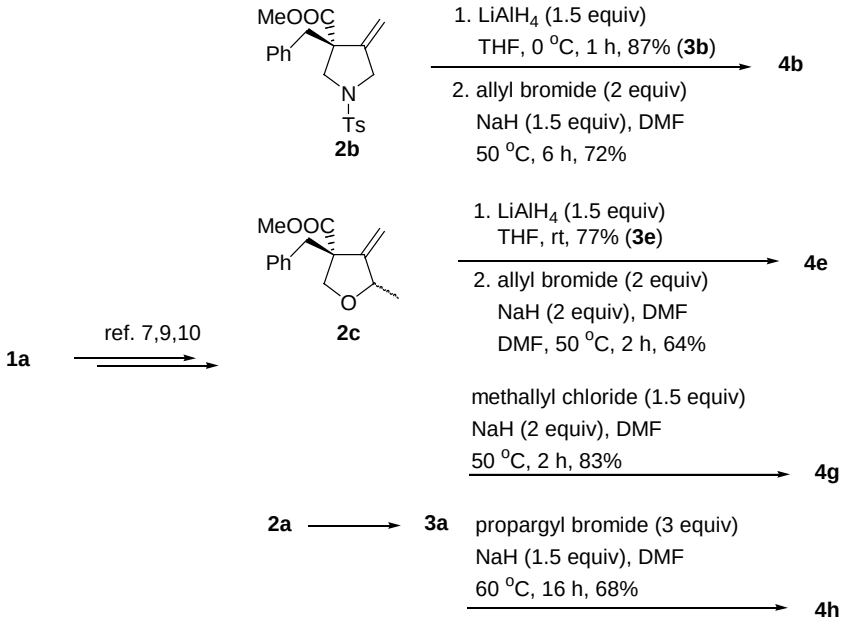
Table 2. Unsuccessful RCM reaction of *exo*-methylene compounds and Grubbs catalyst

Entry	Substrate	Conditions	Product (%)
1	 **4e**[a]	Cat (5 mol%), 12 h	 **5e** (94)[b]
2	 **4f**[a]	Cat (5 mol%), 6 h	 **5f** (85)[b]
3	**4d**	Cat (5 mol%), 1 h	 **5g** (24)[b,c]
4	 **4g**	Cat (10 mol%), 48 h	No reaction
5	 **4h**	Cat (5 mol%), 3 days	**3a** (74)

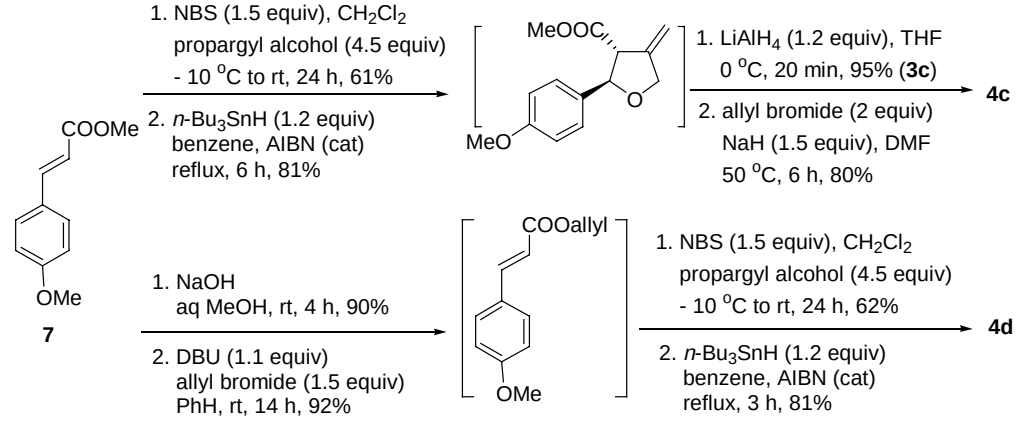
[a] Pure **4e** and **4f** were used, but the stereochemistry is arbitrary.
[b] Pure single isomer was obtained, but we did not assign the stereochemistry.
[c] RCM product **5d** was also isolated in 48% yield.

As shown in Table 1, allyl-substituted starting materials **4b** and **4c** gave the corresponding RCM products **5b** and **5c** successfully in short time in good yields. We could obtain the RCM product **5d**, albeit in low yield, for the allyl ester **4d** (48%, entry 4). In addition, we could isolate the corresponding self-metathesis product **5g** in 24% yield (see also entry 3 in Table 2). Unfortunately, however, we did not obtain the desired RCM products when we used **4e**–**h** as the starting materials as shown in Table 2. The methyl substituent at the 2-position (for **4e**, entry 1) increased the steric crowdedness at the transition state toward RCM product and produced the self-metathesis product **5e**. The situation was same for the allyl ether **4f** (entry 2). For the methallyl-substituted starting material **4g** (entry 4), we failed completely to obtain any product presumably due to the severe steric crowdedness during the reaction progress. As expected, when we compare the differences of reactivity of **4c** and **4e**, the substituent near the metallacyclobutane moiety (like as the methyl group of **4e**) made the RCM reaction difficult, while the substituent far away from the reaction site (like as 4-methoxyphenyl group of **4c**) did not reduce the reactivity toward RCM reaction. For the propargyl ether derivative **4h** (entry 5) we observed the deprotection of propargyl group. Deprotection of propargyl ether moiety has been published recently.[8]

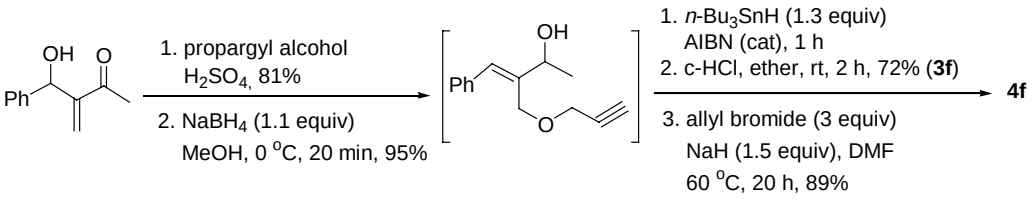
The synthesis of starting materials **4b**–**h** is summarized in Schemes 2–4.[7,9,10] Synthesis of **2a**–**c** was carried out as reported from the corresponding Baylis–Hillman adduct.[7] By following the usual organic laboratory experimental techniques we prepared **4b**, **4e**, **4g**, and **4h** as in Scheme 2 in reasonable yields. Synthesis of **4c** was carried out from methyl 4-methoxycinnamate (**7**) by following bromoetherification with propargyl alcohol (NBS, propargyl alcohol, 61%),[9] radical cyclization (*n*-Bu_3SnH, AIBN, 81%),[9,10] reduction ($LiAlH_4$, 95%), and allylation (allyl bromide, NaH, 80%) as shown in Scheme 3. The compound **4d** was also synthesized from methyl 4-methoxycinnamate by following alkaline hydrolysis (NaOH, 90%), allylation (DBU, allyl bromide, 92%), bromoetherification (NBS, propargyl alcohol, 62%),[9] and radical cyclization (*n*-Bu_3SnH, AIBN, 81%) sequences[9,10] (Scheme 3). Compound **4f** was also synthesized from the Baylis–Hillman adduct of methyl vinyl ketone by following the sequential introduction of propargyl alcohol at the primary position (81%),[7,10] reduction of acetyl group ($NaBH_4$, 95%), radical



Scheme 2.



Scheme 3.



Scheme 4.

cyclization (*n*-Bu_3SnH, AIBN, 72%),[7,10] and allylation (allyl bromide, NaH, 89%) as in Scheme 4.

In summary, we disclosed the first successful RCM reaction of cyclic substrates with *exo*-methylene moiety with the double bond of oxygen atom-containing tether. The steric crowdedness at the metallacyclobutane intermediate stage prohibited the successful RCM reaction in some cases, which afforded the corresponding self-metathesis products. More detailed scope and limitations on the RCM reaction involving *exo*-methylene moiety are currently under study and will be published in due course.

3. Experimental

3.1. General procedure

^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$. The signal positions are reported in parts per million relative to TMS (δ scale) used as an internal standard. IR spectra are reported in cm^{-1}. Mass spectra were obtained from the Korea Basic Science Institute (Gwangju branch). Melting points are uncorrected. The elemental analyses were carried out at Korea Research Institute of Chemical Technology, Taejon, Korea. All

reagents were purchased from commercial sources and used without further treatment. The separations were carried out by flash column chromatography over silica gel (230–400 mesh ASTM). Organic extracts were dried over anhydrous $MgSO_4$ and the solvents were evaporated on a rotary evaporator under water aspirator pressure.

3.2. Synthesis of starting material 2a–c and 3a

Synthesis of the starting materials **2a–c** was carried out according to the reported procedures.[7,9,10] Compound **3a** was prepared from **2a** as follows: to a stirred solution of **2a** (464 mg, 2.0 mmol) in THF (2 mL) was added a solution of $LiAlH_4$ (4 mL, 1 M solution in THF) at 0 °C. The reaction mixture was maintained at room temperature for 2 h. After usual workup and column chromatographic purification process (hexanes/EtOAc, 8:2) we obtained **3a** as colorless oil, 327 mg (80%).

3.2.1. Compound 3a. Eighty percentage; a colorless oil; IR (film) 3464, 1662, 1065 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.76 (br s, 1H), 2.78 (d, $J=13.5$ Hz, 1H), 2.96 (d, $J=13.5$ Hz, 1H), 3.42–3.56 (m, 2H), 3.70 (d, $J=9.0$ Hz, 1H), 3.84 (d, $J=9.0$ Hz, 1H), 4.28–4.45 (m, 2H), 4.87 (t, $J=2.4$ Hz, 1H), 5.10 (d, $J=2.4$ Hz, 1H), 7.15–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.31, 51.86, 64.89, 72.26, 75.34, 105.05, 126.46, 128.13, 130.17, 137.53, 151.94; ESIMS (*m/z*) 205.1 ($M^+ + H$).

3.3. Synthesis of starting materials 4a–h

Synthesis of **4a** was carried out as follows: To a stirred mixture of **3a** (204 mg, 1.0 mmol) and allyl bromide (182 mg, 1.5 mmol) in dry THF (3 mL) was added *t*-BuOK (168 mg, 1.5 mmol) and heated to reflux for 15 h. After usual workup and column chromatographic purification process (hexanes/EtOAc, 95:5) we obtained **4a** as colorless oil, 198 mg (81%). Other compounds **4b**, **4e**, **4g**, and **4h** were synthesized similarly by using the typical experimental procedures (Scheme 2).[7,9,10] The compounds **4c** and **4d** were also prepared from commercial methyl 4-methoxycinnamate by following the typical organic experimental procedures (Scheme 3).[9] Compound **4f** was synthesized from the Baylis–Hillman adduct of methyl vinyl ketone by following the known procedures as in Scheme 4. The spectroscopic data of prepared compounds **4a–h** are as follows. The spectroscopic data of the intermediates (**3b**, **3c**, **3e**, and **3f**) are also reported at the end of this part.

3.3.1. Compound 4a. Eighty-one percentage; a colorless oil; IR (film) 2850, 1072 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.91 (s, 2H), 3.22 (d, $J=9.0$ Hz, 1H), 3.28 (d, $J=9.0$ Hz, 1H), 3.75 (d, $J=9.0$ Hz, 1H), 3.84 (d, $J=9.0$ Hz, 1H), 3.97–4.01 (m, 2H), 4.32–4.35 (m, 2H), 4.64 (t, $J=2.4$ Hz, 1H), 4.97 (t, $J=2.4$ Hz, 1H), 5.16–5.34 (m, 2H), 5.87–6.01 (m, 1H), 7.13–7.29 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.71, 50.60, 72.14, 72.32, 72.82, 76.61, 105.28, 116.66, 126.22, 127.79, 130.61, 134.78, 137.83, 151.18; ESIMS (*m/z*) 245.1 ($M^+ + H$). Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.84; H, 8.18.

3.3.2. Compound 4b. Seventy-two percentage; a colorless oil; IR (film) 2854, 1346, 1165 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.43 (s, 3H), 2.82 (s, 2H), 3.09 (d, $J=9.6$ Hz, 1H), 3.12 (d, $J=9.3$ Hz, 1H), 3.18 (d, $J=9.3$ Hz, 1H), 3.26 (d, $J=9.6$ Hz, 1H), 3.81 (t, $J=2.4$ Hz, 2H), 3.92 (dt, $J=5.4$, 1.5 Hz, 2H), 4.67 (t, $J=2.1$ Hz, 1H), 4.97 (t, $J=2.1$ Hz, 1H), 5.12–5.28 (m, 2H), 5.81–5.94 (m, 1H), 7.04–7.27 (m, 5H), 7.30 (d, $J=8.1$ Hz, 2H), 7.65 (d, $J=8.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.51, 40.16, 50.29, 52.83, 55.79, 72.08, 72.52, 108.30, 116.76, 126.36, 127.84, 127.89, 129.59, 130.51, 132.48, 134.51, 137.12, 143.56, 147.49; ESIMS (*m/z*) 398.2 ($M^+ + H$). Anal. Calcd for $C_{23}H_{27}NO_3S$: C, 69.49; H, 6.85; N, 3.52. Found: C, 69.47; H, 6.94; N, 3.43.

3.3.3. Compound 4c. Eighty percentage; a colorless oil; IR (film) 2839, 1612, 1516, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.85–2.90 (m, 1H), 3.54 (d, $J=1.8$ Hz, 1H), 3.57 (d, $J=2.4$ Hz, 1H), 3.80 (s, 3H), 3.96 (dt, $J=5.7$, 1.5 Hz, 2H), 4.41 (dq, $J=13.2$, 2.4 Hz, 1H), 4.57 (dq, $J=13.2$, 2.1 Hz, 1H), 4.78 (d, $J=7.2$ Hz, 1H), 5.02 (q, $J=2.1$ Hz, 1H), 5.08 (q, $J=2.1$ Hz, 1H), 5.13–5.26 (m, 2H), 5.80–5.94 (m, 1H), 6.88 (d, $J=9.0$ Hz, 2H), 7.29 (d, $J=9.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.59, 55.26, 70.52, 71.24, 72.02, 83.70, 104.89, 113.75, 116.89, 127.68, 133.47, 134.62, 149.34, 159.16; ESIMS (*m/z*) 261.1 ($M^+ + H$). Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.67; H, 7.78.

3.3.4. Compound 4d. Eighty-one percentage; a colorless oil; IR (film) 1736, 1612, 1516, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.49–3.55 (m, 1H), 3.80 (s, 3H), 4.49 (dq, $J=13.2$, 2.4 Hz, 1H), 4.56–4.71 (m, 3H), 5.03–5.34 (m, 5H), 5.83–5.97 (m, 1H), 6.88 (d, $J=9.0$ Hz, 2H), 7.31 (d, $J=9.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.25, 57.01, 65.70, 71.47, 83.24, 106.47, 113.90, 118.66, 127.50, 131.73, 131.79, 146.47, 159.52, 170.42; ESIMS (*m/z*) 275.1 ($M^+ + H$). Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.18; H, 6.54.

3.3.5. Compound 4e. Sixty-four percentage; a colorless oil; IR (film) 2927, 2858, 1099, 1034 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.29 (d, $J=6.3$ Hz, 3H), 2.84 (d, $J=13.2$ Hz, 1H), 2.95 (d, $J=13.2$ Hz, 1H), 3.21 (d, $J=9.0$ Hz, 1H), 3.30 (d, $J=9.0$ Hz, 1H), 3.63 (d, $J=9.0$ Hz, 1H), 3.94–4.00 (m, 3H), 4.38–4.45 (m, 1H), 4.51 (d, $J=2.4$ Hz, 1H), 4.87 (d, $J=2.4$ Hz, 1H), 5.16–5.21 (m, 1H), 5.26–5.34 (m, 1H), 5.87–6.00 (m, 1H), 7.12–7.28 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.33, 40.65, 51.25, 72.15, 73.27, 75.19, 78.28, 105.63, 116.69, 126.18, 127.68, 130.91, 134.78, 137.76, 155.73; ESIMS (*m/z*) 259.2 ($M^+ + H$). Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 78.95; H, 8.48.

3.3.6. Compound 4f. Eighty-nine percentage; a colorless oil; IR (film) 2985, 1115, 1065 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.14 (d, $J=6.3$ Hz, 3H), 2.92 (d, $J=13.2$ Hz, 1H), 3.03 (d, $J=13.2$ Hz, 1H), 3.45 (q, $J=6.3$ Hz, 1H), 3.75 (d, $J=9.3$ Hz, 1H), 3.86–3.93 (m, 1H), 4.06–4.26 (m, 3H), 4.10 (d, $J=9.3$ Hz, 1H), 4.60 (t, $J=2.3$ Hz, 1H), 5.06 (t, $J=2.0$ Hz, 1H), 5.17–5.22 (m, 1H), 5.31–5.38 (m, 1H), 5.93–6.06 (m, 1H), 7.14–7.26 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.95, 40.95, 54.36, 69.93, 72.86, 73.77, 78.70, 105.71, 116.15, 126.14, 127.61, 131.07, 135.28, 137.98,

151.59; ESIMS (*m/z*) 259.2 ($M^+ + H$). Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.12; H, 8.53.

3.3.7. Compound 4g. Eighty-three percentage; a colorless oil; IR (film) 2850, 1103, 1072 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.77 (s, 3H), 2.92 (s, 2H), 3.20 (d, $J=9.3$ Hz, 1H), 3.25 (d, $J=9.3$ Hz, 1H), 3.75 (d, $J=9.0$ Hz, 1H), 3.85 (d, $J=9.0$ Hz, 1H), 3.88 (s, 2H), 4.32 (d, $J=2.1$ Hz, 1H), 4.34 (d, $J=2.1$ Hz, 1H), 4.66 (t, $J=2.4$ Hz, 1H), 4.88–4.91 (m, 1H), 4.96–4.99 (m, 2H), 7.14–7.29 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.54, 39.79, 50.61, 72.34, 72.78, 75.18, 76.54, 105.25, 111.90, 126.22, 127.81, 130.61, 137.87, 142.23, 151.24; ESIMS (*m/z*) 259.1 ($M^+ + H$). Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.20; H, 8.57.

3.3.8. Compound 4h. Sixty-eight percentage; a colorless oil; IR (film) 2117, 1454, 1099 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.44 (t, $J=2.4$ Hz, 1H), 2.87 (d, $J=12.0$ Hz, 1H), 2.92 (d, $J=12.0$ Hz, 1H), 3.33 (d, $J=8.7$ Hz, 1H), 3.39 (d, $J=8.7$ Hz, 1H), 3.76 (q, $J=9.0$ Hz, 1H), 3.84 (q, $J=9.0$ Hz, 1H), 4.18 (d, $J=2.4$ Hz, 2H), 4.33–4.35 (m, 2H), 4.62 (t, $J=2.4$ Hz, 1H), 4.98 (t, $J=2.0$ Hz, 1H), 7.16–7.29 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.64, 50.38, 58.48, 72.29, 72.53, 74.54, 76.58, 79.64, 105.52, 126.29, 127.81, 130.71, 137.60, 150.87; ESIMS (*m/z*) 243.1 ($M^+ + H$). Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.35; H, 7.58.

3.3.9. Compound 3b. Eighty-seven percentage; a colorless oil; IR (film) 3529, 2924, 1342, 1161 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.43 (s, 3H), 2.71 (d, $J=13.5$ Hz, 1H), 2.87 (d, $J=13.5$ Hz, 1H), 3.10 (d, $J=9.9$ Hz, 1H), 3.23 (d, $J=9.9$ Hz, 1H), 3.34–3.49 (m, 2H), 3.79 (dt, $J=14.1$, 2.4 Hz, 1H), 3.87 (dt, $J=14.1$, 2.1 Hz, 1H), 4.85 (t, $J=2.4$ Hz, 1H), 5.09 (t, $J=2.1$ Hz, 1H), 7.08–7.33 (m, 7H), 7.65 (d, $J=8.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.52, 39.90, 51.57, 52.76, 54.53, 64.58, 108.24, 126.61, 127.81, 128.21, 129.67, 130.21, 132.26, 136.83, 143.74, 148.05. Anal. Calcd for $C_{20}H_{23}NO_3S$: C, 67.20; H, 6.49; N, 3.92. Found: C, 67.41; H, 6.53; N, 3.85.

3.3.10. Compound 3c. Ninety-five percentage; a colorless oil; IR (film) 3529, 3313, 1612, 1512 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.66 (br s, 1H), 2.73–2.80 (m, 1H), 3.70–3.75 (m, 1H), 3.80 (s, 3H), 3.82–3.88 (m, 1H), 4.38–4.44 (m, 1H), 4.57–4.63 (m, 1H), 4.79 (d, $J=7.4$ Hz, 1H), 5.06 (q, $J=2.4$ Hz, 1H), 5.10 (q, $J=2.1$ Hz, 1H), 6.89 (d, $J=8.7$ Hz, 2H), 7.32 (d, $J=8.7$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 53.87, 55.26, 61.92, 71.30, 83.18, 104.88, 113.91, 127.70, 133.04, 148.97, 159.33. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 71.01; H, 7.30.

3.3.11. Compound 3e. Seventy-seven percentage; a colorless oil; IR (film) 3440, 2927, 1018 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28 (d, $J=6.3$ Hz, 3H), 2.80 (d, $J=13.5$ Hz, 1H), 2.89 (d, $J=13.5$ Hz, 1H), 3.45–3.58 (m, 2H), 3.62 (d, $J=9.0$ Hz, 1H), 3.96 (d, $J=9.0$ Hz, 1H), 4.43–5.0 (m, 1H), 4.77 (d, $J=2.4$ Hz, 1H), 5.01 (d, $J=2.1$ Hz, 1H), 7.15–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.26, 40.55, 52.61, 65.25, 73.00, 78.18, 105.41, 126.46, 128.05, 130.47, 137.47, 156.64. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.19; H, 8.19.

3.3.12. Compound 3f. Eighty-seven percentage; a colorless oil; IR (film) 3440, 2924, 1072 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.23 (d, $J=6.6$ Hz, 3H), 1.99 (d, $J=3.0$ Hz, 1H), 2.85 (d, $J=13.8$ Hz, 1H), 2.98 (d, $J=13.8$ Hz, 1H), 3.78 (d, $J=9.3$ Hz, 1H), 3.84–3.90 (m, 1H), 4.06 (d, $J=9.3$ Hz, 1H), 4.12 (dt, $J=13.5$, 2.8 Hz, 1H), 4.34 (dt, $J=13.5$, 2.1 Hz, 1H), 4.82 (t, $J=2.4$ Hz, 1H), 5.14 (t, $J=2.1$ Hz, 1H), 7.17–7.29 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.17, 39.81, 54.14, 72.09, 72.97, 74.60, 105.95, 126.44, 128.01, 130.57, 137.72, 151.14. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.09; H, 8.27.

3.4. The reactions of 4a–h and Grubbs catalyst

To a stirred solution of **4a** (122 mg, 0.5 mmol) was added Grubbs catalyst (21 mg, 5 mol%) and the reaction mixture was heated to reflux for 2 h. After usual workup and column chromatographic purification process (hexanes/EtOAc, 85:15) we obtained **5a** as colorless oil, 98 mg (92%). Other entries in Tables 1 and 2 were tried similarly under the similar conditions. The spectroscopic data of prepared compounds are as follows.

3.4.1. Compound 5a. Ninety-two percentage; a colorless oil; IR (film) 2924, 2854, 1103, 1041 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.76 (d, $J=13.2$ Hz, 1H), 2.92 (d, $J=13.2$ Hz, 1H), 3.02 (d, $J=10.8$ Hz, 1H), 3.07 (d, $J=8.4$ Hz, 1H), 3.96 (d, $J=8.4$ Hz, 1H), 3.99 (d, $J=10.8$ Hz, 1H), 4.09–4.46 (m, 4H), 5.54–5.58 (m, 1H), 7.19–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.27, 45.87, 64.59, 67.87, 69.06, 72.58, 115.93, 126.32, 128.15, 130.65, 138.11, 141.94; ESIMS (*m/z*) 217.1 ($M^+ + H$). Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.79; H, 7.58.

3.4.2. Compound 5b. Ninety-one percentage; sticky solid; IR (film) 2924, 2858, 1338, 1157 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.34 (d, $J=9.6$ Hz, 1H), 2.44 (s, 3H), 2.71 (d, $J=13.5$ Hz, 1H), 2.87 (d, $J=10.8$ Hz, 1H), 2.89 (d, $J=13.5$ Hz, 1H), 3.53 (d, $J=9.6$ Hz, 1H), 3.69–3.76 (m, 1H), 3.91 (d, $J=10.8$ Hz, 1H), 4.01–4.31 (m, 3H), 5.49–5.52 (m, 1H), 7.13–7.35 (m, 7H), 7.71 (d, $J=8.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.52, 38.33, 45.16, 50.04, 52.51, 64.78, 67.87, 118.15, 126.52, 127.57, 128.27, 129.71, 130.69, 133.86, 137.21, 138.34, 143.59; ESIMS (*m/z*) 370.1 ($M^+ + H$). Anal. Calcd for $C_{21}H_{23}NO_3S$: C, 68.27; H, 6.27; N, 3.79. Found: C, 68.21; H, 6.38; N, 3.71.

3.4.3. Compound 5c. Ninety-seven percentage; a colorless oil; IR (film) 1516, 1250, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.73–2.79 (m, 1H), 3.28 (t, $J=10.2$ Hz, 1H), 3.81 (s, 3H), 4.05–4.28 (m, 4H), 4.40–4.47 (m, 1H), 4.64–4.71 (m, 1H), 5.60–5.63 (m, 1H), 6.90 (d, $J=9.0$ Hz, 2H), 7.28 (d, $J=9.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 46.31, 55.27, 64.31, 65.89, 66.52, 83.09, 113.96, 116.05, 127.39, 132.17, 138.96, 159.48; ESIMS (*m/z*) 233.1 ($M^+ + H$). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.51; H, 6.79.

3.4.4. Compound 5d. Forty-eight percentage; a colorless oil; IR (film) 1739, 1516, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.23–3.29 (m, 1H), 3.81 (s, 3H), 4.48–4.56 (m, 1H), 4.76–4.93 (m, 3H), 5.06 (d, $J=8.7$ Hz, 1H), 5.88–5.93 (m, 1H), 6.91 (d, $J=9.0$ Hz, 2H), 7.48 (d, $J=9.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.08, 55.28, 68.18, 68.38,

81.22, 112.66, 113.90, 127.73, 131.69, 141.25, 159.51, 169.84; ESIMS (*m*/*z*) 247.1 ($M^+ + H$). Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.41; H, 5.76.

3.4.5. Compound 5e. Ninety-four percentage; a colorless oil; IR (film) 2924, 1103, 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28 (d, $J=6.3$ Hz, 6H), 2.84 (d, $J=13.2$ Hz, 4H), 2.95 (d, $J=13.2$ Hz, 2H), 3.22 (d, $J=9.0$ Hz, 2H), 3.30 (d, $J=9.0$ Hz, 2H), 3.62 (d, $J=9.0$ Hz, 2H), 3.95 (d, $J=9.0$ Hz, 2H), 4.00–4.02 (m, 2H), 4.37–4.44 (m, 2H), 4.50–4.52 (m, 2H), 4.86 (d, $J=2.1$ Hz, 2H), 5.82–5.85 (m, 2H), 7.11–7.28 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.33, 40.65, 51.25, 71.16, 73.36, 75.18, 78.28, 105.67, 126.22, 127.70, 129.10, 130.90, 137.73, 155.72; ESIMS (*m*/*z*) 489.3 ($M^+ + H$). Anal. Calcd for $C_{32}H_{40}O_4$: C, 78.65; H, 8.25. Found: C, 78.80; H, 8.37.

3.4.6. Compound 5f. Eighty-five percentage; a colorless oil; IR (film) 2924, 1115 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.15 (d, $J=6.3$ Hz, 6H), 2.92 (d, $J=13.2$ Hz, 2H), 3.03 (d, $J=13.2$ Hz, 2H), 3.48 (q, $J=6.3$ Hz, 2H), 3.74 (d, $J=9.0$ Hz, 2H), 3.92–4.26 (m, 10H), 4.59–4.64 (m, 2H), 5.06 (t, $J=2.1$ Hz, 2H), 5.93 (t, $J=2.7$ Hz, 2H), 7.14–7.26 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.02, 40.97, 54.37, 69.06, 72.86, 73.76, 78.83, 105.73, 126.16, 127.63, 129.02, 131.07, 137.95, 151.58; ESIMS (*m*/*z*) 489.3 ($M^+ + H$). Anal. Calcd for $C_{32}H_{40}O_4$: C, 78.65; H, 8.25. Found: C, 78.49; H, 8.11.

3.4.7. Compound 5g. Twenty-four percentage; a colorless oil; IR (film) 1736, 1516, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.49–3.53 (m, 2H), 3.79 (s, 6H), 4.44–4.51 (m, 2H), 4.56–4.70 (m, 6H), 5.08–5.11 (m, 2H), 5.14–5.19 (m, 4H), 5.79–5.82 (m, 2H), 6.87 (d, $J=8.7$ Hz, 4H), 7.30 (d, $J=8.7$ Hz, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.25, 56.97, 64.33, 71.46, 83.25, 106.54, 113.92, 127.50, 127.99, 131.69, 146.41, 159.56, 170.34; ESIMS (*m*/*z*) 521.2 ($M^+ + H$). Anal. Calcd for $C_{30}H_{32}O_8$: C, 69.22; H, 6.20. Found: C, 69.10; H, 6.36.

3.5. Synthesis of compound 6

A mixture of **5a** (65 mg, 0.3 mmol) and 5% Pd/C (10 mg) in EtOH (1 mL) was stirred under the atmosphere of H_2 (ballon) at room temperature for 3 h. After filtration, removal of solvent, and column chromatographic purification process (hexanes/EtOAc, 85:15) we obtained **6** as colorless oil, 59 mg (90%).

3.5.1. Compound 6. Ninety percentage; a colorless oil; IR (film) 2924, 2854 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.48–1.51 (m, 1H), 1.90–2.02 (m, 1H), 2.16–2.25 (m, 1H), 2.60 (d, $J=13.5$ Hz, 1H), 3.00 (d, $J=13.5$ Hz, 1H), 3.38 (d, $J=12.0$ Hz, 1H), 3.47 (d, $J=9.0$ Hz, 1H), 3.57–3.74 (m, 4H), 3.84 (t, $J=8.4$ Hz, 1H), 4.06 (t, $J=8.4$ Hz, 1H), 7.11–7.14 (m, 2H), 7.19–7.32 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.31, 29.63, 39.62, 39.90, 64.41, 68.53, 70.63, 73.76, 126.40, 128.22, 130.00, 137.65; ESIMS (*m*/*z*) 219.1 ($M^+ + H$). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.14; H, 8.23.

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$ZrOCl_2 \cdot 8H_2O$: an efficient Lewis acid catalyst for the one-pot multicomponent synthesis of β-acetamido ketones

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Abstract—Aromatic aldehydes were reacted in one-pot with enolisable ketones, acetonitrile and acetyl chloride at ambient temperature in the presence of $ZrOCl_2 \cdot 8H_2O$ to furnish the corresponding β-acetamido ketones in very good to excellent yields. X-ray crystallographic analysis of one *anti*-β-acetamido ketone exhibited a two-dimensional supramolecular framework by a combination of N–H···O, C–H···O and C–H···π (arene) hydrogen bonds.

1. Introduction

Due to several advantages over conventional multi-step synthesis and also because of their promising applications in pharmaceutical chemistry for the generation of structural scaffolds and combinatorial libraries for drug development,[1] one-pot multicomponent reactions have recently drawn the attraction of organic chemists. β-Acetamido or -amino ketones are potential intermediates for the generation of β-amino alcohols[2]—structural units common in natural nucleoside antibiotics such as nikkomycins or neopolyoxins.[3]

The reported one-pot syntheses of the title compounds from aldehydes, enolisable ketones, acetyl chloride and acetonitrile are based on $CoCl_2$,[4a,b] Montmorillonite K-10 Clay,[4c] SiO_2–H_2SO_4[4d] or $BiCl_3$ generated in situ from BiOCl and acetyl chloride.[5] Recently, because of the easy availability in earth crust[6] and low toxicity,[7] Zr(IV) compounds, especially $ZrCl_4$ have received considerable attention in various organic reactions,[8] but reported zirconium oxychloride based reactions are only a few.[9] In one of our earlier reports we have established for the first time that $ZrOCl_2 \cdot 8H_2O$ acts as an efficient Lewis acid catalyst for acylation of alcohols, phenols, amines, thiol and thiophenols.[9a] In further continuation to our ongoing research on metal oxysalt-based organic reactions[5,9a,10] we were prompted to explore the efficacy of $ZrOCl_2 \cdot 8H_2O$ as an activator for the one-pot synthesis of β-acetamido ketones from aromatic aldehydes, enolisable ketones, acetyl chloride and acetonitrile.

2. Results and discussions

2.1. Synthesis

Under the optimized reaction conditions (Table 1, Scheme 1), benzaldehyde (**1**, ~1 equiv) reacted at room temperature with acetophenone (**11**, ~1 equiv), acetyl chloride (~2 equiv) and acetonitrile (reagent as well as solvent) in the presence of $ZrOCl_2 \cdot 8H_2O$ (~20 mol%) to furnish the corresponding β-acetamido ketone (**15**) in excellent yield (90%, entry 2, Table 1 and entry 1, Table 2). Other benzaldehyde derivatives containing electron-withdrawing (entries 5–7, Table 2) and -donating groups (entries 8–10 and 12, Table 2) in the aromatic ring also reacted with acetophenone (**11**), acetyl chloride and acetonitrile affording the corresponding β-acetamido ketones (**16–21** and **23**) in very high to excellent yields with concomitant acetylation of

Table 1. Standardisation of reaction condition

Entry	Metal salts (mol%)	Time (h)	Yield of product (%)
1	$ZrOCl_2 \cdot 8H_2O$ (15)	12	83
2	$ZrOCl_2 \cdot 8H_2O$ (20)	5	90
3	$ZrCl_4$ (20)	5	87

Keywords: One-pot multicomponent synthesis; $ZrOCl_2 \cdot 8H_2O$; Lewis acid catalyzed; β-Acetamido ketone.
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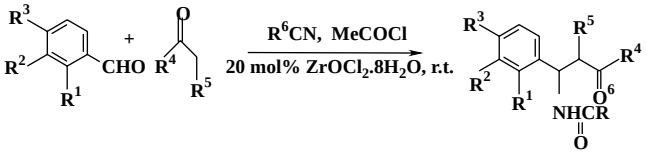
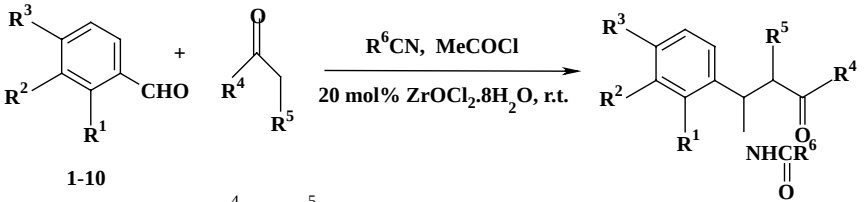


Scheme 1.

the *m*-hydroxy benzaldehyde derived product (entry 10, Table 2). *p*-Dimethylaminobenzaldehyde, however, was inert to the present reaction conditions. Other enolisable ketones (α-unsubstituted and -substituted, **12**–**14**) also served as good substrates for the present one-pot synthesis. Thus, the reaction of benzaldehyde (**1**) with *p*-methoxyacetophenone (**12**), acetyl chloride and acetonitrile in the presence of $ZrOCl_2 \cdot 8H_2O$ proceeded efficiently resulting in the desired product (**22**) in 92% yield (entry 11, Table 2). α-Substituted enolisable ketones such as ethyl methyl ketone (**13**) also reacted with benzaldehyde (**1**) or *p*-tolualdehyde (**8**) resulting in high yields of the title compounds (**26** and **27**), although, with moderate or poor diastereoselectivity in favour of the *anti*-isomers (entries 16 and 17, Table 2). Similarly, propiophenone (**14**) was equally a good substrate to react separately with benzaldehyde (**1**), *p*-chloro-(**5**), *o*-nitro-benzaldehyde (**2**), *p*-tolualdehyde (**8**) or vanilin (**9**) in the presence of other components affording the corresponding β-acetamido ketones (**28**–**32**, entries 18–22, Table 2) with concomitant acetylation of the phenolic –OH groups of the products in relevant system (entry 22, Table 2), but the reactions were either not diastereoselective (entries 18–20) or proceeded with poor diastereoselectivity (entries 21 and 22). The reaction of salicylaldehyde (**10**) with propiophenone (**14**) and other components was, however, tricky; only 31% of the desired acetylated product (**33**) could be isolated (entry 23). The preparative efficacy of this one-pot synthesis was further checked by scaling-up (∼10 folds) of the reaction of benzaldehyde (**1**) with acetophenone (**11**) and other ingredients in solvent as well as in solvent-free conditions (entries 2 and 3, Table 2), which proceeded in 92 and 93% respective yields. The reaction also proceeded with equal efficacy (entry 4, Table 2) with the recovered and isolated $ZrOCl_2 \cdot 8H_2O$. It may be mentioned here that a mixture of benzaldehyde (**1**),

Table 2. $ZrOCl_2 \cdot 8H_2O$ catalyzed one-pot synthesis of β-acetamido ketone



1-10

11, R^4 = Ph, R^5 = H
12, R^4 = *p*-OMe-C_6H_4-, R^5 = H
13, R^4 = Me, R^5 = Me
14, R^4 = Ph, R^5 = Me

15-30

Entry	Aromatic aldehyde	β-Acetamido ketone	Time (h)	Yield (%)[a]	*syn*/*anti*
1	R^1=R^2=R^3=H (**1**)	R^1=R^2=R^3=R^5=H, R^4=Ph, R^6=Me (**15**)	5	90	—
2	R^1=R^2=R^3=H (**1**)	R^1=R^2=R^3=R^5=H, R^4=Ph, R^6=Me (**15**)	5	92[b]	—
3	R^1=R^2=R^3=H (**1**)	R^1=R^2=R^3=R^5=H, R^4=Ph, R^6=Me (**15**)	5	93[c]	—
4	R^1=R^2=R^3=H (**1**)	R^1=R^2=R^3=R^5=H, R^4=Ph, R^6=Me (**15**)	5	90[d]	—
5	R^1=NO_2, R^2=R^3=H (**2**)	R^1=NO_2, R^2=R^3=R^5=H, R^4=Ph, R^6=Me (**16**)	12	85	—
6	R^2=NO_2, R^1=R^3=H (**3**)	R^2=NO_2, R^1=R^3=R^5=H, R^4=Ph, R^6=Me (**17**)	6	92	—
7	R^3=NO_2, R^1=R^2=H (**4**)	R^3=NO_2, R^1=R^2=R^5=H, R^4=Ph, R^6=Me (**18**)	7	69	—
8	R^1=R^2=H, R^3=Cl (**5**)	R^1=R^2=R^5=H, R^3=Cl, R^4=Ph, R^6=Me (**19**)	8	91	—
9	R^1=R^2=H, R^3=OMe (**6**)	R^1=R^2=R^5=H, R^3=OMe, R^4=Ph, R^6=Me (**20**)	7	92	—
10	R^1=R^3=H, R^2=OH (**7**)	R^1=R^3=R^5=H, R^2=OAc, R^4=Ph, R^6=Me (**21**)	4.5	92	—
11	R^1=R^2=R^3=H (**1**)	R^1=R^2=R^3=R^5=H, R^4=*p*-MeO–C_6H_4, R^6=Me (**22**)	4	92	—
12	R^3=Me, R^1=R^2=H (**8**)	R^1=R^2=R^5=H, R^4=Ph, R^3=R^6=Me (**23**)	4	94	—
13	R^2=NO_2, R^1=R^3=H (**3**)	R^1=R^3=R^5=H, R^2=NO_2, R^4=*p*-OMe–C_6H_4, R^6=Me (**24**)	48	61	—
14	R^2=NO_2, R^1=R^3=H (**3**)	R^2=NO_2, R^1=R^3=R^5=H, R^4=R^6=Ph (**25**)	36	86[e]	—
15	R^2=NO_2, R^1=R^3=H (**3**)	R^2=NO_2, R^1=R^3=R^5=H, R^4=R^6=Ph (**25**)	36	89[f]	—
16	R^1=R^2=R^3=H (**1**)	R^1=R^2=R^3=H, R^4=R^5=R^6=Me (**26**)	2	86	1:4.5[g]
17	R^1=R^2=H, R^3= Me (**8**)	R^1=R^2=H, R^3=R^4=R^5=R^6=Me (**27**)	3.5	81	1:1.6[g]
18	R^1=R^2=R^3=H (**1**)	R^1=R^2=R^3=H, R^4=Ph, R^5=R^6=Me (**28**)	6	94	1.1:1[h]
19	R^1=R^2=H, R^3=Cl (**5**)	R^1=R^2=H, R^3=Cl, R^4=Ph, R^5=R^6=Me (**29**)	2	83	1:1[h]
20	R^1=NO_2, R^2=R^3=H (**2**)	R^1=NO_2, R^2=R^3=H, R^4=Ph, R^5=R^6=Me (**30**)	10	80	1.1:1[h]
21	R^1=R^2=H, R^3=Me (**8**)	R^1=R^2=H, R^3=R^5=R^6=Me, R^4=Ph (**31**)	4	94	2.2:1[g]
22	R^1=H, R^2=OMe, R^3=OH (**9**)	R^1=H, R^2=OMe, R^3=OAc, R^4=Ph, R^5=R^6=Me (**32**)	12	74	1.5:1[h]
23	R^1=OH, R^2=R^3=H (**10**)	R^1=OAc, R^2=R^3=H, R^4=Ph, R^5=R^6=Me (**33**)	11	31	1:1[h]

[a] Chromatographed yield.
[b] Scale-up experiment (∼10 fold).
[c] Under neat condition (∼10 fold).
[d] With recovered $ZrOCl^2 \cdot 8H_2O$.[9]
[e] Using PhCN (∼2 equiv) in CH^2Cl_2.
[f] Using PhCN (∼3 equiv) in neat condition.
[g] Ratio of methine protons of *syn* and *anti* isomers (by ^{1}H NMR).
[h] Ratio of isolated yields (by preparative TLC) of *syn* and *anti* isomers.

acetophenone (**11**), acetyl chloride and aceonitrile in the presence of $ZrCl_4$ (~20 mol%) also produced the corresponding β-acetamido ketone (**15**) in excellent yield (entry 3, Table 1), but $ZrOCl_2 \cdot 8H_2O$ was the catalyst of choice because of its moisture stability, recoverability and reusability without any loss of the catalytic activity.

Unlike our earlier report on BiOCl based one-pot synthesis of β-acetamido ketones[5] a mixture of *m*-nitrobenzaldehyde (**3**), acetophenone (**11**), benzoyl chloride in the presence of acetonitrile and $ZrOCl_2 \cdot 8H_2O$ failed to generate the corresponding β-acetamido ketone even after 7 days. But, the use of a different nitrile such as benzonitrile in solvent (CH_2Cl_2) or solvent-free conditions (entries 14 and 15) in a mixture of benzaldehyde, acetophenone and acetyl chloride in the presence of $ZrOCl_2 \cdot 8H_2O$ (~20 mol%) could lead to the expected product (**25**) in similar yields as with the acetonitrile counterpart (entry 1, Table 2) although these reactions proceeded with a much slower rate.

A mixture of chalcone (~1 equiv), acetyl chloride (~2 equiv) and $ZrOCl_2 \cdot 8H_2O$ (20 mol%) in acetonitrile failed to produce any β-acetamido ketone (**15**). Thus, this reaction also follows a similar mechanistic pathway as described in our earlier report of the one-pot synthesis based on BiOCl.[5] It is also noteworthy to mention that neither a mixture of benzaldehyde, acetophenone, acetic anhydride and $ZrOCl_2 \cdot 8H_2O$ in acetonitrile nor a mixture of benzaldehyde acylal, acetophenone and $ZrOCl_2 \cdot 8H_2O$ in acetonitrile could generate any of the corresponding β-acetamido ketone (**15**) even after stirring each mixture for a prolonged time.

2.2. X-ray crystallographic study of *anti*-31

The structures of the *anti*-isomers were confirmed by the X-ray crystallographic analysis of one model *anti*-isomer (*anti*-**31**). Single crystals of *anti*-**31** were grown by slow crystallization from a solution of EtOAc–hexane. The molecular view of compound *anti*-**31** is shown in Figure 1. The torsion angles C1–C7–C8–C10 −158.7(1)° and C7–C8–C10–C13 −179.0(1)° indicate that the propyl chain connecting the two nearby planar phenyl rings, C1–C6 and C13–C18, is almost straight; the dihedral angles between the two phenyl rings is 44.98(3)°. The crystal packing of *anti*-**31** reveals that the molecules are linked into two-dimensional supramolecular framework by a combination of N–H···O, C–H···O and C–H···π (arene) hydrogen bonds.

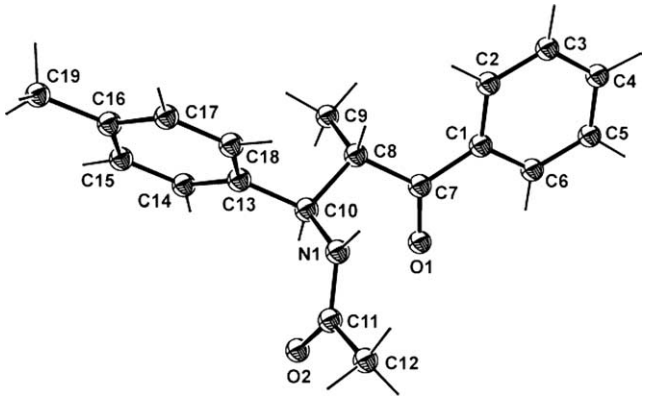


Figure 1. ORTEP diagram of single crystal of *anti*-**31**.

3. Conclusion

The efficacy of $ZrOCl_2 \cdot 8H_2O$ for the one-pot generation of β-acetamido ketones from aromatic aldehyde, enolisable ketone, acetyl chloride and acetonitrile in solvent as well as in solvent-free conditions has been established. The special feature of the present procedure lies in the easy availability, low toxicity, moisture compatibility, recoverability and reusability of the catalyst. Although, it exhibits very low to moderate diastereoselectivity but very high to excellent yields of the products make this procedure a suitable competitor with the other existing methodologies particularly for the synthesis of β-acetamido ketones based on α-unsubstituted ketones. X-ray structure analysis of one model *anti*-isomer exhibits two-dimensional supramolecular assembly by a combination of N–H···O, C–H···O and C–H···π (arene) intermolecular interactions.

4. Experimental

4.1. General

All melting points are uncorrected. IR spectra were recorded on Perkin Elmer 297 spectrophotometer. NMR spectra were recorded on Bruker DPX-300/Mercury 400/Unity 500 spectrometer using $CDCl_3$ as solvent and TMS as the internal standard. Elemental analyses were performed on a Perkin Elmer auto analyzer 2400 II.

4.2. General experimental procedure

(*a*) *In solution*. To a solution of aldehydes (~1 mmol) and acetophenone (~1 mmol) in dry acetonitrile (4 mL) was added $ZrOCl_2 \cdot 8H_2O$ (~20 mol%). To the resulting suspension was finally added acetyl chloride (~2 mmol) and the reaction mixture was stirred at ambient temperature. After the completion of the reaction (checked by TLC with EtOAc-pet.ether (60-80 °C) the mixture was diluted with CH_2Cl_2 (20 mL), washed with brine solution (1×20 mL) and the aqueous layer was then extracted with CH_2Cl_2 (3× 15 mL). The combined organic layer was washed with $NaHCO_3$ solution (1×15 mL) followed by water (1× 20 mL). The organic layer was dried over Na_2SO_4, concentrated to dryness and the crude residue was purified on silica gel column after elution with 3:2 EtOAc–pet. ether (60-80 °C). Mixture of diastereomers were separated by preparative TLC on silica plates using 1:2 EtOAc–pet. ether (60-80 °C).

(*b*) *In solvent-free conditions*. To a mixture of aromatic aldehydes (~1 mmol), acetophenone (~1 mmol) and dry acetonitrile (~3 mmol) was added $ZrOCl_2 \cdot 8H_2O$ (~20 mmol). Finally, acetyl chloride (~2 mmol) was added and the reaction mixture was stirred at ambient temperature. After completion of the reaction, it was diluted with CH_2Cl_2 (15 mL) and then worked-up as described in (a).

4.2.1. *N*-(3-Oxo-1,3-diphenyl-propyl)-acetamide (15).[4c] (Yield 240 mg, 90%). White crystals, (EtOAc-pet.ether, 60-80 °C) mp 104–105 °C, (lit.[4c] mp 102–104 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.03 (s, 3H), 3.40–3.48 (dd, J=6.0, 16.9 Hz, 1H), 3.72–3.79 (dd, J=5.1, 16.9 Hz, 1H), 5.53–5.60 (m, 1H), 6.68–6.70 (br d, J=7.5 Hz, 1H), 7.22–7.35 (m, 5H), 7.42–7.47 (m, 2H), 7.54–7.58 (m, 1H), 7.88–7.91 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.5, 43.3, 50.0, 126.6, 127.5, 128.2, 128.7, 128.8, 133.6, 136.7, 141.6, 169.6, 199.3.

4.2.2. *N*-[1-(2-Nitro-phenyl)-3-oxo-3-phenyl-propyl]-acetamide (16).[4c] (Yield 265 mg, 85%). Off white crystals, (EtOAc-pet.ether, 60-80 °C) mp 191–192 °C, (lit.[4c] mp 186–188 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.02 (s, 3H), 3.60–3.69 (m, 2H), 5.96–5.99 (m, 1H), 7.09 (s, 1H), 7.37–7.50 (m, 3H), 7.56–7.59 (m, 2H), 7.71–7.74 (m, 1H), 7.93–7.96 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.4, 42.3, 47.5, 125.2, 128.4, 128.5, 128.9, 129.9, 133.6, 133.9, 136.3, 136.8, 148.5, 169.5, 198.7.

4.2.3. *N*-[1-(3-Nitro-phenyl)-3-oxo-3-phenyl-propyl]-acetamide (17).[4c] (Yield 287 mg, 92%). White crystals, (EtOAc/pet. ether, 60:80) mp 139–140 °C, (lit.[5] mp 139–140 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.08 (s, 3H), 3.47–3.55 (dd, J=5.4, 17.5 Hz, 1H), 3.77–3.84 (dd, J=4.9, 17.5 Hz, 1H), 5.63–5.69 (m, 1H), 6.95–6.98 (d, J=7.5 Hz, 1H), 7.44–7.51 (m, 3H), 7.57–7.62 (t, J=7.3 Hz, 1H), 7.70–7.73 (d, J=7.5 Hz, 1H), 7.88–7.90 (br d, J=7.3 Hz, 2H), 8.07–8.10 (d, J=8.1 Hz, 1H), 8.22 (br s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.5, 43.0, 49.2, 121.4, 122.4, 128.2, 128.9, 129.6, 133.2, 134.1, 136.3, 143.7, 148.4, 169.9, 198.0.

4.2.4. *N*-[1-(4-Nitro-phenyl)-3-oxo-3-phenyl-propyl]-acetamide (18).[4c] (Yield 215 mg, 69%). White amorphous solid, (EtOAc-pet.ether, 60-80 °C) mp 154 °C, (lit.[4c] mp 148–149 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.08 (s, 3H), 3.46–3.54 (dd, J=5.4, 17.6 Hz, 1H), 3.77–3.85 (dd, J=4.8, 17.6 Hz, 1H), 5.6–5.7 (m, 1H), 6.96–6.98 (d, J=7.7 Hz, 1H), 7.44–7.62 (m, 5H), 7.87–7.90 (d, J=7.3 Hz, 2H), 8.15–8.18 (d, J=8.6 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.5, 42.7, 49.3, 123.9, 127.5, 128.2, 128.9, 134.1, 136.2, 147.1, 148.8, 174.2, 198.1.

4.2.5. *N*-[1-(4-Chlorophenyl)-3-oxo-3-phenyl-propyl]-acetamide (19).[4a] (Yield 274 mg, 91%). White crystals, (EtOAc-pet.ether, 60-80 °C) mp 149–150 °C, (lit.[4a] mp 150 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.00 (s, 3H), 3.37–3.43 (dd, J=5.6, 17.2 Hz, 1H), 3.69–3.74 (dd, J=4.8, 17.1 Hz, 1H), 5.49–5.54 (m, 1H), 6.81–6.83 (d, J=7.6 Hz, 1H), 7.27 (s, 4H), 7.42–7.46 (t, J=7.8 Hz, 2H), 7.54–7.58 (t, J=7.2 Hz, 1H), 7.87–7.89 (d, J=8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.6, 43.1, 49.5, 128.1, 128.3, 128.9, 129.0, 133.4, 133.9, 136.7, 139.8, 169.7, 198.6.

4.2.6. *N*-[1-(4-Methoxy-phenyl)-3-oxo-3-phenyl-propyl]-acetamide (20).[4d] (Yield 273 mg, 92%). White crystals, (EtOAc-pet.ether 60-80 °C) mp 110–112 °C. IR (KBr): 3310, 1690, 1650, 1550, 1510, 1240, 1030, 760, 690 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.98 (s, 3H), 3.36–3.42 (dd, J=6.4, 17.2 Hz, 1H), 3.69–3.75 (dd, J=5.6, 17.2 Hz, 1H), 3.74 (s, 3H), 5.47–5.51 (dd, J=6, 13.2 Hz, 1H), 6.64–6.66 (d, J=7.2 Hz, 1H), 6.80–6.84 (m, 2H), 7.23–7.25 (d, J=8.8 Hz, 2H), 7.41–7.45 (t, J=7.8 Hz, 2H), 7.53–7.57 (t, J=7.6 Hz, 1H), 7.88–7.91 (d, J=8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.6, 43.6, 49.8, 55.5, 114.2, 127.9, 128.3, 128.9, 133.3, 133.6, 136.9, 159.1, 169.6, 198.8.

4.2.7. *N*-[1-(3-Acetoxy-phenyl)-3-oxo-3-phenyl-propyl]-acetamide (21).[4c] (Yield 299 mg, 92%). White crystals, (EtOAc-pet.ether, 60-80 °C) mp 114–115 °C, (lit.[4c] mp 114–115 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.99 (s, 3H), 2.26 (s, 3H), 3.39–3.45 (dd, J=5.8, 17.0 Hz, 1H), 3.68–3.74 (dd, J=5.6, 17.2 Hz, 1H), 5.53–5.58 (m, 1H), 6.73–6.75 (br d, J=8.4 Hz, 1H), 6.95–6.98 (dd, J=2.2, 7.8 Hz, 1H), 7.08–7.09 (t, J=2.0 Hz, 1H), 7.17–7.19 (d, J=8.0 Hz, 1H), 7.27–7.31 (t, J=7.8 Hz, 1H), 7.42–7.46 (m, 2H), 7.53–7.57 (m, 1H), 7.88–7.89 (d, J=7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 23.6, 43.2, 49.7, 120.1, 120.9, 124.2, 128.3, 128.9, 129.8, 133.79, 136.8. 143.0, 151.1, 169.5, 169.7, 198.5.

4.2.8. *N*-[3-(4-Methoxy-phenyl)-3-oxo-1-phenyl-propyl]-acetamide (22). (Yield 273 mg, 92%). White crystals, (EtOAc-pet.ether, 60-80 °C) mp 130 °C. IR (KBr): 3260, 1680, 1640, 1600, 1570, 1255, 1170, 990, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.00 (s, 3H), 3.31–3.39 (dd, J=5.9, 16.6 Hz, 1H), 3.64–3.71 (dd, J=5.3, 16.6 Hz, 1H), 3.84 (s, 3H), 5.50–5.57 (m, 1H), 6.86 (br s, 1H), 6.89 (br d, J=8.8 Hz, 2H), 7.18–7.34 (m, 5H), 7.88 (br d, J=8.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.4, 42.8, 50.0, 55.5, 113.8, 126.4, 127.3, 128.5, 129.7, 130.4, 141.1, 163.8, 169.5, 197.1. Anal. Calcd for $C_{18}H_{19}O_3N$: C, 72.71; H, 6.44; N, 4.71; Found: C, 72.65; H, 6.82; N, 4.67.

4.2.9. *N*-[1-(4-Methyl-phenyl)-3-oxo-3-phenyl-propyl]-acetamide (23). (Yield 264 mg, 94%). White crystals, (EtOAc-pet.ether, 60-80 °C) mp 112 °C. IR (KBr): 3295, 1680, 1650, 1550, 1350, 1200, 810, 755, 690 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.02 (s, 3H), 2.30 (s, 3H), 3.39–3.47 (dd, J=6.2, 16.7 Hz, 1H), 3.71–3.78 (dd, J=5.1, 16.7 Hz, 1H), 5.49–5.56 (m, 1H), 6.61–6.63 (d, J=7.2 Hz, 1H), 7.10–7.23 (m, 4H), 7.42–7.59 (m, 3H), 7.90–7.93 (d, J=7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.8, 23.2, 43.1, 49.6, 126.2, 127.9, 128.5, 129.2, 133.3, 136.5, 136.9, 137.7, 169.4, 198.4. Anal. Calcd for $C_{18}H_{19}O_2N$: C, 76.84; H, 6.80; N, 4.97; Found: C, 76.94; H, 7.18; N, 4.90.

4.2.10. *N*-[3-(4-Methoxy-phenyl)-1-(3-nitro-phenyl)-3-oxo-propyl]-acetamide (24). (Yield 209 mg, 61%). White crystals, (EtOAc-pet.ether, 60-80 °C) mp 132 °C. IR (KBr): 3300, 3065, 2840, 1665, 1645, 1600, 1520, 1350, 1255, 1240, 1170, 1020, 990, 820, 805, 735, 660 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.08 (s, 3H), 3.39–3.47 (dd, J=5.3, 17.2 Hz, 1H), 3.70–3.78 (dd, J=5.0, 17.2 Hz, 1H), 3.86 (s, 3H), 5.60–5.66 (m, 1H), 6.90–6.94 (d, J=8.7 Hz, 2H), 7.05–7.07 (d, J=7.9 Hz, 1H), 7.45–7.50 (t, J=7.9 Hz, 1H), 7.69–7.71 (d, J=7.6 Hz, 1H), 7.86–7.88 (d, J=8.6 Hz, 2H), 8.07–8.09 (d, J=8.1 Hz, 1H), 8.20 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.3, 42.1, 49.1, 55.4, 113.8, 121.1, 122.1, 129.1, 129.3, 130.3, 132.7, 143.4, 164.0, 169.6, 192.9, 196.4. Anal. Calcd for $C_{18}H_{18}O_5N_2$: C, 63.15; H, 5.29; N, 8.18; Found: C; 63.27, H; 5.03, N, 7.98.

4.2.11. *N*-[1-(3-Nitro-phenyl)-oxo-3-phenyl-propyl]-benzamide (25). (Yield 322 mg, 86%). White crystals, (EtOAc-pet.ether, 60-80 °C) mp 194–195 °C. IR (KBr): 3290, 2930, 1685, 1635, 1525, 1355, 1225, 760, 730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.57–3.64 (dd, J=5.4, 17.4 Hz, 1H), 3.87–3.95 (dd, J=4.9, 17.4 Hz, 1H), 5.83–5.88 (m, 1H), 7.44–7.62 (m, 7H), 7.78 (br d, J=7.8 Hz, 1H), 7.84–7.93 (m, 5H), 8.10 (br d, J=8.1 Hz, 1H), 8.28 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 42.5, 49.6, 121.39, 122.5, 127.1, 128.2, 128.7, 128.9, 129.6, 131.9, 132.9, 133.7, 134.1, 136.2, 143.5, 166.9, 198.6. Anal. Calcd for $C_{22}H_{18}N_2O_4$: C, 70.57; H, 4.84; N, 7.48; Found: C, 70.16; H, 4.96; N, 7.23.

4.2.12. *N*-1-[2-Methyl-3-oxo-1-phenyl-butyl]-acetamide (26).[4c] (Yield 188 mg, 86%).

anti-Isomer: (liquid). ^1H NMR (300 MHz, $CDCl_3$): δ 1.08–1.10 (d, J=7.1 Hz, 3H), 1.98 (s, 3H), 2.07 (s, 3H), 3.00–3.07 (m, 1H), 5.34–5.39 (t, J=6.9 Hz, 1H), 6.29–6.32 (d, J=7.9 Hz, 1H), 7.20–7.31 (m, 5H).

syn-Isomer: white crystals, (EtOAc-pet.ether, 60-80 °C) mp 126 °C, (lit.[4c] mp 126–127 °C). ^1H NMR (300 MHz, $CDCl_3$): δ 1.19–1.22 (d, J=7.2 Hz, 3H), 1.96 (s, 3H), 2.05 (s, 3H), 3.08–3.17 (m, 1H), 5.13–5.18 (dd, J=8.9, 5.3 Hz, 1H), 6.91–6.94 (d, J=7.7 Hz, 1H), 7.2–7.3 (m, 5H).

4.2.13. *N*-[2-Methyl-1-(4-methyl-phenyl)-3-oxo-butyl]-acetamide (27).[4c] (Yield 189 mg, 81%).

anti-Isomer: white crystals, (EtOAc-pet.ether, 60-80 °C) mp 162 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 1.19–1.22 (d, J=7.2 Hz, 3H), 1.97 (s, 3H), 2.05 (s, 3H), 2.59 (s, 3H), 3.11–3.16 (m, 1H), 5.12–5.17 (m, 1H), 6.18–6.25 (d, J=12.6 Hz, 1H), 7.21–7.97 (m, 4H).

syn-Isomer: white crystals, (EtOAc-pet.ether, 60-80 °C) mp 134 °C, (lit.[4c] mp 134 °C). ^1H NMR (300 MHz, $CDCl_3$): δ 1.18–1.20 (d, J=7.1 Hz, 3H), 2.03 (s, 3H), 2.08 (s, 3H), 2.31 (s, 3H), 3.08–3.12 (m, 1H), 5.10–5.15 (m, 1H), 6.83–6.86 (d, J=7.9 Hz, 1H), 7.12 (s, 4H).

4.2.14. *N*-(2-Methyl-3-oxo-1,3-diphenyl-propyl)-acetamide (28).[4c] (Yield 264 mg, 94%).

anti-Isomer: white crystals, (EtOAc-pet.ether, 60-80 °C) mp 174 °C, (lit.[4c] mp 140 °C). ^1H NMR (300 MHz, $CDCl_3$): δ 1.38–1.40 (d, J=7.1 Hz, 3H), 2.13 (s, 3H), 4.07–4.16 (m, 1H), 5.37–5.41 (dd, J=3.8, 8.9 Hz, 1H), 7.16–7.54 (m, 9H), 7.75–7.77 (d, J=7.4 Hz, 2H).

syn-Isomer: white crystal. (EtOAc-pet.ether, 60-80 °C) mp 120 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 1.21–1.24 (d, J=6.9 Hz, 3H), 2.00 (br s, 3H), 4.03–4.13 (m, 1H), 5.45–5.50 (t, J=7.7 Hz, 1H), 5.99–6.02 (d, J=5.9 Hz, 1H), 7.23–7.60 (m, 8H), 7.90–7.93 (d, J=7.3 Hz, 2H).

4.2.15. *N*-[1-(4-Chloro-phenyl)-2-methyl-3-oxo-3-phenyl-propyl]-acetamide (29).[4c] (Yield 262 mg, 83%).

anti-Isomer: white crystals, (EtOAc-pet.ether, 60-80 °C) mp 162 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 1.38–1.40 (d, J=7.0 Hz, 3H), 2.12 (s, 3H), 4.05–4.08 (m, 1H), 5.31–5.35 (m, 1H), 7.19 (s, 4H), 7.39–7.44 (t, J=7.6 Hz, 2H), 7.53–7.58 (t, J=7.2 Hz, 1H), 7.55 (s, 1H, exchangeable, –NH), 7.74–7.77 (d, J=7.5 Hz, 2H). ^1H NMR (300 MHz, $CDCl_3$, D_2O-exchange): δ 1.37–1.39 (d, J=7.2 Hz, 3H), 2.12 (s, 3H), 4.04–4.08 (dd, J=3.9, 7.1 Hz, 1H), 5.32–5.33 (d, J=3.7 Hz, 1H), 7.18(s, 4H), 7.38–7.40 (m, 2H), 7.52–7.57 (t, J=7.3 Hz, 1H), 7.74–7.76 (d, J=7.3 Hz, 2H).

syn-Isomer: white crystals, (EtOAc-pet.ether, 60-80 °C) mp 164 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 1.21 1.23 (d, J=6.8 Hz, 3H), 2.01 (s, 3H), 4.00–4.07 (m, 1H), 5.38–5.43 (t, J=7.3 Hz, 1H), 6.03–6.05 (d, J=6.0 Hz, 1H, exchangeable, –NH), 7.28 (s, 4H), 7.42–7.62 (m, 3H), 7.89–7.92 (d, J=7.6 Hz, 2H).

^1H NMR (300 MHz, $CDCl_3$, D_2O-exchange): δ 1.19–1.21 (d, J=6.9 Hz, 3H), 1.98 (s, 3H), 3.99–4.04 (t, J=7 Hz, 1H), 5.37–5.39 (d, J=6.9 Hz, 1H), 7.25 (s, 4H), 7.44–7.49 (m, 2H), 7.55–7.60 (m, 1H), 7.87–7.89 (d, J=7.3 Hz, 2H).

4.2.16. *N*-[2-Methyl-1-(2-nitro-phenyl)-3-oxo-3-phenyl-propyl]-acetamide (30).[4c] (Yield 261 mg, 80%).

anti-Isomer: off white crystals, (EtOAc-pet.ether, 60-80 °C) mp 142 °C, (lit.[4c] mp 122–124 °C). ^1H NMR (300 MHz, $CDCl_3$): δ 1.43–1.46 (d, J=7.1 Hz, 3H), 2.09 (s, 3H), 4.13–4.40 (m, 1H), 5.78–5.82 (dd, J=3.6, 8.0 Hz, 1H), 7.28–7.95 (m, 10H).

syn-Isomer: oil, ^1H NMR (300 MHz, $CDCl_3$): δ 1.25–1.27 (d, J=7.0 Hz, 3H), 2.02 (s, 3H), 4.42–4.47 (m, 1H), 5.71–5.76 (t, J=7.9 Hz, 1H), 6.64–6.66 (d, J=6.7 Hz, 1H), 7.35–7.93 (m, 9H).

4.2.17. *N*-[2-Methyl-1-(4-methyl-phenyl)-3-oxo-3-phenyl-propyl]-acetamide (31). (Yield 278 mg, 94%).

anti-Isomer: white crystals, (EtOAc-pet.ether, 60-80 °C) mp 170 °C. IR (KBr): 3313, 2987, 1685, 1647, 1543, 1367, 1142, 970, 702 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.36–1.38 (d, J=7.16 Hz, 3H), 2.10 (s, 3H), 2.24 (s, 3H), 4.05–4.14 (m, 1H), 5.33–5.37 (m, 1H), 7.01–7.04 (d, J=7.93 Hz, 2H), 7.11–7.14 (d, J=8.01 Hz, 2H), 7.37–7.56 (m, 4H), 7.76–7.79 (d, J=7.68 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.5, 20.9, 23.3, 44.4, 55.5, 126.2, 128.2, 128.6, 129.1, 133.4, 136.4, 136.7, 137.8, 169.9, 204.9. Anal. Calcd for $C_{19}H_{21}O_2N$: C, 77.25; H, 7.16; N, 4.74; Found: C, 77.23; H, 7.14; N, 4.48.

syn-Isomer: white crystals, (EtOAc-pet.ether, 60-80 °C) mp 119 °C. IR (KBr): 3240, 3055, 1678, 1639, 1553, 1371, 1290, 972, 710 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.20–1.22 (d, J=6.96 Hz, 3H), 1.98 (s, 3H), 2.29 (s, 3H), 4.00–4.14 (m, 1H), 5.41–5.46 (t, J=7.64 Hz, 1H), 5.99–6.02 (d, J=7.68 Hz, 1H), 7.08–7.11 (d, J=7.83 Hz, 2H), 7.20–7.28 (d, J=8.0 Hz, 2H), 7.43–7.59 (m, 3H), 7.89–7.92 (d, J=7.38 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 20.9, 23.1, 45.6, 54.8, 126.8, 128.1, 128.6, 129.1, 133.0, 136.3, 136.9, 137.5, 169.7, 201.9. Anal. Calcd for $C_{19}H_{21}O_2N$: C, 77.25; H, 7.16; N, 4.74; Found: C, 77.23; H, 6.94; N, 4.35.

4.2.18. Acetic acid 5-(1-acetylamino-2-methyl-3-oxo-3-phenyl-propyl)-2-methoxy-phenyl ester (32).[11] (Yield 273 mg, 74%).

anti-Isomer: white crystals, (EtOAc/pet. ether, 60:80 °C) mp 177 °C.[11] ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37–1.40 (d, J=7.0 Hz, 3H), 2.12 (s, 3H), 2.26 (s, 3H), 3.72 (s, 3H), 4.08–4.17 (m, 1H), 5.31–5.37 (m, 1H), 6.81–6.91 (m, 3H), 7.40–7.62 (m, 4H), 7.76–7.79 (d, J=7.5 Hz, 2H).

syn-Isomer: oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27–1.29 (d, J=6.6 Hz, 3H), 2.02 (s, 3H), 2.28 (s, 3H), 3.77 (s, 3H), 4.04–4.10 (m, 1H), 5.43–5.49 (t, J=7.6 Hz, 1H), 6.17–6.19 (d, J=6.8 Hz, 1H), 6.80–6.95 (m, 3H), 7.40–7.60 (m, 3H), 7.87–7.90 (d, J=7.4 Hz, 2H).

4.2.19. Acetic acid 3-(1-acetylamino-2-methyl-3-oxo-3-phenyl-propyl)-phenyl ester (33).[4c] (Yield 105 mg, 31%).

anti-Isomer: white crystals, (EtOAc/pet. ether, 60:80) mp 162 °C, (lit.[4c] mp 142 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32–1.35 (d, J=7.1 Hz, 3H), 2.08, (s, 3H), 2.41 (s, 3H), 3.96–4.04 (m, 1H), 5.50–5.54 (dd, J=3.6, 8.4 Hz, 1H), 7.03–7.08 (m, 2H), 7.17–7.22 (t, J=7.1 Hz, 2H), 7.37–7.55 (m, 4H), 7.75–7.78 (d, J=7.4 Hz, 2H).

syn-Isomer: oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29–1.31 (d, J=6.1 Hz, 3H), 1.97 (s, 3H), 2.39 (s, 3H), 4.08 (br s, 1H), 5.74–5.76 (m, 1H), 5.87 (s, 1H), 7.06–7.60 (m, 7H), 7.90–7.92 (d, J=7.5 Hz, 2H).

Crystallographic data of the compound *anti*-**31** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 285299. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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Process development of a disease-modifying antirheumatic drug, TAK-603, based on optimization of Friedel–Crafts reaction and selective substitution of a triazole ring

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Abstract—A practical method for the preparation of **TAK-603**, an antirheumatic drug, has been developed. As a result of optimizing the Friedel–Crafts reaction in the presence of $SnCl_4/POCl_3$, 2-aminobenzophenone skeleton, the key intermediate of **TAK-603**, was formed with good yield. The selective substitution reaction of 1,2,4-triazole was accomplished using 4-amino-1,2,4-triazole and deamination.

1. Introduction

Ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate (**TAK-603**, Fig. 1) was identified as a disease-modifying antirheumatic drug. In our medicinal chemistry research, some original synthetic routes to **TAK-603** were developed.[1] The latter medicinal synthesis route, as shown in Scheme 1, produced a high-purity product.

However, from the viewpoint of the large-scale preparation of **TAK-603**, which requires further evaluation (e.g., toxicological and clinical studies), the original synthetic method for **TAK-603** has some drawbacks, such as low yield in the formation of the benzophenone derivative **4**, low regioselectivity in the substitution reaction of 1,2,4-triazole with **6**, and repeated tedious chromatography for purification. Here, we present an efficient process established by the optimization of 2-aminobenzophenone skeleton formation via Friedel–Crafts reaction, a selective substitution of 1,2,4-triazole using 4-amino-1,2,4-triazole and avoiding chromatography, as outlined in Scheme 2.

2. Results and discussion

2.1. Optimization of the Friedel–Crafts reaction

As shown in Scheme 1, 2-aminobenzophenone intermediate **4** was derived from *N*-(3,4-dimethoxyphenyl)acetamide **2** and 3,4-dimethoxybenzoic acid **3** using polyphosphoric acid (PPA) at 100 °C. In this method, it only yielded 66% because of side reactions, such as the deacetylation of **2** and demethylation at the 3-position of **3**. In addition, PPA has

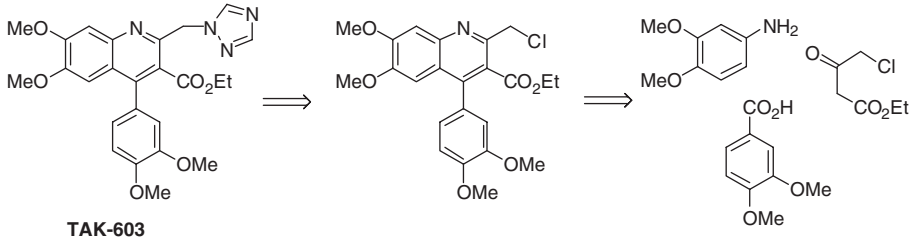

Figure 1.

Keywords: TAK-603; Friedel–Crafts reaction; Selective substitution; 1,2,4-Triazole.
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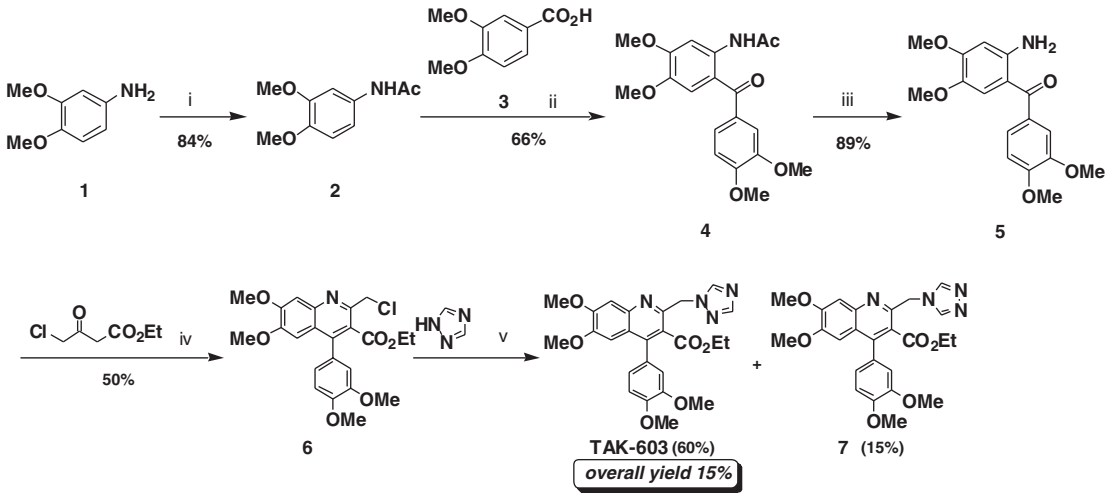


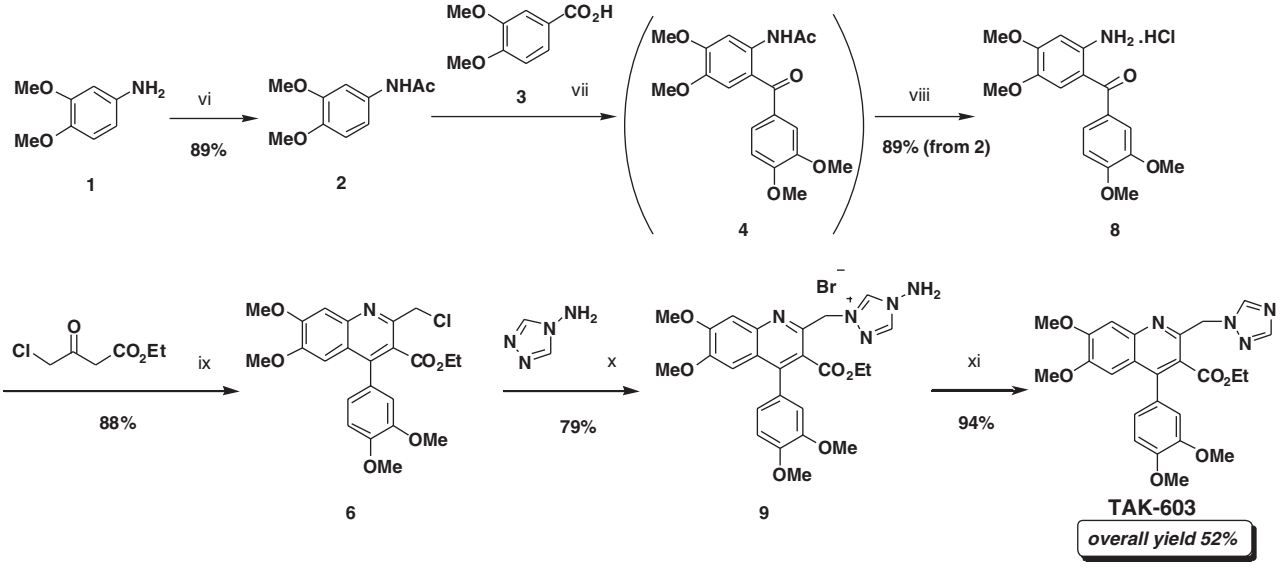
Scheme 1. Reagents and conditions: (i) Ac_2O, pyridine; (ii) PPA, 100 °C; (iii) 6 N HCl, AcOH, reflux; (iv) H_2SO_4, AcOH, 90 °C, then silicagel chromatography; (v) NaH, DMF, 80 °C, then silicagel chromatography.

drawbacks for large scale synthesis because of its viscosity, and significant amounts of water and solvent are needed post-treatment.

To improve these drawbacks, we studied the reaction conditions. In the case of hydroxybenzophenone, it was known that the use of zinc chloride or tin chloride as Lewis acid gave relatively good yield.[2]

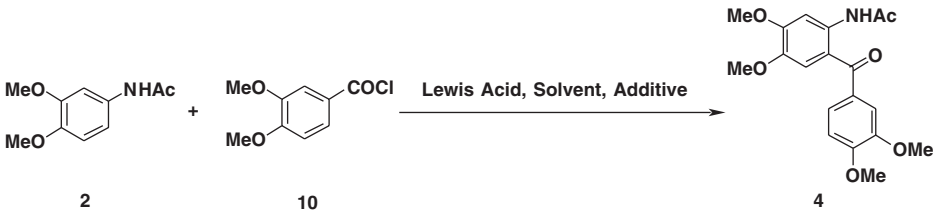
Therefore, we studied Lewis acid and solvents in the reaction of **2** and 3,4-dimethoxybenzoyl chloride **10**, an acid chloride form of **3**, as shown in Table 1. First, we studied Lewis acid as shown in entries 1–4, and established that tin chloride is the best choice. Next, in the presence of tin chloride, we studied solvents as shown in entries 5–11, and established that methylene chloride and ethylene dichloride are excellent solvents; when the 3 equiv of **10** was used in methylene chloride, the yield of **4** was up to 92% (entry 9). This result suggested that more than 1 equiv of **10** was consumed by hydrolysis during the reaction, so the ratio of **10** was fixed at 1.5 equiv to **2**, and we studied the molar ratio of tin chloride and additives as shown in entries 12–17. As a result, the equivalent of tin chloride did not affect the yield of **4**, while an increase in the equivalent of phosphorus oxychloride, which regenerates **10** from **3**, elevated the yield of **4**. In particular, when the 3 equiv of phosphorus oxychloride was used, the yield of **4** was up to 96% (entry 17).

After examining **2** and **10**, we studied the reaction of **2** and **3** in the same way. Optimization of the equivalent of **3**, tin chloride and phosphorus oxychloride was examined as shown in Table 2, and we determined the optimum conditions as shown in entry 4 of Table 2. Thus, we added concd HCl and isobutyl alcohol to the residue of **4** after workup (separation and evaporation) and crystallized to give **8** of high quality and 89% yield based on **2** in two steps.



Scheme 2. Reagents and conditions: (vi) Ac_2O, NaOH, H_2O, 50 °C; (vii) $SnCl_4$, $POCl_3$, CH_2Cl_2, reflux; (viii) concd HCl, EtOH, reflux; (ix) EtOH, reflux; (x) NaBr, DMF, 65 °C; (xi) $NaNO_2$, concd HCl, 5 °C.

Table 1. Study of Lewis acid, solvent and additive; reaction of **2** and **10**



2 10 4

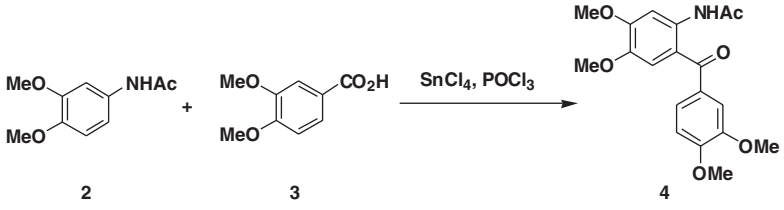
Entry	Lewis acid[a]	Solvent	Molar ratio				Yield of **4** (%)[b]
			2	**10**	Lewis acid	Additive	
1	$SnCl_4$	CH_2Cl_2	1.0	1.5	1.5	—	62
2	$FeCl_3$	CH_2Cl_2	1.0	2.0	2.0	—	47
3	$CF_3SO_3SiMe_3$	CH_2Cl_2	1.0	1.5	1.1	—	2
4	$TiCl_4$	CH_2Cl_2	1.0	1.5	1.5	—	2
5	$SnCl_4$	THF	1.0	1.5	2.0	—	ND[c]
6	$SnCl_4$	$CHCl_3$	1.0	1.5	2.0	—	34
7	$SnCl_4$	CH_2Cl_2	1.0	1.5	2.0	—	64
8	$SnCl_4$	CH_2Cl_2	1.0	2.0	2.0	—	80
9	$SnCl_4$	CH_2Cl_2	1.0	3.0	3.0	—	92
10	$SnCl_4$	$CH_2(Cl)CH_2Cl$	1.0	1.5	2.0	—	66
11	$SnCl_4$	$CH_3(CH_2)_3Cl$	1.0	1.5	1.5	—	ND
12	$SnCl_4$	CH_2Cl_2	1.0	1.5	2.0	—	64
13	$SnCl_4$	CH_2Cl_2	1.0	1.5	3.0	—	61
14	$SnCl_4$	CH_2Cl_2	1.0	1.5	1.5	$AlCl_3$ (0.1)	63
15	$SnCl_4$	CH_2Cl_2	1.0	1.5	1.5	$POCl_3$ (0.4)	74
16	$SnCl_4$	CH_2Cl_2	1.0	1.5	1.5	$POCl_3$ (1.5)	82
17	$SnCl_4$	CH_2Cl_2	1.0	1.5	1.5	$POCl_3$ (3.0)	96

Reaction conditions: CH_2Cl_2-reflux 3–7 h.
[a] We used another Lewis acid (e.g., $AlCl_3$, BF_3/Et_2O, $ZnCl_2$) in $CH_2(Cl)CH_2Cl$, but the yield of **4** was very low.
[b] Isolated yield.
[c] ND, not detected.

2.2. Selective substitution reaction of 1,2,4-triazole

In general, substitution reactions of 1,2,4-triazole produce two regioisomers (N-1 position substitute and N-4 position substitute).[3] Although reaction conditions such as the solvent, temperature or additive were studied to avoid this problem, it was difficult to obtain only one regioisomer. In our preliminary study concerning the reaction of 1,2,4-triazole with **6**, the desired N-1 position substitute was obtained in 60–70% along with about 15% of undesired 4-position substitute as shown in Scheme 1.

Table 2. Reaction of **2** and **3**

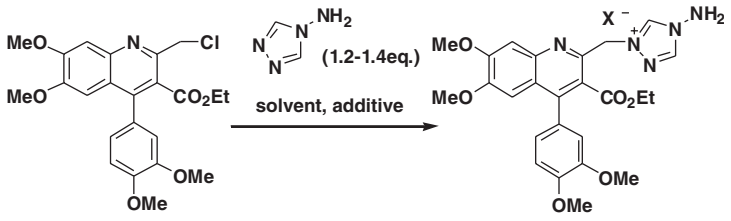


2 3 4

Entry	Molar ratio				Reaction		
	2	**3**	$SnCl_4$	$POCl_3$	Time (h)	Yield of **4** (%)[a]	Ratio by HPLC of **4**[b]
1	1.0	1.1	1.2	8.5	20	68	75
2	1.0	1.1	1.5	8.5	12	87	87
3	1.0	1.1	1.8	5.0	12	83	85
4	1.0	1.1	1.8	5.0	24	94	94
5	1.0	1.1	1.8	8.5	12	93	92
6	1.0	1.3	1.8	8.5	12	99	90
7	1.0	1.5	1.5	8.5	16	84	77
8	1.0	1.5	1.8	8.5	12	96	85
9	1.0	1.5	2.0	8.5	12	97	87

Reaction conditions: CH_2Cl_2-reflux.
[a] Isolated yield.
[b] Determined at 254 nm, YMC A-302 column, 50 mM KH_2PO_4/MeCN=55:45.

Table 3. Reaction of **6** with 4-amino-1,2,4-triazole



6 9 (X=Cl, Br, I)

Entry	Solvent	Additive (equiv)	Reaction		Ratio by HPLC[a]	
			Temperature (°C)	Time (h)	**6**	**9**
1	EtOH	—	Reflux	15	46	49
2	*i*-PrOH	—	Reflux	12	58	39
3	MeCN	—	Reflux	15	7	88
4	DMF	—	100	12	0.2	89
5	MeCN	NaBr (1.1)	70	3	35	61
6	DMF	NaBr (1.1)	70	3	0.01	94
7	DMF	NaI (1.2)	70	2	ND[b]	88

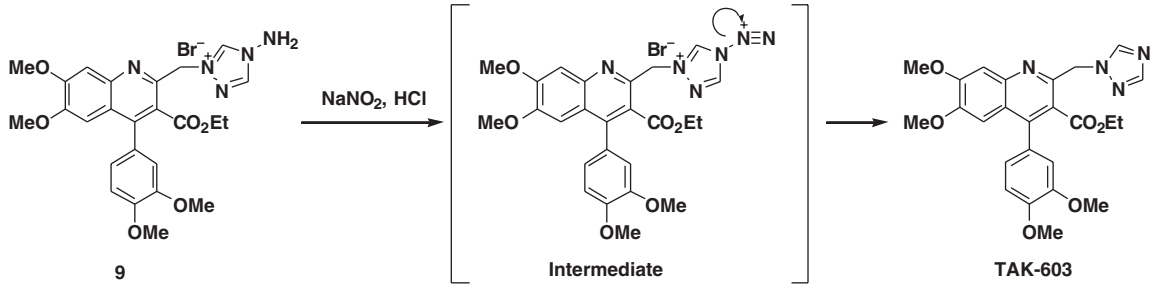
[a] Determined at 254 nm, YMC A-302 column, 50 mM KH_2PO_4/MeCN=55:45.
[b] ND, not detected.

Therefore, we investigated an alternative method to obtain the selectively desired regioisomer, which is the N-1 position substitute of 1,2,4-triazole. Some strategies for selective substitution reactions of 1,2,4-triazole are known, for example, the reaction with 1-trimethylsilyl-1,2, 4-triazole or 1-tributyltin-1,2,4-triazole,[4] isomerization at high temperature,[5] and reaction with 4-amino-1,2, 4-triazole.[6] The former two methods[4,5] require a high temperature (150–180 °C), so we chose the method using 4-amino-1,2,4-triazole. Although the alkylation of 4-amino-1,2, 4-triazole proceeded easily in polar media (isopropyl alcohol, or acetonitrile) exclusively at the N-1 position with good yield with alkyl halides, only small molecules have been identified such as benzyl, benzoylmethyl, 2,4-dichlorobenzoylmethyl and so on.[6] The resulting aminotriazolium salts were deaminated readily with a slight excess of nitrous acid in an essentially quantitative yield.

Our substrate is a relatively large molecule (MW 446), so this is the first application with a large molecular compound. First, as shown in Table 3, we studied solvents, additives and reaction temperatures, and found that dimethylformamide (DMF) is the best solvent compared with other solvents (isopropyl alcohol, or acetonitrile) in the literature.[6] We also discovered that the addition of sodium bromide or sodium iodide was effective in improving the reaction rate. After our studies, we determined the reaction conditions as shown in entry 6 of Table 3, and high quality triazolium salt **9** was obtained containing sodium chloride. Although the deamination of **9** without isolation is possible, we isolated **9** from ethyl acetate as crystals because of the qualification of the product.

After the isolation of triazolium salt **9**, we studied the deamination reaction following the literature method.[6] In the acidic condition at 3 °C, after the solution of sodium nitrite was added gradually for 10 min, the deamination reaction progressed immediately as shown in Table 4. After gradually warming to room temperature for 60 min, the

Table 4. Deamination reaction of **9**



9

Reaction		Ratio by HPLC[a]		
Time (min)	Temperature (°C)	**9**	Intermediate	**TAK-603**
0	3	11	7	79
15	13	ND[b]	4	96
30	20	ND	1	98
60	25	ND	0.2	99

[a] Determined at 254 nm, YMC A-302 column, 50 mM KH_2PO_4/MeCN=55:45.
[b] ND, not detected.

reaction proceeded quantitatively. We speculate that the intermediate, observed on HPLC, is *N*-diazonium salt[7] as shown in Table 4.

2.3. Other improvements for process development

In order to develop a large scale practical preparation, other improvements have been made as shown in Scheme 2 against the former method as shown in Scheme 1, with the exception of the descriptions mentioned above. Concerning the N-acylation reaction, which produces **2** from **1**, sodium hydroxide was used as the base in the water solution instead of pyridine in the methylene chloride solution. Following this modification, it was able to precipitate **2** from the reaction mixture and omit the separation. Concerning the quinoline ring closure reaction, which produces **6**, after refluxing hydrochloride salt **8** in ethanol and the addition of triethyl amine, **6** was precipitated from the reaction mixture. Following this modification, it was able to avoid the chromatographic purification.

3. Conclusion

In conclusion, we have developed a large scale practical preparation method of **TAK-603** based on two main improvements, for example, the optimization of the Friedel–Crafts reaction and the selective substitution reaction of 1,2,4-triazole. Following our new procedure, multikilogram quantities of the bulk substance for toxicological and clinical studies have been prepared without requiring chromatographic purification.

4. Experimental

4.1. General

Melting points were determined on a Yanagimoto micro-melting point apparatus and were uncorrected. Infrared spectra were recorded on a Hitachi IR-215 spectrophotometer. NMR spectra were recorded on a Varian Gemini-200 spectrometer. ^{1}H chemical shifts were referenced to the internal deuterated solvent or tetramethylsilane. Elemental analysis were performed at Takeda Analytical Research Laboratories, Ltd. All commercial chemicals and solvents used were reagent grade and were used without further purification.

4.1.1. *N*-(3,4-Dimethoxyphenyl)acetamide (2). To a suspension of 3,4-dimethoxyaniline (**1**, 50.0 kg) in water (420 L) were alternately added a one-fifth portion of a solution (100 L) of sodium hydroxide (17.0 kg) in water and a one-fifth portion of acetic anhydride (43.3 kg) at less than 65 °C with stirring. After stirring for 20 min at 55–60 °C, the reaction mixture was cooled to about 5 °C and stirred for 1 h to precipitate crystals. The resulting crystals were collected by filtration, washed with water (200 L) and then dried at 50–60 °C for 7 h to give **2** (56.8 kg, yield 89%): mp 130–131 °C; IR (KBr): 1658, 1607, 1520, 1258, 1238 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.16 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 6.79 (d, J=8.4 Hz, 1H), 6.85 (dd, J=8.4, 2.0 Hz, 1H), 7.11 (br s, 1H), 7.30 (d, J=2.0 Hz, 1H).

4.1.2. 2-Acetylamino-3′,4,4′,5-tetramethoxybenzophenone (4). 3,4-Dimethoxybenzoic acid (**3**, 20.0 kg) was added to a suspension of **2** (19.6 kg) in polyphosphoric acid (20.5 kg) with stirring, the mixture was heated at 95–110 °C for 3 h, and then allowed to stand overnight at room temperature. To the mixture was added ice (30 kg) and cold water (500 L, 0–5 °C) at less than 80 °C with stirring and the mixture was extracted with ethyl acetate (530 L, 210 L×2). The extracts were combined and washed with a solution of sodium hydroxide (42.5 kg) in water (500 L) and concentrated in vacuo. After *n*-heptane (200 L) was added to the resulting residue, the mixture was stirred for 1 h at about 5 °C to precipitate crystals. The resulting crystals were collected by filtration, washed with a mixture of ethyl acetate (6 L) and *n*-heptane (24 L) and then dried at room temperature for 95 h to give **4** (23.6 kg, yield 66%): mp 129–130 °C; IR (KBr): 1693, 1610, 1590, 1529, 1518, 1270 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.22 (s, 3H), 3.76 (s, 3H), 3.93 (s, 3H), 3.97 (s, 3H), 4.00 (s, 3H), 6.92 (d, J=8.8 Hz, 1H), 7.08 (s, 1H), 7.27–7.34 (m, 2H), 8.38 (s, 1H), 11.04 (s, br s).

4.1.3. 2-Amino-3′,4,4′,5-tetramethoxybenzophenone hydrochloride (8) from 4. Hydrochloric acid (35%, 180 L) was added to a solution of **4** (50.7 kg) in *i*-butanol (600 L) and the mixture was refluxed for 2 h with stirring. The reaction mixture was cooled and allowed to stand overnight at room temperature and the mixture was stirred for 1 h at about 5 °C. The resulting crystals were collected by filtration, washed with *i*-butanol (180 L) and then dried in vacuo at 30–40 °C for 10 h to give **8** (46.8 kg, yield 94%): mp 172–173 °C; IR (KBr): 3430, 3305, 1621, 1590, 1535, 1510, 1250 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.70 (s, 3H), 3.91 (s, 3H), 3.92 (s, 3H), 3.95 (s, 3H), 6.01 (br s, 2H), 6.22 (s, 1H), 6.90 (d, J=8.6 Hz, 1H), 7.02 (s, 1H), 7.21–7.30 (m, 2H).

4.1.4. 2-Amino-3′,4,4′,5-tetramethoxybenzophenone hydrochloride (8) via 4 from 2. To a suspension of **2** (195.2 g) and **3** (200.4 g) in methylene chloride (800 mL) were added phosphorus oxychloride (766.6 g) and tin chloride (469.0 g) at less than 40 °C. After stirring for 24 h at 49 °C, methylene chloride (2 L) was added to the reaction mixture and cooled to about 10 °C. To the mixture was added water (5 L) at less than 35 °C with stirring and the mixture was extracted. The extract was washed with a solution of sodium hydroxide (60 g) in water (1.94 L) and water (2 L), and then concentrated in vacuo. After hydrochloric acid (35%, 1.154 L) and *i*-butanol (3.86 L) were added to the resulting residue, the mixture was stirred for 2 h at about 75 °C, and then the reaction mixture was stirred for 2 h at about 10 °C. The resulting crystals were collected by filtration, washed with *i*-butanol (1.16 L), and then dried in vacuo at 45 °C for 10 h to give **8** (314.9 g, yield 89% in two steps).

4.1.5. Ethyl 2-chloromethyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline-3-carboxylate (6). Ethyl 4-chloroacetoacetate (11.1 kg) was added to a solution

of **8** (18.1 kg) in ethanol (177 L) and the mixture was stirred for 3 h at 77–80 °C. After cooling, triethylamine (5.3 kg) was added to the reaction mixture and the mixture was stirred for 1 h at 5–15 °C. The resulting crystals were collected by filtration and washed with ethanol (35 L). The crystals were dissolved in dichloromethane (75 L) and the solution was washed with water (60 L×2) and concentrated in vacuo. Ethanol (50 L) was added to the residue and the solution was concentrated in vacuo to remove the residual dichloromethane. Ethanol (50 L) was added to the residue to precipitate crystals. The resulting crystals were collected by filtration, washed with ethanol (35 L) and then dried in vacuo at 40 °C for 8 h to give **6** (20.1 kg, yield 88%): mp 142–143 °C; IR (KBr): 1719, 1518, 1500, 1461, 1425, 1258 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.02 (t, J=7.2 Hz, 3H), 3.80 (s, 3H), 3.88 (s, 3H), 3.97 (s, 3H), 4.05 (s, 3H), 4.10 (q, J=7.2 Hz, 2H), 4.92 (d, J=11.0 Hz, 1H), 4.99 (d, J=11.0 Hz, 1H), 6.90–7.03 (m, 4H), 7.46 (s, 1H); Anal. Calcd for $C_{23}H_{24}NO_6Cl$: C, 61.95; H, 5.43; N, 3.14. Found: C, 61.92; H, 5.42; N, 2.90.

4.1.6. 4-Amino-1-[4-(3,4-dimethoxyphenyl)-3-ethoxycarbonyl-6,7-dimethoxyquinolin-2-ylmethyl]-4*H*-1,2,4-triazolium bromide (9). 4-Amino-1,2,4-triazole (5.0 kg) and sodium bromide (5.0 kg) were added to a suspension of **6** (19.6 kg) in *N*,*N*-dimethylformamide (43 L) and the mixture was stirred for 5 h at 63–67 °C. To the reaction mixture was added ethyl acetate (93 L) and the mixture was stirred for 1 h at 5–15 °C. The resulting crystals were collected by filtration, washed with ethyl acetate (176 L) and then dried in vacuo at 40 °C for 8 h to give **9** (20.0 kg, yield 79%): mp 183–184 °C; IR (KBr): 3196, 1706, 1518, 1472 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 0.92 (t, J=6.9 Hz, 3H), 3.72 (s, 3H), 3.77 (s, 3H), 3.86 (s, 3H), 3.96 (s, 3H), 3.72–4.09 (m, 2H), 5.94 (s, 2H), 6.93–7.31 (m, 7H), 9.28 (s, 1H), 10.41 (s, 1H); Anal. Calcd for $C_{25}H_{28}N_5O_6$-$Br(0.7H_2O)$: C, 51.15; H, 5.05; N, 11.93. Found: C, 51.10; H, 4.91; N, 11.88.

4.1.7. Ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(4*H*-1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate (TAK-603). To a suspension of **9** (20.0 kg) in water (267 L) were added hydrochloric acid (36%, 7.8 kg) and a solution of sodium nitrite (3.1 kg) in water (78 L) at less than 5 °C. After stirring for 3 h at 23 °C, the reaction mixture was adjusted to pH 6.7 with a solution of sodium hydroxide (3.1 kg) in water (15 L) at 10–20 °C. Acetone (73 L) was added to the mixture and the resulting crystals were collected by filtration, washed with a mixture of acetone (15 L) and water (76 L), and then dried in vacuo at 40 °C for 8 h to give **TAK-603** (15.7 kg, yield 94%): mp 174–175 °C; IR (KBr): 1719, 1519, 1502, 1463, 1258 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, J=7.2 Hz, 3H), 3.80 (s, 3H), 3.86 (s, 3H), 3.95 (q, J=7.2 Hz, 2H), 3.97 (s, 3H), 4.06 (s, 3H), 5.74 (s, 2H), 6.80–7.02 (m, 4H), 7.42 (s, 1H), 7.94 (s, 1H), 8.28 (s, 1H); Anal. Calcd for $C_{25}H_{26}N_4O_6$: C, 62.75; H, 5.48; N, 11.71. Found: C, 62.77; H, 5.52; N, 11.48.

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7. Generally, aromatic diazonium salts are stable as a solid and have explosive characteristics. In contrast to this, *N*-diazonium salts are unstable and there is no literature about their isolation and/or explosive nature.

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A quantum chemical study on the mechanism of chiral *N*-oxides-catalyzed Strecker reaction

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Abstract—The mechanism for the Strecker reaction of silyl cyanide (H_3SiCN) and benzaldehyde *N*-methylimine ($PhCH{=}NCH_3$) catalyzed by chiral 3,3′-dimethyl-2,2′-bipyridine *N*,*N*′-dioxide was investigated using the density functional theory (DFT) at the B3LYP/6-31G* level. The calculations revealed that the non-catalyzed reaction proceeded in a concerted way via a five-membered ring transition state, while the catalytic one occurred stepwisely via a hexacoordinate hypervalent silicate intermediate. It was predicted that both non-catalyzed and catalytic Strecker reactions involved two competitive reaction pathways, that is, addition followed by isomerization or isomerization followed by addition. The calculations indicated that two reaction pathways were comparable for both non-catalyzed and catalytic Strecker reactions. In the catalytic reaction, the strong electron donor (N–O) of chiral *N*-oxide played an important role in enhancing the reactivity and nucleophilicity of H_3SiCN by coordinating O atom to the Si atom of H_3SiCN. Chiral *N*-oxide could be used as a good catalyst for the reaction, which was in agreement with the experimental observations.

1. Introduction

Unnatural α-amino acids are expected to play key roles in improving the original properties and the functions of proteins; therefore, the development of efficient methods for the preparation of various types of α-amino acids has attracted considerable attention.[1] Recently, the hydrocyanation of imine (asymmetric Strecker reaction) has become one of the most intensively studied reactions because it is one of the most direct and viable strategies for the asymmetric synthesis of α-amino acids, which involves the reaction of cyanide with imines to produce α-amino nitriles—key intermediates for the synthesis of α-amino acids.[2–4] Several kinds of catalysts have been developed to obtain various α-amino nitriles using Strecker reaction.[5–12] Amine *N*-oxides are one of the most important catalysts among them.[2,13] Because of possessing notable electron-pair donating property,[14,15] amine *N*-oxides have been used in Strecker reaction as efficient catalysts to produce various α-amino nitriles with high yields under mild and practical conditions.[2,13]

A plenty of investigations suggested that the amine *N*-oxides exhibited significant nucleophilicity toward the silicon by coordinating Si atom to *N*-oxides[2,13] to form hypervalent silicon species with high reactivity. Nakajima and co-worker have employed the chiral biquinoline *N*,*N*′-dioxide in asymmetric reaction of aldehydes with allyltrichlorosilanes. The results suggested that the allylation proceeded via cyclic chair-like transition structure, involving hypervalent siliciate where one of two *N*-oxides occupied an axial position. Our previous experimental researches demonstrated the interaction between *N*-oxides and TMSCN by NMR information, and hypervalent silicon intermediate were predicted to be formed in the system.[13] Compared with the widely experimental studies, theoretical investigations on the Strecker reaction are currently very limited. And detailed catalytic performance of amine *N*-oxides in the Strecker reaction remains theoretically unclear.

To understand the mechanism of the Strecker reaction catalyzed by chiral *N*-oxides and provide useful information for the rational design and synthesis of new chiral *N*-oxides catalysts, theoretical investigations on the detailed mechanism for the reaction of benzaldehyde *N*-benzhydrylimine ($PhCH{=}NCHPh_2$) and trimethylsilyl cyanide (TMSCN) (Scheme 1) were performed using the B3LYP method in the present work.

Keywords: Strecker reaction; Chiral *N*-oxide; α-Amino nitriles; Hypervalent silicate.
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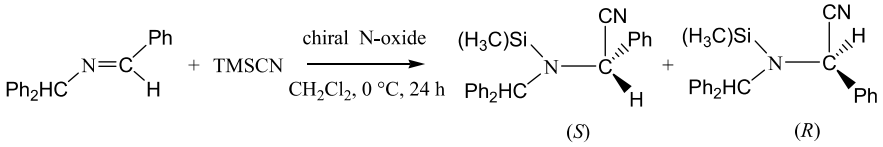
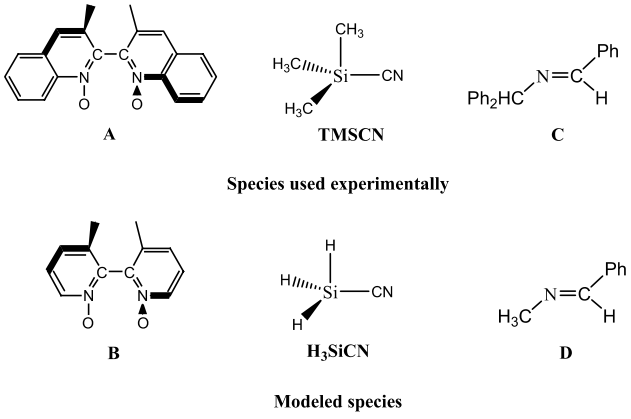


Scheme 1. The Strecker reaction catalyzed by chiral *N*-oxide.

2. Models and computations

Theoretical investigation aiming at the nature of the real catalytic processes based on quantum chemistry approach using gas phase model reaction has been shown to be a useful tool. Because the complexity of the real reaction system causes difficulties for high level computation, investigation on the gas phase reaction of small molecules as model has been adopted and provided very useful information on the reaction mechanism,[16–21] and some successful modeling computations have been performed on the Strecker reaction,[22–25] In the present work, therefore, model molecules were also employed to investigate the mechanism for the Strecker reaction of benzaldehyde *N*-benzhydrylimine ($PhCH{=}NCHPh_2$) and trimethylsilyl cyanide (TMSCN) catalyzed by chiral *N*-oxide **A**. As shown in Scheme 2, silyl cyanide (H_3SiCN) and 3,3′-dimethyl-2,2′-bipyridine *N*,*N*′-dioxide (**B**) were used, respectively, to substitute for TMSCN and 3,3′-dimethyl-2,2′-biquinoline *N*,*N*′-dioxide (**A**), and benzaldehyde *N*-methylimine ($PhCH{=}NCH_3$) (**D**) was used to substitute for benzaldehyde *N*-benzhydrylimine ($PhCH{=}NCHPh_2$) (**C**).



Scheme 2. Real molecules (**A**, TMSCN, **C**) and the corresponding model molecules (**B**, H_3SiCN, **D**) used in the present work.

All calculations were carried out using the Gaussian 03 program.[26] The geometries of all the reactants, products, intermediates and transition states for the Strecker reaction of benzaldehyde *N*-methylimine and H_3SiCN were optimized using the B3LYP method with the 6-31G* basis set. It was rather difficult to carry out intrinsic reaction coordination (IRC) calculation for such a large system. Hence, to confirm the relation between intermediates and transition states, the vibrational modes analysis corresponding to the unique imaginary frequency was adopted. In order to take into account the solvent effect, we also employed the self-consistent reaction field (SCRF) method based on the polarized continuum model (PCM)[27] for the Strecker reaction of benzaldehyde *N*-methylimine and H_3SiCN at B3LYP/6-31G* level. Unless otherwise specified, the single-point energies obtained in CH_2Cl_2 were used in the following discussion. In addition, natural bond orbital (NBO) analysis[28] was performed to obtain a further insight into the mechanism.

3. Results and discussion

The total energies and relative energies of various species in the $PhCH{=}NCH_3 + H_3SiCN$ reaction calculated at the B3LYP/6-31G* level were listed in Table 1. The optimized geometries of various species were depicted in Figures 1–4. In the present work, four reaction pathways (**a** to **d**) were involved. The energy diagrams along the reaction pathways from **a** to **d** were shown in Figures 5 and 6. Selected dominant Wiberg bond indices for each stationary point were presented in Table 2. Some important vibrational frequencies and the corresponding IR intensitives for the reactants, intermediates and transition states were listed in Table 3, and the frequencies were scaled by a factor of 0.963.[29] Experimental data indicated that the racemic α-amino nitriles would be produced in the absence of catalyst.[2,13] Therefore, the processes for the production of α-amino nitriles with (*S*) and (*R*) configuration might be similar. Thus, the following discussion was mainly focused on the pathways producing the (*S*)-enantiomer.

3.1. Investigations on the non-catalyzed Strecker reaction

As shown in Scheme 3, the calculations indicated that the racemic α-amino nitrile might be produced along two different reaction pathways (**a** and **b**), which was discussed, respectively, in detail as follows.

3.1.1. Pathway (a): isomerization followed by addition. The first reaction pathway (**a**) involved the isomerization of H_3SiCN to H_3SiNC firstly followed by the addition to $PhCH{=}NCH_3$ to produce the target α-amino nitrile via a five-membered ring transition state.

In this pathway, the calculations indicated that H_3SiCN was isomerized to H_3SiNC via a three-member ring transition state **TS1a** firstly. For **TS1a**, the distances of C and N to Si atom were 2.009 and 2.101 Å, respectively. The energy barrier for this step was as high as 30.4 kcal/mol, and the reactant H_3SiCN was 6.1 kcal/mol more stable than H_3SiNC. The possible isomerization process above in the present study was in agreement with the theoretical investigations on the mechanism of cyanide exchange for H_3SiCN reported by Wang et al.[30] The calculated characteristic vibrational frequencies for H_3SiCN and H_3SiNC were 2240 cm^{-1} (–C≡N stretch) and 2095 cm^{-1} (–N≡C stretch), respectively, which were close to the values of 2200 and 2098 cm^{-1} determined by Maier and

Table 1. Total energies E (Hartree), relative energies ΔE (kcal/mol) and relative Gibbs free energies ΔG (kcal/mol) in the gas phase and in CH_2Cl_2, respectively, for the stationary points

	E gas	ΔE gas	E solvent	ΔE solvent	ΔG solvent
Background reaction					
H_3SiCN	−384.10354		−384.13967		
$PhCH{=}NCH_3$	−364.85810		−365.01109		
H_3SiNC	−384.09432		−384.12988		
$H_3SiCN + PhCH{=}NCH_3$	−748.96164	0.0	−749.15076	0.0	0.0
TS1a + $PhCH{=}NCH_3$	−784.91636	28.4	−749.10228	30.4	29.1
$H_3SiNC + PhCH{=}NCH_3$	−748.95243	5.8	−749.14096	6.1	5.6
TS2a	−748.89653	40.9	−749.09574	34.5	48.3
P1a	−748.96962	−5.0	−749.162540	−7.4	7.8
TS1b	−748.89815	39.8	−749.096636	34.0	47.9
P1b	−748.94092	13.0	−749.133657	10.7	25.4
TS2b	−748.89799	39.9	−749.096039	34.3	47.2
Strecker reaction catalyzed by chiral *N*-oxide **B**					
B	−724.11569		−724.34517		
B + $H_3SiCN + PhCH{=}NCH_3$	−1473.07733	0.0	−1473.49593	0.0	0.0
$PhCH{=}NCH_3$ + **IM1c**	−1473.08636	−5.7	−1473.50682	−6.8	5.4
TS1c	−1473.04295	21.6	−1473.46747	17.9	47.3
IM2c	−1473.04750	18.7	−1473.47484	13.2	43.6
TS2c	−1473.03150	28.8	−1473.45976	22.7	52.9
IM3c	−1473.06116	10. 2	−1473.48223	8.6	35.8
B + **P1b**	−1473.05662	13.0	−1473.47882	10.7	25.4
TS2b + **B**	−1473.01369	39.9	−1473.44121	34.3	47.2
$PhCH{=}NCH_3$ + **TS1d**	−1473.04148	22.5	−1473.46064	22.1	33.1
$PhCH{=}NCH_3$ + **IM2d**	−1473.07641	0.6	−1473.49661	−0.4	10.3
TS2d	−1473.04004	23.4	−1473.46764	17.8	46.8
IM3d	−1473.04313	21.5	−1473.47161	15.3	45.8
TS3d	−1473.03115	29.0	−1473.46076	22.1	51.6
IM4d	−1473.08978	−7.8	−1473.51092	−9.4	18.0
B + **P1a**	−1473.08531	−5.0	−1473.50771	−7.4	7.8

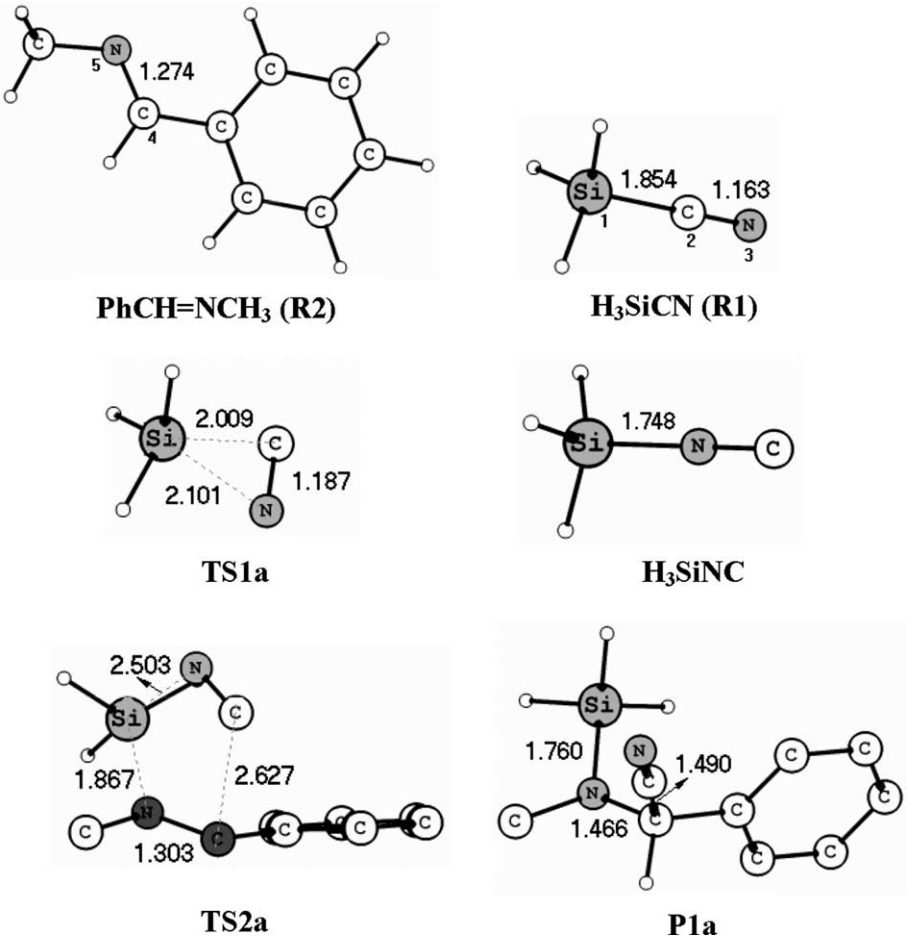


Figure 1. Optimized geometries of the stationary points along with pathway (**a**) in the absence of chiral *N*-oxide **B**.

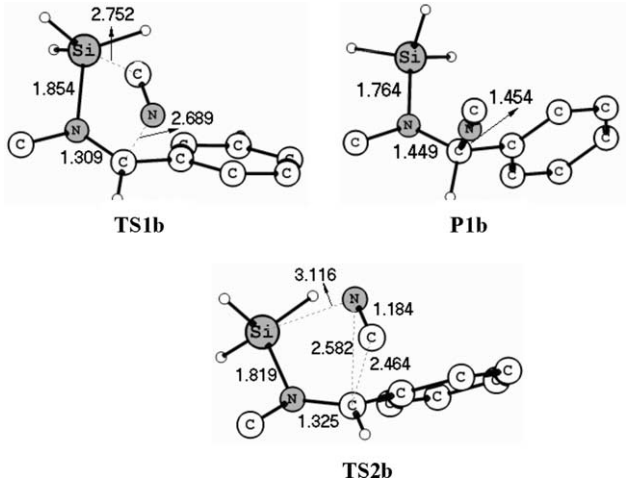


Figure 2. Optimized geometries of the stationary points along with pathway (**b**) in the absence of chiral *N*-oxide **B**.

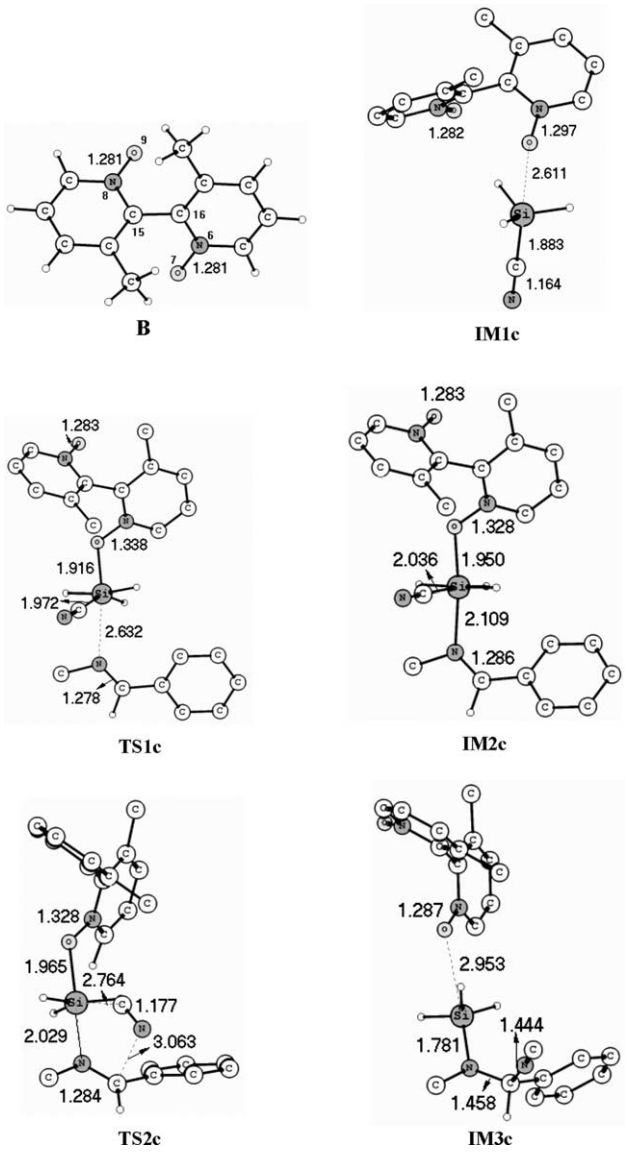


Figure 3. Optimized geometries of the stationary points along with pathway (**c**) in the presence of chiral *N*-oxide **B**.

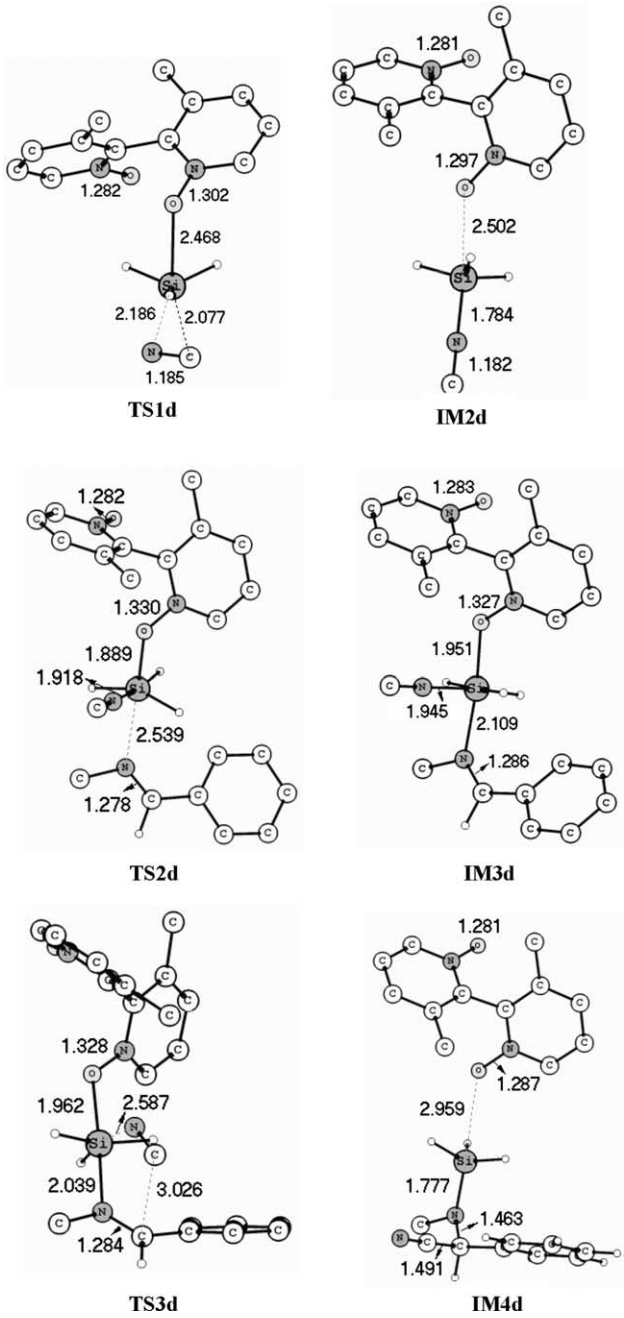


Figure 4. Optimized geometries of the stationary points along with pathway (**d**) in the presence of chiral *N*-oxide **B**.

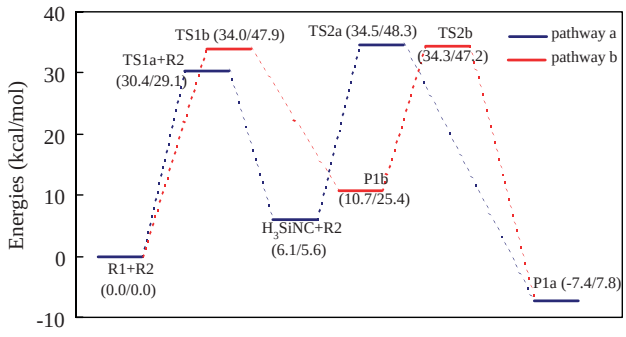


Figure 5. Relative energy/Gibbs free energy profiles for the Strecker reaction of PhCH=NCH$_3$ and H$_3$SiCN (in CH$_2$Cl$_2$) in the absence of chiral *N*-oxide **B** along the pathway (**a**) and (**b**) at the B3LYP/6-31G* level.

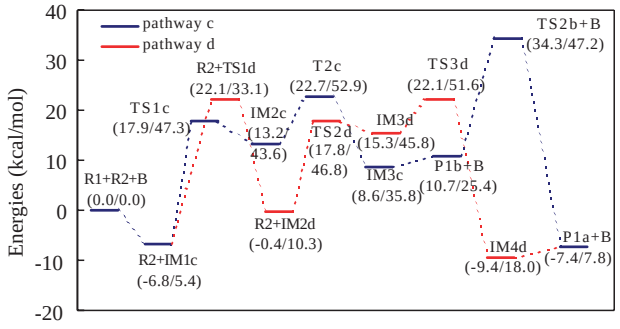


Figure 6. Relative energy/Gibbs free energy profiles for the Strecker reaction of PhCH═NCH_3 and H_3SiCN (in CH_2Cl_2) catalyzed by chiral *N*-oxide **B** along pathway (**c**) and (**d**) at the B3LYP/6-31G* level.

co-workers from photochemical experiments.[31] These results indicated that the present theoretical method of B3LYP/6-31G* was appropriate for this system. In order to testify the efficiency of the modeling molecule, the isomerization process for real reactant $(CH_3)_3SiCN$ was also investigated. Calculations indicated that the process of isomerization from TMSCN to TMSNC was similar to that for modeling molecule H_3SiCN. The energy barrier for the isomerization of TMSCN was 30.0 kcal/mol in CH_2Cl_2 and 27.9 kcal/mol in gas phase, respectively, which were close to those for H_3SiCN (30.4 kcal/mol in CH_2Cl_2 and 28.4 kcal/mol in gas phase).

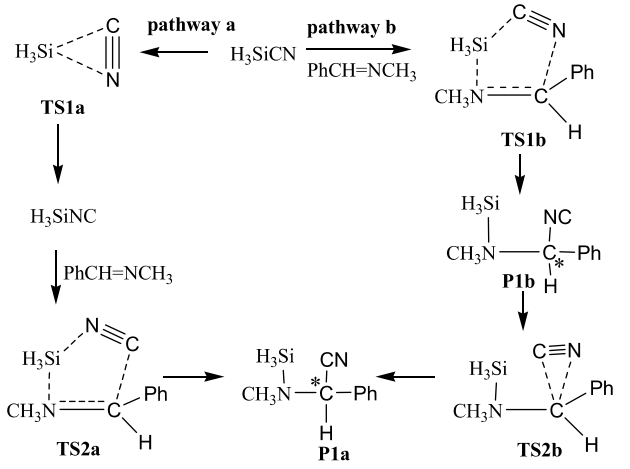
In the following step, the α-amino nitrile would be obtained by the addition of H_3SiNC to PhCH═NCH_3 via the transition state **TS2a**. The calculation gave an exothermicity of about

Table 2. Selected Wiberg bond indices for the stationary points at the B3LYP/6-31G* level

	N8–O9	N6–O7	Si1–C2	C2–N3	C4–N5	Si1–O7	Si1–N3	Si1–N5	C2–C4	N3–C4
B	1.281	1.281								
R1					1.844					
R2			0.846							
TS1a			0.538				0.333			
H_3SiNC							0.656			
TS2a					1.576			0.512	0.117	
P1a					0.973			0.679	1.011	
TS1b			0.201		1.539			0.521		0.069
P1b					1.003			0.675		0.915
TS2b					1.442			0.568	0.176	0.125
IM1c	1.278	1.217	0.797	2.938		0.078				
TS1c	1.276	1.091	0.635	2.902	1.815	0.368		0.147		
IM2c	1.276	1.118	0.562	2.899	1.753	0.335		0.317		
TS2c	1.271	1.117	0.196	2.855	1.736	0.325		0.356		0.010
IM3c	1.280	1.256		2.411	1.014	0.048		0.627		0.908
TS1d	1.280	1.197	0.480				0.279			
IM2d	1.282	1.217		2.421		0.111	0.592			
TS2d	1.278	1.100		2.541	1.809	0.368	0.414	0.167		
IM3d	1.277	1.121		2.570	1.755	0.336	0.397	0.315	0.003	
TS3d	1.270	1.118		2.700	1.734	0.326	0.147	0.351	0.024	
IM4d	1.280	1.257		2.912	0.981	0.047		0.633	1.011	

Table 3. Selected vibrational frequencies (cm^{-1}) and IR intensities (Debye^2/amu Å^2) for all the species involved in the reaction of H_3SiCN and PhCH═NCH_3 catalyzed by chiral *N*-oxide **B**

	Frequencies (cm^{-1})/IR intensities, Debye^2/amu (Å^2)									
	N8–O9	N6–O7	Si1–C2	C≡N	C4–N5	Si1–O7	Si1–N3	Si1–N5	C2–C4	N3–C4
B	1309/179.5	1309/179.5								
R1			581/36.6	2240/10.3						
R2					1679/85.0					
TS1a			517/96.7	2015/5.4						
H_3SiNC				2095/294.3			650/66.6			
TS2a				2065/45.7	1594/222.3			559/4.8		
P1a				2262/1.5	1189/35.1			649/12	912/22.2	
TS1b				2070/22.8	1561/221.8			571/7.9		
P1b				2123/130.5	1196/67.9			648/12.1		895/93.3
TS2b				2037/14.2	1525/273.3			629/6.8		
IM1c	1281/132.7	1311/85.3	538/140.7	2228/5.8		49/2.1				
TS1c	1217/25.9	1312/80.0	429/93.2	2182/2.7	1666/122	591/71.3				
IM2c	1224/44.6	1312/78.8	412/41.3	2173/0.3	1650/165.8	593/86.6		271/58		
TS2c	1227/36.3	1309/76.3		2095/6.8	1655/183.5	591/75.9		280/128.9		
IM3c	1300/172.8	1314/60.9		2121/129.6	1198/84.8			643/10		881/95.5
TS1d	1274/120.7	1311/84.6	428/291.5	2030/5.2						
IM2d	1283/139.8	1314/83.5		2097/335.6		44/14.0				
TS2d	1234/47.4	1310/8/0.2		2092/154.4	1665/113.9	613/131.9	398/77.2			
IM3d	1225/37.9	1313/78.2		2101/118.1	1651/159.9	593/91.2	414/66.1	289/51.0		
TS3d	1227/35.8	1308/76.4		2055/37.1	1654/167.3	591/82.2		279/44.9		
IM4d	1301/173.6	1314/60.2		2258/2.3	1198/84.8			646/8.9	908/55.6	



Scheme 3. Two different reaction pathways (**a** and **b**) to produce α-amino nitrile in the absence of a catalyst.

13.5 kcal/mol, and an energy barrier of 28.4 kcal/mol for this step. For **TS2a**, the Si1–N5 distance of 1.867 Å was close to that for the product **P1a** (1.760 Å). The distance of N5–C4 was remarkably larger than that of the reactant, and the Wiberg bond index of N5–C4 bond was decreased from 1.844 to 1.576. These results indicated that the N=C double bond for the imine was intensively weakened in the transition state **TS2a**. The transition vector of the unique imaginary frequency indicated that the C2 of –CN group got gradually close to C4 and N3 of –CN group moved away from Si1, indicating that the transition state obtained was actually connected with the starting reactant and terminating product as expected.

3.1.2. Pathway (b): addition followed by isomerization. The second reaction pathway to provide the target product α-amino nitrile involved two steps. Firstly, H_3SiCN was reacted with $PhCH{=}NCH_3$ to produce α-amino isonitrile via the transition state **TS1b**. Subsequently, α-amino isonitrile (**P1b**) would be isomerized to α-amino nitrile (**P1a**) via the transition state **TS2b**.

For the transition state **TS1b**, the N5–C4 distance was increased from 1.274 to 1.309 Å, indicating that C=N double bond had been weakened. The Si1–C2 and N3–C4 distances were 2.752 and 2.689 Å, respectively. The energy barrier for the addition of H_3SiCN to $PhCH{=}NCH_3$ was 5.6 kcal/mol higher than that for the addition of H_3SiNC to $PhCH{=}NCH_3$. It was turned out that H_3SiNC was more reactive than H_3SiCN though the former was less stable than the latter.

Next, α-amino isonitrile (**P1b**) would be isomerized to α-amino nitrile (**P1a**) via the transition state **TS2b**. **TS2b** beared close resemblance to **TS2a**, but the distance of N3–Si1 in **TS2b** was 3.116 Å, longer than that in **TS2a**. Si1 atom in **TS2b** was closer to N5 atom than that in **TS2a**, and the vibrational mode of the unique imaginary frequency of 201 cm^{-1} indicated that N3 moved away from C4 and C2 got close to C4 atom.

3.1.3. The mechanism of the non-catalyzed reaction. *Comparison of the activity between H_3SiCN and H_3SiNC*

The facile equilibrium between C-bonded and N-bonded cyanotrialkylsilane has been verified by the spectroscopic studies of Booth and Frankiss.[32] Although the equilibrium concentration of isocyanide in the organic solution is generally low, it is possible for H_3SiNC to participate in the reaction of cyanosilylation of aldimines as a silylcyanide reagent. The positive charge accumulated on Si atom in H_3SiNC is larger than that in H_3SiCN, indicating stronger electrophilicity of Si atom in H_3SiNC. As a result, H_3SiNC may carry out addition reaction more easily than H_3SiCN, which can be verified by the lower energy barrier for the addition of –NC group to C=N double bond. Therefore, H_3SiNC is more reactive than H_3SiCN in the reaction of cyanosilylation of aldimines, and a greater electropositive character of the silicon atom in H_3SiNC has been suggested to be responsible for its increased reactivity.

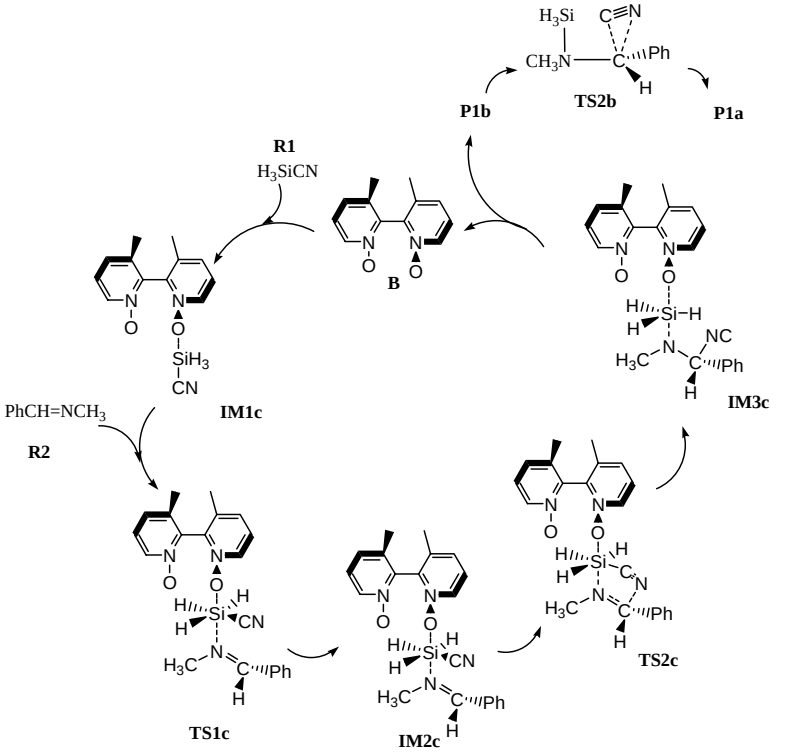
Comparison of the two pathways for the non-catalyzed Strecker reaction

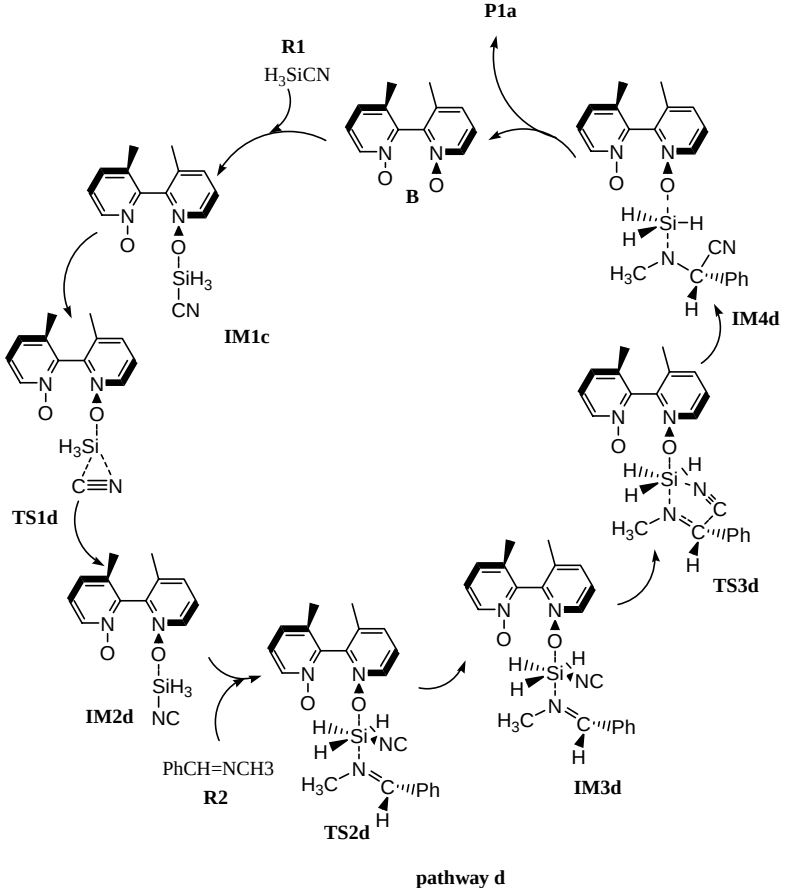
It was noted that the structure of **TS1b** obtained in the present calculation was similar to that of the transition state obtained by Cativiela et al.[22] However, the intermediate containing high coordinated silicon atom presumed by Cainelli et al.[33] was not located as a minimum in the present work. According to the NBO analysis, there were strong interactions between Si1–C2–N3–C4–N5 (or Si1–N3–C2–C4–N5) five atoms in the transition states **TS1b** (or **TS2a**). Therefore, it was reasonable to consider that the reaction was a concerted one, forming five-membered ring transition state. The calculations predicated that the energy barriers of RDS for pathway (**a**) and (**b**) were 35.1 and 39.8 kcal/mol, respectively, and the rate-determining-step (RDS) for both pathways (**a**) and (**b**) was the nucleophilic attack step, that is, the addition of –NC or –CN groups to C=N double bond in the gas phase. Compared with the results obtained in gas phase, the solvent effects significantly lowered the energy barrier of the RDS in CH_2Cl_2 (the energy barrier of the RDS for pathway (**a**) was 30.4 kcal/mol, while that for pathway (**b**) was 34.0 kcal/mol). As shown in Figure 5, the calculations predicted that the relative energies of the highest transition states for pathway (**a**) and (**b**) were similar either in the solvent or in the gas phase. Thus two reaction pathways were competitive with comparable energy maximum. In general, the energy barriers for the addition of –CN or –NC group to C=N double bond were very high for both pathway (**a**) and (**b**) in the absence of a catalyst.

3.2. Investigations on the Strecker reaction catalyzed by chiral *N*-oxide B

It was found experimentally that chiral *N*-oxides were catalytically active for asymmetric cyanosilylation of aldimines.[2,13] The calculations indicated that the production of α-amino nitrile would be realized along two different reaction pathways (**c** and **d**) (as shown in Scheme 4) catalyzed by chiral *N*-oxide **B**, in which the chiral *N*-oxide **B** played a key role to lower the energy barriers of the addition for –CN or –NC group to C=N double bond.

3.2.1. Pathway (c): addition followed by isomerization. In this pathway, H_3SiCN was coordinated to the chiral *N*-oxide **B** and then reacted with $PhCH{=}NCH_3$ to form hexacoordinate silicon species. Next, the cyano group attacked the imine to produce the α-amino isonitrile, which was then isomerized to target α-amino nitrile.





Scheme 4. Two different reaction pathways (**c** and **d**) to produce α-amino nitrile (**P1a**) in the presence of chiral *N*-oxide **B**.

For the reaction pathway (**c**), chiral *N*-oxide **B** was interacted firstly with H_3SiCN, leading to the formation of binary molecular complex **IM1c**, which was stabilized by the interaction between O atom of chiral *N*-oxide **B** and the Si atom of H_3SiCN. For the **IM1c**, the N6–O7 bond interacting directly with H_3SiCN became longer (1.281→1.297 Å), and the negative charge on O7 was increased (−0.529*e*→−0.570*e*). The Si1–C2 distance was longer than that of free H_3SiCN, indicating that Si1–C2 chemical bond was weakened in the binary molecular complex. The charge for the H_3SiCN moiety was −0.06*e*, indicating that the formation of **IM1c** resulted in partial charge transfer from the chiral *N*-oxide **B** moiety to the H_3SiCN moiety. It should be noted that the binary molecular complex **IM1c** was somewhat different from the hypothetical one proposed experimentally, in which the formation of six-coordination hypervalent silicate species by coordinating two O atoms of chiral *N*-oxide to Si atom of TMSCN simultaneously was proposed.[13]

Then, PhCH=NCH_3 was drawn close to the **IM1c** to form stable intermediate **IM2c** via the transition state **TS1c**. This step involved an energy barrier of 24.7 kcal/mol. For the intermediate **IM2c**, C4–N5 and Si1–C2 distances were elongated remarkably, and the Wiberg bond indices of Si1–C2 and C4–N5 were decreased. These results indicated that Si1–C2 and C4–N5 bonds were activated remarkably. **IM2c** was a hexacoordinate silicon species with a greater electropositive character on the hypervalent silicon atom, indicating the increased polarity for Si1–C2 bond. The increase of negative charge on –CN group indicated that the nucleophilicity of –CN group was enhanced.

Next, the highly reactive cyano group attacked the imine to produce **IM3c** via the transition state **TS2c**. The energy barrier for this step was 9.5 kcal/mol, which was remarkably lower than that for the background reaction. For the transition state **TS2c**, Si1–C2 and N3–C4 distances were 2.764 and 3.063 Å, respectively. The vibrational mode of the unique imaginary frequency of 125 cm^{-1} was corresponding to that cyano group was gradually closer to C4 and further away from Si1.

Intermediate **IM3c** could be regarded as the complex formed by chiral *N*-oxide **B** and α-amino isonitrile. The geometrical structure of α-amino isonitrile moiety was very similar to that of free α-amino isonitrile (**P1b**). In the following step, the chiral *N*-oxide **B** was regenerated by leaving the α-amino isonitrile moiety with 2.1 kcal/mol energy gain respected to **IM3c**. The α-amino isonitrile (**P1b**) would be isomerized to target product α-amino nitrile (**P1a**), which was the same as the isomerization process in the pathway (**b**) without chiral *N*-oxide **B**.

3.2.2. Pathway (d): isomerization followed by addition. The calculations indicated that the target product—α-amino nitrile (**P1a**) could also be obtained along with the competitive reaction pathway (**d**), in which H_3SiCN was isomerized to H_3SiNC initially catalyzed by chiral *N*-oxide **B** to produce the intermediate **IM2d**. The energy barrier for the catalytic isomerization of H_3SiCN to H_3SiNC was slightly lower than that without the catalyst, and the energy difference between the binary complexes of H_3SiCN and H_3SiNC with the chiral *N*-oxide **B** was 6.4 kcal/mol, which was slightly higher than the energy difference of 6.1 kcal/mol between H_3SiCN and H_3SiNC. Therefore, the chiral *N*-oxide **B** exerted little influence on the isomerization of H_3SiCN to H_3SiNC.

For the transition state **TS1d**, Si1–C2 and Si1–N3 distances were 2.077 and 2.186 Å, respectively, longer than those for **TS1a**. NBO analysis indicated that there existed interaction in the Si1–C2–N3 three-member ring. Though the energy barrier for this step was rather high, the intermediate **IM2d** was more reactive than **IM1c** because of the greater electropositive character of Si atom. The possibility for the formation of isocyanide as a reactive intermediate in the reaction has also been reported recently in some experimental investigations.[34,35]

For **IM2d**, the higher Wiberg bond index than that for **IM1c** indicated that there was strong interaction between O7–Si1. This effect would weaken the interaction between Si1–N3 and lead to the elongation of Si1–N3 bond. In the following step, PhCH=NCH_3 was drawn close to **IM2d** to form the intermediate **IM3d** via the transition state **TS2d**. The energy barrier for this step was 18.2 kcal/mol.

IM3d was a hexacoordination silicate similar to that for **IM2c**. However, the natural charge for –NC group was −0.693*e*, which was greater than the corresponding value for **IM2c**. This result indicated that the nucleophilicity for –NC group in **IM3d** was stronger than that for –CN group in **IM2c**, which could be verified by the lower energy barrier to carry out nucleophilic attack for imine via the transition state **TS3d**.

The structure of **IM4d** could be regarded as the molecular complex formed by chiral *N*-oxide **B** and the target product α-amino nitrile. In the final step, the chiral *N*-oxide **B** was cleaved from the α-amino nitrile moiety by 2.0 kcal/mol energies gain with respect to **IM4d**.

3.2.3. The reaction mechanism catalyzed by chiral *N*-oxides B. *Comparison of two reaction pathways*. Two competitive pathways (**c** and **d**) for the reaction of H_3SiCN and PhCH=NCH_3 catalyzed by chiral *N*-oxide **B** to furnish α-amino nitrile were rationalized. In the reaction pathway (**c**), the step corresponding to the formation of the three-member complex **IM2c** was predicted to be the rate-determining-step (RDS). In the pathway (**d**), the reaction step from **IM1c** to **IM2d**, which was corresponded to the step of the H_3SiCN isomerizing to H_3SiNC catalyzed by chiral *N*-oxide **B**, was predicted to be the rate-determining-step (RDS) in CH_2Cl_2. Compared with the results obtained in gas phase, the energy barriers of RDS of 24.7 kcal/mol for pathway (**c**) in solvent was lower than the corresponding RDS of pathway (**d**). Although the energy barrier of RDS for pathway (**d**) calculated in CH_2Cl_2 was slightly higher than that in gas phase, the energy maximum along the reaction pathway (**d**) (22.1 kcal/mol for **TS1d**+**R2**) was lower than the energy maximum along the reaction pathway (**c**) (34.3 kcal/mol for **TS2b**). Thus, the solvent had exerted significant influences on the reaction.

Role of the chiral N-oxides **B**. In contrast to carbon, silicon has a marked tendency to increase its coordination number,

and the structures for some penta- and hexacoordinate silicon compounds have been characterized by X-ray diffraction.[36,37] Though the classification of chemical bonds in the multicoordinate silicon remains controversial,[38] the enhanced reactivity for them have been proved by experimental data.[36,37,39] Since amine *N*-oxides are known to exhibit a significant nucleophilicity toward the silicon, some hypervalent silicate intermediates or transition states formed by the O atom of amine *N*-oxides coordinating to Si atom have been proposed in some processes using amine *N*-oxides as the catalyst.[13,15,40,41] For the Strecker reaction between aldimines and trimethylsilyl cyanide catalyzed by chiral *N*-oxides, a mechanistic hypothesis involving the hexacoordinate hypervalent silicate intermediate has been suggested.[13]

The present calculations predicted that chiral *N*-oxide **B** had C_2 symmetry and its dihedral angle of $D_{8\text{–}15\text{–}16\text{–}6}$ was $-113.2°$. The N–O bond was coplanar with aromatic rings in the quinoline and there existed conjugative interactions between them. However, N^+–O^- group was strongly polarizable and the electron density on O atom was higher, which facilitated O atom to interact with the Si atom. This effect would weaken the Si1–C2 bond, leading to the elongation of Si1–C2 distance. As a result, the energy barrier of the isomerization from cyano to isocyano for H_3SiCN moiety was lowered. Compared with the charge on the Si atom for binary complexes of **IM1c** and **IM2d**, the larger electropositive character for Si1 in **IM2d** indicated its stronger electrophilicity, which was in agreement with the lower energy barrier for **IM2d** to form hexacoordinate silicate **IM3d**.

Three-membered complexes **IM3d** and **IM2c** shown in Figures 3 and 4 displayed a similar and somewhat distorted octahedral geometry. Six atoms in the H_3SiCN were almost in the same plane, and the chiral *N*-oxide **B** and imine with larger volume occupied the axial position. Si1–O7 and Si1–N5 distances were in the range normally observed for hexacoordinate silicon compounds.[36] Therefore, they could be treated as hexacoordinate silicate species. Based on the larger Wiberg bond indices for Si1–O7 and Si1–N5, there was strong interactions between chiral *N*-oxide **B** and imine with H_3SiCN, which led to the changes of the stretching modes for N6–O7 of chiral *N*-oxide **B** participating in coordination and for C=N double bond of imine. According to the vibrational analysis, frequencies of 1313 and 1312 cm^{-1}, which were assigned to the asymmetric stretching modes of N6–O7 for **IM3d** and **IM2c**, respectively, were lower than that for free chiral *N*-oxide **B**. Frequencies of 1651 and 1650 cm^{-1}, which were assigned to the asymmetric stretching modes of C=N bond for **IM3d** and **IM2c**, respectively, were lower than that for free imine. According to atomic natural charges of **IM3d** and **IM2c**, there was a charge transfer from O atom of chiral *N*-oxide **B** and N atom of imine to H_3SiCN moiety, and afterward it resulted in a total transfer of 0.342*e* for **IM3d** and 0.357*e* for **IM2c**, respectively, from *N*-oxide **B** and imine moieties to H_3SiCN moiety. This effect would strengthen the interactions between O7 and N5 atoms with Si1 atom and weaken the interaction between Si1 and –NC or –CN group, leading to the elongation of the Si–N(C) or Si–C(N) bond. Simultaneously, the nucleophilicities of the isocyano group or cyano group were enhanced. Consequently, the energy barriers for the attack of –NC or –CN group to C4 atom of imine were lower remarkably than that in the absence of chiral *N*-oxide **B**.

In all, chiral *N*-oxide played a key role for the initial activation of Si–C bond by coordinating O atom to Si atom of silyl cyanide (or silyl isocyanide) and the stabilization of three-membered complex (**IM2c** and **IM3d**). As a result, the energy barrier was decreased remarkably and the reaction was carried out more easily. The formation of hexacoordinate silicate species was very important for the activation of Si1–C2 or Si1–N3 bond, making –CN (or –NC) group more nucleophilic.

4. Conclusion

The main results can be summarized as follows:

1. For the background reaction in the absence of chiral *N*-oxide **B** catalyst, the racemic α-amino nitrile may be produced along two different reaction pathways. The calculations indicated that the two reaction pathways were competitive with comparable energy maximum.
2. For the reaction catalyzed by chiral *N*-oxide **B**—3,3′-dimethyl-2,2′-bipyridine *N*,*N*′-dioxide, although the energy barriers of RDS for pathway (**c**) in solvent was lower than the corresponding RDS of pathway (**d**), the energy maximum along the reaction pathway (**d**) (22.1 kcal/mol for **TS1d**+**R2**) was lower than the energy maximum along the reaction pathway (**c**) (34.3 kcal/mol for **TS2b**). Thus, the two reaction pathways were also comparable.
3. The strong electron donor (N–O) of chiral *N*-oxide **B** played an important role in enhancing reactivity and nucleophilicity of H_3SiCN. The hexacoordinate hypervalent silicate was a stable intermediate. The formation of such hexacoordinate hypervalent silicate intermediate could enhance intensively the nucleophilicity of –NC or –CN group and lower the energy barriers of addition reaction. As a consequence, it facilitated the production of the target α-amino nitrile.

In short, the information obtained from the present work may be useful to investigate further the origin of chiral control for chiral *N*-oxide and provide some hints for the design and synthesis of novel chiral *N*-oxides catalysts for Strecker reaction.

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Facile one-pot syntheses of bromoacetylenes from bulky trialkylsilyl acetylenes

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Abstract—Because haloalkynes are versatile intermediates in synthetic chemistry, the development of new efficient methods for the conversion of 1-trialkylsilylacetylenes to haloacetylenes in situ remains desirable, especially when the corresponding terminal acetylenes are unstable. Using AgF and NBS, we have successfully transformed various 1-(trialkylsilyl)acetylenes, including bulky trialkylsilyl acetylenes, into bromoacetylenes in high yield. The reactions are chemoselective: triisopropylsilyl ethers were not deprotected under these conditions.

1. Introduction

Haloalkynes are useful and versatile intermediates in a variety of organic transformations. They can be used as precursors for the generation of organometallic acetylides, α-keto acid esters, vinyl halides, vinyl organometallic compounds, and other functional groups (Fig. 1);[1] they can also been used as substrates for a variety of metal-mediated coupling reactions.[2] One of the most convenient approaches to the preparation of haloalkynes is the halogenation of terminal acetylenes.[3]

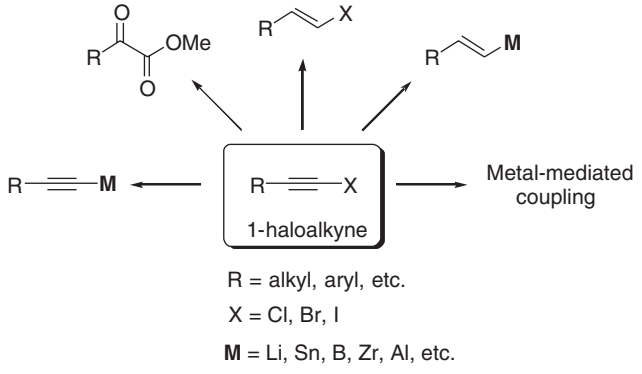

Figure 1. Reaction of haloalkynes.

As part of our ongoing program aimed at the preparation of unsymmetrical polyynes for use in the syntheses of natural products and organic materials, we needed a method to convert 1-(trialkylsilyl)acetylenes into bromoacetylenes. Conceivably, this transformation could be achieved by a protiodesilylation of silyl-protected acetylenes and subsequent halogenation of the resulting terminal acetylenes.[4] Although effective methods are available for this two-step sequence, the major limitation of this conventional approach is the instability of many terminal acetylenes, especially terminal diynes and higher polyynes.[1a,5] To avoid the complications encountered when attempting to isolate sensitive terminal alkynes, we preferred to employ an in situ one-pot desilylative bromination.

In 1994, Isobe and co-workers reported the direct conversion of trimethylsilyl (TMS)-protected acetylenes to haloacetylenes through the use of a catalytic amount of $AgNO_3$ and a halogen source, such as NBS or NIS.[6] This convenient method, which is mild enough to accommodate substrates possessing many different functionalities, has been applied widely in the synthetic community.[7] Unfortunately, this system is effective only for TMS-protected acetylenes and not for bulkier (trialkylsilyl)acetylenes,[4,7a] presumably because of the increased stability of bulkier silyl groups. Under similar conditions, the use of the more highly soluble CF_3CO_2Ag and NBS also leads to the direct desilylative bromination of TMS- and (hydroxypropyl)-silyl-protected acetylenes.[8]

Although less-bulky silyl groups, such as TMS or triethylsilyl (TES) units, are used classically as protecting groups for terminal acetylenes, relatively bulkier

Keywords: Haloalkyne; Trialkylsilyl acetylene; Desilylative bromination; AgF.
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trialkylsilyl protecting groups are also very useful synthetically because the more sterically hindered carbon–carbon triple bonds and carbon–silicon single bonds are inert toward a variety of reagents.[9] As far as we are aware, the direct desilylative bromination of bulky 1-trialkylsilylacetylenes has not been reported previously.[10] In this paper, we present what we believe to be the first example of a technique for the in situ conversion of bulky 1-(trialkylsilyl)acetylenes into 1-bromoacetylenes.[11]

2. Results and discussion

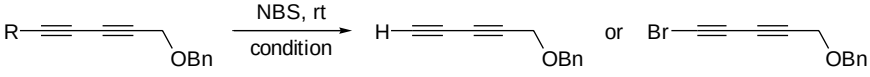
As expected, our initial attempts to effect the in situ desilylative bromination of triisopropylsilyl (TIPS)-protected acetylene **1a**[11] using Isobe's standard NBS/$AgNO_3$ conditions (entry 1, Table 1) led to the recovery only of the starting material. The addition of an oxygenated base, such as NaOH in acetone and K_2CO_3 in THF (entries 2 and 3), to the NBS/$AgNO_3$ mixture also proved futile. Therefore, we chose to use a fluoride source to remove the bulky TIPS group, triggered by the known high affinity of fluoride ions toward silicon atoms. When using a commercial THF solution of tetrabutylammonium fluoride (TBAF) in the presence of a catalytic amount of $AgNO_3$ (0.1 equiv) and a slight excess of NBS (1.2 equiv) in DMF, protiodesilylation occurred, instead of the expected desilylative bromination, to give the terminal acetylene **2** in 73% yield (entry 4). Employing a large excess of NBS (4 equiv), however, led to the formation of the desired bromoacetylene **3**[11] in high yield (95%) either in the presence or absence of $AgNO_3$ (entries 5 and 6, respectively).

Although this NBS/TBAF system permits the facile direct desilylative bromination of bulky 1-(trialkylsilyl)-acetylenes, the basicity of TBAF and use of excess NBS could limit functional group tolerance. Thus, we needed to develop alternative conditions for the reaction. Exposure of **1a** to inorganic fluoride sources, namely CsF, NaF, and AlF_3 (entries 7–9), in the presence of a catalytic amount of $AgNO_3$ and a slight excess of NBS (1.2 equiv) in MeCN resulted in the recovery of the starting material only. On the other hand, when we employed AgF as the fluoride source we obtained the desired bromoacetylene **3** in 99% yield at room temperature (entry 10). Because the redundancy of the additional silver ions in the $AgNO_3$/AgF/NBS system, we found that $AgNO_3$ could be removed from the system to give the desired product **3** in 95% yield (entry 11).

To explore the scope of this AgF/NBS reaction system, we examined the use of other solvents and substrates. Among the solvents examined, DMF gave similar results (91% yield, entry 12) to those obtained using MeCN, but the use of acetone, DMSO, and THF did not yield the desired product **3** presumably because of the low solubility of AgF in those solvents (entries 13–15). Under the optimal reaction conditions (AgF/NBS/MeCN), the acetylenes **1b** and **1c**, which contained TBS and TES protecting groups, respectively, were also smoothly converted to the bromoacetylene **3** in very high yields (entries 16 and 17). Moreover, this system was also effective for converting other substrates (**4a** and **4b**) into their corresponding bromoacetylenes (**5a**[12] and **5b**) in good yields (Scheme 1).

Most interestingly, this AgF/NBS reaction system is chemoselective.[13] Under the optimized conditions, the

Table 1. Desilylative bromination of 1-trialkylsilyl acetylenes[a]

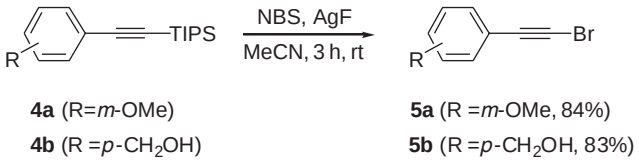


1a (R = TIPS)
1b (R = TBS)
1c (R = TES)

2 **3**

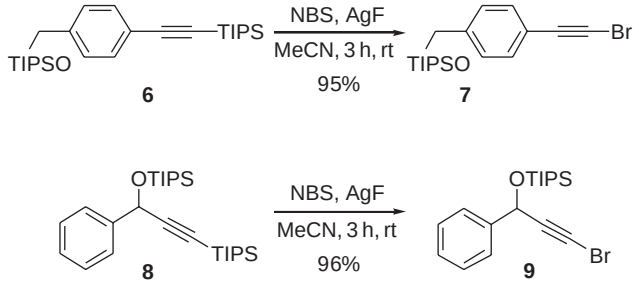
Entry	Reactant	Catalyst	Reagent	NBS (equiv)	Solvent	Product	Yield (%)[b]
1	**1a** (R = TIPS)	$AgNO_3$	—	1.2	Acetone	nd[c]	—
2	**1a**	$AgNO_3$	NaOH	1.2	Acetone	nd	—
3	**1a**	$AgNO_3$	K_2CO_3	1.2	THF	nd	—
4	**1a**	$AgNO_3$	TBAF	1.2	DMF	**2**	73
5	**1a**	$AgNO_3$	TBAF	4.0	DMF	**3**	95
6	**1a**	—	TBAF	4.0	DMF	**3**	95
7	**1a**	$AgNO_3$	CsF	1.2	MeCN	nd	—
8	**1a**	$AgNO_3$	NaF	1.2	MeCN	nd	—
9	**1a**	$AgNO_3$	AlF_3	1.2	MeCN	nd	—
10	**1a**	$AgNO_3$	AgF	1.2	MeCN	**3**	99
11	**1a**	—	AgF	1.2	MeCN	**3**	95
12	**1a**	—	AgF	1.2	DMF	**3**	91
13	**1a**	—	AgF	1.2	Acetone	nd	—
14	**1a**	—	AgF	1.2	DMSO	nd	—
15	**1a**	—	AgF	1.2	THF	nd	—
16	**1b** (R = TBS)	—	AgF	1.2	MeCN	**3**	91
17	**1c** (R = TES)	—	AgF	1.2	MeCN	**3**	95

[a] All reactions were performed on 0.1–0.3 mmol scale. Conditions; 0.1 equiv of catalyst, room temperature, 2–3 h.
[b] Isolated yield.
[c] nd = not dectected.



Scheme 1.

TIPS-protected acetylenes **6** and **8**, which also contained TIPS-protected hydroxyl groups, formed their corresponding bromoacetylenes **7** and **9** in very high yields without any notable *O*-silyl group removal (Scheme 2).



Scheme 2.

3. Conclusion

In conclusion, we have developed an efficient method for the in situ conversion of 1-(trialkylsilyl)acetylenes to bromoacetylenes through the addition of a fluoride source to Isobe's standard NBS/Ag^+ conditions. The optimized reaction conditions (AgF and NBS in MeCN or DMF) afforded high yields of bromoacetylenes from various substrates. This new method provides efficient access to synthetically useful haloalkynes, especially when unstable terminal acetylenes are involved.

4. Experimental

4.1. General

All reagents and solvents were purchased from commercial sources and used without further purification unless otherwise stated. Reactions were monitored through TLC analysis using Merck silica gel 60 F-254 thin layer plates. Flash column chromatography was carried out on Merck silica gel 60 (230–400 mesh). Compounds were visualized on TLC plates under UV light and by spraying with $KMnO_4$ or anisaldehyde solutions. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded in δ units relative to deuterated solvent as internal reference by Varian 300 MHz NMR instrument. Mass spectra (MS) were recorded at 70 or 30 eV using electron impact (EI) and chemical ionization (CI). High-resolution mass spectra (HRMS) were recorded using EI and CI.

4.1.1. General procedure for preparing 1-(trialkylsilyl)-diynes (1). To a degassed solution of 1-bromo-3-(benzyloxy)prop-1-yne[3,11,14] (1.0 equiv), (trialkylsilyl)acetylene (1.2 equiv), $Pd(PPh_3)_2Cl_2$ (0.01 equiv) and CuI (0.01 equiv) in THF (0.3 M) was added diisopropylamine (2.0 equiv). The reaction mixture was stirred for 2 h at room temperature and then quenched with saturated NH_4Cl solution. The mixture was diluted with ether, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 50:1 or 100:1) to give 1-(trialkylsilyl)diyne **1**.

4.1.1.1. 1-(Triisopropylsilyl)-5-(benzyloxy)penta-1,3-diyne (1a). As a yellow oil (131 mg, 91%) from 1-bromo-3-(benzyloxy)prop-1-yne (100 mg, 0.44 mmol): ^1H NMR (300 MHz, $CDCl_3$) δ 1.11 (s, 21H), 4.25 (s, 2H), 4.62 (s, 2H), 7.31–7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.2, 18.5, 57.6, 71.7, 71.8, 72.9, 84.4, 88.9, 127.9, 128.1, 128.4, 137.1; MS (EI) *m/z* (rel int.) 326 (M^+, 1), 284 (68), 141 (56), 91 (100); HRMS (EI) calcd for $C_{21}H_{30}OSi$ (M^+) 326.2066, found 326.2066.

4.1.1.2. 1-(*tert*-Butyldimethylsilyl)-5-(benzyloxy)-penta-1,3-diyne (1b). As a yellow oil (789 mg, 89%) from 1-bromo-3-(benzyloxy)prop-1-yne (697 mg, 3.10 mmol): ^1H NMR (300 MHz, $CDCl_3$) δ 0.18 (s, 6H), 0.99 (s, 9H), 4.25 (s, 2H), 4.62 (s, 2H), 7.31–7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.9, 16.7, 26.0, 57.5, 71.5, 71.7, 73.5, 85.8, 87.9, 127.9, 128.0, 128.4, 137.1; MS (EI) *m/z* (rel int.) 284 (M^+, 2), 227 (42), 139 (87), 91 (100); HRMS (CI) calcd for $C_{18}H_{23}OSi$ ($[M+H]^+$) 283.1518, found 283.1513.

4.1.1.3. 1-(Triethylsilyl)-5-(benzyloxy)penta-1,3-diyne (1c). As a yellow oil (589 mg, 93%) from 1-bromo-3-(benzyloxy)prop-1-yne (500 mg, 2.23 mmol): ^1H NMR (300 MHz, $CDCl_3$) δ 0.69 (q, J=7.8 Hz, 6H), 1.06 (t, J=7.8 Hz, 9H), 4.26 (s, 2H), 4.63 (s, 2H), 7.33–7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 4.0, 7.2, 57.4, 71.5, 71.6, 73.3, 85.1, 88.3, 127.8, 128.0, 128.3, 137.0; MS (EI) *m/z* (rel int.) 284 (M^+, 1), 255 (91), 227 (97), 197 (51), 169 (50), 91 (100); HRMS (CI) calcd for $C_{18}H_{25}OSi$ ($[M+H]^+$) 285.1675, found 285.1671.

4.1.2. 5-(Benzyloxy)penta-1,3-diyne (2). To a solution of **1a** (100 mg, 0.31 mmol) in DMF (3 mL) were added NBS (66 mg, 0.37 mmol), TBAF (0.37 mL, 0.37 mmol, 1.0 M solution in THF) and $AgNO_3$ (5.2 mg, 0.031 mmol). The reaction mixture was stirred for 3 h at room temperature and then quenched with saturated NH_4Cl solution. The mixture was diluted with ether, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 50:1) to give **2** (39 mg, 73%) as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 2.19 (t, J=0.9 Hz, 1H), 4.23 (d, J=1.2 Hz, 2H), 4.61 (s, 2H), 7.30–7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 57.3, 67.5, 68.0, 70.6, 71.8, 72.6, 128.0, 128.1, 128.4, 136.9; MS (CI) *m/z* (rel int.) 169 ($[M-1]^+$, 20), 153 (62), 141 (100), 91 (94); HRMS (CI) calcd for $C_{12}H_9O$ ($[M-M]^+$) 169.0653, found 169.0657.

4.1.3. General procedures for the desilylative bromination. *Method A*. To a solution of the 1-(trialkylsilyl)acetylene (1.0 equiv) in DMF (0.3 M) were added NBS (4.0 equiv), TBAF (1.2 equiv) and $AgNO_3$ (0.1 equiv). The reaction mixture was stirred for 3 h at room temperature

and then quenched with saturated NH_4Cl solution. The mixture was diluted with ether, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to give the 1-bromoalkyne.

Method B. To a solution of the 1-(trialkylsilyl)acetylene (1.0 equiv) in acetonitrile (0.1 M) were added NBS (1.2 equiv) and AgF (1.2 equiv) in the dark. The reaction mixture was stirred at room temperature for 2–3 h and then filtered through a pad of Celite. The filtrate was diluted with ether, washed with water, dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to give the 1-bromoalkyne.

4.1.3.1. 1-Bromo-5-(benzyloxy)penta-1,3-diyne (3). *Method A*. As a yellow oil (83 mg, 95%) from **1a** (114 mg, 0.35 mmol).

Method B. As a yellow oil (73 mg, 95%) from **1a** (101 mg, 0.31 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.22 (s, 2H), 4.60 (s, 2H), 7.32–7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.3, 57.4, 64.9, 71.39, 71.44, 71.8, 128.0, 128.1, 128.5, 136.9; MS (EI) *m/z* (rel int.) 248 (M^+, 2), 218 (34), 139 (76), 91 (100); HRMS (EI) calcd for $C_{12}H_9BrO$ (M^+) 247.9837, found 247.9839.

4.1.4. 1-(Triisopropylsilyl)-2-(3-methoxyphenyl)ethyne (4a). Following the same procedure as for **1**, from 3-iodoanisole (200 mg, 1.02 mmol) in THF (10 mL), (triisopropylsilyl)acetylene (0.24 mL, 1.2 mmol), $Pd(PPh_3)_2Cl_2$ (18 mg, 0.03 mmol), CuI (4.8 mg, 0.03 mmol) and diisopropylamine (0.25 mL, 1.8 mmol), after a reaction time of 2 h, **4a** (190 mg, 77%) was obtained as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (s, 21H), 3.81 (s, 3H), 6.87 (ddd, J=1.2, 2.7, 8.4 Hz, 1H), 6.99 (dd, J=1.2, 2.7 Hz, 1H), 7.08 (ddd, J=1.2, 1.2, 7.2 Hz, 1H), 7.20 (app. t, J=7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.3, 18.7, 55.3, 90.3, 107.0, 114.9, 116.8, 124.5, 124.6, 129.2, 159.2; MS (EI) *m/z* (rel int.) 288 (M^+, 20), 245 (88), 217 (30), 203 (47), 189 (59), 175 (100), 94 (48); HRMS (CI) calcd for $C_{18}H_{29}OSi$ ($[M+H]^+$) 289.1988, found 289.1988.

4.1.5. 1-(Triisopropylsilyl)-2-[4-(hydroxymethyl)phenyl]-ethyne (4b). To a solution of 4-bromobenzyl alcohol (500 mg, 2.67 mmol), (triisopropylsilyl)acetylene (0.72 mL, 3.20 mmol), $PdCl_2(PhCN)_2$ (31 mg, 0.08 mmol), CuI (10 mg, 0.05 mmol), and tri-*tert*-butylphosphine (0.037 mL, 0.16 mmol) in dioxane (6 mL) was added diisopropylamine (0.45 mL, 3.20 mmol). The reaction mixture was stirred for 4 h at room temperature. The reaction mixture diluted with hexane, filtered through Celite, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 10:1) to give **4b** (750 mg, 97%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (s, 21H), 1.73 (t, J=5.7 Hz, 1H), 4.69 (d, J=5.7 Hz, 2H), 7.30 (d, J=8.4 Hz, 2H), 7.47 (d, J=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.3, 18.6, 64.5, 90.4, 106.9, 122.6, 126.6, 132.1, 141.0; MS (EI) *m/z* (rel int.) 288 (M^+, 5), 245 (69), 217 (23), 203 (40), 189 (60), 175 (100), 115 (62); HRMS (CI) calcd for $C_{18}H_{27}OSi$ ($[M-H]^+$) 287.1831, found 287.1827.

4.1.6. 1-Bromo-2-(3-methoxyphenyl)ethyne (5a). Following the same procedure as for desilylative bromination method B. As a colorless oil (109 mg, 84%) from **4a** (177 mg, 0.61 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.80 (s, 3H), 6.90 (ddd, J=1.2, 2.7, 8.1 Hz, 1H), 6.98 (dd, J=1.2, 2.7 Hz, 1H), 7.05 (ddd, J=1.2, 1.2, 7.8 Hz, 1H), 7.22 (app. t, J=8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.6, 55.2, 79.9, 115.3, 116.8, 123.6, 124.4, 129.3, 159.2; MS (EI) *m/z* (rel int.) 210 (M^+, 16), 181 (32), 131 (27), 102 (100); HRMS (CI) calcd for C_9H_8OBr ($[M+H]^+$) 210.9758, found 210.9761.

4.1.7. 1-Bromo-2-[4-(hydroxymethyl)phenyl]ethyne (5b). Following the same procedure as for desilylative bromination method B. As a white solid (162 mg, 83%) from **4a** (267 mg, 0.93 mmol): mp 75–76 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70 (br s, 1H), 4.70 (s, 2H), 7.31 (d, J=8.4 Hz, 2H), 7.45 (d, J=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.8, 64.4, 79.8, 121.6, 126.6, 132.0, 141.3; MS (EI) *m/z* (rel int.) 210 (M^+, 49), 181 (12), 131 (38), 102 (100); HRMS (EI) calcd for C_9H_7OBr (M^+) 210.9758, found 210.9758.

4.1.8. 1-(Triisopropylsilyl)-1-[4-(triisopropylsilyloxy-methyl)phenyl]ethyne (6). To a solution of **4b** (113 mg, 0.40 mmol) in CH_2Cl_2 (4 mL) were added (triisopropylsilyl)chloride (0.10 mL, 0.48 mmol) and imidazole (55 mg, 0.80 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with 1% Na_2CO_3 solution and extracted with hexane (10 mL×2). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/EtOAc, 100:1) to give **6** (167 mg, 94%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06–1.15 (m, 42H), 4.82 (s, 2H), 7.29 (d, J=8.4 Hz, 2H), 7.45 (d, J=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.3, 12.0, 18.0, 18.7, 64.8, 89.8, 107.3, 121.9, 125.4, 131.9, 142.0; MS (EI) *m/z* (rel int.) 444 (M^+, 4), 401 (100), 271 (23); HRMS (CI) calcd for $C_{27}H_{49}OSi_2$ ($[M+H]^+$) 445.3322, found 445.3331.

4.1.9. 1-Bromo-2-[4-(triisopropylsilyloxymethyl)phenyl]-ethyne (7). Following the same procedure as for desilylative bromination method B. As a colorless oil (103 mg, 95%) from **6** (131 mg, 0.29 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06–1.12 (m, 21H), 4.82 (s, 2H), 7.30 (d, J=8.1 Hz, 2H), 7.42 (d, J=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.0, 18.0, 49.0, 64.6, 80.1, 120.9, 125.5, 131.8, 142.4; MS (EI) *m/z* (rel int.) 366 (M^+, 3), 325 (100), 253 (15), 193 (92), 114 (53); HRMS (EI) calcd for $C_{18}H_{28}OBrSi$ ($[M+H]^+$) 367.1092, found 367.1096.

4.1.10. 1-(Triisopropylsilyl)-3-(triisopropylsilyloxy)-3-phenylprop-1-yne (8). To a solution of (triisopropylsilyl)-acethylene (500 mg, 2.74 mmol) in THF (6 mL) was slowly added *n*-BuLi (1.72 mL, 2.75 mmol, 1.6 M solution in hexanes) at −40 °C. The reaction mixture was stirred for 30 min at −40 °C and then a solution of benzaldehyde (278 mg, 2.74 mmol) in THF (3 mL) was added over 5 min. The mixture was warmed to room temperature and stirred for 3 h. The mixture was added saturated NH_4Cl solution at −40 °C and extracted with ether. The organic layer was washed with brine, dried over Na_2SO_4, filtered,

and evaporated to dryness. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 10:1) to give 1-phenyl-3-(triisopropylsilyl)prop-2-yn-1-ol[15] (720 mg, 81%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 21H), 5.49 (s, 1H), 7.30–7.41 (m, 3H), 7.57–7.60 (m, 2H). Following the same procedure as that described for **6**, from 1-phenyl-3-(triisopropylsilyl)prop-2-yn-1-ol (235 mg, 0.82 mmol) in DMF (8 mL), (triisoprophylsilyl)chloride (0.20 mL, 0.90 mmol), and imidazole (140 mg, 2.10 mmol), after a reaction time of 1 h, compound **8** (331 mg, 91%) was obtained as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05–1.13 (m, 42H), 5.60 (s, 1H), 7.28–7.36 (m, 3H), 7.53 (d, J=7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.3, 12.4, 18.1, 18.5, 65.4, 86.2, 108.7, 126.1, 127.4, 128.1, 142.4; MS (EI) *m/z* (rel int.) 444 (M^+, 1), 401 (100); HRMS (CI) calcd for $C_{27}H_{47}OSi_2$ ($[M-H]^+$) 443.3165, found 443.3166.

4.1.11. 1-Bromo-3-(triisopropylsilyloxy)-3-phenylprop-1-yne (9). Following the same procedure as for desilylative bromination method B. As a colorless oil (122 mg, 96%) from **8** (153 mg, 0.34 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05–1.12 (m, 21H), 5.57 (s, 1H), 7.28–7.38 (m, 3H), 7.46–7.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.2, 18.0, 45.7, 65.6, 83.2, 125.8, 127.8, 128.3, 141.5; MS (EI) *m/z* (rel int.) 366 (M^+, 1), 323 (27), 193 (38), 105 (100); HRMS (CI) calcd for $C_{18}H_{28}OBrSi$ ($[M+H]^+$) 367.1092, found 367.1094.

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Antiparasite and antimycobacterial activity of passifloricin analogues

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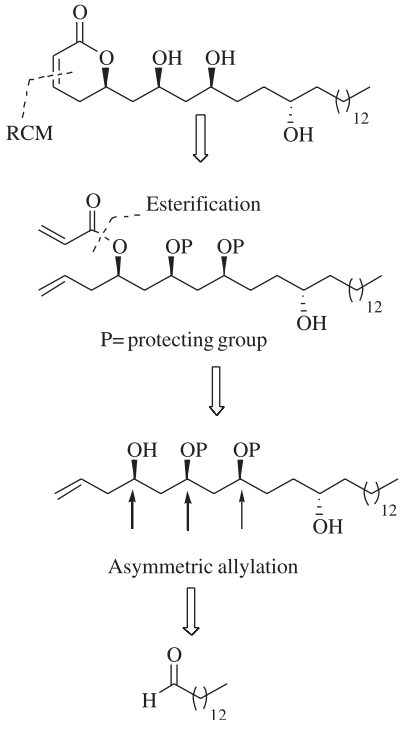
Abstract—Several structural analogues of the polyketide passifloricin lactone were synthesized using asymmetric stereoselective allylations and ring-closing methateses as key reactions. These compounds were active in vitro against intracellular amastigotes of *Leishmania panamensis* (strain UA140), trophozoites of *Plasmodium falciparum* (strain NF54), and *Mycobacterium tuberculosis* (strain $H_{37}Rv$). However, in spite of the significative antiparasitic activity of some synthetic analogues a high cytotoxicity was also observed. Based on these results a lactam derivative was also synthesized. This compound maintained a good level of activity with less toxicity.

1. Introduction

Diseases caused by parasites such as malaria, leishmaniasis, and American trypanosomiasis, and the ones caused by mycobacteria (tuberculosis and leprae) represent approximately a 90% of morbility among the global population, with a higher incidence in developing countries. These ailments affect about 3 billion people, mainly inhabitants of the third world, with very few effective drugs available and with a growing incidence of drug resistant microorganisms. Due to this fact, the World Health Organization through the program 'Tropical Disease Research' (TDR) has classified these diseases as a top priority for research. In this way, it will be possible to find better diagnostic tools, control of vectors, develop vaccines, and alternative treatments.[1] Additionally, it is necessary to search for new molecules using active natural compounds as templates and optimize them through organic synthesis.

It has been reported that natural lactones such as (−)-argentilactone[2] and (+)-boronolide[3] have significant biological activities[4] against some species of *Leishmania* and *Plasmodium*, respectively. Recently, several polyhydroxylated pyrones, named passifloricins, were synthesized[5] and assayed against *Leishmania panamensis* amastigotes.[6] In this article, we describe the synthesis of other passifloricin analogues, their activity against amastigotes of *L. panamensis*



Scheme 1. Retrosynthetic analysis of passifloricin A.

Keywords: Passifloricin; Allylation; Lactone; Antiparasite; Antituberculosis.
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(strain UA140), trophozoites of *Plasmodium falciparum* (strain NF54), and *Mycobacterium tuberculosis* (strain $H_{37}Rv$) as well as their cytotoxic activity.

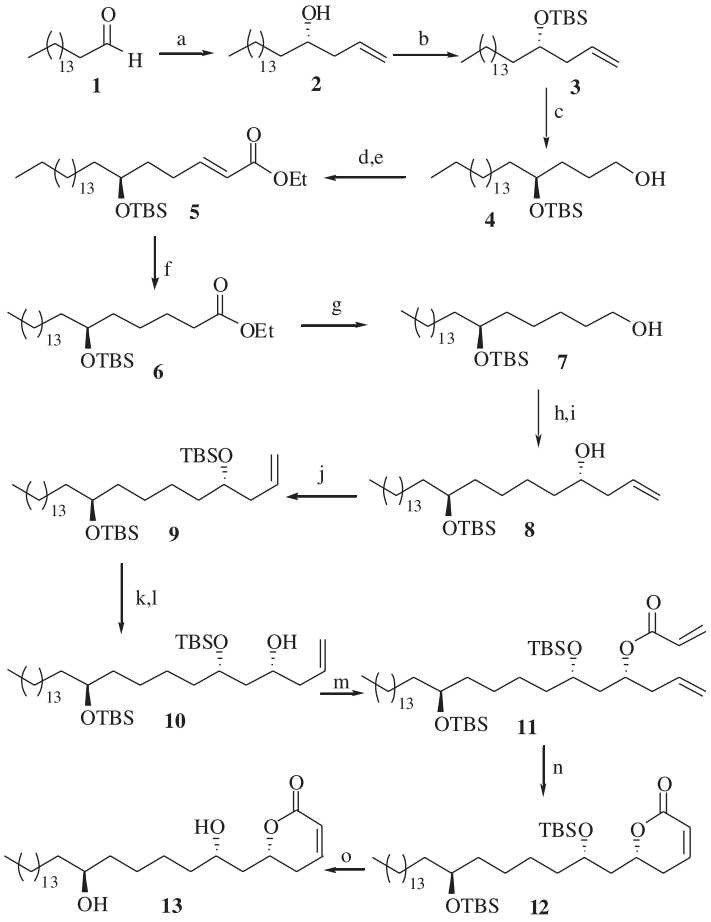
2. Results and discussion

2.1. Synthetic plan

The synthesis of passifloricin analogues was carried out following the methodology described[7] in the literature and according to a retrosynthetic analysis that relied mainly upon asymmetric allylations to create new C–C bonds (Scheme 1).

2.2. Synthesis of δ-lactone of (2*Z*,5*R*,7*S*,12*S*)-trihydroxyheptacos-2-enoic acid (13)

The preparation of passifloricin analogues is exemplified by the synthesis of lactone **13**. Starting with *n*-pentadecanal, an iterative three-step sequence (asymmetric allylation/hydroxyl protection/C=C oxidative cleavage) was proposed to create a new stereogenic carbon atom in each cycle. Acylation of the hydroxyl group generated in the last cycle, followed by ring-closing metathesis, should finally yield the desired unsaturated lactone. Among the existing asymmetric allylation methodologies the Brown chiral allylboranes are the most versatile for the synthesis of this class of compounds due to the relative easy of preparing the allyborane, the efficiency, and the enantiomeric excesses reported.[8] Thus, the synthesis of lactone **13** (Scheme 2) started when *n*-hexadecanal[9] was allowed to react with the B-allyldiisopinocampheylborane (allylBIpc$_2$) prepared from allylmagnesium bromide and (+)-DIP-Cl (diisopinocampheylboron chloride).[10] This gave homoallyl alcohol **2** in a 92:8 enantiomeric ratio, as judged from NMR analysis of the Mosher ester.[11] Protection of the hydroxyl group as the *t*-butyldimethylsilyl (TBS)[12] derivative followed by hydroboration[13] yielded the primary alcohol **4**. Swern oxidation[14] of the latter gave an intermediate γ-silyloxy aldehyde, which was subjected to Horner–Wadsworth–Emmons (HWE)[15] reaction. This provided, without further chromatographic purification, α,β-unsaturated ester **5**, which was transformed into saturated ester **6** upon hydrogenation.[16] Reduction of **6** with DIBAL-H[17] resulted in alcohol **7**, which was submitted to Swern oxidation to give an intermediate silyloxy aldehyde, which, without further chromatographic purification, was subjected to



Scheme 2. Reagents and conditions: (a) allylBIpc$_2$ [from (+)-DIP-Cl and allylmagnesium bromide], Et_2O, −78 °C (80%, 92:8 enantiomeric mixture); (b) TBSCl, DMF, imidazole, rt, 18 h, 80%; (c) 9-BBN, THF, rt, 20 h, then H_2O_2, NaOH, EtOH, 50 °C, 1 h, 80%; (d) Swern oxidation; (e) $(EtO)_2OPCH_2CO_2Et$, LiCl, DIPEA, CH_3CN, 15 h, 70%; (f) Pd–C 10%, H_2, AcOEt, 94%; (g) DIBAL-H, hexane, 0 °C, 95%; (h) Swern oxidation; (i) allylBIpc$_2$ [from (+)-DIP-Cl and allylmagnesium bromide], Et_2O, −78 °C (65% overall for the two steps, 93:7 diastereomeric mixture); (j) TBSOTf, 2,6-lutidine, rt, 1 h, CH_2Cl_2, 88%; (k) O_3, CH_2Cl_2, −78 °C, then PPh_3, 3 h, rt; (l) allylBIpc$_2$ [from (+)-DIP-Cl and allylmagnesium bromide], Et_2O, −78 °C (63% overall for the two steps, 91:9 diastereomeric mixture); (m) acryloyl chloride, Et*N*iPr_2, CH_2Cl_2, −78 °C, 1 h, 81%; (n) 10 mol% PhCH=$RuCl_2(PCy_3)_2$, CH_2Cl_2, 60 °C, 83%; (o) PPTS, aqueous MeOH, 70 °C, 18 h, 94%.

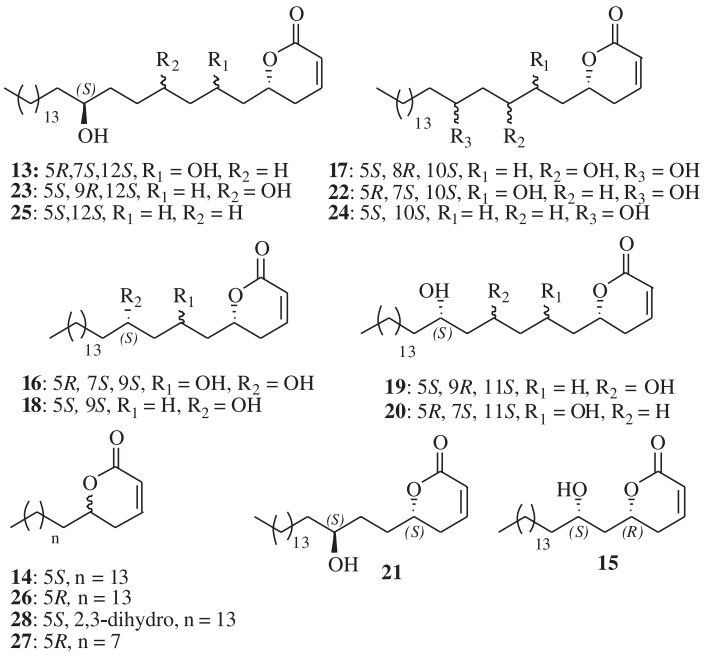


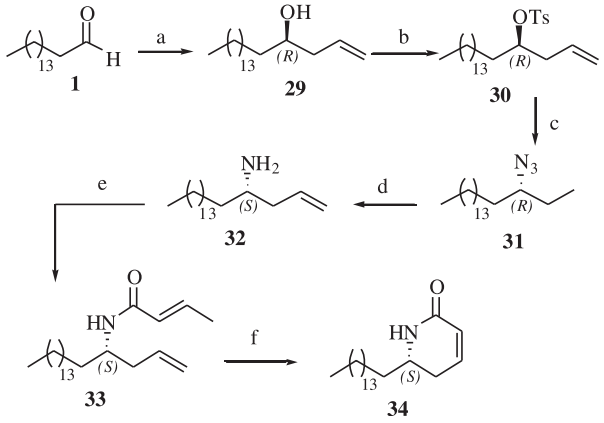
Figure 1. Structures of synthesized lactones.

asymmetric allylation with the same reagent as above. This gave homoallyl alcohol **8**, as a 93:7 diastereomeric mixture, which was then silylated[18] to **9**. Ozonolysis[19] of the olefinic bond in the latter compound was followed by asymmetric allylation with the same reagent as above. This generated the protected triol **10**, which was then treated with acryloyl chloride to produce in good yield the corresponding acrylate.[20] The latter was reactive enough as to undergo RCM with the first generation Grubbs ruthenium catalyst $PhCH{=}RuCl_2(PCy_3)_2$[21] with formation of the unsaturated lactone **12**. Acid-catalyzed cleavage[22] of all the silyl protecting groups in **12** afforded lactone **13** in a 7.3% overall yield from *n*-hexadecanal.

Following similar synthetic strategies a total of 16 lactones, whose structures are shown in Figure 1, were synthesized.[23,24]

2.3. Synthesis of δ-lactam of (2*Z*,5*S*)-hydroxyicos-2-enoic acid (34)

The α,β-unsaturated lactone group is a common feature in many bioactive compounds and it is likely that the electrophilicity of this functional group accounts for their bioactive response. It should be possible to adjust this reactivity through a functional analogue such as a lactam. Therefore we decided to prepare lactam derivative **34**. For the lactam synthesis a similar synthetic strategy was carried out (Scheme 3). Hexadecanal **1** was allowed to react with (−)-B-allyldiisopinocampheylborane, prepared from allylmagnesium bromide and (−)-DIP-Cl, generating homoallyl alcohol **29** as a 90:10 enantiomeric mixture. Tosylation[25] of alcohol **29** following reaction of the corresponding tosylate **30** with sodium azide[26] yielded azide **31**. Reduction of the latter with triphenylphosphine in $THF–H_2O$[27] allowed us to obtain the homoallylic amine **32**, which was subjected to amidation reaction with crotonic acid, DMAP and DCC[28] to yield compound **33**. The latter was reactive enough to undergo RCM using the standard, first generation ruthenium complex with formation of the unsaturated lactam **34**.



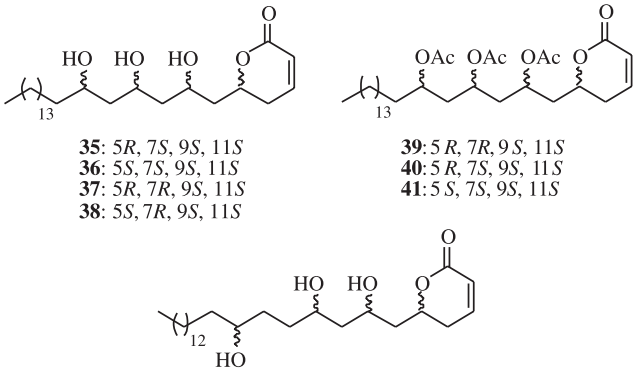
Scheme 3. Reagents and conditions: (a) allylBIpc$_2$ [from (−)-DIP-Cl and allylmagnesium bromide], Et_2O, −78 °C (78%, 90:10 enantiomeric mixture); (b) TsCl, Py, 12 h, 80%; (c) NaN_3, DMF, 25 °C, 16 h, 74%; (d) PPh_3, $THF–H_2O$, 25 °C, 2 days, 80%; (e) crotonic acid, DCC, DMAP, CH_2Cl_2, 25 °C, 6 h, 81%; (f) 10 mol% $PhCH{=}RuCl_2(PCy_3)_2$, CH_2Cl_2, 60 °C, 82%.

2.4. Antiparasite activity studies

The antiprotozoal and antimycobacterial activities of synthetic compounds, as well as passifloricin A are show in the Figure 1. The other synthetic analogues reported previously[29] are shown in Figure 2.

Below are some conclusions concerning the structure and activity:

- In general, all the compounds had a significant activity against *L. panamensis* amastigotes, exhibiting an EC_{50} lower than 1.0 μg/mL (Fig. 3). Related to the selectivity



35: 5*R*, 7*S*, 9*S*, 11*S*
36: 5*S*, 7*S*, 9*S*, 11*S*
37: 5*R*, 7*R*, 9*S*, 11*S*
38: 5*S*, 7*R*, 9*S*, 11*S*

39: 5*R*, 7*R*, 9*S*, 11*S*
40: 5*R*, 7*S*, 9*S*, 11*S*
41: 5*S*, 7*S*, 9*S*, 11*S*

42: 5*R*, 7*S*, 9*S*, 12*R*
43: 5*S*, 7*S*, 9*S*, 12*R*
44: 5*S*, 7*S*, 9*S*, 12*S*
Passifloricina A,**45** : 5*R*, 7*S*, 9*S*, 11*S*

Figure 2. Passifloricin A analogues reported elsewhere.

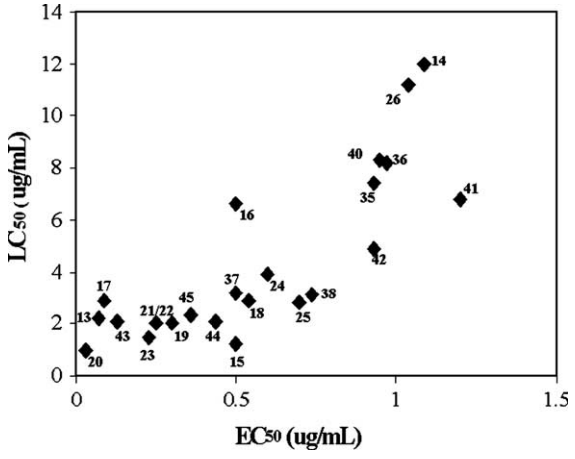


Figure 3. Leishmanicidal activity of passifloricins. Numbering corresponding to structures showed in Figures 1 and 2.

index (SI = $LC_{50}/EC_{50} > 10.0$) compounds **14** (11.0), **16** (13.2), **17** (32,2), **20** (33.7) and **13** (31.4) are the most promising leads, particularly the first one, because simplest structure and lowest LC_{50} (12.0 μg/mL). Passifloricin A, **45**, displayed a SI = 6.4.

Concerning the antiplasmodial activity, compounds with an IC_{50}[†] < 50.0 μg/mL were considered promising.[30] Accordingly, compounds **18** (19.8 μg/mL, 52.1 μM), passifloricin A, **45** (20.9 μg/mL, 47.5 μM), and **23** (26.7 μg/mL, 60.9 μM) exhibit the best activity. Products **20** (39.0 μg/mL, 91.9 μM), **17** (40.1 μg/mL, 97.7 μM), **22** (45.8 μg/mL, 111.6 μM) and **16** (50.1 μg/mL, 126.4 μM) showed marginal activity. The IC_{50} of chloroquine was 1.1 μg/mL (34.5 μM) (Fig. 4).

- Regarding evaluation against *M. tuberculosis* (Table 1) with the green fluorescent protein assay, compounds **13**, **15**, **18**, **19**, **20**, **23** and **24** exhibited an inhibition percentage higher than 90% at 128 μg/mL, while

[†] The IC_{50}: concentration inhibitory dose of the parasite growth in relation to control cultures without compounds.

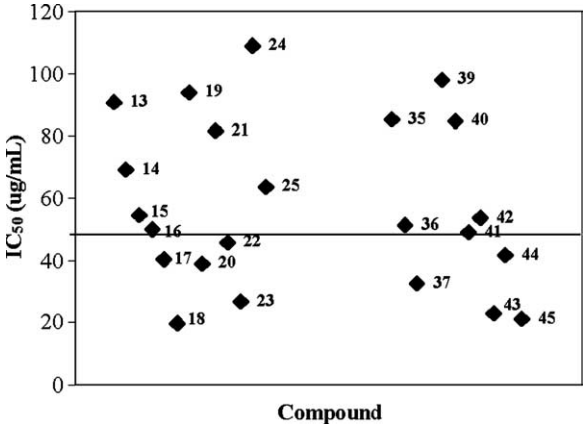


Figure 4. Antiplasmodial activity of passifloricins. Compounds **26**, **27**, **28**, **34**, and **38** were not evaluated.

Table 1. Comparative activity of passifloricins against *M. tuberculosis* $H_{37}Rv$ and Vero cell-line cytotoxicity

Compound	Activity against *M. tuberculosis*		
	Inhibition (%)	MIC (μg/mL, μM)	LC_{50} (μg/mL, μM)
	GFP	MABA	Vero cells
Rifampin	99.6	0.72	117.4
13	97.4	17.31 (39.5)	1.80 (4.1)
14	63.7	> 128	n.e.
15	98.9	35.57 (101.0)	3.07 (8.7)
18	97.4	31.95 (84.0)	2.88 (7.6)
19	95.8	38.04 (89.6)	3.02 (7.2)
20	97.3	48.23 (113.7)	2.20 (5.2)
21	79.1	n.e.	n.e.
22	84.3	n.e.	n.e.
23	98.3	61.47 (140.2)	0.88 (2.0)
24	94.7	24.08 (61.1)	4.60 (12.0)
25	48.1	> 128	n.e.
26	66.3	n.e.	n.e.
27	76.8	n.e.	n.e.
28	53.6	> 128	n.e.
34	74.7	> 128	n.e.
35	81.7	23.4 (53.0)	8.34 (19.0)
45	82.9	29.4 (67.0)	5.61 (13.0)

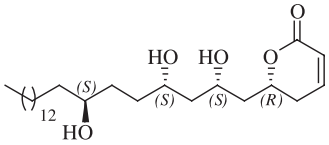
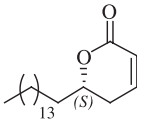
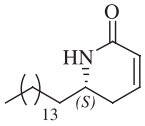
n.e.: no evaluated.

passifloricin A, **45**, reached 82.9%. Additionally, the minimal inhibitory concentration (MIC) of these compounds was lower than 60 μg/mL, except for compound **23**. The other compounds (**14**, **21**, **22**, **25**, **28** and **34**) possesed an inhibition percentage less than 90%. However, the SI of all the compounds was extremely low (0.05–0.36) because their high cytotoxicity levels.

There is not a clear relationship between the antiparasitic activity and other structural facts such as the stereochemistry of the hydroxyl groups and their relative position to the lactone. However, a comparison of the biological profiles of these compounds indicated a tendency to increase the activity against *P. falciparum* and *M. tuberculosis* according to the number of hydroxy groups, but not against *L. panamensis*.

The mechanism of action of these compounds could be originated in the alkylating properties (Michael acceptor) of

Table 2. Comparative activity of lactam **34** against *L. panamensis*

Compound	Structure	Cytotoxicity	Leishmanicidal activity	
		LC $_{50}$ (μg/mL, μM)	EC $_{50}$ (μg/mL, μM)	SI
Glucantime		416.4	6.7	59.6
Passiflorici A, **45**[a]		2.3 (5.2)	0.36 (0.8)	6.4
14		12.0 (39.0)	1.09 (3.5)	11.0
Lactam, **34**		45.1 (146.8)	3.42 (11.1)	13.2

[a] Previous experimental results.

the α,β-unsaturated-δ-lactone; this moiety is widely distributed in nature and have been reported in number bioactivities.[4a,b,31,32]

Lactam **34** exhibited high leishmanicidal activity (3.42 μg/mL, 11.1 μM) versus 0.36 (0.8 μM) and 1.09 (3.5 μM) for passifloricin A and compound **14**, respectively, although it displayed less cytotoxicity (45.1 μg/mL, 146.8 μM vs 2.3 μg/mL, 5.2 μM and 12.0 μg/mL, 39.0 μM) and the SI was almost doubled. However, its profile against *Mycobacterium* was not modified significantly (Table 2).

3. Conclusion

A number of passifloricin analogues have been synthetized and screened. Specific conclusions towards structure–activity relationships point out that the presence of α,β-electrophylic unsaturated lactone moiety is important for the biological actions of these compounds to take place, but the polyhydroxylated side chain seems to have minor influence in their biological profile, as a more simple compound without functionalization on the side chain (compound **14**) is as active as more complex analogues. In addition, this compound displayed a considerable reduction of cytotoxicity. As cytotoxic activity of some synthetic analogues is quite high we intend to screen them as anticancer agents in some cell cancer lines. Work along is in progress and will be the subject of further investigation.

4. Experimental

4.1. General

4.1.1. (*R*)-Nonadec-1-en-4-ol (29). Hexadecanal (1.5 g, 6.25 mmol) was subjected to allyboration with (−)-DIP-Cl as described.[29] Workup as described[29] and column chromatography on silica gel (hexanes/EtOAc, 95:5) provided compound **29** (90:10 mixture of diastereomers, after chromatographic separation 1.37 g, 4.88 mmol, 78%). ^{1}H NMR: δ 0.88 (t, 3H, CH_3, J=6.9 Hz), 1.20–1.36 (m, 26H), 1.40–1.52 (m, 2H, H-5), 2.06 (OH), 2.10–2.19 (m, 1H, H-3′), 2.22–2.31 (m, 1H, H-3), 3.56–3.68 (m, 1H, H-4), 5.09 (d, 1H, H-1, J=9.9 Hz), 5.09 (d, 1H, H-1′, J=17.4 Hz), 5.72–5.92 (m, 1H, H-2); ^{13}C NMR: δ 14.1 (CH_3), 22.7 (CH_2), 25.7 (CH_2), 29.4 (CH_2), 29.7 (×9) (CH_2), 32.0 (CH_2), 36.9 (CH_2), 42.0 (CH_2), 70.8 (CH), 117.7 (CH_2), 135.0 (CH).

4.1.2. (*R*)-4-*p*-Toluensulphonate-nonadec-1-en (30). To a solution of compound **29** (800 mg, 2.83 mmol) in pyridine (2 mL) was added tosyl chloride (1.08 g, 5.67 mmol). The mixture was stirred for 12 h and then CH_2Cl_2 (10 mL) was added and washed with HCl 10% (3×15 mL) of saturated aqueous $NaHCO_3$ and water. Column chromatography on silica gel (hexanes/EtOAc, 95:5) provided compound **30** (987 mg, 2.26 mmol, 80%) oil: $[\alpha]^{20}$ +5.4 (c 1.22, $CHCl_3$); ^{1}H NMR: δ 0.87 (t, 3H, CH_3, J=6.9 Hz), 1.11–1.30 (m, 26H), 1.50–1.52 (m, 2H, H-5), 2.31–2.39 (m, 2H, H-3), 2.43 (s, 3H, Ph-CH_3), 4.50–4.61 (m, 2H, H-4), 5.02 (d, 2H, H-1, J=12.3 Hz), 5.53–5.72 (m, 1H, H-2), 7.31 (d, 2H, Ar, J=8.2 Hz), 7.78 (d, 2H, Ar, J=8.2 Hz); ^{13}C NMR: δ 14.5 (CH_3), 22.0 (CH_3), 23.1 (CH_2), 25.1 (CH_2), 29.6–30.1 (×10) (CH_2), 32.4 (CH_2), 34.1 (CH_2), 39.2 (CH_2), 83.5 (CH), 119.0 (CH_2), 128.2 (×2) (CH), 130.0 (×2) (CH), 132.8 (CH).

4.1.3. (*S*)-4-Azide-nonadec-1-en (31). Compound **30** (800 mg, 1.83 mmol) was dissolved in DMF (5 mL) and NaN_3 (954 mg, 14.67 mmol) was added. The mixture was stirred for 16 h and then AcOEt (10 mL) was added and washed with water. Column chromatography on silica gel (hexanes/EtOAc, 95:5) afforded compound **31** (416 mg, 1.35 mmol, 74%) oil: $[\alpha]^{20}$ −10.6 (c 0.80, $CHCl_3$); ^{1}H NMR: δ 0.82 (t, 3H, CH_3, J=6.9 Hz), 1.15–1.26 (m, 26H), 1.40–1.47 (m, 2H, H-5), 2.19–2.27 (m, 2H, H-3), 3.20–3.30 (m, 1H, H-4), 5.01–5.08 (m, 1H, H-1), 5.09–5.12 (m, 1H, H-1′), 5.65–5.83 (m, 1H, H-2); ^{13}C NMR: δ 14.5 (CH_3), 23.1 (CH_2), 26.5 (CH_2), 29.8–30.1 (×10) (CH_2), 32.4 (CH_2), 34.4 (CH_2), 39.2 (CH_2), 62.8 (CH), 118.4 (CH_2), 134.5 (CH).

4.1.4. (*S*)-Nonadec-1-en-4-amine (32). To a solution of azide **31** (800 mg, 2.83 mmol) in THF (5 mL), PPh_3 (445 mg, 1.71 mmol) and water (28 μL) were added. The mixture was stirred for 12 h and then AcOEt (10 mL) was added and washed with saturated $NaHCO_3$ solution. Column chromatography on silica gel (EtOAc) afforded compound **32** (256 mg, 0.91 mmol, 80%) oil: $[\alpha]^{20}$ −8.6 (*c* 0.84, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}): 3255 (N–H); ^1H NMR: δ 0.88 (t, 3H, CH_3, $J=6.9$ Hz), 1.26–1.55 (m, 26H), 2.08–2.25 (m, 2H, H-5), 2.30–2.50 (m, 2H, H-3), 2.81 (s, 2H, N–H), 2.85–3.10 (m, 1H, H-4), 5.27 (d, 1H, H-1′, $J=$ 9.9 Hz), 5.28 (d, 1H, H-1, $J=17.0$ Hz), 5.93–6.01 (m, 1H, H-2); ^{13}C NMR: δ 14.5 (CH_3), 23.1 (CH_2), 26.5 (CH_2), 26.7 (CH_2), 29.8–30.1 (×9) (CH_2), 32.3 (CH_2), 37.4 (CH_2), 42.3 (CH_2), 51.1 (CH), 117.9 (CH_2), 135.9 (CH).

4.1.5. (*S*)-*N*-(4-Nonadec-1-en)-crotonamide (33). Amine **32** (200 mg, 0.712 mmol) was dissolved in dry CH_2Cl_2 (20 mL), and treated sequentially with crotonic acid (73.5 mg, 0.855 mmol), DMAP (261 mg, 2.14 mmol) and DCC (193 mg, 0.935 mmol). The reaction mixture was stirred for 6 h and filtered. Then CH_2Cl_2 (10 mL) was added and washed with saturated aqueous $NaHCO_3$. Column chromatography on silica gel (hexanes/EtOAc, 6:4) afforded compound **33** (210 mg, 0.577 mmol, 81%) oil: mp: 87–89 °C; $[\alpha]^{20}$ −10.0 (*c* 0.95, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}): 3285 (N–H), 1630 (C═O), 1551 (C–N); ^1H NMR: δ 0.82 (t, 3H, CH_3, $J=6.9$ Hz), 1.15–1.35 (m, 26H), 1.50–1.60 (m, 2H, H-5), 1.78 (d, 3H, Hc, $J=6.9$ Hz), 2.07–2.29 (m, 2H, H-3), 3.95–4.08 (m, 1H, H-4), 4.95–5.10 (m, 2H, H-1/N–H), 5.63–5.80 (m, 2H, H-a/H-2), 6.68–6.82 (m, 1H, Hb); ^{13}C NMR: δ 14.5 (CH_3), 18.1 (CH_3), 23.1 (CH_2), 26.4 (CH_2), 29.8–30.1 (×9) (CH_2), 31.3 (CH_2), 32.3 (CH_2), 34.9 (CH_2), 39.6 (CH_2), 48.9 (CH), 118.1 (CH_2), 125.8 (CH), 134.9 (CH), 140.0 (CH), 166.9 (C═O).

4.1.6. δ-Lactam of (2*Z*,5*S*)-hydroxyicos-2-enoic acid (34). Compound **33** (160 mg, 0.438 mmol) was dissolved under N_2 in dry, degassed CH_2Cl_2 (50 mL) and treated with ruthenium catalyst $PhCH=RuCl_2(PCy_3)_2$ (36 mg, 0.044 mmol). The mixture was heated at reflux until consumption of the starting material (ca. 3 h, TLC monitoring!). Solvent removal in vacuo and column chromatography on silica gel (hexanes/EtOAc, 1:1) furnished **34** (116 mg, 0.36 mmol, 82%): mp: 74–76 °C; $[\alpha]^{20}$ +37.7 (*c* 3.0, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}): 3210 (N–H), 1687 (C═O), 1550 (C–N); ^1H NMR: δ 0.88 (t, 3H, CH_3, $J=6.9$ Hz), 1.20–1.45 (m, 26H), 1.50–1.60 (m, 2H, H-6), 2.01–2.21 (m, 1H, H-4), 2.30–2.46 (m, 1H, H-4′), 3.50–3.66 (m, 1H, H-5), 5.84–5.98 (m, 2H, H-2/N–H), 6.54–6.64 (m, 1H, H-3); ^{13}C NMR: δ 14.5 (CH_3), 23.1 (CH_2), 25.7 (CH_2), 29.8–30.4 (×11) (CH_2), 32.3 (CH_2), 35.9 (CH_2), 51.5 (CH), 125.0 (CH), 141.0 (CH), 166.9 (C═O). HR EIMS, *m/z* (% rel int.) 307.2805 [M^+] (0.7), 240.2678 (2), 96.0417 (100). Calcd for $C_{20}H_{37}NO$, 307.2875.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.09.037. Complete antiparasite and antimycobacterial activity data, NMR and Mass spectra, HPLC analysis and synthetic procedures. This material is available free of charge via the Internet at http://www.sciencedirect.com.

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Stereoselective radical cyclizations of *N*-(2-halobenzoyl)-cyclic ketene-*N*,X(X = O, S)-acetals

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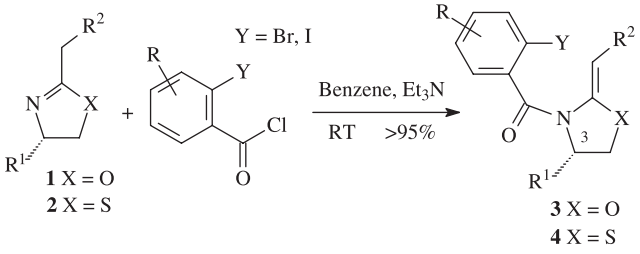
Abstract—2-Alkyloxazolines and 2-alkylthiazolines react with 2-halobenzoyl chlorides to form *N*-(2-halobenzoyl)-cyclic ketene-*N*,*O*-acetals and *N*-(2-halobenzoyl)-cyclic ketene-*N*,*S*-acetals in excellent yields, respectively. These ketene acetals readily undergo stereocontrolled aryl radical cyclizations to afford the central six-membered rings of substituted-2,3,10,10α-tetrahydrooxazolo[3,2-*b*]isoquinolin-5-ones and their 2,3,10,10α-tetrahydrothiazolo[3,2-*b*]isoquinolin-5-one analogs. The tertiary *N*,*O*- and *N*,*S*-radicals formed upon aryl radical reaction at the ketene-*N*,X(X = O, S)-acetal double bond appear to have reasonable stability. The stereoselectivity in hydrogen abstractions by these intermediate radicals from both Bu_3SnH and $(Me_3Si)_3SiH$ was investigated. The *N*,*S*-heterocyclic fused ring products may have potential medical value.

1. Introduction

Radical cyclization is an important route to synthesize heterocyclic compounds and many such methods have been reported.[1–4] Normally radical cyclizations generate a mixture of five- and six-membered-ring products. The product ratio obtained depends on the reagents, solvents, radical initiators and other reaction conditions employed.[5–7] Radical initiators commonly employed in these cyclizations include R_3SnH/AIBN,[8] RSH/AIBN,[9] R_3SiH/AIBN,[10] R_3SnSnR_3[11] and Et_3B.[12]

Despite extensive previous studies, radical cyclizations using electron-rich cyclic ketene-*N*,X(X = O, S)-acetals as a route to make *N*,*S* heterocycles were only recently reported by our group.[13] *N*,*S* Heterocycles, which have important medicinal properties appear to be available through such routes.[13,14]

Cyclic ketene-*N*,X(X = O, S)-acetals are very reactive, electron-rich, nucleophilic compounds because they share enamine and vinyl ether (thioether) structures simultaneously. These compounds and their *O*,*O*-analogs have been under active investigation in our laboratory.[15] They are very sensitive to acids, water or acidic surfaces and are easily protonated. They undergo ready cationic polymerization,[15a–d] but tend to resist radical polymerization. 2-Alkyloxazolines **1** or 2-alkylthiazolines **2** are readily converted to *N*-(2-halobenzoyl)-cyclic ketene-*N*,*O*-acetals **3** or *N*-(2-halobenzoyl)-cyclic ketene-*N*,*S*-acetals **4**, respectively, in excellent yields (>95%), when treated with 1 equiv of 2-halobenzoyl (halogen = Br, I) chlorides and Et_3N in benzene (Scheme 1). Herein, we show that *N*-(2-halobenzoyl)-cyclic ketene-*N*,X(X = O, S)-acetals **3** and **4** are good precursors for intramolecular aryl radical cyclization. When a stereogenic center was inserted at the C-3 position of the 2-alkyloxazolines **1** or 2-alkylthiazolines **2**, the resulting *N*-(2-halobenzoyl)-cyclic ketene-*N*,X(X = O, S)-acetals **3** or **4** formed upon N-benzoylation directly underwent stereocontrolled radical cyclization without need for further purification of **3/4**.



Scheme 1. Reactions of 2-alkyloxazolines **1** and 2-alkylthioazolines **2** with 2-halobenzoyl chlorides.

2. Results and discussions

The syntheses of **1** and **2** with a stereogenic center at C-3 position proceed as shown in Table 1. Natural amino acids **5**

Keywords: Cyclizations; Acetals; Diastereomer; Ketene acetals; Ketene-*N*,*O*-acetals; Ketene-*N*,*S*-acetals.
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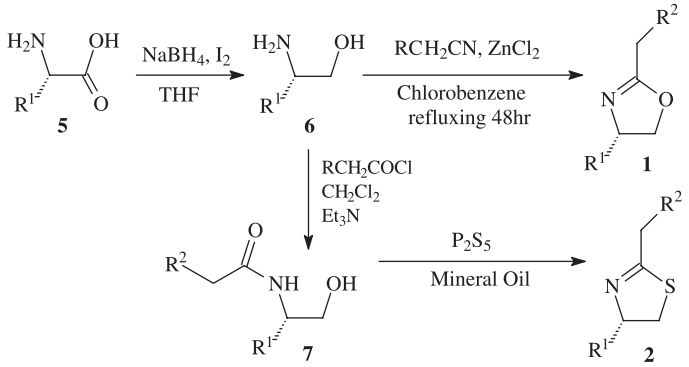
Table 1. The synthesis of 2-alkyloxazolines **1** and 2-alkylthiazolines **2**

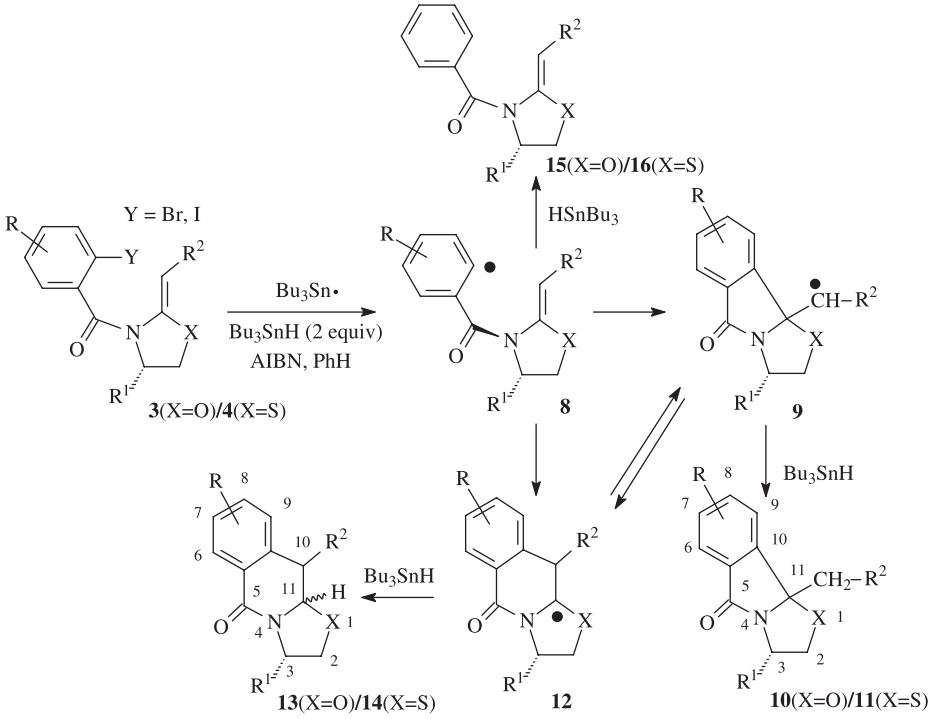


Entry	R^1 in **5**	R^2		Product **1/2**	Yield (%)[a]
1	$-CH(CH_3)_2$	–H	O	**1a**	68
2	$-CH_2CH(CH_3)_2$	–H	O	**1b**	63
3	$-CH(CH_3)_2$	$-CH_3$	O	**1c**	60
4	$-CH_2CH(CH_3)_2$	$-CH_3$	O	**1d**	66
5	$-CH_3$	–Ph	O	**1e**	60
6	$-CH_2Ph$	–H	O	**1f**	67
7	$-CH_2Ph$	–Et	O	**1g**	63
8	$-CH(CH_3)_2$	$-CH_3$	S	**2a**	60
9	$-CH_2CH(CH_3)_2$	$-CH_3$	S	**2b**	63

[a] All are isolated yields, based on **5**, over the entire three-step sequence.

(*S*-configuration) were reduced by $NaBH_4$–I_2 in THF for 18 h to give amino alcohols **6**.[16] Refluxing **6** in chlorobenzene with excess nitrile and $ZnCl_2$ (5%), affords **1** in good isolated yields.[17] Reacting **6** with acid chlorides and Et_3N in CH_2Cl_2 afforded hydroxyamides **7**, which gave **2** upon treatment with P_2S_5 in mineral oil.[18] Treating **1** and **2** with 2-halobenzoyl chloride, filtration and the removal of excess triethylamine and solvent afforded crude **3** and **4** (Scheme 1), which were directly used for aryl radical cyclizations without further purification.

Two aryl radical cyclization pathways appeared possible (Scheme 2). Radical **8**, formed upon halogen atom abstraction by $Bu_3Sn^{\bullet}$, could cyclize to either secondary radical **9**, forming in a new five-membered ring, or to tertiary radical **12**, generating a new six-membered ring. Radicals **9** and **12** would abstract a hydrogen atom from Bu_3SnH, forming **10/11** or **13/14**, respectively. But hydrogen abstraction from Bu_3SnH will be sterically influenced by the location of R^1, R^2 and the stereostructure of the fused ring system. If R^2 stabilizes a radical center, this might facilitate formation of radical **9**



Scheme 2.

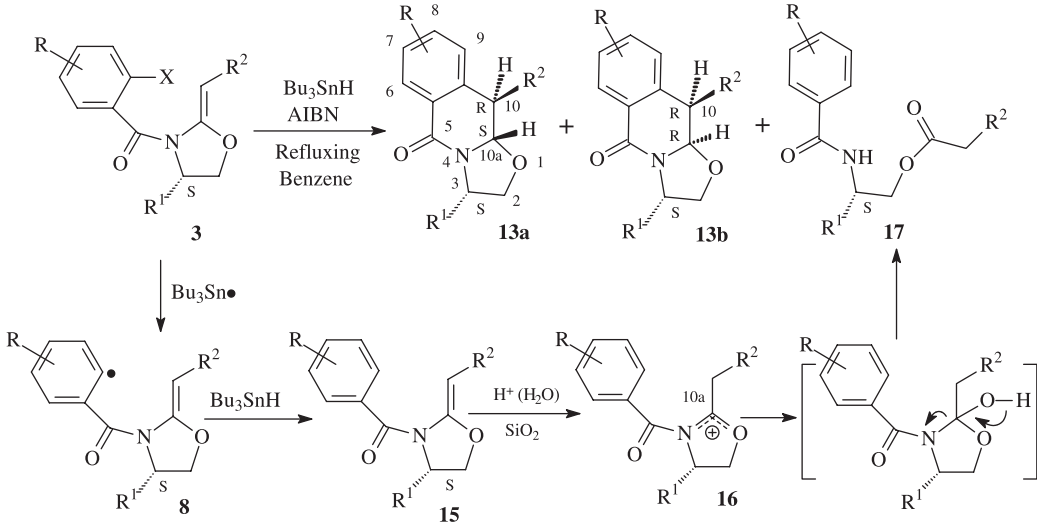
relative to radical **12**, leading to five-membered ring formation and affording **10/11** with $–CH_2R^2$ either cis or trans to R^1. Secondary radical **9** might isomerize to form tertiary radical **12**, however, formation of **9** was never observed. Radical **8** might also abstract hydrogen from $HSnBu_3$ to generate *N*-acyl cyclic ketene acetals **15/16**, which can no longer cyclize. Ring systems **13** (X=O) or **14** (X=S) would form by hydrogen abstraction from Bu_3SnH. Compounds **13** and **14** could exist as four possible diastereomeric structures. The configuration at C-3 is (S), but the C-10 and C-11 positions may be either *S* or *R*.

To study the cyclization's stereoselectivity, the R^1 group was varied (isopropyl, isobutyl, benzyl and methyl) and different R^2 groups were also employed (H, methyl, ethyl and phenyl). Aryl radical cyclizations of *N*-(2-halobenzoyl)-cyclic ketene-*N*,X(X=O, S)-acetals **3** and **4** proceeded smoothly in dry refluxing benzene with Bu_3SnH/AIBN under argon using **3** (or **4**)/Bu_3SnH/AIBN mole ratios of 1:1:0.2 in dry benzene. After refluxing 10 h, benzene was removed and flash chromatography (hexane/ethyl acetate eluent) of the product mixtures afforded two main products and one minor product (Table 2) from **3** and two major products (Table 3) from **4**. These findings were also verified by HPLC. Product structures were determined by a combination of GC–MS, FT-IR, $^1H/^{13}C$ NMR, $DEPT_{135}$, HETCOR and NOESY methods. Cyclizations of **3** are summarized in Table 2 and Scheme 3.

Cyclization of **3** ($R^2=–CH_3$, Table 2) to six-membered rings predominated, generating 2,3,10,10α-tetrahydrooxazolo-[3,2-*b*]isoquinolin-5-one ring systems **13a** and **13b**. No ring closure to generate **10** was detected. However, small amounts of the ring-opened amidoesters **17a–d** (5–9%) were isolated. These were produced by aryl radical hydrogen abstraction to give the corresponding *N*-acyl cyclic ketene-*N*,*O*-acetal **15** (see Table 2). These very acid sensitive ketene acetals were protonated to generate cations **16**, either on silica gel during column separation or during work-up. Attack by water at C-5 of **16** was followed by ring-opening to afford **17a–d**. No attack by water occurred at C-4, adjacent to nitrogen on **16**, during this ring-opening. Cyclization of **8** to **12** predominates, in accord with the greater stability of tertiary radical **12** versus secondary radical **9**. Furthermore, more strain is present in radical **9**, which contains two fused five-membered rings.

The stereochemistries of **13a** and **13b** were established by NOESY experiments (Scheme 3) and coupling constants. Products $\mathbf{13a_1}$ and $\mathbf{13b_1}$ (where $R^1=i$-Pr, $R^2=CH_3$) are given here as representative examples. Large coupling constants (10.5 Hz) were observed between H_a and H_f for $\mathbf{13a_1}$, indicating the dihedral angle ($H_f–C–C–H_a$) is near 180°. No cross-peak existed between H_a and H_e. A weak cross-peak between H_f and H_e indicated that H_f and H_e are located on the same side of the molecule while H_a and H_e are on opposite sides. In contrast to $\mathbf{13a_1}$, an intense cross-peak between H_a and H_e was observed for $\mathbf{13b_1}$, demonstrating that H_e and H_a are on the same side. Furthermore, a small coupling constant (4.5 Hz) was observed between H_a and H_f. There are no correlations from H_g to H_e for $\mathbf{13a_1}$ and

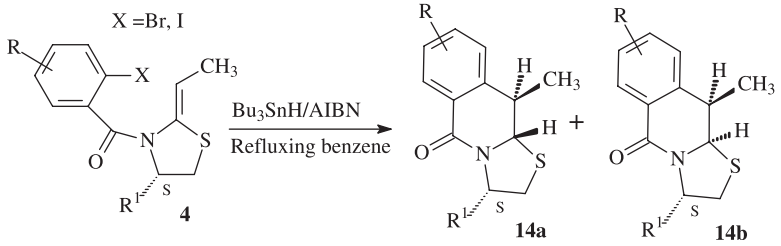
Table 2. Aryl radical cyclizations of *N*-2-halobenzoyl cyclic ketene-*N*,*O*-acetals



Entry	R	R^1	R^2	X	Product yields (%)[a]		
					13a	**13b**	**17**
1	H	$–CH(CH_3)_2$	$–CH_3$	Br	44 ($\mathbf{13a_1}$)	29 ($\mathbf{13b_1}$)	7 (**17a**)
2	H	$–CH(CH_3)_2$	$–CH_3$	I	42 ($\mathbf{13a_1}$)	28 ($\mathbf{13b_1}$)	9 (**17a**)
3	H	$–CH_2CH(CH_3)_2$	$–CH_3$	Br	41 ($\mathbf{13a_2}$)	33 ($\mathbf{13b_2}$)	6 (**17b**)
4	H	$–CH_2CH(CH_3)_2$	$–CH_3$	I	44 ($\mathbf{13a_2}$)	31 ($\mathbf{13b_2}$)	7 (**17b**)
5	*p*-CH_3	$–CH(CH_3)_2$	$–CH_3$	Br	42 ($\mathbf{13a_3}$)	28 ($\mathbf{13b_3}$)	8 (**17c**)
6	*p*-CH_3	$–CH(CH_3)_2$	$–CH_3$	I	40 ($\mathbf{13a_3}$)	29 ($\mathbf{13b_3}$)	6 (**17c**)
7	H	$–CH_2Ph$	$–CH_3$	Br	38 ($\mathbf{13a_4}$)	34 ($\mathbf{13b_4}$)	8 (**17d**)
8	H	$–CH_2Ph$	$–CH_3$	I	37 ($\mathbf{13a_4}$)	35 ($\mathbf{13b_4}$)	8 (**17d**)

[a] All yields are isolated yields based on **3**. $R^2=CH_3$ for each case listed.

Table 3. Aryl radical cyclizations of *N*-2-halobenzoyl cyclic ketene-*N*,*S*-acetals



Entry	R	R^1 in **4**	X	Product yields (%)[a]	
				14a	**14b**
1	H	$-CH(CH_3)_2$	Br	46 (**14a$_1$**)	32 (**14b$_1$**)
2	H	$-CH(CH_3)_2$	I	49 (**14a$_1$**)	33 (**14b$_1$**)
3	H	$-CH_2CH(CH_3)_2$	Br	37 (**14a$_2$**)	33 (**14b$_2$**)
4	H	$-CH_2CH(CH_3)_2$	I	38 (**14a$_2$**)	30 (**14b$_2$**)
5	*p*-CH_3	$-CH(CH_3)_2$	Br	36 (**14a$_3$**)	31 (**14b$_3$**)
6	*p*-CH_3	$-CH_2CH(CH_3)_2$	I	37 (**14a$_4$**)	30 (**14b$_4$**)
7	*m*-OCH_3	$-CH(CH_3)_2$	Br	46 (**14a$_5$**)	33 (**14b$_5$**)

[a] All yields are isolated yields based on **4**.

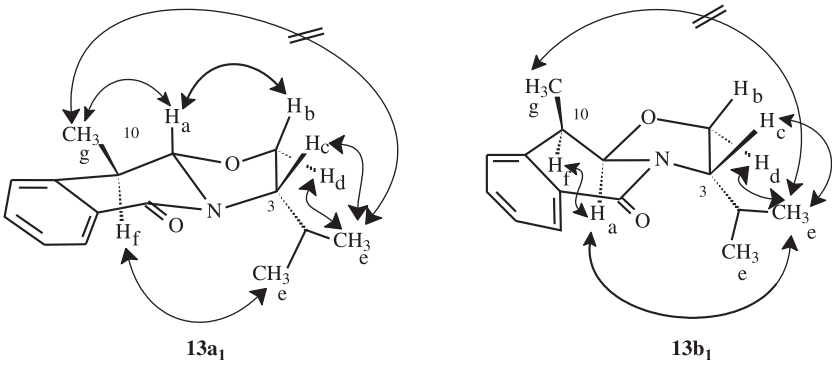
13b$_1$, but correlations from H_e to H_c and from H_e to H_d were evident for both structures.

Of the 4 possible diastereomers of **13**, only two, **13a** and **13b**, were isolated for each example in Table 2. Traces of the other two diastereomers could be present, but we could not separate or identify them. Radical **8** attacks the intramolecular double bond from above stereoselectively (e.g., trans to R^1), resulting in radical **12** where R^2 is trans to R^1. The steric effect from R^1 favors H abstraction from above while R^2 favors abstraction from below, leading to the lower **13a/13b** selectivity observed.

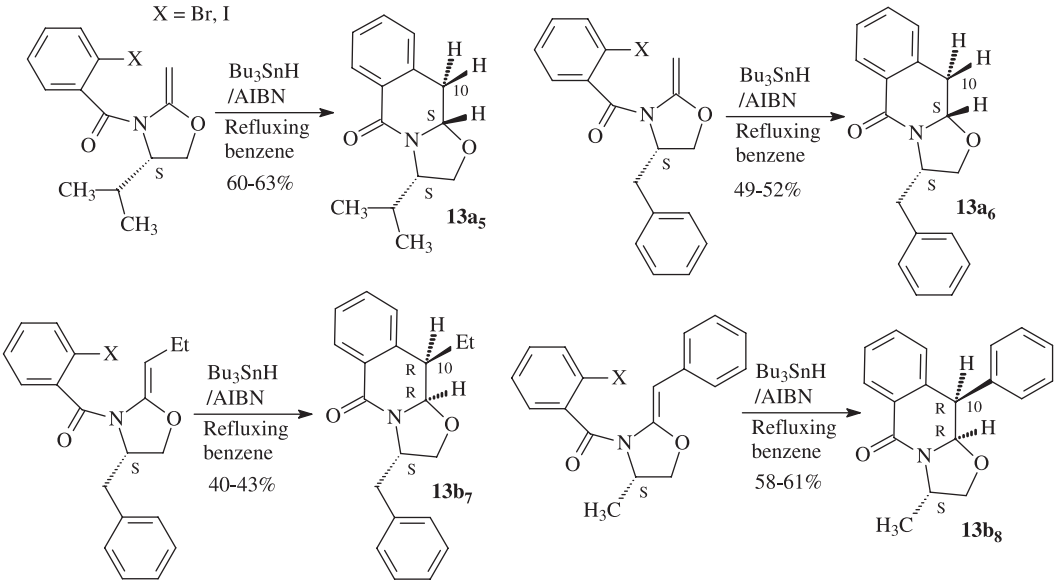
The inherent hydrogen abstraction step's selectivity was probed by replacing the C-10 methyl group (R^2) with R^2=–H, –Ph, and –Et (Scheme 4). When R^1=$-CH(CH_3)_2$, R^2=–H, **13a$_5$** was isolated in yields of 60–63%, while the yield of its diastereomer **13b$_5$** is only 16–18%. When R^1=$-CH_2Ph$, R^2=–H, **13a$_6$** was isolated in 49–52% yields, while its (3*S*,10α*S*) diastereomer, **13b$_6$**, was isolated in 22–25% yields. Clearly, the neighboring C-10 methyl group in radical **12** lowers **13a/13b** ratio obtained on hydrogen abstraction versus when the CH_3 is replaced by R^2=–H. Upon replacing this C-10 CH_3 group in **12** by R^2=–Et or –Ph, hydrogen abstraction trans to R^2 and cis to R^1 predominates, producing **13b** as the major product. Thus, when R^1=$-CH_2Ph$, R^2=–Et, **13b$_7$** was isolated in yields of 40–43% and when R^1=$-CH_3$, R^2=–Ph, **13b$_8$** was isolated in 58–61%. In these cases, no product could be isolated where the 10α hydrogen was up (e.g., cis to R^2). The combined steric effects of R^1 and R^2 clearly control the selectivity of hydrogen abstraction from Bu_3SnH by radical **12**.

The use of a phenyl group for R^2 (in **3** or **4**) is of special interest because it could favor cyclization of **8** to radical **9** due to benzylic radical resonance stabilization. However, no trace of **10** (or **11** when X=S) (Scheme 2) could be detected when R^2=–Ph. It is unlikely that **9** (R^2=–Ph) ever formed, suggesting that tertiary radical **12** is favored kinetically and, possibly, thermodynamically.

Aryl radical cyclizations of seven example *N*-(2-halobenzoyl)-cyclic ketene-*N*,*S*-acetals **4** were also conducted under similar reaction conditions to generate the five pairs of substituted-2,3,10,10α-tetrahydrooxazolo[3,2-*b*]isoquinolin-5-ones **14a** and **14b** (Table 3). After cyclization and flash chromatography purification (hexane/ethyl acetate eluent), product structures were characterized by GC–MS, $^1H/^{13}C$ NMR, $DEPT_{135}$, HETCOR and NOESY methods (Table 3). These cyclizations were similar to those of **3**, except for the absence of acyclic amidothioester formation (analogous to **17**) via aryl radical hydrogen abstraction/ring-opening.



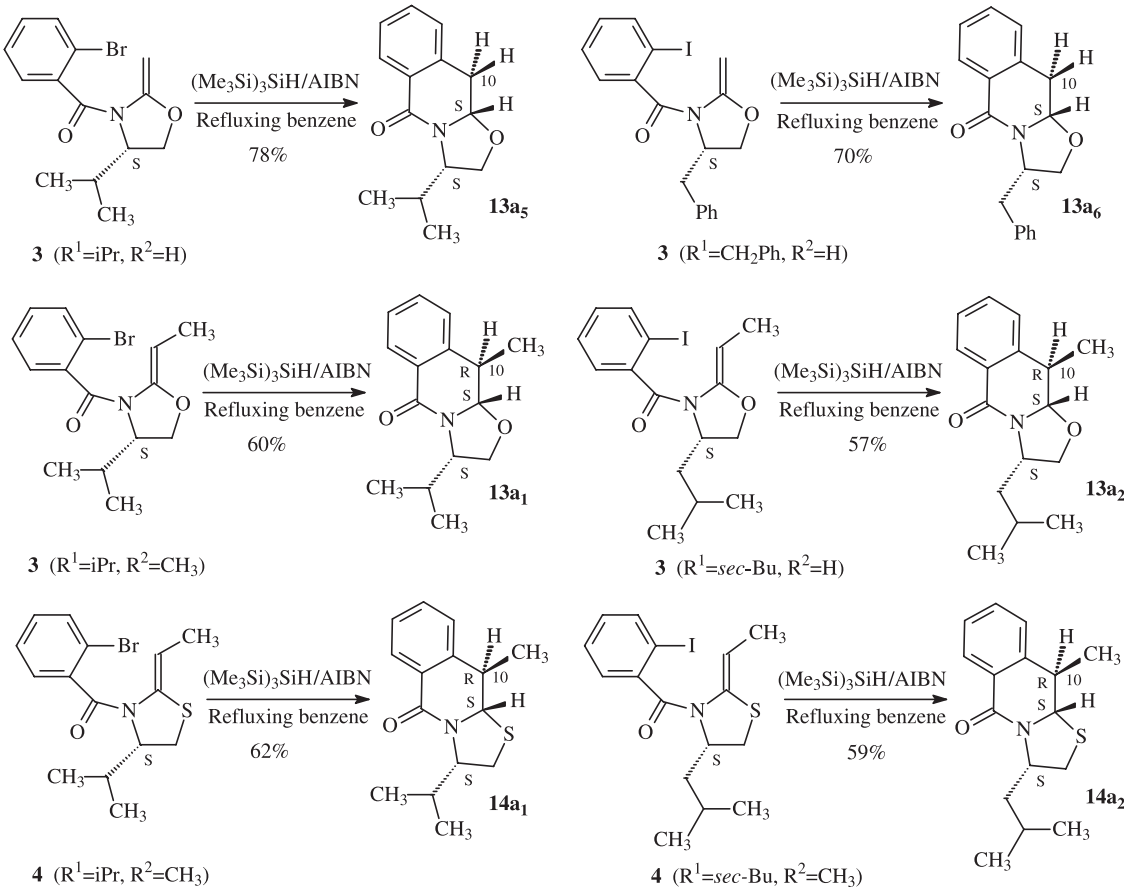
Scheme 3. Selected NOESY correlations for compounds **13a$_1$** and **13b$_1$**.



Scheme 4.

Only six-membered ring formation occurred to produce **14a** and **14b** in each case. No formation of ring system **11** could be detected. This favors the higher relative stability of *N*,*S*-tertiary radical **12** versus **9**.

Both **14a** and **14b** were formed by aryl radical attack trans to R^1 (*i*-Pr, or *sec*-Bu). NOESY experiments again confirmed this stereochemistry in both **14a** and **14b** as with **13a** and **13b**. The methyl group at C-10 on the central ring was trans to the R^2 functional groups of the thiazolidine ring in every case. After cyclization, radical **12** (X=S) abstracted hydrogen from Bu_3SnH both trans and cis to the isopropyl group to generate **14a/14b** (Scheme 2) with the selectivities given in Table 3. Various *N*,*S* heterocyclic analogs exhibit



Scheme 5.

potential biological activity,[14] hence this route may be further exploited to prepare libraries of candidates.

To improve the selectivity in the hydrogen abstraction step by radical **12**, sterically bulky tris(trimethylsilyl)silane was used as the hydrogen atom source in place of tributyltin hydride, This silane is known to react with radicals more slowly than stannanes.[19] The reactions were conducted at 80 °C in refluxing benzene for 8 h, using tris(trimethylsilyl)silane/AIBN/*N*-acyl cyclic ketene-*N*,X-acetals mole ratios of 1.2:1.0:0.2. Half of the AIBN was added at the beginning of the reaction, and the second half was added after 2 h. Example results are summarized in Scheme 5. Using bulky tris(trimethylsilyl)silane as the hydrogen atom donor increases the yields and the selectivities for hydrogen abstraction trans to R^1 to form products **13a** and **14a** (57–78%). The yields of **13b** and **14b** from hydrogen abstraction cis to R^1 decrease to 5–18% in all these reactions. Increasing the steric bulk of the hydrogen atom donor enhances hydrogen abstraction selectivity trans to R^1. Interestingly, unlike Bu_3SnH, the ring-opened products **17** were not found in these reactions, even at only a slight excess of tris(trimethylsilyl)silane over the *N*-acyl cyclic ketene-*N*,X(X=O, S)-acetals. Thus, hydrogen abstraction by aryl radical **8** (Scheme 2) is slowed relative to the use of Bu_3SnH. Cyclization to form the five-membered ring (radical **9**, products **10**, **11**) was also not observed in these reactions. Tris(trimethylsilyl)silane provides higher selectivities than tributylstannane hydride.

3. Conclusions

In conclusion, 2-alkyloxazolines **1** and 2-alkylthiazolines **2** react with 2-halobenzoyl chlorides to form *N*-(2-halobenzoyl)-cyclic ketene-*N*,*O*-acetals **3** and *N*-(2-halobenzoyl)-cyclic ketene-*N*,*S*-acetals **4** in excellent yields, respectively. Both **3** and **4** can then readily undergo stereocontrolled intramolecular aryl radical cyclizations to afford *N*,*O*- and *N*,*S*-heterocycles via six-membered ring formation. These results suggest reasonable stability of *N*,*O*- and *N*,*S*-tertiary radicals, **12**. In contrast, the difficulty encountered in radical initiated polymerizations of 2-methylene-1,3-dioxolanes and 2-methylene-1,3-dioxanes[15a] indicated the corresponding *O*,*O*-tertiary radicals are either formed sluggishly or cannot readily add to a double bond. The selectivity in the hydrogen abstraction step by radical **12** is improved by replacing Bu_3SnH with more bulky $(Me_3Si)_3SiH$.

4. Experimental

4.1. General methods

Melting points were recorded with a Mel-Temp apparatus and were uncorrected (a heating rate of 2 °C/min was used near the mp). The IR spectra were recorded on FT infrared spectrometer as films on KBr plates. The ^1H and ^{13}C NMR spectra were recorded using a 300 MHz spectrometer operating at 300 MHz for proton and 75 MHz for carbon. Chemical shifts were reported in parts per million downfield from Me_4Si used as the internal standard. Splitting patterns are designated as 's, d, t, q, and m'; these symbols indicate 'singlet, doublet, triplet, quartet, and multiplet', respectively. GC–MS instruments were used. All reactions were carried out under a dried argon atmosphere. Acetonitrile and triethylamine were distilled from calcium hydride under nitrogen. Dichloromethane and nitromethane were pre-dried with $CaCl_2$ and then distilled from calcium hydride under nitrogen. Tetrahydrofuran (THF) was distilled from Na metal/benzophenone ketyl. All other commercially obtained reagents were used as received. The silica gel used for the column chromatography was purchased from Aldrich Company (70–230 mesh).

4.1.1. (3*S*,10*R*,10α*S*)-3-Isopropyl-10-methyl-2,3,10,10α-tetrahydrooxazolo[3,2-*b*]isoquinolin-5-one (13a$_1$). 2-Bromobenzoyl chloride (220 mg, 1.00 mmol) was added dropwise to a stirred solution of 2-ethyloxazoline **1a** (157 mg, 1 mmol) and triethylamine (130 mg, 1.20 mmol) in benzene 60 mL at room temperature. Then this solution was stirred for 3 h. The product mixture was filtered and the solvent was removed on a rotary evaporator. Dry benzene (60 mL) was added to the crude residue. Then Bu_3SnH (0.36 mL, 1 mmol) and AIBN (34 mg, 0.2 mmol) were also added. The mixture was refluxed for 10 h and then the solvent was removed by rotary evaporation. The crude product was subjected to flash chromatography on silica gel to afford (3*S*,10*R*,10α*S*)-3-alkyl-10-methyl-2,3,10,10α-tetrahydrooxazolo[3,2-*b*]isoquinolin-5-one (**13a$_1$**, 44%, 107 mg), (3*S*,10*R*,10α*R*)-3-alkyl-10-methyl-2,3,10,10α-tetrahydrooxazolo[3,2-*b*]isoquinolin-5-one (**13b$_1$**, 29%, 70 mg) and propionic acid 2-benzoylamino-3-methylbutyl ester (**17a**, 7%, 17 mg). The same procedure was applied to aryl radical cyclizations of all the *N*-acyl cyclic ketene-*N*,*O*-acetals and *N*-acyl cyclic ketene-*N*,*S*-acetals employed in this work.

Mp 113–115 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.12–7.28 (m, 4H), 4.63 (d, *J*=10.5 Hz, 1H), 4.19 (overlap m, 1H), 4.17 (overlap m, 1H), 3.87 (dd, *J*=7.5, 9.3 Hz, 1H), 3.13 (m, 1H), 2.71 (m, 1H), 1.50 (d, *J*=6.6 Hz, 3H), 0.97 (d, *J*=6.9 Hz, 3H), 0.88 (d, *J*=6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.6, 139.3, 132.3, 129.8, 127.7, 127.1, 124.9, 91.6, 66.6, 60.4, 37.7, 27.3, 19.5, 15.9, 12.9. MS (EI) *m*/*z* (%): 245 (M^+), 202 (100), 158, 132, 104, 77, 51. IR (neat): 2960, 2874, 1658, 1466, 1423, 1352, 1200, 1058, 742 cm^{-1}. Anal. Calcd for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.81; N, 5.71; Found: C, 73.25; H, 7.91; N, 5.86.

4.1.2. (3*S*,10*R*,10α*R*)-3-Isopropyl-10-methyl-2,3,10,10α-tetrahydrooxazolo[3,2-*b*]isoquinolin-5-one (13b$_1$). Mp 113–115 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.00–7.22 (m, 4H), 5.37 (d, *J*=4.5 Hz, 1H), 4.34 (dd, *J*=5.4, 10.8 Hz, 1H), 4.13 (dd, *J*=5.4, 7.8 Hz, 1H), 4.00 (dd, *J*=4.5, 7.8 Hz, 1H), 3.22 (m, 1H), 2.54 (m, 1H), 1.11 (d, *J*=6.9 Hz, 3H), 0.96 (d, *J*=6.9 Hz, 3H), 0.93 (d, *J*=6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.3, 140.7, 132.1, 128.9, 127.9, 127.6, 127.5, 88.6, 67.7, 60.0, 38.6, 29.2, 18.9, 16.8, 15.3. MS (EI) *m*/*z* (%): 245 (M^+), 202 (100), 158, 132, 104, 77, 51. IR (neat): 2962, 2874, 1657, 1465, 1421, 1355, 1207, 1055, 740 cm^{-1}.

4.1.3. Propionic acid 2-benzoylamino-3-methylbutyl ester (17a). Mp 118–120 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.78–7.44 (m, 5H), 6.51 (d, *J*=8.4 Hz, 1H),

4.39 (dd, J=6.9, 11.1 Hz, 1H), 4.34 (m, 1H), 4.13 (dd, J=3.6, 11.1 Hz, 1H), 2.33 (q, J=7.2 Hz, 2H), 1.94 (m, 1H), 1.10 (t, J=7.2 Hz, 3H), 1.02 (d, J=7.8 Hz, 3H), 1.00 (d, J=7.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7, 167.3, 134.6, 131.4, 128.5, 126.8, 64.3, 53.9, 29.8, 27.4, 19.2, 18.6, 9.0. MS (EI) *m/z* (%): 263 (M^+), 189, 146, 105 (100), 86, 77, 51. IR (neat): 3308 (broad), 3030, 2978, 2944, 1738, 1640, 1538, 1183, 1084, 1028, 700 cm^{-1}. Anal. Calcd for $C_{15}H_{21}O_3N$: C, 68.42; H, 8.04; N, 5.32; Found: C, 68.70; H, 7.83; N, 5.18.

4.1.4. (3*S*,10*R*,10α*S*)-3-Isobutyl-10-methyl-2,3,10,10α-tetrahydrooxazolo[3,2-*b*]isoquinolin-5-one (13a$_2$). Mp 115–117 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09–7.27 (m, 4H), 4.62 (d, J=10.5 Hz, 1H), 4.26 (m, 1H), 4.10 (m, 1H), 3.96 (dd, J=6.0, 7.8 Hz, 1H), 3.04 (m, 1H), 2.04 (m, 1H), 1.67 (m, 1H), 1.51 (d, J=6.9 Hz, 3H), 1.01 (d, J=6.9 Hz, 3H), 0.96 (d, J=6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 161.2, 139.2, 132.3, 130.0, 127.7, 127.3, 124.9, 91.3, 70.9, 54.4, 41.7, 38.7, 26.0, 23.6, 21.7, 12.8. MS (EI) *m/z*: 259 (M^+), 244, 203 (100), 132, 104, 77, 63, 51. IR (neat): 2962, 2878, 1657, 1470, 1421, 1350, 1204, 1057, 741 cm^{-1}.

4.1.5. (3*S*,10*R*,10α*R*)-3-Isobutyl-10-methyl-2,3,10,10α-tetrahydrooxazolo[3,2-*b*]isoquinolin-5-one (13b$_2$). Mp 115–117 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07–7.29 (m, 4H), 5.43 (d, J=4.5 Hz, 1H), 4.50 (m, 1H), 4.36 (dd, J=6.6, 8.1 Hz, 1H), 3.89 (dd, J=4.5, 8.1 Hz, 1H), 3.32 (m, 1H), 2.18 (m, 1H), 1.71 (m, 1H), 1.49 (m, 1H), 1.10 (d, J=7.2 Hz, 3H), 1.09 (d, J=6.3 Hz, 3H), 0.99 (d, J=6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 160.9, 140.7, 132.0, 128.9, 127.7, 127.6, 121.3, 87.2, 72.0, 53.8, 41.0, 38.1, 25.6, 23.4, 21.9, 15.3. MS (EI) *m/z*: 259 (M^+), 244, 202 (100), 132, 104, 77, 63, 51. IR (neat): 2960, 2874, 1658, 1466, 1423, 1352, 1200, 1058, 742 cm^{-1}.

4.1.6. Propionic acid 2-benzoylamino-4-methylpentyl ester (17b). Mp 121–123 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77–7.41 (m, 5H), 6.42 (d, J=7.8 Hz, 1H), 4.51 (m, 1H), 4.24 (dd, J=6.3, 11.1 Hz, 1H), 4.13 (dd, J=3.3, 11.1 Hz, 1H), 2.33 (q, J=7.5 Hz, 2H), 1.69 (m, 1H), 1.50 (m, 1H), 1.43 (m, 1H), 1.11 (t, J=7.2 Hz, 3H), 0.96 (d, J=6.3 Hz, 3H), 0.94 (d, J=6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 174.5, 167.0, 134.4, 131.3, 128.4, 126.8, 66.1, 47.2, 40.6, 27.4, 24.8, 22.9, 22.2, 9.0. MS (EI) *m/z*: 277 (M^+), 203, 146, 105 (100), 77, 63, 57, 51. IR (neat): 3303 (broad), 3035, 2983, 2940, 1735, 1642, 1539, 1188, 1080, 1021, 695 cm^{-1}. Anal. Calcd for $C_{16}H_{21}O_2N$: C, 69.29; H, 8.36; N, 5.05; Found: C, 69.11; H, 8.42; N, 5.16.

4.1.7. (3*S*,10*R*,10α*S*)-3-Isopropyl-8,10-dimethyl-2,3,10,10α-tetrahydrooxazolo[3,2-*b*]isoquinolin-5-one (13a$_3$). Mp 116–118 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00–7.17 (m, 3H), 4.60 (d, J=10.8 Hz, 1H), 4.18 (overlap m, 1H), 4.16 (overlap m, 1H), 3.85 (dd, J=7.2, 9.3 Hz, 1H), 3.09 (m, 1H), 2.65 (m, 1H), 2.42 (s, 3H), 1.48 (d, J=6.6 Hz, 3H), 0.96 (d, J=6.9 Hz, 3H), 0.88 (d, J=6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 161.9, 142.8, 139.4, 127.9, 127.2, 125.6, 91.8, 66.7, 60.4, 37.7, 27.4, 21.7, 19.5, 15.9, 12.9. MS (EI) *m/z*: 259 (M^+), 216, 172, 146 (100), 117, 91, 77, 51. IR (neat): 2970, 2880, 1654, 1463, 1420, 1349, 1203, 1056, 738 cm^{-1}. Anal. Calcd for $C_{16}H_{21}O_2N$: C, 74.10; H, 8.16; N, 5.40; Found: C, 73.91; H, 8.03; N, 5.38.

4.1.8. (3*S*,10*R*,10α*R*)-3-Isopropyl-8,10-dimethyl-2,3,10,10α-tetrahydrooxazolo[3,2-*b*]isoquinolin-5-one (13b$_3$). Mp 116–118 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89–7.03 (m, 3H), 5.34 (d, J=4.2 Hz, 1H), 4.31 (dd, J=4.5, 6.8 Hz, 1H), 4.11 (dd, J=6.6, 8.7 Hz, 1H), 4.00 (dd, J=4.5, 8.4 Hz, 1H), 3.16 (m, 1H), 2.53 (m, 1H), 2.38 (s, 3H), 1.09 (d, J=7.2 Hz, 3H), 0.95 (d, J=7.2 Hz, 3H), 0.92 (d, J=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 161.4, 142.6, 140.7, 128.2, 127.9, 126.2, 121.3, 88.6, 67.7, 60.0, 39.3, 38.6, 29.2, 21.4, 18.9, 16.7, 15.3. MS (EI) *m/z*: 259 (M^+), 216, 172, 146 (100), 117, 91, 77, 51. IR (neat): 2968, 2878, 1656, 1461, 1418, 1345, 1200, 1054, 740 cm^{-1}.

4.1.9. Propionic acid 3-methyl-2-(4-methylbenzoylamino)-butyl ester (17c). Mp 123–125 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68–7.25 (m, 4H), 6.25 (d, J=8.2 Hz, 1H), 4.39 (dd, J=6.6, 11.1 Hz, 1H), 4.24 (m, 1H), 4.13 (dd, J=3.3, 11.1 Hz, 1H), 2.40 (s, 3H), 2.32 (q, J=7.5 Hz, 2H), 1.93 (m, 1H), 1.10 (t, J=7.2 Hz, 3H), 1.00 (d, J=6.3 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 161.4, 142.6, 140.7, 128.2, 128.1, 121.3, 88.6, 67.7, 60.0, 39.3, 38.6, 29.2, 18.9, 16.7, 15.3. MS (EI) *m/z*: 278 (M^++H), 262, 203, 161, 146, 119 (100), 91, 77. IR (neat): 3306 (broad), 3029, 2976, 2947, 1739, 1650, 1534, 1187, 1082, 1026, 704 cm^{-1}. Anal. Calcd for $C_{16}H_{23}O_3N$: C, 69.29; H, 8.36; N, 5.05; Found: C, 69.21; H, 8.42; N, 4.93.

4.1.10. (3*S*,10*R*,10α*S*)-3-Benzyl-10-methyl-2,3,10,10α-tetrahydrooxazolo[3,2-*b*]isoquinolin-5-one (13a$_4$). Mp 128–130 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23–7.35 (m, 9H), 4.73 (d, J=10.5 Hz, 1H), 4.51 (m, 1H), 4.23 (m, 1H), 3.91 (dd, J=6.3, 8.1 Hz, 1H), 3.68 (m, 1H), 3.06 (m, 1H), 2.81 (dd, J=10.2, 12.9 Hz, 1H), 1.57 (d, J=6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 161.4, 139.2, 137.9, 132.4, 129.6, 128.7, 128.6, 127.7, 127.3, 126.6, 124.9, 91.6, 69.6, 57.0, 38.4, 38.1, 12.8. MS (EI) *m/z*: 293 (M^+), 278, 202 (100), 174, 158, 132, 115, 104, 91, 77, 65, 51. IR (neat): 2978, 2902, 2884, 1676, 1466, 1398, 1352, 1225, 1057, 727 cm^{-1}.

4.1.11. (3*S*,10*R*,10α*R*)-3-Benzyl-10-methyl-2,3,10,10α-tetrahydrooxazolo[3,2-*b*]isoquinolin-5-one (13b$_4$). Mp 128–130 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14–7.30 (m, 9H), 5.31 (d, J=3.9 Hz, 1H), 4.69 (m, 1H), 4.19 (t, J=6.9 Hz, 1H), 4.00 (dd, J=5.4, 7.8 Hz, 1H), 3.58 (dd, J=1.2, 11.7 Hz, 1H), 3.29 (m, 1H), 2.97 (dd, J=10.2, 12.6 Hz, 1H), 1.18 (d, J=6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 161.3, 140.9, 137.2, 132.3, 129.5, 128.7, 128.6, 127.8, 127.7, 127.5, 126.67, 87.9, 70.6, 56.1, 38.2, 37.2, 15.3. MS (EI) *m/z*: 293 (M^+), 278, 202 (100), 174, 158, 115, 103, 91, 77, 65, 51. IR (neat): 2979, 2904, 2887, 1674, 1464, 1396, 1355, 1228, 1064, 724 cm^{-1}. Anal. Calcd for $C_{19}H_{19}O_2N$: C, 77.79; H, 6.53; N, 4.77; Found: C, 77.70; H, 6.46; N, 4.58.

4.1.12. Propionic acid 2-benzoylamino-3-phenylpropyl ester (17d). Mp 138–140 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80–7.32 (m, 10H), 6.82 (d, J=7.5 Hz, 1H), 4.69 (m, 1H), 4.27 (overlap m, 1H), 4.22 (overlap m, 1H), 3.10 (dd, J=6.0, 13.5 Hz, 1H), 2.96 (dd, J=7.5, 13.5 Hz, 1H), 2.41 (q, J=7.5 Hz, 2H), 1.19 (d, J=6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 174.6, 167.0, 136.9, 134.2, 131.3, 129.1, 128.6, 128.5, 126.8, 126.6, 64.5, 50.2, 37.3, 27.3, 8.9. MS (EI) *m/z*: 312 (M^+), 238 (100), 191, 146, 118, 105, 91, 77, 51. IR (neat): 3345 (broad), 3030, 2967, 2904, 1767, 1643, 1524,

1145, 1037, 1015, 711 cm^{-1}. Anal. Calcd for $C_{19}H_{21}O_3N$: C, 73.29; H, 6.80; N, 4.50; Found: C, 73.57; H, 6.56; N, 4.31.

4.1.13. (3*S*,10α*S*)-3-Isopropyl-2,3,10,10α-tetrahydrooxazolo[3,2-*b*]isoquinolin-5-one (13a$_5$). Mp 110–112 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08–7.39 (m, 4H), 5.06 (dd, *J*=3.6, 11.7 Hz, 1H), 4.19 (overlap m, 1H), 4.17 (overlap m, 1H), 3.88 (dd, *J*=7.8, 9.3 Hz, 1H), 3.26 (dd, *J*=3.6, 15.0 Hz, 1H), 3.09 (m, 1H), 2.70 (m, 1H), 1.62 (s, 3H), 0.97 (d, *J*=6.9 Hz, 3H), 0.88 (d, *J*=6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 161.4, 139.3, 132.1, 129.8, 127.9, 127.5, 124.9, 87.1, 66.9, 60.0, 37.7, 27.2, 15.9, 12.9. MS (EI) *m*/*z* (%): 231 (M^+), 188 (100), 144, 132, 104, 77, 51. IR (neat): 2960, 2874, 1658, 1466, 1423, 1352, 1200, 1058, 742 cm^{-1}. Anal. Calcd for $C_{14}H_{17}O_2N$: C, 72.70; H, 7.41; N, 6.06; Found: C, 72.88; H, 7.27; N, 6.23.

4.1.14. (3*S*,10α*S*)-3-Benzyl-2,3,10,10α-tetrahydrooxazolo[3,2-*b*]isoquinolin-5-one (13a$_6$). Mp 125–127 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15–7.33 (m, 9H), 5.19 (dd, *J*=4.8, 10.8 Hz, 1H), 4.72 (m, 1H), 4.24 (dd, *J*=6.9, 8.7 Hz, 1H), 3.93 (dd, *J*=6.0, 8.4 Hz, 1H), 3.57 (dd, *J*=3.3, 13.2 Hz, 1H), 3.26 (m, 1H), 3.08 (m, 1H), 2.99 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 161.5, 137.1, 133.5, 132.1, 129.5, 128.6, 128.1, 127.7, 127.6, 126.7, 86.2, 70.1, 55.8, 37.2, 34.6. MS (EI) *m*/*z*: 279 (M^+), 188 (100), 160, 144, 118, 103, 91, 65, 50. IR (neat): 2960, 2874, 1658, 1466, 1423, 1352, 1200, 1058, 742 cm^{-1}. Anal. Calcd for $C_{18}H_{17}O_2N$: C, 77.40; H, 6.13; N, 5.01; Found: C, 77.31; H, 6.30; N, 5.13.

4.1.15. (3*S*,10*R*,10α*R*)-3-Benzyl-10-ethyl-2,3,10,10α-tetrahydrooxazolo[3,2-*b*]isoquinolin-5-one (13b$_7$). Mp 130–133 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06–7.26 (m, 9H), 5.26 (d, *J*=3.6 Hz, 1H), 4.58 (m, 1H), 4.11 (dd, *J*=6.9, 8.1 Hz, 1H), 3.90 (dd, *J*=5.4, 8.1 Hz, 1H), 3.49 (dd, *J*=2.4, 13.2 Hz, 1H), 2.89 (overlap m, 1H), 2.85 (overlap m, 1H), 1.87 (m, 1H), 1.25 (m, 1H), 0.77 (t, *J*=7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 161.4, 138.5, 137.2, 131.4, 129.4, 129.2, 129.0, 128.5, 127.7, 127.6, 126.6, 88.3, 70.7, 55.9, 44.9, 39.3, 37.1, 23.3, 21.1, 11.0. MS (EI) *m*/*z*: 308 (M^++H), 278, 216 (100), 198, 172, 165, 131, 115, 91, 77, 65, 51. IR (neat): 2960, 2874, 1658, 1466, 1423, 1352, 1200, 1058, 742 cm^{-1}.

4.1.16. (3*S*,10*R*,10α*R*)-3-Methyl-10-phenyl-2,3,10,10α-tetrahydrooxazolo[3,2-*b*]isoquinolin-5-one (13b$_8$). Mp 122–125 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15–6.98 (m, 9H), 5.63 (d, *J*=4.8 Hz, 1H), 4.44 (d, *J*=4.8 Hz, 1H), 4.18 (m, 1H), 3.47 (dd, *J*=3.3, 8.1 Hz, 1H), 3.25 (dd, *J*=6.3, 7.8 Hz, 1H), 1.36 (d, *J*=6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 161.4, 136.8, 136.1, 132.6, 130.5, 129.5, 129.0, 128.2, 128.1, 127.6, 127.2, 87.3, 72.7, 50.5, 49.1, 17.8. MS (EI) *m*/*z*: 280 (M^++H), 194, 165 (100), 139, 115, 86, 77, 51. IR (neat): 2960, 2874, 1658, 1466, 1423, 1352, 1200, 1058, 742 cm^{-1}. Anal. Calcd for $C_{18}H_{17}O_2N$: C, 77.40; H, 6.13; N, 5.01; Found: C, 77.46; H, 6.02; N, 5.24.

4.1.17. (3*S*,10*R*,10α*S*)-3-Isopropyl-10-methyl-2,3,10,10α-tetrahydrothiazolo[3,2-*b*]isoquinolin-5-one (14a$_1$). Mp 142–144 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14–7.32 (m, 4H), 4.77 (d, *J*=11.70 Hz, 1H), 4.45 (dd, *J*=6.00, 6.20 Hz, 1H), 3.22 (m, 1H), 3.07 (dd, *J*=7.20, 12.30 Hz, 1H), 2.90 (d, *J*=12.30 Hz, 1H), 2.54 (m, 1H), 1.45 (d, *J*=6.90 Hz, 3H), 1.01 (d, *J*=6.90 Hz, 3H), 1.00 (d, *J*=6.90 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 163.6, 142.0, 132.2, 129.8, 128.4, 127.1, 124.1, 69.5, 66.0, 38.9, 30.6, 29.8, 20.0, 18.1 and 15.7. MS (EI) *m*/*z*: 261 (M^+), 218 (100), 159, 132. IR (neat): 2961, 2928, 2873, 1641, 1380 cm^{-1}. Anal. Calcd for $C_{15}H_{19}OSN$: C, 68.93; H, 7.33; N, 5.36; S, 12.27; Found: C, 68.76; H, 7.41; N, 5.51; S, 12.12.

4.1.18. 4(3*S*,10*R*,10α*R*)-3-Isopropyl-10-methyl-2,3,10,10α-tetrahydrothiazolo[3,2-*b*]isoquinolin-5-one (14b$_1$). Mp 142–144 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01–7.17 (m, 4H), 5.21 (d, *J*=3.90 Hz, 1H), 4.79 (dd, *J*=5.70, 8.40 Hz, 1H), 3.07 (dd, *J*=5.70, 10.80 Hz, 1H), 2.99 (m, 1H), 2.87 (d, *J*=10.80 Hz, 1H), 2.24 (m, 1H), 1.26 (d, *J*=7.20 Hz, 3H), 1.03 (d, *J*=7.20 Hz, 3H), 0.98 (d, *J*=6.90 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 162.1, 142.7, 131.8, 128.3, 128.1, 127.1, 126.4, 65.6, 63.6, 39.0, 32.0, 30.6, 23.2, 19.5 and 15.7. MS (EI) *m*/*z*: 261 (M^+), 218 (100), 159, 132. IR (neat): 2959, 2928, 2871, 1645, 1380 cm^{-1}.

4.1.19. (3*S*,10*R*,10α*S*)-3-Isobutyl-10-methyl-2,3,10,10α-tetrahydrothiazolo[3,2-*b*]isoquinolin-5-one (14a$_2$). Mp 144–146 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10–7.27 (m, 4H), 4.72 (d, *J*=12.00 Hz, 1H), 4.67 (m, 1H), 3.15 (m, 1H), 3.15 (m, 1H), 2.85 (d, *J*=12.00 Hz, 1H), 1.82–1.67 (m, 2H), 1.64 (m, 1H), 1.46 (d, *J*=6.80 Hz, 3H), 1.06 (d, *J*=6.34 Hz, 3H), 0.96 (d, *J*=6.30 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 162.4, 141.5, 132.1, 130.0, 128.0, 127.2, 123.9, 68.9, 60.0, 42.6, 39.3, 33.4, 26.3, 23.8, 21.5 and 15.6. MS (EI) *m*/*z*: 275 (M^++H), 260, 219 (100), 132, 104. IR (neat): 2960, 2928, 2869, 1650, 1456, 1385, 752 cm^{-1}.

4.1.20. (3*S*,10*R*,10α*R*)-3-Isobutyl-10-methyl-2,3,10,10α-tetrahydrothiazolo[3,2-*b*]isoquinolin-5-one (14b$_2$). Mp 144–146 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03–7.17 (m, 4H), 5.23 (d, *J*=3.80 Hz, 1H), 5.08 (m, 1H), 3.13 (dd, *J*=5.80, 10.80 Hz, 1H), 2.99 (m, 1H), 2.78 (d, *J*=10.80 Hz, 1H), 1.66–1.63 (m, 2H), 1.38 (m, 1H), 1.27 (d, *J*=6.90 Hz, 3H), 1.06 (d, *J*=5.70 Hz, 3H), 0.96 (d, *J*=5.70 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 162.2, 143.5, 132.5, 130.5, 128.8, 127.7, 127.1, 63.5, 59.1, 41.3, 39.4, 34.1, 26.4, 23.9, 22.3 and 15.8. MS (EI) *m*/*z*: 275 (M^++H), 260, 219 (100), 132, 104. IR (neat): 2956, 2928, 2869, 1651, 1457, 1385, 752 cm^{-1}. Anal. Calcd for $C_{16}H_{21}OSN$: C, 69.78; H, 7.69; N, 5.09; S, 11.64; Found: C, 69.48; H, 7.84; N, 5.22; S, 11.38.

4.1.21. (3*S*,10*R*,10α*S*)-3-Isopropyl-8,10-dimethyl-2,3,10,10α-tetrahydrothiazolo[3,2-*b*]isoquinolin-5-one (14a$_3$). Mp 147–149 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03–7.12 (m, 3H), 4.75 (d, *J*=12.00 Hz, 1H), 4.52 (m, 1H), 3.19 (m, 1H), 3.07 (dd, *J*=7.21, 12.23 Hz, 1H), 2.90 (d, *J*=12.23 Hz, 1H), 2.51 (m, 1H), 2.42 (s, 3H), 1.45 (d, *J*=6.80 Hz, 3H), 1.00 (d, *J*=6.80 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 163.8, 142.8, 142.0, 128.5, 127.9, 127.3, 124.8, 69.6, 65.9, 38.8, 30.7, 29.9, 21.8, 20.0, 18.2 and 15.7. MS (EI) *m*/*z*: 275 (M^++H), 232 (100), 173, 146. IR (neat): 2960, 2928, 2873, 1642, 1381 cm^{-1}.

4.1.22. (3*S*,10*R*,10α*R*)-3-Isopropyl-8,10-dimethyl-2,3,10,10α-tetrahydrothiazolo[3,2-*b*]isoquinolin-5-one (14b$_3$). Mp 146–148 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ

7.90–6.99 (m, 3H), 5.20 (d, J=3.80 Hz, 1H), 4.78 (dd, J=6.20, 8.20 Hz, 1H), 3.06 (dd, J=7.21, 10.96 Hz, 1H), 2.93 (m, 1H), 2.87 (d, J=10.96 Hz, 1H), 2.39 (s, 3H), 2.23 (m, 1H), 1.25 (d, J=7.00 Hz, 3H), 1.03 (d, J=6.70 Hz, 3H), 0.98 (d, J=6.70 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 162.8, 143.3, 142.9, 129.0, 128.5, 127.5, 126.1, 66.0, 64.3, 39.4, 32.6, 31.2, 21.9, 20.1, 20.0 and 16.2. MS (EI) *m/z*: 275 (M^++H), 232 (100), 173, 146. IR (neat): 2960, 2928, 2873, 1650, 1377 cm^{-1}.

4.1.23. (3*S*,10*R*,10α*S*)-3-Isobutyl-8,10-dimethyl-2,3,10,10α-tetrahydrothiazolo[3,2-*b*]isoquinolin-5-one ($14a_4$). Mp 145–147 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00–7.10 (m, 3H), 4.71 (d, J=12.00 Hz, 1H), 4.68 (m, 1H), 3.14 (m, 1H), 3.10 (m, 1H), 2.84 (d, J=12.00 Hz, 1H), 2.41 (s, 3H), 1.78 (m, 2H), 1.64 (m, 1H), 1.44 (d, J=6.80 Hz, 3H), 1.05 (d, J=6.80 Hz, 3H), 0.96 (d, J=6.40 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 162.9, 143.0, 141.9, 128.5, 128.3, 127.5, 125.0, 69.3, 60.3, 43.1, 39.6, 33.8, 26.7, 24.2, 22.0, 21.8 and 16.0. MS (EI) *m/z*: 289 (M^++H), 274, 233, 200, 174, 146 (100), 117. IR (neat): 2956, 2932, 2869, 1650, 1456, 1385 cm^{-1}. Anal. Calcd for $C_{17}H_{23}OSN$: C, 70.55; H, 8.01; N, 4.84; S, 11.08; Found: C, 70.67; H, 7.91; N, 4.68; 11.32.

4.1.24. (3*S*,10*R*,10α*R*)-3-Isobutyl-8,10-dimethyl-2,3,10,10α-tetrahydrothiazolo[3,2-*b*]isoquinolin-5-one ($14b_4$). Mp 145–147 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91–6.99 (m, 3H), 5.20 (d, J=3.60 Hz, 1H), 5.06 (m, 1H), 3.12 (dd, J=5.80, 10.80 Hz, 1H), 2.92 (m, 1H), 2.76 (d, J=10.80 Hz, 1H), 2.39 (s, 3H), 1.71–1.59 (m, 2H), 1.37 (m, 1H), 1.25 (d, J=7.00 Hz, 3H), 1.03 (d, J=6.40 Hz, 3H), 0.98 (d, J=6.40 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 161.9, 143.1, 142.6, 128.4, 128.1, 127.3, 125.6, 63.2, 58.6, 40.9, 39.1, 33.7, 26.0, 23.5, 21.9, 21.5 and 15.4. MS (EI) *m/z*: 288 (M^+), 274, 233, 200, 174, 146 (100), 117. IR (neat): 2960, 2932, 2869, 1654, 1456, 1385 cm^{-1}.

4.1.25. (3*S*,10*R*,10α*S*)-3-Isopropyl-7-methoxy-10-methyl-2,3,10,10a-tetrahydrothiazolo[3,2-*b*]isoquinolin-5-one ($14a_5$). Mp 138–140 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66–7.04 (m, 3H), 4.74 (d, J=12.00 Hz, 1H), 4.52 (t, J=6.10 Hz, 1H), 3.85 (s, 3H), 3.17 (m, 1H), 3.09 (dd, J=7.31, 12.23 Hz, 1H), 2.91 (d, J=12.23 Hz, 1H), 2.51 (m, 1H), 1.43 (d, J=6.80 Hz, 3H), 1.00 (d, J=6.80 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 163.6, 158.8, 134.4, 131.0, 125.4, 119.4, 111.8, 69.8, 66.1, 55.5, 38.3, 30.7, 30.0, 20.1, 18.2 and 15.9. MS (EI) *m/z*: 291 (M^++H), 248 (100), 189, 162, 134, 119, 91. IR (neat): 2961, 2932, 2873, 1653, 1379, 1286, 1033 cm^{-1}.

4.1.26. (3*S*,10*R*,10α*R*)-3-Isopropyl-7-methoxy-10-methyl-2,3,10,10a-tetrahydrothiazolo[3,2-*b*]isoquinolin-5-one ($14b_5$). Mp 137–139 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51–6.97 (m, 3H), 5.18 (d, J=12.00 Hz, 1H), 4.77 (t, J=6.10 Hz, 1H), 3.83 (s, 3H), 3.06 (dd, J=7.31, 12.23 Hz, 1H), 2.92 (m, 1H), 2.85 (d, J=12.23 Hz, 1H), 2.22 (m, 1H), 1.21 (d, J=6.80 Hz, 3H), 1.00 (d, J=6.80 Hz, 3H), 0.96 (d, J=6.80 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 162.3, 159.0, 135.1, 129.4, 127.7, 119.5, 111.9, 65.8, 64.1, 55.6, 38.2, 32.2, 30.8, 19.7, 19.6 and 15.9. MS (EI) *m/z*: 291 (M^++H), 248 (100), 189, 162, 134, 119, 91. IR (neat): 2960, 2931, 2873, 1653, 1380, 1285, 1031 cm^{-1}.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.02.018.

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(*R*)-4-Hydroxymethyl-2-phenyl-4,5-dihydrooxazol-4-ylmethyl acetate: chiral building block for the synthesis of optically active α-substituted α-amino acid derivatives

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Abstract—(*R*)-4-Hydroxymethyl-2-phenyl-4,5-dihydrooxazol-4-ylmethyl acetate was efficiently obtained by lipase-catalyzed asymmetrization of the prochiral diol. (*R*)-4-Hydroxymethyl-2-phenyl-4,5-dihydrooxazol-4-ylmethyl acetate was converted to (*R*)-2-(hydroxymethyl)glutamic acid and a synthetic intermediate of (−)-deoxydysibetaine.

1. Introduction

Recently, compounds containing highly functionalized α-substituted α-amino acid moieties have been reported to possess intriguing biological activity (Fig. 1). For example, myriocin (also known as thermozymocidin and ISP-1) is an α-substituted α-amino acid derivative isolated from the culture broth of *Myriococcum albomyces*, *Mycelia sterilia* and *Isaria sinclairii*, and has reported to possess antifungal and immunosuppressive activity.[1–3] Lactacystin is an α-substituted α-amino acid derivative isolated from the culture broth of *Streptomyces* sp. OM-6519 and first attracted interest due to its ability to inhibit cell proliferation and induce nerve outgrowth in mouse neuroblastoma. The compound exhibits significant neurotropic activity due to its ability to inhibit the 20S proteasome.[4] (*R*)-2-(Hydroxymethyl)glutamic acid is a selective agonist of metabotropic glutamate receptor group II (mGluR3).[5] Dysibetaine is an α-substituted α-amino acid derivative isolated from the marine sponge *Dysidea herbacea* collected in Yap (Micronesia). As this compound is able to induce convulsive behavior in mice, it was suspected of acting on glutamate receptors in the central nervous system.[6] These biological features have prompted many groups to pursue synthetic studies of compounds containing highly functionalized α-substituted α-amino acid moieties.[5,7–9]

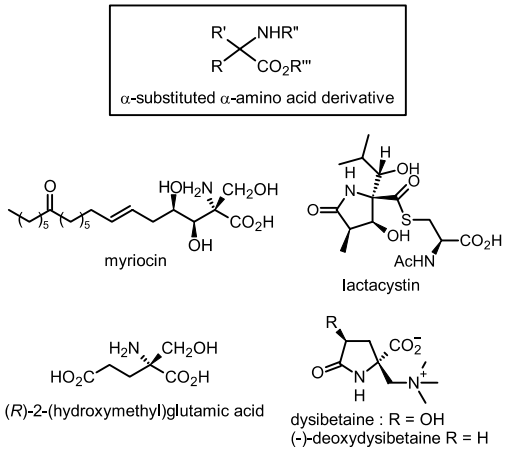

Figure 1. Structure of biologically active compounds containing α-substituted α-amino acid moieties.

The chiral α-substituted α-amino acid derivatives were synthesized using a number of methods including alkylation of chiral enolates,[5a,f,7f,8a–c,e,g,h,k,l] Strecker synthesis,[5c,e,8m] rearrangement of chiral trichloroacetimidates,[7i,8d,f] chiral epoxide-opening with azide[7e,g] or trichloroacetimidates,[7h,8o] and desymmetrization of prochiral compounds.[10]

The synthetic method employed to generate biologically active chiral compounds using chiral building block represents one of the useful methods. Although many chiral building blocks, prepared by enzymatic methods or from the chemical conversion of natural sources (sugars, amino acids etc.), have been developed for the synthesis of versatile

Keywords: Lipase; Chiral building block; α-Substituted α-amino acid; (*R*)-2-(Hydroxymethyl)glutamic acid; (−)-Deoxydysibetaine.
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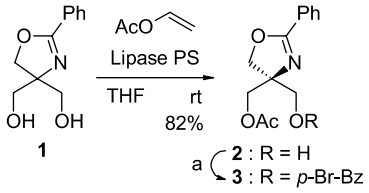
chiral compounds, only a few chiral building blocks have been prepared for the synthesis of highly functionalized α-substituted α-amino acid derivatives.[10]

The authors previously reported the development of chiral building blocks using lipase[11] and the successful synthesis of biologically active natural products from these chiral building blocks.[12] In this paper, the authors developed useful a novel chiral building block for the synthesis of α-substituted α-amino acid derivatives using lipase-catalyzed asymmetrization of the prochiral diol. The chiral building block was converted to (*R*)-2-(hydroxymethyl)-glutamic acid and a synthetic intermediate of (−)-deoxydysibetaine.

2. Results and discussion

Prochiral diol **1**,[13] prepared from 2-amino-2-hydroxymethylpropane-1,3-diol and benzoic acid, was treated with vinyl acetate in THF at rt for 5 days in the presence of Lipase PS® (from *Pseudomonas cepacia*) and gave mono acetate **2** in 82% yield (Scheme 1). Enantiomeric excess of acetate **2** was >99% ee as determined by HPLC using a chiral column. In the case of using Lipase AY® (from *Candida rugosa*) or Lipase AK® (from *Pseudomonas fluorescence*), enantiomeric excess of acetate **2** was 16 or 87% ee. The absolute configuration of acetate **2** was determined by X-ray analysis of *p*-bromobenzoate **3** (Fig. 2),[14] which was derived from **2** and *p*-bromobenzoic acid. The configuration of the chiral center in **2** was thus concluded to be in the *R* configuration. For the assessment of optically active **2** as a potential chiral building block of α-substituted α-amino acid derivatives, (*R*)-2-(hydroxymethyl)glutamic acid and a synthetic intermediate of (−)-deoxydysibetaine were synthesized from acetate **2**.



Scheme 1. Reagents and conditions: (a) *p*-Br–BzOH, DCC, DMAP, CH_2Cl_2, rt, quant.

The primary alcohol **2** was oxidized by DMSO/$(COCl)_2$ to give the aldehyde.[15] This was followed by a Horner–Wadsworth–Emmons reaction to afford (*E*)-α,β-unsaturated ester **4** as the sole product (Scheme 2). Ethanolysis of the acetyl group in ester **4** was carried out by treatment with K_2CO_3 in EtOH to give alcohol **5**. Hydrogenation of the carbon–carbon double bond in **5** in the presence of 10% Pd/C in EtOH gave alcohol (*S*)-**6**. Primary alcohol (*S*)-**6** was oxidized by treatment with 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) and bis(acetoxy)iodobenzene (BAIB) to give the carboxylic acid.[16] Finally, hydrolysis of oxazoline by treatment with 6 M HCl under reflux afforded (*R*)-2-(hydroxymethyl)glutamic acid, $[\alpha]_D^{25}$ −11.9 (*c* 1.17, H_2O).[5]

The primary hydroxy group of acetate **2** was protected to give TBS ether **7** and methanolysis of the acetate

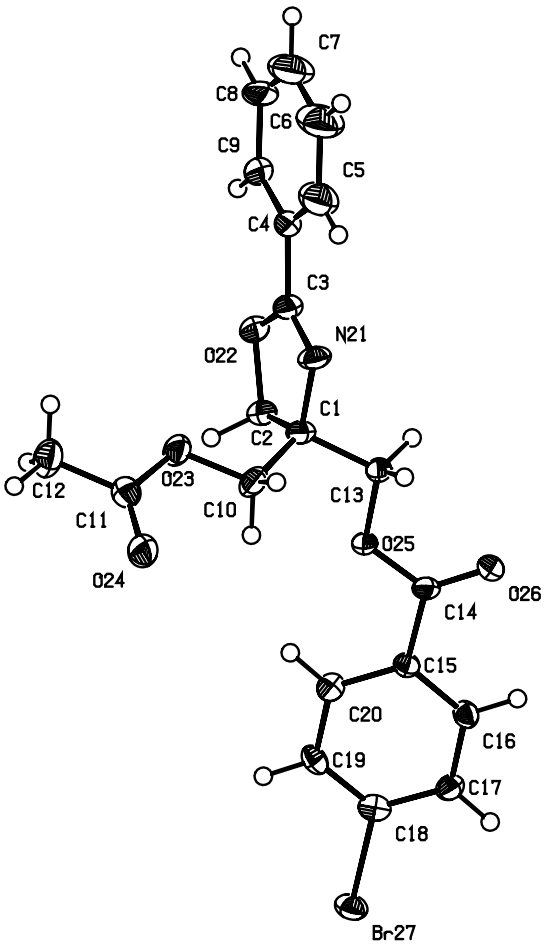
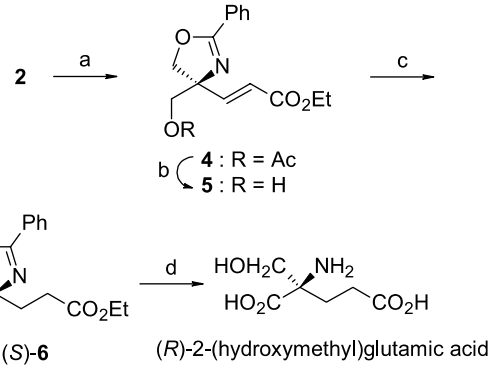
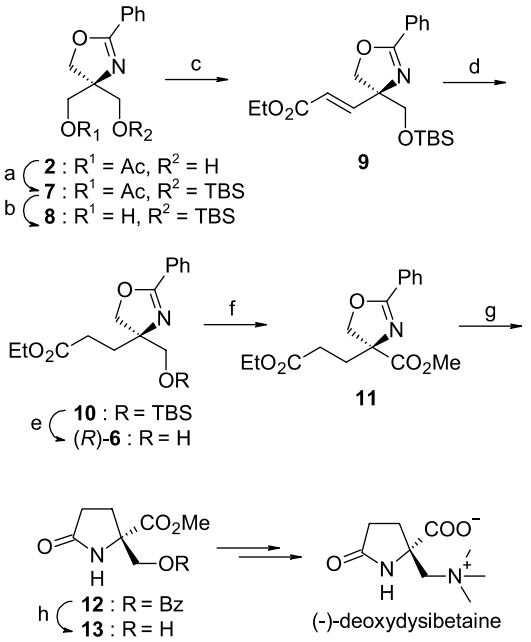


Figure 2. ORTEP drawing of *p*-bromobenzoate **3**.



Scheme 2. Reagents and conditions: (a) (i) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C to rt, (ii) $(^iPrO)_2P(O)CH_2CO_2Et$, NaH, THF, −78 to 0 °C, 86% (two steps); (b) K_2CO_3, EtOH, rt, 96%; (c) H_2, Pd/C, EtOH, rt, quant.; (d) (i) TEMPO, BAIB, H_2O–CH_2Cl_2, rt, (ii) 6 M HCl, reflux, 96% (two steps).

by treatment with K_2CO_3 in MeOH to give alcohol **8** (Scheme 3). Alcohol **8** was oxidized by DMSO/TFAA oxidation followed by a Horner–Wadsworth–Emmons reaction to give (*E*)-α,β-unsaturated ester **9** as a sole product. Hydrogenation of the carbon–carbon double bond in **9** in the presence of 10% Pd/C in EtOH gave ester **10**. Deprotection of the TBS group in ester **10** was carried out by treatment with TBAF in THF to give alcohol (*R*)-**6**. Primary alcohol (*R*)-**6** was oxidized directly into the



Scheme 3. Reagents and conditions: (a) TBSCl, imidazole, DMF, rt, quant.; (b) K_2CO_3, MeOH, rt, 98%; (c) (i) DMSO, TFAA, Et_3N, CH_2Cl_2, −78 °C to rt, (ii) $(^iPrO)_2P(O)CH_2CO_2Et$, NaH, THF, −78 to 0 °C, 95% (two steps); (d) H_2, Pd/C, EtOH, rt, 98%; (e) TBAF, THF, rt, 79%; (f) (i) TEMPO, BAIB, H_2O–CH_2Cl_2, rt, (ii) CH_2N_2, MeOH, 0 °C, 77% (two steps); (g) 1 M HCl, MeOH, 80 °C, 81%; (h) K_2CO_3, MeOH, rt, 81%.

carboxylic acid using TEMPO and BAIB.[16] This was followed by esterification of the carboxylic acid by treatment with CH_2N_2 to afford methyl ester **11**. Hydrolysis of oxazoline in ester **11** by treatment with 1 M HCl gave lactam **12**. Finally, lactam **12** was treated with K_2CO_3 in MeOH at rt to afford alcohol **13**, $[\alpha]_D^{25}$ +34.3 (*c* 0.46, $CHCl_3$), which is a synthetic intermediate of (−)-deoxydysibetaine.[9b,d]

A lipase-catalyzed method for the preparation of optically active oxazoline **2** was established. The present method of desymmetrization of prochiral diol can easily be conducted under mild conditions even in a large-scale experiment. Enantiomeric excess of oxazoline **2** is higher than enantiomeric excess of the chiral compounds provided by the reported enzymatic desymmetrization of prochiral compounds. The optically active oxazoline **2** was clearly shown to be useful as a chiral building block for the synthesis of biologically active chiral compounds containing α-substituted α-amino acid moieties.

3. Experimental

3.1. General

Melting points (mp) were measured using a Yazawa melting point apparatus BY-2 and are uncorrected. Optical rotations were measured using a Jasco P-1030 polarimeter or a Jasco DIP-360 polarimeter. IR spectra were recorded using a Jasco FT-IR/620 spectrometer. UV spectra were recorded using a Jasco V-550 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer. Chemical shifts are given on the δ (ppm) scale using tetramethylsilane (TMS) as the internal standard (s, singlet; d, doublet; t, triplet; m, multiplet; br, broad). ESIMS and high-resolution ESIMS (HRESIMS) spectra were obtained using a Micromass LCT spectrometer. Elemental analysis data were obtained using an Elemental Vavio EL. X-ray diffraction was measured on Bruker MXC18 KHF22 and Rigaku RAXIS-RAPID diffractometers. Flash column chromatography was carried out using Kanto Chemical Silica Gel 60 N (spherical, neutral) 40–50 μm. Reversed phase column chromatography was carried out using Wakosil 25C18 (spherical) 15–30 μm.

3.1.1. (*R*)-4-Hydroxymethyl-2-phenyl-4,5-dihydrooxazol-4-ylmethyl acetate (2). To a solution of diol **1**[12] (33.0 g, 159 mmol) and vinyl acetate (147 mL, 1.59 mol) in THF (318 mL) was added Lipase PS® (6.36 g) and the mixture was stirred for 5 days at rt. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to give a crude solid (40.7 g, >99% ee). The crude solid was purified by recrystallization from acetone–hexane to yield acetate **2** (32.5 g, 82% yield) as colorless plates. Enantiomeric excess of acetate **2** was >99% ee as determined by HPLC analysis (CHIRALPAK AS®, 0.46×25 cm, hexane/2-propanol=93:7, flow rate: 1.0 mL/min, **2**: t_R=22.6 min, *ent*-**2**: t_R=16.8 min), mp: 128 °C; $[\alpha]_D^{26}$ −18.6 (*c* 1.08, $CHCl_3$); IR (KBr) cm^{-1}: 3199, 2962, 1731, 1634; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.80 (2H, m), 7.44 (1H, m), 7.32 (2H, m), 4.39 (1H, d, *J*=8.6 Hz), 4.30 (1H, d, *J*=8.6 Hz), 4.22 (1H, d, *J*=11.3 Hz), 4.18 (1H, d, *J*=11.3 Hz), 3.85 (1H, br dd, *J*=9.2, 15.3 Hz), 3.63 (1H, br dd, *J*=8.1, 15.3 Hz), 3.62 (1H, br s), 2.05 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.8, 165.9, 131.7, 128.4, 128.2, 126.8, 74.7, 71.4, 66.2, 64.7, 20.7; ESIMS *m/z*: 250 (M^++H, 100); HRESIMS *m/z*: 250.1071 (Calcd for $C_{13}H_{16}NO_4$: M^++H, 250.1079). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.73; H, 6.12; N, 5.33.

3.1.2. (*R*)-4-Acetoxymethyl-2-phenyl-4,5-dihydrooxazol-4-ylmethyl 4-bromobenzoate (3). To a solution of alcohol **2** (99.8 mg, 400 μmol) in CH_2Cl_2 (2.00 mL) were added *p*-bromobenzoic acid (88.4 mg, 440 μmol), DCC (90.8 mg, 440 μmol) and DMAP (4.9 mg, 40.0 μmol). Following stirring at rt for 1 h, the reaction mixture was filtered through a thin silica gel pad and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt=4:1) to give *p*-bromobenzoate **3** (173 mg, quantitative yield) as colorless pillars: mp: 118–120 °C; $[\alpha]_D^{25}$ −28.3 (*c* 1.08, $CHCl_3$); IR (KBr) cm^{-1}: 2984, 1739, 1709, 1650; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.96 (2H, m), 7.82 (2H, m), 7.52 (3H, m), 7.42 (2H, m), 4.54 (1H, d, *J*=11.3 Hz), 4.45 (1H, d, *J*=11.3 Hz), 4.44 (1H, d, *J*=9.0 Hz), 4.38 (1H, d, *J*=11.4 Hz), 4.37 (1H, d, *J*=9.0 Hz), 4.32 (1H, d, *J*=11.4 Hz), 2.07 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.6, 165.7, 165.4, 131.9, 131.8 (×2), 131.1 (×2), 128.5, 128.4, 127.0, 73.0, 72.0, 65.9, 66.3, 20.8; ESIMS *m/z*: 432 (M^++H, 100); HRESIMS *m/z*: 432.0421 (Calcd for $C_{20}H_{19}^{79}BrNO_5$: M^++H, 432.0447). Anal. Calcd for $C_{20}H_{18}BrNO_5$: C, 55.57; H, 4.20; N, 3.24. Found: C, 55.58; H, 4.28; N, 3.09.

3.1.3. Ethyl (*R*,*E*)-3-(4-acetoxymethyl-2-phenyl-4,5-dihydrooxazol-4-yl)acrylate (4). To a cold (−78 °C) solution of oxalyl chloride (210 μL, 2.41 mmol) in

CH_2Cl_2 (6.0 mL) was added DMSO (230 μL, 3.21 mmol). Following stirring at −78 °C for 10 min, a solution of alcohol **2** (200 mg, 802 μmol) in CH_2Cl_2 (2.0 mL) was added. Following stirring at −78 °C for 30 min, Et_3N (560 μL, 4.01 mmol) was added. The mixture was warmed to rt for over 15 min and then stirred for 30 min. The reaction mixture was diluted with Et_2O and then washed with saturated aqueous $NaHCO_3$, water and finally saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude aldehyde. The crude aldehyde was subsequently used without further purification.

To a suspension of NaH (55%, 49 mg, 1.12 mmol) in THF (2.0 mL) was added $(^iPrO)_2P(O)CH_2CO_2Et$ (270 μL, 1.20 mmol) at 0 °C and the mixture was stirred at 0 °C for 30 min. A solution of the above crude aldehyde in THF (2.0 mL) was added to the mixture at −78 °C and then the mixture was warmed to 0 °C for over 30 min. The reaction mixture was diluted with Et_2O and then washed with saturated aqueous NH_4Cl, water, and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt=5:2) to give α,β-unsaturated ester **4** (219 mg, 86% yield, two steps) as a colorless oil: $[\alpha]_D^{25}$ −75.9 (*c* 1.56, $CHCl_3$); IR (neat) cm^{-1}: 3064, 2981, 2902, 1745, 1719, 1644, 1603, 1496; UV (EtOH) nm: 242 (ε 11,900); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.97 (2H, m), 7.51 (1H, m), 7.42 (2H, m), 7.07 (1H, d, *J*=15.7 Hz), 6.15 (1H, d, *J*=15.7 Hz), 4.46 (1H, d, *J*=8.7 Hz), 4.26 (1H, d, *J*=8.7 Hz), 4.25 (2H, s), 4.20 (2H, q, *J*=7.1 Hz), 2.06 (3H, s), 1.28 (3H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.6, 166.1, 165.3, 146.5, 131.9, 128.6, 128.4, 127.0, 122.8, 74.0, 73.7, 67.6, 60.7, 20.8, 14.2; ESIMS *m/z*: 318 (M^++H, 100); HRESIMS *m/z*: 318.1345 (Calcd for $C_{17}H_{20}NO_5$: M^++H, 318.1341). Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.29; H, 5.98; N, 4.29.

3.1.4. Ethyl (*S*,*E*)-3-(4-hydroxymethyl-2-phenyl-4,5-dihydrooxazol-4-yl)acrylate (5). To a solution of acetate **4** (34.6 mg, 109 μmol) in EtOH (550 μL) was added K_2CO_3 (5.5 mg, 39.8 μmol). After stirring at rt for 40 min, the reaction mixture was diluted with Et_2O and then washed with saturated aqueous NH_4Cl, water, and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt=3:2) to give alcohol **5** (28.8 mg, 96% yield) as a colorless oil: $[\alpha]_D^{25}$ −56.9 (*c* 0.96, $CHCl_3$); IR (neat) cm^{-1}: 3241, 2980, 2932, 1717, 1641, 1604, 1496; UV (EtOH) nm: 242 (ε 8050); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.85 (2H, m), 7.47 (1H, m), 7.35 (2H, m), 7.00 (1H, d, *J*=15.7 Hz), 6.09 (1H, d, *J*=15.7 Hz), 4.59 (1H, d, *J*=8.4 Hz), 4.28 (1H, d, *J*=8.4 Hz), 4.19 (2H, q, *J*=7.1 Hz), 3.87 (1H, dd, *J*=11.6, 4.8 Hz), 3.64 (1H, dd, *J*=11.6, 9.2 Hz), 3.25 (1H, m), 1.27 (3H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.1, 165.8, 147.5, 131.8, 128.4, 128.2, 126.5, 122.4, 75.9, 73.0, 66.1, 60.6, 14.2; ESIMS *m/z*: 276 (M^++H, 100); HRESIMS *m/z*: 276.1217 (Calcd for $C_{15}H_{18}NO_4$: M^++H, 276.1236). Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.34; H, 6.24; N, 4.90.

3.1.5. Ethyl (*S*)-3-(4-hydroxymethyl-2-phenyl-4,5-dihydrooxazol-4-yl)propionate ((*S*)-6). A solution of α,β-unsaturated ester **5** (158 mg, 574 μmol) in EtOH (5.74 mL) was hydrogenated with 10% Pd/C (57.4 mg). The mixture was stirred at rt under a balloon pressure of H_2 for 1 h. The reaction mixture was diluted with AcOEt and filtered through Celite. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt=2:3) to give ester (*S*)-**6** (159 mg, quantitative yield) as a colorless oil: $[\alpha]_D^{25}$ +13.4 (*c* 1.20, $CHCl_3$); IR (neat) cm^{-1}: 3376, 2927, 1732, 1644, 1579, 1496; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.86 (2H, m), 7.46 (1H, m), 7.38 (2H, m), 4.44 (1H, d, *J*=8.5 Hz), 4.15 (1H, d, *J*=8.5 Hz), 4.11 (2H, dq, *J*=1.7, 7.2 Hz), 3.77 (1H, dd, *J*=11.4, 3.0 Hz), 3.53 (1H, dd, *J*=11.4, 7.8 Hz), 2.38 (2H, m), 2.09 (1H, ddd, *J*=14.2, 8.4, 7.6 Hz), 1.85 (1H, ddd, *J*=14.2, 8.6, 6.6 Hz), 1.20 (3H, t, *J*=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.5, 164.7, 131.5, 128.3, 128.2, 127.0, 74.4, 72.8, 66.9, 60.6, 31.1, 28.6, 14.1; ESIMS *m/z*: 278 (M^++H, 100); HRESIMS *m/z*: 278.1404 (Calcd for $C_{15}H_{20}NO_4$: M^++H, 278.1392). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.89; H, 6.89; N, 4.78.

3.1.6. (*R*)-2-(Hydroxymethyl)glutamic acid. To a solution of alcohol (*S*)-**6** (57.2 mg, 206 μmol) in H_2O–CH_2Cl_2 (2/1, 630 μL) were added TEMPO (9.7 mg, 61.8 μmol) and BAIB (199 mg, 618 μmol). After stirring at rt for 75 min, the reaction mixture was diluted with $CHCl_3$ and then washed with saturated aqueous $Na_2S_2O_3$ and 1 M HCl. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was diluted with $CHCl_3$–MeOH (69/1) and filtered through silica gel using $CHCl_3$–MeOH (69/1–4/1). The filtrate was concentrated under reduced pressure to give the crude carboxylic acid. The crude carboxylic acid was used for the next reaction without further purification.

A solution of the above crude carboxylic acid in 6 M HCl (1.03 mL) was refluxed for 12 h. The reaction mixture was washed with Et_2O. The aqueous layer was concentrated under reduced pressure. The residue was purified by reversed phase column chromatography (H_2O) to give the hydrochloride salt. The hydrochloride salt was passed through a DOWEX® 50W-X8 ion-change resin. Elution with 5% aqueous NH_4OH furnished (*R*)-2-(hydroxymethyl)glutamic acid (35.2 mg, 96% yield, two steps) as colorless needles: $[\alpha]_D^{25}$ −11.9 (*c* 1.17, H_2O). The physical and spectral properties were consistent with the literature values.[5]

3.1.7. (*R*)-4-(*tert*-Butyldimethylsiloxymethyl)-2-phenyl-4,5-dihydrooxazol-4-ylmethyl acetate (7). To a solution of alcohol **2** (2.51 g, 10.1 mmol) in DMF (10.1 mL) were added imidazole (1.31 g, 19.2 mmol) and *tert*-butylchlorodimethylsilane (2.28 g, 15.1 mmol). After stirring at rt for 1 h, the reaction mixture was diluted with Et_2O and then washed with saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt=6:1) to give alcohol TBS ether **7** (3.66 g, quantitative yield) as a colorless oil: $[\alpha]_D^{25}$ −20.6

(c 1.04, $CHCl_3$); IR (neat) cm^{-1}: 2954, 2930, 2858, 1746, 1649, 1604, 1580, 1496; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.93 (2H, m), 7.48 (1H, m), 7.40 (2H, m), 4.44 (1H, d, J=8.6 Hz), 4.28 (1H, d, J=11.4 Hz), 4.25 (1H, d, J=11.4 Hz), 4.23 (1H, d, J=8.6 Hz), 3.84 (1H, d, J=10.0 Hz), 3.63 (1H, d, J=10.0 Hz), 2.05 (3H, s), 0.85 (9H, s), 0.06 (3H, s), 0.03 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.9, 164.9, 131.5, 128.4, 128.3, 127.5, 74.7, 71.9, 66.5, 65.9, 25.7, 20.9, 18.1, −5.5. −5.5; ESIMS m/z: 364 (M^++H, 100); HRESIMS m/z: 364.1948 (Calcd for $C_{19}H_{30}NO_4Si$: M^++H, 364.1944). Anal. Calcd for $C_{19}H_{29}NO_4Si$: C, 62.78; H, 8.04; N, 3.85. Found: C, 62.76; H, 7.87; N, 3.75.

3.1.8. (*S*)-[4-(*tert*-Butyldimethylsiloxymethyl)-2-phenyl-4,5-dihydrooxazol-4-yl]methanol (8). To a solution of acetate **7** (3.61 g, 9.93 mmol) in MeOH (49.7 mL) was added K_2CO_3 (497 mg, 3.60 mmol). After stirring at rt for 10 min, the reaction mixture was diluted with Et_2O and then washed with saturated aqueous NH_4Cl, water and finally saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt=2:1) to give alcohol **8** (3.14 g, 98% yield) as colorless needles: mp: 90 °C; $[\alpha]_D^{25}$ −6.6 (c 1.01, $CHCl_3$); IR (KBr) cm^{-1}: 3214, 2954, 2929, 2657, 1640, 1604, 1496; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.84 (2H, m), 7.45 (1H, m), 7.35 (2H, m), 4.46 (1H, d, J=8.4 Hz), 4.36 (1H, d, J=8.4 Hz), 3.82 (1H, dd, J=11.3, 4.0 Hz), 3.81 (1H, d, J=9.8 Hz), 3.73 (1H, dd, J=11.3, 6.2 Hz), 3.61 (1H, d, J=9.8 Hz), 0.86 (9H, s), 0.07 (3H, s), 0.03 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.4, 131.5, 128.3, 128.2, 127.3, 76.2, 72.0, 66.6, 65.9, 25.7, 18.1, −5.5, −5.5; ESIMS m/z: 322 (M^++H, 100); HRESIMS m/z: 322.1866 (Calcd for $C_{17}H_{28}NO_3Si$: M^++H, 322.1838). Anal. Calcd for $C_{17}H_{27}NO_3Si$: C, 63.51; H, 8.47; N, 4.36. Found: C, 63.28; H, 8.43; N, 4.08.

3.1.9. Ethyl (*S*,*E*) 3-[4-(*tert*-butyldimethylsiloxymethyl)-2-phenyl-4,5-dihydrooxazol-4-yl]acrylate (9). To a cold (−78 °C) solution of TFAA (65.9 μL, 474 μmol) in CH_2Cl_2 (1.0 mL) was added DMSO (44.8 μL, 632 μmol). Following stirring at −78 °C for 30 min, a solution of alcohol **8** (50.7 mg, 158 μmol) in CH_2Cl_2 (580 μL) was added. Following stirring at −78 °C for 30 min, Et_3N (110 μL, 790 μmol) was added. The mixture was warmed to rt for over 15 min and then stirred for 20 min. The reaction mixture was diluted with Et_2O and then washed with saturated aqueous $NaHCO_3$, water and finally saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude aldehyde. The crude aldehyde was used for the next reaction without further purification.

To a suspension of NaH (55%, 20.7 mg, 474 μmol) in THF (1.0 mL) was added $(^iPrO)_2P(O)CH_2CO_2Et$ (120 μL, 553 μmol) at 0 °C. Following stirring at 0 °C for 45 min, a solution of the above crude aldehyde in THF (580 μL) was added to this mixture at −78 °C. The mixture was subsequently warmed to 0 °C for over 15 min. The reaction mixture was diluted with Et_2O and then washed with saturated aqueous NH_4Cl, water, and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt=10:1) to give α,β-unsaturated ester **9** (56.0 mg, 95% yield, two steps) as a colorless oil: $[\alpha]_D^{25}$ +47.6 (c 1.11, $CHCl_3$); IR (neat) cm^{-1}: 2954, 2930, 2857, 1722, 1647, 1580, 1496; UV (EtOH) nm: 242 (ε 15,300); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.95 (2H, m), 7.49 (1H, m), 7.41 (2H, m), 7.15 (1H, d, J=15.8 Hz), 6.11 (1H, d, J=15.8 Hz), 4.61 (1H, d, J=8.4 Hz), 4.19 (2H, q, J=7.1 Hz), 4.19 (1H, d, J=8.4 Hz), 3.76 (1H, d, J=9.9 Hz), 3.71 (1H, d, J=9.9 Hz), 1.28 (3H, t, J=7.1 Hz), 0.84 (9H, s), 0.06 (3H, s), 0.01 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.4, 164.8, 148.1, 131.6, 128.4, 128.3, 127.5, 121.9, 75.9, 74.0, 67.6, 60.4, 25.7, 18.1, 14.2, −5.4, −5.5; ESIMS m/z: 390 (M^++H, 100); HRESIMS m/z: 390.2089 (Calcd for $C_{21}H_{32}NO_4Si$: M^++H, 390.2101). Anal. Calcd for $C_{21}H_{31}NO_4Si$: C, 64.75; H, 8.02; N, 3.60. Found: C, 64.47; H, 8.06; N, 3.47.

3.1.10. Ethyl (*S*)-3-[4-(*tert*-butyldimethylsiloxymethyl)-2-phenyl-4,5-dihydrooxazol-4-yl]-propionate (10). A solution of α,β-unsaturated ester **9** (114 mg, 305 μmol) in EtOH (3.05 mL) was hydrogenated with 10% Pd/C (30.5 mg). The mixture was stirred at rt under a balloon pressure of H_2 for 30 min. The reaction mixture was diluted with Et_2O, filtered through Celite, and the filtrate concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt=8:1) to give ester **10** (112 mg, 98% yield) as a colorless oil: $[\alpha]_D^{25}$ −6.2 (c 1.04, $CHCl_3$); IR (neat) cm^{-1}: 2954, 2930, 2857, 1737, 1649, 1604, 1496; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.91 (2H, m), 7.47 (1H, m), 7.39 (2H, m), 4.44 (1H, d, J=8.6 Hz), 4.10 (2H, dq, J=7.1, 2.2 Hz), 4.08 (1H, d, J=8.6 Hz), 3.68 (1H, d, J=9.9 Hz), 3.61 (1H, d, J=9.9 Hz), 2.42 (1H, ddd, J=16.3, 10.1, 6.3 Hz), 2.36 (1H, ddd, J=16.3, 9.9, 6.3 Hz), 2.07 (1H, ddd, J=14.0, 10.1, 6.3 Hz), 1.95 (1H, ddd, J=14.0, 9.9, 6.3 Hz), 1.20 (3H, t, J=7.1 Hz), 0.84 (9H, s), 0.05 (3H, s), 0.01 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.6, 163.8, 131.3, 128.3, 128.2, 127.8, 74.4, 73.5, 68.2, 60.4, 31.0, 29.0, 25.7, 18.1, 14.1, −5.4, −5.5; ESIMS m/z: 392 (M^++H, 100); HRESIMS m/z: 392.2265 (Calcd for $C_{21}H_{34}NO_4Si$: M^++H, 392.2257). Anal. Calcd for $C_{21}H_{33}NO_4Si$: C, 64.41; H, 8.49; N, 3.58. Found: C, 64.53; H, 8.47; N, 3.47.

3.1.11. Ethyl (*R*)-3-(4-hydroxymethyl-2-phenyl-4,5-dihydrooxazol-4-yl)propionate ((*R*)-6). To TBS ether **10** (66.0 mg, 176 μmol) was added TBAF (1.0 M in THF, 530 μL, 527 μmol). After stirring at rt for 5 min saturated aqueous NH_4Cl was added to the reaction mixture. The mixture was diluted with AcOEt and then washed with water and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/AcOEt=2:1) to give alcohol (*R*)-**6** (38.6 mg, 79% yield) as a colorless oil: $[\alpha]_D^{25}$ −14.6 (c 1.23, $CHCl_3$). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.11; H, 7.09; N, 4.90.

3.1.12. Methyl (*S*)-4-(2-ethoxycarbonylethyl)-2-phenyl-4,5-dihydrooxazole-4-carboxylate (11). To a solution of alcohol (*R*)-**6** (28.8 mg, 104 μmol) in H_2O–CH_2Cl_2 (2/1, 330 μL) were added TEMPO (4.9 mg, 31.2 μmol) and BAIB (100 mg, 312 μmol). After stirring at rt for 75 min, the reaction mixture was diluted with $CHCl_3$ and then

washed with saturated aqueous $Na_2S_2O_3$ and 1 M HCl. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was diluted with $CHCl_3$–MeOH (69/1) and filtered through silica gel using $CHCl_3$–MeOH (69/1–4/1). The filtrate was concentrated under reduced pressure to give the crude carboxylic acid. The crude carboxylic acid was subsequently used without further purification.

To a cold (0 °C) solution of the above crude carboxylic acid in MeOH (1.0 mL) was added a solution of CH_2N_2 in Et_2O until the mixture turned yellow. After stirring at 0 °C for 5 min and then at rt for 50 min, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt=3:1) to give diester **11** (24.5 mg, 77% yield, two steps) as a colorless oil: $[\alpha]_D^{25}$ +18.6 (*c* 0.66, $CHCl_3$); IR (neat) cm^{-1}: 2981, 1735, 1643, 1603, 1496; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.98 (2H, m), 7.50 (1H, m), 7.41 (2H, m), 4.75 (1H, d, J=9.1 Hz), 4.28 (1H, d, J=9.1 Hz), 4.11 (2H, dq, J=1.0, 7.1 Hz), 3.80 (3H, s), 2.52–2.35 (3H, m), 2.19 (1H, m), 1.22 (3H, t, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.1, 172.7, 165.1, 131.9, 128.6, 128.3, 126.9, 77.1, 74.1, 60.6, 52.8, 33.2, 29.0, 14.1; ESIMS *m*/*z*: 306 (M^++H, 100); HRESIMS *m*/*z*: 306.1348 (Calcd for $C_{16}H_{20}NO_5$: M^++H, 306.1341). Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.73; H, 6.26; N, 4.46.

3.1.13. Methyl (*S*)-2-benzoyloxymethyl-5-oxopyrrolidine-2-carboxylate (12). To a solution of diester **11** (752 mg, 2.46 mmol) in MeOH (18.3 mL) was added 1 M HCl (6.1 mL). After stirring at 80 °C for 2.5 h, the reaction mixture was diluted with AcOEt and then washed with saturated aqueous $NaHCO_3$, water and finally saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt=1:3) to give lactam **12** (552 mg, 81% yield) as colorless needles: mp: 140 °C; $[\alpha]_D^{25}$ +37.6 (*c* 0.37, $CHCl_3$); IR (KBr) cm^{-1}: 3232, 2959, 1751, 1723, 1702; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.97 (2H, m), 7.58 (1H, m), 7.44 (2H, m), 6.40 (1H, br s), 4.68 (1H, d, J=11.1 Hz), 4.36 (1H, d, J=11.1 Hz), 3.80 (3H, s), 2.50–2.40 (3H, m), 2.25 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.6, 172.0, 165.7, 133.6, 129.7, 129.0, 128.6, 68.5, 64.7, 53.2, 29.2, 27.7; ESIMS *m*/*z*: 278 (M^++H, 100); HRESIMS *m*/*z*: 278.1054 (Calcd for $C_{14}H_{16}NO_5$: M^++H, 278.1028). Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.52; H, 5.58; N, 4.90.

3.1.14. Methyl (*S*)-2-hydroxymethyl-5-oxopyrrolidine-2-carboxylate (13). To acetate **12** (9.9 mg, 35.7 μmol) was added K_2CO_3 (0.5 g/L in MeOH, 360 μL). After stirring at rt for 1.5 h, the reaction mixture was diluted with $CHCl_3$ and then washed with saturated aqueous NH_4Cl, water, and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH=20:1) to give alcohol **13** (5.0 mg, 81% yield) as colorless pillars: mp: 133°C; $[\alpha]_D^{25}$ +34.3 (*c* 0.46, $CHCl_3$). The physical and spectral properties were consistent with the literature values.[9d]

Acknowledgements

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14. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre with deposition number CCDC 290624.
15. It was determined from the optical purity of **4** from HPLC analysis using a chiral column that migration of an acetyl group in **2** had not taken place in the Swern oxidation process.
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Synthesis of 4-aminomethyl-tetrahydrofuran-2-carboxylates with 2,4-*cis* and 2,4-*trans* relationships

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Abstract—Templated tetrahydrofuran-based γ-azido esters were prepared with the C-2 and C-4 functionalities in cis and trans relative configurations. This was achieved by ring contraction of the suitably protected 2-*O*-triflates of pentono-1,5-lactones (D-ribose and L-arabinose) with subsequent introduction of the azide via the 4-*O*-triflate. Access to a corresponding β-azido ester was achieved in good yield. Little elimination product was observed by introduction of the azide via the 3-*O*-triflate. These azido esters are scaffolds, which may be predisposed to adopt secondary structural motifs, for example, for use as peptidomimetics; they may also be utilised for the preparation of stereodiverse compound libraries.

1. Introduction

Improvement of the pharmacological properties of natural peptides has focused on the structural modification of the constituent amino acids.[1,2] Both β- and γ-peptides (Fig. 1) have been shown to be stable to common proteases.[3] γ-Peptides have been less extensively studied than their β-counterparts.[4–8] Nonetheless, γ-amino acids (both acyclic and cyclic) have been found to adopt secondary structures akin to those observed for α-peptides.

Vinylogous (α,β-unsaturated) γ-peptides adopt parallel sheet structures; with the insertion of a Pro-Gly unit into the backbone, they also adopt novel helical conformations with 10- and 12-membered hydrogen bonded rings.[9] Conformational searching of a γ-hexapeptide and corresponding vinylogous analogue[10] have since been reported and vinylogous peptides identified as a source for γ-peptide foldamers.[11,12] Hanessian and Seebach[13] have prepared an extensive set of acyclic γ-peptides and related substitution patterns and stereochemistry to secondary structural preference for βII′-type turns[14,15] and left and right handed 14-helices.[16–18] The biological importance of such systems has been highlighted by analogues of a γ-dipeptide, which exhibited submicromolar affinities for human somatostatin receptors.[19] Oligomers of ureas, carbamates, phosphodiesters and vinylogous sulfonamidopeptides have also been prepared as γ-peptide analogues.[20]

Rigid cyclic γ-amino acids have been employed in the formation of parallel sheet structures[21] and in the formation of potent γ-amino butyric acid (GABA) antagonists.[22] Several conformationally restricted γ-amino acids have

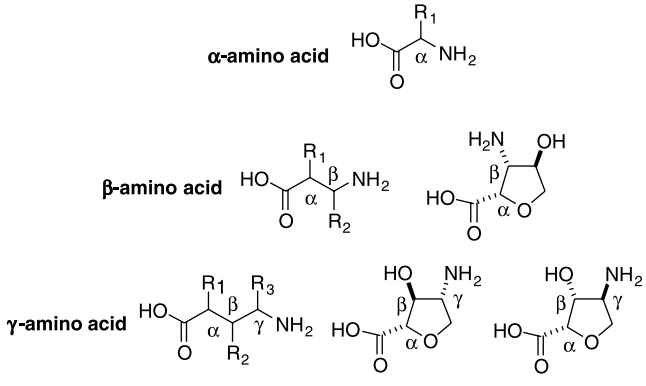

Figure 1. Homologues of α-amino acids.

Keywords: Sugar amino acids; Peptidomimetics; Scaffolds; Gamma amino acids.
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been prepared recently.[23–28] This paper describes the synthesis of conformationally restricted γ-amino acids from sugar starting materials. Sugar amino acids (SAAs) have been frequently employed as peptidomimetic foldamers[29–33] and as library scaffolds with their potential for host–guest chemistry recently explored.[34–38] Compared to δ-SAAs, there are relatively few examples of γ-sugar amino acids (γ-SAAs) in literature.[22,39–45] A pyranose based γ-SAA, which predetermines a β-turn conformation in synthetic peptides has been described.[41] Additionally, a heterooligomer composed of a furanose γ-SAA and GABA exhibited no stable conformation in solution.[44] Furanose and pyranose based γ-SAAs have been utilised to prepare 99-member and 384-member libraries, respectively.[43,46] This paper reports the full synthesis of templated tetrahydrofuran-based γ-azido esters (**1** and **2**) and β-azido ester **3** as SAA precursors for subsequent study of foldamer preference.[47]

2. Results and discussion

2.1. Strategy

Two different synthetic strategies could be employed for the preparation of γ-azido ester **4** as the azide function can be introduced either before of after ring contraction of the activated pentono-1,5-lactone **5** (Fig. 2). This paper reports the synthesis of two γ-azido esters (**1** and **2**) via strategy 1. The key step in the synthesis of γ-azido ester **4** was the ring contraction of a trifluoromethanesulfonyl ester (triflate), from a suitably protected pentono-1,5-lactone (**5**), to form the diol **6**. This method of ring contraction, using either acidic or basic conditions, has been established for the formation of related tetrahydrofuran-2-carboxylates.[48,49] Activation of the C-4 hydroxyl via a sulfonyl ester with subsequent azide displacement from **6** would yield the desired γ-azido ester **4**.

L-Arabinose and D-ribose stereochemistries were employed to give access to γ-azido esters **1** and **2**, which were related at C-2 and C-4 positions by cis and trans stereochemistries, respectively (Fig. 3). The stereochemical relationship between the acid and amine functions of related δ-azido esters has been found to be important in subsequent investigation of conformational preference.[29,30,50,51] Poor selectivity of the C-3 hydroxyl over that at C-4 in **7** generated a suitable precursor (**8**) for synthesis of the corresponding β-azido ester **3**. The β-azido ester **3** has the amine and acid functions in a cis configuration. During synthesis, the methyl ester was converted to the more hindered isopropyl ester where convenient. This was to prevent uncontrolled oligomer and/or lactam formation resulting from nucleophilic attack of the carbonyl group by

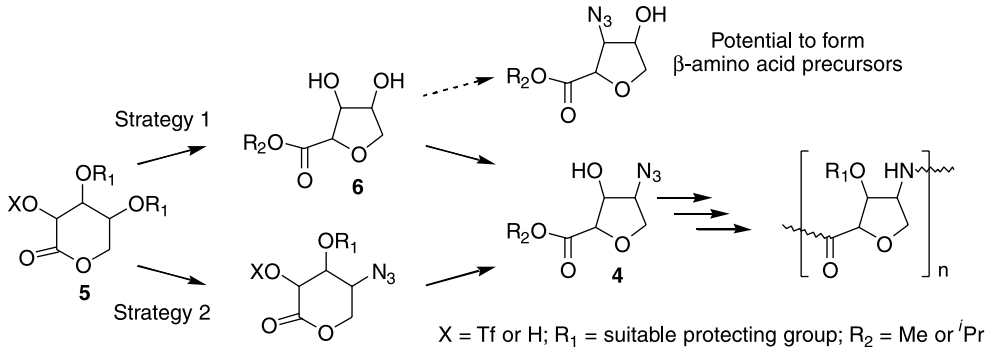


Figure 2. Synthetic strategy for the formation of γ-azido ester **4**.

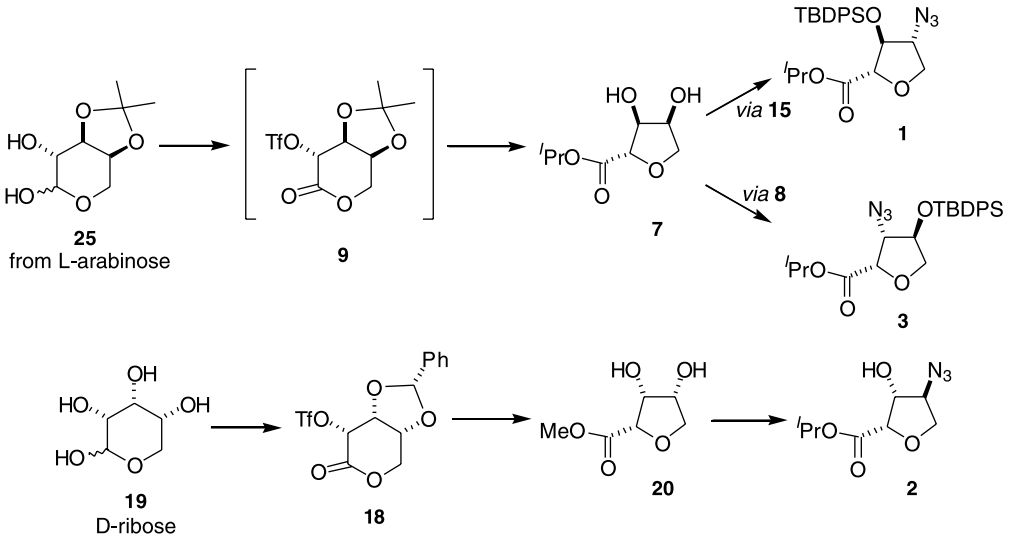


Figure 3. Strategy 1 applied to the formation of **1** and **2**.

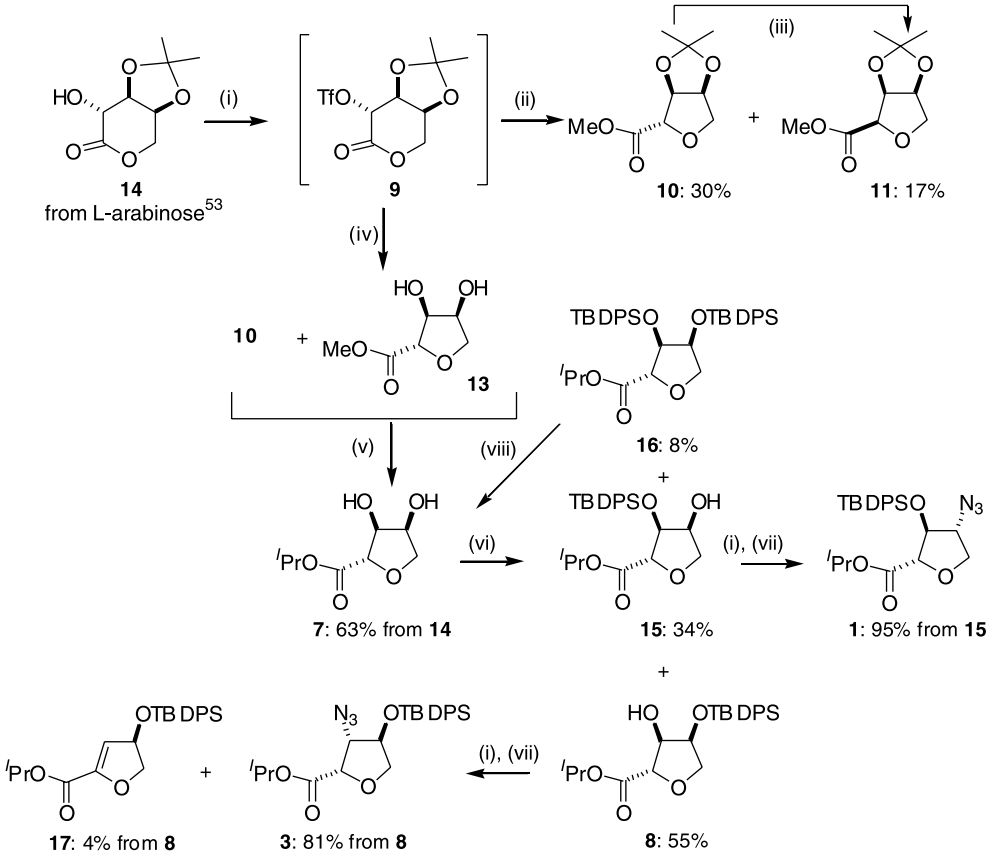
the amine function (by reduction of the azide in later synthesis).[52]

2.2. Synthesis of the β- and γ-azido esters (1 and 3) from L-arabinose stereochemistry

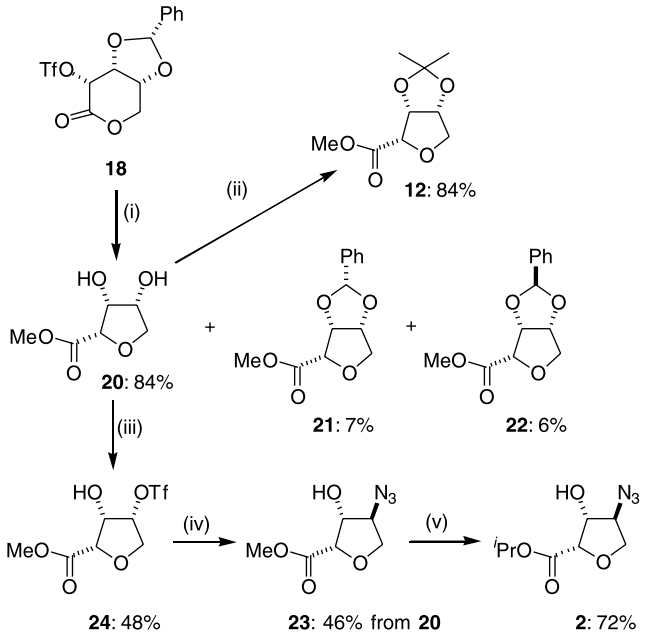
The 2-*O*-trifluoromethanesulfonyl pentono-1,4-lactone (triflate) **9** can be prepared from L-arabinose in three steps using known literature procedures.[53] It was anticipated that the triflate **9** would smoothly undergo the key ring contraction reaction to form **10** upon treatment with methanol in the presence of anhydrous potassium carbonate (K_2CO_3), Scheme 1. However, when the triflate **9** was subjected to basic conditions, the desired product **10** was isolated in 30% yield and a second product **11** in 17% yield, by the K_2CO_3-mediated epimerisation at C-2; in order to confirm this assumption an independent experiment was carried out by the treatment of **10** with methanol containing K_2CO_3. After 13 h, the majority of **10** had been consumed and the more thermodynamically stable C-2 epimer **11** isolated in 89% yield. The stereochemistry of **11** was confirmed by comparison to the physical data of the enantiomer **12** (Scheme 2).

In contrast to basic conditions, acidic conditions obviated epimerisation. Analysis of the reaction mixture by TLC revealed formation of the acetonide **10** (R_f 0.70, ethyl acetate/pet. ether 1:1) together with a second product (R_f 0.20, ethyl acetate/pet. ether 1:1), the diol **13** formed by the deprotection of the acetonide. To achieve complete deprotection of the acetonide to generate the desired diol **13**, hydrochloric acid was added and the reaction mixture warmed to 70 °C. It was convenient at this point to convert the methyl ester to the more sterically hindered isopropyl ester to prevent potential lactone formation. Therefore, the crude diol **13** was subjected to acid-catalysed transesterification with HCl in propan-2-ol (5% v/v) to afford the isopropyl ester **7** as a colourless oil in an overall yield of 63% (over four steps from lactone **14**). Selective reaction of the diol **7** would provide an efficient route to both the γ- and β-azido ester (Fig. 2).

The introduction of azido group at the γ-position, with respect to the carboxyl function on the THF framework, of **7** was investigated. Initial efforts to esterify the C-4 hydroxyl of **7** met with failure as the desired product was found to be highly unstable. It was necessary to protect the free hydroxyls prior to formation of the sulfonyl ester. Introduction of the silyl protecting group was achieved by treatment of the diol **7** with a single equivalent of *tert*-butyl diphenylsilyl chloride (TBDPS-Cl) with imidazole in dimethylformamide. Little selectivity was observed for the hydroxyl at C-3 over that at C-4 giving both the 3-*O*-TBDPS ether **15** and the 4-*O*-TBDPS silyl ether **8** in 34 and 55% yield, respectively. The regio-isomers were easily distinguished from each other by 2D correlated spectroscopy in DMSO-d_6. The formation of the 4-*O*-TBDPS silyl ether **8**, although not part of the desired synthesis for the γ-azido



Scheme 1. Reagents and conditions: (i) Tf_2O, pyridine, DCM, −20 °C; (ii) 1.1 equiv K_2CO_3, MeOH, 0 °C, 1.3 h; (iii) 0.3 equiv K_2CO_3, MeOH, rt, 14 h; (iv) 1% v/v AcCl in MeOH, rt, 13 h; (v) 2 N HCl, 70 °C, 3 h then 5% v/v AcCl in propan-2-ol, 80 °C, 48 h; (vi) TBDPSCl, imidazole, DMF, 0 °C to rt, 10 h; (vii) 4 equiv NaN_3, DMF, rt, 10 h; (viii) 3 equiv TBAF, THF, rt, 14 h.



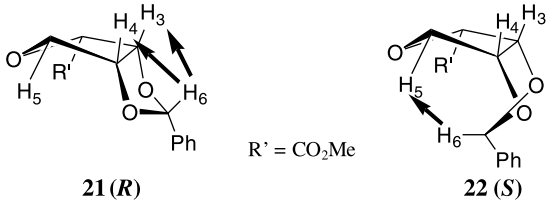
Scheme 2. Reagents and conditions: (i) 5% v/v AcCl in MeOH, rt to 70 °C, 3 h then aq HCl added, 70 °C, 15 h; (ii) CSA, acetone, rt, 24 h; (iii) 1.5 equiv Tf_2O, pyridine, DCM, −25 °C, 4 h then rt, 48 h; (iv) 5 equiv NaN_3, DMF, rt then 85 °C for 15 h; (v) *p*-toluenesulfonic acid, propan-2-ol, 80 °C, 24 h.

ester **1**, was advantageous as the ether **8** is an ideal precursor for the formation of the β-azido ester **3**. A small amount of the disubstituted silyl derivative **16** was isolated (8% yield) and was easily converted back to the diol **7**, albeit in moderate yield (50%), by treatment with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran. A single crystal X-ray structure of **16** was obtained,[54] confirming that ring contraction occurred with complete inversion of configuration at C-2 and thus the relative stereochemistry of the diol.

The 3-*O*-TBDPS ether **15** was esterified using trifluoromethanesulfonic anhydride with pyridine in dichloromethane and was reacted without purification. The 4-*O*-triflate was treated with excess sodium azide in dimethylformamide to yield the γ-azido ester **1** in 95% yield (from **15**) with inversion of configuration at C-4. Following similar protocols, the β-azido ester **3** was obtained via the 3-*O*-triflate in good yield (81% from **8**) together with a small amount (4%) of the β-eliminated product **17**. The effective substitution (with little elimination) is in stark contrast to a related synthesis previously reported.[39]

2.3. Synthesis of γ-azido ester 2 from D-ribose stereochemistry

The 2-*O*-triflate of 3,4-*O*-benzylidene-D-ribono-1,5-lactone (**18**) can be prepared using literature procedures, in three steps starting from D-ribose **19**.[55,56] The preparation of diol **20** from the triflate **18** was achieved by acid-catalysed ring contraction with subsequent deprotection (Scheme 2). Reaction of the crude triflate gave a more complex reaction mixture. Treatment of the recrystallised triflate **18** with methanolic hydrogen chloride (5% v/v) gave the desired ring contraction products and subsequent heating at 70 °C with further addition of hydrochloric acid afforded the unprotected diol **20**, the (*R*)-benzylidene **21** and the (*S*)-benzylidene **22** in 84, 7 and 6% yields, respectively. The stereochemistry of the epimeric centre of the benzylidene group in **21** and **22** was assigned on the basis of NOESY cross-peaks between each benzylidine methane proton and protons of the THF ring (Fig. 4). The diol **20** was treated with acetone and DL-camphor-10-sulfonic acid to yield the acetonide **12** in 83% yield. The formation of **12** confirmed the diol had cis configuration and the physical data is in agreement with the enantiomer **11** (Scheme 1).



21 (*R*) **22 (*S*)**

nOe	21 (*R*)	22 (*S*)
H-6 ↔ H-3	Yes	No
H-6 ↔ H-4	Yes	No
H-6 ↔ H-5	No	Yes

Figure 4. Assignment of *R* and *S* configurations of **21** and **22**.

The preparation of the 4-azido derivative **23** was achieved via S_N2 displacement with sodium azide after selective activation of the C-4 hydroxyl of **20**. The activated ester **24** was obtained in 48% yield by treatment of **20** with trifluoromethanesulfonic anhydride and pyridine in dichloromethane at −25 °C although was observed to be unstable on silica (by 2D TLC). Reaction of the crude triflate **24** with sodium azide in dimethylformamide afforded the azide **23** in 46% yield (over two steps from **20**). Finally, the methyl azido ester **23** was converted to the isopropyl ester **2** in 72% yield by treatment with *p*-toluenesulfonic acid in propan-2-ol at 80 °C.

3. Conclusion

This paper reports the efficient preparation of two diastereomeric γ-azido esters (**1** and **2**) and a β-azido ester **3**. The γ-amino acid precursors have been studied for conformational preference to assess their future role as peptidomimetic foldamers; these results will be published shortly. The efficient displacement of the β-triflate by sodium azide will provide easy access to a range of THF templated β-amino acid building blocks. Furthermore, these orthogonally protected γ- and β-amino acids may be employed for the preparation of novel stereodiverse compound libraries.

4. Experimental

4.1. General

All commercial reagents were used as supplied. *N*-*N*-Dimethylformamide (DMF) was purchased dry from the Aldrich chemical company in sure-seal bottles. All other solvents were used as supplied (Analytical or HPLC grade),

without prior purification. Petroleum ether (pet. ether) refers to the fraction of petroleum ether that boils in the range 40–60 °C and hexane refers to the fraction of petroleum ether that boils in the range 60–80 °C. Reactions were performed under an atmosphere of nitrogen or argon. Thin-layer chromatography (TLC) was performed on aluminium or plastic sheets coated with 60 F_{254} silica. Sheets were visualised using a spray of 0.2% w/v cerium (IV) sulfate and 5% ammonium molybdate in 2 M sulfuric acid. Flash chromatography was performed on Sorbsil C60 40/60 silica. Melting points were recorded on a Kofler hot block and are uncorrected. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a path length of 1 dm. Concentrations are quoted in g $100\,mL^{-1}$. Elemental analyses were performed by the microanalysis service of the Dyson Perrins Laboratory, Oxford or the Inorganic Chemistry Laboratory, Oxford. Infra-red (IR) spectra were recorded on a Perkin–Elmer 1750 IR Fourier Transform spectrophotometer using thin films on NaCl plates (film) or KBr discs. Only the characteristic peaks are quoted and in units of cm^{-1}. Low resolution mass spectra (*m/z*) were recorded on VG MassLab 20-250, Micromass BIOQ-II, Micromass Platform 1, Micromass TofSpec 2E, or Micromass Autospec 500 OAT spectrometers and high resolution mass spectra (HRMS *m/z*) on a Micromass Autospec 500 OAT spectrometer. Techniques used were chemical ionization (CI NH_3), or atmospheric pressure chemical ionization (APCI). Nuclear magnetic resonance (NMR) spectra were recorded on Bruker AMX 500 and DRX 500 spectrometers (^1H: 500 MHz and ^{13}C: 125.7 MHz), a Bruker DPX 400 spectrometer (^1H: 400 MHz and ^{13}C: 100.6 MHz) and a Bruker DPX 200 spectrometer (^1H: 200 MHz and ^{13}C: 50.3 MHz) in the deuterated solvent stated. All chemical shifts (δ) are quoted in parts per million and coupling constants (*J*) given in Hz. Residual signals from the solvents were used as an internal reference. ^{13}C multiplicities were assigned using a DEPT sequence. 3,4-Isopropylidene-L-arabinose **25** was provided by CMS chemicals and the selectively protected lactone **14** prepared according to a literature procedure.[53] 3,4-*O*-Benzylidene-2-*O*-trifluoromethanesulfonyl-D-ribono-1,5-lactone **18** was prepared in three steps from D-ribose using literature procedures.[55,56]

4.1.1. Methyl 2,5-anhydro-3,4-*O*-isopropylidene-L-ribonate 10 and methyl 2,5-anhydro-3,4-*O*-isopropylidene-L-arabinoate 11. Trifluoromethanesulfonic anhydride (0.6 mL, 3.67 mmol) was added dropwise to a stirred solution of the lactone **14** (460 mg, 2.40 mmol) in dichloromethane (5 mL) with freshly distilled pyridine (0.32 mL, 3.90 mmol) at −20 °C. After 40 min, TLC (ethyl acetate/pet. ether, 1:1) showed the absence of starting material (R_f 0.45) and the formation of a single product (R_f 0.73). The reaction mixture was diluted with dichloromethane (10 mL), and then washed sequentially with brine (10 mL), citric acid (1 M aq, 10 mL) and water (10 mL). The organic layer was concentrated in vacuo at low temperature (0–5 °C) to obtain a yellow solid (**9**), which was used without further purification. The triflate **9** was dissolved in methanol (10 mL) containing anhydrous potassium carbonate (360 mg, 2.64 mmol) and stirred at 0–5 °C. After 1.3 h, TLC (ethyl acetate/pet. ether, 1:1) showed the absence of the triflate **9** (R_f 0.73) and the formation of a major (R_f 0.70) and minor (R_f 0.38) product. The reaction mixture was filtered and the residue washed with methanol (2×5 mL). The filtrate was concentrated in vacuo and purified by flash chromatography (ethyl acetate/pet. ether, 1:4) to afford the desired product **10** (150 mg, 30%) as a colourless oil and the C-2 epimer **11** (82 mg, 17%) as a solid.

Compound **10**. $[\alpha]_D^{23}$ +64.6 (*c* 1.2 in $CHCl_3$); (HRMS (CI+): Found 203.092464. $C_9H_{14}O_5$ ($M+H^+$) requires *m/z*, 203.091949); ν_{max} (thin film)/cm^{-1} 1741 (C=O, ester); δ_H ($CDCl_3$, 200 MHz) 1.32 (3H, s, $C(CH_3)_2$), 1.50 (3H, s, $C(CH_3)_2$), 3.75 (3H, s, CO_2CH_3), 4.02 (1H, dd, $J_{5,4}$= 4.3 Hz, $J_{5,5'}$=11.0 Hz, H-5), 4.15 (1H, d, $J_{5',5}$=11.0 Hz, H-5′), 4.60 (1H, br s, H-2), 4.83 (1H, m, H-4), 4.95 (1H, m, H-3); δ_C ($CDCl_3$, 50.3 MHz) 24.8 (q, $C(CH_3)_2$), 26.3 (q, $C(CH_3)_2$), 52.2 (q, CO_2CH_3), 74.0 (t, C-5), 80.7 (d, C-4), 83.2 (d, C-3), 83.9 (d, C-2), 113.1 (s, $C(CH_3)_2$), 170.8 (s, C=O); *m/z* (APCI+): 203.01 ($M+H^+$, 33), 148.88 (100%).

Compound **11**. Mp 61–62 °C; $[\alpha]_D^{23}$ +88.5 (*c* 1.1 in $CHCl_3$): (HRMS (CI+): Found 203.092171. $C_9H_{14}O_5$ ($M+H^+$) requires *m/z*, 203.091949); ν_{max} (thin film)/cm^{-1} 1765 (C=O, ester); δ_H (C_6D_6, 500 MHz) 1.13 (3H, s, $C(CH_3)_2$), 1.48 (3H, s, $C(CH_3)_2$), 2.90 (1H, dd, $J_{5,4}$=4.1 Hz, $J_{5,5'}$= 10.2 Hz, H-5), 3.45 (3H, s, CO_2CH_3), 3.73 (1H, d, $J_{2,3}$= 3.9 Hz, H-2), 3.95 (1H, d, $J_{5',5}$=10.2 Hz, H-5′), 4.05 (1H, m, H-4), 4.43 (1H, m, H-3); δ_C (C_6D_6, 50.3 MHz) 25.7 (q, $C(CH_3)_2$), 26.5 (q, $C(CH_3)_2$), 51.5 (q, CO_2CH_3), 73.0 (t, C-5), 80.9 (d, C-4), 81.9 (d, C-3), 82.2 (d, C-2), 113.30 (s, $C(CH_3)_2$), 168.5 (s, C=O); *m/z* (APCI+): 203.03 ($M+H^+$, 100%).

4.1.2. Conversion of methyl 2,5-anhydro-3,4-*O*-isopropylidene-L-ribonate 10 to methyl 2,5-anhydro-3,4-*O*-isopropylidene-L-arabinoate 11. A catalytic amount of anhydrous potassium carbonate (3 mg, 0.025 mmol) was added to a stirred solution of acetonide **10** (18 mg, 0.089 mmol) in dry methanol (0.5 mL) at room temperature. After 14 h, TLC (ethyl acetate/pet. ether, 1:1) showed the formation of a major product (R_f 0.45) and a trace of starting material (R_f 0.70). The reaction mixture was filtered, concentrated in vacuo and the residue was purified by flash chromatography (ethyl acetate/pet. ether, 1:4) to obtain the *C*-2 epimer **11** (16 mg, 89%); data given above.

4.1.3. Isopropyl 2,5-anhydro-L-ribonate 7. Trifluoromethanesulfonic anhydride (11.6 mL, 70.9 mmol) was added slowly over a period of 15 min to a stirred solution of the lactone **14** (9.52 g, 50.6 mmol) in freshly distilled dry dichloromethane (100 mL) containing dry pyridine (6.13 mL, 75.9 mmol) at −20 °C. After 40 min, TLC (ethyl acetate/pet. ether, 1:1) showed the absence of starting material (R_f 0.45) and the formation of a single product (R_f 0.73). The reaction mixture was diluted with dichloromethane (100 mL), washed sequentially with brine and concentrated in vacuo at low temperature (0–5 °C). The residue (triflate **9**) was dissolved in methanolic hydrogen chloride (1% v/v, 100 mL) and stirred at room temperature. After 13 h, TLC (ethyl acetate/pet. ether, 1:1) showed the absence of the triflate **9** (R_f 0.73) and the formation of two products; R_f 0.70 (**10**) and R_f 0.20 (**13**). Hydrochloric acid

(2 N aq, 15 mL) was added and the reaction mixture warmed to 70 °C. After 3 h, TLC (ethyl acetate/pet. ether, 1:1) indicated the absence of **10** (R_f 0.70). The reaction mixture was concentrated in vacuo and co-evaporated with toluene. The residue was dissolved in 5% v/v HCl in propan-2-ol (100 mL) and heated to 80 °C. After 48 h, TLC (ethyl acetate) showed the formation of a major product (R_f 0.55). The reaction mixture was neutralised by careful addition of solid sodium hydrogen carbonate (30 g) until no more effervescence was observed. The reaction mixture was filtered and the filtrate concentrated in vacuo to obtain an oil, which was purified by flash chromatography (ethyl acetate/pet. ether, 2:3) to afford the title product **7** (6.10 g, 63%) as a colourless oil: $[\alpha]_D^{23}$ +44.3 (*c* 1.01 in $CHCl_3$); (HRMS (CI+): Found 208.118100. $C_8H_{14}O_5$ ($M+NH_4^+$) requires *m/z*, 208.118498); ν_{max} (thin film)/cm^{-1} 3436 (OH) and 1724 (C=O, ester); δ_H ($CDCl_3$, 500 MHz) 1.32 (6H, d, $J=6.3$ Hz, $CH(CH_3)_2$), 3.13 (2H, br s, O*H*), 3.92 (1H, dd, $J_{5,4}=2.7$ Hz, $J_{5,5'}=10.0$ Hz, H-5), 4.16 (1H, dd, $J_{5',4}=4.5$ Hz, $J_{5',5}=10.0$ Hz, H-5′), 4.10 (2H, m, H-2 and H-3), 4.35 (1H, m, H-4), 5.15 (1H, sept, $J=6.3$ Hz, $CH(CH_3)_2$); δ_C ($CDCl_3$, 125.3 MHz) 21.6 (q, $CH(CH_3)_2$), 69.3 (d, $CH(CH_3)_2$), 70.9 (d, C-4), 73.4 (t, C-5), 75.1 (d, C-3), 80.8 (d, C-2), 171.1 (s, C=O); *m/z* (CI+): 208.3 ($M+NH_4^+$, 100%).

4.1.4. Isopropyl 2,5-anhydro-3-*O*-*tert*-butyldiphenylsilyl-L-ribonate 15, isopropyl 2,5-anhydro-4-*O*-*tert*-butyldiphenylsilyl-L-ribonate 8 and isopropyl 2,5-anhydro-3,4-di-*O*-*tert*-butyldiphenylsilyl-L-ribonate 16. *tert*-Butyldiphenylsilyl chloride (5.46 mL, 21.0 mmol) was added to a stirred solution of diol **7** (4.00 g, 21.0 mmol) in dry DMF (20 mL) containing imidazole (1.71 g, 25.2 mmol) at 0 °C. The reaction was allowed to warm to room temperature. After 10 h, TLC (ethyl acetate) showed the absence of starting material (R_f 0.55). Elution of the TLC (with ethyl acetate/pet. ether, 1:9) showed the presence of one minor product (R_f 0.65) and two major products, (R_f 0.32) and (R_f 0.20). The reaction mixture was concentrated in vacuo. The residue was dissolved in ethyl acetate (100 mL) and sequentially washed with brine (100 mL), citric acid (1 M aq, 100 mL), saturated aq sodium hydrogen carbonate (100 mL) and water (100 mL) and then concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate/pet. ether, 1:19) to afford 3-*O*-silyl derivative **15** (3.10 g, 34%) as a colourless oil, the 4-*O*-silyl derivative **8** (5.00 g, 55%) as a colourless oil and the disilylated derivative **16** (1.12 g, 8%) as a white solid.

Compound **15**. $[\alpha]_D^{23}$ +28.9 (*c* 1.9 in $CHCl_3$); (HRMS (CI+): Found 446.234455. $C_{24}H_{32}O_5Si$ ($M+NH_4^+$) requires *m/z*, 446.234934); ν_{max} (thin film)/cm^{-1} 3538 (OH) and 1736 (C=O, ester); δ_H ($(CD_3)_2SO$, 200 MHz) 1.10 (15H, m, $CH(CH_3)_2$ and $SiC(CH_3)_3$), 3.72 (1H, m, H-5), 3.92 (2H, m, H-4 and H-5′), 4.25 (2H, m, H-3 and H-2), 4.82 (1H, sept, $J=6.36$ Hz, $CH(CH_3)_2$), 5.05 (1H, d, O*H*), 7.34–7.65 (10H, m, Ar*H*); δ_C ($(CD_3)_2SO$, 50.3 MHz) 19.9 (s, $SiC(CH_3)_3$), 22.1 (q, $CH(CH_3)_2$), 27.6 (q, $SiC(CH_3)_3$), 68.9 (d, $CH(CH_3)_2$), 71.3 (d, C-4), 73.6 (t, C-5), 77.8 (d, C-3), 82.1 (d, C-2), 128.5, 128.6, 130.8 (3×d, 6×Ar*C*H), 133.6, 133.8 (2×d, 2×Ar*C*), 136.2, 136.4 (2×d, 4×Ar*C*H), 171.3 (s, C=O); *m/z* (CI+): 446.4 ($M+NH_4^+$, 100%).

Compound **8**. $[\alpha]_D^{23}$ +16.5 (*c* 1.6 in $CHCl_3$); (HRMS (CI+): Found 446.236835. $C_{24}H_{32}O_5Si$ ($M+NH_4^+$) requires *m/z*, 446.236277); ν_{max} (thin film)/cm^{-1} 3513 (OH) and 1738 (C=O, ester); δ_H ($(CD_3)_2SO$, 400 MHz) 1.05 (9H, s, $SiC(CH_3)_3$), 1.13 (6H, d, $J=6.2$ Hz, $CH(CH_3)_2$), 3.53 (1H, m, H-5), 3.72 (1H, m, H-5′), 3.95 (1H, m, H-3), 4.12 (1H, m, H-4), 4.20 (1H, d, $J=4.8$ Hz, H-2), 4.90 (1H, sept, $J=6.2$ Hz, $CH(CH_3)_2$), 5.55 (1H, d, O*H*), 7.40–7.75 (10H, m, Ar*H*); δ_C ($(CD_3)_2SO$, 50.3 MHz) 19.8 (s, $SiC(CH_3)_3$), 22.2 (q, $CH(CH_3)_2$), 27.6 (q, $SiC(CH_3)_3$), 68.8 (d, $CH(CH_3)_2$), 72.7 (t, C-5), 73.9 (d, C-4), 75.4 (d, C-3), 82.2 (d, C-2), 128.6, 128.7, 130.7 (3×d, 6×Ar*C*H), 133.8, 134.2 (2×s, 2×Ar*C*), 136.1, 136.2 (2×d, 4×Ar*C*H), 171.3 (s, C=O); *m/z* (CI+): 446.3 ($M+NH_4^+$, 100%).

Compound **16**. Mp 135–136 °C (EtOAc/*n*-hexane, 1:4); $[\alpha]_D^{23}$ +15.1 (*c* 0.5 in $CHCl_3$); (HRMS (CI+): Found 684.354410. $C_{40}H_{50}O_5Si_2$ ($M+NH_4^+$) requires *m/z*, 684.354056); ν_{max} (thin film)/cm^{-1} 1743 (C=O, ester); δ_H ($CDCl_3$, 200 MHz) 1.00 (6H, d, $J=6.7$ Hz, $CH(CH_3)_2$), 1.12, 1.15 (18H, 2×s, 2×$SiC(CH_3)_3$), 3.62 (1H, m, H-5), 3.85 (1H, m, H-5′), 4.13 (1H, m, H-4), 4.22 (1H, d, $J=1.8$ Hz, H-2), 4.35 (1H, m, H-3), 4.75 (1H, sept, $J=6.7$ Hz, $CH(CH_3)_2$), 7.23–7.82 (20H, m, Ar*H*); δ_C ($CDCl_3$, 50.3 MHz) 19.2, 19.4 (2×s, 2×$SiC(CH_3)_3$), 21.4 (q, $CH(CH_3)_2$), 26.9, 27.0 (2×q, 2×$SiC(CH_3)_3$), 68.3 (d, $CH(CH_3)_2$), 70.5 (t, C-5), 73.2 (d, C-4), 76.5 (d, C-3), 82.7 (d, C-2), 127.6, 127.7, 127.7, 127.7, 129.7, 129.9, 129.9 (7×d, 12×Ar*C*H), 133.0, 133.1, 133.5 (3×s, 4×Ar*C*), 135.6, 135.7, 136.0, 136.1 (4×d, 8×Ar*C*H), 170.3 (s, C=O); *m/z* (CI+): 684.4 ($M+NH_4^+$, 35), 589.3 (100%).

4.1.5. Conversion of isopropyl 2,5-anhydro-3,4-di-*O*-*tert*-butyldiphenylsilyl-L-ribonate 16 to isopropyl 2,5-anhydro-L-ribonate 7. Tetrabutylammonium fluoride (1 M solution in THF, 2.2 mL, 2.2 mmol) was added to a stirred solution of disilylated derivative **16** (0.50 g, 0.75 mmol) in dry THF (2 mL) at room temperature. After 14 h, TLC (ethyl acetate) showed the formation of a major product (R_f 0.55). The reaction mixture was concentrated in vacuo and the residue purified by flash chromatography (ethyl acetate/pet. ether, 2:3) to afford the diol **7** (70 mg, 50%) as a colourless oil; data given above.

4.1.6. Isopropyl 2,5-anhydro-4-azido-3-*O*-*tert*-butyldiphenylsilyl-4-deoxy-L-ribonate 1. Trifluoromethanesulfonic anhydride (1.72 mL, 10.5 mmol) was added dropwise over a period of 5 min to a stirred solution of 3-*O*-silyl derivative **15** (3.00 g, 7.0 mmol) in dichloromethane (60 mL) containing freshly distilled dry pyridine (0.96 mL, 11.9 mmol) at −20 °C. After 40 min, TLC (ethyl acetate/pet. ether, 1:9) showed the absence of starting material (R_f 0.20) and the formation of a single product (R_f 0.60). The reaction mixture was diluted with dichloromethane (50 mL), then washed sequentially with brine (50 mL), citric acid (1 M aq, 50 mL) and water (50 mL) and concentrated in vacuo at low temperature (0–5 °C). The residue was dissolved in pre-cooled (0 °C) dry DMF (30 mL) containing sodium azide (1.80 g, 28.0 mmol) and stirred under an atmosphere of nitrogen. After 1 h, the ice bath was removed and the reaction mixture stirred at room temperature. After 10 h, TLC (ethyl acetate/pet. ether, 1:9) showed the formation of a single product (R_f 0.63).

The reaction mixture was filtered and the filtrate concentrated in vacuo and purified by flash chromatography (ethyl acetate/pet. ether, 2:23) to yield the γ-azido ester **1** (3.02 g, 95%) as a colourless oil: $[\alpha]_D^{23}$ +11.3 (*c* 1.15 in $CHCl_3$); (HRMS (CI+): Found 471.242624. $C_{24}H_{31}N_3O_4Si$ ($M+NH_4^+$) requires *m/z*, 471.242759); ν_{max} (thin film)/cm^{-1} 2107 (N_3) and 1753 (C=O, ester); δ_H ($CDCl_3$, 500 MHz) 1.16 (9H, s, $SiC(CH_3)_3$), 1.19 (3H, d, $J=6.2$ Hz, $CH(CH_3)_2$), 1.23 (3H, d, $J=6.2$ Hz, $CH(CH_3)_2$), 3.80 (1H, d, $J=3.5$ Hz, H-4), 4.11 (1H, d, $J_{5,5'}=10.0$ Hz, H-5), 4.30 (1H, dd, $J_{5',4}=4.5$ Hz, $J_{5',5}=10.0$ Hz, H-5′), 4.50 (1H, br s, H-2), 4.58 (1H, br s, H-3), 5.05 (1H, sept, $J=6.2$ Hz, $CH(CH_3)_2$), 7.43–7.67 (10H, m, Ar*H*); δ_C ($CDCl_3$, 50.3 MHz) 19.1 (s, $SiC(CH_3)_3$), 21.6 (q, $CH(CH_3)_2$), 26.8 (q, $SiC(CH_3)_3$), 66.4 (d, $CH(CH_3)_2$), 68.9 (d, C-4), 71.5 (t, C-5), 80.7 (d, C-3), 84.3 (d, C-2), 127.9, 128.0, 130.2, 130.3 (4×d, 6×Ar*C*H), 132.2, 132.7 (2×s, 2×Ar*C*), 135.6, 135.8 (2×d, 4×Ar*C*H), 169.1 (s, C=O); *m/z* (CI+): 471.4 ($M+NH_4^+$, 65), 376.3 (100%).

4.1.7. Isopropyl 2,5-anhydro-3-azido-4-*O*-*tert*-butyldiphenylsilyl-3-deoxy-L-ribonate 3 and isopropyl L-glycero-4-*O*-*tert*-butyldiphenylsilyl-pent-2-enoate 17. Trifluoromethanesulfonic anhydride (1.2 mL, 7.35 mmol) was added dropwise over a period of 5 min to a stirred solution of 4-*O*-silyl derivative **8** (2.10 g, 4.9 mmol) in dichloromethane (60 mL) containing freshly distilled dry pyridine (0.63 mL, 7.8 mmol) at −20 °C. After 40 min, TLC (ethyl acetate/pet. ether, 1:9) showed the absence of starting material (R_f 0.32) and the formation of a single product (R_f 0.58). The reaction mixture was diluted with dichloromethane (50 mL), washed sequentially with brine (50 mL), citric acid (1 M aq, 50 mL) and water (50 mL) and concentrated in vacuo at low temperature (0–5 °C). The residue was dissolved in pre-cooled (0 °C) dry DMF (20 mL) containing sodium azide (1.27 g, 19.6 mmol) and stirred. After 1 h, the ice bath was removed and the reaction mixture stirred at room temperature. After 10 h, TLC (ethyl acetate/pet. ether, 1:9) showed the formation of a minor product (R_f 0.62) and a major product (R_f 0.56). The reaction mixture was filtered and the filtrate concentrated in vacuo and purified by flash chromatography (ethyl acetate/pet. ether, 1:49) to give the β-azido ester **3** (1.80 g, 81%) and the β-elimination product **17** (84 mg, 4%) as colourless oils.

Compound **3**. $[\alpha]_D^{23}$ −12.6 (*c* 1.04 in $CHCl_3$); (HRMS (CI+): Found 471.241851. $C_{24}H_{31}N_3O_4Si$ ($M+NH_4^+$) requires *m/z*, 471.240959); ν_{max} (thin film)/cm^{-1} 2111 (N_3) and 1759 (C=O, ester); δ_H ($CDCl_3$, 500 MHz) 1.15 (9H, s, $SiC(CH_3)_3$), 1.34 (6H, d, $J=6.3$ Hz, $CH(CH_3)_2$), 3.90 (1H, dd, $J_{5,4}=0.9$ Hz, $J_{5,5'}=9.6$ Hz, H-5), 4.03 (1H, t, $J_{3,2}=4.6$ Hz, H-3), 4.08 (1H, dd, $J_{5',4}=3.8$ Hz, $J_{5',5}=9.6$ Hz, H-5′), 4.40 (1H, m, H-4), 4.81 (1H, d, $J_{2,3}=4.6$ Hz, H-2), 5.20 (1H, sept, $J=6.3$ Hz, $CH(CH_3)_2$), 7.42–7.70 (10H, m, 10×Ar*H*); δ_C ($CDCl_3$, 50.3 MHz) 19.0 (s, $SiC(CH_3)_3$), 21.7 (q, $CH(CH_3)_2$), 21.8 (q, $CH(CH_3)_2$), 26.8 (q, $SiC(CH_3)_3$), 69.3 (d, $CH(CH_3)_2$), 69.7 (d, C-4), 74.8 (t, C-5), 77.0 (d, C-3), 79.1 (d, C-2), 128.0, 128.1, 130.2, 130.3 (4×d, 6×Ar*C*H), 132.6 (s, 2×Ar*C*), 135.6 (d, 4×Ar*C*H), 168.3 (s, C=O); *m/z* (APCI+): 454.33 ($M+H^+$, 20), 127.85 (100%).

Compound **17**. $[\alpha]_D^{23}$ −22.3 (*c* 1.75 in $CHCl_3$); (HRMS (TOF MS FI+): Found 410.1973. $C_{24}H_{30}O_4Si$ (M^+) requires *m/z*, 410.1913); ν_{max} (thin film)/cm^{-1} 1737 (C=O, ester); δ_H ($CDCl_3$, 200 MHz) 1.08 (9H, s, $SiC(CH_3)_3$), 1.32 (3H, d, $J=6.3$ Hz, $CH(CH_3)_2$), 1.35 (3H, d, $J=6.3$ Hz, $CH(CH_3)_2$), 4.23 (1H, m, H-5), 4.41 (1H, dd, $J_{5',4}=3.2$ Hz, $J_{5',5}=10.8$ Hz, H-5′), 5.10 (1H, m, H-4), 5.13 (1H sept, $J=6.3$ Hz, $CH(CH_3)_2$), 5.82 (1H, d, $J_{3,4}=2.8$ Hz, H-3), 7.40–7.70 (10H, m, 10×Ar*H*); δ_C ($CDCl_3$, 50.3 MHz) 19.0 (s, $SiC(CH_3)_3$), 21.7 (q, $CH(CH_3)_2$), 26.8 (q, $SiC(CH_3)_3$), 69.2 (d, $CH(CH_3)_2$), 74.8 (d, C-4), 78.4 (t, C-5), 111.5 (d, C-3), 127.7, 127.9, 129.9 (3×d, 6×Ar*C*H), 133.5 (s, 2×Ar*C*), 135.6 (d, 4×Ar-*C*H), 151.0 (s, C-2), 159.9 (s, C=O); *m/z* (TOF MS FI+): 410.19 (M^+, 100%).

4.1.8. Methyl 2,5-anhydro-D-arabinoate 20, methyl 2,5-anhydro-3,4-*O*-(*S*)-benzylidene-D-arabinoate 22 and methyl 2,5-anhydro-3,4-*O*-(*R*)-benzylidene-D-arabinoate 21. 3,4-*O*-Benzylidene-2-*O*-trifluoromethanesulfonyl-D-ribono-1,5-lactone **18** (2.00 g, 5.43 mmol) was dissolved in methanolic hydrogen chloride (5% v/v, 42 mL) and stirred at room temperature. After 1 h, the reaction mixture was heated to 70 °C for 3 h. The reaction mixture was cooled to room temperature, hydrochloric acid (1 M aq, 6 mL) was added and the reaction mixture heated to 70 °C. After 24 h, TLC (chloroform/methanol, 4:1) showed the absence of the starting material (R_f 0.65), the presence of a major product (R_f 0.37) and minor products (R_f 0.71 and 0.68). The reaction mixture was cooled to room temperature and sodium hydrogen carbonate added to neutralize the solution. The mixture was filtered through Celite (eluent: methanol), concentrated in vacuo and purified by flash chromatography (chloroform/methanol, 4:1) to yield the diol **20** (740 mg, 84%) as a white solid. The minor products were purified by further flash chromatography (ethyl acetate/pet. ether, 1:1) to yield the *S*-benzylidene derivative **22** (95 mg, 7%) and the *R*-benzylidene derivative **21** (81 mg, 6%).

Compound **20**. Mp 71–73 °C; $[\alpha]_D^{23}$ +21.7 (*c* 1.0 in $CHCl_3$); (HRMS (CI+ve): Found 163.0614. $C_6H_{11}O_5$ ($M+H^+$) requires *m/z*, 163.0606); (Found C, 44.15; H, 6.52. $C_6H_{10}O_5$ requires C, 44.45; H, 6.22%); ν_{max} (KBr)/cm^{-1} 3491 (OH), 1737 (C=O, ester); δ_H ($CDCl_3$, 400 MHz) 3.31, 3.48 (2H, m, 2×O*H*), 3.81 (3H, s, CO_2CH_3), 4.04–4.07 (2H, m, H-5 and H-5′), 4.26–4.33 (1H, m, H-4), 4.48–4.52 (1H, m, H-3), 4.53 (1H, d, $J_{2,3}=6.4$ Hz, H-2); δ_C ($CDCl_3$, 100 MHz) 53.0 (q, CO_2CH_3), 71.7 (d, C-4), 72.9 (d, C-3), 73.4 (t, C-5), 80.2 (d, C-2), 172.0 (s, C=O); *m/z* (APCI+ve): 163 ($M+H^+$, 80), 103 (100%).

Compound **22**. Mp 125–126 °C; $[\alpha]_D^{24}$ −71.9 (*c* 1.0 in $CHCl_3$): (Found C, 62.55; H, 5.61. $C_{13}H_{14}O_5$ requires C, 62.39; H, 5.64%); ν_{max} (KBr)/cm^{-1} 1756 (C=O, ester); δ_H ($CDCl_3$, 200 MHz) 3.76 (1H, dd, $J_{4,5}=4.0$ Hz, $J_{5,5'}=11.3$ Hz, H-5), 3.84 (3H, s, CO_2CH_3), 4.33 (1H, d, $J_{2,3}=4.3$ Hz, H-2), 4.41 (1H, dd, $J_{4,5'}=0.6$ Hz, $J_{5,5'}=11.3$ Hz, H-5′), 4.98 (1H, ddd, $J_{4,5'}=0.6$ Hz, $J_{4,5}=4.0$ Hz, $J_{3,4}=5.7$ Hz, H-4), 5.08 (1H, dd, $J_{2,3}=4.3$ Hz, $J_{3,4}=5.7$ Hz, H-3), 6.07 (1H, s, Ar-C*H*), 7.35–7.47 (5H, m, 5×Ar*H*); δ_C ($CDCl_3$, 50.3 MHz) 52.6 (q, CO_2CH_3), 74.6 (t, C-5), 80.4 (d, C-4), 81.3 (d, C-3), 82.6 (d, C-2), 106.3 (d, Ar-*C*H), 127.0, 128.6, 129.9, 135.5 (5×d and s, 5×Ar*C*H and Ar*C*), 167.9 (s, C=O); *m/z* (APCI+ve): 121 (100), 251 ($M+H^+$, 35%).

Compound **21**. Mp 79–81 °C: $[\alpha]_D^{23}$ −162.8 (*c* 1.02 in $CHCl_3$): (Found C, 62.19; H, 6.00. $C_{13}H_{14}O_5$ requires C, 62.39; H, 5.64%); ν_{max} (thin film)/cm^{-1} 1764 (C=O, ester); δ_H ($CDCl_3$, 400 MHz) 3.66 (1H, dd, $J_{4,5}=3.5$ Hz, $J_{5,5'}=10.9$ Hz, H-5), 3.78 (3H, s, CO_2CH_3), 4.31 (1H, d, $J_{2,3}=4.3$ Hz, H-2), 4.36 (1H, d, $J_{5,5'}=10.9$ Hz, H-5′), 4.89 (1H, dd, $J_{4,5}=3.5$ Hz, $J_{3,4}=6.3$ Hz, H-4), 5.05 (1H, dd, $J_{2,3}=4.3$ Hz, $J_{3,4}=6.3$ Hz, H-3), 5.76 (1H, s, Ar-CH), 7.37–7.52 (5H, m, 5×ArH); δ_C ($CDCl_3$, 100 MHz) 52.7 (q, CO_2CH_3), 73.0 (t, C-5), 81.6 (d, C-4), 81.9 (d, C-2), 82.3 (d, C-3), 107.1 (d, Ar-CH), 127.8, 128.8, 130.4, 136.0 (5×d and s, 5×ArCH and ArC), 168.1 (s, C=O); *m/z* (APCI+ve): 251 ($M+H^+$, 100%).

4.1.9. Methyl 2,5-anhydro-3,4-*O*-isopropylidene-D-arabinoate 12. DL-Camphor-10-sulfonic acid (182 mg, 0.78 mmol) was added to a stirred solution of the diol **20** (1.27 g, 7.84 mmol) in acetone (6 mL). After 18 h, a white solid had precipitated from solution and TLC (ethyl acetate/hexane, 1:1) showed the absence of starting material (R_f 0.0) and the presence of a major product (R_f 0.2). Sodium hydrogen carbonate was added to the reaction mixture to neutralize the solution and the reaction mixture filtered through Celite (eluent/acetone). The filtrate was concentrated in vacuo and purified by flash chromatography (ethyl acetate/hexane, 1:1) to yield the acetonide **12** (1.19 g, 75%) as a white solid. Mp 60–61 °C; $[\alpha]_D^{23}$ −91.7 (*c* 1.02 in $CHCl_3$): (Found C, 53.48; H, 6.99. $C_9H_{14}O_5$ requires C, 53.46; H, 6.98%); ν_{max} (thin film)/cm^{-1} 1761 (C=O, ester); δ_H (C_6D_6, 400 MHz) 1.13, 1.50 (2×3H, 2×s, $C(CH_3)_2$), 2.85 (1H, dd, $J_{4,5}=3.8$ Hz, $J_{5,5'}=10.6$ Hz, H-5), 3.41 (3H, s, CO_2CH_3), 3.71 (1H, d, $J_{2,3}=4.3$ Hz, H-2), 3.94 (1H, d, $J_{5,5'}=10.6$ Hz, H-5′), 4.04–4.08 (1H, m, H-4), 4.47–4.51 (1H, m, H-3); δ_C (C_6D_6, 100 MHz) 24.9, 25.9 (2×q, $C(CH_3)_2$), 52.2 (q, CO_2CH_3), 72.8 (t, C-5), 80.3 (d, C-4), 81.4 (d, C-3), 81.6 (d, C-2), 113.1 (s, $C(CH_3)_2$), 167.8 (s, C=O); *m/z* (APCI+ve): 203 ($M+H^+$, 100%).

4.1.10. Methyl 2,5-anhydro-4-*O*-trifluoromethanesulfonyl-D-arabinoate 24. Pyridine (374 μL, 4.59 mmol) and trifluoromethanesulfonic anhydride (0.78 mL, 4.64 mmol) were added to a stirred solution of the diol **20** (500 mg, 3.09 mmol) in dichloromethane (25 mL) at −25 °C. The reaction mixture was warmed to room temperature after being stirred for 4 h. After 48 h, TLC (ethyl acetate/pet. ether, 1:1) showed traces of starting material (R_f 0.0) and the presence of a major product (R_f 0.3). The reaction mixture was diluted with dichloromethane (125 mL), washed with hydrochloric acid (1 M aq, 50 mL) and extracted with dichloromethane (3×30 mL). The combined organic extracts were washed with aq buffer (pH 7, 100 mL) and brine (100 mL). The organic layer was dried over magnesium sulfate, filtered, concentrated in vacuo and purified by flash chromatography (ethyl acetate/pet. ether, 1:1) to give the triflate **24** (432 mg, 48%) as a yellow solid. Mp 101–102 °C; $[\alpha]_D^{24}$ −4.6 (*c* 0.53 in $CHCl_3$): (Found C, 28.53; H, 3.11. $C_7H_9F_3O_7S$ requires C, 28.58; H, 3.08%); ν_{max} (thin film)/cm^{-1} 3426 (OH) and 1755 (C=O, ester); δ_H ($(CD_3)_2CO$, 400 MHz) 3.69 (3H, s, CO_2CH_3), 4.22–4.25 (2H, m, H-5 and H-5′), 4.63 (1H, d, $J_{2,3}=6.4$ Hz, H-2), 4.89 (1H, dd, $J_{2,3}=6.4$ Hz, $J_{3,4}=5.4$ Hz, H-3), 5.51–5.55 (1H, m, H-4); δ_C ($(CD_3)_2CO$, 50.3 MHz) 51.6 (q, CO_2CH_3), 69.9 (t, C-5), 71.5 (d, C-3), 79.5 (d, C-2), 86.7 (d, C-4), 119.8 (q, CF_3), 169.5 (s, C=O); *m/z* (TOF CI+ve): 312 ($M+NH_4^+$, 100%).

4.1.11. Methyl 2,5-anhydro-4-azido-4-deoxy-L-xylonate 23. Pyridine (1.0 mL, 12.3 mmol) and trifluoromethanesulfonic anhydride (1.56 mL, 9.23 mmol) were added to a stirred solution of the diol **20** (1.00 g, 6.17 mmol) in dichloromethane (50 mL) at −25 °C. The reaction mixture was warmed to room temperature after being stirred for 4 h. After 48 h, TLC (ethyl acetate/pet. ether, 1:1) showed traces of starting material (R_f 0.0) and the presence of a major product (R_f 0.3). The reaction mixture was diluted with dichloromethane (125 mL), washed with hydrochloric acid (1 M aq, 50 mL) and extracted with dichloromethane (3×30 mL). The combined organic extracts were washed with aq buffer (pH 7, 100 mL) and brine (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo to afford the triflate **24** as a yellow solid, which was used without further purification.

Sodium azide (2.21 g, 34.0 mmol) was added to a stirred solution of the triflate **24** in DMF (95 mL). The reaction mixture was heated to 85 °C after being stirred for 10 h. After 15 h, TLC (ethyl acetate/pet. ether, 1:1) showed the absence of the starting material (R_f 0.3, UV active) and the presence of a major product (R_f 0.3). The reaction mixture was cooled to room temperature and concentrated in vacuo. The resulting residue was dissolved in ethyl acetate (480 mL), washed with water (100 mL) and extracted with ethyl acetate (3×380 mL). The combined organic extracts were dried over magnesium sulfate, filtered, then concentrated in vacuo and purified by flash chromatography (ethyl acetate/pet. ether, 1:1) to yield the title product (528 mg, 46% over two steps) as a white solid. Mp 115–116 °C; $[\alpha]_D^{23}$ +35.9 (*c* 0.99 in $CHCl_3$): (Found C, 38.63; H, 4.82. $C_6H_9O_4N_3$ requires C, 38.51; H, 4.85%); ν_{max} (thin film)/cm^{-1} 3449 (OH), 2127 (N_3) and 1743 (C=O, ester); δ_H ($CDCl_3$, 200 MHz) 2.60 (1H, d, $J=5.0$ Hz, OH), 3.84 (3H, s, CO_2CH_3), 3.95 (1H, dd, $J_{4,5}=2.0$ Hz, $J_{5,5'}=9.8$ Hz, H-5), 4.10–4.15 (1H, m, H-4), 4.35 (1H, dd, $J_{4,5'}=4.9$ Hz, $J_{5,5'}=9.8$ Hz, H-5′), 4.52 (1H, m, H-3), 4.65 (1H, d, $J_{2,3}=4.4$ Hz, H-2); δ_C ($CDCl_3$, 50.3 MHz) 52.7 (q, CO_2CH_3), 66.8 (d, C-4), 71.4 (t, C-5), 76.8 (d, C-3), 80.7 (d, C-2), 170.3 (s, C=O); *m/z* (APCI+ve): 160 ($M-N_2+H^+$, 100%).

4.1.12. Isopropyl 2,5-anhydro-4-azido-4-deoxy-L-xylonate 2. *Method A*. Potassium carbonate (30 mg, 0.22 mmol) was added to a stirred solution of the methyl azido ester **23** (30 mg, 0.16 mmol) in propan-2-ol (2.42 mL). After 72 h, TLC (ethyl acetate/pet. ether, 2:1) showed the absence of the starting material (R_f 0.3) and the presence of a major product (R_f 0.5). The reaction mixture was filtered through Celite (eluent propan-2-ol), concentrated in vacuo and purified by flash chromatography (ethyl acetate/pet. ether, 2:1) to yield isopropyl azido ester **2** (18 mg, 52%) as a white solid.

Method B. *p*-Toluenesulfonic acid monohydrate (160 mg, 0.84 mmol) was added to a stirred solution of methyl azido ester **23** (500 mg, 2.67 mmol) in propan-2-ol (5 mL) at 80 °C. After 24 h, TLC (ethyl acetate/pet. ether, 2:1) showed the absence of the starting material (R_f 0.3) and the presence of a major product (R_f 0.5). The reaction mixture was

cooled to room temperature and sodium hydrogen carbonate added to neutralize the solution. The reaction mixture was filtered, concentrated in vacuo and purified by flash chromatography (ethyl acetate/pet. ether, 2:1) to yield isopropyl azido ester **2** (414 mg, 72%) as a white solid.

Compound **2**. Mp 78–80 °C; $[\alpha]_D^{24}$ +28.9 (*c* 1.07 in $CHCl_3$); (HRMS (CI+ve): Found 216.0987. $C_8H_{14}N_3O_4$ ($M+H^+$) requires *m/z*, 216.0984); ν_{max} (thin film)/cm^{-1} 3431 (OH), 2088 (N_3) and 1728 (C=O, ester); δ_H ($CDCl_3$, 200 MHz) 1.30 (3H, d, $J=6.3$ Hz, $CH(CH_3)_2$), 1.31 (3H, d, $J=6.3$ Hz, $CH(CH_3)_2$), 2.71 (1H, d, $J=5.3$ Hz, OH), 3.92 (1H, dd, $J_{4,5}=2.0$ Hz, $J_{5,5'}=9.9$ Hz, H-5), 4.10–4.13 (1H, m, H-4), 4.34 (1H, dd, $J_{4,5'}=4.7$ Hz, $J_{5,5'}=9.9$ Hz, H-5′), 4.49–4.52 (1H, m, H-3), 4.57 (1H, d, $J_{2,3}=4.4$ Hz, H-2), 5.17 (1H, sept, $J=6.3$ Hz, $CH(CH_3)_2$); δ_C ($CDCl_3$, 50.3 MHz) 22.0 (q, $CH(CH_3)_2$), 66.9 (d, C-4), 69.8 (d, $CH(CH_3)_2$), 71.3 (t, C-5), 76.8 (d, C-3), 80.3 (d, C-2), 169.4 (s, C=O); *m/z* (APCI+ve): 188 ($M-N_2+H^+$, 24), 233 ($M+NH_4^+$, 100%).

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Ground state oxygen in synthesis of cyclic peroxides. Part 1: Benzo fused ketals

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Abstract—A thiol-olefin-cooxygenation (TOCO) radical chain reaction involving ground state molecular oxygen converts 2′-isopropenyl acetophenones directly into cyclic peroxy hemiketal products with three new bonds. Starting with 4-*t*-butylbenzenethiol, this TOCO process proceeds reproducibly on gram scale in 86% yield. Hemiketal → ketal and sulfide → sulfone transformations finally provide a series of sulfonyl cyclic peroxy ketals. The in vitro antimalarial activities of some of these structurally simple benzo-fused cyclic peroxides are reported.

1. Introduction

Among the methods for preparing dialkyl peroxides such as 1,2-dioxetanes and antimalarial 1,2,4-trioxanes, dioxygenation using photochemically-generated singlet molecular oxygen is the most popular.[1–3] Unfortunately, however, preparation of multigram amounts of antimalarial trioxanes is not practical using singlet molecular oxygen due to the short lifetime and high reactivity of this high energy species. Thus, even though our research program of antimalarial trioxane drug development successfully identified two safe, efficacious, and structurally simple antimalarial trioxanes, scale-up synthesis was unsuccessful.[4,5] As part of a general program eventually to synthesize trioxanes using ground state molecular oxygen, we report here non-singlet (i.e., triplet, ground state) molecular oxygen synthesis of simple benzo-fused cyclic peroxy ketals. This research builds on our previous report about some potent antimalarial cyclic peroxy ketals (e.g., sulfone **1** with $IC_{50}=31$ nM)[6] and on the recent successful application of thiol-olefin-cooxygenation (TOCO) chemistry for rapid and efficient conversion of limonene (**2**) into some antimalarially potent sulfonyl endoperoxides (Scheme 1 and Fig. 1).[7,8]

2. Results and discussion

Starting with commercial 2′-bromoacetophenone, Wittig methylenation, lithium–bromide exchange, addition to acetaldehyde, and oxidation produced 2′-isopropenyl acetophenone (**5**) in high yield (Scheme 2). Using a balloon filled with molecular oxygen and a short irradiation time, as recently described in a modified TOCO protocol,[9] TOCO chemistry produced the benzo-fused cyclic peroxy hemiketal **7** in 57% yield as a 9:5 ratio of diastereomers (Scheme 2). The high yield of this TOCO process is due in large part to the ease with which the benzenethiolate radical adds to the isopropenyl group to generate a tertiary benzylic carbon-centered radical; this relatively stable radical reacts with ground-state molecular oxygen to form a peroxy radical, which can abstract a hydrogen atom from benzenethiol, thereby propagating this radical chain reaction. The putative intermediate hydroperoxy ketone **6** is not observed, but it presumably rapidly cyclizes into the isolated peroxy hemiketal product **7**.

Based on our previous finding that cyclic peroxy hemiketals have considerably less antimalarial potency than the

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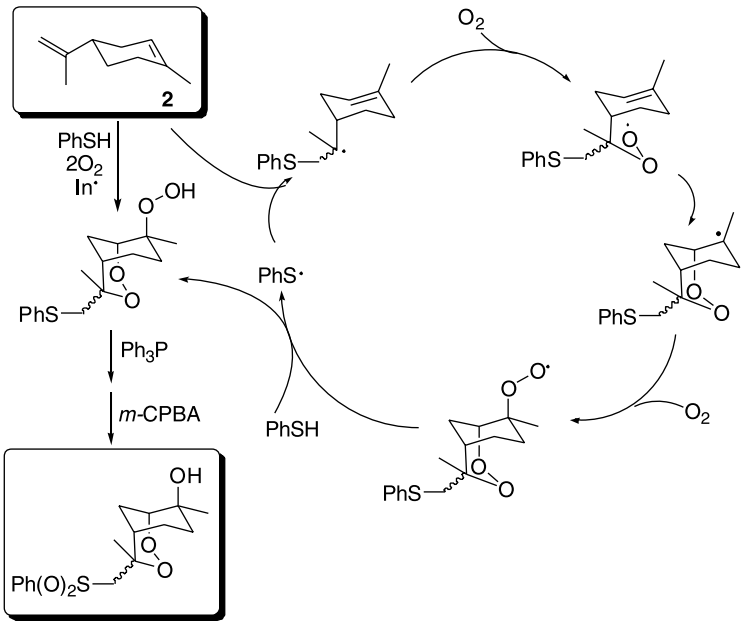


Scheme 1. Thiol olefin cooxygenation (TOCO) followed by sulfide oxidation.

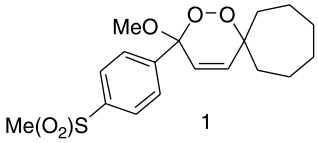
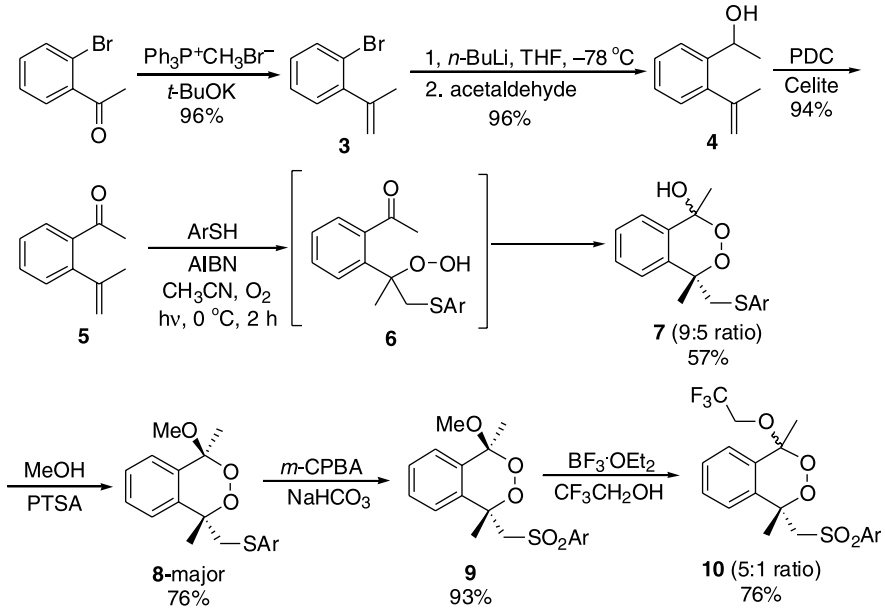


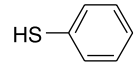
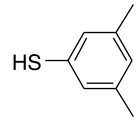
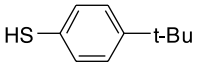
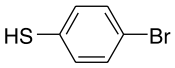
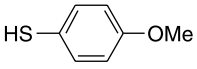
Figure 1.

corresponding ketals,[6] hemiketal **7** was converted directly into ketal **8** (Scheme 2). Based also on the previous finding that sulfanyl endoperoxides have considerably less antimalarial potency than the corresponding sulfonyl endoperoxides,[8] the major diastereomer of sulfide **8** was oxidized into sulfone **9**. Confirmation of the relative stereochemistry of crystalline sulfone **9** by X-ray crystallography revealed that the two methyl groups on the 1,2-dioxin ring are trans-oriented. Dissolved in 40:60 DMSO/H_2O buffered at pH 7.4, sulfone **9** was stable; after 4 days at 25 °C, less than 1% decomposition was determined by calibrated HPLC analysis. Finally, with the intention of further diminishing any possible hydrolysis of the peroxy ketal functionality under physiological (pH 7.4) conditions, the methoxy group was replaced by a less basic (i.e., less easily protonated) trifluoroethoxy group in the form of ketal sulfone **10** (Scheme 2). In this way, a series of commercial benzenethiols led to the series of benzo-fused cyclic peroxy ketals shown in Table 1. The most outstanding chemical result in this series is that 4-*t*-butylbenzenethiol, a mercaptan having almost no unpleasant odor, achieves the 3-bond-forming TOCO process in 86% yield even on gram scale.



Scheme 2. Synthesis of ketal endoperoxides via the TOCO process. Yields and ratios are for Ar=Ph.

Table 1. Benzo fused ketal analogs via the TOCO process

Entry	HS-Ar	Yield (%)			
		7	**8′** major + **8″** minor	**9**	**10′** major + **10″** minor
a		57% (1.8:1)	76% (9:1)	93	76% (5:1)[a]
b		60% (2:1)	76% (2.7:1)	83	74% (5:1)
c		86% (1.4:1)	89% (6:1)	97	65% (5:1)
d		71% (2.8:1)	84% (3.4:1)	89	90% (5:1)
e		72% (1.5:1)	83% (2.4:1)	94	91% (6:1)

[a] Inseparable mixture by HPLC.

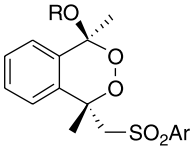
The in vitro antimalarial potencies of several of these sulfonyl cyclic peroxy ketals was determined using our standard protocol[10] and are shown in Table 2.

To encumber the ketal region and thus to retard possible hydrolysis of the peroxy ketal functionality under physiological conditions, a sterically hindered version carrying a tertiary butyl group was prepared in good yield as a 1:1 mixture of diastereomers (Scheme 3). The sulfonyl *t*-butyl peroxy ketal **12** diastereomer where the methoxy is cis to the sulfonyl was only weakly active as an antimalarial.

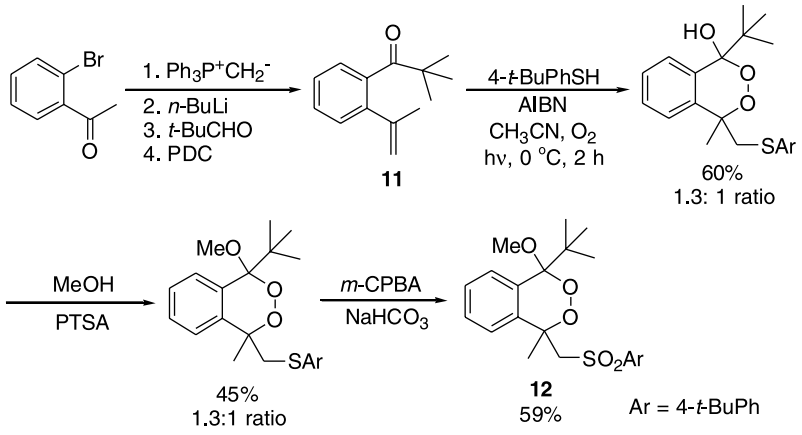
3. Conclusions

In conclusion, TOCO radical chain reactions using ground state molecular oxygen lead, in good yield, to a series of benzo-fused cyclic peroxy ketals. These reactions are easily scaled up to multigram quantities of products. The relatively

Table 2. Antimalarial activity against *Plasmodium falciparum* (NF54)

	Ar	R	IC_{50} (nM)[a]
	4-*t*-BuPh	Me	540
	4-BrPh	Me	820
	Ph[b]	CF_3CH_2	480
	Artemisinin		7.9 ± 0.87

[a] The standard deviation for each set of quadruplicates was an average of 8.0% (≤16%) of the mean. R^2 values for the fitted curves were ≥0.983. Artemisinin activity is the mean ± standard deviation of the concurrent control (n=3).
[b] Mixture of isomers.



Scheme 3. Synthesis of a hindered ketal endoperoxide via the TOCO process.

weak in vitro antimalarial activities of these cyclic peroxy ketals, however, make them unpromising for chemotherapy of malaria.

4. Experimental

4.1. General

4.1.1. 1-Bromo-2-isopropenyl-benzene 3. To a suspension of methyltriphenylphosphonium bromide (8.57 g, 24.0 mmol) in THF (60 mL) at room temperature was added a solution of potassium *tert*-butoxide (1.0 M in THF, 24.0 mL, 24.0 mmol). After being stirred for 5 min, the reaction mixture was treated with a solution of 2′-bromoacetophenone (3.98 g, 20 mmol) in THF (40 mL) via cannula. The reaction mixture was stirred for 3 h at room temperature before it was quenched with the addition of saturated aqueous ammonium chloride (40 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3×40 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified via flash column chromatography (100% hexanes) to give 1-bromo-2-isopropenyl-benzene (3.78 g, 96% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, J=8.0, 1.2 Hz, 1H), 7.26 (dt, J=7.2, 1.2 Hz, 1H), 7.19 (dd, J=7.6, 2.0 Hz, 1H), 7.13–7.09 (m, 1H), 5.24–5.22 (m, 1H), 4.94–4.93 (m, 1H), 2.10–2.09 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 144.8, 132.7, 129.7, 128.3, 127.2, 121.5, 116.0, 23.5; IR (CH_2Cl_2, film) 3081, 3053, 2970, 1917, 1805, 1641, 1469, 1433, 1371, 1025, 903, 758, 653 cm^{-1}; TLC R_f (hexane)=0.83; HRMS (CI) m/z calcd for C_9H_9Br $(M)^+$ 195.9888, found 195.9876.

4.1.2. Alcohol 4. To a solution of 1-bromo-2-isopropenyl-benzene (1.97 g, 10 mmol) in THF (15 mL) at −78 °C, was added a solution of *n*-BuLi (1.6 M in hexanes, 7.5 mL, 12 mmol). After being stirred for 30 min at −78 °C, acetaldehyde (0.84 mL, 15 mmol) was added neat. The reaction mixture was stirred at −78 °C for 30 min then at room temperature for 1 h before it was quenched with the addition of saturated aqueous ammonium chloride (25 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3×40 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified via flash column chromatography (20% ethyl acetate in hexanes) to give alcohol (1.55 g, 96% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (ddd, J=7.6, 1.2, 0.4 Hz, 1H), 7.41 (td, J=7.6, 1.6 Hz, 1H), 7.31 (td, J=7.6, 1.6 Hz, 1H), 7.27 (ddd, J=7.6, 1.2, 0.4 Hz, 1H), 5.25–5.22 (m, 1H), 5.18 (quint, J=1.6 Hz, 1H), 4.90 (m, 1H), 2.10 (br s, 1H), 2.09–2.07 (m, 3H), 1.49–1.45 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 142.3, 142.0, 127.9, 127.4, 127.1, 125.2, 115.5, 66.6, 25.6, 25.0; IR (CH_2Cl_2, film) 3746, 3076, 2971, 2929, 1640, 1486, 1445, 1434, 1372, 1299, 1196, 1073, 1004, 900, 759 cm^{-1}; TLC R_f (hexane/Et_2O 2:1)=0.64; HRMS (EI) m/z calcd for $C_{11}H_{14}O$ $(M)^+$ 162.1039, found 162.1098.

4.1.3. Ketone 5. To a solution of alcohol **4** (1.19 g, 7.36 mmol) in CH_2Cl_2 (25 mL) was added pyridinium dichromate (PDC, 5.54 g, 14.7 mmol) and Celite® (5.50 g) at 25 °C under argon atmosphere. After being stirred for 2 days, the reaction mixture was diluted with EtOAc and filtered through a pad of silica gel. The filtrate was concentrated in vacuo and then purified by flash column chromatography (10% EtOAc in petroleum ether) to give ketone **4** (1.11 g, 94%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (ddd, J=7.6, 1.2, 0.4 Hz, 1H), 7.39 (td, J=7.6, 1.6 Hz, 1H), 7.29 (td, J=7.6, 1.2 Hz, 1H), 7.25 (dd, J=7.6, 1.2 Hz, 1H), 5.16–5.15 (m, 1H), 4.88 (m, 1H), 2.47 (m, 3H), 2.11 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.6, 145.1, 142.5, 139.3, 130.6, 128.4, 127.8, 127.1, 116.2, 29.9, 23.9; IR (neat, film) 3062, 2973, 2918, 2855, 1691, 1635, 1595, 1441, 1355, 1275, 1243, 956, 904, 770, 758 cm^{-1}; TLC R_f (hexane/Et_2O)=0.80; HRMS (EI) m/z calcd for $C_{11}H_{12}O$ $(M)^+$ 160.0883, found 160.0888.

4.1.4. Hemiketal 7c. To a solution of ketone **5** (2.12 g, 13.2 mmol) in acetonitrile (220 mL) under argon was added 2,2′-azobisisobutyronitrile (AIBN, 152 mg, 0.926 mmol) and 4-*tert*-butylthiophenol (2.85 mL, 16.5 mmol). The reaction vessel was flushed with oxygen for 10 min at 0 °C and then kept under a positive pressure of oxygen with two balloons. The reaction mixture was stirred vigorously and irradiated using a mercury UV lamp (450 W, Ace Glass) at a distance of 10 cm at 0 °C. After 2 h, the reaction was flushed with argon and then concentrated in vacuo. The crude product was then purified by flash silica gel column chromatography (10% EtOAc in hexanes) to yield hemiketal **7c** (4.06 g, 11.3 mmol, 86%) as a yellow oil as a mixture of two diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.44 (m, 1H), 7.33–7.26 (m, 7H), 3.78 (s, 1H), 3.70 (d, J=13.6 Hz, 1H), 3.39 (d, J=13.6 Hz, 1H), 1.69 (s, 3H), 1.60 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 137.7, 135.3, 133.4, 129.6, 128.1, 127.6, 125.8, 125.8, 124.7, 99.2, 81.9, 43.4, 34.3, 31.2, 23.8, 22.4; IR (CH_2Cl_2, film) 3415, 2962, 2862, 1492, 1444, 1364, 1148, 1120, 935, 892, 824, 764 cm^{-1}; HRMS (EI) m/z calcd for $C_{21}H_{26}O_3SNa$ $(M+Na)^+$ 381.14948, found 381.14871.

4.1.5. Ketone 11. Ketone **11** was synthesized as above with substitution of trimethylacetaldehyde in place of acetaldehyde. After three steps from 2′-bromoacetophenone, ketone **11** was isolated as a colorless oil (104 mg, 0.512 mmol, 36% from alcohol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.26 (m, 3H), 7.11 (d, J=7.2 Hz, 1H), 5.17 (m, 1H), 4.97 (s, 1H), 2.14 (s, 3H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.0, 144.4, 139.9, 135.8, 128.4, 127.3, 126.5, 125.7, 117.6, 78.6, 27.7, 24.1; IR (CH_2Cl_2, film) 3488.6, 3061.9, 2968.8, 2870.0, 1987.1, 1633.4, 1478.5, 1460.0, 1392.0, 1363.6, 1278.6, 1259.5, 1191.1, 1173.0, 1035.9, 768.0, 734.4 cm^{-1}; HRMS (FAB-MS) m/z calcd for $C_{14}H_{18}O$ $(M+H)^+$ 203.14359, found 203.14416.

4.2. General procedure for the TOCO process

A solution of ketone (1.0 mmol), 2,2′-azobisisobutyronitrile (AIBN, 0.07 mmol) and thiophenol (1.25 mmol) in acetonitrile (17 mL) was thoroughly flushed with oxygen for 10 min at 0 °C and then kept under a positive pressure of pure oxygen with the aid of two oxygen balloons. The reaction mixture was stirred vigorously and UV irradiated at

0 °C using an externally mounted medium-pressure mercury lamp (450 W, Ace Glass) at a distance of 15 cm. After 2 h at 0 °C, the reaction mixture was concentrated in vacuo and the residue was subjected to flash column chromatography to give corresponding hemiketals.

4.3. General procedure for the methylation of the alcohol

To a solution of the above hemiketals (0.15 mmol) in MeOH (3 mL) was added *p*-toluenesulfonic acid monohydrate (0.015 mmol) at 25 °C. After being stirred for 24 h at 25 °C, the reaction mixture was concentrated in vacuo and the residue was subjected to flash column chromatography to give the corresponding methoxy ketal sulfides.

4.4. General procedure for oxidation of methoxy ketal sulfides to methoxy ketal sulfones

To a solution of methoxy ketal sulfide (0.15 mmol) in CH_2Cl_2 (6 mL), was added 3-chloroperoxybenzoic acid (*m*-CPBA, 77% max, 0.36 mmol) and sodium bicarbonate (0.86 mmol). After being stirred for 4 h at 25 °C, the reaction was quenched by the addition of water and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$. After filtration and concentration in vacuo, the residue was purified via flash column chromatography (25% ethyl acetate in hexanes). The products were further purified using normal-phase high-performance liquid chromatography (HPLC) prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 5% EtOAc in hexanes, 2.0 mL/min, 264 nm].

4.5. Conversion of methoxy ketal sulfones to trifluoroethoxy ketal sulfones

To a solution of methoxy ketal (0.13 mmol) in trifluoroethanol (3 mL) at 0 °C, was added dropwise boron trifluoride diethyl etherate (0.066 mmol, 0.5 equiv). After stirring for 3 h at 0 °C, the reaction mixture was warmed to room temperature and further stirred for 1 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (3 mL) and extracted with Et_2O (3×10 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. After filtration and concentration in vacuo, the residue was purified via flash column chromatography (20% ethyl acetate in hexanes). The products were further purified using normal-phase HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 5% EtOAc in hexanes, 2.0 mL/min, 264 nm].

4.5.1. From thiophenol.

4.5.1.1. Compound 8′a. Colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.22 (m, 8H), 7.18–7.13 (m, 1H), 3.69 (d, J=17.6 Hz, 1H), 3.43 (s, 3H), 3.38 (d, J=18.0 Hz, 1H), 1.61 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 137.1, 134.0, 129.4, 128.8, 128.1, 127.6, 126.0, 125.9, 124.5, 101.8, 81.5, 51.2, 43.1, 22.3, 22.3; IR (neat, film) 3060, 2990, 2937, 2832, 1583, 1480, 1439, 1371, 1298, 1275, 1154, 1131, 1043, 875, 763, 739, 691 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{20}O_3SNa$ $(M+Na)^+$339.1025, found 339.1024.

4.5.1.2. Compound 9a. White solid: mp 97–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dm, J=7.6 Hz, 2H), 7.62 (tt, J=7.6, 1.6 Hz, 1H),7.53 (tm, J=7.6 Hz, 2H), 7.34–7.29 (m, 4H), 3.95 (d, J=14.8 Hz, 1H), 3.58 (d, J=14.8 Hz, 1H), 3.30 (s, 3H), 1.87 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 137.5, 133.5, 133.5, 128.9, 128.5, 128.1, 125.9, 124.5, 101.5, 79.7, 61.9, 51.2, 22.5, 22.1; IR ($CDCl_3$, film) 3066, 2996, 2940, 1448, 1375, 1308, 1147, 1085, 1043, 876, 761, 688 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{20}O_5SNa$ $(M+Na)^+$371.0924, found 371.0909.

4.5.1.3. Compound 10′a. Colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94–7.89 (m, 2H), 7.64 (tt, J=7.6, 1.2 Hz, 1H), 7.56–7.51 (m, 2H), 7.42–7.33 (m, 4H), 3.66 (dq, J=12.0, 8.4 Hz, 1H), 3.91 (d, J=14.8 Hz, 1H), 4.02 (dq, J=11.6, 8.8 Hz, 1H), 3.58 (d, J=14.8 Hz, 1H),, 1.90 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 137.9, 133.6, 131.4, 129.2, 129.0, 128.6, 128.1, 126.1, 124.6, 123.6 (q, J=276 Hz), 102.0, 80.0, 62.4 (q, J=35 Hz), 61.6, 23.6, 22.5; IR (neat, film) 3067, 2996, 2942, 2835, 1586, 1448, 1378, 1321, 1286, 1151, 1085, 968, 902, 764, 688 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{19}F_3O_5SNa$ $(M+Na)^+$439.0797, found 439.0808.

4.5.1.4. Compound 8′b. Colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.26 (m, 4H), 6.95 (s, 2H), 6.78 (s, 1H), 3.51 (d, J=13.2 Hz, 1H), 3.43 (s, 3H), 3.38 (d, J=13.2 Hz, 1H), 2.25 (s, 6H), 1.63 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 138.3, 136.6, 134.0, 128.0, 127.8, 127.6, 125.8, 124.6, 101.7, 81.5, 51.2, 43.0, 22.3, 22.3, 21.1; IR (CH_2Cl_2, film) 2989, 2937, 1599, 1582, 1447, 1370, 1298, 1274, 1131, 1043, 896, 875, 762 cm^{-1}; TLC R_f (hexane/Et_2O 2:1)=0.58; HRMS (ESI) *m/z* calcd for $C_{20}H_{24}O_3SNa$ $(M+Na)^+$367.1338, found 367.1328. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 10% EtOAc in hexanes, 2.0 mL/min, 264 nm, t_R =15.3 min].

4.5.2. From 3,5-dimethylthiophenol.

4.5.2.1. Compound 8″b. Colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.31 (m, 3H), 7.22–7.20 (m, 1H), 6.97 (s, 2H), 6.79 (s, 1H), 3.57 (d, J=13.6 Hz, 1H), 3.43 (d, J=13.6 Hz, 1H), 3.33 (s, 3H), 2.26 (s, 6H), 1.69 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 138.4, 136.6, 134.4, 128.0, 128.0, 127.4, 127.3, 125.8, 124.2, 102.9, 82.1, 51.9, 43.4, 24.4, 24.2, 21.2; IR (CH_2Cl_2, film) 2987, 2929, 1594, 1575, 1445, 1369, 1268, 1128, 1042, 849, 762 cm^{-1}; TLC R_f (hexane/Et_2O 2:1)=0.64; HRMS (ESI) *m/z* calcd for $C_{20}H_{24}O_3SNa$ $(M+Na)^+$367.1338, found 367.1332. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 10% EtOAc in hexanes, 2.0 mL/min, 264 nm, t_R=13.5 min].

4.5.2.2. Compound 9b. Colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.50 (m, 2H), 7.35–7.29 (m, 4H), 7.21–7.20 (m, 1H), 3.90 (d, J=14.8 Hz, 1H), 3.61 (d, J=14.8 Hz, 1H), 3.33 (s, 3H), 2.36 (br s, 6H), 1.87 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 139.0, 137.3, 135.0, 133.5, 128.3, 128.0, 125.8, 125.4, 124.7, 101.5, 79.8, 61.9, 51.2, 22.7, 22.0, 21.1; IR (CH_2Cl_2, film)

2972, 2941, 2835, 1608, 1456, 1378, 1318, 1302, 1139, 1104, 1046, 878, 768, 683 cm^{-1}; TLC R_f (hexane/Et_2O 2:1)=0.14; HRMS (ESI) *m/z* calcd for $C_{20}H_{24}O_5SNa$ $(M+Na)^+$ 399.1237, found 399.1237. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 30% EtOAc in hexanes, 3.0 mL/min, 264 nm, t_R=9.5 min].

4.5.2.3. Compound 10′b. Colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (br s, 2H), 7.41–7.33 (m, 4H), 7.22 (br s, 1H), 4.06 (dq, J=11.8, 8.4 Hz, 1H), 3.85 (d, J=14.8 Hz, 1H), 3.68 (dq, J=11.8, 8.8 Hz, 1H), 3.60 (d, J=14.8, 8.8 Hz, 1H), 2.37 (s, 6H), 1.88 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 139.1, 137.8, 135.2, 131.4, 129.0, 128.5, 126.0, 125.4, 124.9, 123.6 (q, J=276 Hz), 62.4 (q, J=35 Hz), 61.6, 23.6, 22.7, 21.1; IR (CH_2Cl_2, film) 2987, 2929, 1608, 1453, 1378, 1321, 1286, 1144, 1083, 967, 902, 858, 765, 684 cm^{-1}; TLC R_f (hexane/EtOAc 2:1)=0.68; HRMS (ESI) *m/z* calcd for $C_{21}H_{23}F_3O_5SNa$ $(M+Na)^+$ 467.1110, found 467.1093. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 30% EtOAc in hexanes, 2.0 mL/min, 264 nm, t_R=13.0 min].

4.5.2.4. Compound 10″b. Colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.48–7.47 (m, 2H), 7.35–7.32 (m, 3H), 7.22–7.18 (m, 2H), 3.78–3.68 (m, 3H), 3.53 (dq, J=12.0, 8.8 Hz, 1H), 2.36 (s, 6H), 1.89 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 139.2, 138.4, 135.3, 132.1, 128.9, 128.2, 125.9, 125.5, 124.1, 123.5 (q, J=276 Hz), 63.1, 62.0 (q, J=35 Hz), 24.4, 24.3, 21.1; IR (CH_2Cl_2, film) 2987, 2929, 1604, 1449, 1372, 1319, 1280, 1140, 966, 898, 855, 763, 681 cm^{-1}; TLC R_f (hexane/EtOAc 2:1)=0.68; HRMS (ESI) *m/z* calcd for $C_{21}H_{23}F_3O_5SNa$ $(M+Na)^+$ 467.1110, found 467.1097. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 30% EtOAc in hexanes, 2.0 mL/min, 264 nm, t_R=13.7 min].

4.5.3. From 4-*t*-butylthiophenol.

4.5.3.1. Compound 8′c. Colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.26 (m, 8H), 3.68 (d, J=13.2 Hz, 1H), 3.43 (s, 3H), 3.36 (d, J=13.6 Hz, 1H), 1.62 (s, 3H), 1.61 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 138.3, 134.0, 133.5, 129.6, 128.0, 127.5, 125.8, 124.5, 101.7, 81.5, 51.1, 43.6, 34.4, 31.2, 22.3; IR (CH_2Cl_2, film) 2962, 1490, 1457, 1371, 1272, 1191, 1130, 1044, 875, 823, 762 cm^{-1}; TLC R_f (hexane/Et_2O 2:1)=0.64; HRMS (ESI) *m/z* calcd for $C_{22}H_{28}O_3SNa$ $(M+Na)^+$ 395.1651, found 395.1641. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 10% EtOAc in hexanes, 3.0 mL/min, 264 nm, t_R=9.5 min].

4.5.3.2. Compound 8″c. Colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.35 (m, 1H), 7.33–7.26 (m, 6H), 7.21–7.18 (m, 1H), 3.58 (d, J=13.6 Hz, 1H), 3.43 (d, J=13.6 Hz, 1H), 3.32 (s, 3H), 1.69 (s, 3H), 1.67 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 139.2, 134.4, 133.6, 130.0, 128.0, 127.4, 125.9, 125.8, 124.1, 102.8, 82.2, 51.9, 44.0, 34.4, 31.2, 24.3, 24.3; IR (CH_2Cl_2, film) 2963, 2868, 1490, 1447, 1369, 1269, 1188, 1120, 1044, 879, 825, 762 cm^{-1}; TLC R_f (hexane/Et_2O 2:1)=0.72; HRMS (ESI) *m/z* calcd for $C_{22}H_{28}O_3SNa$ $(M+Na)^+$ 395.1651, found 395.1648. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 5% EtOAc in hexanes, 2.0 mL/min, 264 nm, t_R=18.4 min].

4.5.3.3. Compound 9c. Colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.84–7.82 (m, 2H), 7.53–7.51 (m, 2H), 7.32–7.26 (m, 4H), 3.90 (d, J=14.8 Hz, 1H), 3.58 (d, J=14.8 Hz, 1H), 3.30 (s, 3H), 1.87 (s, 3H), 1.44 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 137.7, 137.4, 133.5, 128.4, 128.0, 127.9, 125.9, 125.8, 124.6, 101.5, 79.7, 61.9, 51.0, 35.2, 31.0, 22.5, 21.9; IR (CH_2Cl_2, film) 2964, 1595, 1398, 1319, 1151, 1108, 1085, 1043, 762 cm^{-1}; TLC R_f (hexane/EtOAc 2:1)=0.63; HRMS (ESI) *m/z* calcd for $C_{22}H_{28}O_5SNa$ $(M+Na)^+$ 427.1550, found 427.1541. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 30% EtOAc in hexanes, 3.0 mL/min, 264 nm, t_R=12.9 min].

4.5.3.4. Compound 10′c. Colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.84–7.81 (m, 2H), 7.55–7.51 (m, 2H), 7.38–7.32 (m, 4H), 4.03 (dq, J=11.8, 8.8 Hz, 1H), 3.86 (d, J=14.8 Hz, 1H), 3.67 (dq, J=12.0, 8.4 Hz, 1H), 3.59 (d, J=14.8 Hz, 1H), 1.88 (s, 3H), 1.52 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 137.9, 137.7, 131.4, 129.1, 128.5, 127.9, 126.1, 124.8, 123.6 (q, J=280 Hz), 102.0, 80.1, 62.3 (q, J=35 Hz), 61.7, 35.2, 31.1, 23.6, 22.6; IR (CH_2Cl_2, film) 2965, 2872, 1595, 1453, 1320, 1288, 1153, 1084, 968, 902, 842, 765, 573 cm^{-1}; TLC R_f (hexane/EtOAc 2:1)=0.66; HRMS (ESI) *m/z* calcd for $C_{23}H_{27}F_3O_5SNa$ $(M+Na)^+$ 495.1423, found 495.1426. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 30% EtOAc in hexanes, 3.0 mL/min, 264 nm, t_R=7.9 min].

4.5.3.5. Compound 10″c. Colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.82–7.79 (m, 2H), 7.54–7.50 (m, 2H), 7.36–7.33 (m, 3H), 7.21–7.18 (m, 1H), 3.77 (d, J=15.2 Hz, 1H), 3.69 (d, J=15.2 Hz, 1H), 3.68 (dq, J=11.8, 8.8 Hz, 1H), 3.49 (dq, J=11.8, 8.8 Hz, 1H), 1.91 (s, 3H), 1.64 (s, 3H), 1.56 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 138.5, 138.0, 132.0, 129.0, 128.2, 127.9, 126.0, 126.0, 124.1, 123.5 (q, J=276 Hz), 63.2, 62.0 (q, J=35 Hz), 35.2, 31.0, 24.3, 24.1; IR (CH_2Cl_2, film) 2966, 1595, 1493, 1453, 1399, 1375, 1319, 1286, 1152, 1084, 968, 903, 836, 790, 767 cm^{-1}; TLC R_f (hexane/EtOAc 2:1)=0.66; HRMS (ESI) *m/z* calcd for $C_{23}H_{27}F_3O_5SNa$ $(M+Na)^+$ 495.1423, found 495.1408. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 30% EtOAc in hexanes, 3.0 mL/min, 264 nm, t_R=8.2 min].

4.5.3.6. Compound 8′d. Colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 7.26–7.20 (m, 3H), 3.66 (d, J=13.6 Hz, 1H), 3.42 (s, 3H), 3.32 (d, J=13.2 Hz, 1H), 1.61 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 136.3, 133.9, 131.7, 130.9, 128.1, 127.7, 125.9, 124.3, 119.7, 101.7, 81.3, 51.2, 43.1, 22.2, 22.2; IR (CH_2Cl_2, film) 2989, 2927, 2826, 1473, 1368,

1297, 1272, 1126, 1086, 1041, 1006, 870, 805, 760 cm^{-1}; TLC R_f (hexane/Et_2O 2:1)=0.58; HRMS (ESI) *m/z* calcd for $C_{18}H_{19}BrO_3SNa$ $(M+Na)^+$417.0130, found 417.0126. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 20% EtOAc in hexanes, 2.0 mL/min, 264 nm, t_R=11.4 min].

4.5.4. From 4-bromothiophenol.

4.5.4.1. Compound 8″d. Colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.29 (m, 5H), 7.22 (dt, J=8.4, 2.0 Hz, 2H), 7.17–7.14 (m, 1H), 3.56 (d, J=13.6 Hz, 1H), 3.39 (d, J=14.0 Hz, 1H), 3.30 (s, 3H), 1.68 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 136.4, 134.5, 131.8, 131.3, 128.1, 127.5, 125.8, 123.9, 120.0, 102.8, 82.1, 51.7, 43.5, 24.3, 24.0; IR (CH_2Cl_2, film) 2989, 2927, 1474, 1370, 1269, 1189, 1091, 1007, 866, 808, 762 cm^{-1}; TLC R_f (hexane/Et_2O 2:1)=0.64; HRMS (ESI) *m/z* calcd for $C_{18}H_{19}BrO_3SNa$ $(M+Na)^+$417.0130, found 417.0141. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 20% EtOAc in hexanes, 2.0 mL/min, 264 nm, t_R=10.7 min].

4.5.4.2. Compound 9d. Colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J=8.8 Hz, 2H), 7.67 (d, J=8.4 Hz, 2H), 7.34–7.25 (m, 4H), 1.84 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 137.3, 133.3, 132.1, 129.8, 128.7, 128.5, 128.1, 125.9, 124.2, 101.4, 79.5, 61.7, 51.1, 22.2, 21.9; IR (CH_2Cl_2, film) 2990, 2940, 2831, 1574, 1449, 1389, 1320, 1148, 1084, 1067, 1010, 876, 762 cm^{-1}; TLC R_f (hexane/EtOAc 2:1)=0.57; HRMS (ESI) *m/z* calcd for $C_{18}H_{19}BrO_5SNa$ $(M+Na)^+$449.0029, found 449.0031. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 30% EtOAc in hexanes, 2.0 mL/min, 264 nm, t_R=14.1 min].

4.5.4.3. Compound 10′d. White solid: mp 129–130 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81–7.78 (m, 2H), 7.70–7.67 (m, 2H), 7.41–7.31 (m, 4H), 4.01 (dq, J=11.8, 8.4 Hz, 1H), 3.91 (d, J=14.8 Hz, 1H), 3.65 (dq, J=11.6, 8.8 Hz, 1H), 3.54 (d, J=14.8 Hz, 1H), 1.86 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 137.8, 132.3, 131.2, 129.7, 129.3, 128.9, 128.6, 126.2, 124.4, 123.5 (q, J=276 Hz), 62.3 (q, J=35 Hz), 61.5, 23.5, 22.3; IR (CH_2Cl_2, film) 3078, 2991, 2933, 1575, 1451, 1390, 1322, 1277, 1150, 1125, 1083, 1068, 1010, 967 cm^{-1}; TLC R_f (hexane/EtOAc 2:1)=0.73; HRMS (ESI) *m/z* calcd for $C_{19}H_{18}BrF_3O_5SNa$ $(M+Na)^+$516.9903, found 516.9916. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 40% EtOAc in hexanes, 2.0 mL/min, 264 nm, t_R=10.2 min].

4.5.4.4. Compound 10″d. Colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.76–7.73 (m, 2H), 7.66–7.63 (m, 2H), 7.36–7.33 (m, 3H), 7.15–7.13 (m, 1H), 3.74–3.69 (m, 3H), 3.54 (dq, J=11.8, 8.4 Hz, 1H), 1.87 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 137.9, 132.3, 132.2, 129.8, 129.1, 128.3, 127.6, 126.0, 123.9, 123.5 (q, J=276 Hz), 63.1, 61.8 (q, J=35 Hz), 24.2, 23.9; IR (CH_2Cl_2, film) 2920, 2854, 1574, 1390, 1324, 1282, 1150, 1084, 1010, 967, 824, 766 cm^{-1}; TLC R_f (hexane/EtOAc 2:1)=0.73; HRMS (ESI) *m/z* calcd for $C_{19}H_{18}BrF_3O_5SNa$ $(M+Na)^+$516.9903, found 516.9902. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 40% EtOAc in hexanes, 2.0 mL/min, 264 nm, t_R=14.0 min].

4.5.5. From 4-methoxythiophenol.

4.5.5.1. Compound 8′e. Colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.33 (m, 3H), 7.32–7.28 (m, 2H), 7.26–7.23 (m, 1H), 6.83–6.79 (m, 2H), 3.78 (s, 3H), 3.61 (d, J=13.6 Hz, 1H), 3.41 (s, 3H), 3.27 (d, J=13.6 Hz, 1H), 1.59 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 138.4, 133.9, 133.0, 127.9, 127.5, 127.5, 125.8, 124.5, 114.5, 101.7, 81.6, 55.3, 51.2, 45.3, 22.3, 22.2; IR (CH_2Cl_2, film) 2977, 2925, 2820, 1592, 1494, 1443, 1370, 1284, 1245, 1179, 1130, 1042, 875, 762 cm^{-1}; TLC R_f (hexane/Et_2O 2:1)=0.44; HRMS (ESI) *m/z* calcd for $C_{19}H_{22}O_4SNa$ $(M+Na)^+$369.1131, found 369.1129. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 20% EtOAc in hexanes, 2.0 mL/min, 264 nm, t_R=12.2 min].

4.5.5.2. Compound 8″e. Colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.34 (m, 3H), 7.32–7.28 (m, 2H), 7.17–7.15 (m, 1H), 6.81–6.79 (m, 2H), 3.78 (s, 3H), 3.51 (d, J=13.6 Hz, 1H), 3.35 (d, J=13.6 Hz, 1H), 3.31 (s, 3H), 1.66 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 139.2, 134.4, 133.4, 128.0, 127.6, 127.3, 125.8, 124.1, 102.8, 82.3, 55.3, 51.8, 45.6, 24.3, 24.2; IR (CH_2Cl_2, film) 2984, 2937, 2834, 1592, 1494, 1442, 1369, 1284, 1245, 1180, 1129, 1034, 827, 763 cm^{-1}; TLC R_f (hexane/Et_2O 2:1)=0.44; HRMS (ESI) *m/z* calcd for $C_{19}H_{22}O_4SNa$ $(M+Na)^+$369.1131, found 369.1128. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 40% EtOAc in hexanes, 2.0 mL/min, 264 nm, t_R=9.8 min].

4.5.5.3. Compound 9e. White solid: mp 134–135 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86–7.84 (m, 2H), 7.32–7.26 (m, 4H), 6.99–6.97 (m, 2H), 3.92 (d, J=15.2 Hz, 1H), 3.86 (s, 3H), 3.53 (d, J=14.8 Hz, 1H), 3.31 (s, 3H), 1.85 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 137.6, 133.4, 132.4, 130.2, 128.4, 128.0, 125.9, 124.4, 114.1, 101.5, 79.7, 62.0, 55.6, 51.2, 22.4, 22.1; IR (CH_2Cl_2, film) 2983, 2934, 2834, 1596, 1498, 1444, 1320, 1260, 1142, 1087, 804, 741 cm^{-1}; TLC R_f (hexane/EtOAc 2:1)=0.35; HRMS (ESI) *m/z* calcd for $C_{19}H_{22}O_6SNa$ $(M+Na)^+$401.1029, found 401.1029. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 40% EtOAc in hexanes, 2.0 mL/min, 264 nm, t_R=16.9 min].

4.5.5.4. Compound 10′e. Colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.86–7.82 (m, 2H), 7.42–7.33 (m, 4H), 7.01–6.97 (m, 2H), 4.05 (dq, J=11.8, 8.4 Hz, 1H), 3.88 (s, 3H), 3.87 (d, J=14.8 Hz, 1H), 3.66 (dq, J=11.8, 8.8 Hz, 1H), 3.54 (d, J=14.8 Hz, 1H), 1.86 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 138.1, 132.3, 131.3, 130.3, 129.1, 128.5, 126.1, 124.6 (q, J=276 Hz),

114.2, 62.4 (q, $J=35$ Hz), 61.8, 55.7, 23.7, 22.4; IR (CH_2Cl_2, film) 2992, 2938, 2839, 1596, 1498, 1377, 1321, 1286, 1143, 1085, 1024, 967, 901, 836 cm^{-1}; TLC R_f (hexane/EtOAc 2:1)=0.57; HRMS (ESI) *m/z* calcd for $C_{20}H_{21}F_3O_6SNa$ $(M+Na)^+$ 469.0903, found 469.0904. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 50% EtOAc in hexanes, 2.0 mL/min, 264 nm, $t_R=11.5$ min].

4.5.5.5. Compound 12. White solid: mp 120–123 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, $J=8.8$ Hz, 2H), 7.55 (d, $J=8.4$ Hz, 2H), 7.42 (d, $J=7.6$ Hz, 1H), 7.36 (m, 2H), 7.30 (m, 1H), 3.95 (br d, $J=12.0$ Hz, 1H), 3.71 (d, $J=15.2$ Hz, 1H), 3.21 (br s, 3H), 1.81 (br s, 3H), 1.34 (s, 9H), 0.79 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 141.7, 137.8, 128.2, 128.2, 128.0, 127.4, 126.9, 126.0, 124.8, 106.6, 79.5, 50.8, 41.4, 35.2, 31.1, 26.4, 26.2, 23.8; IR (CH_2Cl_2, film) 2964, 2360, 1726, 1595, 1462, 1393, 1319, 1291, 1199, 1150, 1107, 1084, 960, 845, 760, 576, 520 cm^{-1}; HRMS (FAB-MS) *m/z* calcd for $C_{25}H_{34}O_5S$ $(M+Na)^+$ 469.20247, found 469.20237.

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Synthesis of bridged nicotinates having [*n*](2,5)pyridinophane skeletons (*n* = 8–14)

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Abstract—Synthesis of various bridged nicotinates **6** having [*n*](2,5)pyridinophane skeletons (*n* = 8–14) was accomplished by the unique pyridine-formation reaction of methyl propiolate with a series of formyl-substituted (vinylimino)phosphoranes **5**, which were prepared from the corresponding cycloalkanones **1** via Vilsmeier–Haack formylation giving chloro-substituted cycloalkenals **2**, their thermal and photochemical transformation to formyl azirines **4**, and the following ring-opening reactions with triphenylphosphine. The HPLC analysis of [11](2,5)pyridinophane derivatives, (S_p,*S*)-**14** and (R_p,*S*)-**14**, showed that these diastereomers rapidly epimerize themselves at room temperature and that their planar-chirality was thermodynamically less stable as compared to the corresponding [11](2,5)cyclophane systems.

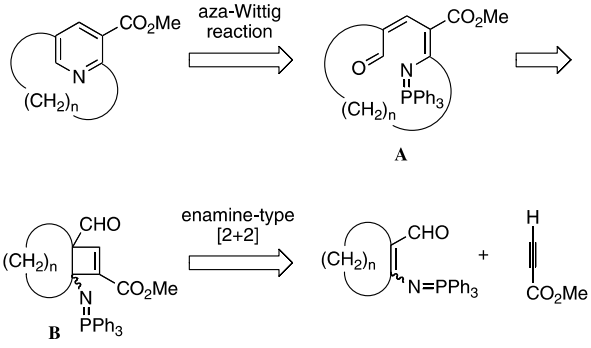
1. Introduction

(Vinylimino)phosphoranes are versatile synthetic synthons of various heteroaromatic compounds,[1] and are particularly useful for the syntheses of pyridine[2–6] and pyridinophane[7–9] derivatives. We have previously reported novel pyridine-formation reactions of formyl-substituted (vinylimino)-phosphoranes with acetylenic esters to give 2- and 2,5-substituted nicotinates,[2] and their synthetic application to a bridged nicotinate having [10](2,5)pyridinophane structure.[7] Our recent studies revealed also that the bridged nicotinate[10] and bridged benzoate[11] are such planar-chiral sources that they are readily accessible by crystallization-induced[11,12] or adsorption-induced[13] asymmetric transformation, and that planar-chiral NADH models, derived from the bridged nicotinate, exhibited one of the highest enantioselectivity in biomimetic asymmetric reduction of pyruvate analogues[7] among a number of NADH-mimicking systems having been reported so far.[14] In the bridged nicoinate systems, the decamethylene chains bridging *para*-positions of the pyridine ring play an extremely important role in shielding either side of two reactive faces and, therefore, the other nicotinates having different sizes of oligomethylene chains became our next target molecules for studying their dynamic motions and the correlation of the bridge lengths with synthetic efficiency. We will report here the detailed results of the synthetic studies on bridged nicotinates having [*n*](2,5)pyridinophane structures (*n* = 8–14) incorporating various lengths of their oligomethylene bridges.

2. Results and discussion

2.1. Synthetic strategy of bridged nicotinates

Scheme 1 illustrates our retrosynthetic route for bridged nicotinates having various lengths of oligomethylene chains,



Scheme 1. Retrosynthetic analysis of bridged nicotinates having various [*n*](2,5)cyclophane skeletons.

Keywords: Planar-chirality; Pyridinophanes; Pyridine-formation reactions; Aza-Wittig reactions; Cycloaddition.
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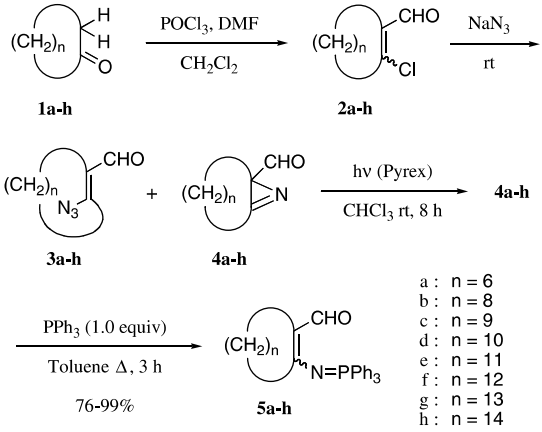
namely methyl [*n*](2,5)pyridinophane-3-carboxylates. The final pyridine-formation is to be accomplished by intramolecular aza-Wittig reactions of intermediates **A** whose diene moieties should be derived from ring-opening isomerizations of cyclobutene intermediates **B**. The enamine-type [2+2] cycloaddition disassembles **B** into methyl propiolate and (vinylimino)phosphorane derivatives, the latter of which are transformed from halo-substituted cycloalkenals being readily available by Vilsmeier–Haack formylation of the corresponding cycloalkanones.

2.2. Preparation of (vinylimino)phosphoranes

The synthetic transformation to formyl-substituted (vinylimino)phosphoranes **5a–h** was achieved by the sequential functionalization from cycloalkanones (**1a–h**) based on our previously reported method giving **5d**[7] (Scheme 2). Vilsmeyer–Haack formylation of cycloalkanones **1a–h** afforded the corresponding (*Z*)- and/or (*E*)-2-chloro-cycloalk-1-enecarbaldehyde (**2a–h**) in good yields (Table 1). At the beginning of our study, we carried out the formylation by using DMF and $POCl_3$ with 1 equiv amount each at a high temperature and, indeed, the reaction of cyclooctanone (**1a**) proceeded smoothly at 70 °C to afford (*Z*)-**2a** exclusively in 84% yield (entry 1). However, significant amounts of by-products (mostly β,γ-unsaturated chloroenals) were co-generated as well as the desired **2b–h** in the similar reaction conditions to those employed for **2a** (entry 2: see footnote). Eventually, we found even milder reaction conditions working very well for the synthesis of **2b–h** where the reactions with excess amounts of DMF and $POCl_3$ at 0 °C effected predominant formation of (*Z*)-**2b–f** in good to moderate isolated yields (entries 2–7). For the reactions giving compounds **2g**,**h**, significant amounts of (*E*)-**2g**,**h** were generated as less reactive isomers in the following steps as well as the desired (*Z*)-**2g**,**h** isolated in moderate yields (entries 8 and 9). In case of compound **2e**, the formylation proceeded with high (*Z*)-selectivity and the product was used for the next step without further purification (entry 6).



Scheme 2. Synthesis of formyl-substituted (vinylimino)phosphoranes **5a–h** from cycloalkanones **1a–h**.

Table 1. Vilsmeier–Haack formylation of **1a–h**

Entry	**1**	Conditions		Yield and ratio of **2**		
		T (°C)	Time (h)	Crude (%)	*E*/*Z*	Isolated (%)
1	**a**	70	6	n/a	0/100	84 (*Z*)
2	**b**	75	6	85[a]	0/100	75 (*Z*)
3	**b**	0	48	Quant	17/83	68 (*Z*)
4	**c**	0	24	99	3/97	90 (*Z*)
5[b]	**d**	0	48	95	18/82	78 (*Z*)
6	**e**	−5	48	91	6/94	n/a[c]
7	**f**	0	48	98	22/78	52 (*Z*)
8	**g**	0	48	92	44/56	53 (*Z*)
9	**h**	0	72	99	48/52	50 (*Z*)

[a] β,γ-Unsaturated chloroenal (15%) was produced as a by-product as well as **2b**.
[b] Previous work. See Ref. 7.
[c] Used in the following steps without further purification.

Then, we initially attempted the conversion of (*Z*)-**2a–h** thus obtained into the corresponding 2-azidocycloalk-1-enecarbaldehyde (**3a–h**), appropriate precursors for the subsequent Staudinger reactions. But the formation of **3a** was not observed in the crude mixture produced by the reaction of **2a** with sodium azide and, instead, formylazirine **4a** was isolated exclusively in 83% yield (entry 1 in Table 2). On the other hand, the reaction of the other chlorocycloalkenals **2b–h** afforded a mixture of (*E*)-**3b–h** and **4b–h**, and none of (*Z*)-**3b–h** was isolated at room temperature. Thus, formation of the azirines **4b–h** was reasonably explained as a result of releasing nitrogen out of less stable (*Z*)-**3b–h**. We have therefore chosen the synthetic route to (vinylimino)-phosphoranes **5a–h** via azirine intermediates as well as the transformation from **2d** to **4d** reported previously.[7] After the reaction of **2b–h** with sodium azide was complete, the crude mixtures containing (*E*)-**3b–h** were irradiated through Pyrex filter (365 nm) to give the compounds **4b–h** in 79–92% isolated yields (entries 2–8). The treatment with triphenylphosphine in refluxing toluene effected the ring-opening reaction of the azirine ring to give the desired formyl-substituted (vinylimino)phosphoranes **5a–h** in 76–99% yields (see Section 3.5). Except for compound **5a**, ^1H NMR spectra of the other iminophosphoranes exhibited two sorts of formyl protons corresponding to (*E*)- and (*Z*)-forms, the chemical shifts of which appeared at δ 9.84–9.93 and 10.57–10.71 ppm, respectively. The former signals were unambiguously assigned to those of (*E*)-**5b–h** whose signals at aliphatic regions were clearly informative of their non-symmetric structures being attributed to highly substituted *trans*-cycloalkenes with planar-chirality.

Table 2. Synthesis of formylazirines **4a–h**

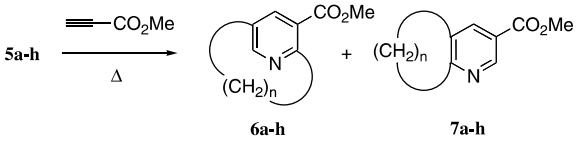
Entry	**2**	Conditions		Isolated yield
		Method[a]	Time (h)	**4** (%)
1	**a**	A	19	83[b]
2	**b**	B	5	79
3	**c**	B	4.5	85
4[c]	**d**	B	5	84
5	**e**	A	3	80
6	**f**	A	3	82
7	**g**	A	3	82
8	**h**	A	3	92

[a] Method A: NaN_3 1.5 equiv, DMF, rt. Method B: NaN_3 1.25 equiv, LiCl 0.1 equiv, wet THF, rt. See Section 3 for details.
[b] Obtained without photolysis.
[c] Previous work. See Ref. 7.

The compounds **5a–c**, having an 11-membered ring or less, exist as (*Z*)-form rich mixtures and, on the other hand, the others exist as (*E*)-form rich mixtures to minimize their ring strain. These compounds were produced as an inseparable mixture and they were used in the following step without further purification (Scheme 3).

2.3. Syntheses of bridged nicotinates

The reactions of the iminophosphoranes **5a–h** with methyl propiolate were thoroughly investigated for synthesizing nicotinates **6a–h** (Scheme 3). Table 3 indicates the reaction conditions and yields of compound **6d**, a representative bridged nicotinates having a [10](2,5)pyridinophane skeleton, as the results of our reinvestigation for seeking more efficient synthetic protocol. Our previous one, where the compound **5d** reacts with 10 equiv amount of methyl propiolate in toluene at 140 °C for 12 h, gave the desired **6d** and its isomer **7d** in 21 and 8% yield, respectively (See entry 4 of Method A in Table 4),[7] and we first examined the solvent effects. After running the reactions of **5d** with 5 equiv amount of methyl propiolate in various solvents at 140 °C, we eventually found that acetonitrile, an aprotic polar solvent, is more suitable for the synthesis of **6d** (entries 1–7). The reactions also work well at 120 °C (entries 8–12), to give **6d** with up to 25% yield (entry 9). The reactions with more or less amount of methyl propiolate did not afford better results for the formation of **6d** (entries 13 and 14). As a result, we were successful in reducing the amount of methyl propiolate to 5 equiv, just a half amount as compared to our original protocol, and in achieving the milder reaction conditions at 120 °C for 10 h (See also Section 3.6).



Scheme 3. Pyridinophane-formation reactions of formyl-substituted (vinylimino)phosphoranes **5a–h** with methyl propiolate.

Table 3. Reaction conditions and the yield of **6d**[a]

Entry	Conditions				Yield[b]
	MP (equiv)[c]	Solvent	*T* (°C)	Time (h)	**6d** (%)
1	5.0	Benzene	140	24	11
2	5.0	Toluene	140	24	17
3	5.0	Xylene	140	24	17
4	5.0	Chlorobenzene	140	24	17
5	5.0	1,1,2-Trichloro-ethane	140	24	19
6	5.0	1,4-Dioxane	140	24	12
7	5.0	Acetonitrile	140	24	22
8	5.0	Acetonitrile	120	12	21[d]
9	5.0	Acetonitrile	120	10	25[d]
10	5.0	Acetonitrile	120	8	24[d]
11	5.0	Acetonitrile	120	6	22[d]
12	5.0	Acetonitrile	120	4	19[d]
13	3.0	Acetonitrile	120	10	17[d]
14	10.0	Acetonitrile	120	8	16[d]

[a] All the reactions were carried out under 0.33 M solution of **5d**.
[b] Isolated yields unless otherwise specified.
[c] Methyl propiolate.
[d] Estimated by ^{1}H NMR spectra.

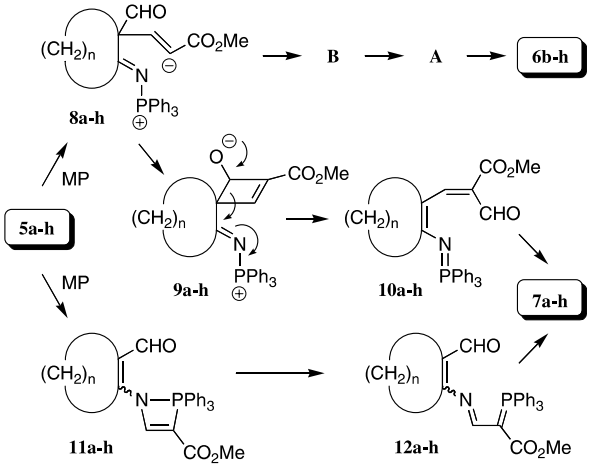
Table 4. Synthesis of bridged nicotinates **6b–h**

Entry	**5**	*n*	Yield (Method A)[a]		Yield (Method B)[b]	
			6 (%)	**7** (%)	**6** (%)	**7** (%)
1	**a**	6	0	5	n/a	n/a
2	**b**	8	4	10	4	25
3	**c**	9	7	4	10	11
4	**d**	10	21[c]	8[c]	25	15
5	**e**	11	26	3	29	8
6	**f**	12	30	3	32	16
7	**g**	13	38	5	41	16
8	**h**	14	40	4	43	16

[a] Method A: reactions were performed with 10 equiv of methyl propiolate in toluene at 140 °C for 12 h in autoclave.
[b] Method B: reactions were performed with 5 equiv of methyl propiolate in acetonitrile at 120 °C for 10 h in autoclave.
[c] Previous work. See Ref. 7.

Table 4 tabulates the yields of bridged nicotinates **6b–h** and their isomers **7a–h** obtained by the reactions of a series of (vinylimino)phosphoranes **5a–h** with methyl propiolate in toluene and acetonitrile as solvent. These reactions also proceeded well to result in the formation of methyl [*n*](2,5)pyridinophane-3-carboxylates **6b–h** having various length of their oligomethylene chains (entries 1–3, 5–8). In each case, the yield of **6b–h** in acetonitrile was better than that in toluene and unidentified by-products formed in these reactions did not seriously disturb the isolation of **6** and **7**. Obviously, the yields of **6b–h** increased as length of the oligomethylene chain becomes longer. Though none of [6](2,5)pyridinophane **6a** was obtained from **5a** (entry 1), the compounds **6b**,**c** were isolated even in relatively low yields due to their higher strain as compared to **6d–h** (entries 2 and 3). The reaction of **5e–h** having a larger ring size reacted with methyl propiolate more smoothly to result in [*n*](2,5)pyridinophane-3-carboxylate **6e–h** (*n*=11–14) in moderate yields (entries 5–8). All the spectral data agree with these proposed structures.

The postulated reaction pathways for the formation of **6b–h** and **7a–h** are shown in Scheme 4. Enamine-type nucleophilic addition[15] of **5a–h** occurs at the β-position of methyl propiolate to form ionic intermediates **8a–h** and the following intramolecular addition onto C=N and C=O produces cyclobutene intermediates **B** and **9**, respectively. The ring-opening reactions of **B** and **9** generate aldehydes **A**



Scheme 4. Postulated reaction pathways for the formation of **6** and **7**.

and **10**, which undergo intramolecular aza-Wittig reactions to give **6b–h** and **7a–h**. The formation of **7a–h** is also explained by the following alternative pathway: [2+2] cycloaddition of methyl propiolate onto N=P double bond of **5a–h** gives intermediates **11** and their subsequent ring-opening to **12** and intramolecular Wittig reaction of **12** afford **7a–h**.[16] Formation of these ionic intermediates shown in Scheme 4 seems to be suitable in an aprotic polar solvent such as acetonitrile, leading to the higher yield of **6** and **7**.

The ^{1}H NMR spectra of parapyridinophanes **6b**,**c** ($n=8$ and 9) showed that some protons at oligomethylene bridges were observed independently with unique chemical shifts and, especially, one of them appeared at δ −0.27 or −0.19 ppm (for **6b** and **6c**, respectively) as a distinctive up-field shift in a shielding region above an aromatic ring. These findings indicate that the compounds **6b**,**c** have a stable planar-chirality as well as [10](2,5)pyridinophane **6d** that we reported previously. As for [11](2,5)pyridinophane **6e**, ^{1}H NMR spectrum exhibited that its rope-skipping mobility of oligomethylene chain is apparently frozen in NMR time scale according to the peak independency of its aliphatic protons appearing at δ 2.62, 2.68, 2.77, and 3.74 ppm (1H each, ArCH_2–) (Fig. 1a).

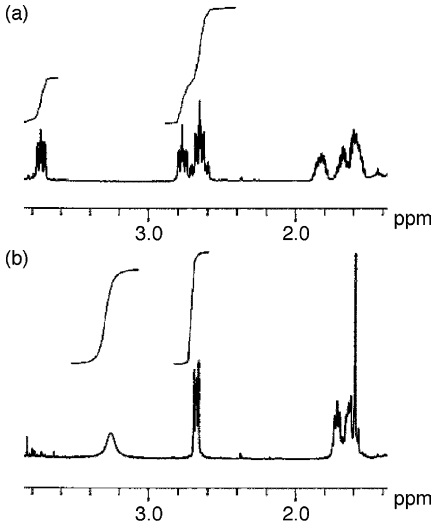
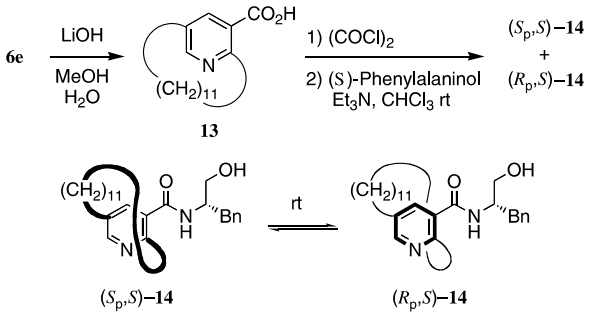


Figure 1. ^{1}H NMR spectra of bridged nicotinates **6e**,**f** at rt: some oligomethylene protons of (a) [11](2,5)pyridinophane **6e** and (b) [12](2,5)pyridinophane **6f**.

On the contrary, HPLC analysis of a diastereomeric mixture of (S_p,*S*)-**14** and (R_p,*S*)-**14**, derived from [11](2,5)pyridinophane-3-carboxylic acid (**13**) (Scheme 5), showed an inseparable single peak at room temperature, which suggests their rapid dynamic interconversion via rope-skipping isomerization in HPLC time scale (Fig. 2).[17] Indeed, at 0 °C, a typical plateau shape was observed in the middle of coalescence peaks of the two diastereoisomers epimerizing themselves.[18] This means that [11](2,5)pyridinophane **6e** also exists as a racemic equilibrium mixture with rapid interconversion and its planar-chirality is not stable enough to be resolved for the synthetic purposes. This is in good contrast to the analogous [11](2,5)cyclophane derivatives, which are reasonably stable against their racemization or epimerization.[11]



Scheme 5. Synthesis of [11](2,5)pyridinophane derivatives, (S_p,*S*)-**14** and (R_p,*S*)-**14**.

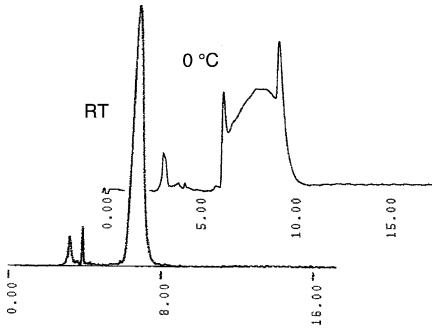


Figure 2. HPLC analyses of a diastereoisomeric mixture of (S_p,*S*)-**14** and (R_p,*S*)-**14** at rt and 0 °C.

On the other hand, ^{1}H NMR spectra of **6f–h** ($n=12$–14) are much simpler than those of **6b–e** and the proton pairs at each methylene unit appear as equivalent signals [see signals appearing at δ 3.26 and 3.93 ppm (2H each, ArCH_2–) for **6f** in Fig. 1b] as well as *Cs*-symmetric isomers of the ortho-bridged **7f–h**. Consequently, undecamethylene or longer bridges ($n\geq 11$) are flexible enough to flip over their pyridine rings and these molecules can hardly retain their planar chirality at room temperature. These findings that we have reported here provide a convenient route for the syntheses of bridged nicotinates having [*n*](2,5)pyridinophane skeletons and unique dynamic behavior of these novel ansa molecules.

3. Experimental

3.1. General

NMR spectra were recorded on Bruker AVANCE600, JEOL JNM-ECA500, JEOL Lambda500, JEOL JNM-A400, JEOL JNM-AL300, or JEOL JNM-EX270 spectrometers. Chemical shifts are reported in parts per million relative to Me_4Si for ^{1}H NMR and to the central line of $CDCl_3$ (77.0 ppm) for ^{13}C NMR as internal standard. Unless otherwise specified, NMR spectra were measured at ambient temperature except for compound **14** (at 50 °C). Mass spectra were recorded on Hitachi M-80, JEOL JMS-SX102, or JEOL-HX110 spectrometers. Thin-layer chromatography was performed using Merck silica gel 60 F_{254} glass plates (Art. 5715, 0.5 mm thick) or Merck aluminum oxide 60 F_{254} glass plates (Art. 5713, 0.25 mm thick). Flash chromatography was performed using Silica gel FL60D

(Fuji Silysia Chemical Ltd) unless otherwise specified. Melting points were recorded on Yanagimoto apparatus and are uncorrected. Cyclooctanone (**1a**), cyclodecanone (**1b**), cylododecanone (**1d**), cyclotridecanone (**1e**), and cyclopentadecanone (**1g**) are commercially available starting materials and were used without further purification. Cycloundecanone (**1c**) was prepared from cyclododecanone according to the literature method.[19]

3.1.1. Cyclotetradecanone (1f). Cyclotetradecanone (**1f**) was prepared from cyclopentadecanone (**1g**) according to the similar method for the preparation of **1c**.[19]

To a solution of cyclopentadecanone (**1g**) (22.4 g, 100 mmol) in toluene (140 ml) and ether (15 ml) was added dropwise bromine (10.0 ml, 200 mmol) and the mixture was stirred with a cooling bath at 20–25 °C for 30 min. After removal of hydrogen bromide generated in vacuo, the residual toluene solution of dibromide was treated with sodium methoxide (18.9 g, 350 mmol) in small portions and the whole mixture was stirred at 20–25 °C for 30 min. After the reaction was complete, the mixture was washed with water (1×50 ml), 5% hydrochloric acid (1×150 ml) and brine (1×50 ml) and the aqueous layer was extracted with ether (3×80 ml). The combined organic layer was dried over sodium sulfate and, after removal of solvent in vacuo, the residue was separated by flash chromatography on silica gel (5% ether in hexane) to give methyl cyclotetradec-1-encarboxylate (24.4 g, 96.7 mmol) in 97% yield: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.23–1.57 (m, 20H), 2.31 (AA′XX′, $J_{AX}+J_{AX'}=11.2$ Hz, 2H), 2.49 (m, 2H), 3.73 (s, 3H), 5.82 (t, $J=7.8$ Hz, 1H). After the product thus obtained was dissolved in sulfuric acid (73 ml) at 5 °C, chloroform (61 ml) was added, sodium azide (9.23 g, 142 mmol) was added in portions at 40 °C, and the reaction mixture was stirred at 35–40 °C for 1 h. The mixture was poured into ice water (200 g each) and was extracted with chloroform (3×100 ml). The combined organic layer was washed with saturated aqueous sodium bicarbonate (2×200 ml) and dried over magnesium sulfate. After removal of solvent in vacuo, the residue was purified by flash chromatography on silica gel (2% ether in hexane) to give cyclotetradecanone (**1f**)[20] (13.7 g, 64.9 mmol) in 69% yield: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.09–1.29 (m, 18H), 1.67 (quint, $J=6.4$ Hz, 4H), 2.44 (t, $J=6.4$ Hz, 4H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 22.8, 24.3, 25.15, 25.20, 25.7, 26.0, 40.7, 212.2.

3.1.2. Cyclohexadecanone (1h). A solution of cyclohexadec-5-enone (11.8 g, 50.0 mmol) (commercially available from Tokyo Kasei Kogyo, TCI Japan) in ethanol (200 ml) was stirred in the presence of Pd/C (5 wt%, 1.18 g) under hydrogen atmosphere at room temperature for 2.5 h. After the reaction was complete, the mixture was filtered through Celite and the filtrate was concentrated in vacuo to give cyclohexadecanone (**1h**)[21] (11.8 g, 49.3 mmol, 99%) as a white solid: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.16–1.38 (m, 22H), 1.64 (quint, $J=6.8$ Hz, 4H), 2.41 (t, $J=6.8$ Hz, 4H).

3.1.3. 2-Chlorocyclooct-1-enecarbaldehyde (2a). To a solution of DMF (1.7 ml, 22.1 mmol) in CH_2Cl_2 (5.0 ml) was added dropwise a solution of phosphorous oxychloride (2.0 ml, 22.0 mmol) in 2.5 ml of CH_2Cl_2 at 0 °C, and the mixture was stirred at room temperature for 30 min. The mixture was cooled down to 0 °C and a solution of cyclooctanone (2.52 g, 20.0 mmol) in CH_2Cl_2 (5.0 ml) was added dropwise at 0 °C. The reaction mixture was heated at 70 °C for 6 h and, then, was poured into ice. The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2, and the combined organic layer was washed with small portions of water, brine and dried over $MgSO_4$. After removal of solvent in vacuo, the residue was distilled (64 °C, 0.3 mmHg) to give chloroaldehyde **2a** (2.92 g, 16.9 mmol) in 84% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44–1.58 (m, 6H), 1.82 (m, 2H), 2.46 (AA′XX′, $J_{AX}+J_{AX'}=12.0$ Hz, 2H), 2.76 (AA′XX′, $J_{AX}+J_{AX'}=12.8$ Hz, 2H), 10.17 (s, 1H). Compound **2a** was reported previously in literature.[22]

3.2. General procedure for the synthesis of 2-chlorocycloalk-1-enecarbaldehyde (2b–h)

To a solution of DMF (4.6 ml, 60.1 mmol) in CH_2Cl_2 (10 ml) was added dropwise a solution of phosphorus oxychloride (9.42 g, 61.4 mmol) in CH_2Cl_2 (10 ml) with ice cooling bath, and the mixture was stirred at room temperature for 30 h. A solution of cycloalkanone **1b–h** (20.1 mmol) in CH_2Cl_2 (10 ml) was added dropwise at 0 °C, and the mixture was stirred at 0 °C for 2 days. Cold water was added and the mixture was extracted with CH_2Cl_2, washed with water and brine, and dried over Na_2SO_4. After removal of solvent in vacuo, the residue gave the crude products of 2-chlorocycloalk-1-enecarbaldehyde (**2b–h**). Compound **2d** was reported previously in literature.[7] Reaction conditions and yields of **2a–h** are summarized in Table 1.

3.2.1. 2-Chlorocyclodec-1-enecarbaldehyde (2b). *Compound* (*Z*)-**2b**. Oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (m, 2H), 1.40–1.52 (m, 6H), 1.62 (m, 2H), 1.90 (br, 2H), 2.53 (t, $J=6.5$ Hz, 2H), 2.83 (br, 2H), 10.29 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.6, 20.8, 24.8, 25.0, 25.2, 25.5, 27.1, 35.7, 135.5, 154.1, 192.4; MS (EI) *m*/*z* (%) 202 (1.1) [M^++2], 200 (3.2) [M^+], 165 (100); HRMS (EI) calcd for $C_{11}H_{17}{}^{35}ClO$ 200.0968, found 200.0971.

3.2.2. 2-Chlorocycloundec-1-enecarbaldehyde (2c). *Compound* (*Z*)-**2c**. Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (m, 2H), 1.27–1.38 (m, 4H), 1.38–1.46 (m, 4H), 1.59 (m, 2H), 1.86 (m, 2H), 2.47 (AA′XX′, $J_{AX}+J_{AX'}=11.9$ Hz, 2H), 2.77 (AA′XX′, $J_{AX}+J_{AX'}=12.2$ Hz, 2H), 10.28 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 23.2, 24.1, 25.2, 25.4, 25.7, 25.8, 32.3, 37.6, 125.5, 154.6, 192.8; MS (EI) *m*/*z* (%) 216 (1.8) [M^++2], 214 (5.3) [M^+], 67 (100). HRMS (EI) calcd for $C_{12}H_{19}{}^{35}ClO$ 214.1124, found 214.1119.

Compound (*E*)-**2c**. Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98–1.18 (m, 3H), 1.18–1.45 (m, 6H), 1.52 (m, 1H), 1.65–1.82 (m, 2H), 1.85–1.99 (m, 2H), 2.40–2.52 (m, 2H), 2.65 (ddd, $J=13.7$, 8.8, 3.9 Hz, 1H), 3.42 (ddd, $J=13.7$, 11.7, 3.4 Hz, 1H), 10.15 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 24.2, 25.07, 25.11, 25.4, 26.4 (2C), 27.0, 35.7, 140.6, 159.2, 188.4. HRMS (EI) calcd for $C_{12}H_{19}{}^{35}ClO$ 214.1124, found 214.1116.

3.2.3. 2-Chlorocyclotridec-1-enecarbaldehyde (2e). *Compound* (*Z*)-**2e**. White solid; mp 38–39 °C (from MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25–1.55 (m, 16H), 1.79 (m, 2H), 2.28 (AA′XX′, $J_{AX}+J_{AX'}=15.4$ Hz, 2H), 2.60 (AA′XX′, $J_{AX}+J_{AX'}=16.1$ Hz, 2H) 10.19 (s, 1H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 24.1, 24.30, 24.34, 24.5, 24.8, 25.0, 25.4, 25.78, 25.84, 26.3, 36.0, 136.2, 154.5, 191.8; MS (EI) *m*/*z* (%) 244 (23) [$M^+ +2$], 242 (73) [M^+], 207 (100); HRMS (EI) calcd for $C_{14}H_{23}{}^{35}ClO$ 242.1437, found 242.1443. Anal. Calcd for $C_{14}H_{23}ClO$: C, 69.26; H, 9.55. Found: C, 69.01; H, 9.56.

Compound (*E*)-**2e**. Obtained as a mixture with (*Z*)-**2e**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 10.03 (s, 1H), and most aliphatic signals are hidden behind those of (*Z*)-**2e** and are unassigned.

3.2.4. 2-Chlorocyclotetradec-1-enecarbaldehyde (2f). *Compound* (*Z*)-**2f**. White solid; mp 42–43 °C (from MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20–1.61 (m, 18H), 1.75 (m, 2H), 2.28 (AA′XX′, $J_{AX}+J_{AX'}=16.6$ Hz, 2H), 2.59 (AA′XX′, $J_{AX}+J_{AX'}=16.6$ Hz, 2H), 10.22 (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 23.5, 24.0, 24.2, 24.9, 25.1, 25.3, 26.0, 26.4, 26.7, 27.1, 36.1, 136.1, 154.4, 192.1. HRMS (EI) calcd for $C_{15}H_{25}{}^{35}ClO$ 256.1594, found 256.1602. Anal. Calcd for $C_{15}H_{25}ClO$: C, 70.15; H, 9.81. Found: C, 69.78; H, 9.76.

Compound (*E*)-**2f**. Oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.98–1.51 (m, 17H), 1.51–1.75 (m, 2H), 1.85 (m, 1H), 2.43–2.55 (m, 2H), 2.66 (dddd, $J=13.2$, 7.3, 3.4, 1.5 Hz, 1H), 3.47 (ddd, $J=14.4$, 11.7, 3.6 Hz, 1H), 10.04 (d, $J=1.0$ Hz, 1H); MS (EI) *m*/*z* (%) 258 (12) [$M^+ +2$], 256 (39) [M^+] 221 (100). HRMS (EI) calcd for $C_{15}H_{25}{}^{35}ClO$ 256.1594, found 256.1601.

3.2.5. 2-Chlorocyclopentadec-1-enecarbaldehyde (2g). *Compound* (*Z*)-**2g**. Oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25–1.42 (m, 18H), 1.50 (quint, $J=6.8$ Hz, 2H), 1.72 (m, 2H), 2.28 (AA′XX′, $J_{AX}+J_{AX'}=15.8$ Hz, 2H), 2.58 (AA′XX′, $J_{AX}+J_{AX'}=16.7$ Hz, 2H), 10.20 (s, 1H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 25.2, 25.5, 25.9, 25.99, 26.02, 26.2, 26.6, 26.7, 26.9, 27.0, 27.1, 27.4, 37.5, 135.7, 154.3, 191.9; MS (EI) *m*/*z* (%) 272 (15) [$M^+ +2$], 270 (44) [M^+], 235 (100); HRMS (EI) calcd for $C_{16}H_{27}{}^{35}ClO$ 270.1750, found 270.1754.

Compound (*E*)-**2g**. Oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04–1.52 (m, 18H), 1.54–1.69 (m, 3H), 1.81 (m, 1H), 2.44 (ddd, $J=12.4$, 7.5, 3.8 Hz, 1H), 2.49 (ddd, $J=14.5$, 4.7, 4.3 Hz, 1H), 2.66 (ddd, $J=12.4$, 9.4, 3.8 Hz, 1H), 3.44 (ddd, $J=14.5$, 11.3, 3.4 Hz, 1H), 10.03 (s, 1H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 25.6, 26.3, 26.6, 26.7, 26.8, 26.99, 27.04, 27.1, 27.48, 27.53, 27.6, 27.8, 34.6, 140.1, 158.9, 188.2; MS (EI) *m*/*z* (%) 272 (18) [$M^+ +2$], 270 (54) [M^+], 235 (100); HRMS (EI) calcd for $C_{16}H_{27}{}^{35}ClO$ 270.1750, found 270.1755.

3.2.6. 2-Chlorocyclohexadec-1-enecarbaldehyde (2h). *Compound* (*Z*)-**2h**. Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11–1.55 (m, 22H), 1.68 (m, 2H), 2.29 (AA′XX′, $J_{AX}+J_{AX'}=15.1$ Hz, 2H), 2.60 (AA′XX′, $J_{AX}+J_{AX'}=16.1$ Hz, 2H), 10.21 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 25.2, 26.07, 26.12, 26.27, 26.34, 26.7, 27.0, 27.3, 27.4, 27.5, 27.6, 28.2, 37.7, 135.8, 154.2, 192.2; MS (EI) *m*/*z* (%) 286 (2.2) [$M^+ +2$], 284 (7.0) [M^+], 55 (100). HRMS (EI) calcd for $C_{17}H_{29}{}^{35}ClO$ 284.1907, found 284.1911.

Compound (*E*)-**2h**. Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15–1.40 (m, 20H), 1.46 (m, 2H), 1.73 (br s, 2H), 2.35–2.60 (br m, 3H), 3.40 (br, 1H), 10.04 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 25.2, 26.1, 26.25, 26.31, 26.56, 25.62, 26.93, 26.97, 27.3, 27.4, 27.6, 28.2, 37.7, 135.8, 154.2, 192.1; MS (EI) *m*/*z* (%) 286 (9) [$M^+ +2$], 284 (27) [M^+], 249 (100). HRMS (EI) calcd for $C_{17}H_{29}{}^{35}ClO$ 284.1907, found 284.1902.

3.3. Representative procedure for the synthesis of formylazirine 4a,e–h (Method A)

A solution of (*Z*)-**2a**,**e**–**h** (4.61 mmol) and NaN_3 (412 mg, 6.33 mmol) in 12.5 ml of DMF was stirred at room temperature for 3 h. Water was added and the mixture was extracted with ether. The combined ethereal layer was washed with water and brine and dried over $MgSO_4$. The filtrate was concentrated in vacuo and the residue was dissolved in 25 ml of $CHCl_3$ and was irradiated through Pyrex filter by using ultraviolet lamp ($\lambda_{max}=365$ nm) for 8 h. After removal of solvent in vacuo, the residue was chromatographed on silica gel by using $CHCl_3$–hexane (1/3) to give azirine **4a**,**e**–**h**. See Table 2 for reaction conditions and yields of **4a**,**e**–**h**.

3.3.1. 9-Azabicyclo[6.1.0]non-8-ene-1-carbaldehyde (4a). Oil; bp 95–96 °C (0.3 mmHg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (m, 1H), 1.36–1.50 (m, 3H), 1.53–1.74 (m, 4H), 2.00 (m, 1H), 2.47 (ddd, $J=15.8$, 11.5, 2.1 Hz, 1H), 2.72 (ddd, $J=15.0$, 10.1, 5.1 Hz, 1H), 3.14 (ddd, $J=15.0$, 6.4, 4.3 Hz, 1H), 8.80 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.6, 23.3, 24.9, 26.6, 27.8, 28.1, 48.8, 168.2, 200.8; MS (EI) *m*/*z* (%) 151 (4) [M^+], 150 (19), 81 (100); HRMS (EI) calcd for $C_9H_{13}NO$ 151.0997, found 151.0996.

3.3.2. 14-Azabicyclo[11.1.0]tetradec-13-ene-1-carbaldehyde (4e). White solid; mp 62–63 °C (from hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (m, 1H), 1.19–1.52 (m, 16H), 1.74 (m, 1H), 2.00 (m, 1H), 2.35 (ddd, $J=14.6$, 8.3, 6.3 Hz, 1H), 2.90 (ddd, $J=17.2$, 6.9, 5.0 Hz, 1H), 3.02 (ddd, $J=17.2$, 9.2, 4.5 Hz, 1H), 8.77 (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 23.5, 23.7, 24.1, 24.4, 24.5, 25.7 (2C), 25.8, 27.0 (2C), 27.7, 49.0, 167.9, 200.9; MS (EI) *m*/*z* (%) 221 (74) [M^+], 192 (100); HRMS (EI) calcd for $C_{14}H_{23}NO$ 221.1780, found 221.1789. Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 75.78; H, 10.67; N, 6.17.

3.3.3. 15-Azabicyclo[12.1.0]pentadec-14-ene-1-carbaldehyde (4f). Yellow solid; mp 38–39 °C (from hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20–1.59 (m, 18H), 1.64–1.80 (m, 2H), 1.98 (dtt, $J=12.7$, 8.3, 6.3 Hz, 1H), 2.10 (ddd, $J=15.1$, 8.3, 6.1 Hz, 1H), 2.87 (ddd, $J=17.1$, 8.3, 5.4 Hz, 1H), 2.96 (ddd, $J=17.1$, 7.8, 5.4 Hz, 1H), 8.76 (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 23.4, 23.9, 25.3, 25.48, 25.54, 25.9, (2C), 26.1, 26.6, 27.19, 27.23, 27.5, 48.9, 168.0, 200.9; MS (EI) m/z (%) 235 (100) [M^+]. HRMS (EI) calcd for $C_{15}H_{25}NO$ 235.1936, found 235.1935. Anal. Calcd for $C_{15}H_{25}NO$: C, 76.55; H, 10.71; N, 5.95. Found: C, 75.98; H, 10.76; N, 5.53.

3.3.4. 16-Azabicyclo[13.1.0]hexadec-15-ene-1-carbaldehyde (4g). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15–1.42 (m, 19H), 1.51 (m, 1H), 1.66 (ddd, J=15.1, 8.8, 6.3 Hz, 1H), 1.75 (dt, J=15.1, 7.3 Hz, 1H), 1.85 (dtt, J=15.1, 7.8, 6.4 Hz, 1H), 2.03 (ddd, J=14.6, 9.3, 7.3 Hz, 1H), 2.88 (dt, J=16.1, 8.1 Hz, 1H), 2.91 (dt, J=16.1, 8.1 Hz, 1H), 8.75 (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 23.4, 24.3, 25.77, 25.83, 25.91, 25.93, 26.0, 26.2, 26.5, 27.1, 27.4, 27.7, 27.8, 49.1, 167.8, 200.5; MS (EI) *m/z* (%) 249 (100) [M^+]; HRMS (EI) calcd for $C_{16}H_{27}NO$ 249.2093, found 249.2092.

3.3.5. 17-Azabicyclo[14.1.0]heptadec-16-ene-1-carbaldehyde (4h). Yellow solid; mp 32–33 °C (from hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10–1.43 (m, 20H), 1.43–1.54 (m, 2H), 1.69 (ddd, J=14.6, 9.0, 6.8 Hz, 1H), 1.76 (dt, J=14.6, 6.8 Hz, 1H), 1.91 (d×quint, J=14.0, 7.2 Hz, 1H), 2.05 (ddd, J=14.6, 8.0, 6.8 Hz, 1H), 2.88 (t, J=6.8 Hz, 2H), 8.76 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 24.3, 26.2, 26.3, 26.39, 26.42, 26.5, 26.9 (2C), 27.3, 27.6, 27.69, 27.74, 27.9, 48.9, 168.0, 200.7; MS (EI) *m/z* (%) 263 (100), [M^+]. HRMS (EI) calcd for $C_{17}H_{29}NO$ 263.2249, found 263.2249.

3.4. Representative procedure for the synthesis of formylazirine 4b–d (Method B)

To a solution of (*Z*)-**2b–d** (10.0 mmol) in THF (20 ml) were added NaN_3 (812 mg, 12.5 mmol), LiCl (42.4 mg, 1.00 mmol), and 60 μl of H_2O, and the mixture was stirred at room temperature for 5 h. After white precipitate was filtered off, the filtrate was concentrated in vacuo and the residue was dissolved in ether (30 ml). The white solid was precipitated again, filtered off, and washed several times with ether. The filtrate was concentrated in vacuo to give a crude mixture of the products containing *trans*-2-azidocycloalk-1-enecarbaldehyde **3b–d** and formyl azirine **4b–d**. The mixture was dissolved in $CHCl_3$ (40 ml) and was irradiated through Pyrex filter by using ultraviolet lamp (λ_{max}=365 nm) for 8 h. The conversion of *trans*-azide was monitored successfully with TLC on silica gel by using $CHCl_3$–hexane (2/1) as a developer. After removal of solvent in vacuo, the residue was chromatographed on silica gel by using ether–hexane (1/4) to give azirine **4b–d**. See Table 2 for reaction conditions and yields of **4b–d**. Compound **4d** was reported previously in literature.[7]

3.4.1. 11-Azabicyclo[8.1.0]undec-10-ene-1-carbaldehyde (4b). Oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20–1.68 (m, 10H), 1.71 (ddd, J=15.4, 9.4, 2.1 Hz, 1H), 1.94 (m, 2H), 2.38 (ddd, J=15.4, 8.6, 2.1 Hz, 1H), 2.92 (ddd, J=16.7, 8.1, 4.3 Hz, 1H), 3.08 (ddd, J=16.7, 7.7, 4.3 Hz, 1H), 8.82 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.5, 22.4, 23.2, 23.8, 26.4, 26.5, 27.0, 28.4, 49.0, 169.4, 201.4; MS (EI) *m/z* (%) 179 (49) [M^+], 150 (100); HRMS (EI) calcd for $C_{11}H_{17}NO$ 179.1310, found 139.1312.

3.4.2. 12-Azabicyclo[9.1.0]dodec-11-ene-1-carbaldehyde (4c). White solid; mp 43–44 °C (from hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12–1.52 (m, 12H), 1.57 (m, 1H), 1.87 (m, 2H), 2.48 (dt, J=14.6, 7.3 Hz, 1H), 2.95 (ddd, J=15.6, 6.8, 5.4 Hz, 1H), 3.10 (ddd, J=15.6, 7.3, 5.4 Hz, 1H), 8.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.72, 22.3, 22.9, 23.1, 24.2, 25.3, 25.5, 27.7 (2C), 49.0, 169.2, 201.1; MS (EI) *m/z* (%) 193 (16) [M^+], 164 (100). HRMS (EI) calcd for $C_{12}H_{19}NO$ 193.1467, found 193.1462. Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.31; H, 10.00; N, 7.18.

3.5. General procedure for the synthesis of iminophosphorane 5a–h

A solution of azirine **4a–h** (18.8 mmol) and PPh_3 (5.03 g, 19.2 mmol) in toluene (20 ml) was heated at reflux for 3 h. After the reaction mixture was concentrated in vacuo, yellow solid precipitated in ether was filtered to give iminophosphorane **5a–h**. Compound **5d** was reported previously in literature.[7]

3.5.1. 2-(Triphenylphosphoranylideneamino)cyclooct-1-enecarbaldehyde (5a). Yield 99%; *Z*-form only; mp 175–176 °C (from toluene); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (m, 2H), 1.34–1.43 (m, 4H), 1.53 (m, 2H), 2.23 (t, J=6.7 Hz, 2H), 2.44 (t, J=6.1 Hz, 2H), 7.48 (td, J_{H-H}=7.3 Hz, J_{P-H}=3.1 Hz, 6H), 7.56 (ttd, J_{H-H}=7.3, 1.8 Hz, J_{P-H}=1.2 Hz, 3H), 7.74 (ddd, J_{H-H}=7.3, 1.8 Hz, J_{P-H}=12.8 Hz, 6H), 10.69 (s, 1H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 23.4 (d, J_{P-C}=2.5 Hz), 26.1, 26.8, 28.6, 30.4, 35.5 (d, J_{P-C}=8.7 Hz), 122.1 (d, J_{P-C}=17.4 Hz), 128.6 (d, J_{P-C}=12.5 Hz, 6C), 131.0 (d, J_{P-C}=102.1 Hz, 3C), 132.0 (d, J_{P-C}=3.1 Hz, 3C), 132.2 (d, J_{P-C}=10.0 Hz, 6C), 171.9, 189.7; MS (EI) *m/z* (%) 413 (44) [M^+], 262 (100); HRMS (EI) calcd for $C_{27}H_{28}NOP$ 413.1908, found 413.1908. Anal. Calcd for $C_{27}H_{28}NOP$: C, 78.43; H, 6.82; N, 3.39. Found: C, 78.21; H, 6.86; N, 3.31.

3.5.2. 2-(Triphenylphosphoranylideneamino)cyclodec-1-enecarbaldehyde (5b). Yield 78%; *E*/*Z*=25:75; mp 162–164 °C (from toluene); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.59 (m, 1H, *E*), 0.96 (m, 1H, *E*), 1.01–1.09 (m, 2H, *E*), 1.15 (m, 2H, *Z*), 1.28–1.43 (m, 8H, *Z*), 1.66 (m, 2H, *Z*), 1.80–1.94 (m, 2H, *E*), 2.27 (br, 2H, *Z*), 2.47 (t, J=6.1 Hz, 2H, *Z*), 2.75–2.85 (m, 2H, *E*), 3.20–3.27 (m, 1H, *E*), 7.46 (ddd, J_{H-H}=7.9, 7.3 Hz, J_{P-H}=3.1 Hz, 6H, *Z*), 7.50 (ddd, J_{H-H}=7.9, 7.3 Hz, J_{P-H}=3.1 Hz, 6H, *E*), 7.55 (td, J_{H-H}=7.9 Hz, J_{P-H}=1.2 Hz, 3H, *Z*), 7.58 (td, J_{H-H}=7.9 Hz, J_{P-H}=1.8 Hz, 3H, *E*), 7.71 (dd, J_{H-H}=7.3 Hz, J_{P-H}=12.2 Hz, 6H, *Z*), 7.78 (dd, J_{H-H}=7.3 Hz, J_{P-H}=12.2 Hz, 6H, *E*), 9.84 (s, 1H, *E*), 10.63 (s, 1H, *Z*) and the other signals of *E*-form (7H) are hidden behind those of (*Z*)-form; ^{13}C NMR (76 MHz, $CDCl_3$) δ 21.4 (*E*), 22.0 (*Z*), 22.3 (*Z*), 23.0 (*E*), 23.1 (*E*), 23.4 (*E*), 24.9 (d, J_{P-C}=1.2 Hz, *Z*), 25.5 (*E*), 25.9 (*E*), 26.0 (*Z*), 26.37 (*Z*), 26.42 (*Z*), 26.6 (*E*), 26.8 (*Z*), 33.2 (d, J_{P-C}=6.2 Hz, *Z*), 34.4 (d, J_{P-C}=9.3 Hz, *E*), 122.9 (d, J_{P-C}=15.6 Hz, *Z*), 126.3 (d, J_{P-C}=21.9 Hz, *E*), 128.6 (d, J_{P-C}=12.5 Hz, 6C, *Z*), 128.7 (d, J_{P-C}=10.6 Hz, 6C, *E*), 130.7, (d, J_{P-C}=101.5 Hz, 3C, *E*), 131.4 (d, J_{P-C}=102.8 Hz, 3C, *Z*), 131.9 (d, J_{P-C}=2.5 Hz, 3C, *Z*), 132.2 (d, J_{P-C}=3.1 Hz, 3C, *E*), 132.3 (d, J_{P-C}=10.0 Hz, 6C, *Z*), 132.5 (d, J_{P-C}=10.6 Hz, 6C, *E*), 170.9 (*Z*), 173.1 (*E*), 187.7 (*E*), 191.9 (*Z*); MS (EI) *m/z* (%) 441 (10) [M^+], 262 (100); HRMS (EI) calcd for $C_{29}H_{32}NOP$ 441.2221, found 441.2227. Anal. Calcd for $C_{29}H_{32}NOP$: C, 78.29; H, 7.51; N, 3.26. Found: C, 78.50; H, 7.33; N, 3.12.

3.5.3. 2-(Triphenylphosphoranylideneamino)cycloundec-1-enecarbaldehyde (5c). Yield 80%; *E*/*Z*=94:6; yellow

solid; mp 171.9–172.4 °C (from toluene); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (m, 1H), 1.04 (m, 1H), 1.09–1.36 (m, 8H), 1.46–1.67 (m, 3H), 1.77 (m, 1H), 2.17 (m, 1H), 2.71 (ddd, J=13.2, 9.8, 3.0 Hz, 1H), 2.79 (ddd, J=13.2, 7.5, 3.1 Hz, 1H), 3.13 (td, J=12.4, 0.4 Hz, 1H), 7.49 (dddd, J_{H-H}=7.5, 7.0, 1.5 Hz, J_{P-H}=3.0 Hz, 6H), 7.57 (tq, J_{H-H}=7.5, 1.5 Hz, J_{P-H}=1.5 Hz, 3H), 7.77 (dtd, J_{H-H}=7.0, 1.5 Hz, J_{P-H}=12.4 Hz, 6H), 9.93 (s, 1H) and most signals for (*Z*)-**5c** were overlapped with (*E*)-**5c** except for δ 1.39 (m, 4H), 2.26 (t, J=6.8 Hz, 2H), 7.71 (dtd, J_{H-H}=7.1, 1.5 Hz, J_{P-H}=12.1 Hz, 6H) and 10.57 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.55, 23.64, 24.3, 24.9, 26.55, 26.63 (2C), 26.9, 34.3 (d, J_{P-C}=8.6 Hz), 127.5 (d, J_{P-C}=20.1 Hz) 128.7 (d, J_{P-C}=12.5 Hz, 6C), 131.2 (d, J_{P-C}=102.6 Hz, 3C), 132.1 (d, J_{P-C}=2.9 Hz, 3C), 132.5 (d, J_{P-C}=10.5 Hz, 6C), 173.2, 188.4 (d, J_{P-C}=3.8 Hz); MS (EI) *m*/*z* (%) 455 (15) [M^+], 262 (100). HRMS (EI) calcd for $C_{30}H_{34}NOP$ 455.2378, found 455.2381.

3.5.4. 2-(Triphenylphosphoranylideneamino)cyclododec-1-enecarbaldehyde (5d).[7] Yield 91% (reported as 84% yield in our previous work); *E*/*Z*=75:25.

3.5.5. 2-(Triphenylphosphoranylideneamino)cyclotridec-1-enecarbaldehyde (5e). Yield 88%; *E*/*Z*=67:33; yellow solid; mp 197–199 °C (from ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75–0.93 (m, 1H for *E* and 2H for *Z*), 0.93–1.62 (m, 16H each, *E* and *Z*), 1.62–1.87 (m, 2H, *E*), 1.98 (AA′XX′, $J_{AX}+J_{AX'}$=17.4 Hz, 2H, *Z*), 2.16 (br AA′XX′, $J_{AX}+J_{AX'}$=14.9 Hz, 2H, *Z*), 2.64 (ddd, J=12.5, 10.6, 2.2 Hz, 1H, *E*), 2.79 (ddd, J=12.5, 6.3, 2.6 Hz, 1H, *E*), 3.05 (ddd, J=11.0, 10.7, 2.6 Hz, 1H, *E*), 7.43–7.53 (m, 6H each, *E* and *Z*), 7.53–7.61 (m, 3H each, *E* and *Z*), 7.72 (dddd, J_{H-H}=7.0, 2.0, 1.5 Hz, J_{P-H}=12.1 Hz, 6H, *Z*), 7.77 (dddd, J_{H-H}=6.8, 2.0, 1.5 Hz, J_{P-H}=12.3 Hz, 6H, *E*), 9.85 (s, 1H, *E*), 10.66 (s, 1H, *Z*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.0 (*Z*), 22.9 (*E*), 23.6 (*E*), 23.9 (*Z*), 24.0 (3C, *Z*), 24.1 (*Z*), 24.2 (*E*), 24.7 (*E*), 25.2 (*E*), 25.3 (*E*), 25.5 (*Z*), 26.3, (*Z*), 26.7 (*Z*), 26.8 (*E*), 26.9 (*Z*), 27.1 (*E*), 27.4 (*E*), 28.1 (*E*), 32.7 (d, J_{P-C}=8.1 Hz, *E*), 35.4 (d, J_{P-C}=7.3 Hz, *Z*), 122.3 (d, J_{P-C}=16.9 Hz, *Z*), 127.0 (d, J_{P-C}=20.1 Hz, *E*), 128.7 (d, J_{P-C}=12.1 Hz, 6C, *E*), 128.8 (d, J_{P-C}=12.1 Hz, 6C, *Z*), 131.0 (d, J_{P-C}=102.3 Hz, 3C, *E*), 131.2 (d, J_{P-C}=102.3 Hz, 3C, *Z*), 132.10 (d, J_{P-C}=3.2 Hz, 3C, *Z*), 132.13 (d, J_{P-C}=3.2 Hz, 3C, *E*), 132.5 (d, J_{P-C}=10.5 Hz, 6C, *Z*), 132.6 (d, J_{P-C}=10.5 Hz, 6C, *E*), 171.8 (*Z*), 172.3 (*E*), 188.3 (d, J_{P-C}=4.0 Hz, *E*), 190.6 (*Z*); MS (EI) *m*/*z* (%) 483 (13.5) [M^+], 262 (100); HRMS (EI) calcd for $C_{32}H_{38}NOP$ 483.2691, found 483.2689. Anal. Calcd for $C_{32}H_{38}NOP$: C, 79.47; H, 7.92; N, 2.90. Found: C, 79.15; H, 8.05; N, 2.88.

3.5.6. 2-(Triphenylphosphoranylideneamino)cyclotetradec-1-enecarbaldehyde (5f). Yield 76%; *E*/*Z*=68:32; yellow solid; mp 171–173 °C (from toluene); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.77 (m, 2H, *Z*), 0.94–1.51 (m, 18H each, *E* and *Z*), 1.53–1.70 (m, 2H, *E*), 1.79 (m, 1H, *E*), 2.07 (AA′XX′, $J_{AX}+J_{AX'}$=17.4 Hz, 2H, *Z*), 2.21 (AA′XX′, $J_{AX}+J_{AX'}$=15.6 Hz, 2H, *Z*), 2.68 (ddd, J=12.8, 8.1, 3.3 Hz, 1H, *E*), 2.90 (ddd, J=12.8, 8.8, 3.1 Hz, 1H, *E*), 3.08 (m, 1H, *E*), 7.44–7.51 (m, 6H each, *E* and *Z*), 7.53–7.60 (m, 3H each, *E* and *Z*), 7.72 (ddd, J_{H-H}=8.2, 1.1 Hz, J_{P-H}=12.3 Hz, 6H, *Z*), 7.77 (ddd, J_{H-H}=8.3, 1.3 Hz, J_{P-H}=12.5 Hz, 6H, *E*), 9.85 (s, 1H, *E*), 10.71 (s, 1H, *Z*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.7 (*Z*), 23.9 (*E*), 24.13 (*Z*), 24.2 (*E*), 24.3 (*E*), 24.76 (*E*), 24.81 (*Z*), 24.9 (*Z*), 25.0 (*Z*), 25.1 (*Z*), 25.4 (*Z*), 25.5 (*E*), 25.9 (*E*), 26.0 (*Z*), 26.4 (*E*), 26.91 (*Z*), 26.93 (*E*), 27.25 (*Z*), 27.33 (*E*), 27.6 (*Z*), 28.0 (*E*), 28.8 (*E*), 32.3 (d, J_{P-C}=7.2 Hz, *E*), 36.9 (d, J_{P-C}=8.3 Hz, *Z*), 122.8 (d, J_{P-C}=15.5 Hz, *Z*), 126.0 (d, J_{P-C}=19.7 Hz, *E*), 128.68 (d J_{P-C}=12.4 Hz, 6C, *E*), 128.70 (d, J_{P-C}=12.4 Hz, 6C, *Z*), 130.9 (d, J_{P-C}=102.4 Hz, 3C, *E*), 131.2 (d, J_{P-C}=102.4 Hz, 3C, *Z*), 132.0 (d, J_{P-C}=3.1 Hz, 3C, *Z*), 132.1 (d, J_{P-C}=3.1 Hz, 3C, *E*), 132.36 (d, J_{P-C}=9.3 Hz, 6C, *Z*), 132.44 (d, J_{P-C}=10.3 Hz, 6C, *E*), 171.3 (*Z*), 171.8 (*E*), 188.3 (d, J_{P-C}=5.2 Hz, *E*), 191.3 (*Z*); MS (EI) *m*/*z* (%) 497 (9) [M^+] 262 (100). HRMS (EI) calcd for $C_{33}H_{40}NOP$ 497.2848, found 497.2850. Anal. Calcd for $C_{33}H_{40}NOP$: C, 79.64; H, 8.10; N, 2.81. Found: C, 79.83; H, 8.22; N, 2.69.

3.5.7. 2-(Triphenylphosphoranylideneamino)cyclopentadec-1-enecarbaldehyde (5g). Yield 85%; *E*/*Z*=67:33; mp 173–176 °C (from toluene); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.70 (m, 2H, *Z*), 0.87–1.65 (m, 22H for *E* and 19H for *Z*), 1.78 (m, 1H, *E*), 2.06 (AA′XX′, $J_{AX}+J_{AX'}$=17.3 Hz, 2H, *Z*), 2.20 (AA′XX′, $J_{AX}+J_{AX'}$=15.0 Hz, 2H, *Z*), 2.71 (ddd, J=12.8, 9.2, 3.7, 1H, *E*), 2.78 (ddd, J=12.8, 5.9, 4.0 Hz, 1H, *E*), 3.04 (ddd, J=13.4, 10.3, 3.3 Hz, 1H, *E*), 7.43–7.61 (m, 9H each, *E* and *Z*), 7.71 (dtd, J_{H-H}=7.0, 1.5 Hz, J_{P-H}=12.5 Hz, 6H, *Z*), 7.75 (dddd, J_{H-H}=7.0, 1.7, 1.5 Hz, J_{P-H}=12.5 Hz, 6H, *E*), 9.85 (s, 1H, *E*), 10.67 (s, 1H, *Z*); ^{13}C NMR (76 MHz, $CDCl_3$) δ 23.9 (*E*), 24.5 (*Z*), 24.7 (*Z*), 24.8 (d, J_{P-C}=1.2 Hz, *Z*), 24.9 (*E*), 25.7 (*Z*), 25.8 (*Z*), 26.1 (*E*), 26.17 (*Z*), 26.24 (*Z*), 26.46 (*E*), 26.51 (*Z*), 26.7 (*E*), 26.9 (*E*), 27.0 (*E*), 27.1 (*Z*), 27.21 (*E*), 27.25 (*E*), 27.9 (*Z*), 28.0 (*E*), 28.3 (*E*), 28.9 (*E*), 31.9 (d, J_{P-C}=8.1 Hz, *E*), 37.1 (d, J_{P-C}=7.5 Hz, *Z*), 122.5 (d, J_{P-C}=16.8 Hz, *Z*), 125.4 (d, J_{P-C}=20.6 Hz, *E*), 128.5 (d, J_{P-C}=12.5 Hz, 6C each, *E* and *Z*), 130.4 (d, J_{P-C}=102.1 Hz, 3C, *E*), 130.9 (d, J_{P-C}=101.5 Hz, 3C, *Z*), 131.8 (d, J_{P-C}=3.1 Hz, 3C, *Z*), 132.0 (d, J_{P-C}=2.5 Hz, 3C. *E*), 132.1 (d, J_{P-C}=10.0 Hz, 6C, *Z*), 132.2 (d, J_{P-C}=10.6 Hz, 6C, *E*), 171.4 (1C each, *E* and *Z*), 187.9 (d, J_{P-C}=3.7 Hz, *E*), 190.8 (*Z*) and two signals of *Z*-form are overlapped; MS (EI) *m*/*z* (%) 511 (28) [M^+], 262 (100); HRMS (EI) calcd for $C_{34}H_{42}NOP$ 511.3004, found 511.3004. Anal. Calcd for $C_{34}H_{42}NOP$: C, 79.81; H, 8.27; N, 2.74. Found: C, 79.57; H, 8.31; N, 2.73.

3.5.8. 2-(Triphenylphosphoranylideneamino)cyclohexadec-1-enecarbaldehyde (5h). Yield 85%; *E*/*Z*=56:44; white solid; mp 97–98 °C (from toluene); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (m, 2H, *Z*), 0.85–0.98 (m, 1H for *E* and 2H for *Z*), 1.12–1.44 (m, 22H for *E* and 18H for *Z*), 1.55–1.76 (m, 2H each, *E* and *Z*), 2.07 (AA′XX′, $J_{AX}+J_{AX'}$=17.1 Hz, 2H, *Z*), 2.21 (br AA′XX′, $J_{AX}+J_{AX'}$=16.6 Hz, 2H, *Z*), 2.65 (ddd, J=12.7, 8.1, 5.1 Hz, 1H, *E*), 2.82 (ddd, J=12.7, 6.7, 5.4 Hz, 1H, *E*), 3.07 (ddd, J=13.0, 9.8, 5.6 Hz, 1H, *E*), 7.43–7.52 (m, 6H each, *E* and *Z*), 7.53–7.61 (m, 3H each, *E* and *Z*), 7.68–7.79 (m, 6H each, *E* and *Z*), 9.85 (s, 1H, *E*), 10.70 (s, 1H, *Z*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 25.2, 25.4, 25.8, 26.1, 26.30, 26.32 (2C), 26.4, 26.6, 26.7, 26.8, 26.98, 27.01, 27.1, 27.4, 27.5 (2C), 27.7, 27.90, 27.93, 28.0, 28.4, 28.6, 29.3, 29.7, 32.9 (d, J_{P-C}=8.3 Hz), 37.7 (d, J_{P-C}=8.3 Hz), 122.8 (d, J_{P-C}=17.6 Hz), 125.8 (d, J_{P-C}=21.2 Hz), 128.7 (d, J_{P-C}=9.9 Hz), 130.9 (d, J_{P-C}=102.6 Hz), 131.3 (d,

J_{P-C}=102.6 Hz), 132.1, 132.2, 132.4 (d, J_{P-C}=9.9 Hz), 132.5 (d, J_{P-C}=9.9 Hz), 171.3, 171.9, 188.1 (d, J_{P-C}=3.3 Hz), 191.4; MS (EI) *m/z* (%) 525 (28) [M^+], 262 (100). HRMS (EI) calcd for $C_{35}H_{44}NOP$ 525.3161, found 525.3154.

3.6. Reaction of 5 with methyl propiolate

Method A. Representative procedure. A solution of iminophosphorane **5g** (4.06 g, 7.93 mmol) and methyl propiolate (6.87 g, 81.7 mmol) in toluene (25 ml) was heated at 140 °C in an autoclave reactor for 12 h. After the mixture was concentrated in vacuo, the residue was separated by flash chromatographed on silica gel (FL60D, Fuji Silysia Chemical Ltd) by using ether–hexane (1/5) to give nicotinates **6g** (741 mg, 2.34 mmol) and **7g** (70.8 mg, 0.223 mmol) in 30 and 3% yields, respectively.

Method B. Representative procedure. A solution of iminophosphorane **5d** (4.70 g, 10.0 mmol) and methyl propiolate (4.21 g, 50.0 mmol) in acetonitrile (30 ml) was heated at 120 °C in an autoclave reactor for 10 h. After removal of solvent and excess methyl propiolate in vacuo, the residue was chromatographed on silica gel (silica gel 60 N spherical, neutral, 40–50 μm, KANTO chemical Co., Inc.) by using acetone–toluene (1/19) to afford a crude mixture of nicotinates **6d** and **7d**. The mixture was further purified by flash chromatography on silica gel (FL60D, Fuji Silysia Chemical Ltd) by using ether–hexane (1/5) to give nicotinates **6d** (688 mg, 2.50 mmol) and **7d** (408 mg, 1.48 mmol) in 25 and 15% yields, respectively.

Compounds **6d** and **7d** were reported previously in literature.[7] See Table 3 for reaction conditions and yields of **6b–h** and **7a–h**.

3.6.1. Methyl [8](2,5)pyridinophane-3-carboxylate (6b). Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.27 (m,1H), 0.14 (m, 1H), 0.41–0.60 (m, 2H), 0.86–1.15 (m, 4H), 1.15–1.39 (m, 2H), 1.58–1.83 (m, 2H), 2.66 (ddd, J=13.0, 8.8, 4.8 Hz, 1H), 2.73 (ddd, J=12.7, 9.9, 4.7 Hz, 1H), 2.75 (ddd, J=13.0, 6.4, 4.8 Hz, 1H), 3.87 (ddd, J=12.7, 6.2, 4.2 Hz, 1H), 3.93 (s,3H), 8.02 (d, J=1.8 Hz, 1H), 8.43 (d, J=1.8 Hz, 1H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 25.3, 25.4, 28.0, 28.7, 29.6, 30.6, 32.3, 36.6, 52.2, 124.8, 133.9, 138.5, 150.6, 163.0, 167.0; MS (EI) *m/z* (%) 247 (100) [M^+]; HRMS (EI) calcd for $C_{15}H_{21}NO_2$ 247.1572, found 247.1579.

3.6.2. Methyl [9](2,5)pyridinophane-3-carboxylate (6c). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.19 (m, 1H), 0.31 (m, 1H), 0.47 (m, 1H), 0.58–0.85 (m, 3H), 0.85–1.12 (m, 4H), 1.28–1.63 (m, 3H), 1.70 (m, 1H), 2.55 (ddd, J=13.2, 8.2, 4.4 Hz, 1H), 2.76–2.85 (m, 2H), 3.79 (ddd, J=12.2, 7.3, 4.4 Hz, 1H), 3.94 (s, 3H), 7.97 (d, J=2.0 Hz, 1H), 8.50 (d, J=2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 23.7, 25.5, 27.4, 27.6, 28.6, 29.7, 32.3, 35.8, 52.3, 125.1, 134.4, 138.6, 151.9, 161.5, 167.3; MS (EI) *m/z* (%) 261 (100) [M^+]. HRMS (EI) calcd for $C_{16}H_{23}NO_2$ 261.1729, found 261.1728.

3.6.3. Methyl [11](2,5)pyridinophane-3-carboxylate (6e). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.55–1.01 (m, 10H), 1.14 (m, 1H), 1.19–1.30 (m, 3H), 1.61–1.74 (m, 3H), 1.83 (m, 1H), 2.62 (ddd, J=13.2, 8.4, 3.2 Hz, 1H), 2.68 (ddd, J=13.2, 8.0, 3.6 Hz, 1H), 2.77 (ddd, J=12.5, 9.4, 3.6 Hz, 1H), 3.74 (ddd, J=12.5, 8.6, 3.6 Hz, 1H), 3.93 (s, 3H), 7.97 (d, J=2.3 Hz, 1H), 8.49 (d, J=2.3 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 25.3, 25.8, 26.4, 26.7, 27.2, 27.77, 27.82, 28.0, 28.5, 32.5, 36.0, 52.3, 125.3, 135.2, 138.6, 151.9, 161.3, 167.3; MS (EI) *m/z* (%) 289 (62) [M^+], 230 (100); HRMS (EI) calcd for $C_{18}H_{27}NO_2$ 289.2042, found 289.2055.

3.6.4. Methyl [12](2,5)pyridinophane-3-carboxylate (6f). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77–0.90 (m, 6H), 0.96–1.17 (m, 10H), 1.63 (m, 2H), 1.71 (quint, J=6.6 Hz, 2H), 2.68 (AA′XX′, $J_{AX}+J_{AX'}$=12.2 Hz, 2H), 3.26 (br, 2H), 3.93 (s, 3H), 7.94 (d, J=2.2 Hz, 1H), 8.47 (d, J=2.2 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 24.7, 25.7, 25.9, 26.2, 26.8, 26.9, 27.36, 27.40, 28.6, 29.2, 31.7, 35.4, 52.1, 125.3, 134.7, 138.3, 151.9, 161.4, 167.4; MS (EI) *m/z* (%) 303 (52) [M^+] 244 (100). HRMS (EI) calcd for $C_{19}H_{29}NO_2$ 303.2198, found 303.2190.

3.6.5. Methyl [13](2,5)pyridinophane-3-carboxylate (6g). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (m, 2H), 0.92–1.19 (m, 16H), 1.67 (m, 2H), 1.75 (m, 2H), 2.66 (AA′XX′, $J_{AX}+J_{AX'}$=12.2 Hz, 2H), 3.24 (AA′XX′, $J_{AX}+J_{AX'}$=12.2 Hz, 2H), 3.93 (s, 3H), 7.94 (d, J=2.4 Hz, 1H), 8.48 (d, J=2.4 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 25.8, 26.5, 26.6, 27.2, 27.3, 27.4, 27.7 (2C), 27.9, 28.6, 29.2, 31.8, 35.6, 52.2, 125.4, 134.6, 138.4, 153.1, 160.9, 167.6; MS (EI) *m/z* (%) 317 (100) [M^+]; HRMS (EI) calcd for $C_{20}H_{31}NO_2$ 317.2355, found 317.2363.

3.6.6. Methyl [14](2,5)pyridinophane-3-carboxylate (6h). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88–1.13 (m, 12H), 1.14–1.35 (m, 8H), 1.67 (m, 2H), 1.74 (m, 2H), 2.69 (AA′XX′, $J_{AX}+J_{AX'}$=12.2 Hz, 2H), 3.24 (AA′XX′, $J_{AX}+J_{AX'}$=12.2 Hz, 2H), 3.92 (s, 3H), 7.93 (d, J=2.2 Hz, 1H), 8.47 (d, J=2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 25.5, 26.3 (2C), 27.0, 27.3, 27.36, 27.44, 28.0 (2C), 28.5, 29.1, 31.4, 35.0, 52.2, 125.5, 134.2, 138.3, 152.0, 160.5, 167.6; MS (EI) m/z (%) 331 (100) [M^+]. HRMS (EI) calcd for $C_{21}H_{33}NO_2$ 331.2511, found 331.2512.

3.6.7. Methyl 5,6,7,8,9,10-hexahydrocycloocta[*b*]pyridine-3-carboxylate (7a). Oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33–1.43 (m 4H), 1.73 (m, 2H), 1.82 (m, 2H), 2.83 (AA′XX′, $J_{AX}+J_{AX'}$=12.8 Hz, 2H), 3.03 (AA′XX′, $J_{AX}+J_{AX'}$=12.5 Hz, 2H), 3.93 (s, 3H), 7.99 (d, J=2.2 Hz, 1H), 8.98 (d, J=2.2 Hz, 1H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 25.8, 25.9, 30.5, 31.8, 32.0, 34.8, 52.2, 123.9, 136.1, 137.4, 148.3, 166.0, 166.3; MS (EI) *m/z* (%) 219 (100) [M^+], 190 (98); HRMS (EI) calcd for $C_{13}H_{17}NO_2$ 219.1259, found 219.1253.

3.6.8. Methyl 5,6,7,8,9,10,11,12-octahydrocyclodeca[*b*]-pyridine-3-carboxylate (7b). White solid; mp 61–63 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06–1.17 (m, 4H), 1.46–1.54 (m, 4H), 1.85 (tt, J=6.4, 6.0 Hz, 2H), 2.00 (m, 2H), 2.91 (t, J=6.4 Hz, 2H), 3.06 (m, 2H), 3.94 (s, 3H), 8.06 (d, J=1.8 Hz, 1H), 9.02 (d, J=1.8 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 20.5, 21.1, 26.1, 26.7, 28.3, 28.8, 29.1, 31.9, 52.2, 123.3, 135.5, 137.6, 147.8, 165.1, 166.1; MS (EI) *m/z* (%) 247 (34) [M^+], 204 (100); HRMS (EI)

calcd for $C_{15}H_{21}NO_2$ 247.1572, found 247.1573. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.86; H, 8.56; N, 5.66. Found: C, 72.36; H, 8.56; N, 5.24.

3.6.9. Methyl methyl 6,7,8,9,10,11,12,13-octahydrocycloundeca[*b*]pyridine-3-carboxylate (7c). White solid; mp 97–98 °C (from ethyl acetate–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09–1.28 (m, 6H), 1.30–1.42 (m, 4H), 1.82 (m, 2H), 1.97 (m, 2H), 2.83 (t, J=6.4 Hz, 2H), 2.97 (t, J=6.0 Hz, 2H), 3.94 (s, 3H), 8.06 (d J=2.3 Hz, 1H), 8.99 (d, J=2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 23.7, 25.4, 26.26, 26.29, 27.5, 28.2, 29.3, 33.0, 52.2, 123.2, 136.3, 137.3, 147.6, 166.1, 166.3; MS (EI) *m*/*z* (%) 261 (29) [M^+], 165 (100). HRMS (EI) calcd for $C_{16}H_{23}NO_2$ 261.1729, found 261.1730.

3.6.10. Methyl 6,7,8,9,10,11,12,13,14,15-decahydrocyclotrideca[*b*]pyridine-3-carboxylate (7e). Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20–1.58 (m, 14H), 1.71 (m, 2H), 1.81 (m, 2H), 2.65 (AA′XX′, $J_{AX}+J_{AX'}$=16.9 Hz, 2H), 2.85 (AA′XX′, $J_{AX}+J_{AX'}$=16.7 Hz, 2H), 3.93 (s, 3H), 8.01 (d, J=2.0 Hz, 1H), 8.95 (d, J=2.0 Hz, 1H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 23.9, 24.0, 24.66, 24.67, 26.2, 26.3, 26.4, 26.5, 27.5, 30.7, 33.9, 52.2, 123.7, 135.7, 138.1, 147.9, 165.5, 166.3; MS (EI) *m*/*z* (%) 289 (46) [M^+], 165 (100); HRMS (EI) calcd for $C_{18}H_{27}NO_2$ 289.2042, found 289.2054.

3.6.11. Methyl 5,6,7,8,9,10,11,12,13,14,15,16-dodecahydrocyclotetradeca[*b*]pyridine-3-carboxylate (7f). White solid; mp 81–83 °C (from ethyl acetate–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22–1.67 (m, 18H), 1.73 (m, 2H), 2.64 (AA′XX′, $J_{AX}+J_{AX'}$=16.5 Hz, 2H), 2.82 (AA′XX′, $J_{AX}+J_{AX'}$=16.9 Hz, 2H), 3.93 (s, 3H), 8.04 (d, J=2.3 Hz, 1H), 8.96 (d, J=2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 24.0, 24.9, 25.2, 25.35, 25.42, 27.1, 27.5, 27.6, 29.2, 31.8, 34.4, 52.1, 123.5, 135.5, 138.1, 147.9, 165.1, 166.2; MS (EI) *m*/*z* (%) 303 (24) [M^+] 165 (100). HRMS (EI) calcd for $C_{19}H_{29}NO_2$ 303.2198, found 303.2208.

3.6.12. Methyl 6,7,8,9,10,11,12,13,14,15,16,17-dodecahydrocyclopentadeca[*b*]pyridine-3-carboxylate (7g). Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22–1.83 (m, 22H), 2.66 (AA′XX′, $J_{AX}+J_{AX'}$=16.5 Hz, 2H), 2.84 (AA′XX′, $J_{AX}+J_{AX'}$=16.5 Hz, 2H), 3.93 (s, 3H), 8.02 (d, J=2.0 Hz, 1H), 8.96 (d, J=2.0 Hz, 1H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 25.4, 25.5, 25.9, 26.0, 26.6, 26.78, 26.83, 27.3, 27.4, 28.1, 29.3, 32.2, 35.2, 52.1, 123.6, 135.6, 137.9, 147.8, 165.3, 166.2; MS (EI) *m*/*z* (%) 317 (75) [M^+], 165 (100); HRMS (EI) calcd for $C_{20}H_{31}NO_2$ 317.2355, found 317.2359.

3.6.13. Methyl 5,6,7,8,9,10,11,12,13,14,15,16,17,18-tetradecahydrocyclohexadeca[*b*]pyridine-3-carboxylate (7h). White solid; mp 57–58 °C (from ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25–1.39 (m, 12H), 1.39–1.52 (m, 8H), 1.59 (m, 2H), 1.71 (m, 2H), 2.66 (AA′XX′, $J_{AX}+J_{AX'}$=16.0 Hz, 2H), 2.84 (AA′XX′, $J_{AX}+J_{AX'}$=16.5 Hz, 2H), 3.93 (s, 3H), 8.04 (d, J=2.3 Hz, 1H), 8.96 (d, J=2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.7 (2C), 26.30, 26.33, 26.36, 26.44, 27.4 (2C), 27.8, 28.0, 28.9, 30.3, 32.2, 35.1, 52.1, 123.5, 135.5, 137.8, 147.9, 165.2, 166.2; MS (EI) m/z (%) 331 (27) [M^+], 165 (100). HRMS (EI) calcd for $C_{21}H_{33}NO_2$ 331.2511, found 331.2501.

3.7. Hydrolysis of [11](2,5)pyridinophane 6e

A solution of **6e** (170 mg, 0.587 mmol) in methanol–water (9/1, 8.0 ml) was stirred in the presence of lithium hydroxide monohydrate (124 mg, 2.94 mmol) at room temperature overnight. After removal of solvent in vacuo, water was added and the solution was washed with ether. The aqueous layer was acidified to pH 3 with hydrochloric acid and extracted with chloroform. The organic layer was dried over magnesium sulfate and was concentrated in vacuo to give compound **13** (138 mg, 0.502 mmol) in 85% yield.

3.7.1. [11](2,5)Pyridinophane-3-carboxylic acid (13). White solid; mp 200–201 °C (from ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.51–1.04 (m, 10H), 1.10–1.35 (m, 4H), 1.46–1.95 (m, 4H), 2.59–2.77 (m, 2H), 2.83 (ddd, J=12.8, 8.7, 3.2 Hz, 1H), 3.91 (m, 1H), 4.14 (br s, 1H), 8.17 (d, J=2.1 Hz, 1H), 8.55 (d, J=2.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 25.6, 26.2, 26.5, 27.1, 27.7, 27.8, 27.9, 28.3, 32.4, 35.0, 126.8, 136.1, 140.3, 150.5, 161.1, 169.0; MS (EI) *m*/*z* (%) 275 (16) [M^+], 230 (20), 69 (100). HRMS (EI) calcd for $C_{17}H_{25}NO_2$ 275.1885, found 275.1879. Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 73.90; H, 9.19; N, 5.02.

3.8. Synthesis of (S_p,*S*)-14 and (R_p,*S*)-14

The compound **13** (207 mg, 0.754 mmol) was treated with oxalyl chloride (132 μl, 1.51 mmol) in chloroform (1.5 ml) and the mixture was stirred at room temperature for 1.5 h. After solvent was removed in vacuo, the acid chloride thus obtained was dissolved in chloroform (1.5 ml) and the solution was added dropwise by syringe to a solution of (*S*)-phenylalaninol (171 mg, 1.13 mmol) and triethylamine (114 mg, 1.13 mmol) in chloroform (2.0 ml) at 0 °C. The reaction mixture was then stirred at room temperature overnight. After the reaction was complete, the mixture was washed with saturated aqueous sodium bicarbonate, was dried over magnesium sulfate, and was concentrated in vacuo. The residue was then chromatographed on silica gel by using ether to give an inseparable mixture of (S_p,*S*)-**14** and (R_p,*S*)-**14** (256 mg, 0.627 mmol) in 83% yield. HPLC analyses, shown in Figure 2, were performed by using SenshuPak PEGASIL Silica 120–5 column (4.6×250 mm) and a UV detector (254 nm) with 20% acetonitrile in ethyl acetate as an eluent (flow rate: 1.0 ml/min).

3.8.1. (*S*)-*N*-(1-Hydroxy-3-phenylpropan-2-yl)-(*S*)-[11](2,5)pyridinophane-3-carboxamide [(S_p,*S*)-14 and (R_p,*S*)-14]. Sticky oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.60 (m, 2H), 0.67–1.10 (m, 18H), 1.10–1.28 (m, 8H), 1.48–1.79 (m, 8H), 2.43–2.55 (m, 2H), 2.59–2.68 (m, 3H), 2.73 (ddd, J=13.2, 8.4, 3.2 Hz, 1H), 2.87 (ddd, J=12.8, 9.2, 3.2 Hz, 1H), 2.90–3.09 (m, 6H), 3.15 (ddd, J=13.2, 9.2, 5.6 Hz, 1H), 3.71–3.75 (m, 2H), 3.80–3.84 (m, 2H), 4.37–4.46 (m, 2H), 6.00 (br, 1H), 6.08 (br, 1H), 7.25–7.38 (m, 12H), 8.39 (d, J=2.4 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$, 50 °C) δ 25.6 (2C), 26.0 (2C), 26.6 (2C), 26.8, 26.9, 27.27, 27.30, 27.47, 27.54, 27.965, 27.973, 27.99 (2C), 28.6 (2C), 32.56,

32.58, 34.9, 35.1, 37.0, 37.1, 53.1, 53.3, 63.8, 64.3, 126.7, 126.8, 128.7 (2C), 128.8 (2C), 129.2 (4C), 131.7, 131.9, 135.30 (2C), 135.32, 135.6, 137.6, 137.6, 150.49, 150.54, 157.4, 157.8, 169.0, 169.2; MS (FAB+) *m/z* (%) 409 (100 [M+H$^+$]), 391 (21), 258 (34). HRMS (FAB+) calcd for $C_{26}H_{37}N_2O_2$ [M+H$^+$] 409.2855, found 409.2856. Anal. Calcd for $C_{26}H_{36}N_2O_2$: C, 76.43; H, 8.88; N, 6.86. Found: C, 76.56; H, 8.80; N, 6.35.

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Reactions of acceptor substituted thiophene-1,1-dioxides with cyclopentadiene: control of selectivity by substitution

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Abstract—Diels–Alder reactions of thiophene-1,1-dioxides with strong electron withdrawing groups (EWG) were studied experimentally and theoretically. Thiophene-1,1-dioxides with two strong EWG behave as dienophiles and regio- and stereoselectively react with cyclopentadiene to give [2+4] cycloadducts **2a–c**, which are derivatives of benzothiophene. In contrast, thiophene-1,1-dioxides with one EWG behave as dienes in the inverse electron demand Diels–Alder reaction yielding dihydro-1*H*-indenes derivatives. Cope [3,3]-sigmatropic rearrangement of adducts **2a–c** was also demonstrated. MP2 calculations successfully rationalize the contrasting regioselectivities of these cycloaddition reactions.

1. Introduction

Thiophene-1,1-dioxides are useful synthetic precursors for different classes of organic compounds because of their high reactivity in the Diels–Alder and 1,3-dipolar cycloadditions reactions.[1–5] The unique opportunity of SO_2-extrusion allows the creation of various complex multifunctional organic molecules.[5,6]

Diels–Alder reactions of thiophene dioxides have been extensively investigated. It has been reported that halogen- and alkyl- containing thiophene-1,1-dioxides undergo cycloadditions with a variety of dienophiles,[1–4] followed by the loss of sulfur dioxide leading to the formation of substituted cyclohexadienes, aromatics or heterocycles.

Reactions of substituted thiophene-1,1-dioxides with cyclopentadiene are of particular interest because the reaction products can be further transformed to 1*H*-indene derivatives, which are valuable building blocks and precursors in polymer chemistry.[7] Unfortunately, the feasibility of this transformation was only studied for the parent thiophene dioxide and a few halogenated derivatives. It was found that while unsubstituted thiophene dioxide acts as a dienophile, only a [2+4] adduct was isolated,[5b] the reaction with halogen containing thiophene dioxides yields a mixture of [4+2] and [2+4] adducts.[1] Factors controlling these variations in selectivity have not been analyzed theoretically.

2. Results and discussion

We previously reported a convenient method for preparation of thiophene-1,1-dioxides bearing electron-withdrawing groups.[8] Furthermore, we found these compounds to be highly reactive towards cycloaddition with various 1,3-dienes.[9] In particular, thiophene-1,1-dioxides bearing EWG act as strong dienophiles that yield [2+4] cycloadducts in the Diels–Alder reaction under mild conditions with 100% chemo-, regio and stereoselectivity.

The extremely high reactivity of these novel dienophiles motivated us to expand our studies to reactions with cyclopentadiene (CPD). Unusual results were observed when we started our investigation of cycloaddition with thiophene-1,1-dioxides **1a** and **1d**. We found that the chemoselectivity of reaction is different in these two cases. Analysis of the crude reaction mixture shows that thiophene-1,1-dioxide **la** bearing two EWG behaves as a dienophile and gives normal Diels–Alder adduct **2a** stereoselectively and in 85% yield. In contrast, the reaction with compound **1d** bearing only one EWG leads to selective formation of dihydro-1*H*-indene **3d**, which is formed as a result of an inverse electron demand Diels–Alder reaction (Scheme 1).

Keywords: Diels–Alder reaction; Thiophene-1,1-dioxides; EWG-groups; Cyclopentadiene; Dihydro-1*H*-indenes; Cope [3,3]-sigmatropic rearrangement; MP2 calculations; FMO coefficients.
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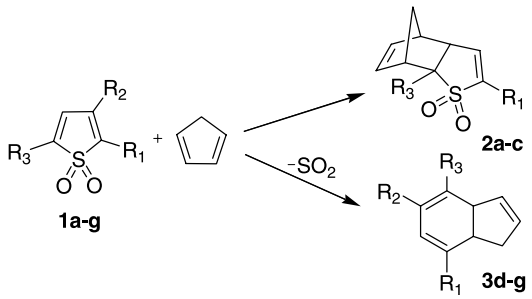


Scheme 1.

The reaction of thiophene dioxide **1a** is strikingly stereoselective. Only one stereoisomer was obtained and the structure of **2a** was unambiguously established from single crystal X-ray analysis. The ORTEP of cycloadduct **2a** is shown in Figure 1. Formation of cycloadduct with the *endo*-orientation of the heterocyclic moiety is consistent with the common *endo*-preference of Diels–Alder reactions known as Alder's rule.[9,10]

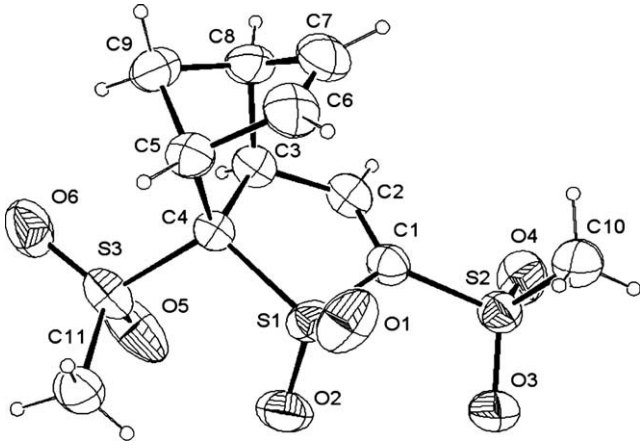
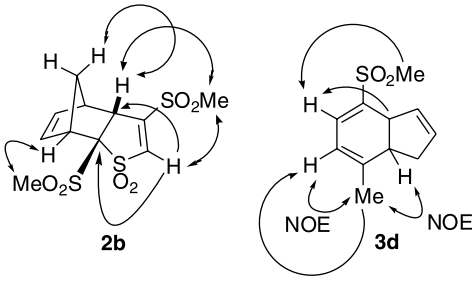


Figure 1. Molecular structure of **2a**.

We investigated a number of thiophene-1,1-dioxides with electron-withdrawing substituents in Diels–Alder reactions with cyclopentadiene. Thiophene-1,1-dioxides **1a–c** having two EWG react with CPD to form norbornene derivatives **2a–c**. On the other hand, the indene derivatives **3d–g** can be prepared exclusively if only one EWG is attached to the thiophene ring. The reaction is carried out in dichloromethane at −10–0 °C to give the respective products **2a–c** and **3d–g** in good yields.

Compounds **1b** and **1c** have been chosen to examine chemo- and regioselectivity in these cycloadditions. Compound **1b** is a very interesting model for the investigation of regiochemistry because it has two $MeSO_2$ groups in the 2,4-positions and, thus, the system contains two differently activated double bonds. Both thiophene dioxides **1b** and **1c** react with CPD 100% selectively to give only one product in each case. Thiophene dioxide **1c** reacts via the more activated double bond bearing the methylsulfonyl substituent. Recently, we found a similar pattern for this compound in reactions with linear 1,3-dienes.[9] We will explain the observed regioselectivity using the FMO theory (see Section 3, vide infra).

The structures of all isolated cycloadducts have been elucidated using ^{13}C, ^{1}H and NOESY NMR spectroscopy. The regiochemistry of **2b** and **2c** was deduced by comparison with ^{1}H NMR spectra of **2a**.[9] All cycloadducts **2a–c** are *exo*-products ($MeSO_2$ orientated towards the bridge). The *exo* stereochemistry was deduced from the value of the coupling constant $J_{3a,4}$, which is in the range 3.5–4.0 Hz for these adducts. Full assignment of the structures of **2b** and **3d** was made by ^{1}H, ^{13}C NMR, COSY, NOE, NOESY, and HMBC measurements. Moreover, NOESY experiments allowed definitive assignment of stereochemistry to the structure **2b**. Scheme 2 shows the important connectivities found in the 1D and 2D spectra of cycloadducts **2b** and **3d**.



Scheme 2. NOE NOESY double pointed arrows and HMBC (single pointed arrows) important correlations in NMR experiments of **2b** and **3d**.

Thus, thiophene-1,1-dioxides containing two strong electron-withdrawing groups (either two methylsulfonyl-or methylsulfonyl- and chloro) **1a–c** give only products **2a–c**, while the thiophene-1,1-dioxides **1d–g** give products **3d–g** (Table 1).

Table 1. Reaction of thiophene-1,1-dioxides **1a–g** with cyclopentadiene

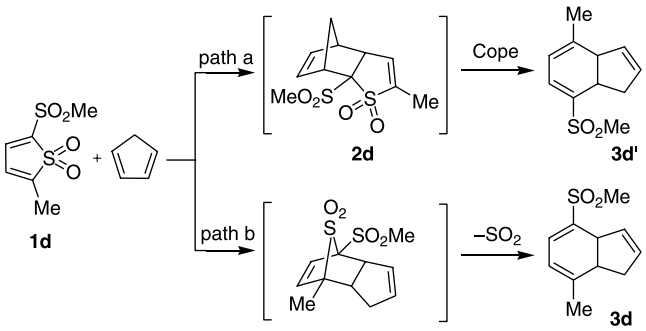
Product	R_1	R_2	R_3	Yield 2 (%)	Yield 3 (%)
a	$MeSO_2$	H	$MeSO_2$	85	
b	H	$MeSO_2$	$MeSO_2$	67	
c	Cl	H	$MeSO_2$	66	
d	Me	H	$MeSO_2$		67
e	Cl	CO_2H	Cl		71
f	Me	H	$MeCO_2$		65
g	Me	H	CN		73

In the first case thiophene dioxides **1a–c** act as dienophiles whereas thiophene-1,1-dioxides **1d–g** behave as dienes. In the latter case, the fast step of the reaction cascade is Diels–Alder reaction with inverse electron demand. In the second step, extrusion of SO_2 gives an unstable intermediate that rearranges to the final dihydro-1*H*-indene products.

Numerous literature precedents for similar electronic systems suggest the probability of [3,3]-Cope rearrangement. For example, vinyl norbomadienes and Diels–Alder adducts of cyclopentadienone undergo the Cope rearrangement to form similar structures.[11] In a similar fashion, substituted cyclopentadiene adducts of

tetrachlorothiophene dioxide (TCTD) also isomerize thermally to dihydro-1*H*-indenes derivatives after SO_2 extrusion.[11b]

Therefore, a very interesting question in the reaction of **1d–g** with cyclopentadiene is the reaction pathway. Two possibilities exist. The first involves Diels–Alder reaction of thiophene dioxide as a dienophile with a subsequent Cope rearrangement (path a). An alternative pathway is cycloaddition with inverse electron demand with thiophene dioxide acting as diene (path b). Detailed investigation of these alternatives was carried out with **1d** as a model compound. Previously, we have demonstrated 100% chemoselectivity of cycloaddition reaction of thiophene dioxide **1d** with non-cyclic dienes towards the more activated double bond. Based on the structure of cycloadduct **3d** and the results of our calculations (see Section 3), it is possible to distinguish between the two possibilities (Scheme 3). If the first mechanism (Diels–Alder reaction followed by Cope rearrangement) takes place, product **3d′** should be formed. Since the exclusive formation of **3d** (structure of which was fully confirmed by 2D NMR study) was observed, the reaction of cyclopentadiene with thiophene dioxide **1d** proceeds along path b. We believe that in all reactions of **1d–g** where indene derivatives **3d–g** are isolated, thiophene dioxides **1d–g** behave as diene components in Diels–Alder reaction.



Scheme 3.

Nevertheless, we found that compounds **2a–c** can also be transformed to indenes **3a–c** since SO_2 can be readily eliminated from adducts **2a–c** even during chromatographic purification of compounds **2a–c** or long-term storage at room temperature. A convenient procedure. for the transformation of **2a–c** into dihydro-1*H*-indenes **4a–c** includes refluxing in acetonitrile for 1–2 min (Table 2). The structure of rearrangement product **3a** was confirmed unambiguously by X-ray analysis (Fig. 2, Scheme 4).

Table 2. Preparation of dihydro-1*H*-indenes **4a–c** by rearrangement of adducts **2a–c**

Products	R_1	R_2	R_3	Yield 4 (%)
a	$MeSO_2$	$MeSO_2$	H	98
b	$MeSO_2$	H	$MeSO_2$	84
c	$MeSO_2$	Cl	H	76

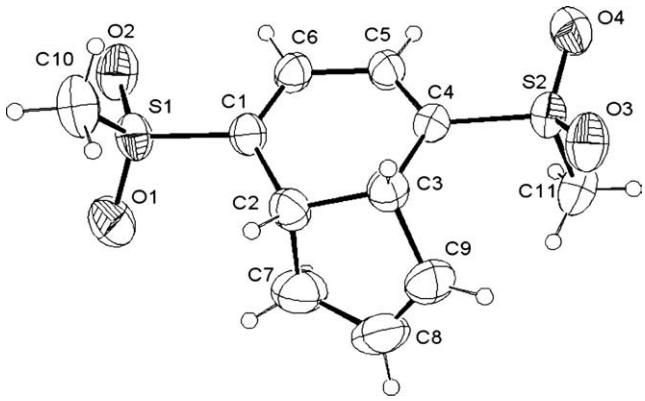
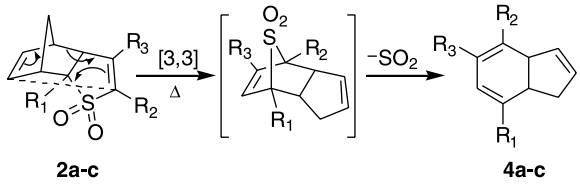


Figure 2. Molecular structure of **4a**.



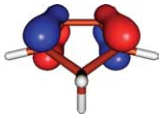
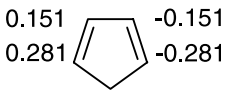
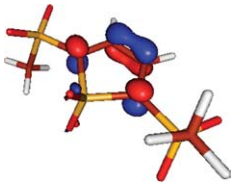
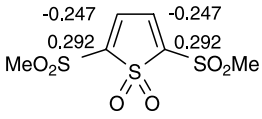
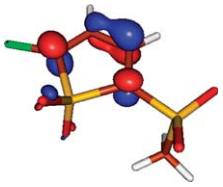
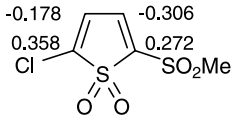
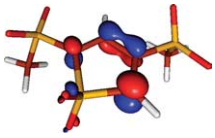
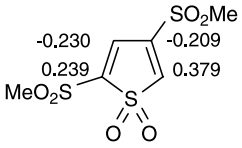
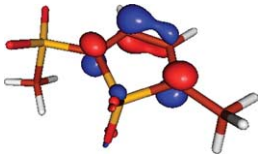
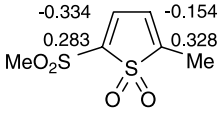
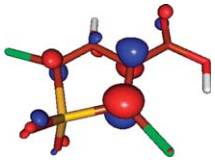
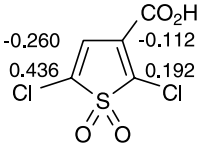
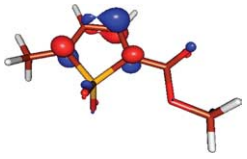
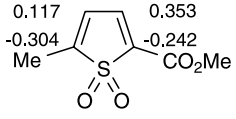
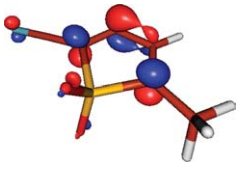
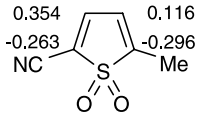
Scheme 4.

3. Computational part

We have used MP2 frontier molecular orbital (FMO) calculation to explain the selectivity of the Diels–Alder reaction of thiophene dioxides.[12] Ab initio all electron correlated resolution of identity second order Moeller–Plesset perturbation theory[13] with B11 basis sets (riMP2(full)/B11//riMP2(full)/B11) has been used to calculate FMOs of thiophene dioxides and cyclopentadiene B11 basis set followed contraction scheme: H-{2,1}/{6,2}; C, N, O-{4,3,1}/{10,7,3}; S,Cl-{5,4,2}/{14,11,6}. All calculations have been performed using PRIRODA-04 quantum chemistry package.[14] Both type of cycloadditions (normal and inverse electron demand Diels–Alder reactions) are HOMO cyclopentadiene-controlled and LUMO thiophene dioxide-controlled. The computer plot of FMO, the corresponding orbital coefficients and HOMO–LUMO energies of cyclopentadiene and thiophene dioxides are presented in Table 3. As can be seen in Table 3 the preferable formation of the **2b** in the case of the reactions of **1b** with CPD is in perfect agreement with 'large–large' molecular orbital overlap in the transition state. The computational data are in very good agreement with experimental results. The regiochemstry of the Diels–Alder reaction is fully controlled by FMO interaction both in the case of normal and in the case of inverse electron demand where the thiophene dioxide plays the role of a diene. For example, the regiochemistry of the Diels–Alder reaction with **1d** can be explained by 'large–large' molecular orbitals overlapping in the transition state (Scheme 5).

Only in the case of reaction of thiophene dioxide **1c** the predicted regiochemistry differ from experimentally observed. We believe that in this case, steric effects modulate electronic preferences. Both sides of thiophene dioxide **1c** are similarly activated, but the 2,3-side is

Table 3. FMO coefficients and energies of HOMO cyclopentadiene and LUMO of thiophene-1,1-dioxides

FMO coefficients		HOMO	LUMO
		−8.46	3.60
	 **1a**	10.62	−0.18
	 **1b**	−11.47	−0.18
	 **1c**	−11.47	−0.29
	 **1d**	−10.69	0.22
	 **1e**	−10.31	0.31
	 **1f**	−10.52	0.69
	 **1g**	−10.10	0.80

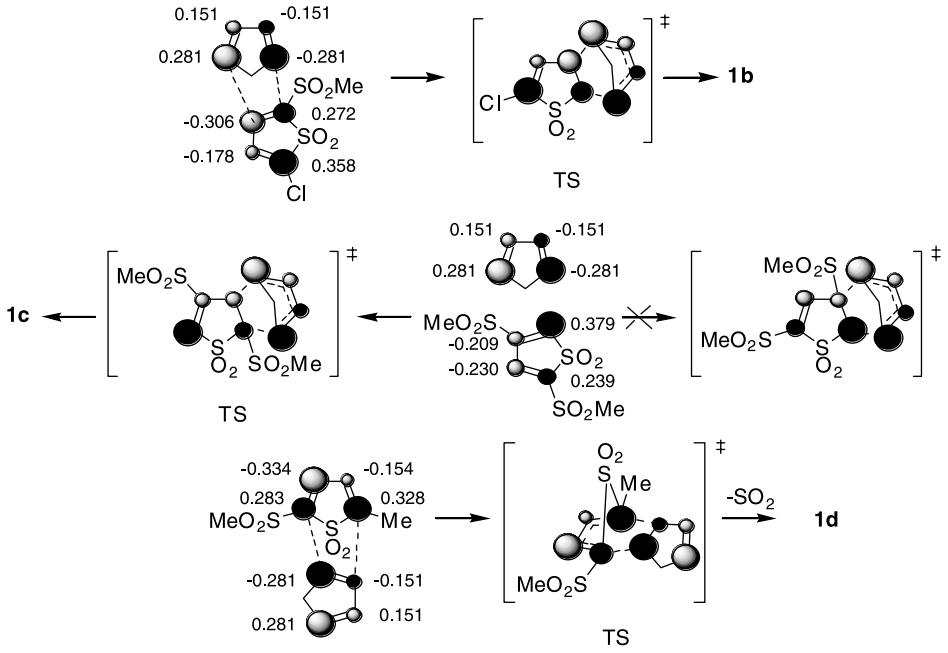
more sterically accessible to the reaction with diene. As a result, the exclusive formation of **2c** is observed.

4. Conclusion

In summary, EWG-containing thiophene-1,1-dioxides were found to be highly active dienophiles in reactions with cyclopentadiene. The reaction pathway depends strongly on the structure of thiophene dioxide, which can behave either as a diene or as a dienophile depending on the substitution pattern. MP2 calculations in conjunction with the FMO analysis successfully rationalize the regioselectivity of cycloaddition.

5. Experimental

All starting materials unless otherwise noted were commercially available. All products unless otherwise noted were identified by comparison NMR spectral and physical data with the data reported in the literature. Melting points are uncorrected. Silica gel 230–400 mesh was used for flash chromatography, all solvents were dried and purified by standard methods. ^{1}H and ^{13}C NMR spectra were recorded on a



Scheme 5.

Varian-400 MHz spectrometer in CD_3COCD_3, $CDC1_3$, and CD_3CN.

5.1. General procedure of preparation of cyclopentadiene adducts 2a–c and 3d–g

To a solution or suspension of corresponding thiophene-1,1-dioxide[5] (1 mmol) in dichloromethane (5 ml) stirred vigorously in an ice-bath was added freshly distilled cyclopentadiene (0.2 ml, 3 mmol). The mixture subsequently was stirred for 1.5 h at −10–0 °C then for an additional hour at room temperature. The clear solution was evaporated in vacuo to afford the crude cycloadducts. The crude products were purified by recrystallization or by flash chromatography using either chloroform or CH_2Cl_2 as eluent to give pure crystalline substances.

5.1.1. 2,7a-Bis(methylsulfonyl)-3a,4,7,7a-tetrahydro-4,7-methano-1-benzothiophene 1,1-dioxide (2a). Yield 85%, mp 231 °C, colorless prisms. IR (neat, υ, cm^{-1}): 1330, 1100 (SO_2). ^1H NMR (δ ppm, CD_3COCD_3): 1.76 (dd, 1H, CH_2, $J=9.4$, 3.2 Hz); 2.76 (dd, 1H, CH_2, $J=9.4$, 3.2 Hz); 3.21 (s, 3H, SO_2CH_3); 3.43 (s, 3H, SO_2CH_3); 3.47 (m, 1H, H-10); 3.83 (m, 1H, H-6); 4.33 (ddd, 1H, H-7, $J=7.1$, 3.5 Hz); 6.34 (dd, 1H, CH═CH, $J=8.5$, 3.2 Hz); 6.49 (dd, 1H, CH═CH, $J=8.5$, 3.2 Hz); 7.66 (d, 1H, H-5, $J=3.5$ Hz). ^{13}C NMR (δ ppm, CD_3COCD_3): 40.6; 43.1; 43.7; 44.0; 115.7; 131.0; 131.4; 132.2; 133.9; 147.4. Anal. Calcd for: $C_{11}H_{14}O_6S_3$ C, 39.04; H, 4.17%. Found: C, 38.79; H, 3.99%.

Crystal data of **2a**. $C_{11}H_{14}O_6S_3$, $M=338.40$, monoclinic, space group $C2/c$, $a=21.067(4)$ Å, $b=12.031(2)$ Å, $c=12.688(3)$ Å, $\beta=120.86(3)°$, $V=2760.6(10)$ $Å^3$, $Z=8$, $D_{calcd}=1.628$ g/cm^3, monochromated Mo K_α radiation, $\lambda=0.71073$ Å. A colorless prism of compound **2a** (from approximate dimensions $0.35\times0.26\times0.14$ mm), mounted on a glass fiber in random orientation, was used for X-ray data collection. Data were collected on Enraf-Nonius CAD-4 diffractometer using $\theta/2\theta$ at a temperature of 20 ± 1 °C. A total of 2270 reflections were collected of which 1624 were unique. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 calculations to give R indices (all data) $R1=0.0578$, $wR2=0.0979$ for 2270 observed independent reflections [$|F_0^2|>3\sigma(F_0)^2$, $2.03°<\Theta<24.97°$]. Crystallographic data for the structure have been deposited with Cambridge Crystallographic Database as supplementary publication number CCDC 293745.[15]

5.1.2. 3,7a-Bis(methylsulfonyl)-3a,4,7,7a-tetrahydro-4,7-methano-1-benzothiophene 1,1-dioxide (2b). Yield 67%, mp 215 °C, colorless prisms. IR (neat, υ, cm^{-1}): 1330, 1100 (SO_2). ^1H NMR (δ ppm, CD_3CN): 1.77 d (1H, CH_2, $J=9.7$ Hz); 2.32 (d, 1H, CH_2, $J=9.7$ Hz); 3.13 (s, 3H, SO_2CH_3); 3.18 (s, 3H, SO_2CH_3); 3.65 (br s, 1H); 3.73 (br s, 1H); 4.49 (d, 1H, $J=3.8$ Hz); 6.31 (dd, 1H, CH═CH, $J=5.4$, 3.3 Hz); 6.46 (dd, 1H, CH═CH, $J=5.4$, 3.3 Hz); 7.45 (s, 1H, CH═C). ^{13}C NMR (δ ppm, CD_3CN): 40.9; 46.2; 48.3; 50.2; 50.8; 69.4; 136.7; 139.4; 143.5; 146.8; 147.1. Anal. Calcd for: $C_{11}H_{14}O_6S_3$ C, 39.04; H, 4.17%. Found: C, 39.01; H, 4.08%.

5.1.3. 2-Chloro-1,1-dioxido-4,7-dihydro-4,7-methano-1-benzothien-7a(3a*H*)-yl methyl sulfone (2c). Yield 66%, mp 203 °C, pale yellow crystalline solid. IR (neat, υ, cm^{-1}): 1330, 1100 (SO_2). ^1H NMR (δ ppm, CD_3COCD_3): 2.09 (d, 1H, CH_2, $J=9.3$ Hz); 2.29 (d, 1H, CH_2, $J=9.3$ Hz); 3.12 (s, 3H, SO_2CH_3); 3.30 (m, 1H); 3.47 (s, 1H); 3.76 (t, 1H, $J=3.5$ Hz); 6.05 (dd, 1H, CH═CH, $J=5.6$, 3.1 Hz); 6.39 (dd, 1H, CH═CH, $J=5.6$, 3.1 Hz); 7.17 (d, 1H, ═C, $J=2.9$ Hz). ^{13}C NMR (δ ppm; CD_3COCD_3): 40.5; 43.2; 44.9; 45.1; 118.1; 129.8; 130.4; 131.1; 135.4; 145.0. Anal. Calcd for: $C_{10}H_{11}ClO_4S_2$ C, 40.75; H, 3.76%. Found: C, 40.79; H, 3.87%.

5.1.4. 4-Methyl-7-(methylsulfonyl)-3a,7a-dihydro-1*H*-indene (3d). Yield 67%, mp 175 °C, colorless crystalline

solid. IR (neat, υ, cm^{-1}): 1330, 1100 (SO_2). ^1H NMR (δ ppm, $CDCl_3$): 1.89 (s, 3H, CH_3); 2.42 (dd, 1H, CH_2, $J=9.4$, 3.2 Hz); 2.85 (dd, 1H, CH_2, $J=9.4$, 3.2 Hz); 2.95 (s, 3H, SO_2CH_3); 3.15 (m, 1H, CH); 3.94 (d, 1H, CH, $J=4.8$ Hz); 5.73 (d, 1H, CH=CH, $J=2.4$ Hz); 5.99 (m, 1H, CH=CH); 6.10 (m, 1H, CH=CH); 7.78 (d, 1H, CH=CH, $J=2.4$ Hz). ^{13}C NMR (δ ppm, $CDCl_3$): 22.4; 40.6; 43.1; 43.7; 44.0; 115.7; 131.0; 131.4; 132.2; 133.9; 147.4. Anal. Calcd for: $C_{11}H_{14}O_2S$ C, 62.83; H, 6.71%. Found: C, 61.80; H, 6.87%.

5.1.5. 4,7-Dichloro-3a,7a-dihydro-1*H*-indene-5-carboxylic acid (3e). Yield 71%, mp 183 °C, yellow crystalline solid. IR (neat, υ, cm^{-1}): 1330, 1100 (SO_2); 3000, 1720 (COOH). ^1H NMR (δ ppm, CD_3COCD_3): 1.76 (dd, 1H, CH_2, $J=9.4$, 3.2 Hz); 2.76 (dd, 1H, CH_2, $J=9.4$, 3.2 Hz); 3.47 (m, 1H, H-10); 3.83 (m, 1H); 4.33 (ddd, 1H, $J=7.1$, 3.5 Hz); 6.34 (dd, 1H, CH=CH, $J=8.5$, 3.2 Hz); 6.49 (dd, 1H, CH=CH, $J=8.5$, 3.2 Hz); 7.66 (d, 1H, $J=3.5$ Hz). ^{13}C NMR (δ ppm, CD_3COCD_3): 32.7; 44.8; 46.0; 120.9; 124.5; 132.1; 133.2; 135.1; 141.9; 166.8. Anal. Calcd for: $C_{10}H_8Cl_2O_2$ C, 51.98; H, 3.49. Found: C, 51.80; H, 3.52.

5.1.6. Methyl 4-methyl-3a,7a-dihydro-1*H*-indene 7-carboxylate (3f). Yield 65%, mp 191 °C, pale yellow crystalline solid. IR (neat, υ, cm^{-1}): 1330, 1100 (SO_2); 1750 (CO_2Me). ^1H NMR (δ ppm, CD_3COCD_3): 1.73 (s, 3H, CH_3), 1.93 (dd, 1H, CH_2, $J=9.4$, 3.2 Hz); 2.76 (dd, 1H, CH_2, $J=9.4$, 3.2 Hz); 3.21 (s, 3H, CO_2CH_3); 3.47 (m, 1H, H-10); 3.83 (m, 1H, H-6); 4.30 (ddd, 1H, H-7, $J=7.0$, 3.2 Hz); 6.31 (dd, 1H, CH=CH, $J=8.5$, 3.2 Hz); 6.51(dd, 1H, CH=CH, $J=8.5$, 3.2 Hz); 7.66 (d, 1H, H-5, $J=$ 3.5 Hz). ^{13}C NMR (δ ppm, CD_3COCD_3): 21.1; 34.0; 39.6; 41.3; 52.1; 115.4; 122.5; 129.3; 131.4; 131.9; 140.7; 169.6. Anal. Calcd for: $C_{12}H_{14}O_{14}$ C, 75.76; H, 7.42%. Found: C, 75.90; H, 7.57%.

5.1.7. 4-Methyl-3a,7a-dihydro-1*H*-indene-7-carbonitrile (3g). Yield 73%, mp 211 °C, colorless prisms. IR (υ, cm^{-1}): 1330, 1100 (SO_2); 2240 (CN). ^1H NMR (δ ppm) (CD_3COCD_3): 1.76 (s, 3H, CH_3); 2.79 (d, IH, CH_2, $J=9.0$, 3.1 Hz); 3.52 (m, 1H); 3.83 (m, 1H); 4.40 (ddd, 1H, $J=6.9$, 3.1 Hz); 6.39 (dd, 1H, CH=CH, $J=8.5$, 3.1 Hz); 6.51 (dd, 1H, CH=CH, $J=8.5$, 3.1 Hz); 7.72 (d, 1H, H-5, $J=$ 3.8 Hz). ^{13}C NMR (δ ppm, CD_3COCD_3): 20.1; 33.4; 36.9; 43.3; 103.7; 115.2; 116.5; 121.0; 129.8; 141.3; 142.9. Anal. Calcd for: $C_{11}H_{11}N$ C, 84.04; H, 7.05. Found: C, 84.43; H, 7.37

5.1.8. 4,7-Bis(methylsulfonyl)-3a,7a-dihydro-1*H*-indene (4a). Yield 98%, mp 221 °C, colorless prisms. IR (neat, υ, cm^{-1}): 1330, 1100 (SO_2). ^1H NMR (δ ppm, CD_3COCD_3): 2.50–2.59 (m, 1H); 2.97–3.04 (m, 1H); 3.01(s, 3H, SO_2CH_3); 3.09 (s, 3H, SO_2CH_3); 3.62–3.72 (m, 1H); 4.15–4.20 (m, 1H); 6.10–6.13 (m, 1H); 6.19–6.22 (m, 1H); 6.97 (br s, 1H); 6.98 (d, 1H, $J=0.7$ Hz). ^{13}C NMR (δ ppm, CD_3COCD_3): 37.4; 41.2; 45.1; 45.8; 128.7; 131.1; 132.0; 132.6; 136.8; 149.2. Anal. Calcd for: $C_{11}H_{14}O_4S_2$ C, 48.16; H, 5.14%. Found: C, 48.13; H, 5.09%.

Crystal data of **4a**. $C_{11}H_{14}O_4S_2$, $M=274.34$, monoclinic, space group $P2_1/n$, $a=10.436(2)$ Å, $b=11.421(2)$ Å, $c=10.691(2)$ Å, $\beta=105.71(3)°$, $V=1226.7(4)$ $Å^3$, $Z=4$, $D_{calcd}=1.486$ g/cm, monochromated Mo K_α radiation, $\lambda=0.71073$ Å. A colorless prism of compound **4a** (from approximate dimensions $0.35\times0.20\times0.17$ mm), mounted on a glass fiber in random orientation, was used for X-ray data collection. Data were collected on Enraf-Nonius CAD-4 diffractometer using $\theta/2\theta$ at a temperature of 20 ± 1 °C. A total of 1396 reflections were collected of which 1314 were unique. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 calculations to give R indices (all data) $R1=0.0261$, $wR2=0.0726$ for 1396 observed independent reflections [$|F_0^2|>3\sigma(F_0)^2$, $2.42°<\Theta<24.97°$] Crystallographic data for the structure have been deposited with Cambridge Crystallographic Database as supplementary publication number CCDC 293746.[15]

5.1.9. 5,7-Bis(methylsulfonyl)-3a,7a-dihydro-1*H*-indene (4b). Yield 84%, mp 203 °C, colorless prisms. IR (neat, υ, cm^{-1}): 1330, 1100 (SO_2). ^1H NMR (δ ppm) ($CDCl_3$): 2.50–2.57 (m, 1H); 2.93 (s, 3H, SO_2CH_3); 3.00 (s, 3H, SO_2CH_3); 3.59–3.66 (m, 1H); 3.91–3.94 (m, 1H); 5.88–5.90 (m, 1H); 6.01–6.04 (m, 1H); 6.97 (d, 1H, $J=3.6$ Hz); 7.13 (s, 1H). ^{13}C NMR (δ ppm, CD_3COCD_3): 36.4; 36.6; 41.6; 44.9; 52.3; 111.4; 121.2, 130.5; 135.7; 143.8; 148.9. Anal. Calcd for: $C_{11}H_{14}O_4S_2$ C, 48.16; H, 5.14%. Found: C, 48.20; H, 5.17%.

5.1.10. 4-Chloro-7-(methylsulfonyl)-3a,7a-dihydro-1*H*-indene (4c). Yield 76%, mp 188°C, pale yellow needles. IR (neat, υ, cm^{-1}): 1330, 1100 (SO_2). ^1H NMR (δ ppm) ($CDCl_3$): 2.71–2.78 (m, 1H); 2.88–2.96 (m, 1H); 2.93 (s, 3H, SO_2CH_3); 3.42–3.49 (m, 1H); 4.04 (dd, 1H, $J=10.1$, 1.7 Hz); 5.95–6.01 (m, 2H); 6.09 (dd, 1H, $J=5.3$, 1.2 Hz); 6.75 (dd, 1H, $J=5.3$, 1.4 Hz). ^{13}C NMR (δ ppm, CD_3COCD_3): 36.4; 41.1; 43.6; 47.3; 125.2; 131.0, 131.8; 132.6; 139.3; 140.1. Anal. Calcd for: $C_{10}H_{11}ClO_2S$ C, 52.06; H, 4.81%. Found: C, 52.1 1; H, 4.77%.

Acknowledgements

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Vinylic nucleophilic substitution in functionalized 2-vinylpyrroles: a route to a new family of stable enols

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Abstract—2-(2-Cyano-1-ethylthioethenyl)pyrroles easy exchange their ethylthio group for hydroxyl (NaOH, H_2O–methanol, 40–45 °C, 1 h) to give 2-(2-cyano-1-hydroxyethenyl)pyrroles, a new family of stable enols, in 50–94% yields. The vinylic nucleophilic substitution proceeds at the double bond of both the starting pyrroles and their cyclic isomers, 3-iminopyrrolizines. X-ray structure analysis and NMR spectra show the enols to be stabilized by exceptionally strong intramolecular H-bonding.

1. Introduction

The chemistry of pyrroles is attracting steady attention because these heterocycles play an important role in nature and, at the same time, possess rich synthetic potential making them valuable synthons for the design of novel materials for optoelectronics,[1] light-harvesting systems and photodynamic cancer diagnostics and therapy.[2] Vinylpyrroles are used for the synthesis of new heterocycles,[3,4] polymers,[5] photocatalysts and biologically active complexes.[6]

Our recent investigations into the reactivity of *C*-ethenylpyrroles with vinyl groups polarized by a push–pull combination of substituents, such as 2-(1-alkylthio-2-cyanoethenyl)pyrroles, have confirmed that these compounds possess synthetic potential, which may be utilized for a variety of synthetic needs.[4c,7]

Meanwhile, *C*-ethenylpyrroles with a hydroxyl group at the double bond still remain virtually unknown. In spite of recent successful synthesis of stable enols of furan and thiophene,[8] attempts to synthesize a corresponding representative with a 2-pyrrolyl substituent failed: instead the tautomeric ketone was isolated in 7% yield and a gamut of unidentified products.[8] Thus, the synthesis of vinylpyrroles with the enol function and their reactivity study represent important issues for both vinylpyrrole and enol chemistries.

As a rule, enols are unstable. However, their stability can be significantly increased by introduction of bulky substituents at the α-position or electron-withdrawing substituents at the β-position relative to the hydroxyl.[9]

Herein, we report on a general approach to the synthesis of a new family of stable enols of the *C*-ethenylpyrrole series based on nucleophilic substitution of an alkylthio group by hydroxyl in 2-(1-alkylthio-2-cyanoethenyl)pyrroles available from 2-pyrrolecarbodithioates.[10]

2. Results and discussion

We have found that in the presence of NaOH, the ethylthio group of *Z*-2-(2-carbamoyl-2-cyano-1-ethylthioethenyl)pyrroles **1a–d** is readily (H_2O/methanol, 1:2, 40–45 °C, 1 h) substituted by the ONa group to form enolates **2a–d** and upon acidification, the corresponding enols **3a–d** in 86–94% yield (Scheme 1).

The reaction is stereospecific (only one isomer with *syn*-disposition of hydroxyl and carbamoyl groups is formed) and chemoselective: the nitrile group is retained (although

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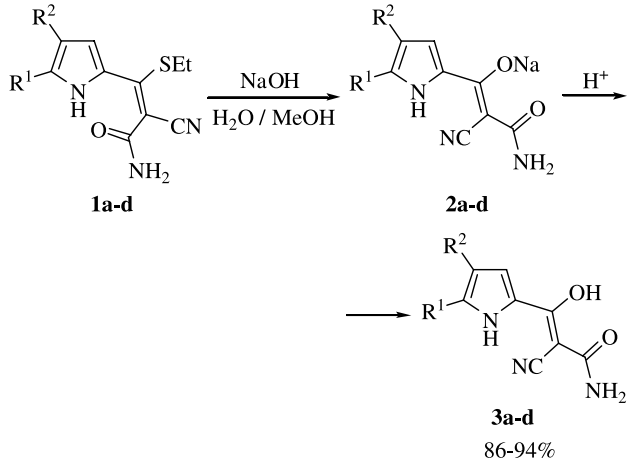
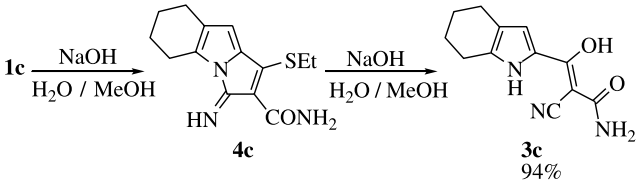


	R^1	R^2
1a-3a	*n*-Pr	E t
1b-3b	*n*-Bu	*n*-Pr
1c-3c	$(CH_2)_4$	
1d-3d	Ph	H

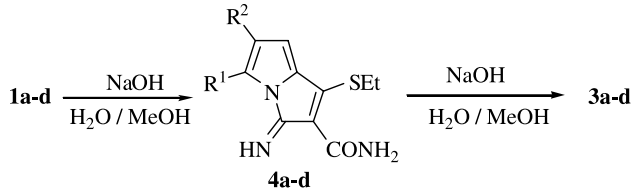
Scheme 1.

transformation of the nitrile to the carbamoyl function under the action of alkali in similar systems is known[11]). TLC monitoring shows the initial formation of intramolecular cyclization products, 3-iminopyrrolizines **4a–d**, which completely disappear by the end of the reaction. In the case of 2-(2-carbamoyl-2-cyano-1-ethylthioethenyl)-4,5,6,7-tetrahydroindole (**1c**), the corresponding 3-imino-pyrrolizine **4c** is quantitatively precipitated after addition of alkali and transformed into the enol **3c** by subsequent treatment with NaOH (H_2O/methanol, 1:2, 40–45 °C, 1 h) (Scheme 2).



Scheme 2.

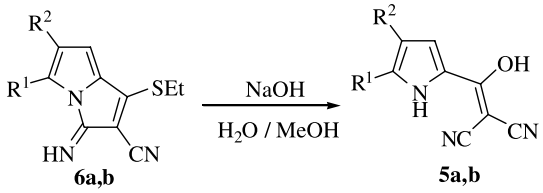
Apparently, the formation of enols **3a–d** occurs through nucleophilic substitution of the ethylthio group in 3-imino-pyrrolizines **4a–d** by hydroxide accompanied by the ring opening (Scheme 3).



	R^1	R^2
4a	*n*-Pr	Et
4b	*n*-Bu	*n*-Pr
4c	$(CH_2)_4$	
4d	Ph	H

Scheme 3.

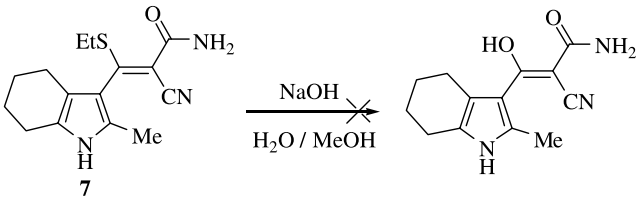
Another evidence for this reaction pathway is the synthesis of enols **5a**,**b** (78 and 90% yield, respectively) from 1-ethylthio-3-imino-2-pyrrolizinecarbonitriles **6a**,**b** under the same conditions (Scheme 4).



	R^1	R^2
5a,6a	*n*-Pr	Et
5b,6b	*n*-Bu	*n*-Pr

Scheme 4.

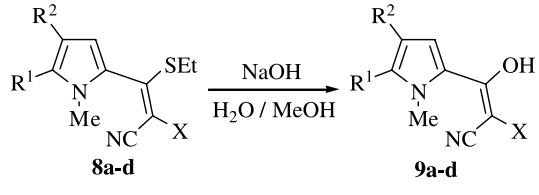
Correspondingly, no ethylthio–hydroxyl exchange in 3-(2-carbamoyl-2-cyano-1-ethylthioethenyl)-2-methyl-4,5,6,7-tetrahydroindole (**7**), which is incapable of cyclization to 3-iminopyrrolizine, is observed (Scheme 5), the starting indole **7** being recovered unchanged.



Scheme 5.

Meanwhile, pyrrolizines **4a–d** can undergo the reversible ring opening to ethenylpyrroles **1a–d**,[5b] hence the parallel direct ethylthio for hydroxide nucleophilic substitution is not ruled out. To verify this assumption, we have studied *N*-methyl-2-(2-cyano-1-ethylthioethenyl)pyrroles **8a–d** in this reaction, which are incapable of cyclization to the pyrrolizines.

Indeed, the experiments have shown that under the same conditions in these pyrroles, the expected ethylthio–hydroxyl exchange does take place to give the corresponding enols **9a–d** in 50–85% yield (Scheme 6).



Pyrrole	R^1	R^2	X
9a	H	H	CN
9b	H	H	$CONH_2$
9c	$(CH_2)_4$		CN
9d	$(CH_2)_4$		$CONH_2$

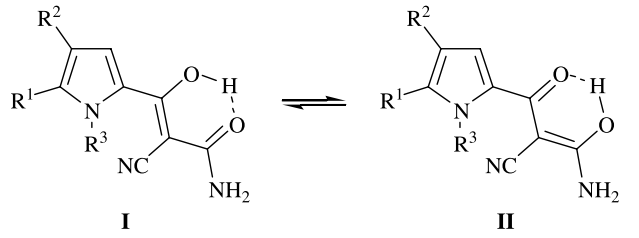
Scheme 6.

Thus, the ethylthio–hydroxyl exchange in 2-cyano-1-ethylthioethenylpyrroles **1a–d** probably proceeds along two competing routes: via 1-ethylthio-3-iminopyrrolizines **4a–d** (Scheme 3) and through the direct vinylic substitution (Scheme 6).

The stability of the tetrahydroindole **7** towards the substitution (Scheme 5) is likely to be associated with a higher electron-donating power of the tetrahydroindol-3-yl substituent compared to that of pyrrol-2-yl and steric hindrance from the 2-methyl and 4-methylene hydrogens.

A structural feature of 2-(2-carbamoyl-2-cyano-1-hydroxyethenyl)pyrroles **3a–d**, **9b**,**d** is a strong intramolecular hydrogen bond between the hydroxyl and carbonyl group showing up in the ^{1}H NMR spectra as a strong downfield-shifted signal of OH hydrogen ($CDCl_3$, 16.4–17.07 ppm).

In the ^{13}C NMR spectra of compounds **3a–d**, **9b**,**d**, the C-2 signal appears in the 66.9–69.7 ppm region, whereas that of C-1 is located at 173.0–178.0 ppm. Such positions of the signals indicate the oxygen atoms to be involved into conjugation with the double bond[12] and there is likely a tautomerism in solution[6a] (Scheme 7).



Scheme 7.

X-ray analysis of monocrystal **9b** shows that in the solid-state it exists solely in the enol form actually stabilized by intramolecular hydrogen bonding. The crystal structure consists of two crystallographically independent molecules, **A** and **B** (Fig. 1), which share same positions.

The OH hydrogen is located between two oxygen atoms at distances of 1.12 and 1.35 Å [these are average values calculated using O–H bond lengths and distances of H···O of both molecules (see Table 1)]. The hexagon O(1)C(6)C(7)C(8)O(2)H(1) has an almost flat conformation: maximum atom deflections are 0.02 and 0.03 Å for O(1A) and C(8B), respectively. Dihedral angles between the planes of the five-membered ring N(1)C(2)C(3)C(4)C(5) and hexagon O(1)C(6)C(7)C(8)O(2)H(1) are 1.2 and 4.2° for molecules **A** and **B**, respectively. Maximum atom deflections from the five-membered ring planes are 0.003 Å [atoms C(3A) and C(3B)]. Dihedral angles between the planes of hexagons and the corresponding substituents N(3)C(9)C(7) are 3.3 and 4.5° for molecules **A** and **B**, correspondingly. The N(2A) and N(2B) atom deflections from corresponding hexagon planes are 0.03 and 0.09 Å.

The length of intramolecular H-bond OH···O=C (1.35 Å) is close to that of the covalent bond O–H (1.12 Å). This, together with the C(6A)–C(7A) double bond elongation (1.393 Å) and C(7A)–C(8A) single bond shortening (1.453 Å), as well as with the flat structure of H-bound ring indicates the remarkably strong H-bonding in this case and significant contribution of the tautomer **II** (Scheme 7). The strength of the H-bond formed and the energy gain from the H-ring closure are likely to be the driving force of the unusually easy nucleophilic substitution of hydroxyl for alkylthio group.

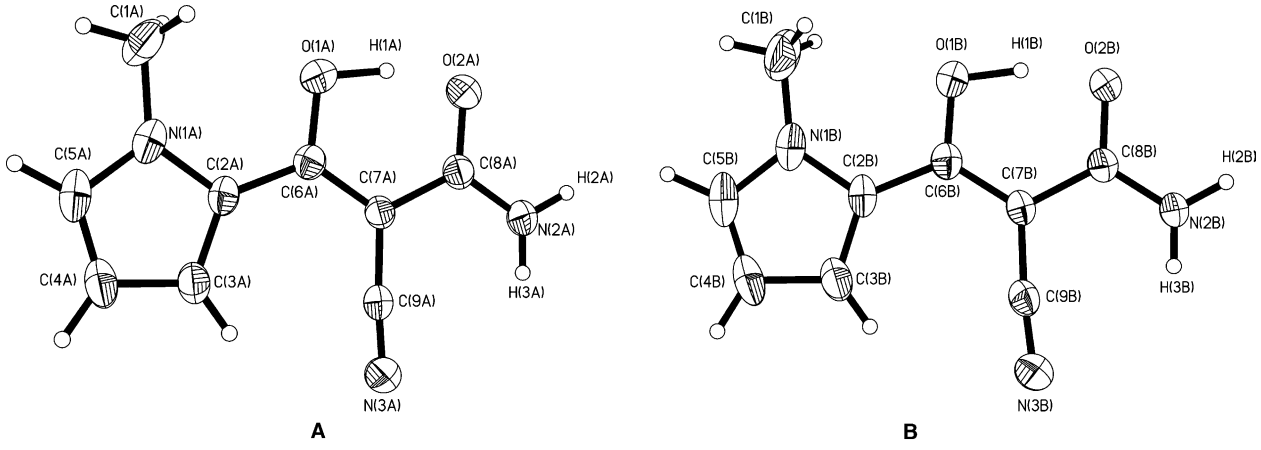


Figure 1. Labelling of atoms in the molecules of **9b**.

Table 1. Parameters of X–H···Y bonds

Contact type	*d*(X–H) (Å)	*d*(H···Y) (Å)	*D*(X···Y) (Å)	∠X–H···Y (°)
N(2AA)–H(2AA)···O(2AB)[a]	0.90(2)	2.14(2)	3.019(2)	165.9
N(2BB)–H(3BB)···N(3AB)[a]	0.88(1)	2.28(1)	3.038(2)	144.8
O(1AA)–H(1AA)···O(2AA)	1.13(2)	1.34(2)	2.435(1)	160.5
O(1BB)–H(1BB)···O(2BB)	1.10(2)	1.36(2)	2.429(1)	162.8

[a] Symmetry operation 1−x, −y, −z.

In conclusion, mild reaction conditions, availability of the starting materials and possibility of varying their structure, good preparative yields and high selectivity make our methods suitable for the synthesis of a new family of stable enols, 2-(2-cyano-1-hydroxyethenyl)pyrroles, rewarding models for basic study of reactivity.

3. Experimental

3.1. General methods

IR spectra of compounds synthesized (400–4000 cm^{-1}) were recorded in KBr pellets on a Bruker IFS-25 spectrometer. ^1H and ^{13}C NMR spectra were taken on a Bruker DPX 250 [250.13 (^1H) and 62.9 (^{13}C) MHz, respectively] and Bruker DPX 400 [400.13 (^1H) MHz] spectrometers using DMSO-d_6 as a solvent and HMDS as an internal reference. Structures of products were determined using 2D ^1H and ^{13}C NMR spectral techniques. ^{13}C resonance assignment was done with the use of 2D HSQC[13] and HMBC[14] heteronuclear correlation methods.

2D HMBC pulse sequence spectra were recorded using delays optimized for the direct $^1J(H,C)=145$ Hz and far $^nJ(H,C)=5$ Hz coupling constants.

Analyses of reaction mixtures and purity control of the compounds obtained were done using TLC on Silufol UV-254 plates with 10:1 diethyl ether/ethanol mixture as an eluent.

The starting 2-(2-cyano-1-ethylthioethenyl)pyrroles including previously unknown **8a–d** were synthesized from pyrrole-2-carbodithioates according to a published procedure.[10]

The X-ray study was performed at room temperature on an Enraf-Nonius CAD-4 ($\omega/2\theta$ scanning, Mo K_α emission, graphite monochromator). Crystalline structure was obtained by direct methods and subsequent Fourier syntheses using SHELXS-97 software.[15] The structure was fine-tuned using least-square technique in anisotropic full-matrix approximation for all non-hydrogen atoms in SHELXL-97 software.[15] Coordinates of hydrogen atoms were determined experimentally and improved in isotropic approximation.

Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with Cambridge Crystallographic Data Centre as supplementary publication number CCDC 277477. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; (fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk).

3.2. Synthesis of 2-(2-cyano-1-ethylthioethenyl)-1-methylpyrroles

3.2.1. 2-(2,2-Dicyano-1-ethylthioethenyl)-1-methylpyrrole (8a). To a stirred (0.5 h) suspension of malononitrile (0.59 g, 9 mmol) and KOH (0.50 g, 9 mmol) in 30 mL of DMSO, methyl 1-methyl-2-pyrrolecarbodithioate[16] (1.03 g, 6 mmol) was added. The reaction mixture was heated at 110 °C for 1.5 h, cooled to room temperature, then ethyl iodide (0.94 g, 6 mmol) was added. After stirring for 2 h, the mixture was diluted with brine (100 mL) and extracted with diethyl ether. After removal of ether, the residue was recrystallized from ethanol to afford 1.11 g (85%) of pyrrole **8a**, yellow solid, mp 68 °C. [Found: C, 60.75; H, 4.89; N, 19.45; S, 14.80. $C_{11}H_{11}N_3S$ requires C, 60.80; H, 5.00; N, 19.34; S, 14.76%]; ν_{max} (KBr): 2217, 1533, 1481, 1472, 1454, 1402, 1374, 1306, 1267, 1246, 1054, 945, 750, 688, 605 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.00 (dd, $^3J=2.6$ Hz, $^4J=1.7$ Hz, 1H, 5-H), 6.69 (dd, $^3J=3.9$ Hz, $^4J=1.7$ Hz, 1H, 3-H), 6.30 (dd, $^3J=3.9$, 2.6 Hz, 1H, 4-H), 3.75 (s, 3H, NMe), 2.79 (q, $^3J=7.3$ Hz, 2H, SCH_2), 1.22 (t, $^3J=7.3$ Hz, 3H, Me); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 168.6 (=*C*-SEt), 131.8 (5-C), 125.2 (2-C), 118.9 (3-C), 114.0 (CN), 113.4 (CN), 110.8 (4-C), 76.3 [=*C*$(CN)_2$], 35.4 (NMe), 29.7 (SCH_2), 14.4 (SCH_2*Me*).

3.2.2. 2-(2-Carbamoyl-2-cyano-1-ethylthioethenyl)-1-methylpyrrole (8b). To a stirred (0.5 h, room temperature) suspension of cyanoacetamide (0.76 g, 9 mmol) and KOH (0.50 g, 9 mmol) in 30 mL of DMSO, methyl 1-methyl-2-pyrrolecarbodithioate (1.03 g, 6 mmol) was added. The reaction mixture was heated at 110 °C for 1.5 h and cooled to room temperature. Ethyl iodide (0.94 g, 6 mmol) was added and stirring was continued for 2 h. The mixture was then diluted with brine (100 mL). Crystalline solid formed was filtered off, dried and recrystallized from ethanol to give 1.06 g (75%) of pyrrole **8b**, *E*/*Z* isomers, 1:5, yellow solid, mp 192 °C. [Found: C, 56.23; H, 5.63; N, 17.90; S, 13.53. $C_{11}H_{13}N_3OS$ requires C, 56.15; H, 5.57; N, 17.86; S, 13.63%]; ν_{max} (KBr): 3394, 3296, 3176, 2210, 1681, 1617, 1546, 1501, 1382, 1306, 1236, 939, 793, 732 cm^{-1}; (*E*)-isomer: ^1H NMR (400 MHz, DMSO-d_6): δ 6.90 (dd, $^3J=2.6$ Hz, $^4J=1.7$ Hz, 1H, 5-H), 6.42 (dd, $^3J=3.8$ Hz, $^4J=1.7$ Hz, 1H, 3-H), 6.28 (dd, $^3J=3.8$, 2.6 Hz, 1H, 4-H), 5.46 (br s, 2H, $CONH_2$), 3.55 (s, 3H, NMe), 2.70 (q, $^3J=7.5$ Hz, 2H, SCH_2), 1.17 (t, $^3J=7.5$ Hz, 3H, Me); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 162.8 (*C*=O), 161.3 (=*C*SEt), 128.4 (5-C), 124.5 (2-C), 116.7 (CN), 114.7 (3-C), 112.1 (4-C), 102.5 [=*C*(CN)$CONH_2$], 34.5 (NMe), 28.5 (SCH_2), 14.6 (SCH_2*Me*); (*Z*)-isomer: ^1H NMR (400 MHz, $CDCl_3$): δ 6.80 (dd, $^3J=2.7$ Hz, $^4J=1.7$ Hz, 1H, 5-H), 6.29 (dd, $^3J=3.8$ Hz, $^4J=1.7$ Hz, 1H, 3-H), 6.23 (dd, $^3J=3.8$, 2.7 Hz, 1H, 4-H), 6.17 (br s, 1H, $CONH_2$), 5.65 (br s, 1H, $CONH_2$), 3.61 (s, 3H, NMe), 2.38 (q, $^3J=7.5$ Hz, 2H, SCH_2), 1.13 (t, $^3J=7.5$ Hz, 3H, Me); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 168.4 (=*C*SEt), 163.9 (*C*=O), 126.0 (2-C), 125.6 (5-C), 117.3 (CN), 112.1 (3-C), 109.0 (4-C), 101.7 [=*C*(CN)$CONH_2$], 34.2 (NMe), 28.1 (SCH_2), 13.6 (SCH_2*Me*).

3.2.3. 2-(2,2-Dicyano-1-ethylthioethenyl)-1-methyl-4,5,6,7-tetrahydroindole (8c). To a stirred (0.5 h, room temperature) suspension of malononitrile (0.59 g, 9 mmol) and KOH (0.50 g, 9 mmol) in 30 mL of DMSO, methyl 1-methyl-4,5,6,7-tetrahydroindole-2-carbodithioate, prepared according to[16] (1.35 g, 6 mmol) was added. The reaction mixture was heated at 110 °C for 1.5 h and cooled to room temperature. Ethyl iodide (0.94 g, 6 mmol) was added and stirring was continued for 2 h. The mixture was then diluted with brine (100 mL) and extracted with ether. After removal of ether, the residue was recrystallized from ethanol to give 1.27 g (78%) of tetrahydroindole **8c**, yellow

solid, mp 104–105 °C. [Found: C, 66.21; H, 6.44; N, 15.60; S, 11.79. $C_{15}H_{17}N_3S$ requires C, 66.39; H, 6.31; N, 15.48; S, 11.81%]; ν_{max} (KBr): 2209, 1491, 1448, 1380, 1356, 1306, 1267, 1221, 1171, 1086, 955, 816, 736, 639 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.64 (s, 1H, 3-H), 3.62 (s, 3H, NMe), 2.95 (q, $^3J=7.3$ Hz, 2H, SCH_2), 2.65 (m, 2H, 7-CH_2), 2.55 (m, 2H, 4-CH_2), 1.88 (m, 2H, 5-CH_2), 1.78 (m, 2H, 6-CH_2), 1.28 (t, $^3J=7.3$ Hz, 3H, Me); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 165.9 (=*C*-SEt), 142.7 (5-C), 125.6 (2-C), 122.0 (4-C), 119.6 (3-C), 115.4 (CN), 114.6 (CN), 71.7 [=*C*$(CN)_2$], 32.3 (NMe), 30.2 (SCH_2), 23.0 (7-CH_2), 22.9 (5-CH_2), 22.8 (6-CH_2), 22.6 (4-CH_2), 14.4 (SCH_2*Me*).

3.2.4. 2-(2-Carbamoyl-2-cyano-1-ethylthioethenyl)-1-methyl-4,5,6,7-tetrahydroindole (8d). To a stirred (0.5 h, room temperature) suspension of cyanoacetamide (0.76 g, 9 mmol) and KOH (0.50 g, 9 mmol) in 30 mL of DMSO, methyl 2-(1-methyl-4,5,6,7-tetrahydroindole)-carbodithioate (1.16 g, 6 mmol) was added. The reaction mixture was heated at 110 °C for 1.5 h and cooled to room temperature. Ethyl iodide (0.94 g, 6 mmol) was added and stirring was continued for 2 h. The mixture was then diluted with brine (100 mL). Crystalline solid formed was filtered off, dried and recrystallized from ethanol to give 1.46 g (84%) of pyrrole **8d**, *E*/*Z* isomers, 1:5, yellow solid, mp 183–184 °C. [Found: C, 62.14; H, 6.88; N, 14.46; S, 11.28. $C_{15}H_{19}N_3OS$ requires C, 62.26; H, 6.62; N, 14.52; S, 11.08%]; ν_{max} (KBr): 3403–3180, 2206, 1688, 1655, 1589, 1512, 1380, 1077, 942, 921, 617 cm^{-1}; (*E*)-isomer: ^1H NMR (400 MHz, $CDCl_3$): δ 6.45 (s, 1H, 3-H), 5.35 (br s, 2H, $CONH_2$), 3.40 (s, 3H, NMe), 2.90 (q, $^3J=7.5$ Hz, 2H, SCH_2), 2.61 (m, 2H, 7-CH_2), 2.55 (m, 2H, 4-CH_2), 1.90 (m, 2H, 5-CH_2), 1.78 (m, 2H, 6-CH_2), 1.17 (t, $^3J=7.5$ Hz, 3H, Me); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 164.0 (*C*=O), 160.0 (=*C*SEt), 139.0 (5-C), 124.9 (2-C), 120.6 (4-C), 116.1 (3-C), 112.4 (CN), 98.2 [=*C*(CN)$CONH_2$], 30.8 (NMe), 29.4 (SCH_2), 23.0 (7-CH_2), 22.9 (5-CH_2), 22.8 (6-CH_2), 22.6 (4-CH_2), 14.4 (SCH_2*Me*); (*Z*)-isomer: ^1H NMR (400 MHz, $CDCl_3$): δ 6.19 (s, 1H, 3-H), 5.09 (br s, 2H, $CONH_2$), 3.48 (s, 3H, NMe), 2.50 (q, $^3J=7.5$ Hz, 2H, SCH_2), 2.61 (m, 2H, 7-CH_2), 2.55 (m, 2H, 4-CH_2), 1.90 (m, 2H, 5-CH_2), 1.78 (m, 2H, 6-CH_2), 1.13 (t, $^3J=7.5$ Hz, 3H, Me); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 167.4 (=*C*SEt), 164.4 (*C*=O), 134.4 (5-C), 124.9 (2-C), 118.9 (4-C), 112.4 (CN), 112.4 (3-C), 99.28 [=*C*(CN)$CONH_2$], 30.8 (NMe), 28.6 (SCH_2), 23.0 (7-CH_2), 22.9 (5-CH_2), 22.8 (6-CH_2), 22.6 (4-CH_2), 13.7 (Me).

3.3. Reaction of 2-(2-cyano-1-ethylthioethenyl)pyrroles 1a–d, 8a–d with NaOH/H_2O

General procedure for the synthesis of enols **3a–d**, **9a–d**. To a heated (45 °C) solution of pyrrole **1a–d** (0.5 mmol) in methanol (2 mL) a solution of NaOH (40 mg, 1 mmol) in water (1 mL) was added, and the mixture was stirred at the same temperature for 1 h. In the case of pyrrole **1c** 3-iminopyrrolizine **4c** is quantitatively precipitated after addition of alkali was isolated and characterised (it's ^1H NMR, IR spectra and mp were identical to those determined earlier[7b]).

Methanol was removed under vacuum, the residue was dissolved in H_2O (10 mL) and acidified with diluted HCl (up to pH 3). Crystalline solid formed was filtered off, washed with water and recrystallized from benzene.

3.3.1. 2-(2-Carbamoyl-2-cyano-1-hydroxyethenyl)-4-ethyl-5-*n*-propylpyrrole (3a). Yield: 114 mg (92%); beige solid, mp 148–149 °C. [Found: C, 62.97; H, 7.18; N, 16.95. $C_{13}H_{17}N_3O_2$ requires C, 63.14; H, 6.93; N, 16.99%]; ν_{max} (KBr): 3483, 3298, 3190, 2200, 1654, 1602, 1559, 1478, 1442, 1362, 1336, 1319, 1284, 1209, 1144, 1003, 953, 833, 769, 720, 660, 527, 457 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 16.45 (s, 1H, OH), 8.97 (br s, 1H, NH), 7.33 (d, $^4J=2.5$ Hz, 1H, 3-H), 5.92 (br s, 1H, $CONH_2$), 5.45 (br s, 1H, $CONH_2$), 2.58 (m, 2H, 1-CH_2 of propyl), 2.42 (q, $^3J=7.3$ Hz, 2H, CH_2 of ethyl), 1.64 (m, 2H, CH_2 of propyl), 1.16 (t, $^3J=7.3$ Hz, 3H, CH_3 of ethyl), 0.96 (t, $^3J=7.4$ Hz, 3H, CH_3 of propyl); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 174.2 ($CONH_2$ or=C–OH), 173.7 (=C–OH or $CONH_2$), 138.1 (5-C), 125.1 (4-C), 121.9 (2-C), 118.8 (CN), 116.7 (3-C), 66.9 [=*C*(CN)$CONH_2$], 27.0 (1-C of propyl), 22.9 (2-C of propyl), 18.3 (1-C of ethyl), 15.4 (Me of ethyl), 13.7 (Me of propyl).

3.3.2. 5-Butyl-2-(2-carbamoyl-2-cyano-1-hydroxyethenyl)-4-*n*-propylpyrrole (3b). Yield: 127 mg (92%); orange solid, mp 154–155 °C. [Found: C, 65.33; H, 7.70; N, 15.40. $C_{15}H_{21}N_3O_2$ requires C, 65.43; H, 7.69; N, 15.26%]; ν_{max} (KBr): 3446, 3416, 3344, 3195, 2198, 1660, 1604, 1555, 1473, 1441, 1366, 1141, 1000, 828, 776, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 16.43 (s, 1H, OH), 8.93 (br s, 1H, NH), 7.30 (d, $^4J=2.4$ Hz, 1H, H-3), 5.92 (br s, 1H, $CONH_2$), 5.43 (br s, 1H, $CONH_2$), 2.60 (m, 2H, 1-CH_2 of butyl), 2.36 (m, 2H, 1-CH_2 of propyl), 1.57 (m, 4H, 2-CH_2 of butyl and propyl), 1.37 (m, 2H, 3-CH_2 of butyl), 0.93 (m, 6H, CH_3 of butyl and propyl); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 174.2 ($CONH_2$ or =C–OH), 173.6 (=C–OH or $CONH_2$), 138.6 (5-C), 123.2 (4-C), 121.9 (2-C), 118.8 (CN), 117.3 (3-C), 66.9 [=*C*(CN)$CONH_2$], 31.8 (2-C of butyl), 27.3 (1-C of propyl), 24.8 (1-C of butyl), 23.9 (2-C of propyl), 21.9 (3-C of butyl), 13.8 (Me of propyl and butyl).

3.3.3. 2-(2-Carbamoyl-2-cyano-1-hydroxyethenyl)-4,5,6,7-tetrahydroindole (3c). Yield: 109 mg (94%); dark orange solid, mp 203–204 °C. [Found: C, 61.94; H, 5.20; N, 17.85. $C_{12}H_{13}N_3O_2$ requires C, 62.3; H, 5.67; N, 18.17%]; ν_{max} (KBr): 3379, 3216, 2203, 1652, 1609, 1479, 1348, 1276, 1212, 1128, 828, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 16.43 (s, 1H, OH), 8.91 (br s, 1H, NH), 7.27 (d, $^4J=1.9$ Hz, 1H, H-3), 5.95 (br s, 1H, $CONH_2$), 5.42 (br s, 1H, $CONH_2$), 2.64 (m, 2H, 7-CH_2), 2.53 (m, 2H, 4-CH_2), 1.79 (m, 4H, 5,6-CH_2); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 174.1 ($CONH_2$ or= C–OH), 173.9 (=C–OH or $CONH_2$), 136.5 (5-C), 120.3 (4-C), 122.5 (2-C), 118.7 (CN), 117.3 (3-C), 66.9 [=*C*(CN)$CONH_2$], 23.0 (7-CH_2), 22.6 (5-CH_2), 22.4 (6-CH_2), 22.4 (4-CH_2).

3.3.4. 2-(2-Carbamoyl-2-cyano-1-hydroxyethenyl)-5-phenylpyrrole (3d). Yield: 109 mg (86%); dark yellow solid, mp 193–194 °C. [Found: C, 66.64; H, 4.59; N, 16.45. $C_{14}H_{11}N_3O_2$ requires C, 66.40; H, 4.38; N, 16.59%]; ν_{max} (KBr): 3469, 3441, 3334, 3276, 3205, 2203, 1652, 1593, 1559, 1469, 1455, 1295, 1072, 790, 756, 687 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 16.69 (s, 1H, OH), 9.47 (br s, 1H, NH), 7.59 (m, 3H, Ph-H_o, 3-H), 7.44 (m, 2H, Ph-H_m),

7.36 (m, 1H, Ph-H_p), 6.68 (m, 1H, 4-H), 6.02 (br s, 1H, $CONH_2$), 5.48 (br s, 1H, $CONH_2$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.03 (br s, 1H, NH), 9.25 (br s, 1H, $CONH_2$), 7.77 (m, 2H, Ph-H_o), 7.32 (m, 2H, Ph-H_m), 7.16 (m, 1H, Ph-H_p), 7.00 (m, 1H, H-3), 6.49 (m, 1H, H-4), 6.00 (br s, 1H, $CONH_2$); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 174.8 ($CONH_2$ or =C–OH), 173.8 (=C–OH or $CONH_2$), 137.8 (5-C), 131.0 (Ph-C_i), 128.8 (Ph-C_m), 127.7 (Ph-C_p), 127.0 (CN), 125.5 (Ph-C_o), 109.1 (4-C), 119.3 (2-C), 117.0 (3-C), 69.1 [=*C*(CN)$CONH_2$].

3.3.5. 2-(2,2-Dicyano-1-hydroxyethenyl)-1-methylpyrrole (9a). Yield: 43 mg (50%); dark-pink solid, mp 114–115 °C ($CHCl_3$). [Found: C, 62.01; H, 4.77; N 24.08. $C_9H_7N_3O$ requires C, 62.42; H, 4.07; N, 24.26%]; ν_{max} (KBr): 3114, 2227, 2205, 1550, 1508, 1482, 1401, 1388, 1292, 1244, 1212, 1069, 892, 858, 760, 698 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.83 (dd, ^3J=2.4 Hz, ^4J=1.8 Hz, 1H, 5-H), 6.70 (dd, ^3J=3.8 Hz, ^4J=1.8 Hz, 1H, 3-H), 5.96 (dd, ^3J=3.8, 2.4 Hz, 1H, 4-H), 3.72 (s, 3H, NMe); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 178.5 (=C–OH), 129.2 (2-C), 127.0 (5-C), 122.3 (CN), 120.9 (CN), 113.7 (3-C), 106.3 (4-C), 47.7 [=*C*$(CN)_2$], 36.0 (NMe).

3.3.6. 2-(2-Carbamoyl-2-cyano-1-hydroxyethenyl)-1-methylpyrrole (9b). Yield: 81 mg (85%); yellow solid, mp 161–162 °C (MeOH). [Found: C, 57.01; H, 4.97; N, 22.08. $C_9H_9N_3O_2$ requires C, 56.54; H, 4.74; N, 21.98%]; ν_{max} (KBr): 3410, 3347, 3286, 2200, 1667, 1603, 1559, 1532, 1466, 1407, 1353, 1236, 1158, 1108, 1070, 1024, 743, 669 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 18.38 (s, 1H, OH), 8.23 (br s, 1H, $CONH_2$), 7.23 (m, 1H, 3-H), 7.11 (m, 1H, 5-H), 6.19 (m, 1H, 4-H), 5.62 (br s, 1H, $CONH_2$), 3.83 (s, 3H, NMe); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 178.0 (=C–OH), 174.3 ($CONH_2$), 131.5 (5-C of pyrrole), 124.9 (CN), 118.6 (3-C), 118.4 (2-C), 108.4 (4-C), 69.7 [=*C*(CN)$CONH_2$], 37.5 (NMe). Crystal data for **9b** $C_9H_9N_3O_2$: M_w=191.19, a=11.859(2) Å, b=13.6319(2) Å, c=11.870(2) Å, α=90°, β=102.67(1), γ=90°, V=1872.1(5), D_{calcd}=1.36 g cm^{-3}, μ=0.100 mm^{-1}, Z=8, monoclinic, space group $P2_1/c$, λ=0.71073, 3028 total reflections, 2872 total independent reflections, 2347 total reflections with [$F_0>4\sigma(F_0)$], number of parameters 326, $(2\theta)_{max}$=47.94°, interval for h $-13\le h\le 13$, interval for k $0\le k\le 15$, interval for l $0\le l\le 13$, R-factor ($F_0>4\sigma(F_0)$) 0.030.

3.3.7. 2-(2-Dicyano-1-hydroxyethenyl)-1-methyl-4,5,6,7-tetrahydroindole (9c). Yield: 68 mg (60%); orange solid, mp 181–182 °C. [Found: C, 58.80; H, 5.56; N, 18.55. $C_{13}H_{13}N_3O$ requires C, 68.71; H, 5.77; N, 18.49%]; ν_{max} (KBr): 3140, 2223, 2205, 1533, 1514, 1468, 1456, 1409, 1253, 1223, 1200, 1100, 1073, 1028, 870, 810, 714 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.56 (s, 1H, 3-H), 3.47 (s, 3H, NMe), 2.49 (m, 2H, 7-CH_2), 2.35 (m, 2H, 4-CH_2), 1.70 (m, 2H, 6-CH_2), 1.59 (m, 2H, 5-CH_2); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 175.4 (=C–OH), 137.2 (5-C), 124.0 (2-C), 118.2 (CN), 117.9 (4-C), 117.3 (CN), 115.6 (3-C), 52.8 [=*C*$(CN)_2$], 32.1 (NMe), 27.9 (7-CH_2), 22.5 (4-CH_2), 22.4 (6-CH_2), 21.6 (5-CH_2).

3.3.8. 2-(2-Carbamoyl-2-cyano-1-hydroxyethenyl)-1-methyl-4,5,6,7-tetrahydroindole (9d). Yield: 103 mg (84%); orange solid, mp 191–192 °C (benzene). [Found: C, 63.56; H, 6.06; N, 16.90. $C_{13}H_{15}N_3O_2$ requires C, 63.66; H, 6.16; N, 17.13%]; ν_{max} (KBr): 3351, 3197, 2934, 2844, 2204, 1669, 1602, 1546, 1469, 1430, 1381, 1351, 1194, 1153, 1080, 1058, 985, 828, 810, 778, 707, 673 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 16.92 (s, 1H, OH), 7.30 (s, 1H, 3-H), 5.99 (br s, 1H, $CONH_2$), 5.47 (br s, 1H, $CONH_2$), 3.69 (s, 3H, NMe), 2.56 (m, 2H, 7-CH_2), 2.50 (m, 2H, 4-CH_2), 1.84 (m, 2H, 6-CH_2), 1.71 (m, 2H, 5-CH_2); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 177.2 (=C–OH or $CONH_2$), 174.5 ($CONH_2$ or =C–OH), 138.5 (5-C), 123.3 (2-C), 118.9 (CN), 118.5 (4-C), 116.8 (3-C), 68.5 [=*C*(CN)$CONH_2$].

3.4. Reaction of 1-(ethylthio)-3-imino-3*H*-pyrrolizines 4c, 6a,b with NaOH/H_2O

General procedure for the synthesis of enols **3c**, **5a**,**b**. To a heated (45 °C) solution (suspension in the case of 3-iminopyrrolisine **4c**) of 1-(ethylthio)-3-imino-3*H*-pyrrolizine (**6a** or **6b**) (0.5 mmol) in methanol (2 mL) a solution of NaOH (40 mg, 1 mmol) in water (1 mL) was added, and the mixture was stirred at the same temperature for 1 h. After the end of the reaction, methanol was removed under vacuum, the residue was dissolved in H_2O (10 mL), acidified with diluted HCl (up to pH 3). Crystalline solid formed was filtered off, washed with water and recrystallized from benzene.

3.4.1. 2-(2,2-Dicyano-1-hydroxyethenyl)-4-ethyl-5-*n*-propylpyrrole (5a). Yield: 89 mg (78%); yellow solid, mp 150–151 °C. [Found: C, 68.22; H, 6.57; N, 18.31. $C_{13}H_{15}N_3O$ requires C, 68.10; H, 6.59; N, 18.33%]; ν_{max} (KBr): 3280, 2233, 2214, 1580, 1526, 1481, 1205, 1158, 1009, 853, 837 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.07 (s, 1H, NH), 6.85 (d, ^4J=2.7 Hz, 1H, 3-H), 5.71 (br s, 1H, OH), 2.52 (m, 2H, CH_2 of propyl), 2.36 (q, ^3J=7.5 Hz, 2H, CH_2 of ethyl), 1.53 (m, 2H, CH_2 of propyl), 1.08 (t, ^3J=7.5 Hz, 3H, Me of ethyl), 0.86 (t, ^3J=7.0 Hz, 3H, Me of propyl); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 172.0 (=C–OH), 137.2 (5-C), 124.6 (4-C), 122.4 (2-C), 118.9 (CN), 117.6 (CN), 116.1 (3-C), 48.9 [=*C*$(CN)_2$], 27.1 (1-C of propyl), 22.8 (2-C of propyl), 18.3 (1-C of ethyl), 15.4 (Me of ethyl), 13.7 (Me of propyl).

3.4.2. 5-*n*-Butyl-2-(2,2-dicyano-1-hydroxyethenyl)-4-*n*-propylpyrrole (5b). Yield: 116 mg (90%); yellow crystals, mp 148–149°C. [Found: C, 69.80; H, 7.48; N, 16.10. $C_{15}H_{19}N_3O$ requires C, 70.01; H, 7.44; N, 16.33%]; ν_{max} (KBr): 3287, 2225, 2204, 1579, 1525, 1509, 1479, 1340, 1221, 1192, 1155, 1073, 861, 837 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.98 (br s, 1H, NH), 7.32 (m, 1H, 3-H), 2.61 (m, 2H, CH_2 of butyl), 2.36 (m, 2H, CH_2 of propyl), 1.56 (m, 4H, CH_2 of propyl and butyl), 1.36 (m, 2H, CH_2 of butyl), 0.93 (m, 6H, CH_3 of propyl and butyl); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 173.0 (=C–OH), 136.7 (5-C), 123.6 (2-C of pyrrole), 122.1 (4-C), 119.9 (CN), 118.6 (CN), 115.8 (3-C), 47.8 [=*C*$(CN)_2$], 31.8 (1-C of butyl), 27.3 (1-C of propyl), 24.8 (2-C of propyl), 23.9 (2-C of butyl), 21.9 (3-C of butyl), 13.80 (Me of butyl and propyl).

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Studies in stereoselective [2+2]-cycloadditions with dichloroketene

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Abstract—During the investigation of the reaction of dichloroketene with cyclic enoxy-lactones and acyclic enoxy-ester substrates it was found that only the acylic variants effectively participated in the [2+2]-cycloaddition. Although a complete understanding of the reasons for this are lacking, molecular mechanics calculations do suggest that an out of plane twist of the cabonyl group in the acyclic compounds may be partially responsible. After screening a variety of chiral auxiliaries it was found that useful levels of diastereoselectivity (2.6–10.8:1) could be obtained in this cycloaddition reaction when (*R*)-2,2-diphenylcyclopentanol was used as the chiral auxiliary.

1. Introduction

(+)-Cryptosporiopsin **1**, a chlorine containing fungal metabolite was isolated in 1969 from *Sporormia affinis*, *Cryptosporiopsis* sp. and *Periconia macrospinosa*.

Bio-assay[1–3] of this natural product against a variety of wood-rotting and other filamentous fungi[2] demonstrated that (+)-cryptosporiopsin was comparable to nystatin in its antibiotic activity. These results strongly suggested that cryptosporiopsin could be used to control microorganisms associated with tree diseases and wood decay.[2]

The first total synthesis of racemic cryptosporiopsin was reported by Strunz and Court in 1973 by a formally biomimetic route.[4] Although the synthesis had the merit of being very concise, the key ring contraction step was a capricious and low yielding process. An improved synthesis was reported by Henderson and Hill a decade later, however, it was rather lengthy.[5]

As a result of the difficulties in the original syntheses, Kabanyane and co-workers[6] recently revisited this natural product, and in 2000, accomplished a new concise synthesis of related chlorine containing fungal metabolites. This synthesis consisted of a total of eight steps and involved a [2+2]-cycloaddition between dichloroketene and a silyl enol ether as one of the key steps. The new strategy provided a quick and efficient route to the carbon framework of this group of natural products, and importantly, in contrast to the original ring contraction approach, opened the way to an asymmetric synthesis. In this context, it should be noted that in a quantitative bioassay, the racemic product was only half as active as the natural material, suggesting that the dextrorotatory enantiomer alone was endowed with the bioactivity.[4]

Upon examination of the Kabanyane route, it is apparent that the crucial stereochemistry is introduced at the [2+2]-cycloaddition stage (Fig. 1). In considering methods to achieve an asymmetric [2+2]-cycloaddition, two options presented themselves; the chirality could be introduced via a substrate-based approach, that is, an optically pure chiral auxiliary covalently bonded to the ketene or the olefin, or, alternatively, the chirality could be derived from an additive such as a chiral Lewis acid. The literature contains examples of each of these strategies. [7–10] Excellent enantioselectivity was achieved in some of the methods described, however, none of the substrate types employed seemed to be directly applicable per se, to the synthesis of our target chlorine

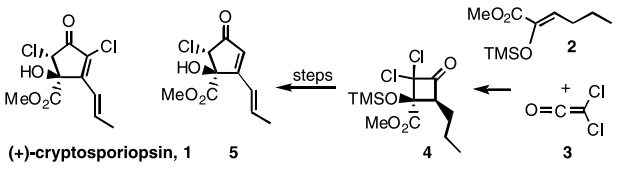

Figure 1. Attempted Kabanyane route to the synthesis of cryptosporiopsin.

Keywords: [2+2]-Cycloaddition; Diastereoselective; Chiral auxiliaries; Dioxolanones.
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containing metabolites since the substrates studied were either of limited scope or under functionalized.

To produce an optically enriched cyclobutanone like **4** (Fig. 1), it was clear that an optically pure equivalent of the enol-ether ester **2** (a tri-substituted olefin) must be employed as the precursor. To achieve this end, we realized that some type of rigid cyclic substrate such as a dioxolanone or lactone might be exploited with advantage, or drawing upon Greene[11] and Kabanyane's[6] work, presumably a suitable acyclic chiral analogue of **2** could be developed (Fig. 2). The following work describes our efforts in trying to design an appropriate substrate to achieve this goal.

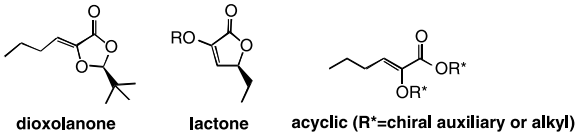
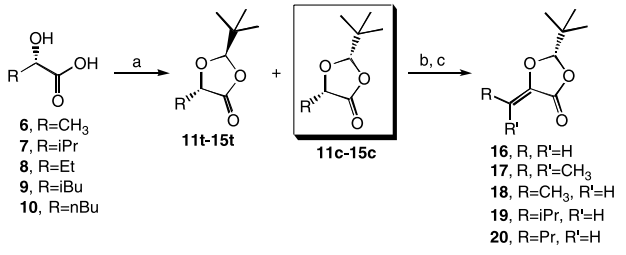


Figure 2. Potential substrates for asymmetric [2+2]-cycloaddition.

2. Results and discussion

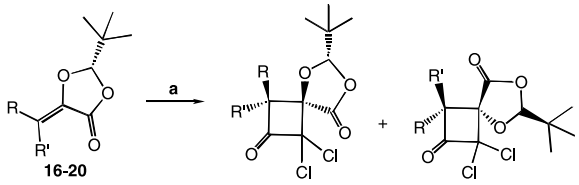
It is well established that asymmetric induction tends to be much higher when the 'chiral inducer' is held in a fixed position. With this in mind, it appeared that optimum selectivity could be obtained by using a chiral dioxolanone substrate possessing the appropriate latent functionality, such as that depicted in Figure 2. Compounds of this type are well known in the literature and have served as excellent substrates in [4+2]-cycloadditions.[12] Examples of their use in [2+2]-cycloaddition chemistry, however, are unknown so it was hoped that dichloroketene would be sufficiently reactive to add to the dioxolanone olefin with similar excellent stereoselectivity.

To initiate this study, a variety of chiral α-hydroxy acids, **6–10**, were condensed with pivaldehyde[13] under acidic catalysis to give a mixture of *cis* and *trans*-dioxolanones **11–15** (**c** and **t**) (4–8:1, 66–74% yields) with the cis-isomer always predominating (Scheme 1). The two isomers in each case were easily separated by silica gel column chromatography. The stereochemistry of the major diastereomer was assigned as the *cis*-dioxolanone by NOE difference experiments and by comparing with literature results.[13] The *cis*-dioxolanones were readily transformed[14] into the requisite olefins **16–20** by bromination with *N*-bromosuccinimide (NBS, 97–99% yields) followed by dehydrobromination with DBU (30–65% yields).



Scheme 1. (a) $(CH_3)_3CCHO$, H_2SO_4, *p*TSA, pentane, Δ; (b) NBS, CCl_4, Δ; (c) DBU, C_6H_6, rt.

With five different olefin substrates made, each was subjected to standard cycloaddition conditions (Cl_3CCOCl, Zn, Et_2O, rt)[15] (Scheme 2). The results are summarized in Table 1. The cyclobutanone obtained from cycloaddition with the dioxolanone olefin **16**, derived from lactic acid **6**, was a 2:1 diastereomeric mixture, as clearly evidenced by ^1H NMR. Thus, for example, the protons on the cyclobutanone gave rise to an AB quartet with the signals for the major diastereomer at δ 3.82 and 3.64 and those for the minor one at δ 2.95 and 2.75. Given the low stereoselectivity one comes to the disappointing conclusion that the *t*-butyl group is not providing facial discrimination to the same extent as in other cycloaddition chemistry. This was very surprising.



Scheme 2. (a) Cl_3CCOCl, Zn, Et_2O, 0 °C–rt.

Table 1. Cycloaddition results of the dioxolanone olefins

Olefin dioxolanone	R′	R″	dr	Yield (%)
16	H	H	2:1	33
17	Me	Me	—	0
18	Me	H	—	0
19	*i*Pr	H	1.4:1	13
20	*n*Pr	H	>95:1	7

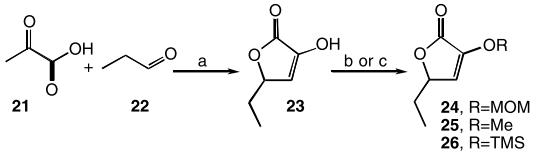
The olefin **17** derived from 2-hydroxy-3-methylbutanoic acid did not undergo cycloaddition; only starting dioxolanone olefin was recovered. This was perhaps not astonishing since **17** is a tetra-substituted alkene and therefore much less reactive towards cycloaddition. Like **17**, the tri-substituted alkene **18** also failed to react. On the other hand, tri-substituted dioxolanone olefins **19** and **20** reacted with dichloroketene to give cycloadducts in very modest yields, ranging from poor (1.4:1) to excellent (>95:5), diastereoselectivity. The reason for the differences in stereoselectivity with these tri-substituted alkenes was not obvious, however, the alkyl chain may confer a preference for a particular rotamer that gives rise to higher levels of selectivity.

Although the dioxolanone olefin cycloaddition approach was conceptually attractive, all cycloadditions were plagued with extremely low yields (0–33%). Attempts to eliminate side reactions[16] in the cycloaddition by using solvents such as dichloromethane or hexane proved fruitless. Additionally, efforts to increase the yield of the cycloadduct by using an excess of trichloroacetyl chloride and zinc, added all at once or in aliquots over a period of time, or using ultrasound and TMSCl[17] also failed.

To explain the reluctance of these cyclic olefins to participate in [2+2]-cycloadditions it was considered that geometric constraints in the rigid ring system might prevent appropriate alignment of the lone pair on the ether oxygen for activation of

the olefin. To gain insight, energy minimization of **20** was done at the MMFF94 (molecular mechanics force field 1994) level. The results indicate that the five-membered ring was essentially planar and co-planar with the olefin (a 2° deviation from co-planarity was not considered significant). Accordingly, adequate donation indeed appeared to be possible.

Although it was initially believed that sterics might not affect reactivity in a major way, it appears that in fact it does. While the unsubstituted dioxolanone **16** gave the highest yield of cycloadduct, tri-substituted olefins **19** and **20** gave diminished product whereas tetra-substituted olefin **17** did not react at all. Coupled with this steric effect was the fact that all alkene substrates studied here contained an alkyl enol-ether, rather than a trimethylsilyloxy-derivative as used by Kabanyane.[6] This change, although minor, might have contributed to the reduced reactivity of these olefins since the ether oxygen would be expected to have less electron density, and therefore be less reactive. To investigate these subtle electronic effects, an alternative cyclic substrate **24** was considered (Scheme 3). This substrate separated the two electronic factors that were potentially influencing the cycloaddition, namely the electron withdrawing nature of the carbonyl and the electron donating nature of the acyclic enol ether.



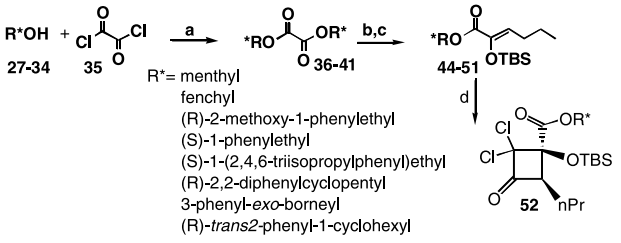
Scheme 3. (a) Concd H_2SO_4, 0 °C–rt; (b) P_2O_5, dimethoxymethane, rt; (c) AgO, CH_3I, CH_3CN, Δ.

Although several asymmetric routes to this substrate can be envisaged, including oxidation of the Mori lactone[18] or degradation of D-ribose[19] or D-mannose,[20] it was considered prudent to test the reactivity of this type of compound first using racemic models. Accordingly, pyruvic acid was condensed with propanal under acidic conditions[21] to give lactone **23** in 17% yield (Scheme 3). Attempts to protect the hydroxyl group under basic conditions resulted in the complete decomposition of starting material. Fortunately the MOM-ether, **24**, and methyl-ether, **25**, could be formed under acid conditions in 57 and 38% yields, respectively.[22,23] Unfortunately, all endeavors aimed at producing silyl ether **26** under acidic[24] or neutral[25,26] conditions failed. Subjection of lactones **24** and **25** to the standard cycloaddition conditions once again proved unsuccessful and only the starting material was recovered.

Given the reluctance of both classes of cyclic compounds investigated above to undergo cycloaddition, it appeared that the electron withdrawing ability of the carbonyl group was overriding any electron donating effect of the ether oxygen. Simple molecular mechanics (MMFF94) calculations on the Kabanyane alkene, methyl 2-trimethylsilyloxyhex-2-enoate, showed that the carbonyl carbon was twisted slightly out of plane (ca. 5°), and although this was only a minimal amount of twisting it would help render the alkene less electron deficient. This twisting effect is not possible in the dioxolanones or lactones. That said, the effect of the silyl group could not be completely dismissed. These results seemed to indicate that we could not take advantage of a rigid cyclic structure to achieve enhanced chiral induction and were thus limited to the use of chiral modifications of the acyclic Kabanyane alkene.

In view of the demonstrated efficiency of dichloroketene cycloaddition to 2-silyloxy-2-enoate esters[6] and because of potential difficulties associated with introduction of chirality into the enol ether moiety in these compounds, we were encouraged to focus on installation of chirality in the ester group. In order to furnish the appropriate compounds the respective α-keto esters had to be first generated.

There were numerous literature reports that described the synthesis of α-keto esters,[27–31] many of which we initially used to generate the various chiral compounds, **44–51**, shown in Scheme 4. However, we eventually found that these compounds could be most conveniently produced via a Grignard addition to oxalates **36–43**.[32] The oxalates themselves were generated in a straightforward manner from oxalyl chloride **35** and enantioenriched alcohols **27–34**. Once synthesized the α-keto esters were then converted to their respective silyl enol ethers following Kabanyane's protocol[6] (Scheme 4). Notably in each case only the *Z*-alkene was formed, this was important since it helped simplify analysis of the cycloaddition products.



Scheme 4. (a) Pyridine, CH_2Cl_2, rt, 24 h; (b) 1.5 equiv *n*BuMgCl, THF, 40 °C, 2 h; (c) TBSCl, DBU, C_6H_6, Δ, 2 h; (d) Cl_3CCOCl, Zn, Et_2O, 0 °C–rt.

With the chiral ester silyl enol ethers synthesized, their utility in the asymmetric [2+2]-cycloaddition reaction was probed. The TBS-enol ethers (**44–51**) were allowed to react, with dichloroketene to give cycloadducts in yields ranging from 31 to 88% (Table 2). The dramatic rise in yield realized with these substrates leant credence to our earlier observations and predictions concerning the influence of electronic effects. Examination of Table 2 shows that simple terpene based auxiliaries gave moderate levels of selectivity, 1-phenylethanol and 'synthetic' auxiliary derived

Table 2. Cycloaddition results of the enoxy-ester olefins

Entry	R*	dr	Yield (%)
1	Menthyl	1.7:1	88
2	Fenchyl	2.2:1	77
3	(*R*)-2-Methoxy-1-phenylethyl	1.3:1	35
4	(*S*)-1-Phenylethyl	1.2:1	31
5	(*S*)-1-(2,4,6-Triisopropylphenyl)ethyl	4:1	83
6	(*R*)-2,2-Diphenylcyclopentyl	7.5:1	79
7	3-Phenyl-isoborneol	2.4:1	31
8	(*R*)-*trans* 2-Phenyl-1-cyclohexyl	2.8:1	65

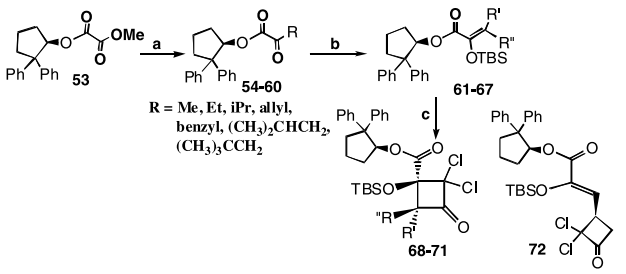
substrates ranged from poor (entries 3 and 4) to moderate (entries 7 and 8) to acceptable levels of selectivities (entries 5 and 6).

It was observed that the *trans* 2-phenyl-1-cyclohexanol derivative, entry 8, was consumed immediately after complete addition of trichloroacetyl chloride. This was not observed in any of the other cycloadditions: in fact, all other cycloadditions took 18–24 h to go to completion. Since this cycloaddition occurred at a significantly greater rate, a temperature study was done to see if the stereoselectivity could be improved. It was found that at 0 °C a 3.5:1 dr was obtained while at −30 °C no observable reaction was detected, even after 24 h.

It was gratifying to find that Denmark's diphenylcyclopentanol auxiliary,[33] present in entry 6, gave acceptable levels of asymmetric induction. Since the cycloadduct was crystalline, simple recrystallization from hexane increased the diasteromeric ratio to 11.5:1. Although not pursued, presumably further recrystallizations would produce a diastereomerically pure cycloadduct.

Since it was not evident how important a role the silyloxy function played in determining the course of the cycloaddition, either in rate or stereoselectivity, a quick investigation into the use of other silyl groups was pursued. Upon changing to the less robust trimethylsilyl ether (TMS) no change in reaction rate or stereoselectivity was observed. However, when the *t*-butyldiphenylsilyl ether (TBDPS) was used only starting silyl enol ether was recovered. This was surprising but presumably meant that both faces of the alkene were now effectively blocked from reaction.

Given the success of the diphenylcyclopentyl auxiliary it remained to be seen how limited the scope of this cycloaddition was. To probe this a variety of substrates were generated that explored both the electronic and steric limitations of this reaction (Scheme 5). When compounds **61**–**67** were subjected to the standard cycloaddition several trends became abundantly clear (Table 3). First, successful cycloaddition is only possible if the olefin is not overly hindered. For example, when the olefin is tetrasubstituted or R is very bulky (*t*Bu) then either no reaction is observed or the rate is greatly diminished. Second, if alternative alkenes are present in the molecule then they react in preference to the enoxy-alkene. Third, additional conjugation of the enoate with a phenyl group completely inactivates the reaction. Finally, diastereomeric ratios improve as R



Scheme 5. (a) 1.5 equiv RMgCl, THF, 40 °C, 2 h; (b) TBSCl, DBU, C_6H_6, Δ, 2 h; (d) Cl_3CCOCl, Zn, Et_2O, 0 °C–rt.

Table 3. Cycloaddition results of different alkyl substituted dioxolanone olefins

Olefin dioxolanone	R′	R″	dr	Yield (%) (product)
61	H	H	3.5:1	80 (**68**)
62	H	Me	3.8:1	68 (**69**)
63	Me	Me	—	No reaction
64	H	Vinyl	2.6:1	44 (**72**)
65	H	Ph	—	No reaction
66	H	*i*Bu	10.8:1	94 (**70**)
67	H	*t*Bu	8.2:1	32 (**71**)

increases in size, at least to a point. This suggests that the observed good levels of diasteroselectivities in this reaction are the result of a balancing of nonbonding steric interactions between the chiral auxiliary, the silyl ether and the alkyl group attached to the alkene.

Molecular modeling of the (*R*)-2,2-diphenylcyclopentyl chiral enol ether† using the MMFF94 force field was performed in order to ascertain some type of transition state model. These calculations allowed prediction that *Si*-face addition of dichloroketene should be more favorable than the *Re*-face addition when using (*R*)-2,2-diphenylcyclopentanol as the chiral auxiliary (Fig. 3). Although there were many low energy conformations (approximately 20 within 2.5 kcal/mol) 15 of them adopted the *s*-trans conformation with all having the *Si*-face more accessible for cycloaddition. Of the remaining five low energy conformations they all had the *s*-cis arrangement, again with the *Si*-face most accessible.

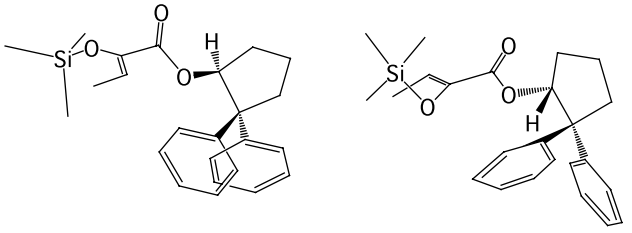


Figure 3. Molecular mechanics (MMFF94) calculated structures of *S*-diphenylcyclopentyl TMS-enol ester.

Of particular interest in these calculations was that a dihedral angle of 139° between the carbonyl and the carbon–carbon double bond (O═C–C═C) was observed. This twist, reducing the electron-attracting effect of the ester carbonyl, once again helps to explain the enhanced reactivity of this alkene towards [2+2]-cycloaddition. Although these calculations were not performed on the other enoxy-ester models we believe that the same subtleties exist, but to varying degrees, and thus account for the reactivities and stereoselectivities that were observed.

Lastly, the absolute stereochemistry was shown to coincide with our transition state model by conversion[34]

† A modified version of enoxy-ester **62** was used in order to simplify the calculations; the TBS-group was replaced with a TMS-group.

of cycloadduct **52** into (−)-cryptosporiopsin, a known natural product.[35] Since the (−)-enantiomer was generated this indeed meant that dichloroketene added to the *Si*-face of **49**, consistent with the molecular mechanics calculations.

3. Conclusion

During the investigation of the reaction of dichloroketene with cyclic enoxy-lactones and acyclic enoxy-ester substrates it was found that only the acylic variants effectively participated in the [2+2]-cycloaddition. Although complete understanding of this discrepancy is lacking at this time, molecular mechanics calculations do suggest that an out of plane twist of the cabonyl group (up to 41° see Fig. 3) in the acyclic compounds may be partially responsible. An additional factor may be the nucleophilicty of the enoxy oxygen since only the silyloxy derivatives gave efficient reaction. Acyclic silyl enol ether substrates bearing a chiral auxiliary on the ester proved to be viable candidates for the production of optically enriched cycloadducts with diastereomeric ratios ranging from 1.5–10.8:1. Effort to further improve the diastereoselection is currently in progress.

4. Experimental

4.1. General experimental procedures

All reactions except those stated otherwise were performed under inert atmospheres of either argon or nitrogen in flame dried glassware (Pyrex). All solvents were dried according to established procedures prior to use.[36] Standard techniques were used in handling air sensitive reagents. All commercially available reagents and solvents were used without further purification. All oxalates required for the preparation of 2-enoxy-esters **44**–**51** and **61**–**67** were synthesized according to literature,[32] Silicycle Ultra Pure Silica Gel was used for all flash chromatography. All ^{1}H and ^{13}C NMR spectra were performed on a Varian UNITY 400 MHz or Varian (INOVA 300 MHz) spectrometer. Optical rotation measurements were taken on a Perkin-Elmer 241 Polarimeter using the Na lamp. All IR spectra were recorded on a Bruker IFS 25 instrument and all mass spectra were run on a Kratos MS50 instrument and were done under electron impact conditions at 80 eV unless stated otherwise.

4.2. General preparation of olefin dioxolanone, 16–20

A mixture of α-hydroxy acid (10 mmol), pivaldehyde (2.2 mL, 20 mmol), *p*TSA (50 mg), and concd H_2SO_4 (2 drops) in pentane (70 mL) was heated to reflux with azeotropic removal of the water using a Dean Stark apparatus. After complete reaction, the mixture was diluted with ether and washed with H_2O (1×), brine (1×), dried over $MgSO_4$ and the solvent evaporated. Purification by SiO_2 chromatography using hexane/ethyl acetate as eluant furnished the *cis*-dioxolanones as colorless oils.

N-Bromosuccinimide (1.33 g, 7.4 mmol) in carbon tetrachloride (20 mL) was combined with *cis*-dioxolanone (5 mmol) in carbon tetrachloride (5 mL). The reaction mixture was heated at reflux for 3 h, cooled and then filtered. The solvent was removed in vacuo to provide the bromo-dioxolanones as pale green oils of sufficient purity to be used directly in the next step.

To a solution of brominated dioxolanone (5 mmol) in benzene (20 mL) was added DBU (0.85 mL, 5.75 mmol) dropwise over 5 min at rt. After complete addition, the mixture was stirred for 20 min then filtered and the solvent was removed. The crude product was purified by SiO_2 chromatography using 20:1 hexane/ethyl acetate to furnish the olefins as pale yellow oils.

4.2.1. (*S*)-2-*tert*-Butyl-5-methylene-[1,3]dioxolan-4-one, 16. 39% overall yield from (*S*)-lactic acid. ^{1}H NMR ($CDCl_3$): δ 1.00 (s, 9H), 4.86 (d, J=2.6 Hz, 1H), 5.13 (d, J=2.6 Hz, 1H), 5.44 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 22.8, 35.9, 90.8, 144.2, 162.5. IR (NaCl plates, cm^{-1}): 3020, 2972, 2940, 2883, 1796, 1670, 1475, 1311, 1133, 992. MS: m^{+}/z=156.0787 (calculated 156.0787). $[\alpha]_D^{22}$ −1.9 (*c* 1.1, CH_2Cl_2).

4.2.2. (*Z*)-(*S*)-2-*tert*-Butyl-5-ethylidene-[1,3]dioxolan-4-one, 17. 22% yield from (*S*)-2-hydroxybutanoic acid. ^{1}H NMR ($CDCl_3$): δ 0.97 (s, 9H), 1.77 (d, J=7.8 Hz, 3H), 5.42 (s, 1H), 5.60 (q, J=7.6 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 10.7, 22.8, 35.8, 105.0, 109.5, 139.2, 163.0. IR (NaCl plates, cm^{-1}): 2970, 2924, 2876, 1798, 1702, 1478, 1342, 1240, 1134, 1086, 968. MS: m^{+}/z=170.0941 (calculated=170.0943). $[\alpha]_D^{22}$ +33.7 (*c* 1.55, CH_2Cl_2).

4.2.3. (*Z*)-(*S*)-2-*tert*-Butyl-5-(2-methylpropylidene)-1,3-dioxolan-4-one 18. 44% yield from (*S*)-2-hydroxy-4-methylpentanoic acid. ^{1}H NMR ($CDCl_3$): δ 0.92 (s, 9H) 1.79 (s, 3H), 2.04 (s, 3H), 5.29 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 16.7, 19.2, 23.0, 35.8, 108.3, 121.5, 133.4, 162.9. IR (NaCl plates, cm^{-1}): 2958, 2912, 2876, 1774, 1678, 1490, 1276, 1216, 1158, 1074, 980, 730. MS: m^{+}/z=184.1094 (calculated 184.1099). $[\alpha]_D^{25}$ −16.6 (*c* 2.7, CH_2Cl_2).

4.2.4. (*Z*)-(*S*)-2-*tert*-Butyl-5-(3-methylbutylidene)-1,3-dioxolan-4-one, 19. 21% yield from (*S*)-2-hydroxy-5-methylhexanoic acid. ^{1}H NMR ($CDCl_3$): δ 0.99 (s, 9H) 1.10 (d, J=6.1 Hz, 6H), 2.72 (d of heptet, J=4.4, 6.2 Hz, 1H), 5.42 (s, 1H), 5.49 (d, J=4.5 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 22.1, 23.0, 25.8, 36.2, 109.7, 116.9, 137.0, 163.7. IR (NaCl plates, cm^{-1}): 2958, 2918, 2854, 1794, 1690, 1478, 1362, 1302, 1216, 1150, 1076, 988, 732. MS: m^{+}/z= 198.1254 (calculated=198.1256). $[\alpha]_D^{25}$ −34.0 (*c* 1.72, CH_2Cl_2).

4.2.5. (*Z*)-(*S*)-2-*tert*-Butyl-5-butylidene-[1,3]dioxolan-4-one 20. 31% yield from (*S*)-2-hydroxyhexanoic acid. ^{1}H NMR ($CDCl_3$): δ 0.95 (t, J=7.3 Hz, 3H), 0.98 (s, 9H), 1.49 (heptet, J=7.4 Hz, 2H), 2.19 (q, J=7.1 Hz, 2H), 5.42 (s, 1H) 5.59 (t, J=7.7 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 13.9, 22.0, 23.0, 27.5, 36.1, 109.7, 110.2, 138.7, 163.4. IR (NaCl plates, cm^{-1}): 2978, 2918, 2854, 1794, 1690, 1478, 1406, 1368, 1310, 1208, 1090, 974, 740. MS: m^{+}/z=198.1260 (calculated=198.1256). $[\alpha]_D^{25}$ −28.4 (*c* 1.02, CH_2Cl_2).

4.2.6. Preparation of 5-ethyl-3-methoxymethoxy-5*H*-furan-2 one, 24. In a flask cooled in an ice bath was put

concd H_2SO_4 (30 mL) followed by a mixture of pyruvic acid (7.85 mL, 0.114 mol) and propanal (8.19 mL, 0.11 mol) dropwise over 30 min. The temperature of the reaction mixture was maintained below 5 °C. After complete addition the dark colored mixture was poured into cold H_2O (60 mL) and extracted with ether (3×). The combined organic extracts were washed with H_2O, 5% HCl, brine, dried over $MgSO_4$ and solvent evaporated. The residue was purified by SiO_2 chromatography (3:1 hexane/ethyl acetate) to give lactone **23** (2.54 g, 17%) as a brown oil.

To a solution of enol lactone **23** (500 mg) and CH_2Cl_2 (20 mL) was added dimethoxymethane (23 mL, 264 mmol) and P_2O_5 (1.95 g, 17.0 mmol). The reaction mixture was stirred overnight, diluted with ether and then poured into a cold Na_2CO_3 solution. The organic layer was then washed with brine, dried over Na_2SO_4 and the solvent evaporated. The oily residue was purified by SiO_2 chromatography (3:1 hexane/ethyl acetate) to give MOM-lactone **24** (510 mg, 76%) as a tan colored oil. ^{1}H NMR ($CDCl_3$): δ 1.00 (t, J=7.5 Hz, 3H), 1.76 (dq, J=7.2, 11.0 Hz, 2H), 3.50 (s, 3H), 4.90 (dt, J=1.9, 6.3 Hz, 1H), 5.11 (s, 2H) 6.38 (d, J=1.9 Hz, 1H). ^{13}C NMR ($CDC1_3$): δ 8.8, 27.2, 56.6, 80.0, 96.0, 121.0, 143.7, 168.2. IR (NaCl plates, cm^{-1}): 2958, 2901, 2832, 1772, 1654, 1456, 1236, 1156, 1128, 1084, 958. MS: m^+/z=172.0739 (calculated=172.0736).

4.3. General preparation of TBS-enoxy esters 44–51 and 60–67

A mixture of α-keto ester[32] (1.9 g, 5.5 mmol) and TBS-Cl (1.0 g, 6.6 mmol) in THF (35 mL) was added dropwise to a solution of DBU (1.24 mL, 8.3 mmol) in THF (5 mL). The reaction mixture was stirred at rt for 12 h then diluted with ether and filtered through Celite®. The filtrate was washed with cold HCl (5%, 2×), H_2O (1×), brine (1×), dried over $MgSO_4$ and the solvent removed in vacuo. Purification by SiO_2 chromatography provided silyl enol ethers **44–51** and **61–67**.

4.3.1. (*Z*)-(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexy 2-*tert*-butyldimethylsilyloxyhex-2-enoate, 44. Colorless oil, 65% yield. ^{1}H NMR ($CDCl_3$): δ 0.15 (s, 3H), 0.17 (s, 3H), 0.75 (d, J=6.8 Hz, 3H), 0.89 (t, J=6.3 Hz, 3H), 0.92 (d, J=7.5 Hz, 3H), 0.94 (d, J=7.4 Hz, 3H), 0.96 (s, 9H), 1.02 (m, 2H), 1.43 (q, J=2.7 Hz, 1H), 1.68 (m, 2H), 1.88 (m, 1H), 2.00 (m, 1H), 2.17 (m, 2H), 4.73 (t of d, J=4.4, 10.9 Hz, 1H), 5.98 (t, J=7.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ −4.3, −4.2, 14.0, 16.4, 18.6, 20.6, 22.0, 22.1, 23.3, 25.9, 26.3, 27.8, 31.4, 34.3, 40.8, 47.1, 74.8, 122.5, 140.9, 164.5. IR (NaCl plates, cm^{-1}): 2936, 2854, 1712, 1648, 1464, 1150, 834. MS: [$m^+/z-C_6H_{15}Si$]=267.1960 (calculated=267.1964). $[\alpha]_D^{25}$ −36.5 (*c* 2.6, EtOH).

4.3.2. (*Z*)-(1*R*)-1,3,3-Trimethylbicyclo[2.2.1]heptan-2-yI 2-*tert*-butyldimethylsilyloxyhex-2-enoate, 45. Colorless oil, 42% yield. ^{1}H NMR ($CDCl_3$): δ 0.17 (s, 3H), 0.17 (s, 3H), 0.78 (s, 3H), 0.94 (t, J=7.4 Hz, 3H), 0.97 (s, 9H), 1.05 (s, 2H), 1.11 (s, 2H), 1.21 (m, 2H), 1.4 (m, 3H), 1.59 (d of d, J=1.7, 10.3 Hz, 1H), 1.74 (m, 3H), 2.19 (q, J=7.4 Hz, 2H), 4.44 (d, J=1.9 Hz, 1H), 6.00 (t, J=7.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ −4.3, 13.9, 18.6, 19.4, 20.4, 22.1, 25.5, 25.9, 26.8, 27.7, 29.8, 39.8, 41.4, 48.3, 48.5, 76.3, 86.4, 122.2, 140.7, 165.1. IR (NaCl plates, cm^{-1}): 2958, 2874, 1720, 1640, 1464, 1252, 1150, 842. MS: [$m^+/z-C_6H_{15}Si$]=265.1804 (calculated=265.1804). $[\alpha]_D^{25}$ +14.9 (*c* 2.37, EtOH).

4.3.3. (*Z*)-(*R*)-2-Methoxy-1-phenylethyl 2-*tert*-butyldimethylsilyloxyhex-2-enoate, 46. Colorless oil, 67% yield. ^{1}H NMR ($CDCl_3$): δ 0.09 (s, 3H), 0.14 (s, 3H), 0.93 (t, J=3.6 Hz, 3H), 0.94 (s, 9H), 1.43 (q, J=7.5 Hz, 2H), 2.17 (q, J=7.3 Hz, 2H), 3.36 (s, 3H), 3.59 (d of d, J=4.1, 10.9 Hz, 1H), 3.75 (d of d, J=7.9, 10.8 Hz, 1H), 6.01 (d of d, J=3.9, 7.9 Hz, 1H), 6.11 (t, J=7.5 Hz, 1H), 7.30 (m, 5H). ^{13}C NMR ($CDCl_3$): δ −4.4, 14.0, 18.5, 22.0, 25.8, 27.9, 59.0, 74.7, 75.3, 123.5, 126.7, 128.2, 137.5, 140.6, 164.1. IR (NaCl plates, cm^{-1}): 2936, 1728, 1648, 1456, 1150, 834, 702. MS: [$m^+/z-C_6H_{15}Si$]=378.2226 (calculated=378.2226). $[\alpha]_D^{25}$ −28.4 (*c* 1.05, EtOH).

4.3.4. (*Z*)-(*R*)-1-Phenylethyl2-*tert*-butylydimethylsilyloxyhex-2-enoate, 47. Colorless oil, 77% yield. ^{1}H NMR ($CDCl_3$): δ 0.09 (s, 3H), 0.13 (s, 3H), 0.95 (t, J=7.5 Hz, 3H), 0.95 (s, 9H), 1.43 (sextet, J=7.5 Hz, 2H), 1.58 (d, J=5.0 Hz, 3H), 2.17 (d of q, J=0.9, 7.2 Hz, 2H), 5.94 (q, J=6.3 Hz, 1H), 6.08 (t, J=7.5 Hz, 1H), 7.25–7.4 (m, 5H). ^{13}C NMR ($CDCl_3$): δ −3.98, −3.93, 14.3, 18.9, 22.4, 22.5, 26.2, 28.2, 73.2, 123.5, 126.5, 128.2, 128.8, 141.2, 141.9, 164.6. IR (NaCl plates, cm^{-1}): 2946, 2855, 1720, 1640, 1456, 1368, 1258, 1142, 834. MS: [$m^+/z-C_{12}H_{18}$]=186.0717 (calculated=186.0712), $[C_8H_9]^+$=105.0705 (calculated=105.0704). $[\alpha]_D^{25}$ +2.2 (*c* 1.08, CH_2Cl_2).

4.3.5. (*Z*)-(*R*)-1-(2,4,6-Triisopropylphenyl)ethyl 2-*tert*-butyldimethylsilyloxyhex-2-enoate, 48. Colorless waxy solid, 72% yield. ^{1}H NMR (DMSO, 80 °C): δ 0.06 (s, 3H) 0.12 (s, 3H), 0.88 (t, J=7.3 Hz, 3H), 0.92 (s, 9H), 1.19 (d, J=7.0 Hz, 12H) 1.24 (d, J=6.8 Hz, 6H), 1.37 (h, J=7.5 Hz, 2H), 1.59 (d, J=7.0 Hz, 3H), 2.13 (q, J=7.5 Hz, 2H), 2.84 (heptet, J=6.8 Hz, 1H), 3.52 (broad heptet, J=6.7 Hz, 2H) 5.96 (t, J=7.5 Hz, 1H), 6.47 (q, J=6.8 Hz, 1H), 7.00 (s, 2H). ^{13}C NMR (DMSO, 80 °C): δ −4.8, −4.7, 13.1, 17.7, 21.0, 21.4, 23.21, 23.24, 23.7, 24.1, 25.3, 26.8, 28.3, 32.9, 35.9, 68.2, 121.2, 121.4, 131.4, 140.3, 147.3, 163.1. IR (NaCl plates, cm^{-1}): 2948, 2855, 1722, 1644, 1452, 1367, 1268, 1060, 834. MS: (30 eV): [m^+/z]=473.3451 (calculated=473.3451). $[\alpha]_D^{25}$ +3.2 (*c* 1.45, CH_2Cl_2).

4.3.6. (*Z*)-(*R*)-2,2-Diphenylcyclopentyl 2-*tert*-butyldimethylsilyloxyhex-2-enoate, 49. Colorless oil, 70% yield. ^{1}H NMR ($CDCl_3$): δ 0.108 (s, 3H), 0.11 (s, 3H), 0.79 (t, J=7.4 Hz, 3H), 0.92 (s, 9H), 1.24 (m, 2H) 1.57 (m, 1H), 1.75 (m, 1H), 1.95 (m, 1H), 2.23 (m, 1H) 2.47 (m, 1H), 2.63 (m, 1H), 5.33 (t, J=7.9 Hz, 3H), 6.01 (m, 1H), 7.17 (m, 10H). ^{13}C NMR ($CDCl_3$): δ −4.4,−4.3, 13.8, 14.1, 18.5, 20.4, 21.8, 22.7, 25.8, 27.5, 30.6, 31.6, 35.5, 59.1, 80.3, 123.0, 125.8, 126.1, 127.88, 127.9, 128.4, 140.4, 145.0, 145.6, 164.4. IR (NaCl plates, cm^{-1}) 2936, 1720, 1648, 1376, 1252, 1150, 834. MS: [$m^+/z-C_6H_{15}Si$]=349.1791 (calculated=349.1804). $[\alpha]_D^{25}$ −37.0 (*c* 3.0, CH_2Cl_2).

4.3.7. (*Z*)-(1*R*,2*R*,3*S*,4*S*)-4,7,7-Trimethyl-3-phenylbicyclo[2.2.1]heptan-2-yl 2-*tert*-butyldimethylsilyloxyhex-2-enoate, 50. Colorless of 77% yield. ^{1}H NMR ($CDCl_3$):

δ −0.05 (s, 3H), 0.04 (s, 3H), 0.61 (t, J=7.4 Hz, 3H), 0.82 (s, 9H), 0.88 (m, 2H), 1.01 (s, 3H), 1.30 (s, 3H), 1.32 (s, 3H), 1.55 (m, 2H), 1.71 (m, 3H), 1.94 (m, 1H), 2.03 (d, J= 5.1 Hz, IH), 4.09 (d, J=8.7 Hz, 1H), 4.25 (t, J=7.0 Hz, 1H), 5.39 (d, J=8.7 Hz, 1H), 7.41 (m, 3H), 7.66 (m, 2H), 7.76 (d of d, J=1.4, 8.0 Hz, 1H), 8.00 (d, J=8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ −4.8, −4.5, 13.7, 14.8, 18.4, 21.6, 21.7, 23.9, 23.93, 25.8, 26.1, 27.2, 42.6, 48.2, 49.3, 51.1, 55.4, 76.3, 80.3, 122.4, 123.3, 124.3, 125.0, 126.1, 126.6, 126.8, 128.8, 133.4, 133.5, 135.9, 139.9, 163.7. IR (NaCl plates, cm^{-1}): 2948, 1726, 1632, 1466, 1252, 1146, 836, 778. MS: [$m^+/z-C_6H_{15}Si$]=391.2274 (calculated= 391.2273). $[\alpha]_D^{25}$ −53.5 (c 1.05, EtOH).

4.3.8. (*Z*)-(1*R*,2*S*)-2-Phenylcyclohexyl 2-*tert*-butyldimethylsilyloxyhex-2-enoate, 51. Colorless oil 75% yield. ^{1}H NMR ($CDCl_3$): δ −0.04 (s, 3H), 0.02 (s, 3H), 0.86 (t, J=9.8 Hz, 3H), 0.91 (s, 9H), 1.23–1.65 (m, 4H), 1.31 (q, J=9.8 Hz, 2H), 1.78–2.21 (m, 4H), 2.02 (dq, J=1.1, 10.1 Hz, 2H), 2.72 (ddd, J=5.0, 17.2, 16.4 Hz, 1H) 4.96 (dt, J=6.1, 14.0 Hz, 1H), 5.66 (t, J=9.9 Hz, 1H), 7.18 (m, 5H). ^{13}C NMR ($CDCl_3$): δ −4.4, −4.2, 10.7, 14.0, 18.7, 22.1, 24.9, 26.0, 27.7, 32.5, 34.1, 50.0, 122.7, 126.5, 127.1, 128.4, 140.7, 143.3, 164.4. IR (NaCl plates, cm^{-1}): 2946, 1730, 1630, 1456, 1250, 1146, 832, 778. MS: (30 eV): [$m^+/z-C_4H_9$]=345.1886 (calculated=345.1886). $[\alpha]_D^{25}$ −11.6 (c 3.1, CH_2Cl_2).

4.3.9. (*R*)-2,2-Diphenylcyclopentyl 2-(*tert*-butyldimethylsilyloxy)acrylate, 61. Colorless oil, 71%. ^{1}H NMR ($CDCl_3$): δ 0.00 (s, 3H), 0.04 (s, 3H), 0.84 (s, 9H), 1.54 (m, 1H), 1.67–1.89 (m, 2H), 2.14 (m, 1H), 2.45–2.62 (m, 2H), 4.60 (d, J=1.0 Hz, 1H), 4.95 (d, J=1.0 Hz, 1H), 6.04 (dd, J=2.6, 0.9 Hz, 1H), 7.01–7.26 (m, 10H). ^{13}C NMR ($CDCl_3$): δ −5.1, −5.0, 18.2, 20.4, 25.5, 30.5, 35.1, 59.2, 80.7, 103.6, 125.8, 126.1, 126.5, 127.8, 127.9, 128.4, 144.8, 145.4, 147.3, 163.8. IR (NaCl plates, cm^{-1}): 3059, 3032, 2955, 2884, 2857, 1730, 1624, 1599, 1485, 1463, 1447, 1377, 1322, 1253, 1169, 1031, 1005. MS: [$m^+/z-C_6H_{15}Si$]=307.1330 (calculated=307.1334). $[\alpha]_D^{25}$ −76 (c 0.48, EtOH).

4.3.10. (*Z*)-(*R*)-2,2-Diphenylcyclopentyl 2-(*tert*-butyldimethylsilyloxy)but-2-enoate, 62. Colorless oil, 69%. ^{1}H NMR ($CDCl_3$): δ 0.11 (s, 3H), 0.13 (s, 3H), 0.94 (s, 9H), 1.56 (d, J=7.1 Hz, 3H), 1.61–1.79 (m, 2H), 1.91 (m, 1H), 2.20 (m, 1H), 2.48–2.67 (m, 2H), 5.49 (q, J=7.1 Hz, 1H), 6.04 (dd, J=5.3, 2.6 Hz, 1H), 7.07–7.31 (m, 10H). ^{13}C NMR ($CDCl_3$): δ −4.37, −4.28, 11.3, 18.5, 20.4, 25.8, 30.5, 35.3, 59.1, 80.3, 117.6, 125.8, 126.1, 126.6, 127.9, 128.4, 141.5, 144.9, 145.6, 164.1. IR (NaCl plates, cm^{-1}): 3087, 3059, 3024, 2956, 2884, 2857, 1717, 1648, 1598, 1494, 1472, 1447, 1389, 1343, 1264, 1145, 1090. MS: [$m^+/z-C_6H_{15}Si$]=321.1503 (calculated=321.1491). $[\alpha]_D^{25}$ −73 (c 0.95, EtOH).

4.3.11. (*R*)-2,2-Diphenylcyclopentyl 2-(*tert*-butyldimethylsilyloxy)-3-methylbut-2-enoate, 63. White solid, 44%. Mp: 56–58 °C. ^{1}H NMR ($CDCl_3$): δ 0.07 (s, 3H), 0.09 (s, 3H), 0.93 (s, 9H), 1.43 (s, 3H), 1.59 (m, 1H), 1.68 (s, 3H), 1.75–1.99 (m, 2H), 2.18 (m, 1H), 2.53–2.69 (m, 2H), 6.27 (d, J=4.9 Hz, 1H), 7.05–7.27 (m, 8H), 7.36 (d, J=8.2 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ −4.3, −4.2, 18.4, 19.2, 20.3, 20.7, 25.9, 30.8, 35.0, 59.2, 80.9, 125.7, 126.1, 126.4, 128.8, 127.9, 128.0, 128.4, 136.2, 145.10, 145.13, 165.3. IR (NaCl plates, cm^{-1}): 3059, 3023, 2955, 2929, 2857, 1704, 1634, 1472, 1463, 1371, 1300, 1250, 1192, 1090. MS: [$m^+/z-C_6H_{15}Si$]=335.1645 (calculated=335.1647). $[\alpha]_D^{25}$ −63 (c 0.40, EtOH).

4.3.12. (*Z*)-(*R*)-2,2-Diphenylcyclopentyl 2-(*tert*-butyldimethylsilyloxy)penta-2,4-dienoate, 64. Colorless oil, 16%: ^{1}H NMR ($CDCl_3$): δ 0.14 (s, 3H), 0.143 (s, 3H), 0.94 (s, 9H), 1.56–1.82 (m, 2H), 1.92 (m, 1H), 2.26 (m, 1H), 2.48 (m, 1H), 2.67 (dt, J=12.9, 9.3 Hz, 1H), 5.13 (m, 2H), 5.83 (d, J=11.0 Hz, 1H), 6.03 (dd, J=5.7, 3.1 Hz, 1H), 6.60 (ddd, J=17.0, 11.0, 10.0 Hz, 1H), 7.09–7.34 (m, 10H). ^{13}C NMR ($CDCl_3$): δ −4.3, −4.1, 18.6, 20.4, 25.8, 30.7, 35.5, 59.1, 80.6, 120.2, 120.6, 125.9, 126.2, 126.6, 127.9, 128.0, 128.4, 130.4, 140.3, 144.9, 145.6, 164.4. IR (NaCl plates, cm^{-1}): 3060, 3024, 2956, 2929, 2857, 1726, 1645, 1599, 1495, 1471, 1390, 1362, 1255, 1151. MS: [$m^+/z-C_6H_{15}Si$]=333.1489 (calculated=333.1491). $[\alpha]_D^{25}$ −40 (c 0.70, EtOH).

4.3.13. (*Z*)-(*R*)-2,2-Diphenylcyclopentyl 2-(*tert*-butyldimethylsilyloxy)-3-phenylacrylate, 65. Colorless oil, 44%. ^{1}H NMR ($CDCl_3$): δ 0.12 (s, 3H), 0.13 (s, 3H), 0.91 (s, 9H), 1.66 (m, 1H), 1.77–1.98 (m, 2H), 2.30 (m, 1H), 2.51 (m, 1H), 2.72 (dt, J=12.3, 9.1 Hz, IH), 6.05 (t, J=2.9 Hz, 1H), 6.07 (s, 1H), 7.13–7.33 (m, 13H), 7.49 (d, J=7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ −3.9, −3.8, 18.6, 20.4, 25.8, 30.6, 35.6, 59.1, 80.7, 118.5, 125.9, 126.1, 126.6, 127.8, 127.9, 128.0, 128.4, 129.7, 129.8, 134.1, 140.3, 144.9, 145.6, 164.9. IR (NaCl plates, cm^{-1}): 3058, 3024, 2956, 2929, 2883, 2857, 1717, 1634, 1598, 1494, 1463, 1386, 1321, 1254, 1130, 1071, 1006. MS: [$m^+/z-C_6H_{15}Si$]=383.1643 (calculated=383.1647). $[\alpha]_D^{25}$ −81 (c 0.99, EtOH).

4.3.14. (*Z*)-(*R*)-2,2-Diphenylcyclopentyl 2-(*tert*-butyldimethylsilyloxy)-4-methylpent-2-enoate, 66. Colorless oil, 61%. ^{1}H NMR ($CDCl_3$): δ 0.12 (s, 3H), 0.13 (s, 3H), 0.77 (d, J=6.7 Hz, 3H), 0.86 (d, J=6.7 Hz, 3H), 0.93 (s, 9H), 1.59 (m, 1H), 1.78 (m, 1H), 1.90 (m, 1H), 2.27 (m, 1H), 2.45 (ddd, J=12.3, 7.9, 1.7 Hz, 1H), 2.59–2.72 (m, 2H), 5.08 (d, J=9.7 Hz, 1H), 6.00 (dd, J=5.7, 2.7 Hz, 1H), 7.08–7.34 (m, 10H). ^{13}C NMR ($CDCl_3$): δ −4.4, −4.3, 18.6, 20.5, 22.0, 22.1, 24.8, 25.8, 30.7, 35.6, 59.3, 80.3, 125.8, 126.1, 126.6, 127.9, 128.0, 128.3, 129.8, 138.5, 145.0, 145.6, 164.6. IR (NaCI, plates, cm^{-1}): 3088, 3060, 3025, 2957, 2857, 1716, 1643, 1599, 1494, 1471, 1447, 1387, 1362, 1303, 1257, 1157, 1113, 1032, 1007. MS: [$m^+/z-C_6H_{15}Si$]=349.1802 (calculated=349.1804). $[\alpha]_D^{25}$ −66 (c 0.92, EtOH).

4.3.15. (*Z*)-(*R*)-2,2-Diphenylcyclopentyl 2-(*tert*-butyldimethylsilyloxy)-4,4-dimethylpent-2-enoate, 67. White Solid, 21%. Mp: 94–96 °C. ^{1}H NMR (C_6D_6): δ 0.16 (s, 3H), 0.18 (s, 3H), 0.92 (s, 9H), 0.96 (s, 9H), 1.68–1.98 (m, 2H), 2.27 (m, 1H), 2.44 (m, 1H), 2.64 (m, 1H), 4.99 (s, 1H), 5.95 (dd, J=2.3, 5.5 Hz, 1H), 7.08–7.28 (m, 10H). ^{13}C NMR (C_6D_6): δ 165.4, 146.1, 145.5, 139.9, 129.3, 128.7, 126.4, 126.1, 80.8, 59.6, 36.0, 31.7, 31.1, 30.0, 29.9, 26.7, 20.7, 19.4, −2.6, −2.7. IR (NaCl, plates, cm^{-1}): 3088, 3050, 3022, 2950, 2863, 1716, 1645, 1601, 1495, 1471, 1447, 1377, 1361, 1303, 1027, 1005. MS: [$m^+/z-$

$C_6H_{15}OSi]=347.2011$ (calculated=347.2024). $[\alpha]_D^{25}$ −123 (*c* 2.2, CH_2Cl_2).

4.4. General cycloaddition reaction

4.4.1. Preparation of 1-*tert*-butyldimethylsilyloxy-2,2-dichloro-3-oxo-4-*n*-propyl-cyclobutanecarboxylic acid (*S*)-(2,2-diphenyl)cyclopentyl ester, 52. Zn dust was activated by vigorously stirring with HCl (10%) for 1–2 min, filtered, then washed with H_2O (3×) followed by acetone (3×). The activated Zn was stored in an oven heated at approximately 140–150 °C. To a flask of activated Zn dust (1.12 g, 17.1 mmol) and ether (10 mL) was added a mixture of trichloroacetyl chloride (1.53 mL, 13.7 mmol) and alkene **49** (3.20 g, 6.9 mmol) dropwise over 4–5 h. The heterogeneous solution was stirred for 16 h at rt, diluted with diethyl ether and filtered through Celite®. The filtrate was concentrated to 1–5 mL by rotary evaporation, diluted with pentane (15 mL) then vigorously stirred for 5 min to induce precipitation of Zn salts. After allowing the precipitate to settle, the pentane solution was decanted from the Zn salts. This decanting/washing protocol was repeated twice more. The combined pentane extracts were washed with cold saturated $NaHCO_3$ (5%, 2×), H_2O (1×), brine (1×), dried over Na_2SO_4, and the solvent evaporated. The crude residue was purified by filtration through SiO_2 (20:1 hexane/ethyl acetate) followed by recrystallization from hexanes to furnish cycloadduct **52** (3.07 g, 79% yield) as a colorless solid. Mp: 76–78 °C. ^{1}H NMR ($CDCl_3$). δ 0.22 (s, 3H), 0.36 (s, 3H), 0.73 (t, J=7.3 Hz, 3H), 0.92 (s, 9H), 1.29 (m, 2H), 1.51 (m, 3H), 1.87 (m, 1H), 2.04 (m, 1H), 2.31 (m, 1H), 2.47 (m, 1H), 2.65 (m, 1H), 2.95 (t, J=7.7 Hz, lH), 6.24 (d, J=4.8 Hz, 1H), 7.23 (m, 10H). ^{13}C NMR ($CDCl_3$): δ −2.8, 14.1, 19.9, 20.7, 21.2, 26.3, 26.7, 28.8, 30.3, 35.2, 59.9, 64.3, 83.9, 126.3, 126.5, 126.7, 126.8, 127.6, 128.4, 128.5, 128.7, 128.8, 144.5, 145.1, 168.2, 194.8. IR (NaCl plates, cm^{-1}): 3030, 2878, 1818, 1735, 1518, 1460, 1225, 920. $[\alpha]_D^{25}$ −65.2 (*c* 2.5, CH_2Cl_2).

4.4.2. Preparation of 1-*tert*-butyldimethylsilyloxy-2,2-dichloro-3-oxocyclobutanecarboxylic acid (*S*)-(2,2-diphenyl)cyclopentyl ester, 68. Starting with alkene **61** a clear yellow oil was produced in 80% as a 3.5:1 ratio of diastereoisomers. ^{1}H NMR ($CDCl_3$): δ 7.12–7.37 (m, 10H), 6.29 (d, J=4.6 Hz, 0.78H), 6.16 (dd, J=5.2, 2.8 Hz, 0.22H), 3.49 (d, J=17.6 Hz, 0.22H), 3.20 (d, J=17.7 Hz, 0.2H), 3.03 (d, J=17.1 Hz, 0.78H), 2.57–2.65 (m, 1H), 2.16–2.48 (m, 2H), 2.06 (d, J=17.5 Hz, 0.78H), 1.82–2.07 (m, 2H), 1.44–1.62 (m, 1H), 0.95 (s, 7.02H), 0.93 (s, 1.98H), 0.26 (s, 2.34H), 0.16 (s, 0.66H), 0.06 (s, 0.66H), −0.01 (s, 2.34H). ^{13}C NMR ($CDCl_3$): Major diastereomer δ 188.8, 167.9, 145.1, 144.1, 128.54, 128.52, 127.3, 126.4, 126.2, 126.0, 91.8, 83.6, 78.1, 59.8, 53.8, 34.9, 29.9, 25.7, 20.5, 18.5, −3.6, −4.0. Minor diastereomer (visible peaks) δ 189.1, 168.0, 145.2, 143.8, 128.5, 128.2, 128.0, 126.5, 126.3, 91.2, 83.3, 78.6, 58.6, 53.7, 30.6, 25.8, 25.6, 19.8, 18.4, −3.7. IR (NaCl plates, cm^{-1}): 3088, 3059, 3024, 2955, 2931, 2885, 2858, 1813, 1756, 1598, 1472, 1463, 1388, 1300, 1252, 1220, 1181, 1132, 1103, 1032. MS: $[m^+/z-C_6H_{15}Si]=417.0670$ (calculated=417.0660). $[\alpha]_D^{25}$ −36 (*c* 0.99 EtOH).

4.4.3. Preparation of 1-*tert*-butyldimethylsilyloxy-2,2-dichloro-4-methyl-3-oxo-cyclobutanecarboxylic acid (*S*)-(2,2-diphenyl)cyclopentyl ester, 69. Starting with alkene **62** a colorless oil was produced in 68% as a 3.8:1 ratio of inseparable diastereoisomers. ^{1}H NMR ($CDCl_3$): δ 7.10–7.33 (m, 10H), 6.19 (d, J=5.3 Hz, 0.79H), 6.06 (m, 0.21H), 3.50 (q, J=7.2 Hz, 0.21H), 3.07 (q, J=7.6 Hz, 0.79H), 2.44–2.60 (m, 2H), 2.22–2.34 (m, 1H), 1.97–2.07 (m, 1H), 1.80–1.92 (m, 1H), 1.47–1.66 (m, 1H), 1.02 (d, J=7.2 Hz, 0.63H), 0.89 (s, 7.11H), 0.87 (s, 1.89H), 0.81 (d, J=7.5 Hz, 2.37H), 0.34 (s, 3H), 0.15 (s, 2.37H), 0.08 (s, 0.63H). ^{13}C NMR ($CDCl_3$): Major diastereomer δ 195.0, 167.4, 144.8, 144.3, 128.5, 128.4, 127.5, 126.4, 126.3, 126.1, 90.7, 83.4, 80.4, 59.7, 58.6, 35.3, 30.4, 26.4, 20.6, 19.6, 9.5, −2.8, −3.0. Minor diastereomer (visible peaks) δ 194.2, 162.0, 145.0, 144.2, 128.5, 128.2, 127.9, 126.5, 89.8, 82.7, 80.9, 58.9, 57.2, 35.5, 30.7, 26.0, 20.1, 19.1, 7.6, −3.0, −3.6. IR (NaCl plates, cm^{-1}): 3059, 2958, 2932, 2884, 2858, 1817, 1744, 1494, 1472, 1463, 1448, 1258, 1252, 1207, 1156, 1111, 1054, 1031. MS: $[m^+/z-C_6H_{15}Si]=325.0431$ (calculated=325.0430). $[\alpha]_D^{25}$ −45 (*c* 1.10, EtOH).

4.4.4. Preparation of 1-*tert*-butyldimethylsilyloxy-2,2-dichloro-3-oxo-4-isopropyl-cyclobutanecarboxylic acid (*S*)-(2,2-diphenyl)cyclopentyl ester, 70. Starting with alkene **66** a colorless oil was produced in 94% as a 10.8:1 ratio of inseparable diastereoisomers. ^{1}H NMR ($CDCl_3$) δ 7.22 (m, 1H), 6.21 (d, J=5.0 Hz, 0.92H), 6.03 (dd, J=5.9, 3.4 Hz, 0.08H), 3.32 (d, J=10.6 Hz, 0.08H), 2.44–2.63 (m, 2H), 2.40 (d, J=10.6 Hz, 0.92H), 1.98–2.26 (m, 3H), 1.80–1.91 (m, 1H), 1.49–1.64 (m, 1H), 0.98 (s, 0.72H), 0.91 (s, 8.28H), 0.82 (d, J=6.8 Hz, 2.76H), 0.71 (d, J=6.3 Hz, 0.24H), 0.62 (d, J=6.3 Hz, 0.24H), 0.41 (d, J=6.4 Hz, 2.76H), 0.33 (s, 2.76H), 0.27 (s, 2.76H), 0.18 (s, 0.24H), 0.04 (s, 0.24H). ^{13}C NMR ($CDCl_3$): Major diastereomer δ 193.5, 168.3, 144.8, 144.3, 128.57, 128.55, 127.4, 126.4, 126.2, 83.7, 80.7, 70.8, 59.6, 35.0, 30.0, 28.0, 26.6, 26.0, 21.8, 20.4, 20.3, 19.7, −2.6, −2.8. Minor diastereomer (visible peaks) δ 193.8, 167.0, 144.7, 144.1, 128.8, 128.4, 128.3, 128.2, 128.1, 126.6, 91.1, 82.4, 68.1, −3.4, −3.7. IR (NaCl plates, cm^{-1}): 2960, 2927, 2847, 1808, 1754, 1722, 1643, 1568, 1494, 1470, 1388, 1362, 1254, 1200, 1110, 1031. MS: $[m^+/z-C_6H_{15}Si]=459.1130$ (calculated=459.1130). $[\alpha]_D^{25}$ −31 (*c* 0.60, EtOH).

4.4.5. Preparation of 1-*tert*-butyldimethylsilyloxy-2,2-dichloro-4,4-dimethyl-3-oxo-cyclobutanecarboxylic acid (*S*)-(2,2-diphenyl)cyclopentyl ester 71. Starting with 220 mg (0.46 mmol) of alkene **67**, a 4:1 inseparable mixture of starting material and cycloadduct was produced. Based on consumed starting material (determined by ^{1}H NMR) **71** was produced as a colorless oil in 32% yield in a 8.2:1 ratio of inseparable diastereosiomers. ^{1}H NMR (C_6D_6): Major diastereosiomer δ 6.87–7.21 (m, 10H), 6.16 (d, J=3.6 Hz, 1H), 3.45 (s, 1H), 1.23–2.61 (m, 6H), 1.08 (s, 9H), 0.92 (s, 9H), 0.55 (s, 3H), 0.53 (s, 3H). ^{13}C NMR (C_6D_6): Major diastereomer δ 194.6, 169.0, 145.3, 144.7, 129.0, 128.9, 127.9, 127.6, 126.54, 126.5, 84.5, 83.9, 73.4, 35.1, 34.6, 32.4, 30.2, 30.1, 29.9, 28.7, 28.5, 27.2, 23.2, 20.3, 14.4, −1.8. IR (NaCl plates, cm^{-1}); most distinguishable peak for cycloadduct **71**: 1814.

4.4.6. Preparation of (*Z*)-(*R*)-diphenylcyclopentyl 2-(*tert*-butyldimethylsilyloxy)-3-(3,3-dichloro-2-oxocyclobutyl)acrylate, 72. Starting with alkene **64**, a colorless oil was produced in 44% as a 2.6:1 ratio of inseparable diastereoisomers. ^{1}H NMR ($CDCl_3$): δ 7.05–7.27 (m, 10H), 6.01–6.06 (m, 1H), 5.33 (d, J=9.2 Hz, 0.28H) 5.08 (d, J=9.5 Hz, 0.72H), 3.80 (d, J=4.8 Hz, 0.28H), 3.46 (m, 0.72H), 3.38 (dd, J=17.8, 10.1 Hz, 0.72H), 3.00 (dd, J=17.9, 8.6 Hz, 0.28H), 2.86 (dd, J=18.0, 4.9 Hz, 0.28H), 2.78 (dd, J=17.8, 8.6 Hz, 0.72H), 2.59–2.71 (m, 1H), 2.45–2.56 (m, 1H), 2.23–2.41 (m, 1H), 2.07 (m, 0.28H), 1.77–1.96 (m, 1.72H), 1.36–1.47 (m, 1H), 1.01 (s, 2.52H), 0.94 (s, 6.48H), 0.38 (s, 0.84H), 0.30 (s, 0.84H), 0.19 (s, 2.16H), 0.18 (s, 2.16H). ^{13}C NMR ($CDCl_3$): Major diastereomer δ 192.2, 163.4, 145.1, 144.3, 143.7, 130.9, 128.8, 128.4, 128.2, 127.8, 126.5, 126.3, 81.5, 68.1, 59.6, 48.7, 41.8, 35.7, 30.4, 25.8, 20.7, 18.6, −4.2. Minor diastereomer (visible peaks) δ 132.5, 128.7, 128.1, 127.3, 126.2, 125.8, 81.1, 66.4, 59.5, 45.9, 44.1, 35.7, 30.2, 25.8, 20.5, −2.2, −2.5. IR (NaCl plates, cm^{-1}): 3060, 3024, 2957, 2930, 2858, 1815, 1760, 1725, 1645, 1599, 1495, 1447, 1386, 1291, 1254, 1212, 1162, 1124, 1071. MS: $[m^{+}/z-C_6H_{15}Si]$=337.0417 (calculated=337.0430). $[\alpha]_D^{25}$ −69 (*c* 0.26, EtOH).

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Chiral discrimination of ibuprofen isomers in β-cyclodextrin inclusion complexes: experimental (NMR) and theoretical (MD, MM/GBSA) studies

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Abstract—In this paper, we analyze the energetic and conformational preferences involved in the chiral discrimination of ibuprofen (**Ibu**) isomers by beta-cyclodextrin (β-CD) when forming inclusion complexes in water. This study was performed by means of atomistic molecular mechanics simulations upon four different penetration modes of the guest, and a structural 2D NMR experiment. The trajectories of these simulations were treated with the MM/GBSA method in order to obtain the relative weights of the different free energy components. The resulting values of the free energy of binding and other geometrical features indicate that this chiral selectivity is influenced by a preferred penetration mode involving the *S*-(+)-**Ibu** isomer. The calculated $\Delta\Delta G$ of binding is in good agreement with published experiments.

1. Introduction

Chiral discrimination is one of the most intriguing phenomena in chemistry. It is of great importance in analytic, organic, and biological chemistry. Stereoselective recognition is the basis of asymmetric synthesis, chromatography techniques, enzymatic catalysis, and origin of the chiral composition of the molecules constituting biological systems.[1] Despite the fundamental importance of this effect, its origin and nature are still far from being well understood at the atomic level. Chiral cyclodextrin (CD) hosts have been used extensively as models for investigating chiral and molecular recognition. Solution studies of CD inclusion complexes[2,3] and binding constants,[4] have provided thermodynamic data useful for chromatographic applications.[5] However, despite intense efforts, the mechanism of the recognition is not fully understood and many essential data are missing.

In pharmacology chirality is an important factor in drug efficacy. About 56% of the drugs currently in use are chiral compounds, and about 88% of these chiral synthetic drugs are used therapeutically as racemates. Unfortunately, there are many racemic drugs where the stereospecificity of the metabolism and/or pharmacodynamic effect of the enantiomers is not known. Studying the chiral recognition by CDs is of considerable importance in view of its enantiodifferentiation of drugs. A large number of experimental[6–10] and theoretical works have been performed over the past few years on CDs drug complexes.[11–13]

Besides experimental measurements, it is possible to accurately estimate the free energy of binding ($\Delta G_{\text{binding}}$) between small druglike molecules and a larger target molecule using computer simulation methods. One way is to use the very CPU intensive methods like the free energy perturbation (FEP) and thermodynamic integration (TI) techniques. Another way is to use the MM-PBSA/GBSA method[14] that in the last decade has been applied successfully to estimate the binding free energies of different biological systems.[15,16] This approach combine molecular mechanics energies for the solute with a continuum solvation approach and normal mode analysis

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to evaluate the total free energy. Depending on whether the continuum solvation model is based in solving the Poisson–Boltzmann equation or the Generalized Born equation is called MM-PBSA or MM-GBSA. The MM-PBSA/GBSA method is faster by at least a factor of 10 than the traditional FEP and TI techniques. Furthermore, it does not require any experimental data or fitting of parameters, it calculates the free energies of the end states directly, avoiding the time-consuming simulation of intermediate states as in FEP and TI methods.[17]

Given that in the chiral recognition process the guest molecules being discriminated have the same size, same molecular charges, same physicochemical properties, etc. they can only be discerned when different diasteromeric responses take place when they associate with another chiral molecule. It is generally accepted that the intermolecular forces responsible for enantiomer discrimination are the same as those involved in other types of molecular recognition, although the differences in binding energies of the enantiomers are much smaller in magnitude. In spite of this belief the so called three-point interaction model[18–20] between one enantiomer and the chiral selector, and the induced fit effect on chiral discrimination must be studied in more detail.

In this study, we used β-cyclodextrin (β-CD) as the chiral host and the two ibuprofen (4-isobutyl-2-phenyl-propionic acid) isomers as the chiral guests. β-CD is a cyclic oligomer made of seven α-D-glucose residues arranged in a donut-shaped ring with a dipole moment of about 2.311 D. The specific coupling and conformation of these glucose units give the cyclodextrin a rather rigid, toroidal molecular structure with a hollow interior of specific volume. The lining of the cavity is formed by hydrogen atoms and glycosidic bridging oxygen atoms; consequently this surface is fairly hydrophobic. The unique shape and physical–chemical properties of the cavity allows the formation of inclusion complexes with organic molecules, where the extent of the complex formation depends on the polarity of the absorbed molecules. The hydrophilic characteristic of β-CD is provided by its two different rims: one narrower (N) or primary hydroxyl rim and another wider (W) or secondary hydroxyl rim. These features are shown in Figure 1. Ibuprofen (**Ibu**) is a drug molecule containing a single chiral center, a long non-polar (NP) chain and a polar (P) end; properties that are useful for constructing a simple and good model in which study chiral discrimination. **Ibu** is one of the most effective and widely used non-steroidal analgesic and anti-inflammatory agent. **Ibu** is a polar molecule with a dipole moment around 1.8 D (computed with PM3 method). It is marketed as a racemic mixture though it is known that the pharmacological activity resides in the *S*-(+)-**Ibu** (**Ibu***S*) enantiomer only. However, in vivo testing the presence of an isomerase can convert the *R*-(−)-**Ibu** (**Ibu***R*) to the active **Ibu***S* enantiomer. Complexes of **Ibu** with β-CD and modified β-CD have been reported.[21]

Most of the experimental studies around **Ibu** chiral separation have been carried out in aqueous solution using a large variety of techniques such as: fluorescence measurements,[22,23] differential scanning calorimetry,[24] crystallography,[25] capillary electrophoresis,[26] potentiometric studies,[27] spectroscopy,[28] and supercritical fluid chromatography.[29] In turn, the number of theoretical studies on the complexation of **Ibu** by β-CD are few. These include use of MC/SD,[27] simulated annealing,[30] AM1 semi-empirical calculations,[24] and semi-empirical PM3 calculations.[31] Both experimental and theoretical studies suggest that features such as guest fit to the CD cavity, solvent interactions, hydrogen bonding potential of the guest molecules, and van der Waals forces combine to play a significant role in chiral discrimination. However, none of those studies furnish data regarding the specific role of the enantiomeric interactions and the spatial arrangements involved in the chiral discrimination of the guest molecules.

This article describes the results of several 4.5 ns molecular dynamics simulations, carried out on four different penetration modes of the **Ibu** isomers into the β-CD cavity

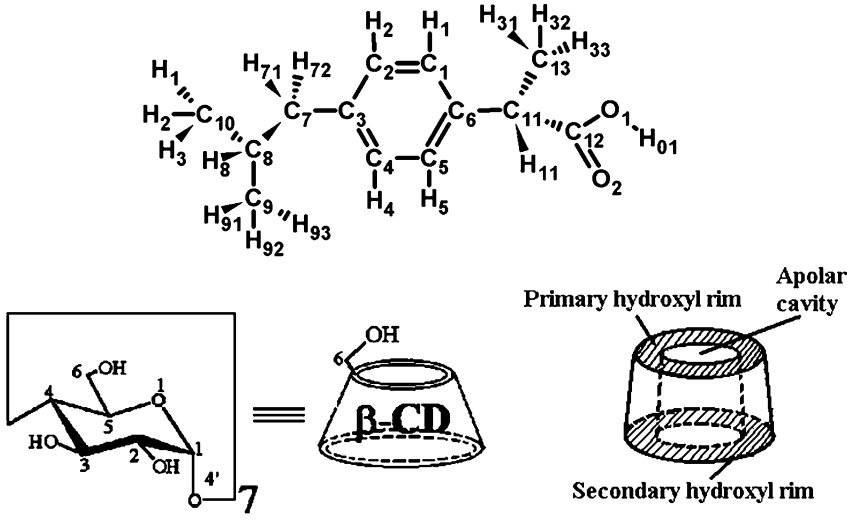

Figure 1. Structures of ibuprofen and β-CD.

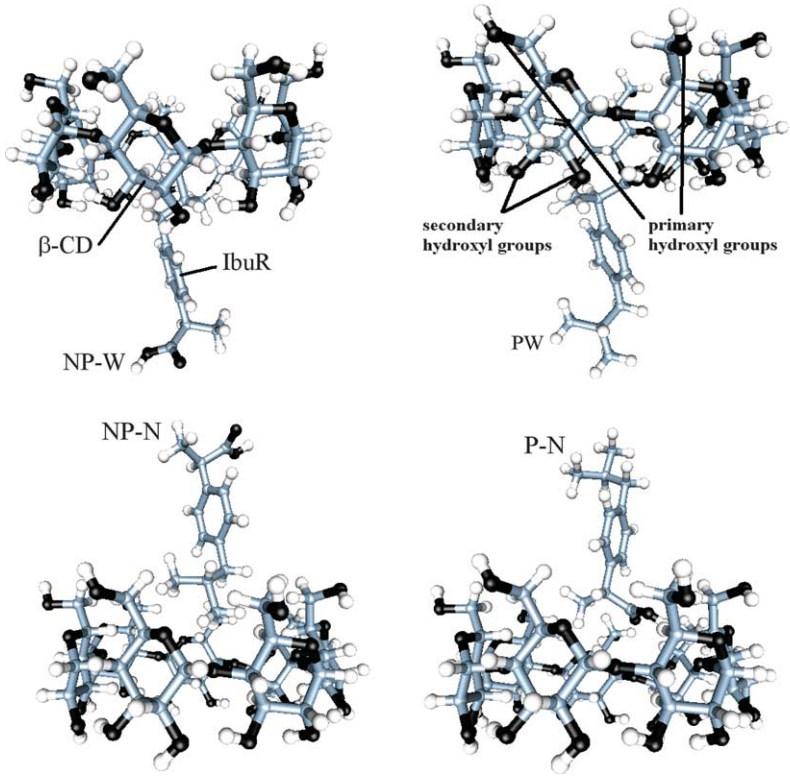

Figure 2. An schematic representation of the four different penetration modes of **Ibu** into β-CD. The corresponding minimized geometries are used as the starting points for the MD simulations.

in the presence of explicit solvent (Fig. 2). Detailed analyses of our results reveal that among the four penetration modes, there is one that appears to possess the most predominant discriminating features. During most of the simulation time, this penetration mode produces a large number of hydrogen bonds between the carboxyl group of **Ibu***S* and the secondary hydroxyl groups of β-CD. A trace analysis shows that for this penetration mode there are evident differences in occupancy and orientation between the two **Ibu** enantiomers inside the β-CD cavity, which in turn plays an important role in maximizing hydrogen bonding. The results of the remaining three penetration modes are also presented and we discuss how they contribute to the average $\Delta\Delta G_{\text{binding}}$ that facilitate the chiral discrimination of **Ibu** in a racemic mixture.

It is known that the carboxylic group of benzoic acid (BA) binds well within α-CDs,[32] especially in its non-ionized form, and that ionization of the carboxylic group leads to a much weaker binding.[33] Recent studies on the crystal structure of the inclusion complex of β-CD with BA show that the COOH groups of the BA molecules protrude at the β-CD O-6 sides,[34] and maintained in position by hydrogen bonding to the surrounding O-6-H groups. However, conflicting views are expressed in the literature regarding the stereoselectivity of inclusion of benzoic acid derivatives. Thus, in order to gain some extra information about the intermolecular interactions accompanying complexation we also report the results of association experiments via electronic absorption spectroscopy and a NMR 2D-NOESY study on complexes of the ionic form of ibuprofen ($\mathbf{Ibu}^{-1}$) with β-CD. We expected that NMR results would give structural information about the system by showing any particular interaction as a corresponding cross peak.

2. Results and discussion

2.1. MM/GBSA analysis

The results of the MM/GBSA analysis upon the 4.5 ns MD trajectories on the four penetration modes are gathered in Tables 1–3. In Table 1, we show the free energy contribution of the ligands alone. Solvation energies ($G_{\text{solvation}}$) for isolated **Ibu***R* and **Ibu***S* are identical for all arrangements (about −8.2 kcal/mol), however, small differences of about 1–4 kcal/mol are observed among the different conformers of β-CD (Table 1) and the respective complexes (Table 2). These results suggest that solvation by itself does not contribute significantly to the chiral selectivity; instead they suggest that chiral selectivity arises mainly from a delicate balance between internal energies. According to these calculated results, the complexes formed with the **Ibu***S* enantiomer are more stable than those for **Ibu***R*; however, if we consider the stability of the guests relative to the host we find that both the complex and the guest favor the [**Ibu***S*⊂β-CD] complex, while the host favors the [**Ibu***R*⊂β-CD] complex.

The results shown in Table 3 indicate that the initial arrangements P–W, NP–N and P–N have no clear chiral selectivity, while the initial orientation NP–W is responsible for a reasonable degree of enantioselectivity. Our

Table 1. Energy contribution of the ligands alone [**A** ≡ β-CD, **B** ≡ **Ibu**]

	Energy (kcal/mol)	NP–W_R (std)[a]	NP–W_S (std)	P–W_R (std)	P–W_S (std)	NP–N_R (std)	NP–N_S (std)	P–N_R (std)	P–N_S (std)
A	E_{electr}	439 (0.4)	446.3 (0.4)	444.3 (0.4)	438.0 (0.4)	441.9 (0.4)	441.7 (0.4)	443.3 (0.1)	445.1 (0.4)
	E_{vdW}	16.2 (0.2)	14.8 (0.2)	15.7 (0.2)	16.8 (0.2)	16.0 (0.2)	16.3 (0.2)	16.3 (0.2)	16.2 (0.2)
	$G_{(non\text{-}polar\ GB)}$	8.7 (0.0)	8.7 (0.0)	8.7 (0.0)	8.7 (0.0)	8.7 (0.0)	8.7 (0.0)	8.7 (0.0)	8.7 (0.0)
	G_{GB}	−71.5 (0.2)	−75.0 (0.2)	−75.0 (0.2)	−71.3 (0.2)	−72.3 (0.2)	−76.3 (0.2)	−73.1 (0.3)	−75.4 (0.2)
	$G_{solvation}$	−62.8 (0.2)	−66.3 (0.2)	−66.3 (0.2)	−62.6 (0.2)	−63.6 (0.2)	−65.0 (0.2)	−64.4 (0.2)	−66.7 (0.2)
	$E_{(total,\ GB)}$	543.5 (0.5)	549.6 (0.4)	546.7 (0.4)	554.0 (0.3)	552.2 (0.3)	549.8 (0.4)	555.7 (0.2)	554.3 (0.3)
	$\Delta E_{(total,\ GB)}$	**6.1**		**7.3**		**−3.4**		**−1.4**	
B	E_{electr}	−36.5 (0.1)	−48.5 (0.1)	−46.4 (0.1)	−48.6 (0.1)	−46.5 (0.1)	−46.5 (0.1)	−46.8 (0.1)	−48.6 (0.1)
	E_{vdW}	6.0 (0.0)	6.0 (0.0)	5.9 (0.0)	6.2 (0.0)	6.1 (0.0)	6.1 (0.0)	6.2 (0.0)	6.1 (0.0)
	$G_{(non\text{-}polar\ GB)}$	3.3 (0.0)	3.3 (0.0)	3.2 (0.0)	3.3 (0.0)	3.3 (0.0)	3.3 (0.0)	3.3 (0.0)	3.3 (0.0)
	G_{GB}	−11.4 (0.0)	−11.4 (0.0)	−11.4 (0.0)	−11.4 (0.0)	−11.5 (0.0)	−11.4 (0.0)	−11.3 (0.0)	−11.3 (0.0)
	$G_{solvation}$	−8.1 (0.0)	−8.2 (0.0)	−8.2 (0.0)	−8.1 (0.0)	−8.2 (0.0)	−8.1 (0.0)	−8.0 (0.0)	−8.0 (0.0)
	$E_{(total,\ GB)}$	−18.1 (0.1)	−29.5 (0.1)	−27.8 (0.1)	−28.2 (0.1)	−26.7 (0.1)	−27.2 (0.1)	−26.0 (0.1)	−28.5 (0.1)
	$\Delta E_{(total,\ GB)}$	**−11.4**		**−0.4**		**0.5**		**−2.5**	

The notation used for the four different penetration modes is that described in the text. The subindexes *R* and *S* have been added in order to make reference to the data obtained for **Ibu***R* and **Ibu***S*, respectively.
[a] Standard errors of the mean values.

Table 2. Energy contribution of the complex [**AB** ≡ **Ibu**(*R*,*S*)⊂β-CD]

	Energy (kcal/mol)	NP–W_R (std)[a]	NP–W_S (std)	P–W_R (std)	P–W_S (std)	NP–N_R (std)	NP–N_S (std)	P–N_R (std)	P–N_S (std)
AB	E_{electr}	399.8 (0.4)	392.3 (0.4)	396.5 (0.4)	388.0 (0.4)	394.1 (0.4)	394.0 (0.4)	393.4 (0.4)	392.1 (0.4)
	E_{vdW}	7.9 (0.3)	2.4 (0.3)	4.2 (0.3)	6.5 (0.3)	6.0 (0.3)	6.6 (0.3)	5.3 (0.3)	4.6 (0.3)
	$G_{(non\text{-}polar\ GB)}$	8.4 (0.0)	8.0 (0.0)	8.1 (0.0)	8.2 (0.0)	8.2 (0.0)	8.2 (0.0)	8.1 (0.0)	8.1 (0.0)
	G_{GB}	−78.9 (0.2)	−78.8 (0.2)	−81.6 (0.2)	−77.9 (0.2)	−79.3 (0.2)	−80.9 (0.2)	−78.4 (0.2)	−79.8 (0.2)
	$G_{solvation}$	−70.5 (0.2)	−70.9 (0.2)	−73.5 (0.3)	−69.7 (0.2)	−71.1 (0.2)	−72.7 (0.2)	−70.2 (0.3)	−71.7 (0.2)
	$E_{(total,\ GB)}$	508.8 (0.7)	499.7 (0.5)	501.0 (0.5)	509.0 (0.4)	508.7 (0.5)	506.0 (0.5)	511.5 (0.4)	506.7 (0.4)
	$\Delta E_{(total,\ GB)}$	**−9.1**		**8.0**		**−2.7**		**−4.8**	

[a] Standard errors of the mean values.

Table 3. Energy difference of the complex formation [$\Delta_{Binding}$ ≡ **AB** − (**A** + **B**)]

	Energy (kcal/mol)	NP–W_R (std)[a]	NP–W_S (std)	P–W_R (std)	P–W_S (std)	NP–N_R (std)	NP–N_S (std)	P–N_R (std)	P–N_S (std)
$\Delta_{Binding}$	E_{electr}	−2.7 (0.1)	−5.5 (0.1)	−1.5 (0.1)	−1.4 (0.1)	−1.3 (0.1)	−1.2 (0.1)	−3.2 (0.1)	−4.3 (0.1)
	E_{vdW}	−14.4 (0.3)	−18.5 (0.3)	−17.4 (0.3)	−16.5 (0.3)	−16.2 (0.3)	−15.9 (0.3)	−17.2 (0.3)	−17.8 (0.3)
	$G_{(non\text{-}polar\ GB)}$	−3.6 (0.0)	−4.0 (0.0)	−3.8 (0.0)	−3.8 (0.0)	−3.8 (0.0)	−3.8 (0.0)	−3.8 (0.0)	−3.8 (0.0)
	G_{GB}	4.1 (0.1)	7.6 (0.1)	4.8 (0.1)	4.8 (0.1)	4.5 (0.1)	4.1 (0.1)	6.0 (0.1)	6.8 (0.1)
	$G_{solvation}$	0.4 (0.1)	3.6 (0.2)	1.0 (0.1)	1.0 (0.1)	0.7 (0.1)	0.4 (0.1)	2.2 (0.1)	3.0 (0.1)
	$E_{(total,\ GB)}$	−16.6 (0.3)	−20.4 (0.2)	−17.9 (0.2)	−16.9 (0.2)	−16.8 (0.2)	−16.6 (0.2)	−18.2 (0.2)	−19.1 (0.2)
	$\Delta E_{(total,\ GB)}$	**−3.8**		**1.0**		**0.2**		**−0.9**	

[a] Standard errors of the mean values.

calculations suggest that the total chiral selectivity action by β-CD favors the **Ibu***S* enantiomer by about 0.9 kcal/mol. The computed average binding energies of −17.4 kcal/mol for the **Ibu***R* and of −18.3 kcal/mol for the **Ibu***S*, are about three times larger than the more recent experimentally available $\Delta G_{complex\_formation}$ data of −5.45 kcal/mol[22] and of −5.35 kcal/mol[23] for **Ibu** racemic mixtures.

The calculated $-T\Delta S$ values for the complexes [**Ibu***R*⊂β-CD] and [**Ibu***S*⊂β-CD] are 8.282 and 8.373 cal/mol, respectively. Thus the resulting $\Delta(T\Delta S)$ was too small to have an effective contribution to the overall $\Delta G_{binding}$ and it was not included in the present energy analysis. Recent thermodynamic studies on several enantiomeric pairs forming inclusion complexes with natural occurring CDs also report small differences on $\Delta\Delta S$ and $\Delta\Delta H$ in the overall complexation process.[35]

2.2. Hydrogen bond analysis

A full analysis of all possible hydrogen bonds formed between the primary or secondary hydroxyl groups of β-CD with the carboxylic group of **Ibu***R* and **Ibu***S* was carried out with the help of the PTRAJ subroutine of AMBER. For this analysis, the carboxyl group of **Ibu** was considered to act either as acceptor (through the CO or through the OH) or as donor (through the OH); similar properties were considered for the hydroxyl groups of β-CD. We used Jeffrey's hydrogen bond distance and bond angle criterion[36] to classify these from strong to weak hydrogen bonds. Table 4 compares the total number of hydrogen bonds present in all penetration modes studied.

Since the NP–W penetration mode was computed to contribute the most in the chiral selection process, only

Table 4. Hydrogen bonds formed per picosecond of simulation time during the complexation process for all penetration modes

			Moderate	Moderate + weak
NP–W		β-CD donor	0.40	1.21
	Ibu*R*	β-CD acceptor	0.06	0.46
		Total	**0.46**	**1.67**
		β-CD donor	0.73	1.88
	Ibu*S*	β-CD acceptor	0.08	0.56
		Total	**0.81**	**2.44**
P–W		β-CD donor	0.02	0.17
	Ibu*R*	β-CD acceptor	0.01	0.14
		Total	**0.03**	**0.31**
		β-CD donor	0.45	1.41
	Ibu*S*	β-CD acceptor	0.66 (0.48)[a]	1.04
		Total	**1.11 (0.92)**[a]	**2.45**
NP–N		β-CD donor	0.04	0.20
	Ibu*R*	β-CD acceptor	0.02	0.10
		Total	**0.06**	**0.30**
		β-CD donor	0.02	0.15
	Ibu*S*	β-CD acceptor	0.02	0.08
		Total	**0.04**	**0.23**
P–N		β-CD donor	0.50	1.42
	Ibu*R*	β-CD acceptor	0.11	0.64
		Total	**0.61**	**2.06**
		β-CD donor	0.56	1.56
	Ibu*S*	β-CD acceptor	0.14	0.64
		Total	**0.70**	**2.20**

[a] Number of H-bonds formed without considering the contacts with the O4 oxygen.

the results obtained in this arrangement are going to be described here. The results from the penetration modes and their intricate hydrogen bonding pattern formed during the simulation are discussed and depicted in the Supplementary material (Figs. 1–4).

In the NP–W penetration mode no strong hydrogen bonds were observed in any of the [**Ibu**(*R*,*S*)⊂β-CD] inclusion complexes, however, only moderate and weak H-bonds were detected. Upon further analysis, we observed that in both [**Ibu**(*R*,*S*)⊂β-CD] complexes the hydroxyl group on **Ibu** formed fewer hydrogen bonds than the corresponding carbonyl oxygen. Moreover, the first were classified as weak while the second were classified as moderate-weak. In most cases the hydrogen bonds were bifurcated between the hydroxyl groups of C3 and C2 of any glucose moiety.

Figure 1 of Supplementary material shows that more hydrogen bonds (moderate plus moderate-weak) were formed between the β-CD and the **Ibu*S*** enantiomer than with the **Ibu*R*** enantiomer in the NP–W penetration mode. The average number of total H-bonds in the [**Ibu*R*** ⊂β-CD] complex is 2.07 h bonds/ps while in the [**Ibu*S*** ⊂β-CD] complex the number raises up to 3.37 h bonds/ps; this is about 50% more hydrogen bonds than in the former. When moderate H-bonds are considered only, the difference between both isomers is even larger (about twice).

A sample of the hydrogen bonding trajectory is shown in Figure 3. This figure depicts the trajectory for the O···H distances between the carbonyl oxygen of **Ibu*S*** and the hydroxylic hydrogen corresponding to the OH in position 2 for any glucose residue in the NP–W penetration mode. This figure shows that the C═O forms a single H-bond with one of the secondary OH most of the simulation time, and that the H-bond position alternates between three different glucose units: two adjacent and a third one separated from the other two by one residue of glucose. After careful analysis of the geometries involving the H-bonds shown in this figure, we saw that they tend to be linear with O–H···O bond angles between 140 and 180° and H···O distances between 1.6 and 2.0 Å, these parameters are in agreement within those assigned to strong H-bonds. This analysis also indicates that when intermolecular H-bonds are formed between **Ibu** and the host, the intramolecular H-bonds between the O2 and O3 of β-CD are broken.

2.3. Trace of the chiral atom

The course followed by the chiral atom of **Ibu** in its corresponding [**Ibu**(*R*,*S*)⊂β-CD] complexes (hereinafter called trace) along the whole MD trajectory was computed with the help of the gOpenMol[37] program. The results for the trace in the NP–W inclusion mode are shown in Figure 4. The β-CD and corresponding **Ibu** isomer structure are the average structures computed over the 4500 ps of simulation, while the **Ibu** trace shown corresponds to the nonaveraged isomers and it is the trajectory of the chiral atom within the β-CD cavity.

The trace for **Ibu*R*** is more spherical than the one for **Ibu*S***. This is an indication that the latter has a more restricted motion within the CD cavity. The difference in the cavity volume explored by **Ibu** isomers is consistent with the results of the MM/GBSA and hydrogen bond analyses. Moreover, the average structure for the β-CD is more distorted in the [**Ibu*R*** ⊂β-CD] complex than in the

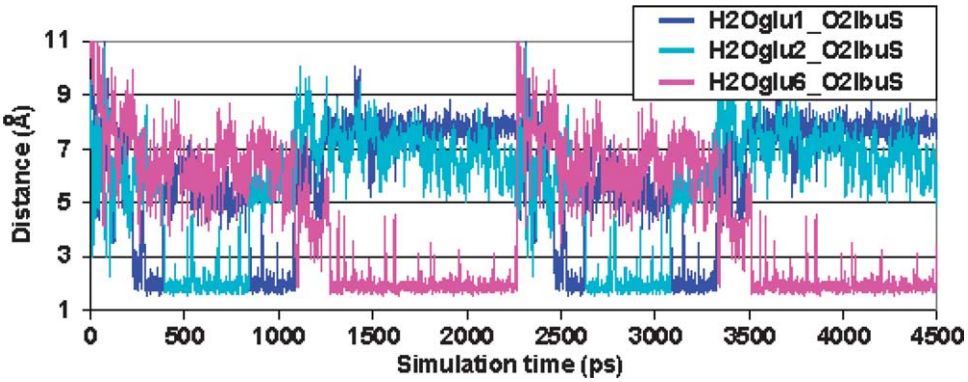

Figure 3. Distances between the carbonyl oxygen of **Ibu*S*** and the hydroxylic oxygen of the OH in position 2 for three specific glucose units.

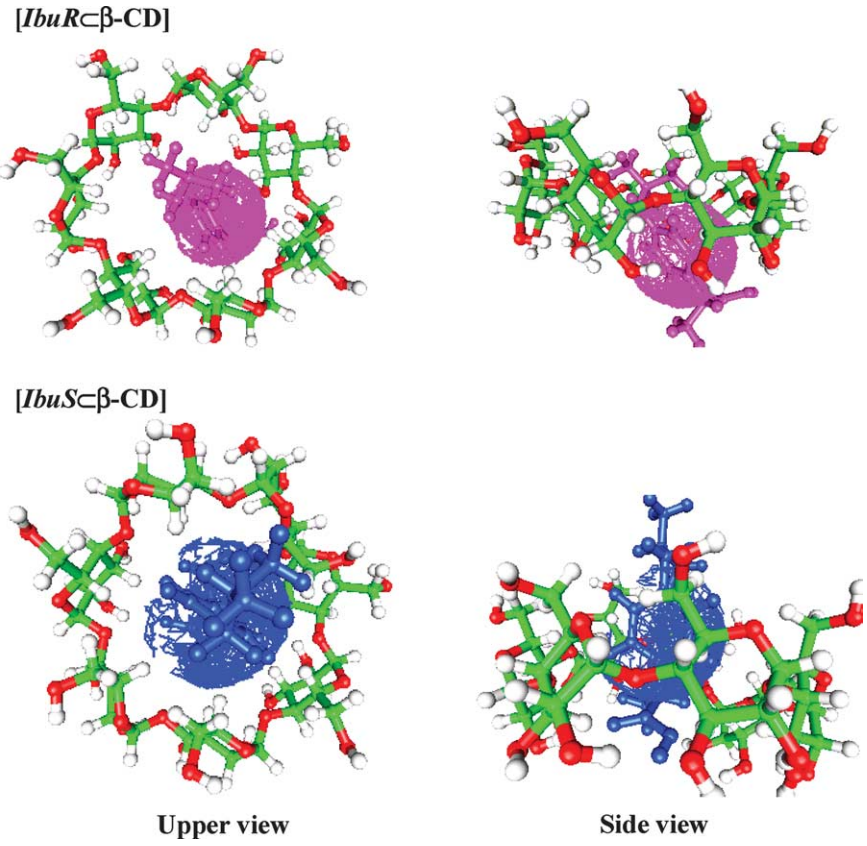

Figure 4. Trace followed by the chiral atom of **Ibu** in the [**Ibu***R*⊂β-CD] and [**Ibu***S*⊂β-CD] complexes in the NP–W arrangement in both upper and side view.

[**Ibu***S*⊂β-CD] one. Upon further observation, we saw that the first complex presents two glucose units that have lost their parallel arrangement and are tilted (with the secondary hydroxyls pointing towards the interior of the cavity), while the second complex presents only one of such tilted glucoses.

2.4. Structural features

In this section, we present the structural aspects for the average structures of the [**Ibu**(*R*,*S*)⊂β-CD] inclusion complexes as arising from 4.5 ns molecular dynamics simulations relative to available experimental thermodynamic and X-ray data.

All penetration modes formed a 1:1 inclusion complex in the first 10 ps of simulation, and they remained as such thereafter. However, in the P–W penetration mode an association complex was observed for the **Ibu***S* isomer. Since the energetic analysis shows the NP–W penetration mode as the most representative of the inclusion complexes formed (see Table 3), in Figure 5a and b we present the averaged structures of **Ibu***R* and **Ibu***S* as obtained from MOIL-View for this arrangement. The RMSd for the best fit of the non-minimized structures [**Ibu***R*⊂β-CD] versus [**Ibu***S*⊂β-CD] and the corresponding minimized structures are 2.042 and 1.867, respectively. The superimposition of the non-minimized and minimized structures of **Ibu***R* is shown in Figure 5c and the corresponding structures of **Ibu***S* in Figure 5d. The RMSd for their best fit are 0.9615 and 0.7524, respectively. It is noteworthy that after minimization, in the absence of explicit solvent, **Ibu***R* moves into the β-CD cavity where the aromatic ring and the polar group suffer a better orientation due to electrostatics, while **Ibu***S* suffers minor geometric adjustments. The preferred NP–W penetration mode of **Ibu** inclusion correlates well with ^{1}H NMR results.[28b] Moreover, in similar solvent, temperature and pH conditions our simulation predicts the correct elution order of the enantiomers in capillary electrophoresis experiments.[26a]

A recent crystallographic study of the inclusion complex between pure **Ibu***S* and β-CD[25] presents a 2:1 host–guest stoichiometry in a head-to-head dimer, where the carboxylic end of the **Ibu***S* molecule faces the narrower rim of β-CD, position further stabilized by a hydrogen bond with one of the primary hydroxyl groups of the host. This mode of inclusion is opposite to the one we report and to the ^{1}H NMR results.[28b] The disagreement might originate because our simulations correspond to a solvated inclusion complex in a 1:1 host–guest stoichiometry, while in the crystal structure the formation of a 2:1 host–guest stoichiometry favors a channel type structure that could give extra stability to the **Ibu***S* orientation. Since the crystallographic structure does not indicate the direction of inclusion, we hypothesize that only the P–W and NP–N penetration modes could favor this orientation.

2.5. Electronic absorption data

Ibuprofen forms 1:1 inclusion complexes with α, β and γ cyclodextrins, in pH 7.5 buffer aqueous solutions. The interaction constant of [**Ibu**$^{-1}$⊂β-CD] at 298 K is

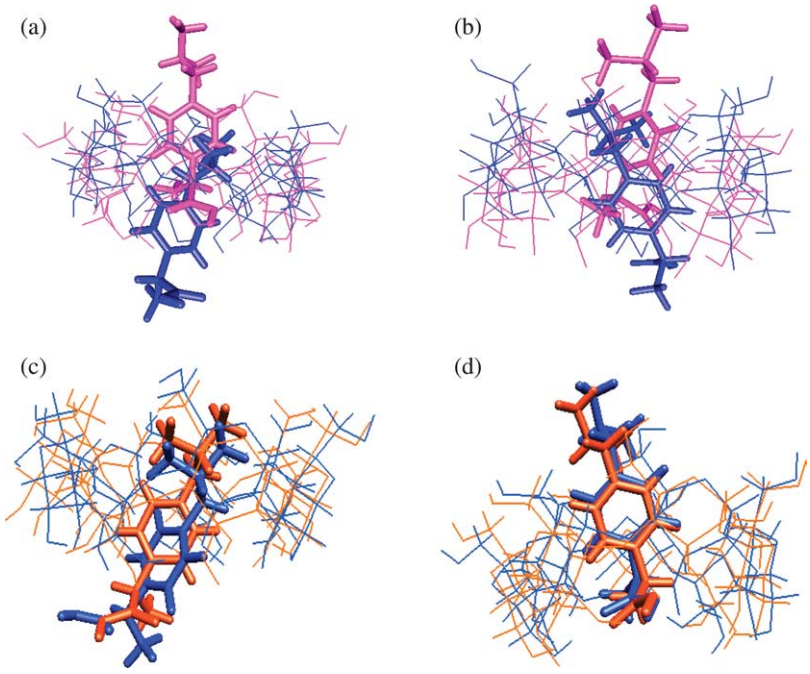

Figure 5. Average structures of the [**Ibu***R*⊂β-CD] and [**Ibu***S*⊂β-CD] complexes after 4.5 ns of simulation of the initial NP–W arrangement. (a) Nonminimized structures, in blue that of the **Ibu***R* enantiomer and in magenta that of the **Ibu***S* enantiomer. (b) Minimized structures of the same complexes shown in (a). (c) Comparison of the nonminimized (blue) and minimized (orange) average structure of [**Ibu***R*⊂β-CD]. (d) Comparison of the nonminimized (blue) and minimized (orange) average structure of [**Ibu***S*⊂β-CD].

$170\pm10\ M^{-1}$; some of its thermodynamic parameter values were determined: $\Delta H_{interaction}$ and $\Delta S_{interaction}$, $+2.82$ kcal mol^{-1} and $+0.019$ kcal mol^{-1} K^{-1}, respectively. While the values of the corresponding interaction constants for [**Ibu**$^{-1}$⊂α-CD] and [**Ibu**$^{-1}$⊂γ-CD] complexes, under the same reaction conditions, are: 190 ± 10 and $170\pm15\ M^{-1}$, respectively.[38] Therefore, the magnitude of these interaction constants for the 1:1 complexes seems to indicate that the cavity size of the cyclodextrins is not an important factor for the **Ibu** complexation. Additionally, these interaction constants are small in comparison with other reported values for anti-inflammatory-cyclodextrin binding constants.[39] There are several reports[40] in the literature about the complexation of guest molecules containing alkyl chains and cyclodextrins, where the alkyl moieties are included into the cyclodextrin cavity; in these cases the binding constants are also small.

2.6. Two dimensional NMR spectra

The alkyl chain of **Ibu** is part of its hydrophobic moiety involved in the complexation. The negatively charged group of this guest species drives the direction in which it is oriented during the inclusion process. The carboxylate group remains in contact with the aqueous solution and the uncharged moiety is included in the cyclodextrin cavity.

The NOESY spectrum (see Fig. 5 of the Supplementary material) shows changes corresponding to the signals of H-3 of the β-CD. Significant changes in the corresponding signals of the H-2 and H-4 are also observed on cyclodextrin external protons. This NOESY spectrum is indication of a weak interaction between the **Ibu** molecule and the β-CD. Both, the aromatic and the alkyl moieties are included into the cyclodextrin ring and are protected from the aqueous solution and the β-CD hydroxylic groups. The interaction of the guest with H-3, localized in the interior of the β-CD cavity and close to its wide part, and is due to the *iso*-alkyl group and the aromatic ring, when **Ibu** is included. The *iso*-butyl chain is completely included; however, the characteristic band associated with the interaction of H-5 of β-CD is absent in this spectrum. Perhaps, the great difference between the *iso*-butyl chain size and the internal cyclodextrin diameter, (≈4.3 and 7.8 Å, respectively) is responsible for this weak interaction.

The β-CD external section is also affected by the interaction with the *iso*-butyl chain of the guest molecule. When the [**Ibu**$^{-1}$⊂β-CD] complex is formed the *iso*-butyl chain is completely included, the –CH_2 group and the benzene ring remain close to H-5 and H-3, respectively. However, only the interaction with H-3 can be inferred in this spectrum, since the ibuprofen –CH_2 group weakly interacts with the internal H-5 of the host molecule.

The –CH group of the *iso*-butyl chain displays a small interaction signal with the H-6 of the β-CD, the remaining methyl and C-H groups of the guest that are not included within the confinement of the cyclodextrin, interact with the host external hydrogen atoms.

It can be suggested that the small interaction constant values is due to the small surface contact between the guest and host molecules, since ibuprofen is small for the cavity.

3. Conclusions

The main driving forces for complexation are dominated by non-bonded van der Waals intermolecular interactions and

the non-polar contributions to solvation, although the relative orientation of the interacting molecules and the presence of topical H-bonds between the polar part of the drug and the OH groups of the β-CD rims play a further role in stabilizing the supramolecular assemblies. Calculations of the energy components showed that under the conditions considered all 1:1 inclusion complexes are stable and, that a preferential way of insertion was detected, exception made for **Ibu***S* in the P–W penetration mode in which an association complex was formed.

The preferred penetration mode found corresponds to a geometry where the non-polar group of **Ibu** faces the wider cavity of the β-CD (NP–W). In this geometry, the **Ibu***R* enantiomer moves more freely inside the host cavity after insertion, while the **Ibu***S* enantiomer presents a more restricted motion. Moreover, the **Ibu***S* enantiomer forms a significant number of moderate to strong hydrogen bonds with the secondary hydroxyl groups of β-CD during the entire simulation time, while the **Ibu***R* enantiomer does not present such feature. In general, the energetic analysis reveals that the **Ibu***S* enantiomer is about 1 kcal/mol more tightly bonded than the **Ibu***R* enantiomer. This rather small energy difference is not enough to explain the chiral selectivity shown by β-CD upon **Ibu** isomers, however, the apparent geometrical differences shown by the [**Ibu**(*R*,*S*)⊂β-CD] molecular complexes suggest that the **Ibu** chiral discrimination is also due to an induced fit effect.

In summary, we have shown that the recognition process is based upon four steps. Step1: formation of the guest–host complex. Step 2: positioning of both guest and host to optimize interactions (conformational adjustments). Step 3: formation of secondary interactions (activation of the complexes). Step 4: expression of molecular fit (chiral recognition). Within the limits of this study we did not detect any three-point recognition process.

The small contact surface formed from the inclusion complexes of $\mathbf{Ibu}^{-1}$ ion and the cyclodextrin cavity discards van der Waals interactions as a stabilizing factor of the inclusion complex. The positive values of the $\Delta H_{\text{interaction}}$ and $\Delta S_{\text{interaction}}$, computed from the absorption electronic spectroscopic data, lead to the identification of the hydrophobic effect as the driving force for the formation of the [$\mathbf{Ibu}^{-1}$⊂β-CD] complex in aqueous solution; while the geometry of this inclusion complex was established by the $\text{ion}_{\text{ibuprofen}}$–$\text{dipole}_{\beta\text{-CD}}$ interaction. The $\mathbf{Ibu}^{-1}$ ion produces 1:1 inclusion complexes with the smallest interaction constant values, when compared with other anti-inflammatory-cyclodextrin complexes.

4. Construction of models

The atomic coordinates for the *S*-(+)-**Ibu** enantiomer (**Ibu***S*) were obtained from the 3D Pharmaceutical Structure Database (3DPSD).[41] The *R*-(−)-**Ibu** enantiomer (**Ibu***R*) was obtained from reflection of the first one. The β-CD molecule was built using the PREP/LINK/EDIT/PARM modules of the AMBER v.5 programs[42] suite, by connecting seven D-glucopyranose units from the GLYCAM_93 fragment library[43] through the α-(1,4) glycosidic linkages.

The starting orientations for the inclusion complexes were built by the combination of all the insertion possibilities, thereby identified as the penetration modes NP–W, NP–N, P–W and P–N shown in Figure 2. For instance, NP–W means that the non-polar chain of **Ibu** is placed at the entrance of the wide rim, or secondary hydroxyl rim, of β-CD. The rest of the labels are self explanatory.

The 1:1 inclusion complexes were constructed between β-CD and each one of the two **Ibu** enantiomers in the neutral moiety. The corresponding geometries were achieved with the aid of the docking module of the InsightII program package.[44] Unfavorable interactions within these structures were relieved by energy minimization with steepest descent followed by conjugate gradient energy minimization until the RMS of the elements of the gradient vector was less than 10^{-4} kcal/(mol Å).

5. Computational methodology

The parm94 force field,[45] the GLYCAM_93[43] set of parameters and the AMBER program[42] were used throughout this work. The partial atomic charges for the neutral **Ibu** isomers were obtained following the RESP methodology.[46] Accordingly, four low energy conformations of each **Ibu** enantiomer were minimized with the DFT method (B3LYP/6-31G**)[47] implemented in the Jaguar program,[48] and the electrostatic potential (ESP) was calculated at the HF/6-31G* level. For a better estimation of the guest atomic charges in the hydrophobic interior of β-CD, the ESP mesh was computed as if the **Ibu** molecule was immersed in cyclohexane. This was accomplished using the corresponding solvation module of Jaguar. In these calculations the solute is represented by a set of atomic charges and the solvent as a layer of charges at the solute molecular surface. The final set of atomic charges used in these computations is the result of averaging a total of eight conformations (four for each enantiomer). The atomic charges for β-CD were taken from the literature.[43]

The 1:1 inclusion complexes were solvated by a cubic box of 35 Å per side of TIP3P[49] water molecules, equivalent to a 0.001 M solution of pH 4.5. These conditions resemble those reported on capillary electrophoresis experiments.[50,51] The water imbibed models were gradually heated from 0 to 300 K in three steps of 100 K each. Each step had duration of 5 ps with diminishing restrains for the solute. The full system with no-restrains was equilibrated for approximately 20 ps at 300 K. This was followed by 4500 ps of data collection runs in order to examine the complex dynamics and structure. The temperature was maintained at 300 K by the Berendsen coupling algorithm,[52] with separate solute–solvent and solvent–solvent coupling. A total of 4500 snapshots were saved during the data collection period, one snapshot per 1 ps of MD simulation. Visual inspection showed that the 1:1 inclusion complex was formed within the first picoseconds of simulation and that it was stable during the entire simulation period. In order to compare with experimental results, various physical properties associated with the host molecule were calculated using the various modules present in the AMBER v.5 suite of programs.[42]

The MD simulations were carried out under an NPT ensemble. Periodic boundary conditions with a primary cutoff of 9 and 15 Å for a secondary cutoff for non-bonded interactions were applied. The long range electrostatic interactions were evaluated by the Ewald method.[53] The leap-frog algorithm with a time step of 1 fs with sampling taken every 1 ps was used. SHAKE was used for all bonds containing hydrogens.[54]

To estimate the binding free energy on the complex formation we employed the MM-PBSA/GBSA methodology[14,55,56] since it has been successfully applied to study the binding of small druglike molecules[57,58] to proteins,[59,60] RNA[61] and DNA.[16] In the frame of this methodology the free energy of binding for the association reaction A + B → AB is calculated using the following thermodynamic cycle:

$$\begin{array}{ccccc} A_{aqu} & + & B_{aqu} & \xrightarrow{\Delta G_{binding}} & AB_{aqu} \\ \downarrow{\scriptstyle -\Delta G^{A}_{solv}} & & \downarrow{\scriptstyle -\Delta G^{B}_{solv}} & & \downarrow{\scriptstyle \Delta G^{AB}_{solv}} \\ A_{gas} & + & B_{gas} & \xrightarrow{\Delta G_{gas}} & AB_{gas} \end{array}$$

$$\begin{aligned} \Delta G_{\text{binding}} &= \Delta G_{\text{gas}} - \Delta G^{\text{A}}_{\text{solv}} - \Delta G^{\text{B}}_{\text{solv}} + \Delta G^{\text{AB}}_{\text{solv}} \\ &= \Delta H_{\text{gas}} - T\Delta S - \Delta G^{\text{A}}_{\text{GBSA}} - \Delta G^{\text{B}}_{\text{GBSA}} + \Delta G^{\text{AB}}_{\text{GBSA}} \end{aligned}$$

where ΔG_{gas} is the interaction energy between A and B in the gas phase and $\Delta G^{\text{A}}_{\text{solv}}$, $\Delta G^{\text{B}}_{\text{solv}}$ and $\Delta G^{\text{AB}}_{\text{solv}}$ are the solvation free energies of A, B and AB, which are estimated using a continuum approach, that is, $\Delta G^{\text{A}}_{\text{solv}} = \Delta G^{\text{A}}_{\text{GBSA}} = \Delta G^{\text{A}}_{\text{GB}} + \Delta G^{\text{A}}_{\text{SA}}$, etc. Therefore,

$$\Delta G_{\text{binding}} = \Delta H_{\text{gas}} - T\Delta S + \Delta\Delta G_{\text{GB}} + \Delta\Delta G_{\text{SA}}$$

where

$$\Delta H_{\text{gas}} \approx \Delta E_{\text{gas}} = \Delta E_{\text{intra}} + \Delta E_{\text{electrostatic}} + \Delta E_{\text{vdw}} = E_{\text{MM}}$$

and

$$\Delta\Delta G_{\text{GB}} = \Delta G^{\text{AB}}_{\text{GB}} - \left(\Delta G^{\text{A}}_{\text{GB}} + \Delta G^{\text{B}}_{\text{GB}}\right)$$

$$\Delta\Delta G_{\text{SA}} = \Delta G^{\text{AB}}_{\text{SA}} - \left(\Delta G^{\text{A}}_{\text{SA}} + \Delta G^{\text{B}}_{\text{SA}}\right)$$

The polar solvation energy contribution is computed in continuum solvent with the Generalized Born (G_{GB}) model using the PARSE van der Waals radii,[62] with interior and exterior dielectric constants of 1 and 80, respectively; while the non-polar solvation energy contribution or the solvent accessible surface area (SASA) for each isolated state (host, guest, or complex) is calculated as $G_{\text{SA}} = \gamma\text{SA} + b$, where $\gamma = 0.00542$ kcal/(mol Å^2) and $b = 0.92$ kcal/mol, and SA is estimated with the MSMS program.[63]

The change of solute entropy upon binding, $-T\Delta S$, was estimated using the NMODE module of AMBER and the MOIL-View program[64] v.10.0. With MOIL-View we performed a cluster analysis of the [**Ibu**(*R*,*S*)⊂β-CD] complex structures within a RMSD of 1 Å during the MD trajectories. We focused on the six most populated clusters and obtained an average structure for each one of these clusters. These structures were minimized using a distance dependent dielectric constant of $\varepsilon = 4r_i$, to account for solvent screening, and its entropy was calculated using classical statistical formulas and normal mode analysis.

We also assumed that if one wishes to calculate the binding free energy difference between two similar guests bound to the same host, this process can be described by the following thermodynamic cycle:

$$\begin{array}{ccccc} IbuR & + & \beta CD & \xrightarrow{\Delta G^{R}_{binding}} & IbuR:\beta\ CD \\ \downarrow{\scriptstyle \Delta G_{solv}} & & & & \downarrow{\scriptstyle \Delta G_{B}} \\ IbuS & + & \beta\ CD & \xrightarrow{\Delta G^{S}_{binding}} & IbuS:\beta\ CD \end{array}$$

In such a way that,

$$\Delta\Delta G = \Delta G^{\text{R}}_{\text{binding}} - \Delta G^{\text{S}}_{\text{binding}} = \Delta G_{\text{solv}} - \Delta G_{\text{B}},$$

where $\Delta G^{\text{R}}_{\text{binding}}$ and $\Delta G^{\text{S}}_{\text{binding}}$ are the binding free energies for the R and S isomers of **Ibu**, respectively, and ΔG_{solv} and ΔG_{B} are the nonphysical transmutation free energy from the *R* to the *S* isomer of **Ibu** in free and bound states. Since we are interested in learning about the structural and energetic features that lead to chiral discrimination, we propose that we can calculate the binding free energy difference of the two enantiomers as $\Delta\Delta G = \Delta G^{\text{R}}_{\text{binding}} - \Delta G^{\text{S}}_{\text{binding}}$, where the $\Delta G_{\text{binding}}$ is calculated using the MM/GBSA methodology as described above. The ensemble of structures was generated by sampling the MD trajectory every 4 ps.

The hydrogen bond analysis was done with the hbond subroutine the PTRAJ module of AMBER. The maximum distance between acceptor oxygen and donor oxygen was considered to be 4.05 Å, and resulting hydrogen bonds were classified as strong, moderate and weak according to Jeffrey.[36]

AMBER MD calculations were performed on a SGI Onix R4400 with OS IRIX 6.5 and the MM/GBSA calculations were carried out in a PC Pentium III computer with Linux v.7.1.

6. Experimental

6.1. Chemical reagents

Ibuprofen (Boehringer-Ingelheim Promeco laboratories, Mexico City); β-CD was a donation from Arancia Mexico. The buffer components, Na_2HPO_4 and KH_2PO_4, and D_2O (99.9 at.% D) were supplied by Aldrich. NaCl, R.A. was purchased from Mallinckrodt. Water was distilled in a Barnstead Thermolyne System and given a second treatment in the Easypure RF Compact Ultrapure Water System. All chemical reagents were used without further purification except for β-CD. A 2% aqueous solution of β-CD was left to stand at room temperature for a long time in order to promote aggregation of insoluble impurities and complexes; the solution was then filtered off before recrystallization. β-CD was recrystallized from boiling water and it was then rinsed several times with ethanol, acetone and cold water.[65]

6.2. Preparation of the inclusion complexes

Prior to the inclusion complex study, we prepared a series of ibuprofen solutions in the calculated concentration range in aqueous solution to generate a calibration curve. The calibration curve was used to determine the absorbance of the guest at 10^{-5} mol dm^{-3}. In aqueous solution, the absorbance of β-CD in the concentration range studied (10^{-3}–10^{-2} mol dm^{-3}) was also known. Inclusion compounds were prepared by direct dissolution. The 10^{-5} mol dm^{-3} guest solutions were employed to dissolve increasing concentrations of cyclodextrin. In this way, the inclusion compound solutions were prepared. The buffer solution, pH 7.5, consists of Na_2HPO_4/KH_2PO_4 (0.07895 mol dm^{-3}) with constant ionic strength of 0.1 mol dm^{-3} NaCl. At this pH the carboxylic group of ibuprofen takes the ionic form of the ibuprofenate ion (**Ibu**$^{-1}$).

The absorption spectra of each solution series were measured 24 h after their preparation using a 1 cm path length cell. Each solution was measured several times. Thus, the resulting absorption data are average values, to minimize the measurement errors. The same general procedure was followed for the formation of inclusion complexes in the other reaction media.

6.3. Spectroscopic measurements

The UV–vis electronic absorption spectra were determined using a Hewlett Packard 8452A Diode Array Spectrophotometer. The temperature was kept constant by means of a Peltier Hewlett Packard 89090A system. Water was used as blank in all measurements.

^{1}H NMR experiments were carried out in non-buffered D_2O solutions. 1D ^{1}H NMR spectra were collected on a 300 MHz Varian Unity Plus spectrometer using a frequency of 299.95 MHz, with a 45° pulse (6.7 μs), spectral width of 3229.5 Hz, 3.002 s of acquisition time and 298 K. The number of transients acquired (32–128) depended on the sample sensitivity. Nuclear Overhauser Effect (NOESY) data were collected with the same 300 MHz Varian Unity Plus spectrometer, with a broad band switchable probe. Spectral width was 2731.5 Hz in both dimensions, with an acquisition time of 0.187 s.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.02.010. Distribution of the hydrogen bonding pattern of the NP–W, P–W and P–N penetration modes, the average structure of the **Ibu***S*:β-CD association complex as obtained from the MD for the P–W arrangement, and the NOESY spectrum of the [**Ibu**$^{-1}$⊂β-CD] complex in D2O at 298 K are given.

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New heterotopic, linked macrocyclic systems derived from selectively protected macrocycles

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Abstract—The use of orthogonally protected cyclam and 1,9-dithia-5,13-diazacyclohexadecane macrocycles, in combination with aza-18-crown-6, has enabled the efficient synthesis of a new heterotritopic macrocyclic ligand incorporating N_4-, N_2S_2- and NO_5-donor sites. A similar strategy has allowed the incorporation of cyclam and 1,9-dithia-5,13-diazacyclohexadecane into a cofacial ligand. Further, the synthesis of novel tetramacrocyclic ligands has been achieved in which the macrocycles are linked in a cyclic arrangement. The availability of different binding sites in the respective products makes the latter suitable candidates for the synthesis of a range of mixed-metal multinuclear complexes.

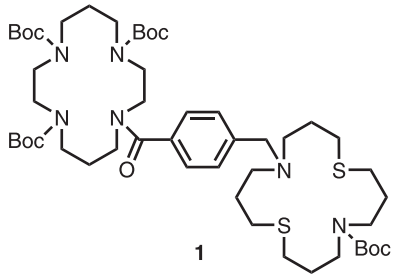
1. Introduction

A major thrust in recent macrocyclic ligand research has been the development of multi-component structures in which individual macrocyclic units are linked.[1–5] Examples of such systems exist that display a range of molecular architectures that include, linear, branched, stacked, and dendritic arrangements of their macrocyclic components. Such nanometre-scale structures have been employed in a range of studies for binding two or more metal ions simultaneously in defined positions with respect to each other.

The majority of the investigations in the above area have involved linked systems incorporating macrocycles of a similar type.[1–5] Examples include linked crown,[6–8] aza-crown,[7,9–16] thiaazacrown[17,18a–c] and porphyrin-derived systems[19,20]—in part, reflecting the ease of synthesis of suitably functionalised derivatives involving these macrocyclic types.

Examples incorporating hetero-macrocyclic rings are much less common even though such compounds have the potential to produce new hetero-metal systems exhibiting unusual properties, including unusual spectral, photoactive and redox properties.[21] Beside their considerable intrinsic interest, linked di- or polynuclear macrocyclic complexes may also serve as models for the charge transfer, electron transport and allosteric behaviour found in many metal-containing biochemical systems.[22,23]

Previously, we have reported the facile synthesis of a number of new linked, homo-[17,24,25] and heteroditopic[26] macrocycles obtained via simple protecting group strategies. For example, in one study, tris(*N*-Boc) cyclam and *N*-Boc protected S_2N_2-donor macrocycles were linked via unsymmetrical linking agents to yield intermediates such as **1**.[26]



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Based on the methodology developed in the above studies, an aim of the investigation now reported was to undertake the synthesis of structurally more elaborate linked species such as the heterotritopic and cofacial derivatives exemplified by **2** and **3**. Motivation for the synthesis of such species included the desire to obtain ligand systems capable of promoting the binding of different metal ions in sterically defined spatial and electronic environments.

Keywords: Linked macrocycle; Cofacial; Heterotopic; Orthogonal protection; Cyclam.
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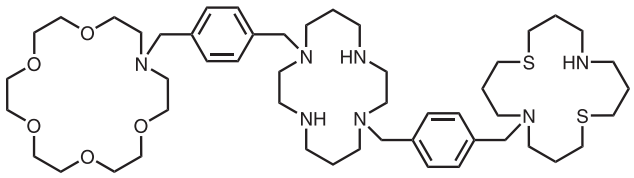

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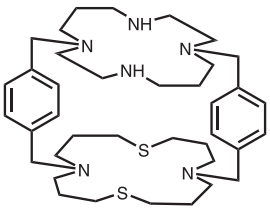

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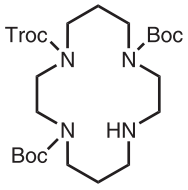
2. Results and discussion

2.1. Protected macrocyclic precursors

The synthesis of **2** and **3** required the N-protection of cyclam with two orthogonal protecting groups such that two (*trans*) nitrogens could be separately functionalised. Protected cyclams of this general type have been reported.[27,28] However, these were not suitable for our purposes since they require somewhat harsh conditions for deprotection and, in any case, the isolation of the starting diprotected macrocycle is not necessarily straightforward. Both of these potential difficulties were satisfactorily circumnavigated by synthesising the trihetero-protected cyclam **4**.



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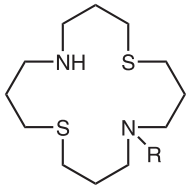
Access to *trans*-diprotected cyclams in large quantities and high yields was made possible via the procedure reported by Guilard et al. for the synthesis of **5**.[29] Subsequently, **5** was reacted with 2 equiv of di-*tert*-butyl dicarbonate and the benzyl groups removed by hydrogenation over palladium catalyst to give **7** (Scheme 1). It appeared not to be possible to use **5** directly for formation of the proposed linked hetero-ring systems as our experience is that removal of benzyl groups by hydrogenation is difficult in the presence of sulfur-containing macrocycles due to poisoning of the catalyst.

The 2,2,2-trichloroethoxycarbonyl (Troc) protecting group was chosen for protection of one of the nitrogens of **7** since this group can be readily removed under mild conditions in the presence of the *tert*-butoxycarbonyl group.[17] Thus, addition of 0.8 equiv of Troc chloride to 1,8-di-Boc(cyclam) **7** gave the required triprotected cyclam **4** in 46% yield (based on **7**) (Scheme 2). This product was readily characterised by ^{1}H NMR, the *t*-butyl singlet at δ 1.46 and Troc methylene resonance at δ 4.75 being diagnostic. Attempts to increase the yield of **4** by using more Troc chloride were unsuccessful and led instead to increased isolation of the di-Troc derivative **8**. The symmetry of **8** allows it to be easily distinguished from **4** by the presence of a single resonance for the ring methylene groups β- to nitrogen (δ 1.83).

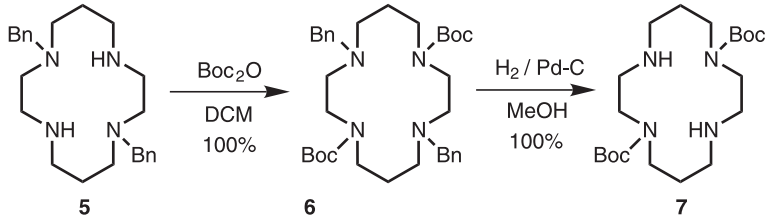
Alternatively, tetra-protected cyclam **8** was obtained in 85% yield by reaction of **7** with excess Troc chloride. After removal of the Boc groups from **8** to give **9** in 95% yield, subsequent reaction with 0.8 equiv of Boc_2O allowed the isolation of the alternative triprotected cyclam **10**, in 78% yield (based on **9**) (Scheme 3). This species, while not used in the current synthesis, represents an alternative trihetero-protected cyclam.[30]

The second macrocyclic component chosen for incorporation into the planned heterotopic systems was the 16-membered S_2N_2-donor macrocycle **11**. Macrocycle **11** was a desirable component for the proposed systems as it provides a very different coordination environment compared to cyclam. The parent (unsubstituted) macrocycle was originally reported by Kaden et al.[31] However, the synthetic approach employed in this previous study was not suitable for our present purpose since it did not allow easy chemical differentiation between the two ring nitrogen sites.



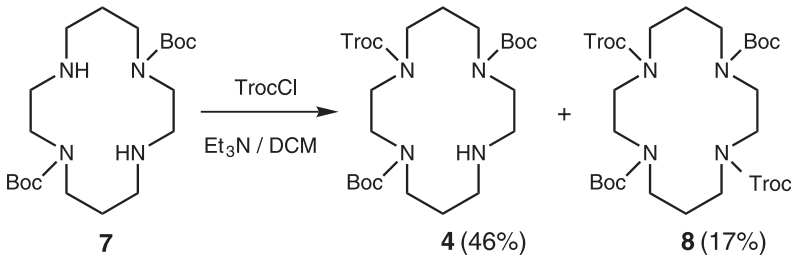
11 R = H
12 R = Boc
13 R = Troc

Incorporation of **11** into linked homotopic systems, including dendrimers, has been demonstrated previously by our group,[17,32] aided by the availability of syntheses for

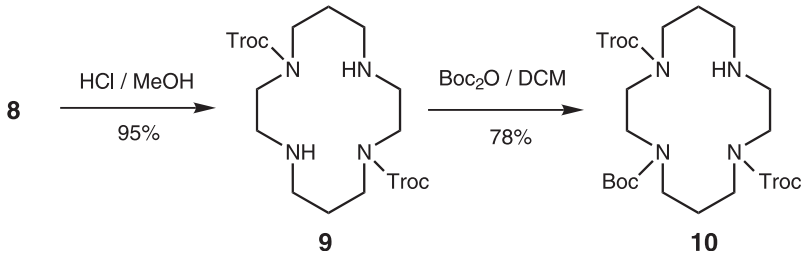


5 6 7

Scheme 1.



Scheme 2.



Scheme 3.

several mono-protected derivatives that include **12** and **13**. The latter species appeared suitable for incorporation into hetero-ring, ditopic systems of the type of interest in the present study.

2.2. Synthesis of orthogonally protected linked intermediates

Since different macrocyclic ring systems were to be linked, a stepwise synthetic approach was employed as we have previously demonstrated that such an approach is generally applicable for obtaining linked hetero-ditopic macrocyclic systems.[26] 4-(Chloromethyl)benzoyl chloride **14** was employed as a difunctional linking reagent in our previous studies,[26] and was again used for the current synthesis. Selectivity tends to be facilitated when using this linking reagent due to the greater tendency for acylation, rather than alkylation, to occur at the secondary amino groups present in the (partially) protected macrocycles of interest.

A solution of triprotected cyclam **4** in dichloromethane containing triethylamine was reacted with 4-(chloromethyl)benzoyl chloride **14** to give chloroamide **15** in 95% yield (Scheme 4). As expected, the signals for the methylene groups α- to the secondary nitrogen in **4** (δ 2.16 and 2.78) are absent from the ^{1}H spectrum of the amide **15**. Instead, these resonances are shifted downfield to ca. δ 3.2 such that they overlap with the signals for the methylene groups α- to carbamate nitrogens. The benzylic protons of **15** appear at δ 4.59.

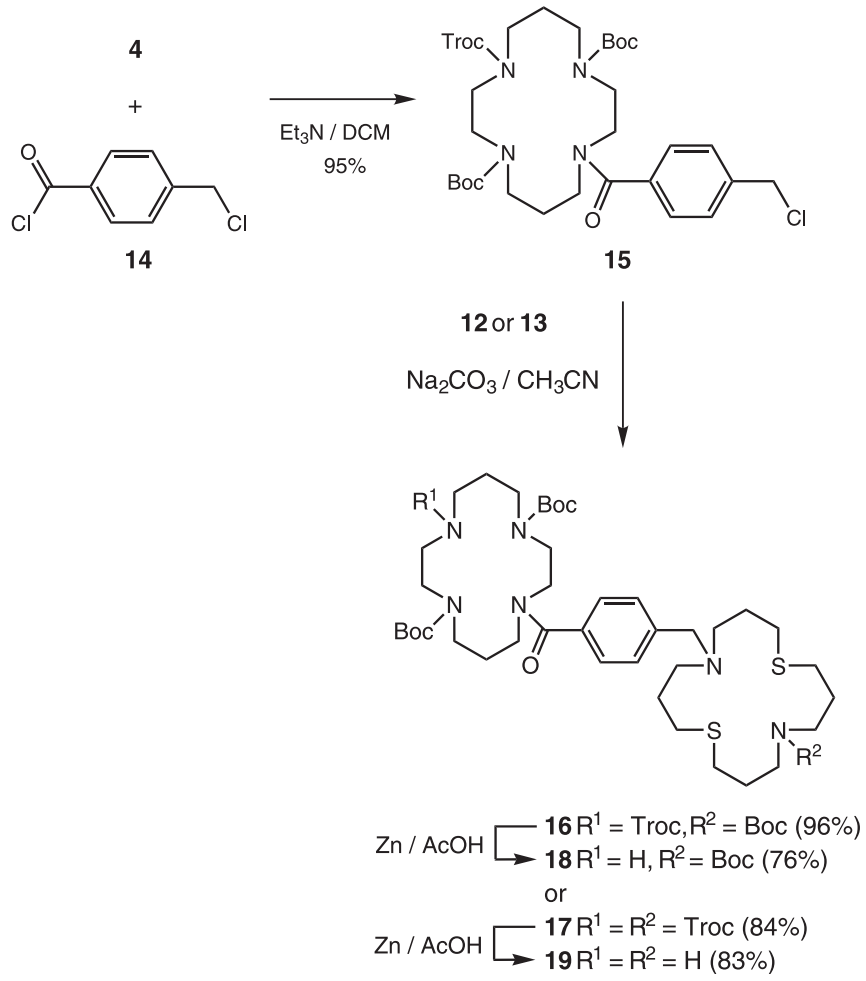
For the synthesis of the heterotritopic ligand **2**, it was necessary that the protecting group on the S_2N_2-donor macrocycle be orthogonal to the Troc group of the cyclam moiety in order to facilitate further functionalisation of the latter. Thus, the *N*-Boc-S_2N_2-derivative **12** was alkylated with **15** to give the tris(Boc)-Troc-protected amide **16** (Scheme 4). The reaction was carried out in refluxing acetonitrile in the presence of sodium carbonate over a period of 24 h and **16** was isolated in 96% yield. The ^{1}H NMR spectrum of the product was in accord with the expected product; in particular, the benzylic proton signal of **15** (δ 4.59) was replaced by a singlet at δ 3.51, characteristic of a benzylamine derivative. The Troc-protected S_2N_2-donor macrocycle **13** was alkylated with **15** under the same conditions; the corresponding linked amide **17** was obtained in 84% yield after chromatography (Scheme 4).

Selective removal of the Troc group of **16** was achieved by zinc reduction in glacial acetic acid to give **18** in 76% yield (Scheme 4). As expected, deprotection was accompanied by the disappearance of the Troc methylene resonance at δ 4.75 in the ^{1}H spectrum of **16**. Removal of the Troc protecting groups from **17** was again effected by treatment with zinc/glacial acetic acid, with the desired product **19** being isolated in 83% yield (Scheme 4).

2.3. Synthesis of a heterotritopic ligand

The selective Troc-deprotection of **16** enabled functionalisation of the resulting secondary amine ring of intermediate **18**. Thus, acylation of **18** with **14** (triethylamine/dichloromethane) gave the chloroamide **20** in 93% yield (Scheme 5).

Based on the success of the above procedures, it was decided to attempt the synthesis of a heterotritopic system in which a third macrocycle was incorporated that had different coordination characteristics to those of either the (essentially) soft-donor character of the S_2N_2-donor macrocycles or the intermediate character of the N_4-donor set of cyclam. The monoaza crown ether macrocycle 1-aza-18-crown-6 **21**, with its five hard ether donors, appeared to be an ideal precursor for the third ring. This system also had the advantage that it contains a single secondary amine linkage site without the need to protect other amino groups. Accordingly, **21** was alkylated with **20** in acetonitrile in the presence of sodium carbonate to give **22** in 50% yield after chromatography on silica gel (Scheme 5). A second, lower R_f component with a similar ^{1}H NMR spectrum to that of **22** was also isolated from the chromatography. This lower R_f



Scheme 4.

component was much less soluble in chloroform. The only discernable difference in the ^{1}H NMR spectra of the respective fractions was associated with proton signals arising from the azacrown moiety.[33] In view of this, it was concluded that the lower R_f compound was likely the sodium adduct of **22**, with the sodium ion originating from the sodium carbonate used in the synthesis. The chromatography of sodium adducts of azacrowns has been performed previously by our group.[34]

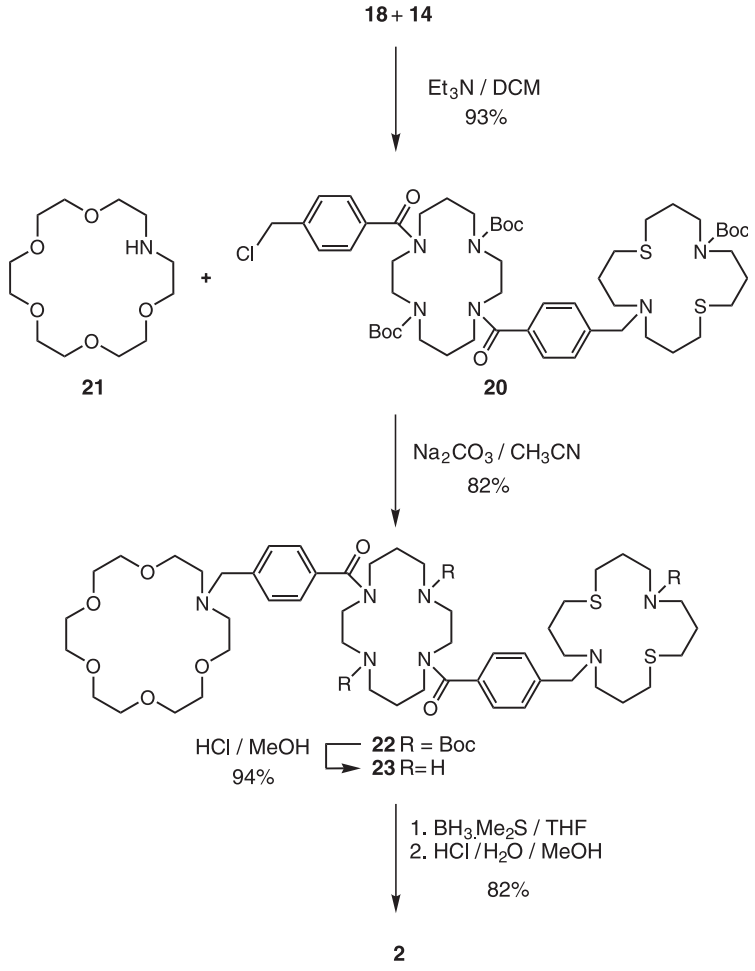
The suspected sodium adduct was converted to the metal-free product by partitioning it between chloroform and water and continuously extracting the organic phase with water (using a continuous extractor for liquid–liquid extraction by upward displacement) over 3 days. The material in the organic layer then ran at an identical R_f to the initial crop of **22** and also displayed an identical ^{1}H NMR spectrum to it. Combining the two fractions gave an overall yield of **22** of 82%. This combined product was dried by azeotropic distillation of a toluene solution (rather than over sodium sulfate).

A two-step deprotection/reduction protocol (Scheme 5) was used to obtain the target heterotritopic ligand **2** (even though it has been reported that in a related synthesis both steps could be accomplished simultaneously).[35] In our case, the two step procedure had the advantage that it made the intermediate diamide **23** available for possible future metal coordination studies. This latter product was obtained by deprotection of **22** with methanolic hydrochloric acid. Work-up involved basifying the reaction mixture with aqueous ammonium hydroxide, instead of sodium or potassium hydroxide, to avoid alkali metal adduct contamination.

The final step in the synthesis of **2**, the reduction of the amide groups of **23** by borane–dimethylsulfide complex in tetrahydrofuran, was achieved in 82% yield (Scheme 5) and corresponded to the disappearance of the amide carbon resonance (δ 171.7) originally present in the ^{13}C NMR spectrum of **23**. Likewise, a strong absorption at 1621.8 cm^{-1} in the infrared spectrum of **23**, consistent with an amide stretching frequency, was absent in the corresponding spectrum of **2**. HRMS data also supported the proposed structure.[†]

The ^{1}H NMR spectrum of **2** is noticeably sharper than that of **23** reflecting the absence of amide rotamers in the

[†] A preliminary metal-ion coordination study led to isolation of a dinuclear copper(II) complex whose microanalysis corresponded to $[Cu_2L](ClO_4)_4\cdot H_2O$ (L=2). This complex was then treated with sodium perchlorate to give the sodium derivative, analysing as $[Cu_2NaL](ClO_4)_4\cdot 5H_2O$ (L=2)].



Scheme 5.

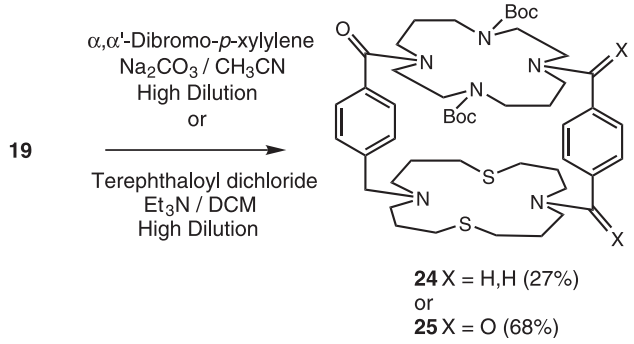
former;[26] nevertheless, numerous chemical shift overlaps were evident. The three types of protons for macrocyclic ring methylene groups not adjacent to heteroatoms appear as a complex multiplet between δ 1.6 and 1.9. When the spectrum was run at 333 K, three resonances were just resolved in this region, with the other spectral resonances remaining largely unchanged. A complex multiplet in the region δ 2.4–2.8 is assigned to a combination of the macrocyclic ring methylene protons adjacent to the sulfur and amino groups. The complex multiplet between δ 3.5 and 3.8 corresponds to the methylene protons adjacent to oxygen as well as to the benzylic protons. The aromatic protons occur as a broad multipet in the region δ 7.3–7.5.

2.4. Synthesis of a hetero-ring cofacial ligand

Conversion of the linked bis(macrocycle) species **19** to its cofacial analog required intramolecular linking of its two secondary amino groups. The cyclisation involved the simultaneous addition of **19** and α,α'-dibromo-*p*-xylylene by means of a dual syringe pump to a suspension of sodium carbonate in refluxing acetonitrile over 110 h under high dilution conditions (Scheme 6). After chromatography, the desired 1 + 1 cyclisation product **24** was obtained in 27% yield, with HRMS supporting the target structure.

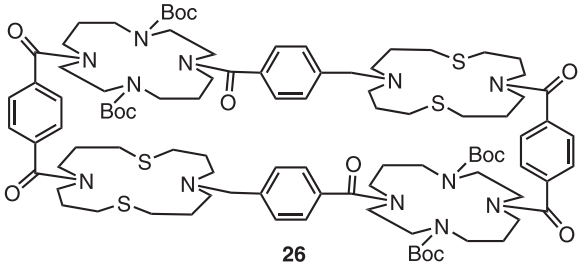
In light of the initial low yield obtained for the cyclised product, a further attempt was made to effect the cyclisation via a bis-acylation reaction employing terephthaloyl dichloride. Thus, addition of **19** and terephthaloyl dichloride via the dual syringe pump to a solution of triethylamine in dichloromethane under high dilution was carried out over 110 h (Scheme 6). After chromatography, the desired tricyclic ligand **25** was this time isolated in 68% yield.

A small amount (11% yield) of a product was also isolated during the above chromatographic procedure which had a

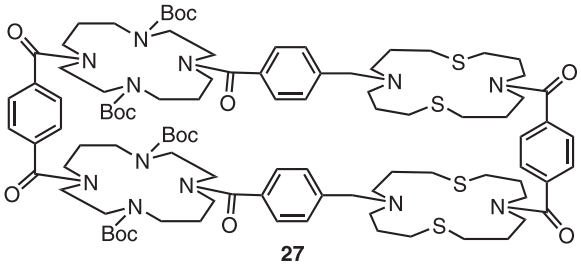


Scheme 6.

HRMS corresponding to a 2+2 cyclisation product. Isomers are possible for such stoichiometry, the most likely of which are given by **26** and **27**. It is assumed that neither one of these products would be favoured under the reaction conditions employed. Nevertheless, only one component was observed by TLC analysis using a variety of mobile phases.[36] As might be predicted, due to severe spectral overlap the NMR spectra of the product were uninformative with respect to possible isomeric composition. It is noted that while a catenane consisting of two interlocked 1+1 cyclisation products would also yield the same mass, it appears unlikely that such a product would form in preference to products of type **26** and **27**.



26



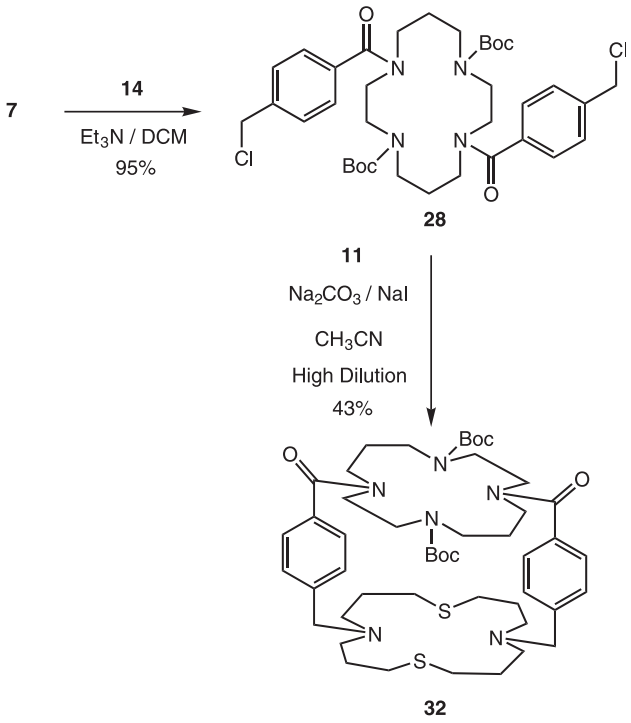
27

2.5. Synthesis of a cofacial ligand from a di-functionalised cyclam

The use of 4-(chloromethyl)benzoyl chloride **14** as a difunctional linking reagent was again used for bis-acylation of **7** to produce **28** in 95% yield after chromatography (Scheme 7).

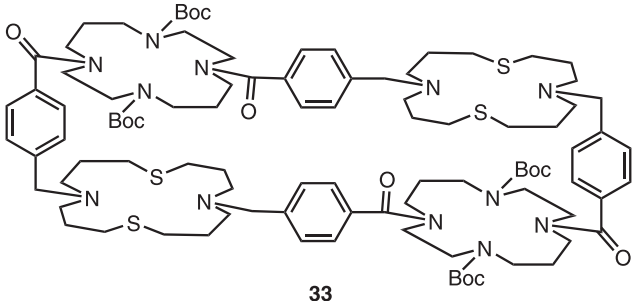
The possibility of bis-N-alkylation of the parent 16-membered S_2N_2-donor macrocycle **11** by the benzyl chloride functionalities present in **28** was also explored. The preparation of **11** was originally reported by Kaden et al.[31] However, in the present study a synthesis of **11** was devised which employed intermediates already prepared in the authors' laboratory.[17] Thus, cyclisation of *N*-Boc-dichloride **29** and *N*-Boc-dithiol **30** afforded the di-*N*-Boc macrocycle **31** in 60% yield (Scheme 8). Complete deprotection of **31** with trifluoroacetic acid in dichloromethane subsequently gave the desired macrocycle **11** in 96% yield.

Once again, using high-dilution conditions, macrocycle **11** and the bis(chloroamide) **28** were added simultaneously via a dual syringe pump to a suspension of potassium carbonate and sodium iodide in a large volume of refluxing acetonitrile over 110 h (Scheme 7). After workup and chromatography, the desired cofacial ligand **32** was isolated in 43% yield. Interestingly, a second, lower R_f component was isolated in 11% yield from the chromatographic procedure employed.



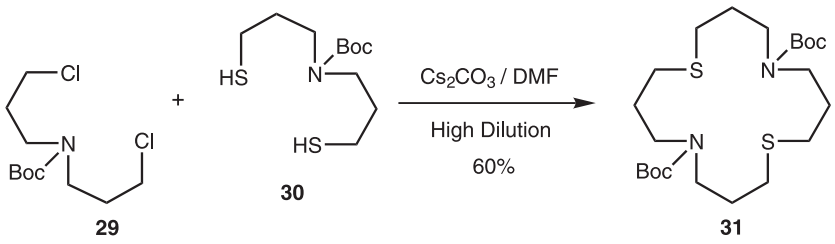
Scheme 7.

The ES-HRMS was in accord with this species being the 2+2 cyclisation product **33**.



33

The identification of **32** by electrospray mass spectrometry is complicated by the fact that this method may produce dimers during the ionisation process. A singly protonated dimer of **32** would give the same *m/z* parent ion as a singly protonated molecular ion of **33**, with an identical isotopic distribution. However, it is suggested that this did not occur as the mass spectra of **32** and **33** were dissimilar under the same ionisation conditions. The spectrum of **32** is unequivocal, with $[M+H]^+$ and $[M+Na]^+$ ions at *m/z* 895.5200 and 917.4958, respectively, with each peak displaying the predicted isotopic distribution. Neither $[2M+2H]^{2+}$ nor $[2M+H]^+$ ions were observed. For **33** $[M+H]^+$ and $[M+Na]^+$ ions at *m/z* 1789.9126 and 1811.8831 were observed; peaks at this *m/z* were not observed for **32** under the same ionisation conditions. Also, a peak occurs at *m/z* 895.5177 for **33**, with an isotopic distribution corresponding to that of a doubly protonated ion, consistent with the presence of $[M+2H]^+$. Other parent molecular ions corresponding to $[M+H+Na]^{2+}$ and

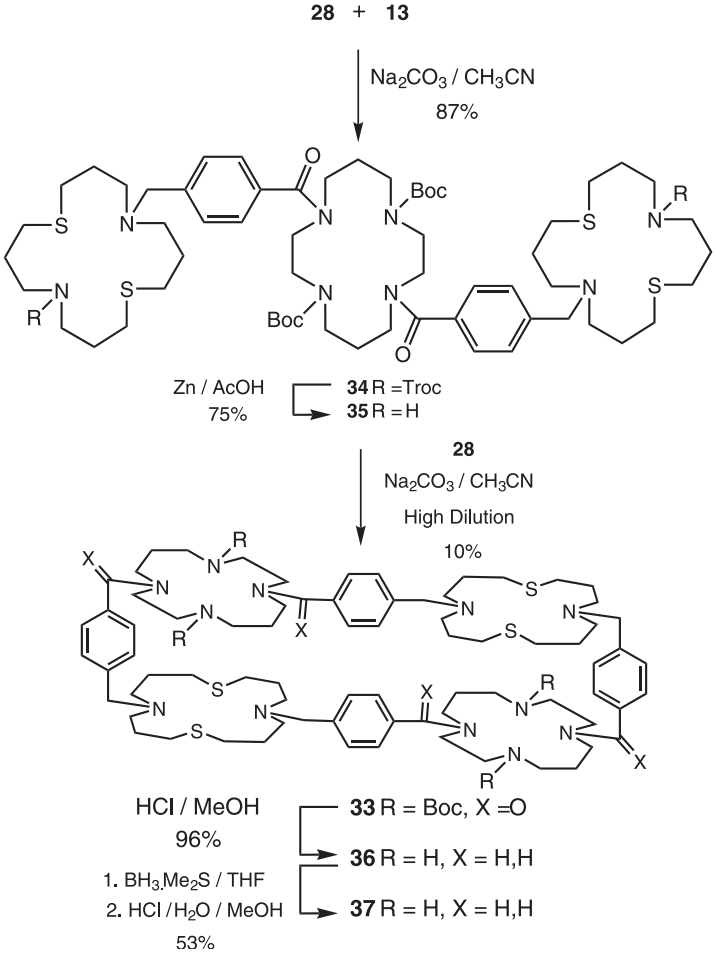


Scheme 8.

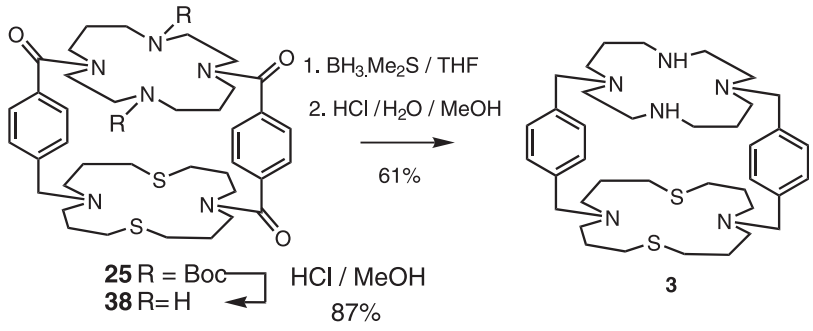
$[M+2Na]^{2+}$ were also observed, at *m*/*z* values of 906.5088 and 917.5900, respectively.

The ^{1}H NMR of **32** suffers from extreme broadening, most likely due to slow rotation of the amide rotamers.[26] The Boc singlet at δ 1.46 is broader than the analogous resonance for the linear bis(macrocycles) described above. Two broad signals at δ 1.74 and 1.89 are assigned to the macrocyclic ring methylenes not adjacent to a heteroatom. Two broad overlapping signals are found at δ 2.41 and 2.59 which are due to the ring methylenes adjacent to sulfur or a benzylamino group. A number of overlapping broad signals occur in the region δ 3.2–3.8 for the ring methylenes adjacent to amide nitrogens and the benzylic protons. Finally, two broad signals at δ 7.34 and 7.39 are due to the aromatic protons. The ^{1}H NMR spectrum of **33** in the present study was not able to be distinguished from that of **32**. The small chemical shift differences that might be expected between these two compounds are presumably masked by the broadness of the spectra.

The serendipitous isolation of the novel tetramacrocycle species **33** described above encouraged an attempt to synthesise this compound by means of a more considered (and hopefully higher yielding) strategy. To this end, the bis-alkylating agent **28** was reacted with two equivalents of the mono-Troc-protected macrocycle **13** to give the hetero-protected species **34** in 86% yield (Scheme 9). Removal of the Troc groups from **34** was performed with zinc in glacial acetic acid in 75% yield to give the tris(macrocyclic) species **35** containing two terminal NH groups.



Scheme 9.



Scheme 10.

Subsequent reaction of **28** with **35** under high dilution conditions was successful in affording the tetra-macrocyclic species **33**, but in the disappointingly low yield of 10% (Scheme 9). This low yield (and presumably also that for the product from the reaction of **28** with **11**) is attributed to the relatively large distance between the reacting termini of **35**, which lowers the prospect of ring closure but increases the tendency for oligomerisation. Obviously, this procedure is less than satisfactory for obtaining significant quantities of **33**.

2.6. Completion of target syntheses

Deprotection of **33** was accomplished in hydrochloric acid/methanol to give the tetraamide **36** in 96% yield (Scheme 9) while the bis(Boc) cofacial ligand **25** was also readily deprotected to give the cofacial amide **38** in 87% yield (Scheme 10). Reduction of the respective amides was performed with borane dimethyl sulfide complex in tetrahydrofuran. Reduction of **36** gave **37** in 53% yield (Scheme 9). To obtain the unsubstituted cofacial derivative **3**, amide **38** was reduced with borane dimethyl sulfide complex to yield **3** in 67% yield (Scheme 10).[37]

In contrast to the observations made for the linear tritopic ligand **2**, final reduction of the amide groups of **38** did not lead to the expected sharpening of the ^{1}H NMR spectrum of the reduced product **3**—possibly a result of the cyclic nature of **3** restricting bond rotation to an intermediate rate on the NMR time scale. Obtaining the spectrum at higher temperatures did not result in a significant improvement. Nevertheless, the spectrum could be reasonably assigned in terms of the types of protons present. The macrocyclic ring methylene protons not adjacent to a heteroatom give a broad resonance at δ 1.74 while the remaining ring methylene resonances are found at δ 2.4–2.8 (as broad overlapping signals). Two distinct singlets at δ 3.50 and δ 3.68 are assigned to the two types of non-equivalent benzylic protons. The aromatic protons give rise to a multiplet spanning δ 7.1–7.3. Under the conditions employed, the ^{1}H NMR spectrum of **37** was essentially indistinguishable from that of **3**.

In gauging the success of the various strategies for synthesising **3**, two aspects deserve comment. These are (i) the yield of the cyclisation step, and (ii) the ease of synthesis of the precursors required for this cyclisation. While **25** can be formed in a superior yield of 68%, the synthesis of the precursor **19** represents an involved procedure. Conversely, **32** was synthesised in the lower yield of 43%, but its precursor **28** is synthesised in three fewer steps. Further, the high-dilution conditions required for **25** (room temperature, dichloromethane) are perhaps preferred over those for **32** (refluxing acetonitrile). On balance, the synthesis of **3** is most efficiently achieved via **32**; however, of course, this route can not be applied to systems with unsymmetrical linkers.

3. Conclusions

The present paper describes the facile synthesis of new heterotopic macrocyclic ligands, including a heterotritopic tris(macrocyclic) ligand and a heteroditopic cofacial ligand. This has been achieved via the development of new orthogonal protecting group strategies enabling the selective linking of different macrocyclic components—including the linkage of four macrocycles incorporating two different donor sets, in a cyclic arrangement. Based on the known metal-ion chemistry of the constituent macrocycles, the described ligands incorporate sites that will clearly exhibit different affinities for particular metal ions. The new derivatives thus lead the way for the synthesis of a range of new hetero-metal complexes. Our efforts in this direction will be reported in due course.

4. Experimental

4.1. General

Where available, all reagents were of analytical grade. 1,4,8,11-Tetraazacyclotetradecane (cyclam),[38a,b] *N*-*tert*-butoxycarbonylbis(3-chloropropyl)amine **29**,[17] *N*-*tert*-butoxycarbonylbis(3-mercaptopropyl)amine **30**,[17] 1,8-dibenzyl-1,4,8,11-tetraazacyclotetradecane **5**,[29] 5-*tert*-butoxycarbonyl-1,9-dithia-5,13-diazacyclohexadecane **12**,[17] 5-(2,2,2-trichloroethoxycarbonyl)-1,9-dithia-5,13-diazacyclohexadecane **13**[17] and 1-aza-18-crown-6 **21**[39] were synthesised as described previously. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately prior to use. Acetonitrile and dichloromethane were distilled from calcium hydride. All reactions were carried out under an inert atmosphere of dry nitrogen. NMR spectra were recorded on a Bruker AM-300 spectrometer. Chemical shifts are quoted in δ units (ppm) relative to the residual proton signal in $CDCl_3$ (δ_H 7.26) or to $CDCl_3$ (δ_C 77.0). The majority of compounds prepared in this study were viscous

oils and elemental composition (of chromatographically homogeneous materials) is mainly supported by high-resolution mass spectrometry (HRMS). High-resolution electrospray ionisation mass spectra (ESI-MS) were obtained on a Bruker BioApex 47e FTICR mass spectrometer. In some cases, the most abundant peak in the spectra corresponded to the sodium adduct.

4.1.1. 1,8-Dibenzyl-4,11-bis(*tert*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane 6. To a solution of 1,8-dibenzyl-1,4,8,11-tetraazacyclotetradecane **5** (27.4 g, 0.072 mol) in dichloromethane was added di-*tert*-butyl dicarbonate (39.3 g, 0.18 mol) in dichloromethane and the mixture was stirred at room temperature for 4 h. The solvent was removed under reduced pressure and the resulting oily residue purified by column chromatography on silica gel (eluting with 1% MeOH–DCM). The title compound was isolated as a colourless oil (41.8 g, 100%). [Found $(M+H)^+$, 581.4067 (ES). $C_{34}H_{52}N_4O_4$ requires $(M+H)^+$, 581.4061]; δ_H ($CDCl_3$; 300 MHz) 1.38 (18H, br s, ^tBu), 1.77 (4H, br m, $CH_2CH_2CH_2NH$), 2.4–2.7 (8H, br m, $ArCH_2NCH_2$), 3.2–3.6 (8H, br m, CH_2NBoc), 3.55 (4H, s, $ArCH_2$), 7.30 (10H, br s, ArH).

4.1.2. 1,8-Bis(*tert*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane 7. 1,8-Dibenzyl-4,11-bis(*tert*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane **6** (20.9 g, 36.0 mmol) was dissolved in methanol (100 cm^3) and glacial acetic acid (2 cm^3, 36.0 mmol) in a pressure hydrogenation vessel under a stream of N_2. Palladium on charcoal (10%) (3.8 g, 3.6 mmol) was carefully added to the solution and the mixture was then agitated under H_2 (3 atm) for 12 h. The catalyst was removed by filtration through Celite and the solvent was evaporated under reduced pressure. The residue was partitioned between 10% aqueous sodium hydroxide (100 cm^3) and dichloromethane (300 cm^3) then the aqueous layer was re-extracted with dichloromethane (2×250 cm^3). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give an oily residue, which was purified by column chromatography on silica gel (eluting with 5% MeOH–DCM). The title compound was isolated as colourless oil (14.4 g, 100%). The ^1H NMR spectrum was as previously reported.[40]

4.1.3. 1,8-Bis(*tert*-butoxycarbonyl)-4-(2,2,2-trichloroethoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane 4. 1,8-Bis(*tert*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane **7** (2.27 g, 5.67 mmol) was dissolved in dry dichloromethane (80 cm^3). Triethylamine (0.69 g, 6.8 mmol) and then 2,2,2-trichloroethyl chloroformate (0.96 g, 4.54 mmol) in dichloromethane (30 cm^3) were added. The reaction mixture was stirred at room temperature for 12 h. The organic layer was washed with water (2×50 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. Purification of this material was achieved by column chromatography on silica gel (eluting with 1% MeOH–DCM). The title compound was isolated as a yellow oil (1.50 g, 72%). [Found $(M+Na)^+$, 597.2014 (ES). $C_{23}H_{41}N_4O_6Cl_3$ requires $(M+Na)^+$, 597.1984]; δ_H ($CDCl_3$; 300 MHz) 1.46 (18H, br s, ^tBu), 1.71 (2H, br m, $BocNCH_2CH_2CH_2NH$), 1.95 (2H, br m, $BocNCH_2CH_2CH_2NBoc$), 2.61 (2H, br m, $CH_2CH_2CH_2NH$), 2.78 (2H, br m, $BocNCH_2CH_2NH$), 3.2–3.6 (12H, br m, CH_2NBoc), 4.73 (2H, s, Cl_3CCH_2OCO); δ_C ($CDCl_3$; 75 MHz) 28.5, 29.6, 30.8, ~45–50 (broad overlapping signals), 75.1, 79.6, 95.7, 155.4, 156.2.

4.1.4. 1,8-Bis(*tert*-butoxycarbonyl)-4,11-bis(2,2,2-trichloroethoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane 8. 1,8-Bis(*tert*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane **7** (1.00 g, 2.50 mmol) was dissolved in dry dichloromethane (50 cm^3). Triethylamine (0.76 g, 7.5 mmol) and then 2,2,2-trichloroethyl chloroformate (1.32 g, 6.25 mmol) were added by syringe. The reaction mixture was stirred at room temperature for 2 h. The organic layer was then washed with water (2×30 cm^3), dried (sodium sulfate) and evaporated under reduced pressure. Purification of this material was achieved by column chromatography on silica gel (eluting with 1% MeOH–DCM). The title compound was isolated as a yellow oil (1.59 g, 85%). [Found $M+Na^+$, 771.1008 (ES). $C_{26}H_{42}N_4O_8Cl_6$ requires $M+H^+$, 771.1026]; δ_H ($CDCl_3$; 300 MHz) 1.45 (18H, br s, ^tBu), 1.83 (4H, br m, $CH_2CH_2CH_2$), 3.3–3.5 (16H, br m, CH_2NCO), 4.74 (4H, s, Cl_3CCH_2OCO); δ_C ($CDCl_3$; 75 MHz) 28.3, ~45–50 (broad overlapping signals), 75.0, 80.1, 95.3, 154.0, 155.8.

4.1.5. 1,8-Bis(2,2,2-trichloroethoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane 9. Tetra-substituted cyclam **8** (3.50 g, 4.66 mmol) was dissolved in methanol (80 cm^3) and stirred with concentrated hydrochloric acid (4.7 cm^3, 365 g/L, 47 mmol) at room temperature for 2 h. The methanol was removed in vacuo and the residue partitioned between 10% aqueous sodium hydroxide (50 cm^3) and dichloromethane (100 cm^3). The layers were separated and the aqueous layer re-extracted with dichloromethane (2× 100 cm^3). The combined organic extracts were dried (sodium sulfate) and evaporated under reduced pressure to give the title compound as a yellow oil; this product was used without further purification (2.20 g, 85%). [Found $M+H^+$, 549.0148 (ES). $C_{16}H_{26}N_4O_4Cl_6$ requires $M+H^+$, 549.0158]; δ_H ($CDCl_3$; 300 MHz) 1.84 (4H, br m, CH_2CH_2N), 2.73 (4H, br m, $CH_2CH_2CH_2NH$), 2.88 (4H, br m, $TrocNCH_2CH_2NH$), 3.4–3.6 (8H, br m, CH_2NTroc), 4.75 (2H, s, Cl_3CCH_2OCO); δ_C ($CDCl_3$; 75 MHz) 28.9, ~45–50 (broad overlapping signals), 74.7, 95.5, 154.5.

4.1.6. 4-*tert*-Butoxycarbonyl-1,8-bis(2,2,2-trichloroethoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane 10. Bis(Troc)-cyclam **9** (2.10 g, 3.81 mmol) was dissolved in dry dichloromethane (40 cm^3) to which was added di-*tert*-butyl dicarbonate (0.67 g, 3.05 mmol) in dry dichloromethane (20 cm^3) and the reaction mixture was stirred for 12 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (eluting with 1% MeOH–DCM). The title compound was isolated as a colourless oil [1.94 g, 78% (based on **9**)]. [Found $M+Na^+$, 671.0493 (ES). $C_{21}H_{34}N_4O_6Cl_6$ requires $M+Na^+$, 671.0502]; δ_H ($CDCl_3$; 300 MHz) 1.46 (9H, br s, ^tBu), 1.77 (2H, br m, $TrocNCH_2CH_2CH_2NH$), 2.05 (2H, br m, $TrocNCH_2CH_2CH_2NBoc$), 2.65 (2H, br m, $CH_2CH_2CH_2NH$), 2.87 (2H, br m, $TrocNCH_2CH_2NH$), 3.2–3.6 (12H, br m, CH_2NBoc), 4.76 (2H, s, Cl_3CCH_2OCO); δ_C ($CDCl_3$; 75 MHz) 28.2, 29.4, ~45–50 (broad overlapping signals), 74.7, 79.4, 95.6, 154.0, 155.1.

4.1.7. 1,8-Bis(*tert*-butoxycarbonyl)-4-[4-(chloromethyl)-benzoyl]-11-(2,2,2-trichloroethoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane 15. Bis(Boc)-Troc-cyclam **4** (1.96 g, 3.40 mmol) was dissolved in dry dichloromethane (80 cm^3). Triethylamine (0.45 g, 4.42 mmol) and then 4-(chloromethyl)benzoyl chloride **14** (0.775 g, 4.08 mmol) were added by syringe. The reaction mixture was stirred at room temperature for 12 h. The organic layer was washed with water (2×50 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. Purification of this material was achieved by column chromatography on silica gel (eluting with 2% MeOH–DCM). The title compound was isolated as a colourless glass (2.40 g, 95%). [Found $(M+Na)^+$, 749.2037 (ES). $C_{31}H_{46}N_4O_7Cl_4$ requires $(M+Na)^+$, 749.2013]; δ_H ($CDCl_3$; 300 MHz) 1.47 (18H, br s, ^{t}Bu), 1.6–2.0 (4H, br m, $CH_2CH_2CH_2N$), 3.1–3.7 (16H, br m, CH_2NBoc), 4.58 (2H, s, $ArCH_2Cl$), 4.75 (2H, s, Cl_3CCH_2OCO), 7.3–7.5 (4H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 28.4, 45.3, ~45–50 (broad overlapping signals), 75.1, 80.2, 95.3, 126.6, 128.6, 136.3, 138.5, 154.2, 155.8, 171.2.

4.1.8. 5-*tert*-Butoxycarbonyl-13-(4-{[4,11-bis(*tert*-butoxycarbonyl)-8-(2,2,2-trichloroethoxycarbonyl)-1,4,8,11-tetraazacyclotetradecan-1-yl]carbonyl}benzyl)-1,9-dithia-5,13-diazacyclohexadecane 16. 5-*tert*-Butoxycarbonyl-1,9-dithia-5,13-diazacyclohexadecane **12** (1.24 g, 3.43 mmol) was dissolved in dry acetonitrile (15 cm^3) and added to a refluxing mixture of chloroamide **15** (2.08 g, 2.86 mmol), sodium carbonate (0.455 g, 4.29 mmol) and sodium iodide (0.086 g, 0.57 mmol) in dry acetonitrile (5 cm^3). The reaction was allowed to reflux for 24 h after which the solvent was removed under reduced pressure and the residue partitioned between dichloromethane (50 cm^3) and water (20 cm^3). The aqueous layer was extracted with dichloromethane (3×50 cm^3), the combined organic layers were dried (Na_2SO_4), then evaporated under reduced pressure to give a brown oil that was purified by column chromatography on silica gel (eluting with 2% MeOH–DCM). The title compound was isolated as a colourless glass (2.90 g, 96%). [Found $(M+H)^+$, 1053.4485 (ES). $C_{48}H_{79}N_6S_2O_9Cl_3$ requires $(M+H)^+$, 1053.4488]; δ_H ($CDCl_3$; 300 MHz) 1.46 (27H, br s, ^{t}Bu), 1.74 (4H, br m, $CH_2CH_2NCH_2Ar$), 1.89 (8H, br m, $CH_2CH_2CH_2NCO$), 2.3–2.6 (12H, m, CH_2S, CH_2NCH_2Ar), 3.1–3.7 (16H, br m, CH_2NCO), 3.52 (2H, s, $ArCH_2N$), 4.75 (2H, s, Cl_3CCH_2OCO), 7.3–7.4 (4H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 27.7, 28.5, ~45–50 (broad overlapping signals), 47.5, 52.8, 58.9, 75.2, 79.4, 80.1, 95.4, 126.3, 128.7, 135.0, 141.1, 154.3, 155.6, 171.7.

4.1.9. 5-(4-{[4,11-Bis(*tert*-butoxycarbonyl)-8-(2,2,2-trichloroethoxycarbonyl)-1,4,8,11-tetraazacyclotetradecan-1-yl]carbonyl}benzyl)-13-(2,2,2-trichloroethoxycarbonyl)-1,9-dithia-5,13-diazacyclohexadecane 17. 5-(2,2,2-Trichloroethoxycarbonyl)-1,9-dithia-5,13-diazacyclohexadecane **13** (0.29 g, 0.66 mmol) was dissolved in dry acetonitrile (5 cm^3) and this solution was added to a refluxing mixture of chloroamide **15** (0.40 g, 0.55 mmol), sodium carbonate (0.09 g, 0.83 mmol) and sodium iodide (0.02 g, 0.11 mmol) in dry acetonitrile (5 cm^3). The reaction mixture was heated at reflux for 24 h after which the solvent was removed under reduced pressure and the residue partitioned between dichloromethane (30 cm^3) and water (10 cm^3). The aqueous layer was extracted with dichloromethane (3×50 cm^3), the combined organic layers were dried (sodium sulfate) and evaporated under reduced pressure to give a brown oil that was purified by column chromatography on silica gel (eluting with 2% MeOH–DCM). The title compound was isolated as a colourless glass (0.52 g, 84%). [Found $(M+H)^+$, 1127.2973 (ES). $C_{46}H_{72}N_6S_2O_9Cl_6$ requires $(M+H)^+$, 1127.3006]; δ_H ($CDCl_3$; 300 MHz) 1.46 (18H, br s, ^{t}Bu), 1.75 (4H, br m, $CH_2CH_2NCH_2Ar$), 1.97 (8H, br m, $CH_2CH_2CH_2NCO$), 2.4–2.7 (12H, m, CH_2S, CH_2NCH_2Ar), 3.1–3.8 (22H, br m, CH_2NCO, $ArCH_2N$), 4.76 (4H, s, Cl_3CCH_2OCO), 7.2–7.4 (4H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 27.7, 28.5, 29.2, 29.6, 29.7, 30.0, ~45–50 (broad overlapping signals), 47.5, 48.2, 52.8, 58.9, 75.0, 80.2, 94.4, 95.7, 126.3, 128.7, 135.0, 141.0, 154.3, 156.0, 171.7.

4.1.10. 5-*tert*-Butoxycarbonyl-13-(4-{[4,11-bis(*tert*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecan-1-yl]carbonyl}benzyl)-1,9-dithia-5,13-diazacyclohexadecane 18. Tris(Boc)-Troc amide **16** (2.90 g, 2.75 mmol) was dissolved in glacial acetic acid (30 cm^3) and stirred with activated zinc dust (9.0 g, 140 mmol) at room temperature for 12 h. The reaction mixture was filtered through Celite with excess glacial acetic acid; the acid was then removed in vacuo. The residue was partitioned between 10% aqueous sodium hydroxide (50 cm^3) and dichloromethane (50 cm^3) at 0 °C. The layers were separated and the aqueous layer was re-extracted with DCM (2×20 cm^3). The combined dichloromethane extract was dried (Na_2SO_4) and evaporated under reduced pressure to give a brown oil. This material was purified by column chromatography on silica gel (eluting with 1% MeOH–DCM). The title compound was isolated as a colourless glass (1.84 g, 76%). [Found $(M+H)^+$, 879.5458 (ES). $C_{45}H_{78}N_6S_2O_7$ requires $(M+H)^+$, 879.5446]; δ_H ($CDCl_3$; 300 MHz) 1.46 (27H, br s, ^{t}Bu), 1.73 (6H, br m, $CH_2CH_2NCH_2Ar$, $CH_2CH_2CH_2NH$), 1.90 (6H, br m, $CH_2CH_2CH_2NCO$), 2.4–2.8 (16H, m, CH_2S, CH_2NH, CH_2NCH_2Ar), 3.2–3.7 (16H, br m, CH_2NCO), 3.51 (2H, s, $ArCH_2N$), 7.2–7.4 (4H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 27.7, 28.5, 29.7, 29.9, ~43–50 (broad overlapping signals), 47.4, 52.7, 58.8, 79.2, 79.4, 79.6, 126.4, 128.6, 135.4, 141.0, 154.5, 171.7.

4.1.11. 5-(4-{[4,11-Bis(*tert*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecan-1-yl]carbonyl}benzyl)-1,9-dithia-5,13-diazacyclohexadecane 19. Bis(Boc)-bis(Troc) amide **17** (3.50 g, 3.10 mmol) was dissolved in glacial acetic acid (20 cm^3) and stirred with activated zinc dust (6.5 g, 100 mmol) at room temperature for 2 h. The reaction mixture was filtered through Celite with excess glacial acetic acid; the acid was then removed in vacuo. The residue was partitioned between 10% aqueous sodium hydroxide (50 cm^3) and dichloromethane (50 cm^3) at 0 °C. The layers were separated and the aqueous layer was re-extracted with dichloromethane (2×50 cm^3). The combined organic extracts were dried (sodium sulfate) and evaporated under reduced pressure to give a brown oil. This material was purified by column chromatography on silica gel (eluting with 5% MeOH–DCM). The title compound was isolated as a colourless glass (2.0 g, 83%). [Found $(M+H)^+$, 779.4888 (ES). $C_{40}H_{70}N_6S_2O_5$ requires $(M+H)^+$, 779.4921]; δ_H ($CDCl_3$; 300 MHz) 1.48 (18H, br s, ^{t}Bu), 1.6–1.9 (8H, br m,

CH_2CH_2S), 2.13 (4H, br m, $CH_2CH_2CH_2NCO$), 2.3–2.9 (20H, m, CH_2S, CH_2NH, CH_2NCH_2Ar), 3.2–3.8 (12H, br m, CH_2NCO), 3.51 (2H, s, $ArCH_2N$), 7.2–7.4 (4H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 25.8, 27.5, 28.4, 28.5, 29.7, 30.0, ~45–50 (broad overlapping signals), 45.6, 52.5, 58.7, 79.7, 126.6, 128.8, 135.1, 140.7, 155.8, 171.8.

4.1.12. 5-*tert*-Butoxycarbonyl-13-[4-({4,11-bis(*tert*-butoxycarbonyl)-8-[4-(chloromethyl)benzoyl]-1,4,8,11-tetraazacyclotetradecan-1-yl}carbonyl)benzyl]-1,9-dithia-5,13-diazacyclohexadecane 20. Tris(Boc) amide **18** (1.82 g, 2.07 mmol) was dissolved in dry DCM (30 cm^3). Triethylamine (0.27 g, 2.7 mmol) and then 4-(chloromethyl)benzoyl chloride (0.470 g, 2.48 mmol) were added by syringe. The reaction mixture was stirred at room temperature for 12 h. The organic layer was then washed with water (2×20 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. Purification of this material was achieved by column chromatography on silica gel (eluting with 1% MeOH–DCM). The title compound was isolated as a colourless glass (1.99 g, 93%). [Found $(M+H)^+$, 1031.5491 (ES). $C_{31}H_{46}N_4O_7Cl_4$ requires $(M+H)^+$, 1031.5475]; δ_H ($CDCl_3$; 300 MHz) 1.46 (27H, br s, ^{t}Bu), 1.74 (4H, br m, $CH_2CH_2CH_2NCH_2Ar$), 1.90 (8H, br m, $CH_2CH_2CH_2NCO$), 2.2–2.6 (12H, m, CH_2S, CH_2NCH_2Ar), 3.0–3.8 (20H, br m, CH_2NCO), 3.51 (2H, s, $ArCH_2N$), 4.58 (2H, s, $ArCH_2Cl$), 7.3–7.5 (8H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 27.4, 28.2, 29.4, 29.6, ~45–50 (broad overlapping signals), 45.2, 47.2, 52.6, 58.6, 79.1, 79.7, 126.0, 126.4, 128.4, 134.7, 136.2, 138.3, 140.9, 154.2, 170.9, 171.5.

4.1.13. 16-(4-{[4,11-Bis(*tert*-butoxycarbonyl)-8-{4-[(13-*tert*-butoxycarbonyl-1,9-dithia-5,13-diazacyclohexadecan-5-yl)methyl]benzoyl}-1,4,8,11-tetraazacyclotetradecan-1-yl]carbonyl}benzyl)-1,4,7,10,13-pentaoxa-16-azacyclooctadecane 22. 1-Aza-18-crown-6 **21** (0.38 g, 1.44 mmol) was dissolved in dry acetonitrile (20 cm^3) and added to a refluxing mixture of chloroamide **20** (1.24 g, 1.20 mmol), sodium carbonate (0.190 g, 1.80 mmol) and sodium iodide (0.036 g, 0.24 mmol) in dry acetonitrile (10 cm^3). The reaction mixture was heated at reflux for 24 h after which the solids were filtered off and washed with dichloromethane (3×50 cm^3). The filtrate and washings were combined and the solvent removed under reduced pressure. The resulting residue was partitioned between chloroform (50 cm^3) and water (20 cm^3) and continuously extracted with water (using a continuous liquid-liquid extractor, by upward displacement) for 3 days. The organic layer was separated, and evaporated to give a colourless oil that was purified by column chromatography on silica gel (eluting with 2% MeOH–DCM). The product was dried by azeotropic distillation involving toluene. The title compound was isolated as a colourless glass (1.20 g, 80%). [Found $(M+H)^+$, 1258.7474 (ES). $C_{67}H_{107}N_7S_2O_{13}$ requires $(M+H)^+$, 1258.7440]; δ_H ($CDCl_3$; 300 MHz) 1.46 (27H, br s, ^{t}Bu), 1.74 (4H, br m, $CH_2CH_2NCH_2Ar$), 1.90 (8H, br m, $CH_2CH_2CH_2NCO$), 2.4–2.6 (12H, m, CH_2S, CH_2NCH_2Ar), 2.84 (4H, br m, NCH_2CH_2O), 3.1–3.8 (44H, br m, CH_2NCO, $ArCH_2N$, CH_2O), 7.3–7.5 (8H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 27.6, 28.3, 28.4, 29.6, 29.8, ~45–50 (broad overlapping signals), 47.4, 52.7, 54.1, 68.2, 99.9, 70.2, 70.3, 79.3, 80.1, 126.2, 126.3, 128.6, 129.4, 135.0, 141.0, 155.4, 171.6.

4.1.14. 16-[4-({8-[4-(1,9-Dithia-5,13-diazacyclohexadecan-5-ylmethyl)benzoyl]-1,4,8,11-tetraazacyclotetradecan-1-yl}carbonyl)benzyl]-1,4,7,10,13-pentaoxa-16-azacyclooctadecane 23. Tris(Boc) diamide **22** (0.90 g, 0.71 mmol) was dissolved in methanol (15 cm^3) and stirred with concentrated HCl (2.1 mL, 365 g/L, 21 mmol) at room temperature for 2 h. The methanol was removed in vacuo and the residue partitioned between saturated aqueous ammonia solution (20 cm^3) and dichloromethane (50 cm^3). The layers were separated and the aqueous layer re-extracted with dichloromethane (2×50 cm^3). The combined dichloromethane extract was dried (Na_2SO_4) and evaporated under reduced pressure to give the title compound as a colourless oil that was used without further purification (0.64 g, 94%). [Found $(M+H)^+$, 958.5848 (ES). $C_{50}H_{83}N_7S_2O_7$ requires $(M+H)^+$, 958.5868]; δ_H ($CDCl_3$; 300 MHz) 1.4–2.0 (12H, br m, $CH_2CH_2CH_2$), 2.4–3.0 (30H, br m, CH_2S, CH_2NH, CH_2NCH_2Ar, NCH_2CH_2O), 3.2–3.8 (32H, br m, CH_2NCO, $ArCH_2N$, CH_2O), 7.3–7.5 (8H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 27.2, 28.9, 29.4, 29.6, ~45–50 (broad overlapping signals), 47.0, 52.3, 53.5, 58.6, 59.3, 69.5, 69.9, 70.3, 70.5, 126.0, 128.2, 135.1, 140.7, 171.7.

4.1.15. 16-[4-({8-[4-(1,9-Dithia-5,13-diazacyclohexadecan-5-ylmethyl)benzyl]-1,4,8,11-tetraazacyclotetradecan-1-yl}methyl)benzyl]-1,4,7,10,13-pentaoxa-16-azacyclooctadecane 2. Diamide **23** (0.64 g, 0.67 mmol) was dissolved in dry THF (5 cm^3). A 2.0 mol dm^{-3} solution of $BH_3 \cdot SMe_2$ (5 mL, 10 mmol) was added slowly and the solution then heated to reflux for 24 h. The solution was allowed to cool and the excess borane destroyed by careful addition of methanol. The THF was removed under reduced pressure and the residue hydrolysed in refluxing MeOH–H_2O–concentrated HCl (20:10:10; 30 cm^3) for 1 h. The methanol was removed under reduced pressure and the resulting solution partitioned between saturated aqueous ammonia (20 cm^3) and dichloromethane (50 cm^3). The aqueous layer was extracted with dichloromethane (2×50 cm^3) and the combined organic layers dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the resulting material was achieved by column chromatography on silica gel (eluting with 5% MeOH–DCM with 1% saturated NH_3 solution). The title compound was isolated as a colourless oil (0.51 g, 82%). [Found $(M+H)^+$, 930.6258 (ES). $C_{50}H_{87}N_7S_2O_5$ requires $(M+H)^+$, 929.6282]; δ_H ($CDCl_3$; 300 MHz) 1.6–1.9 (12H, br m, $CH_2CH_2CH_2$), 2.4–2.8 (36H, br m, CH_2S, CH_2NH, CH_2NCH_2Ar, NCH_2CH_2O), 3.5–3.8 (28H, br m, CH_2NCO, $ArCH_2N$, CH_2O), 7.3–7.5 (8H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 24.6, 27.5, 28.9, 29.6, 29.9, 47.2, 47.4, 48.1, 50.3, 51.1, 52.5, 53.6, 58.6, 58.8, 59.4, 69.7, 70.1, 70.5, 70.6, 128.5, 128.6, 129.2, 135.6, 135.7, 138.4, 138.6.

4.1.16. Bis(Boc)-tricyclic amide 24. Bis(Boc) amide **19** (0.413 g, 0.53 mmol) in dry acetonitrile (50 cm^3) and α,α-dibromo-*p*-xylene (0.14 g, 0.53 mmol) in dry acetonitrile (50 cm^3) were added simultaneously by syringe pump to a suspension of potassium carbonate (0.73 g, 5.3 mmol) in dry acetonitrile (2900 cm^3) at reflux over a period of 110 h. The reaction mixture was refluxed for a further 72 h and then the solvent removed under reduced pressure. The residue was dissolved in dichloromethane (80 cm^3) and then

washed with water (2×20 cm^3), dried (sodium sulfate) and evaporated under reduced pressure. Purification of this material was achieved by column chromatography on silica gel (eluting with 3% MeOH–DCM). The product was isolated as a colourless glass (0.128 g, 27%). [Found $(M+H)^+$, 881.5394 (ES). $C_{48}H_{76}N_6S_2O_5$ requires $(M+H)^+$, 881.5391] (difference between isotope peaks 1.0 amu); δ_H ($CDCl_3$; 300 MHz) 1.2–1.5 (18H, br s, ^{t}Bu), 1.5–2.0 (12H, br m, $CH_2CH_2CH_2$), 2.0–2.9 (20H, m, CH_2S, CH_2NCH_2Ar), 3.0–3.8 (18H, br m, CH_2NCO, $ArCH_2N$), 7.2–7.6 (8H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 27.6, 28.6, 29.1, 29.6, 30.0, ~45–50 (broad overlapping signals), 52.7, 58.7, 75.2, 80.3, 95.5, 126.1, 128.6, 135.1, 141.2, 154.5, 171.7.

4.1.17. Bis(Boc)-tricyclic triamide 25. Bis(Boc) amide **19** (0.617 g, 0.79 mmol) in dry dichloromethane (50 cm^3) and terephthaloyl dichloride (0.161 g, 0.79 mmol) in dry dichloromethane (50 cm^3) were added simultaneously by syringe pump to a solution of triethylamine (0.40 g, 3.96 mmol) in dry dichloromethane (2900 cm^3) over a period of 110 h at room temperature. The reaction mixture was stirred for a further 36 h at room temperature and then concentrated to a volume of approximately 50 cm^3 under reduced pressure. The organic layer was then washed with water (2×20 cm^3), dried (sodium sulfate) and evaporated under reduced pressure. Purification of this material was achieved by column chromatography on silica gel (eluting with 3% MeOH–DCM). The title compound was isolated as a colourless glass (0.49 g, 68%). [Found $(M+Na)^+$, 931.4785 (ES). $C_{48}H_{72}N_6S_2O_7$ requires $(M+Na)^+$, 931.47796]; δ_H ($CDCl_3$; 300 MHz) 1.44 (18H, br s, ^{t}Bu), 1.5–2.1 (12H, br m, $CH_2CH_2CH_2$), 2.2–2.7 (12H, m, CH_2S, CH_2NCH_2Ar), 3.1–3.8 (20H, br m, CH_2NCO), 3.48 (2H, s, $ArCH_2N$), 7.2–7.6 (8H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 27.7, 28.5, 29.2, 29.7, 30.0, ~43–50 (broad overlapping signals), 52.8, 58.9, 75.0, 80.2, 95.7, 126.3, 128.7, 135.0, 141.0, 154.3, 155.9, 171.7.

A small amount of lower R_f material isolated from this chromatography was identified as 2+2 cyclisation products (0.08 g, 11%). [Found $(M+2H)^{2+}$, 909.5000 (ES). $C_{96}H_{144}N_{12}S_4O_{14}$ requires $(M+2H)^{2+}$, 909.4977]. The NMR spectra were indistinguishable from those of **25**.

4.1.18. 1,8-Bis(*tert*-butoxycarbonyl)-4,11-bis[4-(chloromethyl)benzoyl]-1,4,8,11-tetraazacyclotetradecane 28. To a solution of 1,8-bis(*tert*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane **7** (1.91 g, 4.77 mmol) and triethylamine (1.25 g, 12.4 mmol) in dry dichloromethane (50 cm^3) was added a solution of 4-(chloromethyl)benzoyl chloride **14** (2.16 g, 11.4 mmol) in dry DCM (20 cm^3). The reaction mixture was stirred at room temperature for 12 h after which the reaction mixture was washed with water (2×50 cm^3), dried (sodium sulfate) and evaporated under reduced pressure. Purification of this material was achieved by column chromatography on silica gel (eluting with 2% MeOH–DCM). The title compound was isolated as a colourless glass (3.20 g, 95%). [Found $(M+Na)^+$, 727.2997 (ES). $C_{36}H_{50}N_4O_6Cl_2$ requires $(M+Na)^+$, 727.3000]; δ_H ($CDCl_3$; 300 MHz) 1.46 (18H, br s, ^{t}Bu), 1.7–2.1 (4H, br m, $CH_2CH_2CH_2$), 3.2–3.8 (16H, br m, CH_2NCO), 4.58 (4H, s, $ArCH_2Cl$), 7.3–7.5 (8H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 28.5, 30.1, 45.5, ~45–50 (broad overlapping signals), 80.4, 126.7, 128.6, 136.3, 138.7, 155.7, 171.4.

4.1.19. 1,9-Dithia-5,13-diazacyclohexadecane 11. (a) A solution of dichloro compound **29**[17] (6.0 g, 23.0 mmol) and dithiol **30**[17] (6.1 g, 23.0 mmol) in dry *N*,*N*-dimethylformamide (500 cm^3) was added over a period of 36 h to a stirred suspension of caesium carbonate (16.9 g, 51.8 mmol) in dry *N*,*N*-dimethylformamide (2.3 dm^3) at 85 °C. The reaction mixture was stirred at this temperature for a further 24 h. The solvent was removed in vacuo, the residue taken up in dichloromethane and the solids removed by filtration through Celite. Evaporation of the solvent under reduced pressure gave a brown oily crystalline solid that was purified by column chromatography on silica gel (eluting with EtOAc–petroleum ether, 1:9). 5,13-Bis(*tert*-butoxycarbonyl)-1,9-dithia-5,13-diazacyclohexadecane **31** was obtained as a low melting solid (6.4 g, 60%). δ_H ($CDCl_3$, 300 MHz) 1.38 (18H, s, ^{t}Bu), 1.79 (8H, quin, $CH_2CH_2CH_2$), 2.48 (8H, t, CH_2S), 3.27 (8H, br s, CH_2N). δ_C ($CDCl_3$, 75 MHz) 28.3, 29.7, 47.2, 79.3. This material was used without further characterisation as described below.

(b) Trifluoroacetic acid (0.91 g, 8.0 mmol) was added slowly to di-*N*-Boc macrocycle **31** (0.463 g, 1.0 mmol) in wet dichloromethane. The solution was stirred for 2 h after which excess acid was neutralised with 10% aqueous sodium hydroxide (25 cm^3) and the aqueous layer extracted with dichloromethane (3×50 cm^3). The combined organic layers were dried (sodium sulfate) and evaporated under reduced pressure. Purification of the residue was achieved by column chromatography on silica gel (eluting with 5% MeOH–DCM) to give the title compound as a colourless oil (0.25 g, 95%). The ^{1}H NMR spectrum was as previously reported.[31]

4.1.20. Bis(Boc)-tricyclic diamide 32. Bis(chloroamide) **28** (1.31 g, 1.86 mmol) in dry acetonitrile (50 cm^3) and 1,9-dithia-5,13-diazacyclohexadecane **11** (0.487 g, 1.86 mmol) in dry dichloromethane (50 cm^3) were added simultaneously by syringe pump to a suspension of potassium carbonate (2.6 g, 18.56 mmol) in dry refluxing acetonitrile (2900 cm^3) over a period of 110 h. The reaction mixture was refluxed for a further 60 h and the solvent removed under reduced pressure. The residue was partitioned between dichloromethane (50 cm^3) and water (20 cm^3) and the aqueous layer was extracted with dichloromethane (3×20 cm^3). The combined organic layers were dried (sodium sulfate), and evaporated under reduced pressure to give a brown oil that was purified by column chromatography on silica gel (eluting with 2% MeOH–DCM). The title compound was isolated as a colourless glass (0.72 g, 43%). [Found $(M+H)^+$, 895.5200; $(M+Na)^+$, 917.4958 (ES). $C_{48}H_{74}N_6S_2O_6$ requires $(M+H)^+$, 895.5189; $(M+Na)^+$, 917.5009]; δ_H ($CDCl_3$; 300 MHz) 1.46 (18H, br s, ^{t}Bu), 1.74 and 1.89 (12H, 2×br s, $CH_2CH_2CH_2$), 2.41 and 2.59 (16H, 2×br s, CH_2S, $ArCH_2NCH_2$), 3.2–3.8 (20H, br m, CH_2NCO, $ArCH_2N$), 7.34 and 7.39 (8H, 2×br s, ArH); δ_C ($CDCl_3$; 75 MHz) 28.5, 30.0, 46.5, ~45–50 (broad overlapping signals), 52.6, 59.4, 80.3, 126.7, 128.6, 136.3, 138.7, 155.7, 171.4.

A small amount of the [2+2] reaction product **33** was also isolated (0.19 g, 11%). [Found $(M+2H)^{2+}$, 895.5177 (ES). $C_{96}H_{148}N_{12}S_4O_{12}$ requires $(M+2H)^{2+}$, 895.5189. Other parent ions were observed at *m/z* 1789.9126 $(M+H)^+$, 1811.8831 $(M+Na)^+$, 906.5088 $(M+H+Na)^{2+}$, and 917.5900 $(M+2\ Na)^{2+}$]; the ^1H and ^{13}C NMR spectra were indistinguishable from those of **32**.

4.1.21. Tetrakis(Boc)-pentacyclic tetraamide 33. Bis(-chloroamide) **28** (0.49 g, 0.69 mmol) in dry acetonitrile (50 cm^3) and bis(Boc) diamide **35** (see below) (0.80 g, 0.69 mmol) in dry dichloromethane (50 cm^3) were added simultaneously by syringe pump to a suspension of sodium carbonate (0.37 g, 3.45 mmol) in dry refluxing acetonitrile (2900 cm^3) over a period of 110 h. The reaction mixture was refluxed for a further 60 h and the solvent removed under reduced pressure. The residue was partitioned between dichloromethane (50 cm^3) and water (20 cm^3) and the aqueous layer was extracted with dichloromethane (3× 20 cm^3). The combined organic layers were dried (sodium sulfate), and evaporated under reduced pressure to give a brown oil that was purified by column chromatography on silica gel (eluting with 2% MeOH–DCM). The title compound was isolated as a colourless glass (0.12 g, 10%). [Found $(M+2H)^{2+}$, 895.5180 (ES). $C_{96}H_{148}N_{12}S_4O_{12}$ requires $(M+2H)^+$, 895.5189]; δ_H ($CDCl_3$; 300 MHz) 1.46 (18H, br s, ^{t}Bu), 1.6–2.1 (12H, br m, $CH_2CH_2CH_2$), 2.4–2.7 (16H, br m, CH_2S, $ArCH_2NCH_2$), 3.2–3.8 (20H, br m, CH_2NCO, $ArCH_2N$), 7.3–7.5 (8H, br m, ArH).

4.1.22. 5-(4-{[4,11-Bis(*tert*-butoxycarbonyl)-8-(4-{[13-(2,2,2-trichloroethoxycarbonyl)-1,9-dithia-5,13-diazacyclohexadecan-5-yl]methyl}benzoyl)-1,4,8,11-tetraazacyclotetradecan-1-yl]carbonyl}benzyl)-13-(2,2,2-trichloroethoxycarbonyl)-1,9-dithia-5,13-diazacyclohexadecane 34. 5-(2,2,2-Trichloroethoxycarbonyl)-1,9-dithia-5,13-diazacyclohexadecane **13** (2.30 g, 5.25 mmol) was dissolved in dry acetonitrile (25 cm^3) and this solution was added to a refluxing mixture of bis(chloroamide) **28** (1.77 g, 2.50 mmol) and sodium carbonate (0.61 g, 5.75 mmol) in dry acetonitrile (50 cm^3). The reaction solution was allowed to reflux for 24 h after which the solvent was removed under reduced pressure and the residue partitioned between dichloromethane (70 cm^3) and water (30 cm^3). The aqueous layer was extracted with dichloromethane (3×50 cm^3), the combined organic layers were dried (sodium sulfate) and evaporated under reduced pressure to give a brown oil that was purified by column chromatography on silica gel (eluting with 1% MeOH–DCM). The title compound was isolated as a colourless glass (3.28 g, 87%). [Found $(M+H)^+$, 1505.4798 (ES). $C_{66}H_{102}N_8S_4O_{10}Cl_6$ requires $(M+H)^+$, 1505.4805]; δ_H ($CDCl_3$; 300 MHz) 1.46 (18H, br s, ^{t}Bu), 1.6–2.1 (20H, br m, $CH_2CH_2CH_2$), 2.4–2.6 (24H, br m, CH_2S, $ArCH_2NCH_2$), 3.2–3.7 (28H, br m, CH_2NCO, $ArCH_2N$), 4.76 (4H, s, Cl_3CCH_2OCO), 7.2–7.4 (8H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 27.7, 28.6, 29.3, 30.0, ~45–50 (broad overlapping signals), 48.1, 52.7, 58.7, 75.2, 80.3, 95.4, 126.5, 128.5, 135.0, 141.3, 154.1, 155.9, 171.5.

4.1.23. 5-[4-({4,11-Bis(*tert*-butoxycarbonyl)-8-[4-(1,9-dithia-5,13-diazacyclohexadecan-5-ylmethyl)benzoyl]-1,4,8,11-tetraazacyclotetradecan-1-yl}carbonyl)benzyl]-1,9-dithia-5,13-diazacyclohexadecane 35. Bis(Boc)-bis-(Troc) diamide **34** (1.00 g, 0.66 mmol) was dissolved in glacial acetic acid (30 cm^3) and stirred with activated zinc dust (0.87 g, 1.3 mmol) at room temperature for 12– h. The reaction mixture was filtered through Celite with excess glacial acetic acid, which was then removed in vacuo. The residue was partitioned between 10% aqueous sodium hydroxide (50 cm^3) and dichloromethane (50 cm^3) at 0 °C. The layers were separated and the aqueous layer re-extracted with dichloromethane (2×20 cm^3). The combined organic extracts were dried (sodium sulfate) and evaporated under reduced pressure to give a brown oil. This material was purified by column chromatography on silica gel (eluting with 5% MeOH–DCM). The title compound was isolated as a colourless glass (0.57 g, 75%). [Found $(M+H)^+$, 1167.28 (ES). $C_{60}H_{100}N_8S_4O_6$ requires $(M+H)^+$, 1157.6721]; δ_H ($CDCl_3$; 300 MHz) 1.46 (18H, br s, ^{t}Bu), 1.7–2.1 (20H, br m, $CH_2CH_2CH_2$), 2.4–2.8 (32H, br m, CH_2S, $ArCH_2NCH_2$, CH_2NH), 3.2–3.8 (20H, br m, CH_2NCO, $ArCH_2N$), 7.3–7.5 (8H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 27.5, 28.5, 29.1, 29.9, 46.8, ~45–50 (broad overlapping signals), 52.5, 59.2, 126.9, 128.3, 136.7, 138.5, 155.6, 171.3.

4.1.24. Pentacyclic tetraamide 36. Tetrakis(Boc)-pentacyclic tetraamide **33** (0.10 g, 0.056 mmol) was dissolved in methanol (30 cm^3) and stirred with concentrated hydrochloric acid (5 cm^3, 10 M, 50 mmol) at room temperature for 4 h. The methanol was removed in vacuo and the residue partitioned between 10% aqueous sodium hydroxide (20 cm^3) and dichloromethane (50 cm^3). The layers were separated and the aqueous layer re-extracted with dichloromethane (2×50 cm^3). The combined organic extracts were dried (sodium sulfate) and evaporated under reduced pressure to give the title compounds as a colourless glass that was used without further purification (0.075 g, 96%). [Found $(M+H)^+$, 1389.8200 (ES). $C_{76}H_{116}N_{12}S_4O_4$ requires $(M+H)^+$, 1389.8197]; δ_H ($CDCl_3$; 300 MHz) 1.4–2.1 (24H, br m, $CH_2CH_2CH_2$), 2.1–3.1 (42H, br m, CH_2S, CH_2NH, CH_2NCH_2Ar), 3.1–3.8 (28H, br m, CH_2NCO, $ArCH_2N$), 7.2–7.6 (16H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 27.6, 28.8, 29.0, 29.8, ~43–50 (broad overlapping signals), 52.7, 53.1, 58.7, 59.1, 126.1, 126.3, 128.4, 135.4, 137.3, 137.5, 137.7, 140.5, 141.0, 170.6, 171.0, 171.7.

4.1.25. Tetramacrocyclic ligand 37. Pentacyclic tetraamide **36** (0.050 g, 0.036 mmol) was dissolved in dry tetrahydrofuran (5 cm^3). A 2.0 M solution of borane dimethylsulfide complex (10 cm^3, 20 mmol) was added slowly and the solution then heated at reflux for 24 h. The solution was allowed to cool and the excess borane was destroyed by careful addition of methanol. The solvent was removed under reduced pressure and the residue was hydrolysed in refluxing methanol–water–concentrated hydrochloric acid (20:10:10; 40 cm^3) for 1 h. The methanol was removed under reduced pressure and the resulting solution was partitioned between 10% aqueous sodium hydroxide (50 cm^3) and dichloromethane (50 cm^3). The aqueous layer was extracted with dichloromethane (2× 25 cm^3) and the combined organic layers were dried (sodium sulfate) and evaporated under reduced pressure.

Purification of the resulting material was achieved by column chromatography on silica gel (eluting with 5% MeOH–DCM containing 1% saturated NH_3 solution). The title compound was isolated as a colourless glass (0.025 g, 53%). [Found $(M+H)^+$, 1333.9001 (ES). $C_{76}H_{124}N_{12}S_4$ requires $(M+H)^+$, 1333.9027]; δ_H ($CDCl_3$; 300 MHz) 1.6–1.9 (24H, m, $CH_2CH_2CH_2N$), 2.4–2.8 (66H, CH_2N, CH_2S), 3.50 (8H, s, $ArCH_2N$), 3.68 (8H, s, $ArCH_2N$), 7.1–7.3 (16H, m, ArH); δ_C ($CDCl_3$; 75 MHz) 25.8, 27.6, 30.0, 47.5, 49.9, 51.6, 52.5, 53.8, 59.1, 128.4, 128.5, 129.2, 129.3, 135.6, 135.9, 138.2, 138.3.

4.1.26. Tricyclic triamide 38. Bis(Boc)-tricyclic triamide **26** (0.436 g, 0.49 mmol) was dissolved in methanol (80 cm^3) and stirred with concentrated hydrochloric acid (15 cm^3, 10 M, 150 mmol) at room temperature for 6 h. The methanol was removed in vacuo and the residue partitioned between 10% aqueous sodium hydroxide (30 cm^3) and dichloromethane (70 cm^3). The layers were separated and the aqueous layer re-extracted with dichloromethane (2× 50 cm^3). The combined organic extracts were dried (sodium sulfate) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluting with 5% MeOH–DCM containing 1% saturated NH_3 solution). The title compound was isolated as a colourless glass (0.30 g, 87%). [Found $M+H^+$, 709.3919 (ES). $C_{38}H_{56}N_6S_2O_3$ requires $(M+H)^+$, 709.3928]; δ_H ($CDCl_3$; 300 MHz) 1.4–2.1 (12H, br m, $CH_2CH_2CH_2$), 2.1–3.0 (20H, br m, CH_2S, CH_2NH, CH_2NCH_2Ar), 3.1–3.8 (14H, br m, CH_2NCO, $ArCH_2N$), 7.2–7.6 (8H, br m, ArH); δ_C ($CDCl_3$; 75 MHz) 27.6, 28.8, 29.0, 29.8, ~43–50 (broad overlapping signals), 52.7, 53.1, 58.7, 59.1, 126.1, 126.3, 128.4, 135.4, 137.3, 137.5, 137.7, 140.5, 141.0, 170.6, 171.0, 171.7.

4.1.27. Cofacial ligand 3. Tricyclic diamide **38** (0.190 g, 0.27 mmol) was dissolved in dry tetrahydrofuran (2 cm^3). A 2.0 mol dm^{-3} solution of borane dimethylsulfide complex (2.7 cm^3, 5.36 mmol) was added slowly and the solution was then heated at reflux for 24 h. The solution was allowed to cool and the excess borane was destroyed by careful addition of methanol. The solvent was removed under reduced pressure and the residue was hydrolysed in refluxing methanol–water–concentrated hydrochloric acid (10:5:5; 20 cm^3) for 1 h. The methanol was removed under reduced pressure and the resulting solution was partitioned between 10% aqueous sodium hydroxide (30 cm^3) and dichloromethane (70 cm^3). The aqueous layer was extracted with dichloromethane (2×25 cm^3) and the combined organic layers were dried (sodium sulfate) and evaporated under reduced pressure. Purification of the resulting material was achieved by column chromatography on silica gel (eluting with 5% MeOH–DCM containing 1% saturated NH_3 solution). The title compound was isolated as a colourless glass (0.12 g, 67%). [Found $(M+H)^+$, 667.4529 (ES). $C_{38}H_{62}N_6S_2$ requires $(M+H)^+$, 667.4550]; δ_H ($CDCl_3$; 300 MHz) 1.6–1.9 (12H, m, $CH_2CH_2CH_2N$), 2.4–2.8 (32H, m, CH_2N, CH_2S), 3.50 (4H, s, $ArCH_2N$), 3.68 (4H, s, $ArCH_2N$), 7.1–7.3 (8H, m, ArH); δ_C ($CDCl_3$; 75 MHz) 25.8, 27.6, 28.4, 30.0, 47.5, 49.9, 53.8, 128.5, 129.2, 135.9, 138.2.

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'Push–Pull' and spirobicyclic structures by reacting *N*-methyl cyclic ketene-*N*,X (X = S, O)-acetals with isocyanates and isothiocyanates

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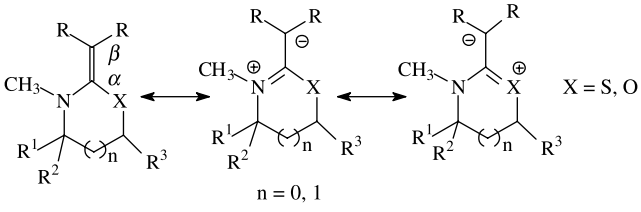
Abstract—Nucleophilic *N*-methyl cyclic ketene-*N*,X (X = S, O)-acetals can react with electrophilic aryl isocyanates and aryl isothiocyanates to form 'push–pull' mono-adducts, di-adducts and spirobicyclic 6/5 ring compounds.

1. Introduction

N-Methyl cyclic ketene-*N*,X (X = S, O)-acetals are electron-rich nucleophilic agents, which have the ability to react with electron deficient electrophiles.[1–8] *N*-Methyl cyclic ketene-



Scheme 1.

N,X (X = S, O)-acetals exhibit extremely electron-rich double bonds with highly polarized exocyclic β carbon atoms (β position is defined in Scheme 1), due to their dual character as both an enamine and a vinyl ether (or vinyl thioether). The electron-rich double bonds of cyclic ketene (*O*,*O*-, *N*,*O*- and *N*,*S*-)-acetals can be easily protonated by protons from moisture and acids.[1]

The earliest report of acyclic ketene-*O*,*N*-acetal, which we are aware of appeared in McElvain's 1949 review.[2] Subsequently, others described the use of acyclic and cyclic ketene-*N*,*O*-acetals as reactants or reaction intermediates.[3–17] In contrast to acyclic and cyclic ketene-*N*,*O*-acetals, only a few reports exist concerning the syntheses and uses of acyclic or cyclic ketene-*N*,*S*-acetals.[18–22] Hiroki first demonstrated the reaction of acyclic ketene-*N*,*S*-acetals with phenyl isocyanate.[19,20] Later, Endo briefly reported the reactions of cyclic ketene-*N*,*O*-acetals with phenyl isocyanate[11] and thioisocyanate.[8] Other than these few reports, no detailed studies of these nucleophiles have appeared. Therefore, our laboratory has undertaken a general investigation of cyclic ketene acetal polymerization[23,25] and reactions with electrophiles and dielectrophiles.[22,24,26–29] Unique cyclizations to fused heterocyclic ring systems and high yield ring-opening reactions suitable for combinatorial applications have been observed.[31] Since a more complete exploration of these reactions is needed, we explored the reactions of aryl isocyanates and aryl isothiocyanates with various cyclic ketene-*N*,*O*-acetals at different temperatures. Cyclic ketene-*N*,*S*-acetals were synthesized and their reactions with isocyanates and thioisocyanates were also studied.

An important capability of both ketene-*N*,*O*- and -*N*,*S*-acetals is the ability to regenerate the acetal double bond by elimination of a proton after addition of the β-carbon to an electrophile gives the resulting zwitterion. Thus, a new ketene acetal function is available for further reaction. This opens many synthetic possibilities,[22,24,26–28] such as cyclization with diacid chlorides[28] and chlorocarbonyl isocyanate.[27]

2. Results and discussion

The detailed syntheses of *N*-methyl cyclic ketene-*N*,X-acetals **1** (X = S), **2** and **3** (X = O) can be easily found in our previous papers and dissertations.[22–30] The three classes of *N*-methyl

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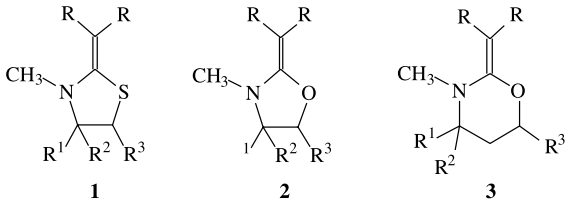


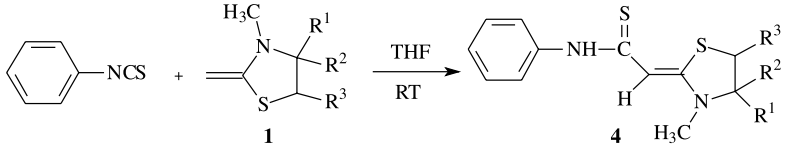
Scheme 2.

cyclic ketene-*N*,X (X=S, O)-acetals represented in structures **1–3** (Scheme 2) were synthesized in this research. These *N*-methyl cyclic ketene-*N*,X (X=S, O)-acetals are all very sensitive to acid and water. Protonation at the exocyclic β-carbon readily generates the corresponding stable heterocyclic cations, which readily react with water. Since the β-carbon is nucleophilic, we explored the reactions of **1–3** with electrophilic isocyanates and isothiocyanates.

N-Methyl cyclic ketene-*N*,*S*-acetals reacted readily with phenyl isothiocyanate at ambient temperature in THF via nucleophilic attack at the electron-deficient isothiocyanate carbon. For example, the four *N*-methyl-2-methylene-1,3-thiazolanes **1a–d** afforded excellent isolated yields of the α,β-unsaturated thioamide monoadducts **4a–d** (Scheme 3). In these substituted 2-(3-methylthiazolidin-2-ylidene)-*N*-phenylthioacetamides, the strong electron-donating enamine and thiovinyl ether functions are conjugated to the electron-withdrawing thioamide function to form a 'push–pull' conjugated system. NOESY experiments proved that the vinyl proton in **4** was cis to the ring nitrogen, because there is a cross-peak between the vinyl proton and protons of the *N*-methyl group. This requires that these protons are spatially near each other, confirming the cis geometry.

Both five- and six-membered ring *N*-methyl cyclic ketene-*N*,*O*-acetals **2** and **3** also react with aryl isothiocyanates to generate monoadducts **5** and **6**, respectively (Scheme 4). For example, 2-methylene-*N*-methyl-1,3-oxazolanes **2a–b** and 3,4,4,6-tretamethyl-2-methylene-1,3-oxazine **3** give the corresponding substituted 2-(3-methyloxazolidin-2-ylidene)-*N*-arylthioacetamides **5a–b** and 2-(3,4,4,6-tetramethyloxazan-2-ylidene)-*N*-arylthioacetamide **6** in CH_2Cl_2 in very good isolated yields at 25, −50 and −78 °C. The *N*-arylthioamide function is found exclusively cis to the oxygen and trans to ring nitrogen in **5** and **6**. This assignment was clear from NOESY experiments and X-ray crystal structures (Fig. 1) of compounds **5b** and **6a**. NOSEY experiments on **5a–b** and **6** exhibited cross-peaks between the vinyl proton and protons of the *N*-methyl group, as was previously found with **4a–d**. Protons are spatially near each other.

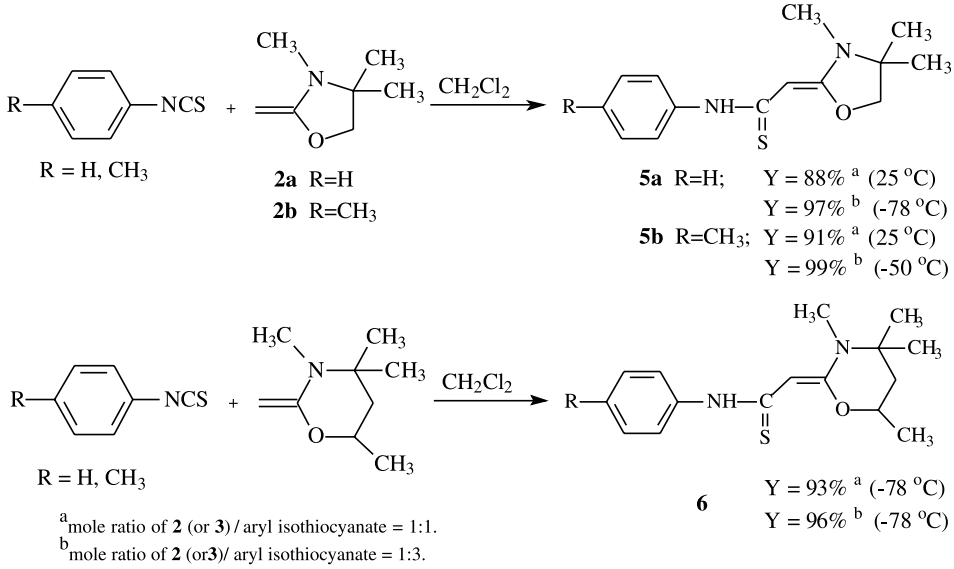
Thioamide adducts **4**, **5** and **6** are not nucleophilic enough to react with a second equivalent of aryl isothiocyanate to give the corresponding 'push–pull' bis-adducts at room temperature. The use of high aryl isothiocyanate to **1**, **2** or **3**



1a R^1=H; R^2=H; R^3=H
1b R^1=H; R^2=H; R^3=CH_3
1c R^1=H; R^2=Et; R^3=H
1d R^1=CH_3; R^2=CH_3; R^3=H
mole ratio of **1** / ArNCS = 1:2

4a R^1=H; R^2=H; R^3=H; Y = 88%
4b R^1=H; R^2=H; R^3=CH_3; Y = 79%
4c R^1=H; R^2=Et; R^3=H Y = 80%
4d R^1=CH_3; R^2=CH_3; R^3=H; Y = 80%

Scheme 3.



[a] mole ratio of **2** (or **3**) / aryl isothiocyanate = 1:1.
[b] mole ratio of **2** (or**3**)/ aryl isothiocyanate = 1:3.

Scheme 4.

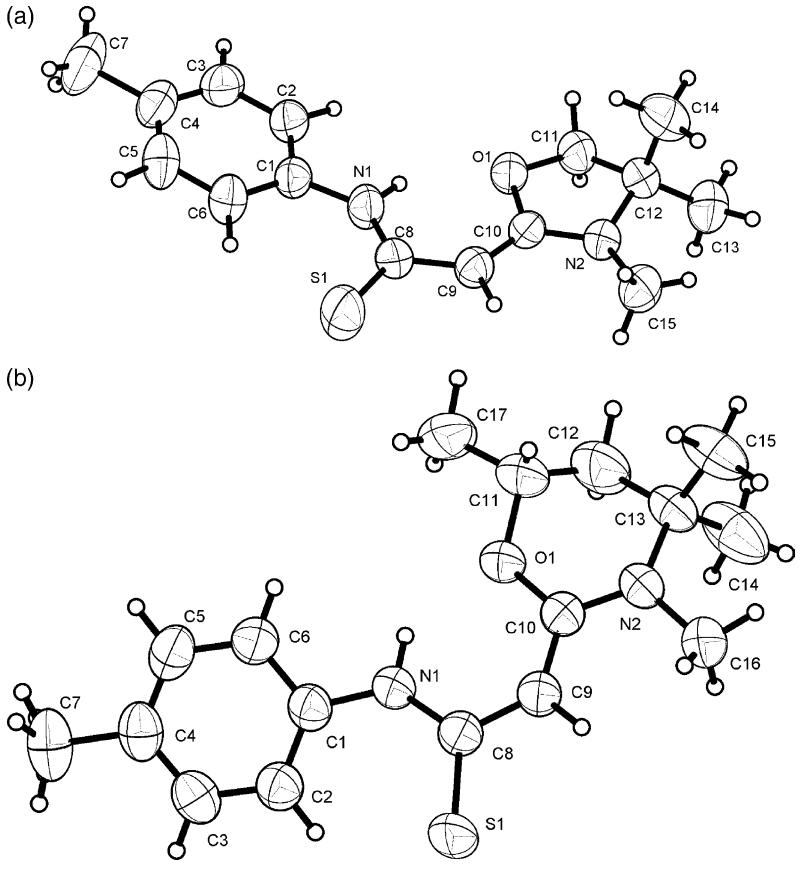
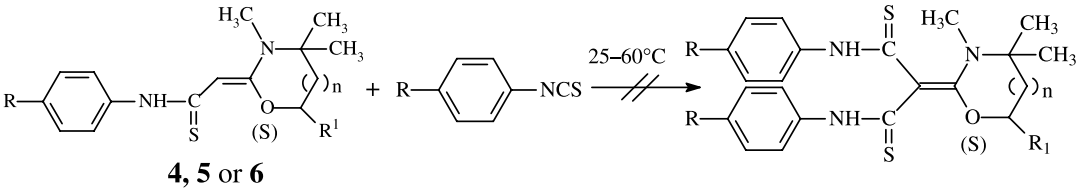
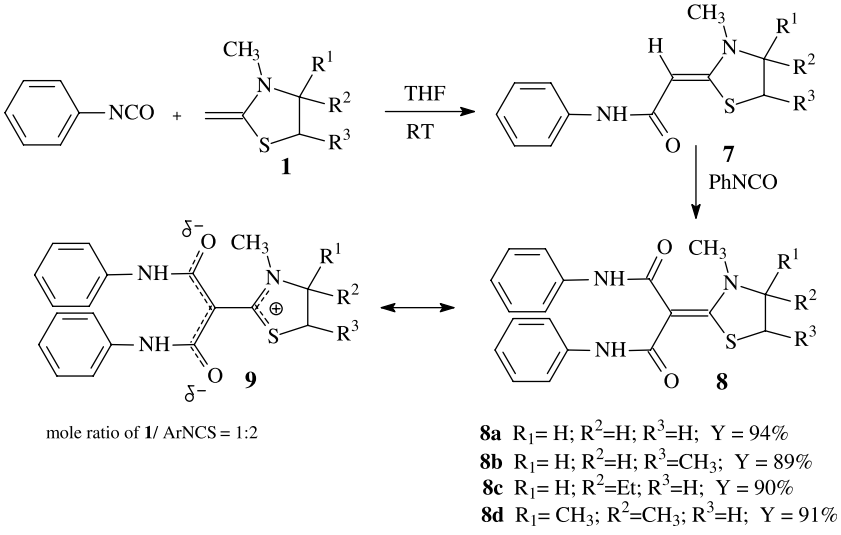


Figure 1. (a) X-ray crystal structure of compound **5b**. (b) X-ray crystal structure of compound **6**.



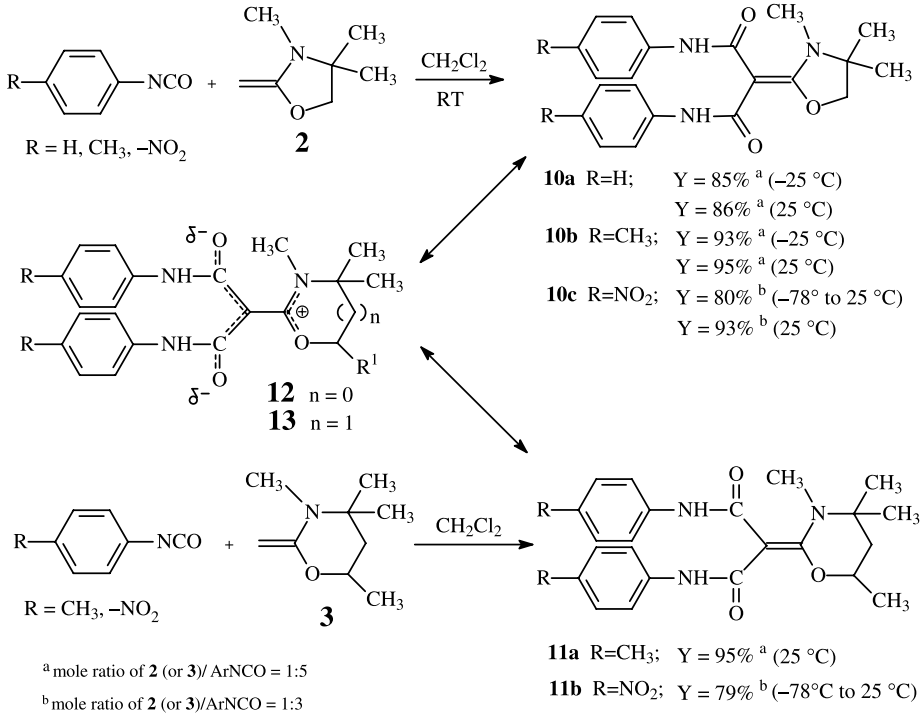
Scheme 5.



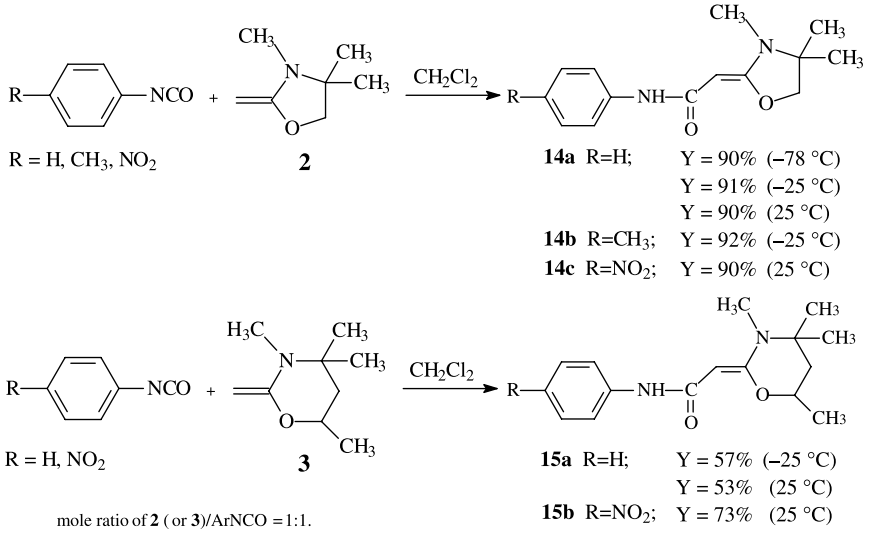
Scheme 6.

mole ratios or raising the temperature to 60 °C did not generate the corresponding bis-adducts (Scheme 5).

Aryl isocyanates are more electrophilic than their corresponding aryl isothiocyanates. Aryl isocyanate reactions with cyclic ketene-*N*,*O* (and *N*,*S*)-acetals **1**, **2**, or **3** did not stop at the monoadduct stage in the presence of excess aryl isocyanate. Thus, the initially formed monoadducts **4**, **5** and **6** add to a second equivalent of aryl isocyanate to afford bis-adducts **8** (Scheme 6), **10** and **11** (Scheme 7), respectively. These reactions all proceed readily in excellent isolated yields in THF or CH_2Cl_2, at, or below, 25 °C. The 'push–pull' bis-amide adducts **8**, **10** and **11** exhibit zwitterionic resonance contributions from hybrid structures **9** (Scheme 6), **12** and **13** (Scheme 7), respectively. The enamine, vinylether and thioether functions provide strong electron donation towards the two amide functions. The charge is localized more on the amide carbonyl oxygens in these zwitterions and β-carbons resemble ordinary vinyl carbons more than they did in the original ketene acetals. This is indicated by the substantial downfield shifts in the ^{13}C NMR spectra experienced by the original α-carbons of **1**, **2** and **3** upon conversion to **8**, **10** and **11**. The β-carbons are also shifted downfield considerably due to substantial charge delocalization to the amide carbonyls. The chemical shifts of the original β-carbons in **1**, **2** and **3** are found at 45–65 ppm. These move downfield to 75–95.5 ppm in **8**, **10** and **11**. Example changes in β-carbon chemical shifts are **8a**: $\Delta\delta=$ 37.9 ppm; **8d**: $\Delta\delta=26.5$ ppm; **10a**: $\Delta\delta=23.1$ ppm; **11a**: $\Delta\delta=22.1$ ppm. The solubilities of **8**, **10** and **11** in hexane



Scheme 7.



Scheme 8.

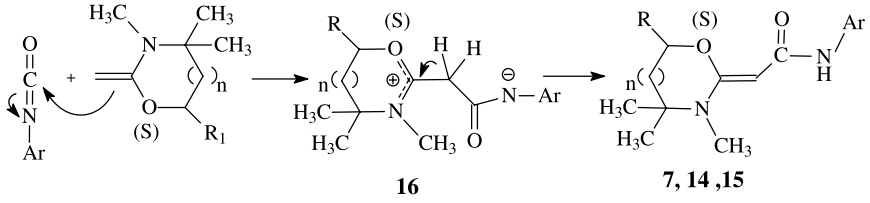
and even ethyl acetate are very low, in accord with the high polarity of these compounds. Hexane is used to precipitate reaction product **8**, **10** and **11**.

When the cyclic ketene acetal/aryl isocyanate ratio was held at 1:1, mono-adducts **14** and **15** were also readily prepared from **2** and **3**, respectively (Scheme 8). Thus, it is clear that bis-adducts **8**, **10**, and **11** are formed by two-step reactions. First, the *N*-methyl cyclic ketene-*N*,X (X=S, O)-acetals **1**, **2**, and **3** rapidly form the monoadduct. Monoadduct formation is much faster than the second aryl isocyanate addition to give the bis-adducts **8**, **10** and **11**.

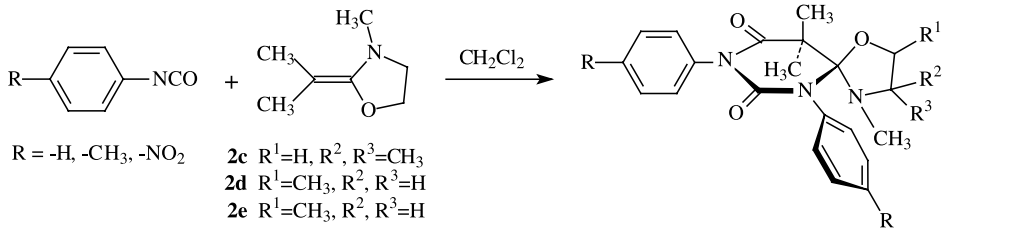
Monoadduct formation occurs as shown in Scheme 10. Nucleophilic attack by the acetal's β-carbon on the isocyanate (or isothiocyanate) function's carbon generates the zwitterionic intermediate **16**, which now features an acidic proton adjacent to the ring. Loss of this acidic proton and proton capture by the amide nitrogen regenerates the cyclic ketene-*N*,X-acetal function in the product (Scheme 9).

N-Methyl cyclic ketene-*N*,*O*-acetals **2** and **3**, which contain two methyl groups at the β-carbon atom of the acetal double bond, behaved differently. When examples of **2** and **3**, which contain two β-methyls, were reacted with aryl isocyanate in CH_2Cl_2 at room temperature or −25 °C, instead of giving bis-adducts, the reactions produced the spirobicyclic 6/5 and 6/6 ring systems **17** and **18** (Scheme 10). In sharp contrast, *N*-methyl cyclic ketene-*N*,*S*-acetals containing two methyl groups on the β-carbon did not afford spirobicyclic rings systems when reacted with aryl isocyanates. Instead, many spots were observed on TLC plates. No major product was formed or isolated and these reactions were not further investigated.

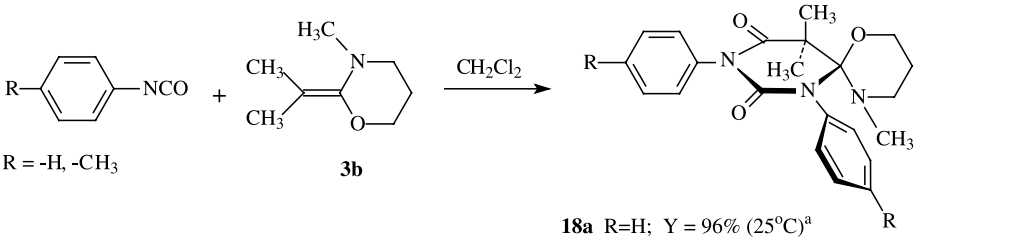
The 6/5 spirobicyclic products, **17c**, **17d** and **17f**, each have two diastereomers, because each contains two carbons (C-3



Scheme 9.



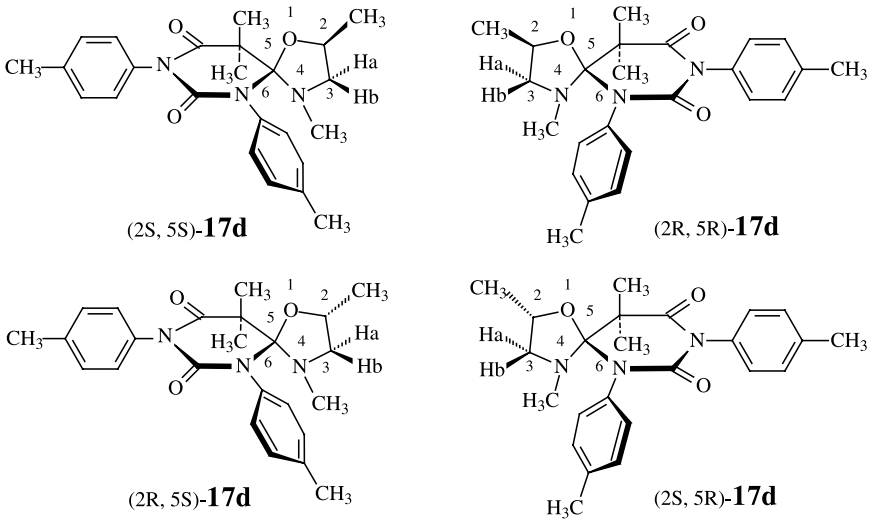
17a R=H; R^1=H, R^2, R^3=CH_3; Y = 94% (–25 °C)[a]
Y = 98% (25 °C)[a]
17b R=CH_3; R^1=H, R^2, R^3=CH_3; Y = 91% (–25 °C)[a]
Y = 92% (25 °C)[a]
17c R= H; R^1=CH_3, R^2, R^3=H; Y = 92% (–25 °C)[a]
Y = 94% (25 °C)[a]
17d R=CH_3; R^1=CH_3, R^2, R^3=H; Y = 95% (–25 °C)[a]
Y = 97% (25 °C)[a]
17e R=NO_2; R^1=H, R^2, R^3=CH_3; Y = 92% (–20 °C)[b]
Y = 95% (25 °C)[b]
17f R=NO_2; R^1=CH_3, R^2, R^3=H; Y = 91% (–20 °C)[b]
Y = 93% (25 °C)[b]



18a R=H; Y = 96% (25°C)[a]
18b R=CH_3; Y = 93% (-25°C)[a]
Y = 97% (25°C)[a]

[a] mole ratio of **2** (or **3**)/ ArNCO = 1:5
[b] mole ratio of **2** (or **3**)/ArNCO = 1:3.

Scheme 10.



Scheme 11.

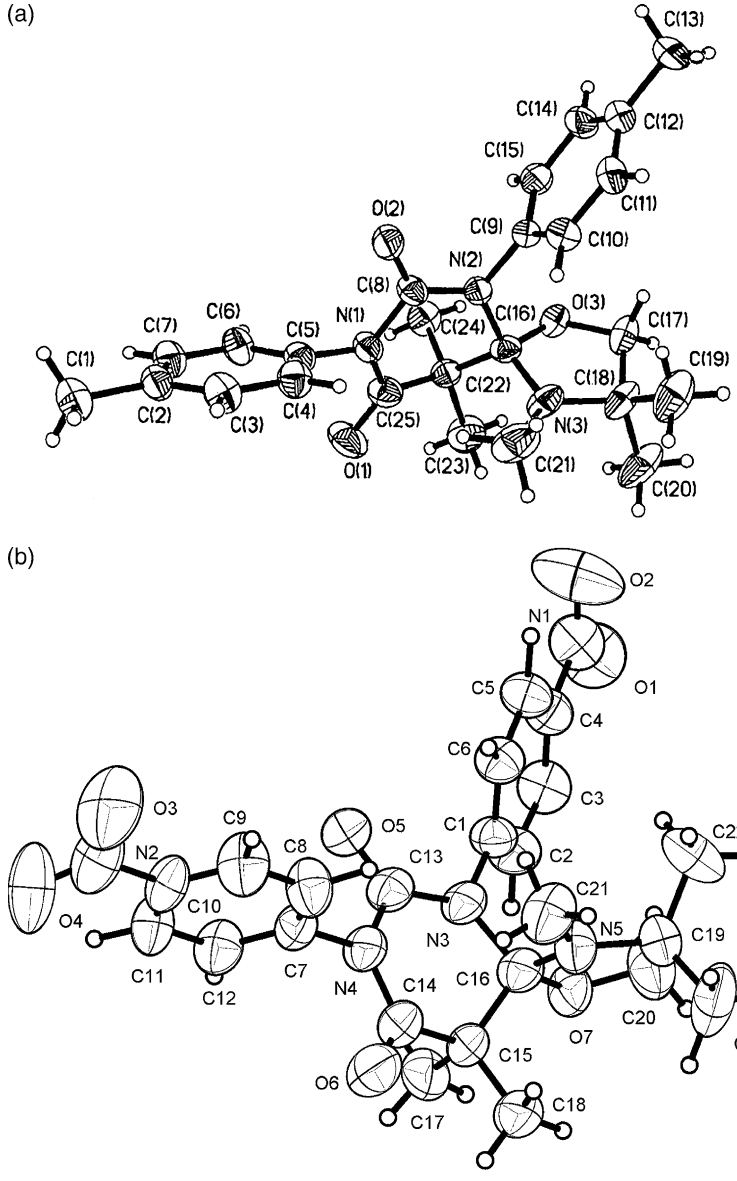
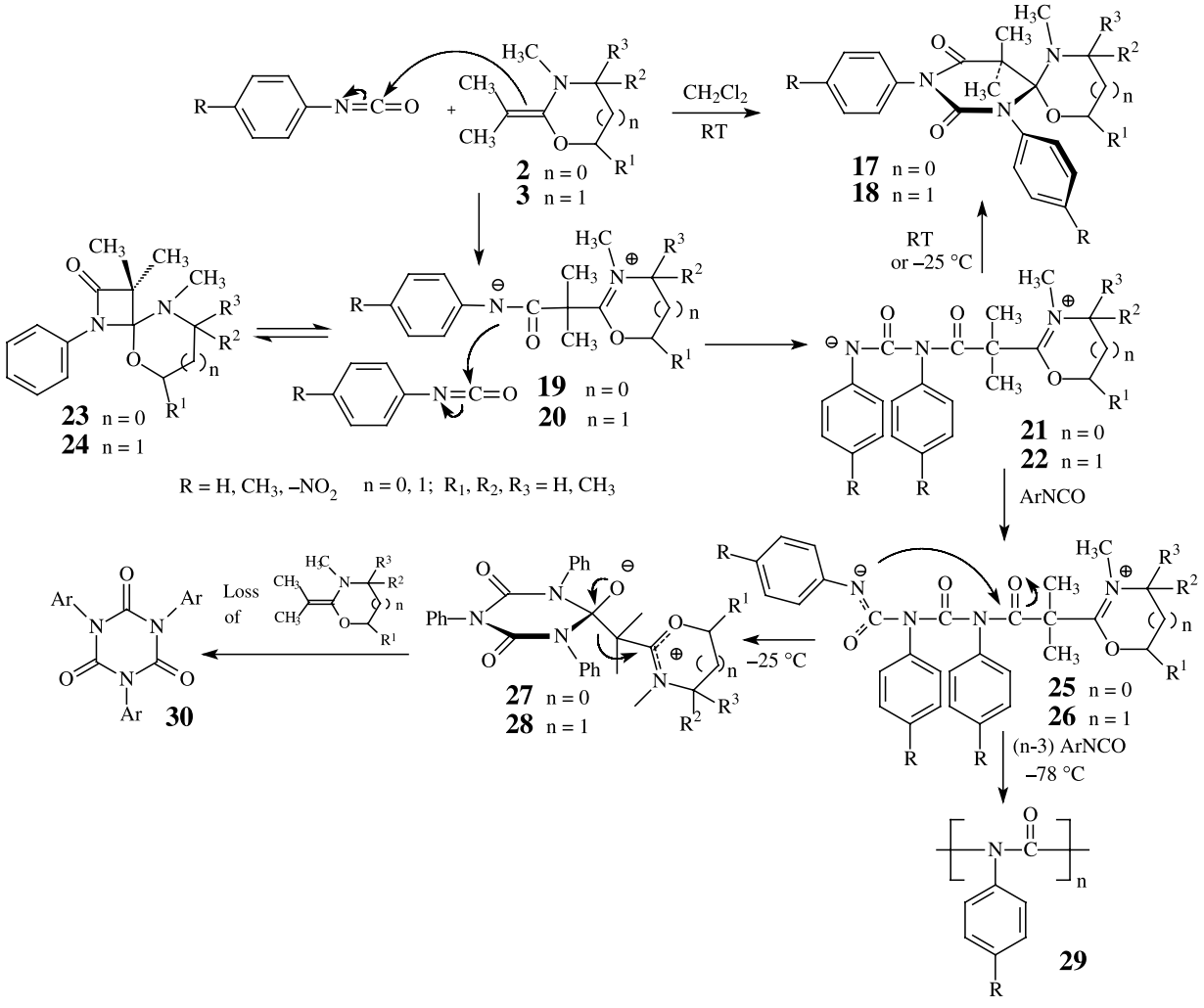


Figure 2. (a) X-ray crystal structure of compound **17b**. (b) X-ray crystal structure of compound **17e**.

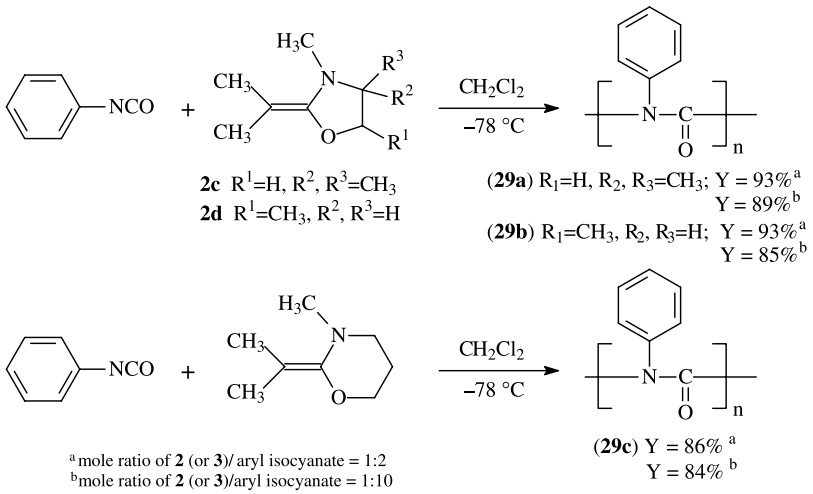
and C-5) whose configurations can be *R* or *S*. The ^{1}H and ^{13}C NMR spectra of each of these three diastereomer mixtures, prior to separation by flash chromatography over silica gel, clearly exhibited two sets of peaks corresponding to each diastereomer. The mole ratio of two diasteromers is nearly 1:1 for all three cases. Integration of the methyl peaks from ^{1}H NMR spectroscopy (protons from R^1, R^2, R^3) versus the aromatic protons demonstrated that **17/18** contained two molecules of ArNCO.

The diastereomers of **17d** are used here as the example pair to illustrate how stereochemistry was assigned by use of their NMR spectra. Scheme 11 shows the structures of the diastereomers of **17d**. These diastereomers exist as two racemic sets of enantiomers (e.g., (2*S*,5*S*)-**17d** and (2*R*,5*R*)-**17d** along with (2*R*,5*S*)-**17d** and (2*S*,5*R*)-**17d**. These two diastereomers were easily separated by flash chromatography. The configuration at C-2 was decided by proton chemical shift of the methyl group bound to C-2. These methyl resonances were observed at 1.11 and 0.46 ppm. The upfield doublet at 0.46 ppm belongs to the C-2 methyl of the 2*S*,5*S*-**17d** and 2*R*,5*R*-**17d** enantiomer pair, because this methyl group lies in the face of this phenyl ring on N-6. Therefore, it experiences a strong upfield shift. In contrast, the methyl protons of the 2*R*,5*S*-**17d** and 2*S*,5*R*-**17d** enantiomer pair lie outside this shielding zone. Therefore, this C-2 methyl doublet's chemical shift is assigned to the at 1.12 ppm resonance. The proton bound to C-2 in each diastereomer also fit this pattern. Thus, the proton chemical shifts on C-2 for (2*S*,5*S*)-**17d** and (2*R*,5*R*)-**17d** is a multiplet at 4.11 ppm. However, the C-2 proton in 2*R*,5*S*-**17d** and 2*S*,5*R*-**17d** is found substantially upfield at 3.35 ppm, because it lies within the shielding anisotropy region of the aryl ring at N-6. X-ray crystal structures of **17b** and **17e** in Figure 2, provide further support to these assignments. Both crystal structures demonstrate that the plane of the phenyl ring at N-6 is approximately perpendicular to central ring in these compounds. Models show this conformation is also favored in solution, because the spiroheterocyclic five-membered ring interferes sterically with the *ortho*-hydrogen on the N-6 aryl ring.

The mechanism for spirobicyclic ring formation is shown in Scheme 12. Reaction of **2** or **3** (two β-methyls) with the first aryl isocyanate affords the zwitterions **19/20**. These zwitterions cannot undergo transfer of an acidic proton to nitrogen to form monoadducts as was the case during the formation of **4**, **5**, **6**, **7**, **14** and **15** (e.g., Schemes 3, 4, 6, 7 and 8). However **19** or **20** could reversibly cyclize to form spirobicyclic lactams, **23** or **24**. However, these lactams were not observed or isolated.



Scheme 12.

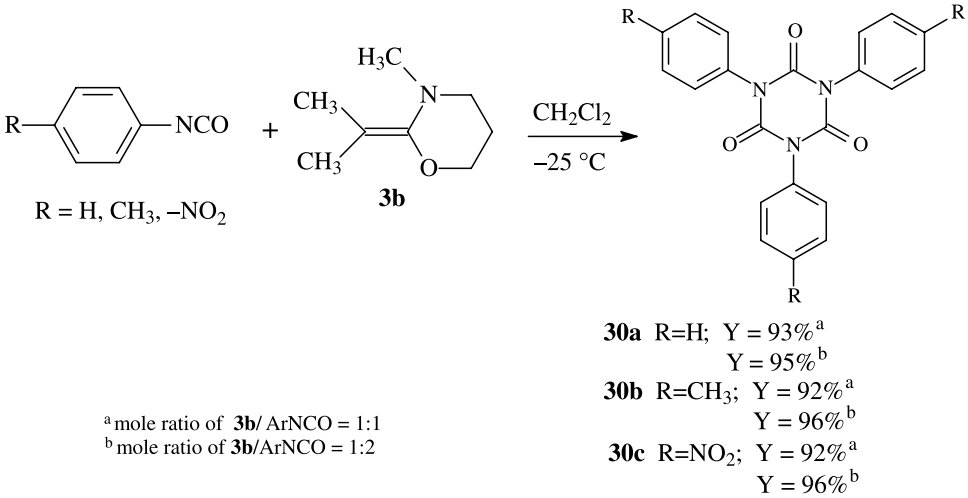


Scheme 13.

Instead, a second equivalent of aryl isocyanate reacts by nucleophilic attack of **19/20** on the isocyanate carbon to form zwitterion **21/22**. Cyclization of **21/22** then occurs to form the stable spiro-six-membered ring in **17/18** at temperatures between −25 and 25 °C. Cyclization to **17/18** occurs more rapidly than another nucleophilic addition of the negatively charged amide nitrogen of **21**, **22** to a third equivalent of aryl isocyanate to form the zwitterions **25/26**. Thus, the spirobicyclic 6/5 and 6/6 ring products, **17** and **18**, were obtained. X-ray crystal structures of **17b** and **17d** confirmed the formation spirobicyclic structures (Fig. 2). These structures also fit the detailed NMR analyses described earlier.

The reaction pathways change when cyclic ketene-*N*,*O*-acetals with two methyl groups at the β-carbon are reacted at −78 °C. At this low temperature, these *N*,*O*-acetals, **2** and **3** do not form the spirobicyclic 6/5 and 6/6 ring products upon reacting with isocyanates. Instead of cyclizing to **17/18**, zwitterions **21/22** (shown in Scheme 12) continue to react with additional phenyl isocyanate to generate poly(phenylisocyanate) **29** (Scheme 13). Molecular weights of 2000–4000 were observed when substantial or stoichiometric amounts of **2** (R=CH_3) were employed, indicating that this polymerization is very fast relative to the initial addition of **2** to phenylisocyanate. Adding only trace amounts of **2** to phenylisocyanate gives higher molecular weight polymers.

Curiously, the six-membered ring cyclic ketene-*N*,*O*-acetal **3b** does not generate poly(aryl isocyanates) when reacted with aryl isocyanates at −25 °C in CH_2Cl_2. Instead 1,3,5-triaryl-[1,3,5]triazinan-2,4,6-triones **30** were produced (Scheme 14). While **3b** acts as an anionic polymer initiator at −78 °C, **3b** leads to **30** at −25 °C because each of the cyclizations of zwitterions **26** (R=H, CH_3, NO_2) occur faster then the addition of **26** to a fourth aryl isocyanate. Cyclization of **26** gives intermediates **28** (Scheme 12), which eliminate the original cyclic ketene-*N*,*O*-acetal **3b** to form 1,3,5-triaryl-[1,3,5]triazinane-2,4,6-triones **30a–c**. The structures of **30a–c** were established by NMR and IR spectroscopy



Scheme 14.

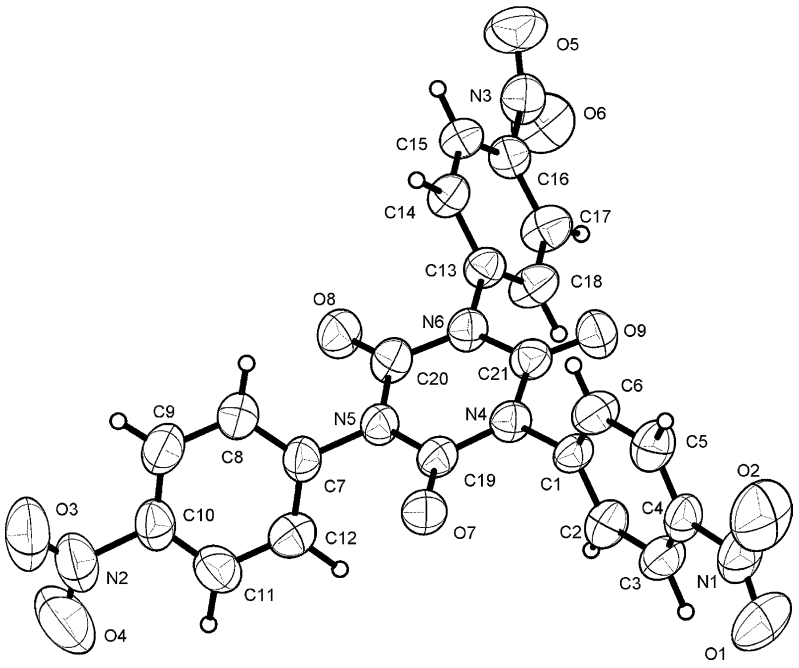


Figure 3. X-ray crystal structure of compound **30c**.

and melting points. Furthermore, the crystal structure was obtained for **30c** (Fig. 3).

3. Conclusions

The nucleophilic character of the exocyclic β-carbon of cyclic ketene-*N*,X (X=O, S)-acetals was established and demonstrated in nucleophilic reactions with aryl isocyanates, and aryl isothiocyanates, at different temperatures. Mono-α,β-unsaturated thioamides and both mono- and bis-α,β-unsaturated amide electronic 'push–pull' products were obtained when the β-carbon of the cyclic ketene acetal contained two hydrogens. However, when no hydrogens were present at the β-carbon, spirobicyclic six/five and six/six-membered ring systems were formed in reactions of cyclic ketene-*N*,*O*-acetals with aryl isocyanates at 25−−25 °C. At −78 °C, however, both five- and six-membered ring *N*,*O*-acetals initiated aryl isocyanate polymerizations. A third reaction pathway was also observed, six-membered ring *N*,*O*-acetal **3a** generated 1,3,5-triaryl-[1,3,5]triazinane-2,4,6-triones when reacted with aryl isocyanates. All these reactions proceed under mild conditions to give excellent isolated yields in most cases.

4. Experimental

4.1. General methods

Melting points were recorded with a Mel-Temp apparatus and were uncorrected (using a heating rate of 2 °C/min near the mp). The IR spectra were recorded on FT infrared spectrometer as films on KBr plates. The ^{1}H and ^{13}C NMR spectra were recorded using 300 MHz spectrometer operating at 300 MHz for proton and 75 MHz for carbon. Chemical shifts were reported in ppm downfield from Me_4Si used as the internal standard. Splitting patterns are designated as 's, d, t, q, and m'; these symbols indicate 'singlet, doublet, triplet, quartet, and multiplet', respectively. All reactions were carried out under a dried nitrogen atmosphere. Acetonitrile and triethylamine were distilled from calcium hydride under nitrogen. Dichloromethane and nitromethane were pre-dried with $CaCl_2$ and then distilled from calcium hydride under nitrogen. Tetrahydrofuran (THF) was distilled from Na metal/benzophenone ketyl. All other commercially obtained reagents were used as received. The silica gel used for the column chromatography was purchased from Aldrich Company (70–230 mesh).

4.1.1. (2*Z*)-(3-Methylthiazolidin-2-ylidene)-*N*-phenylthioacetamide (4a). The *N*-methyl cyclic ketene-*N*,*S*-acetal (3-methyl-2-methylenethiazolidine) (0.23 g, 2.0 mmol) was directly added into THF (40 mL). While stirring, phenyl isothiocyanate (0.54 g, 4.0 mmol) was added to this THF solution under nitrogen at room temperature. An immediate exothermic reaction occurred. The reaction mixture was stirred at room temperature under nitrogen for 3 h and then poured into *n*-hexane (100 mL) to precipitate the product. 2-(3-Methyl-thiazolidin-2-ylidene)-*N*-phenylthioacetamide **4a** was obtained in an isolated yield of 88% (0.45 g). The same procedure was used for compounds **4b–d**, **5a–b**, **6**, **14** and **15**.

Mp 157–159 °C. ^{1}H NMR (300 MHz, DMSO): δ 10.30 (s, 1H), 7.67–7.07 (m, 5H), 5.95 (s, 1H), 3.59 (t, J=7.8 Hz, 2H), 2.80 (t, J=7.8 Hz, 2H), 2.90 (s, 3H). ^{13}C NMR (DMSO): δ 188.0, 166.1, 140.7, 128.1, 123.7, 122.6, 95.5, 55.3, 35.3, 28.2. IR (neat): 3400–3300, 2932, 2857, 1587, 1515, 1452, 1351, 1195, 738 cm^{-1}.

4.1.2. (2*Z*)-(3,5-Dimethylthiazolidin-2-ylidene)-*N*-phenylthioacetamide (4b). Mp 158–160 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.37 (s, 1H), 7.33–7.13 (m, 5H), 5.83 (s, 1H), 3.59 (dd, J=7.2, 10.2 Hz, 1H), 3.59 (m, 1H), 3.26 (dd, J=7.2, 10.2 Hz, 1H), 2.81 (s, 3H), 1.38 (d, 3H). ^{13}C NMR ($CDCl_3$): δ 188.5, 168.8, 139.2, 128.8, 125.3,

124.2, 92.4, 62.8, 38.9, 35.4, 19.2. IR (neat): 3400–3300, 2962, 2924, 1595, 1530, 1495, 1301, 1230, 1183, 911, 750, 697 cm^{-1}. Anal. Calcd for $C_{13}H_{16}N_2S_2$: C, 59.08; H, 6.05; N, 10.60; S 24.26. Found: C, 59.23; H, 5.93; N, 10.77; S, 23.92.

4.1.3. (2*Z*)-(4-Ethyl-3-methylthiazolidin-2-ylidene)-*N*-phenylthioacetamide (4c). Mp 162–164 °C. ^1H NMR (300 MHz, acetone-d_6): δ 9.45 (s, 1H), 7.70–7.07 (m, 5H), 5.93 (s, 1H), 3.81 (m, 1H), 3.12 (dd, $J=7.8$, 11.1 Hz, 1H), 2.90 (s, 3H), 2.80 (dd, $J=3.6$, 11.1 Hz, 1H), 1.72–1.56 (m, 2H), 0.91 (t, $J=7.5$ Hz, 3H). ^{13}C NMR (acetone-d_6): δ 190.5, 167.3, 142.1, 129.3, 125.0, 124.0, 96.0, 68.4, 34.8, 33.1, 24.4, 10.1. IR (neat): 3400–3300, 2964, 1595, 1524, 1494, 1299, 1231, 1191, 756, 695 cm^{-1}. Anal. Calcd for $C_{14}H_{18}N_2S_2$: C, 60.43%; H, 6.47; N, 10.06; S, 23.04. Found: C, 60.24; H, 6.64; N, 9.88; S, 23.43.

4.1.4. (2*Z*)-(3,4,4-Trimethylthiazolidin-2-ylidene)-*N*-phenylthioacetamide (4d). Mp 164–166 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.35–7.15 (m, 5H), 5.82 (s, 1H), 2.90 (s, 2H), 2.66 (s, 3H), 1.31 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 188.5, 168.2, 139.2, 128.8, 125.3, 124.3, 93.1, 66.2, 41.9, 30.80, 23.9. IR (neat): 3400–3300, 2970, 1590, 1520, 1494, 1297, 1236, 1183, 910, 757, 715 cm^{-1}. Anal. Calcd for $C_{14}H_{18}N_2S_2$: C, 60.43; H, 6.47; N, 10.06; S, 23.04. Found: C, 60.26; H, 6.67; N, 10.25; S, 22.76.

4.1.5. (2*Z*)-(3,4,4-Trimethyloxazolidin-2-ylidene)-*N*-phenylthioacetamide (5a). Mp 136–137 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 9.14 (s, 1H), 7.61–7.11 (m, 5H), 5.11 (s, 1H), 4.21 (s, 2H), 2.69 (s, 3H), 1.28 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.3, 166.1, 140.1, 128.3, 125.2, 124.5, 82.6, 79.0, 60.3, 26.5, 22.8. IR (neat): 3376, 2976, 1588, 1507, 1433, 1343, 1147, 936, 764, 699 cm^{-1}.

4.1.6. *N*-*p*-Tolyl-(2*Z*)-(3,4,4-trimethyloxazolidin-2-ylidene)-thioacetamide (5b). Mp 153–154 °C. ^1H NMR (600 MHz, $CDCl_3$): δ 9.37 (s, 1H), 7.44–7.14 (m, 4H), 5.12 (s, 1H), 4.23 (s, 2H), 2.71 (s, 3H), 2.33 (s, 3H), 1.31 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 190.6, 162.2, 137.5, 135.2, 129.1, 124.9, 83.2, 79.0, 60.3, 26.6, 22.9, 22.0. IR (neat): 3378, 2971, 2927, 1583, 1522, 1438, 1338, 1260, 1137, 925, 748, 697 cm^{-1}.

4.1.7. 2-(3,4,4,6-Tetramethyl-[1,3]oxazinan-2-ylidene)-*N*-*p*-tolylthioacetamide (6). Mp 170–172 °C. ^1H NMR (600 MHz, $CDCl_3$): δ 9.85 (s, 1H), 7.52–7.14 (m, 4H), 5.20 (s, 1H), 4.43 (m, 1H), 2.80 (s, 3H), 1.97–1.79 (m, 2H), 1.46 (d, $J=6.2$ Hz, 3H), 1.34 (s, 3H), 1.29 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 190.4, 156.5, 138.0, 134.7, 129.0, 124.1, 88.7, 69.6, 55.0, 44.9, 32.1, 27.8, 26.6, 21.0, 20.4. IR (neat): 3348, 2968, 2924, 2360, 1594, 1537, 1442, 1256, 1137, 1309, 1142, 1120, 985 cm^{-1}.

4.1.8. Preparation of 2-(3-methylthiazolidin-2-ylidene)-*N*,*N*′-diphenylmalonamide (8a). The *N*-methyl cyclic ketene-*N*,*S*-acetal (3-methyl-2-methylenethiazolidine) (0.23 g, 2.0 mmol) was directly added into THF (60 mL). Phenyl isocyanate (0.48 g, 4.00 mmol) was added to this solution while stirring under nitrogen at room temperature. An immediate exothermic reaction occurred. The reaction mixture was stirred at room temperature under nitrogen for 3 h and then poured into *n*-hexane (100 mL) to precipitate the product. 2-(3-Methyl-thiazolidin-2-ylidene)-*N*,*N*′-diphenylmalonamide **8a** was obtained in an isolated yield of 94% (0.67 g). The same procedure was used for compounds **8b–d**, **10a–c**, **11a–b**, **17**, **18**, **29** and **30**.

Mp 188–190 °C. ^1H NMR (300 MHz, DMSO): δ 9.37 (s, 2H), 7.61–6.88 (m, 10H), 3.49 (t, $J=6.9$ Hz, 2H), 2.90 (s, 3H), 2.80 (t, $J=7.8$ Hz, 2H). ^{13}C NMR (DMSO): δ 168.0, 166.1, 140.7, 128.1, 123.7, 122.6, 95.5, 55.3, 35.3, 28.2. IR (KBr): 3400–3200, 2932, 2857, 1587, 1515, 1452, 1351, 1195, 738 cm^{-1}. Anal. Calcd for $C_{19}H_{19}N_3O_2S$: C, 64.61; H, 5.38; N, 11.89; O, 9.06; S, 9.06. Found: C, 64.73; H, 5.27; N, 11.71; S, 8.93.

4.1.9. 2-(3,5-Dimethylthiazolidinylidene)-*N*,*N*′-diphenylmalonamide (8b). Mp 190–192 °C. ^1H NMR (300 MHz, DMSO): δ 10.02 (s, 2H), 7.62–7.00 (m, 10H), 3.90 (m, 1H), 3.50 (m, 1H), 3.44 (m, 1H), 2.95 (s, 3H), 1.30 (d, $J=6.0$ Hz, 3H). ^{13}C NMR (DMSO): δ 167.6, 165.6, 139.1, 128.6, 122.7, 119.2, 92.6, 63.6, 38.6, 35.5, 19.7. IR (KBr): 3400–3200, 2937, 2849, 1583, 1521, 1447, 1355, 1198, 741 cm^{-1}. Anal. Calcd for $C_{20}H_{21}N_3O_2S$: C, 65.41; H, 5.72; N, 11.44; O, 8.71; S, 8.71. Found: C, 65.10; H, 5.91; N, 11.33; S, 8.78.

4.1.10. 2-(4-Ethyl-3-methylthiazolidin-2-ylidene)-*N*,*N*′-diphenylmalonamide (8c). Mp 194–196 °C. ^1H NMR (300 MHz, DMSO): δ 9.88 (s, 2H), 7.61–6.99 (m, 10H), 3.82 (m, 1H), 3.18 (dd, $J=8.1$, 10.8 Hz, 1H), 2.95 (s, 3H), 2.77 (dd, $J=4.8$, 10.8 Hz, 1H), 1.85–1.60 (m, 2H), 0.89 (t, $J=6.9$ Hz, 3H). ^{13}C NMR (DMSO): δ 168.3, 165.8, 139.2, 128.6, 122.7, 119.0, 93.0, 69.9, 39.9, 30.4, 25.1, 9.8. IR (KBr): 3400–3200, 2967, 1643, 1589, 1521, 1436, 1309, 1243, 905, 749, 693 cm^{-1}. Anal. Calcd for $C_{21}H_{23}N_3O_2S$: C, 66.16; H, 6.03; N, 11.02%; O, 8.39; S, 8.39. Found: C, 66.40; H, 6.01; N, 10.73; S, 8.56.

4.1.11. *N*,*N*′-Diphenyl-2-(3,4,4-trimethylthiazolidin-2-ylidene)-malonamide (8d). Mp 197–199 °C. ^1H NMR (300 MHz, DMSO): δ 9.85 (s, 2H), 7.61–7.01 (m, 10H), 3.00 (s, 2H), 2.80 (s, 3H), 1.33 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 168.9, 165.9, 139.2, 128.6, 122.6, 119.1, 91.7, 67.8, 40.2, 34.30, 23.6. IR (KBr): 3400–3200, 2970, 1590, 1520, 1494, 1297, 1236, 1183, 910, 757, 715 cm^{-1}. Anal. Calcd for $C_{21}H_{23}N_3O_2S$: C, 66.16; H, 6.03; N, 11.02; O, 8.39; S, 8.39. Found: C, 65.88; H, 6.34; N, 10.84; S, 8.13.

4.1.12. *N*,*N*′-Diphenyl-2-(3,4,4-trimethyloxazolidin-2-ylidene)-malonamide (10a). Mp 161–162 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 9.99 (s, 2H), 7.56–7.03 (m, 10H), 4.25 (s, 2H), 2.95 (s, 3H), 1.44 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 169.7, 167.0, 140.7, 130.1, 124.4, 121.9, 82.1, 78.5, 63.6, 32.4, 25.0. IR (KBr): 3330, 3020, 2960, 1640, 1595, 1540, 1440, 1320, 1250, 1055, 960, 760 cm^{-1}. Anal. Calcd for $C_{21}H_{23}O_3N_3$: C, 69.05; H, 6.30; N, 11.27. Found: C, 68.86; H, 6.54; N, 11.27.

4.1.13. *N*,*N*′-Di-*p*-tolyl-2-(3,4,4-trimethyloxazolidin-2-ylidene)-malonamide (10b). Mp 168–170 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 9.92 (s, 2H), 7.42–7.09 (m, aromatic H, 8H), 4.21 (s, 2H), 2.93 (s, 3H), 2.29 (s, 6H), 1.40 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 167.8, 165.6, 136.5, 129.2, 120.7, 79.4, 62.1, 60.3, 31.0, 23.6, 20.8. IR (KBr): 3427, 3027,

1660, 1625, 1521, 1437, 1326, 1242, 1065, 814, 786 cm^{-1}. Anal. Calcd for $C_{23}H_{27}N_3O_3$: C, 70.24; H, 6.87; N, 10.69. Found: C, 70.03; H, 7.06; N, 10.62.

4.1.14. *N*,*N*′-Bis-(4-nitrophenyl)-2-(3,4,4-trimethyloxazolidin-2-ylidene)-malonamide (10c). Mp 195–196 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 10.58 (s, 2H), 8.19–7.87 (m, 8H), 4.66 (s, 2H), 3.08 (s, 3H), 1.54 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 169.8, 166.6, 149.7, 147.4, 125.6, 119.4, 78.7, 78.5, 64.5, 30.2, 23.6. IR (KBr): 3581, 3238, 2968, 1697, 1625, 1575, 1507, 1335, 1257, 1118, 1056, 867, 761 cm^{-1}.

4.1.15. *N*,*N*′-Bis-(4-tolyl)-2-(3,4,4,6-tetramethyl-[1,3]-oxazinan-2-ylidene)-malonamide (11a). Mp 166–168 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 10.03 (s, 2H), 7.40–7.08 (m, 8H), 4.57–4.45 (m, 1H), 3.11 (s, 3H), 2.29 (s, 6H), 2.04–1.91 (m, 2H), 1.55 (d, J=5.2 Hz, 3H), 1.48 (s, 3H), 1.47 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 169.6, 166.3, 137.0, 132.1, 129.2, 120.3, 88.5, 70.9, 57.7, 45.1, 35.5, 27.5, 27.2, 20.7, 20.0. IR (KBr): 3435, 2927, 1638, 1507, 1313, 1245, 1052, 821, 728, 505 cm^{-1}.

4.1.16. *N*,*N*′-Bis-(4-nitrophenyl)-2-(3,4,4,6-tetramethyl-[1,3]oxazinan-2-ylidene)-malonamide (11b). Mp 205–208 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 10.64 (s, 2H), 8.16–7.66 (m, 8H), 4.73 (m, 1H), 3.21 (s, 3H), 2.15–2.02 (m, 2H), 1.65 (d, J=5.2 Hz, 3H), 1.56 (s, 3H), 1.55 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 170.7, 165.9, 147.4, 145.8, 142.1, 129.9, 125.1, 124.8, 119.7, 118.8, 82.7, 72.3, 58.8, 44.4, 36.1, 27.5, 27.0, 20.3. IR (KBr): 3412, 3074, 2990, 1720, 1650, 1600, 1536, 1491, 1407, 1335, 1257, 1118, 1056, 846, 744 cm^{-1}.

4.1.17. *N*-Phenyl-2-(3,4,4-trimethyloxazolidin-2-ylidene)-acetamide (14a). Mp 151–152 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.26 (s, 1H), 7.55–6.99 (m, 4H), 4.18 (s, 2H), 4.03 (s, 1H), 2.63 (s, 3H), 1.27 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 166.0, 161.7, 139.6, 128.6, 122.3, 119.5, 78.6, 70.4, 60.0, 26.5, 22.5. IR (KBr): 3289, 2964, 1757, 1532, 1255, 1038, 831, 743, 521 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_2N_2$: C, 68.31; H, 7.31; N, 11.38. Found: C, 68.48; H, 7.11; N, 11.24.

4.1.18. *N*-*p*-Tolyl-2-(3,4,4-trimethyloxazolidin-2-ylidene)-acetamide (14b). Mp 160–162 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.19 (s, 1H), 7.42–7.07 (m, 4H), 4.17 (s, 2H), 4.02 (s, 1H), 2.62 (s, 3H), 2.29 (s, 3H), 1.26 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 166.0, 161.6, 137.0, 131.8, 129.1, 119.7, 78.5, 70.4, 60.0, 26.6, 22.5, 20.7. IR (KBr): 3295, 2976, 1760, 1523, 1253, 1041, 821, 731, 510 cm^{-1}. Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.24; H, 7.69; N, 10.77. Found: C, 69.10; H, 7.93; N, 10.53.

4.1.19. *N*-*p*-Nitrophenyl-2-(3,4,4-trimethyloxazolidin-2-ylidene)-acetamide (14c). Mp 190–193 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.58 (s, 1H), 8.16–7.70 (m, 4H), 4.24 (s, 2H), 4.07 (s, 1H), 2.68 (s, 3H), 1.32 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 168.9, 162.4, 146.2, 142.2, 125.1, 118.3, 80.4, 70.3, 56.1, 26.7, 22.8. IR (neat): 3567, 3198, 2982, 1709, 1633, 1537, 1515, 1324, 1237, 1131, 1061, 911, 864, 757 cm^{-1}.

4.1.20. *N*-Phenyl-2-(3,4,4,6-tetramethyl-[1,3]oxazinan-2-ylidene)-acetamide (15a). Mp 164–166 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.82 (s, 1H), 7.54–6.95 (m, 5H), 4.42 (m, 1H), 4.10 (s, 1H), 2.70 (s, 3H), 1.90–1.70 (m, 2H), 1.51 (d, J=6.2 Hz, 3H), 1.32 (s, 3H), 1.25 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 161.3, 154.3, 128.7, 125.4, 118.7, 119.1, 71.3, 67.6, 55.4, 46.7, 28.6, 26.9, 22.4, 17.2.

4.1.21. *N*-*p*-Nitrophenyl-2-(3,4,4,6-tetramethyl-[1,3]-oxazinan-2-ylidene)-acetamide (15b). Mp 194–196 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 9.14 (s, 1H), 8.16–7.62 (m, 4H), 4.45 (m, 1H), 4.12 (s, 1H), 2.74 (s, 3H), 1.99–1.82 (m, 2H), 1.56 (d, J=6.2 Hz, 3H), 1.35 (s, 3H), 1.32 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 165.0, 157.5, 132.5, 125.2, 119.6, 117.9, 72.5, 69.7, 55.6, 47.5, 30.5, 27.8, 26.7, 20.6. IR (neat): 3587, 3191, 2974, 1703, 1625, 1538, 1502, 1335, 1257, 1112, 1056, 861, 761 cm^{-1}.

4.1.22. 3,3,4,10,10-Pentamethyl-6,8-diphenyl-1-oxa-4,6,8-triazaspiro[4,5]decane-7,9-dione (17a). Mp 147–148 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.16–7.44 (m, 10H), 3.49 (d, J=6.8 Hz, 1H), 2.67 (d, J=6.8 Hz, 1H), 2.64 (s, 3H), 1.71 (s, 3H), 1.33 (s, 3H), 1.06 (s, 3H), 0.78 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 174.7, 152.4, 136.2, 135.8, 131.4, 131.3, 131.1, 128.9, 128.4, 127.9, 108.2, 77.7, 59.3, 48.1, 26.3, 26.1, 24.7, 24.6, 19.0. IR (KBr): 2980, 2940, 1710, 1660, 1595, 1490, 1390, 1315, 1180, 1081, 840, 690 cm^{-1}. Anal. Calcd for $C_{23}H_{27}O_3N_3$: C, 70.24; H, 6.87; N, 10.69. Found: C, 70.01; H, 7.24; N, 10.39.

4.1.23. 3,3,4,10,10-Pentamethyl-6,8-di-*p*-tolyl-1-oxa-4,6,8-triazaspiro[4,5]decane-7,9-dione (17b). Mp 165–167 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.26–7.03 (m, 10H), 3.48 (d, J=7.7 Hz, 1H), 2.71 (d, J=7.7 Hz, 1H), 2.61 (s, 3H), 2.35 (s, 6H), 1.68 (s, 3H), 1.32 (s, 3H), 1.06 (s, 3H), 0.8 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 174.7, 152.5, 137.8, 133.5, 131.1, 130.7, 129.5, 129.3, 128.7, 128, 108.1, 77.6, 59.2, 48.1, 26.3, 26.2, 24.8, 24.7, 21.1, 19.0. IR (KBr): 2985, 1735, 1678, 1507, 1393, 1327, 1189, 1034, 821, 723, 519 cm^{-1}. Anal. Calcd for $C_{25}H_{31}N_3O_3$: C, 71.27; H, 7.36; N, 9.98. Found: C, 71.04; H, 7.60; N, 9.77.

4.1.24. 2,4,10,10-Tetramethyl-6,8-bis-(4-phenyl)-1-oxa-4,6,8-triazaspiro[4,5]decane-7,9-dione (17c). Compound **17c** consists of two diastereomers. They are (2*R*,5*R*)/(2*S*,5*S*)-2,4,10,10-tetramethyl-6,8-(4-nitrophenyl)-1-oxa-3,6,8-triazospiro[4,5]decane-7,9-dione (**17c**).

Mp 129–133 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.45–7.14 (m, 10H), 4.11(m, 1H), 3.02 (m, 1H), 2.76 (s, 3H), 2.58 (m, 1H), 1.69 (s, 3H), 1.33 (s, 3H), 0.46 (d, J=6.0 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 176.3, 154.1, 137.2, 133.8, 132.5, 132.2, 129.9, 129.7, 129.5, 129.1, 108.1, 76.1, 60.7, 49.1, 34.5, 26.0, 19.7, 18.5. Anal. Calcd for $C_{22}H_{25}O_3N_3$: C, 69.67; H, 6.59; N, 11.08. Found: C, 69.53; H, 6.77; N, 11.21.

4.1.25. (2*S*,5*R*)/(2*R*,5*S*)-2,4,10,10-Tetramethyl-6,8-(4-nitrophenyl)-1-oxa-3,6,8-triazospiro[4,5]decane-7,9-dione (17c). Mp 129–133 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.45–7.14 (m, 10H), 3.30 (m, 1H), 3.02 (m, 2H), 2.76 (s, 3H), 2.70 (m, 1H), 1.69 (s, 3H), 1.33 (s, 3H), 1.12 (d, J=6.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 176.3, 154.2, 139.3,

133.8, 132.8, 132.5, 130.3, 129.7, 129.7, 129.1, 108.1, 73.4, 60.5, 48.6, 34.6, 26.2, 22.0, 19.7.

4.1.26. 2,4,10,10-Tetramethyl-6,8-bis-(4-*p*-tolyl)-1-oxa-4,6,8-triazaspiro[4,5]decane-7,9-dione (17d). Compound **17d** consists of two diastereoisomers. They are (2*R*,5*R*)/(2*S*,5*S*)-2,4,10,10-tetramethyl-6,8-(4-*p*-tolyl)-1-oxa-3,6,8-triazospiro[4,5]decane-7,9-dione (**17d**).

Mp 171–173 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26–7.02 (m, 8H), 4.11 (m, 1H), 3.00 (m, 1H), 2.74 (s, 3H), 2.59 (m, 1H), 2.35 (s, 6H), 1.66 (s, 3H), 1.32 (s, 3H), 0.46 (d, J= 6.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 174.7, 152.7, 137.8, 135.2, 132.0, 130.4, 129.5, 129.1, 128.8, 128.0, 106.4, 74.6, 59.3, 47.6, 33.2, 24.6, 21.1, 18.4, 17.1.

4.1.27. (2*S*,5*R*)/(2*R*,5*S*)-2,4,10,10-Tetramethyl-6,8-(4-nitrophenyl)-1-oxa-3,6,8-triazospiro[4,5]decane-7,9-dione (17d). Mp 171–173 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-7.02 (m, 8H), 3.35 (m, 1H), 3.02 (m, 2H), 2.73 (s, 3H), 2.69 (m, 1H), 2.35 (s, 6H), 1.66 (s, 3H), 1.31 (s, 3H), 1.11 (d, J=6.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 174.7, 152.7, 137.4, 136.0, 133.2, 130.4, 129.5, 129.1, 128.8, 128.0, 106.4, 71.8, 59.1, 47.1, 33.1, 24.7, 21.1, 18.3. Anal. Calcd for $C_{24}H_{29}O_3N_3$: C, 70.77; H, 7.12; N, 10.32. Found: C, 70.65; H, 7.31; N, 10.14.

4.1.28. 3,3,4,10,10-Pentamethyl-6,8-bis-(4-nitrophenyl)-1-oxa-4,6,8-triaza-spiro[4,5]decane-7,9-dione (17e). Mp 195–197 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35–8.31 (m, aromatic H, 8H), 3.61 (d, J=8.0 Hz, 1H), 2.85 (d, J= 8.0 Hz, 1H), 2.64 (s, 3H), 1.74 (s, 3H), 1.37 (s, 3H), 1.11 (s, 3H), 0.76 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 174.0, 151.5, 147.8, 147.3, 143.8, 133.7, 132.6, 132.0, 129.7, 123.9, 109.0, 78.1, 59.6, 48.7, 26.4, 25.8, 24.6, 19.0, 14.7. IR (KBr): 2979, 1725, 1675, 1615, 1603, 1530, 1502, 1397, 1335, 1274, 1123, 1023, 833 and 744 cm^{-1}.

4.1.29. 2,4,10,10-Tetramethyl-6,8-bis-(4-nitrophenyl)-1-oxa-4,6,8-triaza-spiro[4,5]decane-7,9-dione (17f). Compound **17f** consists of two diastereomers. They are (2*R*,5*R*)/(2*S*,5*S*)-2,4,10,10-(-tetramethyl-6,8-(4-nitrophenyl)-1-oxa-3,6,8-triazospiro[4,5]decane-7,9-dione (**17f**).

Mp 193–195 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–8.31 (m, 8H), 4.17–4.20 (m, 1H), 3.10 (m, 1H), 2.79 (s, 3H), 2.78 (m, 1H), 1.72 (s, 3H), 1.37 (s, 3H), 0.57 (d, J=6.0 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 174.0, 151.3, 147.1, 144.4, 141.1, 132.4, 131.1, 129.8, 124.3, 123.8, 106.9, 76.8, 59.3, 48.0, 33.4, 24.6, 18.4, 17.5. IR (KBr): 2985, 1735, 1681, 1614, 1530, 1502, 1402, 1335, 1319, 1274, 1190, 1118, 1040, 845, 800, 733 cm^{-1}.

4.1.30. (2*S*,5*R*)/(2*R*,5*S*)-2,4,10,10-Tetramethyl-6,8-(4-nitrophenyl)-1-oxa-3,6,8-triazospiro[4,5]decane-7,9-dione (17f). Mp 193–195 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–8.31 (m, 8H), 3.39 (m, 1H), 3.09 (m, 2H), 2.78 (s, 3H), 3.00 (m, 1H), 1.72 (s, 3H), 1.35 (s, 3H), 1.16 (d, J= 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 177.1, 151.6, 147.5, 147.1, 143.5, 133.5, 132.2, 132.0, 129.7, 123.9, 107.1, 75.3, 58.8, 47.7, 33.4, 24.8, 20.2, 18.3. IR (KBr): 2984, 1735, 1679, 1507, 1391, 1327, 1185, 1034, 828, 723, 521 cm^{-1}.

4.1.31. 5,5,11-Trimethyl-1,3-diphenyl-7-oxa-1,3,11-triazaspiro[5,5]undecane-2,4-dione (18a). Mp 138–140 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.14 (m, 10H), 3.53 (m, 1H), 3.03 (m, 2H), 2.88 (m, 2H), 2.70 (s, 3H), 1.72 (m, 1H), 1.63 (s, 3H), 1.39 (s, 3H), 1.28 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 175.4, 152.5, 138.3, 135.9, 131.3, 128.8, 128.5, 128.3, 128.0, 127.8, 100.4, 61.7, 49.9, 47.5, 37.8, 24.8, 22.9, 20.6, 18.0 cm^{-1}. Anal. Calcd for $C_{22}H_{25}O_3N_3$: C, 69.67; H, 6.59; N, 11.08. Found: C, 69.59; H, 6.77; N, 10.92.

4.1.32. 5,5,11-Trimethyl-1,3-di-*p*-tolyl-7-oxa-1,3,11-triazaspiro[5,5]undecane-2,4-dione (18b). Mp 155–157 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30–7.01 (m, 8H), 3.53 (m, 1H), 3.00 (m, 2H), 2.87 (m, 2H), 2.67 (s, 3H), 2.36 (s, 3H), 2.34 (s, 3H), 1.71 (m, 1H), 1.60 (s,3H), 1.37 (s, 3H), 1.29 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 175.0, 152.3, 137.3, 137.1, 135.1, 132.7, 130.5, 129.0, 128.7, 127.4, 99.7, 61.3, 49.3, 47.1, 37.4, 24.4, 22.5, 20.6, 17.6. IR (KBr): 2971, 1725, 1688, 1521, 1419, 1326, 1186, 1056, 814, 749, 526 cm^{-1}. Anal. Calcd for $C_{24}H_{29}O_3N_3$: C, 70.77; H, 7.12; N, 10.32. Found: C, 70.54; H, 7.31; N, 10.18.

4.1.33. 1,3,5-Triphenyl-[1,3,5]triazinane-2,4,6-trione (30a). Mp 269–270 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51–7.24 (aromatic H). ^{13}C NMR ($CDCl_3$): δ 148.6, 133.9, 129.3, 129.2, 128.4. MS (CI): Calcd for $C_{21}H_{15}O_3N_3$: 357.4 (M). Found: 358.4 (M+1). IR (KBr): 1717, 1596, 1503, 1429, 1224, 964, 760, 713, 593 cm^{-1}.

4.1.34. 1,3,5-Tri-*p*-tolyl-[1,3,5]triazinane-2,4,6-trione (30b). Mp 281–282 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (aromatic H, 12H), 2.38 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 148.8, 139.2, 131.0, 129.9, 128.0, 21.2. IR (KBr): 1719, 1409, 964, 813, 756, 544 cm^{-1}. Anal. Calcd for $C_{24}H_{21}O_3N_3$: C, 72.19; H, 5.26; N, 10.53. Found: C, 72.26; H, 5.34; N, 10.33.

4.1.35. 1,3,5-Tris-(4-nitrophenyl)-[1,3,5]triazinane-2,4,6-trione (30c). Mp 286 °C (decomposed). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.43–7.76 (aromatic H). ^{13}C NMR ($CDCl_3$): δ 149.2, 148.9, 140.9, 131.3, 125.2. IR (KBr): 2929, 1720, 1525, 1430, 1352, 817, 767 cm^{-1}.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.02.011. Crystallographic data (excluding structure factors) for the structure in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 285465–285468 (**5b**, **6**, **17e**, **30c**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or deposit@ccdc.cam.ac.uk].

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Ph_2S_2–CaH_2 in *N*-methyl-2-pyrrolidone as an efficient protocol for chemoselective cleavage of aryl alkyl ethers

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Dedicated to Professor Srinivasan Chandrasekaran on his 60th birth anniversary.

Abstract—CaH_2 was been found, for the first time, as a mild reducing agent to generate thiophenolate anion from Ph_2S_2 in *N*-methyl-2-pyrrolidone (NMP) for deprotection of aryl alkyl ethers. Excellent chemoselctivity was observed for substrates having chloro and nitro groups without displacement of the chlorine atom and the nitro group. Selective ether cleavage took place in the presence of α,β-unsaturated carbonyl and nitro groups without reduction and conjugate addition (to the α,β-unsaturated carbonyl group).

1. Introduction

The phenolic moiety constitutes an important pharmacophore due to the wide spread biological activity of compounds containing phenolic hydroxyl group. Thus, the cleavage of aryl alkyl ethers is a versatile organic reaction keeping in view the ease of the generation of aryl alkyl ethers.[1] Although various methods such as nucleophilic,[2] reductive,[3] and photo/electrochemical cleavage[4] of aryl alkyl ethers are available, alkaline thiolates have been the commonly employed reagents for this purpose.[5] However, due to their obnoxious smell and radical generation ability, handling of thiols become difficult. The requirement of stoichiometric amount of bases such as NaH or MeLi to generate the thiolate anions do not make these procedures attractive. Moreover, the propensity of the thiolate anion to undergo oxidation to form the corresponding disulfides also necessitates special attention in using alkaline thiolates. Recently, Me_3SiSNa has been introduced for aryl alkyl ether cleavage.[6] However, the use of Me_3SiSNa requires stringent reaction conditions such as heating in sealed tube in DMEU/DMPU and is not compatible with functional groups (e.g., NO_2) that are susceptible to reduction. Recently, we have demonstrated Ph_2S_2 and Na in NMP as an efficient protocol for in situ generation of thiophenolate anion for selective deprotection of aryl alkyl ethers.[7] Although excellent results were obtained using this method, we felt that the use of highly moisture sensitive sodium metal still demands milder reagent for reductive generation of the thiophenolate anion from Ph_2S_2. This led us to develop a better reducing agent for in situ generation of thiophenolate anion from Ph_2S_2 and we report herein, for the first time, CaH_2 as a mild reducing agent to generate thiophenolate anion from Ph_2S_2 in NMP for chemoselective cleavage of aryl alkyl ethers.[8]

In the pursuit for a suitable reducing agent, we came across the use of potassium triisopropoxyborohydride[9] and lithium tri-*tert*-butoxyaluminiumhydride[10] for generation of thiolate anions from the corresponding disulfides and subsequent reaction with various alkyl halides. However, these reducing agents are not suitable for substrates bearing reducible functionalities such as carbonyl and nitro groups. Recently lanthanoid metals,[11] transition metal complex and salt such as benzyltriethylammonium tetrathiomolybdate[12] and indium(I) chloride[13] have been used for generation of thiolate anions from the corresponding disulfides. However, the high cost of these reagents does not make them attractive for routine applications. Other methods involve the treatment with Cu_2O-bpy (10 mol%) and Mg (0.6 equiv) in DMF at 110 °C for 18–72 h[14] and $NiBr_2$-bpy (10 mol%) and zinc (200 mol%) in DMF at 110 °C for 48 h.[15] In all of these reports the thiolate anion has been used either for conjugate addition to α,β-unsaturated carbonyl compounds[11,12,13b] or aryl sulfide formation by reaction with aromatic halides.[13a,14,15]

Keywords: Ether cleavage; Diphenyl disulfide; Calcium hydride; Chemoselective; Thiophenolate anion.
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2. Results and discussion

To find out the best reducing agent(s), 2-methoxynaphthalene (**1**) was treated with Ph_2S_2 in NMP in the presence of various metals such as Mg, Fe and In under varied experimental conditions such as the amount of Ph_2S_2 and the reducing agent, reaction temperature and time. The reactions conditions providing the optimum results in each case are provided in Table 1. In each occasion, the progress of the reaction was monitored by GCMS and HPLC. Moderate result was obtained in using Fe affording 2-hydroxynaphthalene (**2**) in 38% yield. The use of Mg and In were proved to be ineffective as evidenced by the formation of **2** in 2 and 1% yields, respectively (GCMS and HPLC). As calcium metal (Ca) has been reported to be a milder reducing agent compared to the alkali metals,[16] we planned to use Ca as the reducing agent. However, the use of Ca afforded 46% conversion to **2**. We next choose NaH and CaH_2 as alkali metal hydrides were known to possess reducing property[17] and generated alkali selenoates from diorganodiselenides.[18] We were delighted to observe that 95 and 90% conversion (HPLC) to **2** took place in the presence of NaH and CaH_2, respectively. The best result was obtained by the treatment of **1** (1 equiv) with Ph_2S_2 (0.6 equiv) and MH (1.6 equiv) in NMP by heating under reflux for 30 min.

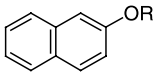
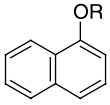
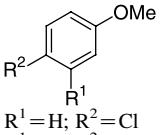
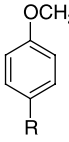
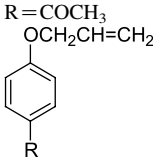
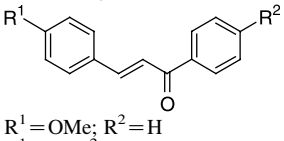
Table 1. Reaction of **1** with Ph_2S_2 in NMP in the presence of various reducing agents[a]

Entry	Reducing agent	Time (min)	Yield (%)[b]
1	Mg	30	2
2	Fe	30	38
3	In	30	1
4	Ca	30	48
5	NaH	30	96
6	CaH_2	30	90
7	CaH_2	15	64

[a] **1** (1 mmol) was treated with Ph_2S_2 (0.6 equiv) and the reducing agent (1.6 equiv) by heating under reflux in NMP (~220 °C).
[b] GCMS and HPLC yields of **2**.

To establish the generality, various aryl alkyl ethers were subjected to the treatment with Ph_2S_2 and CaH_2 in NMP (Table 2). Although the use of NaH afforded marginally better result than that of CaH_2 (compare the results of entries 5 and 6, Table 1), we planned to carry out the remaining reactions with CaH_2 as NaH is highly moisture sensitive and its strong basic property may induce sulfenylation as major side reaction with substrates bearing enolisable proton. Excellent results were obtained with methyl, ethyl and benzyl ethers. However, allyl and propargyl ethers afforded moderate yields (Table 2: entries 3, 4 and 7). In each occasion, the isolated (after aqueous work up) product was pure (GCMS, NMR) and the reaction temperature had no detrimental effect on purity of the product. The rate of ether cleavage was affected by the steric and electronic factors of the alkyl group. Inferior yield was obtained during the cleavage of ethyl ether compared to that of methyl ether under identical reaction conditions (compare entries 1 and 2, Table 2). The cleavage of benzyl ether was more facile compared to that of methyl ether (compare the results of entry 1 with that of 5 and the result of entry 6 with that of 8, Table 2). The presence of an electron withdrawing group made the ether cleavage facile as evidenced by the excellent

Table 2. Chemoselective deprotection of aryl alkyl ethers[a]

Entry	Ether	Yield (%)[b,c]
		
1	R=Me	80
2	R=Et	69
3	R=CH_2–CH=CH_2	42
4	R=CH_2–C≡CH	35
5	R=CH_2-Ph	100
		
6	R=Me	76
7	R=CH_2–CH=CH_2	47
8	R=CH_2-Ph	95
		
9	R^1=H; R^2=Cl	99
10	R^1=H; R^2=COMe	88
11	R^1=$COCH_3$; R^2=H	83
12	R^1=H; R^2=CHO	98
13	R^1=H; R^2=CN	100
14	R^1=H; R^2=NO_2	100
		
15	R=CN	100
16	R=$COCH_3$	88
		
17	R=CN	100
18	R=$COCH_3$	100
		
19	R^1=OMe; R^2=H	100
20	R^1=H; R^2=OMe	100

[a] The ether (1 mmol) was treated with Ph_2S_2 (0.6 equiv) and CaH_2 (1.6 equiv) by heating under reflux in NMP (~220 °C) for 30 min.
[b] Isolated yields of the corresponding phenol.
[c] The products were characterized by GCMS and NMR.

(83–100%) yields of the phenolic products for substrates bearing electron withdrawing groups such as Cl, COMe, CHO, CN, NO_2, and α,β-unsaturated carbonyl (Table 2: entries 9–20). Excellent chemoselectivity was observed with substrates that are susceptible to undergo competitive aromatic nucleophilic substitution, conjugate addition and reduction. Exclusive ether cleavage took place for 4-chloro anisole (Table 2: entry 9) and 4-nitro anisole (Table 2: entry 14) without displacement of the chlorine atom[19] and the nitro group.[20] No reduction of the nitro group (Table 2: entry 14)[6b,c] and α,β-unsaturated double bond (Table 2: entries 19 and 20)[16,21] was observed although thiolate anions have reducing properties.[22] The reactions with the 1,3-diaryl-2-propenones (Table 2: entries 19 and 20) further

demonstrated chemoselectivity of ether cleavage without any competitive conjugate addition.[23,24]

3. Conclusion

In conclusions, we have described Ph_2S_2–CaH_2 in NMP as a highly efficient protocol for in situ generation of thiophenolate anion for chemoselective deprotection of aryl alkyl ethers. We have demonstrated, for the first time, the use of CaH_2 as a reducing agent to generate thiolate anion from disulfides. The mildness of CaH_2 should find its application in various other organic transformations.

4. Experimental

4.1. General

The ^1H and ^{13}C spectra were recorded on Bruker Avance DPX 300 (300 MHz) spectrometer in $CDCl_3$ using TMS as internal standard. The IR spectra were recorded on Nicolet Impact 400 spectrometer as KBr pellets for solid and neat for liquid samples. Mass spectra were recorded on QCP 5000 (Shimadzu) GCMS. The reactions were monitored by TLC (Merck). Evaporation of solvents were performed under reduced pressure using a Büchi rotary evaporator. Indium and calcium metals, 2-methoxynaphthalene, 4-methoxyacetophenone, 3-methoxyacetophenone, 4-methoxybenzaldehyde were purchased from Aldrich, India. Magnesium and iron metals, NaH, CaH_2 and *N*-methyl 2-pyrrolidone were from S-D Fine Chemicals, India. 4-Methoxychlorobenzene,[25] 4-methoxynitrobenzene,[25] 4-methoxybenzonitrile,[25] 2-ethoxynaphthalene,[25] 2-benzyloxynaphthalene,[26] 1-benzyloxynaphthalene,[27] 2-allyloxynaphthalene,[28] 1-allyloxynaphthalene,[29] 2-propynyloxynaphthalene,[30] 4-benzyloxyacetophenone,[31] 4-allyloxyacetophenone,[32] 4-allyloxybenzonitrile,[33] 1-phenyl-3-(4-methoxyphenyl)-2-propenone[34] and 1-(4-methoxyphenyl)-3-phenyl-2-propenone[34] were prepared following reported procedures.

4.1.1. Representative experimental procedure. 2-Methoxynaphthalene (**1**) (158 mg, 1 mmol) in NMP (0.4 mL) was added to a magnetically stirred mixture of Ph_2S_2 (130 mg, 0.6 mmol) and CaH_2 (70 mg, 1.6 mmol) in NMP (0.6 mL) under N_2 and the mixture was heated under reflux for 30 min. The cooled reaction mixture was diluted with water (10 mL) and extracted with Et_2O (3×10 mL) to separate any neutral component. The combined ethereal extracts were washed with 5% aqueous NaOH (10 mL) and the alkaline washing was added to the aqueous portion. The aqueous part was acidified in the cold (ice bath) with 6 N HCl and extracted with Et_2O (3×15 mL). The combined ethereal extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated under vacuum to afford the crude product which on crystallization (MeOH) afforded 2-hydroxynaphthalene (**2**) (115 mg, 80%). Mp 121 °C; IR (KBr) cm^{-1}: 3300,1630, 1601; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.1 (dd, 1H, J=2.5, 8.8 Hz), 7.18 (d, 1H, J=2.5 Hz), 7.36 (ddd, 1H, J=1.24, 6.88, 6.96 Hz), 7.46 (ddd, 1H, J=1.2, 6.88, 6.92 Hz), 7.71 (d, 1H, J=8.28 Hz), 7.77–7.81 (m, 2H); MS (EI): m/z=144 (M^+), 115 (M^+-29); identical with an authentic sample.[5g,35] The remaining reactions were carried out following this general procedure and the isolated product was purified either by crystallization (MeOH) or passing through a column of silica gel and eluting with eluting with hexane–EtOAc (9/1). The physical data (mp, IR, NMR and MS) of 1-hydroxynaphthalene,[35] 4-chlorophenol,[35] 4-hydroxyacetophenone,[35] 3-hydroxyacetophenone,[35] 4-hydroxybenzaldehyde,[35] 4-cyanophenol,[35] 4-nitrophenol,[35] 1-phenyl-3-(4-hydroxyphenyl)-2-propenone[5f] and 1-(4-hydroxyphenyl)-3-phenyl-2-propenone[5f] were in complete agreement with those of authentic samples.

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Further studies on the constituents of the gorgonian octocoral *Pseudopterogorgia elisabethae* collected in San Andrés and Providencia islands, Colombian Caribbean: isolation of a putative biosynthetic intermediate leading to erogorgiaene

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Abstract—Chemical investigations of the MeOH–CH_2Cl_2 extract of *Pseudopterogorgia elisabethae* specimens collected in the islands of San Andrés and Providencia, Colombian Caribbean, yielded four new diterpenes (**1**, **3**, **5**, **7**) along with seco-pseudopterosin J (**8**), and amphilectosins A (**9**) and B (**10**). The structures of the new compounds were established through spectral studies as an elisabethatriene analog named elisabethatrienol (**1**), 10-acetoxy-9-hydroxy- and 9-acetoxy-10-hydroxy-amphilecta-8,10,12,14-tetraenes (isolated as an interconverting mixture) (**3**), amphilecta-8(13),11,14-triene-9,10-dione (**5**), and a *seco*-pseudopterosin 7-*O*-α-L-fucopyranoside named *seco*-pseudopterosin K (**7**). Elisabethatrienol can be regarded as a biosynthetic intermediate leading to erogorgiaene.

1. Introduction

The purple sea feather, *Pseudopterogorgia elisabethae*, is a gorgonian octocoral found in protected reef environments throughout the Caribbean Sea. This species has been the subject of numerous chemical and biological studies (SciFinder search revealed more than 50 papers published on this matter up to date), particularly in regard of its diterpene and diterpene glycoside content. Among the latter compounds, the pseudopterosins and *seco*-pseudopterosins are of particular interest due to their excellent anti-inflammatory properties superior even to the activity shown by the commercial drug indomethacin.

There are several studies showing the great degree of variability in pseudopterosin (Ps) composition from specimens of *P. elisabethae* collected at different Caribbean locations. For instance, PsA–PsD, PsE–PsL and PsM–PsO were obtained from animals collected at the Bahamas,[1] Bermuda[2] and in the Florida Keys,[3] respectively. Recently, as a part of our continuous search for biologically active compounds from marine organisms,[4,5] we examined the extracts of *P. elisabethae* collected in San Andrés and Providencia islands (SW Caribbean) by LC–MS, finding two distinct chemotypes that were characterized based on their pseudopterosin and related compounds composition and correlated quite well with the geographical distribution.[6] Chemotype 1, found almost exclusively in Providencia island, was mainly characterized by the presence of PsP–PsV,[7] PsG and PsK and two *seco*-pseudopterosins (compounds **7** and **8** in this text). Chemotype 2, found in San Andrés island, was revealed to contain several non-glycosylated diterpenes (compounds **1**, **3** and **5** in this text) structurally related to pseudopterosins, along with much smaller amounts of the pseudopterosins found in Chemotype 1. Recently, Rodríguez et al. reported the isolation of PsP–PsZ from *P. elisabethae* collected at San Andrés and Providencia islands.[8,9]

The structurally related *seco*-pseudopterosins, named *seco*-PsA–*seco*-PsD, were isolated from *P. kallos* collected in the Florida Keys.[10] Subsequently, the isolation of *seco*-PsE–*seco*-PsG from *P. elisabethae* collected in the Florida Keys was reported.[3] Recently, *seco*-PsH and *seco*-PsI were found in *P. elisabethae* specimens collected at Providencia island.[8]

Keywords: Pseudopterosin; Seco-pseudopterosin; *Pseudopterogorgia elisabethae*; Elisabethatrienol; Seco-pseudopterosin K.
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In continuation of our recent work on the constituents of *P. elisabethae* from San Andrés and Providencia islands, Colombian Caribbean,[6,7] we report here the isolation and structure elucidation of the new non-glycosylated diterpenes (**1**, **3**, **5**) and one new *seco*-pseudopterosin (*seco*-pseudopterosin K) (**7**) together with the known *seco*-pseudopterosin J (**8**) and amphilectosins A (**9**) and B (**10**).

2. Results and discussion

The MeOH–CH_2Cl_2 (1/1) extract of the animal tissue was separated on silica gel column chromatography and reversed-phase HPLC to yield compounds **1**, **3**, **5** from chemotype 2 specimens from San Andrés island, and compounds **7**–**10** from chemotype 1 specimens from Providencia island. The structures of these compounds were elucidated by spectral means including 2D NMR experiments. Four compounds, out of seven, were characterized as new diterpene derivatives: elisabethatrienol (**1**), 10-acetoxy-9-hydroxy- and 9-acetoxy-10-hydroxy-amphilecta-8,10,12,14-tetraenes (isolated as an interconverting mixture) (**3**), amphilecta-8(13),11,14-triene-9,10-dione (**5**), and a *seco*-pseudopterosin 7-*O*-α-L-fucopyranoside named *seco*-pseudopterosin K (**7**), whereas the other compounds were identified as the recently reported *seco*-pseudopterosin J (**8**),[11] and amphilectosins A (**9**) and B (**10**) (Fig. 1).[11]

Compound **1** was isolated as a white amorphous solid. The molecular formula of **1** was determined to be $C_{20}H_{32}O$ by HREIMS. The UV absorption was found at 236 nm probably due to a conjugated diene. The ^{1}H NMR of **1** exhibited signals for two doublet methyls (δ 0.91 and 0.84), two olefinic methyls (δ 1.67 and 1.57), two olefinic protons (δ 5.92 and 5.01), exomethylene protons (δ 5.06 and 4.80), and one oxymethine proton (δ 4.20). The ^{13}C NMR data, assisted by the DEPT spectrum, indicated the presence of three double bonds [δ 147.6 (C), 143.9 (C), 131.2 (C), 125.6 (CH), 124.9 (CH) and 105.0 (CH_2)]. These spectral features were reminiscent of (+)-elisabethatriene (**2**),[12] a bicyclic, biosynthetic intermediate of pseudopterosin arising from geranylgeranyl diphosphate. Compound **1** is thus suggested to be a hydroxylated derivative of **2**.

The H–H COSY spectrum of **1** indicated that the oxymethine proton was correlated with the methylene protons at δ 1.52 and 1.91, and the exomethylene protons. The methylene protons were further connected to a methine proton at δ 2.56 (H-9), which in turn showed allylic coupling with the olefinic proton at δ 5.92 (H-5). The olefinic proton was further correlated with the exomethylene protons. These COSY correlations clearly showed the C-7 location of the hydroxyl group. HMBC correlations (Fig. 2) fully supported the structure formulation. Coupling patterns of 8α-H at δ 1.52 (q-like, J=12.0 Hz) and 8β-H at δ 1.91 (dt, J=12.0, 6.0 Hz) helped us to assign the pseudo-axial β-orientation of H-7 ($J_{7\text{-H},8\alpha\text{-H}}$=12.0 Hz) and pseudo-equatorial α-orientation of the C-7 hydroxyl group. The β-axial orientation of H-9 was also evident from the coupling constants of $J_{\text{H-9,H-8}\alpha}$=12.0 Hz and $J_{\text{H-9,H-8}\beta}$=6.0 Hz. A small coupling constant of $J_{\text{H-1,H-9}}$ (ca. 4 Hz), estimated from the shape of H-9, further indicated that H-1 is β-equatorially oriented. It was difficult to assign the orientation of H-4 on the basis of decoupling studies, although the H-4 resonance appeared at δ 1.82 as a broad doublet with J=ca. 10.0 Hz. Extensive NOE studies afforded useful information on the stereochemistry at the chiral centers. The pertinent NOE correlations are depicted in Figure 3. In particular, H-9 and H-5 showed NOE correlations with H-11 and H-4, respectively. The findings established the 4α-orientation of H-4. The C-4/C-11 relative stereochemistry was assumed from the biogenesis of pseudopterosins and the similarity of the ^{13}C data (C-11, C-12 and C-18) of **1** with those of **2**,[12,13] serrulatane

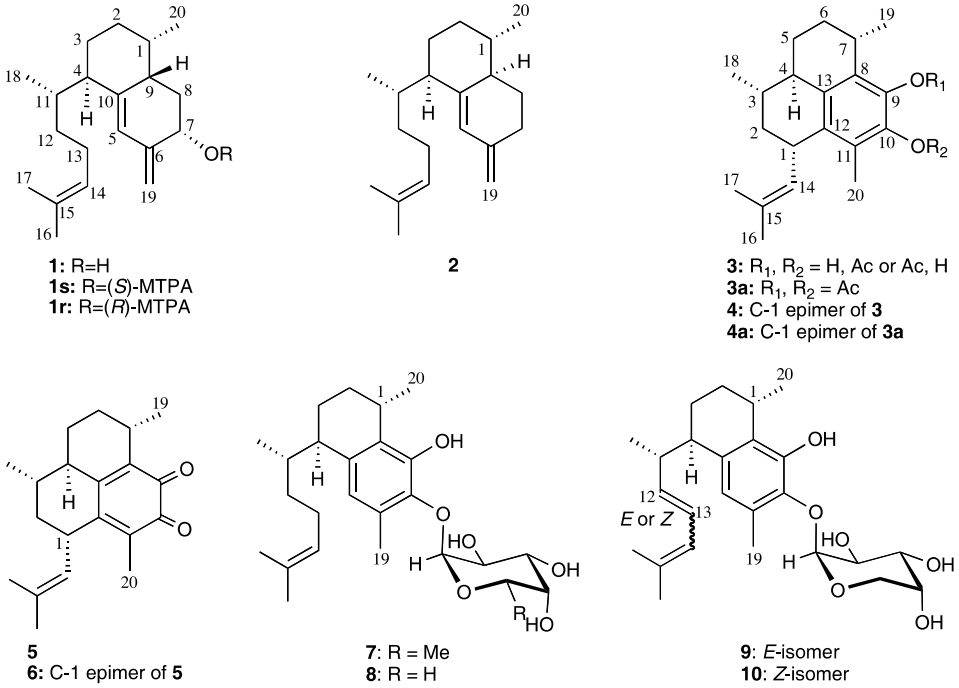
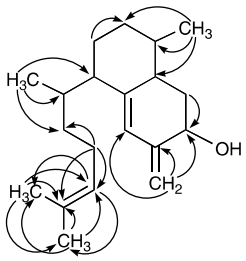


Figure 1. Chemical structures of compounds.



1

Figure 2. HMBC correlations from H to C for elisabethatrienol **1**.

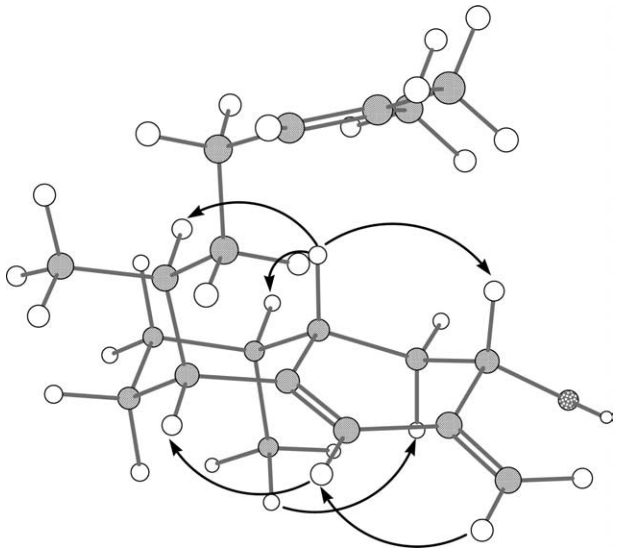


Figure 3. Pertinent NOE correlations and most stable conformation of elisabethatrienol **1**.

diterpenes,[14] and seco-pseudopterosins.[3] On the basis of these data the structure of **1** was determined as shown in Figure 1. The most stable conformation of the molecule, deduced by MM2 calculation, is also illustrated in Figure 3. It should be noted that the olefinic bond-containing six-membered ring adopts a half-chair conformation. Assignments of the NMR signals are listed in Table 1.

Mosher's ester method[15] was applied to determine the absolute configuration of this molecule. The ^{1}H NMR data for the (*S*)- and (*R*)-MTPA esters of **1** (**1s** and **1r**) are summarized in Table 2. The data clearly established the 7*S* configuration of **1**. Hence, the absolute configuration of the chiral centers in **1** was determined to be 1*S*,4*R*,7*S*,9*S*,11*S*. The new diterpene was named elisabethatrienol.[16] The possibility that compound **1** is 9-*epi*-elisabethatrienol, which is suggested from the structure of elisabethatriene **2**, was ruled out, since the observed NOE data was incompatible with the structure. Elisabethatrienol is an interesting molecule from a biosynthetic point of view and this will be discussed later.

Compound **3** was isolated as a yellow amorphous solid. Interestingly, it showed two distinct peaks when analyzed on reversed-phase HPLC. However, the samples separated by HPLC again showed the original two peaks in HPLC analysis. The phenomenon suggested that compound **3** should be a readily interconverting mixture of two components. The molecular formula of **3** was determined to be $C_{22}H_{30}O_3$ (MW 342) on the basis of HREIMS. The UV absorption maxima at 230 and 276 nm were similar to those of pseudopterosins. The ^{1}H NMR of **3** displayed pairs of signals in a 54:46 ratio, suggesting a mixture of two structurally related constituents. The ^{13}C NMR spectrum also showed a series of paired signals, including an acetoxy group (δ_C 20.6/20.9, 169.2/169.6). The HMBC spectrum (Fig. 4) helped us to propose that compound **3** is a mixture of 10-acetoxy-9-hydroxy- and 9-acetoxy-10-hydroxy-amphilecta-8,10,12,14-tetraenes[17] with the former being a major constituent. For the purpose of rigorous identification, **3** was acetylated to furnish a single compound **3a** having two acetyl groups (EIMS, M^+, 384), which was fully characterized by spectral methods, including 2D NMR. The coupling patterns of H-1 and H-7 of **3a** were closely similar to those of the pseudopterosin aglycone with 1β-H configuration, and different from those of 1α-H epimers.[18] Furthermore, the ^{13}C NMR chemical shifts of C-1–C-7 and C-14–C-19 in **3a** were in excellent agreement with those of pseudopterosins with 1β-H configuration,[7] thus indicating 1*S**,3*S**,4*R**,7*S** relative configuration of **3a**. Compound **3a** was therefore determined to be 9,10-diacetoxyamphilecta-8,10,12,14-tetraene. Accordingly, compound **3** was established to be a mixture of 10-acetoxy-9-hydroxy- and 9-acetoxy-10-hydroxy-amphilecta-8,10,12,14-tetraenes. It is likely that **3** has the 1*S*,3*S*,4*R*,7*S* absolute stereochemistry, since compound **3** ($[\alpha]_D^{25}$ +77.5) and known 9-methoxy-10-hydroxy-amphilecta-8,10,12,14-tetraene (lit.[18] +90) have the positive sign of optical rotation. The C-1 epimer of **3** (**4**) was previously isolated, also as an interconverting mono-acetate mixture, from the same species collected in the Bahamas islands and characterized in the form of the acetyl derivative, 9,10-diacetoxy-1-*epi*-amphilecta-8,10,12,14-tetraene (**4a**).[19] The ^{1}H NMR data of **3a** showed diagnostic difference from those reported for **4a**: H-14, δ 4.99 for **3a** versus δ 5.18 for **4a**.[18,19] The diacetate **4a** was also prepared from pseudopterosin C[20] and chemically synthesized.[21]

Compound **5** was isolated as an orange oil. Its molecular formula was determined as $C_{20}H_{26}O_2$ on the basis of HREIMS, which requires eight degree of unsaturation, one additional unsaturation expected for pseudopterosin aglycones. The ^{1}H NMR spectrum showed signals of two doublet methyls assignable to H_3-18 (δ 1.02) and H_3-19 (δ 1.14), two singlet methyls and an olefinic proton due to the isobutenyl group, and two methine protons assignable to H-1 (δ 3.70, td, J=9.1, 4.9 Hz) and H-7 (δ 2.77, sextet-like, J=6.4 Hz). The singlet methyl at δ 1.84, presumably due to H_3-20, was appreciably shifted upfield compared to that of pseudopterosins (ca. δ 2.2–2.3), suggesting that the aromatic ring is modified. In the ^{13}C NMR spectrum compound **5** exhibited eight sp^2 carbons, two of which (δ 181.0 and 180.8) could be assigned to carbonyl groups, most likely α,β-unsaturated carbonyls. In the HMBC spectrum, H_3-20 (δ 1.84) showed correlations to the carbonyl (δ 180.8) and two other sp^2 carbons (δ 132.2, 151.8), while H_3-19 was correlated with an sp^2 carbon (δ 138.8), C-6 and C-7. These NMR data agreed with the structure in which the catechol aromatic ring of a pseudopterosin aglycone was oxidized to an *ortho*-quinone. HMBC correlations depicted in Figure 5

Table 1. NMR ($CDCl_3$) data for compounds **1**, **3**, **3a** and **5**

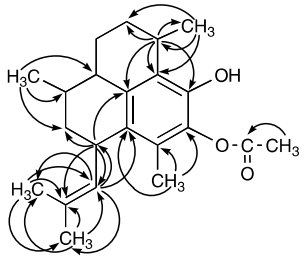
No.[a]	**1**		**3**		**3a**		**5**	
	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
1/7	1.96 (m)	32.6	3.18 (sextet-like, 7.2)/2.94 (sextet-like, 7.2)	28.8/28.4	2.95 (sextet-like, 7.2)	28.7	2.77 (sextet-like, 6.4)	28.7
2/6	1.35 (m) 1.75 (m)	28.5	1.33 (m) 2.13 (m)/2.07 (m)	31.7/31.5	1.36 (m) 2.10 (m)	31.3	1.23 (m) 1.95 (m)	29.8
3/5	1.60 (m) 1.65 (m)	21.8	0.92 (m) 2.03 (m)	27.5	0.97 (m) 2.07 (m)	27.2	1.13 (m) 1.96 (m)	25.4
4/4	1.82 (br d, 10.0)	47.8	2.05 (m)	44.6/44.0	2.05 (m)	44.2	2.04 (m)	43.0
5/12	5.92 (s)	125.6	—	130.6/136.9	—	137.0	—	151.8
6/11	—	147.6	—	126.7/122.8	—	128.0	—	132.2
7/10	4.20 (m)	69.7	—	136.0/143.4	—	139.5	—	181.0
8/9	1.52 (q-like, 12.0) 1.91 (dt, 12.0, 6.0)	36.4	—	143.0/135.6	—	138.8	—	180.8
9/8	2.56 (m)	38.7	—	127.2/131.4	—	132.4	—	138.8
10/13	—	143.9	—	137.9/132.2	—	137.9	—	152.3
11/3	1.65 (m)	32.4	1.20 (m)	33.7/33.9	1.33 (m)	33.6	1.40 (m)	31.8
12/2	1.31 (m) 0.88 (m)	34.6	1.18 (m) 1.96 (m)	40.0/39.9	1.23 (dd, 13.0, 3.3) 1.97 (ddd, 13.0, 8.1, 2.8)	39.9	1.28 (dd, 13.6, 4.9) 2.14 (ddd, 13.6, 9.0, 6.0)	37.7
13/1	2.02 (m) 1.82 (m)	25.5	3.68 (q-like, 8.8)/ 3.72 (q-like, 8.8)	36.9/37.3	3.71 (q-like, 8.8)	37.4	3.70 (td, 9.1, 4.9)	36.0
14/14	5.01 (t, 7.1)	124.9	4.97 (d, 9.2)/4.95 (d, 9.2)	130.9/130.6	4.99 (dt, 9.3, 1.2)	130.2	5.11 (dt, 9.2, 1.3)	126.5
15/15	—	131.2	—	128.6/128.8	—	129.2	—	132.0
16/16	1.67 (s)	25.7	1.71 (s)/173 (s)	25.4	1.71 (d, 1.2)	25.4	1.72 (br s)	25.6
17/17	1.57 (s)	17.7	1.66 (s)/1.67 (s)	17.5	1.66 (d, 1.2)	17.5	1.72 (br s)	17.9
18/18	0.91 (d, 6.6)	17.5	1.02 (d, 6.6)/ 1.01 (d, 6.6)	20.0/19.9	1.03 (d, 6.3)	19.9	1.02 (d, 6.6)	20.5
19/20	4.80 (s), 5.06 (s)	105.0	1.92 (s)/2.05 (s)	13.0/12.1	1.93 (s)	12.9	1.84 (s)	11.0
20/19	0.84 (d, 7.1)	14.6	1.26 (d, 6.8)/ 1.19 (d, 6.8)	23.1/23.4	1.19 (d, 6.9)	23.3	1.14 (d, 7.0)	21.3
Ac			2.34 (s)/2.35 (s)	20.6/20.9 169.2/169.6	2.27 (s) 2.29 (s)	20.4 20.6 168.6 168.3		

[a] Seco-type numbering/pseudopterosin numbering.

supported the *o*-quinone structure. The assignments of ^{1}H and ^{13}C signals are listed in Table 2. The shape (septet-like) of H-7 was similar to those of pseudopterosins with 1β-H,[7] thus indicating the β orientation of 7-H. NOE correlation between H_3-18 and H-4 evidenced the *syn*-orientation of the two groups. This compound was thus suggested to be 1-amphilecta-8(13),11,14-triene-9,10-dione (**5**) or its C-1 epimer **6**. However, the coupling pattern of H-1 was somewhat different from those of pseudopterosins with 1β-H (typically ddd, J=7.2, 7.2, 7.2 Hz).[7] Fortunately, 1-*epi*-amphilecta-8(13),11,14-triene-9,10-dione (**6**), was previously prepared from natural pseudopterosin C[20] and chemically synthesized.[21] Comparison of the NMR data of **5** and **6** showed considerable differences (e.g., H-14: δ 5.06 for **6**[21] vs δ 5.11 for **5**, H-1: δ 3.61 for **6**[21] vs δ 3.70 for **5**). Hence, compound **5** was determined to be amphilecta-8(13),11,14-triene-9,10-dione. Definitive proof of the structure came from the chemical correlation of **5** with **3**. Compound **3** was reduced by $LiAlH_4$ in ether and the reaction mixture was worked up in the usual extractive

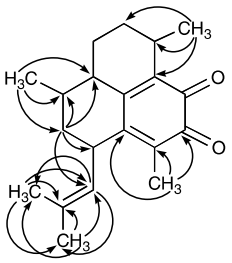
Table 2. ^{1}H NMR ($CDCl_3$) data for the MTPA esters **1s** and **1r**

No.	**1s**	**1r**	Δ (δ**1s**–δ**1r**)
1	1.94 (m)	1.97 (m)	−0.03
5	5.93 (s)	5.90 (s)	+0.03
7	5.40 (br d, 12.5)	5.56 (br d, 12.3)	
8	1.98 (ddd, 12.0, 6.1, 4.2)	2.02 (ddd, 11.5, 5.6, 4.2)	−0.04
	1.63 (m)	1.72 (m)	−0.09
9	2.64 (m)	2.66 (m)	−0.02
11	1.65 (m)	1.65 (m)	0.00
12	1.37 (m)	1.36 (m)	+0.01
	0.88 (m)	0.87 (m)	+0.01
14	5.06 (br t, 12.4)	5.05 (br t, 12.0)	+0.01
16	1.60 (s)	1.60 (s)	0.00
17	1.69 (s)	1.69 (s)	0.00
18	0.91 (d, 6.6)	0.91 (d, 6.6)	0.00
19	4.87 (s)	4.69 (s)	+0.18
	4.79 (s)	4.60 (s)	+0.19
20	0.79 (d, 7.0)	0.83 (d, 7.1)	−0.04
OMe	3.58 (br s)	3.62 (br s)	



3

Figure 4. HMBC correlations from H to C for the major constituent of compound **3**.



5

Figure 5. HMBC correlations from H to C for compound **5**.

manner to give the *ortho*-quinone **5** (identified by co-TLC and ^{1}H NMR) in 63% yield. It is likely that an air-oxidation of the initially formed diol yielded **5**. The optical rotation ($[\alpha]_D^{25}$ +134) of **5** derived from **3** was practically identical with that of natural sample **5**, thus establishing the 1*S*,3*S*,4*R*,7*S* absolute configuration of **5**. Compound **5** was a sensitive material and gradually decomposed even when stored in a freezer, as reported for **6**.

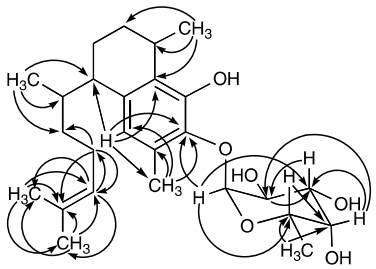
Compound **7** was isolated as a white amorphous solid. The molecular formula of **7** was determined to be $C_{26}H_{40}O_6$ on the basis of HREIMS. The UV spectrum showed absorption maxima at 208 and 280 nm due to a substituted benzene ring. In the EIMS spectrum, an intense fragment ion at *m/z* 302 arising from loss of 146 mass units from the molecular ion peak at *m/z* 448 suggested that **7** could be a seco-type pseudopterosin containing a deoxy-hexose moiety. Interpretation of the ^{1}H and ^{13}C NMR data (Table 3) indicated that the signals for the aglycone moiety were in good agreement with those reported for *seco*-pseudopterosin J,[11] while those for the sugar moiety were essentially identical with the data of α-fucopyranosyl moiety found in pseudopterosin-P,[7] which has recently been isolated from the same organism by us. HMBC correlation between the anomeric proton (δ 5.04) and C-7 (δ 142.1) gave evidence for the C-7 glycosylation (Fig. 6). The C-7 resonance was unequivocally assigned by HMBC cross peaks between C-7 and both H_3-19 (δ 2.29) and H-5 (δ 6.49). Chirality of fucose was assumed to be L, since the L-form of fucose, a sugar moiety of pseudopterosin-P, was unambiguously established in our previous paper.[7] Hence, the structure of **7** was established to be *seco*-pseudopterosin with the α-L-fucopyranosyl moiety linked at C-7, as shown in Figure 1. Compound **7** was named *seco*-pseudopterosin K. Previously reported *seco*-pseudopterosins E-G are 2-*O*-acetyl, 3-*O*-acetyl and 4-*O*-acetyl derivatives at the fucose moiety of **7**.[3]

Compound (**8**), $C_{25}H_{38}O_6$, showed a molecular ion peak at *m/z* 434. Interpretation of the NMR data, including HMQC and HMBC spectra, established that compound **8** is a *seco*-pseudopterosin with a β-D-arabinopyranosyl group attached to C-7 (evidenced by the HMBC correlation from the

Table 3. NMR ($CDCl_3$) data for compounds **7–10**

No.[a]	**7**		**8**		**9**		**10**
	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H
1/7	3.14 (m)	27.0	3.12 (m)	27.1	3.15 (m)	27.0	3.17 (m)
2/6	1.46 (m) 1.87 (tdd, 12.7, 5.9, 3.4)	27.9	1.45 (m) 1.85 (tdd, 12.7, 5.9, 3.3)	27.9	1.46 (m) 1.87 (m)	27.3	1.48 (m) 1.99 (tdd, 12.7, 6.0, 3.5)
3/5	1.66 (m) 1.79 (tdd, 12.7, 6.4, 3.3)	18.5	1.66 (m) 1.77 (tdd, 12.7, 6.3, 3.3)	18.5	N[b] 1.81 (m)	19.4	N 1.87 (tdd, 12.7, 5.8, 3.4)
4/4	2.63 (m)	39.5	2.62 (m)	39.6	2.65 (m)	42.5	2.62 (m)
5/12	6.49 (s)	120.8	6.49 (s)	121.2	6.49 (s)	121.9	6.53 (s)
6/11	—	127.8	—	127.9	—	127.6	—
7/10	—	142.1	—	141.9	—	142.1	—
8/9	—	146.6	—	146.5	—	146.6	—
9/8	—	128.9	—	129.2	—	129.0	—
10/13	—	136.7	—	137.1	—	135.4	—
11/3	1.97 (m)	38.5	1.97 (m)	38.6	2.66 (m)	41.3	2.99 (m)
12/2	1.34 (m) 1.46 (m)	35.6	1.33 (m) 1.46 (m)	35.7	5.61 (dd, 15.2, 6.4)	137.4	5.31 (t, 10.3)
13/1	1.95 (m) 2.07 (m)	26.2	1.95 (m) 2.06 (m)	26.3	6.15 (dd, 15.2, 10.5)	125.2	6.08 (dd, 11.5, 10.3)
14/14	5.15 (t, 7.1)	124.9	5.14 (t, 7.2)	124.9	5.81 (d, 10.5)	125.5	5.91 (d, 11.5)
15/15	—	131.1	—	131.2	—	133.0	—
16/16	1.71 (s)	25.6	1.71 (s)	25.7	1.77 (s)	25.9	1.77 (s)
17/17	1.63 (s)	17.6	1.62 (s)	17.7	1.73 (s)	18.3	1.72 (s)
18/18	0.71 (d, 7.0)	16.4	0.70 (d, 6.9)	16.4	0.89 (d, 6.8)	16.3	0.92 (d, 6.7)
19/20	2.29 (s)	16.9	2.25 (s)	17.2	2.23 (s)	17.1	2.28 (s)
20/19	1.19 (d, 6.8)	20.8	1.15 (d, 6.9)	21.0	1.18 (d, 6.9)	20.9	1.19 (d, 6.5)
1′	5.04 (d, 3.8)	103.9	5.13 (d, 3.4)	103.7	5.14 (d, 3.0)	103.3	5.14 (d, 3.1)
2′	3.96 (dd, 10.0, 3.8)	69.0	4.17 (br d 10.0)	69.7	4.16 (br d, 9.3)	69.6	4.17 (br d, 9.6)
3′	4.07 (dd, 10.0, 3.2)	70.2	4.12 (dd, 10.0, 3.6)	69.8	4.10 (br d, 9.3)	70.1	4.10 (br d, 9.6)
4′	3.86 (br d, 3.2)	67.2	4.10 (br s)	69.3	4.13 (br s)	69.1	4.13 (br s)
5′	4.51 (q, 6.6)	71.9	3.84 (dd, 12.0, 1.7) 4.34 (d, 12.0)	63.8	3.89 (d, 11.9) 4.40 (d, 11.9)	63.7	3.90 (d, 11.9) 4.41 (d, 11.9)
6′	1.34 (d, 6.6)	16.1					
OH	8.33 (br)		8.38 (br)		8.19 (br)		8.11 (br)

[a] Seco-type numbering/pseudopterosin numbering.
[b] ^{1}H NMR resonances not assigned.



7

Figure 6. HMBC correlations from H to C for compound **7**.

anomeric proton to C-7). This *seco*-pseudopterosin (*seco*-pseudopterosin J) was quite recently reported from *P. elisabethae* collected in the Florida Keys (no ^{13}C assignments were reported).[11] The accurate ^{13}C assignments for compounds **7** and **8** are listed in Table 3. It should be noted that the ^{13}C data of the aglycone moieties for 7-*O*-glycosylated seco-pseudopterosins[11] (e.g., **7** and **8**) and 8-*O*-glycosylated congeners (seco-PsA–seco-PsD[10]) are coincidentally closely similar to each other. The C-7 and C-8 signals for the former isomer resonate at ca. 142.0 and 146.5 ppm, respectively,[10] while the C-7 and C-8 for the latter appear at ca. 146.5 and 142.0 ppm, respectively.[8,11] It is therefore essential to assign unambiguously the two carbon chemical shifts on the basis of long-range C–H correlations for distinguishing 7-*O*- and 8-*O*-glycosylated seco-pseudopterosin structures. Otherwise, chemical conversion of glycosylated seco-pseudopterosins to the known 7-hydroxy-8-methoxy- or 8-hydroxy-7-methoxy-serrulat-14-ene is necessary for the structure determination.[8,10,11] The absolute configurations at the chiral centers of most seco-pseudopterosins can be assumed as 1*S*,4*R*,11*S* from biosynthetic consideration. However, no rigorous stereochemical study has been reported until now.

Compound **9** was identified as amphilectosin A, a recently isolated (*E*)-12,13-didehydro derivative of seco-pseudopterosin J,[11] while compound **10** was identified as amphilectosin B,[11] (*Z*)-12,13-didehydro derivative of *seco*-pseudopterosin J. Our ^{1}H and ^{13}C NMR data and the assignments of signals for compound **9** are listed in Table 3.[22] The ^{13}C NMR data of **10** was not available due to the scarcity of the sample.

Kerr and his co-workers have reported a pioneering work on the biosynthesis of pseudopterosins, demonstrating that geranylgeranyl diphosphate is cyclized to give elisabethatriene **2** as the first isolable intermediate.[12,23] The bicyclic intermediate was reported to be converted to erogorgiaene presumably via dehydrogenation and aromatization.[24] Coleman et al. initially proposed a biosynthetic pathway, which involved isomerization of **2** into the isomeric 5(6),9(10)-diene, but failed to obtain evidence supporting the double-bond isomerization pathway.[24] Among the compounds isolated in the present study, elisabethatrienol **1** is interesting, since the hydroxylated structure can be considered as a biosynthetic intermediate leading to erogorgiaene (Fig. 7). If this is the case, 9-*epi*-elisabethatriene must be a precursor of **1** in place of elisabethatriene **2**. We would like to propose the biosynthetic pathway, which involves 9-*epi*-elisabethatriene and elisabethatrienol as shown in Figure 7. Elisabethatrienol can be converted to erogorgiaene by dehydration followed by double bond isomerization (aromatization). As proposed by Kohl et al.,[23] subsequent oxidation of the benzene ring would produce the catechol (*seco*-pseudopterosin aglycone). The co-occurrence of compounds **7** and **8** (both are 7-*O*-glycoside) suggests that the glycosylation should take place at this stage using either D-arabinose, D-xylose or L-fucose. Glycosylation at C-8 would be also possible so that pseudopterosins and *seco*-pseudopterosins glycosylated at the C-8 position can be formed. Acetylation onto the sugar may proceed just after glycosylation, which can explain the co-occurrence of variously acetylated *seco*-pseudopterosins. The glycosylated intermediate will then

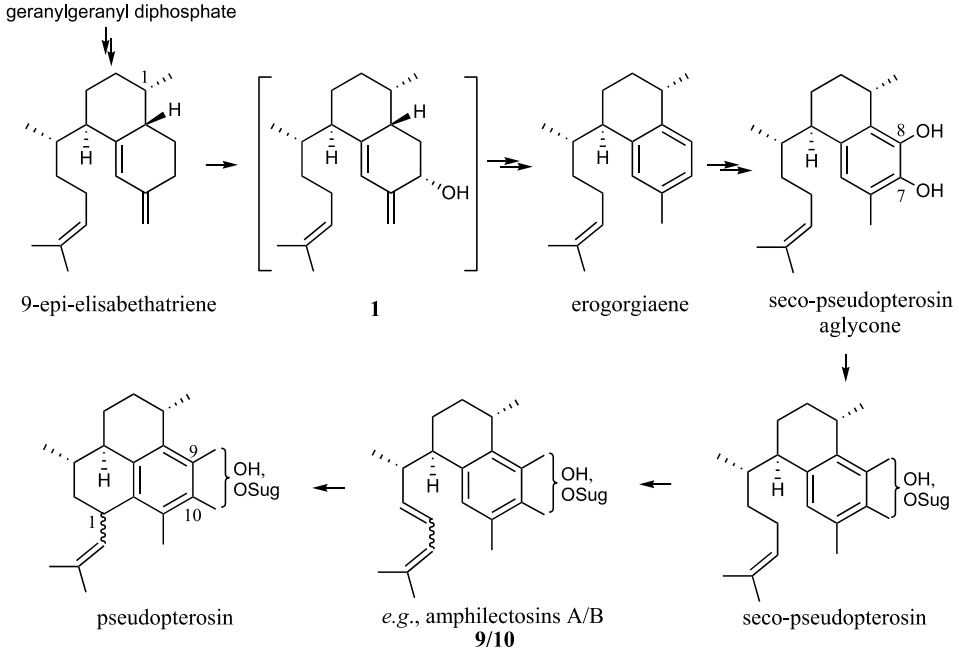


Figure 7. Postulated biosynthetic pathway of pseudopterosins involving elisabethatrienol **1** and 9-epi-elisabethatriene as putative intermediates.

undergo dehydrogenation to give the *E* and *Z* dienes (amphilectosins A/B **9**/**10**).[11] Fern et al.[11] recently described important findings that **8** is converted into **9** and **10** with a cell-free extract of *P. elisabethae*, which are further metabolized into pseudopterosin Y (1β-H) and pseudopterosin F (1α-H), respectively. The formation of the dienes **9** and **10** seems to be an obligatory step, since the activation at the C-13 position is reasonably explained by the presence of the double bond.

It should be noted that the C-9 configuration of elisabethatrienol **1** is different from that of elisabethatriene **2**. An early stage of the biosynthesis of pseudopterosins may involve either 9β-H compounds or 9α-H counterparts, and the discrepancy of the C-9 configuration in **1** and **2** needs to be clarified. A further investigation is highly awaited to see if **1** can be metabolized into erogorgiaene.

3. Experimental

3.1. General

Optical rotations were measured on a JASCO DIP-360 polarimeter. UV spectra were recorded on a Shimadzu UV-1600PC spectrophotometer. IR spectra were recorded on a Perkin-Elmer FT-IR Paragon 500 spectrophotometer. ^{1}H and ^{13}C NMR (one- and two-dimensional) spectra were recorded on a Bruker DRX500 (500 MHz for ^{1}H and 125 MHz for ^{13}C) spectrometer in $CDCl_3$ solution. ^{13}C chemical shifts are referenced to the solvent signal ($\delta=$ 77.0). EIMS and HREIMS were obtained on a JEOL JMS-700 spectrometer. HPLC-MS on APCI mode was carried out on a Shimadzu QP-8000α spectrometer with a Thermo Hypersil-Keystone RP-18 (100×2 mm i.d., 3 μm) column. Preparative HPLC was conducted with a Merck-Hitachi instrument with a UV/vis L-4250 detector (detected at 210 nm) using a Nucleosil 120 10 C-18 (300×8 mm i.d., 10 μm) column with a gradient of 70% aq acetonitrile to 100% acetonitrile within 30 min as mobile phase at a flow rate of 1 ml/min. Final HPLC purification was performed with a Shimadzu LC-6A apparatus equipped with a UV detector (detected at 254 nm) under a Shimadzu Shim-Pack CLC-ODS (150×6 mm i.d., 5 μm) using MeOH–water (9/1) as mobile phase at a flow rate of 1.0–1.5 ml/min.

3.2. Animal material

Fragments of individual colonies of *Pseudopterogorgia elisabethae* were collected by SCUBA (ca. 20–30 m depth) at four sites at the leeward portion of San Andrés island (SW Caribbean) and 12 sites at the leeward portion of Providencia island, between June and September, 2002. Colony fragments were cut off along the main gorgonian axis with sharp scissors. Ten replicates were collected on average per site. Gorgonian fragments were air-dried under the shade, and stored in the freezer until the moment of extraction. Animals were identified as *P. elisabethae* by Dr. M. Puyana, and voucher specimens were deposited at the invertebrate collection of MHNMC (Museo de Historia Natural Marina Colombiano) at INVEMAR (Instituto de Investigaciones Marinas de Punta de Betín), coded as INV CNI 1612, INV CNI 1613 and INV CNI 1614.

3.3. Extraction and separation of compounds

Dried colony fragments were cut in small pieces, weighed and repeatedly extracted with a dichloromethane–methanol (1/1) mixture. Resultant extracts were filtered and concentrated by rotary evaporation obtaining a dark green oily extract. HPLC analysis with the aid of HPLC-MS (APCI mode) was carried out for each colony extract from each location in order to determine chemical variability between the different collection sites.[6] Crude extracts obtained from each chemotype (chemotype 1 from Providencia island and chemotype 2 from San Andrés island) were pooled, until substantial amounts of individual extracts were accumulated. The crude extracts thus obtained (4.0 g for each chemotype) were subjected to silica gel column chromatography eluting with a solvent of increasing polarity consisting of hexane/CH_2Cl_2, AcOEt/CH_2Cl_2, and AcOEt/MeOH to yield eight fractions.

Fraction 6 (eluted with AcOEt) from the extract of chemotype 1 contained compounds **7**–**10**. The fraction was further separated on preparative reversed-phase HPLC (solvent gradient acetonitrile/water, 70:100% in 30 min; flow rate 1 ml/min) to give compounds **9** (retention time, 15.5–16.5 min), **10** (16.6–17.8 min), **7** (21–22 min), and **8** (25–26 min). Final HPLC purification of these samples yielded pure compounds **7** (6 mg), **8** (4 mg), **9** (4 mg) and **10** (1 mg).

Fraction 4 [eluted with AcOEt–CH_2Cl_2 (4/1)] from the extract of the chemotype 2 contained compounds **1**, **3** and **5**. The fraction was further chromatographed on a C-18 open column with a discontinuous gradient of acetonitrile–water (50/50, 70/30, 85/15, 90/10) to give a mixture (500 mg) of **1**, **3** and **5** in the fraction eluted with acetonitrile–water (85/15). A part of that mixture (200 mg) was then separated by preparative reversed-phase HPLC (solvent, acetonitrile; flow rate, 1.5 ml/min) to give **3** (50 mg), and a mixture of compounds **1** and **5**, which were further purified by reversed-phase HPLC (solvent, acetonitrile/water, 85:15; flow rate 1 ml/min), to obtain 5 mg of each. Compounds **1** and **5** were purified by *p*-TLC prior to spectral analysis since these compounds decomposed slowly.

3.3.1. Compound 1. White amorphous solid; $[\alpha]_D^{25}$ −44.8 (*c*, 0.14, MeOH); UV λ_{max}^{MeOH} (ε): 236 (16,800) nm; IR ($CHCl_3$) ν_{max} 3600, 3525, 3020, 2970, 2930, 2880, 1675, 1450, 1385, 1070, 890 cm^{-1}; EI-MS *m*/*z* (relative intensity): 288 (M^+, 100), 270 (14), 255 (8), 227 (8), 213 (7), 204 (45), 177 (70), 160 (60), 159 (33), 131 (59), 117 (60), 105 (49), 91 (36), 79 (37); HREIMS *m*/*z*: 288.2415 (M^+), $C_{20}H_{32}O$ requires 288.2453; ^{1}H and ^{13}C NMR: see Table 1.

3.3.2. MTPA esters of 1 (1s and 1r). (*S*)- and (*R*)-MTPA ester derivatives of **1** were prepared by reacting **1** (0.3 mg) in pyridine (30 μl) with (*R*)- and (*S*)-MTPA chlorides (1.5 μl), respectively, at room temperature for 1 h. The reaction mixture was diluted with methanol and directly applied to silica gel *p*-TLC plate. The plate was developed with hexane–AcOEt (20/1) and elution of the major band furnished the desired ester as an oil in a good yield. ^{1}H NMR data, see Table 2. HRFABMS **1s** *m*/*z*: 505.2919

$[M+H]^+$ and **1r** *m/z*: 505.2914 $[M+H]^+$. $C_{30}H_{40}O_3F_3$ requires 505.2930.

3.3.3. Compound 3. Yellow amorphous solid; $[\alpha]_D^{25}$ +77.5 (*c*, 0.21, MeOH); UV λ_{max}^{MeOH} (*ε*): 207 (36,900), 230 (shoulder), 276 (2000) nm; IR ($CHCl_3$) ν_{max} 3590, 3030, 2970, 2930, 2880, 1765, 1450, 1440, 1370, 1040 cm^{-1}; EI-MS *m/z* (relative intensity): 342 (M^+, 10), 300 (9), 286 (39), 244 (100), 229 (35), 187 (13), 109 (14); HREIMS *m/z*: 342.2166 (M^+), $C_{22}H_{30}O_3$ requires 342.2195; ^1H and ^{13}C NMR: see Table 1.

3.3.4. Acetate derivative of 3 (3a). Compound **3** (4 mg) was allowed to stand in pyridine (100 μl) and acetic anhydride (50 μl) at room temperature for 2 h. After addition of 0.2 ml of methanol, the whole mixture was concentrated by flushing nitrogen. The orange oily residue was analyzed by NMR without purification. Yellow oil; $[\alpha]_D^{25}$ +66.4 (*c*, 0.71, MeOH); UV λ_{max}^{MeOH} (*ε*): 206 (35,800), 227 (shoulder) nm; IR ($CHCl_3$) ν_{max} 3030, 2970, 2930, 2880, 1760, 1440, 1370, 1050 cm^{-1}; EI-MS *m/z* (relative intensity): 384 (M^+, 4), 342 (5), 328 (50), 300 (8), 286 (90), 244 (100), 229 (20), 187 (9); HREIMS *m/z*: 384.2293 (M^+), $C_{24}H_{32}O_4$ requires 384.2301; ^1H and ^{13}C NMR: see Table 1.

3.3.5. Conversion of 3–5. $LiAlH_4$ (1 mg) was added to a stirred solution of compound **3** (2.0 mg) in dry ether (1 ml) and the mixture was reacted for 10 min when the starting material disappeared and a polar spot presumably due to a catecol was monitored by TLC analysis. Several drops of water and satd aq NH_4Cl were added to the mixture. TLC analysis of the organic layer showed practically single spot corresponding to the quinone with disappearance of the polar spot. The organic layer was separated and the water layer was re-extracted with ether. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to dryness. The residue was chromatographed on silica gel with *n*-hexane–AcOEt (4/1) to give **5** (1.1 mg, 63%) as a yellow oil; $[\alpha]_D^{25}$ +134 (*c*, 0.13, MeOH). The compound was identified with compound **5** by ^1H NMR and TLC analysis.

3.3.6. Compound 5. Orange oil; $[\alpha]_D^{25}$ +146.0 (*c*, 0.10, MeOH); UV λ_{max}^{MeOH} (*ε*): 208 (27,700), 285 (2100) nm; IR ($CHCl_3$) ν_{max} 3600, 3525, 3020, 2970, 2930, 2880, 1675, 1450, 1385, 1070, 890 cm^{-1}; EI-MS *m/z* (relative intensity): 298 (M^+, 100), 283 (59), 255 (24), 244 (93), 229 (65), 197 (28), 187 (25); HREIMS *m/z*: 298.1894 (M^+), $C_{20}H_{26}O_2$ requires 298.1933; ^1H and ^{13}C NMR: see Table 1.

3.3.7. Compound 7. White amorphous solid; $[\alpha]_D^{25}$ −121.3 (*c*, 0.43, MeOH); UV λ_{max}^{MeOH} 208 (42,000), 230 (shoulder), 280 (1500) nm; IR ($CHCl_3$) ν_{max} 3330, 3020, 2970, 2930, 2880, 1090 cm^{-1}; EI-MS *m/z* (relative intensity): 448 (M^+, 15), 303 (96), 302 (75), 218 (90), 192 (84), 173 (90), 161 (41), 157 (40), 145 (71), 129 (61), 115 (31), 91 (28), 75 (100), 73 (81), 69 (91); HREIMS *m/z*: 448.2816 (M^+), $C_{26}H_{40}O_6$ requires 446.2825; ^1H and ^{13}C NMR: see Table 3.

3.3.8. Compound 8. White amorphous solid; $[\alpha]_D^{25}$ −120.0 (*c*, 0.70, MeOH); UV λ_{max}^{MeOH} 207 (42,000), 230 (shoulder), 280 (1300) nm; EI-MS *m/z* (relative intensity): 434 (M^+, 37), 303 (100), 302 (51), 244 (66), 218 (95), 192 (84), 173 (78), 157 (35), 145 (53), 129 (40), 115 (37), 91 (19), 73 (90), 69 (65); HREIMS *m/z*: 434.2711 (M^+), $C_{25}H_{38}O_6$ requires 434.2668; ^1H and ^{13}C NMR: see Table 3.

3.3.9. Compound 9. Colorless oil; $[\alpha]_D^{25}$ −102.3 (*c*, 0.19, MeOH); UV λ_{max}^{MeOH} 206 (32,000), 233 (19,500), 280 (1400) nm; EI-MS *m/z* (relative intensity): 432 (M^+, trace), 365 (1), 323 (75), 316 (41), 298 (40), 229 (37), 192 (97), 173 (99), 157 (39), 145 (67), 129 (50), 109 (100), 91 (33), 73 (82), 67 (41); HRFABMS (negative mode) *m/z*: 431.2454 ($M-H^-$), $C_{25}H_{35}O_6$ requires 431.2434; ^1H and ^{13}C NMR: see Table 3.

3.3.10. Compound 10. Colorless oil; $[\alpha]_D^{25}$ −64.4 (*c*, 0.07, MeOH); UV λ_{max}^{MeOH} 205 (29,300), 230 (13,700), 281 (1400) nm; EI-MS *m/z* (relative intensity): 432 (3), 365 (4), 323 (22), 316 (8), 298 (26), 229 (22), 192 (75), 191 (100), 173 (29), 157 (22), 145 (14), 129 (11), 109 (34), 91 (8), 73 (13), 67 (7); HRFABMS (negative mode) *m/z*: 431.2472 ($M-H^-$), $C_{25}H_{35}O_6$ requires 431.2434; ^1H and ^{13}C NMR: see Table 3.

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Synthesis of cicerfuran, an antifungal benzofuran, and some related analogues

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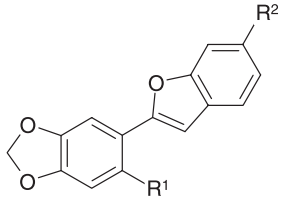
Abstract—Routes were investigated for the synthesis of cicerfuran, a hydroxylated benzofuran from wild chickpea implicated in resistance to Fusarium wilt, and some of its analogues. A novel method is described for the synthesis of oxygenated benzofurans by epoxidation and cyclisation of 2′-hydroxystilbenes. The stilbene intermediates required could be synthesised by palladium-catalysed coupling of styrenes with mono-oxygenated aryl halides but not with di-oxygenated aryl halides. Stilbenes corresponding to the latter were synthesised by Wittig reactions.

1. Introduction

Benzofurans and their analogues constitute a major group of naturally-occurring compounds that are of particular interest because of their biological activity and role in plant defence systems.[1] The hydroxylated benzofuran cicerfuran (**1a**, Fig. 1) was first obtained from the roots of a wild species of chickpea, *Cicer bijugum*, and reported to be a major factor in the defence system against Fusarium wilt.[2]



1a R^1=OMe, R^2=OH
1b R^1=H, R^2=H
1c R^1=OMe, R^2=H
1d R^1=Me, R^2=H
1e R^1=H, R^2=OH
1f R^1=Me, R^2=OH

Figure 1. Structures of cicerfuran (**1a**) and analogues (**1b–f**).

Several methodologies are available for the synthesis of simple benzofurans[3] but less attention has been given to the synthesis of hydroxylated benzofurans. Methodologies reported to date for the synthesis of natural hydroxylated benzofurans involve formation of a C–C bond between benzofuran and a substituted aryl halide,[4] arylation of a benzofuranone,[5] cyclisation of an arylbenzylketone,[6] coupling of cuprous acetylides with aryl halides,[7] Sonogashira coupling of terminal acetylenes with aryl halides,[8] coupling of a diphenylketone with the lithium salt of trimethylsilyldiazomethane[9] and use of an intramolecular Wittig reaction.[10]

Recently, the first synthesis of cicerfuran (**1a**) was reported by Sonogashira coupling of 2-methoxy-4,5-methylenedioxyphenylacetylene with dioxygenated aryl halides.[11] Our study employs an alternative strategy for the production of both cicerfuran and related analogues and was developed independently of the work of Novak and colleagues.[11] The essential features (Scheme 1) are palladium-catalysed coupling of a styrene and a 2-hydroxyaryl halide to generate a stilbene, followed by epoxidation, cyclisation and dehydration.

Two analogues (**1c**, **1d**) of cicerfuran (**1a**) were synthesised successfully by this method, but the palladium coupling step did not proceed with the dioxygenated aryl halides that are required for synthesis of cicerfuran itself (Scheme 1, R_2=OH). Palladium-catalysed coupling of the more reactive aryl acetylenes[12–14] with 2-iodophenol proceeded well to give two analogues (**1b**, **1c**) of cicerfuran directly. Use of this approach, essentially as described by Novak

Keywords: Cicerfuran; Arylbenzofuran; Palladium-catalysed coupling; Wittig reaction.
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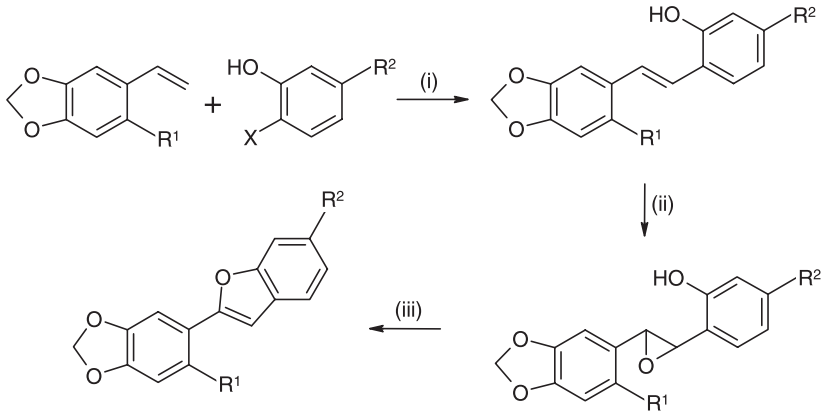


Scheme 1. Reagents and conditions: (i) palladium catalyst; (ii) epoxidation; (iii) mild acid.

et al.[11] gave cicerfuran (**1a**) only in low yields. Returning to the original synthetic plan, the stilbene required was synthesised by a Wittig reaction between 2-methoxy-4,5-methylenedioxybenzyltriphenylphosphonium bromide and 2,4-di-*tert*-butyldimethylsiloxy-benzaldehyde. Epoxidation and cyclisation gave an alternative route to cicerfuran (**1a**) in quantities sufficient for further biological assays. In addition, the synthetic and natural cicerfuran were compared directly and shown to have identical spectroscopic and chromatographic properties, confirming the proposed structure for the natural compound. Two further analogues (**1e**, **1f**) of cicerfuran were prepared by this route but were not characterised fully due to decomposition during the purification.

2. Results and discussion

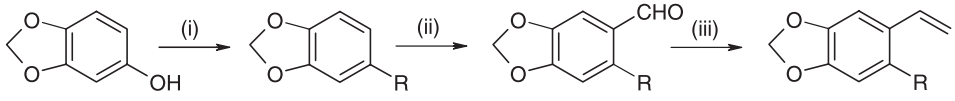
2.1. Synthesis of benzofurans via palladium-catalysed coupling of styrenes and aryl halides

2.1.1. Synthesis of styrenes. Styrene precursors for use in palladium-catalysed coupling (Scheme 1) were styrene itself (**5**) and methylenedioxystyrenes (**6a–c**) prepared from the corresponding benzaldehydes (**4a–c**) by a Wittig reaction with methyltriphenylphosphonium bromide and *n*-butyllithium (Scheme 2). 3,4-Methylenedioxystyrene (**6a**) was obtained in 97% yield from piperonal (3,4-methylenedioxybenzaldehyde) (**4a**).

Sesamol (3,4-methylenedioxyphenol) (**2**) was *O*-methylated using sodium hydroxide and dimethylsulphate to give anisole **3a** in 99% yield. Formylation[15] of **3a** gave benzaldehyde **4b** in 90% yield as shown in Scheme 2. The benzaldehyde **4b** was then converted to the desired styrene **6b** by a Wittig reaction in 98% yield.

2-Methyl-4,5-methylenedioxybenzaldehyde (**4c**) was similarly obtained in 96% yield by formylation of commercially-available 3,4-methylenedioxytoluene (**3b**) and 2-methyl-4,5-methylenedioxyphenyl-ethene (**6c**) was obtained in 96% yield via a Wittig reaction of **4c** under the same reaction conditions (Scheme 2).

2.1.2. Palladium-catalysed coupling of styrenes with aryl halides. Palladium-catalysed reactions are among the most frequently used methods for carbon–carbon bond formation and have been applied to synthesis of both natural and non-natural compounds.[16–19] Experiments were carried out to optimise the reaction conditions for the palladium-catalysed coupling of styrenes **5** and **6a** with simple aryl halides and then with multioxygenated aryl halides (Scheme 3, Table 1).

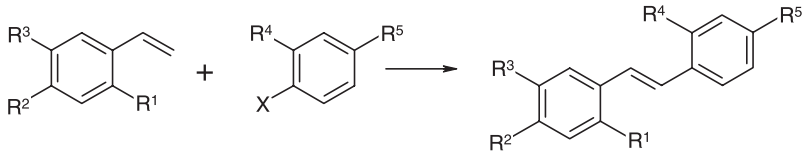


3a R=OMe (99%)
3b R=Me

4a R=H
4b R=OMe (90%)
4c R=Me (96%)

6a R=H (97%)
6b R=OMe (98%)
6c R=Me (96%)

Scheme 2. Reagents and conditions: (i) NaOH, $(CH_3)_2SO_4$; (ii) α,α-dichloromethylmethyl ether, $TiCl_4$; (iii) *n*-BuLi, THF, methyltriphenylphosphonium bromide.



5, 6a-c **7a-k** **8a-j**

Scheme 3. Palladium-catalysed coupling of styrenes with aryl halides.

Table 1. Palladium-catalysed coupling of styrenes with aryl halides

Styrene (**5**)				Aryl halide (**7**)				Solvent	Cat	Temperature (°C)	Time	Stilbene product (%)
	R_1	R_2	R_3		X	R_4	R_5					
5	H	H	H	**7a**	I	H	H	Et_3N	—	100	24 h	**8a** (60%)
5	H	H	H	**7b**	I	OH	H	Et_3N	B	100	13 h	**8b** (50%)
5	H	H	H	**7d**	I	H	OMe	Et_3N	B	100	3 days	**8c** (65%)
5	H	H	H	**7e**	I	OMe	OMe	DMA	B	130	4 days	**8d** (31%)
5	H	H	H	**7f**	Cl	OH	OH	DMA	A	130	5 days	—
5	H	H	H	**7g**	Cl	OAc	OAc	DMA	A	130	4 days	—
5	H	H	H	**7h**	Br	OH	OH	DMA	A	130	4 days	—
5	H	H	H	**7i**	Br	OAc	OAc	DMA	A	130	4 days	—
6a	H	OCH_2O		**7a**	I	H	H	Et_3N	—	100	18 h	**8e** (50%)
6a	H	OCH_2O		**7b**	I	OH	H	Et_3N	B	100	18 h	**8f** (42%)
6a	H	OCH_2O		**7c**	I	OAc	H	Et_3N	B	100	18 h	**8g** (49%)
6a	H	OCH_2O		**7d**	I	H	OMe	Et_3N	B	100	5 h	**8h** (60%)
6b	OMe	OCH_2O		**7b**	I	OH	H	Et_3N	B	100	5 h	**8i** (68%)
6b	OMe	OCH_2O		**7j**	I	OH	OH	Et_3N	B	100	5 h	—
6b	OMe	OCH_2O		**7k**	I	OAc	OAc	Et_3N	B	100	5 h	—
6c	Me	OCH_2O		**7b**	I	OH	H	Et_3N	B	100	5 h	**8j** (54%)

Catalyst (Cat) was palladium acetate with triphenylphosphine (A) or tri-*o*-tolylphosphine (B).

Palladium acetate with either triphenylphosphine or tri-*o*-tolylphosphine was used as catalyst and the different ligands had no obvious effect on yield. However, the solvent used for the coupling reaction was found to be important. Styrene (**5**) polymerised at temperatures above 100 °C when triethylamine was used as solvent, but with dimethylacetamide and sodium acetate no polymerisation of **5** was observed at temperatures above 120 °C.

After optimisation of the conditions for palladium-catalysed coupling using simple styrenes **5** and **6a** (Scheme 3) two stilbenes 1-(2-methoxy-4,5-methylenedioxyphenyl)-2-(2-hydroxyphenyl)ethene (**8i**) and 1-(2-methyl-4,5-methylenedioxyphenyl)-2-(2-hydroxyphenyl)ethene (**8j**) were obtained in 68 and 54% yield by palladium-catalysed coupling of 2-iodophenol (**7b**) with styrenes **6b** and **6c**, respectively. Two equivalents of 2-iodophenol were used for the coupling to ensure complete reaction of the styrene. The stilbenes were shown to be the *E* isomers by ^{1}H NMR spectroscopy.

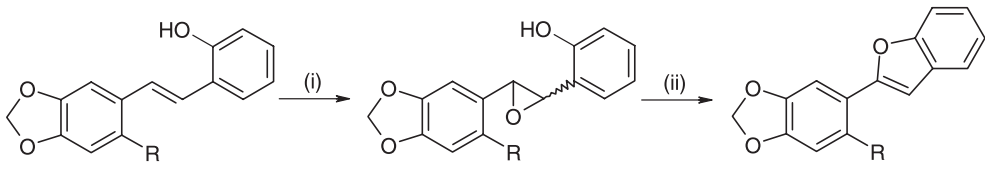
Stilbenes **8i** and **8j** were epoxidised with 3-chloroperbenzoic acid in dichloromethane (Scheme 4). Stilbene **8j** underwent sequential epoxidation and cyclisation under these conditions to give 2-(2-methyl-4,5-methylenedioxyphenyl)benzofuran (**1d**, Fig. 1) in 50% yield after stirring overnight. The same process applied to **8i** resulted in complete decomposition. Thus, the epoxide **9a** was isolated and then subjected to acid-catalysed ring-opening, cyclisation and dehydration with *p*-toluenesulphonic acid in chloroform to give 2-(2-methoxy-4,5-methylenedioxyphenyl)benzofuran (**1c**, Fig. 1). The 2-methoxy group in **1c** makes this benzofuran much less stable to acid than **1d** with the 2-methyl group.

As indicated in Table 1, palladium-catalysed coupling of styrenes could be carried out with aryl halides having one oxygenated functionality. However, introduction of a second oxygenated functionality deactivated the halide towards nucleophilic substitution, and several unsuccessful attempts were made to couple styrene **6b** with 4-iodoresorcinol (**7j**). The reaction still failed after acetylation of the hydroxyl groups which was expected to increase the reactivity of the halide.

2.2. Synthesis of benzofurans via palladium-catalysed coupling of acetylenes with aryl halides

Palladium catalysed coupling of terminal acetylenes with *o*-hydroxy aryl halides is reported to give the benzofurans in a single step reaction.[12–14] As aryl acetylenes are more reactive in palladium-catalysed coupling than the corresponding styrenes,[20] it was considered that this approach might be more successful with the multioxygenated aryl halides required for synthesis of cicerfuran and its analogues (Scheme 5).

2.2.1. Synthesis of acetylenes. 3,4-Methylenedioxyphenylethyne (**10b**) was obtained in 56% yield by bromination of the corresponding styrene **6a**, synthesised previously, with bromine in dichloromethane at 0 °C followed by dehydrohalogenation with potassium *t*-butoxide and 18-crown-6 ether. Similar treatment of 2-methoxy-3,4-methylenedioxystyrene (**6b**) resulted in bromination of the aryl ring. However, bromination in chloroform at room temperature then at 40 °C, followed by dehydrohalogenation gave acetylene **10c** in 51% yield. The use of chloroform rather

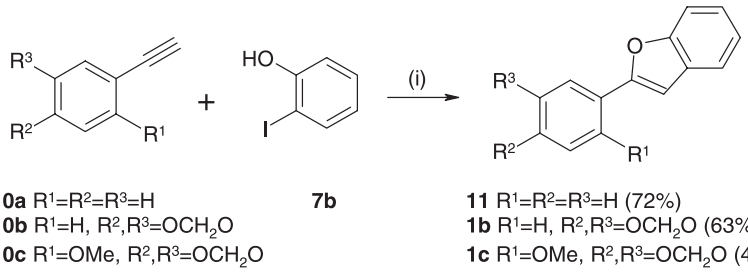


8i R=OMe
8j R=Me

9a R=OMe (67%)
9b R=Me

1c R=OMe (76%)
1d R=Me (50%)

Scheme 4. Reagents and conditions: R=Me (i), (ii) 3-CPBA, DCM; R=OMe (i) 3-CPBA, DCM; (ii) *p*TSA, $CHCl_3$.



Scheme 5. Reagents and conditions: (i) $Pd(Ph_3P)_2Cl_2$, CuI, Et_3N, DMF.

than dichloromethane was reported to enhance the bromination of styrenes.[21]

2.2.2. Palladium-catalysed coupling of aryl acetylenes. Three arylbenzofurans, **11**, **1b** and **1c**, were synthesised by palladium-catalysed coupling of acetylenes **10a–c** with 2-iodophenol (**7b**) as shown in Scheme 5. While this approach worked well with the monohydroxyaryl iodide **7b**, attempts to couple acetylene (**10c**) with 4-iodoresorcinol (**7j**) were unsuccessful.

Acetylation of the hydroxyl groups was expected to make the aryl halide more reactive to nucleophilic attack, and the synthesis of cicerfuran was therefore attempted by palladium-catalysed coupling[7] of acetylene (**10c**) with the diacetate of iodoresorcinol (**7k**), as shown in Scheme 6.

Iodoresorcinol (**7j**) was obtained in 70% yield by reaction of resorcinol with iodine monochloride, and was acetylated with acetic anhydride and pyridine to give the diacetate **7k**. Coupling of **7k** with acetylene **10c** was carried out in DMF in the presence of $Pd(PPh_3)_2Cl_2$, CuI, and diisopropylamine at 60 °C. The diarylacetylene **12** was 15% of the total reaction mixture as shown by GC-MS analysis. The other major products were 2-methoxy-4,5-methylenedioxybenzene, a decomposition product of acetylene **10c**, and diacetoxybenzene formed by reduction of **7k**. Acetylene **12** could not be isolated by flash chromatography, and the crude product was used for the further reaction. Deacetylation of **12** with anhydrous potassium carbonate in methanol was followed by cyclisation to give cicerfuran (**1a**). However, this was present as only 5% of the mixture by GC–MS and attempted isolation by chromatography on silica gel was unsuccessful.

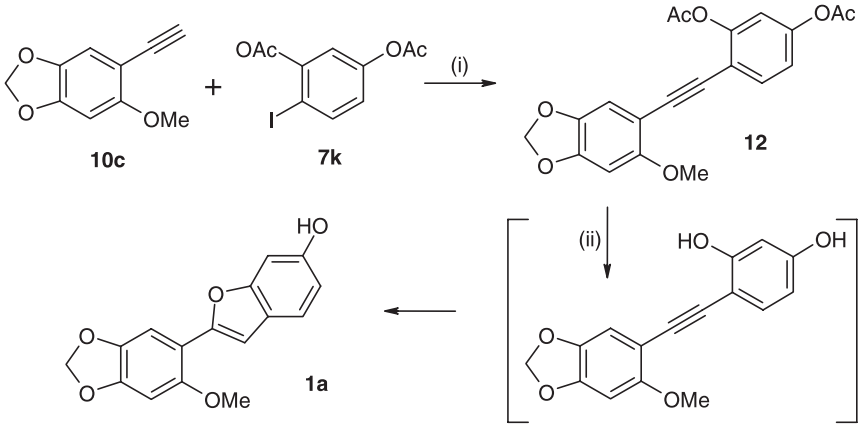
Novak et al.[11] used a similar approach to synthesise cicerfuran and also noted the instability of the acetylenic intermediates.

2.3. Synthesis of cicerfuran via the Wittig reaction

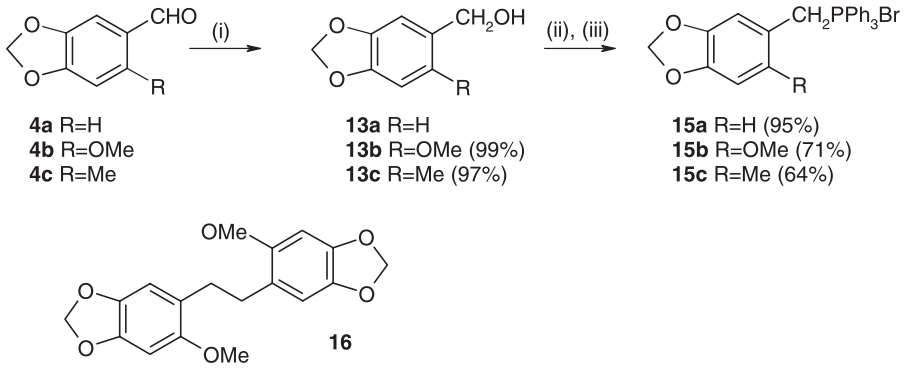
Returning to the original reaction scheme (Scheme 1), the stilbenes with the multioxygenated functionalities required for synthesis of cicerfuran and analogues were synthesised by a Wittig reaction, an olefination reaction relatively independent of the nature of the substituents on the moieties to be coupled. The hydroxyl groups were protected as *tert*-butyldimethylsiloxy (TBDMS) derivatives during the Wittig coupling.

For synthesis of the required phosphonium salts **15a–c**, benzaldehydes **4a–c** were reduced to the corresponding benzyl alcohols **13a–c** with sodium borohydride in ethanol (Scheme 7). For the reduction of 2-methoxy-4,5-methylenedioxybenzaldehyde (**4b**) the volume of ethanol was found to be critical. When solvent was used at 0.1 g of benzaldehyde mL^{-1} ethanol, 1,2-di-(2-methoxy-4,5-methylenedioxyphenyl)ethane (**16**) was formed. When the concentration of benzaldehyde was halved, benzyl alcohol (**13b**) was obtained in 96% yield and only 2% of dimer **16** was found in the reaction mixture.

For the conversion of benzyl alcohols **13a**,**c** to the corresponding triphenylphosphonium bromides **15a**,**c**, a two-step procedure[22] was initially used. This involved



Scheme 6. Reagents and conditions: (i) $Pd(Ph_3P)_2Cl_2$, CuI, $(iPr)_2NH$, DMF; (ii) K_2CO_3, MeOH. Intermediates and product were not purified or fully characterised.



Scheme 7. Reagents and conditions: (i) $NaBH_4$, MeOH; (ii) PBr_3, toluene; (iii) PPh_3.

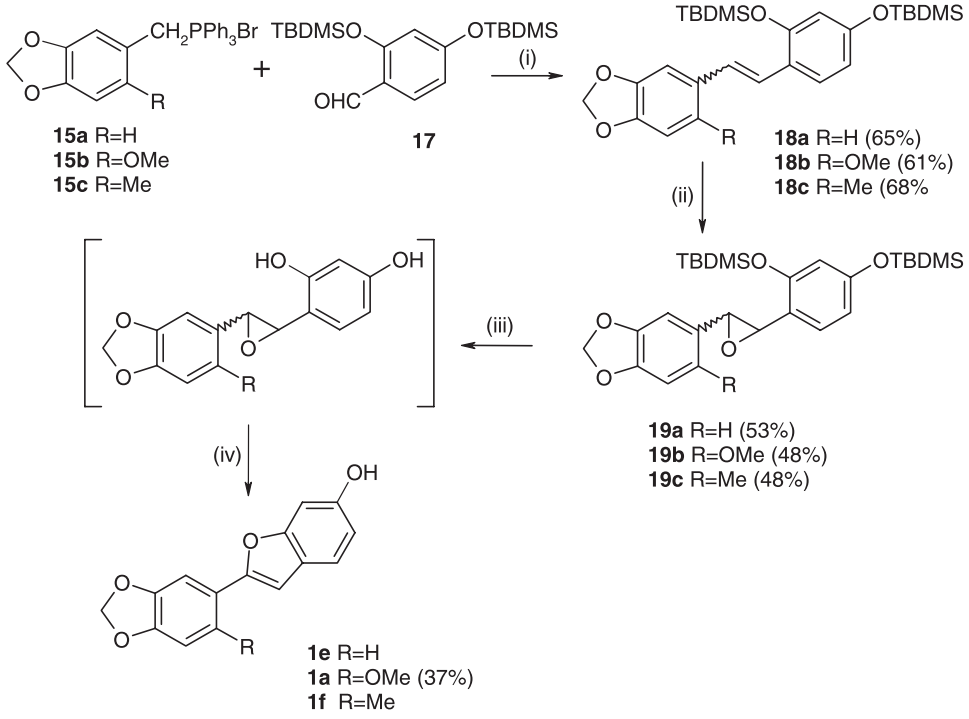
bromination with 1.2 equiv of phosphorus tribromide in dichloromethane, isolation of the bromides **14a**,**c** and conversion to the phosphonium bromides **15a**,**c** with triphenylphosphine in refluxing toluene. However, attempted bromination of 2-methoxy-4,5-methylenedioxybenzyl alcohol (**13b**) in dichloromethane gave the dimer **16** in 73% yield (Scheme 7).

The method was improved by bromination of benzyl alcohol **13b** with 0.5 equiv of phosphorous tribromide in toluene. After aqueous workup and drying, the toluene solution was refluxed directly with triphenylphosphine and phosphonium salt **15b** was obtained in 71% yield. Use of this procedure gave phosphonium bromide **15a** in 95% overall yield and **15c** in 64% overall yield (Scheme 7).

Phosphonium bromides **15a–c** and benzaldehyde **17** were coupled by Wittig reactions. Use of butyllithium as base was unsuccessful, but sodium hexamethyldisilazide in THF gave the desired stilbenes **18a–c**. Analyses by GC and TLC indicated these were approximately 1:1 mixtures of the *E* and *Z* isomers (Scheme 8).

The stilbenes **18a–c** were epoxidised with 3-chloroperbenzoic acid in dichloromethane (Scheme 8). Yields were low presumably due to the instability of the epoxides **19a–c**. There was also removal of TBDMS groups by the 3-chlorobenzoic acid and formation of the *tert*-butyldimethylsilyl ester of 3-chlorobenzoic acid was confirmed by GC–MS.

Conventional methods for removing the TBDMS protecting groups with tetrabutyl ammonium fluoride or mild acid[7,23,24] led to decomposition of the desired products. A more neutral deprotection procedure[25] using cupric chloride in acetone–water (95/5) under gentle reflux for 24–48 h was successful and the crude products were immediately cyclised with a few crystals of *p*-toluenesulphonic acid in chloroform (Scheme 8).



Scheme 8. Reagents and conditions: (i) NaHMDS, THF; (ii) 3-CPBA, DCM; (iii) $CuCl_2$, acetone, water; (iv) pTSA, $CHCl_3$.

The dihydroxyepoxides and final products were highly acid sensitive. Traces of 3-chlorobenzoic acid from the epoxidation greatly reduced yields, and significant decomposition was observed during flash chromatography on silica gel. Cicerfuran (**1a**) was obtained in 37% yield from the protected stilbene, but the two analogues **1d** and **1e** could not be isolated by chromatography on silica gel due to decomposition, even though they were shown to be present by GC–MS at 16 and 10% of the reaction mixture, respectively.

2.4. Comparison of synthetic and natural cicerfuran

Cicerfuran was isolated from roots of wild chickpea, *C. bijugum* as described previously.[2] The natural and synthetic compounds were shown to have identical chromatographic retention times on GC using a non-polar column and on HPLC using a reversed phase column. They also had the same UV spectra as recorded online by HPLC coupled with diode array detection, the same EI mass spectrum in GC-MS, and identical ^{1}H and ^{13}C NMR spectra.

3. Conclusions

Cicerfuran (**1a**), an antifungal agent isolated from roots of wild chickpea,[2] has been synthesised from sesamol (3,4-methylenedioxyphenol) (**2**) in seven steps and 37% overall yield. The route involved epoxidation and cyclisation of a dihydroxystilbene intermediate. Two analogues (**1e**, **1f**) were also prepared and characterised by GC–MS. Although they could be recovered in small quantities by HPLC for some bioassays [20] their instability meant it was not possible to isolate enough for NMR analysis. The intermediate stilbenes were synthesised by a Wittig reaction. These could not be synthesised by palladium-catalysed coupling of appropriate styrenes and dioxygenated aryl halides, as originally planned, because of deactivation of the halides to nucleophilic attack. The limitations of this approach have been explored and two deoxy analogues (**1c**, **1d**) of cicerfuran were synthesised by this route in good yield. As reported previously,[20] the more reactive aryl acetylenes could be used in palladium-catalysed coupling with dihydroxy-aryl halides if the hydroxyl groups are converted to the more electron-withdrawing acetoxy functions.

Both the benzofurans (**1a–f**) and the corresponding stilbene intermediates synthesised here have been shown to have antifungal and antibacterial activities[20,26] and details of these will be reported separately.

4. Experimental

4.1. General

Thin layer chromatography was performed using Merck 60F-254 aluminium sheets and compounds were visualised under UV light. Gas chromatograms were recorded on a Carlo Erba Strumentazione HRGC with fused silica capillary column (25 m×0.32 mm i.d.) coated with either polar CP Wax 52CB (Carbowax 20 M equiv, Chrompack) or non polar CPSil 5CB (methyl silicone, Chrompack) and flame ionisation detection. Split injection was used with the injector at 220 °C and detector at 250 °C. Typical oven temperature programmes were 60 °C for 2 min then at 10 °C/min–250 °C for the polar column and 280 °C for the non-polar. GC–MS analyses were carried out on a Hewlett–Packard HP 6890 GC System linked directly to a HP 5973 mass selective detector operated in electron impact (EI) mode at 70 eV. A fused silica capillary column (25 m× 0.22 mm i.d.) coated with non polar HP-MS5, split/splitless injector and helium carrier gas (1 mL min^{-1}) were used with oven temperature programme as above. High resolution mass spectra were provided by the EPSRC National Mass Spectrometry Service Centre, Chemistry Department, University of Wales, Swansea, UK. HPLC was carried out with a Waters 600E pump, Waters 996 photodiode array detector and Waters 717 autosampler with Spherisorb 5ODS analytical column (250 mm×4.6 mm i.d.). The binary solvent system consisted of 2% acetic acid in water (A) with 2% acetic acid in acetonitrile with 70% A at $t=0$ min, 50% A at $t=20$ min and 30% A at $t=30$ min. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Jeol EX270 spectrometer at 270 and 67.5 MHz, respectively or a Bruker Avance 400 MHz instrument. Spectra acquired in $CDCl_3$ were referenced to TMS and those in DMSO-d_6 to internal solvent resonances at δ_H 2.50 and δ_C 39.50 ppm. IR spectra were recorded as thin films (liquids), nujol mulls or solutions in ethanol-free chloroform (solids) on a Perkin–Elmer 298 grating spectrophotometer. Melting points were recorded in open capillary tubes in a heating block. Silica gel (230–400 mesh) was used for flash chromatography.

4.2. Synthesis of styrenes (6a–c)

4.2.1. 3,4-Methylenedioxyanisole (3a). A solution of 3,4-methylenedioxyphenol (sesamol) (6.0 g, 43.5 mmol) in water (30 mL) was treated with sodium hydroxide (1.7 g, 43.5 mmol) while the flask was kept in an ice bath. The reaction mixture was stirred for 15 min after which dimethyl sulphate (6.3 g, 43.5 mmol) was added dropwise. The reaction mixture was then heated under reflux for 1 h, allowed to cool down to room temperature and extracted with diethyl ether (3×100 mL). The extract was washed with 2 M NaOH (100 mL), dried, filtered and concentrated. The crude product was purified by flash chromatography and pure anisole (**3a**) obtained as an amber oil in 99% yield (6.6 g); IR (film) ν_{max}: 2905, 2860, 2720, 1585, 1565, 1458, 1441, 1200, 1155, 1133, 1088, 995 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.42 (m, 3H), 5.88 (s, 2H), 3.72 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.3, 148.4, 141.6, 107.9, 104.7, 101.1, 97.5, 56.0; MS *m/z* (% relative intensity, ion): 152(100, $[M]^+$), 137(100), 121(5), 107(50), 79(50), 69(5), 63(10), 51(30).

4.3. General method for formylation

α,α-Dichloromethylmethyl ether (2 equiv) was added dropwise via syringe to a stirred solution of anisole **3a** or 3,4-methylenedioxytoluene (**3b**) (37.3 mmol) in DCM (50 mL) at 0 °C. After stirring for 15 min titanium tetrachloride solution (1.2 equiv) in DCM (50 mL) was added dropwise via a dropping funnel. On complete addition, the reaction mixture was allowed to warm to room temperature and stirring continued for 1 h.

The reaction mixture was poured into ice-cold water (100 mL) and extracted with diethyl ether (3×100 mL) and ethyl acetate (3×100 mL). The combined organic extracts were washed with brine (1×100 mL), aqueous $NaHCO_3$ (3×100 mL), dried and passed through silica gel. The eluent was concentrated under vacuum and the crude product purified by flash chromatography.

4.3.1. 2-Methoxy-4,5-methylenedioxybenzaldehyde (4b). Light yellow crystals (90%), mp 108–110 °C; IR (nujol mull) ν_{max}: 1625, 1584, 1466, 1385, 1338, 1230, 1201, 1165, 1123, 1110, 1043, 995 cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.27 (s, 1H), 7.25 (s, 1H), 6.53 (s, 1H), 5.99 (s, 2H), 3.87 (s, 3H); MS *m/z* (% relative intensity, ion): 180(100, $[M]^+$), 163(20), 149(20), 134(50), 120(25), 107(50), 93(18), 79(35), 69(20), 62(30), 53(60).

4.3.2. 2-Methyl-4,5-methylenedioxybenzaldehyde (4c). Yellow solid (96%), mp 85–88 °C; IR (nujol mull) ν_{max}: 2905, 1641, 1581, 1563, 1460, 1215, 1152, 1111, 1070, 1012, 1001, 961 cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.12 (s, 1H), 7.24 (s, 1H), 6.65 (s, 1H), 5.99 (s, 2H), 2.57 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 189.8, 152.3, 146.6, 138.1, 128.5, 111.2, 108.7, 101.8, 18.8; MS *m/z* (% relative intensity, ion): 163(100, $[M-1]^+$), 155(1), 149(1), 135(40), 123(6), 105(12), 95(1), 86(1), 77(32), 51(36), 40(1).

4.4. General method for synthesis of styrenes

n-Butyl lithium in hexane (29 mmol) was added dropwise to a stirred solution of methyltriphenylphosphonium bromide (30 mmol) in THF (50 mL) at 0 °C. After stirring for 30 min, a cold solution of benzaldehyde **4a–c** (30 mmol) in THF (50 mL) was added dropwise from a dropping funnel to the reaction mixture. The yellow suspension produced was stirred for a further 4 h, then treated with saturated ammonium chloride solution, dried, filtered and concentrated under vacuum. The resulting viscous solution was purified by flash chromatography using hexane as eluent.

4.4.1. 3,4-Methylenedioxyphenylethene (6a). Light yellow oil (97%); IR (film) ν_{max}: 2865, 2800, 2685, 1645, 1581, 1558, 1458, 1440, 1399, 1303, 1202, 1072, 1051, 995 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.94 (br s,1H), 6.83 (dd, J=7.9, 1.5 Hz, 1H), 6.75 (d, J=7.9 Hz, 1H), 6.62 (dd, J=17.6, 10.9 Hz, 1H), 5.95 (s, 2H), 5.57 (d, J=17.6 Hz, 1H), 5.13 (d, J=10.9 Hz, 1H); ^{13}C NMR ($CDCl_3$): 148.2, 136.4, 132.1, 128.7, 121.0, 112.0, 108.2, 105.4, 101.1; MS *m/z* (% relative intensity, ion): 148(100, $[M]^+$), 89(35), 74(5), 63(20), 51(10).

4.4.2. 2-Methoxy-4,5-methylenedioxyphenylethene (6b). Yellow oil (98%); IR (film) ν_{max}: 2860, 2685, 1635, 1458, 1440, 1303, 1202, 995 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.98 (dd, J=17.8, 11.1 Hz, 1H), 6.97 (s, 1H), 6.50 (s, 1H), 5.91 (s, 2H,), 5.53 (dd, J=17.8, 1.2 Hz, 1H), 5.13 (dd, J=11.1, 1.2 Hz,1H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 152.1, 148.4, 141.6, 131.0, 119.6, 111.9, 105.2, 106.2, 94.9, 56.7; MS *m/z* (% relative intensity, ion): 178(80, $[M]^+$), 163(20), 133(100), 105(20), 77(30), 63(15), 53(30); HRMS (EI) *m/z*=178.0624 $[M]^+$, calcd for $C_{10}H_{10}O_3$=178.0625.

4.4.3. 2-Methyl-4,5-methylenedioxyphenylethene (6c). Yellow oil (96%); IR (film) ν_{max}: 2860, 2675, 1581, 1562, 1458, 1440, 1381, 1303, 1202, 1120, 995 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.96 (s, 1H), 6.83 (dd, J=17.3, 10.9 Hz, 1H), 6.59 (s, 1H), 5.86 (s, 2H), 5.48 (d, J=17.3 Hz, 1H), 5.15 (d, J=10.9 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 147.1, 146.1, 134.2, 130.0, 129.3, 113.1, 110.2, 105.1, 100.8, 19.5; MS *m/z* (% relative intensity, ion): 162(100 $[M]^+$), 147(5), 131(37), 115(2), 103(38), 91(19), 77(18), 63(9), 51(18); HRMS (EI) *m/z*=162.0675 $[M]^+$, calcd for $C_{10}H_{10}O_2$=162.0672.

4.5. Palladium-catalysed coupling of styrenes 5, 6a–c with aryl halides (Table 1)

To a stirred solution of aryl halide (10 mmol) and styrene **5**, **6a–c** (15 mmol) in dimethyl acetamide or triethylamine (20 mL) as indicated in Table 1, was added palladium acetate (28 mg, 0.12 mmol) and triphenylphosphine (68 mg, 0.25 mmol) or tri-*o*-tolylphosphine (80 mg, 0.26 mmol). The reaction mixture was stirred at room temperature for 1 h and then heated at the required temperature as shown in Table 1. After completion the reaction was quenched by addition of water (50 mL), extracted with diethyl ether (3×50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was then purified by flash chromatography.

4.5.1. 1,2-Diphenylethene (8a). ^1H NMR ($CDCl_3$): δ 7.55–7.49 (br s, 4H), 7.40–7.33 (br s, 4H) 7.30–7.26 (br s, 2H), 7.11 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 128.7, 127.6, 126.5; MS *m/z* (% relative intensity, ion): 180(100 $[M^+]$), 165(30), 102(2), 77(10), 51(15); (identical to commercially-available material).

4.5.2. 1-(2-Hydroxyphenyl)-2-phenylethene (8b). ^1H NMR ($CDCl_3$): δ 7.55–7.50 (m, 3H), 7.38–7.32 (m, 2H), 7.36 (d, J=16.5 Hz, 1H), 7.26 (m, 1H), 7.15 (td, J=7.8, 1.5 Hz, 1H), 7.12 (d, J=16.5 Hz, 1H), 6.95 (td, J=7.8, 1.5 Hz, 1H), 6.80 (dd, J=7.8, 1.5 Hz, 1H) 1.59 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 153.0, 137.7, 130.2, 128.7, 127.6, 127.2, 126.6, 124.8, 123.0, 121.2, 115.9; MS *m/z* (% relative intensity, ion): 196(100, $[M]^+$), 179(15), 165(33), 152(22), 139(7), 128(7), 118(11), 106(1), 98(7), 89(15), 76(7), 63(6), 51(6), 41(1).[27]

4.5.3. 1-(4-Methoxyphenyl)-2-phenylethene (8c). IR ($CHCl_3$) ν_{max}: 3000, 2830, 1610, 1510, 1310, 1300, 1250, 1180, 1150, 1055, 970, 960 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.51–7.43 (m, 4H), 7.37–7.31 (m, 2H), 7.26–7.20 (m, 1H), 7.07 (d, J=15.4 Hz, 1H), 6.97 (d, J=15.4 Hz, 1H), 6.93–6.87 (m, 2H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 128.7, 128.2, 127.7, 127.2, 126.6, 126.3, 114.2, 55.3; MS *m/z* (% relative intensity, ion): 210(90, $[M]^+$), 177(20), 162(100), 134(2), 114(2), 100(2), 87(2), 65(2) 52(2).[28]

4.5.4. 1-(2,4-Dimethoxyphenyl)-2-phenylethene (8d). ^1H NMR ($CDCl_3$): δ 7.51–7.48 (m, 3H), 7.40, (d, J=15.3 Hz, 1H), 7.35–7.29 (m, 2H), 7.23–7.16 (m, 1H), 7.0 (d, J=15.3 Hz, 1H), 6.42–6.52 (m, 2H), 3.85 (s, 3H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 160.5, 158.0, 138.3, 128.5, 127.2, 127.0, 126.9, 126.3, 123.3, 105.0, 98.5, 55.5; MS *m/z* (% relative intensity, ion): 240(100, $[M]^+$), 225(5), 209(7),

197(21), 182(16), 165(64), 153(27), 139(13), 121(20), 104(21), 91(20), 76(13), 63(10), 51(10).[27]

4.5.5. 1-(3,4-Methylenedioxyphenyl)-2-phenylethene (8e). IR ($CHCl_3$) ν_{max}: 2900, 1605, 1495, 1450, 1360, 1255, 1100, 1040, 960, 935, 870, 610 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.46 (dt, J=7.2, 1.5 Hz; 2H), 7.33 (tt, J=7.2, 1.5 Hz, 2H), 7.22 (tt, J=7.2, 1.5 Hz, 1H), 7.05 (d, J=1.5 Hz, 1H), 7.01 (d, J=16.3 Hz, 1H), 6.92 (dd, J=8.5, 1.5 Hz, 1H), 6.91 (d, J=16.3 Hz, 1H), 6.78 (d, J=8.5 Hz, 1H), 5.93 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 148.2, 147.3, 137.4, 131.9, 128.7, 128.4, 127.4, 127.0, 126.3, 121.5, 108.4, 105.6, 101.1; MS *m/z* (% relative intensity, ion): *m/z* 224(100, $[M]^+$), 193(15), 165(85), 139(13), 115(10), 82(10), 63(10).[29]

4.5.6. 1-(3,4-Methylenedioxyphenyl)-2-(2-hydroxyphenyl)ethene (8f). ^1H NMR ($CDCl_3$): δ 7.94 (dd, J=8.2, 1.5 Hz, 1H,), 7.23 (d, J=8.2 Hz, 1H), 7.16–7.05 (m, 3H), 6.99–6.90 (m, 2H), 6.79 (d, J=8.2 Hz, 2H), 5.96 (s, 2H), 1.70 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 152.9, 148.1, 147.3, 132.2, 129.8, 128.4, 127.1, 124.8, 121.5, 121.3, 121.1, 115.9, 108.4, 105.7, 101.1; MS *m/z* (% relative intensity, ion): 240(100 $[M]^+$), 225(5), 211(7), 193(7), 181(36), 165(18), 152(38), 139(5), 122(7), 105(3), 91(15), 76(16), 63(13), 51(7), 40(1); HRMS (EI) *m/z*: 240.0852 $[M]^+$ ($C_{15}H_{12}O_3$ requires 240.0786).

4.5.7. 1-(3,4-Methylenedioxyphenyl)-2-(2-acetoxyphenyl)ethene (8g). White solid, mp 68–70 °C; IR (nujol mull) ν_{max}: 1701, 1581, 1460, 1442, 1333, 1210, 1187, 1175,1135, 1045, 1001, 982 cm^{-1}; MS *m/z* (% relative intensity, ion): 282(51, $[M]^+$), 265(1), 240(100), 211(4), 181(24), 152(37), 131(53), 103(4), 86(1), 63(20).

4.5.8. 1-(3,4-Methylenedioxyphenyl)-2-(4-methoxyphenyl)ethene (8h). White solid, mp 139–141 °C; IR ($CHCl_3$) ν_{max}: 2900, 2840, 1610, 1510, 1590, 1450, 1360, 1310, 1285, 1255, 1180, 1040, 960, 935, 850, 825, 610 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.41 (dt, J=8.9, 2.0 Hz, 2H), 7.03 (d, J=1.5 Hz, 1H), 6.92–6.82 (m, 5H), 6.81 (d, J=8.2 Hz, 1H), 5.94 (s, 2H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 159.2, 148.3, 147.2, 132.4, 130.2, 127.5, 126.6, 126.3, 121.0, 114.1, 108.4, 105.4, 101.1, 55.3; MS *m/z* (% relative intensity, ion): 254(100, $[M]^+$), 223(5), 181(20), 152(50), 127(50), 98(10), 76(10), 51(10).[30]

4.5.9. 1-(2-Methoxy-4,5-methylenedioxyphenyl)-2-(2-hydroxyphenyl)ethene (8i). To a stirred solution of 2-iodophenol (**7b**) (0.99 g, 4.5 mmol) in triethylamine (10 mL) was added styrene **6b** (0.8 g, 4.5 mmol), palladium acetate (28 mg, 0.12 mmol) and tri-*o*-tolylphosphine (80 mg, 0.26 mmol). The reaction mixture was stirred at room temperature for 1 h and then the temperature was increased to 100 °C. After 4 h of heating, a further equivalent of **7b** (0.99 g, 4.5 mmol) was added and stirring was continued for a further 16 h. The reaction was monitored by following the disappearance of styrene **6b** by TLC and GC. On completion, the reaction was quenched by addition of water (50 mL) and extracted with ethyl acetate (50 mL) and diethyl ether (3×50 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography and stilbene **8i** was obtained as yellow solid in 68% yield (810 mg), mp 137–139 °C; IR ($CHCl_3$) ν_{max}: 3680, 3300, 3000, 2890, 1625, 1600, 1590, 1400, 1485, 1430, 1320, 1290, 1260, 1170, 1160, 1040, 1015,975, 940, 870, 840 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.51 (dd, J=7.7, 1.5 Hz, 1H), 7.40 (d, J=16.6 Hz, 1H), 7.14 (d, J=16.6 Hz, 1H), 7.13–7.08 (m, 2H), 6.94–6.89 (m, 1H), 6.79 (d, J=7.2 Hz, 1H), 6.53 (s, 1H), 5.93 (s, 2H), 5.15 (br s, 1H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 152.8, 152.7, 147.7, 141.8, 128.2, 127.1, 125.4, 124.6, 121.0, 121.0, 119.6, 115.8, 105.3, 101.3, 95.0, 56.8; MS *m/z* (% relative intensity, ion): 270(100, $[M]^+$), 255(5), 227(40), 197(20), 181(50), 169(20), 152(15), 133(20), 115(20), 105(5), 91(10), 77(10), 63(10), 53(2); HRMS (EI) *m/z* 271.0965 $[M+H]^+$, calcd for $C_{16}H_{15}O_4$ 271.0970.

4.5.10. 1-(2-Methyl-4,5-methylenedioxyphenyl)-2-(2-hydroxyphenyl)ethene (8j). To a stirred solution of 2-iodophenol (**7b**) (6.6 g, 30 mmol) in triethylamine (50 mL) was added styrene **6c** (3.42 g, 21 mmol), palladium acetate (31 mg, 0.13 mmol) and tri-*o*-tolylphosphine (85 mg, 0.27 mmol). The reaction mixture was stirred for 1 h at room temperature and then the temperature increased to 100 °C. After 4 h of heating, a further equivalent of 2-iodophenol (**7b**) was added and stirring continued for 16 h. The reaction was monitored by following the disappearance of styrene (**6d**) by TLC and GC. After completion, the reaction was quenched by adding water (50 mL) and extracted with ethyl acetate (1×50 mL) and diethyl ether (3×50 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was then purified by flash chromatography and stilbene **8j** was obtained as a white solid (2.77 g, 54%), mp 147–149 °C; IR ($CHCl_3$) ν_{max}: 3600, 3300, 3000, 2890, 1610, 1505, 1485, 1460, 1370, 1320, 1255, 1170, 1045, 970, 940, 875 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.48 (dd, J=7.9, 1.7 Hz, 1H), 7.26 (d, J=16.3 Hz, 1H), 7.13 (td, J=7.9, 1.7, 1H), 7.12 (s, 1H), 7.08 (d, J=16.3 Hz, 1H), 6.94 (td, J=7.9, 0.7 Hz, 1H), 6.81 (dd, J=7.9, 1.5 Hz, 1H), 6.66 (s, 1H), 5.94 (s, 2H), 2.33 (s, 3H), 1.58 (br s, 1H,); ^{13}C NMR ($CDCl_3$): δ 152.9, 146.9, 130.9, 129.9, 129.9, 128.4, 127.9, 127.3, 125.1, 122.4, 121.1, 115.9, 110.4, 105.2, 100.9, 19.8; MS *m/z* (% relative intensity, ion): 254(100, $[M]^+$), 239(27), 225(7), 209(8), 195(13), 181(15), 165(27), 152(33), 135(13), 115(13), 102(8), 89(15), 77(13), 63(12), 51(14), 40(5); HRMS (EI) *m/z* 254.0937 $[M]^+$, calcd for $C_{16}H_{14}O_3$ 254.0943.

4.6. Epoxidation and acid-catalysed cyclisation of stilbenes

4.6.1. 1-(2-Methoxy-4,5-methylenedioxyphenyl)-2-(2-hydroxyphenyl)ethene oxide (9a). 3-Chloroperbenzoic acid (276 mg, 2 equiv) was added stepwise to a stirred solution of stilbene **8i** (220 mg, 0.8 mmol) in DCM (10 mL) at 0 °C. After addition, the reaction mixture was warmed to 35 °C and stirring continued for 2 h. The reaction was quenched by the addition of water (50 mL) and extracted with DCM. The combined organic extracts were dried and concentrated under vacuum and purified by flash chromatography. The epoxide **9a** was obtained as a yellow solid (150 mg, 67%), mp 118–122 °C; IR ($CHCl_3$) ν_{max}: 3520, 3080, 2900, 1580, 1490, 1430, 1280, 1260, 1170, 1080,

1040, 940, 910 cm^{-1}; MS *m/z* (% relative intensity, ion): 286(21, $[M]^+$), 268(100), 253(60), 239(1), 225(60), 207(2), 195(15), 179(5), 167(30), 151(40), 139(70), 126(10), 112(15), 99(10), 87(10), 78(10), 69(20), 53(40), 44(50).

4.6.2. 2-(2-Methoxy-4,5-methylenedioxyphenyl)benzofuran (1c). To a stirred solution of epoxide **9a** (50 mg, 0.17 mmol) in chloroform (10 mL), a few crystals of *p*-toluenesulphonic acid were added. The reaction was stirred at 40 °C for 1 h and then quenched by the addition of water (50 mL), extracted with chloroform (3×30 mL) and the extracts washed with aqueous sodium bicarbonate solution. Benzofuran **1c** was obtained as a white solid in 76% yield (35 mg), mp 114–116 °C; IR ($CHCl_3$) ν_{max}: 2900, 1630, 1580, 1510, 1490, 1450, 1380, 1260, 1180, 1160, 1145, 1045, 1030, 940, 910, 880, 845 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.53–7.52 (m, 3H), 7.23–7.20 (m, 3H), 6.60 (s, 1H), 5.96 (s, 2H), 3.91 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 153.6, 152.8, 152.3, 148.4, 141.6, 138.3, 130.2, 123.7, 122.4, 120.7, 112.2, 106.4, 104.6, 101.5, 94.7, 56.3: MS *m/z* (% relative intensity, ion): 268(100, $[M]^+$), 253(90), 239(2), 225(50), 209(3), 195(15), 181(5), 167(20), 155(15), 139(60), 131(15), 112 (20), 99(10), 87(12), 79(2), 69(10), 53(40), 44(10); HRMS (EI) *m/z* 268.0729 $[M]^+$, calcd for $C_{16}H_{12}O_4$ 268.0736.

4.6.3. 2-(2-Methyl-4,5-methylenedioxyphenyl)benzofuran (1d). To a stirred solution of stilbene (**8j**) (2 g, 7.8 mmol) in DCM (10 mL), 3-chloroperbenzoic acid (2 g, 12 mmol) was added. The reaction mixture was stirred overnight at 35 °C. The reaction was quenched by the addition of water (50 mL) and extracted with DCM. The combined organic extracts were dried, filtered and concentrated under vacuum. The crude product was purified by flash chromatography and pure benzofuran **1d** was obtained as a white solid in 50% yield (1.0 g), mp 73–76 °C; IR ($CHCl_3$) ν_{max}: 2900, 1625, 1510, 1490, 1460, 1375, 1250, 1170, 1090, 1045, 940, 870 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.58 (dd, J=7.4, 1.2 Hz, 1H), 7.50 (br d, J=7.9 Hz, 1H), 7.32 (s, 1H), 7.31–7.20 (m, 2H), 6.77 (br s, 2H), 5.98 (s, 2H), 2.49 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 155.4, 154.1, 147.7, 146.0, 130.4, 129.3, 124.0, 122.8, 122.7, 120.7, 111.2, 111.0, 108.1, 104.3, 101.2, 21.8; MS *m/z* (% relative intensity, ion): 252(100, $[M]^+$), 221(9), 207(10), 194(18), 181(8), 165(40), 152(5), 139(11), 126(15), 115(8), 82(10), 63(5), 51(5), 44(2); HRMS (EI) *m/z* 252.0783 $[M]^+$, calcd for $C_{16}H_{12}O_3$ 252.0786).

4.7. Synthesis of benzofurans via palladium-catalysed coupling of acetylenes with aryl halides

4.7.1. 4-Iodoresorcinol (7j). Iodine monochloride was added to a stirring solution of resorcinol (0.68 g, 6.25 mmol) in diethyl ether (7 mL) at room temperature. After stirring for 1 h the reaction was quenched by adding water (30 mL) and excess iodine monochloride was destroyed by adding Na_2SO_3 (1 g, 7.9 mmol). The aqueous phase was extracted with diethyl ether (3×50 mL). The combined organic extracts were dried, filtered and concentrated under vacuum and the crude product was purified by flash chromatography. 4-Iodoresorcinol (**7j**) was obtained as a colourless oil in 70% yield (1.1 g); ^1H NMR ($CDCl_3$): δ 7.44 (d, J=8.6 Hz, 1H), 6.52 (d, J=2.7 Hz, 1H), 6.24 (dd, J=8.6, 2.7 Hz, 1H); ^{13}C NMR($CDCl_3$): δ 157.8, 145.1, 138.3, 110.4, 107.7, 102.6; MS *m/z* (% relative intensity, ion): 236(100, M^+), 227(1), 219(1), 207(2), 195(1), 187(1), 179(1), 165(1), 152(1), 144(1), 135(1), 127(62), 118(5), 119(6), 96(1), 81(19), 69(10), 61(1), 53(14).[8]

4.7.2. 2,4-Diacetoxyiodobenzene (7k). To a stirring solution of 4-iodoresorcinol (**7j**) (0.57 g, 2.4 mmol) in acetic anhydride (1.6 g, 20 mmol), pyridine (2 g, 20 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 1 h, quenched by adding water (30 mL) and extracted with diethyl ether (3×50 mL). The extracts were washed with 2 N HCl (50 mL), dried, filtered and concentrated under vacuum. The crude product was purified by flash chromatography to give diacetate **7k** as a colourless oil (0.58 g, 76%); IR (film): ν_{max} 3000, 2940, 2905, 2850, 1731, 1670, 1562, 1540, 1453, 1430, 1329, 1253, 1142, 1105, 1081, 995 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.78 (d, J=8.7 Hz, 1H), 6.97 (brs, 1H), 6.79 (m, 1H), 2.33 (s, 3H), 2.25 (s, 3H); MS *m/z* (% relative intensity, ion): 320(19, M^+), 294(1), 278(62), 254(1), 236(100), 207(5), 179(1), 151(8), 127(10), 108(10), 81(10), 51(8).

4.7.3. 3,4-Methylenedioxyphenylethyne (10b). Bromine (1.4 mL, 27.5 mmol) dissolved in DCM (25 mL) was added dropwise to a stirring solution of 3,4-methylenedioxyphenylethene (**6a**) (3.7 g, 25 mmol) in DCM (25 mL) at 0 °C. The ice bath was removed after the complete addition of bromine and the reaction mixture was kept stirring for 1 h. The excess bromine was destroyed by adding 10% sodium thiosulphate solution. The organic phase was dried, filtered and concentrated under vacuum. Potassium *t*-butoxide (6.25 g, 55 mmol) and 18-crown-ether (200 mg, 0.76 mmol) were suspended in cyclohexane (50 mL) and crude brominated styrene was added to this suspension. The resultant slurry was refluxed for 2 h, then cooled to room temperature and filtered through a thick pad of TLC grade silica gel. The filtrate was dried and concentrated under vacuum. The crude product was purified by flash chromatography and the acetylene **10b** was obtained as yellow oil in a yield of 56% (1 g); IR (film): ν_{max} 3200, 2810, 2010, 1582, 1460, 1441, 1382, 1291, 1202, 1145, 1077, 1049, 995 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.04–6.73 (m, 3H), 5.98 (s, 2H), 3.01 (s, 1H); MS *m/z* (% relative intensity, ion): 146(100, $[M]^+$), 89(20), 73(10), 62(65), 50(20).

4.7.4. 2-Methoxy-4,5-methylenedioxyphenylethyne (10c). Bromine (3.52 g, 22 mmol) dissolved in $CHCl_3$ (30 mL) was added dropwise to a stirred solution of 2-methoxy-4,5-methylenedioxyphenylethene (**6b**) (2.0 g, 11 mmol) in $CHCl_3$ (30 mL) at room temperature. The addition was completed in 1 h at which point the temperature of the reaction mixture was increased to 40 °C and stirring was continued for a further 2 h. Excess bromine was destroyed by the addition of 10% sodium thiosulphate. The organic phase was dried and concentrated under vacuum to give the crude brominated styrene as a yellow solid. Potassium *t*-butoxide (5.0 g, 44 mmol) and 18-crown ether (200 mg, 0.76 mmol) were suspended in cyclohexane (50 mL). The crude brominated styrene was added to this suspension and the resultant slurry was heated under reflux for 1 h. The reaction mixture was cooled to

room temperature and the slurry was passed through a thick pad of silica gel and then concentrated. The crude product was obtained as a yellow oil and was further purified by flash chromatography yielding acetylene **10c** as yellow solid (1.0 g, 51%); ^{1}H NMR ($CDCl_3$): δ 6.88 (s, 1H), 6.51 (s, 1H), 5.94 (s, 2H), 3.85 (s, 3H), 3.23 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 157.5, 150.2, 140.9, 112.5, 102.3, 101.6, 94.4, 80.2, 79.8, 56.6; MS *m/z* (% relative intensity, ion): 176(100, $[M]^+$), 161(73), 131(20), 103(25), 87(20), 75(30), 69(10), 63(10), 53(40), 44(5); HRMS (EI) *m/z* 176.0471 $[M]^+$, calcd for $C_{10}H_8O_3$ 176.0473.

4.8. General method for palladium-catalysed coupling of acetylenes with 2-iodophenol

To a stirred solution of 2-iodophenol (**7b**) (6 mmol) in DMF (15 mL), $Pd(Ph_3P)_2Cl_2$ (0.21 mmol), CuI (0.30 mmol) and Et_3N (12 mmol) were added. The mixture was stirred for 1 h at room temperature. One of the acetylenes **10a–c** (12 mmol) was added to the reaction mixture and stirring continued at room temperature for 1 h after which the temperature was increased to 60 °C and stirring maintained overnight. The mixture was then cooled and poured into water (30 mL) and extracted with DCM (3×30 mL). The combined organic extract was washed with 10% NaOH (30 mL) and water (30 mL), dried and concentrated under vacuum. The products were obtained as yellow solids after flash chromatography and further purified by recrystallisation from aqueous ethanol.

4.8.1. 2-Phenylbenzofuran (11). Light yellow solid (72%); MS *m/z* (% relative intensity, ion): 194(100, $[M]^+$), 165(58), 150(1), 139(13), 126(2), 115(6), 105(1), 97(13), 82(7), 74(2), 63(3), 51(4), 40(1). [12]

4.8.2. 2-(3,4-Methylenedioxyphenyl)benzofuran (1b). (63%), mp 78–80 °C; IR ($CHCl_3$) ν_{max}: 2900, 1620, 1585, 1510, 1490, 1455, 1365, 1320, 1290, 1250, 1170, 1150, 1110, 1040, 935, 870 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.58–7.47 (m, 2H), 7.39 (dd, J=8.2, 1.7 Hz, 1H), 7.32 (d, J=1.7 Hz, 1H), 7.25–7.20 (m, 2H), 6.88 (d, J=8.2 Hz, 2H), 6.00 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 155.9, 154.7, 148.1, 135.6, 129.3, 124.8, 124.0, 122.9, 120.7, 119.2, 111.0, 108.7, 105.5, 101.3, 100.2; MS *m/z* (% relative intensity, ion): 238(100, $[M]^+$), 209(2), 181(20), 152(40), 119(15), 102(5), 86(1), 63(5); HRMS (EI) *m/z* 238.0630 $[M]^+$, calcd for $C_{15}H_{10}O_3$ 238.0630.

4.8.3. 2-(2-Methoxy-4,5-methylenedioxyphenyl)benzofuran (1c). To a stirring solution of 2-iodophenol (**7b**) (0.22 mg, 1 mmol) in DMF (5 mL), $Pd(Ph_3P)_2Cl_2$ (10 mg, 0.05 mmol), CuI (24 mg, 0.03 mmol) and Et_3N (0.3 mL, 2.9 mmol) were added and further stirred for 1 h at room temperature. Acetylene **10c** (200 mg, 1.1 mmol) was added to the reaction mixture and stirred for a further 1 h at room temperature and then the temperature was increased to 60 °C and stirring continued overnight. The mixture was then cooled and poured into water (30 mL) and extracted with DCM (3×30 mL). The combined extracts were washed with 10% NaOH (30 mL) and water (30 mL), dried and concentrated under vacuum. Benzofuran **1c** was obtained as a white solid after flash chromatography and was further purified by recrystallisation from aqueous ethanol (140 mg, 46%), mp 114–116 °C; IR ($CHCl_3$) ν_{max}: 2900, 1630, 1580, 1510, 1490, 1450, 1380, 1260, 1180, 1160, 1145, 1045, 1030, 940, 910, 880, 845 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.53–7.52 (m, 3H), 7.23–7.20 (m, 3H), 6.60 (s, 1H), 5.96 (s, 2H), 3.91 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 153.6, 152.8, 152.3, 148.4, 141.6, 130.2, 123.7, 122.4, 120.7, 112.2, 110.6, 106.4, 104.6, 101.5, 94.7, 56.3; MS *m/z* (% relative intensity, ion): 268(100 $[M]^+$), 253(90), 239(2), 225(50), 209(3), 195(15), 181(5), 167(20), 155(15), 139(60), 131(15), 112(20), 99(10), 87(12), 79(2), 69(10), 53(40), 44(10); HRMS (EI) *m/z* 268.0729 $[M]^+$, calcd for $C_{16}H_{12}O_4$ 268.0736.

4.8.4. 1-(2-Methoxy-4,5-methylenedioxyphenyl)-2-(2,4-diacetoxyphenyl)ethyne (12). A mixture of 2-methoxy-4,5-methylenedioxyphenylethyne (**10c**) (176 mg, 1 mmol), 2,4-diacetoxyiodobenzene (**7k**) (384 mg, 1.2 mmol), $PdCl_2(PPh_3)_2$ (36 mg, 0.06 mmol) and disiopropylamine (0.22 mL, 1.4 mmol) in DMF (6 mL) was stirred at 60 °C for 1 h. Water (30 mL) was added to the reaction mixture which was extracted with ethyl acetate (2×50 mL) and chloroform (2×50 mL). The combined organic extracts were dried, filtered and concentrated under vacuum. The crude product **12** was used without any further purification for the next reaction; MS *m/z* (% relative intensity, ion): 368(50, $[M]^+$), 337(1), 326(26), 310(1), 295(20), 284(75), 269(100), 253(2), 241(27), 225(2), 211(7), 197(6), 183(12), 169(3), 155(10), 139(9), 126(15), 115(10), 99(5), 87(5), 69(18), 55(8), 43(78).

4.8.5. 2-(2-Methoxy-4,5-methylenedioxyphenyl)-6-hydroxybenzofuran (cicerfuran) (1a). Anhydrous potassium carbonate (2.5 equiv) was added to the stirring solution of diarylacetylene **12** in methanol (10 mL). The reaction was stirred for a further 2 h at room temperature and concentrated under vacuum. GC–MS analysis showed cicerfuran (**1a**) as 5% of the mixture which could not be further purified by column chromatography; MS *m/z* (% relative intensity, ion): 284(100, $[M]^+$), 269(90), 253(1), 241(60), 225(2), 211(10), 197(5), 183(15), 171(8), 155(22), 142(37), 134(2), 115(10), 102(11), 91(11), 77(13), 69(20), 53(25), 44(20).[11]

4.9. Synthesis of stilbene intermediates by Wittig reactions

4.9.1. 2,4-Di-*O*-*tert*-butyldimethylsiloxybenzaldehyde (17). *tert*-Butyldimethylsilyl chloride (6.94 g, 40 mmol) was stirred for 10 min in DMF (30 mL). To this stirring solution diisopropylamine (6.94 mL, 40 mmol) was added dropwise and allowed to stir for 10 min. 2,4-Dihydroxybenzaldehyde (3.0 g, 20 mmol) was then added with further stirring for 1 h. The reaction was stopped by addition of water (50 mL) and extracted with a mixture of petroleum ether and diethyl ether (9:1). The organic layer was dried and concentrated yielding benzaldehyde **19** as an oil in 99.8% yield (8.03 g); IR (film): ν_{max} 2870, 2840, 2800, 2775, 1648, 1550, 1535, 1430, 1410, 1345, 1250, 1230, 1210, 1195, 1042 cm^{-1}; MS *m/z* (% relative intensity, ion): 365(1, $[M-H]^+$), 351(5), 309(100), 293(2), 279(2), 265(1), 251(8), 25.8(2), 221(1), 208(1), 195(13), 178(10), 165(6), 149(7), 133(8), 117(5), 104(2), 91(5), 73(50), 57(10), 41(9).

4.10. General method for reduction of benzaldehydes

Sodium borohydride (75 mmol) was added stepwise to stirred solutions of benzaldehydes **4a–c** (50 mmol) in ethanol (200 mL) at 0 °C. After complete addition, the reaction mixture was allowed to warm to room temperature and stirring continued for 2 h. The reaction was quenched by adding water (100 mL), ethanol was removed under reduced pressure and the aqueous phase extracted with dichloromethane (3×100 mL). The combined organic phase was then washed with water (100 mL) and aqueous $NaHCO_3$ (100 mL). The organic extract was dried, filtered and concentrated. The products were recrystallised from diethyl ether/petroleum ether as white solids.

4.10.1. 2-Methoxy-4,5-methylenedioxybenzyl alcohol (13b). White solid (99%), mp 53–55 °C; IR (nujol mull) ν_{max}: 1465, 1235, 1148, 1134, 1110, 1035, 982 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.79 (s, 1H), 6.54 (s, 1H), 5.91 (s, 2H), 4.57 (s, 2H), 3.80 (s, 3H,), 2.27 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 152.7, 147.6, 140.8, 121.3, 109.0, 101.1, 94.4, 61.7, 56.2; MS *m/z* (% relative intensity, ion): 182(100, $[M]^+$), 165(90), 149(23), 135(14), 81(23), 69(23), 53(45), 41(5); HRMS (CI) *m/z* 200.0917 $[M+ NH_4]^+$, calcd for $C_9H_{14}NO_4$ 200.0923.

4.10.2. 2-Methyl-4,5-methylenedioxybenzyl alcohol (13c). Yellow solid (97%) mp 53 °C; IR ($CHCl_3$) ν_{max}: 3590, 2870, 1622, 1510, 1490, 1370, 1260, 1160, 1045, 940, 870 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.94 (s, 1H), 6.68 (s, 1H), 5.67 (s, 2H), 4.36 (s, 2H), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 146.0, 145.1, 131.9, 127.9, 109.8, 107.7, 100.2, 57.2, 17.9; MS *m/z* (% relative intensity, ion): 166(100, $[M]^+$), 148(83), 135(30), 123(8), 107(50), 93(30), 77(42), 65(20), 51(33), 44(8).

4.10.3. Two-step synthesis of 3,4-methylenedioxybenzyltriphenylphosphonium bromide (15a). To a stirred solution of 3,4-methylenedioxybenzyl alcohol (piperonyl alcohol) (**13a**) (8.45 g, 55.5 mmol) in CH_2Cl_2 (50 mL) was added phosphorous tribromide (17.98 g, 1.2 equiv) dropwise at 0 °C. When addition was complete, the ice bath was removed and the reaction mixture allowed to stir at room temperature. After stirring for 2 h, bromination was terminated by careful addition of aqueous $NaHCO_3$ at 0 °C. The organic phase was separated, dried and concentrated under vacuum, affording 3,4-methylenedioxybenzyl bromide (**14a**) as a white solid in 67% yield (7.8 g), mp 45–47 °C; ^1H NMR ($CDCl_3$): δ 6.86 (d, J=7.6 Hz, 2H), 6.74 (d, J=7.6 Hz, 1H), 5.96 (s, 2H), 4.52 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 147.9, 147.8, 131.5, 122.7, 109.5, 108.3, 101.3, 34.2; MS *m/z* (% relative intensity, ion): 245(7, $[M]^+$), 229(1), 180(2), 165(100), 151(34), 135(20), 121(15), 107(10), 93(10), 77(20), 53(18), 40(5). To the stirred suspension of 3,4-methylenedioxybenzyl bromide (7.8 g, 36.5 mmol) in toluene (100 mL) was added triphenylphosphine (11.45 g, 1.2 equiv). After stirring for 30 min at room temperature the reaction mixture was heated to reflux for 2 h. After cooling to room temperature the precipitates were filtered and washed with excess diethyl ether. Phosphonium salt **15a** was obtained as a white crystalline solid in 60% yield (16 g), mp 242–244 °C; IR (nujol mull): ν_{max} 2950, 2695, 1574, 1581, 1538, 1455, 1435, 1385, 1332, 1250, 1141, 1108, 1064, 1039, 988 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.78–7.63 (m, 15H), 6.64–6.52 (m, 3H), 5.87 (s, 2H), 5.30 (d, J=13.8 Hz, 2H).

4.10.4. Attempted synthesis of 2-methoxy-4,5-methylenedioxybenzyltriphenylphosphonium bromide (15b). To a stirred solution of 2-methoxy-4,5-methylenedioxybenzyl alcohol (**13b**) (3 g, 16.5 mmol) in CH_2Cl_2 (50 mL) was added phosphorous tribromide dropwise (5.34 g, 1.2 equiv). After stirring for 5 h bromination was terminated by careful addition of aqueous $NaHCO_3$. The organic phase was separated, dried and concentrated under vacuum to give 1,2-di-(2-methoxy-4,5-methylenedioxyphenyl)ethane (**16**) in 73% yield (4 g); ^1H NMR ($CDCl_3$): δ 6.57 (s, 2H), 6.51 (s, 1H), 5.85 (s, 2H), 3.78 (s, 2H), 3.75 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 152.3, 146.1, 140.8, 121.7, 110.1, 100.9, 94.7, 56.5, 29.3.

4.11. Improved method for the synthesis of phosphonium bromides

A solution of phosphorous tribromide (0.5 equiv) in toluene (50 mL) was added dropwise to a stirred solution of piperonyl alcohol (66 mmol) in toluene (100 mL) at 0 °C. After addition, the reaction mixture was allowed to warm to room temperature and the stirring was continued for 30 min. Bromination was terminated by careful addition of aqueous $NaHCO_3$ at 0 °C. The organic phase was separated, dried, filtered and passed through a thick pad of Celite®. To the filtrate (100 mL) was added triphenylphosphine (1.2 equiv). The reaction mixture was stirred for 30 min at room temperature and then heated to reflux for 2 h. After cooling to room temperature, the precipitates were filtered and washed with excess diethyl ether.

4.11.1. 3,4-Methylenedioxybenzyltriphenylphosphonium bromide (15a). White crystalline solid (95%), mp 242–244 °C; IR (nujol mull): ν_{max} 2950, 2695, 1574, 1581, 1538, 1455, 1435, 1385, 1332, 1250, 1141, 1108, 1064, 1039, 988 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.78–7.63 (m, 15H), 6.64–6.52 (m, 3H), 5.87 (s, 2H), 5.30 (d, J=13.8 Hz, 2H).

4.11.2. 2-Methoxy-4,5-methylenedioxybenzyltriphenylphosphonium bromide (15b). White crystalline solid (71%), mp 256–258 °C; IR (nujol mull): ν_{max} 1581, 1538, 1455, 1435, 1355, 1332, 1250, 1142, 1108, 1064, 988 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.81–7.76 (m, 15H), 6.86 (s, 1H), 6.24 (s, 1H), 5.87 (s, 2H), 5.09 (d, J=14.5 Hz, 2H), 3.12 (s, 3H).

4.11.3. 2-Methyl-4,5-methylenedioxytriphenylphosphonium bromide (15c). Light yellow solid (64%); IR (nujol mull): ν_{max} 2950, 1581, 1538, 1455, 1435, 1355, 1332, 1250, 1141, 1108, 1064, 988 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.84–7.64 (m, 15H), 6.55 (d, J=2 Hz, 1H), 6.46 (s, 1H), 5.87 (s, 2H), 5.17 (d, J=14.6 Hz, 2H), 1.55 (s, 3H).

4.12. Synthesis of stilbenes by the Wittig reaction

Sodium hexamethyldisilazide (15 mL of 1 M soln in THF, 15 mmol) was added by syringe to a stirred suspension of phosphonium salt (12.6 mmol) in THF (50 mL) at 0 °C, and

allowed to stir for a further 1 h. 2,4-Di-*tert*-butyldimethylsilyloxybenzaldehyde (**17**) (8 mmol) in THF (50 mL) was then added dropwise using a dropping funnel. After addition, the reaction mixture was allowed to warm to room temperature and stirring was continued for 2 h. The reaction mixture was then washed with aqueous NH_4Cl, filtered, dried and concentrated under vacuum. The crude product was dissolved in 1 mL of diethyl ether and excess petroleum ether added to precipitate the remaining triphenylphosphonium oxide. The filtrate was concentrated under vacuum to give the required product.

4.12.1. 1-(3,4-Methylenedioxyphenyl)-2-(2,4-di-*O*-*tert*-butyldimethylsiloxyphenyl)ethene (18a). Yellow oil (65%); IR (film): ν_{max} 2875, 2843, 2800, 2815, 1560, 1523, 1463, 1450, 1405, 1360, 1211, 1159, 1133, 995 cm^{-1}; MS *m/z* (% relative intensity, ion): 484(60, $[M]^+$), 469(2), 427(50), 411(1), 397(2), 369(8), 351(2), 341(3), 325(2), 305(10), 295(2), 283(1), 263(2), 249(1), 239(5), 223(3), 214(1), 203(8), 185(10), 170(12), 156(10), 145(5), 135(10), 117(10), 105(1), 91(1), 73(100), 59(10), 41(10).

4.12.2. 1-(2-Methoxy-4,5-methylenedioxyphenyl)-2-(2,4-di-*O*-*tert*-butyl-dimethylsiloxyphenyl)-ethene (18b). Yellow oil (61%); MS *m/z* (% relative intensity, ion): 514(60, $[M]^+$), 457(6), 426(4), 400(2), 385(10), 369(2), 351(2), 327(8), 311(8), 281(5), 233(4), 207(12), 185(10), 165(13), 115(2), 89(7), 73(100), 44(50).

4.12.3. 1-(2-Methyl-4,5-methylenedioxyphenyl)-2-(2,4-di-*O*-*tert*-butyldimethylsiloxyphenyl)-ethene (18c). Yellow oil (68%); IR (film) ν_{max}: 2875, 2845, 2809, 2790, 1560, 1523, 1441, 1379, 1211, 1132, 995 cm^{-1}; MS *m/z* (% relative intensity, ion): 498(88, $[M]^+$), 483(2), 441(22), 425(1), 411(2), 383(10), 380(8), 355(5), 326(2), 305(8), 293(10), 281(2), 263(1), 249(5), 217(4), 205(2), 192(6), 177(7), 165(6), 149(16), 135(10), 117(5), 103(5), 91(1), 73(100), 59(16), 41(10).

4.13. Epoxidation of stilbenes

3-Chloroperbenzoic acid (4 mmol) was added portionwise to a stirred solution of stilbene (2.06 mmol) in dichloromethane at 0 °C. After addition, the reaction was allowed to warm to room temperature and stirring continued for 1 h. The reaction was then quenched by addition of water. The organic phase was washed three times with aqueous $NaHCO_3$ dried, filtered and concentrated under vacuum. The crude product was purified by adding excess petroleum ether that resulted in precipitation of 3-chlorobenzoic acid as a white solid. Precipitates were filtered off and the filtrate was concentrated under vacuum and used for the next reaction without further purification.

4.13.1. 1-(3,4-Methylenedioxyphenyl)-2-(2,4-di-*O*-*tert*-butyldimethylsiloxyphenyl)ethene oxide (19a). Yellow oil (53%); MS *m/z* (% relative intensity, ion): 500(3, $[M]^+$), 471(100), 443(13), 415(2), 357(2), 299(1), 179(5), 135(13), 105(2), 73(67), 41(5).

4.13.2. 1-(2-Methoxy-4,5-methylenedioxyphenyl)-2-(2,4-di-*O*-*tert*-butyldimethylsiloxyphenyl)ethene oxide (19b). Yellow oil (48%); MS *m/z* (% relative intensity, ion): 530(2, $[M]^+$), 501(100), 473(5), 457(1), 430(1), 387(7), 355(10), 314(8), 297(1), 281(1), 265(1), 241(3), 222(2), 193(8), 165(13), 135(5), 105(2), 89(1), 73(80), 57(10), 41(10); HRMS (E1) *m/z* 531.2593 $[M+H]^+$, calcd for $C_{28}H_{43}O_6Si_2$ 531.2595.

4.13.3. 1-(2-Methyl-4,5-methylenedioxyphenyl)-2-(2,4-di-*O*-*tert*-butyldimethylsiloxyphenyl)ethene oxide (19c). Yellow oil (48%); MS *m/z* (% relative intensity, ion): 514(2, $[M]^+$), 485(100), 457(10), 429(2), 399(2), 373(3), 351(13), 335(1), 313(2), 297(1), 267(1), 239(2), 214(1), 193(4), 165(4), 149(18), 133(4), 115(2), 91(2), 73(88), 57(6), 41(6).

4.14. Deprotection and acid-catalysed cyclisation

Epoxides (**19a**,**b** and **c**) (1 mmol) were each dissolved in acetone–water (95/5, 10 mL). To this solution was added $CuCl_2 \cdot H_2O$ (2 mmol) and the homogeneous mixture was heated under gentle reflux for 48 h. The solvent was removed under vacuum and the crude product immediately dissolved in chloroform (5 mL) and a few crystals of *p*-toluenesulphonic acid added. The reaction was heated at 35 °C for 1 h to give the required product.

4.14.1. 2-(3,4-Methylenedioxyphenyl)-6-hydroxybenzofuran (1e). The product decomposed completely during the work up and purification process; MS *m/z* (% relative intensity, ion): 254(100, $[M]^+$), 225(4), 207(2), 196(14), 181(1), 168(14), 139(22), 127(18), 112(8), 98(4), 89(4), 75(6), 63(7), 51(3), 41(1).

4.14.2. 2-(2-Methoxy-4,5-methylenedioxyphenyl)-6-hydroxybenzofuran (cicerfuran) (1a). White solid (37%); GC-MS retention time 26.45 min; HPLC retention time 22.5 min, λ_m 285.4, 337.8 nm); IR ($CHCl_3$): ν_{max} 3600, 3300, 3000, 2900, 1630, 1510, 1492, 1450, 1380, 1320, 1275, 1175, 1150, 1120, 1045, 960, 940, 910, 880, 850, 830 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.36 (d, $J=8.4$ Hz, 1H), 7.34 (s, 1H), 7.09 (d, $J=1.0$ Hz, 1H), 6.94 (s, 1H), 6.90 (m, 1H), 6.71 (dd, $J=8.4$, 2.1 Hz, 1H), 6.04 (s, 2H), 3.90 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 155.5, 154.0, 151.8, 150.0, 147.7, 141.0, 121.1, 120.7, 112.1, 111.3, 104.6, 104.3, 101.3, 97.1, 95.5, 56.3; MS *m/z* (% relative intensity, ion): 284(100, $[M]^+$), 269(90), 253(1), 241(30), 232(1), 225(2), 211(6), 195(2), 183(10), 171(10), 162(5), 155(10), 142(30), 134(10), 126(10), 115(6), 102(4), 91(5), 84(2), 77(5), 69(10), 62(5), 53(10), 44(2); HRMS (E1) *m/z* 285.0757 $[M+H]^+$, calcd for $C_{16}H_{13}O_5$ 285.0763.

4.14.3. 2-(2-Methoxy-4,5-methylenedioxyphenyl)-6-hydroxybenzofuran (1f). The product decomposed completely during the work up and purification process; MS *m/z* (% relative intensity, ion): 268(100, $[M]^+$), 251(9), 239(7), 221(7), 207(22), 197(6), 181(17), 165(9), 152(35), 139(14), 126(5), 115(9), 105(17), 91(6), 76(14), 63(10), 51(10).

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Cyanosilylation of aldehydes catalyzed by *N*-heterocyclic carbenes

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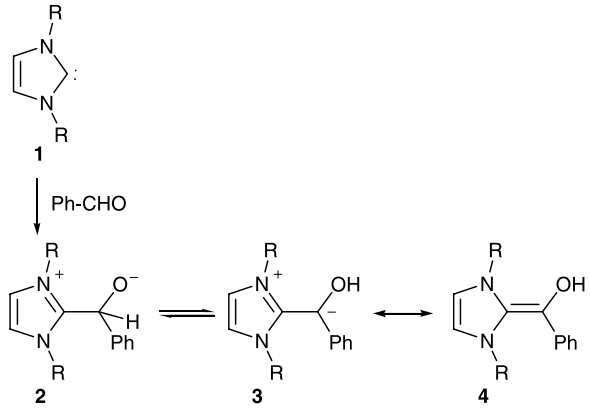
Abstract—*N*-Heterocyclic carbenes produced in situ from salts of imidazolium, benzimidazolium, pyrido[1,2-*c*]imidazolium, imidazolinium, thiazolium, and triazolium catalyze the addition of trimethylsilylcyanide to aldehydes to yield cyanohydrin trimethylsilyl ethers. The use of C_2-symmetric imidazolidenyl carbene derived from (*R*,*R*)-1,3-bis[(1-naphthyl)ethyl]imidazolium chloride led to enantioselective cyanosilylation.

1. Introduction

Cyanohydrin trimethylsilyl ethers are versatile intermediates because they can be transformed into a number of important building blocks such as α-hydroxyacids and β-hydroxyamines. One of the common methods to prepare silylated cyanohydrins is the addition reaction of trimethylsilylcyanide (TMS-CN) to aldehydes. It has been known that Lewis acids catalyze the cyanosilylation of aldehydes by activating them,[1] while Lewis bases catalyze the reaction by the activation of TMS-CN.[2] In this paper, we report *N*-heterocyclic carbenes (NHCs) **1** as catalysts for the cyanosilylation of aldehydes.

NHCs are excellent σ-donors, and their use as ligands for transition metal catalysts enhances catalytic performance and stability.[3] In addition, they are effective organocatalysts for important reactions such as benzoin condensation,[4,5] Stetter reactions,[6] and acylation/transesterification reactions.[7] Our research group has reported NHC-catalyzed reactions such as nucleophilic aroylation and asymmetric acylation.[5,8,9]

In benzoin condensation, the nucleophilic addition of the NHC to a carbonyl carbon atom of an aldehyde produces intermediate **2** (Scheme 1). A tautomer of **2** is an acyl anion equivalent **4**, which reacts with another aldehyde to produce benzoin. We anticipated intermediate **2** to react with TMS-CN to produce cyanosilyl ethers and the NHCs to catalyze the cyanosilylation reaction.



Scheme 1.

2. Results and discussion

To examine the catalytic ability of the NHCs for cyanosilylation, a reaction of *p*-chlorobenzaldehyde (**5a**) and TMS-CN was carried out in the presence of 1,3-dibenzylimidazolinylidene (5 mol%) generated in situ from imidazolium bromide **6** (Table 1, entry 1). After the mixture of **6** and potassium *tert*-butoxide in tetrahydrofuran was stirred at room temperature to generate the carbene, **5a** and TMS-CN were added. The reaction mixture was stirred continuously at room temperature, and the generation of cyanohydrin trimethylsilyl ether **7a** was observed by silica gel thin-layer chromatography. The reaction mixture was treated with dilute HCl, and the product was isolated as a form of cyanohydrin **8a** (80%). The cyanosilylation reaction of other aromatic aldehydes **5b–e**, conjugated aldehyde **5f**, and aliphatic aldehydes **5g–i** also proceeded to produce

Keywords: Cyanosilylation; Cyanohydrin; *N*-Heterocyclic carbene; Organocatalysis; Asymmetric cyanosilylation.
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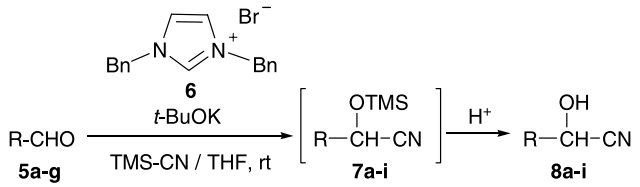
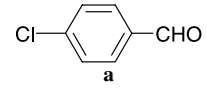
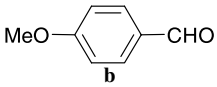
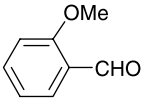
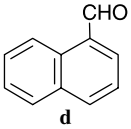
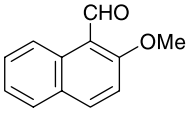
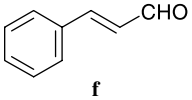
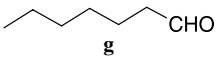
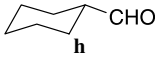
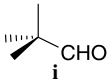
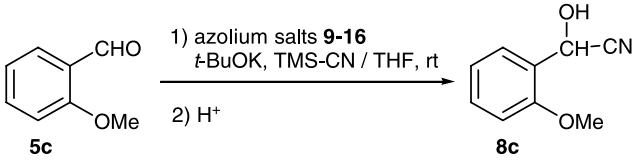
Table 1. Cyanosilylation of aldehydes catalyzed by 1,3-dibenzylimidazolidenyl carbene

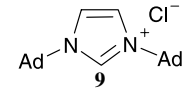
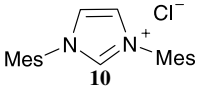
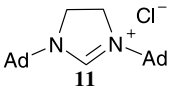
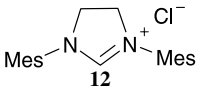
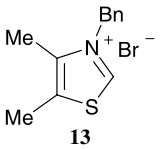
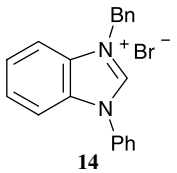
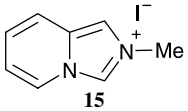
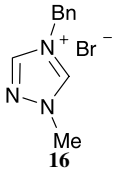


Entry	5	Time (h)	Yield (%)[a]
1	 **a**	2	80
2	 **b**	0.5	69
3	 **c**	0.5	93
4	 **d**	0.5	94
5	 **e**	3	85
6	 **f**	0.5	75
7	 **g**	0.5	77
8	 **h**	0.5	81
9	 **i**	0.5	65

[a] Isolated yield as a cyanohydrin.

Table 2. Cyanosilylation of *o*-methoxybenzaldehyde



Entry	Azolium salt	Time (h)	Yield (%)[a]
1	 **9**	8	85
2	 **10**	1.5	98
3	 **11**	8	65
4	 **12**	1.3	96
5	 **13**	20	59
6	 **14**	20	60
7	 **15**	2	82
8	 **16**	2	87

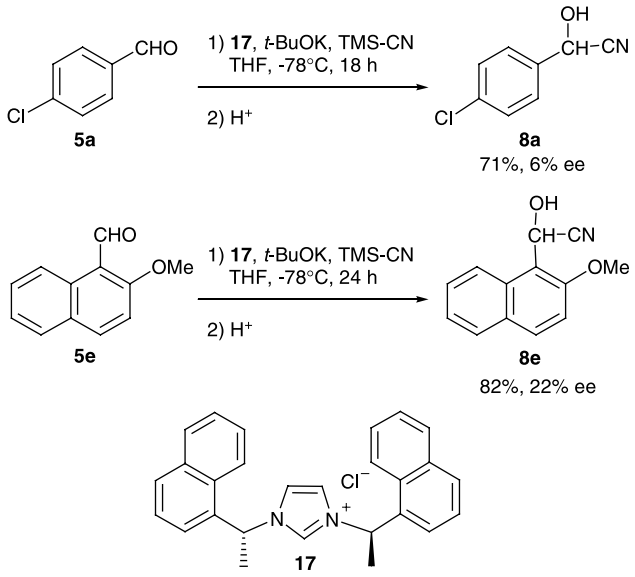
[a] Isolated yield as a cyanohydrin.

corresponding cyanohydrins **8b–i** in good yields (Table 1, entries 2–8).

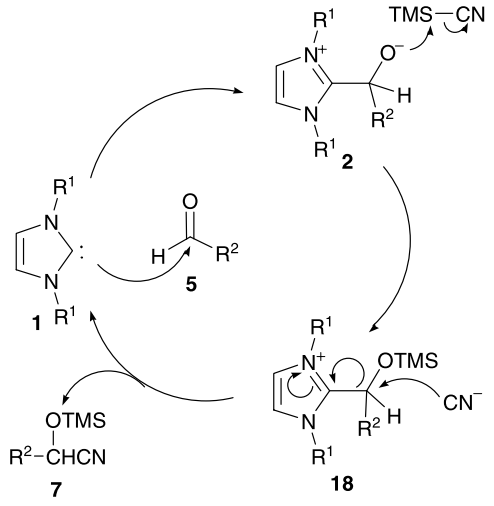
In the acylation reaction of alcohols, imidazolidinylidenes (derived from imidazolinium salts) were reported to exhibit less catalytic ability than imidazolinylidenes (derived from imidazolium salts).[10] To compare the catalytic abilities of imidazolidinylidenes and imidazolinylidenes, the cyanosilylation of *o*-methoxybenzaldehyde (**5c**) was examined using imidazolium and imidazolinium salts **9–12** with adamantyl and mesityl groups as *N*-substituents (Table 2, entries 1–4) because imidazolidinylidenes without bulky substituents gradually dimerize.[11] In contrast to the acylation of alcohols, the NHCs generated from imidazolium and imidazolinium chlorides with the same *N*-substituents exhibited comparable catalytic abilities in the cyanosilylation of **5c**.

The cyanosilylation of **5c** was also conducted by using other azolium salts **13–16** (Table 2, entries 5–8). The reaction rates were low and the yields were moderate with thiazolium salt **13** and benzimidazolium salt **14** (entries 5 and 6). Reactions with pyrido[1,2-*c*]imidazolium salt **15** and triazolium salt **16** produced cyanohydrin **8c** in good yields (entries 7 and 8).

Many reports have described asymmetric reactions catalyzed by chiral NHCs such as asymmetric benzoin condensation and the Stetter reaction.[9,12–15] The cyanosilylation of aldehyde **5a** was carried out in the presence of chiral NHC generated from imidazolium salt **17**[16] at −78 °C for 18 h (Scheme 2). Cyanohydrin **8a** was obtained with a yield



Scheme 2. Asymmetric cyanosilylation catalyzed by chiral NHC.

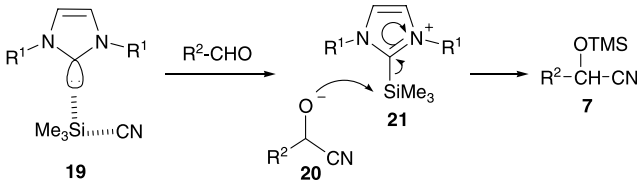


Scheme 3. Postulated reaction pathway.

of 71% and 6% ee. The reaction of **5e** at −78 °C for 24 h produced **8e** with a yield of 82% and 22% ee.

A possible reaction pathway of cyanosilylation is shown in Scheme 3. The formation of intermediate **2** has been widely accepted in NHCs' catalysis.[12,15b,17] Intermediate **2** reacts with TMS-CN to produce intermediate **18** and cyanide anion. The cyanide anion nucleophilically attacks a carbon atom (derived from aldehyde carbonyl carbon) of **18**. The imidazolium moiety of **18** acts as a leaving group, and nucleophilic substitution occurs to produce cyanohydrin silyl ether **7**. In the case of the chiral NHC, **1** added to **5** face selectively to produce diastereoisomeric intermediates **2** with an excess of a favored isomer.

It should be noted that an alternative catalytic mechanism possibly exists. In particular, the NHCs activate TMS-CN by coordination (Scheme 4). The chemical behavior of the NHCs is similar to those of tertiary amines and phosphines. All these species are used as ligands, nucleophilic reagents, and catalysts. Tertiary amines and phosphines catalyze the cyanosilylation of aldehydes by activating TMS-CN.[2] Mukaiyama et al. reported that the reaction of TMS-CN with cyclohexanecarboxyaldehyde in the presence of a catalytic amount of chiral amine, (+)-cinchonine, produced optically active cyanohydrin.[18]



Scheme 4. Alternative reaction pathway.

Song et al. reported NHC-catalyzed trifluoromethylation of carbonyl compounds.[19] They implied NHCs catalyze trifluoromethyl transfer by activation of trifluoromethyltrimethylsilane (TMS-CF_3). There are also two types of mechanism proposed for NHC-catalyzed transesterification. One mechanism involves a nucleophilic attack of NHC to a carbonyl carbon.[7] The other involves an activation of alcohols by NHCs.[20]

3. Conclusion

We have shown that the NHCs catalyze the cyanosilylation reaction between aldehydes and TMS-CN. In addition, we have proposed possible reaction mechanisms. One involves the nucleophilic addition of the NHCs to the carbonyl carbon atoms of aldehydes, followed by O-silylation and the replacement of an azolium moiety with a cyano group by S_N2 substitution. The other involves the activation of TMS-CN by coordination of NHCs. Although the optical yield was not satisfactory, the use of chiral NHC resulted in asymmetric cyanosilylation. Further investigations to clarify the reaction mechanism and increase optical yields in asymmetric cyanosilylation are in progress.

4. Experimental

4.1. General

Melting points are determined using a Yazawa Micro Melting Point Apparatus without correction. ^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra were recorded on a JEOL ECA-500 NMR spectrometer. IR spectra were recorded on a SHIMADZU IR Prestige-21. HRMS (FAB) spectra were recorded on a JEOL MStation JMS-700 mass spectrometer using *m*-nitrobenzyl alcohol as a matrix. Column chromatography was performed with Merck Silica Gel 60 and Silica Gel 60 N (spherical, neutral; Kanto Chemical Co., Inc.).

4.2. Typical procedure for cyanosilylation of aldehydes

To a suspension of azolium salt (0.05 mmol) in THF (2 mL), 1 M *t*-BuOK/THF (0.05 mmol) was added at room temperature, and the mixture was stirred for 30 min. Subsequently, the aldehyde (1 mmol) and TMS-CN (1.1 mmol) were added. This mixture was stirred at room temperature for the indicated time and then treated with dilute HCl. The crude product was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by silica gel chromatography using hexane/ethyl acetate as an eluent in order to produce cyanohydrin.

The enantiomeric excess of **8a**,**e** was determined by chiral HPLC analysis after the conversion to acetate.

4.2.1. 4-Chloromandelonitrile (8a).[21] Colorless granules (recrystallized from $CHCl_3$/hexane); Mp 35–37 °C; ^{1}H NMR ($CDCl_3$) δ: 3.16 (1H, br s, CHO*H*), 5.52 (1H, s, C*H*OH), 7.41 (2H, d, J=8.6 Hz), 7.46 (2H, d, J=8.6 Hz); ^{13}C NMR ($CDCl_3$) δ: 63.0, 118.5, 128.1, 129.5, 133.6, 136.1; IR (KBr) 2255 (CN), 3401 (OH) cm^{-1}.

4-Chloromandelonitrile, acetate: Analytical chiral HPLC: Chiralcel OD-H column, 0.46×25 cm, hexane–2-propanol (99/1), 0.5 mL min^{-1}; 21.5, 25.2 min.

4.2.2. 4-Methoxymandelonitrile (8b).[22] Colorless oil; ^{1}H NMR ($CDCl_3$) δ: 3.81 (3H, s, OCH_3), 5.44 (1H, s, C*H*OH), 6.92 (2H, d, J=4.6 Hz), 7.42 (2H, d, J=4.6 Hz); ^{13}C NMR ($CDCl_3$) δ: 55.5, 63.2, 114.5, 119.3, 127.8, 128.4, 160.6; IR (neat) 2245 (CN), 3414 (OH) cm^{-1}.

4.2.3. 2-Methoxymandelonitrile (8c).[22] Colorless granules (recrystallized from CH_2Cl_2/hexane); Mp 64–67 °C; ^{1}H NMR ($CDCl_3$) δ: 3.62 (1H, d, J=8.9 Hz, CHO*H*), 3.94 (3H, s, OCH_3), 5.56 (1H, d, J=8.9 Hz, C*H*OH), 6.97 (1H, d, J=8.6 Hz), 7.01 (1H, t, J=7.5 Hz), 7.38–7.42 (2H, m); ^{13}C NMR ($CDCl_3$) δ: 55.9, 60.4, 111.3, 119.0, 121.2, 123.8, 128.2, 131.3, 156.8; IR (KBr) 2251 (CN), 3377 (OH) cm^{-1}.

4.2.4. α-Hydroxy-1-naphthaleneacetonitrile (8d).[21] Yellow oil; ^{1}H NMR ($CDCl_3$) δ: 2.93 (1H, d, J=6.3 Hz, CHO*H*), 6.18 (1H, d, J=6.3 Hz, C*H*OH), 7.51 (1H, dd, J=8.0, 7.5 Hz), 7.57 (1H, dd, J=8.0, 6.9 Hz), 7.61–7.64 (1H, m), 7.83 (1H, d, J=7.5 Hz), 7.91 (1H, d, J=8.6 Hz), 7.94 (1H, d, J=8.0 Hz), 8.15 (1H, d, J=8.6 Hz); ^{13}C NMR ($CDCl_3$) δ: 62.2, 119.0, 123.0, 125.3, 125.8, 126.6, 127.5, 129.1, 130.0, 130.3, 131.0, 134.0; IR (neat) 2249 (CN), 3399 (OH) cm^{-1}.

4.2.5. α-Hydroxy-1-(2-methoxynaphthalene)acetonitrile (8e). Colorless needles (recrystallized from CH_2Cl_2/hexane); Mp 95–97 °C; ^{1}H NMR ($CDCl_3$) δ: 3.94 (1H, d, J=9.7 Hz, CHO*H*), 4.09 (3H, s, OCH_3), 6.34 (1H, d, J=9.7 Hz, C*H*OH), 7.32 (1H, d, J=9.2 Hz), 7.41–7.44 (1H, m), 7.58–7.61 (1H, m), 7.84 (1H, d, J=8.0 Hz), 7.94 (1H, d, J=9.2 Hz), 8.04 (1H, d, J=8.6 Hz); ^{13}C NMR ($CDCl_3$) δ: 56.6, 56.9, 112.9, 116.4, 119.3, 121.8, 124.5, 128.4, 129.1, 129.4, 130.8, 132.4, 155.6; IR (KBr) 2241 (CN), 3453 (OH) cm^{-1}; HRMS (FAB) Calcd for $C_{13}H_{11}NO_2$ (M^+): 213.0790, found: 213.0814.

α-Acetyloxy-1-(2-methoxynaphthalene)acetonitrile: colorless prisms (recrystallized from CH_2Cl_2/hexane); Mp 133–135 °C; ^{1}H NMR ($CDCl_3$) δ: 2.14 (3H, s, CH_3), 4.03 (3H, s, OCH_3), 7.28 (1H, d, J=9.2 Hz), 7.42–7.45 (1H, m), 7.53 (1H, s, C*H*OAc), 7.60–7.63 (1H, m), 7.83 (1H, d, J=8.0 Hz), 7.95 (1H, d, J=9.2 Hz), 8.25 (1H, d, J=8.6 Hz); ^{13}C NMR ($CDCl_3$) δ: 20.6, 55.1, 56.9, 112.2, 112.9, 116.9, 123.3, 124.4, 128.1, 129.0, 129.3, 131.8, 133.3, 155.6, 169.1; IR (KBr) 1749 (CO) cm^{-1}; HRMS (FAB) Calcd for $C_{15}H_{13}NO_3$ (M^+): 255.0895, found: 255.0875; Analytical chiral HPLC: Chiralcel OD-H column, 0.46×25 cm, hexane–2-propanol (98/2), 0.5 mL min^{-1}; 29.9, 40.3 min.

4.2.6. 2-Hydroxy-4-phenyl-3-butenenitrile (8f).[22] Pale yellow powder (recrystallized from CH_2Cl_2/hexane); Mp 71–74 °C; ^{1}H NMR ($CDCl_3$) δ: 2.65 (1H, d, J=6.3 Hz, CHO*H*), 5.17 (1H, t, J=6.3 Hz, C*H*OH), 6.26 (1H, dd, J=16.0, 6.3 Hz, olefinic H), 6.92 (1H, dd, J=16.0, 1.1 Hz, olefinic H), 7.30–7.40 (3H, m), 7.42 (2H, d, J=8.6 Hz); ^{13}C NMR ($CDCl_3$) δ: 62.0, 118.4, 122.3, 127.2, 129.0, 129.2, 134.8, 135.4; IR (KBr) 2253 (CN), 3358 (OH) cm^{-1}.

4.2.7. 2-Hydroxyoctanenitrile (8g).[23] Yellow oil; ^{1}H NMR ($CDCl_3$) δ: 0.87 (3H, t, J=6.9 Hz, Me), 1.24–1.38 (6H, m), 1.44–1.50 (2H, m), 1.81 (2H, q, J=6.9 Hz), 3.64 (1H, br s, CHO*H*), 4.44 (1H, t, J=6.9 Hz, C*H*OH); ^{13}C NMR ($CDCl_3$) δ: 14.1, 22.6, 24.6, 28.7, 31.6, 35.2, 61.3, 120.3; IR (neat) 2247 (CN), 3447 (OH) cm^{-1}.

4.2.8. 2-Cyclohexyl-2-hydroxyacetonitrile (8h).[21] Colorless oil; ^{1}H NMR ($CDCl_3$) δ: 1.01–1.28 (5H, m), 1.62–1.89 (6H, m), 3.87 (1H, br s, CHO*H*), 4.22 (1H, dd, J=6.3, 5.7 Hz, C*H*OH); ^{13}C NMR ($CDCl_3$) δ: 25.5, 25.5, 26.0, 27.9, 28.2, 42.2, 66.2, 119.6; IR (neat) 2245 (CN), 3435 (OH) cm^{-1}.

4.2.9. 2-Hydroxy-3,3-dimethylbutanenitrile (8i).[24] Yellow oil; ^{1}H NMR ($CDCl_3$) δ: 1.05 (9H, s, CH_3), 3.28 (1H, br s, CHO*H*), 4.11 (1H, s, C*H*OH). ^{13}C NMR ($CDCl_3$) δ: 25.0, 35.5, 70.6, 119.3.

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Reactivity and regioselectivity in the synthesis of spiroindoles via indole *o*-quinodimethanes. An experimental and computational study

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Abstract—The 1,3-dipolar cycloaddition reactions of stable nitrile oxides with indole *o*-quinodimethanes have been examined. In all cases the '*exo–anti*' addition products, dispiroisoxazolines, were isolated in moderate to good yields (25–47%). In addition, from the reaction of one of the indole quinodimethanes with mesitonitrile oxide the '*exo–syn*' addition product was isolated in 7% yield along with the remarkable indole quinodimethane dimerization and cycloaddition product, which was isolated in 13% yield. An analogous dimerization and cycloaddition product was isolated in 18% yield from the reaction of the *N*-acetyl-indole quinodimethane with mesitonitrile oxide. In the case of the reaction of the *N*-benzoylindole quinodimethane with the 2,6-dichlorobenzonitrile oxide an oxime was also isolated in 13% yield. The proposed reaction mechanism is supported by semiempirical (AM1) MO calculations via FMO interactions. The observed selectivity was explained by an investigation of the transition states carried out also for analogous dispiroisoxazolines.

1. Introduction

The chemistry of heterocyclic *o*-quinodimethanes (*o*-QDMs) has gained increasing interest in the last decade.[1] *o*-QDMs have been widely used as intermediates[2] in the synthesis of lignans,[3] terpenes, anthracyclines, alkaloids,[4] steroids and other natural products.[5–7] The study of their reactivity, applied in organic synthesis, is still an important issue.[1] However, although the utilization of *o*-QDM/Diels–Alder methodology in the synthesis of complex polycyclic compounds and the factors controlling the stereochemistry of the reaction have been studied extensively,[1,8] the 1,3-dipolar nitrile oxide cycloaddition to *o*-QDMs and moreover the 1,3-dipolar cycloaddition reactions with 1,3-dienes are rare.[9] To our knowledge, the only example of 1,3-dipolar cycloaddition to *o*-QDMs leading to spiro derivatives has been reported by us.[10]

Against this background, we have explored the reactivity of the stable nitrile oxides mesitonitrile oxide and 2,6-dichlorobenzonitrile oxide towards indole *o*-quinodimethanes speculating the formation of new spiroindoles, since spiroindole derivatives show interesting biological activities.[11–13] Our results revealing the facile formation of novel spiroindoles are presented here along with a reactivity and regioselectivity investigation of the reaction.

2. Results and discussion

The *N*-substituted 2,3-bis(bromomethyl)indoles **2** were synthesized by known procedures.[14,15] From these bisbromides **2** by treatment with sodium iodide in DMF at 150 °C the corresponding indole quinodimethanes **3** were generated in situ and were trapped with 2 mol equiv of nitrile oxide to afford moderate to good yields (31–47%) of products, by addition to the two exomethylenic double bonds (Scheme 1). In all cases the '*exo–anti*' dispiroindoles **5** were isolated (20–46% yield). It is of interest to note that from the reaction of the indole *o*-quinodimethane **3a** with mesitonitrile oxide the '*exo–syn*' dispiroindole **6a** was also isolated (7% yield) along with a third product, the dispiroindole compound **7a** in 13% yield. This very interesting product is most probably produced by 1,3-dipolar cycloaddition of a mesitonitrile oxide molecule to the exomethylene double bond $C_2{=}CH_2$ followed by the [4+2] cycloaddition of *o*-QDM to the remaining exomethylene double bond (see Section 2.2). An analogous product **7b** was isolated in 18% yield from the reaction of QDM **3b** with **4a**.

Keywords: Spiroindoles; *o*-Quinodimethanes; Diels–Alder reactions; Reactivity; Regioselectivity.
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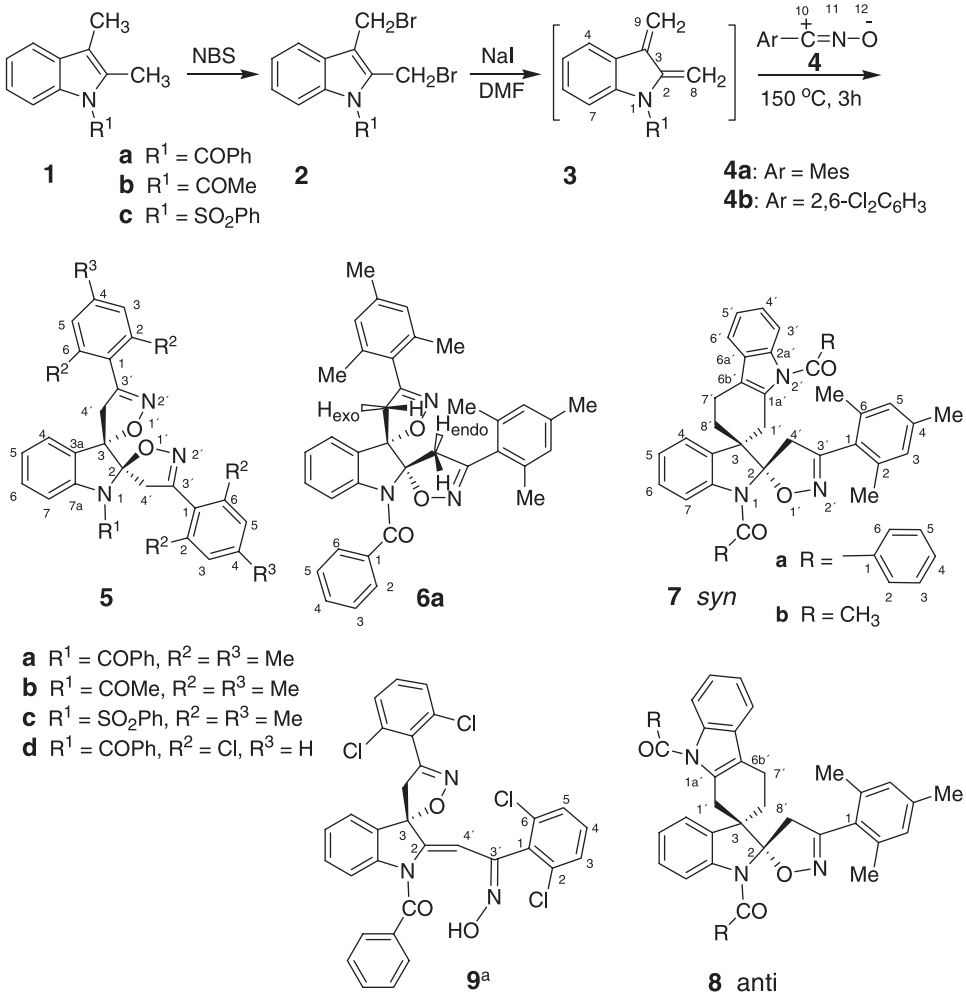


[a] The numbering of the substituent at C-2 is set analogously to the other derivatives.

Scheme 1. Preparation of *o*-QDMs **3**, their reaction with the stable nitrile oxides **4** and atom numbering at the reaction sites and the products **5**–**9**.

It is also worth mentioning that an exomethylenic dimeric [4+2] product was always isolated from the reaction of *N*-benzoyl indole *o*-quinodimethane with less reactive dienophiles.[16] Finally, from the reaction of quinodimethane **3a** with 2,6-dichlorobenzonitrile oxide, the oxime **9** was isolated in 13%, instead of the '*exo–syn*' dispiroindole.

2.1. Structure assignments by NMR spectra investigations

The assigned molecular structures of all new compounds **5**–**9** are based on rigorous spectroscopic analysis including IR, NMR (^{1}H, ^{13}H, COSY, NOESY, HETCOR and COLOC), MS and elemental analysis data.

Regarding the structure of the *anti* dispiroindoles **5** the assignment of **5a** is described. From the molecular ion at *m*/*z* 570 (corresponding to $M^+ + 1$) the conclusion could be drawn that **5a** is produced from the reaction of one molecule of **3a** with two molecules of mesitonitrile oxide, a fact that was also confirmed from the ^{13}C NMR spectrum where 29 different signals were observed (Table 1). Furthermore, from the C–H correlated spectrum in the saturated region, the presence of six mesito methyl groups, of two methylene groups with their carbons at 42.5 and 45.3 ppm and of two quaternary carbons at 92.1 and 107.4 ppm, connected with one and two heteroatoms, respectively, was established thus leading to the conclusion that a dispiroisoxazolinic indole derivative was formed.

Concerning the indole ring aromatic protons, COLOC correlations of the proton at δ 7.07 with the quaternary carbon at 130.9 ppm and of the proton at δ 7.46 with the quaternary carbon at 141.9 ppm and with CH carbon at 129.7 ppm were found. The first methylene group protons (δ 3.48 and 4.24) correlate with carbon at 158.0, whereas only the proton at δ 3.48 correlates with carbon at 130.9 ppm, indicating the position of methylene group (3-C4′) and the *exo* orientation of this proton, being coplanar with C-3a. The second methylene group protons (δ 3.91 and 4.07) correlate with carbon at 158.9. In addition, the correlation between proton at δ 4.07 and carbon at 92.1 ppm indicates the *endo* orientation of this proton. The *endo–exo* orientation of the methylene protons refers towards or in reverse to the neighbor isoxazoline ring (Scheme 1). The *o*-aromatic protons of CO-Ph group are deshielded (δ 7.70) and are easily distinguished from the rest of the aromatics. The COSY and COLOC correlations of these protons with the

Table 1. ^{1}H, ^{13}C and COLOC NMR data for compound **5a**

Position[a]	C	H[b]	COLOC[c]
2	107.4		
3	92.1		
3a	130.9		
4	123.6	7.46 (d, 7.8)[d]	141.9, 129.7
5	124.2	7.07 (m)[d]	130.9
6	129.7	7.00 (m)[d]	123.6
7	115.3	6.05 (d, 7.6)	
7a	141.9		
1-(CO)	168.7		
1-(1)	135.5		
1-(2,6)	128.8	7.70 (m)	168.7, 132.1
1-(3,5)	128.9	7.45 (m)[d]	135.5
1-(4)	132.1	7.57 (m)	128.8
2-(3′)	158.9		
2-(4′)	42.5	4.07 (d, 18.8)[e]	158.9, 92.1
		3.91 (d, 18.8)	158.9
2-(1)[f]	125.3		
2-(2,6)	137.7		
2-(3,5)	128.9	6.92 (s)	125.3, 21.1, 20.6
2-(4)	139.3		
2-(Me-2,6)	20.6	2.48 (s)	137.7, 128.9
2-(Me-4)	21.1	2.32 (s)	139.3, 128.9
3-(3′)	158.0		
3-(4′)	45.3	4.24 (d, 18.8)[e]	158.0, 92.1
		3.48 (d, 18.8)	158.0, 130.9
3-(1)[f]	125.2		
3-(2,6)	136.9		
3-(3,5)	128.9	6.95 (s)	125.2, 21.1, 20.3
3-(4)	139.0		
3-(Me-2,6)	20.3	2.38 (s)	136.9, 125.2, 128.9
3-(Me-4)	21.1	2.30 (s)	139.0, 128.9

[a] For carbon numbering see Scheme 1. The first number refers to indole ring position, the number in parenthesis refers to the substituent.
[b] Multiplicities and coupling constants (in Hertz) in parentheses.
[c] Long range ($^{2}J_{C-H}$ and $^{3}J_{C-H}$) correlations between the protons on the left and the carbons stated on this column.
[d] Overlaped multiplets, distinguished by homo- and hetero-COSY.
[e] In the order of *endo*, *exo* orientation.
[f] The mesito groups may be interchanged.

rest of aromatic protons and carbons lead to their assignment (Table 1). The two singlets at δ 6.92 and 6.95 belong to mesito groups and correlate with the aromatic and methyl carbons. By combination of these data the carbon sequence given in Scheme 1 for compound **5a** can be proposed.

In an analogous manner the structure assignment of the '*syn*' dispiroindole derivative **6a** was possible.

The assignment of **5a** to the'*exo–anti*' and of **6a** to the '*exo–syn*' addition product, respectively, was made in conjunction with the crystallographic results obtained[10] in the case of dispiroisoxazoline derivatives **12** and **13** (Scheme 2), where by analogy to **12**, the isomer, which is faster moving on TLC with a lower melting point corresponds to the '*exo–anti*' addition product **5a**.

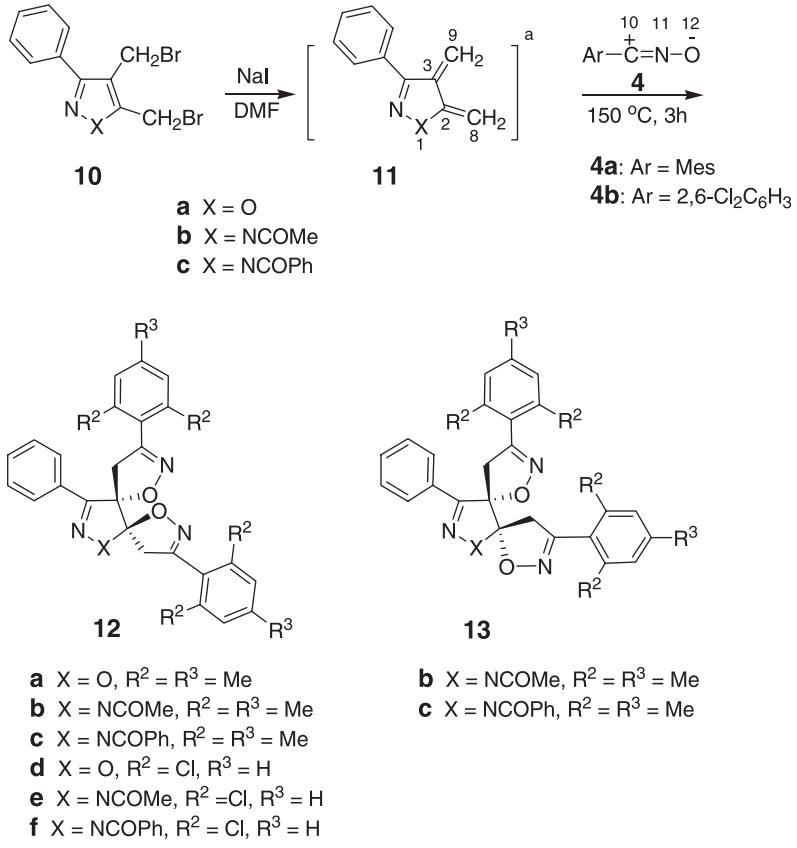
Concerning the assignment of the dispiro derivative **7a** it was supported by the following data. The molecular ion at *m/z* 655 indicated the presence of two molecules of indole quinodimethane reacting with one molecule of mesitonitrile oxide. This was confirmed from the C–H correlated spectrum, where in the saturated region four methylene groups with their carbons resonating at 18.3, 27.9, 29.6 and 39.7, three methyl groups at 20.8 and 21.1 ppm (2:1) and two quaternary carbons at 50.7 and 110.5 ppm were observed. The quaternary carbon at 110.5 ppm, the methylene carbon at 39.7 ppm and the quaternary carbon at 157.3 could be attributed to a spiro isoxazoline ring, most likely formed from the quinodimethane exomethylene group next to the nitrogen, on account of the analogous chemical shifts observed for **5a** and **6a** (see also Section 2.2). In addition, the COLOC correlations observed between the carbon resonating at 157.3 ppm with the methylene group protons (δ 3.50 and 4.10) and between the carbon at 110.5 ppm with the methylene proton at δ 4.10 supported the formation of this isoxazoline ring.

Concerning the three remaining methylene groups, the one with its carbon at 27.9 ppm gave a very narrow AB system ($\nu_A = 3.24$, $\nu_B = 3.27$, $J_{AB} = 18.4$ Hz), whereas the remaining two at 29.6 and 18.3 ppm gave a complicated NMR spectrum thus indicating their vicinity.[17] Obviously, the methylene group with its carbon resonating at 29.6 ppm should be assigned to C-7′ next to aromatic indole ring. Moreover, all three methylene group protons gave COLOC correlations with carbon at 117.5 ppm. From these COLOC data the conclusion could be drawn that the second exomethylene group was used for the formation of a [4+2] *o*-quinodimethane dimmer creating thus the cyclohexene ring of compound **7** or **8**, from *syn* or *anti* approaching of the QDM moiety excluding thus all other possible adducts.

Finally, the assignment of oxime **9** was possible on account of the following data. From the combination of the molecular ion in mass spectrum with the 25 different carbon signals in the ^{13}C NMR, it was concluded that compound **9** was formed from one molecule of **3a** with two molecules of 2,6-dichlorobenzonitrile oxide. Furthermore, from the C–H correlated spectra in the saturated region the presence of only one methylene group and of a quaternary carbon at 88.2 ppm indicated the formation of only one isoxazoline ring. In addition, the methylene group protons gave COLOC correlations with the quaternary carbons at 156.2, 171.4, 128.7 and 88.2, whereas the indole ring proton at δ 7.42 is correlated with the quaternary carbon at 136.3 indicating thus the position of the isoxazoline ring. Concerning the addition of the second nitrile oxide molecule, the presence in the infrared spectrum of a hydroxyl at 3390 cm^{-1}, of a quaternary carbon at 171.4 ppm and of a proton at δ 6.45 (with its carbon resonating at 105.2 ppm), correlating with carbons at 171.4 and 159.1 ppm, led us to the structure **9**. Moreover, this structure was supported by the presence of a hydrogen bond between the hydroxyl proton at δ 9.27 and the amide oxygen (*N*–C=O at 165.3 ppm), as was revealed from their COLOC correlation. The stabilization of the COPh conformation, almost perpendicular to the indole ring, due to this hydrogen bond results to the very low field shift (δ 8.26) of indole proton H7 (Fig. 5).

2.2. Computational methods

Searching for the stereoselectivity reasons and since the X-ray crystallographic data for the quinodimethane adducts of **11** were available,[10] we attempted to investigate the reactions of *o*-QDMs **3** and **11** with mesito- and 2,6-dichlorobenzonitrile oxides (**4**) by studying the FMO



[a] The carbon numbering is analogous to QDM **3**.

Scheme 2. Preparation of *o*-QDMs **11** and their reaction with the nitrile oxides **4**.

interactions and the transition structures of the intermediates (AM1).

Experimentally, the *exo* addition products were isolated from the reaction of *o*-QDMs **3a–c** and **11a–c** with the nitrile oxides **4a–b**. We take for granted that the initial formation of the diene moiety is synchronous. In order to investigate the '*endo–exo*' and '*syn–anti*' addition selectivity of nitrile oxides to the two exomethylenic groups, the transition structures (TS) of the successive adducts at bonds $C_2{=}C_8$ and $C_3{=}C_9$ were located and examined in connection with HOMO–LUMO interactions of the reactants. Full geometry optimizations were carried out for nitrile oxides **4** and *o*-QDMs **3** and **11** as well as for the possible adducts at the AM1 level of theory. For each located TS after complete optimization only one negative eigenvalue was calculated corresponding to one imaginary frequency about 600–620 cm^{-1} and assigned to the new forming bonds[18] at methylene carbons C-8 or C-9. In Table 2 are presented the calculated HOMO–LUMO energies and the orbital coefficients (eigenvectors) for the atoms involved in the [2+3] cycloaddition reaction.

According to FMO interactions the additions of nitrile oxides **4a** and **4b** to *o*-QDMs **3** (Fig. 1) and **11** are predicted to be $HOMO_{(QDM)}$–$LUMO_{(dipole)}$ controlled, except in the case of QDM **11a**, where the addition of mesitonitrile oxide is predicted to be $HOMO_{(dipole)}$ controlled. The opposite attacking process is predicted to be energetically disfavored by 17.89 and 40.75 kcal/mol for **4a** and **4b**, respectively (Table 3). Looking at the $\Delta E(L_{dipole})$ values in Table 3, we notice that in all cases there is a difference of ~0.5 eV (~11.5 kcal/mol) favoring the reaction with nitrile oxide **4b**, validating the argument that **4b** is more reactive than **4a**.

In order to examine the *exo* selectivity of the reaction we carried out AM1 calculations for locating the TS for *exo* and *endo* addition of both nitrile oxides **4** to compound **3a** (Figs. 2 and 3). From Figure 2 it is observed that the new forming bond C_8–C_{10} (or C_9–C_{10}) is shorter than the second one C_2–O_{12} (or C_3–O_{12}) supporting the hypothesis of great asynchronicity in the above dipolar cycloaddition. In the case of *exo* approaching of **4a** to **3a** the C_8–C_{10}-Ar angle was calculated to be 109.1° in **TS1** and the C_9–C_{10}-Ar angle 111.2° in **TS2**, whereas for the *exo* approaching of **4b** to **3a** the corresponding angles were calculated to be 107.4° (**TS3**) and 110.4° (**TS4**), respectively. To the contrary, in *endo* approaching of **4a** to $C_2{=}C_8$ bond of **3a** the C_2–C_{10}-Ar angle was increased to 122.0° (**TS5**) and to $C_3{=}C_9$ bond the C_3–C_{10}-Ar angle was increased to 121.8° (**TS6**). Analogous angle increase was calculated for **4b** approach (**TS7–TS8**) revealing an increasing Van der Waals interaction. In addition, the $\Delta\Delta H^{\#}$ differences between the corresponding activation energies of *endo–exo* TS is 8.42 and 2.54 kcal/mol for the reaction of **3a** with **4a** at $C_2{=}C_8$ and $C_3{=}C_9$, respectively, and 8.50 and 4.46 kcal/mol for the reaction of **3a** with **4b** (Figs. 2 and 3). The energy differences between the $C_2{=}C_8$ and $C_3{=}C_9$ approaches can be attributed mostly to the Van der Waals interaction of CO-Ph substituent of **3a**. The energy profiles of the reactions are depicted in Figure 4.

Table 2. Calculated HOMO–LUMO energies (eV) and orbital coefficients (eigenvectors) for the atoms involved in new bond formations[a] for the reaction of *o*-QDMs **3a–c** and **11a–c** with nitrile oxides **4a** and **4b** (in gas phase at 298 K, AM1)

Comp.	HOMO	LUMO
3a	−8.396[b]	−0.328
C-8	0.4242[c]	0.2708
C-2	0.2163	−0.1508
C-3	−0.1838	−0.2996
C-9	−0.3646	0.4812
3b	−8.468	−0.381
C-8	−0.4263	−0.2654
C-2	−0.2267	0.1422
C-3	0.1910	0.2954
C-9	0.3713	−0.4798
3c	−8.646[b]	−0.391[d]
C-8	−0.4052	0.3329
C-2	−0.1987	−0.2116
C-3	0.2128	−0.3145
C-9	0.3933	0.5025
11a	−9.066	−0.652
C-8	0.4461	−0.3705
C-2	0.2518	0.2187
C-3	−0.2278	0.3085
C-9	−0.3929	−0.5134
11b	−8.598[b]	−0.590
C-8	−0.4664	0.2931
C-2	−0.2466	−0.1539
C-3	0.1812	−0.2654
C-9	0.3618	0.4565
11c	−8.602	−0.580
C-8	−0.4610	0.2793
C-2	−0.2435	−0.1475
C-3	0.1821	−0.2628
C-9	0.3617	0.4510
4a	−9.053[b]	−0.447
C-10	−0.3114	−0.2249
N-11	−0.2572	0.3454
O-12	0.4368	−0.2114
4b	−9.548	−0.943
C-10	0.3826	−0.1833
N-11	0.2637	0.3274
O-12	−0.4947	−0.2097

[a] For atom numbering of the diene moiety and nitrile oxides see Scheme 2.
[b] HOMO–LUMO energies (eV).
[c] Orbital coefficients (eigenvectors).
[d] NN–LUMO.

For the same type of reactions at the same temperature the factor $T\Delta S^{\#}$ is approximately the same, so $\Delta\Delta H^{\#}$ differences could be referred to as the $\Delta\Delta G^{\#}$ differences for Gibbs free energies of the TS.

Studying the MO coefficients in Table 2 the first attacking position of nitrile oxides can be predicted. The p_z orbital coefficients for the $C_2{=}C_8$ atoms of the reacting double bond of QDMs **3** and **11** are larger than those of the $C_3{=}C_9$ atoms. As a consequence, the $C_2{=}C_8$ bond most probably should be the first target for nitrile oxide addition. By examination of the corresponding TS for the reaction at the two different double bonds the same conclusion is extracted, since the addition at $C_2{=}C_8$ bond has 3.72 kcal/mol lower activation energy than the corresponding addition at $C_3{=}C_9$ bond (Fig. 4). This energy difference gives via the Boltzmann distribution equation a ratio of 536:1 preference at $C_2{=}C_8$ over $C_3{=}C_9$ (C_2/C_3) for a kinetically controlled reaction. An analogous preference for $C_2{=}C_8$ addition is predicted for all cycloadditions as presented in Table 4. For compound **3c** the preference for the first addition is reduced to 79:1. This can be attributed to the orientation of the N–SO_2-Ph group perpendicularly to the indole ring, so the approach to both double bonds is undisturbed from the opposite site of indole ring.

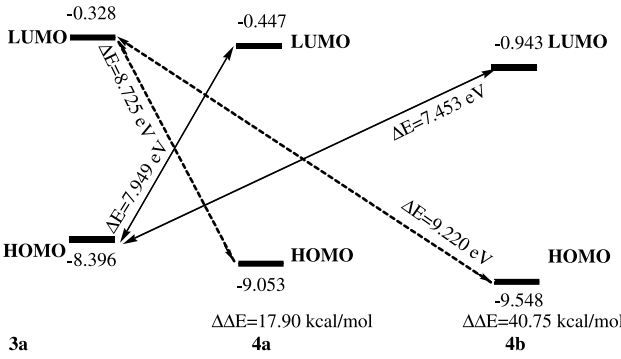


Figure 1. Molecular orbital correlation diagram for the interaction of *o*-QDM **3a** with the stable nitrile oxides **4a** and **4b**.

Concerning the *syn*/*anti* addition of the second nitrile oxide molecule at $C_3{=}C_9$ bond the energies and activation parameters for the transition structures have been calculated and presented in Table 5. From the $\Delta\Delta H^{\#}$ values a slight preference of *anti* over *syn* addition is always predicted for kinetically controlled reactions. The nitrile oxide **4b** is reactive enough to follow this reaction path and tries to approach and react to both reaction sites almost simultaneously, the *syn* approaching, however, being stereochemically disfavored. In agreement with this theoretical study, experimentally only the *anti* final products were isolated (Table 6). Nevertheless, from the reaction of **3a** with **4b** compound **9** was also isolated, possibly produced by almost simultaneous *syn* addition of two molecules of **4b** at reaction sites $C_2{=}C_8$ and $C_3{=}C_9$, respectively. As we noticed before, there is a great asynchronicity in the formation of the bonds C_8–C_{10} and C_2–O_{12} (see Fig. 2, **TS1**). Before the isoxazoline ring closure is completed at $C_2{=}C_8$ a second molecule of **4b** reacts at $C_3{=}C_9$, with *syn* or *anti* addition, since the energy difference between them is practically negligible. In the $C_3{=}C_9$ *syn* adduct, the bulky substituent at C-8 cannot be accommodated easily and fast between the two other substituents and finally oxygen abstracts, possibly via a free radical process, a hydrogen atom from the nearby methylene group giving the oxime **9**, depicted in Figure 5, which is 5.4 kcal more stable than the corresponding bis adduct **6d**.

Table 3. Energy differences for the various HOMO–LUMO interactions between quinodimethanes (**3a–c** and **11a–c**) and nitrile oxides **4a–b** (in gas phase at 298 K, AM1)

Reaction with			4a			4b		
QDM	HOMO	LUMO	$\Delta E(L_{dipole})$[a]	$\Delta E(H_{dipole})$	$\Delta\Delta E$[b]	$\Delta E(L_{dipole})$	$\Delta E(H_{dipole})$	$\Delta\Delta E$
3a	−8.396	−0.328	7.949	8.725	17.89	7.453	9.220	40.75
3b	−8.468	−0.381	8.021	8.672	15.01			
3c	−8.646	−0.391	8.199	8.662	10.68			
11a	−9.066	−0.652	8.619	8.401	−5.03	8.123	8.896	17.83
11b	−8.598	−0.590	8.151	8.463	7.19	7.655	8.958	30.05
11c	−8.606	−0.579	8.159	8.474	7.26	7.663	8.969	30.12

[a] $\Delta E(L_{dipole}) = E(LUMO_{dipole}) - E(HOMO_{QDM})$; $\Delta E(H_{dipole}) = E(HOMO_{dipole}) - E(LUMO_{QDM})$, (in eV/mol).
[b] $\Delta\Delta E = \Delta E(H_{dipole}) - \Delta E(L_{dipole})$, (in kcal/mol, 1 eV = 23.06 kcal/mol).

On the other hand, since the nitrile oxide **4a** is less reactive than **4b**, there is enough time to accommodate the groups of substituents after the first addition in $C_2{=}C_8$ bond. As a result, the second nitrile oxide molecule can approach from both sites giving '*exo–syn*' and '*exo–anti*' addition products. Considering the thermodynamics of the reaction and since reaction times were prolonged and therefore the reactions were thermodynamically controlled, the $\Delta\Delta H^o$ values of '*exo–syn*' and '*exo–anti*' addition products should also be taken into consideration. From the $\Delta\Delta H^o$ values given in Table 5 a small preference of '*exo–anti*' over '*exo–syn*' addition can be anticipated. In connection with the previous aspect of monoproduct accommodation both *syn* and *anti* products are derived. Experimentally, this was observed in the case of the QDMs **3a**, **11b** and **11c**. However, in the case of QDMs **3c** and **11a**, because of the higher values of $\Delta\Delta H^{\#}$ and (or) $\Delta\Delta H^o$ (Table 5a), '*exo–anti*' products were only isolated (Table 6).

Although we did not take into account the solvent effect, the above results show a good approximation with the experimental ones. In all computations presented in Table 5 the approaching of nitrile oxide **4a** takes place to the fully relaxed and energy minimized monoadduct, a situation that most probably is true only in the case of **4a**. Moreover, the formation of product **7** supports the prediction that the cycloaddition begins at $C_2{=}C_8$ followed by the addition of a second molecule of *o*-QDM at $C_3{=}C_9$. This is a consequence of the smaller reactivity of the nitrile oxide **4a** in comparison to **4b**.

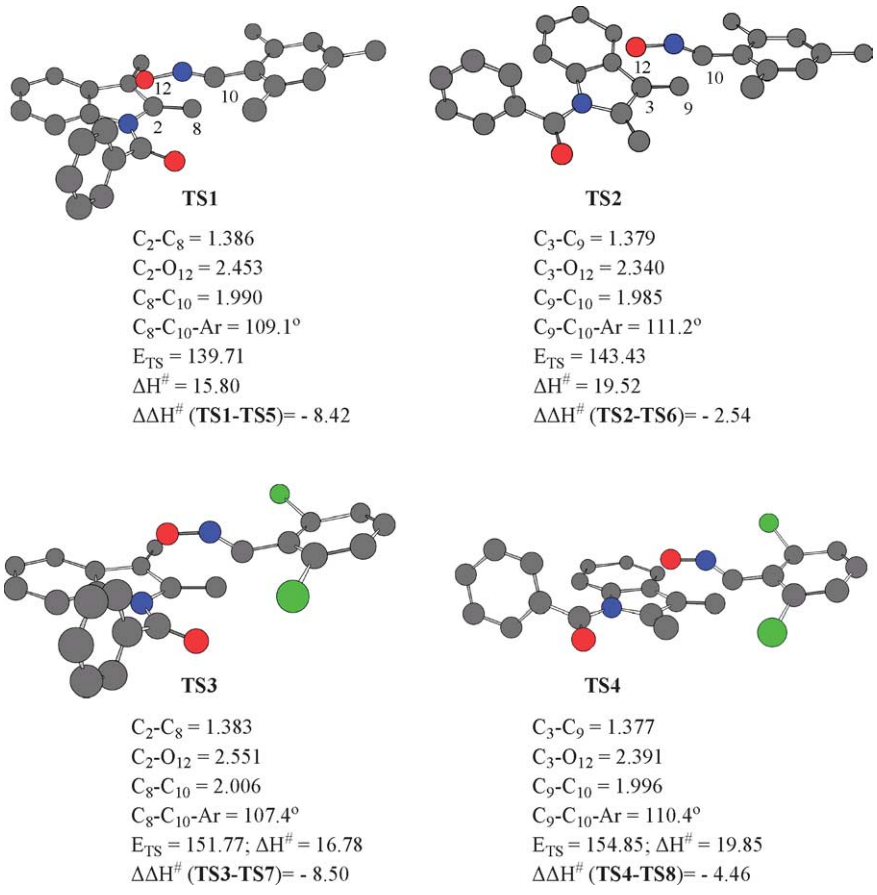


Figure 2. *exo* Transition structures optimized at AM1 level for the interaction of *o*-QDM **3a** with the stable nitrile oxides **4a** (**TS1**, **TS2**) and **4b** (**TS3**, **TS4**) at $C_2{=}C_8$ and at $C_3{=}C_9$ double bonds. $\Delta\Delta H^{\#}$ is the difference of $\Delta H^{\#}$ between the *exo* and *endo* approaching in the TS (see also Fig. 3). All bond lengths are in angstroms (Å), bond angles in degrees (°), energies in kcal/mol. For the numbering of reacting atoms see Scheme 1.

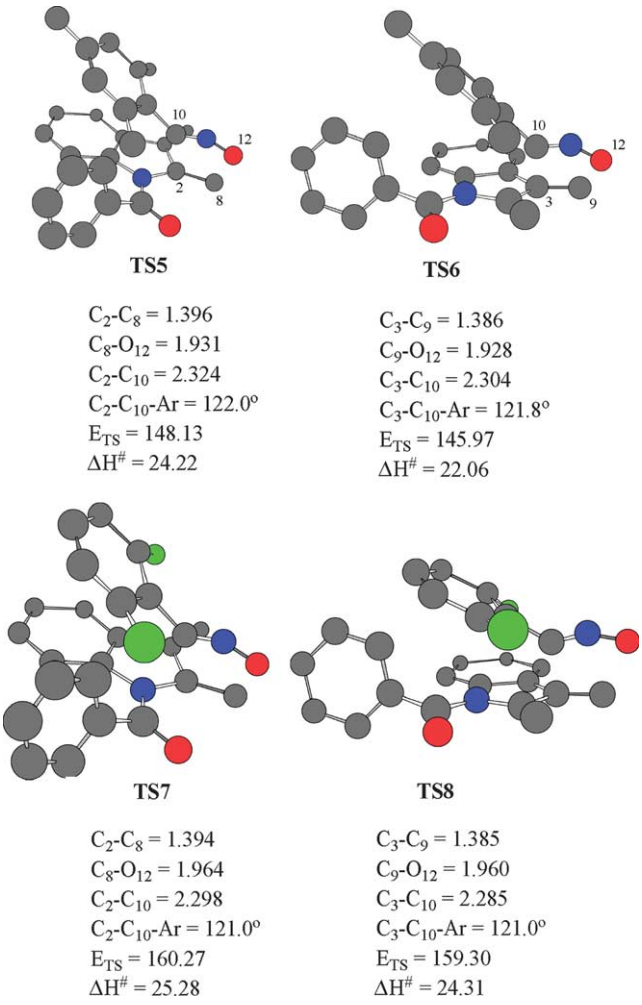


Figure 3. *endo* Transition structures for the interaction of *o*-QDM **3a** with the stable nitrile oxides **4a** and **4b** at C_2=C_8 and C_3=C_9 double bonds (AM1).

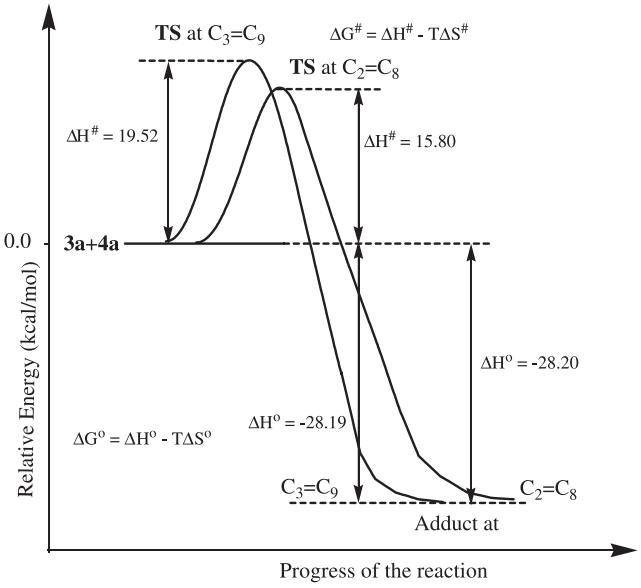


Figure 4. Reaction coordinate diagram of potential energy surface for the reaction **3a**+**4a** (*exo* monoadduct) at the two reaction sites C_2=C_8 and C_3=C_9 (energies in kcal/mol).

3. Conclusion

In conclusion, we have studied the reaction of some indole *o*-quinodimethanes with stable nitrile oxides **4**. Although these nitrile oxides are short lived at high temperatures and comparatively less reactive, it is remarkable that they reacted with the transient intermediate indole *o*-quinodimethanes giving in all cases the otherwise inaccessible *anti* indole dispiroisoxazolines, as the main or the only reaction products. In the case of reaction of quinodimethane **3a** with **4a** the '*exo–syn*' dispiroisoxazoline **6a** was also formed, whereas with **4b** the oxime **9** was isolated as a final product instead of **6d**. The very interesting indole quinodimethane dimerization and cycloaddition products **7** were also isolated. For all new compounds full assignment of proton and carbon NMR chemical shifts was achieved.

AM1 MO calculations support the experimental results concerning the '*endo–exo*' and '*syn–anti*' preference. The regioselectivity of the reactions is in accordance with the regioselectivity reported for the additions of nitrile oxides to 1,1-disubstituted alkenes.[19] The first nitrile oxide approaches the C_2=C_8 group freely from both sites only in *exo* configuration. The second nitrile oxide moiety approaches the C_3=C_9 bond preferentially in '*exo–anti*' configuration to the previously inserted group, as it was concluded from the X-ray structures[10] of adducts **12** and **13**.

4. Experimental

4.1. General

Melting points were measured on a Kofler hot-stage and are uncorrected. Column chromatography was carried out using Merck silica gel. Petroleum ether refers to the fraction boiling between 60 and 80 °C. NMR spectra were recorded at rt on a Bruker AM 300 spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C, respectively, using $CDCl_3$ as solvent. Chemical shifts are expressed in δ values (ppm) relative to TMS as internal standard for ^{1}H and relative to TMS (0.00 ppm) or to $CDCl_3$ (77.05 ppm) for ^{13}C NMR spectra. Coupling constants ^nJ are reported in Hertz. IR spectra were recorded on a Perkin-Elmer 297 spectrometer and are reported in wave numbers (cm^{-1}). Low-resolution electron impact mass spectra (EIMS) were obtained on a VG TS-250 instrument and elemental analyses performed with a Perkin-Elmer 2400-II CHN analyzer. Structural assignments of the derived compounds were established by analysis of their IR, MS and NMR spectra (^{1}H, ^{13}C, COSY, NOESY, HETCOR and COLOC). The MO calculations for minimum energy conformation of compounds were computed with the AM1 method as implemented in the MOPAC package[20] version 6.3. All stationary points were refined by minimization of the gradient norm of the energy to at least 0.005 kcal/mol. The ^{13}C and ^{1}H NMR data of compounds **5b–d**, **6a**, **7a–b** and **9** are summarized and presented also for comparison in Tables S1 and S2 as supplementary data in supporting information.

Table 4. Calculated energies of formation ΔH_f[a] and activation parameters for the *exo* transition structures and products for the reactions of *o*-QDMs **3a–c** and **11a–c** to form monoadduct: (a) with mesitonitrile oxide and (b) with 2,6-dichlorobenzonitrile oxide (in gas phase, 298 K, AM1)

	Addition at C_2=C_8					Addition at C_3=C_9					
QDM	$\Sigma\Delta H_{f(r)}$	$\Delta H_{f(p)}$	ΔH^{o}[b]	E_{TS}[c]	$\Delta H^{\#}$[d]	$\Delta H_{f(p)}$	ΔH^{o}	E_{TS}	$\Delta H^{\#}$	$\Delta\Delta H^{\#}$[e,f]	C_2/C_3[g]
(a)											
3a	123.91	95.71	−28.20	139.71	15.80	95.72	−28.19	143.43	19.52	−3.72	536
3b	87.69	59.55	−28.14	104.37	16.68	59.55	−28.14	107.26	19.58	−2.90	134
3c	89.45	63.49	−25.96	107.47	18.02	61.85	−27.60	110.06	20.61	−2.59	79
11a	135.36	97.98	−37.38	152.11	16.75	107.37	−27.99	155.93	20.58	−3.83	645
11b	128.20	99.86	−28.34	144.34	16.14	99.26	−28.94	147.99	19.79	−3.65	476
11c	164.77	136.62	−28.15	180.98	16.21	135.94	−28.83	184.92	20.50	−4.29	1404
(b)											
3a	134.99	107.07	−27.92	151.77	16.78	105.87	−29.12	154.85	19.86	−3.08	182
11a	146.44	108.23	−38.21	163.65	17.21	117.42	−29.02	167.42	20.98	−3.77	583
11b	139.28	111.16	−28.12	156.71	17.43	109.38	−29.90	159.46	20.18	−2.75	104
11c	175.85	147.94	−27.91	193.28	17.43	146.06	−29.79	196.46	20.61	−3.18	215

[a] ΔH_f for the reactants (in kcal/mol): **3a**=81.33; **3b**=45.11; **3c**=46.87; **11a**=92.78; **11b**=85.62; **11c**=122.19; **4a**=42.58; **4b**=53.66.
[b] $\Delta H^{o}=\Delta H_{f(p)}-\Sigma\Delta H_{f(r)}$, where $\Sigma\Delta H_{f(r)}=\Delta H_{f(n.o)}+\Delta H_{f(QDM)}$,(r=reactants, p=products, n.o=nitrile oxide).
[c] E_{TS} is the calculated ΔH_f for the transition state.
[d] $\Delta H^{\#}=E_{TS}-\Sigma\Delta H_{f(r)}$.
[e] $\Delta\Delta H^{\#}=\Delta H^{\#}_{(\text{adduct at } C_2=C_8)}-\Delta H^{\#}_{(\text{adduct at } C_3=C_9)}$ is the relative activation energy.
[f] A negative value means a more stable TS at C_2=C_8 and the corresponding adduct is favored kinetically.
[g] C_2/C_3 is the relative calculated ratio of adducts at C_2=C_8 versus C_3=C_9 by the Boltzmann equation for equilibrium distribution.

Table 5. Calculated energies ΔH_f and activation parameters for the transition structures for the reactions of monoadducts of *o*-QDMs **3** and **11** at C_2=C_8 with a second molecule of (a) mesitonitrile oxide and (b) 2,6-dichlorobenzonitrile oxide in *exo–syn* and *exo–anti* configuration (in gas phase, at 298 K, AM1)[a]

QDM	$\Sigma\Delta H_{f(r)}$	$\Delta H_{f(p)}$	ΔH^{o}	E_{TS}	$\Delta H^{\#}$	$\Delta H_{f(p)}$	ΔH^{o}	E_{TS}	$\Delta H^{\#}$	$\Delta\Delta H^{ob}$	$\Delta\Delta H^{\#c}$
(a) Adduct of **4a** at C-2:			*exo–syn* addition at C-3				*exo–anti* addition at C-3				
3a	138.29	113.76	−24.53	160.17	21.88	109.02	−28.89	159.73	21.44	4.36	0.44
3b	102.13	77.69	−24.44	123.83	21.70	73.13	−29.00	123.67	21.54	4.56	0.16
3c	106.07	78.27	−27.80	128.80	22.73	74.45	−31.62	127.89	21.82	3.82	0.91
11a	140.56	113.12	−27.44	163.04	22.48	108.99	−31.57	161.07	20.51	4.13	1.97
11b	142.44	115.92	−26.52	164.30	21.86	111.87	−30.57	163.40	20.96	4.05	0.90
11c	179.20	152.49	−26.71	200.95	21.75	148.04	−31.16	200.26	21.06	4.45	0.69
(b) Adduct of **4b** at C-2:			*exo–syn* addition at C-3				*exo–anti* addition at C-3				
3a	160.73	135.34	−25.39	182.98	22.25	131.23	−29.50	182.85	22.12	4.11	0.13
11a	161.89	133.96	−27.93	184.59	22.70	129.79	−32.10	183.00	21.11	4.17	1.59
11b	164.82	137.94	−26.88	187.21	22.39	133.49	−31.33	186.70	21.88	4.45	0.51
11c	201.60	174.66	−26.94	223.70	22.10	171.10	−30.50	223.55	21.95	3.55	0.15

[a] The symbols have the same meaning as in Table 4.
[b] $\Delta\Delta H^{o}=\Delta H^{o}_{(syn\ \text{product})}-\Delta H^{o}_{(anti\ \text{product})}$, relative energy of formation. A positive value means the corresponding *anti* product is more stable and is favored thermodynamically.
[c] $\Delta\Delta H^{\#}=\Delta H^{\#}_{(syn\ \text{product})}-\Delta H^{\#}_{(anti\ \text{product})}$ relative activation energy. A positive value means a more stable TS for the *anti* approach and the corresponding adduct is favored kinetically.

4.2. Reaction of 1-benzoyl-2,3-bis(bromomethyl)indole (2a) with mesitonitrile oxide. General procedure

Sodium iodide (0.30 g, 2.0 mmol) was added in one portion to a stirred solution of 1-benzoyl-2,3-bis(bromomethyl)indole (**2a**) (0.41 g, 1.0 mmol) and mesitonitrile oxide (0.335 g, 2.1 mmol) in dry DMF (30 mL). The reaction mixture was stirred under reflux (153 °C) for 3 h, the solvent was evaporated under reduced pressure, and the residue was extracted with dichloromethane. The suspension was washed with saturated aqueous sodium hydrogen sulfite and then with water. The organic layer was separated, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using petroleum ether/EtOAc as eluent, slowly increasing the polarity to give in order of elution.

Table 6. The various addition products with their yields (%) from the studied reactions

Reactants		Products (%)				
3a+**4a**	**5a**	20	**6a**	7	**7a**	13
3a+**4b**	**5d**	25			**9**	13
3b+**4a**	**5b**	29			**7b**	18
3c+**4a**	**5c**	46				
11a+**4a**[a]	**12a**	31				
11a+**4b**	**12d**	43				
11b+**4a**	**12b**	19	**13b**	15		
11b+**4b**	**12e**	37				
11c+**4a**	**12c**	21	**13c**	19		
11c+**4b**	**12f**	46				

[a] Reactions with QDMs **11** were carried out at 120–130 °C for 2 h in DMF (Ref. 10).

4.2.1. (3′*S*,5*R* or 3′*R*,5*S*)-1′-Benzoyl-3,3″-dimesityl-1′*H*,4*H*,4″*H*-dispiro[isoxazole-5,2′-indole-3′,5″-isoxazole] 5a.

0.115 g, 20% Yield, white solid, mp 184–185 °C (EtOH); IR (Nujol) ν_{max}: 1660 cm^{-1}. ^1H NMR: 2.30 (s, 3H, 3-(Me-4)), 2.32 (s, 3H, 2-(Me-4)), 2.38 (s, 6H, 3-(Me-2,6)), 2.48 (s, 6H, 2-(Me-2,6)), 3.48 (d, J=18.8 Hz, 1H, *exo*-3-C(4′)), 3.91 (d, J=18.8 Hz, 1H, *exo*-2-C(4′)), 4.07 (d, J=18.8 Hz, 1H, *endo*-2-C(4′)), 4.24 (d, J=18.8 Hz, 1H, *endo*-3-C(4′)), 6.05 (d, J=7.6 Hz, 1H, C(7)), 6.92 (s, 2H, 2-C(3,5)), 6.95 (s, 2H, 3-C(3,5)), 7.00 (m, 1H, C(6)), 7.07

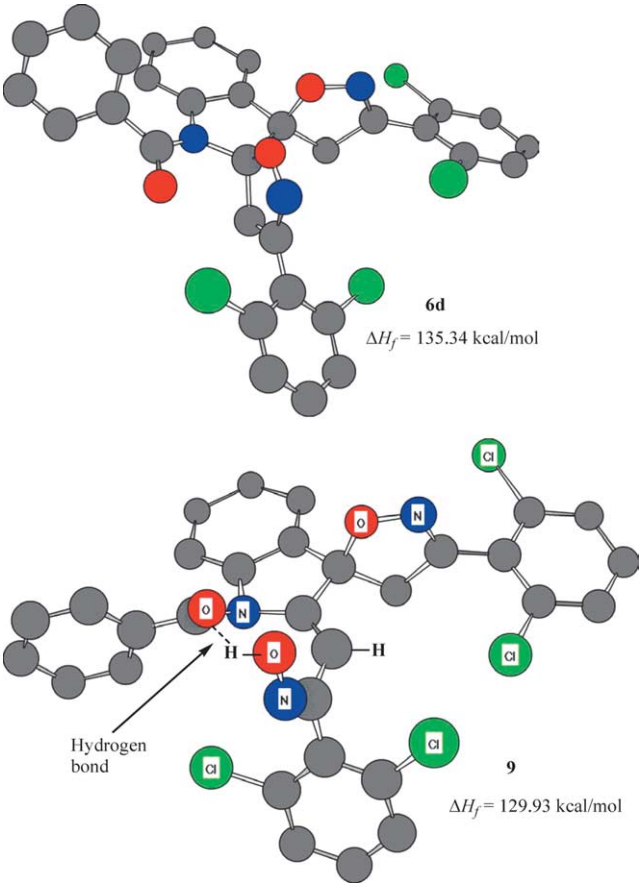


Figure 5. Energy minimized molecular models for compound **9**, where the hydrogen bond between C=*O*···*H*O–N can be distinguished, and for the corresponding bis adduct **6d**.

(m, 1H, C(5)), 7.45 (m, 2H, 1-C(3,5)), 7.46 (d, J=7.8 Hz, 1H, C(4)), 7.57 (m, 1H, 1-C(4)), 7.70 (m, 2H, 1-C(2,6)). ^{13}C NMR: 20.3 (3-(Me-2,6)), 20.6 (2-(Me-2,6)), 21.1 (2-(Me-4)), 21.1 (3-(Me-4)), 42.5 (2-(4′)), 45.3 (3-(4′)), 92.1 (3), 107.4 (2), 115.3 (7), 123.6 (4), 124.2 (5), 125.2 (3-(1)), 125.3 (2-(1)), 128.8 (1-(2,6)), 128.9 (1-(3,5)), 128.9 (2-(3,5)), 128.9 (3-(3,5)), 129.7 (6), 130.9 (3a), 132.1 (1-(4)), 135.5 (1-(1)), 136.9 (3-(2,6)), 137.7 (2-(2,6)), 139.0 (3-(4)), 139.3 (2-(4)), 141.9 (7a), 158.0 (3-(3′)), 158.9 (2-(3′)), 168.7 (1-(CO)). EIMS *m*/*z* (%) 570 (13, $M^{+\cdot}$+1), 464 (4), 450 (100), 434 (43), 408 (26), 221 (19), 105 (85), 77 (6). Anal. Calcd for $C_{37}H_{35}N_3O_3$ (569.67): C, 78.00; H, 6.19; N, 7.38%. Found: C, 77.81; H, 6.08; N, 7.47%.

4.2.2. 1′,9-Dibenzoyl-3″-mesityl-1,3,4,9-tetrahydro-1′*H*,4″*H*-dispiro[carbazole-2,3′-indole-2′,5″-isoxazole] 7a (or 8a). 0.085 g, 13% Yield, white solid, mp 248–250 °C (EtOH); IR (Nujol) ν_{max}: 1665, 1590 cm^{-1}. ^{1}H NMR: 2.03 (ddd, J=12.0, 4.0, 1.0 Hz, 1H, 3-C(8′)), 2.19 (ddd, J=12.0, 12.0, 5.0 Hz, 1H, 3-C(8′)), 2.30 (s, 3H, 2-(Me-4)), 2.53 (s, 6H, 2-(Me-2,6)), 2.66 (ddd, J=16.3, 12.0, 4.0 Hz, 1H, 3-C(7′)), 2.99 (ddd, J=16.3, 5.0, 1.0 Hz, 1H, 3-C(7′)), 3.24 (d, J=18.4 Hz, 1H, 3-C(4′)), 3.27 (d, J=18.4 Hz, 1H, 3-C(4′)), 3.50 (d, J=19.3 Hz, 1H, 2-C(4′)), 4.10 (d, J=19.3 Hz, 1H, 2-C(4′)), 6.07 (m, 1H, C(7)), 6.79 (m, 1H, C(5)), 6.85 (m, 1H, C(6)), 6.86 (m, 1H, C(4)), 6.92 (s, 2H, 2-C(3,5)), 7.00 (m, 1H, 3-C(3′)), 7.11 (m, 1H, 3-C(4′)), 7.23 (m, 1H, 3-C(5′)), 7.46 (m, 2H, 3-C(3,5)), 7.50 (m, 2H, 1-C(3,5)), 7.50 (m, 1H, 3-C(6′)), 7.55 (m, 1H, 1-C(4)), 7.62 (m, 1H, 3-C(4)), 7.68 (m, 2H, 1-C(2,6)), 7.76 (m, 2H, 3-C(2,6)). ^{13}C NMR: 18.3 (3-(8′)), 20.8 (2-(Me-2,6)), 21.1 (2-(Me-4)), 27.9 (3-(1′)), 29.6 (3-(7′)), 39.70 (2-(4′)), 50.7 (3), 110.5 (2), 114.7 (3-(3′)), 116.0 (7), 117.5 (3-(6b′)), 118.2 (3-(6′)), 122.7 (3-(5′)), 123.5 (5), 123.6 (4), 123.7 (3-(4′)), 126.0 (2-(1)), 127.4 (6), 128.8 (2-(3,5)), 128.9 (1-(3,5)), 128.9 (1-(2,6)), 128.9 (3-(3,5)), 129.5 (3-(2,6)), 131.2 (3-(6a′)), 132.0 (1-(4)), 132.9 (3-(4)), 134.8 (3-(1a′)), 135.1 (3a), 135.4 (1-(1)), 136.0 (3-(1)), 137.2 (3-(2a′)), 137.7 (2-(2,6)), 138.8 (2-(4)), 141.7 (7a), 157.3 (2-(3′)), 169.0 (1-(CO)), 169.1 (3-(CO)). EIMS *m*/*z* (%) 655 (<1, $M^{+\cdot}$), 640 (6), 450 (33), 392 (89), 105 (100), 77 (68). Anal. Calcd for $C_{44}H_{37}N_3O_3$ (655.78): C, 80.59; H, 5.69; N, 6.41%. Found: C, 80.75; H, 5.82; N, 6.34%.

4.2.3. (3′*R*,5*R* or 3′*S*,5*S*)-1′-Benzoyl-3,3″-dimesityl-1′*H*,4*H*,4″*H*-dispiro[isoxazole-5,2′-indole-3′,5″-isoxazole] 6a. 0.040 g, 7% Yield, white solid, mp 218–220 °C (EtOH); IR (Nujol) ν_{max}: 1655 cm^{-1}. ^{1}H NMR: 2.30 (s, 3H, 2-(Me-4)), 2.30 (s, 3H, 3-(Me-4)), 2.31 (s, 6H, 3-(Me-2,6)), 2.48 (s, 6H, 2-(Me-2,6)), 3.42 (d, J=18.5 Hz, 1H, *exo*-3-C(4′)), 3.44 (d, J=18.2 Hz, 1H, *exo*-2-C(4′)), 3.78 (d, J=18.5 Hz, 1H, *endo*-3-C(4′)), 4.11 (d, J=18.2 Hz, 1H, *endo*-2-C(4′)), 6.10 (m, 1H, C(7)), 6.92 (s, 2H, 2-C(3,5)), 6.92 (s, 2H, 3-C(3,5)), 6.99 (m, 1H, C(6)), 7.07 (m, 1H, C(5)), 7.45 (m, 2H, 1-C(3,5)), 7.45 (d, J=7.3 Hz, 1H, C(4)), 7.57 (m, 1H, 1-C(4)), 7.70 (m, 2H, 1-C(2,6)). ^{13}C NMR: 20.0 (3-(Me-2,6)), 20.2 (2-(Me-2,6)), 21.1 (2-(Me-4)), 21.1 (3-(Me-4)), 41.7 (2-(4′)), 47.7 (3-(4′)), 91.8 (3), 107.8 (2), 116.0 (7), 122.5 (4), 124.3 (5), 125.1 (3-(1)), 125.5 (2-(1)), 128.6 (2-(3,5)), 128.8 (3-(3,5)), 128.9 (1-(3,5)), 128.9 (1-(2,6)), 129.2 (6), 132.7 (3a), 132.4 (1-(4)), 135.2 (1-(1)), 136.5 (3-(2,6)), 137.7 (2-(2,6)), 139.0 (2-(4)), 139.4 (3-(4)), 141.8 (7a), 156.5 (3-(3′)), 156.8 (2-(3′)), 165.0 (CO). EIMS *m*/*z* (%) 569 (20, $M^{+\cdot}$), 449 (37), 433 (16), 408 (10), 105 (100), 77 (22). Anal. Calcd for $C_{37}H_{35}N_3O_3$ (569.67): C, 78.00; H, 6.19; N, 7.38%. Found: C, 78.13; H, 6.28; N, 7.27%.

4.3. Reaction of 1-acetyl-2,3-bis(bromomethyl)indole (2b) with mesitonitrile oxide

The reaction was carried out as described above with 1.0 mmol of 1-acetyl-2,3-bisbromomethylindole (**2b**) and 2.1 mmol of mesitonitrile oxide to afford after column chromatography in order of elution.

4.3.1. (3′*R*,5*S* or 3′*S*,5*R*)-1′-Acetyl-3,3″-dimesityl-1′*H*,4*H*,4″*H*-dispiro[isoxazole-5,2′-indole-3′,5″-isoxazole] 5b. White solid, mp 234–236 °C (EtOH), 0.147 g, 29% yield. IR (Nujol) ν_{max}: 1650 cm^{-1}. ^{1}H NMR: 2.29 (s, 3H, 2-(Me-4)), 2.30 (s, 3H, 3-(Me-4)), 2.33 (s, 6H, 2-(Me-2,6)), 2.38 (s, 6H, 3-(Me-2,6)), 2.51 (s, 3H, CO–Me), 3.18 (d, J=18.7 Hz, 1H, *exo*-3-C(4′)), 3.49 (d, J=19.1 Hz, 1H, *exo*-2-C(4′)), 4.34 (d, J=19.1 Hz, 1H, *endo*-2-C(4′)), 4.38 (d, J=18.7 Hz, 1H, *endo*-3-C(4′)), 6.91 (s, 2H, 2-C(3,5)), 6.92 (s, 2H, 3-C(3,5)), 7.20 (m, 1H, C(5)), 7.36 (m, 1H, C(6)), 7.45 (d, J=7.5 Hz, 1H, C(4)), 7.81 (br, 1H, C(7)). ^{13}C NMR: 19.9 (2-(Me-2,6)), 20.4 (3-(Me-2,6)), 21.1 (2-(Me-4)), 21.1 (3-(Me-4)), 25.0 (CO–Me), 44.9 (2-(4′)), 47.4 (3-(4′)), 92.7 (3), 106.3 (2), 116.2 (7), 123.3 (4), 124.9 (2-(1)), 125.0 (3-(1)), 125.1 (5), 128.7 (2-(3,5)), 129.0 (3-(3,5)), 130.3 (6), 131.0 (3a), 137.0 (2-(2,6)), 137.3 (3-(2,6)), 139.3 (2-(4)),

139.4 (3-(4)), 140.5 (7a), 158.5 (3-(3′)), 160.4 (2-(3′)), 169.2 (CO). EIMS *m/z* (%) 508 (13, $M^{+\cdot}$), 466 (10), 347 (32), 105 (85), 77 (100). Anal. Calcd for $C_{32}H_{33}N_3O_3$ (507.61): C, 75.71; H, 6.55; N, 8.28%. Found: C, 75.81; H, 6.38; N, 8.64%.

4.3.2. 1′,9-Diacetyl-3″-mesityl-1,3,4,9-tetrahydro-1′*H*,4″*H*-dispiro[carbazole-2,3′-indole-2′,5″-isoxazole] 7b (or 8b). White solid, mp 240–242 °C (EtOH), 0.096 g, 18% yield. ^{1}H NMR: 1.77 (m, 1H, 3-C(8′)), 2.02 (m, 1H, 3-C(8′)), 2.29 (s, 3H, 2-(Me-4)), 2.46 (s, 6H, 2-(Me-2,6)), 2.49 (m, 1H, 3-C(7′)), 2.55 (s, 3H, CO–Me), 2.72 (s, 3H, 3-(CO–Me)), 2.87 (m, 1H, 3-C(7′)), 3.28 (d, *J*=18.2 Hz, 1H, 3-C(4′)), 3.44 (d, *J*=18.6 Hz, 1H, 2-C(4′)), 3.49 (d, *J*=18.2 Hz, 1H, 3-C(4′)), 4.27 (d, *J*=18.6 Hz, 1H, 2-C(4′)), 6.89 (m, 1H, C(7)), 6.90 (m, 1H, C(4)), 6.90 (m, 1H, 3-C(4′)), 6.91 (s, 2H, 2-C(3,5)), 7.21 (m, 1H, C(6)), 7.31 (m, 1H, 3-C(5′)), 7.35 (m, 1H, 3-C(6′)), 7.37 (m, 1H, C(5)), 8.17 (m, 1H, 3-C(3′)). ^{13}C NMR: 18.0 (3-(8′)), 20.6 (2-(Me-2,6)), 21.0 (2-(Me-4)), 25.7 (1-COMe), 27.2 (3-COMe), 28.9 (3-(1′)), 29.4 (3-(7′)), 40.1 (2-(4′)), 50.4 (3), 110.1 (2), 115.2 (3-(3′)), 115.8 (7), 118.2 (3-(6′)), 118.2 (3-(6b′)), 123.3 (3-(5′)), 124.1 (4), 124.1 (5), 124.7 (3-(4′)), 125.7 (2-(1)), 128.1 (6), 128.9 (2-(3,5)), 129.0 (3-(6a′)), 133.2 (3-(1a′)), 135.6 (3a), 136.6 (3-(2a′)), 137.4 (2-(2,6)), 138.9 (2-(4)), 140.4 (7a), 157.9 (2-(3′)), 169.6 (1-(CO)), 169.7 (3-(CO)). EIMS *m/z* (%) 531 (3, $M^{+\cdot}$), 516 (10), 488 (22), 412 (5), 372 (90), 105 (100), 77 (67). Anal. Calcd for $C_{34}H_{33}N_3O_3$ (531.64): C, 76.81; H, 6.26; N, 7.90%. Found: C, 76.60; H, 6.38; N, 8.04%.

4.4. Reaction of 1-sulfonyl-2,3-bis(bromomethyl)indole (2c) with mesitonitrile oxide

The reaction was carried out as described above with 1.0 mmol of 1-sulfonyl-2,3-bisbromomethylindole (**2c**) and 2.1 mmol of mesitonitrile oxide to afford after column chromatography compound **5c**.

4.4.1. (3′*S*,5*R* or 3′*R*,5*S*)-3,3″-Dimesityl-1′-(phenylsulfonyl)-1′*H*,4*H*,4″*H*-dispiro[isoxazole-5,2′-indole-3′,5″-isoxazole] 5c. White solid, mp 126–128 °C (EtOH), 0.278 g, 46% yield. ^{1}H NMR: 2.26 (s, 6H, 3-(Me-2,6)), 2.28 (s, 3H, 2-(Me-4)), 2.30 (s, 3H, 3-(Me-4)), 2.42 (s, 6H, 2-(Me-2,6)), 3.03 (d, *J*=18.8 Hz, 1H, *exo*-3-C(4′)), 3.85 (d, *J*=18.8 Hz, 1H, *endo*-3-C(4′)), 4.00 (d, *J*=19.3 Hz, 1H, *exo*-2-C(4′)), 4.40 (d, *J*=19.3 Hz, 1H, *endo*-2-C(4′)), 6.88 (s, 2H, 2-C(3,5)), 6.92 (s, 2H, 3-C(3,5)), 7.15 (m, 1H, C(5)), 7.35 (m, 1H, C(6)), 7.37 (d, *J*=7.6 Hz, 1H, C(4)), 7.45 (m, 2H, 1-C(3,5)), 7.53 (m, 1H, 1-C(4)), 7.69 (d, *J*=8.3 Hz, 1H, C(7)), 8.07 (m, 2H, 1-C(2,6)). ^{13}C NMR: 20.1 (3-(Me-2,6)), 20.3 (2-(Me-2,6)), 21.1 (2-(Me-4)), 21.1 (3-(Me-4)), 46.8 (2-(4′)), 47.1 (3-(4′)), 93.0 (3), 108.2 (2), 114.4 (7), 123.5 (4), 124.8 (5), 124.5 (2-(1)), 124.8 (3-(1)), 127.7 (1-(2,6)), 128.8 (3-(3,5)), 128.9 (1-(3,5)), 128.9 (2-(3,5)), 130.2 (3a), 130.8 (6), 133.3 (1-(4)), 136.9 (3-(2,6)), 137.6 (2-(2,6)), 139.3 (2-(4)), 139.3 (3-(4)), 139.9 (7a), 140.3 (1-(1)), 158.0 (3-(3′)), 160.4 (2-(3′)). EIMS *m/z* (%) 605 (7, $M^{+\cdot}$), 463 (58), 319 (51), 157 (55), 103 (100), 77 (56). Anal. Calcd for $C_{36}H_{35}N_3O_4S$ (605.75): C, 71.38; H, 5.82; N, 6.94%. Found: C, 71.48; H, 5.66; N, 7.11%.

4.5. Reaction of 1-benzoyl-2,3-bis(bromomethyl)indole (2a) with 2,6-dichloronitrile oxide

The reaction was carried out as described above with 1.0 mmol of 1-benzoyl-2,3-bisbromomethylindole (**2a**) and 2.1 mmol of 2,6-dichloronitrile oxide to afford after column chromatography compound in order of elution.

4.5.1. (3′*R*,5*S* or 3′*S*,5*R*)-1′-Benzoyl-3,3″-bis(2,6-dichlorophenyl)-1′*H*,4*H*,4″*H*-dispiro[isoxazole-5,2′-indole-3′,5″-isoxazole] 5d. White solid, mp 233–235 °C (EtOH), 0.156 g, 25% yield. IR (Nujol) ν_{max}: 1660 cm^{-1}. ^{1}H NMR: 3.93 (d, *J*=19.1 Hz, 1H, *exo*-3-C(4′)), 3.95 (d, *J*=19.1 Hz, 1H, *endo*-3-C(4′)), 4.01 (d, *J*=19.2 Hz, 1H, *exo*-2-C(4′)), 4.26 (d, *J*=19.2 Hz, 1H, *endo*-2-C(4′)), 6.11 (m, 1H, C(7)), 7.07 (m, 1H, C(5)), 7.07 (m, 1H, C(6)), 7.30 (m, 1H, 3-C(4)), 7.36 (m, 1H, 2-C(4)), 7.41 (m, 2H, 3-C(3,5)), 7.45 (m, 2H, 2-C(3,5)), 7.48 (m, 2H, 1-C(3,5)), 7.58 (m, 1H, 1-C(4)), 7.62 (m, 1H, C(4)), 7.75 (m, 2H, 1-C(2,6)). ^{13}C NMR: 39.5 (2-(4′)), 40.7 (3-(4′)), 93.5 (3), 107.6 (2), 115.6 (7), 124.1 (4), 124.2 (5), 127.7 (2-(1)), 127.7 (3-(1)), 128.6 (1-(3,5)), 128.7 (2-(3,5)), 128.9 (1-(2,6)), 128.9 (3-(3,5)), 130.1 (3a), 130.2 (6), 131.0 (3-(4)), 131.4 (2-(4)), 132.2 (1-(4)), 135.3 (1-(1)), 135.3 (2-(2,6)), 135.7 (3-(2,6)), 143.2 (7a), 153.9 (3-(3′)), 154.7 (2-(3′)), 168.7 (1-(CO)). EIMS *m/z* (%) 629/627/625/623/621 (7, $M^{+\cdot}$), 505/503/501 (6), 467 (13), 465 (13), 345 (9), 331 (11), 214 (25), 196 (75), 171 (46), 105 (97), 77 (100). Anal. Calcd for $C_{31}H_{19}Cl_4N_3O_3$ (623.31): C, 59.73; H, 3.07; N 6.74%. Found: C, 59.54; H, 2.99; N, 6.83%.

4.5.2. (1*E*,2*Z*)-2-[(3*R*)-1-Benzoyl-3′-(2,6-dichlorophenyl)-4′*H*-spiro[indole-3,5′-isoxazol]-2(1*H*)-ylidene]-1-(2,6-dichlorophenyl)ethanone oxime 9. White solid, mp 200–202 °C (EtOH), 0.081 g, 13% yield. IR (Nujol) ν_{max}: 3400, 1660 cm^{-1}. ^{1}H NMR: 4.14 (d, *J*=16.8 Hz, 1H, 3-C(4′)), 4.17 (d, *J*=16.8 Hz, 1H, 3-C(4′)), 6.45 (s, 1H, 2-C(4′)), 7.27 (m, 1H, C(5)), 7.29 (m, 1H, 3-C(4)), 7.31 (m, 1H, 2-C(4)), 7.34 (m, 2H, 2-C(3,5)), 7.34 (m, 2H, 3-C(3,5)), 7.42 (m, 1H, C(6)), 7.49 (m, 2H, 1-C(3,5)), 7.52 (d, *J*=7.3 Hz, 1H, C(4)), 7.54 (m, 1H, 1-C(4)), 7.95 (m, 2H, 1-C(2,6)), 8.26 (d, *J*=8.1 Hz, 1H, C(7)), 9.27 (s, 1H, OH). ^{13}C NMR: 48.1 (3-(4′)), 88.2 (3), 105.2 (2-(4′)), 125.2 (5), 125.5 (7), 127.0 (2-(1)), 127.2 (1-(2,6)), 127.4 (6), 127.7 (3-(1)), 128.2 (2-(3,5)), 128.2 (3-(3,5)), 128.7 (3a), 128.9 (1-(3,5)), 130.4 (4), 131.2 (3-(4)), 131.7 (2-(4)), 132.1 (1-(4)), 134.2 (1-(1)), 135.0 (3-(2,6)), 135.5 (2-(2,6)), 136.3 (7a), 156.2 (3-(3′)), 159.1 (2-(3′)), 165.3 (1-(CO)), 171.4 (2). EIMS *m/z* (%) 629/627/625/623/621 (39, $M^{+\cdot}$), 329 (37), 214 (98), 196 (100), 171 (46), 105 (97). Anal. Calcd for $C_{31}H_{19}Cl_4N_3O_3$ (623.31): C, 59.73; H, 3.07; N 6.74%. Found: C, 59.59; H, 2.95; N, 6.59%.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.01.064.

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A scheme estimating the energy of intramolecular hydrogen bonds in diols

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Abstract—The relative energies of conformers of 1,2-ethanediol, 1,3-propanediol, and 1,4-butanediol are split into a sum of five different terms including the intramolecular OH···O interaction. This scheme allows to estimate the energy of the O–H···O intramolecular hydrogen bond of the tGG′g and gGG′g conformers of 1,3-propanediol, the g′GG′Gt and g′GG′Gg conformers of 1,4-butanediol, and the energy of the non-bonded O–H···O interaction in the g′Gt, g′Gg and g′Gg′ conformers of 1,2-ethanediol. This scheme provides pure hydrogen bond energies without assuming the geometry and/or electronic features to be constant between the conformation having a IHB and a reference conformation. The fitted energies show a perfect linear correlation with the corresponding $r(\mathrm{H}\cdots\mathrm{O})^{-1}$ values. QTAIM atomic electron population and energies of the donor hydrogen calculated along the H–O–C–C internal rotation are found to be linearly correlated. These linear correlations display small changes at the BCP formation in 1,3-propanediol.

1. Introduction

The sequence of stability of the different conformers of 1,2-diols and 1,3-diols have been traditionally explained by the presence of O–H···O intramolecular hydrogen bonds[1–8] (IHBs), however, other important features can play an important role in the stability of these compounds.

The energy of most intermolecular hydrogen bonds can be calculated to a good approximation as the difference between the energies of dimer and monomers (as long as no other important interactions or geometry distortions accompany the dimer formation and the basis set superposition error, BSSE, correction is included in the calculation[9]). However, when a similar formula is applied to IHB (in this case using the energies of conformers with and without hydrogen bonding), it yields a very crude estimation, principally owing to the fact that other internal interactions display significant changes and appear or disappear from one conformer to another (as those mentioned below for 1,2-diols and 1,3-diols). Thus, most of the IHB energies provided previously were obtained by assuming that IHB was the sole structural feature that modified the energy with regard to an arbitrary chosen reference conformation in which the IHB is broken. Therefore, several different IHB energies could only be given for a certain conformer of a given molecule.

In a previous work, Lipkowski et al. estimated the energy of O–H···N IHBs in chloro-derivates of 2-(*N*-dimethylamino-methyl)-phenols[10] by using the energies of several conformers, which display different steric effects. They were able to separate these steric effects from the energy of the IHB. The so obtained values were correlated with the donor/acceptor distances, $r(\mathrm{N}\cdots\mathrm{H})$. This work aims to achieve this goal in diols by splitting relative conformational energies into several energy terms. These terms were selected on the basis of the variations displayed by atomic energies computed within the framework of the quantum theory of atoms in molecules (QTAIM)[11,12] for diverse conformers and molecules.

The conformational features of 1,2-ethanediol and 1,3-propanediol were largely studied by Bultinck et al.[3] who described all the conformers of both compounds. However, as this work dates from 1995, only HF levels were employed for geometry optimizations, using 6-31++G** and 4-31+G* bassis sets for 1,2-ethanediol and 1,3-propanediol, respectively. The energies of the different conformers were also calculated at the MP2 level and two possible IHBs were characterized (only using geometrical criteria) for the g′Gt and g′Gg conformers of 1,2-ethanediol and tGG′g and g′GG′g conformers of 1,3-propanediol.

Keywords: QTAIM; Hydrogen bond; Diols.
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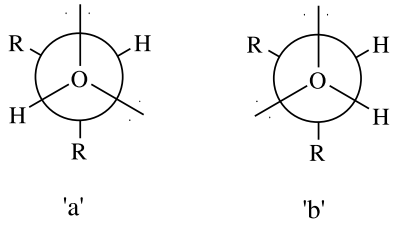
Other works have also treated the issue of the IHB in diols using only geometrical criteria. Thus, Reiling et al.[4] proposed the presence of a double IHB in the g′Gg′ conformer of 1,2-ethanediol.

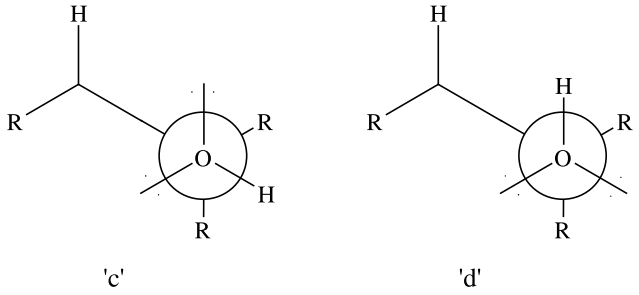
The QTAIM supplies a rigorous way to characterize IHBs. The presence of a hydrogen bond requires a bond critical point (BCP) placed between donor and acceptor atoms and a bond path linking them[13,14]. This topological criterion was applied in diols by Klein[15,16], and more recently by Mandado et al.[17] No topological hydrogen bond was found in these studies for the conformers of 1,2-ethanediol. On the contrary, some conformers of 1,3-propanediol display BCP′s associated to IHB.[15]

It has recently been found, using the framework of the QTAIM, that the stability of the gauche conformers in anomeric molecules, such as methanediol, can be explained by the migration of some electron population from the methylene hydrogens to the central carbon and oxygens.[18] This migration takes place when the hydrogens are gauche with respect to the lone pairs (LPs) of the oxygens (conformation 'a' in Scheme 1). The reduction of electron population increases the energies of the hydrogens but is accompanied by a larger decrease of the energies of the central carbons and oxygens, yielding conformer stabilization. The two hydroxyl groups in diols can adopt different conformations with respect to their α-methylene, where such stabilization may be present or not, playing an important role for the relative conformational energy.



Scheme 1.

Also, for the same arrangement of the molecular backbone formed by C and O atoms, the disposition of the hydroxyl group gives rise to very different steric interactions with its β-methylene (conformations 'c' and 'd' in Scheme 2) as indicated by the corresponding OH···HC distances. Obviously, they can alter significantly the conformational energy, with hydrogens being stabilized in the 'c' conformation.



Scheme 2.

In the present study, we have performed an estimation of the energy of bonding and non-bonding OH···O interactions in 1,4-butanediol, 1,3-propanediol, and 1,2-ethanediol using the energies of different conformers and considering the main conformational features, which govern the order of stability in these compounds. All stable conformers of 1,2-ethanediol were considered, nevertheless only the stable nGG′n (with n=t,g,g′) conformers of 1,3-propanediol and the nGG′Gn conformers of 1,4-butanediol were considered as they are the only ones in which allow the possibility of an IHB. We have also investigated the relations between these energies and the donor/acceptor distances, r(O···H), and have compared them with those in the intermolecular bonding in the methanol dimer.

1.1. Methodology and geometrical features

The geometries and electron densities of all stable conformers of 1,2-ethanediol were determined at the B3LYP/6-311++G(2d,2p) level. Ten different conformers (shown in Fig. 1) were obtained and are named using the nomenclature presented by Radom et al.[2] The values of r(OH···O) distances are shown in Figure 1 for all the conformers, which are susceptible to have an OH···O IHB. The hydrogen or carbon atoms stabilized by '*gauche*' interactions with oxygen lone pairs (as mentioned in the introduction) and those stabilized by the hydroxyl arrangement with regard to β-methylene, are also indicated in Figure 1 by displaying the atoms in question in parenthesis or brackets, respectively.

Although the OH···O distance is not exactly the same in g′Gt and g′Gg conformers, the difference is so small that we consider the OH···O interaction to be the same in both molecules (referred to as $\Delta E_{\mathrm{OH\cdots O}}$ in this work). This interaction is certainly different in the g′Gg′ conformer, where the two OH···O distances are quite different with respect to those of g′Gt and g′Gg. Therefore, a different energy will be given to this interaction in this conformer.

On the other hand, '*gauche*' interactions are supposed to be very similar in different conformers. Consequently, a common value denoted by, respectively, $\Delta E_{\mathrm{g(H)}}$ and $\Delta E_{\mathrm{g(C)}}$, for hydrogens and another for carbons are given to these interactions. In order to simplify the calculations, the energy difference between c and d conformations (Scheme 2), due to the different interactions among β-methylenes and the hydroxyl group, is represented by a common value for all the conformers, $\Delta E_{\mathrm{OH\cdots HC}}$. This is equivalent to use average values for both terms. The results obtained for $\Delta E_{\mathrm{OH\cdots O}}$, which will be commented on in the next chapter, indicate this is not too crude an approximation.

Thus, the equation employed in this study to rationalize the interactions in the different conformers is:

$$\Delta E_{\mathrm{conf}}^{C_1-C_2} \approx \Delta E_{\mathrm{OH\cdots O}} + (n^{C_1} - n^{C_2})_{\mathrm{OH\cdots HC}} \Delta E_{\mathrm{OH\cdots HC}} + (n^{C_1} - n^{C_2})_{\mathrm{g(H)}} \Delta E_{\mathrm{g(H)}} + (n^{C_1} - n^{C_2})_{\mathrm{g(C)}} \Delta E_{\mathrm{g(C)}} + \Delta E' \quad (1)$$

When the two conformations compared have the same backbone conformations, both G or both T, $\Delta E'$ is equal to

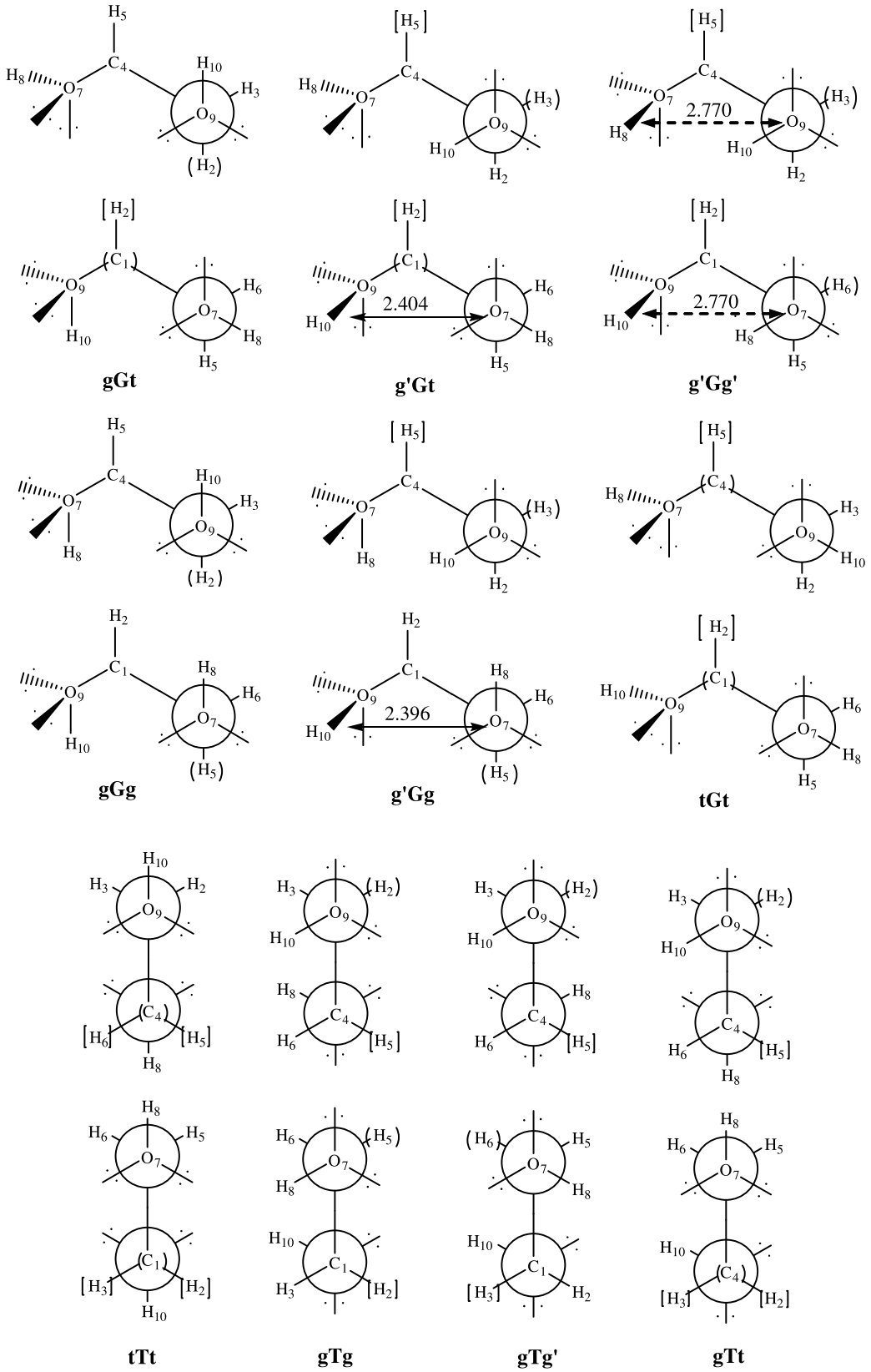


Figure 1. Plot of all stable conformers of 1,2-ethanediol. The nomenclature, atomic numbering and OH···O distances are shown. The '*gauche*' stabilizations of hydrogens and carbons are marked by displaying the corresponding atoms in parenthesis, while stabilizations due to the relative arrangements of β-methylene and hydroxyl groups are indicated by displaying the corresponding atoms in brackets.

zero, as is $\Delta E_{OH\cdots O}$ for those conformations where no IHB is present. $(n^{C_1}-n^{C_2})_{OH\cdots HC}$ represent the difference in the number of OH⋯HC interactions in conformations 1 (n^{C_1}) and in conformation 2 (n^{C_2}). Terms involving g(H) and g(C) have a similar meaning.

Calculations of atomic populations, $N(\Omega)$, and atomic energies, $E(\Omega)$, of all the conformers studied for 1,2-ethanediol and 1,3-propanediol have been performed in order to interpret the results provided by the energy partitioning proposed by Eq. 1. These atomic properties were obtained within the framework of the QTAIM[11,12]. We have paid special attention on the atomic properties of hydrogens as these atoms are involved in all the interactions included in Eq. 1, and the effect of the conformational changes will reflect on them.

The B3LYP/6-311++G(2d,2p) level was also employed to calculate the geometries and electron densities of the conformers of 1,3-propanediol and 1,4-butanediol that are susceptible to present IHB. Thus, only the nGG′n and nGG′Gn arrangements were considered for 1,3-propanediol and 1,4-butanediol, respectively, yielding three stable conformers for each molecule, which are shown in Figure 2 together with their r(OH⋯O) distances. The '*gauche*' stabilization of hydrogens or carbons due to the oxygen lone pairs and those due to the hydroxyl arrangement with regard to β-methylene, are also indicated in Figure 2 similarly as in Figure 1 for 1,2-ethanediol. The gGG′g conformation of 1,3-propanediol was not characterized as a stable conformer, contradicting the results obtained by Bultinck et al.[3] at HF level of theory. The estimation of $\Delta E_{OH\cdots O}$ in 1,3-propanediol and 1,4-butanediol was performed constraining

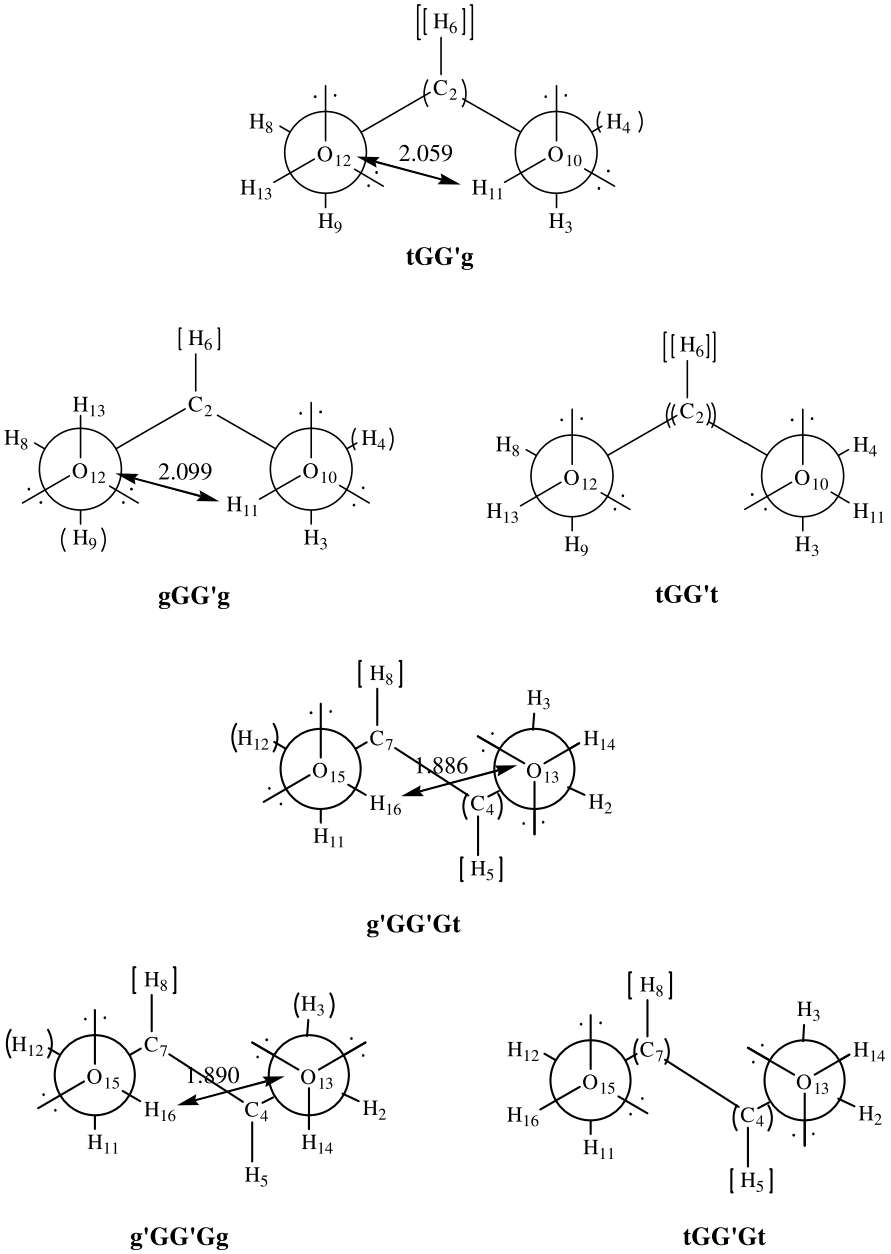


Figure 2. Plot of the conformers of 1,3-propanediol and 1,4-butanediol here studied. The nomenclature, atomic numbering and OH⋯O distances are shown. The '*gauche*' stabilizations of hydrogens and carbons are marked by displaying the corresponding atoms in parenthesis while stabilizations due to the relative arrangements of β-methylene and hydroxyl groups are indicated by displaying the corresponding atoms in brackets.

Table 1. Molecular total energies (E) and energy differences (ΔE) relative to the stablest conformation, energy differences calculated using QTAIM theory (ΔE^{AIM}) and their differences to ΔE in parenthesis, energy differences calculated using Eq. 1 (ΔE^{conf}) and their differences to ΔE in parenthesis, for all conformers of 1,2-ethanediol and the nGG′n and nGG′Gn conformers of 1,3-propanediol and 1,4-butanediol, respectively

	E (au)	ΔE (kcal mol^{-1})	ΔE^{AIM} (kcal mol^{-1})	ΔE^{conf} (kcal mol^{-1})
g′Gt	−230.3465	0.00[a]	0.00 (0.00)	0.00 (0.00)
g′Gg	−230.3460	0.32[a]	0.14 (−0.18)	0.10 (−0.22)[b]
g′Gg′	−230.3452	0.83[a]	0.41 (−0.42)	0.80 (−0.03)
gGg	−230.3421	2.77[a]	2.45 (−0.32)	2.78 (0.01)
tGt	−230.3419	2.94[a]	2.74 (−0.20)	2.94 (0.00)
gGt	−230.3412	3.35[a]	3.20 (−0.15)	3.04 (−0.31)[b]
gTg′	−230.3427	2.43[a]	2.36 (−0.07)	2.47 (0.04)
tTt	−230.3426	2.47[a]	2.56 (−0.09)	2.47 (0.00)
gTt	−230.3425	2.52[a]	2.33 (−0.19)	2.57 (0.05)[b]
gTg	−230.3423	2.64[a]	2.55 (−0.09)	2.67 (0.03)
tGG′g	−269.6738	0.00[c]	0.00 (0.00)	0.00 (0.00)
gGG′g	−269.6737	0.05[c]	−0.30 (−0.35)	0.00 (−0.05)
tGG′t	−269.6652	5.37[c]	5.12 (0.29)	5.37 (0.00)
g′GG′Gt	−309.0009	0.00[d]		0.00 (0.00)
g′GG′Gg	−309.0005	0.25[d]		0.00 (−0.25)
tGG′Gt	−308.9901	6.78[d]		6.78 (0.00)

[a] Values calculated with respect to the g′Gt conformer.
[b] Conformers, which were not used to calculate ΔE^{conf} parameters.
[c] Values calculated with respect to the tGG′g conformer.
[d] Values calculated with respect to the g′GG′Gt conformer.

$\Delta E_{OH\cdots HC}$, $\Delta E_{g(H)}$, and $\Delta E_{g(C)}$ to their values obtained for 1,2-ethanediol. This assumption is based on the fact that the values of r(OH⋯HC) distances and the QTAIM atomic properties, are all quite similar.

Finally, some conformational interchange processes of 1,2-ethanediol and 1,3-propanediol were studied, in particular we have studied the changes displayed by the atomic properties of hydrogens involved in IHB.

The geometrical optimization and the calculation of the electron density were performed with Gaussian03 program.[19] The atomic properties were determined using the AIMPAC suite of programs[20] and the drawings of the electron density were plotted using the MORPHY program.[21] All calculated atomic properties were obtained with integrated values of the laplacian of the charge density, $L(\Omega)$, which did not differ from zero (the ideal value[12]) by more than 10^{-3} au.

2. Results and discussion

2.1. Calculation of intramolecular interactions

Table 1 collects the relative energies calculated from the total electronic energies, ΔE, those calculated by summing the QTAIM atomic energies, ΔE^{AIM}, and those calculated by using Eq. 1, ΔE^{conf}. The source of error giving rise to differences between ΔE and ΔE^{AIM} is the numerical integration performed to obtain the latter. As the integration was done with a large number of grid points and using second and third intersections to delimitate the interatomic surfaces, these differences never exceed 0.5 kcal mol^{-1}. Differences between ΔE and ΔE^{conf} are inherent to the partitioning shown in Eq. 1 and due to considering constant $\Delta E_{OH\cdots HC}$, $\Delta E_{g(H)}$ and $\Delta E_{g(C)}$ values for all the conformers. The differences between ΔE and ΔE^{conf} are only noticeable for g′Gg and gGt conformers of 1,2-ethanediol and for g′GG′Gg conformer of 1,4-butanediol. The g′Gg and gGt are two of the three conformers (within a total of ten) not used in the calculation of $\Delta E_{OH\cdots O}$, $\Delta E_{OH\cdots HC}$, $\Delta E_{g(H)}$, $\Delta E_{g(C)}$, and $\Delta E'$ with Eq. 1. The small deviations of ΔE^{conf} with respect to ΔE for these two conformers (−0.22 and −0.31 kcal mol^{-1} in g′Gg and gGt, respectively) indicate that the use of Eq. 1 was not too rough an approximation. Moreover, the highest deviation of ΔE^{conf} (−0.31 kcal mol^{-1}) is smaller than that of ΔE^{AIM} (−0.42 kcal mol^{-1}), so that one can establish that the deviations on the conformational energy due to the model proposed are smaller that those due to the accuracy of the numerical integration within the QTAIM atoms.

Two different $\Delta E_{OH\cdots O}$ values were calculated for 1,2-ethanediol, one for g′Gt and g′Gg conformers (2.19 kcal mol^{-1}) and another one for g′Gg′ (0.12 kcal mol^{-1}). The latter conformer shows a double interaction (Fig. 1), which, according to its very small energy, can be considered almost negligible. Only one $\Delta E_{OH\cdots O}$ value was calculated for 1,3-propanediol (4.40 kcal mol^{-1} for tGG′g and gGG′g) and 1,4-butanediol (5.79 kcal mol^{-1} for g′GG′Gt and g′GG′Gg) as r(OH⋯O) distances are very similar for the two conformers of each molecule and the conformational energy only differs in 0.05 and 0.25 kcal mol^{-1}, respectively. The calculated values for the different parameters used to model the IHB′s using Eq. 1 are given in Table 2.

Table 2. Calculated values for the parameters of Eq. 1

$\Delta E_{OH\cdots O}$	$\Delta E_{OH\cdots CH}$	$\Delta E_{g(H)}$	$\Delta E_{g(C)}$	$\Delta E'$
2.19 (g′Gt)[a] 0.12 (g′Gg′) 4.40 (tGG′g)[b] 5.79 (g′GG′Gt)[c]	0.97	1.52	0.55	1.47

All values in kcal mol^{-1}.
[a] The same value for g′Gg.
[b] The same value for gGG′g.
[c] The same value for g′GG′Gg.

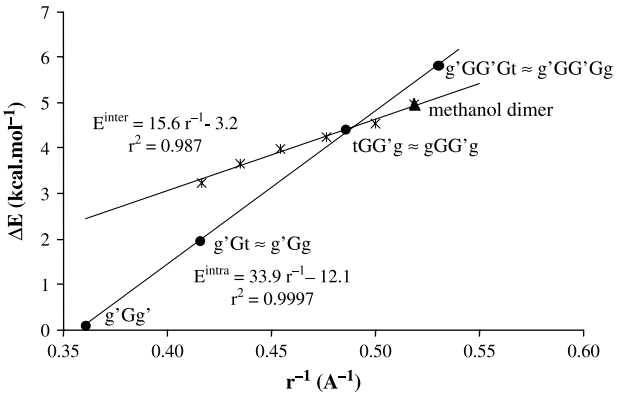


Figure 3. Plots of $\Delta E_{OH\cdots O}$ versus $r(O\cdots H)^{-1}$ linear correlations for diols studied and for the methanol dimer. Boldface circles represent the conformers of 1,2-ethanediol, 1,3-propanediol and 1,4-butanediol. The boldface triangle represents the optimized geometry of methanol dimer and crosses represent the methanol dimer at different $r(O\cdots H)$ distances.

A very good linear correlation was found relating $\Delta E_{OH\cdots O}$ values to $r(OH\cdots O)^{-1}$. Figure 3 shows this linear correlation for the conformers of Table 1 as well as that calculated for the methanol dimer. It is noticed that the data obtained for formally 'bonding' IHB conformers in 1,3-propanediol and 1,4-butanediol lie on the same line as those computed for formally 'non bonding' IHB conformers in 1,2-ethanediol. This shows that the formal QTAIM distinction between IHBs featuring a BCP and those that do not, does not imply any significant energy variation as was previously shown.[22,24]

As mentioned in the introduction, the $\Delta E_{OH\cdots O}$ values for the intermolecular HB in methanol dimer were calculated as differences between dimer and monomer energies, correcting the BSSE error by using the counterpoise method.[9] The calculations were done on geometries where the $r(OH\cdots O)$ distance was fixed while the rest of the geometrical parameters were optimized. The geometry of minimum

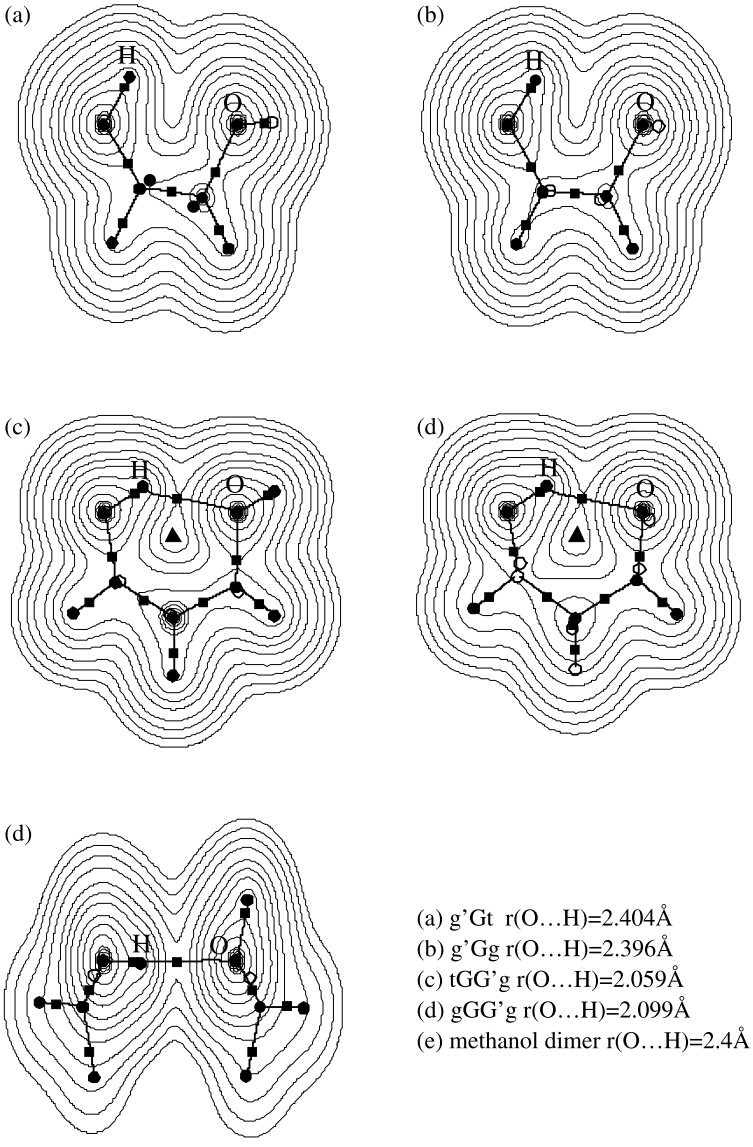


Figure 4. Plots of the electron density in the O–H···O plane for different conformers of 1,2-ethanediol and 1,3-propanediol and for the methanol dimer at $r(O\cdots H)=2.4$ Å. Bond critical points and ring critical points are represented by ■ and ▲, respectively.

energy of the dimer was taken from a previous work[22] at B3LYP/6-311++G(d,p) level and re-optimized at the B3LYP/6-311++G(2d,2p) level.

The decrease of the HB energy as the O···H distance increases is steeper for the intramolecular case (Fig. 3) than for the intermolecular case. This is in line with ring-strain effects involved in the cyclic IHB structures of diols, which favor stronger (more stabilizing) IHBs for larger (more flexible) rings. The different behavior found for the topology of the electron density (Fig. 4): the dimer of methanol displays a BCP associated with the HB when the O···H distance is (or even exceeds) 2.4 Å, while no BCP is obtained for 1,2-ethanediol at the O···H distances presented by g′Gt and g′Gg conformers (2.404 and 2.396 Å, respectively) can be considered a consequence of these ring-strain effects. Thus, according to the electron density drawn Figure 4, the OH···O interaction in 1,2-ethanediol represents a non-bonding situation whereas it is a topological IHB in 1,3-propanediol, with the corresponding BCP on a pathway linking donor and acceptor atoms and a ring critical point (RCP) associated to a six member ring.

2.2. Variations on the atomic properties upon the conformational changes

Figure 5 shows the process of interconformational change studied for 1,2-ethanediol and 1,3-propanediol. Those corresponding to 1,2-ethanediol are named $1,2^n$ and those corresponding to 1,3-propanediol $1,3^n$ ($n=1$ or 2). Two processes were studied for 1,2-ethanediol, in both processes a conformer with non-bonding OH···O interaction turns into a conformer without any OH···O interaction. Other two processes were studied for 1,3-propanediol, nevertheless one of them, $1,3,^2$ involves two conformers with OH···O IHB (see Fig. 5).

Table 3 collects the variations of atomic electron population and energy upon the processes plotted in Figure 5. The values of ΔN(H) and ΔE(H) can be rationalized approximately in terms of Eq. 1.

Processes $\mathbf{1,2}^1$ and $\mathbf{1,2}^2$: the main variations of ΔN(H) and ΔE(H) correspond to H_2, H_3, H_5, and H_{10}. H_2 and H_3 present '*gauche*' stabilization at gGt and g′Gt, respectively, so that when the gGt turns into g′Gt these atoms display similar

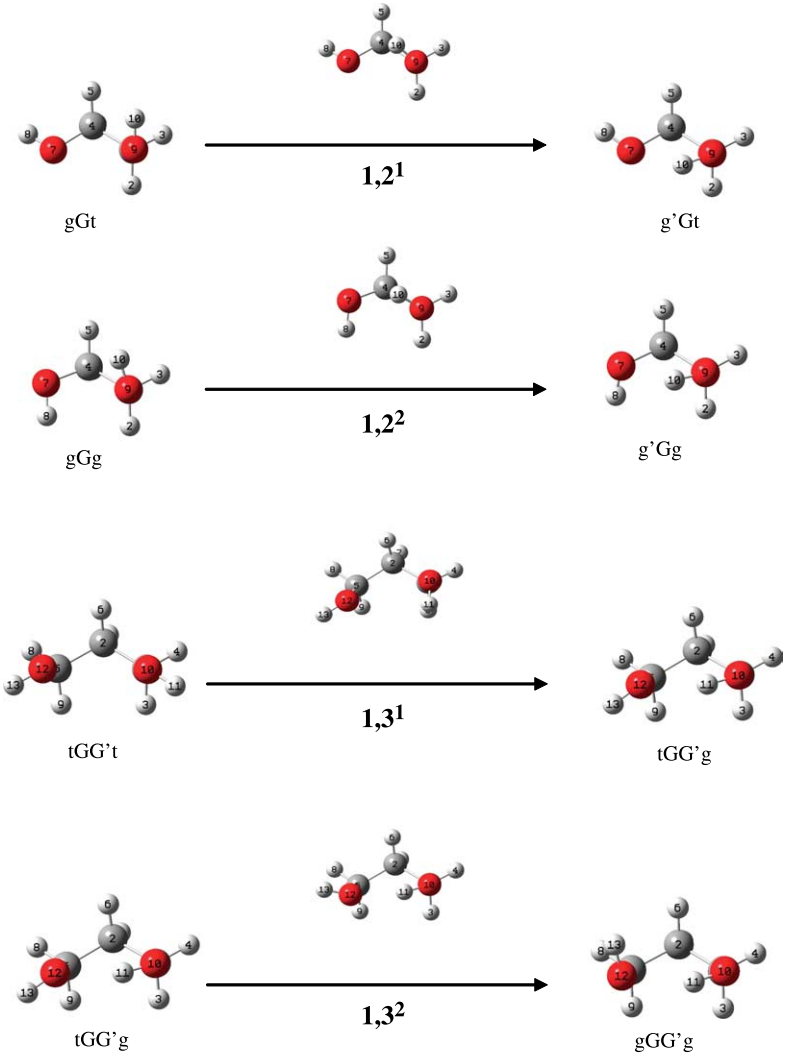


Figure 5. Process of interconformational change of 1,2-ethanediol and 1,3-propanediol studied in this work.

Table 3. Variations of atomic electron populations and atomic energies for the process of interconformational change for 1,2-ethanediol and 1,3-propanediol drawn in Figure 3

	$1,2^1$		$1,2^2$			$1,3^1$		$1,3^2$	
	$10^2\Delta N$	ΔE (kcal mol^{-1})	$10^2\Delta N$	ΔE (kcal mol^{-1})		$10^2\Delta N$	ΔE (kcal mol^{-1})	$10^2\Delta N$	ΔE (kcal mol^{-1})
C1	−0.2	−3.23	−0.6	−2.01	C1	−1.0	2.24	0.3	−1.87
C4	1.9	−10.31	2.0	−11.63	C2	1.4	−5.67	0.7	−2.68
H2	2.8	−5.40	2.2	−3.07	C5	3.0	−13.28	−0.3	−0.82
H3	−2.5	4.60	−1.8	3.20	H3	0.2	0.24	−0.4	0.81
H5	−2.1	4.08	−2.2	5.09	H4	−2.2	4.39	−0.1	0.44
H6	−0.4	1.08	0.0	0.11	H6	1.1	−2.96	2.0	−4.07
H8	−0.7	2.44	0.2	−1.38	H7	−0.5	2.65	−0.1	0.73
H10	−2.4	8.24	−1.4	5.03	H8	−1.3	3.37	0.0	0.31
O7	1.6	0.09	0.3	5.30	H9	−0.9	1.62	−2.3	4.44
O9	1.7	−5.05	1.0	−3.19	H11	−4.1	14.47	0.5	−1.28
					H13	−1.4	4.87	0.5	−1.12
					O10	3.9	−12.79	−0.1	1.02
					O12	2.1	−4.01	−0.9	3.68

values of ΔN(H) and ΔE(H) with opposite sing. H_5 presents an OH···HC interaction at g′Gt, so that when the gGt turns into g′Gt this atom is destabilized and its electron population decreases. H_{10} presents OH···O non-bonding interaction at g′Gt, so that when the gGt turns into g′Gt this atom is destabilized (with larger destabilization comparing to the H_5) and its electron population decreases.

Process **1**,**3**^{1}: the main variations of ΔN(H) and ΔE(H) correspond to H_4 and H_{11}. H_4 presents a '*gauche*' stabilization for tGG′g, so that when the tGG′t conformer turns into tGG′g this atom is destabilized and its electron population decreases. H_{11} presents OH···O IHB at tGG′g, so that when the tGG′t turns into tGG′g this atom is destabilized and its electron population decreases (with larger destabilization comparing to H_{10} in $1,2^1$ and $1,2^2$).

Process **1**,**3**:^{2} the main variations of ΔN(H) and ΔE(H) correspond to H_6, H_9. H_6 presents an OH···HC interaction in tGG′t, so that when the tGG′t turns into tGG′g this atom is stabilized and its electron population increases. H_9 presents '*gauche*' interaction in tGG′g, so that when tGG′t turns into tGG′g this atom is destabilized and its electron population decreases.

Notice that according to the QTAIM atomic properties the 'stabilizing interactions' in these systems always are concurrent with a destabilization of the hydrogens and a decrease in the electron population as previously found at hydrogen bonding systems.[23,17,24]

Figure 6 displays the values of N(H) versus w(C–C–O–H), where w(C–C–O–H) is the reaction coordinate for the $1,2^n$ and $1,3^n$ processes. N(H) corresponds to the electron population of the H involved in the O–H···O non-bonding or bonding interaction in the process considered. Some differences between the behavior on $1,2^n$ and $1,3^n$ were found. For instance, the total variation of N(H) is larger for $1,3^1$ in agreement with stronger interactions. In contrast, the values of N(H) hardly change for $1,3^2$ as both the conformers display IHB. On the other hand, the values of N(H) at $1,2^n$ display a minimum before reaching the final conformer. This is due to the fact that the shortest O···H distance (2.264 and 2.304 Å at $1,2^1$ and $1,2^2$, respectively) does not correspond to any of the stable conformers, but to the lowest N(H) value.

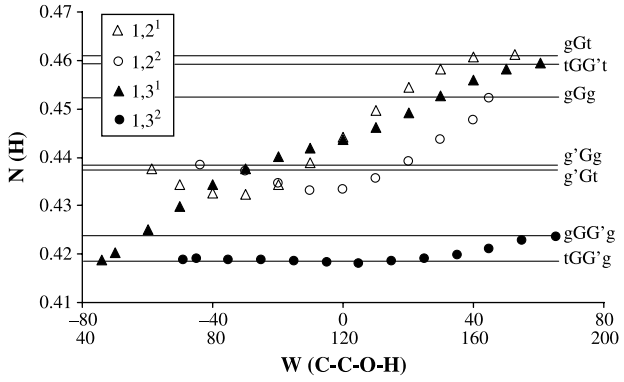


Figure 6. Plots of the atomic population (in au) of the hydrogen involved in IHB, N(H), versus the C–C–O–H dihedral angle (in degrees), w(C–C–O–H), for the processes drawn in Figure 5. The first row at the 'x' axis represents the values of w(C–C–O–H) for $1,2^n$ while the second row represents the values of w(C–C–O–H) for $1,3^n$. Horizontal lines correspond to the different conformers.

In a previous work on β-hydroxyethoxy and β-hydroxyethylperoxy radicals[24] linear correlations between E(H) and N(H) were found when the O and H atoms approached one another by rotating around dihedral angles or shortening the O···H distance. Moreover, the slope of these linear correlations changed when a BCP linking the O and H was formed. Similar linear correlations have been found for 1,2-ethanediol and 1,3-propanediol in as depicted in Figure 7, where the N(H) values are those collected in Figure 6. Good linear correlations were found for $1,2^1$, $1,2^2$ and $1,3^1$, those corresponding to 1,2-ethanediol do not present changes on the slope while a small change on the slope appears for $1,3^1$ at the point where the BCP is formed. The very small changes on N(H) and E(H) at $1,3^2$ make the representation of both properties appear as an accumulation of points (see Fig. 7).

3. Conclusions

The conformational energy of 1,2-ethanediol, 1,3-propanediol, and 1,4-propanediol can be split to a very good approximation into four different contributions: OH···O interactions, $\Delta E_{OH\cdots O}$, '*gauche*' stabilization of hydrogens and carbons due to the oxygen lone pairs, $\Delta E_{g(H)}$ and $\Delta E_{g(C)}$, and stabilizations due to the relative arrangement of hydroxyl and β-methylene groups, $\Delta E_{OH\cdots HC}$.

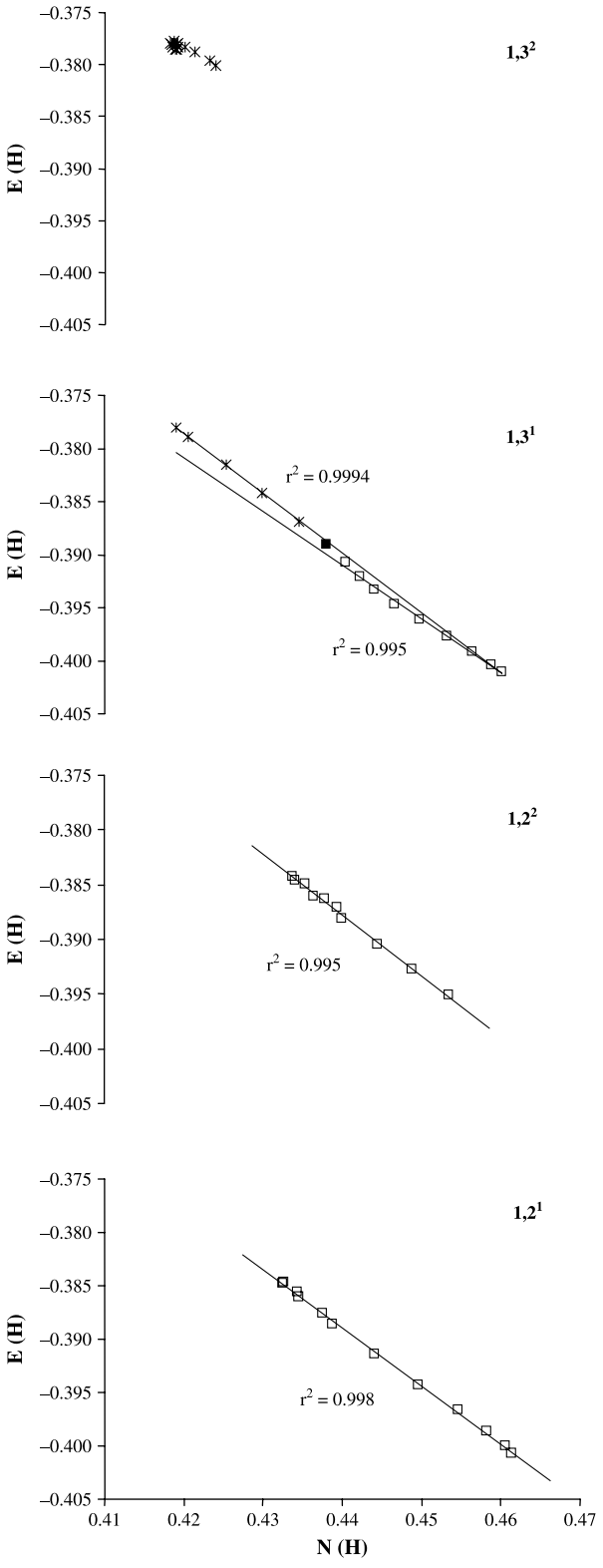


Figure 7. Plots of the atomic energy (in au) of the hydrogen involved in IHB, E(H), versus its atomic electron population, N(H), (in au) for several points along the processes drawn in Figure 5. Black squares represent the geometry for which the BCP is formed, white squares and crosses represent geometries before and after the BCP formation, respectively.

An additional term has to be included when comparing conformers with different arrangement of the O–C–C–O unit in 1,2-ethanediol ($\Delta E'$). This partitioning scheme allows to estimate and rationalize the energy due to the O–H···O interactions, $\Delta E_{OH\cdots O}$, from the relative electronic energies of the conformers without neglecting important structural changes between them nor introducing arbitrary chosen reference conformations. Moreover, the topological analysis of the electron density along with the $\Delta E_{OH\cdots O}$ values shows that the OH···O interaction must be considered non-bonding at 1,2-ethanediol and bonding in 1,3-propanediol and 1,4-butanediol.

Both the values of $\Delta E_{OH\cdots O}$ for intramolecular and intermolecular (for instance the dimer of methanol) interactions display a very good linear correlation with the $r(O\cdots H)^{-1}$ values. These linear correlations indicate a steeper decrease of $\Delta E_{OH\cdots O}$ when r(O···H) increases for the intramolecular case than for the intermolecular case, which can be attributed to ring-strain effects. These effects explain also why the donor/acceptor BCP remains present in the methanol dimer for r(O···H) distances where BCPs are not present in 1,2-ethanediol.

The linear correlations displayed by N(H) and E(H) along the rotation over the w(C–C–O–H) dihedral angles can be employed to characterize O···H topological hydrogen bonds in these compounds.

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Reaction of magnesium cyclopropylidene with *N*-lithio arylamines: a method for generation of α-amino-substituted cyclopropylmagnesiums and a study for their reactivity with electrophiles

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Abstract—Magnesium cyclopropylidene was generated from 1-chlorocyclopropyl phenyl sulfoxide with *i*-PrMgCl in THF at −78 °C in high yield by a sulfoxide–magnesium exchange reaction. The generated magnesium cyclopropylidene was found to be reactive with *N*-lithio arylamines to give α-amino-substituted cyclopropylmagnesiums. The reaction of the α-amino-substituted cyclopropylmagnesiums with several electrophiles was examined and a new method for a synthesis of cyclopropane amino acid derivatives was realized.

1. Introduction

Carbenes and carbenoids have long been recognized as highly reactive carbon species and are frequently used as useful intermediates in organic synthesis.[1] In the synthetic viewpoint, however, many carbenes are relatively short-lived and are too reactive to control. Recently, carbene–metal complexes (metal carbenes or metallocarbenes) were found to be controllable and highly effective carbenoids and are used widely in organic synthesis.[1b]

Cyclopropylidenes (carbenacyclopropanes) are the carbenes or carbenoids of cyclopropanes and are also known as interesting reactive intermediates. Cyclopropylidenes are usually known as the fleeting intermediates of the reaction of 1,1-dihalocyclopropanes with alkylmetals giving allenes.[2] These reactions are called the Doering–Moore–Skattebol reaction or the Doering–LaFlamme allene synthesis.[3]

Recently, we are interested in the chemistry of the magnesium carbenoids derived from α-haloalkyl sulfoxides[4] or α-haloalkenyl sulfoxides[5] by the sulfoxide–magnesium exchange reaction.[6] In the studies, we have found that the magnesium cyclopropylidenes **2**, which were derived from 1-chlorocyclopropyl phenyl sulfoxides **1** with a Grignard reagent by the sulfoxide–magnesium exchange reaction, are much more stable and controllable compared to the corresponding lithium cyclopropylidenes and could be used in organic synthesis.[7]

In continuation of our interest in the use of the magnesium cyclopropylidenes in organic synthesis we investigated the reaction of the magnesium cyclopropylidenes **2** with several nucleophiles and found that the reaction with *N*-lithio arylamines gave α-amino-substituted cyclopropylmagnesiums **3**. We also investigated the reaction of the cyclopropylmagnesiums **3** with several electrophiles and developed this chemistry to a new method for a synthesis of cyclopropane amino acid derivatives **4** (E=$COOCH_3$) (Scheme 1).

Cyclopropane amino acids (1-aminocyclopropane-1-carboxylic acid) and their derivatives have recently received considerable attention.[8] The reaction described below is worth noting as a unique way for the synthesis of cyclopropane amino acid derivatives.

Keywords: Sulfoxide; Sulfoxide–magnesium exchange; Magnesium cyclopropylidene; α-Amino-substituted cyclopropylmagnesium; Cyclopropane amino acid.
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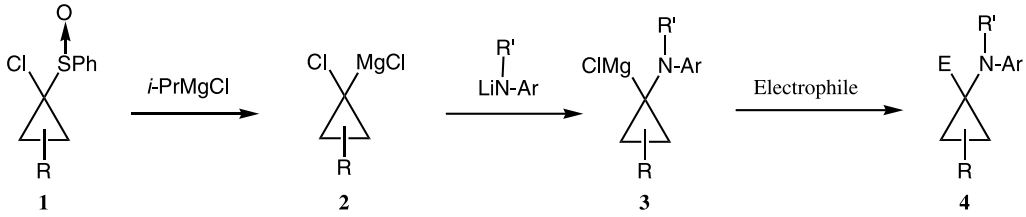


Scheme 1.

2. Results and discussion

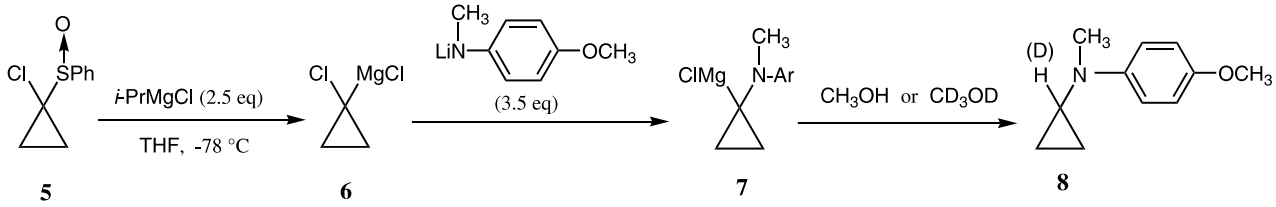
2.1. Generation of magnesium cyclopropylidene 6 from 1-chlorocyclopropyl phenyl sulfoxide 5 by the sulfoxide–magnesium exchange reaction and their reaction with *N*-lithio arylamines

First, 1-chlorocyclopropyl phenyl sulfoxide **5** was synthesized from commercially available cyclopropyl phenyl sulfide[7b] and it was treated with 2.5 equiv of *i*-PrMgCl in THF at −78 °C. The sulfoxide–magnesium exchange reaction took place instantaneously to afford 1-chlorocyclopropyl magnesium chloride **6** in high yield.[7] To this reaction mixture, 3.5 equiv of *N*-lithio *N*-methyl *p*-anisidine (prepared from *N*-methyl *p*-anisidine with *n*-BuLi in THF) was added through a cannula and the reaction mixture was slowly allowed to warm to −50 °C (Scheme 2, entry 1).

Fortunately, the desired *N*-cyclopropyl *N*-methyl *p*-anisidine **8** was obtained in 42% yield. When the temperature of the reaction was allowed to warm to −40 °C, the yield of **8** was improved to 82% (entry 2). Interestingly, quenching of this reaction with CD_3OD gave the deuterated compound **8** (D) and the deuterium incorporation was measured to be 98% by ^1H NMR. This result indicated that the intermediate of this reaction is α-amino-substituted cyclopropylmagnesium **7**.

The temperature of the reaction mixture was further allowed to warm to room temperature (entries 3–5); however, the yields were the same within experimental error. The results in entries 2–5 implied that the reaction of **6** with *N*-lithio *N*-methyl *p*-anisidine was almost completed at about −40 °C and the resulting α-amino-substituted cyclopropylmagnesium **7** is stable at room temperature. When this reaction was conducted with 2 equiv of *N*-lithio *N*-methyl *p*-anisidine, the same yield of **8** was obtained (entry 6). It is noted that the reaction with 1.5 equiv of the amine gave a diminished yield (61%) of **8**.

Encouraged by these results, we investigated the reaction of magnesium cyclopropylidene **6** with other *N*-lithioamines and the results are summarized in Table 1. *N*-Methylaniline, 4-chloro-*N*-methylaniline, and *N*-benzyl-*p*-anisidine gave 60–67% yield of the desired *N*-cycloproyl aryl amines (**9a**–**9c**) and quenching with CD_3OD gave the deuterated compounds with high deuterium content (entries 1–3). Diphenylamine gave the desired cyclopropyl amine **9d**; however, the yield was not satisfactory (entry 4). Interestingly, dibenzylamine did not afford any

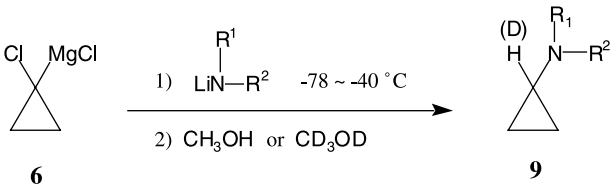


Entry	Temperature	Electrophiles	**8**	
			Yield / %	D-content / %
1	-78 ~ -50 °C	CH_3OH	42	--
2	-78 ~ -40 °C	CD_3OD	82	98
3	-78 ~ -30 °C	CH_3OH	76	--
4	-78 ~ 0 °C	CH_3OH	79	--
5	-78 ~ room temp.	CD_3OD	82	98
6[a]	-78 ~ -40 °C	CH_3OH	82	--

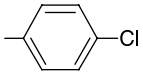
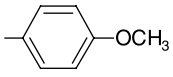
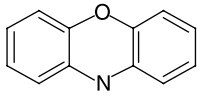
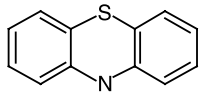
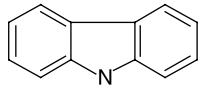
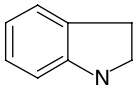
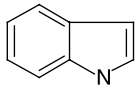
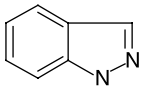
[a] The reaction was carried out with 2.0 equivalents of *N*-lithio *N*-methyl *p*-anisidine.

Scheme 2. Generation of magnesium cyclopropylidene **6** and reation with *N*-lithio *N*-methyl *p*-anisidine followed by CH_3OH or CD_3OD.

Table 1. Reaction of magnesium cyclopropylidene **6** with *N*-lithio amines followed by CH_3OH or CD_3OD



6 **9**

Entry	R^1	R^2	Equiv of amine	**9**		
					Yield (%)	D-content (%)
1	CH_3		3.5	**9a**	67	93
2	CH_3		3.5	**9b**	60	90
3	CH_2Ph		3.5	**9c**	60	98
4			3.5	**9d**	42	92
5	CH_2Ph	CH_2Ph	3.5	**9e**	0	
6[a]			2.0	**9f**	87	99
7[a]			2.0	**9g**	55	—[b]
8[a]			2.0	**9h**	43	—[b]
9[a]			2.0	**9i**	75	—[b]
10[a]			2.0	**9j**	21	—[b]
11[a]			2.0	**9k**	12	—[b]

[a] Temperature of the reaction mixture was allowed to warm to room temperature.
[b] The reaction was quenched with methanol.

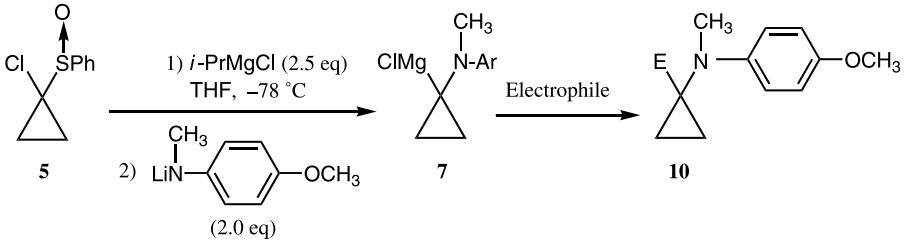
cyclopropylamine at all (entry 5). Only isopropyl phenyl sulfoxide and dibenzylamine were observed from the reaction mixture. This result indicated that the magnesium cyclopropylidene **6** only reacts with *N*-lithio arylamines. This result consistents with that of the reaction of *N*-lithio amines with the magnesium carbenoids generated from 1-chloroalkyl phenyl sulfoxides reported before.[4c]

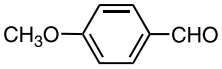
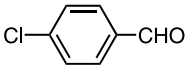
Further, we investigated the reaction of **6** with *N*-lithio nitrogen-containing heterocyclic compounds. In these cases, we used 2 equiv of the nucleophiles. Phenoxazine gave excellent yield of **9f** with perfect deuterium incorporation (entry 6). Phenothiazine and carbazole gave moderate yields of the desired compounds **9g** and **9h** (entries 7 and 8). Indoline gave good yield of the desired compound **9i**; however, indole and indazole gave very poor yields (entries 10 and 11). These results implied that the yields of the reaction of **6** with *N*-lithio nitrogen-containing heterocyclic compounds are fairly variable with the used heterocyclic compounds.

2.2. Investigation of the reactivity of the α-amino-substituted cyclopropylmagnesiums 7 with electrophiles and a new synthesis of cyclopropane amino acid derivatives

As described above, the reaction of the magnesium cyclopropylidene **6** with *N*-lithio arylamines gave α-amino-substituted cyclopropylmagnesiums, which were deuterated with high deuterium incorporation. If these

Table 2. Generation of α-amino-substituted cyclopropylmagnesium **7** and reaction with several electrophiles



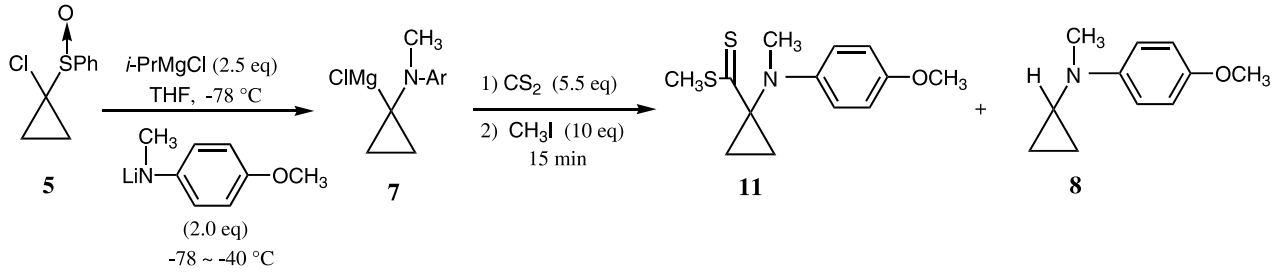
Entry	Electrophile	Equiv	Conditions	**10**	
					Yield (%)
1	PhCHO	5.5	−40 to −20 °C, 1 h	**10a**	40
2		5.5	−40 to −20 °C, 1 h	**10b**	53
3		5.5	−40 to −20 °C, 1 h	**10c**	0[a]
4	CH_3CH_2CHO	5.5	−40 to −20 °C, 1 h		0[a]
5	$ClCOOC_2H_5$	3.0	−40 °C, 10 min	**10d**	10
6[b]	$ClCOOC_2H_5$	5.5	−40 °C, 10 min	**10d**	20
7[b]	$ClCOOCH_3$	5.5	−40 °C, 10 min	**10e**	11
8[b]	$NCCOOC_2H_5$	5.5	−40 °C, 10 min		0[a]
9[b]	CO_2	5.5	−40 °C, 10 min		Complex

[a] No reaction was observed.
[b] 3.5 equiv of *N*-lithio *N*-methyl *p*-anisidine was used in this reaction.

cyclopropylmagnesiums have enough nucleophilicity to several electrophiles, addition of the electrophiles to the reaction mixture was expected to give *N*-cyclopropylamines having a substituent at the α-position **10** (Table 2). We tried to trap the α-amino-substituted cyclopropylmagnesium **7** with several electrophiles and the results are summarized in Table 2.

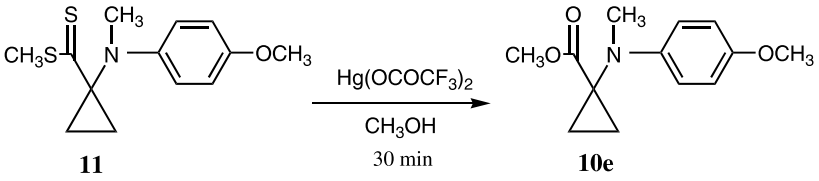
Benzaldehyde and *p*-anisaldehyde gave the desired adduct **10a** and **10b** in moderate yield; however, *p*-chlorobenzaldehyde and propionaldehyde gave none of the desired adduct (entries 1–4). These results implied that the nucleophilicity of **7** is quite low. Next, with great anticipation, we investigated the reaction of **7** with ethyl chloroformate; however, only maximum 20% yield of the desired cyclopropane amino acid derivative **10d** was obtained. Methyl chloroformate, ethyl cyanoformate, and carbon dioxide were not effective (entries 7–9).

Finally, we investigated the reaction of **7** with carbon disulfide (Scheme 3).[9] α-Chlorocyclopropyl phenyl sulfoxide **5** was treated with 2.5 equiv of *i*-PrMgCl followed by *N*-lithio *N*-methyl *p*-anisidine (2.0 equiv) and the



Entry	Conditions for the treatment with CS_2	**11** / yield %	**8** / yield %
1	-40 °C, 10 min	Trace	75
2	-40 °C, 1 h	17	61
3	-40 ~ -20 °C, 1 h	72	10
4	-40 ~ room temp., 2 h	91	0

Scheme 3. Generation of α-amino-substituted cyclopropylmagnesium chloride **7** and reaction with CS_2 followed by iodomethane.



Entry	Conditions	$Hg(OCOCF_3)_2$ (equiv)	**10e** / yield %
1	Room temperature	2	40[a]
2	Room temperature	3	53
3	0 °C	3	71
4	-20 °C	3	92

[a] Dithioester **11** was recovered in 16% yield.

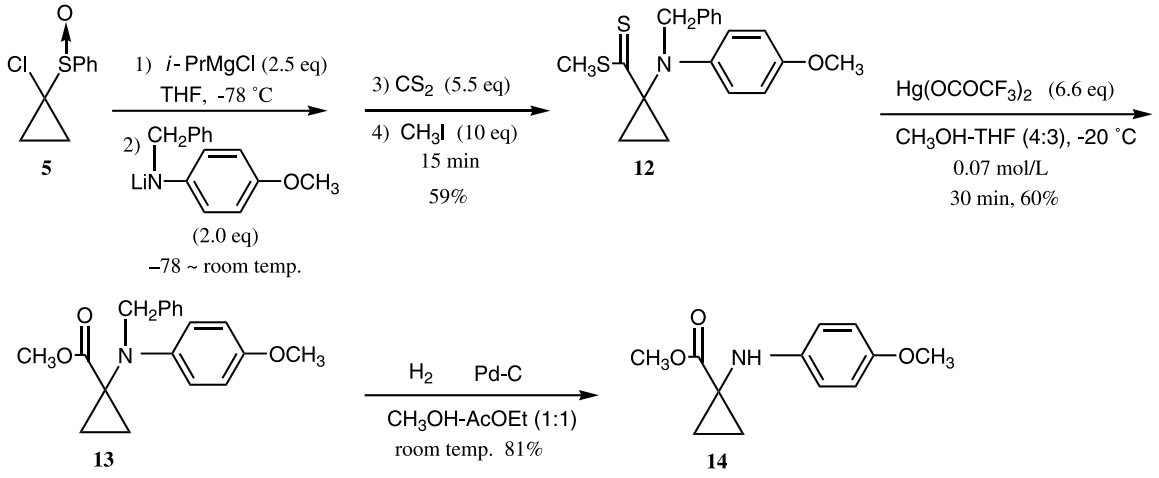
Scheme 4. Methanolysis of the dithioester **11** with $Hg(OCOCF_3)_2$ in methanol.

temperature of the reaction mixture was allowed to warm to −40 °C. To this reaction mixture was added 5.5 equiv of carbon disulfide and the reaction mixture was stirred at −40 °C for 10 min. Iodomethane (10 equiv) was added finally to this reaction mixture (Scheme 3, entry 1). From this reaction the desired dithioester **11** was obtained; however, cyclopropylamine **8** was found to be the main product.

The reaction time for the treatment with carbon disulfide was prolonged to 1 h (entry 2) or the reaction temperature was allowed to warm to −20 °C and stirred 1 h (entry 3) to give the desired dithioester **11** in up to 72% yield. The best yield was obtained when the reaction with carbon disulfide was warmed to room temperature and stirred for 2 h (entry 4).

Methanolysis of the dithioester **11** was successfully carried out with mercury(II) trifluoroacetate in methanol[10] at the concentration of 0.2 mol/L and the results are summarized in Scheme 4. The reaction did not complete with 2 equiv of $Hg(OCOCF_3)_2$ at room temperature (entry 1). The reaction completed with 3 equiv of $Hg(OCOCF_3)_2$; however, the reaction gave some byproducts and the yield was not satisfactory (entry 2). The reaction was conducted with 3 equiv of $Hg(OCOCF_3)_2$ at 0 and −20 °C, and the best yield (92%) of the cyclopropane amino acid derivatives **10e** was obtained at −20 °C (entry 4).

As the generality of this reaction, we further investigated the reaction of **5** with *N*-benzyl-*p*-anisidine (Scheme 5). Treatment of **5** with *i*-PrMgCl followed by *N*-lithio *N*-benzyl-*p*-anisidine gave the α-amino-substituted cyclopropylmagnesium. Carbon disulfide followed by iodomethane was added to the reaction mixture as above to afford the desired dithioester **12** in 59% overall yield from **5**. As the solubility of **12** was found to be low in methanol, methanolysis of the dithioester **12** was carried out in a mixture of CH_3OH–THF with excess $Hg(OCOCF_3)_2$ to give the methylester **13** in 60% yield. Finally, the benzyl group was hydrogenolized with hydrogen in the presence of Pd–C to give cyclopropane amino acid derivative **14** in 81% yield.



Scheme 5. A synthesis of cyclopropane amino acid derivative **14** from **5** with *N*-benzyl-*p*-anisidine.

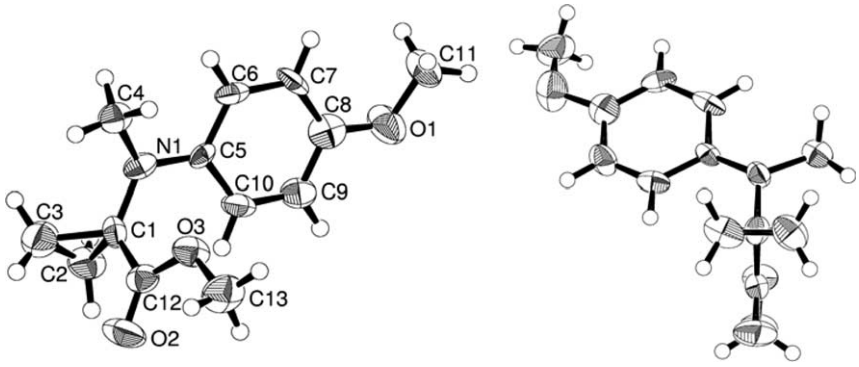


Figure 1. An ORTEP view for the structure of **10e** showing the atom labeling diagram (left), together with a view perpendicular to the cyclopropane ring showing the location of the (4-methoxyphenyl)methylamino group with regard to the cyclopropane ring (right).

2.3. X-ray crystallographic analysis of the cyclopropane amino acid derivative 10e

During the course of this work, we encountered an unusual phenomenon in the ^{1}H NMR spectrum measured in a $CDCl_3$ solution of the cyclopropane amino acid derivative **10e**. If the rotational motion of the (4-methoxyphenyl)methylamino moiety about the N–C(cyclopropane) bond axis is undertaken very rapidly within a timescale much shorter than the timescale of ^{1}H NMR, the structure of **10e** should be regarded as symmetrical leading to the observation of two sets of magnetically non-equivalent protons on the cyclopropane ring. In spite of the fact that three methyl groups of **10e** showed quite sharp signals, four protons on the cyclopropane ring are observed at δ 1.20 with a broad signal (two protons) and at δ 1.47 and 1.81 as two very broad signals (each one proton), indicating that the two carbon atoms on its 2- and 3-positions are not equivalent magnetically. In order to better understand the structure of **10e** and to elucidate the unusual observation described above, the crystal structure of **10e** has been determined by X-ray diffraction. The ORTEP diagram of **10e** is shown in Figure 1.[11]

Obviously, the crystal structure is not symmetrical with regard to the cyclopropane ring. The result also indicates that the methoxycarbonyl moiety is so bulky that the fast rotation of the (4-methoxyphenyl)methylamino moiety around the N–C (cyclopropane) bond is prohibited. The molecular modeling studies using either the crystal structure or a computed structure (density functional method) also showed that such a rotation mode is not favored due to the steric contacts between these bulky moieties. It is also noteworthy that compound **8** whose structure is given by the substitution of the methoxycarbonyl unit in **10e** by a proton shows two sets of symmetrical signals in its ^{1}H NMR. As a whole, the unexpected ^{1}H NMR signals of **10e** can be understood from the structure in Figure 1.

3. Experimental

3.1. General

^{1}H NMR spectra were measured in a $CDCl_3$ solution with JEOL JNM-LA 300 and 500 spectrometer. Electron-impact mass spectra (MS) were obtained at 70 eV by direct insertion. Silica gel 60 (MERCK) containing 0.5% fluorescence reagent 254 and a quartz column were used for column chromatography and the products having UV absorption were detected by UV irradiation. In experiments requiring a dry solvent, THF was distilled from benzophenone ketyl.

3.1.1. 1-Chlorocyclopropyl phenyl sulfoxide (5). To a solution of cyclopropyl phenyl sulfide (3 g; 19.9 mmol) in CH_2Cl_2 (80 mL) was added *m*-chloroperbenzoic acid (about 70% purity; 5.4 g; 21.9 mmol) with stirring at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. To the reaction mixture was added aq Na_2SO_3 to reduce excess *m*-chloroperbenzoic acid and the solution was diluted with CH_2Cl_2 and the organic layer was washed with 5% NaOH followed by satd aq NH_4Cl. The organic layer was dried over $MgSO_4$ and the solvent was evaporated to give an oil, which was purified by silica gel column chromatography to afford 3.3 g (99%) of cyclopropyl phenyl sulfoxide as a cololess oil; IR (neat) 3007, 1652, 1478, 1444, 1087, 1044, 1022 (SO), 880, 750, 692 cm^{-1}.

A solution of the cyclopropyl phenyl sulfoxide (2.14 g; 13 mmol) in CCl_4 (26 mL) was stirred with *N*-chlorosuccinimide at room temperature for 13 h. The precipitate was filtered off and the solvent was evaporated to give an oil, which was purified by silica gel column chromatography to afford 2.5 g (96%) of **5** as a colorless crystals; mp 49–50 °C (AcOEt–hexane); IR (KBr) 3084, 1477, 1443, 1089 (SO), 1059 (SO), 754, 691 cm^{-1}; ^{1}H NMR δ 1.21–1.27 (1H, m), 1.36–1.42 (1H, m), 1.65–1.72 (2H, m), 7.52–7.59 (3H, m), 7.70–7.73 (2H, m). MS *m*/*z* (%) 200 (M^+, 8), 125 (100), 97 (19), 77 (20), 51 (13). Calcd for C_9H_9ClOS: M, 200.0061. Found: *m*/*z* 200.0054. Anal. Calcd for C_9H_9ClOS; C, 53.86; H, 4.52; Cl, 17.67; S, 15.98. Found: C, 53.94; H, 4.17; Cl, 17.58; S, 15.97.

3.1.2. *N*-Cyclopropyl-*N*-(4-methoxyphenyl)methylamine (8). To a solution of *i*-PrMgCl (0.75 mmol) in THF (1.5 mL) at −78 °C was added a solution of **5** (60 mg; 0.3 mmol) in 1.5 mL of THF dropwise with stirring. After 10 min, a solution of *N*-lithio *N*-methyl *p*-anisidine (prepared from *N*-methyl *p*-anisidine (1.05 mmol) and *n*-BuLi (1.16 mmol) in 1.5 mL of THF at 0 °C) was added to a solution of the magnesium cyclopropylidene **6** through a cannula and the reaction mixture was slowly allowed to warm to −40 °C over 1 h. The reaction was quenched with MeOH and the

whole was extracted with $CHCl_3$ and the organic layer was washed with satd aq NH_4Cl and dried over $MgSO_4$. After removal of the solvent, the product was purified by silica gel column chromatography to give **8** (43.6 mg; 82%) as a light yellow oil; IR (neat) 3004, 2933, 1513, 1455, 1361, 1245, 1040, 818 cm^{-1}; ^1H NMR δ 0.58 (2H, m), 0.77 (2H, m), 2.27 (1H, m), 2.92 (3H, s), 3.77 (3H, s), 6.84 (2H, d, J=9.2 Hz), 6.97 (2H, d, J=9.2 Hz). MS m/z (%) 177 (M^+, 100), 176 (60), 162 (80), 146 (18), 134 (16), 121 (57). Calcd for $C_{11}H_{15}NO$: M, 177.1154. Found: m/z 177.1135.

3.1.3. *N*-Cyclopropyl-*N*-methylphenylamine (9a). Light yellow oil; IR (neat) 2933, 1601, 1503, 1363, 751, 692 cm^{-1}; ^1H NMR δ 0.61 (2H, m), 0.81 (2H, m), 2.37 (1H, m), 2.97 (3H, s), 6.76 (1H, t, J=7.3 Hz), 6.99 (2H, d, J=8.0 Hz), 7.21–7.26 (2H, m). MS m/z (%) 147 (M^+, 100), 146 (89), 132 (46), 120 (20), 104 (23), 91 (40), 77 (42). Calcd for $C_{10}H_{13}N$: M, 147.1048. Found: m/z 147.1057.

3.1.4. *N*-(4-Chlorophenyl)-*N*-cyclopropylmethylamine (9b). Colorless amorphous; IR (neat) 2935, 1599, 1497, 1360, 1115, 813, 668 cm^{-1}; ^1H NMR δ 0.60 (2H, m), 0.81 (2H, m), 2.36 (1H, m), 2.95 (3H, s), 6.89 (2H, d, J=8.9 Hz), 7.17 (2H, d, J=8.9 Hz). MS m/z (%) 181 (M^+, 100), 180 (86), 166 (67), 146 (50), 144 (50), 140 (68), 125 (47), 111 (59), 91 (39). Calcd for $C_{10}H_{12}ClN$: M, 181.0659. Found: m/z 181.0659.

3.1.5. *N*-Benzyl-*N*-cyclopropyl(4-methoxyphenyl)amine (9c). Colorless amorphous; IR (neat) 2943, 1513, 1454, 1366, 1243, 1043, 818, 729 cm^{-1}; ^1H NMR δ 0.65 (2H, m), 0.78 (2H, m), 2.52 (1H, m), 3.74 (3H, s), 4.55 (2H, s), 6.79 (2H, d, J=9.2 Hz), 6.87 (2H, d, J=9.2 Hz), 7.15–7.30 (5H, m). MS m/z (%) 253 (M^+, 84), 252 (44), 162 (99), 147 (26), 134 (54), 132 (70), 91 (100). Calcd for $C_{17}H_{19}NO$: M, 253.1465. Found: m/z 253.1463.

3.1.6. *N*-Cyclopropyldiphenylamine (9d). Colorless oil; IR (neat) 3022, 1590, 1491, 1358, 1298, 1267, 1025, 748, 693 cm^{-1}; ^1H NMR δ 0.64 (2H, m), 0.85 (2H, m), 2.75 (1H, m), 6.99 (2H, m), 7.07 (4H, m), 7.28 (4H, m). MS m/z (%) 209 (M^+, 100), 208 (82), 193 (19), 167 (28), 117, (88), 104 (63), 91 (38), 77 (91). Calcd for $C_{15}H_{15}N$: M, 209.1203. Found: m/z 209.1203.

3.1.7. 10-Cyclopropyl-10*H*-phenoxazine (9f). To a solution of *i*-PrMgCl (0.5 mmol) in THF (1.0 mL) at −78 °C was added a solution of **5** (40 mg; 0.2 mmol) in 1.0 mL of THF dropwise with stirring. After 10 min, a solution of *N*-lithio phenoxazine (prepared from phenoxazine (0.4 mmol) and *n*-BuLi (0.44 mmol) in 0.6 mL of THF at 0 °C) was added to the solution of the magnesium cyclopropylidene **6** through a cannula and the reaction mixture was slowly allowed to warm to room temperature over 2 h. The reaction was quenched with MeOH and the whole was extracted with $CHCl_3$ and the extract was washed with aq NH_4Cl and dried over $MgSO_4$. After removal of the solvent, the product was purified by silica gel column chromatography to give **9f** (38.9 mg; 87%) as colorless crystals; mp 111–112 °C (AcOEt–hexane); IR (KBr) 2956, 1590, 1483, 1338, 1268, 745 cm^{-1}; ^1H NMR δ 0.72 (2H, m), 1.10 (2H, m), 2.38 (1H, m), 6.75 (4H, m), 6.86–6.91 (2H, m), 6.98 (2H, d, J=8.0 Hz). MS m/z (%) 223 (M^+, 65), 222 (100), 207 (10), 182 (41), 127, (10). Calcd for $C_{15}H_{13}NO$: M, 223.0996. Found: m/z 223.0998.

3.1.8. 10-Cyclopropyl-10*H*-phenothiazine (9g). Colorless crystals; mp 118–121 °C (AcOEt–hexane); IR (KBr) 3055, 1572, 1459, 1313, 1243, 1023, 755 cm^{-1}; ^1H NMR δ 0.72 (2H, m), 1.15 (2H, m), 2.79 (1H, m), 6.93 (2H, t, J=5.5 Hz), 7.11 (2H, dd, J=1.2, 7.6 Hz), 7.14–7.25 (4H, m). MS m/z (%) 239 (M^+, 86), 238 (100), 223 (17), 210 (12), 198 (35), 154 (9). Calcd for $C_{15}H_{13}NS$: M, 239.0768. Found: m/z 239.0770. Anal. Calcd for $C_{15}H_{13}NS$: C, 75.28; H, 5.47; N, 5.85; S, 13.40. Found: C, 74.93; H, 5.83; N, 5.58; S, 12.98.

3.1.9. 9-Cyclopropyl-9*H*-carbazole (9h). Colorless crystals; mp 118–120 °C (AcOEt–hexane); IR (KBr) 3063, 1596, 1480, 1457, 1375, 1317, 1233, 1158, 1034, 753, 748, 723 cm^{-1}; ^1H NMR δ 1.11 (2H, m), 1.26 (2H, m), 3.30 (1H, m), 7.23 (2H, ddd, J=0.9, 7.4, 7.5 Hz), 7.46 (2H, ddd, J=1.3, 7.4, 8.6 Hz), 7.65 (2H, d, J=8.3 Hz), 8.06 (2H, d, J=7.6 Hz). MS m/z (%) 207 (M^+, 63), 206 (100), 204 (18), 180 (15), 166 (12), 140 (10). Calcd for $C_{15}H_{13}N$: M, 207.1046. Found: m/z 207.1041.

3.1.10. 1-Cyclopropyl-2,3-dihydro-1*H*-indole (9i). Colorless oil; IR (neat) 2926, 2822, 1607, 1488, 1453, 1368, 1277, 1021, 869, 748 cm^{-1}; ^1H NMR δ 0.64 (2H, m), 0.67 (2H, m), 2.11 (1H, m), 2.90 (2H, t, J=8.3 Hz), 3.36 (2H, t, J=8.3 Hz), 6.70 (1H, dt, J=0.9, 7.3 Hz), 6.83 (1H, dd, J=0.9, 7.3 Hz), 7.08 (2H, m). MS m/z (%) 159 (M^+, 87), 158 (100), 144 (66), 130 (48), 117 (27), 91 (24), 77 (18). Calcd for $C_{11}H_{13}N$: M, 159.1047. Found: m/z 159.1043.

3.1.11. 1-Cyclopropyl-1*H*-indole (9j). Colorless oil; IR (neat) 3013, 2925, 1509, 1476, 1464, 1370, 1314, 1235, 765, 741 cm^{-1}; ^1H NMR δ 0.99–1.09 (4H, m), 3.34 (1H, m), 6.42 (1H, dd, J=0.6, 3.0 Hz), 7.08–7.13 (2H, m), 7.19–7.25 (1H, m), 7.55–7.61 (2H, m). MS m/z (%) 157 (M^+, 75), 156 (100), 130 (21), 128 (10). Calcd for $C_{11}H_{11}N$: M, 157.0891. Found: m/z 157.0886.

3.1.12. 1-Cyclopropyl-1*H*-indazole (9k). Colorless oil; IR (neat) 2925, 1615, 1466, 1425, 1218, 768, 743 cm^{-1}; ^1H NMR δ 1.17 (2H, m), 1.24 (2H, m), 3.59 (1H, m), 7.16 (1H, t, J=7.4 Hz), 7.39 (1H, t, J=7.4 Hz), 7.61 (1H, d, J=8.2 Hz), 7.71 (1H, d, J=7.4 Hz), 7.94 (1H, s). MS m/z (%) 158 (M^+, 82), 157 (58), 131 (100), 130 (60), 104 (37), 103 (24), 77 (21), 76 (28). Calcd for $C_{10}H_{10}N_2$: M, 158.0844. Found: m/z 158.0847.

3.1.13. {1-[(4-Methoxyphenyl)methylamino]cyclopropyl}-phenylmethanol (10a). To a solution of *i*-PrMgCl (0.75 mmol) in THF (1.5 mL) at −78 °C was added a solution of **5** (60 mg; 0.3 mmol) in 1.5 mL of THF dropwise with stirring. After 10 min, a solution of *N*-lithio *N*-methyl-*p*-anisidine (prepared from *N*-methyl-*p*-anisidine (0.6 mmol) and *n*-BuLi (0.66 mmol) in 0.9 mL of THF at 0 °C) was added to a solution of the magnesium cyclopropylidene **6** through a cannula and the reaction mixture was slowly allowed to warm to −40 °C for 1 h. Benzaldehyde (1.65 mmol) was added to the reaction mixture dropwise with stirring and the solution was slowly allowed to warm to −20 °C over 1 h. The reaction was

quenched with MeOH and the whole was extracted with $CHCl_3$ and the extract was washed with aq NH_4Cl and dried over $MgSO_4$. After removal of the solvent, the product was purified by silica gel column chromatography to give **10a** (34.5 mg; 40%) as a colorless oil; IR (neat) 3446 (OH), 2904, 1512, 1453, 1242, 1039, 818, 745, 702 cm^{-1}; ^1H NMR δ 0.80 (2H, s), 0.94 (1H, br s), 1.11 (1H, br s), 2.62 (3H, br s), 3.77 (3H, s), 5.01 (1H, s), 6.78–6.84 (4H, m), 7.26–7.35 (5H, m). MS *m/z* (%) 283 (M^+, 21), 177 (21), 176 (100), 146 (13), 145 (17), 144 (15), 121 (75). Calcd for $C_{18}H_{21}NO_2$: M, 283.1571. Found: *m/z* 283.1577.

3.1.14. *N*-(4-Methoxyphenyl)-*N*-[1-{(4-methoxyphenyl)-hydroxymethyl}cyclopropyl]methylamine (10b). Colorless oil; IR (neat) 3469 (OH), 2934, 1514, 1464, 1243, 1036, 818 cm^{-1}; ^1H NMR δ 0.77–0.80 (2H, m), 0.93 (1H, br s), 1.07–1.12 (1H, m), 2.62 (3H, br s), 3.76 (3H, s), 3.80 (3H, s), 4.97 (1H, s), 6.77–6.85 (6H, m), 7.22 (2H, d, J=8.6 Hz). MS *m/z* (%) 313 (M^+, 14), 176 (100), 145 (22), 144 (17), 135 (12), 121 (71), 77 (11). Calcd for $C_{19}H_{23}NO_3$: M, 313.1676. Found: *m/z* 313.1669.

3.1.15. Ethyl 1-[(4-methoxyphenyl)methylamino]cyclopropanecarboxylate (10d). To a solution of *i*-PrMgCl (0.75 mmol) in THF (1.5 mL) at −78 °C was added a solution of **5** (60 mg; 0.3 mmol) in 1.5 mL of THF dropwise with stirring. After 10 min, a solution of *N*-lithio *N*-methyl-*p*-anisidine (prepared from *N*-methyl-*p*-anisidine (1.05 mmol) and *n*-BuLi (1.16 mmol) in 1.5 mL of THF at 0 °C) was added to a solution of the magnesium cyclopropylidene **6** through a cannula and the reaction mixture was slowly allowed to warm to −40 °C for 1 h. Ethyl chloroformate (1.65 mmol) was added to the reaction mixture dropwise with stirring and the reaction mixture was stirred for 10 min. The reaction was quenched with MeOH and the whole was extracted with $CHCl_3$ and the extract was washed with aq NH_4Cl and dried over $MgSO_4$. After removal of the solvent, the product was purified by silica gel column chromatography to give **10d** (14.8 mg; 20%) as a colorless oil; IR (neat) 2936, 1723 (CO), 1513, 1294, 1245, 1186, 1143, 1039, 818 cm^{-1}; ^1H NMR δ 1.14 (3H, t, J=7.0 Hz), 1.19 (2H, br s), 1.45 (1H, br s), 1.78 (1H, br s), 3.03 (3H, s), 3.75 (3H, s), 4.09 (2H, q, J=7.0 Hz), 6.74 (2H, d, J=9.2 Hz), 6.81 (2H, d, J=9.2 Hz). MS *m/z* (%) 249 (M^+, 43), 220 (59), 176 (68), 175 (27), 144 (18), 135 (21), 121 (100). Calcd for $C_{14}H_{19}NO_3$: M, 249.1363. Found: *m/z* 249.1368.

3.1.16. Methyl 1-[(4-methoxypenyl)methylamino]cyclopropanecarboxylate (10e). Colorless crystals; mp 59–61 °C (AcOEt–hexane); IR (KBr) 2958, 1722 (CO), 1512, 1433, 1301, 1248, 1195, 1035, 817 cm^{-1}; ^1H NMR δ 1.20 (2H, br s), 1.47 (1H, br s), 1.81 (1H, br s), 3.03 (3H, s), 3.63 (3H, s), 3.75 (3H, s), 6.74 (2H, d, J=8.9 Hz), 6.82 (2H, d, J=8.9 Hz). MS *m/z* (%) 235 (M^+, 49), 220 (42), 176 (72), 175 (49), 121 (100). Calcd for $C_{13}H_{17}NO_3$: M, 235.1208. Found: *m/z* 235.1213. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.93. Found: C, 66.29; H, 7.33; N, 5.88.

3.1.17. 1-[*N*-Methyl-(4-methoxylphenyl)amino]cyclopropanecarbodithioic acid methyl ester (11). To a solution of *i*-PrMgCl (0.75 mmol) in THF (1.5 mL) at −78 °C was added a solution of **5** (60 mg; 0.3 mmol) in 1.5 mL of THF dropwise with stirring. After 10 min, a solution of *N*-lithio *N*-methyl-*p*-anisidine (prepared from *N*-methyl-*p*-anisidine (0.6 mmol) and *n*-BuLi (0.66 mmol) in 0.9 mL of THF at 0 °C) was added to solution of the magnesium cyclopropylidene **6** through a cannula and the reaction mixture was slowly allowed to warm to −40 °C over 1 h. Carbon disulfide (1.65 mmol) was added to the reaction mixture dropwise with stirring and the solution was slowly allowed to warm to room temperature over 2 h. Iodomethane (3.0 mmol) was added to the reaction mixture dropwise with stirring and the reaction mixture was stirred for 15 min. The reaction was quenched with MeOH and the whole was extracted with $CHCl_3$ and the extract was washed with aq NH_4Cl and dried over $MgSO_4$. After removal of the solvent, the product was purified by silica gel column chromatography to give **11** (72.8 mg; 91%) as a colorless light yellow amorphous; IR (KBr) 2910, 1516, 1343, 1278, 1246, 1175, 1030, 814 cm^{-1}; ^1H NMR δ 1.32 (1H, br s), 1.55 (1H, br s), 2.03 (1H, br s), 2.44 (1H, br s), 2.51 (3H, s), 3.08 (3H, s), 3.76 (3H, s), 6.66 (2H, d, J=9.2 Hz), 6.84 (2H, d, J=9.2 Hz). MS *m/z* (%) 267 (M^+, 100), 252 (47), 219 (27), 174 (19), 122 (22), 121 (27). Calcd for $C_{13}H_{17}NOS_2$: M, 267.0751. Found: *m/z* 267.0757.

3.1.18. Methyl 1-[(4-methoxypenyl)methylamino]cyclopropanecarboxylate (10e). To a solution of **11** (80 mg; 0.3 mmol) in MeOH (1.5 mL) at −20 °C was added mercury (II) trifluoroacetate (0.9 mmol) with stirring and the reaction mixture was stirred for 30 min. The reaction mixture was diluted with $CHCl_3$ and the solution was washed with 10% NaOH and dried over $MgSO_4$. After removal of the solvent, the product was purified by silica gel column chromatography to give **10e** (65 mg; 92%) as colorless crystals. Melting point and all the spectral data were identical with the product described above.

3.1.19. 1-[*N*-Benzyl-*N*-(4-methoxyphenyl)amino]cyclopropanecarbodithioic acid methyl ester (12). Light yellow amorphous; IR (neat) 3000, 2930, 1511, 1440, 1353, 1278, 1236, 1186, 1147, 1036, 955, 817, 757 cm^{-1}; ^1H NMR δ 1.59 (2H, m), 1.84 (1H, m), 2.55 (3H, s), 2.66 (1H, m), 3.72 (3H, s), 4.75 (1H, d, J=18.0 Hz), 4.95 (1H, d, J=18.0 Hz), 6.60 (2H, d, J=9.2 Hz), 6.77 (2H, d, J=9.2 Hz), 7.11 (2H, d, J=8.0 Hz), 7.21–7.34 (3H, m). MS *m/z* (%) 343 (M^+, 52), 252 (100), 218 (27), 205 (19), 204 (34), 160 (55), 91 (89). Calcd for $C_{19}H_{21}NOS_2$: M, 343.1064. Found: *m/z* 343.1071.

3.1.20. Methyl 1-[*N*-Benzyl-(4-methoxyphenyl)amino]-cyclopropanecarboxylate (13). To a solution of **12** (34 mg; 0.1 mmol) in MeOH (0.82 mL) and THF (0.61 mL) at −20 °C was added mercurry (II) trifluoroacetate (0.66 mmol) and the reaction mixture was stirred for 30 min. The reaction mixture was diluted with $CHCl_3$ and the solution was washed with 10% NaOH and dried over $MgSO_4$. After removal of the solvent, the product was purified by silica gel column chromatography to give **13** (18.6 mg; 60%) as a colorless amorphous; IR (neat) 2950, 2832, 1726 (CO), 1509, 1451, 1291, 1244, 1163, 1044, 819 cm^{-1}; ^1H NMR δ 1.25–1.43 (3H, m), 1.91 (1H, br s), 3.69 (3H, s), 3.72 (3H, s), 4.66 (2H, d, J=14.4 Hz), 6.63 (2H, d, J=9.5 Hz), 6.75 (2H, d, J=9.5 Hz), 7.16 (2H, d, J=7.6 Hz), 7.22 (1H, t, J=7.6 Hz), 7.30 (2H, t, J=7.6 Hz). MS *m/z* (%) 311 (M^+, 30), 252 (27), 220 (43), 190 (55), 160

(24), 92 (22), 91 (100). Calcd for $C_{19}H_{21}NO_3$: M, 311.1519. Found: *m/z* 311.1517.

3.1.21. Methyl 1-(4-methoxyphenylamino)cyclopropanecarboxylate (14). To a solution of **13** (21 mg; 0.07 mmol) in MeOH (0.7 mL) and AcOEt (0.7 mL) at room temperature was added 10%-Pd/C (21 mg). The reaction mixture was stirred for 5 h under hydrogen atmosphere. The catalyst was filtered off and the solvent was removed. The product was purified by silica gel column chromatography to give **14** (13 mg; 81%) as a colorless oil; IR (neat) 3380 (NH), 2953, 1725 (CO), 1512, 1236, 1038, 822, 754 cm^{-1}; ^1H NMR δ 1.16 (2H, m), 1.56 (2H, m), 3.65 (3H, s), 3.74 (3H, s), 4.32 (1H, br s), 6.65 (2H, d, $J=8.9$ Hz), 6.77 (2H, d, $J=8.9$ Hz). MS *m/z* (%) 221 (M^+, 53), 190 (56), 162 (100), 161 (55), 160 (52), 146 (49), 130 (42), 121 (29). Calcd for $C_{12}H_{15}NO_3$: M, 221.1051. Found: *m/z* 221.1059.

Acknowledgements

The authors thank Professor Isamu Shiina of this university for helpful discussions.

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11. $C_{13}H_{17}NO_3$, $M=235.28$, Orthorhombic, space group *Pbca* (#61), $a=12.8035(12)$, $b=7.7201(8)$, $c=24.955(2)$ Å, $V=2466.7(4)$ Å^3, $Z=8$, $F(000)=1008$, $D_{calc}=1.267$ g cm^{-3}, μ(Mo K_α)$=0.9$ cm^{-1}, $T=296$ K, radiation$=0.71073$ Å, $R1=0.2567$ for $I>2.0\sigma(I)$, $wR2=0.3582$ for all data (2824 reflections), GOF$=1.508$ (157 parameters), crystal dimensions $0.3\times0.08\times0.08$ mm^3. A quality single crystal of the compound (colorless prism) was mounted on a glass fiber. Diffraction data were measured on a Bruker APEX CCD-Detector X-ray diffractometer with monochromated Mo K_α radiation. The data reduction, structure solution and refinement, and all the necessary computational data processes were performed using SMART, SAINT, SHELXTL, KENX, and TEXSAN programs. Data deposited at the Cambridge Crystallographic Data Centre; deposition number CCDC 285997.

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A structure–activity relationship study of brusatol, an antitumor quassinoid

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Abstract—Analogues of brusatol (**2**) were prepared and examined for their cytotoxic activity by using P-388 murine leukemia cells. The following structure–activity relationships were noted: (i) an enone carbonyl oxygen or an enolic oxygen at C-2 is essential, but an oxygen at C-3 not essential for the activity; (ii) the C-11 β-hydroxyl group is important for the activity; and (iii) the length of the ester alkoxy side chain at C-21 seems to have a slight effect on the activity.

1. Introduction

Bruceantin (**1**, NSC 165563),[1] isolated from *Brucea antidysenterica* (Simaroubaceae), is a quassinoid having a promising antitumor activity (Fig. 1).[2] Its mode of action is attributed to inhibition of protein synthesis through interference at the peptidyl transferase site.[3,4] Phase I and II clinical trials of **1** were conducted in the late 1970s and early 1980s in the United States.[5–9] Brusatol (**2**),[10] a closely related congener of **1**, having also a potent antitumor activity,[11] and a different ester side chain at C-15, has been obtained from *B. sumatrana*[10] and *B. javanica*.[12] In spite of their promising antitumor activity, no systematic structure–activity relationship (SAR) studies have been reported: such information should be inevitable for designing their analogues with more improved medicinal profiles.[13]

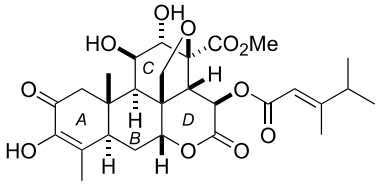
In the present report, we describe preparation of analogues of **2** with a modified ring A or ring C structure, or different C-21 alkoxy chain lengths and some observations on the chemical reactivity of the ring C moiety, and on the effects of chemical structures on the cytotoxic activity.

2. Results and discussion

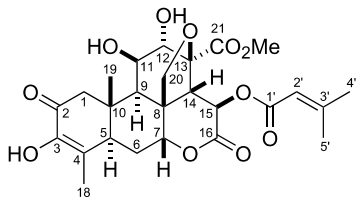
Brusatol (**2**) was obtained from the ground seeds of *B. javanica* as it was[14] or by partial hydrolysis of bruceoside-A,[15] the 2-*O*-glucoside of **2**, also obtained more abundantly from this plant source. Throughout the present transformation reactions, the senecioyl side chain at C-15 of brusatol (**2**) was retained, as it is reported to be essential for the compound to express potent antitumor activity.[1,13a,16]

2.1. Modification of ring A

Brusatol (**2**) possesses a diosphenol (3-hydroxy-3-en-2-one) group in the ring A. An earlier SAR study by Lee et al.[16]



bruceantin (**1**)



brusatol (**2**)

Figure 1.

Keywords: Bruceantin; Brusatol; Quassinoid; SAR; Cytotoxicity.
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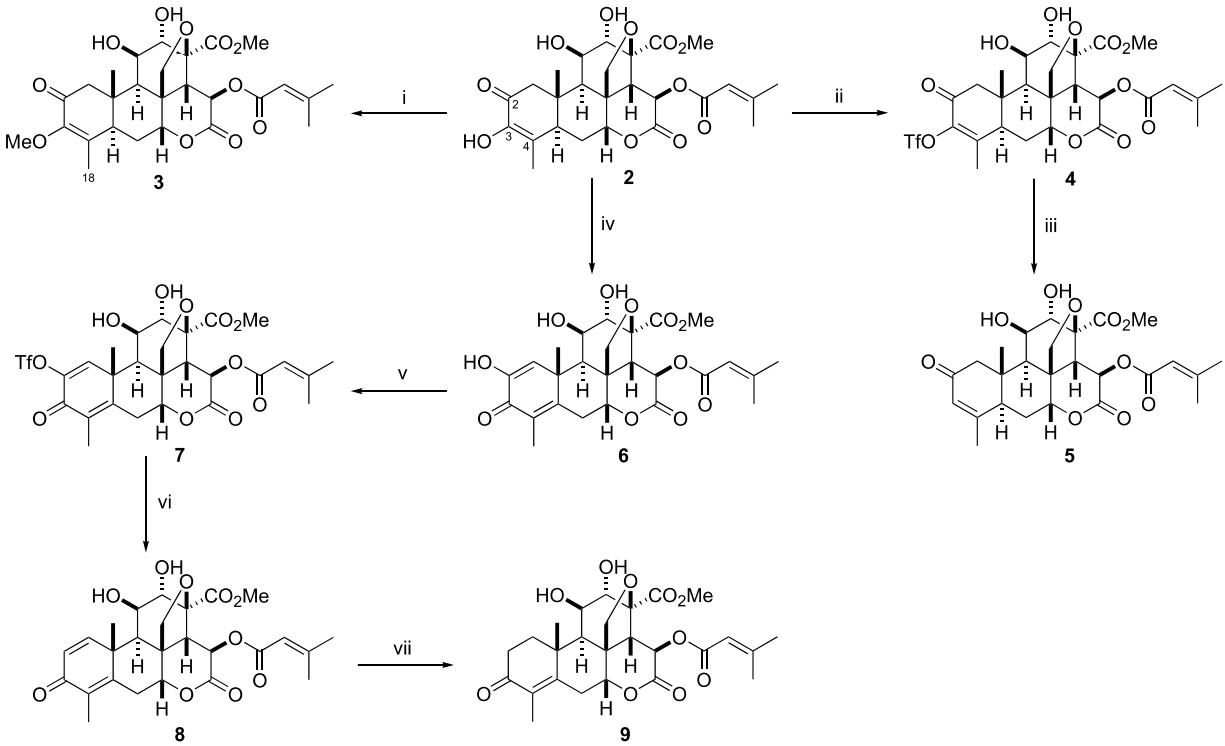
revealed that saturation of the 3,4-double bond resulted in loss of the antitumor activity, which indicates that the presence of a π bond system in this region is essential. Therefore, in the present study, we first prepared several analogues in which the tautomerizable diosphenol structure in **2** was modified. Analogue **3** in which this conjugate system was fixed and delineated was prepared by introduction of a methyl group onto the enolic oxygen (Scheme 1). Confirmation of the structure of **3** was made by observation of a NOESY correlation between the methoxyl protons and H_3-18. Enone **5** was prepared by treatment of brusatol (**2**) with *N*-phenyl-bis(trifluoromethanesulfonimide) to afford 3-*O*-trifrate **4**, and subsequent palladium-mediated reduction of **4**.[17] Dehydrobrusatol (**6**), having a ketone group at C-3, obtainable also as a minor quassinoid from this plant source, was prepared by DDQ oxidation of **2**.[18] A series of C-3 carbonyl analogues were prepared as shown in Scheme 1: **8** was prepared by converting the enol group in **6** into hydrogen via 2-*O*-trifrate **7**, by the same procedure used for the conversion of **2** into **5**. Partial hydrogenation of **8** by using Wilkinson's rhodium catalyst provided enone **9**.

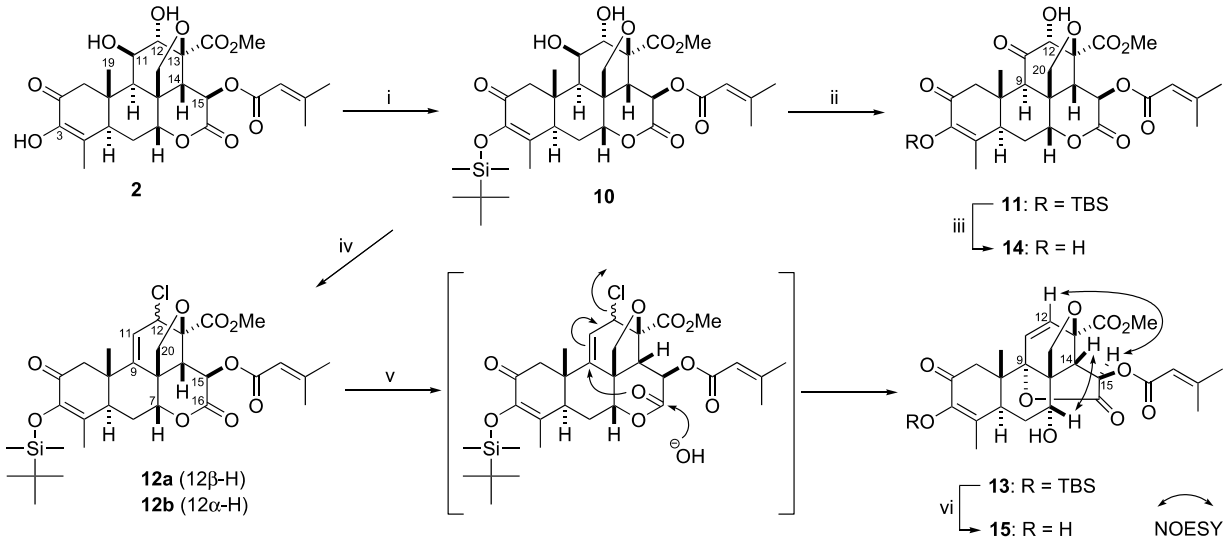
2.2. Modification of ring C

The ring C of brusatol (**2**) is characterized by the C-11 β- and C-12 α-hydroxyl groups. As regards the modification involving those hydroxyl groups, several acylated analogues have been prepared, which are reported to have a lower antitumor activity.[16] In the present work, prior to performing transformations of the ring C structure, the enolic hydroxyl group at C-3 was selectively protected as a *tert*-butyldimethylsilyl (TBS) ether, **10** (Scheme 2).[19] Oxidation of **10** with Jones reagent afforded a ketone, **11**, in 77% yield. The location of the ketone group in **11** was determined by the HMBC cross-peaks observed between the carbonyl signal (δ_C 201.5) and H-9 and H-12. The H-9 signal observed as a singlet signal in the ^{1}H NMR spectrum also supported this structure. The selective oxidation of the C-11 hydroxyl group may be due to its steric environment. Of the two hydroxyl groups on the ring C, both axially oriented, the C-11 hydroxyl group is sterically more congested than the C-12 hydroxyl group. The C-11 hydroxyl group is influenced by three 1,3-diaxial interactions involving the carbon atoms, C-19 and C-20, and the oxygen atom at C-13, whereas the C-12 hydroxyl group suffers only one 1,3-diaxial interaction with the C-15 atom. Steric congestion is known to accelerate oxidation of hydroxyl groups by chromium(VI) oxidation.[20]

Chlorination of those hydroxyl groups with thionyl chloride caused simultaneous elimination of the C-11 hydroxyl group to afford two epimeric allyl chlorides **12a** and **12b** in 54 and 25% yields, respectively (Scheme 2). The presence of an olefinic bond between C-9 and C-11 was confirmed by the HMBC experiments. The α- and β-orientations of the chlorine atoms of **12a** and **12b** at C-12 were determined by observation of NOESY correlations between H-12 and H_a-20 for **12a** and between H-12 and H-15 for **12b**, respectively. Steric congestion around the C-11 hydroxyl group mentioned above may facilitate the elimination of the axial hydroxyl group at C-11. Several attempts at the



Scheme 1. Reagents and conditions: (i) *p*-TsOMe, K_2CO_3, acetone, 50 °C, 7 days, 37%; (ii) Tf_2NPh, Et_3N, DMAP, dioxane, room temperature, 30 min, 75%; (iii) $Pd(OAc)_2$, 1,1′-bis(diphenylphosphino)ferrocene, HCO_2H, Et_3N, DMF, 45 °C, 2 h, 68%; (iv) DDQ, dioxane, room temperature, 1 h, 55%; (v) Tf_2NPh, Et_3N, DMAP, dioxane, room temperature, 1 h, 90%; (vi) $Pd(OAc)_2$, 1,1′-bis(diphenylphosphino)ferrocene, HCO_2H, Et_3N, DMF, 50 °C, 1 h, 87%; (vii) H_2, $(PPh_3)_3RhCl$, benzene, 45 °C, 30 h, 62%.



Scheme 2. Reagents and conditions: (i) *tert*-butyl(chloro)dimethylsilane, imidazole, DMF, room temperature, 24 h, 91%; (ii) Jones reagent, acetone, room temperature, 1 h, 77%; (iii) *n*-Bu_4NF, THF, room temperature, 15 min, 46%; (iv) $SOCl_2$, pyridine, $CHCl_3$, 60 °C, 10 h, 54% of **12a** and 25% of **12b**; (v) K_2CO_3, acetone–H_2O (10/1), room temperature, 6 h, 54%; (vi) *n*-Bu_4NF, THF, room temperature, 20 min, 46%.

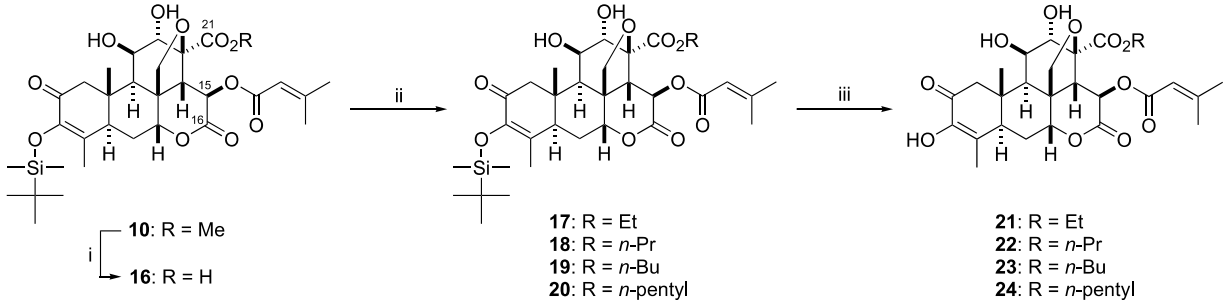
nucleophilic displacement at C-12 of **12a**,**b** were unsuccessful. Treatment of **12a**,**b** with potassium carbonate in aqueous acetone at room temperature, however, unexpectedly produced lactone **13** in 54% yield. Its structure was established by the spectroscopic methods. The molecular formula, $C_{32}H_{44}O_{10}Si$, determined by the HRESIMS, suggested that a hydroxyl group substituted the chlorine atom in the reaction. Its HMBC spectra showed the presence of an olefinic bond between C-11 (δ_H 6.10, d, J=9.8 Hz; δ_C 128.1) and C-12 (δ_H 6.38, dd, J=9.8, 1.2 Hz; δ_C 130.5) in **13**. The chemical shift value of C-9 (δ 85.4) and a DEPT experiment indicated that C-9 was an oxygen-bearing sp^3 quaternary carbon. The chemical shift of H-7 (δ 4.21) was in higher field than that in **10** (δ 4.78) or in **12a**,**b** (δ 5.00, 4.92), suggesting deacylation at the C-7 oxygen. NOESY correlations between H-7 and H-14 and between H-12 and H-15 indicated that the configuration at C-7 and C-15 did not change through the reactions. From these observations, structure **13** given in Scheme 2 was assigned for this product. The possible steps from **12** to **13** are shown in Scheme 2. The hydroxide anion first attacked the C-16 carbonyl carbon, and the resultant oxide anion subsequently attacked the proximal C-9 carbon in an intramolecular S_N' displacement fashion to give **13**. Compound **13** is unique in that it has an unusual 9,16-lactone linkage. Desilylation of **11** and **13** produced analogues **14** and **15**, respectively.

2.3. Modifications at C-21 ester side chain

Brusatol (**2**) possess a methyl ester group at C-21 along with two other ester functionalities at the C-15 side chain and C-16. Of those three ester groups, the C-15 side chain ester is the most susceptible to alkaline hydrolysis.[21] Therefore, to modify the C-21 ester side chain, first, we had to establish a method of selective cleavage of the C-21 ester group. This problem was successfully solved by an S_N2 displacement reaction on the ester–methyl group.[22] When compound **10** was treated with lithium iodide in pyridine at 100 °C for 24 h, acid **16** was obtained in 72% yield (Scheme 3), which was then converted by O-alkylation of the carboxylic acid into brusatol analogues having different alkyl chains. By treatment with potassium carbonate and iodoethane, 1-iodopropane, 1-iodobutane, and 1-iodopentane at 50 °C, it afforded corresponding esters **17**, **18**, **19**, and **20**, respectively, in yields of 88–92%, which were then desilylated to afford ethyl (**21**), propyl (**22**), butyl (**23**), and pentyl (**24**) ester analogues, respectively.

2.4. Cytotoxicity of brusatol analogues on P-388 leukemia cells

Brusatol (**2**) and its analogues thus prepared were evaluated for their cytotoxicity by using P-388 murine leukemia cells.



Scheme 3. Reagents and conditions: (i) LiI, pyridine, 100 °C, 24 h, 72%; (ii) RI, K_2CO_3, acetone, 50 °C, 6–24 h, 88–92%; (iii) *n*-Bu_4NF, THF, room temperature, 15 min, 61–79%.

Table 1. Cytotoxicity of brusatol (**2**) and its analogues **3**, **5**, **6**, **8**, **9**, **14**, **15**, and **21**–**24** on P-388 leukemia cells

Compound	IC_{50} (μg/mL)
Brusatol (**2**)	0.0061
3	0.23
5	0.057
6	0.072
8	1.5
9	5.0
14	10
15	18
21	0.014
22	0.050
23	0.063
24	0.071

The results are summarized in Table 1. As regards modifications of ring A (**3**, **5**, **6**, **8**, and **9**), replacement of the enol group with a methoxyl group (**3**) gave a marked decrease in activity, but replacement with a hydrogen atom (**5**) gave less decrease. In dehydrobrusatol (**6**), the decrease was less, whereas in **8**, with the enol group oxygen of **6** replaced by a hydrogen atom, and in **9**, with the 1,2-double bond of **8** saturated, the decrease in activity was more significant. Thus, the presence of an enone carbonyl oxygen or an enolic oxygen at C-2 appears to be essential for the compounds to express the activity, but the oxygen at C-3 not essential.

As regards the ring C-modified analogues, 11-ketone analogue **14** showed only a very weak activity, indicating that disposition of a β-hydroxyl group at C-11 is important, and the 9,16-lactone analogue **15** also only a marginal activity.

The table shows that the lengths of the ester alkyl side chains at C-21 apparently had a weak effect on the activity: the activity generally decreases as the alkyl chain length increases from methyl (**2**) to pentyl (**24**).

In the present study, we prepared several analogues of brusatol (**2**) and evaluated their cytotoxic activity. Thus, we established methods of preparation of new analogues of **2**, having modified ring A conjugate systems, modified ring C structures, or different C-21 alkoxy chain lengths, and by detailed assay of their effect on leukemia cells, obtained information on the relation between the chemical structure and the cytotoxic activity of the compounds of this series. Such knowledge should be useful for designing and synthesizing novel analogues of brusatol (**2**) and bruceantin (**1**).

3. Experimental

3.1. General

Optical rotations were measured on a JASCO DIP-360 digital polarimeter, IR spectra on a Perkin-Elmer 1710 spectrophotometer, mass spectra on a Micromass LCT spectrometer, and NMR spectra on a Bruker DRX-500 spectrometer at 300 K. ^{1}H chemical shifts in $CDCl_3$ or methanol-d_4 were referenced to the residual $CHCl_3$ (7.26 ppm) or CD_2HOD (3.31 ppm); ^{13}C chemical shifts were referenced to the solvent ($CDCl_3$, 77.03 ppm; methanol-d_4, 49.0 ppm). Preparative HPLC was performed on a Shimadzu LC-6AD system equipped with a SPD-10A UV detector (at 254 nm) and a reverse-phase column, Inertsil PREP-ODS (10 μm, 20×250 mm), by using a mixed solvent system of MeOH–H_2O or MeCN–H_2O, at a flow rate of 10 mL/min.

3.2. Material

Brusatol (**2**) was obtained by chromatographic separation of a methanol extract of the seeds of *Brucea javanica* (L.) Merr. as described before[14] or by acid hydrolysis of bruceoside-A from the same plant source, according to the reported procedure.[15]

3.3. Synthesis of brusatol analogues

3.3.1. 3-*O*-Methylbrusatol (3). To a solution of brusatol (**2**) (30 mg, 0.058 mmol) in acetone (1 mL) were added potassium carbonate (16 mg, 0.12 mmol) and methyl *p*-toluenesulfonate (88 μL, 0.58 mmol). After stirring at 50 °C under an argon atmosphere for 7 days, the reaction mixture was diluted with chloroform (10 mL) and filtered. The solvent was removed in vacuo, and the crude product was purified by preparative ODS-HPLC using MeOH–H_2O (33/67) as an eluent to afford **3** (11.4 mg, 37%) as a colorless amorphous solid: $[\alpha]_D^{24}$ +35.2 (*c* 0.66, $CHCl_3$); IR (film) ν_{max} 3473, 1736, 1671 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.28 (1H, br s, H-15), 5.62 (1H, s, H-2′), 4.79 (1H, s, H-7), 4.73 (1H, d, J=7.9 Hz, H_a-20), 4.26 (1H, m, H-11), 4.19 (1H, s, H-12), 3.79 (1H, dd, J=7.9, 1.3 Hz, H_b-20), 3.79 (3H, s, CH_3O-21), 3.64 (3H, s, CH_3O-3), 3.13 (1H, br s, H-14), 2.96 (1H, d, J=13.0 Hz, H-5), 2.93 (1H, d, J=15.9 Hz, H_β-1), 2.38 (1H, dt, J=14.6, 2.8 Hz, H_α-6), 2.36 (1H, d, J=15.9 Hz, H_α-1), 2.19 (3H, d, J=0.8 Hz, H-5′), 2.07 (1H, br s, H-9), 1.93 (3H, d, J=1.0 Hz, H-4′), 1.87 (3H, d, J=1.4 Hz, H-18), 1.77 (1H, ddd, J=14.6, 13.0, 2.5 Hz, H_β-6), 1.39 (3H, s, H-19); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.4 (C-2), 172.0 (C-21), 167.0 (C-16), 164.5 (C-1′), 161.1 (C-3′), 149.4 (C-3), 143.4 (C-4), 114.0 (C-2′), 82.4 (C-7), 81.4 (C-13), 75.9 (C-12), 74.1 (C-20), 70.9 (C-11), 65.7 (C-15), 59.9 (CH_3O-3), 53.1 (CH_3O-21), 51.8 (C-14), 51.2 (C-1), 45.4 (C-8), 42.7 (C-5), 42.0 (C-9), 40.5 (C-10), 29.1 (C-6), 27.7 (C-4′), 20.6 (C-5′), 15.4 (C-19), 14.0 (C-18); HRESIMS *m*/*z* 535.2147 $[M+H]^+$ (calcd for $C_{27}H_{35}O_{11}$, 535.2179).

3.3.2. Compound 4. A solution of brusatol (**2**) (100 mg, 0.192 mmol) and *N*-phenyl-bis(trifluoromethanesulfonimide) (206 mg, 0.577 mmol) in 1,4-dioxane (1 mL) was treated with triethylamine (81 μL, 0.58 mmol) and 4-(dimethylamino)pyridine (23 mg, 0.19 mmol), and the resulting reaction mixture was stirred at room temperature under an argon atmosphere for 30 min. The mixture was diluted with chloroform (30 mL), washed sequentially with 1 M HCl (5 mL), water (5 mL), and brine (5 mL), dried over Na_2SO_4, and filtered. The solvent was removed in vacuo, and the crude product was purified by preparative ODS-HPLC using MeOH–H_2O (54/46) as an eluent to afford **4** (94.2 mg, 75%) as a colorless amorphous solid: $[\alpha]_D^{24}$ +31.8 (*c* 0.60, $CHCl_3$); IR (film) ν_{max} 3526, 1733, 1697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.26 (1H, br s, H-15), 5.63

(1H, s, H-2′), 4.82 (1H, s, H-7), 4.72 (1H, d, J=8.0 Hz, H_a-20), 4.27 (1H, s, H-11), 4.20 (1H, s, H-12), 3.81 (1H, d, J=8.0 Hz, H_b-20), 3.79 (3H, s, OCH_3), 3.16 (1H, br s, H-14), 3.11 (1H, d, J=12.9 Hz, H-5), 3.08 (1H, d, J=16.4 Hz, H_β-1), 2.47 (1H, d, J=16.4 Hz, H_α-1), 2.43 (1H, dt, J=14.6, 2.8 Hz, H_α-6), 2.19 (3H, d, J=0.9 Hz, H-5′), 2.10 (1H, br s, H-9), 2.00 (3H, s, H-18), 1.94 (3H, d, J=1.1 Hz, H-4′), 1.88 (1H, ddd, J=14.6, 12.9, 2.4 Hz, H_β-6), 1.46 (3H, s, H-19); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.2 (C-2), 171.8 (C-21), 166.7 (C-16), 164.4 (C-1′), 161.5 (C-3′), 149.4 (C-3), 141.9 (C-4), 118.5 (CF_3SO_2), 113.9 (C-2′), 81.7 (C-7), 81.2 (C-13), 75.8 (C-12), 73.8 (C-20), 70.8 (C-11), 65.7 (C-15), 53.1 (OCH_3), 51.7 (C-14), 49.9 (C-1), 45.3 (C-8), 43.7 (C-5), 41.6 (C-9), 40.4 (C-10), 28.8 (C-6), 27.7 (C-4′), 20.7 (C-5′), 15.6 (C-18), 15.4 (C-19); HRESIMS m/z 653.1509 $[M+H]^+$ (calcd for $C_{27}H_{32}O_{13}F_3S$, 653.1516).

3.3.3. Compound 5. Triethylamine (64 μL, 0.46 mmol) and formic acid (17 μL, 0.45 mmol) were added to a solution of compound **4** (30 mg, 0.046 mmol), 1,1′-bis(diphenylphosphino)ferrocene (38 mg, 0.069 mmol), and palladium(II) acetate (10.3 mg, 0.046 mmol) in *N*,*N*-dimethylformamide (0.5 mL), and the resulting mixture was stirred at 45 °C under an argon atmosphere for 2 h. The volatiles were removed in vacuo, and the residue was dissolved in chloroform (30 mL). The solution was washed sequentially with 1 M HCl (5 mL), saturated aqueous $NaHCO_3$ (5 mL), and brine (5 mL), dried over Na_2SO_4, and filtered. The solvent was removed in vacuo, and the crude product was purified by preparative ODS-HPLC using MeOH–H_2O (37/63) as an eluent to afford **5** (15.8 mg, 68%) as a colorless amorphous solid: $[\alpha]_D^{24}$ +35.6 (*c* 0.67, $CHCl_3$); IR (film) ν_{max} 3466, 1738, 1650 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.27 (1H, br s, H-15), 5.97 (1H, s, H-3), 5.63 (1H, s, H-2′), 4.79 (1H, s, H-7), 4.74 (1H, d, J=7.9 Hz, H_a-20), 4.28 (1H, m, H-11), 4.20 (1H, s, H-12), 3.80 (1H, dd, J=7.9, 1.4 Hz, H_b-20), 3.79 (3H, s, OCH_3), 3.13 (1H, br s, H-14), 2.85 (1H, d, J=15.7 Hz, H_β-1), 2.85 (1H, d, J=13.0 Hz, H-5), 2.41 (1H, dt, J=14.6, 2.8 Hz, H_α-6), 2.29 (1H, d, J=15.7 Hz, H_α-1), 2.19 (3H, d, J=1.0 Hz, H-5′), 2.10 (1H, br s, H-9), 1.93 (3H, d, J=1.1 Hz, H-4′), 1.91 (3H, s, H-18), 1.78 (1H, ddd, J=14.6, 13.0, 2.6 Hz, H_β-6), 1.38 (3H, s, H-19); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.1 (C-2), 172.0 (C-21), 167.0 (C-16), 164.5 (C-1′), 161.1 (C-3′), 160.1 (C-4), 127.4 (C-3), 114.0 (C-2′), 82.4 (C-7), 81.3 (C-13), 75.8 (C-12), 74.1 (C-20), 70.9 (C-11), 65.8 (C-15), 53.1 (OCH_3), 51.8 (C-14), 50.6 (C-1), 45.5 (C-8), 43.2 (C-5), 42.1 (C-9), 40.9 (C-10), 28.6 (C-6), 27.7 (C-4′), 22.2 (C-18), 20.6 (C-5′), 15.5 (C-19); HRESIMS m/z 527.1880 $[M+Na]^+$ (calcd for $C_{26}H_{32}O_{10}Na$, 527.1893).

3.3.4. Dehydrobrusatol (6). To a solution of brusatol (**2**) (25 mg, 0.048 mmol) in 1,4-dioxane (1 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (11 mg, 0.048 mmol), and the resulting mixture was stirred at room temperature for 1 h. After dilution with chloroform (30 mL), the mixture was washed successively with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried over Na_2SO_4, and filtered. The solvent was removed in vacuo, and the crude product was purified by preparative ODS-HPLC using MeOH–H_2O (36/64) as an eluent to afford dehydrobrusatol (**6**) (13.6 mg, 55%) as a colorless amorphous solid, whose ^{1}H and ^{13}C NMR spectra were identical with those in the literature.[18]

3.3.5. Dehydrobrusatol 2-*O*-triflate (7). A solution of compound **6** (90 mg, 0.17 mmol) and *N*-phenylbis(trifluoromethanesulfonimide) (186 mg, 0.52 mmol) in 1,4-dioxane (1 mL) was treated with triethylamine (73 μL, 0.52 mmol) and 4-(dimethylamino)pyridine (21 mg, 0.17 mmol), and the resulting reaction mixture was stirred at room temperature under an argon atmosphere for 1 h. The mixture was diluted with chloroform (30 mL), washed successively with 1 M HCl (5 mL), water (5 mL), and brine (5 mL), dried over Na_2SO_4, and filtered. The solvent was removed in vacuo, and the crude product was purified by preparative ODS-HPLC using MeOH–H_2O (49/51) as an eluent to afford **7** (102 mg, 90%) as a colorless amorphous solid: $[\alpha]_D^{21}$ +51.2 (*c* 0.25, $CHCl_3$); IR (film) ν_{max} 3510, 1736, 1658 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (1H, s, H-1), 5.98 (1H, br s, H-15), 5.61 (1H, s, H-2′), 4.88 (1H, s, H-7), 4.84 (1H, d, J=8.0 Hz, H_a-20), 4.37 (1H, br s, H-11), 4.25 (1H, s, H-12), 3.93 (1H, dd, J=8.0, 1.1 Hz, H_b-20), 3.79 (3H, s, OCH_3), 3.34 (1H, dd, J=15.0, 3.1 Hz, H_α-6), 3.22 (1H, br s, H-14), 2.60 (1H, d, J=15.0 Hz, H_β-6), 2.16 (3H, d, J=0.8 Hz, H-5′), 2.09 (1H, br s, H-9), 2.02 (3H, s, H-18), 1.92 (3H, d, J=0.8 Hz, H-4′), 1.77 (3H, s, H-19); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.4 (C-3), 171.4 (C-21), 166.0 (C-16), 164.5 (C-1′), 161.3 (C-3′), 153.9 (C-5), 143.9 (C-2), 140.6 (C-1), 133.2 (C-4), 118.7 (CF_3SO_2), 113.9 (C-2′), 82.8 (C-7), 81.5 (C-13), 75.8 (C-12), 73.3 (C-20), 73.0 (C-11), 65.7 (C-15), 53.2 (OCH_3), 51.2 (C14), 45.9 (C-8), 44.9 (C-10), 40.5 (C-9), 32.4 (C-6), 27.7 (C-4′), 22.9 (C-19), 20.6 (C-5′), 11.1 (C-18); HRESIMS m/z 651.1343 $[M+H]^+$ (calcd for $C_{27}H_{30}O_{13}F_3S$, 651.1359).

3.3.6. Compound 8. Triethylamine (100 μL, 0.72 mmol) and formic acid (27 μL, 0.72 mmol) were added to a solution of compound **7** (47 mg, 0.072 mmol), 1,1′-bis(diphenylphosphino)ferrocene (60 mg, 0.11 mmol), and palladium(II) acetate (16 mg, 0.071 mmol) in *N*,*N*-dimethylformamide (0.5 mL), and the resulting mixture was stirred at 50 °C under an argon atmosphere for 1 h. The volatiles were removed in vacuo, and the residue was dissolved in chloroform (30 mL). The solution was washed successively with 1 M HCl (5 mL), saturated aqueous $NaHCO_3$ (5 mL), and brine (5 mL), dried over Na_2SO_4, and filtered. The solvent was removed in vacuo, and the crude product was purified by preparative ODS-HPLC using MeOH–H_2O (44/56) as an eluent to afford **8** (31.6 mg, 87%) as a colorless amorphous solid: $[\alpha]_D^{24}$ +87.2 (*c* 0.87, $CHCl_3$); IR (film) ν_{max} 3478, 1742, 1659 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (1H, d, J=10.1 Hz, H-1), 6.35 (1H, d, J=10.1 Hz, H-2), 6.01 (1H, br s, H-15), 5.60 (1H, s, H-2′), 4.85 (1H, d, J=8.0 Hz, H_a-20), 4.84 (1H, s, H-7), 4.42 (1H, d, J=4.2 Hz, H-11), 4.23 (1H, s, H-12), 3.90 (1H, d, J=8.0 Hz, H_b-20), 3.78 (3H, s, OCH_3), 3.32 (1H, dd, J=14.8, 3.0 Hz, H_α-6), 3.15 (1H, br s, H-14), 2.56 (1H, d, J=14.8 Hz, H_β-6), 2.15 (3H, d, J=0.7 Hz, H-5′), 2.02 (1H, br s, H-9), 1.96 (3H, s, H-18), 1.91 (3H, s, H-4′), 1.65 (3H, s, H-19); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.6 (C-3), 171.7 (C-21), 166.3 (C-16), 164.5 (C-1′), 161.0 (C-3′), 152.8 (C-5), 152.4 (C-1), 133.4 (C-4), 127.5 (C-2), 114.0 (C-2′), 83.3 (C-7), 81.6 (C-13), 75.9 (C-12), 73.5 (C-20), 72.9 (C-11), 65.8 (C-15), 53.1 (OCH_3), 51.4 (C-14), 45.9 (C-8), 43.3

(C-10), 40.2 (C-9), 32.2 (C-6), 27.7 (C-4′), 22.6 (C-19), 20.6 (C-5′), 10.8 (C-18); HRESIMS *m/z* 503.1868 $[M+H]^+$ (calcd for $C_{26}H_{31}O_{10}$, 503.1917).

3.3.7. Compound 9. Compound **8** (32 mg, 0.064 mmol) and tris(triphenylphosphine)rhodium(I) chloride (59 mg, 0.064 mmol) were dissolved in benzene (5 mL), and the mixture was stirred at 45 °C under a hydrogen atmosphere for 30 h. The solvent was removed in vacuo, and the residue was separated by preparative ODS-HPLC using MeOH–H_2-O (38/62) as an eluent to afford **9** (19.8 mg, 62%) as a colorless amorphous solid: $[\alpha]_D^{24}$ +120.8 (*c* 0.59, $CHCl_3$); IR (film) ν_{max} 3486, 1742, 1659 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.16 (1H, br s, H-15), 5.62 (1H, s, H-2′), 4.80 (1H, d, J=7.9 Hz, H_a-20), 4.78 (1H, s, H-7), 4.38 (1H, m, H-11), 4.23 (1H, s, H-12), 3.88 (1H, dd, J=7.9, 1.5 Hz, H_b-20), 3.79 (3H, s, OCH_3), 3.23 (1H, dd, J=15.5, 3.5 Hz, H_α-6), 3.11 (1H, br d, J=10.9 Hz, H-14), 2.53 (1H, ddd, J=16.7, 14.2, 5.1 Hz, H_β-2), 2.48 (1H, ddd, J=16.7, 5.4, 3.4 Hz, H_α-2), 2.41 (1H, d, J=15.5 Hz, H_β-6), 2.34 (1H, m, H_α-1), 2.18 (3H, d, J=1.1 Hz, H-5′), 1.99 (1H, br s, H-9), 1.97 (1H, dd, J=14.4, 5.6 Hz, H_β-1), 1.92 (3H, d, J=1.1 Hz, H-4′), 1.83 (3H, d, J=0.8 Hz, H-18), 1.68 (3H, s, H-19); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.2 (C-3), 171.9 (C-21), 166.5 (C-16), 164.5 (C-1′), 161.0 (C-3′), 154.3 (C-5), 132.6 (C-4), 114.1 (C-2′), 82.3 (C-7), 81.6 (C-13), 75.9 (C-12), 73.6 (C-20), 71.3 (C-11), 65.9 (C-15), 53.1 (OCH_3), 51.9 (C-14), 45.7 (C-8), 42.4 (C-9), 39.9 (C-10), 34.9 (C-1), 32.8 (C-2), 32.0 (C-6), 27.7 (C-4′), 21.1 (C-19), 20.6 (C-5′), 11.3 (C-18); HRESIMS *m/z* 505.2074 $[M+H]^+$ (calcd for $C_{26}H_{33}O_{10}$, 505.2074).

3.3.8. Compound 10. To a solution of **2** (100 mg, 0.192 mmol) in *N*,*N*-dimethylformamide (0.5 mL) were added *tert*-butyl(chloro)dimethylsilane (87 mg, 0.58 mmol) and imidazole (90 mg, 1.3 mmol), and the mixture was stirred at room temperature under an argon atmosphere for 24 h. The mixture was diluted with water (0.5 mL), and the precipitate was collected by filtration. This was purified by preparative ODS-HPLC using MeOH–H_2O (76/24) as an eluent to afford **10** (111 mg, 91%) as a colorless amorphous solid: $[\alpha]_D^{24}$ +18.5 (*c* 0.44, $CHCl_3$); IR (film) ν_{max} 3475, 1743, 1676 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.25 (1H, br s, H-15), 5.63 (1H, s, H-2′), 4.78 (1H, s, H-7), 4.72 (1H, d, J=7.9 Hz, H_a-20), 4.25 (1H, br s, H-11), 4.19 (1H, s, H-12), 3.79 (1H, d, J=7.9 Hz, H_b-20), 3.78 (3H, s, OCH_3), 3.13 (1H, br s, H-14), 2.93 (1H, br d, J=14 Hz, H-5), 2.89 (1H, d, J=16.0 Hz, H_β-1), 2.38 (1H, dt, J=14.7, 2.7 Hz, H_α-6), 2.33 (1H, d, J=16.0 Hz, H_α-1), 2.19 (3H, d, J=0.8 Hz, H-5′), 2.07 (1H, br s, H-9), 1.92 (3H, d, J=0.8 Hz, H-4′), 1.84 (3H, d, J=1.7 Hz, H-18), 1.75 (1H, ddd, J=14.7, 13.8, 2.5 Hz, H_β-6), 1.39 (3H, s, H-19), 0.95 (9H, s, Me_3CSi), 0.17 and 0.13 (3H each, s, Me_2Si); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.0 (C-2), 172.0 (C-21), 167.1 (C-16), 164.5 (C-1′), 160.9 (C-3′), 145.0 (C-3), 135.7 (C-4), 114.1 (C-2′), 82.5 (C-7), 81.4 (C-13), 75.8 (C-12), 74.1 (C-20), 70.9 (C-11), 65.8 (C-15), 53.0 (OCH_3), 51.7 (C-14), 50.6 (C-1), 45.4 (C-8), 42.7 (C-5), 42.0 (C-9), 40.4 (C-10), 29.4 (C-6), 27.7 (C-4′), 26.0 (Me_3CSi, 3C), 20.6 (C-5′), 18.8 (Me_3CSi), 15.5 (C-19), 14.4 (C-18), −3.8, −3.9 (Me_2Si); HRESIMS *m/z* 635.2880 $[M+H]^+$ (calcd for $C_{32}H_{47}O_{11}Si$, 635.2888).

3.3.9. Compound 11. To an ice-cooled solution of **10** (50 mg, 0.079 mmol) in acetone (0.5 mL) was added Jones reagent [30 μL, prepared by dissolving chromium(VI) oxide (267 mg) in sulfuric acid–H_2O (23/77, 1 mL)], and the mixture was stirred at room temperature for 1 h. The mixture was diluted with chloroform (30 mL), which was washed sequentially with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried over Na_2SO_4, and filtered. The solvent was removed in vacuo, and the crude product was purified by silica gel column chromatography using chloroform–methanol (20/1) as an eluent to afford **11** (38.3 mg, 77%) as a colorless amorphous solid: $[\alpha]_D^{24}$ +52.0 (*c* 0.78, $CHCl_3$); IR (film) ν_{max} 3446, 1734, 1672 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.36 (1H, br s, H-15), 5.68 (1H, s, H-2′), 4.89 (1H, s, H-7), 4.30 (1H, s, H-12), 4.29 (1H, d, J=8.2 Hz, H_a-20), 3.80 (1H, d, J=8.2 Hz, H_b-20), 3.78 (3H, s, OCH_3), 3.47 (1H, d, J=16.5 Hz, H_β-1), 3.38 (1H, br s, H-14), 3.02 (1H, s, H-9), 2.97 (1H, d, J=12.9 Hz, H-5), 2.41 (1H, dt, J=14.8, 3.0 Hz, H_α-6), 2.21 (3H, d, J=0.7 Hz, H-5′), 2.18 (1H, d, J=16.5 Hz, H_α-1), 1.95 (3H, d, J=0.9 Hz, H-4′), 1.85 (3H, d, J=1.7 Hz, H-18), 1.64 (1H, ddd, J=14.8, 12.9, 2.3 Hz, H_β-6), 1.21 (3H, s, H-19), 0.95 (9H, s, Me_3CSi), 0.18 and 0.14 (3H each, s, Me_2Si); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.5 (C-11), 191.8 (C-2), 169.7 (C-21), 166.7 (C-16), 164.7 (C-1′), 161.4 (C-3′), 145.4 (C-3), 134.8 (C-4), 114.0 (C-2′), 81.3 (C-13), 80.7 (C-7), 77.8 (C-12), 73.6 (C-20), 65.8 (C-15), 53.1 (OCH_3), 51.3 (C-14), 51.2 (C-1), 50.6 (C-9), 46.7 (C-8), 40.7 (C-5), 38.9 (C-10), 28.6 (C-6), 27.7 (C-4′), 26.0 (Me_3CSi, 3C), 20.7 (C-5), 18.9 (Me_3CSi), 14.3 (C-18), 13.3 (C-19), −3.7, −3.9 (Me_2Si); HRESIMS *m/z* 633.2723 $[M+H]^+$ (calcd for $C_{32}H_{45}O_{11}Si$, 633.2731).

3.3.10. Treatment of 10 with thionyl chloride. Thionyl chloride (12 μL, 0.16 mmol) and pyridine (26 μL, 0.32 mmol) were added to a solution of **10** (20 mg, 0.032 mmol) in chloroform (0.5 mL) at 0 °C, and the resultant mixture was stirred at 60 °C under an argon atmosphere for 10 h. After dilution with chloroform (30 mL), the mixture was washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried over Na_2SO_4, filtered and evaporated in vacuo. The residue was shown to be a mixture of **12a** and **12b** in a ratio of ca. 2:1. The mixture was subjected to preparative ODS-HPLC using MeOH–H_2-O (70/30) as an eluent to afford **12a** (10.8 mg, 54%) and **12b** (5.0 mg, 25%). Compound **12a**: colorless amorphous solid, $[\alpha]_D^{24}$ −113.5 (*c* 0.18, $CHCl_3$); IR (film) ν_{max} 1752, 1677 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.91 (1H, d, J=4.4 Hz, H-11), 5.75 (1H, s, H-2′), 5.24 (1H, br s, H-15), 5.00 (1H, s, H-7), 4.71 (1H, d, J=4.4 Hz, H-12), 4.01 (1H, d, J=7.2 Hz, H_a-20), 3.86 (1H, d, J=7.2 Hz, H_b-20), 3.81 (3H, s, OCH_3), 3.66 (1H, br s, H-14), 3.07 (1H, br d, J=13.0 Hz, H-5), 2.91 (1H, d, J=16.1 Hz, H_β-1), 2.49 (1H, dt, J=14.3, 2.9 Hz, H_α-6), 2.47 (1H, d, J=16.1 Hz, H_α-1), 2.18 (3H, s, H-5′), 1.93 (3H, s, H-4′), 1.90 (3H, d, J=1.1 Hz, H-18), 1.77 (1H, dd, J=14.3, 13.0 Hz, H_β-6), 1.16 (3H, s, H-19), 0.95 (9H, s, Me_3CSi), 0.16 (6H, s, Me_2Si); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.1 (C-2), 167.1 (C-21), 166.6 (C-16), 165.3 (C-1′), 159.6 (C-3′), 145.3 (C-3), 144.1 (C-9), 136.0 (C-4), 122.3 (C-11), 115.0 (C-2′), 83.2 (C-13), 79.6 (C-7), 78.4 (C-20), 67.1 (C-15), 53.3 (C-12), 53.0 (OCH_3), 49.6 (C-1), 47.2 (C-8), 45.2 (C-14), 40.8 (C-10), 38.2 (C-5), 28.7 (C-6), 27.6 (C-4′), 26.0 (Me_3CSi, 3C), 23.0

(C-19), 20.6 (C-5′), 18.8 (Me_3CSi), 14.6 (C-18), −3.8×2 (Me_2Si); HRESIMS *m/z* 635.2415 $[M+H]^+$ (calcd for $C_{32}H_{44}O_9ClSi$, 635.2443). Compound **12b**: colorless amorphous solid, $[\alpha]_D^{24}$ +27.8 (*c* 0.19, $CHCl_3$); IR (film) ν_{max} 1742, 1675 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.73 (1H, d, *J*=2.3 Hz, H-11), 5.70 (1H, br s, H-15), 5.67 (1H, s, H-2′), 5.30 (1H, s, H-12), 4.92 (1H, s, H-7), 4.38 (1H, d, *J*=7.3 Hz, H_a-20), 4.12 (1H, dd, *J*=7.3, 0.9 Hz, H_b-20), 3.75 (3H, s, OCH_3), 3.11 (1H, d, *J*=12.6 Hz, H-14), 2.96 (1H, d, *J*=13.0 Hz, H-5), 2.91 (1H, d, *J*=16.1 Hz, H_β-1), 2.48 (1H, dt, *J*=14.7, 3.0 Hz, H_α-6), 2.43 (1H, d, *J*=16.1 Hz, H_α-1), 2.22 (3H, d, *J*=1.0 Hz, H-5′), 1.96 (3H, d, *J*=1.0 Hz, H-4′), 1.88 (3H, d, *J*=1.8 Hz, H-18), 1.79 (1H, ddd, *J*=14.7, 13.0, 2.2 Hz, H_β-6), 1.21 (3H, s, H-19), 0.95 (9H, s, Me_3CSi), 0.18 and 0.15 (3H, each, s, Me_2Si); HRESIMS *m/z* 635.2444 $[M+H]^+$ (calcd for $C_{32}H_{44}O_9ClSi$, 635.2443).

3.3.11. Treatment of 12a and 12b with potassium carbonate. To a solution of a mixture of **12a** and **12b** (a product of Section 3.3.10 without HPLC, a ca. 2:1 mixture, 20 mg, 0.031 mmol) in acetone–H_2O (10/1, 1 mL) was added potassium carbonate (85 mg, 0.62 mmol), and the mixture was stirred at room temperature for 6 h. The mixture was diluted with chloroform (20 mL), washed sequentially with 1 M HCl (5 mL) and brine (5 mL), dried over Na_2SO_4, and filtered. The solvent was removed in vacuo, and the crude product was purified by preparative ODS-HPLC using MeCN–H_2O (65/35) as an eluent to afford **13** (10.4 mg, 54%) as a colorless amorphous solid: $[\alpha]_D^{24}$ −106.0 (*c* 0.20, $CHCl_3$); IR (film) ν_{max} 3444, 1753, 1731, 1680 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.38 (1H, dd, *J*=9.8, 1.2 Hz, H-12), 6.10 (1H, d, *J*=9.8 Hz, H-11), 5.77 (1H, s, H-2′), 5.41 (1H, d, *J*=1.9 Hz, H-15), 4.21 (1H, br s, H-7), 4.18 (1H, d, *J*=9.8 Hz, H_a-20), 3.83 (3H, s, OCH_3), 3.78 (1H, d, *J*=9.8 Hz, H_b-20), 3.74 (1H, br d, *J*=13.1 Hz, H-5), 3.19 (1H, d, *J*=16.2 Hz, H_α-1), 2.72 (1H, dd, *J*=1.9, 1.2 Hz, H-14), 2.56 (1H, br s, HO-7), 2.52 (1H, d, *J*=16.2 Hz, H_β-1), 2.18 (1H, d-like, *J*=14.3 Hz, H_α-6), 2.18 (3H, d, *J*=0.6 Hz, H-5′), 1.92 (3H, d, *J*=0.6 Hz, H-4′), 1.85 (3H, d, *J*=1.7 Hz, H-18), 1.64 (1H, ddd, *J*=14.3, 13.1, 2.6 Hz, H_β-6), 1.07 (3H, s, H-19), 0.94 (9H, s, Me_3CSi), 0.15 (6H, s, Me_2Si); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.4 (C-2), 169.1 (C-21), 167.2 (C-16), 164.4 (C-1′), 159.9 (C-3′), 144.6 (C-3), 136.0 (C-4), 130.5 (C-12), 128.1 (C-11), 114.7 (C-2′), 85.4 (C-9), 82.2 (C-13), 72.8 (C-7), 71.1 (C-20), 63.1 (C-15), 54.5 (C-14), 53.2 (OCH_3), 48.2 (C-8), 45.0 (C-1), 44.4 (C-10), 34.2 (C-5), 30.5 (C-6), 27.6 (C-4′), 26.0 (Me_3CSi, 3C), 20.6 (C-5′), 18.9 (Me_3CSi), 17.3 (C-19), 14.5 (C-18), −3.8×2 (Me_2Si); HRESIMS *m/z* 617.2754 $[M+H]^+$ (calcd for $C_{32}H_{45}O_{10}Si$, 617.2782).

3.3.12. Compound 14. A tetrabutylammonium fluoride solution (1.0 M in tetrahydrofuran, 120 μL, 0.120 mmol) was added to a solution of **11** (15 mg, 0.024 mmol) in tetrahydrofuran (0.5 mL), and the mixture was stirred at room temperature under an argon atmosphere for 15 min. The mixture was diluted with chloroform (30 mL), washed sequentially with water (5 mL) and brine (5 mL), dried over Na_2SO_4, and filtered. The solvent was removed in vacuo, and the crude product was purified by preparative ODS-HPLC using MeCN–H_2O (35/65) as an eluent to afford **14** (5.6 mg, 46%) as a colorless amorphous solid: $[\alpha]_D^{24}$ +52.8 (*c* 0.04, $CHCl_3$); IR (film) ν_{max} 3431, 1735, 1644 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.38 (1H, br s, H-15), 5.68 (1H, s, H-2′), 4.89 (1H, s, H-7), 4.31 (1H, d, *J*=8.4 Hz, H_a-20), 4.30 (1H, s, H-12), 3.79 (3H, s, OCH_3), 3.78 (1H, d, *J*=8.4 Hz, H_b-20), 3.58 (1H, d, *J*=16.8 Hz, H_β-1), 3.40 (1H, br s, H-14), 3.05 (1H, s, H-9), 2.98 (1H, d, *J*=13.1 Hz, H-5), 2.41 (1H, dt, *J*=14.8, 3.0 Hz, H_α-6), 2.24 (1H, d, *J*=16.8 Hz, H_α-1), 2.21 (3H, d, *J*=1.1 Hz, H-5′), 1.95 (3H, d, *J*=1.1 Hz, H-4′), 1.85 (3H, d, *J*=1.9 Hz, H-18), 1.65 (1H, ddd, *J*=14.8, 13.1, 2.4 Hz, H_β-6), 1.21 (3H, s, H-19); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.2 (C-11), 191.9 (C-2), 169.9 (C-21), 166.6 (C-16), 164.7 (C-1′), 161.6 (C-3′), 144.4 (C-3), 126.7 (C-4), 113.9 (C-2′), 81.2 (C-13), 80.6 (C-7), 77.8 (C-12), 73.7 (C-20), 65.7 (C-15), 53.2 (OCH_3), 51.4 (C-14), 50.5 (C-9), 49.3 (C-1), 46.8 (C-8), 39.9 (C-5), 39.7 (C-10), 28.3 (C-6), 27.7 (C-4′), 20.7 (C-5′), 13.2×2 (C-18, C-19); HRESIMS *m/z* 519.1853 $[M+H]^+$ (calcd for $C_{26}H_{31}O_{11}$, 519.1866).

3.3.13. Compound 15. To a solution of **13** (15 mg, 0.024 mmol) in tetrahydrofuran (0.5 mL) was added a tetrabutylammonium fluoride solution (1.0 M in tetrahydrofuran, 120 μL, 0.120 mmol), and the mixture was stirred at room temperature under an argon atmosphere for 20 min. The mixture was diluted with chloroform (30 mL), washed sequentially with water (5 mL) and brine (5 mL), dried over Na_2SO_4, and filtered. The solvent was removed in vacuo, and the crude product was purified by preparative ODS-HPLC using MeCN–H_2O (35/65) as an eluent to afford **15** (5.6 mg, 46%) as a colorless amorphous solid: $[\alpha]_D^{24}$ −113.4 (*c* 0.11, $CHCl_3$); IR (film) ν_{max} 3429, 1745, 1643 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.39 (1H, d, *J*=9.8 Hz, H-12), 6.08 (1H, d, *J*=9.8 Hz, H-11), 5.78 (1H, s, H-2′), 5.43 (1H, d, *J*=1.5 Hz, H-15), 4.20 (1H, s, H-7), 4.16 (1H, d, *J*=9.8 Hz, H_a-20), 3.82 (3H, s, OCH_3), 3.78 (1H, d, *J*=9.8 Hz, H_b-20), 3.73 (1H, d, *J*=12.8 Hz, H-5), 3.20 (1H, d, *J*=16.5 Hz, H_α-1), 2.74 (1H, s, H-14), 2.59 (1H, d, *J*=16.5 Hz, H_β-1), 2.22 (1H, br d, *J*=14.5 Hz, H_α-6), 2.18 (3H, s, H-5′), 1.93 (3H, s, H-4′), 1.84 (3H, d, *J*=1.1 Hz, H-18), 1.59 (1H, dd, *J*=14.5, 12.8 Hz, H_β-6), 1.06 (3H, s, H-19); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.4 (C-2), 169.0 (C-21), 167.9 (C-16), 164.5 (C-1′), 159.8 (C-3′), 143.5 (C-3), 130.7 (C-12), 128.5 (C-4), 127.8 (C-11), 114.8 (C-2′), 85.6 (C-9), 82.1 (C-13), 72.5 (C-7), 71.0 (C-20), 63.1 (C-15), 54.4 (C-14), 53.1 (OCH_3), 48.2 (C-8), 45.1 (C-10), 43.3 (C-1), 33.5 (C-5), 30.0 (C-6), 27.6 (C-4′), 20.6 (C-5′), 17.3 (C-19), 13.4 (C-18); HRESIMS *m/z* 503.1882 $[M+H]^+$ (calcd for $C_{26}H_{31}O_{10}$, 503.1917).

3.3.14. Compound 16. A solution of **10** (60 mg, 0.095 mmol) and lithium iodide (63 mg, 0.47 mmol) in pyridine (1 mL) was stirred at 100 °C under an argon atmosphere for 24 h. The solvent was removed in vacuo, and the residue was dissolved in chloroform (30 mL). The solution was washed sequentially with 1 M HCl (5 mL) and brine (5 mL), dried over Na_2SO_4, and filtered. The solvent was removed in vacuo, and the crude product was purified by preparative ODS-HPLC using MeCN–H_2O–AcOH (51/48/1) as an eluent to afford acid **16** (42.4 mg, 72%) as a colorless amorphous solid: $[\alpha]_D^{24}$ +15.3 (*c* 0.85, $CHCl_3$); IR (film) ν_{max} 3467, 1728, 1672 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 6.20 (1H, br s, H-15), 5.69 (1H, s, H-2′), 4.91 (1H, s, H-7), 4.70 (1H, br s, H_a-20), 4.17 (1H, s, H-11), 4.12 (1H, s, H-12), 3.74 (1H, br s, H_b-20), 3.24 (1H, br s, H-14),

2.99 (1H, d, J=12.2 Hz, H-5), 2.82 (1H, d, J=15.9 Hz, H_β-1), 2.51 (1H, d, J=15.9 Hz, H_α-1), 2.31 (1H, dd, J=14.6, 2.4 Hz, H_α-6), 2.19 (1H, s, H-9), 2.15 (3H, s, H-5′), 1.92 (3H, s, H-4′), 1.89 (3H, s, H-18), 1.88 (1H, m, H_β-6), 1.39 (3H, s, H-19), 0.97 (9H, s, Me_3CSi), 0.17 and 0.12 (3H each, s, Me_2Si); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.1 (C-2), 174.6 (C-21), 170.0 (C-16), 166.5 (C-1′), 160.0 (C-3′), 146.0 (C-3), 139.1 (C-4), 116.1 (C-2′), 84.9 (C-7), 82.6 (C-13), 77.1 (C-12), 74.5 (C-20), 72.4 (C-11), 68.1 (C-15), 51.4×2 (C-1, C-14), 46.6 (C-8), 44.0 (C-5), 42.6 (C-9), 41.7 (C-10), 30.3 (C-6), 27.5 (C-4′), 26.5 (Me_3CSi, 3C), 20.5 (C-5′), 19.7 (Me_3CSi), 15.9 (C-19), 14.8 (C-18), −3.4, −3.6 (Me_2Si); HRESIMS m/z 621.2755 $[M+H]^+$ (calcd for $C_{31}H_{45}O_{11}Si$, 621.2731).

3.3.15. Compound 17. To a solution of **16** (20 mg, 0.032 mmol) in acetone (0.5 mL) were added potassium carbonate (22 mg, 0.16 mmol) and iodoethane (26 μL, 0.33 mmol), and the mixture was stirred at 50 °C under an argon atmosphere for 6 h. The mixture was diluted with chloroform (20 mL) and the insoluble matter was removed by filtration. The filtrate was concentrated in vacuo, and the crude product was purified by silica gel column chromatography using chloroform–methanol (20/1) as an eluent to afford **17** (18.9 mg, 90%) as a colorless amorphous solid: $[\alpha]_D^{24}$ +11.3 (c 0.23, $CHCl_3$); IR (film) ν_{max} 3473, 1739, 1676 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.29 (1H, br s, H-15), 5.63 (1H, s, H-2′), 4.78 (1H, s, H-7), 4.72 (1H, d, J=7.9 Hz, H_a-20), 4.28–4.20 (3H, m, H-11 and H-1″), 4.18 (1H, s, H-12), 3.79 (1H, d, J=7.9 Hz, H_b-20), 3.10 (1H, br s, H-14), 2.93 (1H, d, J=12.5 Hz, H-5), 2.90 (1H, d, J=15.9 Hz, H_β-1), 2.38 (1H, dt, J=14.7, 2.7 Hz, H_α-6), 2.33 (1H, d, J=15.9 Hz, H_α-1), 2.19 (3H, s, H-5′), 2.07 (1H, br s, H-9), 1.92 (3H, s, H-4′), 1.84 (3H, d, J=1.6 Hz, H-18), 1.75 (1H, ddd, J=14.7, 12.5, 2.5 Hz, H_β-6), 1.39 (3H, s, H-19), 1.32 (3H, t, J=7.2 Hz, H-2″), 0.95 (9H, s, Me_3CSi), 0.17 and 0.14 (3H each, s, Me_2Si); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.9 (C-2), 171.7 (C-21), 167.1 (C-16), 164.5 (C-1′), 161.0 (C-3′), 145.1 (C-3), 135.6 (C-4), 114.1 (C-2′), 82.5 (C-7), 81.3 (C-13), 75.9 (C-12), 74.1 (C-20), 70.9 (C-11), 65.8 (C-15), 62.5 (C-1″), 51.7 (C-14), 50.6 (C-1), 45.4 (C-8), 42.7 (C-5), 42.0 (C-9), 40.5 (C-10), 29.4 (C-6), 27.7 (C-4′), 26.0 (Me_3CSi, 3C), 20.6 (C-5′), 18.8 (Me_3CSi), 15.5 (C-19), 14.4 (C-18), 14.0 (C-2″), −3.8, −3.9 (Me_2Si); HRESIMS m/z 649.3077 $[M+H]^+$ (calcd for $C_{33}H_{49}O_{11}Si$, 649.3044).

3.3.16. Compound 18. As described for **17**, the reaction of compound **16** (10 mg, 0.016 mmol), potassium carbonate (11 mg, 0.080 mmol), and 1-iodopropane (16 μL, 0.16 mmol) in acetone (0.5 mL) at 50 °C for 16 h afforded **18** (9.7 mg, 91%) as a colorless amorphous solid: $[\alpha]_D^{24}$ +10.8 (c 0.19, $CHCl_3$); IR (film) ν_{max} 3460, 1738, 1674 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.30 (1H, br s, H-15), 5.62 (1H, s, H-2′), 4.79 (1H, s, H-7), 4.72 (1H, d, J=7.9 Hz, H_a-20), 4.25 (1H, m, H-11), 4.18 (1H, s, H-12), 4.12 (2H, m, H-1″), 3.79 (1H, d, J=7.9 Hz, H_b-20), 3.09 (1H, br s, H-14), 2.93 (1H, d, J=12.6 Hz, H-5), 2.90 (1H, d, J=15.9 Hz, H_β-1), 2.38 (1H, dt, J=14.7, 2.8 Hz, H_α-6), 2.33 (1H, d, J=15.9 Hz, H_α-1), 2.18 (3H, d, J=0.9 Hz, H-5′), 2.07 (1H, br s, H-9), 1.92 (3H, d, J=1.1 Hz, H-4′), 1.84 (3H, d, J=1.7 Hz, H-18), 1.75 (1H, ddd, J=14.7, 12.6, 2.6 Hz, H_β-6), 1.75–1.67 (2H, m, H-2″), 1.39 (3H, s, H-19), 0.96 (3H, t, J=7.5 Hz, H-3″), 0.95 (9H, s, Me_3CSi), 0.18 and 0.14 (3H each, s, Me_2Si); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.9 (C-2), 171.8 (C-21), 167.1 (C-16), 164.5 (C-1′), 160.9 (C-3′), 145.1 (C-3), 135.6 (C-4), 114.1 (C-2′), 82.5 (C-7), 81.4 (C-13), 76.0 (C-12), 74.1 (C-20), 70.9 (C-11), 68.0 (C-1″), 65.8 (C-15), 52.0 (C-14), 50.6 (C-1), 45.4 (C-8), 42.7 (C-5), 42.0 (C-9), 40.5 (C-10), 29.4 (C-6), 27.7 (C-4′), 26.0 (Me_3CSi, 3C), 21.8 (C-2″), 20.6 (C-5′), 18.8 (Me_3CSi), 15.5 (C-19), 14.4 (C-18), 10.3 (C-3″), −3.8, −3.9 (Me_2Si); HRESIMS m/z 663.3204 $[M+H]^+$ (calcd for $C_{34}H_{51}O_{11}Si$, 663.3201).

3.3.17. Compound 19. As described for **17**, the reaction of compound **16** (10 mg, 0.016 mmol), potassium carbonate (11 mg, 0.080 mmol), and 1-iodobutane (18 μL, 0.16 mmol) in acetone (0.5 mL) at 50 °C for 16 h afforded **19** (10 mg, 92%) as a colorless amorphous solid: $[\alpha]_D^{24}$ +2.0 (c 0.20, $CHCl_3$); IR (film) ν_{max} 3483, 1730, 1672 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.30 (1H, br s, H-15), 5.63 (1H, s, H-2′), 4.79 (1H, s, H-7), 4.72 (1H, d, J=7.9 Hz, H_a-20), 4.25 (1H, m, H-11), 4.17 (1H, s, H-12), 4.16 (2H, m, H-1″), 3.79 (1H, d, J=7.9 Hz, H_b-20), 3.08 (1H, br s, H-14), 2.93 (1H, d, J=12.5 Hz, H-5), 2.90 (1H, d, J=15.9 Hz, H_β-1), 2.38 (1H, dt, J=14.7, 2.8 Hz, H_α-6), 2.32 (1H, d, J=15.9 Hz, H_α-1), 2.19 (3H, d, J=1.0 Hz, H-5′), 2.07 (1H, br s, H-9), 1.92 (3H, d, J=1.0 Hz, H-4′), 1.84 (3H, d, J=1.7 Hz, H-18), 1.75 (1H, ddd, J=14.7, 12.5, 2.6 Hz, H_β-6), 1.66 (2H, m, H-2″), 1.39 (3H, s, H-19), 1.38 (2H, m, H-3″), 0.95 (3H, t, J=7.5 Hz, H-4″), 0.95 (9H, s, Me_3CSi), 0.18 and 0.14 (3H each, s, Me_2Si); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.9 (C-2), 171.8 (C-21), 167.1 (C-16), 164.4 (C-1′), 160.9 (C-3′), 145.1 (C-3), 135.6 (C-4), 114.2 (C-2′), 82.5 (C-7), 81.4 (C-13), 76.0 (C-12), 74.1 (C-20), 70.9 (C-11), 66.4 (C-1″), 65.8 (C-15), 51.8 (C-14), 50.6 (C-1), 45.4 (C-8), 42.7 (C-5), 42.0 (C-9), 40.5 (C-10), 30.4 (C-2″), 29.4 (C-6), 27.7 (C-4′), 26.0 (Me_3CSi, 3C), 20.6 (C-5′), 19.1 (C-3″), 18.8 (Me_3CSi), 15.5 (C-19), 14.4 (C-18), 13.7 (C-4″), −3.8, −3.9 (Me_2Si); HRESIMS m/z 677.3362 $[M+H]^+$ (calcd for $C_{35}H_{53}O_{11}Si$, 677.3357).

3.3.18. Compound 20. As described for **17**, the reaction of compound **16** (10 mg, 0.016 mmol), potassium carbonate (11 mg, 0.080 mmol), and 1-iodopentane (21 μL, 0.16 mmol) in acetone (0.5 mL) at 50 °C for 24 h afforded **20** (9.8 mg, 88%) as a colorless amorphous solid: $[\alpha]_D^{24}$ −11.8 (c 0.26, $CHCl_3$); IR (film) ν_{max} 3417, 1739, 1672 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.29 (1H, br s, H-15), 5.62 (1H, s, H-2′), 4.79 (1H, s, H-7), 4.72 (1H, d, J=7.9 Hz, H_a-20), 4.25 (1H, m, H-11), 4.18 (1H, s, H-12), 4.15 (2H, m, H-1″), 3.78 (1H, d, J=7.9 Hz, H_b-20), 3.09 (1H, br s, H-14), 2.93 (1H, d, J=12.3 Hz, H-5), 2.90 (1H, d, J=15.8 Hz, H_β-1), 2.38 (1H, d, J=14.5 Hz, H_α-6), 2.32 (1H, d, J=15.8 Hz, H_α-1), 2.18 (3H, s, H-5′), 2.06 (1H, br s, H-9), 1.91 (3H, s, H-4′), 1.84 (3H, d, J=1.2 Hz, H-18), 1.75 (1H, ddd, J=14.5, 12.3, 2.6 Hz, H_β-6), 1.68 (2H, m, H-2″), 1.39 (3H, s, H-19), 1.37–1.28 (4H, m, H-3″ and H-4″), 0.95 (9H, s, Me_3CSi), 0.92 (3H, t, J=7.0 Hz, H-5″), 0.17 and 0.13 (3H each, s, Me_2Si); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.0 (C-2), 171.7 (C-21), 167.1 (C-16), 164.5 (C-1′), 160.9 (C-3′), 145.1 (C-3), 135.7 (C-4), 114.2 (C-2′), 82.5 (C-7), 81.4 (C-13), 75.9 (C-12), 74.0 (C-20), 70.9 (C-11), 66.7 (C-1″), 65.8 (C-15), 51.8 (C-14), 50.6 (C-1), 45.4 (C-8), 42.7 (C-5), 42.0 (C-9), 40.5 (C-10), 29.4 (C-6), 28.0 (C-2″), 27.9 (C-3″),

27.7 (C-4′), 26.0 (Me_3CSi, 3C), 22.3 (C-4″), 20.6 (C-5′), 18.8 (Me_3CSi), 15.5 (C-19), 14.4 (C-18), 13.9 (C-5″), −3.8, −3.9 (Me_2Si); HRESIMS *m/z* 691.3505 $[M+H]^+$ (calcd for $C_{36}H_{55}O_{11}Si$, 691.3514).

3.3.19. Compound 21. To a solution of **17** (10 mg, 0.015 mmol) in tetrahydrofuran (0.5 mL) was added a tetrabutylammonium fluoride solution (1.0 M solution in tetrahydrofuran, 80 μL, 0.080 mmol), and the mixture was stirred at room temperature under an argon atmosphere for 15 min. Water (5 mL) was added to the mixture, and the whole was extracted with chloroform (3×10 mL). The combined organic layers were washed sequentially with water (5 mL) and brine (5 mL), dried over Na_2SO_4, and filtered. The solvent was removed in vacuo, and the crude product was purified by preparative ODS-HPLC using MeCN–H_2O (30/70) as an eluent to afford **21** (6.3 mg, 76%) as a colorless amorphous solid: $[\alpha]_D^{24}$ +2.4 (*c* 0.13, $CHCl_3$); IR (film) ν_{max} 3452, 1731, 1644 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.31 (1H, br s, H-15), 5.63 (1H, s, H-2′), 4.79 (1H, s, H-7), 4.72 (1H, d, *J*=8.0 Hz, H_a-20), 4.27–4.23 (3H, m, H-11 and H-1″), 4.19 (1H, s, H-12), 3.80 (1H, dd, *J*=8.0, 1.2 Hz, H_b-20), 3.11 (1H, br s, H-14), 2.98 (1H, d, *J*=16.2 Hz, H_β-1), 2.96 (1H, d, *J*=12.6 Hz, H-5), 2.39 (1H, d, *J*=16.2 Hz, H_α-1), 2.39 (1H, d, *J*=15.1 Hz, H_α-6), 2.19 (3H, d, *J*=0.8 Hz, H-5′), 2.12 (1H, br s, H-9), 1.92 (3H, d, *J*=0.8 Hz, H-4′), 1.85 (3H, d, *J*=1.8 Hz, H-18), 1.76 (1H, ddd, *J*=15.1, 12.6, 2.6 Hz, H_β-6), 1.40 (3H, s, H-19), 1.32 (3H, t, *J*=7.2 Hz, H-2″); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.9 (C-2), 171.7 (C-21), 167.0 (C-16), 164.5 (C-1′), 161.1 (C-3′), 144.1 (C-3), 127.6 (C-4), 114.1 (C-2′), 82.3 (C-7), 81.3 (C-13), 75.9 (C-12), 74.1 (C-20), 70.9 (C-11), 65.7 (C-15), 62.6 (C-1″), 51.8 (C-14), 48.7 (C-1), 45.5 (C-8), 42.0 (C-9), 41.9 (C-5), 41.2 (C-10), 29.1 (C-6), 27.7 (C-4′), 20.6 (C-5′), 15.5 (C-19), 14.0 (C-2″), 13.3 (C-18); HRESIMS *m/z* 535.2159 $[M+H]^+$ (calcd for $C_{27}H_{35}O_{11}$, 535.2179).

3.3.20. Compound 22. As described for **21**, desilylation of **18** (10 mg, 0.015 mmol) afforded **22** (6.5 mg, 79%) as a colorless amorphous solid: $[\alpha]_D^{24}$ −1.3 (*c* 0.15, $CHCl_3$); IR (film) ν_{max} 3442, 1731, 1644 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.32 (1H, br s, H-15), 5.62 (1H, s, H-2′), 4.79 (1H, s, H-7), 4.72 (1H, d, *J*=7.9 Hz, H_a-20), 4.25 (1H, s, H-11), 4.19 (1H, s, H-12), 4.13 (2H, m, H-1″), 3.80 (1H, d, *J*=7.9 Hz, H_b-20), 3.10 (1H, br s, H-14), 2.99 (1H, d, *J*=16.2 Hz, H_β-1), 2.96 (1H, d, *J*=12.8 Hz, H-5), 2.39 (1H, d, *J*=16.2 Hz, H_α-1), 2.39 (1H, d-like, *J*=15.2 Hz, H_α-6), 2.19 (3H, s, H-5′), 2.11 (1H, br s, H-9), 1.92 (3H, s, H-4′), 1.85 (3H, d, *J*=1.4 Hz, H-18), 1.76 (1H, ddd, *J*=15.2, 12.8, 2.4 Hz, H_β-6), 1.71 (2H, m, H-2″), 1.40 (3H, s, H-19), 0.96 (3H, t, *J*=7.5 Hz, H-3″); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.0 (C-2), 171.7 (C-21), 167.1 (C-16), 164.4 (C-1′), 161.0 (C-3′), 144.1 (C-3), 127.6 (C-4), 114.1 (C-2′), 82.3 (C-7), 81.4 (C-13), 75.9 (C-12), 74.1 (C-20), 70.9 (C-11), 68.0 (C-1″), 65.8 (C-15), 51.8 (C-14), 48.7 (C-1), 45.5 (C-8), 42.0 (C-9), 41.9 (C-5), 41.2 (C-10), 29.1 (C-6), 27.7 (C-4′), 21.8 (C-2″), 20.6 (C-5′), 15.5 (C-19), 13.3 (C-18), 10.3 (C-3″); HRESIMS *m/z* 549.2338 $[M+H]^+$ (calcd for $C_{28}H_{37}O_{11}$, 549.2336).

3.3.21. Compound 23. As described for **21**, desilylation of **19** (10 mg, 0.015 mmol) afforded **23** (6.1 mg, 73%) as a colorless amorphous solid: $[\alpha]_D^{24}$ 0 (*c* 0.04, $CHCl_3$); IR (film) ν_{max} 3443, 1732, 1645 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.33 (1H, br s, H-15), 5.63 (1H, s, H-2′), 4.79 (1H, s, H-7), 4.72 (1H, d, *J*=8.0 Hz, H_a-20), 4.25 (1H, br s, H-11), 4.19 (1H, s, H-12), 4.17 (2H, m, H-1″), 3.80 (1H, d, *J*=8.0 Hz, H_b-20), 3.09 (1H, br s, H-14), 2.99 (1H, d, *J*=16.2 Hz, H_β-1), 2.96 (1H, d, *J*=12.3 Hz, H-5), 2.39 (1H, d, *J*=16.2 Hz, H_α-1), 2.39 (1H, d, *J*=14.9 Hz, H_α-6), 2.20 (3H, s, H-5′), 2.12 (1H, br s, H-9), 1.93 (3H, s, H-4′), 1.85 (3H, d, *J*=1.8 Hz, H-18), 1.76 (1H, ddd, *J*=14.9, 12.3, 2.6 Hz, H_β-6), 1.67 (2H, m, H-2″), 1.41 (3H, s, H-19), 1.38 (2H, m, H-3″), 0.96 (3H, t, *J*=7.4 Hz, H-4″); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.9 (C-2), 171.8 (C-21), 167.1 (C-16), 164.5 (C-1′), 161.1 (C-3′), 144.1 (C-3), 127.5 (C-4), 114.1 (C-2′), 82.3 (C-7), 81.4 (C-13), 76.0 (C-12), 74.1 (C-20), 70.9 (C-11), 66.4 (C-1″), 65.7 (C-15), 51.9 (C-14), 48.7 (C-1), 45.5 (C-8), 42.0 (C-9), 41.9 (C-5), 41.2 (C-10), 30.4 (C-2″), 29.1 (C-6), 27.7 (C-4′), 20.6 (C-5′), 19.1 (C-3″), 15.5 (C-19), 13.7 (C-4″), 13.3 (C-18); HRESIMS *m/z* 563.2471 $[M+H]^+$ (calcd for $C_{29}H_{39}O_{11}$, 563.2492).

3.3.22. Compound 24. As described for **21**, desilylation of **20** (25 mg, 0.036 mmol) afforded **24** (12.7 mg, 61%) as a colorless amorphous solid: $[\alpha]_D^{24}$ −2.8 (*c* 0.25, $CHCl_3$); IR (film) ν_{max} 3452, 1731, 1644 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.31 (1H, br s, H-15), 5.62 (1H, s, H-2′), 4.79 (1H, s, H-7), 4.72 (1H, d, *J*=8.0 Hz, H_a-20), 4.25 (1H, br s, H-11), 4.19 (1H, s, H-12), 4.15 (2H, m, H-1″), 3.80 (1H, d, *J*=8.0 Hz, H_b-20), 3.09 (1H, br s, H-14), 2.98 (1H, d, *J*=16.1 Hz, H_β-1), 2.96 (1H, d, *J*=12.8 Hz, H-5), 2.39 (1H, d, *J*=16.1 Hz, H_α-1), 2.39 (1H, d, *J*=15.2 Hz, H_α-6), 2.19 (3H, s, H-5′), 2.12 (1H, br s, H-9), 1.92 (3H, s, H-4′), 1.85 (3H, d, *J*=1.5 Hz, H-18), 1.76 (1H, ddd, *J*=15.2, 12.8, 2.4 Hz, H_β-6), 1.68 (2H, m, H-2″), 1.40 (3H, s, H-19), 1.38–1.28 (4H, m, H-3″ and H-4″), 0.92 (3H, t, *J*=7.0 Hz, H-5″); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.0 (C-2), 171.7 (C-21), 167.1 (C-16), 164.4 (C-1′), 161.0 (C-3′), 144.1 (C-3), 127.6 (C-4), 114.1 (C-2′), 82.3 (C-7), 81.4 (C-13), 75.9 (C-12), 74.1 (C-20), 70.9 (C-11), 66.7 (C-1″), 65.7 (C-15), 51.9 (C-14), 48.7 (C-1), 45.5 (C-8), 42.1 (C-9), 41.9 (C-5), 41.2 (C-10), 29.1 (C-6), 28.0 (C-2″), 27.9 (C-3″), 27.7 (C-4′), 22.3 (C-4″), 20.6 (C-5′), 15.5 (C-19), 13.9 (C-5″), 13.3 (C-18); HRESIMS *m/z* 577.2626 $[M+H]^+$ (calcd for $C_{30}H_{41}O_{11}$, 577.2649).

3.4. Cytotoxicity assays

The MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) colorimetric assay was performed on a 96-well plate. Murine P-388 leukemia cells (3×10^3 cells) in 100 μL of RPMI-1640 medium (Nissui Pharmaceutical Company, Ltd, Tokyo, Japan) supplemented with 5% fetal calf serum (Mitsubishi Chemical Industry Co., Ltd, Tokyo, Japan) and kanamycin (100 μg/mL) were inoculated into each well and incubated at 37 °C in a humidified atmosphere of 7% CO_2. Test samples of various concentrations (10 μL) were added to the cultures 24 h after incubation. The medium was incubated for 48 h at 37 °C and then 20 μL of the MTT solution (5 mg/mL) was added to each well. After a further incubation for 4 h, 100 μL of 10% sodium dodecyl sulfate–0.01 M HCl solution was added to each well, and the formazan crystals that were formed in each well were dissolved by stirring with a pipette. Optical density was

recorded on a microplate reader (Tosoh MPR-A4i) at 550 nm. In the assay for cytotoxicity, each data point represents the average of three replicate measurements.

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Corrigendum

Corrigendum to "Photoinduced cycloadditions of *N*-methyl-1,8-naphthalenedicarboximides with alkynes" [Tetrahedron 62 (2006) 1131]

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In the experimental section, the X-ray structure analysis of compound **3b** should be as follows:

X-ray structure analysis: $C_{21}H_{14}BrNO_2$, $M=392.24$. Triclinic, space group P-1, $a=9.849(1)$ Å, $b=12.677(2)$ Å, $c=14.493(2)$ Å, $\alpha=90.55(1)$, $\beta=102.96(1)$, $\gamma=107.09(1)°$, $V=1680.0(4)$ Å^3, $Z=4$, $D_c=1.551$ g cm^{-3}, $F(000)=792$, absorption coefficient 2.461 mm^{-1}, scan range for data collection $1.45\leq\theta\leq25.00°$, 6514 measured reflections, 5848 independent reflections, 3555 reflections with $I>2\sigma(I)$, $R_{int}=0.0098$, 454 refinable parameters, $R[F^2>2\sigma(F^2)]=0.0330$, $wR_2(F^2)=0.0726$.

In the X-ray structure analysis of compound **7e**, the cell parameter b should be replaced by $b=10.465(2)$.

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