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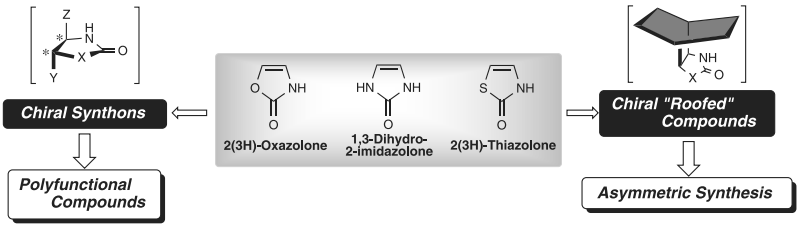
Tetrahedron Vol. 61, No. 34, 2005

Contents

REPORT



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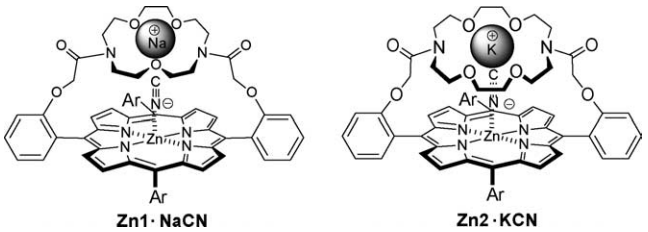
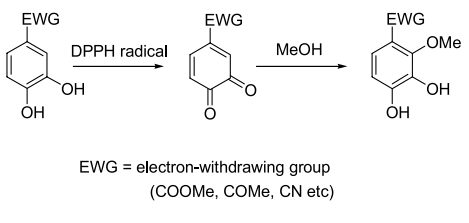
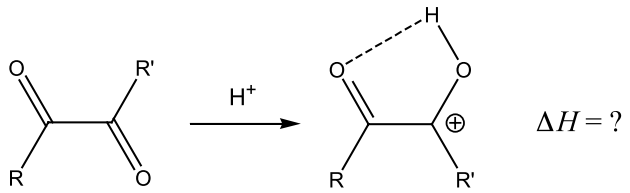
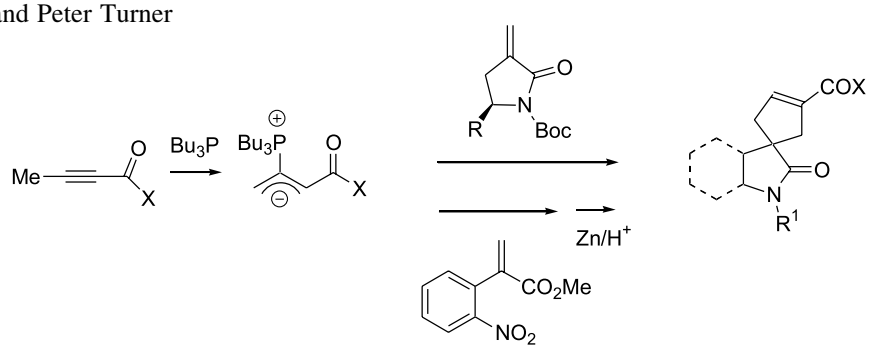
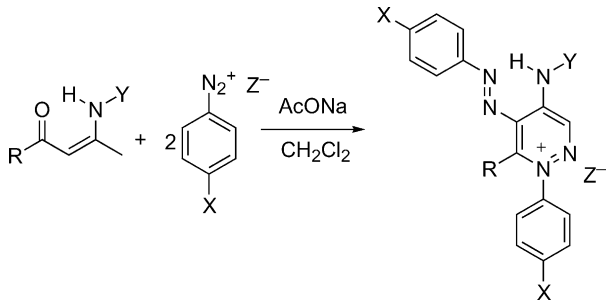
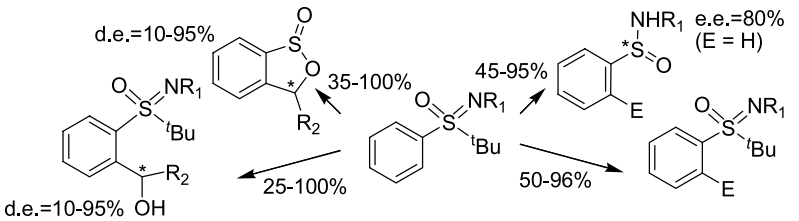


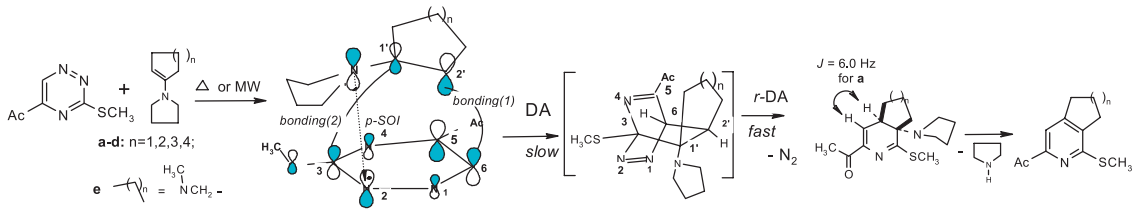


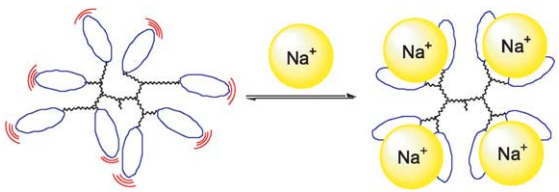


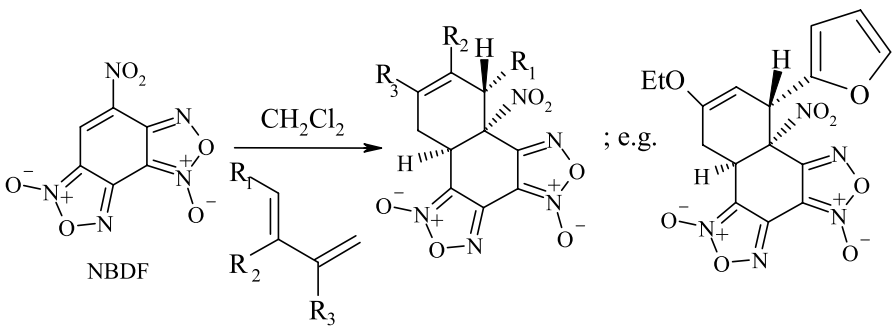


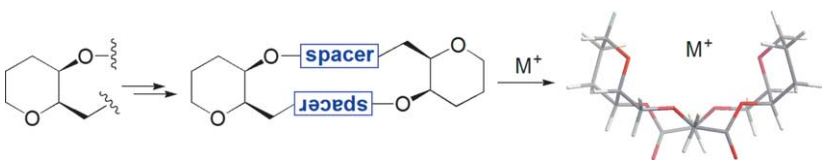


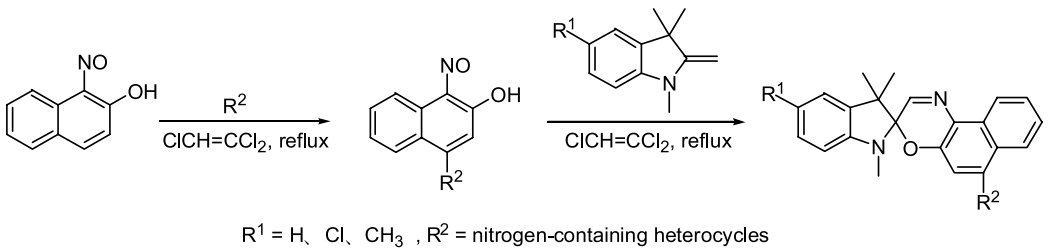


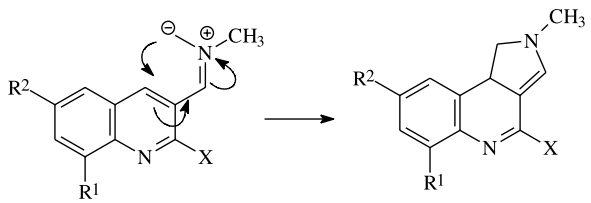


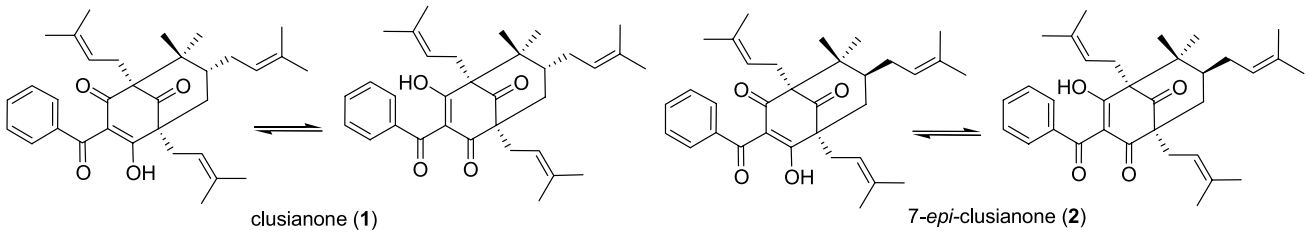


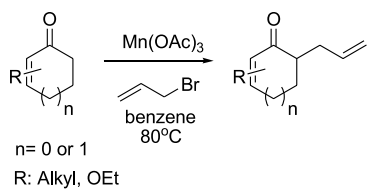


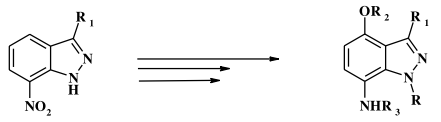


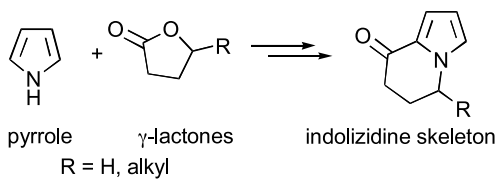




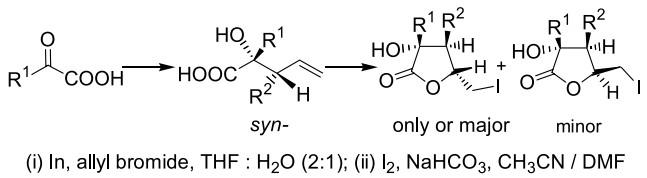


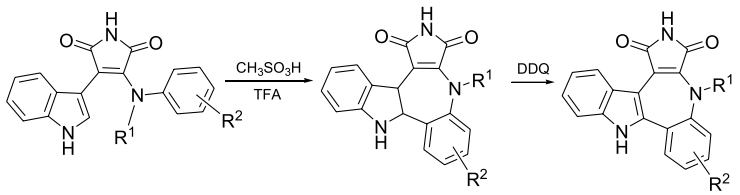


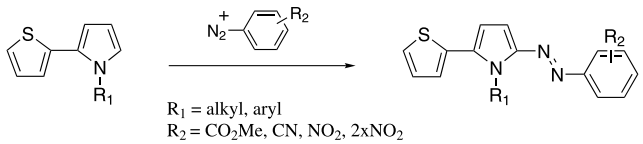


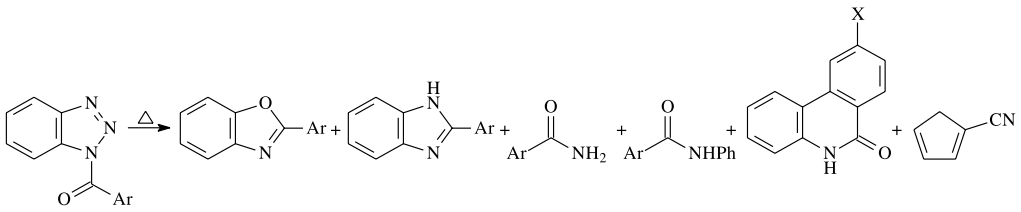


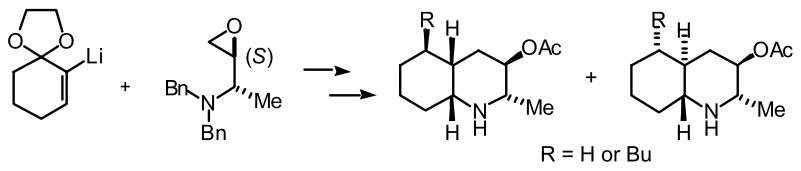
The unusual ring opening of γ-lactones with pyrrole has been exploited in the synthesis of indolizidine natural products.



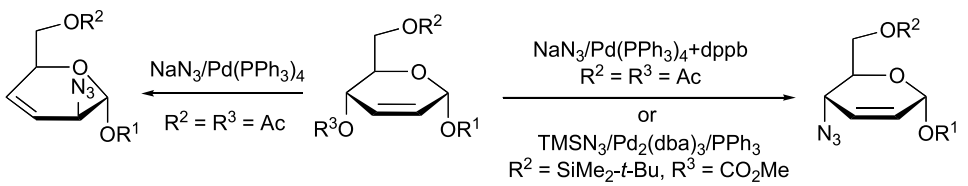


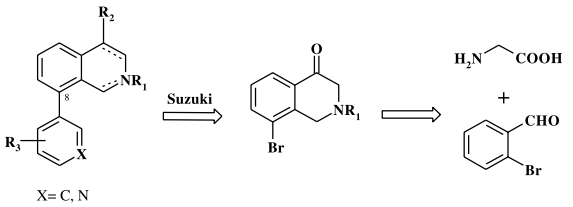


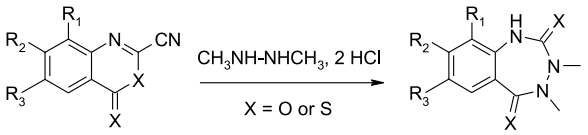




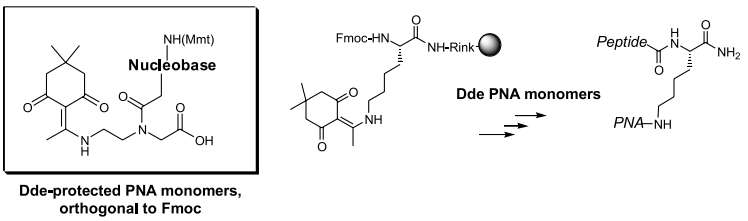
The same sequence was carried out using the (2*R*) epoxide leading to the corresponding epimeric decahydroquinolines at C(3).







Synthesis of novel oxygen and sulfur containing 1,3,4-benzotriazepine derivatives was performed.



OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Efficient solution phase synthesis of the four 1-(4,4-dimethyl-2,6-dioxacyclohexylidene)ethyl/4-methoxytrityl (Dde/Mmt) protected PNA monomers allows the preparation of PNA-peptide conjugates through a Dde deprotection strategy, fully orthogonal to Fmoc chemistry. This approach now allows the preparation of PNA-peptide conjugates for interfacing to DNA micro-array technology and cellular delivery applications. *Tetrahedron* **2005**, *61*, 8295–8305.

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Synthetic utility of five-membered heterocycles—chiral functionalization and applications

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1. Introduction

Highly stereoselective and high-yield bond formations are an absolute necessity for the chiral synthesis of architecturally complex molecules that contain multiple stereogenic centers.[1] Therefore, efficient and practical methodologies continue to be needed for such reactions, which play a key role in highly enantio-controlled bond formation.

Simple five-membered heterocycles such as 2(3*H*)-oxazolone **1**,[2,3] 1,3-dihydro-2-imidazolone **2**[4] and 2(3*H*)-thiazolone **3**[5] contain hydroxy, amino and mercapto functional groups, which are masked by the carbonyl moiety as enol, enamine and enethiol structures. A variety of conceivable addition modes at olefinic moieties are indicative of their synthetic potential as versatile building blocks for polyfunctional compounds. Thus, addition reactions with ionic and radical species as well as pericyclic reactions provide synthetic tools for the preparation of a variety of chiral 2-aminoalcohols,[6] 1,2-diamines[7] and 2-aminothiols[8] as well as functionalized heterocyclic chiral auxiliaries,[1] provided the reactions are enantiomerically controlled (Scheme 1).

This article describes the synthetic utility of simple heterocycles, 4,5-unsubstituted 2-azolones **1**–**3**, from the viewpoint of the chiral synthesis of polyfunctional compounds via versatile chiral synthons and the development of a new class of 'roofed' type chiral sources.[3a,9]

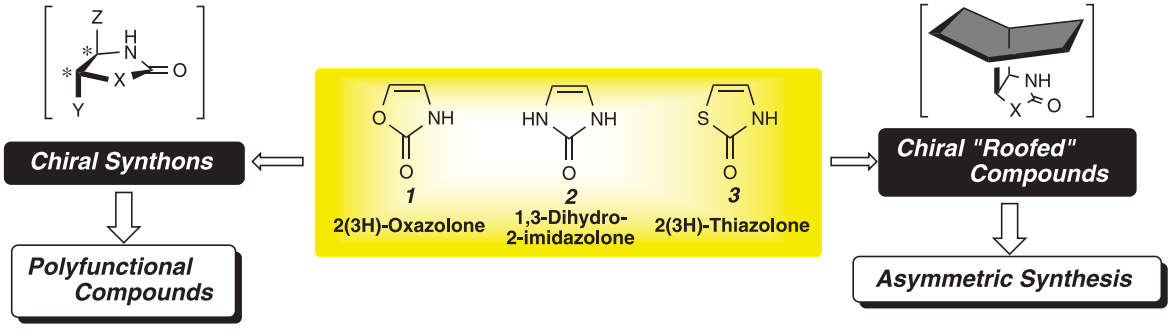
2. Preparation of 2(3*H*)-oxazolone, 1,3-dihydro-2-imidazolone and 2(3*H*)-thiazolone

The 4,5-unsubstituted heterocycles **1**–**3** used in this study are not currently commercially available, although they are quite simple and have been known for some decades. Among the synthetic methods reported, a 2-oxazolone **1** might be most conveniently synthesized in 60–80% overall yield by way of the anodic oxidation of 2-oxazolidinone **4** in methanol,[2b] which is obtainable from the pyrolysis of tris(2-hydroxyethyl)isocyanuric acid **6**,[10] followed by the elimination of methanol. This electrochemical oxidation–elimination procedure has been successfully employed for the practical synthesis of 1,3-dihydro-2-imidazolone **2** from 2-imidazolidinone **5**.[4b] The 2-thiazolone **3** is readily obtainable from the hydrolysis of commercially available 2-bromothiazole **7** under basic conditions.[5] The *N*-acetyl heterocycles of **1**–**3** thus obtained are sufficiently stable to be stored below room temperature (Scheme 2).

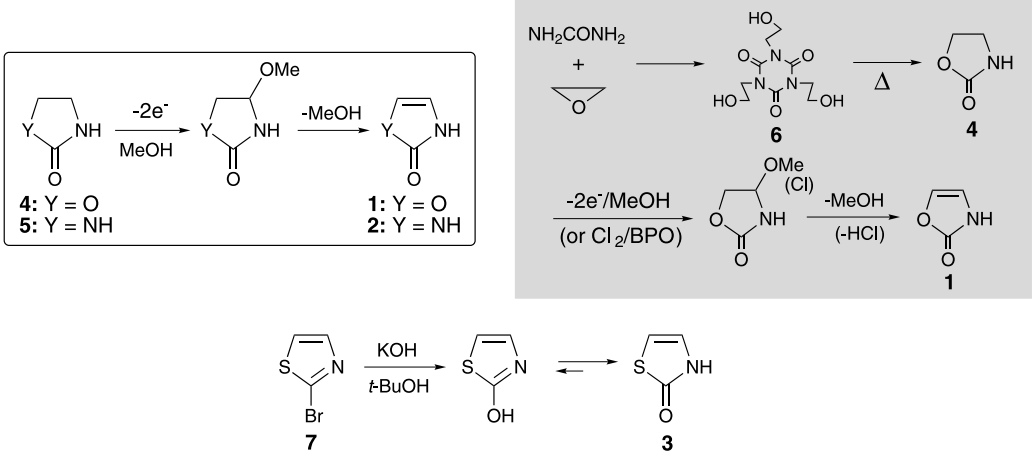
3. Chiral synthons and their use

3.1. Synthetic strategy

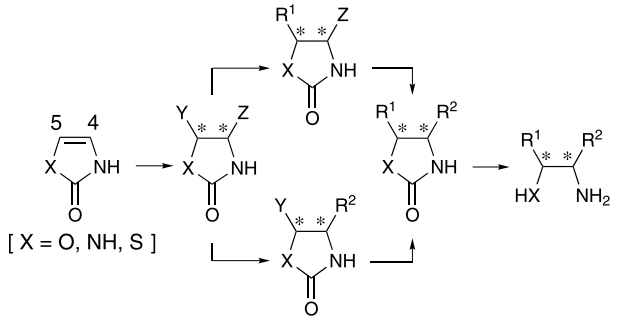
Scheme 3 shows some versatile routes for the chiral synthesis of polyfunctional amino compounds via chiral synthons derived from the efficient chiral functionalization



Scheme 1.



Scheme 2.



Scheme 3.

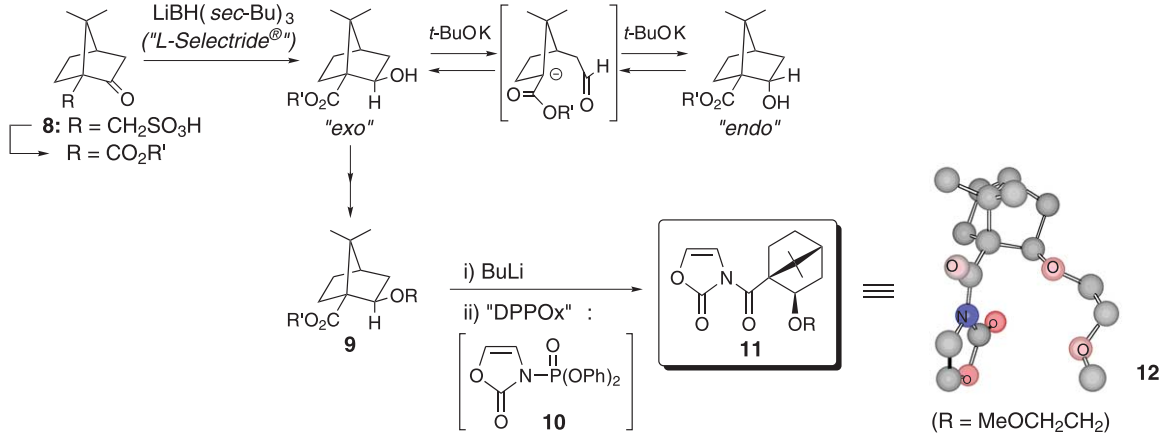
of heterocycles **1**–**3**. The procedure involves, as a key step, the regio- and stereoselective introduction of easily replaceable groups (Y and Z), followed by stepwise and stereospecific substitution with appropriate moieties under the control of the adjacent stereogenic center and subsequent ring opening.

The efficient chiral functionalization of the heterocycles might be achieved by diastereoselective electrophilic additions with the aid of chiral *N*-acyl auxiliaries. Among the chiral sources examined including conventional α-*N*-protected α-amino acids, conformationally rigid 2-*exo*-alkoxy-1-apocamphanecarboxylic acids **9**[11] with a quaternary stereogenic center, derived from (*S*)- and (*R*)-10-camphorsulfonic acids **8**, are promising chiral auxiliaries of choice for achieving a high degree of chiral induction and efficiency.

X-ray crystallographic analysis shows that the predominant conformers of *N*-(2-*exo*-alkoxy-1-apocamphanecarbonyl)-2-oxazolones **11** are rigid *transoid*-forms, depicted as **12**.[12] A series of hindered *N*-acyl-2-oxazolone derivatives are readily accessible from diphenyl 2-oxazolonylphosphonate (DPPOx, **10**)[13] and the bulky carboxylic acids **9**. This type of conformers resulting from dipolar repulsion between the imido-carbonyl groups might be predominantly operative during addition reactions to olefinic moieties, indicative of the effective shielding of the enantiotopic faces (Scheme 4).

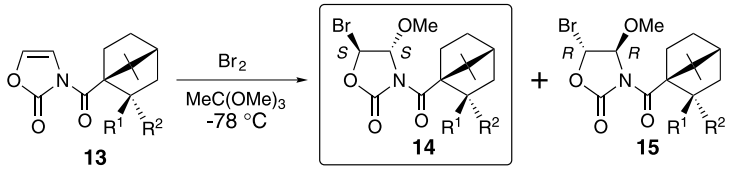
3.2. Electrophilic addition

3.2.1. Bromo-methoxylation.[9b,14,15] A series of *N*-((1*S*)-2-*exo*-alkoxy-1-apocamphanecarbonyl)-2-oxazolones react smoothly with NBS or Br_2 in methanol to yield a diastereomeric mixture of *trans*-5-bromo-4-methoxy derivatives (**14**, **15**) with only moderate selectivity. The diastereoselectivity was greatly improved when trimethyl orthoacetate was used in place of methanol as the methoxy-donating agent. Table 1 shows that the diastereoselectivity for this reaction is dependent on the configuration and bulkiness of the 2-alkoxy groups. Thus, the 2-*exo*-ethoxymethoxy derivative gave the highest selectivity of 96% de, in favor of the (4*S*,5*S*)-adduct **14**, as



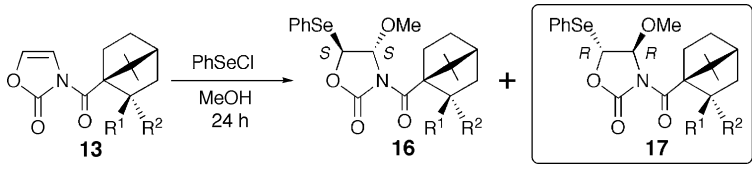
Scheme 4.

Table 1. Diastereoselective bromo-methoxylation



Entry	R^1 (*exo*)	R^2 (*endo*)	Yield (%)	**14**:**15**	de (%)
1	=O		58	9:1	80
2	OMe	H	89	12:1	85
3	OBu	H	85	12:1	85
4	OCH_2CH_2OMe	H	79	17:1	89
5	OCH_2OEt	H	79	46:1	96
6	H	OMe	36	1:1	0
7	Me	H	80	1:1	0

Table 2. Diastereoselective seleno-methoxylation



Entry	R^1 (*exo*)	R^2 (*endo*)	T (°C)	Yield (%)	**16**:**17**	de (%)
1	=O		0	52	1:6	71
2	OMe	H	0	83	1:4	60
3	OBu	H	0	76	1:12	85
4	OCH_2CH_2OMe	H	0	94	1:18	90
5	OCH_2OEt	H	−20	82	1:45	96
6	H	OMe	0	94	1:1	0
7	Me	H	0	80	1:1	0

verified by X-ray crystal analysis. On the other hand, the 2-*endo*-alkoxy- and 2-*exo*-alkyl-apocamphane derivatives were of almost no use as chiral auxiliaries. The oxygen atoms at the 2-*exo*-position appear to play a significant role in achieving a high degree of chiral induction.

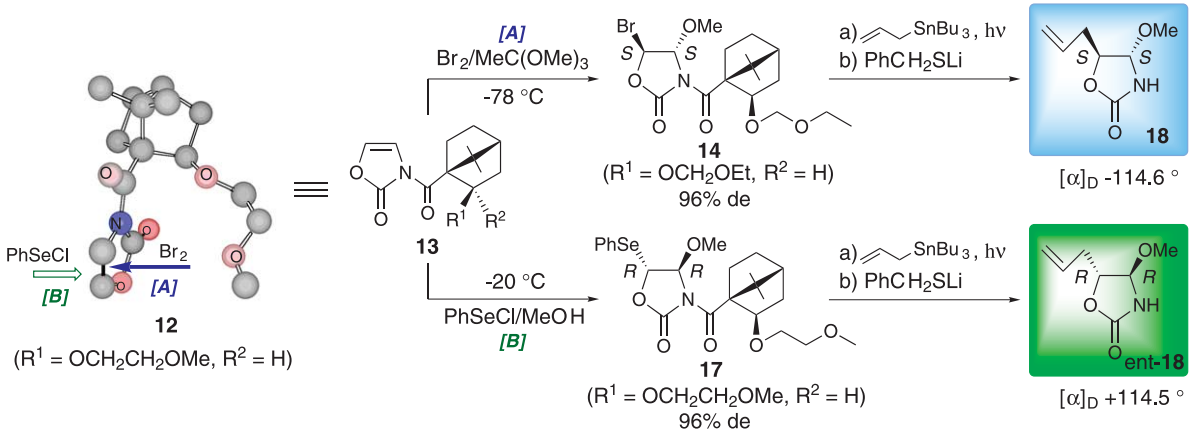
3.2.2. Seleno-methoxylation.[9b,15] The electrophilic addition of **13** with phenylselenenyl chloride in methanol similarly proceeded to give (4*R*,5*R*)-4-methoxy-5-phenylselenenyl adducts **17** in excellent selectivity, in excess of 96% de (Table 2). The stereochemistry of the adducts was confirmed by conversion into 5-allyl-4-methoxy-2-oxazolidinone (*ent*-**18**), which was enantiomeric with compound **18** derived from the methoxy-bromination products **14** (Scheme 5).

Both of the electrophilic addition reactions are generally accepted to proceed via bromonium and selenenium cation intermediates,[16] followed by an anti-periplanar attack of a methoxy group. The observed stereoselectivity is consistent with the postulation that phenylselenenium ions approach from the less hindered face to give the thermodynamically favored selenenium intermediates, while coordination of the bromine molecule with the oxygens of the 2-*exo*-alkoxy substituents accelerates the attack from the sterically shielded side to give the bromonium species.[17] Subsequent back-attacks of the methoxy groups to the active intermediates thus formed should afford the major isomers with completely opposite configurations. The reaction paths are depicted as in Scheme 5, provided that the conformations determined by the X-ray crystal analysis are retained during the reactions.

Electrophilic addition to the 2-thiazolone derivatives **19** proceeds analogously, with virtually the same high diastereoselectivity (Table 3),[18] while it is difficult to control the reactions with reasonable regio- and diastereoselectivity in the case of 2-imidazolone.

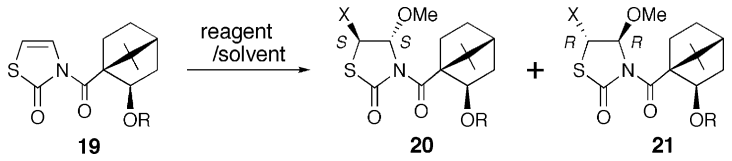
3.2.3. Dialkoxylation. Chiral *trans*-4,5-dialkoxy derivatives of 2-oxazolidinones and 2-imidazolidinones, which are regarded as α-methoxyglycinal and glycinamide equivalents, respectively, represent good candidates for a new class of chiral synthons for use in the preparation of a variety of optically active α-amino acids,[19] α-amino aldehydes[20] and *threo*-1,2-diamines.[7]

The 4,5-dialkoxy derivatives were conventionally prepared from *N*-acetyl-2-oxazolone **22** by bromo-alkoxylation with NBS/ROH (R=Me or *t*-Bu) followed by alcoholysis. Both enantiomers of (+) and (−)-4,5-dimethoxy-2-oxazolidinones (DMOx; **25**, *ent*-**25**) were obtained by kinetic optical resolution through the oxazaborolidine-catalyzed enantioselective deacylation of *N*-acetyl-2-oxazolidinones **23** with borane. On the other hand, the optical resolution of 4-benzyloxy-5-methoxy-2-oxazolidinone (BMOx; **26**) into

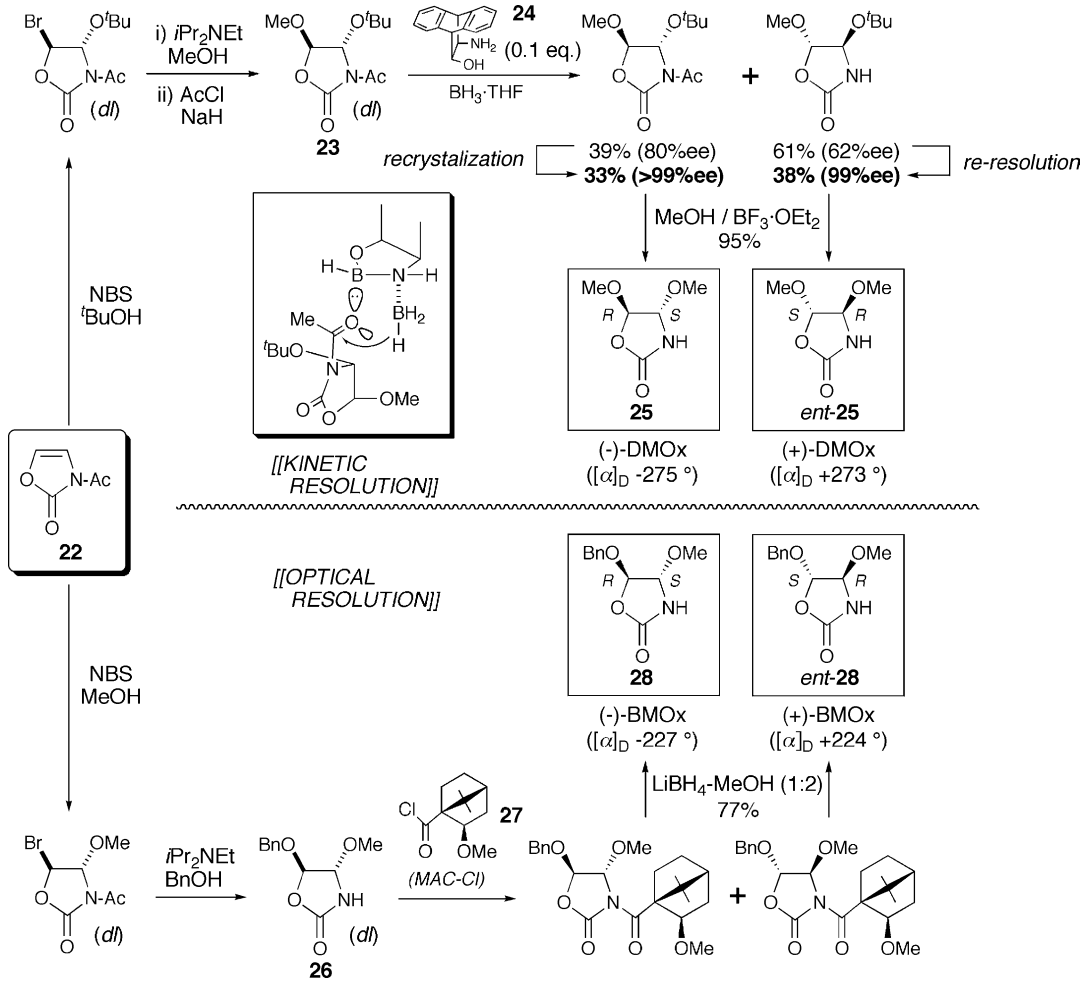


Scheme 5.

Table 3. Diastereoselective bromo-methoxylation and seleno-methoxylation of 3-acyl-2-thiazolones



Entry	R	Reagent/solvent	X	T (°C)	*t* (h)	Yield (%)	**20**:**21**	de (%)
1	Me	Br_2/MeC(OMe)$_3$	Br	−78	2	66	3:1	50
2	Pr	Br_2/MeC(OMe)$_3$	Br	−78	2	59	2:1	33
3	C_2H_4OMe	Br_2/MeC(OMe)$_3$	Br	−78	2	60	20:1	90
4	$C_2H_4OC_2H_4OMe$	Br_2/MeC(OMe)$_3$	Br	−78	2	70	35:1	94
5	Me	PhSeCl/MeOH–CH_2Cl_2	PhSe	−20	24	90	1:2	33
6	Pr	PhSeCl/MeOH–CH_2Cl_2	PhSe	−20	24	82	1:3	50
7	C_2H_4OMe	PhSeCl/MeOH–CH_2Cl_2	PhSe	−20	24	81	1:9	80
8	$C_2H_4OC_2H_4OMe$	PhSeCl/MeOH–CH_2Cl_2	PhSe	−20	24	84	1:7	75



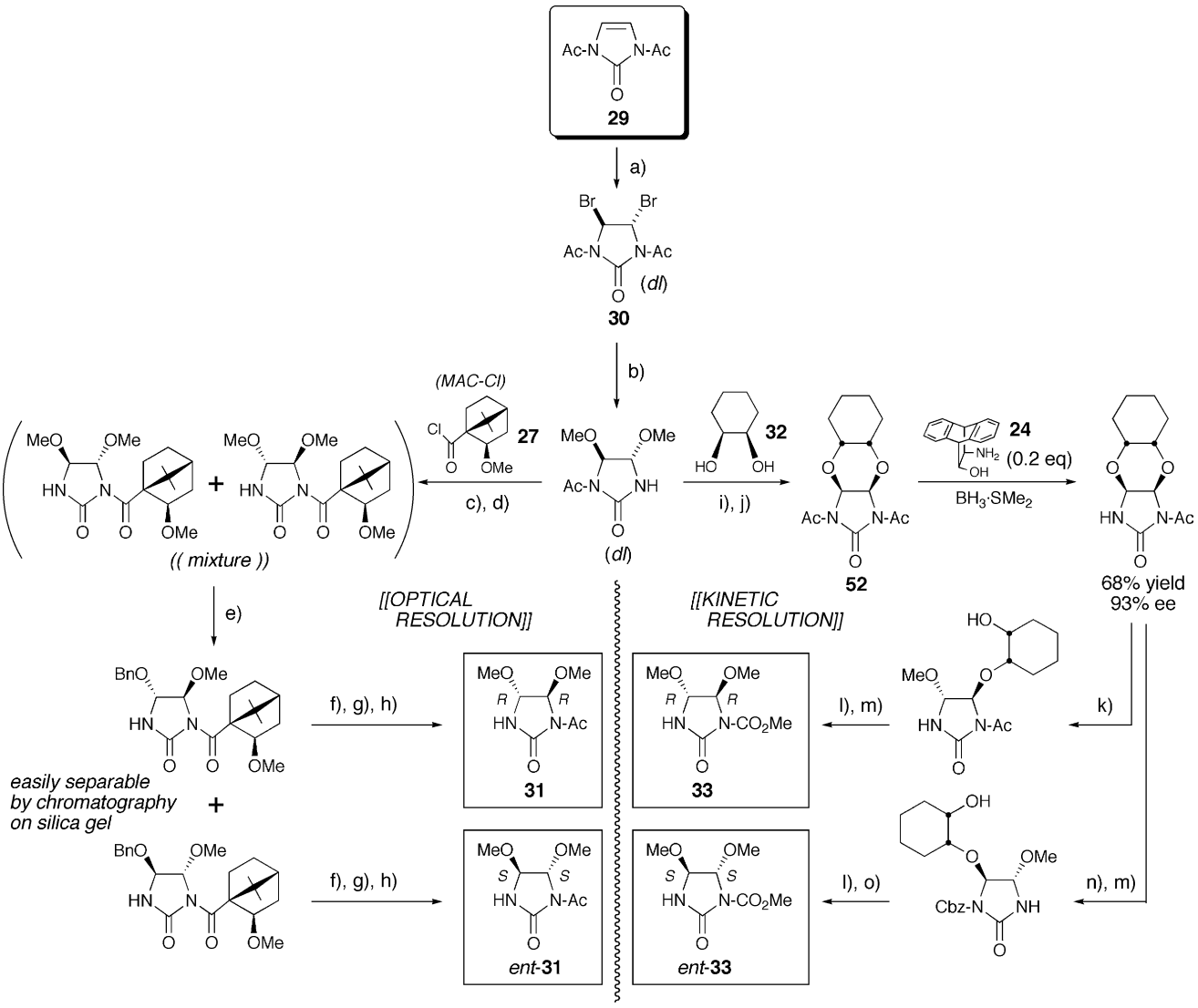
Scheme 6.

the (+) and (−)-isomers (**28**, *ent*-**28**) was conveniently performed with the aid of 2-*exo*-methoxy-1-apocamphanecarboxylic acid (MAC acid) (Scheme 6).[21]

The 4,5-dimethoxy-2-imidazolidinones (**31**, *ent*-**31**; **33**, *ent*-**33**), which are readily accessible from simple 1,3-dihydro-2-imidazolone heterocycles **29** via 4,5-dibromide **30** followed by methanolysis, serve as chiral synthons for the chiral preparation of biologically and synthetically important *threo*-1,2-diamines. This methodology has applicability to the chiral synthesis of C_2-2-imidazolidinone auxiliaries and C_2-1,2-diamine ligands (Scheme 7).[22,23]

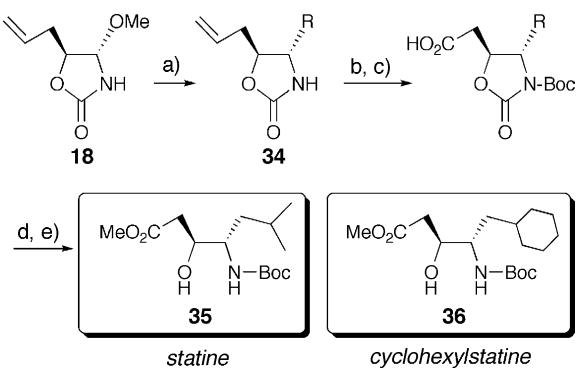
3.2.4. Applications.

3.2.4.1. Statine and its analogs. The (*S*,*S*)-adduct **18** was found to be a good precursor for statine



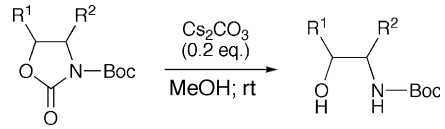
Scheme 7. (a) Br_2, CH_2Cl_2; (b) *i*-Pr_2NEt, MeOH; (c) **27**, NaH, THF; (d) Cs_2CO_3, MeOH; (e) BnOH, $BF_3{\cdot}OEt_2$, CH_2Cl_2; (f) Pd-black, H_2, MeOH; (g) $LiBH_4$–MeOH; (h) AcCl, NEt_3, DMAP; (i) **32**, $BF_3{\cdot}OEt$, CH_2Cl_2 (j) Ac_2O, NEt_3, DMAP; (k) Amberlyst 15, MeOH, 50 °C; (l) $ClCO_2Me$, NEt_3, CH_2Cl_2; (m) Amberlyst® 15, MeOH, reflux; (n) Cbz–Cl, NEt_3, CH_2Cl_2; (o) Pd–C, H_2, Amberlyst® 15, MeOH.

[(3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid], a key component of pepstatins exhibiting inhibitory activity against proteases.[24] Thus, on treatment of compound **18** with the isobutyl cuprate–$BF_3{\cdot}OEt_2$ reagent, the isobutyl group was directly introduced with full retention of configuration to give **34**. Oxidative cleavage of the allyl group, followed by opening of the 2-oxazolidinone ring with catalytic amounts of Cs_2CO_3, yielded (3*S*,4*S*)-*N*-Boc-statine derivative **35**. The cyclohexylstatine[25] derivative **36** was easily prepared (Scheme 8).[26] The *N*-*t*-butoxycarbonylation



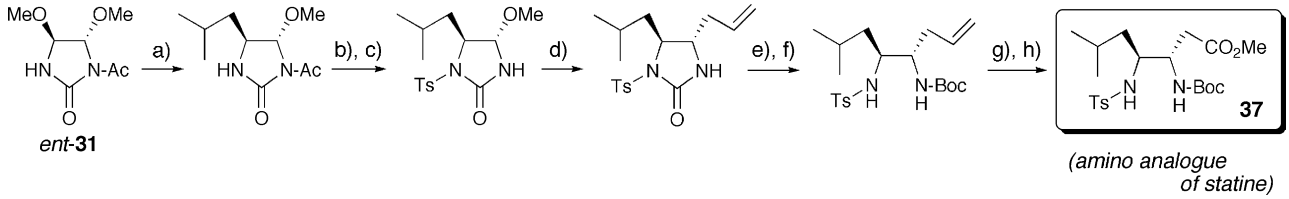
Scheme 8. (a) RCuCNMgBr, $BF_3{\cdot}OEt_2$; (b) $(Boc)_2O$; (c) $RuCl_3$–$NaIO_4$; (d) Cs_2CO_3, MeOH; (e) CH_2N_2.

Table 4. Ring cleavage of *N*-Boc-2-oxazolidinone to 1,2-amino alcohols

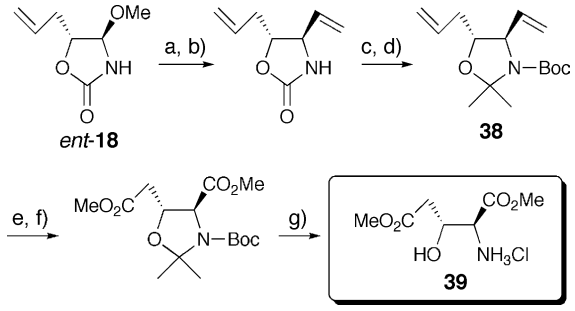


Entry	R^1	R^2	*t* (h)	Yield (%)[a]
1	H	H	3	77
2	CO_2Me	H	2	72
3	Ph	H	1	94
4	H	OMe	2	75
5[b]	H	CO_2H	18	73[c]
6	Me (*trans*)	CO_2Me	3	70
7	Me (*cis*)	CO_2Me	3	76

[a] Isolated yields.
[b] 1.2 equiv of Cs_2CO_3 was used.
[c] The value refers to methyl ester.



Scheme 9. (a) *i*-BuMgBr, CuCN, LiCl, $BF_3{\cdot}OEt_2$, THF; (b) TsCl, BuLi, THF; (c) CS_2CO_3, MeOH; (d) allylTMS, $BF_3{\cdot}OEt_2$, CH_2Cl_2; (e) $Ba(OH)_2{\cdot}8H_2O$, EtOH; (f) $(Boc)_2O$, NEt_3, CH_2Cl_2; (g) $KMnO_4$, $NaIO_4$ acetone, H_2O; (h) CH_2N_2.

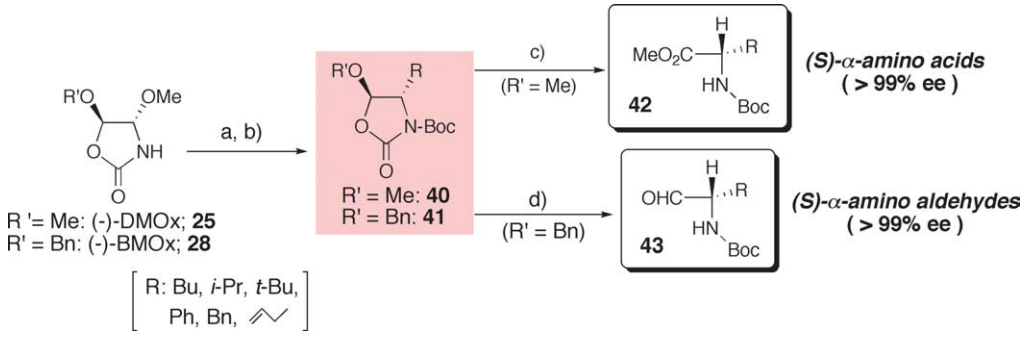


Scheme 10. (a) $(Vinyl)_2CuCNMgBr$, $BF_3{\cdot}OEt_2$; (b) $(Boc)_2O$, DMAP; (c) Cs_2CO_3, MeOH; (d) dimethoxypropane, TsOH; (e) $KMnO_4$, $NaIO_4$; (f) CH_2N_2; (g) HCl/MeOH.

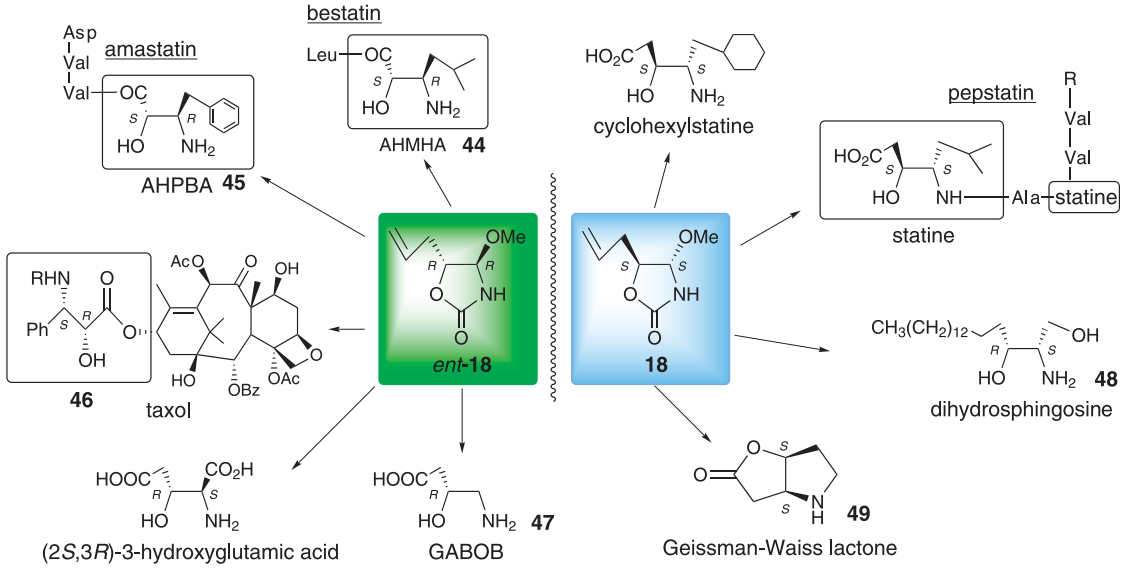
of the 2-oxazolidinones is essential for a facile ring opening under very mild conditions and the generality is exemplified by some other examples, as shown in Table 4.[27]

Analogously, the amino analog of statine **37** is readily synthesized starting from the 2-imidazolidinone synthon (*ent*-**31**), as shown in Scheme 9.[28]

3.2.4.2. 3-Hydroxyglutamic acid.[29] This acid is a component of the peptidic antibiotic S-520.[30] Starting from the intermediate (*ent*-**18**), dimethyl (2*S*,3*S*)-3-hydroxyglutamate **39** was synthesized by conversion into the (4*R*,5*R*)-5-allyl-4-vinyl derivative **38**, followed by the simultaneous cleavage of both double bonds with $KMnO_4$–$NaIO_4$, as outlined in Scheme 10.



Scheme 11. (a) RLi or RMgX, CuCN, LiCl, $BF_3{\cdot}OEt_2$, THF (R = allyl; allylTMS, $TiCl_4$, CH_2Cl_2); (b) $(Boc)_2O$, NEt_3, DMAP, CH_2Cl_2; (c) $KMnO_4$, KOH, *t*-BuOH, H_2O then CH_2N_2 or PDC, MeOH, KOH, DMF; (d) H_2, Pd–C, MeOH.



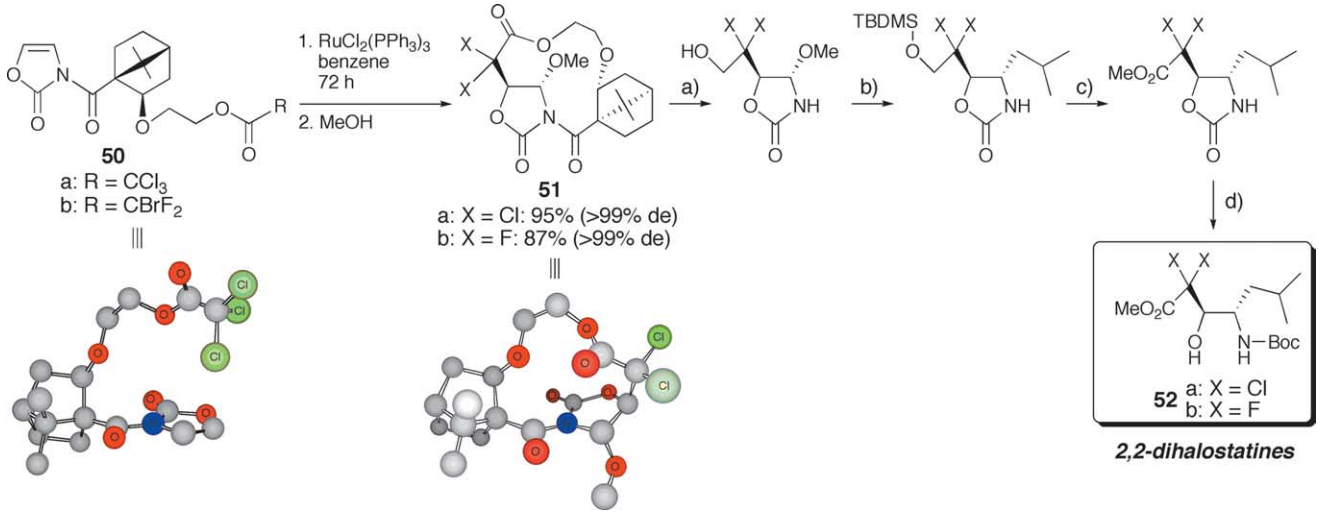
Scheme 12.

3.2.4.3. α-Amino acids and α-amino aldehydes.[21] Treatment of DMOx **25** with organocuprates/$BF_3 \cdot OEt_2$ resulted in the regioselective replacement of the 4-methoxy group with *prim*- to *tert*-alkyls and aryls with full retention of configuration. Optically pure (*S*)-*N*-Boc-α-amino acids **42** were synthesized by the direct oxidation of *N*-Boc-4-substituted 5-methoxy-2-oxazolidinones **40** with either $KMnO_4$ or PDC under basic conditions. Hydrogenolysis of the *N*-Boc-4-substituted 5-benzyloxy-2-oxazolidinones **41** with H_2/Pd–C under strictly neutral conditions gave the (*S*)-*N*-Boc-α-amino aldehydes **43** in optically pure form (Scheme 11).

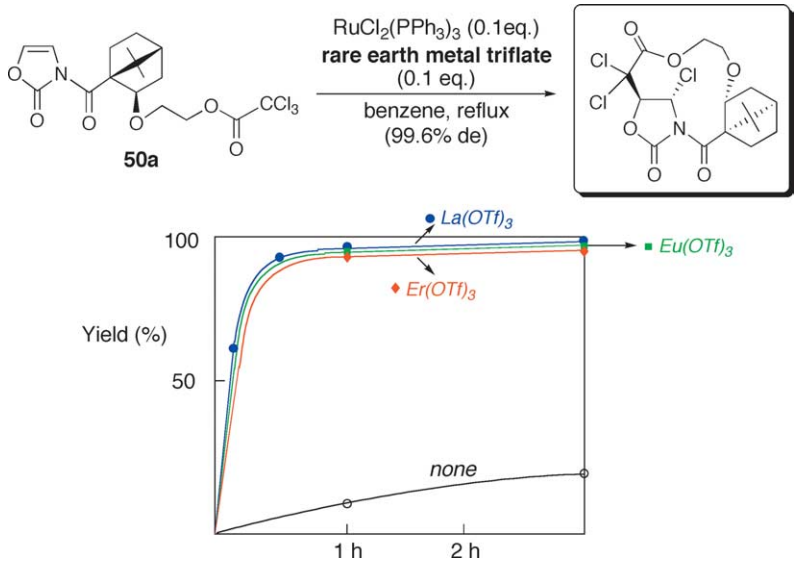
3.2.4.4. Others. Among the polyfunctional compounds synthesized by this methodology are the chiral amino alcohols such as (2*S*,3*R*)-3-amino-2-hydroxy-5-methylhexanoic acid (AHMHA, **44**)[31] and (2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanoic acid (AHPBA, **45**),[31] which are components of the enzyme inhibitors, amastatin[32] and bestatin,[33] respectively, (2*R*,3*S*)-3-amino-2-hydroxy-3-phenylpropanoic acid **46**,[34] a component of taxol,[35] (3*R*)-3-amino-2-hydroxybutylic acid (GABOB, **47**),[27,36] (2*S*,3*R*)-dihydrosphingosine **48**[34,37] and the Geissman–Waiss lactone **49**[38,39] (Scheme 12).

3.3. Intramolecular atom-transfer cyclization

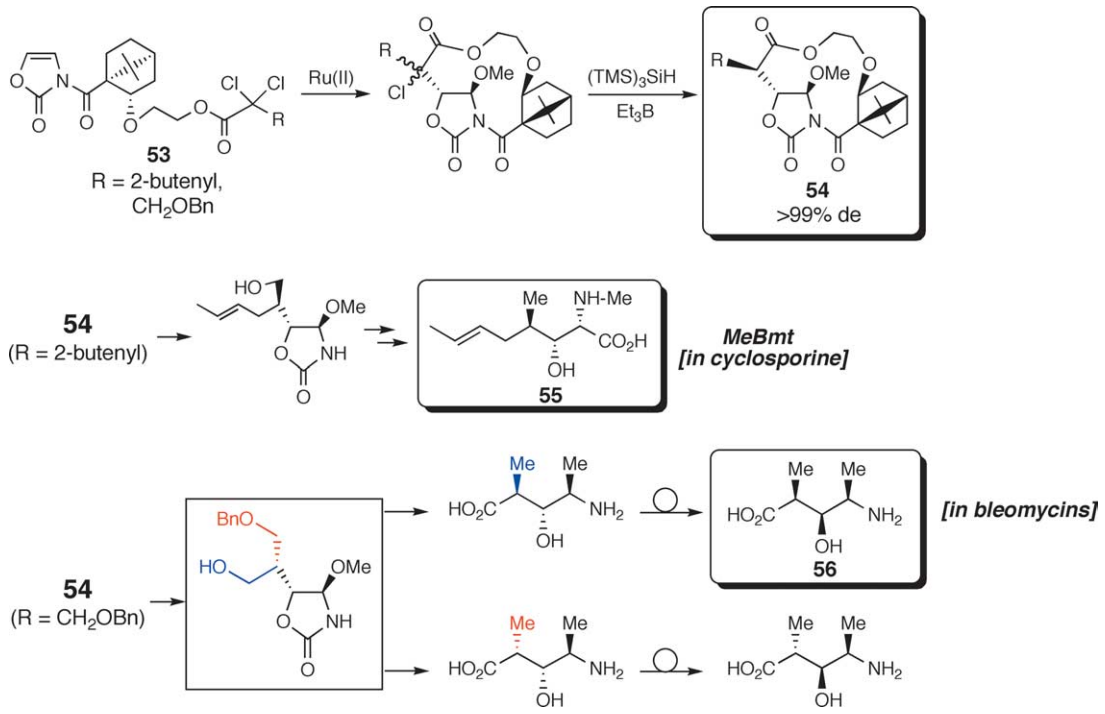
3-[(1*S*)-2-*exo*-trihaloacetoxyethoxy-1-apocamphanecarbonyl]-2-oxazolone **50** underwent a smooth intramolecular cyclization to the 12-membered lactone with perfect regio- and diastereoselectivity, on heating with a catalytic amount of $RuCl_2(PPh_3)_3$ in benzene (Scheme 13).[40] The addition of a catalytic amount of lanthanoid triflates resulted in a considerable reduction in the reaction time (Scheme 14).[41] The structure of the 4-methoxy-cycloadduct **51a** was confirmed by X-ray analysis, and the extremely high diastereoselectivity observed can be rationalized by assuming a favored conformer with the *anti*-coplanar amido carbonyl groups.



Scheme 13. (a) (1) $LiBH_4$/MeOH, (2) TBDMS–Cl/imidazole; (b) *i*-BuCuCNMgBr, LiCl, $BF_3 \cdot OEt_2$; (c) (1) TBAF, (2) CrO_3, H_2SO_4–acetone–H_2O, (3) CH_2N_2; (d) (1) HCl, Δ, (2) $(Boc)_2O$, NEt_3, DMAP, (3) CH_2N_2.



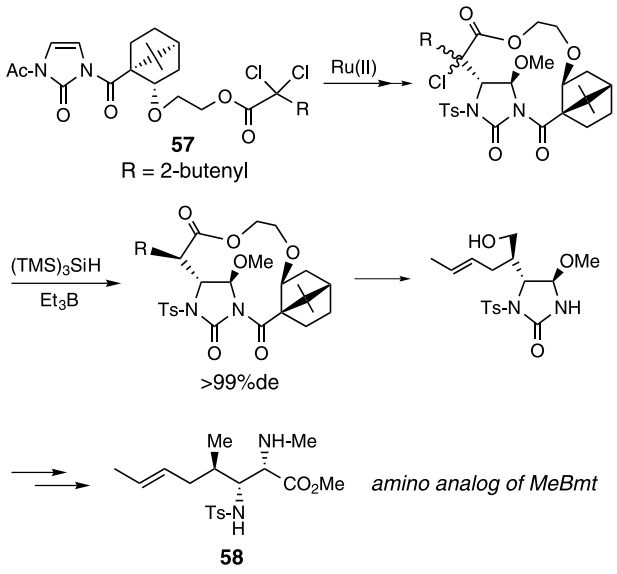
Scheme 14.



Scheme 15.

The macrolides **51** thus obtained have potential for serving as chiral building blocks for halogenated analogs of 3-hydroxy-4-aminocarboxylic acids of biological interest and thus have been successfully employed in the synthesis of optically active statine and dihalostatine[42] analogs **52**, as outlined in Scheme 13.[40]

This cyclization reaction provides a convenient synthetic tool for the preparation of amino hydroxy acids with three contiguous chiral centers such as MeBmt **55**[43] and **56**,[44] which are components of cyclosporine[45] and bleomycin,[46] when the 2-oxazolone derivatives **53** contain 2,2-dichloroacyl moieties as pendant groups (Scheme 15).



Scheme 16.

Similarly, the amino analogue of MeBmt **58** is available from the 2-imidazolone derivative **57** through an intramolecular cyclization catalyzed by $RuCl_2(PPh_3)_3$ with perfect regio- and diastereoselectivity (Scheme 16).[47]

3.4. Pericyclic addition[48,49]

The thermal cycloaddition of the 2-oxazolones **59** to dialkyl azodicarboxylates **60** proceeds smoothly under mild conditions (at 80 °C) to give the regiocontrolled cycloadducts (**61**, **62**) exclusively, in spite of other conceivable addition modes, to give diazetidines **63** (1,2-addition) and isoxazolidines **64** (1,3-addition).[50]

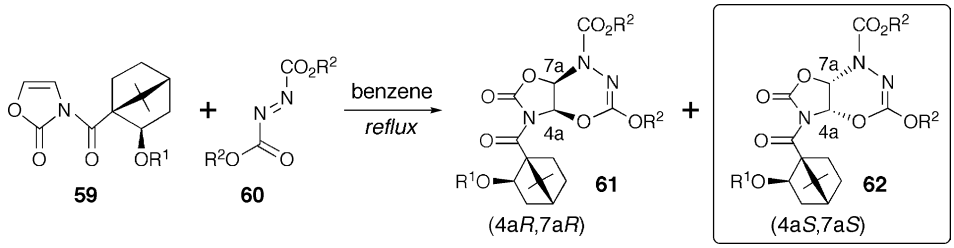
The diastereoselectivity is dependent on the bulkiness of the ester moieties R^2 and R^1 and a selectivity of 72% de was obtained when the neopentyloxy derivative was reacted with dibenzyl azodicarboxylate. The cyclization promoted by UV irradiation proceeds with slightly higher diastereoselectivity at room temperature (Table 5).

The cycloadducts **62** are readily converted into (4*R*,5*S*)-5-hydrazino-4-methoxy-2-oxazolidinones **65**, which serve as chiral 'α-methoxyglycinal' equivalents for the alternative synthesis of α-amino acids **66**, 2-amino alcohols **67** and 2-oxazolidinones **68** (Scheme 17).

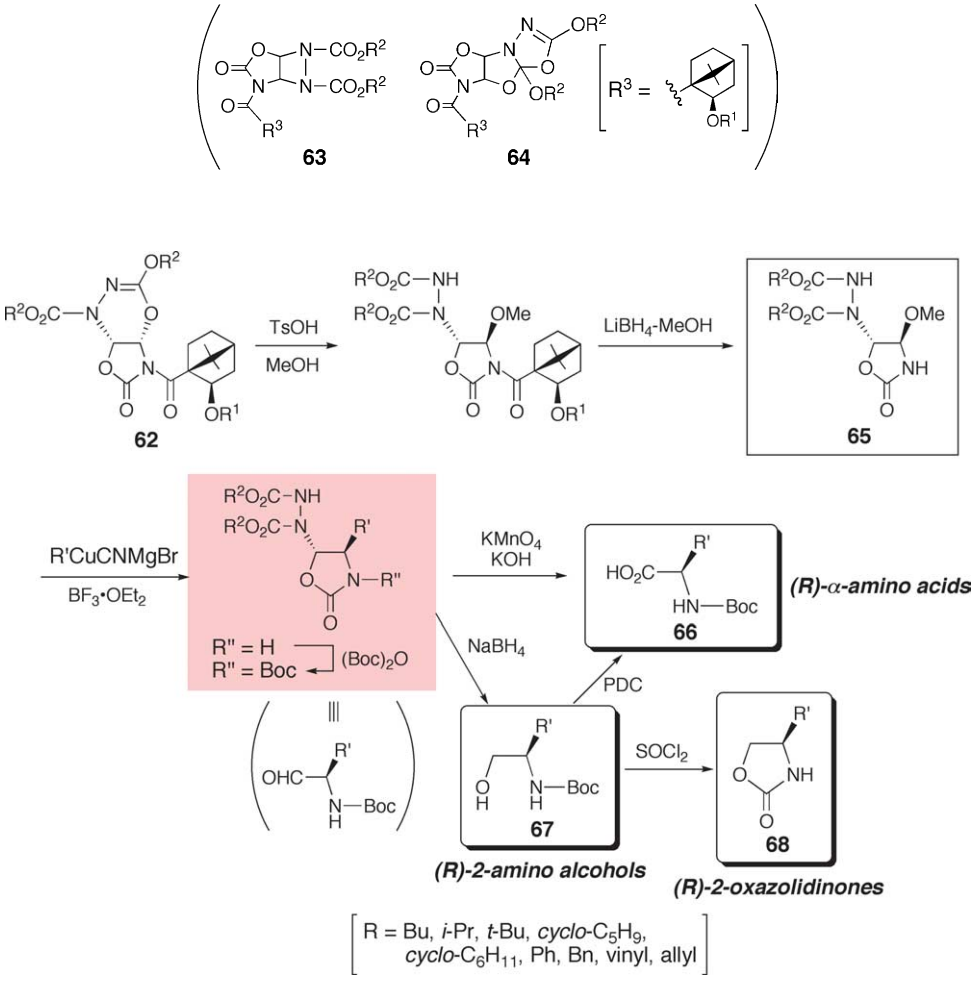
4. 'Roofed' type chiral sources

Apart from natural chiral sources which are of restricted versatility, compounds that are carefully designed on the basis of the mechanism for enantiocontrol play an increasingly important role in achieving a high degree of asymmetric induction.[51]

Table 5. Cycloaddition of *N*-acyl-2-oxazolones to azodicarboxylates



Entry	R^1	R^2	*t* (h)	Yield (%)	**61**:**62**	de (%)
1	Me	Me	6	83	34:66	32
2	Me	*i*-Pr	12	93	24:76	52
3	Pr	*i*-Pr	12	76	22:78	56
4	Pr	Bn	6	86	18:82	64
5	CH_2CMe_3	*i*-Pr	19	85	15:85	70
6	CH_2CMe_3	Bn	18	93	14:86	72



Scheme 17.

The successful auxiliary should be readily accessible in both enantiomeric forms and preferably be a crystalline compound. In addition, the auxiliary should be introduced in high yield, provide a high level of chiral induction, which is most important, and be easily removed under mild conditions, to permit recycling of the chiral unit. Based on the above considerations, we designed sterically constrained 'roofed' type chiral auxiliaries.

Cycloadditions of simple heterocycles **1**–**3** to cyclic dienes afford a new class of 'roofed' tricyclic 2-oxazolidinone, 2-imidazolidinone and 2-thiazolidinone heterocycles, which are conformationally rigid and sterically congested. The 'roofed' type chiral sources with unique skeletons are expected to efficiently block the attack of reactants from one diastereotopic face of the heterocycles and, therefore, excellent chiral control of a wide variety of reactions should be expected when they are used as chiral auxiliaries. Ring openings of the tricyclic cycloadducts give the bicyclic 'roofed' type of 2-amino alcohols, 1,2-diamines and

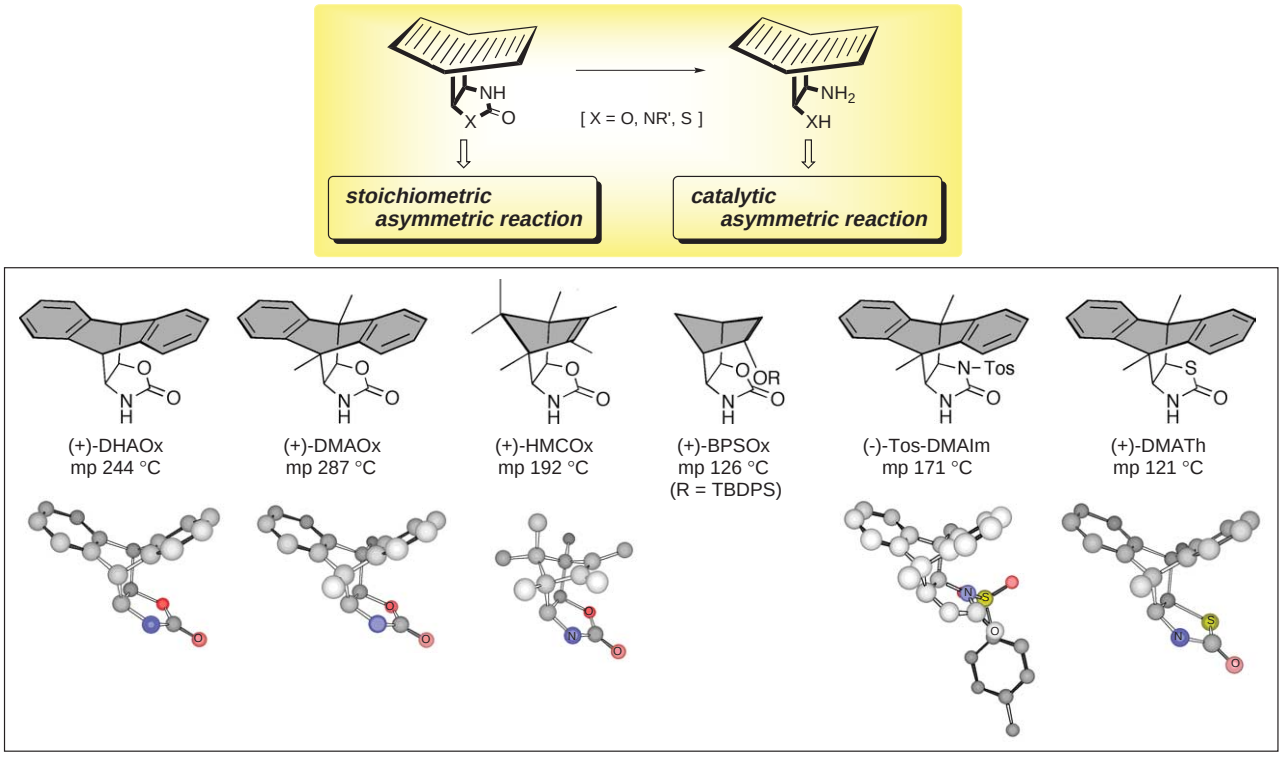


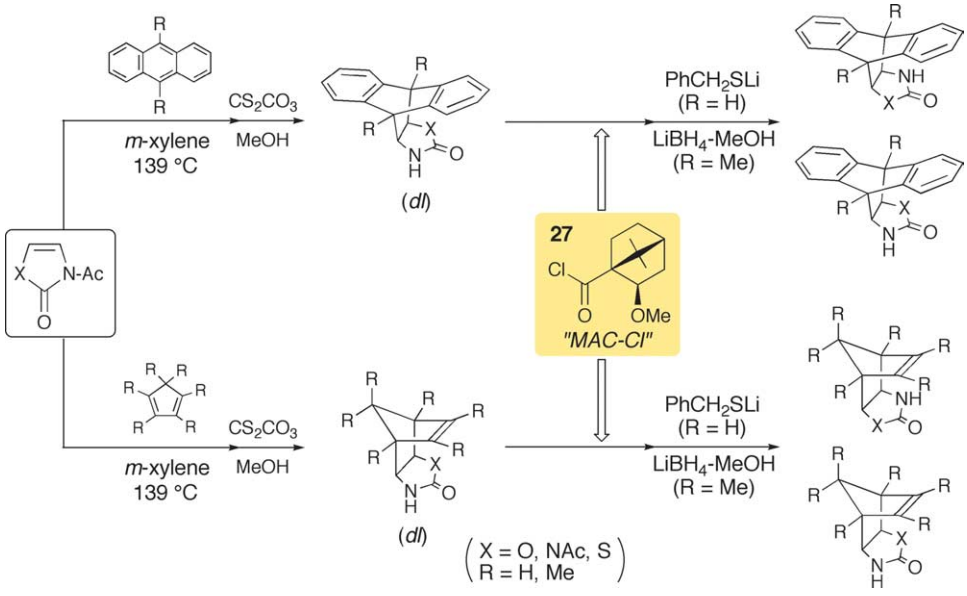
Figure 1. X-ray crystal structures of 'roofed' chiral sources.

2-amino thiols, respectively, with steric congestion and conformational rigidity, which would also serve as chiral ligands for catalytic asymmetric reactions (Fig. 1).

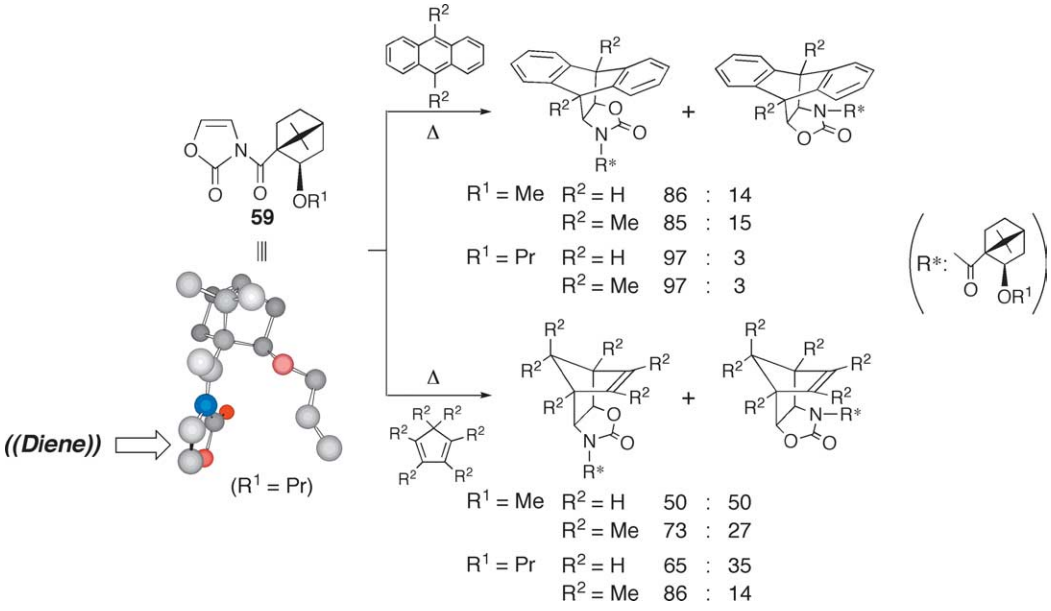
4.1. Preparation

The 'roofed' type heterocycles can be readily obtained by the thermal cycloaddition of the five-membered heterocycles **1**–**3** to cyclic dienes such as anthracene, cyclopentadiene and derivatives thereof. The cycloaddition proceeded smoothly on heating in xylene at 139 °C. The optical resolution of the cycloadducts has been performed by three types of practical methods.

4.1.1. Optical resolution with MAC acid.[52–56] The first method is shown in Scheme 18. The camphor-derived MAC acid served as an excellent resolving agent for this type of heterocycles[57] and gave the readily separable diastereomers as *N*-MAC derivatives, from which both enantiomers were obtained in nearly quantitative yield.

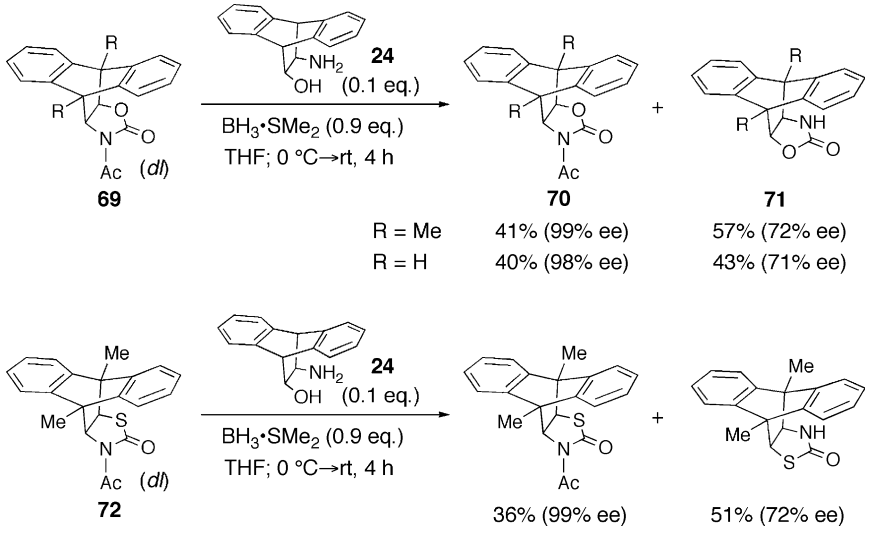


Scheme 18.

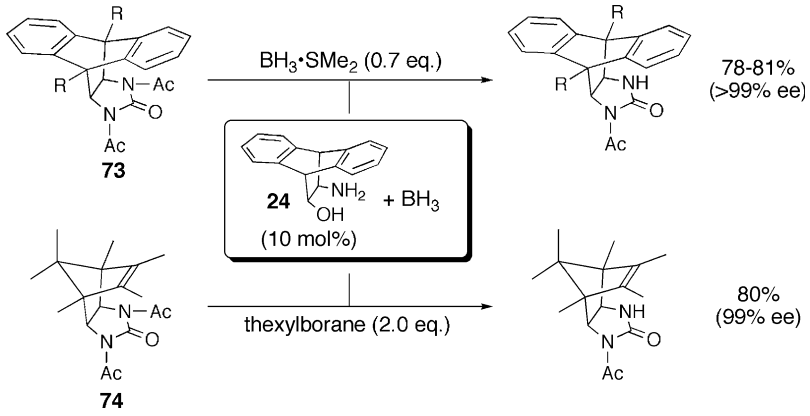


Scheme 19.

4.1.2. Diastereoselective Diels–Alder reaction.[52–54] Another procedure for chiral auxiliaries is based on the diastereoselective cycloaddition of chiral 2-oxazolone derivatives **59**. When an equimolar mixture of 2-oxazolone derivatives **59** and anthracene or dimethylanthracene was simply heated in xylene, a surprisingly high selectivity (>94% de) was obtained, indicating that the conformers could be preserved as the predominant form, even at 139 °C.



Scheme 20.



Scheme 21.

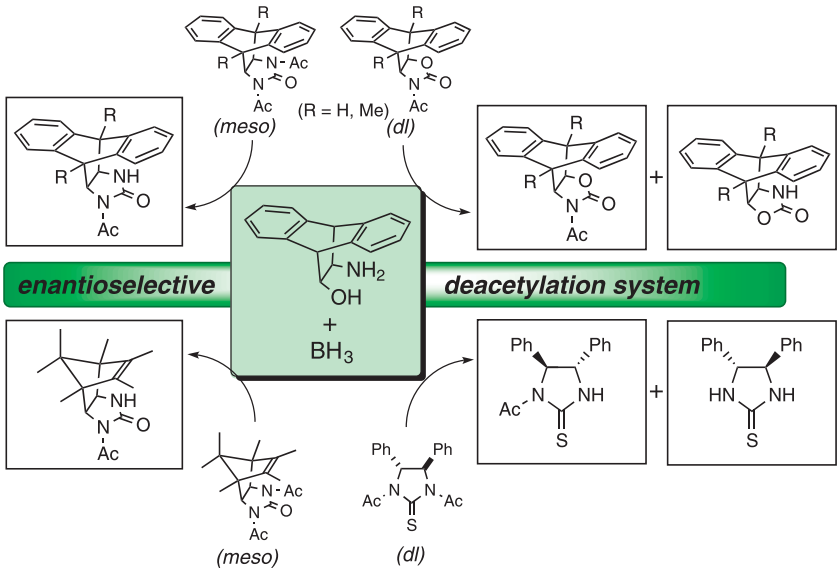


Figure 2. Catalytic process for enantioselective deacetylation.

On the other hand, the cycloaddition to cyclopentadiene and the hexamethyl derivative resulted in a poorer selectivity of 72% de (Scheme 19).

4.1.3. Catalytic kinetic resolution.[58,59] The third method involves the enantioselective deacetylation of **69**, catalyzed by oxazaborolidine with borane, in which catalytic kinetic resolution gives the *N*-acetyl enantiomer **70** with 99% ee, while the deacylated NH-isomer **71** was obtained only in moderate selectivity. This single catalytic step was also successfully applied to the optical resolution of compound **72** (Scheme 20). This kinetic resolution method is particularly useful for enantiodivergence of *meso*-*N*,*N*-diacetyl-2-imidazolidinones (**73**, **74**) as shown in Scheme 21. Successful examples of resolutions using this enantioselective deacylation system are summarized in Figure 2. A plausible mechanism for the disymmetrization of *meso*-imidazolidone compounds would be similar to that proposed for the enantioselective reduction of ketones with borane[60] (Fig. 3).

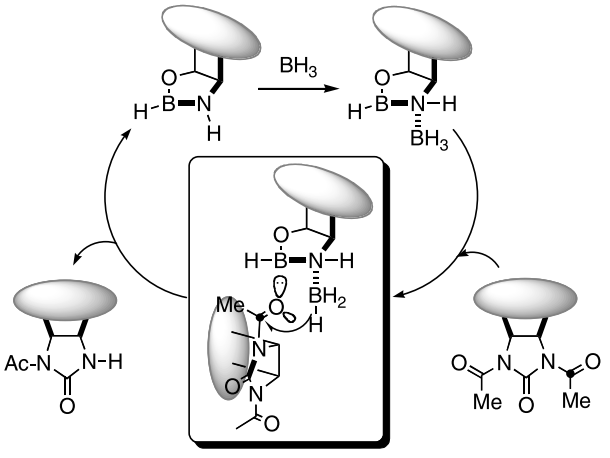


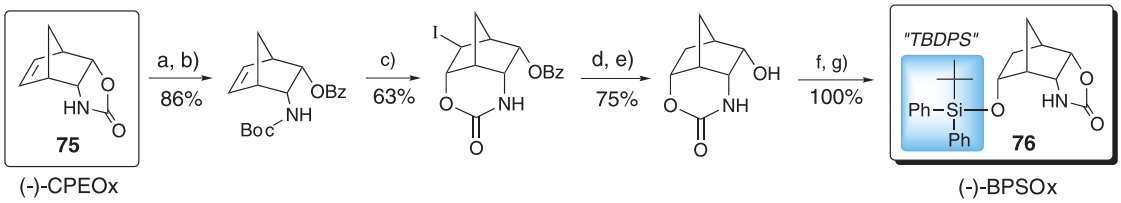
Figure 3. Plausible mechanism for the disymmetrization of *meso*-imidazolidones.

4.1.4. Miscellaneous.[61] Another type of 2-oxazolidinone auxiliary, BPSOx **76**, was prepared from the auxiliary **75** through an iodolactonization step (Scheme 22).

4.2. Use as chiral auxiliaries

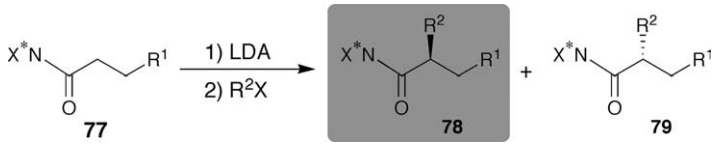
As clearly shown by their X-ray crystal structures, one side of the heterocycle face is effectively and firmly shielded and, as a result, a high level of chiral induction might be expected in a variety of transformations. The utility of the chiral auxiliaries thus obtained has been evaluated by fundamental reactions such as alkylations, cycloadditions, Aldol reactions and conjugate additions through stoichiometric or catalytic processes.

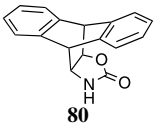
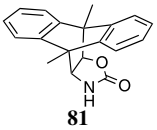
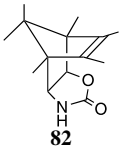
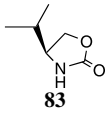
4.2.1. Alkylation of enolates. Table 6 shows the effect of chiral auxiliaries on diastereoselectivity in the alkylation of enolates with benzyl and allyl bromide. The 'roofed' type auxiliaries (**81**, **82**) gave excellent selectivity, over 500 to 1 ratio, while a more conventional auxiliary such as **83** resulted in a much lower selectivity under identical conditions.[62] In contrast to the alkylations mentioned



Scheme 22. (a) $(Boc)_2O$, NEt_3; (b) PhLi; (c) I_2; (d) AIBN, Bu_3SnH; (e) Cs_2CO_3, MeOH; (f) NaH; (g) TBDPS–Cl.

Table 6. Diastereoselective alkylation of **77** via lithium enolates



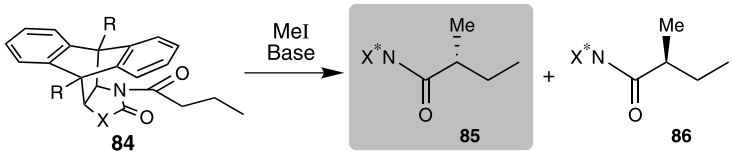
Entry	X*NH	R^1	R^2X	T (°C)	Yield (%)	**78**:**79**	de (%)
1	 **80**	H	CH_2=$CHCH_2Br$	−30	55	36:1[a]	94.6
2		H	$PhCH_2Br$	0	71	120:1[a]	98.3
3		Me	MeI	−30	97	2.5:1[a]	42.9
4	 **81**	H	CH_2=$CHCH_2Br$	0	92	>500:1[a]	>99.6
5		H	$PhCH_2Br$	0	76	>500:1[a]	>99.6
6		Me	MeI	−30	96	155:1[a]	98.4
7	 **82**	H	CH_2=$CHCH_2Br$	0	100	>500:1[b]	>99.6
8		H	$PhCH_2Br$	0	100	>500:1[b]	>99.6
9		Me	MeI	−30	85	139:1[b]	98.6
10	 **83**	H	CH_2=$CHCH_2Br$	0	71	49:1	96
11		H	$PhCH_2Br$	0	75	120:1	98.3
12		Me	MeI	−30	—	9.9:1	81.7

[a] Determined by HPLC analysis.
[a] Determined by capillary GC.

above, methylation via lithium enolates is widely recognized as being quite difficult to control with a high selectivity. Thus, the auxiliary DHAOx **80** gave an isomer ratio of only 3:1, while the auxiliaries, DMAOx **81** and HMCOx **82**, with bridgehead methyl substituents gave excellent selectivity, indicative of the remarkable beneficial effect of the methyl group at the bridgehead position. Thus, this type of chiral auxiliary could be conveniently evaluated by sterically undemanding methylation reactions. As summarized in Table 6, it is apparent that the 'roofed' type auxiliaries are much more promising than the conventional auxiliaries.[52–54]

The corresponding 2-imidazolidinone and 2-thiazolidinone auxiliaries work equally well. As seen in Table 7, a small structural variation in the chiral 2-imidazolidinone auxiliaries may induce a large effect on asymmetric induction and the selectivity was greatly dependent on the *N*-substituents. The bulky *N*-2,4,6-trimethylbenzenesulfonyl auxiliary gave perfect selectivity, with a ratio in excess of 500:1 (entry 6).

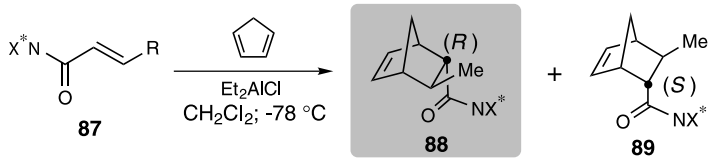
Table 7. Diasteroselective methylation of **84** via enolates

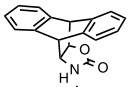
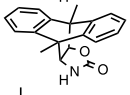
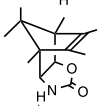
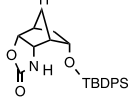
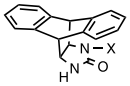
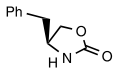


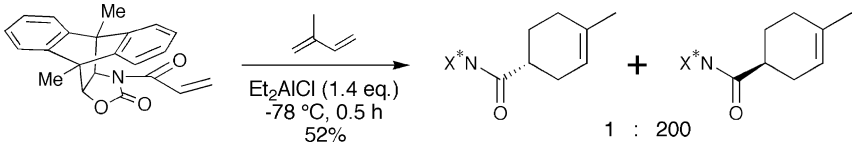
Entry	R	X	Base	Yield (%)[a]	**85**:**86**[b]
1	H	N–Me	LHMDS	80	2:1
2	H	N-SO_2- 	LHMDS	90	9:1
3	H	N-SO_2- 	LHMDS	84	31:1
4	H	O	LDA	97	2.5:1
5	Me	N–Me	LHMDS	99	46:1
6	Me	N-SO_2- 	LHMDS	82[c]	>500:1
7	Me	O	LDA	96	155:1
8	Me	S	LHMDS	93	32:1

[a] Isolated yields.
[b] Determined by HPLC analysis.
[c] Determined by ^{1}H NMR (500 MHz) spectra.

Table 8. Diastereoselective Diels–Alder reactions of **87**



Entry	X*NH		R	Yield (%)	*endo*:*exo*	*endo* ds **88**:**89**
1		**80** (DHAOx)	Me	100	49:1	55:1
2		**81** (DHAOx)	Me	97	99:1	327:1
3		**82** (HMCOx)	Me	100	99:1	>500:1
4		*ent*-**76** (BPSOx)	Me	100	99:1	>500:1
5	 (DHAIm)	**90**:X=Me	H	98	74:1	>500:1
6		**91**:X=Te	H	97	43:1	17:1
7		**92** (Evans' auxillary)	Me	100	55:1	32:1
8			H	100	>100:1	19:1

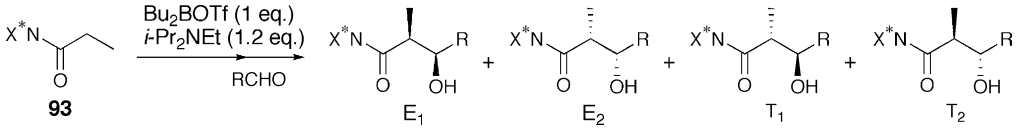


Scheme 23.

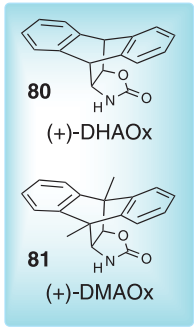
To our knowledge, the *N*-2,4,6-trimethylbenzenesulfonyl 'roofed' auxiliaries are the most promising and powerful chiral auxilaries developed to date. Unfortunately, we cannot currently explain such a remarkable remote control by the *N*-substituents, which are located a considerable distance from the site of the reaction.[55,56,63]

4.2.2. Diels–Alder reaction. In the thermal cycloaddition of

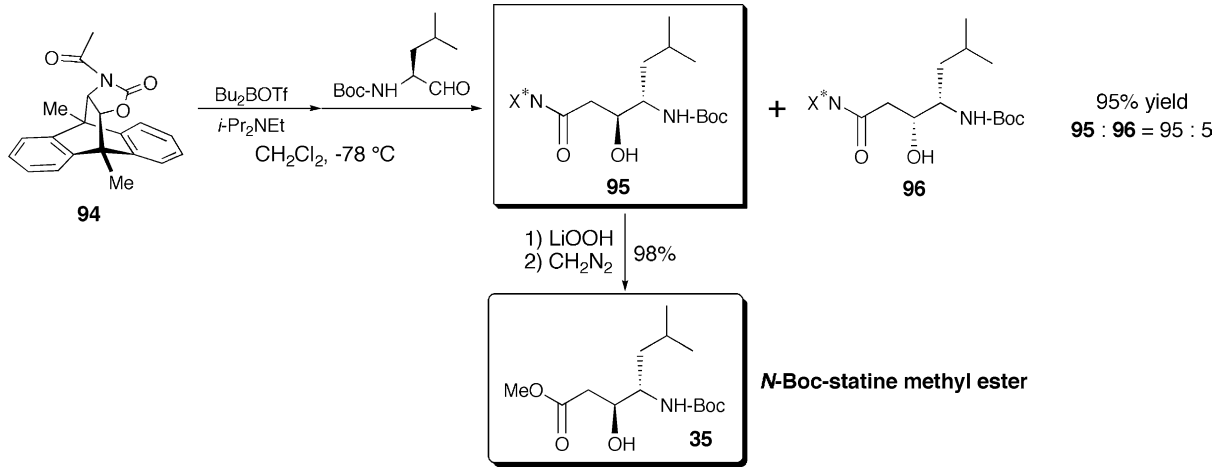
Table 9. Diasteroselective reactions of propionyl derivates **93**



X*NH	Solvent	Additive	R	Yield (%)	E_1:E_2:T_1:T_2[a]
(+)-DHAOx	CH_2Cl_2	—	Ph	89	100:0:0:0
(+)-DMAOx	CH_2Cl_2	—	Ph	93	100:0:0:0
(+)-DHAOx	CH_2Cl_2	—	*i*-Pr	86	91:3:6:0
(+)-DMAOx	CH_2Cl_2	—	*i*-Pr	96	98:0:2:0
(+)-DMAOx	CH_2Cl_2	$TiCl_4$ (3 equiv)	Ph	73	1:88:11:0
(+)-DHAOx	THF	—[b]	Ph	100	7:3:90:0



[a] Determined by HPLC.
[b] Bu_2BOTf (2 equiv) and *i*-Pr_2NEt (2.2 equiv) were used.



Scheme 24.

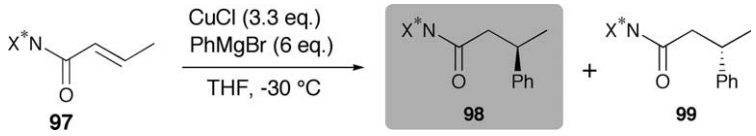
cyclopentadiene to the *N*-alkenoyl compounds **87**, these 'roofed' auxiliaries gave perfect selectivity,[52–55,61] while the conventional auxiliary **92** resulted in only moderate selectivity[64] (Table 8). In a Lewis acid-promoted Diels–Alder reaction with isoprene, the auxiliary **81**, which contains angular methyl groups, showed a much higher selectivity than the auxiliaries **80** and **92** (Scheme 23).[9c]

4.2.3. Aldol reaction.[65] Table 9 shows a diastereoselective Aldol reaction via boron enolates. In this system, the 'roofed' auxiliaries, DHAOx **80** and DMAOx **81**, are effective enough to show a significant advantage. Of the four possible isomers, a particular isomer E1, E2 or T1, except for T2, could be preferentially obtained, depending on the reaction conditions used.

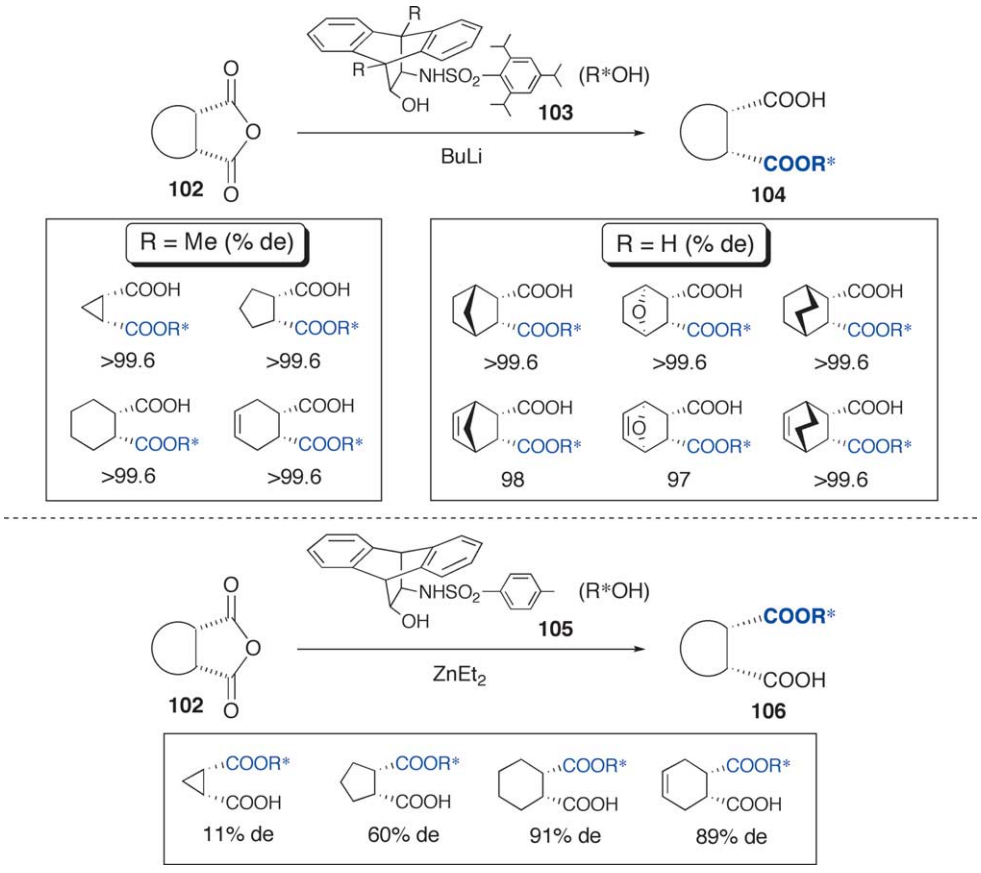
The *N*-acetyl-DMAOx derivative **94** serves well as a chiral enol acetate equivalent, as shown for the synthesis of statine **35** (Scheme 24).

4.2.4. Michael-type addition.[9c,61] Of the variety of chiral auxiliaries examined for conjugate additions, the 2-oxazolidones are generally inferior in terms of selectivity.[66] We have examined some diastereoselective conjugate addition reactions using a copper reagent (Table 10). A satisfactory selectivity was obtained when sterically

Table 10. Diastereoselective Michael-type additions of crotonyl derivatives **97**



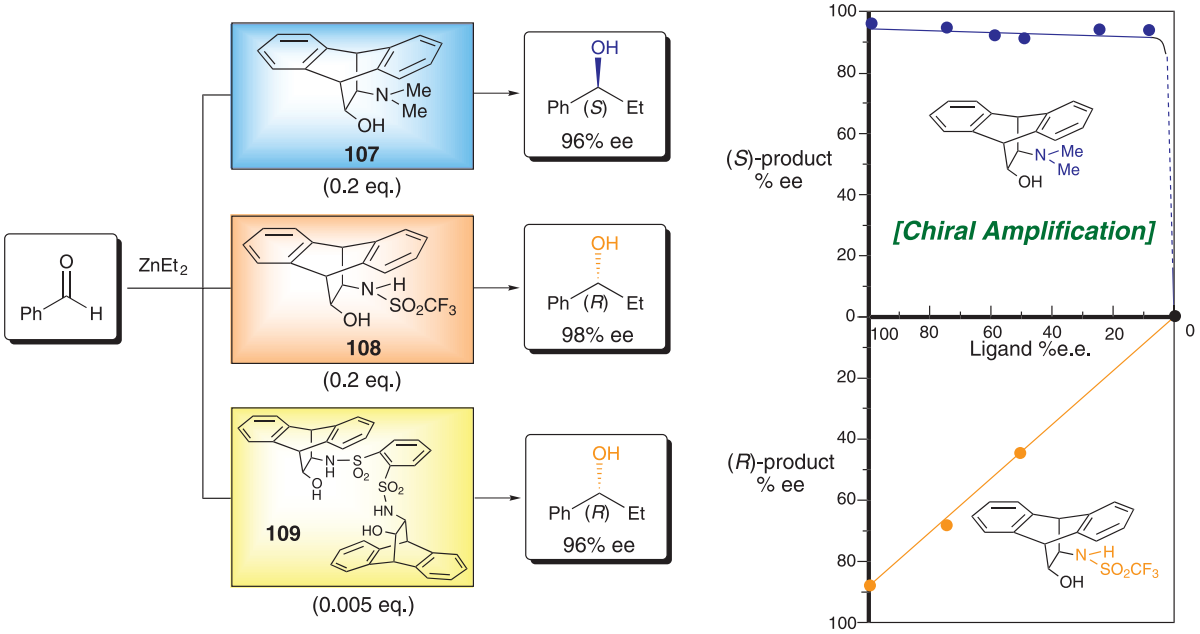
Entry	X*NH	Yield (%)	**98**:**99**	de (%)
1	**81** (DMAOx)	96	24:1	92
2	**82** (HMCOx)	100	12:1	85
3	*ent*-**76** (BPSOx)	99	116:1	98
4	**80** (DHAOx)	96	1.4:1	17
5	**100** (DMATh)	97	13:1	86
6	**101** (HMCTh)	99	32:1	94
7	**83** (Evan's aux.)	87	1.7:1	26



Scheme 25.

congested auxiliaries were used, while the auxiliaries, DHAOx **80** and the conventional Evans' auxiliary **83**, were unsatisfactory. The data clearly show that the DMAOx, BPSOx and HMCTh auxiliaries (**81**, *ent*-**76** and **101**) are able to effectively shield the β-carbon for the addition of cuprates.

4.2.5. Diastereodifferentiation of *meso*-dicarboxylic anhydrides.[67,68] The differentiation between enantiotopic carbonyl groups of *meso*-dicarboxylic anhydrides **102** was successfully performed with the lithium salts of bulky amino-alcohols. The heavily congested 2,4,6-tri-isopropyl-benzenesulfonyl derivative **103** was the reagent of choice



Scheme 26.

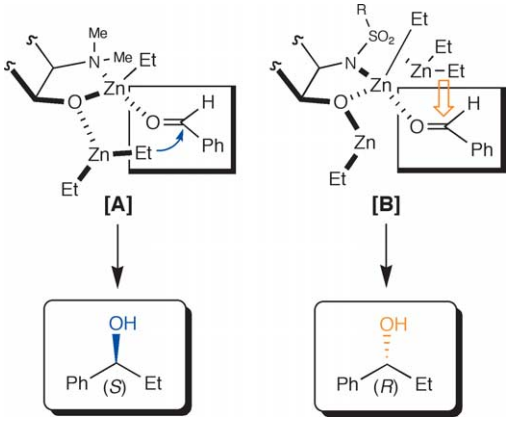


Figure 4. Plausible mechanism for the reversal of the enantioselectivity.

for asymmetric ring opening to achieve a thorough chiral differentiation. On the other hand, the zinc complexes generated in situ from *N*-tosyl-amino alcohol **105** and $ZnEt_2$ afforded a mono-ester **106** of the opposite configuration with a good de value (Scheme 25).

4.3. Catalytic use as chiral ligands

4.3.1. Ethylation of aldehydes.[69] It is well known that *N*,*N*-dialkylamino alcohols catalyze the alkylation of aldehydes with organozinc reagents.[70] As shown here, both *N*,*N*-dimethyl- and *N*-sulfonyl-amino alcohols (**107**, **108**) are good catalysts, giving excellent enantioselectivity of 96–98% ee, respectively, and, interestingly, with the opposite enantioselection. The dimeric catalyst **109** appears to be more promising than the monomeric *N*-tosyl catalyst **108**. It is quite interesting that the *N*-sulfonyl derivative had an excellent catalytic ability for this type of reactions (Scheme 26), contrary to previous findings.[71]

Typical chiral amplification[72] was observed in the *N*,*N*-dimethylamino alcohol-catalyzed reaction, as expected. On the other hand, the *N*-sulfonyl compound did not show such an effect, indicative of the different aggregation states of zinc complexes in solution (Scheme 26).

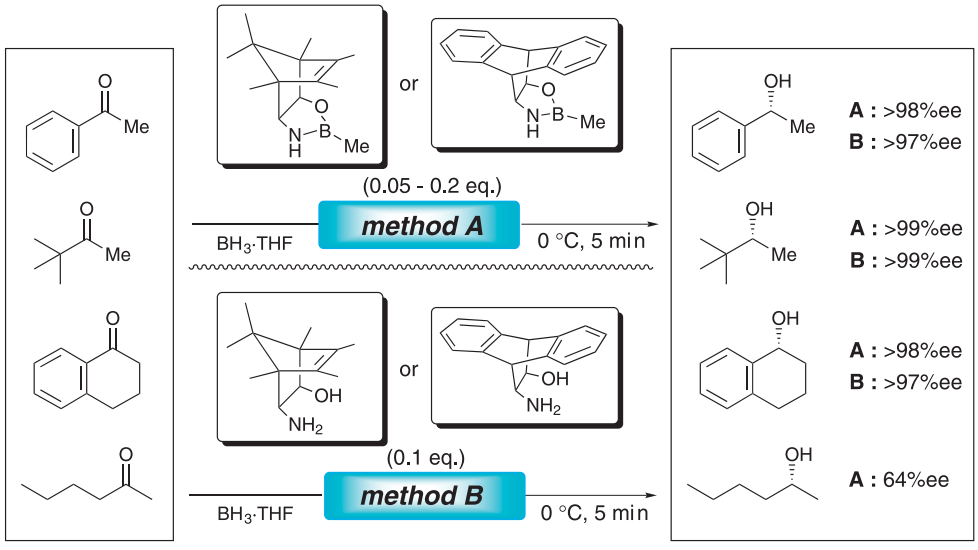
The reversal of the enantioselectivity can be rationalized by postulating the transition complexes shown in Figure 4. [A] shows the well-established mechanism for the reaction catalyzed by an *N*,*N*-dimethylamino alcohol, while, in the sulfonamide-catalyzed reactions, the coordination of a third zinc reagent with the sulfonyl groups would be responsible for the opposite enantioselection observed, as shown in [B].

4.3.2. Reduction of ketones.[73] A number of oxazaborolidine-catalyzed reductions of ketones have been extensively explored.[74] It is noteworthy that the enantioselective reduction proceeded smoothly within 5 min without any pretreatment for oxazaborolidine formation when the ketones were directly added to a mixture of 'roofed' type amino alcohols and borane complexes. This is a practical and convenient process for the preparation of optically active secondary alcohols (Scheme 27).

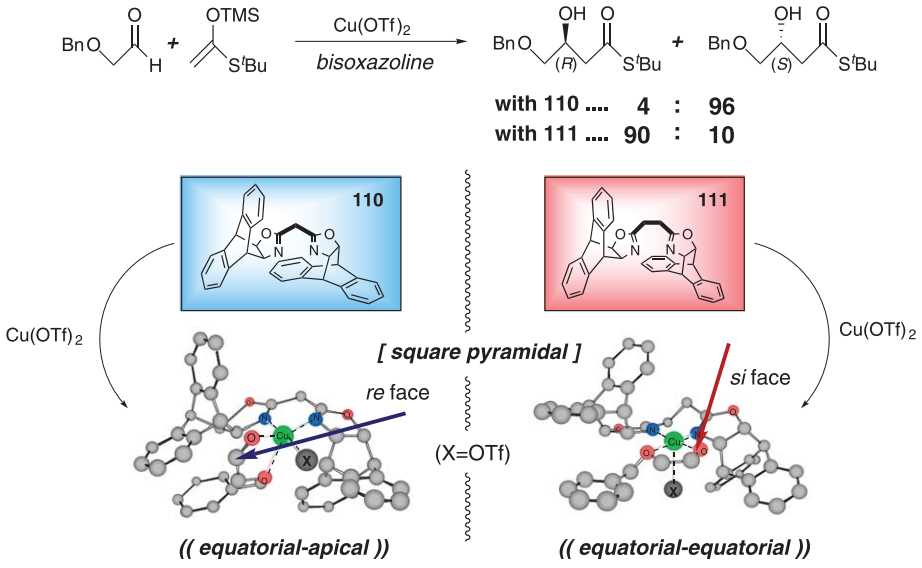
4.3.3. Aldol reaction.[75] The spacer length between the sterically congested oxazoline rings has a considerable effect on the chiral environment at the catalytic site.[76] In the copper complex-catalyzed aldol reaction, the use of the methylene- and ethylene-bridged bisoxazoline ligands **110** and **111** led to the preferential formation of the *S*- and *R*-isomer, respectively, resulting in the reversal of enantioselection. The observation, which is dependent on the ring-size of the chelates, may be due to the geometrical change in the coordination with an aldehyde on the square-pyramidal metal geometry (Scheme 28).

5. Conclusion

The five-membered heterocycles **1**–**3** are sufficiently reactive to serve as versatile building blocks for the facile synthesis of polyfunctional compounds, as well as the 'roofed' chiral sources. The 'roofed' type of sterically congested and conformationally fixed auxiliaries and ligands have a great and unique potential for use in challenging synthetic transformations, for which existing auxiliaries are unsatisfactory, in addition to practical



Scheme 27.



Scheme 28.

advantages such as facile preparation, high crystallinity and ease of recovery.

In addition to the reactivities described here, simple five-membered heterocycles such as 2-oxazolone, 1,3-dihydro-2-imidazolone and 2-thiazolone show interesting behavior towards polymerization and condensation, leading to homopolymers and telomers, and condensation reagents.[77]

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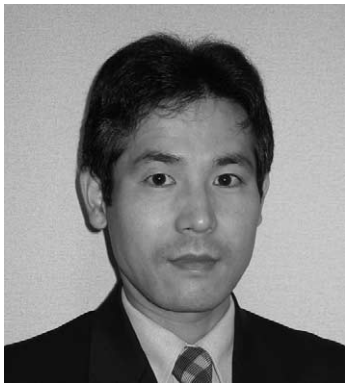
Biographical sketch



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Selective recognition of sodium cyanide and potassium cyanide by diaza-crown ether-capped Zn-porphyrin receptors in polar solvents

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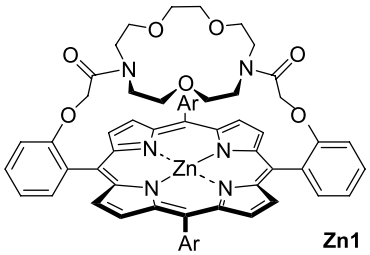
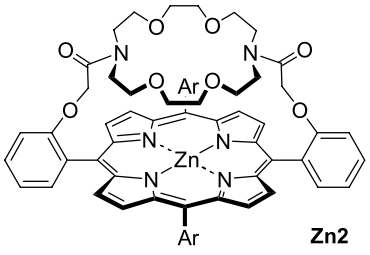
Abstract—Two new ditopic porphyrin receptors **Zn1**, incorporating a diaza-15-crown-5 unit, and **Zn2**, incorporating a diaza-18-crown-6 unit, have been prepared and characterized. UV–vis study in polar methanol has revealed that **Zn1** is able to selectively recognize sodium cyanide over potassium cyanide (the ratio of their binding constant is ca. 56), whereas **Zn2** exhibits a higher binding affinity for potassium cyanide over sodium cyanide (the ratio of their binding constant is ca. 12). In contrast, both receptors display substantially weaker binding affinity for sodium thiocyanate and potassium thiocyanate presumably due to a monotopic binding fashion.

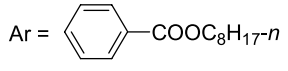
1. Introduction

Considerable attention has been focused upon the design of synthetic receptors for the detection of biologically and environmentally important small species.[1,2] A large number of receptors have been reported, which can bind simple inorganic cations or anions. However, the development of receptors for selective recognition of ion pairs in competitive solvents would be of more importance, because the physical, chemical, and biological properties of any ionic molecule are always controlled by both its cation and anion.[3]

Sodium cyanide and potassium cyanide are among the most concerned inorganic salts in the environment because of their high toxicity and wide applications in industries. Development of selective and sensitive receptors for both salts in polar solvent should be of special value, because efficient detection of these salts are potentially useful for monitoring their metabolism in nature,[4] the analysis of drinking water,[5] and environment protection.[6] Recently, several synthetic receptors for complexing cyanide anion in dichloromethane or aqueous media have been reported.[7] A Zn-porphyrin-crown ether conjugate for ion pair recognition of sodium cyanide in nonpolar organic solvent has also been developed.[8] Herein, we describe the selective complexation of NaCN and KCN in polar solvents by two novel aza-crown ether-capped porphyrins **Zn1** and **Zn2**. To the best of our knowledge, this represents the first example of synthetic receptors that are able to discriminate between NaCN and KCN in polar solvents.







Keywords: Hydrogen bonding; Foldamer; Aromatic amide; Molecular recognition; Alkyl ammonium ion.
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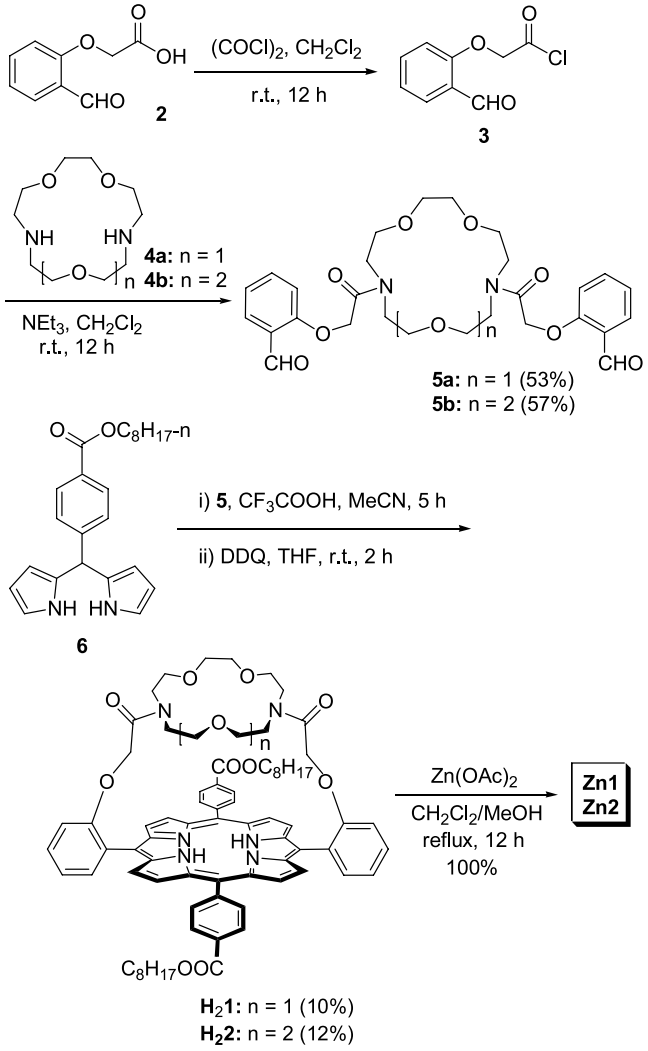
2. Results and discussion

The design of the new receptors are based on the ditopic feature of the well-established crown ether-capped porphyrins.[9] The crown ether moiety is typical binding units for alkaline metal ions, whereas the Zn-porphyrin moiety is well-known to coordinate nitrogen ligand. The synthesis of **Zn1** and **Zn2** is provided in Scheme 1. In brief, compounds **5a** and **5b** were first prepared from acyl chloride **3** and diaza-crown ether **4a** or **4b**, respectively, and then coupled with dipyrrole **6** with trifluoroacetic acid as catalyst, followed by oxidation by 2,3-dichloro-5,6-dicyano-1,4-quinone (DDQ), to afford $\mathbf{H_2 1}$ and $\mathbf{H_2 2}$. Treatment of $\mathbf{H_2 1}$ and $\mathbf{H_2 2}$ with zinc acetate in dichloromethane and methanol produced **Zn1** and **Zn2** in quantitative yield. Compounds **Zn1** and **Zn2** had been characterized by the ^{1}H NMR, ^{13}C NMR, mass spectroscopy, and elemental analysis.



Scheme 1.

The proximate location of the diaza-crown ether moiety to the porpyirin unit of both molecules is confirmed by the ^{1}H NMR spectrum in $CDCl_3$, which revealed substantial upfield shifts (up to 4.5 ppm) for the crown ether methylene signals. Molecular modeling revealed a distance of ca. 3.2 and 3.6 Å between the porphyrin moiety and the diazo-crown ether unit for **Zn1** and **Zn2**, respectively. The Soret bands of both compounds (at 403 and 424 nm) in chloroform (2.5 μM) were not split, indicating that the crown ether does not present significant perturbation.[10] The Soret bands maintained a constant shape and gave unchanged ε value (4.09×10^5 M^{-1} cm^{-1}) over the concentration range of 0.5–100 μM, ruling out any important intermolecular aggregation in this range.

When NaCN was added to the CD_3OD solution of **Zn1** (1.0 mM), the signals of the pyrrole protons shifted upfield pronouncedly (ca. −0.12 ppm with 10 equiv of NaCN) as a result of coordination between the cyanide ion and the central zinc of **Zn1**, whereas the crown ether ethylene proton signals shifted downfield (0.11 ppm) owing to the binding of cation Na^+ to the oxygen atoms of the aza-crown ether. These results indicate that NaCN is complexed by **Zn1** in a ditopic fashion (Fig. 1).[11,12] The addition of NaCN to the solution of **Zn1** (3.0 μM) in methanol also caused the solution color to change from purple to pale green (Fig. 2). In contrast, addition of potassium or sodium fluoride did not cause similar significant shifting. UV–vis study revealed a remarkable red shift (ca. 17 and 14 nm for the major Soret band and the Q band of the Zn-porphyrin. Moreover, the UV–vis absorption spectra recorded as a function of the NaCN) concentration displayed two clear isosbestic points at 434 and 565 nm, which also confirms a two-component equilibrium (Fig. 3).[11,12] By fitting the UV–vis titration data to a function containing K_{assoc} as a variable parameter,[13,14] the association constant K_{assoc} of complex **Zn1**·NaCN was determined to be approximately 7.4×10^5 M^{-1} (Table 1).

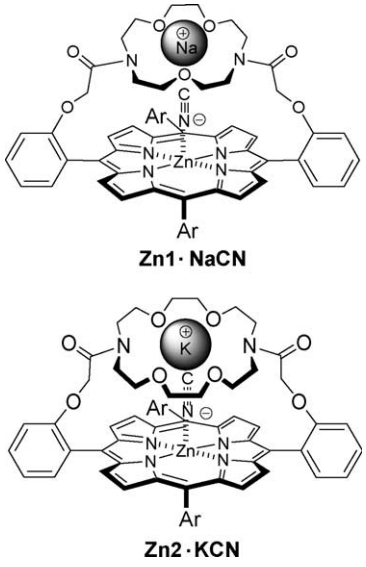


Figure 1. Proposed ditopic binding modes (another two aryl groups are not shown for clarity).

Adding KCN (10 equiv) to the solution of **Zn1** (1.0 mM) in CD_3OD caused the ^{1}H NMR signals of the pyrrole and diazo-crown ether protons to shift upfield (ca. 0.11 ppm) and downfield (0.06 ppm), respectively. Red shift was also observed for the Soret and Q bands (up to 15 and 13 nm) of the Zn-porphyrin moiety when adding KCN to the solution of **Zn1** in methanol. These results also indicate that a 1:1

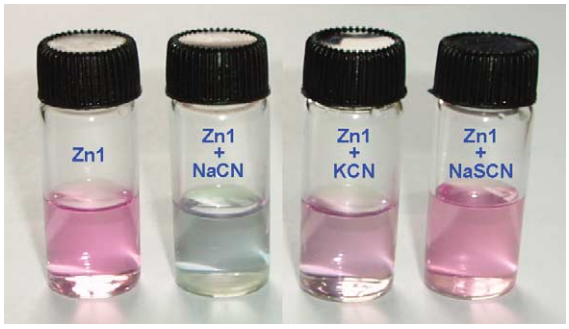


Figure 2. Color changes of the methanol solution of **Zn1** (3.0×10^{-6} M) after addition of inorganic salts (0.5 mM) at 25 °C.

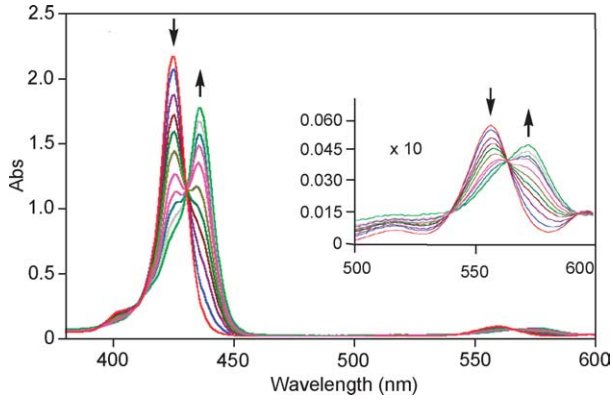


Figure 3. Absorption spectral changes of **Zn1** (5.5×10^{-6} M) in MeOH upon addition of NaCN (1.0×10^{-6}–1.0×10^{-3} M).

complex, that is, **Zn1**·KCN, was formed between the two compounds. From the UV–vis titration experiments, we determined the K_{assoc} of **Zn1**·KCN to be ca. 1.3×10^{4} M^{-1}. This value is significantly lower than that observed for NaCN, revealing a binding selectivity of **Zn1** for NaCN over KCN.

The binding behaviors of **Zn2** with both salts were then investigated. Addition of KCN to the solution of **Zn2** in CD_3OD led to significant upfield shifting of one of the crown ether signals (Fig. 4). The signals of the aromatic protons of **Zn2** also notably shifted upfield (albeit to a smaller extent) as a result of complexation. Similar changes were also observed for the system of **Zn2** and NaCN. The association constants of complexe between **Zn2** and NaCN and KCN in methanol were obtained also with the UV–vis

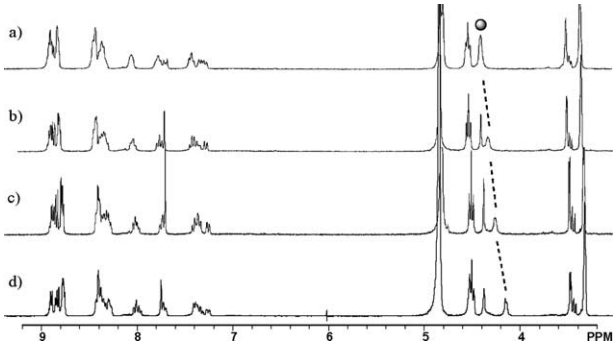


Figure 4. Partial ^{1}H NMR (500 MHz, [**Zn2**] = 1.0 mM) spectra of (a) **Zn2**, (b) **Zn2** + KCN (0.2 equiv), (c) **Zn2** + KCN (0.5 equiv), and (d) **Zn2** + KCN (5.0 equiv) in methanol-*d* at 23 °C.

titration method. The results are provided in Table 1. It can be found that the values of both **Zn2**·NaCN and **Zn2**·KCN are larger than that of the related complexes **Zn1**·NaCN and **Zn1**·KCN. However, different from receptor **Zn1**, which exhibited a binding selectivity for NaCN, receptor **Zn2** showed a remarkably higher binding affinity to KCN. It has been reported that the binding ability of diaza-15-crown-5 to both Na^+ and K^+ is lower than that of diaza-18-crown-6 in methanol.[15] If we assume that the diacylated diazo-15-crown-5 and diaza-18-crown-6 units in the present receptors possess a similar binding affinity, the above results imply that the steric effect, produced in **Zn1** by the reduced ring size of the diazacrown ether and consequently the shorter distance between the porphyrin and diazacrown ether units compared to **Zn2**, might play a crucial role for the selective recognition of **Zn1** to the smaller NaCN. The distance between the porphyrin and diazo-crown ether in **Zn1** is more suitable for the smaller NaCN, while the larger KCN suffers a greater steric hindrance. As expected, the complexing affinity of both **Zn1** and **Zn2** for both NaCN and KCN was remarkably decreased when water or DMSO of higher polarity was added to the solvent (Table 1). However, the complexing selectivity of **Zn1** for NaCN and **Zn2** for KCN did not change.

The binding ability of **Zn1** and **Zn2** to NaSCN and KSCN in methanol was also investigated. As shown in Table 1, all the 1:1 complexes between the receptors and the salts displayed comparable binding stability, which suggests a simple monotopic binding fashion between **Zn1** and **Zn2** and these larger salts. That is, the SCN^- anion bound the porphyrin zinc from the diaza-crown ether-free side, while the cation played a negligible role for the stability of the complexes.

Table 1. Association constants (M^{-1}) and the associated free energy change (kcal/mol) for the complexes between **Zn1** and **Zn2** and inorganic salts obtained from UV–vis titration experiments in methanol at 25 °C[a]

Salt	**Zn1**	ΔG	Salt	**Zn2**	ΔG
NaCN	7.4×10^5	8.0	NaCN	8.0×10^5	8.1
NaCN[b]	1.9×10^5	7.2	NaCN[b]	2.0×10^5	7.3
NaCN[c]	8.5×10^4	6.7	KCN	9.5×10^6	9.5
KCN	1.3×10^4	5.6	KCN[b]	1.8×10^6	8.5
KCN[b]	2.5×10^3	4.6	NaSCN	1.4×10^3	4.3
KCN[c]	1.9×10^3	4.5	KSCN	1.6×10^3	4.4
NaSCN	1.1×10^3	4.1			
KSCN	9.3×10^2	4.0			

[a] Values are the average of two separate measurements and with error of ±15%.
[b] Obtained in MeOH–water (v/v 19:1).
[c] Obtained in MeOH–DMSO (v/v 9:1).

3. Conclusion

We have reported the synthesis and characterization of two new aza-crown ether-capped porphyrins **Zn1** and **Zn2**. The new artificial receptors are able to selectively recognize sodium cyanide and potassium cyanide in a ditopic binding fashion in polar methanol solvent. The binding selectivity of receptor **Zn1** for sodium cyanide is ca. 56 times as high as that for potassium cyanide, whereas the selectivity of receptor **Zn2** for potassium cyanide is ca. 12 times as high as that for sodium cyanide. In contrast, both receptors display remarkably reduced binding affinity for sodium thiocyanate and potassium thiocyanate, presumably due to a monotopic binding fashion. Current efforts will be focused on the modification of the Zn-porphyrin receptors to explore the selective recognition of cyanides in aqueous media.

4. Experimental

4.1. General methods

Melting points are uncorrected. All reactions were performed under an atmosphere of dry nitrogen. The ^{1}H NMR spectra were recorded on 400, or 300 MHz spectrometers in the indicated solvents. Chemical shifts are expressed in parts per million (δ) using residual solvent protons as internal standards. Chloroform (δ 7.27 ppm) was used as an internal standard for chloroform-*d*. Elemental analysis was carried out at the SIOC analytical center. Unless otherwise indicated, all starting materials were obtained from commercial suppliers and were used without further purification. All solvents were dried before use following standard procedures. Compounds **4a**[16] and **4b**[17] were prepared according to reported methods.

4.1.1. Compound 3. To a stirred solution of salicylaldehyde (6.00 g, 49.2 mmol) and chloroacetic acid (4.65 g, 49.2 mmol) in water (10 mL) was slowly added sodium hydroxide (3.60 g, 90.0 mmol) within 3 h at room temperature. The solution was stirred at 70 °C for 1.5 h and then acidified with dilute hydrochloric acid (2 N) to pH=7. The resulting solid was filtered and purified by recrystallization from water to give (2-formyl-phenoxy)-acetyl acid **2** as a white solid (6.00 g, 68%). Mp 129–130 °C [129–131 °C].[18] ^{1}H NMR (DMSO-d_6): δ 4.91 (s, 2H), 7.10 (m, 2H), 7.64 (m, 2H), 10.47 (s, 1H), 13.08 (br, 1H). ME (EI): *m*/*z* 180 $[M]^+$. To a solution of the above acid (3.60 g, 20.0 mmol) in dichloromethane (20 mL) was added oxalyl chloride (2 mL, 25.0 mmol) and drops of DMF. The mixture was stirred at room temperature for 12 h and then evaporated in vacuo to give **3** as a crude product, which was used directly for the next step without further purification.

4.1.2. Compound 5a. To a stirred solution of compound **4a** (2.18 g, 10.0 mmol) and triethylamine (1.0 mL) in dichloromethane (40 mL) was added a solution of the above **3** in dichloromethane (10 mL). The mixture was stirred at room temperature for 12 h and then washed with dilute hydrochloric acid, water, brine, and dried over magnesium sulfate. After the solvent was removed in vacuo, the crude product was purified by column chromatography (CH_2Cl_2/MeOH, 20:1) to give **5a** as a white solid (2.87 g, 53%). ^{1}H NMR ($CDCl_3$): δ 3.53–3.81 (m, 20H), 4.84 (s, 4H), 6.97 (d, J=7.5 Hz, 2H), 7.04 (t, J=6.5 Hz, 2H), 7.52 (t, J=6.5 Hz, 2H), 7.83 (d, J=7.5 Hz, 2H), 10.53 (s, 2H). IR (KBr): ν 2870, 1712, 1660, 1600 cm^{-1}. MS (ESI): *m*/*z* 543 $[M+H]^+$. Anal. Calcd for $C_{28}H_{34}N_2O_9\cdot 0.5H_2O$: C, 60.97; H, 6.40, N, 5.08. Found: C, 60.92; H, 6.36, N, 4.78.

4.1.3. Compound 5b. This intermediate was synthesized from the reaction of compounds **3** and **4b** in 57% yield by using the same procedure described for preparing compound **5a**. ^{1}H NMR ($CDCl_3$): δ 3.67–3.96 (m, 24H), 4.69 (s, 4H), 6.96 (d, J=7.5 Hz, 2H), 7.18 (t, J=6.5 Hz, 2H), 7.59 (t, J=6.5 Hz, 2H), 7.81 (d, J=7.5 Hz, 2H), 10.53 (s, 2H). MS (ESI): *m*/*z* 587 $[M+H]^+$, 610 $[M+Na]^+$. Anal. Calcd for $C_{30}H_{38}N_2O_{10}$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.08; H, 6.41; N, 4.59.

4.1.4. Compound 6. The solution of *n*-octyl 4-formylbenzoate[19] (8.70 g, 33.2 mmol) and pyrrole (23 mL, 66.4 mmol) in toluene (250 mL) was degassed by a stream of nitrogen for 30 min. Hot saturated *p*-toluenesulfonic acid solution in toluene (1.0 mL) was added in one portion. The solution was heated under reflux for 1.5 h and cooled to room temperature. The solution was washed with aqueous potassium carbonate solution (2 N), water, brine, and dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave a brown oil, which was purified by column chromatography (chloroform) and recrystallization (chloroform/hexane) to give compound **6** (8.13 g, 65%) as a white solid. Mp 84–85 °C. ^{1}H NMR ($CDCl_3$): δ 0.89 (t, J=6.7 Hz, 3H), 1.27–1.44 (m, 10H), 1.71–1.78 (m, 2H), 4.30 (t, J=6.6 Hz, 2H), 5.53 (s, 1H), 5.90 (s, 2H), 6.15–6.18 (m, 2H), 6.70–6.73 (m, 2H), 7.24–7.30 (m, 2H), 7.97 (s, 2H), 8.00 (s, 2H). MS (EI): *m*/*z* 378 $[M]^+$. Anal. Calcd for $C_{24}H_{30}N_2O_2$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.25; H, 7.99; N, 7.29.

4.1.5. Compound $H_2$1. Compounds **5a** (5.42 g, 10.0 mmol) and **6** (7.56 g, 20.0 mmol) were dissolved in acetonitrile (1000 mL). The solution was degassed for 30 min and the trifluoroacetic acid (0.2 mL) was added in one portion. The solution was shielded from light and stirred at room temperature for 5 h. Then, a solution of DDQ (5.26 g) in THF (100 mL) was added and the mixture was stirred at room temperature for another 2 h. The solvent was evaporated in vacuo and the residue was triturated with chloroform (300 mL). The solution was washed with diluted sodium carbonate solution, water, brine, and dried over sodium sulfate. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography (dichloromethane/methanol, 40:1) to afford compound **$H_2$1** (1.26 g, 10%). Mp >235 °C. ^{1}H NMR ($CDCl_3$): δ −2.71 (s, 2H), 0.96 (t, J=6.5 Hz, 6H), 1.24 (br, 8H), 1.36–1.62 (m, 20H), 1.92 (p, J=6.8 Hz, 4H), 2.13 (br, 4H), 2.87 (br, 8H), 4.50 (t, J=7.0 Hz, 4H), 4.67 (s, 4H), 7.20–7.25 (m, 2H), 7.44–7.49 (m, 2H), 7.73–7.79 (m, 2H), 8.04–8.08 (m, 2H), 8.30–8.34 (m, 4H), 8.42–8.48 (m, 4H), 8.81–8.86 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 14.3, 22.9, 26.4, 29.1, 29.5 (d), 32.0, 46.5 (d), 49.6, 63.2, 65.7, 66.9, 67.2, 67.4, 68.0 (d), 69.1, 70.2, 70.9 (d), 111.9, 113.0, 116.1 (d), 119.2, 121.3 (d), 121.8, 128.3 (d), 130.2, 130.7 (d), 131.2, 131.6 (d), 132.9, 134.7 (d), 135.1 (d), 134.0, 146.6 (d), 157.2, 158.3, 166.2, 167.0 (d), 167.2. IR (KBr): ν 2924,

1718, 1653, 1272, 1112 cm^{-1}. MS (MALDI): *m/z*: 1257 $[M+H]^+$, 1279 $[M+Na]^+$. HRMS: Calcd for $C_{76}H_{85}N_6O_{11}$: 1257.6276. Found: 1257.6268 $[M+H]^+$. Anal. Calcd for $C_{76}H_{84}N_6O_{11}\cdot H_2O$: C, 72.06; H, 6.78; N, 6.64. Found: C, 72.06; H, 6.47; N, 6.52.

4.1.6. Porphyrin $H_2$2. This compound was prepared (12%) as purple solid from the reaction of **5b** and **6** by a method analogous to $\mathbf{H_2}$**1**. Mp >230 °C. ^{1}H NMR ($CDCl_3$): δ −2.71 (s, 2H), 0.96 (t, J=7.0 Hz, 6H), 1.24 (br, 8H), 1.36–1.62 (m, 20H), 1.92 (p, J=7.0 Hz, 4H), 2.13 (br, 8H), 2.87 (s, 8H), 4.50 (t, J=7.1 Hz, 4H), 4.67 (s, 4H), 7.22–7.25 (m, 2H), 7.46–7.49 (m, 2H), 7.76–7.80 (m, 2H), 8.04–8.06 (m, 2H), 8.30–8.33 (m, 4H), 8.44–8.47 (m, 4H), 8.81–8.85 (m, 8H). IR (KBr): ν 2925, 1718, 1653, 1271, 1115 cm^{-1}. MS (MALDI): *m/z*: 1300 $[M]^+$. Anal. Calcd for $C_{78}H_{88}N_6O_{12}$: C, 71.98; H, 6.81; N, 6.46. Found: 71.69; H, 6.70; N, 6.31.

4.1.7. Porphyrin Zn1. The free base porphyrin $\mathbf{H_2}$**1** (1.00 g, 0.08 mmol) was dissolved in dichloromethane/methanol (3:1, 200 mL) and zinc acetate (0.60 g, 5.00 mmol) was added with stirring. The mixture was stirred under reflux overnight. The solvent was removed in vacuo, and the product was subjected to column chromatography (dichloromethane/methanol 40:1) to afford porphyrin **Zn1** as a purple solid in quantitative yield. Mp >260 °C. ^{1}H NMR ($CDCl_3$): δ −0.85 (t, J=7.0 Hz, 4H), 0.32 (t, J=7.0 Hz, 4H), 0.98 (br, 8H), 1.36–1.90 (m, 22H), 2.89 (s, 8H), 4.23–4.67 (m, 12H), 7.20–7.25 (m, 2H), 7.40–7.43 (m, 2H), 7.71–7.72 (m, 2H), 8.00–8.09 (m, 2H), 8.31–8.33 (m, 4H), 8.46–8.49 (m, 4H), 8.80–8.85 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 14.1, 22.7, 26.1, 28.8, 29.3 (d), 31.8, 43.6, 46.8, 62.6, 65.5, 67.3 (d), 68.8, 69.4, 70.4, 71.0, 72.2, 115.2, 115.9, 117.4, 119.7, 119.8, 122.1, 127.7 (d), 129.6, 130.3, 131.6, 132.0 (d), 133.7, 134.3 (d), 134.6, 147.4, 149.4 (d), 150.0 (d), 157.1, 159.1, 166.0, 166.8 (d), 167.5. IR (KBr): ν 2926, 1719, 1647, 1271, 1116 cm^{-1}. MS (MALDI): *m/z* 1320 $[M+H]^+$. Anal. Calcd for $C_{76}H_{82}N_6O_{11}Zn$: C, 69.11; H, 6.26; N, 6.36. Found: C, 69.50; H, 6.43; N, 5.98.

4.1.8. Porphyrin Zn2. This compound was prepared as a purple solid from the reaction of $\mathbf{H_2}$**2** and zinc acetate by a method similar to that for **Zn1**. Mp >250 °C. ^{1}H NMR ($CDCl_3$): δ 0.72 (br, 4H), 0.96 (t, J=6.7 Hz, 8H), 1.11–1.58 (m, 18H), 1.84–1.96 (m, 8H), 2.81–2.31 (m, 8H), 4.36–4.42 (m, 4H), 4.50 (t, J=6.5 Hz, 12H), 7.17–7.27 (m, 2H), 7.37–7.48 (m, 2H), 7.71–7.80 (m, 2H), 7.97–8.10 (m, 2H), 8.29 (d, J=7.8 Hz, 4H), 8.43 (d, J=7.8 Hz, 4H), 8.75–8.91 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 14.1, 22.7, 26.2, 28.9, 29.3 (d), 31.8, 45.8 (d), 47.1 (d), 65.5, 65.7, 67.4, 67.7, 68.2, 68.9, 69.3, 69.7, 70.3, 112.9, 114.6, 116.3, 116.5, 119.4 (d), 120.9, 121.3, 127.7 (d), 129.6, 130.0, 131.7, 132.5, 133.0, 134.3, 134.8, 135.4 (d), 147.6, 149.4 (d), 150.2 (d), 157.6, 158.0, 166.9 (d), 167.1. IR (KBr): ν 2924, 1718, 1653, 1271, 1114 cm^{-1}. MS (MALDI): *m/z*: 1363 $[M+H]^+$. HRMS: Calcd for $C_{78}H_{86}N_6O_{12}Zn$: 1363.5673. Found: 1363.5689. Anal. Calcd for $C_{78}H_{86}N_6O_{12}Zn$: C, 68.64; H, 6.35, N, 6.16. Found: C, 68.42; H, 6.39; N, 6.11.

4.2. Binding studies

For the UV–vis absorption titration experiments, typically a methanol solution of **Zn1** or **Zn2** was prepared at a fixed concentration. Methanol solutions of inorganic salts were prepared at concentrations of 0.1 M, 2.5 mL of the mixture solution with the fixed [**Zn1**] or [**Zn2**] and the changing concentration of guests was placed in a cuvette and the UV–vis absorption spectrum were sequentially recorded. The values of the absorbance at fixed wavelengths were used. Origin6.0 software was used to fit the data to a 1:1 binding isotherm: $\Delta A=(\Delta A_{max}/[\mathbf{Zn1}\cdot\mathbf{Zn1}])\times\{0.5[G]+0.5([\mathbf{Zn1}\cdot\mathbf{Zn1}]+K_d)-0.5[[G]^2+(2[G](K_d-[\mathbf{Zn1}\cdot\mathbf{Zn1}])+(K_d+[\mathbf{Zn1}\cdot\mathbf{Zn1}])^2)^{1/2}]\}$, where [G] is the salt guest concentration, $K_d=(K_{assoc})^{-1}$. Association constants reported are the average of two experiments.[14]

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Effects of electron-withdrawing substituents on DPPH radical scavenging reactions of protocatechuic acid and its analogues in alcoholic solvents

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Abstract—The DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging activity of protocatechuic acid (3,4-dihydroxybenzoic acid) and its related catechols was examined. Compounds possessing strong electron-withdrawing substituents showed high activity. NMR analysis of the reaction mixtures of catechols and DPPH radical in methanol showed the formation of methanol adducts. The results suggest that high radical scavenging activity of catechols in alcohol is due to a nucleophilic addition of an alcohol molecule on *o*-quinones, which leads to a regeneration of a catechol structure. Furthermore, the radical scavenging activity in alcohols would largely depend on the electron-withdrawing/donating substituents, since they affect the susceptibility toward nucleophilic attacks on *o*-quinone.

1. Introduction

Polyphenols such as hydroxybenzoic and hydroxycinnamic acids derivatives are known to exhibit potent antioxidant activities. In particular, catechol-type *o*-diphenols such as protocatechuic acid (3,4-dihydroxybenzoic acid, **1**) and caffeic acid show high antiradical activity,[1–4] since they would be readily converted to the corresponding *o*-quinones and further complex products.[1,5] In recent years, kinetic studies on reactions of phenolic antioxidants with radicals, including substituents effects,[6–8] have been extensively investigated.[6–10] However, to understand the whole antioxidant mechanisms of catechols and explain why they show high radical scavenging activity, it is necessary to study the reaction events after the formation of *o*-quinones. Previously, we reported the solvent dependency of radical scavenging activity of protocatechuic acid and its esters.[11] In non-alcoholic acetone or acetonitrile, protocatechuic acid and its esters consumed two radicals and were converted to their quinones. In contrast, protocatechuic esters rapidly scavenged more than four radicals with a concomitant conversion to the corresponding quinones, 3-hemiacetals,[12] and their alcohol adducts at C-2 in methanol or ethanol. We found that regeneration of catechol structures by a nucleophilic addition of a solvent alcohol molecule on *o*-quinones is a key reaction for the higher radical scavenging activity of protocatechuic esters in alcoholic solvents than in non-alcoholic solvents.[11,13] Interestingly, **1** showed significantly low activity in alcohol compared to its methyl ester (**2**), and no alcohol adduct was formed. In addition, the radical scavenging activity of 3′,4′-dihydroxyacetophenone (**3**), 3,4-dihydroxybenzaldehyde (**4**) and 3,4-dihydroxybenzonitrile (**5**), which bear electron-withdrawing groups (–COMe, –CHO, –CN) at C-1 of the catechol ring, was comparable to that of **2**.[14] It seems that the radical scavenging activity is greatly affected by the C-1 substituents on the catechol ring. Therefore, in the present study, we extended our investigation on radical scavenging reactions to other C-1 substituted catechols. The objective of this study is to determine whether the radical scavenging mechanisms of protocatechuic ester analogues, possessing electron-withdrawing/donating groups at C-1, are similar or different to that of **2**, and to examine the effects of the electronic properties of the substituents on the radical scavenging reactions beyond the formation of *o*-quinones. In this study, the DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging activity of protocatechuic acid and its related compounds, which bear electron-withdrawing/donating substituents on the catechol ring (Fig. 1), was compared in acetonitrile and methanol. In addition, the reaction mixtures of catechols and DPPH radical were

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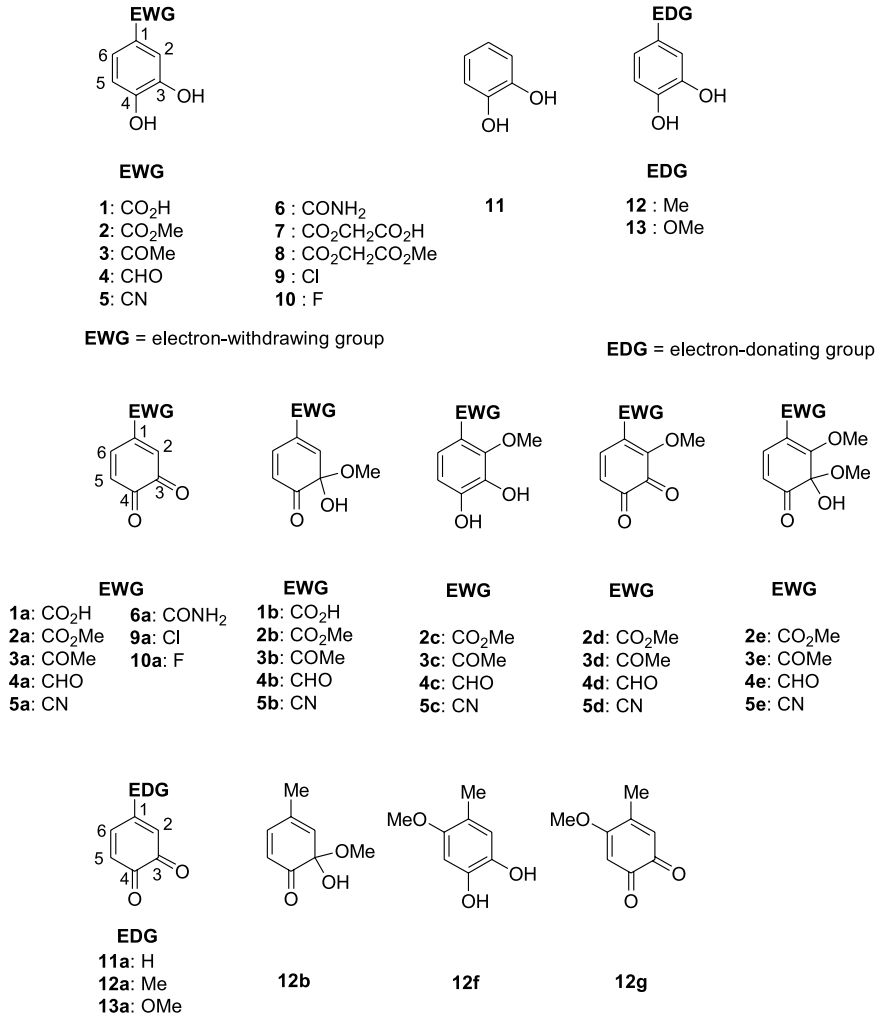


Figure 1. Structures of protocatechuic acid and its related compounds, and their oxidation products.

analyzed by NMR and HPLC, to determine what went on after the quinone formation with the aid of molecular orbital calculations, and the radical scavenging mechanism of protocatechuic ester analogues in alcoholic solvents is proposed.

Table 1. DPPH radical scavenging equivalence in methanol and acetonitrile after 30 min, and the Hammett σ_p values

Compound	Radical scavenging equivalence[a] MeOH	MeCN	σ_p[b]
1	2.5	2.2	0.45 (COOH) 0.00 (COO^-)
2	5.0	2.2	0.45
3	4.8	2.2	0.50
4	5.7	2.2	0.42
5	5.5	2.1	0.66
6	4.9	—[c]	0.36
7	4.9	2.1	—
8	5.2	2.3	—
9	3.0	2.0	0.23
10	2.5	1.8	0.06
11	2.7	1.9	0.00
12	2.8	1.9	−0.17
13	2.1	1.8	−0.27

[a] The equivalence is expressed as the values relative to that of DL-α-tocopherol as 2.0.
[b] σ_p Values according to Ref. 15.
[c] Not tested due to low solubility.

2. Results and discussion

The DPPH radical scavenging activity of catechols (**1**–**13**), which possess electron-withdrawing/donating substituents at C-1 of the aromatic ring except **11**, was evaluated in methanol and acetonitrile. The relative radical scavenging equivalences of compounds **1**–**13**, when that of DL-α-tocopherol as standard was designated as 2.0, are listed in Table 1. In inert acetonitrile, all test compounds scavenged approximately two radicals in 30 min, and there was no significant difference in activity among these compounds. On the other hand, in nucleophilic methanol, all compounds showed relatively high activity compared to that in acetonitrile, and consumed more than two radical in 30 min. As shown in Figure 2, the DPPH radical scavenging equivalences of compounds possessing electron-withdrawing substituents (**1**–**10**) and **11** in methanol correlated well with their Hammett substituents σ_p values.[15] It clearly shows that compounds bearing strong electron-withdrawing substituents at C-1 exhibit high radical scavenging activity. Considering that the high radical scavenging activity of protocatechuic esters is due to their regeneration of the catechol structures via a nucleophilic attack of an alcohol molecule on *o*-quinones, it is indicated that the strong electron-withdrawing substituents enhance the electrophilic

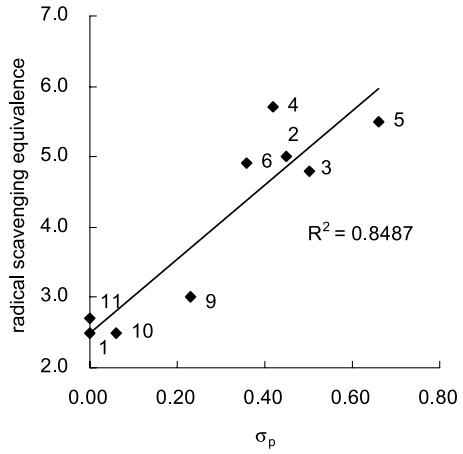


Figure 2. Correlation between DPPH radical scavenging equivalence in methanol after 30 min and the Hammett σ_p values.

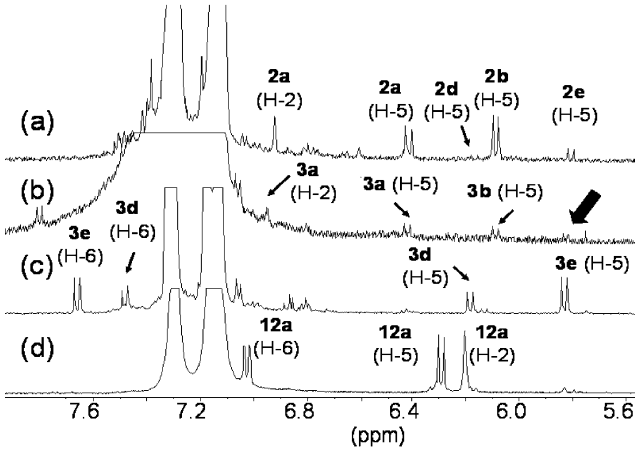
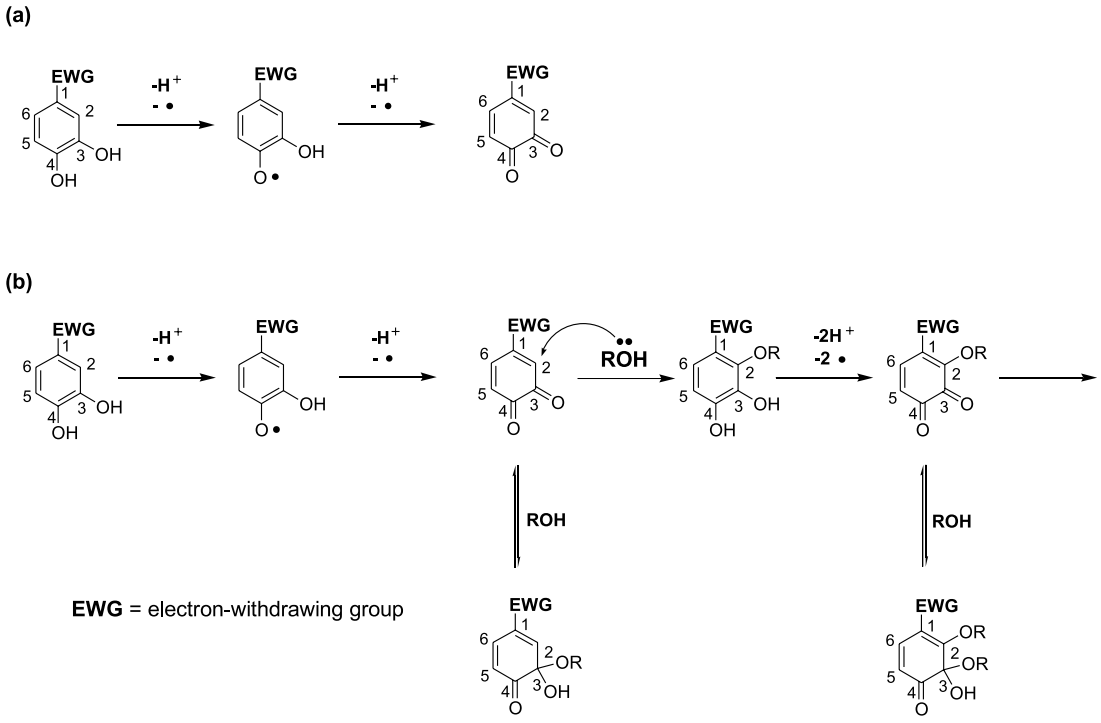


Figure 3. ^{1}H NMR spectra of **2** (a), **3** (b), **3c** (c) and **12** (d) reacted with DPPH radical in methanol-d_4/acetone-d_6 (3:1) 10 min after being mixed.The intense signals in the range of 7.1–7.5 ppm are due to 2,2-diphenyl-1-picrylhydrazine.

nature of the quinone rings, and thus facilitate the nucleophilic addition of an alcohol molecule on *o*-quinones, which leads to the high radical scavenging activity. Since the Hammett σ_p value of COO^- is much smaller than those of COOH and COOMe, the low activity of **1** compared to its methyl ester (**2**) in methanol can be due to the dissociation of the free carboxylic group to the carboxylate ion, which is accelerated by the strong electron-withdrawing property of the quinone carbonyls. Moreover, the radical scavenging equivalence of 3,4-dihydroxybenzoyloxyacetic acid (**7**), which also has a free carboxylic acid ($-CO_2CH_2CO_2H$) at C-1, was comparable to that of **2** and **8**, indicating that the presence of a nonconjugated carboxylic group does not affect the reactivity toward the nucleophilic attack on the quinone ring. It is known that electron-donating substituents reduce the O–H bond dissociation enthalpies of phenols, and hence, facilitate hydrogen atom abstractions, whereas electron-withdrawing groups have the opposite effect.[6,7,16,17] In the present study, however, the radical scavenging activity of compounds **12** and **13**, which bear electron-donating substituents at C-1, exhibited relatively low activity compared to compounds, possessing strong electron-withdrawing groups (**2**–**8**). The result indicates that although electron-withdrawing substituents have negative effects toward initial hydrogen atom abstraction, they contribute to the total radical scavenging ability of catechols by enhancing the electrophilicity of the *o*-quinones.

To elucidate the radical scavenging mechanism, the reaction mixtures of catechols and DPPH radical were directly analyzed by NMR. Since the time course of the DPPH radical scavenging activity of compounds **2**–**5** reached steady state within 10 min,[14] the reaction mixtures were analyzed by NMR 10 min after mixing. The ^{1}H NMR spectrum of the mixture of **3** and DPPH radical in acetone-d_6 showed only signals of the corresponding *o*-quinone (**3a**), as was seen for **1** and **2**.[14] As shown in Figure 3b, the ^{1}H NMR spectrum of the reaction mixture of **3** and DPPH radical in methanol-d_4/acetone-d_6 (3:1) was also similar to that of the mixture of **2** and DPPH radical (Fig. 3a), which showed signals of **2a**, **2b** and its methanol adducts at C-2 (**2d** and **2e**). Together with the characteristic signals of H-5 of the *o*-quinone (**3a**) and its acetal (**3b**) at δ 6.45 (d, $J=10.3$ Hz) and δ 6.12 (d, $J=10.3$ Hz), respectively, a doublet signal at δ 5.85 ($J=10.3$ Hz) was observed. The last doublet signal was assumed to be a methanol adduct, since it corresponded to the signal of H-5 of **2e** (Fig. 3a). To confirm the formation of the methanol adduct, the mixture of authentic **3c** and DPPH radical was analyzed (Fig. 3c). The ^{1}H NMR spectrum showed two sets of doublet signals at δ 6.20 and 7.49 ($J=10.3$ Hz), and δ 5.85 and 7.67 ($J=10.3$ Hz), which correspond to the signals of **2d** and **2e**, respectively.[11] These doublet signals had typical large coupling constants compared to the catechol (**3c**, $J=$ 8.6 Hz), indicating the formation of *o*-quinones and its 3-hemiacetals.[14] Furthermore, the HMBC spectrum showed a correlation between H-5 and C-3 acetal carbon at δ 92.5. Hence, the doublet signal at δ 5.85 in Figure 3b was assigned as H-5 of 2-methoxy adduct (**3e**). Similarly, the NMR analysis of the reaction mixture of **5** and DPPH radical revealed the formation of a methanol adduct at C-2 (**5e**), together with **5a** and **5b**. The results indicate that the radical scavenging reactions of protocatechuic esters and analogues, which possess strong electron-withdrawing substituents at C-1, are very similar, and that methanol additions occur at C-2 of the *o*-quinones.

The ^{1}H NMR spectrum of the mixture of **12** and DPPH radical in methanol-d_4/acetone-d_6 (3:1) showed peaks at δ 6.23 (1H, d, $J=2.0$ Hz), δ 6.32 (1H, d, $J=10.1$ Hz), and δ 7.05 (1H, dd, $J=10.1$, 2.0 Hz) (Fig. 3d). The signals at δ 6.32 and δ 7.05 showed $^3J_{CH}$ HMBC correlation with two distinct carbonyls of C-3 (δ 180.4) and C-4 (δ 181.3), respectively, indicating the formation of the *o*-quinone (**12a**). The result was in agreement with the report for the formation of **12a** from **12** and DPPH radical in acetonitrile.[18] Interestingly, unlike **1**–**5**, no signal due to an acetal (**12b**) was observed. Similarly, the spectrum of the mixture of **11** (or **13**) and DPPH radical in methanol-d_4/acetone-d_6 (3:1) after 10 min showed only the signals of its *o*-quinone (**11a**, **13a**). It can be speculated that the absence of an electron-withdrawing substituent at C-1 increases the stability of the *o*-quinone, and hence, a nucleophilic attack of a methanol molecule at C-3 carbonyl of **12a** to form the corresponding 3-hemiacetal (**12b**) is unlikely to occur. The stability of **12a** was supported by the result of ^{1}H NMR analysis in which the signals of **12a** remained unchanged for



Scheme 1. Plausible radical scavenging mechanism of methyl protocatechuate and its analogues in non-alcoholic solvents (a) and alcoholic solvents (b).

3 h, whereas those of **2a**–**5a** disappeared within 1 h in methanol-d_4/acetone-d_6 (3:1). Moreover, in the ^{1}H NMR spectrum of the mixture of **12** and DPPH radical in methanol-d_4/acetone-d_6 (3:1) after 5 h, new singlet signals appeared at δ 5.82 and δ 6.29, which showed $^3J_{CH}$ HMBC correlation with two distinct carbonyls of C-3 (δ 181.1) and C-4 (δ 180.4), respectively, indicating the formation of a methanol adduct at C-6 (**12g**). Suzuki et al. also reported the formation of an ethanol adduct at C-6 of **12** by reacting **12** and DPPH radical in ethanol.[18] This indicates that the position of nucleophilic attack differs by the electron-withdrawing/donating substituents on the quinone ring.

Formation of methanol adducts by oxidation of **3** and **5** in methanol were further confirmed by HPLC analysis of the reaction mixtures. After reacting catechols and DPPH radical in methanol for 5 min, sodium dithionite was added to the reaction mixture to reduce *o*-quinones and 3-hemiacetals to their catechol-forms. The HPLC analysis of the mixture of **5** and DPPH radical showed a peak at 10.8 min, together with the peak of **5** at 9.2 min. The peak at 10.8 min was identical with that of authentic **5c**. Similarly, in the HPLC analysis of the reaction mixture of **3** and DPPH radical, peaks at 6.5 and 7.2 min, which correspond to those of authentic **3** and **3c**, were observed. The NMR and HPLC studies of the reaction mixtures clearly show that the radical scavenging reactions of **3** and **5** proceed in the similar manner as that of **2**.

The DPPH radical scavenging activity of **2c**–**5c**, which are the oxidation products of **2**–**5**, was evaluated in methanol. The radical scavenging equivalence after 30 min was **2c**, 3.1; **3c**, 2.8; **4c**, 3.7 and **5c**, 3.5, which was approximately 2 equiv lower than that of **2**–**5** (Table 1). Taking into account that **2c**–**5c** are derived from an addition of a methanol molecule to *o*-quinones (**2a**–**5a**), which were produced from **2**–**5** by reacting with two radicals, **2c**–**5c** could largely contribute to the total radical scavenging activity of **2**–**5**. Previously, we reported that thiol adducts at C-2 of **1**–**5**, formed by oxidation of **1**–**5** in the presence of a thiol nucleophile, undergo a second nucleophilic attack at C-5.[14] Therefore, a methanol addition on the *o*-quinones of **2c**–**5c** would also occur. However, since **2c**–**5c** consumed less than four radicals, the second addition of a methanol molecule might be limited by steric hindrance.

The plausible radical scavenging reaction of a protocatechuic ester and its analogues, bearing strong electron-withdrawing groups at C-1, is shown in Scheme 1a and b. In inert solvents, such as acetone and acetonitrile, catechols only scavenge two radicals to yield the corresponding *o*-quinones (Scheme 1a). In contrast, in alcoholic solvents, catechols react with two radicals and are converted to their quinones and 3-hemiacetals (Scheme 1b). Then, subsequent nucleophilic addition of an alcohol molecule at C-2 of the quinone leads to a regeneration of the catechol structure, which can scavenge two additional radicals. In the present study, *o*-quinones, which bear strong electron-withdrawing groups at C-1, preferentially underwent nucleophilic attacks at C-2. In addition, we previously reported that oxidations of **1**–**5** in the presence of thiols form adducts at C-2.[14] To substantiate the position of the nucleophilic attacks, electron density of LUMO of *o*-quinones (**1a**–**6a**, **9a**–**13a**) was calculated by semiempirical method (Table 2). All of the compounds **2a**–**6a**, which possess strong electron-withdrawing groups at C-1, had largest LUMO electron density at C-2. The result indicates that C-2 of the *o*-quinones (**2a**–**6a**) is the most susceptible position for the nucleophilic attack. On the other hand, the LUMO electron density of C-2 of **9a**–**13a** was lower than that of **2a**–**6a** and nearly equal to the C-5 and C-6, hence the regioselectivity of **9a**–**13a** toward nucleophilic attacks seems to be lower than **2a**–**6a**.

Table 2. LUMO energy and electron density at each carbon of *o*-quinones (**1a–6a**, **9a–13a**)

Compound	**1a**		**2a**	**3a**	**4a**	**5a**	**6a**	**9a**	**10a**	**11a**	**12a**	**13a**
	COOH	COO^-										
LUMO	−2.339	1.656	−2.086	−2.041	−2.090	−2.184	−2.000	−1.904	−1.900	−1.640	−1.577	−1.612
C-1	0.34	0.21	0.30	0.31	0.31	0.29	0.32	0.28	0.26	0.26	0.26	0.25
C-2	0.41	0.17	0.41	0.40	0.41	0.36	0.36	0.29	0.25	0.27	0.26	0.19
C-3	0.19	0.26	0.20	0.20	0.20	0.20	0.20	0.20	0.18	0.21	0.21	0.18
C-4	0.14	0.29	0.14	0.14	0.14	0.16	0.16	0.19	0.20	0.21	0.21	0.23
C-5	0.22	0.18	0.21	0.20	0.20	0.23	0.23	0.27	0.30	0.27	0.26	0.30
C-6	0.16	0.31	0.16	0.16	0.15	0.19	0.19	0.24	0.27	0.26	0.26	0.30

This was supported by the report that catechin, an analogous compound of **12** forms three isomers of mono-glutathione adducts at C-2′, 5′, and 6′.[19] Moreover, **2a–6a** had relatively low LUMO energy compared to **11a–13a**. The result indicates that strong electron-withdrawing substituents at C-1 of *o*-quinones facilitate the reactivity toward nucleophilic attacks. Furthermore, the low reactivity toward a nucleophilic attack of **1** could be explained by the increase of LUMO energy of **1a** by dissociation of the free carboxylic group to the carboxylate ion.

3. Conclusion

In conclusion, the radical scavenging mechanisms of catechols, bearing strong electron-withdrawing substituents such as –COMe, –CN at C-1, were similar to that of methyl protocatechuate. Moreover, the results suggested that the radical scavenging activity largely depends on the electron-withdrawing/donating properties of the substituents, since they affect the susceptibility toward nucleophilic attack on the *o*-quinones. In this study, nitrogen-centered DPPH radical was used as a model radical. Therefore, it is of interest to examine whether the reactions with oxygen-centered peroxyl radicals in biological aqueous system are similar to the DPPH radical scavenging reaction shown in this paper.

4. Experimental

4.1. Chemicals

3,4-Dihydroxybenzaldehyde, 3′,4′-dihydroxyacetophenone, 4-fluoro-1,2-dimethoxybenzene, and 4-chlorocatechol were purchased from Tokyo Kasei Kogyo Co. 3,4-Dihydroxybenzonitrile and 4-methylcatechol were obtained from Aldrich Chemical Co. and protocatechuic acid from Sigma Chemical Co. Methyl protocatechuate (**2**) and methyl 3,4-dihydroxy-2-methoxybenzoate (**2c**) were prepared by the method described previously.[11] 2,2-Diphenyl-1-picrylhydrazyl (DPPH) radical and other reagents were purchased from Wako Pure Chemical Industries. All solvents used were of reagent grade.

4.1.1. 3′,4′-Dihydroxy-2′methoxyacetophenone (3c). A mixture of 2′,3′,4′-trihydroxyacetophenone (1.68 g, 10 mmol), benzyl bromide (2.1 mL, 18 mmol, 1.8 equiv), and potassium carbonate (2.48 g, 18 mmol, 1.8 equiv) in acetone (30 mL) was refluxed for 6 h. After cooling to room temperature, the reaction mixture was filtered. The filtrate was concentrated in vacuo, and the residue was subjected to silica gel column chromatography (hexane/ethyl acetate = 3:1) to afford 3′,4′-dibenzyloxy-2′-hydroxyacetophenone (3.0 g, 86%). The dibenzyl ether (1.5 g, 4.3 mmol) in acetonitrile/methanol (4:1, 15 mL) was methylated with 2 M trimethylsilyldiazomethane solution in hexane (3.0 mL, 6 mmol, 1.4 equiv) in the presence of *N*,*N*-diisopropylethylamine (1.0 mL, 6 mmol, 1.4 equiv) for 12 h at room temperature. The reaction mixture was concentrated under reduced pressure. After acidification with 2 M HCl, water was added and the mixture was extracted with ethyl acetate. The organic layer was evaporated under reduced pressure, and the residue was subjected to silica gel column chromatagraphy (hexane/ethyl acetate = 2:1) to afford 3′,4′-dibenzyloxy-2′-methoxyacetophenone (1.1 g, 70%). The resultant dibenzyl methyl ether (1.1 g, 3.0 mmol) was deprotected by hydrogenation at an atmospheric pressure with a catalytic amount of 10% palladium on carbon. The crude product was subjected to silica gel column chromatography (hexane/ethyl acetate = 2:1) to afford **3c** (454 mg, 83%) as a yellow crystal; EI-HR-MS, *m/z* $[M]^+$ 182.0542, calcd $C_9H_{10}O_4$, 182.0579; mp: 87–88 °C; ^{1}H NMR (methanol-d_4): δ 2.55 (3H, s, $COCH_3$), 3.85 (3H, s, 2′-OCH_3), 6.60 (1H, d, J = 8.6 Hz, H-5′), 7.18 (1H, d, J = 8.6 Hz, H-6′); ^{13}C NMR (methanol-d_4): δ 30.4 ($COCH_3$), 61.6 (2′-OCH_3), 111.7 (C-5′), 122.5 (C-6′), 125.1 (C-1′), 139.6 (C-3′), 150.6 (C-2′), 152.8 (C-4′), 200.6 (C=O).

4.1.2. 3,4-Dihydroxy-2-methoxybenzaldehyde (4c). To a suspended solution of 2,3,4-trihydroxybenzaldehyde (2.3 g, 15 mmol) in dichloromethane (20 mL) was added *N*,*N*-diisopropylethylamine (5.6 mL, 32 mmol, 2.1 equiv), and stirred for 15 min at 0 °C. Methoxymethylchloride (2.4 mL, 32 mmol, 2.1 equiv) was then added dropwise. The mixture was stirred at 0 °C for 15 min, and subsequently at room temperature for 45 min. The reaction mixture was poured into water and extracted with chloroform. The organic layer was concentrated under reduced pressure, and the residue was subjected to silica gel column chromatography (hexane/ethyl acetate = 2:1) to afford 2-hydroxy-3,4-bis(methoxymethoxy)benzaldehyde (2.7 g, 74%). The bismethoxymethyl ether (2.1 g, 8.7 mmol) in acetonitrile/methanol (4:1, 20 mL) was methylated with 2 M trimethylsilyldiazomethane solution in hexane (6.0 mL, 12 mmol, 1.4 equiv) in the presence of *N*,*N*-diisopropylethylamine (2.1 mL, 12 mmol, 1.4 equiv) for overnight at room temperature. The reaction mixture was concentrated under reduced pressure. After acidification with 2 M HCl, water was added and the mixture was extracted with ethyl acetate. The organic layer was evaporated under reduced pressure, and the residue was subjected to silica gel column chromatography (hexane/ethyl acetate = 3:1) to

afford 2-methoxy-3,4-bis(methoxymethyloxy)benzaldehyde (1.6 g, 72%). The resultant 2-methoxy-3,4-bis(methoxymethyloxy)benzaldehyde (1.6 g, 6.3 mmol) was suspended in methanol (4 mL) and 1 M HCl (6 mL), and refluxed for 1 h. The reaction mixture was concentrated under reduced pressure, and the crude product was subjected to silica gel column chromatography (hexane/ethyl acetate = 2:1) to afford **4c** (0.93 g, 89%) as a pale yellow powder; EI-HR-MS, *m/z* $[M]^+$168.0469, calcd $C_8H_8O_4$, 168.0423; mp: 110–111 °C; ^{1}H NMR (methanol-d_4): δ 3.93 (3H, s, 2-OCH_3), 6.66 (1H, d, J=8.6 Hz, H-5), 7.23 (1H, d, J=8.6 Hz, H-6), 10.1 (1H, s, CHO); ^{13}C NMR (methanol-d_4): δ 61.4 (2-OCH_3), 112.4 (C-5), 121.7 (C-6), 123.7 (C-1), 139.3 (C-3), 153.2 (C-2), 155.0 (C-4), 190.8 (CHO).

4.1.3. 3,4-Dihydroxy-2-methoxybenzonitrile (5c). Compound **5c** was prepared by the method of Shirai et al.[20] To a solution of hydroxylamine-*O*-sulfonic acid (204 mg, 1.8 mmol, 1.2 equiv) in water (2 mL) was added **4c** (252 mg, 1.5 mmol) at 0 °C, and stirred for 30 min. Then, the reaction mixture was stirred for another 2 h at 60 °C. After cooling, the reaction mixture was extracted with ethyl acetate. The crude product was subjected to silica gel column chromatography (hexane/ethyl acetate = 1:1) to afford **5c** (220 mg, 89%) as a pale yellow powder; EI-HR-MS, *m/z* $[M]^+$165.0443, calcd $C_8H_7NO_3$, 165.0426; mp: 136–138 °C; ^{1}H NMR (methanol-d_4): δ 3.95 (3H, s, 2-OCH_3), 6.62 (1H, d, J=8.4 Hz, H-5), 6.96 (1H, d, J=8.4 Hz, H-6); ^{13}C NMR (methanol-d_4): δ 61.9 (2-OCH_3), 97.7 (C-1), 112.7 (C-5), 118.3 (CN), 125.3 (C-6), 139.8 (C-3), 152.0 (C-2), 153.3 (C-4).

4.1.4. 3,4-Dihydroxybenzamide (6). To 12 M HCl (15 mL) was added 3,4-dihydroxybenzonitrile 675 mg (5.0 mmol), and stirred for 3 h at 40 °C. The reaction mixture was poured into ice-water and washed with ethyl acetate. The water layer was concentrated in vacuo to afford **6** as a white powder (616 mg, 81%); EI-HR-MS, *m/z* $[M]^+$153.0446, calcd $C_7H_7NO_3$, 153.0426; mp: 216–218 °C; ^{1}H NMR (methanol-d_4): δ 6.81 (1H, d, J=8.1 Hz, H-5), 7.27 (1H, dd, J=8.1, 2.2 Hz, H-6), 7.32 (1H, d, J=2.2 Hz, H-2).

4.1.5. (3,4-Dihydroxybenzoyloxy)acetic acid (7). Compound **7** was prepared by the method of Wijesekera and Ratnayake.[21] To a solution of protocatechuic acid (1.54 g, 10 mmol) in water (10 mL) was added 10 M aqueous sodium hydroxide (1 mL) and benzyl chloroacetate (3.1 mL, 20 mmol, 2 equiv), and refluxed for 24 h. After cooling, the reaction mixture was extracted with ethyl acetate, and then washed with water and saturated aqueous sodium hydrogen carbonate. The organic layer was concentrated under reduced pressure, and the residue was subjected to silica gel column chromatography (hexane/ethyl acetate = 2:1) to afford (3,4-dihydroxybenzoyloxy)-acetic acid benzyl ester. The resultant benzyl ester was deprotected by hydrogenation at an atmospheric pressure with a catalytic amount of 10% palladium on carbon. The crude product was subjected to silica gel column chromatography (hexane/ethyl acetate = 1:2) to afford **7** (0.84 g, 40%) as a white powder; EI-HR-MS, *m/z* $[M]^+$212.0280, calcd $C_9H_8O_6$, 212.0321; mp: 194–196 °C; ^{1}H NMR (methanol-d_4): δ 4.75 (2H, s, CH_2), 6.84 (1H, d, J=8.4 Hz, H-5), 7.51 (2H, m, H-2, and 6).

4.1.6. (3,4-Dihydroxybenzoyloxy)acetic acid methyl ester (8). Compound **8** was prepared by the method of Wijesekera and Ratnayake.[21] To a solution of protocatechuic acid (1.54 g, 10 mmol) in water (10 mL) was added 10 M aqueous sodium hydroxide (1 mL) and chloroacetic acid methyl ester (1.75 mL, 20 mmol, 2 equiv), and refluxed for 24 h. After cooling, the reaction mixture was extracted with ethyl acetate, and then washed with water and saturated aqueous sodium hydrogen carbonate. The organic layer was concentrated under reduced pressure, and the residue was subjected to silica gel column chromatography (hexane/ethyl acetate = 2:1) to afford **8** (0.70 g, 31%) as a pale yellow powder; EI-HR-MS, *m/z* $[M]^+$226.0486, calcd $C_{10}H_{10}O_6$, 226.0477; mp: 171–173 °C; ^{1}H NMR (methanol-d_4): δ 3.76 (3H, s, CH_3), 4.80 (2H, s, CH_2), 6.81 (1H, d, J=8.4 Hz, H-5), 7.46 (2H, m, H-2 and 6).

4.1.7. 4-Fluorocatechol (10). To a solution of 4-fluoro-1,2-dimethoxybenzene (1.0 g, 6.4 mmol) in dichloromethane (20 mL) at −80 °C, 1 M boron tribromide dichloromethane solution (38.4 mL, 6 equiv) was added, and stirred for 1 h. The reaction mixture was kept for another 12 h at room temperature. The mixture was poured into ice-water, and extracted with ethyl acetate. The organic layer was washed with water, and then evaporated under reduced pressure to give **10** (0.71 g, 86%) as a white powder; EI-HR-MS, *m/z* $[M]^+$128.0278, calcd $C_6H_5FO_2$, 128.0274; mp: 90–91 °C; ^{1}H NMR (acetone-d_6): δ 6.42 (1H, ddd, J=8.6, 3.0 Hz, J_{HF}=8.6 Hz, H-5), 6.59 (1H, dd, J=3.0 Hz, J_{HF}=9.8 Hz, H-3), 6.77 (1H, dd, J=8.6 Hz, J_{HF}=5.7 Hz, H-6), 7.83 (1H, s, OH), 8.17 (1H, s, OH).

4.1.8. 4-Methoxycatechol (13). A mixture of 3,4-dihydroxybenzaldehyde (5.5 g, 40 mmol), potassium carbonate (11.0 g, 80 mmol, 2 equiv), and benzyl bromide (9.5 mL, 80 mmol, 2 equiv) in acetone (100 mL) was refluxed for 4 h. After cooling, the reaction mixture was filtered. The filtrate was concentrated under reduced pressure, and the residue was subjected to silica gel column chromatography (hexane/ethyl acetate = 2:1) to afford 3,4-dibenzyloxybenzaldehyde (10.7 g, 84%). The resultant dibenzyl ether was converted to the corresponding phenol by the method of Roy et al.[22] To a mixture of boric acid (3.1 g, 50 mmol, 5 equiv) and 30% hydrogen peroxide (2.5 g, 22 mmol, 2.2 equiv) in THF (30 mL) was added concentrated H_2SO_4 (1 mL), and stirred at room temperature for 0.5 h. A solution of 3,4-dibenzyloxybenzaldehyde (3.18 g, 10 mmol) in THF (10 mL) was added, and the reaction mixture was further stirred at room temperature for 12 h. The mixture was filtered, and the filtrate was neutralized with aqueous saturated sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer was washed with water, and evaporated under reduced pressure. The residue was subjected to silica gel column chromatography (hexane/ethyl acetate = 2:1) to afford 3,4-dibenzyloxyphenol (2.3 g, 75%). To a solution of 3,4-dibenzyloxyphenol (1.0 g, 3.3 mmol) in acetone (15 mL) was added potassium carbonate (0.46 g, 3.3 mmol, 1 equiv) and iodomethane (0.2 mL, 3.3 mmol, 1 equiv), and refluxed for 6 h. After cooling, the reaction mixture was filtered. The filtrate was concentrated under reduced pressure, and the residue was subjected to silica gel column chromatography (hexane/ethyl acetate = 2:1) to afford 1,2-dibenzyloxy-4-methoxybenzene

(0.70 g, 67%). The resultant 1,2-dibenzyloxy-4-methoxybenzene (0.70 g, 2.2 mmol) was deprotected by hydrogenation at an atmospheric pressure with a catalytic amount of 10% palladium on carbon. The crude product was subjected to column chromatography (hexane/ethyl acetate = 2:1) to afford **13** (0.24 g, 77%) as a yellow oil; EI-HR-MS, *m/z* $[M]^+$, 140.0499, calcd $C_7H_8O_3$, 140.0474; ^{1}H NMR (acetone-d_6): δ 3.66 (3H, s, OMe), 6.24 (1H, dd, J = 8.6, 3.0 Hz, H-5), 6.42 (1H, d, J = 3.0 Hz, H-3), 6.70 (1H, d, J = 8.6 Hz, H-6).

4.2. Apparatus

NMR spectra were recorded on a Bruker AMX500 spectrometer (^{1}H, 500 MHz; ^{13}C, 125 MHz); chemical shifts are expressed relative to the residual signals of methanol-d_4 (δ_H 3.30, δ_C 49.0) and acetone-d_6 (δ_H 2.04, δ_C 29.8). Electron ionization mass spectra (EI-MS) were obtained with a JEOL JMS-AX500 instrument. Optical absorbance was acquired using a HITACHI U-3210 spectrophotometer. Melting point data were measured with a hot-stage apparatus and are uncorrected. Analytical thin-layer chromatography was performed on silica gel plates Merck 60 F_{254} (0.25 mm thickness). Ordinary phase column chromatography was performed with silica gel, Wakogel C-300 (Wako Pure Chemical Industries).

4.3. Colorimetric radical scavenging tests

DPPH radical scavenging activity was measured as described previously.[11,14] To a solution of a test compound (12.5 μM, 4 mL) was added 1 mL of DPPH radical (500 μM) in a test tube. The solution was immediately mixed vigorously for 10 s by a Vortex mixer and transferred to a cuvette. The absorbance reading at 517 nm was taken at 30 min after initial mixing. Acetonitrile and methanol were chosen as inert non-alcoholic and nucleophilic alcoholic solvents, respectively. A solution of DL-α-tocopherol in the same concentration was measured as a positive control. A reduction of the absorbance, 0.228, by the positive control was regarded as corresponding to the consumption of two molecules of DPPH radical. All experiments were performed in triplicate.

4.4. NMR analyses

4.4.1. NMR measurements of the reaction mixtures of catechols and DPPH radical. To a catechol (2.5 μmol) was added DPPH radical (5.0 mg, 13 μmol, 5 equiv) in methanol-d_4/acetone-d_6 (3:1) or acetone-d_6 (0.4 mL). In the case of the methanol-d_4 solution, acetone-d_6 was added as a cosolvent for enhancing a solubility of DPPH radical. The mixture was immediately transferred to a NMR tube and mixed vigorously. ^{1}H NMR spectra were recorded at 10 min after mixing.

4.4.1.1. Reaction of 2 and DPPH radical. 2a: ^{1}H NMR (methanol-d_4/acetone-d_6 (3:1)): δ 6.44 (1H, d, J = 10.3 Hz, H-5), 6.94 (1H, s, H-2), 7.51 (1H, d, J = 10.3 Hz, H-6), **2b**: ^{1}H NMR (methanol-d_4/acetone-d_6 (3:1)): δ 6.11 (1H, d, J = 10.3 Hz, H-5), 7.43 (1H, d, J = 10.3 Hz, H-6), **2d**: ^{1}H NMR (methanol-d_4/acetone-d_6 (3:1)): δ 6.19 (1H, d, J = 10.3 Hz, H-5), **2e**: ^{1}H NMR (methanol-d_4/acetone-d_6 (3:1)): δ 5.83 (1H, d, J = 10.3 Hz, H-5), 7.53 (1H, d, J = 10.3 Hz, H-6).

4.4.1.2. Reaction of 3 and DPPH radical. 3a: ^{1}H NMR (methanol-d_4/acetone-d_6 (3:1)): δ 6.45 (1H, d, J = 10.3 Hz, H-5), 6.94 (1H, d, J = 2.2 Hz, H-2), **3b**: ^{1}H NMR (methanol-d_4/acetone-d_6 (3:1)): δ 6.12 (1H, d, J = 10.3 Hz, H-5), **3e**: ^{1}H NMR (methanol-d_4/acetone-d_6 (3:1)): 5.85 (1H, d, J = 10.3 Hz, H-5), 7.67 (1H, d, J = 10.3 Hz, H-6).

4.4.1.3. Reaction of 5 and DPPH radical. 5a: ^{1}H NMR (methanol-d_4/acetone-d_6 (3:1)): δ 6.49 (1H, d, J = 10.3 Hz, H-5), **5b**: ^{1}H NMR (methanol-d_4/acetone-d_6 (3:1)): δ 6.19 (1H, d, J = 10.1 Hz, H-5), **5e**: ^{1}H NMR (methanol-d_4/acetone-d_6 (3:1)): δ 5.90 (1H, d, J = 10.1 Hz, H-5).

4.4.1.4. Reaction of 11 and DPPH radical. 11a: ^{1}H NMR (methanol-d_4/acetone-d_6 (3:1)): δ 6.35 (2H, m, H-2 and 5), 7.14 (2H, m, H-1 and 6); ^{13}C NMR (methanol-d_4/acetone-d_6 (3:1)): δ 131.7 (C-2 and 5), 140.9 (C-1 and 6), 181.3 (C-3 and 4); HMBC correlation peaks: H-1 (6)/C-3 (4), C-5 (2), H-2 (5)/C-4 (3), C-6 (1).

4.4.1.5. Reaction of 12 and DPPH radical. 12a: ^{1}H NMR (methanol-d_4/acetone-d_6 (3:1)): δ 2.17 (3H, s, CH_3), 6.23 (1H, d, J = 2.0 Hz, H-2), 6.32 (1H, d, J = 10.1 Hz, H-5), 7.05 (1H, dd, J = 10.1, 2.0 Hz, H-6); ^{13}C NMR (methanol-d_4/acetone-d_6 (3:1)): δ 21.3 (CH_3), 128.4 (C-2), 129.4 (C-5), 144.3 (C-6), 153.6 (C-1), 180.4 (C-3), 181.3 (C-4); HMBC correlation peaks: H-2/C-4, C-6, H-5/C-1, C-3, H-6/C-2, C-4, CH_3/C-1, C-2, C-6, **12g**: ^{1}H NMR (methanol-d_4/acetone-d_6 (3:1)): δ 2.14 (3H, s, CH_3), 5.82 (1H, s, H-5), 6.29 (1H, s, H-2); ^{13}C NMR (methanol-d_4/acetone-d_6 (3:1)): δ 17.3 (CH_3), 102.5 (C-5), 129.3 (C-2), 151.5 (C-1), 171.3 (C-6), 180.4 (C-4), 181.1 (C-3); HMBC correlation peaks: H-2/C-1, C-4, H-5/C-1, C-3, C-6, CH_3/C-1, C-2, C-6.

4.4.1.6. Reaction of 13 with DPPH radical. 13a: ^{1}H NMR (methanol-d_4/acetone-d_6 (3:1)): δ 3.91 (3H, s, CH_3), 5.86 (1H, d, J = 2.7 Hz, H-2), 6.43 (1H, d, J = 10.3 Hz, H-5), 7.00 (1H, dd, J = 10.3, 2.7 Hz, H-6); ^{13}C NMR (methanol-d_4/acetone-d_6 (3:1)): δ 57.5 (CH_3), 103.5 (C-2), 131.8 (C-5), 140.7 (C-6), 171.1 (C-1), 179.2 (C-3), 182.0 (C-4); HMBC correlation peaks: H-2/C-4, C-6, H-5/C-1, C-3, H-6/C-2, C-4, CH_3/C-1, C-2, C-6.

4.4.2. NMR measurements of the reaction mixtures of catechols (2c, 3c, and 5c) and DPPH radical. To a catechol (2.5 μmol) was added DPPH radical (3.0 mg, 7.6 μmol, 3 equiv) in methanol-d_4/acetone-d_6 (3:1, 0.4 mL). The mixture was immediately transferred to a NMR tube and mixed vigorously. ^{1}H NMR spectra were recorded at 10 min after mixing.

4.4.2.1. Reaction of 2c and DPPH radical. 2d: ^{1}H NMR (methanol-d_4/acetone-d_6 (3:1)): δ 6.19 (1H, d, J = 10.3 Hz, H-5), 7.38 (1H, d, J = 10.3 Hz, H-6), **2e**: ^{1}H NMR (methanol-d_4/acetone-d_6 (3:1)): δ 5.83 (1H, d, J = 10.3 Hz, H-5), 7.53 (1H, d, J = 10.3 Hz, H-6).

4.4.2.2. Reaction of 3c and DPPH radical. 3d: ^{1}H NMR (methanol-d_4/acetone-d_6 (3:1)): δ 2.52 (3H, s, $COCH_3$), 4.16 (3H, s, 2-OCH_3), 6.20 (1H, d, J = 10.3 Hz, H-5), 7.49 (1H, d,

$J=10.3$ Hz, H-6), **3e**: ^{1}H NMR (methanol-d_4/acetone-d_6 (3:1)): δ 2.44 (3H, s, $COCH_3$), 4.33 (3H, s, 2-OCH_3), 5.85 (1H, d, $J=10.3$ Hz, H-5), 7.67 (1H, d, $J=10.3$ Hz, H-6).

4.4.2.3. Reaction of 5c and DPPH radical. 5e: ^{1}H NMR (methanol-d_4/acetone-d_6 (3:1)): δ 5.90 (1H, d, $J=10.1$ Hz, H-5).

4.5. HPLC analyses

4.5.1. HPLC analyses of the reaction mixtures of catechols and DPPH radical. To a catechol (1.7 μmol) was added DPPH radical (2.0 mg, 5.1 μmol, 3 equiv) in methanol (0.2 mL). After 5 min, an aqueous solution (10 μL) of sodium dithionite (0.9 mg, 5.2 μmol, 3 equiv) was added to the reaction mixture. The resulting solution was passed through a filter (0.45 μm), and analyzed by HPLC (Inertsil ODS-2 (GL Sciences Inc.), 4.6 mm i.d.×250 mm, 20% MeCN/H_2O containing 0.1% HCOOH, detected by UV at 254 nm).

4.6. Molecular orbital calculations

Electron density and energy of LUMO were calculated by AM1 method using MOPAC 2000 program combined in Chem3D package, CambridgeSoft Co.

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Proton affinities of ketones, vicinal diketones and α-keto esters: a computational study

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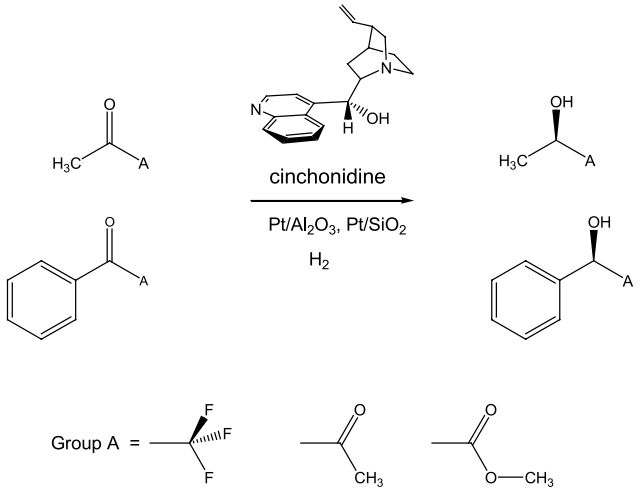
Abstract—The proton affinities of seven different ketones, vicinal diketones, and α-keto esters (acetophenone, 2,2,2-trifluoroacetophenone, 2,3-butanedione, 1-phenyl-1,2-propanedione, methyl pyruvate, ethyl benzoylformate, and ketopantolactone) have been evaluated theoretically using the conventional ab initio HF and several post-HF methods (MP2, MP4, CCSD), density functional methods with the B3LYP hybrid functional, as well as some ab initio model chemistries [CBS-4M, G2(MP2), and G3(MP2)//B3LYP]. The chemical compounds studied are frequently used substrates in the asymmetric hydrogenation over chirally modified platinum catalysts where the protonation properties of the chiral modifier and the substrates are of great interest. In most cases, the proton affinities (PAs) evaluated with the CCSD/6-311+G(d,p)//B3LYP/TZVP and G2(MP2) methods are in good agreement with the existing experimental ones. However, the previously reported PA of 2,3-butanedione seems to be too high by 10–15 kJ mol^{-1}. The B3LYP/TZVP//B3LYP/TZVP and MP2/6-311+G(d,p)//B3LYP/TZVP model chemistries predict proton affinities that are systematically higher and lower than the experimental PAs, respectively. If proton affinities are evaluated as the average of the PAs calculated with these two theoretical methods a very good agreement with the experimental results is obtained. The mean absolute deviation (MAD) from experiment of this combination method for the PAs of 13 test molecules is 4.0 kJ mol^{-1}. For 9 molecules composed only of first-row atoms the MAD is 2.5 kJ mol^{-1}. The B3LYP/TZVP//B3LYP/TZVP and MP2/6-311+G(d,p)//B3LYP/TZVP methods provide significant savings in computational time and disk space compared to the CCSD/6-311+G(d,p)//B3LYP/TZVP and G2(MP2) models. Therefore, it is suggested that if no experimental or highly accurate theoretical data is available (due to computational cost), the proton affinities of similar compounds as investigated in this paper, can be evaluated with the combination method. For the studied molecules, this method gives the following PAs (in kJ mol^{-1}): 788 (2,3-butanedione, exptl 802); 798 (2,2,2-trifluoroacetophenone, exptl 799); 811 (ketopantolactone); 813 (methyl pyruvate); 825 (1-phenyl-1,2-propanedione); 862 (acetophenone, exptl 861); 865 (ethyl benzoylformate).

1. Introduction

Asymmetric hydrogenation of prochiral ketones, vicinal diketones and α-keto esters over cinchona alkaloid modified platinum catalysts (Orito reaction[1], Scheme 1) is an example of heterogeneous enantioselective catalysis, which is actively investigated[2–5] by groups working in the field of catalysis, organic chemistry, surface science, and quantum chemistry. Reduction of a prochiral α-keto ester (e.g., ethyl pyruvate) over the Orito catalyst (Pt modified with cinchonidine) to corresponding alcohols gives stereoselectively the other product enantiomer with over 95% enantiomeric excess (ee),[6] defined as ee = 100%*([*R*]−[*S*])/([*R*]+[*S*]), where [*R*] and [*S*] are the concentrations of the (*R*)- and (*S*)-product enantiomers.



Scheme 1. Examples of substrates, which can be hydrogenated enantioselectively over cinchonidine modified Pt catalysts.

Keywords: Proton affinity; Ab initio calculation; DFT; Enantioselective hydrogenation; α-Keto ester; Model chemistry.
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The commonly accepted Orito reaction[1] mechanism involves a one-to-one hydrogen bonding interaction between a chiral cinchona alkaloid modifier in protonated form (in acidic media) and a reactant on the catalyst metal surface. The reaction mechanism, albeit actively investigated, is not fully understood and the present-day mechanistic models cannot comprehensively explain the involvement of carboxylic acids (proton donors) or other solvent effects on the experimentally observed reaction rates and ees. For example, comparison with literature data reveals very different ee dependences on the solvent used (protic vs aprotic); acetic acid is by far the best solvent for ethyl pyruvate[6,7] whereas in the case of ketopantolactone[8] and 1-phenyl-1,2-propanedione[9] enantioselectivity is lost when the solvent is changed from toluene to acetic acid. Therefore, more information of the solute–solvent–surface interactions present in this complex system is needed to refine the mechanistic models.

Absolute gas-phase basicity, expressed in terms of proton affinity (PA), is an intrinsic property of individual molecules in contrast to the situation in solution where the acid–base properties belong to the phase as a whole due to interactions between solute and solvent molecules.[10] Solution-phase basicities as well as solvation reflect solvent effects. Thus, basicities measured under solvent-free conditions must be available before the interplay between solute properties and solvent effects can be studied.[10] In other words, it is important to know the intrinsic basicity in order to understand, for example, how the surrounding molecular environment can affect the ability of the solute molecule to transfer or accept a proton. Therefore, the proton affinities are important in mechanistic studies of proton transfer reactions and in reactions involving protons, protonated and unprotonated organic molecules.

Pulsed high pressure mass spectrometry (PHPMS)[11] and Fourier transform ion cyclotron resonance (FT-ICR)[12] method are examples of experimental techniques that can accurately evaluate proton affinities for many molecular systems. It is also possible to get reliable PAs computationally with theoretical methods designed for modeling the energies of molecular processes with chemical accuracy (4–8 kJ mol^{-1}). Examples of such methods are Gaussian-*n* (G*n*) methods of Pople and co-workers[13] and complete basis set (CBS) methods of Petersson and co-workers.[14] Very recently, Martin and de Oliveira[15] proposed the W1 and W2 methods, which are designed to achieve 'calibration accuracy', that is, better than 1 kJ mol^{-1}.

The thermodynamic proton affinity of a compound A is defined as the negative of the enthalpy change, $-\Delta_r H°$, for the following gas phase reaction at standard conditions (usually at 298 K under pressure of 1 atm)

$$A + H^+ \rightarrow AH^+ \quad (1)$$

Theoretically, the proton affinities at 0 K are obtained from the calculated electronic energies, E_0^{el}, and the zero-point vibrational energies, E_0^{vib}. The values at temperature T are determined by using in addition the thermal corrections to the vibrational energy, $E^{vib}(T)$, and thermal corrections for translational and rotational energy, $\frac{1}{2}RT$ per degree of freedom. If both AH^+ and A are non-linear species, the proton affinity is given by Eq. 2

$$PA = -\Delta H_{prot}(T)$$

$$= -\Delta E_0^{el} - \Delta E_0^{vib} - \Delta E^{vib}(T) + \frac{5}{2}RT \quad (2)$$

where ΔE is the energy difference between AH^+ and A. If A is linear but AH^+ not, the last term in Eq. 2 is $2RT$ instead of $5/2RT$.

For a fundamental understanding of solvent effects especially in protic media it is important to know the proton affinities of the solute molecules under solvent-free conditions. To best of our knowledge, for most reactants frequently used in the Orito reaction[1] neither experimental nor theoretical PAs have been published. The aim of the present work is to fill this gap in fundamental knowledge. The gas-phase proton affinities of some compounds relevant to the Orito reaction are determined by using various computational methods. The results are compared with previously reported experimental PAs (when available) and the efficiency and the accuracy of the model chemistries are evaluated. Furthermore, experimentally obtained ees and solvent effects are discussed in the light of calculated proton affinities.

2. Computational methods

All calculations were performed with computational methods incorporated in the Gaussian 98 program suite.[16] The molecular structures of the studied species were optimized by using density functional theory (DFT) with the B3LYP hybrid exchange-correlation functional[17–19] and the TZVP basis set.[20] The B3LYP functional is known to behave particularly well when applied to minimum-energy molecular structures composed only of first-row atoms.[21] Frequency calculations of all species were done at the B3LYP/TZVP level to verify that the geometries were minima on the potential energy surface and to obtain zero-point and thermal corrections (298.15 K, 1 atm) for the determination of the proton affinities. For comparison purposes, some geometry optimizations and frequency calculations were performed at the B3LYP/6-31G(d), HF/6-311+G(d), and HF/6-311+G(d,p) levels. The scaling factors[22] 0.95 and 0.893 were used for computing zero-point energy corrections with DFT and HF methods, respectively. The scaling factor 0.95 has been applied previously, for example, by Nicholas and Haw[23] to correct B3LYP/TZVP calculated frequencies for anharmonicity.

Single-point energies of the optimized geometries were obtained with Hartree–Fock (HF) theory, Møller-Plesset perturbation theory with second- and fourth-order corrections (MP2 and MP4, respectively)[24–26] as well as coupled cluster method including single and double excitations (CCSD).[27,28] The 6-311+G(d) and 6-311+G(d,p) basis sets were used in combination with these methods. The single-point calculations with DFT/B3LYP were performed with the TZVP, 6-31G(d) and 6-311+G(2df,2p) basis sets.

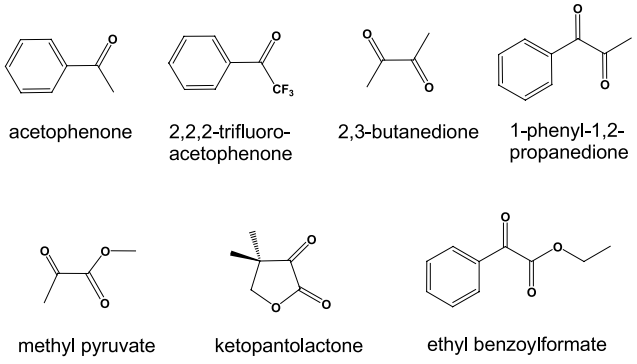
The highly accurate CBS-4M, G2(MP2) and G3(MP2)// B3LYP models[14,29,30] were also used to compute proton affinities of some molecules. These models are compound methods consisting of a number of pre-defined component calculations whose results are combined in a specified manner. This way they attempt to achieve the accuracy of a single, very high level computation, which is much too expensive to be practical. The average absolute deviation from the eight experimental proton affinities in the G2/97 test set[31,32] is only 3.2 and 3.7 kJ mol^{-1} for the G2(MP2) and G3(MP2)//B3LYP results,[30,33] respectively, and 7.3 kJ mol^{-1} for the CBS-4M results.[14]

The CBS-4M model chemistry[14] employes the very fast UHF/3-21G(d) method for geometry optimization and zero-point energies. This makes studies of large and flexible molecules practical.[34] However, the UHF/3-21(d) geometries are sometimes inaccurate, which in many cases leads to large errors in the final results.[14] Further, CBS-4M uses a large basis set SCF calculation as a base energy, and an MP2 calculation with complete basis set extrapolation to correct the energy through second order. An MP4(SDQ)/6-31G calculation is used to approximate higher order contributions. The model includes some additional empirical corrections, too.

G2(MP2) theory uses geometries from second-order perturbation theory with full electron correlation [MP2(FU)/6-31G(d)] and scaled zero-point energy corrections from Hartree–Fock theory [HF/6-31G(d)] followed by single-point calculations at the QCISD(T)/6-311G(d,p) and MP2/6-311+G(3df,2p) levels of theory.[29] In addition, an empirical higher level correction (HLC) term is included to account for remaining (basis set) deficiencies.[29] The steps in G3(MP2)//B3LYP theory are essentially the same as in G2(MP2) theory. However, the geometries and zero-point energy corrections are obtained at the B3LYP/6-31G(d) level.[30]

3. Results and discussion

The structural formulae of the molecules studied in this work are represented in Scheme 2. The three-dimensional minimum energy geometries of the protonated and unprotonated molecules, calculated at the B3LYP/TZVP level, are shown in Figures 1 and 2. In addition, these



Scheme 2. The structural formulas of the ketones, vicinal diketones and α-keto esters studied.

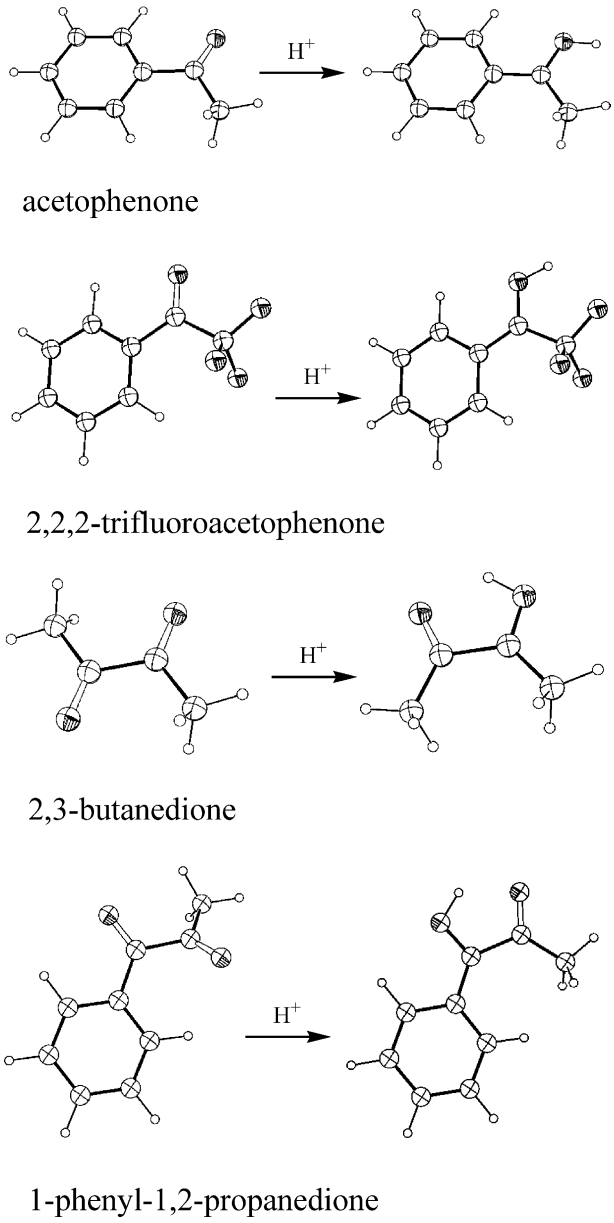


Figure 1. B3LYP/TZVP optimized structures of the most stable conformers of the protonated and unprotonated ketones and vicinal diketones.

structures are given in the Supplementary data as Gaussian output files, which can be viewed, for example, with Molden[35] molecular visualization program. The Supplementary data also contains Gaussian output files of all competing structural and conformational isomers of the protonated molecules, which were considered as well as a table showing the relative stabilities of the various structures.

In the most stable protonated species, the proton is bound to one of the carbonyl oxygens in the molecule. The preferred site depends on the molecule. In two α-keto esters (methyl pyruvate and ketopantolactone) the carbonyl oxygen of the ester group is protonated. In the case of ethyl benzoylformate and the asymmetric vicinal diketone, 1-phenyl-1,2-propanedione, it is the carbonyl oxygen next to the phenyl group, which forms a more stable bond with the proton. These phenomena can be understood in terms of resonance

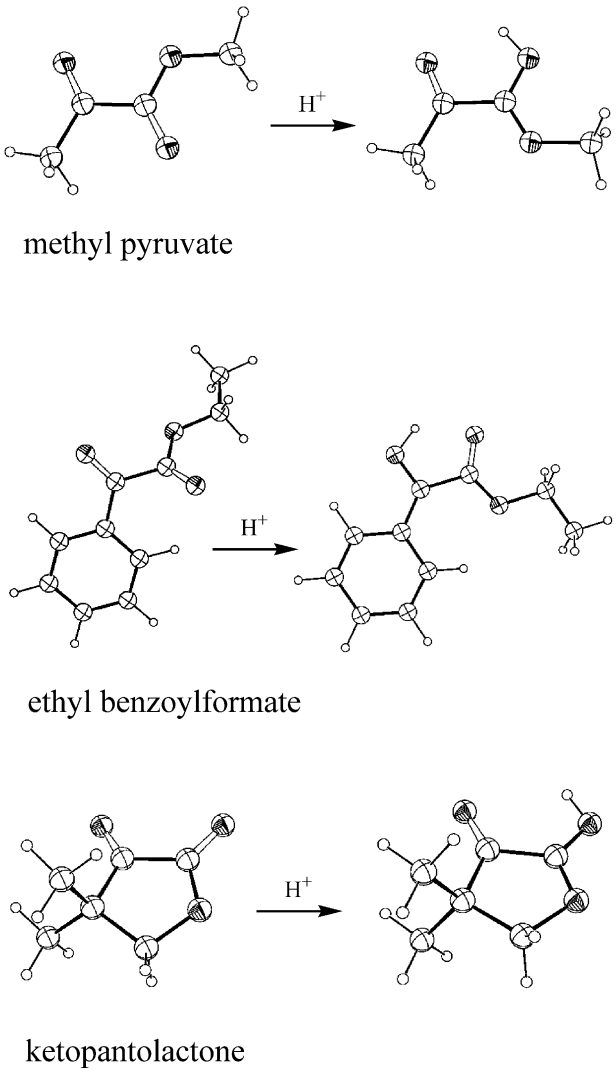


Figure 2. B3LYP/TZVP optimized structures of the most stable conformers of the protonated and unprotonated α-keto esters.

stabilization of the resulting cations. For example, the benzyl cation $C_6H_5C^+(OH)C(O)CH_3$ is resonance stabilized by the phenyl group C_6H_5 while the other possible cation $C_6H_5C(O)C^+(OH)CH_3$ is not. Also the Mulliken charges of the carbonyl oxygen atoms are mostly in harmony with the preferred protonation sites when assuming that the proton binds to the more negative oxygen. In the α-keto esters, the carbonyl oxygen of the ester group has a slightly (0.04–0.09 units) more negative charge than the carbonyl oxygen next to the alkyl group while in 1-phenyl-1,2-propanedione the oxygen atom closer to the phenyl group is more negative. In 2,3-butanedione the partial atomic charges of the carbonyl oxygens are of equal magnitude because the molecule is symmetric. Due to the hydrogen bonding, in all protonated diketones and α-keto esters the whole $O{=}C{-}C{-}OH^+$ system is planar and the $O{-}H^+$ proton is at a distance of ca. 200 pm from the carbonyl oxygen.

Before considering the proton affinities of 2,3-butanedione and other compounds mentioned, we will briefly discuss the PA of water, which has been studied extensively elsewhere.[36,37] It is interesting to compare the experimental and previous theoretical results for water with the ones obtained with some of the computational methods used in this study.

3.1. Proton affinity of water

The theoretical and experimental geometrical parameters for H_2O and H_3O^+ are considered first. For H_2O, the bond distance 96.40 pm and the bond angle 105.50° obtained at the B3LYP/TZVP level are slightly larger than the experimental values[38] of 95.72 pm and 104.52°. The geometry for H_3O^+ is nonplanar with the calculated values of 98.30 pm for the bond distance and 112.82° for the bond angle. The experimental values[39] are again somewhat smaller, 97.58 pm and 111.3°, respectively.

The experimentally obtained range for the proton affinity of water at 298 K is 697 ± 4 and 694 ± 8 kJ mol^{-1}.[36,40] Many calculations for the PA have also been done, the most recent and accurate values being $PA(H_2O)=691\pm1$ and 680 kJ mol^{-1},[36,37] that is, slightly lower than the experimentally determined values. The archivally suggested value from the NIST database[41] is 691 kJ mol^{-1}. It has been proposed that the experimental values are too high and should be corrected by 6–12 kJ mol^{-1}.[36,37] However, it seems that in the study of Jursic[37] the term $5/2RT$ ($\approx$6.2 kJ mol^{-1} at 298.15 K) in Eq. 2 has been neglected when evaluating the proton affinity, thus, yielding to such a low estimate (680 kJ mol^{-1}).

Our results for the PA of water (Table 1) fall in the experimentally[40] obtained range 694 ± 8 kJ mol^{-1} if electron correlation is treated adequately (e.g., at the MP4/6-311+G(d,p) level of theory). The importance of

Table 1. Calculated proton affinities (kJ mol^{-1}) of water

Method	PA	Method	PA
Experimental[a]	691	MP2/6-311+G(d,p)//HF/6-311+G(d,p)	696
B3LYP/TZVP//B3LYP/TZVP	692	MP4/6-311+G(d,p)//HF/6-311+G(d,p)	700
HF/6-311+G(d)//B3LYP/TZVP	702	CCSD/6-311+G(d,p)//HF/6-311+G(d,p)	703
HF/6-311+G(d,p)//B3LYP/TZVP	705	B3LYP/TZVP//HF/6-311+G(d,p)	691
MP2/6-311+G(d)//B3LYP/TZVP	694	B3LYP/6-31G(d)//B3LYP/6-31G(d)	709
MP2/6-311+G(d,p)//B3LYP/TZVP	696	B3LYP/6-11+G(2df,2p)//B3LYP/6-31G(d)	687
MP4/6-311+G(d)//B3LYP/TZVP	696	G1	690
MP4/6-311+G(d,p)//B3LYP/TZVP	700	G2	688
CCSD/6-311+G(d)//B3LYP/TZVP	699	G2(MP2)	688
CCSD/6-311+G(d,p)//B3LYP/TZVP	703	G3(MP2)//B3LYP	689
HF/6-311+G(d,p)//HF/6-311+G(d,p)	706		

[a] Ref. 41.

Table 2. Calculated proton affinities (kJ mol^{-1}) of 2,3-butanedione

Method	PA	Method	PA	Method	PA
Experimental[a]	802	CCSD/6-311+G(d)//B3LYP/TZVP	762	B3LYP/TZVP//HF/6-311+G(d,p)	786
B3LYP/TZVP//B3LYP/TZVP	795	CCSD/6-311+G(d,p)//B3LYP/TZVP	792	B3LYP/6-311+G(d,p)//HF/6-311+G(d,p)	783
HF/6-311+G(d)//B3LYP/TZVP	770	HF/6-311+G(d)//HF/6-311+G(d)	775	B3LYP/6-311+G(d)//HF/6-311+G(d,p)	767
HF/6-311+G(d,p)//B3LYP/TZVP	791	MP2/6-311+G(d)//HF/6-311+G(d)	745	B3LYP/6-31G(d)//HF/6-311+G(d,p)	792
HF/6-311++G(d,p)//B3LYP/TZVP	792	MP4/6-311+G(d)//HF/6-311+G(d)	753	B3LYP/6-31G(d)//B3LYP/6-31G(d)	801
MP2/6-311+G(d)//B3LYP/TZVP	750	CCSD/6-311+G(d)//HF/6-311+G(d)	759	B3LYP/6-311+G(2df,2p)//B3LYP/6-31G(d)	796
MP2/6-311+G(d,p)//B3LYP/TZVP	781	B3LYP/TZVP//HF/6-311+G(d)	785	G2(MP2)	787
MP2/6-311++G(d,p)//B3LYP/TZVP	782	HF/6-311+G(d,p)//HF/6-311+G(d,p)	794	G3(MP2)//B3LYP	789
MP4/6-311+G(d)//B3LYP/TZVP	757	MP2/6-311+G(d,p)//HF/6-311+G(d,p)	775	CBS-4M	780
MP4/6-311+G(d,p)//B3LYP/TZVP	788	MP4/6-311+G(d,p)//HF/6-311+G(d,p)	783		
MP4/6-311++G(d,p)//B3LYP/TZVP	789	CCSD/6-311+G(d,p)//HF/6-311+G(d,p)	788		

[a] Ref. 41.

electron correlation effects in determination of PAs was already found by Nicholas and Haw[23] when they studied theoretically a wide variety of olefins and aromatics. The traditional ab initio methods, which take electron correlation into account (MP2, MP4, CCSD) give proton affinities of water in the range of 694–703 kJ mol^{-1}. The PAs depend only slightly on whether polarization functions on hydrogen have been used or not in the single-point calculation. For example, the difference between the values predicted by the CCSD/6-311+G(d,p)//B3LYP/TZVP and CCSD/6-311+G(d)//B3LYP/TZVP levels is 4 kJ mol^{-1}. The geometry optimization method (B3LYP/TZVP vs HF/6-311+G(d,p)) does not affect the results. The proton affinities estimated by Gaussian-*n* models (G1[42], G2[43], G2(MP2), G3(MP2)//B3LYP) are around 689 kJ mol^{-1}, that is, very close to the PA reported in the NIST Chemistry WebBook[41] (691 kJ mol^{-1}). Results at the B3LYP/TZVP//B3LYP/TZVP and B3LYP/6-311+G(2df,2p)//B3LYP/6-31G(d) levels are in agreement with the G*n* results. Instead, the HF/6-311+G(d,p)//HF/6-311+G(d,p) and B3LYP/6-31G(d)//B3LYP/6-31G(d) models predict too large values for the proton affinity of water.

3.2. Proton affinity of 2,3-butanedione

The proton affinities of 2,3-butanedione (Scheme 2) calculated using several theoretical methods are reported in Table 2. The PAs calculated at the B3LYP/TZVP//B3LYP/TZVP, B3LYP/6-31G(d)//B3LYP/6-31G(d) and B3LYP/6-311+G(2df,2p)//B3LYP/6-31G(d) levels (795, 801 and 796 kJ mol^{-1}, respectively) are in the closest agreement with the experimental[41] value of 802 kJ mol^{-1}. The compound methods G2(MP2) and G3(MP2)//B3LYP predict ca. 10 kJ mol^{-1} lower PAs, 787 and 789 kJ mol^{-1}. Also the MP4 and CCSD methods with the 6-311+G(d,p) basis set and the B3LYP/TZVP optimized structures and frequencies give proton affinities around 790 kJ mol^{-1} (788 and 792 kJ mol^{-1}, respectively). The PA suggested by CBS-4M (780 kJ mol^{-1}) is lower than the experimental value, too. As the G*n* and CCSD methods are expected to be very accurate, the obtained results imply that the experimental[41] PA of 2,3-butanedione is too high by 10–15 kJ mol^{-1}.

Unlike the proton affinity of water, the PA of 2,3-butanedione calculated with traditional ab initio methods depends considerably on the basis set used in the single-point energy calculation (see Table 2 and Fig. 3). With the 6-311+G(d) basis set, which includes polarization functions only on carbon and oxygen atoms (in the case of 2,3-butanedione), the PAs are evaluated to be ca. 20 kJ mol^{-1} (HF) and 30 kJ mol^{-1} (MP2, MP4, CCSD) lower than with the 6-311+G(d,p) basis set. This effect must solely be a consequence of the single-point energies of the protonated and unprotonated species since the molecular geometries and the zero-point and thermal corrections to the total energies are calculated at the same B3LYP/TZVP level. For example, the CCSD single-point (total) energy of the B3LYP/TZVP optimized 2,3-butanedione decreases by 116 kJ mol^{-1} when the basis set is changed from 6-311+G(d) to 6-311+G(d,p) while in the case of protonated 2,3-butanedione the corresponding energy decrease is 145 kJ mol^{-1}, that is, 29 kJ mol^{-1} more. This is a reasonable result since the inclusion of hydrogen polarization functions (i.e., the *p* functions) is expected to play a more important role in the energy of the protonated 2,3-butanedione than in the energy of the neutral species. The O–H$^+$ bond and the interaction between the O–H$^+$ hydrogen and, for example, the carbonyl oxygen atom is

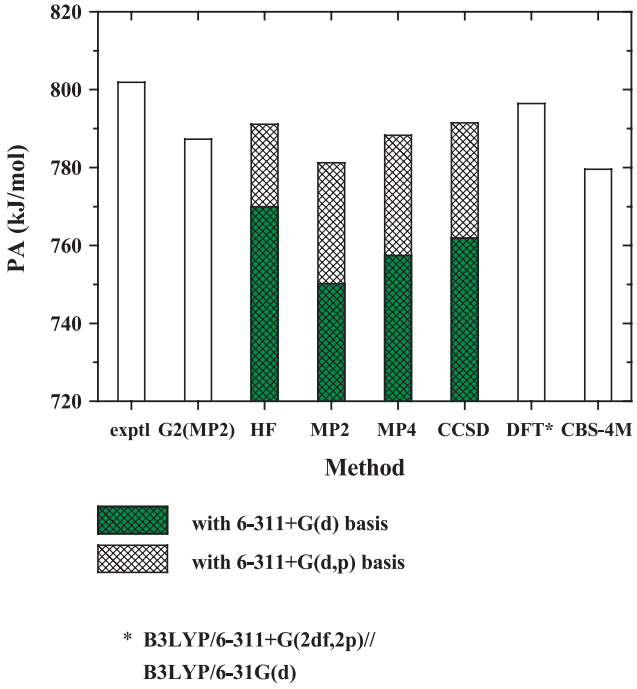


Figure 3. Proton affinity of 2,3-butanedione calculated with selected methods. The diagram shows clearly the considerable effect of the basis set on proton affinity.

Table 3. Proton affinities (kJ mol^{-1}) of some ketones, vicinal diketones, and α-keto esters computed with different methods

Method	Compound						
	Aceto-phenone	2,2,2-Tri-fluoroaceto-phenone	2,3-Butane-dione	1-Phenyl-1,2-propane-dione	Methyl-pyruvate	Ethyl benzoyl-formate	Ketopanto-lactone
Experimental[a]	861	799	802	—	—	—	—
B3LYP/TZVP//B3LYP/TZVP	875	811	795	838	818	880	817
HF/6-311+G(d)//B3LYP/TZVP	865	793	770	806	808	852	812
HF/6-311+G(d,p)//B3LYP/TZVP	883	811	791	825	828	870	832
MP2/6-311+G(d)//B3LYP/TZVP	821	756	750	780	777	820	774
MP2/6-311+G(d,p)//B3LYP/TZVP	848	785	781	812	808	850	805
MP4/6-311+G(d)//B3LYP/TZVP	827	—	757	—	784	—	780
CCSD/6-311+G(d)//B3LYP/TZVP	836	—	762	—	798	—	791
CCSD/6-311+G(d,p)//B3LYP/TZVP	863	797	792	821	821	n.a.	820
B3LYP/6-31G(d)//B3LYP/6-31G(d)	879	829	801	864	826	891	823
B3LYP/6-311+G(2df,2p)//B3LYP/6-31G(d)	876	816	796	857	820	881	820
G2(MP2)	857	n.a.	787	n.a.	815	n.a.	816
CBS-4M	845	783	780	829	799	851	802

Not available (n.a.) due to computational cost.
[a] Ref. 41.

described satisfactorily only if the polarization functions are used on hydrogen. However, diffuse functions are not required on hydrogen since the proton affinity of 2,3-butanedione increases only by ca. 1 kJ mol^{-1} if the basis set in single-point calculations is changed from 6-311+G(d,p) to 6-311++G(d,p) (see Table 2). This is reasonable because the evaluation of the PA of 2,3-butanedione does not include any calculations of species such as anions, highly excited electronic states or loose supermolecular complexes where the diffuse functions are necessary in basis sets to allow a weakly bound electron to localize far from the remaining density.[21]

Let us now have a look at what kind of effect the computational methods and the basis sets have on ΔE_0^{vib} and $\Delta E^{vib}(T)$ of 2,3-butanedione, that is, the zero-point vibrational energy change $[=E_0^{vib}(AH^+)-E_0^{vib}(A)]$ and the change in the thermal corrections to the vibrational energy $[=E^{vib}(AH^+, T)-E^{vib}(A, T)]$ in Eq. 2. The unscaled values for ΔE_0^{vib} and $\Delta E^{vib}(298.15\ K)$ are, respectively, 31.2 and 0.0 kJ mol^{-1} (B3LYP/TZVP), 31.1 and 0.0 kJ mol^{-1} [B3LYP/6-31G(d)], 35.1 and 0.4 kJ mol^{-1} [HF/6-311+G(d)], as well as 34.7 and 0.4 kJ mol^{-1} [HF/6-311+G(d,p)]. These values suggest that the computational method (DFT/B3LYP vs HF) has a more important effect on both ΔE_0^{vib} and $\Delta E^{vib}(T)$ than the basis set does. This is evidently true as long as the various basis sets lead to the same molecular geometry.

3.3. Proton affinities of the other compounds

The proton affinities of all ketones, vicinal diketones and α-keto esters studied in this work (Scheme 2) are reported in Table 3. Some of the results are also shown graphically (Fig. 4) to make comparison easier. Previously reported (experimental) PAs exist only for 2,3-butanedione, acetophenone and 2,2,2-trifluoroacetophenone.[41] Excluding the proton affinity of 2,3-butanedione, the B3LYP/TZVP//B3LYP/TZVP and B3LYP/6-311+G(2df,2p)//B3LYP/6-31G(d) model chemistries result in 12–17 kJ mol^{-1} higher PAs than observed experimentally. The largest overestimates are given at the B3LYP/6-31G(d)//B3LYP/6-31G(d) level; the proton affinity of 2,2,2-trifluoroacetophenone is calculated to be 829 kJ mol^{-1}, which is 30 kJ mol^{-1} higher than the previously reported value.[41] Excellent agreement is obtained between the experimental result for acetophenone (861 kJ mol^{-1}) and the CCSD/6-311+G(d,p)//B3LYP/TZVP as well as the G2(MP2) calculations (863 and 857 kJ mol^{-1}, respectively). Also the PA of acetophenone evaluated at the HF/6-311+G(d)//B3LYP/TZVP level of theory (865 kJ mol^{-1}) is close to the

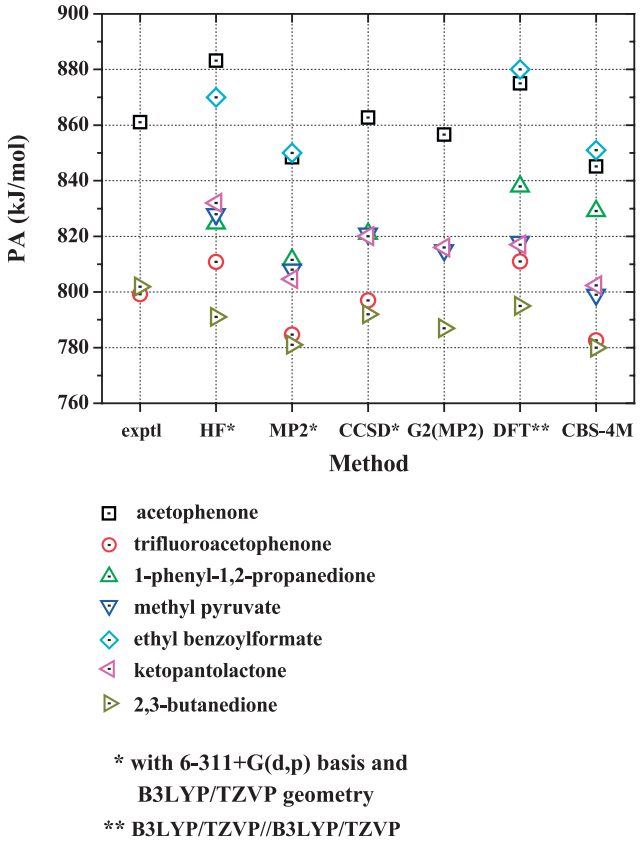


Figure 4. Some experimental and calculated proton affinities of the ketones, vicinal diketones and α-keto esters studied in this work. The figure shows, for example, that the PAs predicted by the CCSD and G2(MP2) methods lie between those given by MP2 and DFT.

experimental value. However, this has to be due to a favourable cancellation of errors because the same model with an extended basis set [6-311+G(d,p)] in the single-point calculation overestimates the proton affinity by 22 kJ mol^{-1}. It is often the case that basis set incompleteness and failure to account for electron correlation introduce errors of opposite sign.[21] If those errors are also of similar magnitude, then fortuitously good results can be obtained.

As was already observed for 2,3-butanedione, the proton affinities of all molecules in Table 3 calculated with traditional ab initio methods (HF, MP2, CCSD) depend considerably on the basis set that is used in the single-point energy calculation; the change of the basis set from 6-311+G(d) to 6-311+G(d,p) increases the PA of the studied molecules by ca. 20–30 kJ mol^{-1}. The 6-311+G(d) basis set is obviously not adequate in these calculations and therefore, we have not evaluated the PAs of some compounds at the MP4/6-311+G(d)//B3LYP/TZVP and CCSD/6-311+G(d)//B3LYP/TZVP levels of theory. From Table 3 it is also noted that the model chemistries B3LYP/TZVP//B3LYP/TZVP and B3LYP/6-311+G(2df,2p)//B3LYP/6-31G(d) predict proton affinities, which differ just a few kJ mol^{-1} from each other. A similar trend is observed for the PAs evaluated by the MP2/6-311+G(d,p)//B3LYP/TZVP and CBS-4M calculations. The only exception to these observations is caused by the PA of 1-phenyl-1,2-propanedione. For example, CBS-4M calculation suggests a proton affinity (829 kJ mol^{-1}), that is 17 kJ mol^{-1} higher than the MP2 value (812 kJ mol^{-1}). A possible explanation for this is that the CBS-4M method predicts a planar conformation for 1-phenyl-1,2-propanedione (with respect to heavy atoms, remember that the geometry optimization is done at the HF/3-21G(d) level) whereas the torsional angle of the O=C–C=O system in the molecule is ca. 135° according to the B3LYP/TZVP level and previous experimental and theoretical studies.[44,45] However, a similar phenomenon is not observed in the case of the proton affinity of ethyl benzoylformate although the CBS-4M model again predicts a planar equilibrium structure, which is far from the optimal geometry evaluated at the B3LYP/TZVP level [the torsional angle D(O=C–C=O)=118°]. The B3LYP/6-31G(d) level of theory gives ca. 20° larger value for D(O=C–C=O) in 1-phenyl-1,2-propanedione and ethyl benzoylformate than the B3LYP/TZVP level does.

Investigation of the components contributing to PA (see Eq. 2) reveals that the $\Delta E_0^{\mathrm{vib}}$ term is of the same size (ca. 30 kJ mol^{-1} or slightly higher) for almost all molecules studied, irrespective of whether it is calculated at the B3LYP/TZVP or B3LYP/6-31G(d) level. Since the absolute value of the $\Delta E^{\mathrm{vib}}(T)$ term is small (<2 kJ mol^{-1}), the differences in proton affinities are almost entirely governed by the electronic energy term, ΔE_0^{el}. 1-phenyl-1,2-propanone is the only exception. In this case, $\Delta E_0^{\mathrm{vib}}$ is 54 kJ mol^{-1} at the B3LYP/TZVP level but conventional 35 kJ mol^{-1} at the B3LYP/6-31G(d) level (these are unscaled values), which explains why the B3LYP/6-311+G(2df,2p)//B3LYP/6-31G(d) method predicts 19 kJ mol^{-1} higher proton affinity than the B3LYP/TZVP//B3LYP/TZVP method does.

Although the proton affinity of a molecule depends considerably on the computational method in some cases, it is interesting to note that with only a few exceptions the differences between the PAs of various molecules are approximately the same regardless of the method applied (Fig. 4). It is seen, for example, that the PA of acetophenone is higher than the PA of methyl pyruvate by 42 kJ mol^{-1} [G2(MP2)], 42 kJ mol^{-1} [CCSD/6-311+G(d,p)//B3LYP/TZVP], 40 kJ mol^{-1} [MP2/6-311+G(d,p)//B3LYP/TZVP], 57 kJ mol^{-1} (B3LYP/TZVP//B3LYP/TZVP), and 46 kJ mol^{-1} (CBS-4M). This behaviour allows us to evaluate the proton affinities of those compounds, for which there is no experimental data available. Of course, methods such as CCSD/6-311+G(d,p)//B3LYP/TZVP, G2(MP2), and G3(MP2)//B3LYP are expected to predict proton affinities with high accuracy but these methods are computationally very expensive and thus, not practical for studies of 'large' molecules, especially with desktop computers. For example, the G2(MP2) calculation on protonated acetophenone takes ca. 12 times more cpu time and needs ca. 200 times more disk space (total of 20 GB) than the B3LYP/TZVP//B3LYP/TZVP calculation. The CCSD/6-311+G(d,p) single point calculations on 1-phenyl-1,2-propanedione and 2,2,2-trifluoroacetophenone take ca. 80 and 90 GB disk space, respectively, while the largest molecule studied, ethyl benzoylformate with 13 heavy atoms, needs ca. 150 GB disk space!

Table 3 shows that the proton affinities given by the B3LYP/6-311+G(2df,2p)//B3LYP/6-31G(d) and CBS-4M models represent the upper and lower limits, respectively, of the experimental proton affinities as well as the PAs calculated with the CCSD/6-311+G(d,p)//B3LYP/TZVP and G2(MP2) methods (i.e., the most probable PAs), and that the average difference between them is 25 kJ mol^{-1}. We have shown, however, that the CBS-4M model has problems in predicting some molecular structures. Therefore, the MP2/6-311+G(d,p)//B3LYP/TZVP method is regarded as a more reliable candidate for representing the lower limit of PA for the molecules studied in this work. For the evaluation of the upper limit one can equally use the B3LYP/TZVP//B3LYP/TZVP method instead of the B3LYP/6-311+G(2df,2p)//B3LYP/6-31G(d) method. The average difference between the proton affinities predicted by the B3LYP/TZVP//B3LYP/TZVP and MP2/6-311+G(d,p)//B3LYP/TZVP models is 21 kJ mol^{-1}. It is suggested that the proton affinities of compounds similar to those studied in this paper and without any experimental or highly accurate theoretical data available can be evaluated by taking the average value of the proton affinities calculated with these models. This procedure should give a reliable estimate of the 'true' proton affinity quickly and efficiently. In Table 4 we have reported the PAs of various compounds evaluated with this combination method, which is referred to as ½(DFT+MP2). As can be seen, these PAs are in close agreement with the PAs calculated with the high level CCSD/6-311+G(d,p)//B3LYP/TZVP and G2(MP2) model chemistries.

3.4. Performance of the combination method

The combination method ½(DFT+MP2) we have suggested for predicting PAs computationally works

Table 4. Calculated and some experimental proton affinities (kJ mol^{-1}) of the reactants in increasing order and experimental values for ee (%) in acetic acid and in toluene

Method	Compound						
	2,3-Butane-dione	2,2,2-Tri-fluoroaceto-phenone	Ketopanto-lactone	Methyl-pyruvate	1-Phenyl-1, 2-propane-dione	Aceto-phenone	Ethyl benzoyl-formate
Experimental[a]	802	799	—	—	—	861	—
½(DFT+MP2)[b]	788	798	811	813	825	862	865
CCSD/6-311+G(d,p)//B3LYP/TZVP	792	797	820	821	821	863	n.a.
G2(MP2)	787	n.a.	816	815	n.a.	857	n.a.
ee in AcOH	14[c]	92[d,e]	35[f]	90[g]	6[h]	—	95[i]
ee in toluene	47[c]	62[d]	79[f]	74[g]	65[h]	17[j]	98[k]

Not available (n.a.) due to computational cost.
[a] Ref. 41.
[b] The combination method as described in the text. The proton affinity of a molecule is evaluated as the average of the PAs calculated with the B3LYP/TZVP//B3LYP/TZVP and MP2/6-311+G(d,p)//B3LYP/TZVP methods.
[c] Ref. 50.
[d] Ref. 51.
[e] Toluene with some trifluoroacetic acid (the molar ratio trifluoroacetic acid/cinchonidine=9.6).
[f] Ref. 8.
[g] Ref. 52.
[h] Ref. 9.
[i] Ref. 54.
[j] Ref. 53.
[k] Ref. 55.

reasonably well, at least for the seven molecules studied previously (Table 4). To get a better picture of the performance of the model, it was applied to 11 additional compounds, for which there exist experimental[41] proton affinities. Thus, our final test set consists of the 8 proton affinities in the G3/99 test set[46] and the 6 PAs of compounds with a carbonyl group (formaldehyde, acetaldehyde, 2-propanone, acetophenone, 2,2,2-trifluoroacetophenone and 2,3-butanedione). The experimental PAs together with the calculated ones (at 298.15 K) are given in Table 5. A summary of the mean absolute deviations for the DFT, MP2 and combination methods is given in Table 6.

The B3LYP functional works well for the molecules in the G3/99 test set; the mean absolute deviation (MAD) from the experimental PAs is only 2.9 kJ mol^{-1}. This is not surprising since the B3LYP functional uses parameters fitted to the data in the previous G2 test set,[42] which contains seven of the eight proton affinities in the G3/99 test set. For carbonyl oxygen bases (i.e., compounds with a C=O group) the B3LYP functional performs slightly worse and generally overestimates the PAs by ca. 10 kJ mol^{-1}; the MAD is 9.1 kJ mol^{-1} for all carbonyl oxygen bases and 7.9 kJ mol^{-1} for carbonyl oxygen bases without 2,3-butanedione. As mentioned above, the experimental PA of 2,3-butanedione is very likely 10–15 kJ mol^{-1} too high and that increases the MAD of all computational results notably.

The results given by the combination method ½(DFT+MP2), by which we mean the average of the proton affinities evaluated at the B3LYP/TZVP//B3LYP/TZVP and MP2/6-311+G(d,p)//B3LYP/TZVP levels, are very close to the experimental ones. This method seems to work especially well for the carbonyl oxygen bases we have studied; the

Table 5. Calculated proton affinities and their deviations from experiment[a]

Species	Proton affinity				Deviation		
	Exptl[b]	DFT[c]	MP2[d]	½(DFT+MP2)	DFT[c]	MP2[d]	½(DFT+MP2)
NH_3	853.6	856.2	861.8	859.0	−2.6	−8.2	−5.4
H_2O	691.0	691.7	696.0	693.9	−0.7	−5.0	−2.9
C_2H_2	641.4	645.6	638.9	642.3	−4.2	2.5	−0.9
SiH_4	639.7	642.8	646.1	644.5	−3.1	−6.4	−4.8
PH_3	785.0	785.8	806.0	795.9	−0.8	−21.0	−10.9
SH_2	705.0	707.3	722.9	715.1	−2.3	−17.9	−10.1
ClH	556.9	552.8	569.5	561.2	4.1	−12.6	−4.3
H_2	422.3	416.9	421.5	419.2	5.4	0.8	3.1
HCHO	712.9	711.2	707.0	709.1	1.7	5.9	3.8
CH_3CHO	768.5	778.3	764.2	771.3	−9.8	4.3	−2.8
CH_3COCH_3	812.0	822.5	806.0	814.3	−10.5	6.0	−2.3
Acetophenone	861.1	874.5	848.4	861.5	−13.4	12.7	−0.4
2,2,2-Trifluoroacetophenone	799.2	811.2	784.7	798.0	−12.0	14.5	1.3
2,3-Butanedione	801.9	794.7	781.2	788.0	7.2	20.7	13.9

All values in kJ mol^{-1}.
[a] Deviation=experiment−theory.
[b] Ref. 41.
[c] B3LYP/TZVP//B3LYP/TZVP.
[d] MP2/6-311+G(d,p)//B3LYP/TZVP.

Table 6. Mean absolute deviations from experimental proton affinities (kJ mol^{-1}) for the DFT[a], MP2[b], and combination methods

Test set	DFT[a]	MP2[b]	½(DFT+MP2)
G3/99 (8)	2.9	9.3	5.3
Carbonyl oxygen bases in Table 5 (6)	9.1	10.7	4.1
Carbonyl oxygen bases without 2,3-butanedione (5)	7.9	7.2	1.7
All molecules (14)	5.6	9.9	4.8
All without 2,3-butanedione (13)	5.4	9.1	4.0
Molecules containing first-row atoms without 2,3-butanedione (9)	6.7	6.7	2.5

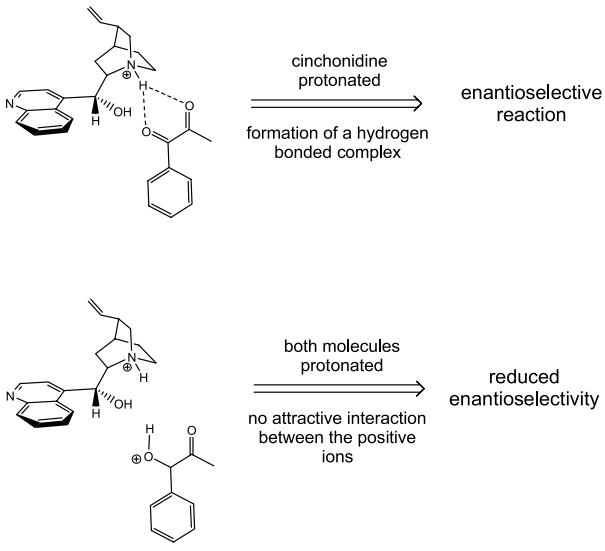
[a] B3LYP/TZVP//B3LYP/TZVP.
[b] MP2/6-311+G(d,p)//B3LYP/TZVP.

mean absolute deviation is just 1.7 kJ mol^{-1} if the PA of 2,3-butanedione is excluded. The MAD from the PAs in the G3/99 test set[46] is higher, 5.3 kJ mol^{-1}, mainly because the MP2/6-311+G(d,p)//B3LYP/TZVP method overestimates the PAs of PH_3, SH_2, and ClH by 13–21 kJ mol^{-1}. If all 14 molecules in our test set are considered, the MAD is the lowest for the ½(DFT+MP2) method (4.0 kJ mol^{-1} if 2,3-butanedione is excluded) and slightly higher for the B3LYP/TZVP//B3LYP/TZVP model. For 9 molecules composed only of first-row atoms the MAD for the combination method is 2.5 kJ mol^{-1}, which is 4.2 kJ mol^{-1} lower than the MADs for either the B3LYP/TZVP//B3LYP/TZVP or MP2/6-311+G(d,p)//B3LYP/TZVP methods. Based on these results, it is suggested that the combination method ½(DFT+MP2) can be used to get reliable approximations for the PAs of similar compounds as studied in this paper.

3.5. Implications on enantioselective hydrogenation over the Pt/Cinchonidine system

The most widely accepted mechanistic models postulate that a one-to-one hydrogen bonded complex between cinchonidine and the reactant is the source of enantiodifferentiation in the catalytic hydrogenation reaction (Orito reaction[1], Scheme 1). Interactions between protonated cinchonidine and substrates have been investigated theoretically by ab initio methods, for example, for methyl pyruvate,[47,48] 1-phenyl-1,2-propanedione,[9] and ketopantolactone.[47] As long as proton donors are available the protonation of the quinuclidine *N* of cinchonidine is very likely due to its high proton affinity (ca. 1000 kJ mol^{-1}),[9] which is about 150 kJ mol^{-1} higher than the PA of ammonia. Under typical experimental conditions the proton donors could be, for example, traces of water as an impurity in the aprotic solvent (e.g., toluene), the protic solvent (e.g., acetic acid, trifluoroacetic acid), adsorbed hydrogen on Pt or acidic sites on the Al_2O_3 or SiO_2 support commonly used in the experiments.

The proton affinity of cinchonidine is 130–200 kJ mol^{-1} higher than the PA of any of the reactants (Table 4) indicating that the modifier has higher affinity towards protonation than any reactant considered and is protonated first under reaction conditions if proton donors are available. Further protonation of the substrate molecule would lead to a non-favourable situation with respect to the attractive modifier-substrate interaction as the protonated substrate molecule cannot interact with the already protonated modifier due to the repulsion of positive charges—at least not that easily. This weakened interaction between the modifier and the reactant could lead to reduced ee (under such conditions that the reactants can be protonated as well). The idea is clarified in Scheme 3. If the enantioselectivity of the hydrogenation reaction is influenced by the proton affinity of the reactant molecule, in protic solvent the ee is expected to decrease as the PA of the reactant increases. The higher the PA of the reactant is, the more there are protonated reactant molecules in acidic media. They are not expected to react enantioselectively but lead to a racemate of the (*R*)- and (*S*)-product enantiomers thus lowering the observed ee. The protonation of the reactant could be a contributing factor, for example, for the decrease of ee in ethyl pyruvate hydrogenation observed in stronger acids than trifluoroacetic acid.[49] However, comparison of the proton affinities with the ees observed experimentally in the enantioselective hydrogenation of the reactants over cinchonidine modified platinum surface in toluene and in acetic acid[8,9,50–55] (Table 4) reveals that PA alone cannot be utilized to rationalize solvent effects in the inherently complex asymmetric hydrogenation, where many other factors, such as modifier conformation, adsorption mode etc., may contribute simultaneously to the observed ee.



Scheme 3. A possible reason for reduced enantioselectivity in protic solvent. Protonation of both the modifier and the reactant in acidic solvent hinders the formation of a reactant–modifier complex, which is believed to be crucial for enantiodiscrimination.

4. Conclusions

In this study, fundamental knowledge of the acid–base properties of some ketones, vicinal diketones and α-keto esters, commonly used as reactants in the enantioselective

hydrogenation over chirally modified platinum surface, was reported. The calculated gas-phase proton affinities (PAs) at 298.15 K varied between 750–890 kJ mol^{-1} depending on the molecule and the model chemistry applied. We noted that in order to get reliable results, electron correlation had to be modelled very accurately. It is essential that the basis set used in the calculations includes polarization functions on all atoms. The CCSD/6-311+G(d,p)//B3LYP/TZVP, G2(MP2) and G3(MP2)//B3LYP models gave PAs with the lowest absolute deviation from experimental ones. However, these models are computationally very expensive and therefore, not practical for molecules with more than about 12 heavy atoms. On the other hand, the CBS-4M, B3LYP/6-311+G(2df,2p)//B3LYP/TZVP, B3LYP/TZVP//B3LYP/TZVP and MP2/6-311+G(d,p)//B3LYP/TZVP methods are computationally much less demanding and can be applied to larger molecules but they may suffer from inaccuracy. The results showed, however, that in the studied molecular systems the CBS-4M, MP2, and hybrid DFT methods are competitive with the expensive G2(MP2), MP4, and CCSD methods. Very accurate predictions for the proton affinities can be made if they are evaluated as the average of the PAs calculated with the B3LYP/TZVP//B3LYP/TZVP and MP2/6-311+G(d,p)//B3LYP/TZVP models. For this combination method, the mean absolute deviation from the experimental PAs of 13 test molecules containing first- and second-row atoms is 4.0 kJ mol^{-1}.

Comparison of the experimentally observed ees in acetic acid and in toluene with the calculated proton affinities of the reactants revealed that the positive or negative influence of acetic acid on the ee cannot straightforwardly be correlated with the PA. This implies that the decrease of ee in acidic media, for example, in the case of ketopantolactone and vicinal diketones, cannot solely be explained by simultaneous protonation of both the modifier and the substrate molecules that would hinder the important substrate–modifier (attractive) interactions and, consequently, would result in racemic rather than enantioselective reaction. Nevertheless, proton affinities play an important role in fundamental understanding of the solute–solvent interactions and they are required to explain solvation and solvent effects in enantioselective hydrogenation as well.

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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.2005.06.049. The minimum energy geometries of the protonated and unprotonated molecules studied in this work (Scheme 2) are provided as Gaussian output files. The structures have been optimized at the B3LYP/TZVP level of theory. They can be viewed, for example, with Molden[35] molecular visualization program. The supplementary data also contains Gaussian output files of all competing structural and conformational isomers of the protonated molecules, which were considered as well as a table showing the relative stabilities of the various structures.

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Synthesis of 2-azaspiro[4.4]nonan-1-ones via phosphine-catalysed [3+2]-cycloadditions

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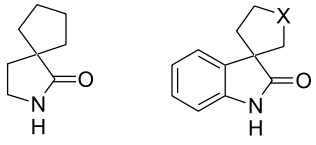
Abstract—The phosphine-catalyzed [3+2]-cycloaddition of the 2-methylene γ-lactams **4** and **5** and the acrylate **6** with the ylides derived from the ethyl ester, the amide or the chiral camphor sultam derivative of 2-butynoic acid (**7a–c**) give directly, or indirectly after reductive cyclization, spiro-heterocyclic products. The acid **32** underwent Curtius rearrangement and then acid hydrolysis to give two novel spirocyclic ketones, **41** and **42**.

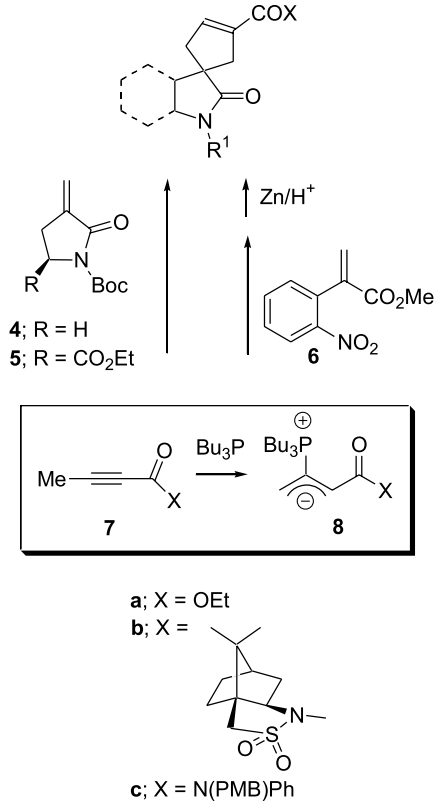
1. Introduction

The 2-azaspiro[4.4]nonan-1-one structure (**1**) is found in several bioactive natural products, including alkaloids, where it forms part of a spiro[cyclopentane-1,1′-[1H]isoindol]-3′(2′H)-one (**2**) or spiro[3H-indole-3,3′-pyrrolidin]-2(1H)-one (**3**) ring system.[1,2]



1 **2**; X = CH_2 **3**; X = NH

We report here, a new strategy for the synthesis of both racemic and enantio-enriched versions of the 2-azaspiro-[4.4]nonan-1-one and spiro[cyclopentane-1,1′-[1H]isoindol]-3′(2′H)-one ring systems using the phosphine-catalyzed [3+2]-cycloaddition of the ethyl ester (**7a**), the chiral camphor sultam (**7b**) or the amide (**7c**) derivative of 2-butynoic acid with either 2-methylene γ-lactams **4** or **5** or the acrylate **6**, followed by reductive cyclization with zinc (Scheme 1). Enantiomerically enriched versions of **2** can be obtained using or the chiral (1*S*)-camphor sultam analogue



Scheme 1.

Keywords: Phosphine-catalyzed; [3+2]-Cycloaddition; 2-Methylene γ-lactams; Spiro-heterocyclics; Curtius rearrangement.
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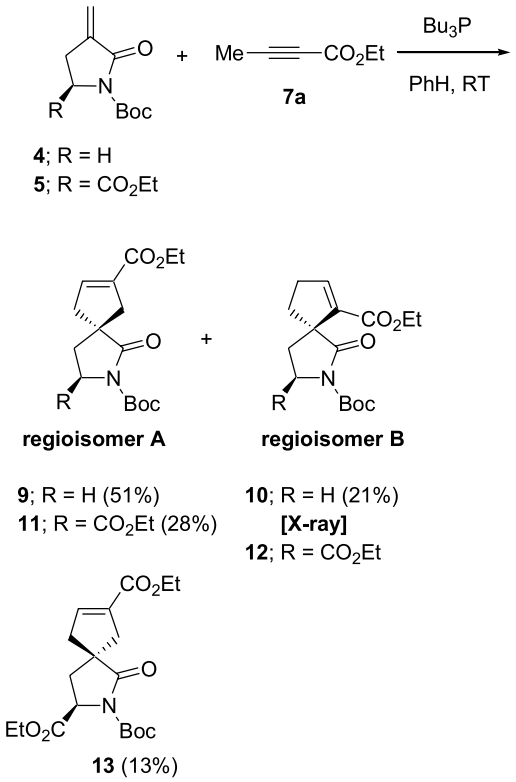
7b to generate the key spiro-heterocyclic system of these target molecules (Scheme 1). The phosphine-catalyzed cycloaddition of ethyl buta-2,3-dienoate or ethyl 2-butynoate with electron-deficient alkenes has been established as a useful method for preparing substituted cyclopentenes[3–13] both in racemic and enantio-enriched forms.[14] However, only a few examples of preparing spiro-heterocyclic derivatives using this method have been reported.[7,11–13] During the initial phase of our study, Lu et al. reported the triphenylphosphine-catalyzed cycloaddition reaction of **4** and **7a**.[13]

2. Results and discussion

The results of the phosphine-catalyzed [3+2]-cycloaddition reactions of the 2-methylene γ-lactams **4** and **5** with the ylide **8a** (X=OEt), that was generated in situ from the reaction of ethyl 2-butynoate **7a** and tributylphosphine (TBP) are shown in Scheme 2. The reaction of **4**[13] with ethyl 2-butynoate (2 equiv) and TBP (1 equiv) in benzene solution at rt for 15 h gave a mixture (ca. 80:20) of two racemic regio-isomeric cycloadducts, **9** and **10**, that were isolated in yields of 51 and 21%, respectively, after column chromatography. We found that the use of a stoichiometric amount of TBP was required to obtain a good conversion to **9** and **10**. The structures of **9** and **10** were confirmed by extensive 2D NMR experiments and the structure of **10** was established by single-crystal X-ray structural analysis (Fig. 1).[15] The spectroscopic data of these compounds agreed well with that reported by Lu et al.[13] who reported a combined yield for **9** and **10** (dr=62:38) of only 33% when the more hindered and less nucleophilic catalyst, triphenyl-



Scheme 2. Compounds **9** and **10** are racemic.

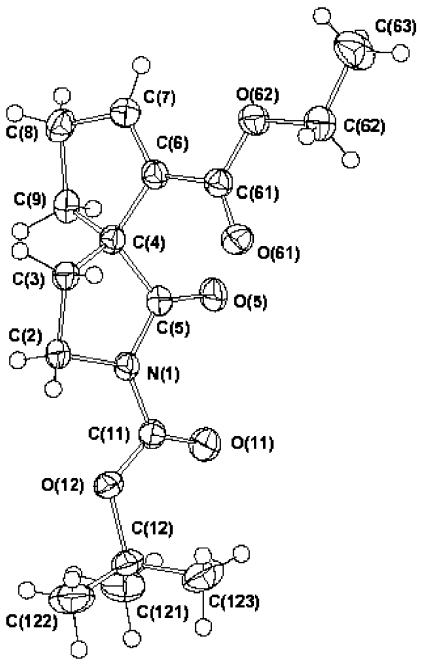
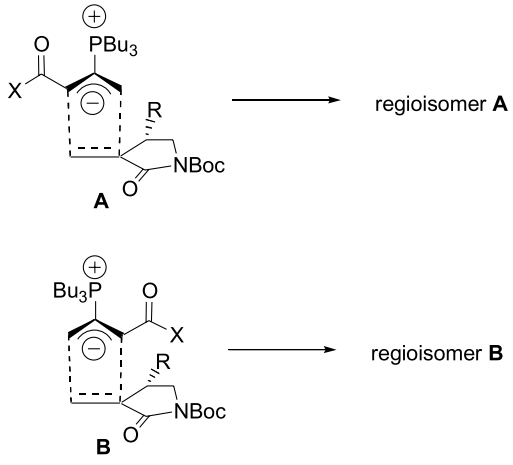


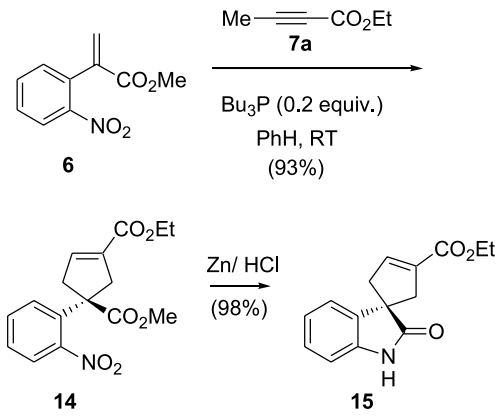
Figure 1. Molecular projection of **10**.

phosphine (0.1 equiv), was employed. Based on steric considerations alone, the regiochemical outcome of this reaction can be rationalised as occurring via the transition state **A** (R=H, X=OEt), which would be expected to be favoured over the more sterically demanding transition state **B** (R=H, X=OEt, Scheme 3).[12,13]

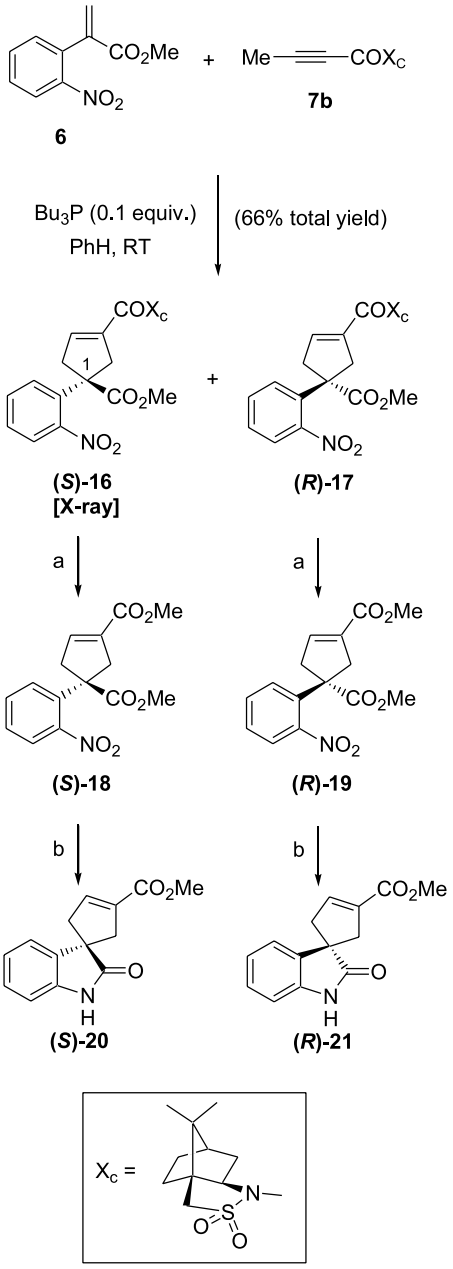


Scheme 3.

Under similar conditions the chiral 2-methylene γ-lactam **5**[16] reacted with the ylide **8a** (X=OEt) to produce three cycloadducts, **11**, **12** and **13**, in a ratio of 63:17:30, respectively, from ^{1}H NMR analysis of the crude reaction mixture (Scheme 2). Diastereomerically pure samples of **11** (28% yield) and **13** (13% yield) could be obtained after extensive purification, however, a pure sample of **12** could not be obtained due to difficulties in separating **12** from **11** and **13**. Although the absolute stereochemistries of **11** and **13** could not be unequivocally proven from 2D NMR experiments we assume that the major cycloadduct



Scheme 4. Compounds **14** and **15** are racemic.



Scheme 5. Reagents and conditions: (a) $Sm(OTf)_3$ (1 equiv), MeOH, 50 °C, 18 h, 67% ((*S*)-**18**), 68% ((*R*)-**19**); (b) Zn dust (24 equiv), 8.9 M HCl, $MeOH/H_2O$, reflux, 2 h, 69% ((*S*)-**20**), 56% ((*R*)-**21**).

11 arises from attack of the ylide onto the face of the 2-methylene group of **5** that is *anti* to the ethyl ester substituent (via transition state **A**, R=CO_2Et, X=OEt, Scheme 3).

Treatment of ethyl 2-(2-nitrophenyl)propenoate **6**[17] with ethyl 2-butynoate **7a** and TBP (0.2 equiv) gave the racemic cycloadduct **14** as a single regio-isomer in 93% yield (Scheme 4). Upon exposure to zinc/aqueous HCl, **14** underwent reductive cyclization to give the spiro[cyclopentane-1,1′-[1H]isoindol]-3′(2′H)-one derivative **15** in 98% yield (Scheme 4).

In order to prepare enantiomerically enriched versions of **15**, the corresponding cycloaddition reaction of **6** with the chiral alkyne **7b**, derived from Oppolzer's (1*S*)-chiral sultam,[18] was examined (Scheme 5). This reaction produced a 3.3:1 mixture of the diasteromeric cycloadducts **16** and **17** from, which pure samples could be obtained after column chromatography, along with mixed fractions in a combined yield of 66% (Scheme 5). The absolute (1*S*)-configuration of the cyclopentane ring of **16** ($[\alpha]_D^{26}$ −22.0 (*c* 0.3, $CHCl_3$)) was established by a single-crystal X-ray structural analysis, (Fig. 2)[15] which then allowed assignment of the 1*R*-configuration to this ring of the minor diastereomer **17** ($[\alpha]_D^{24}$ +19.0 (*c* 0.6, $CHCl_3$)). The chiral auxiliary was then removed by methanolysis of (*S*)-**16** and (*R*)-**17** in the presence of samarium(III) triflate[19] to give the methyl esters, (−)-(*S*)-**18** and (+)-(*R*)-**19** in yields of 67 and 68%,

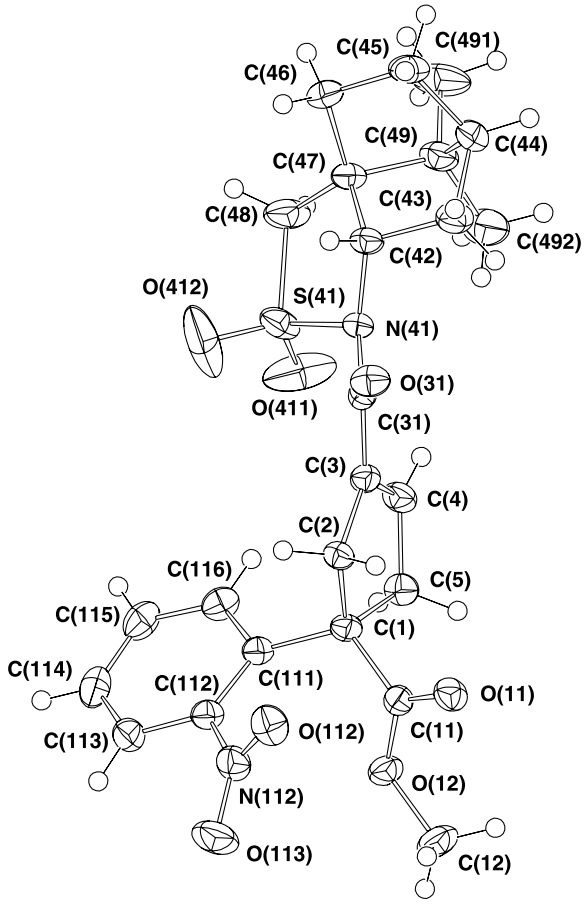
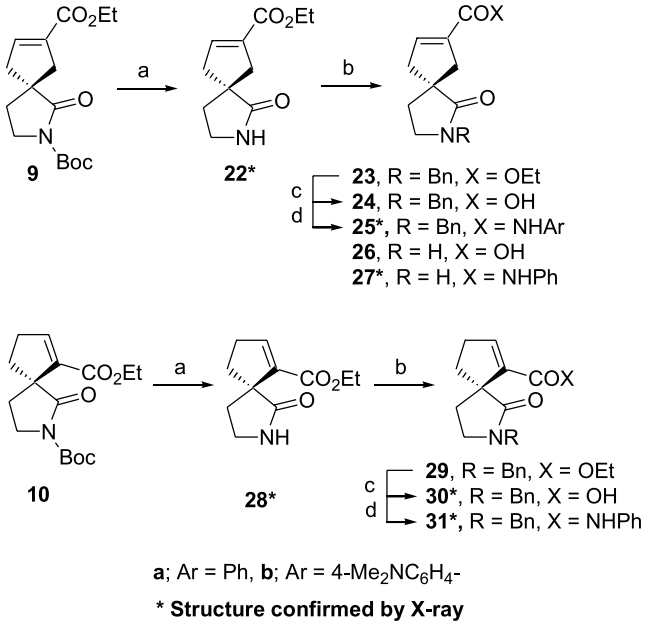


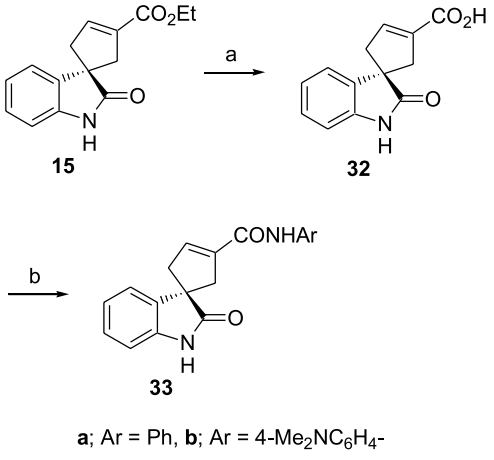
Figure 2. Molecular projection of **16**.

respectively. Reductive cyclization of (−)-(*S*)-**18** or (+)-(*R*)-**19** by treatment with zinc/aqueous HCl gave the tricyclic lactams, (−)-(*S*)-**20** or (+)-(*R*)-**21**, respectively (Scheme 5).

The spiro-cyclic compounds **9**, **10** and **15** have three functional groups that can be further derivatised to provide compounds with increased structural diversity. For example, the *N*-Boc protecting group in racemic **9** and **10** was readily removed upon exposure to trifluoroacetic acid (TFA) to give compounds **22** and **28**, respectively (Scheme 6). Both compounds gave single crystals for X-ray structural analysis (not shown).[15] The nitrogen atom of **22** and **28** was readily *N*-benzylated with benzyl bromide under



Scheme 6. All compounds are racemic. Reagents and conditions: (a) TFA, DCM, 2.5 h, 91% (**22**), 86% (**28**); (b) NaH (1.3 equiv), Bu_4NI (0.1 equiv), BnBr (1.5 equiv), dry THF, rt, 1–5 h, 74% (**23**), 47% (**29**); (c) K_2CO_3 (2 equiv), MeOH/H_2O, high pressure tube, 60 °C, 1 day, 93% (**24**), 53% (**26**), 80% (**30**); (d) aniline or 4-*N*,*N*-dimethylaminoaniline (1.2 equiv), HOBT (1 equiv), EDCI (1 equiv), dry MeCN, 0–60 °C, 1–2 days, 54% (**25a**), 64% (**25b**), 91% (**27**), 91% (**31a**).

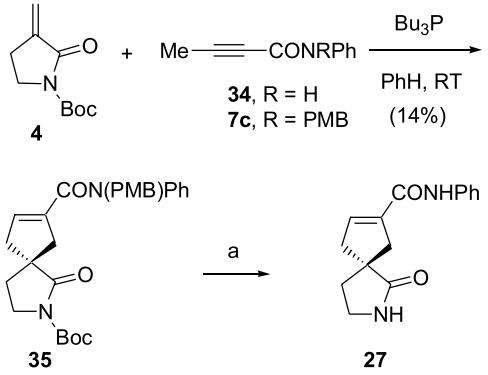


Scheme 7. All compounds are racemic. Reagents and conditions: (a) K_2CO_3 (2 equiv), MeOH/H_2O, high pressure tube, 60 °C, 5 h, 94%; (b) aniline or 4-*N*,*N*-dimethylaminoaniline (1.7 equiv), HOBT (1 equiv), EDCI (1 equiv), MeCN, 0 °C→rt, 15 h, 92% (**33a**), 44% (**33b**).

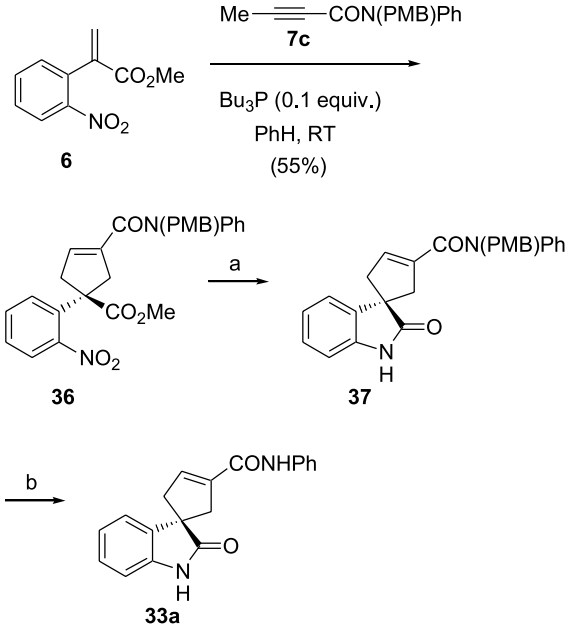
basic conditions and the resulting compounds **23** and **29**, respectively, were converted to the *N*-aryl amide derivatives **25a**,**b**[15] and **31a**, respectively, through amide bond formation between their respective carboxylic acids, **24** and **30**[15] and aniline and 4-*N*,*N*-dimethylaminoaniline (Scheme 6). Amide **27**[15] was obtained from the coupling reaction of aniline and the carboxylic acid **26** obtained from base catalyzed hydrolysis of ester **22**.

Using related chemistry, the ester **15** was converted to the *N*-aryl amides **33a**,**b** via the carboxylic acid **32** (Scheme 7).

To explore a more direct method to these *N*-aryl amide derivatives, the phosphine-catalyzed [3+2]-cycloaddition reactions of the 2-methylene γ-lactam **4** and acrylate **6** with the ylide **8** (X=NHPh), that was generated in situ from the reaction of *N*-phenyl 2-butynamide **34**, was examined (Schemes 8 and 9). These reactions were unsuccessful, presumably due to internal quenching of the ylide **8** (X=NHPh) by the relatively acidic secondary amide NH. In accordance with this hypothesis was the fact that the



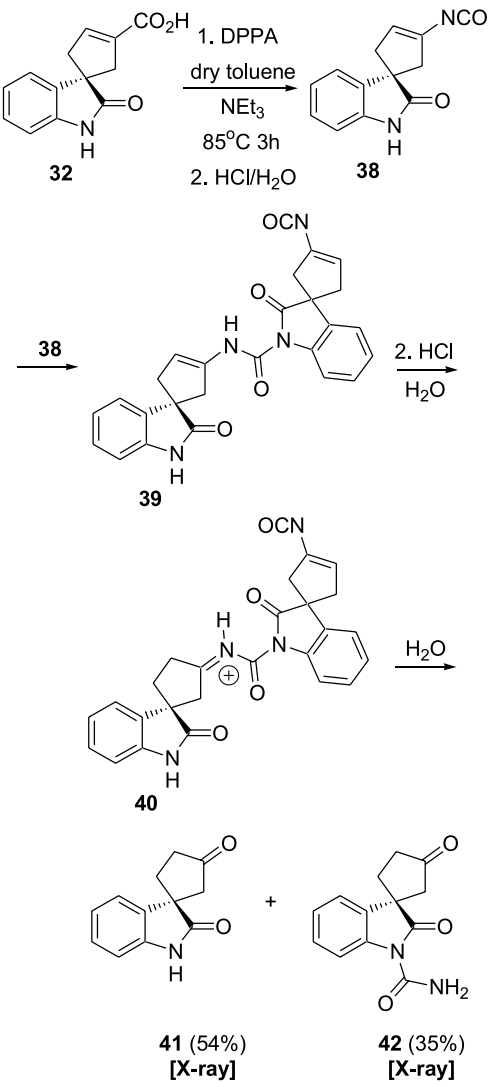
Scheme 8. All compounds are racemic. Reagents and conditions: (a) anisole (10 equiv), TFA (125 equiv), DCM, 15 h, 57%.



Scheme 9. All compounds are racemic. Reagents and conditions: (a) activated Zn dust (3.4 equiv), acetic acid, 1.5 h, 16%; (b) anisole (10 equiv), TFA (125 equiv), DCM, 15 h, 52%.

corresponding *N*-PMB protected ylide **8c** (X=N(PMB)Ph), generated in situ from the tertiary amide **7c**, gave the racemic cycloadducts **35** and **36**, in yields of 14 and 55%, respectively (Schemes 8 and 9). These reactions, while poor to modest in yields, were completely regioselective, presumably due to the increased steric bulk of the ylide, **8c**, which would further destabilize transition state **B** over transition state **A** (Scheme 3). Treatment of the cycloladdition product **35** with TFA, gave *N*-phenyl amide **27** (Scheme 8) that was identical to the compound **27** prepared according to Scheme 6. Similarly, reductive cyclization of **36** followed by deprotection of the product **37** with TFA gave **33a** (Scheme 9) that was identical to the compound **33a** prepared according to Scheme 7. To the best of our knowledge the phosphine-catalyzed [3+2]-cycloaddition reactions of alkenes and 2-butynamides has not been previously reported.

With the aim of preparing the novel spiro-cyclic ketone **41**, the racemic carboxylic acid **32** was converted to the corresponding acyl azide by treatment with diphenylphosphoryl azide (DPPA),[20] which was then heated under Curtius rearrangement conditions. Acid hydrolysis of the resulting product mixture gave ca. a 1:1 mixture of the spiro-cyclic ketones **41** and **42** (Scheme 10). These compounds were readily separated by column chromatography and were isolated in yields of 54 and 35%, respectively. The ^{1}H NMR spectrum of **42** showed two distinct N–H resonances (δ_H (C_6D_6) 7.96 (br s), 4.84 (br s)) and a deshielded aromatic proton (δ_H (C_6D_6) 8.64 (d, J= 8 Hz), consistent with the presence of the *N*-aminocarbonyl group with internal H-bonding to the lactam carbonyl group. The structures of **41** and **42** were confirmed by a single crystal X-ray structural analysis (**42**: Fig. 3).[15] We assume that the unexpected product **42** arises from self-condensation of the intermediate vinyl isocyanate **38** to give the carbamate derivative **39**. Acid hydrolysis of **39** then gives, via **40**, the spiro-cyclic ketones **41** and **42** (Scheme 10). We have not, however, attempted to isolate or characterize the intermediates involved.



Scheme 10. All compounds are racemic.

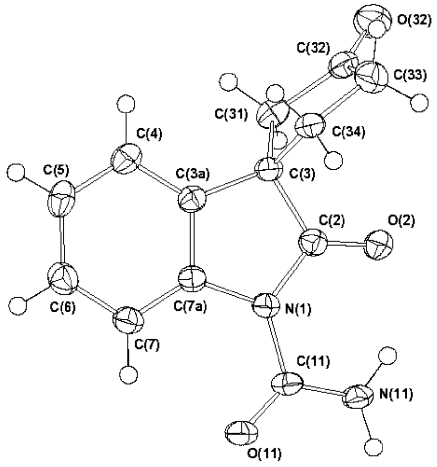
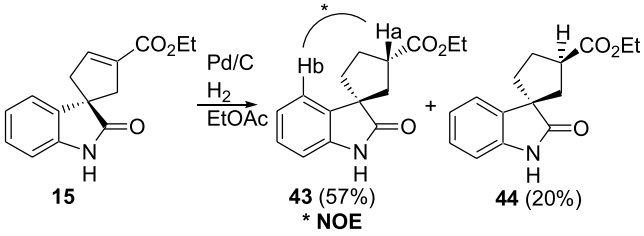


Figure 3. Molecular projection of **42**.

Catalytic hydrogenation of the alkene moiety of racemic **15** gave a 1.8:1 mixture of the diastereomers **43** and **44**, respectively, that were readily separated by column chromatography (Scheme 11). The relative stereochemistry of **43** was determined by 1D NOE experiments that showed a significant enhancement of the signal for the methine proton Ha upon radiation of the aromatic proton Hb and vice versa.



Scheme 11. All compounds are racemic.

2.1. Cytotoxicity studies

Compounds **15**, **25a**,**b**, **27**, **31**, **33a**,**b**, **41**, **42**, **43** and **44** were all tested for their cytotoxic activity against the cancer cell lines H460 (human non small cell lung), MCF-7 (human breast) and SF-268 (human CNS) at the Peter MacCallum Cancer Centre, St Andrew's Place, East Melbourne, Vic, 3002, Australia. Biological testing was performed using

standard NCI procedures at a drug concentration of 25 μM (5 mM drug stocks were prepared in DMSO. Cells were then exposed to 25 μM of each drug for 72 h. The cells were then fixed, stained with SRB and the percentage cell growth relative to the solvent control determined). Percent cell growth calculated from this testing showed little or no cytotoxic activity. The best activity was 50% cell growth at 25 μM for **33b** against H460.

In conclusion, we have developed a new strategy for the synthesis of both racemic and enantio-enriched versions of the 2-azaspiro[4.4]nonan-1-one and spiro[cyclopentane-1, 1′-[1H]isoindol]-3′(2′H)-one ring systems using the phosphine-catalyzed [3+2]-cycloaddition of both ester (**7a**) and amide derivatives (**7c**) of 2-butynoic acid. Enantiomerically enriched versions of **2** can be obtained using a chiral (1*S*)-camphor sultam derivative **7b** of 2-butynoic acid. We have also demonstrated the potential of these compounds as scaffolds for developing libraries of novel spiro-heterocyclic compounds.

3. Experimental

3.1. General

For X-ray structure determinations see Supplementary data. All ^{1}H NMR spectra were performed at 300 MHz and all ^{13}C NMR (DEPT) spectra at 75 MHz in $CDCl_3$ solution, unless otherwise noted.

Abbreviations: PS (petroleum spirit, bp 40–60 °C) and DCM (dichloromethane).

3.1.1. Ethyl (5*S) 2-(*tert*-butoxycarbonyl)-1-oxo-2-azaspiro[4.4]non-7-ene-7-carboxylate (9) and ethyl (5*R**) 2-(*tert*-butoxycarbonyl)-1-oxo-2-azaspiro[4.4]non-6-ene-6-carboxylate (10).** To a solution of **4** (200.7 mg, 1.02 mmol) in dry benzene (3 mL) was added ethyl 2-butynoate (0.13 mL, 1.12 mmol) and tributylphosphine (0.25 mL, 1.01 mmol). The reaction mixture was allowed to stir at rt for 15 h, under an atmosphere of N_2. The solvent was then evaporated in vacuo. An 82:18 mixture of the two regioisomers, **9** and **10** respectively, resulted (determined from analysis of the ^{1}H NMR spectrum of the crude reaction product). Compounds **9** and **10** were purified by column chromatography using 10–30% EtOAc:PS as the eluent. These compounds were further purified by PTLC (30% EtOAc:PS). Compound **9**: a yellow oil (161.7 mg, 0.52 mmol, 51%), R_f 0.78 (30% EtOAc:PS). ^{1}H NMR (C_6D_6, 500 MHz) δ 6.37 (t, J=2 Hz, 1H, C*H*=), 3.98 (dd, J=14, 7.5 Hz, 2H, CH_2CH$_3$), 3.20 (ddd, J=13, 6, 6 Hz, 2H, NCH_2), 3.04 (dq, J=16.5, 2.5 Hz, 1H, C*H*-6$_\beta$), 2.71 (dq, J=18.5, 2.5 Hz, 1H, C*H*-9$_\beta$), 2.13 (d, J=16.5 Hz, 1H, C*H*-6$_\alpha$), 1.73 (d, J=18 Hz, 1H, C*H*-9$_\alpha$), 1.48 (s, 9H, C(CH_3)$_3$), 1.12 (ddd, J=13, 6, 6 Hz, 1H, CH_ACH$_B$-4), 1.04 (ddd, J=13, 6, 6 Hz, 1H, CH$_A$CH_B-4), 0.97 (t, J=7.5 Hz, 3H, CH_3CH$_2$). ^{13}C NMR (C_6D_6, 75 MHz) δ 175.4 (C-1), 163.7 (*C*O$_2$Et), 151.0 (N*C*O$_2$), 139.8 (*C*H=), 134.3 (C-7), 82.1 (*C*(CH$_3$)$_3$), 60.1 (*C*H$_2$CH$_3$), 51.6 (C-5), 43.3 (*C*H$_2$-9), 42.9 (N*C*H$_2$), 42.3 (*C*H$_2$-6), 33.2 (*C*H$_2$-4), 28.1 (C(*C*H$_3$)$_3$), 14.3 (*C*H$_3$CH$_2$). MS (ES) *m*/*z* 348 ([M$^+$ +K], 15%), 332.1 ([M$^+$ +Na], 60%), 310.0 ([MH$^+$], 32%), 254.1 ([MH$^+$ -C(CH$_3$)$_3$], 100%), 210.1 ([MH$^+$ −Boc], 85%); HRMS (CI) Calcd for $C_{16}H_{24}NO_5$ [MH$^+$] 310.1654. Found: 310.1664. NMR data for **9** agreed well with literature when performed under the literature conditions.[13] Compound **10**: a white crystalline solid (44.3 mg, 0.14 mmol, 21%), mp 100–102 °C (lit.[13] 107–110.5 °C), R_f 0.58 (30% EtOAc:PS). ^{1}H NMR (500 MHz) δ 6.99 (t, J=2.5 Hz, 1H, C*H*=), 4.17 (ddd, J=14.5, 7, 0.5 Hz, 2H, CH_2CH$_3$), 3.90 (ddd, J=10.5, 9.5, 3.5 Hz, 1H, NCH_ACH$_B$), 3.63 (ddd, J=10.5, 8.5, 8.5 Hz, 1H, NCH_BCH$_A$), 2.62–2.69 (m, 1H, CH_ACH$_B$-8), 2.51–2.58 (m, 1H, CH_BCH$_A$-8), 2.38–2.46 (om, 2H, CH_ACH$_B$-9 and CH_ACH$_B$-4), 1.98 (ddd, J=13, 8.5, 4.5 Hz, 1H, CH_BCH$_A$-9), 1.92 (ddd, J=12.5, 8.5, 4 Hz, 1H, CH_BCH$_A$-4), 1.54 (s, 9H, (C(CH_3)$_3$), 1.26 (dt, J=7.5, 2.5 Hz, 3H, CH_3CH$_2$). ^{13}C NMR δ 176.8 (C-1), 163.6 (*C*O$_2$Et), 150.6 (N*C*O$_2$), 147.5 (*C*H=), 138.0 (C-6), 83.0 (*C*(CH$_3$)$_3$), 60.8 (*C*H$_2$CH$_3$), 59.7 (C-5), 44.2 (N*C*H$_2$), 37.4 (*C*H$_2$-9), 31.7 (*C*H$_2$-8), 29.8 (*C*H$_2$-4), 28.4 (C(*C*H$_3$)$_3$), 14.5 (*C*H$_3$CH$_2$). MS (ES) *m*/*z* 310.2 ([MH$^+$], 53%), 332.1 ([M$^+$+Na$^+$], 29%), 348.1 ([M$^+$+K$^+$], 23%), 254.1 ([MH$^+$-C(CH$_3$)$_3$], 100%), 209.8 ([MH$^+$−Boc], 95%); HRMS (ES) Calcd for $C_{16}H_{24}NO_5$ [MH$^+$] 310.1654. Found: 310.1654. The NMR data collected for **10** agreed well with those found in literature.[13]

3.1.2. 2-*tert*-Butyl 3,7-diethyl (3*S*,5*S*)-1-oxo-2-azaspiro[4.4]non-7-ene-2,3,7-tricarboxylate (11) and 2-*tert*-butyl 3,7-diethyl (3*S*,5*R*)-1-oxo-2-azaspiro[4.4]non-7-ene-2,3,7-tricarboxylate (13). To a solution of **5** (125.8 mg, 0.47 mmol) in dry benzene (3 mL) was added ethyl-2-butynoate (0.06 mL, 1.12 mmol) and tributylphosphine (0.25 mL, 1.01 mmol). The reaction was allowed to stir at rt for 15 h, under an atmosphere of N_2. The solvent was evaporated in vacuo and ^{1}H NMR analysis showed a mixture of the two diastereomers, **11** and **12**, and one regioisomer **13** (**11/12/13**=63:17:30). Compounds **11** and **13** were purified by column chromatography using 20–90% EtOAc:PS as eluent and further by PTLC (30% EtOAc:PS). A pure sample of **12** was unable to be isolated. Compound **11**: a yellow oil (50.5 mg, 0.13 mmol, 28%), $[\alpha]_D^{22}$ −17.5 (*c* 4.6, $CHCl_3$), R_f 0.57 (30% EtOAc:PS). ^{1}H NMR (500 MHz) δ 6.57 (s, 1H, C*H*=), 4.54 (dd, J=9.5, 4.5 Hz, 1H, C*H*-5), 4.21 (dq, J=6.5, 1.5 Hz, 2H, NCHCO$_2$CH_2), 4.16 (q, J=6.7 Hz, 2H, CCO$_2$CH_2), 3.15 (dd, J=16.5, 2 Hz, 1H, C*H*-6$_\beta$), 3.04 (dd, J=18.5, 1.5 Hz, 1H, C*H*-9$_\beta$), 2.55 (d, J=16.5 Hz, 1H, C*H*-6$_\alpha$), 2.39 (d, J=17.5 Hz, 1H, C*H*-9$_\alpha$), 2.33–2.55 (m, 1H, CH_ACH$_B$-4), 2.09 (dd, J=13, 4 Hz, 1H, CH_BCH$_A$-4), 1.49 (s, 9H, C(CH_3)$_3$), 1.23–1.29 (m, 6H, CH$_2$CH_3). ^{13}C NMR δ 176.9 (C-1), 171.5 (NCH*C*O$_2$Et), 164.3 (C*C*O$_2$Et), 149.6 (N*C*O$_2$) 139.8 (*C*H=), 134.4 (C-7), 84.0 (*C*(CH$_3$)$_3$), 61.9 (NCHCO$_2$*C*H$_2$), 60.7 (CCO$_2$*C*H$_2$), 56.7 (*C*H-5), 51.0 (C-3), 45.2 (*C*H$_2$-9), 43.5 (*C*H$_2$-6), 37.9 (*C*H$_2$-4), 28.1 (C(*C*H$_3$)$_3$), 14.4 (*C*H$_3$CH$_2$), 14.3 (*C*H$_3$CH$_2$). MS (ES) *m*/*z* 382.2 ([MH$^+$], 5%); HRMS (ES) Calcd for $C_{19}H_{28}NO_7$ [MH$^+$] 382.1866. Found: 382.1892. **13**: a yellow oil (24 mg, 63 μmol, 13%), $[\alpha]_D^{23}$ −1.88 (*c* 0.14, $CHCl_3$), R_f 0.36 (30% EtOAc:PS). ^{1}H NMR (500 MHz) δ 6.65 (s, 1H, C*H*=), 4.57 (dd, J=9.5, 3.5 Hz, 1H, C*H*-5), 4.21–4.29 (m, 2H, NCHCO$_2$CH_2), 4.18 (q, J=7.5 Hz, 2H, CCO$_2$CH_2), 3.12–3.17 (m, 1H, C*H*-6$_\beta$), 3.08–3.12 (m, 1H, C*H*-9$_\beta$), 2.51 (d, J=16.5 Hz, 1H, CH-6$_\alpha$), 2.45 (d, J=18.5 Hz, 1H, C*H*-9$_\alpha$), 2.33 (dd, J=13.5, 9.5 Hz, 1H, CH_ACH$_B$-4), 2.20 (dd, J=13.5, 4 Hz, 1H, CH_BCH$_A$-4),

1.51 (s, 9H, C(CH_3)$_3$), 1.31 (t, J=7 Hz, 3H, CCO$_2$CH$_2$-CH_3), 1.27 (t, J=7 Hz, 3H, NCHCO$_2$CH$_2$CH_3). ^{13}C NMR δ 177.0 (C-1), 171.1 (NCHCO$_2$Et), 164.3 (CCO$_2$Et), 149.4 (NCO$_2$), 139.9 (C-8), 133.8 (C-7), 83.8 (C(CH$_3$)$_3$), 61.8 (NCHCO$_2$$CH_2$), 60.4 (CCO$_2$$CH_2$), 56.4 ($C$H-5), 50.7 (C-3), 44.8 ($CH_2$-9), 43.6 ($CH_2$-6), 37.8 ($CH_2$-4), 27.8 (C($CH_3$)$_3$), 14.2 ($CH_3CH_2$), 14.1 ($CH_3CH_2$). MS (ES) m/z 382.2 ([MH$^+$], 5%); HRMS (ES) Calcd for $C_{19}H_{28}NO_7$ [MH$^+$] 382.1866. Found: 382.1914.

3.1.3. 3-Ethyl, 1-methyl 1-(2-nitrophenyl)-cyclopent-3-ene-1,3-dicarboxylate (14). To a solution of alkene **6** (1.013 g, 4.9 mmol) and ethyl 2-butynoate (0.63 mL, 5.4 mmol) in dry benzene (35 mL) was slowly added tributylphosphine (0.24 mL, 0.98 mmol). The reaction was left to stir for 6 h. Upon evaporation in vacuo of volatiles, the resulting crude product was purified by column chromatography using 20–50% EtOAc:PS as eluent to yield a peach coloured oil (1.45 g, 4.5 mmol, 93%), R_f 0.81 (50% EtOAc:PS). ^{1}H NMR δ 7.93 (dd, J=8.1, 1.5 Hz, 1H, ArH-3), 7.58 (dt, J=7.8, 1.8 Hz, 1H, ArH-5), 7.42 (dt, J=7.6, 1.5 Hz, 1H, ArH-4), 7.40 (d, J=7.8 Hz, 1H, ArH-6), 6.74 (t, J=1.8 Hz, 1H, CH=), 4.20 (q, J=6.9 Hz, 2H, CH_2CH$_3$), 3.64 (s, 3H, CO$_2$CH_3), 3.62 (dq, J=19.2, 2.7 Hz, 1H, CH-5′$_\alpha$), 3.52 (dq, J=17.4, 2.5 Hz, 1H, CH-2′$_\alpha$), 3.21 (dm, J=17.1 Hz, 1H, CH-2′$_\beta$), 2.99 (dt, J=19.2, 2.4 Hz, 1H, CH-5′$_\beta$),1.29 (t, J=6.9 Hz, 3H, CH_3CH$_2$). ^{13}C NMR δ 174.0 (CO$_2$Me), 164.0 (CO$_2$Et), 148.1 (ArC-2), 140.1 (CH=), 138.1 (ArC-1), 133.8 (C-3′), 133.2 (ArCH-5), 128.3 (ArCH-6), 128.0 (ArCH-4), 125.3 (ArCH-3), 60.6 (CH$_2$CH$_3$), 55.6 (C-1′), 52.4 (CO$_2$$CH_3$), 45.8 ($CH_2$-5′), 44.2 ($CH_2$-2′), 14.2 (CH$_2$$CH_3$). MS (CI) m/z $C_{16}H_{18}NO_6$ 320 ([MH$^+$], 100%), 288 ([MH$^+$−Et], 41%), 206 (68%), 246 (22%), 188 (21%); HRMS (CI) Calcd for $C_{16}H_{18}NO_6$ [MH$^+$] 320.1134. Found: 320.1132.

3.1.4. Ethyl 2-oxo-spiro[3′-cyclopentene-1′,3-[3H] indole]-3′-carboxylate (15). To a solution of **14** (29.5 mg, 0.092 mmol) in EtOH (0.7 mL) and H_2O (0.18 mL) was added activated Zn dust (96 mg, 1.5 mmol) and 8.9 M HCl (0.14 mL). The reaction was heated at reflux for 2 h. Another portion of activated Zn dust (96 mg, 1.5 mmol) was added and the reaction was left at reflux for an additional 4 h. The mixture was then filtered through Celite and diluted with H_2O. The filtrate was then extracted with EtOAc and the organic extracts were combined and dried over $MgSO_4$ to yield a creamy brown oil (23.4 mg, 0.091 mmol, 98%), R_f 0.5 (50% EtOAc:PS). ^{1}H NMR (500 MHz) δ 9.15 (br s, 1H, NH), 7.21 (d, J=7.5 Hz, 1H, ArH-4), 7.20 (t, J=8 Hz, 1H, ArH-6), 7.01 (t, J=7.7 Hz, 1H, ArH-5), 6.93 (d, J=8 Hz, 1H, ArH-7), 6.86 (br s, 1H, CH=), 4.23 (q, J=7 Hz, 2H, CH_2CH$_3$), 3.27 (dd, J=16.5, 2.5 Hz, 1H, CH-2′$_\alpha$), 3.19 (dd, J=18.7, 2.25 Hz, 1H, CH-5′$_\alpha$), 2.90 (d, J=16.5 Hz, 1H, CH-2′$_\beta$), 2.80 (d, J=18.5 Hz, 1H, CH-5′$_\beta$), 1.31 (t, J=7.25 Hz, 3H, CH_3CH$_2$). ^{13}C NMR δ 183.2 (C-2), 164.2 (CO$_2$Et), 140.6 (CH=), 139.7 (C-7a), 136.6 (C-3a), 134.8 (C-3′), 128.1 (ArCH-6), 123.0 (ArCH-5), 122.1 (ArCH-4), 109.9 (ArCH-7), 60.5 (CH$_2$CH$_3$), 52.5 (C-3), 44.9 (CH$_2$-5′), 43.4 (CH$_2$-2′), 14.2 (CH$_3$CH$_2$). MS (CI) m/z 258 ([MH$^+$], 100%), 212 ([M$^+$−OEt], 12%), 184 ([M$^+$−CO$_2$Et], 12%); HRMS (EI) Calcd for $C_{15}H_{15}NO_3$ [M$^+$] 257.1052. Found: 257.1048.

3.1.5. (3a*S*,6*R*,7a*R*,4′*S*)-Hexahydro-4′-methoxycarbonyl-4′-(2″-nitrophenyl)-1 ((*S*)-16)-(cyclopenten-1′-ylcarbonyl)-8,8-dimethyl-2,2-dioxide-3*H*-3a,6-methano-2,1-benzisothiazole) and (3a*S*,6*R*,7a*R*,4′*R*)-hexahydro-4′-methoxycarbonyl-4′-(2″-nitrophenyl)-1′-(cyclopenten-1′-ylcarbonyl)-8,8-dimethyl-2,2-dioxide-3*H*-3a,6-methano-2,1-benzisothiazole ((*R*)-17). To a solution of **6** (147 mg, 0.709 mmol) and **7b** (198 mg, 0.706 mmol) in dry benzene (1.5 mL) under a N_2 atmosphere was added tributylphosphine (0.02 mL, 71 μmol). The reaction was stirred at rt for 18 h and then the solvent was removed in vacuo. The diastereomeric products were obtained in a ratio of 3.3:1 (*S*)-**16**/(*R*)-**17** from ^{1}H NMR analysis of the crude reaction mixture. The crude mixture was purified by column chromatography using 15% EtOAc:PS as eluent, yielding pure diastereomeric products (*S*)-**16** (140.6 mg, 0.29 mmol, 13%) and (*R*)-**17** (154 mg, 0.32 mmol, 15%) and a mixture (400 mg, 0.82 mmol, 38%) containing both diastereomeric products in a ratio of 4.3:1 (*S*)-**16**/(*R*)-**17**. Further purification by PTLC (20% EtOAc:PS) could yield the pure diastereomeric products. (*S*)-**16**: a colourless crystal, mp 196–200 °C, $[\alpha]_D^{26}$ −22.0 (c 0.3, CHCl$_3$), R_f 0.53 (30% EtOAc:PS). ^{1}H NMR (500 MHz) δ 7.94 (d, J=7.5 Hz, 1H, ArH-3″ 7.56 (br s, 2H, ArH-5″, ArH-6″), 7.41 (br s, 1H, ArH-4″), 6.74 (br s, 1H, CH=), 4.07 (t, J=5.5 Hz, 1H, CH-7a), 3.74 (d, J=19.5 Hz, 1H, CH-3′$_\alpha$), 3.66 (s, 3H, CO$_2$CH_3), 3.64 (d, J=19.0 Hz, 1H, CH-5′$_\alpha$), 3.45 (ABq, J=13.5 Hz, 2H, CH_2-3), 3.19 (d, J=19.0 Hz, 1H, CH-5′$_\beta$), 3.06 (d, J=19.5 Hz, 1H, CH-3′$_\beta$), 2.09–1.99 (m, 2H, H-7$_\alpha$, CH-7$_\beta$), 1.97–1.91 (m, 3H, CH-4$_\beta$, CH-5$_\beta$, CH-6), 1.44–1.37 (m, 2H, CH-4$_\alpha$, CH-5$_\alpha$), 1.24 (s, 3H, CH_3-9), 1.00 (s, 3H, CH_3-10). ^{13}C NMR (125 MHz) δ 174.8 (CO$_2$Me), 171.3 (=CCO), 148.5 (ArC-2″), 141.6 (CH=), 138.4 (ArC-1″) 134.7 (C-1′), 133.4 (ArCH-5″), 129.2 (ArCH-6″), 128.0 (ArCH-4″), 125.1 (ArCH-3″), 65.6 (CH-7a), 54.6 (C-4′), 53.7 (CH$_2$-3), 52.4 (CO$_2$$CH_3$), 48.1 (C-3a), 47.7 (C-8), 47.0 (CH$_2$-3′), 45.5 (CH$_2$-5′), 45.2 (CH-6), 38.3 (CH$_2$-7), 33.3 (CH$_2$-4), 26.5 (CH$_2$-5), 21.3 (CH$_3$-9), 19.9 (CH$_3$-10). LRMS (EI) m/z 488 ([M$^+$], 5%); HRMS (CI) Calcd for $C_{24}H_{29}N_2O_7S$ [MH$^+$] 489.1695. Found: 489.1690. (*R*)-**17**: a colourless crystal, mp 198–202 °C, $[\alpha]_D^{24}$ +19.0 (c 0.6, CHCl$_3$), R_f 0.43 (30% EtOAc:PS). ^{1}H NMR (500 MHz) δ 7.95 (d, J=8.0 Hz, 1H, ArH-3″), 7.60 (t, J=7.5 Hz, 1H, ArH-5″), 7.54 (d, J=8.0 Hz, 1H, ArH-6″), 7.43 (t, J=7.5 Hz, 1H, ArH4′), 6.66 (s, 1H, CH=), 4.07 (m, 1H, CH-7a), 3.80 (d, J=19.0 Hz, 1H, CH-3′$_\beta$), 3.68 (s, 3H, CO$_2$CH_3), 3.50 (d, J=13.5 Hz, 1H, CH-3$_A$), 3.46–3.42 (m, 3H, CH-5′$_\beta$, CH-5′$_\alpha$, CH-3$_B$), 2.97 (d, J=19.0 Hz, 1H, CH-3′$_\alpha$), 2.06–2.00 (m, 2H, CH-7$_\alpha$, CH-7$_\beta$), 1.98–1.90 (m, 3H, CH-4$_\beta$, CH-5$_\beta$, CH-6), 1.42 (m, 2H, CH-4$_\alpha$, CH-5$_\alpha$), 1.23 (s, 3H, CH_3-9), 1.00 (s, 3H, CH_3-10). ^{13}C NMR (125 MHz) δ 173.9 (CO$_2$Me), 165.7 (=CCO), 148.2 (ArC-2″), 139.9 (CH=), 138.1 (ArC-1″), 134.7 (C-1′), 133.3 (ArCH-5″), 128.6 (ArCH-6″), 128.0 (ArCH-4″), 125.4 (ArCH-3″), 65.5 (CH-7a), 55.9 (C-4″), 53.6 (CH$_2$-3), 52.5 (CO$_2$$CH_3$), 48.1 (C-3a), 47.7 (C-8), 46.3 (CH$_2$-3′), 44.8 (CH$_2$-5′), 45.2 (CH-6), 38.4 (CH$_2$-7), 33.2 (CH$_2$-4), 26.5 (CH$_2$-5), 21.3 (CH$_3$-9), 19.9 (CH$_3$-10). MS (EI) m/z 488 ([M$^+$], 2.6%); HRMS (CI) Calcd for $C_{24}H_{29}N_2O_7S$ [MH$^+$] 489.1695. Found: 489.1713.

3.1.6. Dimethyl (1*S*)-1-(2′-nitrophenyl)-3-cyclopentene-1,3-dicarboxylate ((*S*)-18). To a solution of (*S*)-**16**

(199 mg, 0.4 mmol) in dry MeOH (10.2 mL) was added $Sm(OTf)_3$ (258 mg, 0.43 mmol). The reaction was heated at 50 °C for 15 h. The mixture was then cooled and the solvent was removed in vacuo. The residue was then diluted with DCM. The mixture was then washed with brine and saturated $NaHCO_3$, dried and solvent removed in vacuo. The crude mixture was purified by column chromatography using 8:11:1 (DCM:PS:EtOAc) as eluent to afford (*S*)-**18** as a peach oil (82.4 mg, 0.27 mmol, 67%) and the recovered chiral auxiliary as white crystals. (*S*)-**18**: $[\alpha]_D^{24}$ −42.5 (*c* 0.1, $CHCl_3$), R_f 0.42 (20% EtOAc:PS). ^1H NMR δ 7.95 (dd, J= 7.8, 1.5 Hz, 1H, Ar*H*-3′), 7.59 (dt, J=7.5, 1.5 Hz, 1H, Ar*H*-5′), 7.44 (dt, J=7.5, 1.5 Hz, 1H, Ar*H*-4′), 7.42 (dd, J=7.8, 1.5 Hz, 1H, Ar*H*-6′), 6.76 (m, 1H, C*H*=), 3.77 (s, 3H, =CCO_2CH_3), 3.67 (s, 3H, $PhCCO_2CH_3$), 3.62 (dddd, J= 19.5, 5.1, 5.1, 2.7 Hz, 1H, C*H*-5_α), 3.51 (dddd, J=17.4, 5.1, 5.1, 2.4 Hz 1H, C*H*-2_α), 3.22 (dt, J=17.1, 1.5 Hz, 1H, C*H*-2_β), 2.98 (dddd, J=19.1, 2.4, 2.4, 0.9 Hz, 1H, C*H*-5_β). ^{13}C NMR (125 MHz) δ 174.0 (PhCCO_2Me), 164.4 (=CCO_2Me), 148.2 (Ar*C*-2′), 140.4 (*C*H=), 138.0 (Ar*C*-1′), 133.6 (C-3), 133.2 (Ar*C*H-5′), 128.3 (Ar*C*H-6′), 128.1 (Ar*C*H-4′), 125.3 (Ar*C*H-3′), 55.7 (C-1), 52.4 ($PhCCO_2$-CH_3), 51.7 (=CCO_2CH_3), 45.8 (CH_2-5), 44.2 (CH_2-2). MS (ES) *m/z* 306 ([MH^+], 13%); HRMS (ES) Calcd for $C_{15}H_{16}NO_6$ [MH^+] 306.0978. Found: 306.0966.

3.1.7. Dimethyl (1*R*)-1-(2′-nitrophenyl)-3-cyclopentene-1,3-dicarboxylate ((*R*)-19). The title compound was prepared using a similar method to that described above for the synthesis of (*S*)-**18** using (*R*)-**17** (81.9 mg, 0.17 mmol). Purification by column chromatography in solvent system 8:11:1 (DCM:PS:EtOAc) gave (*R*)-**19** as a brown oil (34.7 mg, 0.1 mmol, 68%) and recovered chiral auxiliary as white crystals. (*R*)-**19**: $[\alpha]_D^{26}$ +50.0 (*c* 0.7, $CHCl_3$), R_f=0.26 in 20% EtOAc:PS). MS (ES+ve) *m/z* 306 (26%) [MH^+]; HRMS (ES+ve) Calcd for $C_{15}H_{16}NO_6$ [MH^+] 306.0978. Found: 306.0984. The ^1H NMR spectrum of (*R*)-**19** was identical to that of its enantiomer (*S*)-**18**.

3.1.8. Methyl (1′*S*)-2-oxo-spiro[3′-cyclopentene-1′,3-[3*H*]indole]-3′-carboxylate (*S*)-20). To a solution of (*S*)-**18** (21.7 mg, 0.07 mmol) in MeOH (0.5 mL) and H_2O (0.17 mL) was added activated Zn dust (112 mg, 1.7 mmol) and 8.9 M HCl (0.1 mL). The reaction was heated at reflux for 2 h. The mixture was then cooled and filtered through Celite, and the precipitate was washed with H_2O and MeOH. The filtrate was evaporated in vacuo. The crude product was purified by column chromatography using 30% EtOAc:PS as eluent and further purified by PTLC (30% EtOAc:PS). Compound (*S*)-**20** was obtained as a yellow oil (11.9 mg, 0.049 mmol, 69%), $[\alpha]_D^{24}$ −40.8 (*c* 1.2, $CHCl_3$), R_f 0.23 (30% EtOAc:PS). ^1H NMR δ 8.73 (br s, 1H, N*H*), 7.21 (dd, J=7.5, 1.2 Hz, 1H, Ar*H*-4), 7.20 (td, J=7.8, 1.2 Hz, 1H, Ar*H*-6), 7.01 (td, J=7.8, 0.9 Hz, 1H, Ar*H*-5), 6.92 (d, J=7.8 Hz, 1H, Ar*H*-7), 6.88–6.84 (m, 1H, C*H*-4′), 3.79 (s, 3H, CH_3), 3.26 (ddd, J=18.3, 5.1, 2.7, 2.4 Hz, 1H, C*H*-$2'_\alpha$), 3.20 (ddd, J=20.3, 5.1, 2.7, 2.4 Hz, 1H, C*H*-$5'_\alpha$), 2.90 (ddd, J=18.3, 2.4, 1.5 Hz, 1H, C*H*-$2'_\beta$), 2.80 (m, 1H, C*H*-$5'_\beta$). ^{13}C NMR δ 182.9 (C-2), 164.6 (CO_2Me), 140.9 (*C*H=), 139.7 (C-7a), 136.5 (C-3a), 134.5 (C-3′), 128.1 (Ar*C*H-6), 123.0 (Ar*C*H-5), 122.2 (Ar*C*H-4), 109.8 (Ar*C*H-7), 52.5 (C-3), 51.7 (CH_3), 45.0 (CH_2-5′), 43.4 (CH_2-2′). MS (EI) *m/z* 243 ([M^+], 11%); HRMS (ES) Calcd for $C_{14}H_{14}NO_3$ [MH^+] 244.0974. Found: 244.0966.

3.1.9. Methyl (1′*R*)-2-oxo-spiro[3′-cyclopentene-1′,3-[3*H*]indole]-3′-carboxylate ((*R*)-21). The title compound was prepared using a similar method to that described above for the synthesis of (*S*)-**20** using (*R*)-**19** (14.6 mg, 0.048 mmol). Compound (*R*)-**21** was obtained as a peach oil (6.5 mg, 0.027 mmol, 56%), $[\alpha]_D^{23}$ +57.4 (*c* 1.0, $CHCl_3$), R_f 0.52 (30% EtOAc:PS). The ^1H NMR spectrum of (*R*)-**21** was identical to that of (*S*)-**20**. MS (EI) *m/z* 243 ([M^+], 50%); HRMS (ES) Calcd for $C_{14}H_{14}NO_3$ [MH^+] 244.0974. Found: 244.0963.

3.1.10. Ethyl (5*S)-1-oxo-2-azaspiro[4.4]non-7-ene-7-carboxylate (22).** To a solution of **9** (852.4 mg, 2.76 mmol) in dry DCM (2.5 mL), was added TFA (2.5 mL). The solution was left to stir for 2.5 h under an atmosphere of N_2. The solvent was removed in vacuo, and the oily residue was then treated with saturated $NaHCO_3$ solution (2×10 mL) and extracted with DCM (2×20 mL). The organic portions were dried, and evaporated in vacuo to yield **22** as brown needle-like crystals (524.2 mg, 2.5 mmol, 91%), mp 70–78 °C, R_f 0.26 (70% EtOAc:PS). ^1H NMR δ 7.50 (br s, 1H, NH), 6.69 (t, J=2.7 Hz, 1H, C*H*=), 4.19 (q, J=7.2 Hz, 2H, CH_2CH_3), 3.35 (t, J=7.1 Hz, 2H, NCH_2), 3.02 (od, J=16.5, Hz, 2H, C*H*-6_β, C*H*-9_β), 2.59 (d, J= 15.9 Hz, 1H, C*H*-6_α), 2.46 (d, J=18.9 Hz, 1H, C*H*-9_α), 2.14–2.16 (m, 2H, CH_2-4), 1.32 (t, J=7.0 Hz, 3H, CH_2CH_3). ^{13}C NMR δ 182.35 (C-1), 164.65 (CO_2Et), 140.9 (*C*H=), 134.5 (C-7), 60.4 (CH_2CH_3), 49.4 (C-5), 43.5 (CH_2-9), 42.0 (CH_2-6), 39.5 (NCH_2), 37.8 (CH_2-4), 14.4 (CH_2CH_3). MS (CI) *m/z* 210 ([MH^+], 100%); HRMS (CI) Calcd for $C_{11}H_{16}NO_3$ [MH^+] 210.1130. Found: 210.1132.

3.1.11. Ethyl (5*S)-2-benzyl-1-oxo-2-azaspiro[4.4]non-7-ene-7-carboxylate (23).** To a stirred solution of **22** (255.7 mg, 1.22 mmol) in dry THF (15 mL), under an atmosphere of N_2, was added in quick succession, NaH (76 mg, 1.6 mmol, 50% dispersion in paraffin oil), tetrabutylammonium iodide (45 mg, 0.12 mmol) and benzyl bromide (0.22 mL, 1.85 mmol). The reaction mixture was left stirring for 1 h. The reaction mixture was then quenched with H_2O (50 mL) and extracted with DCM (3×40 mL). The combined organic extracts were then dried and evaporated in vacuo. The crude product was purified by column chromatography using 40–60% EtOAc:PS as the eluent to give **23** as a brown oil (271.5 mg, 0.91 mmol, 74%), R_f 0.56 (50% EtOAc:PS). ^1H NMR δ 7.21–7.34 (m, 5H, ArH), 6.69 (s, 1H, C*H*=), 4.46 (ABq, J=14.5 Hz, 2H, NCH_ACH_BPh), 4.19 (dq, J=6.9, 2.4 Hz, 2H, CH_2CH_3), 3.16–3.21 (m, 2H, CH_2-3), 3.05 (od, J=16.2 Hz, 2H, C*H*-6_β, C*H*-9_β), 2.56 (d, J=15.3 Hz, 1H, C*H*-6_α), 2.43 (d, J=18.9 Hz, 1H, C*H*-9_α), 1.91–2.04 (m, 2H, CH_2-4), 1.28 (dt, J=2.4, 7.2 Hz, 3H, CH_2CH_3). ^{13}C NMR δ 178.0 (C-1), 164.6 (CO_2Et), 141.0 (*C*H=), 136.6 (C-7), 134.4 (Ar*C*-*i*), 128.9 (Ar*C*H-*m*), 128.2 (Ar*C*H-*o*), 127.8 (Ar*C*-*p*), 60.5 (CH_2CH_3), 50.3 (C-5), 47.1 (NCH_2Ph), 43.81 (CH_2-9), 43.78 (CH_2-3), 42.2 (CH_2-6), 35.5 (CH_2-4), 14.5 (CH_2CH_3). MS (CI) *m/z* 300 ([MH^+], 8%); HRMS (EI) Calcd for $C_{18}H_{21}NO_3$ [M^+] 299.1521. Found: 299.1508.

3.1.12. (5*S)-2-Benzyl-1-oxo-2-azaspiro[4.4]non-7-ene-7-carboxylic acid (24).** A solution of a **23** (271.5 mg, 0.91 mmol) in MeOH (2 mL) contained within a sealed tube was added a solution of K_2CO_3 (251 mg, 1.82 mmol) in water (2.5 mL). The mixture was left stirring at 40 °C for 4 days, another equivalent of K_2CO_3 was added and temperature was raised to 60 °C for 1 day. The solvent was removed in vacuo and the oily residue was dissolved in H_2O (15 mL) and washed with Et_2O (2×25 mL). The aqueous fraction was acidified (pH∼1) with 10% HCl and extracted with EtOAc (3×25 mL). The organic portions were combined, dried and evaporated in vacuo to yield a white solid (229.7 mg, 0.85 mmol, 93%), R_f 0.06 (50% EtOAc:PS). ^{1}H NMR δ 9.16 (br s, 1H, OH); 7.24–7.35 (m, 3H, ArH), 7.22 (d, J=6.3 Hz, 2H, Ar*H*-*o*), 6.81 (s, 1H, C*H*=), 4.49 (ABq, J=14.7 Hz, 2H, NCH_ACH_BPh), 3.17–3.23 (m, 2H, CH_2-3), 3.11 (ddd, J=18.3, 4.9, 2.2 Hz, 1H, C*H*-9$_\beta$), 3.05 (d, J=16.5, 4.9, 2.2, Hz, 1H, C*H*-6$_\beta$), 2.56 (d, J=17.1 Hz, 1H, C*H*-6$_\alpha$), 2.45 (d, J=18.6 Hz, 1H, C*H*-9$_\alpha$), 1.92–2.08 (m, 2H, CH_2-4). ^{13}C NMR δ 178.1 (C-1), 168.8 (*C*O_2H), 143.5 (*C*H=), 136.4 (C-7), 133.9 (Ar*C*-*i*), 128.9 (Ar*C*H-*m*), 128.2 (Ar*C*H-*o*), 127.8 (Ar*C*H-*p*), 50.7 (C-5), 47.4 (NCH_2Ph), 44.1 (*C*H_2-9), 44.0 (*C*H_2-3), 42.0 (*C*H_2-6), 35.6 (*C*H_2-4). MS (CI) *m*/*z* 272 ([MH$^+$], 100%); HRMS (CI) Calcd for $C_{16}H_{17}NO_3$ [M$^+$] 271.1208. Found: 271.1123.

3.1.13. (5*S)-2-Benzyl-1-oxo-*N*-phenyl-2-azaspiro[4.4]non-7-ene-7-carboxamide (25a).** To a solution of **24** (52.2 mg, 0.21 mmol) and HOBT (26 mg, 0.2 mmol) in dry MeCN (2 mL) at 0 °C, was added aniline (0.02 mL, 0.25 mmol). The solution was stirred for 10 min at 0 °C before the addition of EDCI (38.2 mg, 0.2 mmol) and left to stir at rt for 15 h and then at 60 °C for 2 h. The solvent was then removed, and the residue was extracted with DCM and washed successively with H_2O and brine. The organic portions was then dried and evaporated in vacuo. Purification of the crude product was achieved through column chromatography using 70% EtOAc:PS as the eluent to yield **25a** as white crystals (36.2 mg, 0.11 mmol, 54%), mp 148–150 °C, R_f 0.32 (60% EtOAc:PS). ^{1}H NMR (500 MHz) *(* 7.55 (d, J=8 Hz, 2H, Ar*H*-*o*), 7.29–7.34 (m, 5H, Ar*H*), 7.23 (d, J=7.5 Hz, 2H, Ar*H*-*m*), 7.11 (t, J=7.25 Hz, 1H, Ar*H*-*p*), 6.50 (s, 1H, C*H*=), 4.49 (ABq, J=14.5 Hz, 2H, NCH_2), 3.21 (q, J=7 Hz, 2H, CH_2-3), 3.15 (d, J=16 Hz, 1H, C*H*-6$_(_), 3.08 (d, J=18 Hz, 1H, C*H*-9$_(_), 2.68 (d, J=15 Hz, 1H, C*H*-6$_(_), 2.49 (d, J=18 Hz, 1H, C*H*-9$_(_), 2.00–2.11 (m, 2H, CH_2-4). ^{13}C NMR (125 MHz) *(* 177.6 (C-1), 162.7 (*C*ONHPh), 137.8 (Ar*C*-*i*), 137.7 (C-7), 136.2 (Ar*C*-*i*′), 135.0 (*C*H=), 128.8 (Ar*C*H), 128.6 (Ar*C*H-*m*), 127.9 (Ar*C*H), 127.5 (Ar*C*H), 124.2 (Ar*C*H-*p*), 119.9 (Ar*C*H-*o*), 50.3 (C-5), 47.1 (NCH_2), 43.7 (*C*H_2-3 and *C*H_2-9), 42.4 (*C*H_2-6), 35.3 (*C*H_2-4). MS (CI) *m*/*z* 347 ([MH$^+$], 80%); HRMS (CI) Calcd for $C_{22}H_{22}N_2O_2$ [M$^+$] 346.1681. Found: 346.1632.

3.1.14. Spiro[cyclopentane-1′,3-[3H]indole]-2,3′(1H)-dione (41) and spiro[cyclopentane-1′,3-[3H]indole]-2,3′(1H)-dione-1-carboxamide (42). A solution of racemic acid **32** (55.6 mg, 0.24 mmol), diphenylphosphoryl azide (DPPA) (0.11 mL, 4.8×10^{-4} mol) and NEt_3 (0.07 mL, 0.48 mmol) in anhydrous toluene (3 mL) was heated at 85 °C for 3 h. The mixture was then heated at reflux for 30 min then 8.9 M HCl (0.05 mL) was cautiously added. The mixture was then heated at reflux for another 1 h before allowing to cool to rt with stirring for 15 h. The solvent was removed in vacuo. NMR analysis of the crude mixture revealed a 1:1 mixture of **41/42**, respectively. The crude mixture was purified by column chromatography in 30–50% EtOAc:PS and then a second time with 2:1:1 (DCM:PS:EtOAc). **41**: a semi-crystalline yellow oil (26.5 mg, 0.13 mmol, 54%), R_f 0.28 (50% EtOAc:PS). ^{1}H NMR (C_6D_6, 500 MHz) δ 8.81 (br s, 1H, NH), 6.96 (t, J=7.8 Hz, 1H, Ar*H*-6), 6.79 (t, J=7.8 Hz, 1H, Ar*H*-5), 6.66 (d, J=7.5 Hz, 1H, Ar*H*-4), 6.55 (d, J=7.5 Hz, 1H, Ar*H*-7), 2.53–2.62 (m, 1H, C*H*-4′$_\alpha$), 2.51 (d, J=17.5 Hz, 1H, C*H*-2′$_\alpha$), 2.06–2.15 (m, 1H, C*H*-4′$_\beta$), 2.05 (d, J=18 Hz, 1H, C*H*-2′$_\beta$), 2.01–2.06 (m, 1H, C*H*-5′$_\alpha$), 1.60 (dt, J=13, 8.5 Hz, 1H, C*H*-5′$_\beta$). ^{13}C NMR (C_6D_6, 125 MHz) δ 214.0 (C-3′), 182.7 (C-2), 141.0 (C-7a), 133.4 (C-3a), 128.4 (Ar*C*H-6), 122.7 (Ar*C*H-5), 122.5 (Ar*C*H-4), 110.3 (Ar*C*H-7), 51.1 (C-3), 46.7 (*C*H_2-2′), 36.5 (*C*H_2-4′), 33.4 (*C*H_2-5′). MS (EI) *m*/*z* 201 ([M$^+$], 67%), 145 ([M$^+$-(CH$_2$)$_2$CO], 100%); HRMS (EI) Calcd for $C_{12}H_{12}NO_2$ [MH$^+$] 202.0868. Found: 202.0874. **42**: white crystals (21.1 mg, 0.086 mmol, 35%), mp 139–143 °C, R_f 0.73 (50% EtOAc:PS). ^{1}H NMR (C_6D_6, 500 MHz) δ 8.64 (d, J=8 Hz, 1H, Ar*H*-7), 7.96 (br s, 1H, NH_AH$_B$), 7.08 (t, J=8 Hz, 1H, Ar*H*-6), 6.85 (t, J=7.5 Hz, 1H, Ar*H*-5), 6.55 (d, J=7.5 Hz, 1H, Ar*H*-4), 4.84 (br s, 1H, NH$_A$$H_B$), 2.37 (ddd, J=18, 9, 9 Hz, 1H, C*H*-4′$_\alpha$), 2.22 (d, J=18.5 Hz, 1H, C*H*-2′$_\alpha$), 2.01 (ddd, J=18.5, 9, 6 Hz, 1H, C*H*-4′$_\beta$), 1.87 (d, J=18.5 Hz, 1H, C*H*-2′$_\beta$), 1.68–1.74 (m, 1H, 1H, C*H*-5′$_\alpha$), 1.37–1.43 (m, 1H, 1H, C*H*-5′$_\beta$). ^{13}C NMR (C_6D_6, 125 MHz) δ 212.5 (C-3′), 182.0 (C-2), 152.1 (*C*ONH$_2$), 139.9 (C-7a), 131.5 (C-3a), 128.8 (Ar*C*H-6), 125.0 (Ar*C*H-5), 121.6 (Ar*C*H-4), 117.0 (Ar*C*H-7), 51.3 (C-3), 47.0 (*C*H_2-2′), 36.1 (*C*H_2-4′), 34.0 (*C*H_2-5′). LRMS (EI) *m*/*z* 244 ([M$^+$], 2%), 201 ([M$^+$ -CONH$_2$], 36%); HRMS (EI) Calcd for $C_{13}H_{12}N_2O_3$ [M$^+$] 244.0848. Found: 244.0823.

3.1.15. Ethyl (*S)-2-oxo-spiro[3′-cyclopentane-1′,3-[3H]indole]-(3′*S**)-carboxylate (43) and ethyl (*R**)-2-oxo-spiro[3′-cyclopentane-1′,3-[3H]indole]-(3′*R**)-carboxylate (44).** To a mixture of spiroalkene **15** (34.9 mg, 0.136 mmol) in EtOAc (2.2 mL) was added 10 wt% palladium on activated carbon (9.4 mg). The system was then flushed with H_2 gas and left stirring under a H_2 atmosphere for 15 h. The crude reaction mixture was filtered on Celite and washed multiple times with EtOAc. These organic extracts were evaporated in vacuo. NMR analysis of crude mixture revealed a 1.75:1 (**43/44**). The crude product was purified by column chromatography in 20–30% EtOAc:PS and then further by PTLC in 30% EtOAc:PS. **43**: a creamy white oil (20.1 mg, 0.78 μmol, 57%), R_f 0.28 (30% EtOAc:PS). ^{1}H NMR (500 MHz) δ 8.91 (br s, 1H, NH), 7.20 (t, J=7.7 Hz, 1H, Ar*H*-6), 7.18 (d, J=7 Hz, 1H, Ar*H*-4), 7.02 (t, J=7.7 Hz, 1H, Ar*H*-5), 6.93 (d, J=7.5 Hz, 1H, Ar*H*-7), 4.18 (q, J=7.3 Hz, 2H, CH_2CH$_3$), 3.25 (m, 1H, *C*H-3′$_\beta$), 2.51 (dd, J=13, 10 Hz, 1H, C*H*-2′$_\alpha$), 2.28–2.40 (m, 3H, CH_2-4′ and C*H*-5′$_\alpha$), 2.14 (dd, J=13, 8 Hz, 1H, C*H*-2′$_\beta$), 1.84–1.95 (m, 1H, C*H*-5′$_\beta$), 1.28 (t, J=7.3 Hz, 3H, CH_3CH$_2$). ^{13}C NMR (125 MHz) δ 183.1 (C-2), 174.4 (*C*O_2Et), 140.1 (C-7a), 136.1 (C-3a), 127.7 (Ar*C*H-6), 122.53 (Ar*C*H-4), 122.49 (Ar*C*H-5), 109.8 (Ar*C*H-7), 60.6 (*C*H$_2$CH$_3$), 54.3 (C-3), 44.8 (*C*H-3′$_\beta$), 40.8 (*C*H_2-2′), 37.3

(CH_2-5′), 29.6 (CH_2-4′), 14.2 (CH_3CH_2). MS (EI) *m/z* 259 ([M^+], 72%), 260 ([MH^+], 12%); HRMS (EI) Calcd for $C_{15}H_{17}NO_3$ [M^+] 259.1208. Found: 259.1219. **44**: a yellow oil (6.9 mg, 0.26 μmol, 20%), R_f 0.38 (30% EtOAc:PS). ^{1}H NMR (C_6D_6, 500 MHz) δ 8.14 (br s, 1H, NH), 7.22 (d, 1H, J=7.5 Hz, Ar*H*-4) 6.96 (dt, J=7.5, 1 Hz, 1H, Ar*H*-6), 6.86 (dt, J=7.5, 1 Hz, 1H, Ar*H*-5), 6.48 (d, J=8 Hz, 1H, Ar*H*-7), 3.99 (q, J=7 Hz, 2H, CH_2CH$_3$), 3.38 (ddd, J=16, 16, 8 Hz, 1H, C*H*-3′$_\alpha$), 2.43 (dd, J=13.5, 8.5 Hz, 1H, C*H*-2′$_\alpha$), 2.33–2.38 (m, 1H, C*H*-4′$_\alpha$), 2.31 (dd, J=14, 8 Hz, 1H, C*H*-2′$_\beta$), 2.19–2.25 (m, 1H, C*H*-4′$_\beta$), 2.10 (dt, J=13, 7.5 Hz, 1H, C*H*-5′$_\alpha$) 1.87 (dt, J=12.5, 7.5 Hz, 1H, C*H*-5′$_\beta$), 0.96 (t, J=7 Hz, 3H, CH_3CH$_2$). ^{13}C NMR (C_6D_6, 125 MHz) δ 183.6 (C-2), 175.2 (CO_2Et), 140.9 (C-7a), 135.6 (C-3a), 123.4 (Ar*C*H-4), 127.7 (Ar*C*H-6), 122.7 (Ar*C*H-5), 109.5 (Ar*C*H-7), 60.3 (CH_2CH_3), 54.3 (C-3), 44.5 (*C*H-3′$_\alpha$), 40.6 (CH_2-2′), 38.1 (CH_2-5′), 30.8 (CH_2-4′), 14.2 (CH_3CH_2). LRMS (EI) *m/z* 259 ([M^+], 64%), 260 ([MH^+], 12%); HRMS (EI) Calcd for $C_{15}H_{17}NO_3$ [M^+] 259.1208. Found: 259.1220.

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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.2005.06.050

Details of the X-ray crystal/refinement data and experimental procedures for the synthesis of compounds **25b**-**37**.

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Synthesis, NMR and X-ray characterisation of 6-substituted 4-amino-5-aryldiazenyl-1-arylpyridazinium salts

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Abstract—A new simple method has been used to prepare 6-substituted 4-(subst. amino)-5-aryldiazenyl-1-arylpyridazinium salts from *N*-methyl- or *N*-aryl-3-amino-1-phenylbut-2-en-1-ones and 4-aminopent-3-en-2-ones and substituted benzenediazonium tetrafluoroborates or hexafluorophosphates. The structure of selected derivatives was studied by means of ^{15}N NMR spectra and X-ray.

1. Introduction

In our previous paper,[1] we stated that the reaction of 1-phenyl-3-(2,4-dimethoxyphenylamino)but-2-en-1-one or 1-phenyl-3-methylaminobut-2-en-1-one with substituted benzenediazonium tetrafluoroborates produces, besides the expected products of attack of diazonium ion on methine carbon of enaminone, also the side products 4-(2,4-dimethoxyphenylamino)- or 4-methylamino-1-aryl-5-phenyldiazenylpyridazinium tetrafluoroborates in the yields of 17–22%. The mechanism for formation of these pyridazinium salts has not been reliably proven. The aim of the present paper is to explore the scope and limitations of this reaction, inclusive of the effect of the anion of the diazonium salt upon the yield of the pyridazinium salt, and to find out whether the reaction can also be applied to other enaminones than benzoylacetone derivatives.

2. Results and discussion

In contrast to our previous findings, now we have used benzenediazonium hexafluorophosphates instead of benzenediazonium tetrafluoroborates. This change in the anion approximately doubled the yield. The X-ray diffraction studies on a single crystal of product **10** (Figs. 1 and 2) unequivocally proved the presumed structure of the pyridazinium salt. The proton and carbon NMR spectra of the hexafluorophosphates are practically identical with those of the corresponding tetrafluoroborates (see Section 5).

The reaction of enaminone **1** with 4-methoxybenzenediazonium tetrafluoroborate did not give the respective

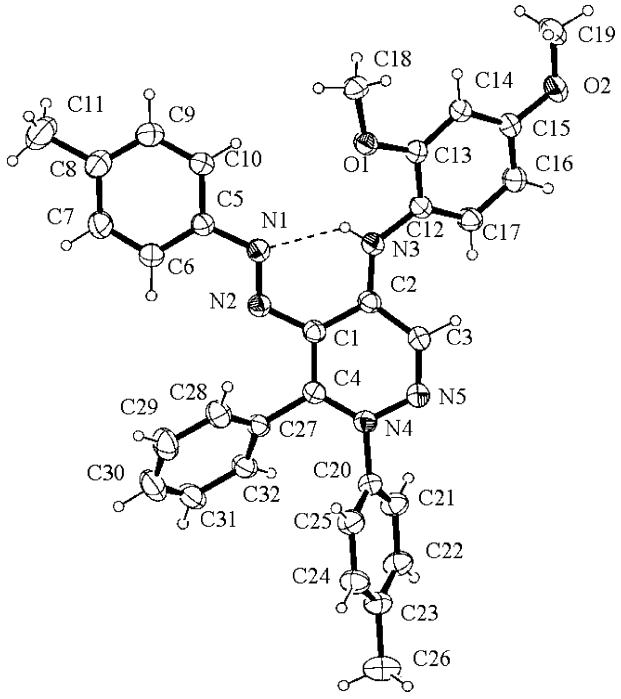

Figure 1. ORTEP view of the cation of compound **10**. Thermal ellipsoids are drawn at 30% probability level.

Keywords: Enaminones; Pyridazinium salts; Azo coupling; NMR; X-ray.
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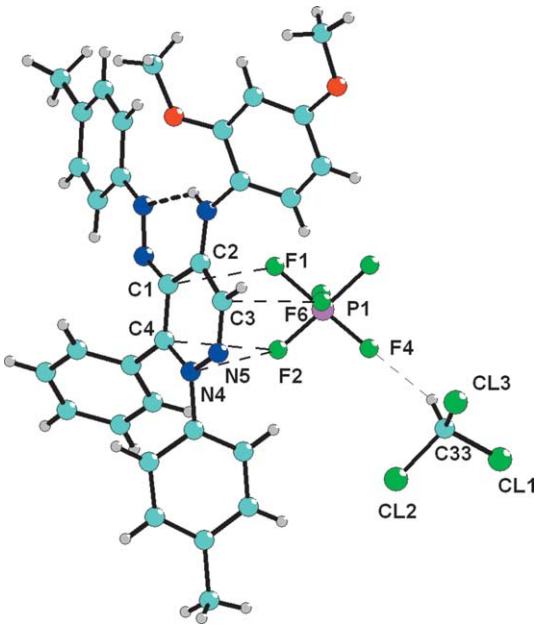


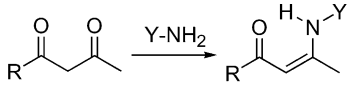
Figure 2. Crystal structure of compound **10** showing the most significant intermolecular interactions.

pyridazinium salts.[1] The increase in yield of pyridazinium salt **10** after replacement of the tetrafluoroborate by hexafluorophosphate of the diazonium salt led us to believe that it could be possible to prepare the 4-methoxy derivative too (Scheme 1). This turned out to be the case and 4-(2,4-dimethoxyphenylamino)-1-(4-methoxyphenyl)-5-(4-methoxyphenyldiazenyl)-6-phenylpyridazinium hexafluorophosphate (**12**) was obtained in a relatively good yield (40%) when the starting material molar ratios were 2:1.

The pyridazinium salts can only be prepared from diazonium salts with electropositive substituents (according to the Hammett σ constants up to the non-substituted benzenediazonium tetrafluoroborate). With hexafluorophosphates the reaction applicability expanded to the 4-Cl derivative. However, it was proved that the 4-nitro derivative is not formed even with the application of 4-nitrobenzenediazonium hexafluorophosphate.

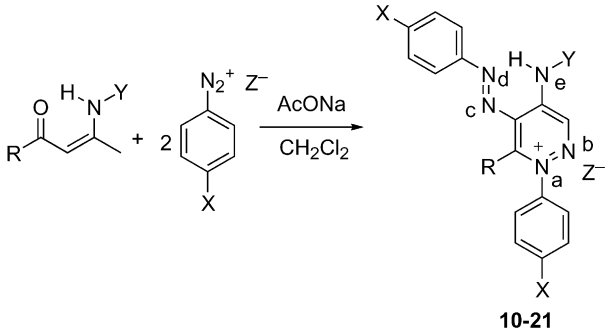
For a survey and characterization of the 6-arylpyridazinium hexafluorophosphates prepared, see Scheme 1, Table 1 and Section 5.

It was found that the reaction leading to formation of pyridazinium salts (Scheme 1) was not limited to enaminones derived from benzoylacetone alone. The reaction between 4-methylaminopent-3-en-2-one **5** and 4-methoxybenzenediazonium hexafluorophosphate also gave the respective 6-methylpyridazinium hexafluorophosphate (**17**), shown in Figures 3 and 4. Compound **17**, which is the first representative of 6-methyl derivatives, was also characterised by its ^{1}H and ^{13}C, ^{19}F, ^{31}P spectra (see Section 5 and Table 1) and ^{15}N NMR spectra (see Table 1 and Fig. 5). For more details about NMR of related compounds see Ref. 1. It was found that using this method is also possible to prepare related 6-methyl substituted pyridazinium hexafluorophosphates and tetrafluoroborates with various substituents at the amino group and aryl group,



1-9

R = C_6H_5, Y = 2,4-$(OCH_3)_2C_6H_3$ (**1**); R = C_6H_5, Y = 4-$(OCH_3)C_6H_4$ (**2**); R = Y = C_6H_5 (**3**); R = C_6H_5, Y = CH_3 (**4**); R = Y = CH_3 (**5**); R = CH_3, Y = 2,4-$(OCH_3)_2C_6H_3$ (**6**); R = CH_3, Y = CH_2-2,4-$(OCH_3)_2C_6H_3$ (**7**); R = CH_3, Y = 4-ClC_6H_5 (**8**); R = CH_3, Y = 4-$(CH_3)C_6H_5$ (**9**).



10-21

R = C_6H_5, Y = 2,4-$(OCH_3)_2C_6H_3$, X = CH_3, Z = PF_6^- (**10**); R = C_6H_5, Y = 2,4-$(OCH_3)_2C_6H_3$, X = H, Z = PF_6^- (**11**)
R = C_6H_5, Y = 2,4-$(OCH_3)_2C_6H_3$, X = OCH_3, Z = PF_6^- (**12**);
R = C_6H_5, Y = CH_3 , X = OCH_3, Z = PF_6^- (**13**); R = C_6H_5, Y = 2,4-$(OCH_3)_2C_6H_3$, X = Cl, Z = PF_6^- (**14**);
R = C_6H_5, Y = 4-$(OCH_3)C_6H_4$, X = CH_3, Z = BF_4^- (**15**); R = CH_3, Y = CH_3, X = OCH_3, Z = BF_4^- (**16**);
R = CH_3, Y = CH_3, X = OCH_3, Z = PF_6^- (**17**); R = CH_3, Y = CH_3, X = H, Z = BF_4^- (**18**);
R = CH_3, Y = CH_3, X = H, Z = PF_6^- (**19**); R = CH_3, Y = 2,4-$(OCH_3)_2C_6H_3$, X = OCH_3, Z = PF_6^- (**20**);
R = CH_3, Y = 4-$(CH_3)C_6H_4$, X = CH_3, Z = PF_6^- (**21**).

Scheme 1.

Table 1. ^{15}N, ^{19}F, ^{31}P and ^{11}B NMR parameters of the representative pyridazinium salts[a]

Compound	N_a	N_b	N_c	N_d	N_e	^{19}F[b]	^{31}P[c]	^{11}B
10 ($CDCl_3$)	−163.0	−32.5	[d]	107.7	−265.5	−73.90	−144.0	
16 (DMSO)	−164.7	−33.6	[d]	107.7	−276.0	−147.87[e] −147.93[f]		−1.82
17 (DMSO)	−164.7	−33.6	[d]	107.7	−276.2	−69.73	−143.1	

[a] For ^{1}H and ^{13}C see Section 5.
[b] Values of $^{1}J(^{19}F, ^{31}P)$: 713.4 Hz (**10**), 711.0 Hz (**17**).
[c] Values of $^{1}J(^{31}P, ^{19}F)$: 712.6 Hz (**10**), 711.3 Hz (**17**).
[d] Not detected.
[e] $^{19}F–^{10}B$.
[f] $^{19}F–^{11}B$.

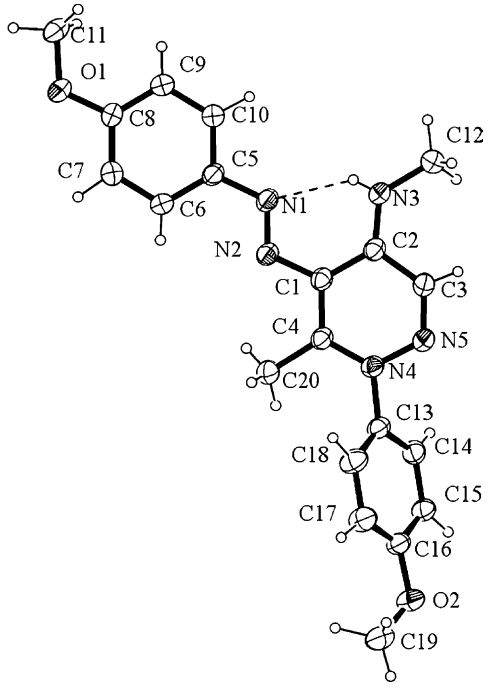


Figure 3. ORTEP view of the cation of compound **17**. Thermal ellipsoids are drawn at 30% probability level.

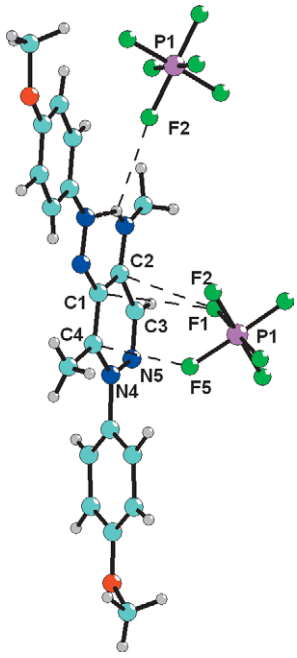


Figure 4. Crystal structure of compound **17** showing the most significant intermolecular interactions.

depending on the starting enaminone and diazonium salts (substances **16–21**).

3. Crystallography

ORTEP[2] diagrams of compounds **10** and **17** are shown in Figures 1 and 3, respectively. The structures of both organic cations are very similar to those recently published.[1] The pyridazinium rings are essentially planar and display extended conjugation with the positive charge mainly located on nitrogen N4. Both compounds form short intramolecular N–H···N hydrogen bond assisted by resonance between the aminic N3–H group and the nitrogen N1 of the diazenyl moiety. The N1···N3 distances of 2.625(2) and 2.645(3) Å in **10** and **17**, respectively, are in agreement with those of analogue structures recently reported.[1] In compound **17** the N3–H aminic group forms also a bifurcated weak hydrogen bond with a fluorine atom (F2) of the PF_6^- anion [N3···F2 = 3.083(4) Å]. In both structures the PF_6^- anions are involved in short electrostatic interactions with pyridazinium rings as shown in Figures 2 and 4 and in Table 3.

4. Conclusions

The described way of preparation of pyridazinium salts is simple: the reaction proceeds under mild conditions and the separation of product being easy, too. The reaction can be

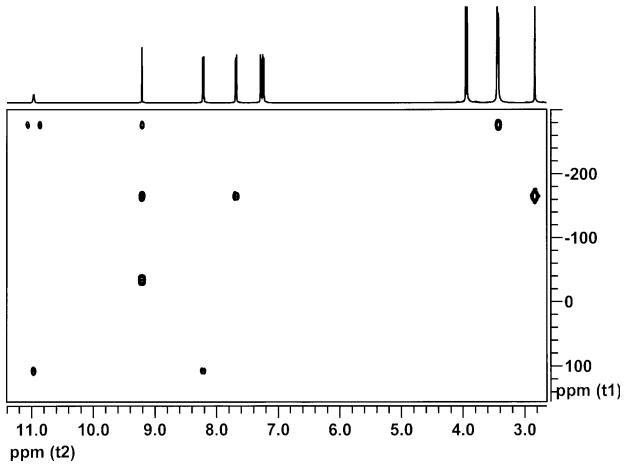


Figure 5. 500 MHz $^{1}H–^{15}N$ gs HMBC spectrum of the compound **17** in DMSO-d_6 optimised for 5 Hz. One of azo nitrogens has not been detected at the natural abundance.

applied to both diazonium tetrafluoroborates and diazonium hexafluorophosphates: the latter gave higher yields in the majority of cases. The method can be used to prepare various 1-(substituted aryl)-4-(substituted amino)pyridazinium salts substituted at 6-position by a phenyl or methyl group. The reaction is affected by substituent type both in the diazonium salt and in the amino group of the starting enaminone. Electron-donating substituents in diazonium salts are usually more appropriate for the formation of the pyridazinium salt, but exceptions were also observed in the reactions of *N*-arylenaminones with diazonium tetrafluoroborates. The reaction is restricted to enaminones with a secondary amino group; the compounds with a primary amino group only give products of a single azo coupling, and the enaminones with a tertiary amino groups show double azo coupling.[3]

5. Experimental

5.1. General

The NMR spectra were measured at 298 K with a Bruker AVANCE 500 spectrometer equipped with a 5 mm broadband probe with a gradient of magnetic field in the direction of z axis at the frequencies of 500.13 MHz (^{1}H), 125.77 MHz (^{13}C), 50.69 MHz (^{15}N), 470.56 MHz (^{19}F), 202.46 MHz (^{31}P) and with a Bruker AMX 360 spectrometer at the frequency of 360.14 MHz (^{1}H), 90.57 MHz (^{13}C), 115.55 MHz (^{11}B). The ^{1}H NMR spectra were calibrated in $CDCl_3$ on hexamethyldisiloxane (δ 0.05) and in DMSO-d_6 on the central signal of the solvent multiplet (δ 2.55). The ^{13}C NMR spectra were calibrated on the central signal of the solvent multiplet (δ 39.6 for DMSO and δ 76.9 for $CDCl_3$). The carbon NMR spectra were measured in standard way and by means of the APT pulse sequence (spectral width 26.455 kHz, acquisition time 1.238 s, zero filling to 64 K and line broadening 1 Hz prior Fourier transformation). The ^{15}N NMR spectra were calibrated on external neat ^{15}N nitromethane placed in a coaxial capillary (δ 0.0). The ^{11}B NMR spectra were calibrated on external $B(OCH_3)_3$ placed in a co-axial capillary (δ 18.1). In order to suppress the signals of ^{11}B nuclei from NMR tube glass, the measurements were carried out in teflon sample tube liners (Aldrich) inserted into 5 mm tubes whose bottom part of about 25 mm length was cut off. The ^{19}F NMR spectra were calibrated on internal $CFCl_3$ (δ 0.0, central signal of multiplet of the standard) and were measured using 5 mm ^{1}H/^{19}F dual probehead with proton noise decoupling. The $\delta(^{15}N)$ values were measured with the help of techniques with inversion detection (^{1}H–^{15}N HMBC) processed in the magnitude mode. The gradient ratios were 70:30:50.1. Experiments were performed with the NH one-bond coupling 90 Hz, and NH long-range coupling 5 Hz, 2k$\times$160k zero filled to 2k$\times$1k, sinebell squared in both dimensions.

Melting points were determined with a Kofler hot stage microscope and were not corrected. The elemental analyses were carried out with a FISONS EA 1108 automatic analyser.

Dichloromethane was pre-dried by standing with anhydrous calcium chloride and subsequent distillation with phosphorus pentoxide. The anhydrous sodium acetate was fused on a porcelain dish and left to cool in a desiccator. The diazonium tetrafluoroborates used were prepared by procedures described elsewhere[4] and diazonium hexafluorophosphates were prepared in the same manner as corresponding tetrafluoroborates with using sodium hexafluorophosphate instead of sodium tetrafluoroborate.

The crystal data for compounds **10** and **17** were collected at room temperature using a Nonius Kappa CCD diffractometer with graphite monochromated Mo K_α radiation and corrected for Lorentz and polarization effects. The structures were solved by direct methods (SIR97[5]) and refined using full-matrix least-squares. In compound **10** all non-hydrogen atoms were refined anisotropically and hydrogens included on calculated positions, riding on their

Table 2. Crystal data

Compound	**10**	**17**
Formula	$(C_{32}H_{30}N_5O_2)^+\cdot(PF_6)^-\cdot CHCl_3$	$(C_{20}H_{22}N_5O_2)^+\cdot(PF_6)^-$
M	780.95	509.40
System	Orthorhombic	Monoclinic
Space group	$Pna2_1$	Cc
a (Å)	30.1530(3)	11.8255(3)
b (Å)	14.4669(1)	23.3472(7)
c (Å)	8.2887(1)	9.3110(2)
α (°)	90	90
β (°)	90	117.684(2)
γ (°)	90	90
U (Å^3)	3615.7(1)	2276.4(1)
Z	4	4
D_c (g cm^{-3})	1.435	1.486
T (K)	295	295
μ (cm^{-1})	3.667	1.978
θ_{min}–θ_{max} (°)	3.9–28.0	1.7–30.0
Unique reflections	8324	6067
R_{int}	0.041	0.056
Observed reflections [$I>2\sigma(I)$]	6986	4193
R (observed reflections)	0.0624	0.0499
wR (all reflections)	0.1828	0.1437
S	1.023	1.028
$\Delta\rho_{max}$; $\Delta\rho_{min}$ (e Å^{-3})	0.38; −0.45	0.34; −0.22

carrier atoms except for N3–H hydrogen, which was refined isotropically. The PF_6^- anion was found disordered and the six fluorine atoms were refined with two independent orientations with occupancies of 0.6 and 0.4, respectively. The asymmetric unit contains also a molecule of solvent $CHCl_3$. In compound **17** all non-hydrogen atoms were refined anisotropically and hydrogens isotropically.

All the calculations were performed using SHELXL-97[6] and PARST[7] implemented in WINGX[8] system of programs. The crystal data and refinement parameters are summarized in Table 2. Selected bond and short contact distances are given in Table 3 and hydrogen bond parameters are shown in Table 4.

CCDC-266954 and 266955 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk] (Table 4).

5.1.1. 3-(2,4-Dimethoxyphenylamino)-1-phenylbut-2-en-1-one (1). Compound **1** was prepared according to the procedure described in Ref. 1.

5.1.2. 3-(4-Methoxyphenylamino)-1-phenylbut-2-en-1-one (2). Compound **2** was prepared by the same method as **1**. Crystallisation from toluene, yield 77%; mp 106–107 °C. ^{1}H NMR (360.14 MHz, $CDCl_3$) 2.00 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 5.83 (s, 1H, =CH), 6.83 (m, 2H, Ar), 7.05 (m, 2H, Ar), 7.39 (m, 3H, Ar), 7.89 (m, 2H, Ar), 12.94 (br s, 1H, NH). ^{13}C NMR (90.57 MHz, $CDCl_3$) 19.89 (CH_3), 55.11 (OCH_3), 93.42 (=CH), 114.02 (CH Ar), 126.19 (CH Ar), 126.72 (CH Ar), 127.95 (CH Ar), 130.46 (CH Ar), 131.08 (C_q Ar), 139.82 (C_q Ar), 157.51 (C_q Ar), 162.81 (=C–N), 187.47 (C=O). Anal. Calcd for $C_{17}H_{17}NO_2$ (267.33): C, 76.38; H, 6.41; N, 5.24. Found: C, 76.34; H, 6.60; N, 5.47.

Table 3. Selected bond and short contact distances (Å)

	10	17
N1–N2	1.268(3)	1.266(3)
N2–C1	1.395(3)	1.405(3)
C1–C2	1.431(3)	1.426(3)
N3–C2	1.330(3)	1.322(4)
C1–C4	1.401(3)	1.400(4)
N4–C4	1.346(3)	1.361(3)
N4–N5	1.348(3)	1.352(3)
N5–C3	1.298(3)	1.303(4)
C2–C3	1.415(3)	1.424(4)
N4···F2	3.130(11)	
C1···F1	3.196(8)	
C3···F6	3.149(12)	
C4···F2	3.128(11)	
C1···F1		3.194(5)
C2···F1		3.187(5)
C4···F5		3.193(6)

5.1.3. 3-Phenylamino-1-phenylbut-2-en-1-one (3). Compound has been prepared according to method described in Ref. 9. Yield 85%; mp 107–108.5 °C (Ref. 9; mp 110.5–111.5 °C). ^{1}H NMR (360.14 MHz, $CDCl_3$) 2.10 (s, 3H, CH_3), 5.87 (s, 1H, =CH), 7.14 (m, 2H, Ar), 7.20 (m, 1H, Ar), 7.33 (m, 2H, Ar), 7.40 (m, 3H, Ar), 7.90 (m, 2H, Ar), 13.09 (br s, 1H, NH). ^{13}C NMR (90.57 MHz) 20.21 (CH_3), 94.45 (=CH), 124.55 (CH Ar), 125.57 (CH Ar), 126.87 (CH Ar), 128.08 (CH Ar), 128.97 (CH Ar), 130.70 (CH Ar), 138.46 (C_q Ar), 139.84 (C_q Ar), 162.00 (=C–N), 188.47 (C=O).

5.1.4. 3-Methylamino-1-phenylbut-2-en-1-one (4). Compound **4** was prepared according to the procedure described in Ref. 10.

5.1.5. 4-Methylaminopent-3-en-2-one (5). Compound **5** was prepared according to procedure described in Ref. 11.

5.1.6. 4-(2,4-Dimethoxyphenylamino)pent-3-en-2-one (6). A mixture of acetylacetone (0.1 mol) and 2,4-dimethoxyaniline (0.1 mol) was heated in 50 ml toluene to boiling. The water formed in reaction was distilled off as an azeotrope with toluene. The toluene thus removed was replenished by adding fresh toluene. After the reaction, the solvent was distilled off, and the residue was submitted to vacuum distillation. Yield 84%, bp 165 °C/5 mBar. ^{1}H NMR (360.14 MHz, $CDCl_3$): 1.87 (s, 3H, CH_3), 2.07 (s, 3H, CH_3CO), 3.79 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 5.15 (s, 1H, =CH), 6.42 (dd, 1H, CH_{Ar}, J=8.6, 2.7 Hz), 6.48 (d, 1H, CH_{Ar}, J=2.6 Hz), 7.00 (d, 1H, CH_{Ar}, J=8.6 Hz), 12.04 (br s, 1H, NH). ^{13}C NMR (90.57 MHz, $CDCl_3$): 19.43, 28.91 (2×CH_3), 55.35, 55.55 (2×OCH_3), 96.69, 99.08, 103.62, 120.80, 126.75 (5×CH), 154.50, 158.73, 161.70 (3×C_q), 195.48 (C=O). Anal. Calcd for $C_{13}H_{17}NO_3$ (235.28): C, 66.36; H, 7.28; N, 5.95. Found: C, 66.47; H, 7.23; N, 5.99.

5.1.7. 2,4-Dimethoxybenzaldoxime. A 250 ml three-necked flask equipped with a reflux condenser, thermometer and dropping funnel was charged with a solution of 2, 4-dimethoxy-benzaldehyde (16.6 g, 0.1 mol) in 75 ml ethanol, and a solution of hydroxylamine hydrochloride (7 g, 0.1 mol) in 20 ml water. The mixture was stirred, and a solution of anhydrous sodium carbonate (5.3 g, 0.05 mol) in 20 ml water was added drop by drop from the funnel. After addition of all the carbonate, the mixture was refluxed 5 h, whereupon it was cooled in ice bath, and the separated

Table 4. Hydrogen bond parameters (Å and degrees)

D–H···A	D–H	H···A	D···A	D–H···A
Compound **10**				
N3–H···N1	0.75(4)	2.04(3)	2.625(2)	135(3)
C33–H33[a]···F4	0.98	2.18	3.084(12)	153
Compound **17**				
N3–H···N1	0.70(3)	2.08(3)	2.645(3)	140(4)
N3–H···F2($x,-y,z-1/2$)	0.70(3)	2.68(4)	3.083(4)	119(3)

[a] Calculated hydrogen.

product was collected by suction and dried in air. Yield 10.8 g (60%); mp 103–105 °C (Ref. 12; mp 104–105 °C).

5.1.8. 2,4-Dimethoxybenzylamine. 2,4-Dimethoxybenzaldoxime (10.8 g) was hydrogenated at atmospheric pressure in ethyl acetate with RaneyNi as catalyst for 48 h. The solvent was removed by distillation, and the evaporation residue was distilled in vacuum to give 4.5 g (45%) liquid, bp 110–120 °C/10 mBar (Ref. 13, bp 142–143 °C/20 mBar). ^{1}H NMR (500.13 MHz, $CDCl_3$): 3.73 (s, 2H, CH_2), 3.78 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 6.41 (dd, 1H, CH_{Ar}, $J=8.1$, 2.4 Hz), 6.44 (d, 1H, CH_{Ar}, $J=2.3$ Hz), 7.08 (d, 1H, CH_{Ar}, $J=8.1$ Hz). ^{13}C NMR (125.77 MHz, $CDCl_3$): 42.02 (CH_2), 55.00, 5.19 (2×OCH_3), 98.42, 103.44 (2×CH_{Ar}), 124.38 (C_q), 128.83 (CH_{Ar}), 158.22, 159.76 (2×C_q).

5.1.9. 4-(2,4-Dimethoxybenzylamino)pent-3-en-2-one (7). A 100 ml three-necked flask equipped with azeotropic distillation head was charged with acetylacetone (29 mmol), 2,4-dimethoxybenzylamine (29 mmol), 30 ml toluene and 4-methylbenzenesulphonic acid (1 mmol). The mixture was heated to boiling on an oil bath while intermittently removing the toluene–water azeotrope, until the distillate was clear toluene. Then a part of toluene was distilled off and the residue was cooled. The separated crystals were collected by suction. The product was purified by vacuum distillation (173–176 °C/6–7 mBar). Yield 66%. ^{1}H NMR (360.14 MHz, $CDCl_3$): 1.93 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.33 (d, 2H, CH_2, $J=6.4$ Hz), 4.96 (s, 1H, =CH), 6.40–6.44 (m, 2H, CH_{Ar}), 7.06 (d, 1H, CH_{Ar}, $J=8.4$ Hz), 11.03 (br s, 1H, NH). ^{13}C (90.57 MHz, $CDCl_3$): 18.60 (CH_3), 28.65 (CH_3), 41.74 (CH_2), 55.20, 55.23 (2×OCH_3), 95.23, 98.43, 103.83 (3×CH_{Ar}), 118.57 (C_q), 128.54 (CH_{Ar}), 157.85, 160.30, 162.84 (3×C_q), 194.57 (C=O). Anal. Calcd for $C_{14}H_{19}NO_3$ (249.31): C, 67.45; H, 7.68; N, 5.62. Found: C, 67.69; H, 7.51; N, 5.64.

5.1.10. 4-(4-Chlorophenylamino)pent-3-en-2-one (8). This compound has been prepared according to procedure described in Ref. 14. Product has been purified by vacuum distillation, (bp 123–132 °C/4 mBar) and by crystallization from *n*-hexane; mp 55.5–57 °C (Ref. 14; mp 60–61 °C). ^{1}H NMR (360.14 MHz, $CDCl_3$): 1.95 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 5.18 (s, 1H, =CH), 6.98–7.05 (m, 2H, AA′), 7.25–7.28 (m, 2H, XX′), 12.43 (br s, 1H, NH). ^{13}C (90.57 MHz, $CDCl_3$): 19.44, 28.89 (2×CH_3), 97.86 (=CH), 125.46, 128.88 (2×CH), 130.60, 137.06 (3×C_q), 159.34 (=C–N), 196.15 (C=O).

5.1.11. 4-(4-Methylphenylamino)pent-3-en-2-one (9). Compound has been prepared according to procedure described in Ref. 14. Product has been purified by crystallisation from *n*-hexane; mp 63.5–64.5 °C (Ref. 14 68–69 °C). ^{1}H NMR (360.14 MHz, $CDCl_3$): 1.93 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 5.14 (s, 1H, =CH), 6.97 (m, 2H, AA′), 7.11 (m, 2H, XX′), 12.38 (br s, 1H, NH). ^{13}C (90.57 MHz, $CDCl_3$): 19.64, 20.79, 29.00 (3×CH_3), 97.11 (=CH), 124.74, 129.55 (2×CH_{Ar}), 135.37, 135.97 (2×C_q), 160.56 (=C–N), 195.77 (C=O).

5.2. General procedure of azo coupling reactions

Re-melted sodium acetate (30 mmol) and the respective benzenediazonium tetrafluoroborate or hexafluorophosphate (10 mmol) were added to a solution of enaminone (5 mmol) in 30 ml dichloromethane with stirring. The reaction mixture was stirred at room temperature 72 h, whereupon the solids were collected by suction on a sintered-glass filter and the filter cake was washed with dichloromethane. The filtrate was evaporated in vacuum, and the evaporation residue was either recrystallized or submitted to column chromatography (in the case of compounds **13** and **16–19** and **21** washing by ethylacetate was performed instead of column chromatography). The following compounds were prepared by the procedure described.

5.2.1. 4-(2,4-Dimethoxyphenylamino)-1-(4-methylphenyl)-5-(4-methylphenyldiazenyl)-6-phenylpyridazinium hexafluorophosphate (10). This compound was obtained as red crystalline solid after crystallization of evaporation residue from ethanol. Yield 43%; mp 243–245 °C. ^{1}H NMR (500.13 MHz, $CDCl_3$): 2.26 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 6.58 (dd, 1H, CH_{Ar}, $J=2.6$, 8.7 Hz), 6.61 (d, 1H, CH_{Ar}, $J=2.5$ Hz), 7.04–7.05 (m, 2H, AA′), 7.18–7.20 (m, 2H, AA′), 7.24–7.26 (m, 2H, XX′), 7.28–7.32 (m, 2H, CH_{Ar}), 7.35–7.42 (m, 5H, CH_{Ar}), 7.63 (d, 1H, CH_{Ar}, $J=8.7$ Hz), 8.81 (s, 1H, CH), 12.83 (s, 1H, NH). ^{13}C NMR (125.77 MHz, $CDCl_3$): 20.99 (CH_3), 21.55 (CH_3), 55.69 (OCH_3), 56.04 (OCH_3), 99.59, 105.35 (2×CH_{Ar}), 115.70 (C_q), 123.34, 126.20, 126.24, 127.72 (4×CH_{Ar}), 128.74, 128.89 (2×C_q), 129.59, 130.10, 130.13, 130.69 (4×CH_{Ar}), 139.28, 139.85, 140.32 (3×C_q), 141.33 (CH), 144.35, 149.71, 154.02, 158.04, 161.27 (5×C_q). ^{31}P NMR (202.45 MHz, $CDCl_3$): −143.99 (sp, $J=712.6$ Hz). ^{19}F NMR (470.56 MHz): −73.88 (d, $J=713.4$ Hz). Anal. Calcd for $C_{32}H_{30}F_6N_5O_2P$ (661.58): C, 58.10; H, 4.57; N, 10.59. Found: C, 58.01; H, 4.72; N, 10.31.

5.2.2. 4-(2,4-Dimethoxyphenylamino)-1-phenyl-5-phenyldiazenyl-6-phenylpyridazinium hexafluorophosphate (11). This compound was obtained as red crystalline solid after column chromatography (silica/chloroform/ethylacetate 3:1) and recrystallization from ethanol. Yield 38%; mp 236–240 °C. ^{1}H NMR (500.13 MHz, $CDCl_3$): 3.85 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 6.61–6.63 (m, 2H, CH_{Ar}), 7.28–7.32 (m, 5H, CH_{Ar}), 7.36–7.46 (m, 8H, CH_{Ar}), 7.48–7.5 (m, 2H, CH_{Ar}), 7.69 (d, 1H, CH_{Ar}, $J=8.72$ Hz), 8.86 (s, 1H, CH_{Ar}), 12.87 (br s, 1H, NH). ^{13}C NMR (125.77 MHz, $CDCl_3$): 55.73 (OCH_3), 56.04 (OCH_3), 99.75, 105.21 (2×CH_{Ar}), 115.66 (C_q), 123.34, 126.44, 126.57, 127.79 (4×CH_{Ar}), 128.57, 128.81 (2×C_q), 129.11, 129.40, 129.64, 130.29, 130.75, 133.03 (6×CH_{Ar}), 139.42 (C_q), 141.61 (CH), 142.64, 151.43, 153.98, 158.45, 161.36 (5×C_q). Anal. Calcd for $C_{30}H_{26}F_6N_5O_2P$ (633.53): C, 56.88; H, 4.14; N, 11.05. Found: C, 57.04; H, 4.15; N, 10.92.

5.2.3. 4-(2,4-Dimethoxyphenylamino)-1-(4-methoxyphenyl)-5-(4-methoxyphenyldiazenyl)-6-phenylpyridazinium hexafluorophosphate (12). This compound was obtained as red crystalline solid after column chromatography (silica/chloroform/ethylacetate 4:1) and recrystallization

from ethanol. Yield 40%; mp 129–134 °C. ^{1}H NMR (500.13 MHz, $CDCl_3$): 3.73 (s, 3H, OCH_3), 3.84 (s, 6H, 2×OCH_3), 3.84 (s, 3H, OCH_3), 6.58–6.60 (m, 2H, 2×CH_{Ar}), 6.74–6.75 (m, 2H, AA′), 6.87–6.89 (m, 2H, AA′), 7.27–7.30 (m, 2H, XX′), 7.30–7.33 (m, 3H, CH_{Ar}), 7.35–7.40 (m, 4H, CH_{Ar}), 7.45–7.48 (m, 2H, XX′), 7.63 (d, 1H, CH_{Ar}, J=9 Hz), 8.79 (s, 1H, CH), 12.80 (br s, 1H, NH). ^{13}C NMR (125.77 MHz, $CDCl_3$): 55.40 (OCH_3), 55.70 (2×OCH_3), 56.02 (OCH_3), 99.64, 105.20, 114.08, 114.75 (4×CH_{Ar}), 115.84 (C_q), 125.61, 126.14, 127.74, 127.77 (4×CH_{Ar}), 128.93, 129.11 (2×C_q), 130.05, 130.63 (2×CH_{Ar}), 135.70, 139.28 (2×C_q), 140.98 (CH), 145.96, 153.95, 157.58, 159.93, 161.13, 163.90 (6×C_q). Anal. Calcd for $C_{32}H_{30}F_6N_5O_4P$ (693.58): C, 55.42; H, 4.36; N, 10.10. Found: C, 55.71; H, 4.25; N, 9.91.

5.2.4. 1-(4-Methoxyphenyl)-4-methylamino-5-(4-methoxyphenyldiazenyl)-6-phenylpyridazinium hexafluorophosphate (13). This compound was obtained as orange solid after recrystallization from ethanol. Yield 33%; mp 215–218 °C. ^{1}H NMR (500.13 MHz, DMSO-d_6): 3.51 (d, 3H, NCH_3, J=5.5 Hz), 3.78 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3) 6.99–7.00 (m, 2H, AA′), 7.11–7.14 (m, 2H, AA′), 7.44–7.52 (m, 7H, CH_{Ar}), 7.74–7.77 (m, 2H, XX′), 9.39 (s, 1H, CH), 10.97 (q, 1H, NH, J=5.5 Hz). ^{13}C NMR (125.77 MHz, DMSO-d_6): 30.95 (NCH_3), 55.82, 56.18 (2×OCH_3), 114.42, 115.21, 125.60, 127.96, 128.41 (5×CH_{Ar}), 129.01, 129.85 (2×C_q), 130.30, 130.84 (2×CH_{Ar}), 136.17, 141.33 (2×C_q), 141.46 (CH), 146.50, 156.72, 159.92, 163.71 (4×C_q). ^{31}P NMR (202.45 MHz, DMSO-d_6): −143.14 (sp, J=711.5 Hz). ^{19}F NMR (470.56 MHz, DMSO-d_6): −69.72 (d, J=711.8 Hz). Anal. Calcd for $C_{25}H_{24}F_6N_5O_2P$ (571.46): C, 52.55; H, 4.23; N, 12.26. Found: C, 52.79; H, 4.42; N, 12.19.

5.2.5. 4-(2,4-Dimethoxyphenylamino)-1-(4-chlorophenyl)-5-(4-chlorophenyldiazenyl)-6-phenylpyridazinium hexafluorophosphate (14). This compound was obtained as dark purple solid after column chromatography (silica/$CHCl_3$) and recrystallization from ethanol. Yield 32%; mp 245–249 °C. ^{1}H NMR (500.13 MHz, $CDCl_3$): 3.83 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 6.57–6.59 (m, 2H, CH_{Ar}), 7.21–7.23 (2H, m, CH_{Ar}), 7.31–7.41 (m, 11H, CH_{Ar}), 7.64 (d, 1H, CH_{Ar}, J=9.5 Hz), 8.83 (s, 1H, =CH), 12.75 (br s, 1H, NH). ^{13}C NMR (125.77 MHz, $CDCl_3$): 55.69, 56.05 (2×OCH_3), 99.65, 105.23 (2×CH_{Ar}), 115.43 (C_q), 124.38, 126.08, 127.91, 127.96 (4×CH_{Ar}), 128.27, 128.77 (2×C_q), 129.25, 129.73, 130.54, 130.62 (4×CH_{Ar}), 135.73, 139.24, 139.26, 140.99 (4×C_q), 141.75 (CH), 149.77, 153.89, 158.47, 161.42 (4×C_q). Anal. Calcd for $C_{30}H_{24}Cl_2F_6N_5O_2P$ (702.42): C, 51.30; H, 3.44; N, 9.97. Found: C, 51.05; H, 3.40; N, 9.65.

5.2.6. 4-(4-Methoxyphenylamino)-1-(4-methylphenyl)-5-(4-methylphenyldiazenyl)-6-phenylpyridazinium tetrafluoroborate (15). This compound was obtained as orange solid after column chromatography (silica/$CHCl_3$/ethylacetate 3:2) and washing by hot ethylacetate. Yield 9%; mp 207–215 °C. ^{1}H NMR (500.13 MHz, $CDCl_3$): 2.20 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 6.92–6.94 (m, 2H, AA′), 6.95–6.97 (m, 2H, AA′), 7.13–7.14 (m, 2H, AA′), 7.23–7.26 (m, 2H, CH_{Ar}), 7.30–7.32 (m, 3H, CH_{Ar}), 7.34–7.36 (m, 2H, XX′), 7.45–7.46 (m, 2H, CH_{Ar}), 7.47–7.49 (m, 2H, XX′), 8.69 (s, 1H, CH), 12.71 (br s, 1H, NH). ^{13}C NMR (125.77 MHz, $CDCl_3$): 20.88, 21.44, 55.41 (3×CH_3), 115.30, 123.20 (2×CH_{Ar}), 126.18 (C_q), 126.33, 126.79, 127.44 (3×CH_{Ar}), 128.55, 128.79 (2×C_q), 129.31, 129.81, 129.88, 130.65 (4×CH_{Ar}), 139.52, 140.21, 140.37 (3×C_q), 141.05 (CH), 144.00, 149.62, 158.35, 159.72 (4×C_q). Anal. Calcd for $C_{31}H_{28}BF_4N_5O$ (573.40): C, 64.94; H, 4.92; N, 12.21. Found: C, 64.97; H, 4.87; N, 12.10.

5.2.7. 1-(4-Methoxyphenyl)-4-methylamino-5-(4-methoxyphenyldiazenyl)-6-methylpyridazinium tetrafluoroborate (16). This compound was obtained as orange solid after recrystallization from methanol. Yield 20%; mp 210–213.5 °C. ^{1}H NMR (360.14 MHz, DMSO-d_6): 2.82 (s, 3H, CH_3), 3.41 (d, 3H, NCH_3, J=5.4 Hz), 3.92 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 7.20–7.28 (m, 4H, 2×AA′), 7.65–7.70 (m, 2H, XX′), 8.18–8.22 (m, 2H, XX′), 9.18 (s, 1H, =CH), 10.97 (br q, 1H, NH, J=5.4 Hz). ^{13}C NMR (90.57 MHz, DMSO-d_6): 17.04 (CH_3), 30.53 (NCH_3), 55.07, 56.24 (2×OCH_3), 115.18, 115.27, 125.88, 127.82 (4×CH_{Ar}), 128.21, 135.38, 140.23 (3×C_q), 140.82 (CH), 146.50, 157.18, 160.75, 163.71 (4×C_q). Anal. Calcd for $C_{20}H_{22}F_4N_5O_2B$ (451.23): C, 53.24; H, 4.91; N, 15.52. Found: C, 53.41; H, 4.96; N, 15.27.

5.2.8. 1-(4-Methoxyphenyl)-4-methylamino-5-(4-methoxyphenyldiazenyl)-6-methylpyridazinium hexafluorophosphate (17). This compound was obtained as orange solid after recrystallization from ethanol. Yield 26%; mp 217–221 °C. ^{1}H NMR (360.14 MHz, DMSO-d_6): 2.84 (s, 3H, CH_3), 3.43 (d, 3H, NCH_3, J=5.4 Hz), 3.93 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 7.23–7.25 (m, 2H, AA′), 7.26–7.29 (m, 2H, AA′), 7.67–7.70 (m, 2H, XX′), 8.21–8.23 (m, 2H, XX′), 9.22 (s, 1H, =CH), 10.97 (br q, 1H, NH, J=5.4 Hz). ^{13}C NMR (90.57 MHz, DMSO-d_6): 16.94 (CH_3), 30.44 (NCH_3), 55.82, 56.02 (2×OCH_3), 115.03, 125.65, 127.55 (3×CH_{Ar}), 128.07 (C_q), 135.18 (CH_{Ar}), 139.79, 139.95 (2×C_q), 140.78 (CH), 146.30, 156.99, 160.48, 163.54 (4×C_q). Anal. Calcd for $C_{20}H_{22}F_6N_5O_2P$ (509.39): C, 47.16; H, 4.35; N, 13.75. Found: C, 47.17; H, 4.43; N, 13.98.

5.2.9. 1-Phenyl-4-methylamino-5-phenyldiazenyl-6-methylpyridazinium tetrafluoroborate (18). This compound was obtained as orange solid after recrystallization from ethanol. Yield 3%; mp 220.5–224 °C. ^{1}H NMR (360.14 MHz, DMSO-d_6): 2.86 (s, 3H, CH_3), 3.43 (d, 3H, NCH_3, J=5.5 Hz), 7.68–7.70 (m, 3H, CH_{Ar}), 7.76–7.77 (m, 5H, CH_{Ar}), 8.17–8.20 (m, 2H, CH_{Ar}), 9.24 (s, 1H, CH), 11.08 (br q, 1H, NH, J=5.4 Hz). ^{13}C NMR (90.57 MHz, DMSO-d_6): 17.16 (CH_3), 30.75 (NCH_3), 123.53, 126.48 (2×CH), 128.09 (C_q), 130.04, 130.42, 131.13, 133.36 (4×CH), 140.23, 142.40, 152.16, 157.93 (4×C_q). Anal. Calcd for $C_{18}H_{18}F_4N_5BF_4$ (391.18): C, 55.27; H, 4.64; N, 17.90. Found: C, 55.24; H, 4.53; N, 17.92.

5.2.10. 1-Phenyl-4-methylamino-5-phenyldiazenyl-6-methylpyridazinium hexafluorophosphate (19). This compound was obtained as orange solid and were not recrystallized. Yield 54%; mp 210–214.5 °C. ^{1}H NMR (360.14 MHz, DMSO-d_6): 2.86 (s, 3H, CH_3), 3.45 (d, 3H, NCH_3, J=5.5 Hz), 7.67–7.71 (m, 3H, CH_{Ar}), 7.74–7.78 (m, 5H, CH_{Ar}), 8.18–8.21 (m, 2H, CH_{Ar}), 9.26 (s, 1H,

=CH), 11.09 (br q, 1H, NH, $J=5.4$ Hz). ^{13}C NMR (90.57 MHz, DMSO-d_6): 17.04 (CH_3), 30.67 (NCH_3), 123.44, 126.36 ($2\times CH_{Ar}$), 127.98 (C_q), 129.90, 130.32, 131.01, 133.24 ($4\times CH_{Ar}$), 140.12 (C_q), 141.55 (CH), 142.31, 152.06, 157.79 ($3\times C_q$). Anal. Calcd for $C_{18}H_{18}F_6N_5P$ (449.34): C, 48.12; H, 4.04; N, 15.59. Found: C, 48.33; H, 4.26; N, 15.81.

5.2.11. 1-(4-Methoxyphenyl)-4-(2,4-dimethoxyphenylamino)-5-(4-methoxyphenyldiazenyl)-6-methylpyridazinium hexafluorophosphate (20). This compound was obtained as dark red solid after column chromatography (silica/chloroform/ethylacetate 4:1) and recrystallization from ethanol. Yield 37%; mp 126–131 °C. ^{1}H NMR (360.14 MHz, $CDCl_3$): 2.89 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.90 (s, 6H, $2\times OCH_3$), 6.56–6.59 (m, 2H, CH_{Ar}), 7.00–7.06 (m, 4H, $2\times AA'$), 7.46–7.50 (m, 3H, $XX'+CH_{Ar}$), 7.84–7.86 (m, 2H, XX'), 8.59 (s, 1H, =CH), 12.75 (br s, 1H, NH). ^{13}C NMR (90.57 MHz, $CDCl_3$): 16.71 (CH_3), 55.51, 55.57, 55.69, 55.91 ($4\times OCH_3$), 99.30, 105.21, 114.80, 114.84 ($4\times CH_{Ar}$), 115.48 (C_q), 125.49, 125.61, 126.97 ($3\times CH_{Ar}$), 128.71, 134.70, 137.94 ($3\times C_q$), 140.29 (CH), 145.76, 153.89, 157.85, 160.73, 160.96, 164.00 ($6\times C_q$). Anal. Calcd for $C_{27}H_{28}F_6N_5O_4P$ (631.51): C, 51.35; H, 4.47; N, 11.09. Found: C, 51.51; H, 4.19; N, 10.97.

5.2.12. 1-(4-Methylphenyl)-4-(4-methylphenylamino)-5-(4-methylphenyldiazenyl)-6-methylpyridazinium hexafluorophosphate (21). This compound was obtained as orange solid after recrystallization from ethanol. Yield 34%; mp 223–227 °C. ^{1}H NMR (360.14 MHz, $CDCl_3$): 2.35 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.86 (s, 3H, NCH_3), 7.20–7.31 (m, 8H, CH_{Ar}), 7.39–7.42 (m, 2H, XX'), 7.69–7.72 (m, 2H, XX'), 8.51 (s, 1H, CH), 12.78 (br s, 1H, NH). ^{13}C NMR (90.57 MHz, $CDCl_3$): 16.70, 20.96, 21.05, 21.51 ($4\times CH_3$), 123.23, 125.10, 125.44 ($3\times CH_{Ar}$), 128.31 (C_q), 130.07, 130.35, 130.82 ($3\times CH$), 130.83, 138.93, 139.23, 139.52 ($4\times C_q$), 140.30 (CH), 140.90, 144.41, 149.64, 158.72 ($4\times C_q$). Anal. Calcd for $C_{26}H_{26}F_6N_5P$ (553.49): C, 56.42; H, 4.73; N, 12.65. Found: C, 56.60; H, 4.82; N, 12.62.

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ortho-Lithiation of *S*-*tert*-butyl-*S*-phenylsulfoximines. New route to enantiopure sulfinamides via a de-*tert*-butylation reaction

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Abstract—The sulfoximine group proved to be an excellent *ortho*-directing group in lithiation reactions. Several electrophiles were used to afford the corresponding *ortho*-functionalized aryl sulfoximines in good yields. The use of prochiral electrophiles lead to modest to good diastereoselectivities up to 95%. During this study, we observed a side reaction due to a *S*-de-*tert*-butylation. After optimization of this *S*-de-*tert*-butylation reaction, the corresponding enantiopure sulfinamides could be obtained in good yields.

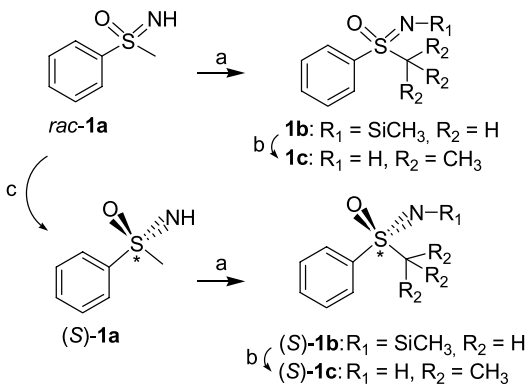
1. Introduction

The directed *ortho*-lithiation reaction is a very powerful method for the functionalization of aromatic compounds and synthesis of polysubstituted homoaromatic and heteroaromatic compounds.[1] In a previous paper,[2] we reported our first results concerning the sulfoximine[3a] group as an *ortho*-directing group[3b] for the lithiation reaction of homoaromatic systems. The reaction with *n*-butyllithium in THF at −78 °C afforded the corresponding *ortho*-lithiated species, which could be trapped with different electrophiles in good yields. Addition of benzaldehyde proceeded with modest diastereoselectivity (de=52%). The aim of this paper is to provide full details concerning the scope and limitations of this new *ortho*-directing group and to improve the stereoselectivity in the case of prochiral electrophiles. During the course of this study, we observed a troubleshooting de-*tert*-butylation side-reaction leading to sulfinamides or in some cases to cyclic sulfinic esters. We found it interesting to define optimal conditions leading to enantiopure *ortho*-substituted sulfinamides.

2. Results and discussion

2.1. Synthesis of *N*-substituted sulfoximines 1a–i

Racemic sulfoximine **1c** has been prepared as described in our previous paper.[2] The starting material for the synthesis was *rac*-**1a**, which was converted quantitatively into **1b** (Scheme 1). Repeated lateral lithiation of **1b** followed by quenching with CH_3I afforded **1c** in 86% yield. We also turned our interest in the stereoselective preparation of sulfoximine (*S*)-**1c** by using the same procedure. For that purpose, (*S*)-*S*-phenyl-*S*-methylsulfoximine ((*S*)-**1a**) was prepared in 80% optical purity by resolution of the racemic (±)-**1a** according to a published procedure.[4] In order to study the influence of the *N*-substituent sulfoximine on the *ortho*-lithiation properties, we first prepared a series of *N*-functionalized sulfoximines **1d–i** (Table 1). *N*-silylation could be achieved by reacting **1c**[2] with HMDS leading to compound **1d** in a quantitative yield (Table 1, entry 1). First attempts to alkylate sulfoximine **1c** in the presence of



Scheme 1. (a) HMDS (5 equiv), 85 °C, 40 min (100%); (b) *n*-BuLi, THF, 0 °C then CH_3I, 30 min, 20 °C repeated twice (86%); (c) (1*S*)-(+)-camphorsulfonic acid, acetone.[4]

Keywords: Sulfoximine; Lithiation; Sulfinamide; Asymmetric synthesis.
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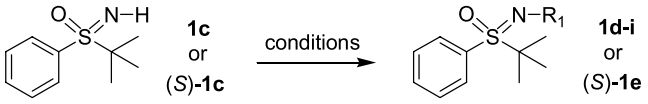
Table 1. *N*-functionalization of sulfoximine **1c** and (*S*)-**1c**



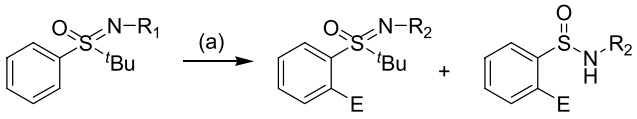
Entry	Conditions	Product	R_1	Yield%
1	HMDS (5 equiv), 85 °C, 40 min (100%)	**1d**	$Si(CH_3)_3$	100
2	KH (1 equiv), DME, 20 °C, 1 h then CH_3I, PTC, 20 °C, 12 h	**1e**	CH_3	86
3	KH (1 equiv), DME, 20 °C, 1 h then CH_3I, PTC, 20 °C, 12 h	(*S*)-**1e**	CH_3	86
4	KH (1 equiv), DME, 20 °C, 1 h then Br-$(CH_2)_2OCH_3$, PTC, 20 °C, 12 h	**1f**	$(CH_2)_2OCH_3$	92
5	KH (1 equiv), DME, 20 °C, 1 h then Br–CH_2–CH=CH_2, PTC, 20 °C, 12 h	**1g**	CH_2–CH=CH_2	95
6	KH (1 equiv), DME, 20 °C, 1 h then Boc_2O, PTC, 20 °C, 12 h	**1h**	COO^tBu	63
7	$(CH_3)_3COCl$, Na_2CO_3, CH_2Cl_2, 20 °C, 2 h	**1i**	CO^tBu	44

sodium hydride afforded low yields, most likely due to steric hindrance of the *tert*-butyl group and the poor nucleophilicity of the sulfoximine nitrogen. Finally, sulfoximine **1c** could be alkylated with success according to a literature procedure by deprotonation with potassium hydride in DME[5] in the presence of tetrabutylammonium bromide and quenching with various electrophiles to afford the *N*-substituted sulfoximines **1e–h** in good yields (Table 1, entries 2, 4–6). *tert*-Butylsulfoximine[2] (*S*)-**1e** (Table 1, entry 3) was obtained without erosion of the optical purity (ee = 80%) by using this procedure. Treatment of sulfoximine **1c** with pivaloyl chloride and sodium carbonate in a biphasic mixture of water and dichloromethane afforded, in a moderate yield, the instable[6] crude *N*-pivaloyl sulfoximine **1i** (Table 1, entry 7).

2.2. Metalation reaction of sulfoximines 1c–g

Preliminary experiments using various conditions have been described before by us.[2] We summarize here the main results. With the *N*-unprotected sulfoximine **1c**, 2 equiv of *n*-BuLi followed by quenching with methyl iodide or methanol-*d* afforded, respectively, products **2a** and **2b** in low yields (Table 2, entries 1 and 2). To examine the scope of this reaction with several other electrophiles, we then studied the *ortho*-functionalization of the *N*-protected sulfoximines **1d–g** (Table 2, entries 3–18). *ortho*-Lithiation of the *N*-trimethylsilyl sulfoximine **1d** with *n*-BuLi at −78 °C is very fast and, the intermediate lithio species was quenched after 10 min with methanol-*d* to afford compound **2f** in 95% yield (Table 2, entry 7). However, a small amount

Table 2. Metalation reaction of sulfoximines **1c–g** and quenching with electrophiles

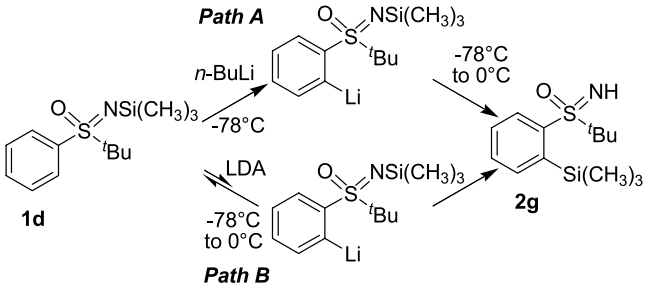


Entry	Sulfoximine	R_1	Electrophile	E	R_2	Product	Yield%
1	**1c**	H	CH_3I	CH_3	H	**2a**	50
2	**1c**	H	CH_3OD	D	H	**2b**	60
3	**1d**	$Si(CH_3)_3$	CH_3I	CH_3	H	**2a**	90
4	**1d**	$Si(CH_3)_3$	$(CH_3)_2S_2$	SCH_3	H	**2c**	95
5	**1d**	$Si(CH_3)_3$	I_2	I	H	**2d**	75
6	**1d**	$Si(CH_3)_3$	C_2Cl_6	Cl	H	**2e**	76
7	**1d**	$Si(CH_3)_3$	CH_3OD	D	$Si(CH_3)_3$	**2f**	95[a]
8	**1d**	$Si(CH_3)_3$	—	$Si(CH_3)_3$	H	**2g**	95
9	**1e**	CH_3	CH_3I	CH_3	CH_3	**2h**	95
10	**1e**	CH_3	$(CH_3)_2S_2$	SCH_3	CH_3	**2i**	78
11	**1e**	CH_3	I_2	I	CH_3	**2j**+**3a**[b]	—
12	**1e**	CH_3	C_2Cl_6	Cl	CH_3	**2k**+**3b**[b]	—
13	**1e**	CH_3	CH_3OD	D	CH_3	**2l**	92[a]
14	**1f**	$(CH_2)OCH_3$	CH_3I	CH_3	$(CH_2)OCH_3$	**2m**	55
15	**1f**	$(CH_2)OCH_3$	$(CH_3)_2S_2$	SCH_3	$(CH_2)OCH_3$	**2n**	65
16	**1g**	$CH_2CH=CH_2$	CH_3I	CH_3	$CH_2CH=CH_2$	**2o**	96
17	**1g**	$CH_2CH=CH_2$	$(CH_3)_2S_2$	SCH_3	$CH_2CH=CH_2$	**2p**	90
18	**1g**	$CH_2CH=CH_2$	CH_3OD	D	$CH_2CH=CH_2$	**2q**	95[a]

(a) Reaction performed with *n*-BuLi (1.2 equiv), THF, −78 °C (2 equiv of *n*-BuLi with **1c** to obtain **2a**, **2b**; 0 °C with **1d** to obtain **2g**), 10 min then electrophile, 2 h (1 h for **1d**), −78 °C.
[a] Conversion determined by ^1H NMR.
[b] Conversion into the sulfinamide occured during the purification.

of compound **2g** corresponding to the migration of the trimethylsilyl group could be isolated. When the *ortho*-lithiated species was allowed to reach 0 °C, compound **2g** was obtained in 95% yield (Table 2, entry 8).

It is interesting to note that this migration also occurred when LDA is used as lithiating agent. When a lithium amide is employed, the formation of **2g** probably proceeded via an equilibrium between the starting sulfoximine **1d** and the *ortho*-lithiated sulfoximine, which is trapped by the trimethylsilyl group shifting the equilibrium to the formation of **2g** (Scheme 2).



Scheme 2. Lithiation of *N*-trimethylsilysulfoximine **1d**: Path A: Non-reversible conditions (*n*-BuLi). Path B: Reversible conditions (LDA).

Trapping of the intermediate lithio species obtained from **1d–g** with methyl iodide and dimethyl disulfide, afforded the corresponding *ortho*-substituted sulfoximines in good yields (Table 2, respectively, entries 3, 9, 14, and 16 and entries 4, 10, 15, and 17). These last results clearly show that *N*-protected sulfoximines **1d–g** are superior to the *N*-unprotected sulfoximine **1c** to provide satisfactory yields. Use of iodine or hexachloroethane as electrophiles proceeded smoothly with the *N*-silylated sulfoximine **1d** (Table 2, entries 5 and 6). With sulfoximine **1e**, an unseparable mixture of *ortho*-substituted sulfoximines **2j**,**k** and their corresponding sulfinamides **3a**,**b** was observed (Table 2, entries 11 and 12). Optimization of this reaction giving rise to the exclusive formation of sulfinamides will be further described in this paper.

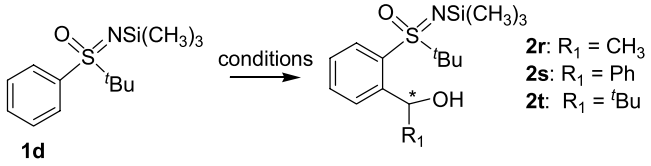
2.3. Quenching with prochiral electrophiles

In order to investigate the potential of the chiral sulfoximine *ortho*-directing group as a new synthetic tool for asymmetric induction, we decided to test various prochiral electrophiles. The first experiments were carried out with sulfoximine **1d** in THF and various aldehydes (Table 3). Acetaldehyde and pivaldehyde (Table 3, entries 1 and 7) gave satisfactory yields and medium stereocontrol, while no stereocontrol was obtained with benzaldehyde (Table 3, entry 2). Decreasing the solvent polarity by means of toluene in the presence of *sec*-BuLi/TMEDA allowed us to improve somewhat the level of stereocontrol (de=50%) with benzaldehyde (Table 3, entry 6). Under the same conditions, *N*-methylsulfoximine **1e** afforded along with the desired *ortho*-functionalized sulfoximines **2u**,**v**, sulfinic esters **4a–c** (Table 4). These by-products result from a de-*tert*-butylation reaction followed by an intramolecular cyclisation of the resultant sulfinamide with the hydroxy group. With acetaldehyde, the sulfinic ester **4a** is the sole product observed with modest diastereoselectivity (Table 4, entry 1). In the case of benzaldehyde, alcohol **2u** was recovered quantitatively in the crude reaction mixture, but flash chromatography led to the sulfinic ester **4b** in a quantitative yield and once again with a modest diastereoisomeric excess (Table 4, entry 2). Pivaldehyde gave a 1/1 mixture of *ortho*-substituted sulfoximine **2v** and sulfinic ester **4c** in moderate yields and excellent stereocontrol in both cases (Table 4, entry 3). It is interesting to point out that this de-*tert*-butylation reaction seems to be easier with *ortho*-substituted sulfoximines. Indeed, no de-*tert*-butylation reaction is detected during flash chromatography of the starting material **1e**. In spite of these interesting results in terms of stereocontrol, the de-*tert*-butylation reaction limits the yields and the reproducibility of this *ortho*-functionalization of aryl-sulfoximines. Since we could not get away from this side reaction, we optimized the conditions to obtain a clean stereoselective de-*tert*-butylation reaction to improve the overall yield of this process. Given the impressive applications of chiral sulfinamides reported these last years in literature,[7] efficient stereoselective routes to new *ortho*-substituted sulfinamides may be highly desirable.

2.4. Optimization of the de-*tert*-butylation reaction

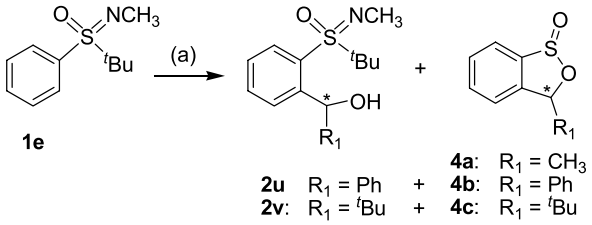
Many papers[8–11] report the conversion of sulfoximines into sulfinamides. These include the preparation of epoxides and cyclopropanes from β-hydrosulfoximines[10] and γ-ketosulfoximines,[8b] respectively, which is accompanied in both cases by the formation of sulfinamides (Scheme 3a

Table 3. Metalation reaction of sulfoximine **1d** followed by trapping with prochiral electrophiles



Entry	Conditions	Product	Yield%	de%
1	*n*-BuLi (1.2 equiv), THF, −78 °C, 10 min then CH_3CHO, −78 °C, 1 h	**2r**	76	50
2	*n*-BuLi (1.2 equiv), THF, −78 °C, 10 min then PhCHO, −78 °C, 1 h	**2s**	60	0
3	*n*-BuLi (1.2 equiv), TMEDA, THF, −78 °C, 10 min then PhCHO, −78 °C, 1 h	**2s**	60	25
4	*n*-BuLi (1.2 equiv), TMEDA, ether, −78 °C, 10 min then PhCHO, −78 °C, 1 h	**2s**	60	40
5	*n*-BuLi (1.2 equiv), TMEDA, toluene, −78 °C, 10 min then PhCHO, −78 °C, 1 h	**2s**	60	40
6	*sec*-BuLi (1.2 equiv), TMEDA, toluene, −78 °C, 10 min then PhCHO, −78 °C, 1 h	**2s**	60	50
7	*n*-BuLi (1.2 equiv), THF, −78 °C, 10 min then ^{t}BuCHO, −78 °C, 1 h	**2t**	71	67

Table 4. Quenching of the *ortho*-lithiated *N*-methylsulfoximine **1e** with prochiral electrophiles



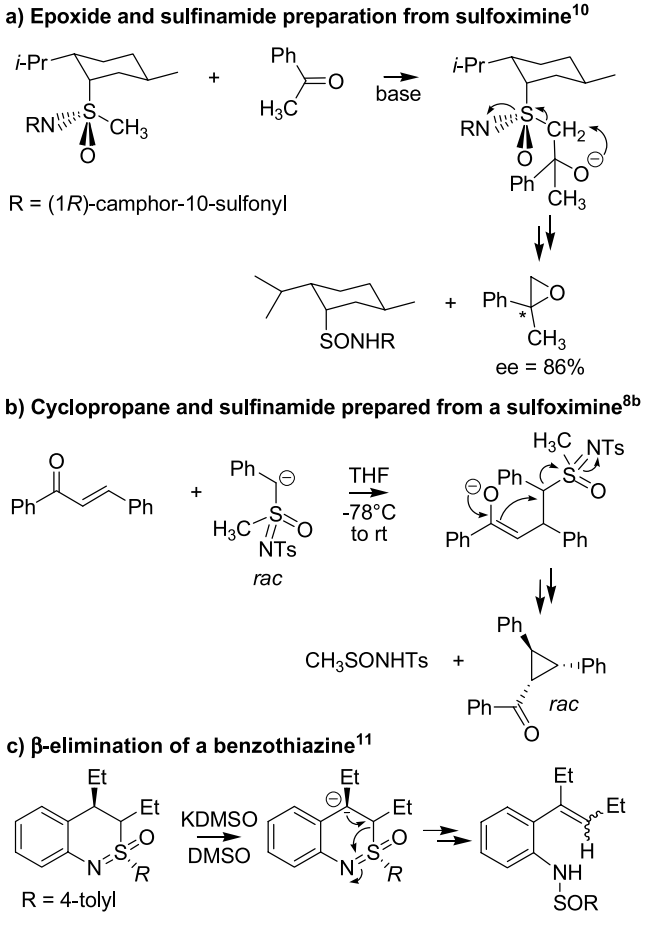
Entry	Electrophile	Product	Yield%	de%[a]	Product	Yield%	de%[b]
1	CH_3CHO	—	—	—	**4a**	100	13
2	PhCHO	**2u**	100[c]	10	**4b**	100[c]	10
3	^{t}BuCHO	**2v**	25	95	**4c**	25	95

(a) Reaction performed with *n*-BuLi (1.2 equiv), THF, −78 °C, 10 min, then electrophile, −78 °C, 2 h.
[a] Determined by ^{1}H NMR from the crude product.
[b] After purification on silica gel.
[c] Before purification.

and b). More closely related to our case, is the β-elimination of benzothiazines reported by Harmata[11] in the presence of KDMSO (Scheme 3c). The driving force of this rearrangement seems to be the apparition of an anion at the β- or γ-position related to the sulphur atom generated by the use of a base. A second driving force might also appear after complexation of the lone pair of the nitrogen atom by an electron poor species (proton or Lewis acid).[12] This fact would explain the observed instability of **1i** bearing an electron withdrawing group on the nitrogen atom.[6] Sulfoximine **1e** was first subjected to Harmata conditions[10] using KDMSO at 50 °C. The racemic sulfinamide **3c** was obtained in 70% yield (Table 5, entry 1). A weaker base such as potassium *tert*-butoxide yielded the starting sulfoximine **1e** besides traces of the desired sulfinamide **3c**. During the course of our study, Bolm et al.[13] described the conversion of C_2 symmetric bis(sulfoximines) into bis(sulfinamides) by using diborane. These results prompted us to test these new conditions with the sulfoximine **1e** (Table 5, entry 2). A clean de-*tert*-butylation reaction was achieved with 2 equiv of BH_3 affording sulfinamide **3c** in 76% yield. The formation of sulfinamide **3c** could be explained by both the Lewis acid property and the hydride donor ability of diborane.

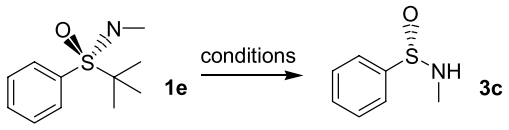
We also tried other hydride donors such as lithium tetrahydruroaluminate or sodium cyanoborohydride (Table 5, entries 3–7). The best result was obtained with 3 equiv of lithium tetrahydruroaluminate in THF affording **3c** in 60% yield (Table 5, entry 7) whereas other reducing agents gave only poor yields. Finally, the de-*tert*-butylation reaction was studied in the presence of Brönsted or Lewis acids. Strong Brönsted acids (2 M hydrochloric acid or Amberlyst® 15) gave rise to degradation products. Similarly, zinc or magnesium bromides and copper(II) chloride (Table 5, entries 8–10) afforded sulfinamide **3c** in a poor yield together with degradation products while magnesium perchlorate in THF gave sulfinamide **3c** in 76% yield (Table 5, entry 12).

Having at hand good conditions (BH_3 or $Mg(ClO_4)_2$) to convert *tert*-butyl-arylsulfoximines to racemic arylsulfinamides, we focused then our attention on the stereoselectivity of this de-*tert*-butylation reaction. The sulfinamide (*S*)-**3c** was obtained using diborane or magnesium perchlorate in 76% yield, and this, without detectable loss in optical purity (ee = 80%). Comparison of the optical rotation with literature data[14] allowed us to assign the *S*-absolute configuration showing that the de-*tert*-butylation reaction proceeded with complete retention of configuration.



Scheme 3. Conversion of sulfoximines into sulfinamides. (a) Epoxide and sulfinamide preparation from sulfoximine;[10] (b) Cyclopropane and sulfinamide prepared from a sulfoximine;[8b] (c) β-elimination of a benzothiazine.[11]

Table 5. Study of the de-*tert*-butylation reaction of **1e** to obtain sulfinamide **3c**

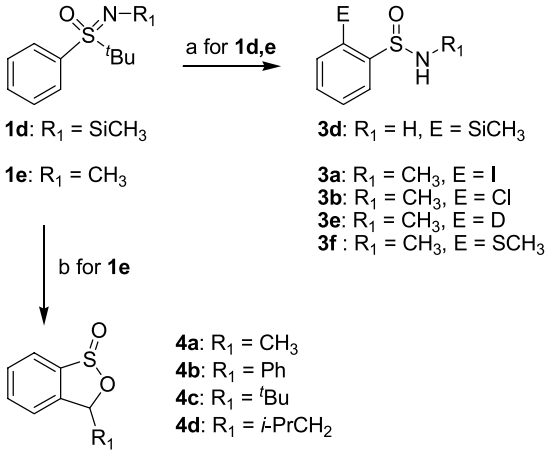


Entry	Conditions	Solvent	Yield%
1	KDMSO (2 equiv), 30 min, 50 °C	DMSO	70[a]
2	BH_3 (2 equiv), 12 h, 20 °C	THF	76[a]
3	$NaBH_4$ (1 equiv), 5 days, 20 °C	$CDCl_3$	5[b]
4	$NaBH_3CN$ (1 equiv), 5 days, 20 °C	$CDCl_3$	5[b]
5	$LiAlH_4$ (1 equiv), 5 days, 20 °C	$CDCl_3$	10[b]
6	$LiAlH_4$ (1 equiv), 24 h, 20 °C	THF	20[b]
7	$LiAlH_4$ (3 equiv), 24 h, 20 °C	THF	60[b]
8	$ZnBr_2$ (1 equiv), 5 days, 20 °C	$CDCl_3$	35[b,c]
9	$MgBr_2$ (1 equiv), 5 days, 20 °C	$CDCl_3$	43[b,c]
10	$CuCl_2$ (1 equiv), 5 days, 20 °C	$CDCl_3$	—[c]
11	$Mg(ClO_4)_2$ (1 equiv), 24 h, 20 °C	$CDCl_3$	—[c]
12	$Mg(ClO_4)_2$ (1 equiv), 24 h, 20 °C	THF	84[b] (76[a])

[a] Isolated yield.
[b] Determined by ^1H NMR.
[c] Degradation.

2.5. Optimization of the *ortho*-functionalization/de-*tert*-butylation sequence

We next examined various conditions in order to develop a procedure affording the *ortho*-substituted sulfinamides from sulfoximines **1d**,**e**. The best results were obtained by treating the residue of the *ortho*-lithiation step in THF with magnesium perchlorate (Scheme 4). According to this procedure, the sulfinamides **3a**,**b**,**d**–**f** were obtained in fair to good yields (Table 6). In the case of prochiral electrophiles, the sulfinic esters **4a** and **4c**,**d** were obtained in moderate yields and 28–95% diastereoisomeric excess (Scheme 4, Table 7). At this stage of the study, it seems difficult to provide additional information on the origin of the stereoselectivity. Curiously, no stereocontrol was observed with benzaldehyde (Table 7, entry 2).



Scheme 4. (a) *n*-BuLi (1.5 equiv), THF, −78 °C, 10 min then electrophile (Table 6), 2 h, 0 °C and quenching with NH_4Cl, extraction, evaporation then $Mg(ClO_4)_2$ (1 equiv), THF, 24 h (66 to 95%); (b) *n*-BuLi (1.5 equiv), THF, −78 °C, 10 min then aldehyde (Table 7), 2 h, −78 °C and quenching with NH_4Cl, extraction, evaporation then $Mg(ClO_4)_2$ (1 equiv), THF followed for **4b**–**d** by $MgBr_2$ (1 equiv) in $CHCl_3$ (35 to 58%).

3. Conclusion

The sulfoximine group has shown to be an excellent *ortho*-directing group in lithiation reactions. Several electrophiles were used to afford the corresponding *ortho*-functionalized arylsulfoximines in good yields. We had better to use *N*-substituted sulfoximines. The use of prochiral electrophiles afford modest to good diastereoselectivities up to 95%. During this study, we observed a side reaction due to a *S*-de-*tert*-butylation. This side *S*-de-*tert*-butylation reaction has been optimized and allowed us to open a new route to *ortho*-substituted enantiopure sulfinamides and sulfinic esters.

Table 6. *ortho*-Functionalization/de-*tert*-butylation sequence

Entry	Sulfoximine	Electrophile	Product	Yield%
1	**1d**	—[a]	**3d**	71
2	**1e**	I_2	**3a**	80
3	**1e**	C_2Cl_6	**3b**	82
4	**1e**	CH_3OD	**3e**	95[b]
5	**1e**	$(CH_3)_2S_2$	**3f**	66

[a] The electrophile is sulfoximine **1d** itself.
[b] Conversion determined by ^1H NMR

Table 7. Synthesis of sulfinic esters **4a**–**d**

Entry	Electrophile	Product	Yield%	de%
1	CH_3CHO	**4a**	58	28
2	PhCHO	**4b**	45	0
3	^{t}BuCHO	**4c**	40	>95
4	*i*-$PrCH_2CHO$	**4d**	35	48

4. Experimental

4.1. General details

Infrared spectra were recorded on a Beckmann IR 4250 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a

200 or 300 MHz Bruker apparatus and calibrated with the residual undeuterated solvent. Spectra were recorded in deuteriochloroform. Chemicals were purchased from Aldrich Co. and Janssen Co. and, unless otherwise stated, were used without further purification. Tetrahydrofuran was distilled from sodium–benzophenone ketyl. Flash chromatography was performed with silica gel 60 (70–230 mesh from Merck) and monitored by thin layer chromatography (TLC) with silica plates (Merck, Kieselgel 60 F254).

4.1.1. *S*-Methyl-*S*-phenylsulfoximine (1a). In a 500 mL round-bottomed flask were introduced NaN_3 (4.8 g, 73.7 mmol), $CHCl_3$ (20 mL) and methyl-phenylsulfoxide[15] (9.4 g, 67 mmol) previously dissolved in $CHCl_3$ (60 mL). The mixture was cooled at 0 °C and concentrated H_2SO_4 (17.5 mL) was added dropwise. The solution was stirred and heated at 45 °C for 5 h. After cooling at 0 °C, 150 mL of water were added and stirring was continued until dissolution is complete. The aqueous layer was extracted three times with CH_2Cl_2 (100 mL). The combined organic layers were dried on $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (AcOEt) to yield 8.1 g (78%) of **1a** as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.70 (br s, 1H), 3.10 (s, 3H), 7.60 (m, 3H), 8.06 (d, J= 8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 46.5, 128.0, 129.7, 133.5, 143.7. IR (cm^{-1}, KBr): ν=3269, 1645, 1445, 1221, 1099. Anal. Calcd for C_7H_9NOS: C, 54.17; H, 5.84; N, 9.02; S, 20.66. Found: C, 54.40; H, 5.72; N, 9.02; S, 20.31. Conditions for the separation of the two enantiomers: CHIRALCEL OJ. Eluent: heptane/isopropanol 90:10. Temperature: 18 °C. λ=230 nm, flow rate: 1 mL min^{-1}. Retention times: 24 min (*R*) and 30 min (*S*).

4.1.2. *N*-Trimethylsilyl-*S*-methyl-*S*-phenylsulfoximine (1b). In a 250 mL round-bottomed flask were introduced the sulfoximine **1a** (3.4 g, 22.0 mmol) and HMDS (23.3 mL, 110 mmol). The mixture was heated at 85 °C for 40 min under a vigorous stirring. The solvent was removed under reduced pressure. The compound **1b** was obtained as a yellow oil in a quantitative yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.10 (s, 9H), 3.00 (s, 3H), 7.50 (m, 3H), 8.00 (d, J=8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 2.7, 49.7, 127.4, 129.3, 132.7, 145.2. IR (cm^{-1}, KBr): ν= 3270, 2955, 1446, 1320, 1285, 1247, 1228, 1151, 1089. Anal. Calcd for $C_{10}H_{17}NOSSi$: C, 52.82; H, 7.54; N, 6.16; S, 14.10. Found: C, 52.83; H, 7.26; N, 5.98; S, 14.16.

4.1.3. *S-tert*-Butyl-*S*-phenylsulfoximine (1c). To a solution of sulfoximine **1b** (4.98 g, 21.9 mmol) in anhydrous THF (50 mL) under a nitrogen atmosphere at −0 °C, a 2.5 M solution of *n*-BuLi in hexanes (8.76 mL, 21.9 mmol) was slowly added. Then, methyl iodide (1.36 mL, 21.9 mmol) was added and the mixture was stirred for 30 min at 20 °C. The solution was cooled at 0 °C and the same procedure was repeated two more times. Hydrolysis was carried out with MeOH (20 mL) and stirred for an additional 30 min. So, a saturated aqueous solution of NH_4Cl (20 mL) and water (20 mL) were added. The mixture was extracted with CH_2Cl_2 (3×100 mL). The collected organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oil. The residue was purified by flash chromatography on silica gel (AcOEt/cyclohexane 1:1). The sulfoximine **1c** was obtained as a yellow oil (3.72 g, 86%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.34 (s, 9H), 2.50 (br s, 1H), 7.54 (m, 3H), 7.94 (d, J=8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4, 60.7, 128.9, 131.1, 133.3, 138.2. IR (cm^{-1}, KBr): ν=3256, 2975, 1476, 1448, 1366, 1210, 1107, 1075. MS (IC$^+$, isobutane, *m/z*): M+H$^+$=198. Conditions for the separation of the two enantiomers: CHIRALCEL OJ. Eluent: heptane/isopropanol 90:10. Temperature: 19 °C. λ=220 nm, flow rate: 1 mL min^{-1}. Retention times: 13 and 16 min.

4.1.4. *S-tert*-Butyl-*N*-trimethylsilyl-*S*-phenylsulfoximine (1d). As described for **1b** starting from sulfoximine **1c** (2.0 g, 10.1 mmol) and HMDS (10.7 mL, 50.5 mmol). The compound **1d** was obtained as a yellow oil in a quantitative yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.08 (s, 9H), 1.25 (s, 9H), 7.51 (m, 3H), 7.85 (d, J=6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 2.6, 23.8, 60.9, 128.2, 130.4, 132.1, 140.1. IR (cm^{-1}, KBr): ν=3066, 2955, 2897, 1445, 1286, 1137, 1083, 837, 756, 694, 633. Anal. Calcd for $C_{13}H_{23}NOSSi$: C, 57.94; H, 8.60; N, 5.20; S, 11.90. Found: C, 58.19; H, 8.31; N, 5.07; S, 12.27.

4.1.5. *S-tert*-Butyl-*N*-methyl-*S*-phenylsulfoximine (1e). In a 250 mL round-bottomed flask were introduced DME (40 mL) and sodium hydride (30% dispersion in mineral oil, 2.04 g, 15.2 mmol). A solution of *S*-phenyl-*S-tert*-butylsulfoximine (**1c**) (3.0 g, 15.2 mmol) in DME (20 mL) was then added dropwise in the sodium hydride solution. The mixture was stirred for 1 h at 20 °C. Methyl iodide (4.7 mL, 76 mmol) was added and the solution stirred for 12 h at 20 °C. The mixture was quenched with a saturated aqueous solution of NH_4Cl (100 mL), and extracted with CH_2Cl_2 (3×100 mL). The collected organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica gel (AcOEt/cyclohexane 1:1). The sulfoximine **1e** was obtained as a white solid (2.76 g, 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 9H), 2.64 (s, 3H), 7.55 (m, 3H), 7.75 (d, J=8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4, 30.2, 60.3, 129.2, 132.1, 133.0, 134.3. IR (cm^{-1}, KBr): ν=1446, 1232, 1130, 1101, 1068. Anal. Calcd for $C_{11}H_{17}NOS$: C, 62.52; H, 8.05; N, 6.63; S, 15.17. Found: C, 62.46; H, 7.98; N, 6.72; S, 15.10. Conditions for the separation of the two enantiomers: CHIRALCEL OJ. Eluent: heptane/isopropanol 95:5. Temperature: 19 °C. λ=220 nm, flow rate: 1 mL min^{-1}. Retention times: 6 and 9 min.

4.1.6. *S-tert*-Butyl-*N*-2-methoxyethyl-*S*-phenylsulfoximine (1f). In a 250 mL round-bottomed flask were introduced DME (30 mL) and potassium hydride (30% dispersion in mineral oil, 1.35 g, 10.1 mmol). A solution of *S*-phenyl-*S-tert*-butylsulfoximine (**1c**) (2.0 g, 10.1 mmol) in DME (15 mL) was then added dropwise in the potassium hydride solution. The mixture was stirred for 1 h at 20 °C. Tetrabutylammonium bromide (150 mg, 0.5 mmol) and 2-bromoethylmethylether (1.9 mL, 20.2 mmol) were then added and the resulting mixture was stirred for 12 h. The mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3×100 mL). The work-up was the same as above. The product was purified by flash chromatography on silica gel (AcOEt/

cyclohexane 1:2). Product **1f** was obtained as a colorless oil (2.37 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 9H), 3.12 (m, 2H), 3.31 (s, 3H), 3.49 (m, 2H), 7.50 (m, 3H), 7.80 (d, $J=8.0$ Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4, 43.8, 59.2, 60.4, 75.0, 129.1, 132.1, 133.0, 135.1. IR (cm^{-1}, KBr): 3220, 2927, 1444, 1123, 1087, 1055. Anal. Calcd for $C_{13}H_{21}NO_2S$: C, 61.14; H, 8.29; N, 5.48; S, 12.56. Found: C, 60.86; H, 8.34; N, 5.68; S, 12.46.

4.1.7. *N*-Allyl-*S*-*tert*-butyl-*S*-phenylsulfoximine (1g). As above reaction of *S*-phenyl-*S*-*tert*-butylsulfoximine (**1c**) (2 g, 10.1 mmol) in DME (20 mL), potassium hydride (30% dispersion in mineral oil, 1.35 g, 10.1 mmol) in DME (30 mL), tetrabutylammonium bromide (150 mg, 0.5 mmol) and allyl bromide (1.7 mL, 20.2 mmol) afforded after flash chromatography on silica gel (AcOEt/cyclohexane 1:2) product **1g** as a colorless oil (2.27 g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 9H), 3.45 (ddt, $J=16$, 5, 2 Hz, 1H), 3.64 (ddt, $J=16$, 5, 2 Hz, 1H), 5.05 (dq, $J=10$, 2 Hz, 1H), 5.25 (dq, $J=17$, 2 Hz, 1H), 5.96 (dq, $J=17$, 5 Hz, 1H), 7.55 (m, 3H), 7.76 (d, $J=8$ Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4, 46.3, 60.6, 114.0, 129.1, 132.0, 133.0, 135.0, 138.9. IR (cm^{-1}, KBr): 2976, 1444, 1266, 1214, 1133, 1083. Anal. Calcd for $C_{13}H_{19}NOS$: C, 65.78; H, 8.01; N, 5.90; S, 13.51. Found: C, 65.93; H, 8.40; N, 6.07; S, 13.57.

4.1.8. *S*-*tert*-Butyl-*N*-*tert*-butyloxycarbonyl-*S*-phenylsulfoximine (1h). As above, reaction of *S*-phenyl-*S*-*tert*-butylsulfoximine (**1c**) (1.0 g, 5 mmol) in DME (10 mL), potassium hydride (30% dispersion in mineral oil, 0.70 g, 5.2 mmol) in DME (20 mL), tetrabutylammonium bromide (75 mg, 0.25 mmol) and di-*tert*-butyl dicarbonate (2.18 g, 10 mmol) afforded, after purification by chromatography on silica gel (AcOEt/petroleum ether 1:2), the product **1h** as a sticky colorless oil (0.95 g, 63%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 9H), 1.37 (s, 9H), 7.56 (m, 3H), 7.83 (d, $J=8$ Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.7, 28.3, 61.6, 80.4, 129.3, 130.6, 133.7, 134.7, 158.4. IR (cm^{-1}, KBr): 2977, 1693, 1668, 1274, 1154. Anal. Calcd for $C_{15}H_{23}NO_3S$: C, 60.58; H, 7.74; N, 4.71; S, 10.78. Found: C, 60.56; H, 7.34; N, 4.68; S, 10.46.

4.2. General procedure A for the metalation reaction of compounds 1d–g

To a cooled (−78 °C) solution of the corresponding *N*-protected-*S*-phenyl-*S*-*tert*-butylsulfoximine **1d–g** (0.71 mmol) in anhydrous THF (10 mL) under a nitrogen atmosphere was added a 2.5 M solution in hexanes of *n*-BuLi (0.34 mL, 0.85 mmol) while maintaining the temperature at −78 °C. The mixture was stirred for 10 min at this temperature before addition of the appropriate electrophile. The resulting solution was then stirred for 1 h at −78 °C with **1d** and 2 h with **1e–g**. The reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL) and extracted with dichloromethane (3×10 mL). The organic layers were dried on $MgSO_4$ and the solvent was removed under reduced pressure. The residues obtained from **1e–g** were purified by flash chromatography on silica gel (AcOEt/cyclohexane) whereas the oil obtained from **1d** was dissolved in methanol and stirred for 1 h at 20 °C. Methanol was removed under reduced pressure and the product was purified by flash chromatography on silica gel (AcOEt).

4.2.1. *S*-*tert*-Butyl-*S*-(2-tolyl)sulfoximine (2a). According to the general procedure A from **1d**, the electrophile was MeI (0.22 mL, 3.55 mmol). The yield was 0.135 g (90%) of an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.33 (s, 9H), 2.74 (s, 3H), 7.30–7.48 (m, 3H), 8.00 (d, $J=11$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3, 24.4, 62.1, 126.4, 133.3, 133.6, 134.0, 136.8, 141.0. IR (cm^{-1}, KBr): $\nu=3200$, 2974, 2931, 1478, 1459, 1221, 1189, 1065, 976, 775. Anal. Calcd for $C_{11}H_{17}NOS$: C, 62.52; H, 8.11; N, 6.63; S, 13.51. Found: C, 62.15; H, 8.10; N, 6.67; S, 13.37.

4.2.2. *S*-*tert*-Butyl-*S*-(2-methylthiophenyl)sulfoximine (2c). According to the general procedure A from **1d**, the electrophile was Me_2S_2 (0.32 mL, 3.55 mmol). The yield was 0.164 g (95%) of an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.42 (s, 9H), 2.43 (s, 3H), 7.25 (m, 2H), 7.50 (t, $J=11$ Hz, 1H), 8.00 (d, $J=11$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9, 24.2, 62.8, 123.6, 125.1, 133.0, 134.4, 134.5, 143.2. IR (cm^{-1}, KBr): $\nu=3273$, 2968, 2919, 1447, 1432, 1217, 1072, 971, 774. HRMS (IE, *m*/*z*): calcd for $C_{11}H_{17}NOS_2$: 243.0752. Found: 243.0748.

4.2.3. *S*-*tert*-Butyl-*S*-(2-iodophenyl)sulfoximine (2d). According to the general procedure A from **1d**, the electrophile was I_2 (0.432 g, 1.7 mmol). The yield was 0.172 g (75%) of a white solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.44 (s, 9H), 7.16 (t, $J=11$ Hz, 1H), 7.51 (t, $J=11$ Hz, 1H), 8.17 (d, $J=11$ Hz, 1H), 8.25 (d, $J=11$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.0, 54.9, 93.9, 125.7, 129.0, 132.5, 140.1, 147.1. HRMS (IE, *m*/*z*): calcd for $C_{10}H_{14}INOS$: 322.9841. Found: 322.9842.

4.2.4. *S*-*tert*-Butyl-*S*-(2-chlorophenyl)sulfoximine (2e). According to the general procedure A from **1d**, the electrophile was C_2Cl_6 (0.113 mL, 0.99 mmol). Yield 0.125 g (76%) of a white solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.39 (s, 9H), 7.40 (m, 3H), 8.13 (d, $J=11$ Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.1, 62.5, 126.7, 132.7, 133.9, 134.7, 135.2, 136.0. HRMS (IE, *m*/*z*): calcd for $C_{10}H_{14}ClNOS$: 231.0485. Found: 231.0480.

4.2.5. *S*-*tert*-Butyl-*N*-trimethylsilyl-*S*-(2-^{2}*H*-phenyl)sulfoximine (2f) According to the general procedure A from **1d**, the electrophile was MeOD (0.144 mL, 3.55 mmol). No methanolysis at the end of the reaction. The yield was 95% determined by ^{1}H NMR. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.11 (s, 9H), 1.28 (s, 9H), 7.52 (m, 3H), 7.90 (d, $J=8$ Hz, 1H).

4.2.6. *S*-*tert*-Butyl-*S*-(2-trimethylsilylphenyl)-sulfoximine (2g). In a round-bottomed flask flushed with nitrogen, a solution of *N*-trimethylsilyl-*S*-phenyl-*S*-*tert*-butylsulfoximine (**1d**) (0.2 g, 0.74 mmol) in THF (5 mL) was cooled at −78 °C. A 2.5 M solution in hexanes of *n*-BuLi (0.35 mL, 0.87 mmol) was then added. The mixture was allowed to warm to 0 °C and stirred for 1 h. Hydrolysis was carried out with a saturated aqueous solution of NH_4Cl (5 mL) and the aqueous layer was extracted with dichloromethane (3× 5 mL). The yield was 0.19 g (95%) of **2g** as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.41 (s, 9H), 1.35 (s, 9H), 7.54 (m, 2H), 7.85 (d, $J=9$ Hz, 1H), 8.01 (d, $J=9$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 2.5, 24.7, 61.5, 129.0, 131.8, 131.9, 136.9, 143.0, 143.7. IR (cm^{-1}, KBr): $\nu=3333$, 3256, 2955, 1245, 1214, 1109, 966, 846, 760. Anal. Calcd for

$C_{13}H_{23}NOSSi$: C, 57.94; H, 8.60; N, 5.20; S, 11.90. Found: C, 58.03; H, 8.40; N, 5.07; S, 12.37.

4.2.7. *S*-*tert*-Butyl-*N*-methyl-*S*-(2-tolyl)sulfoximine (2h). According to the general procedure A from **1e**, the electrophile was MeI (88 μL, 1.42 mmol). The yield was 0.152 g (95%) of a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 9H), 2.65 (s, 3H), 2.69 (s, 3H) 7.29 (m, 2H), 7.42 (t, J=8 Hz, 1H), 7.76 (d, J=8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.3, 30.0, 60.3, 61.7, 126.3, 128.7, 132.6, 134.0, 134.6, 142.0. Anal. Calcd for $C_{12}H_{19}NOS$: C, 63.96; H, 8.50; N, 6.22; S, 14.23. Found: C, 63.93; H, 8.39; N, 6.07; S, 14.57.

4.2.8. *S*-*tert*-Butyl-*N*-methyl-*S*-(2-methylthiophenyl)sulfoximine (2i). According to the general procedure A from **1e**, the electrophile was Me_2S_2 (0.32 mL, 3.55 mmol). The yield was 0.142 g (78%) of a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 9H), 2.40 (s,3H), 2.68 (s, 3H), 7.18 (t, J=7 Hz, 1H), 7.26 (d, J=8 Hz, 1H), 7.47 (t, J=7 Hz, 1H), 7.75 (d, J=8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.8, 24.3, 29.9, 62.7, 123.5, 125.3, 130.9, 132.8, 135.2, 144.4. HRMS (IE, *m*/*z*): calcd for $C_{12}H_{19}NOS_2$: 257.0908. Found: 257.0904.

4.2.9. *S*-*tert*-Butyl-*N*-(2-methoxyethyl)-*S*-(2-tolyl)sulfoximine (2m). According to the general procedure A from **1f**, the electrophile was MeI (88 μL, 1.42 mmol). The yield was 0.105 g (55%) of an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 9H), 2.69 (s, 3H), 3.00–3.20 (m, 2H), 3.32 (s, 3H), 3.49 (m, 2H), 7.28 (m, 1H), 7.41 (t, J=7 Hz, 1H), 7.54 (m, 1H), 7.78 (d, J=7 Hz, 1H). IR (cm^{-1}, KBr): ν=2974, 2928, 1455, 1245, 1191, 1124, 763. ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5, 24.0, 43.4, 58.8, 61.5, 74.6, 125.9, 132.6, 133.2, 133.5, 134.2, 141.7. Anal. Calcd for $C_{14}H_{23}NO_2S$: C, 62.42; H, 8.61; N, 5.20; S, 11.90. Found: C, 62.59; H, 8.41; N, 5.07; S, 12.27.

4.2.10. *S*-*tert*-Butyl-*N*-(2-methoxyethyl)-*S*-(2-methylthiophenyl)sulfoximine (2n). According to the general procedure A from **1f**, the electrophile was Me_2S_2 (0.32 mL, 3.55 mmol). The yield was 0.14 g (65%) of an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 9H), 2.39 (s, 3H), 3.04–3.16 (m, 2H), 3.32 (s, 3H), 3.50 (m, 2H), 7.22 (m, 1H), 7.41 (m, 2H), 7.81 (d, J=7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.7, 24.1, 43.4, 58.8, 62.7, 74.4, 123.4, 125.2, 131.4, 132.7, 134.9, 144.3. IR (cm^{-1}, KBr): ν=2923, 2872, 1436, 1246, 1120, 768. HRMS (IE, *m*/*z*): calcd for $C_{14}H_{23}NO_2S_2$: 301.1170. Found: 301.1166.

4.2.11. *N*-Allyl-*S*-(2-tolyl)-*S*-*tert*-butylsulfoximine (2o). According to the general procedure A from **1g**, the electrophile was MeI (88 μL, 1.42 mmol). The yield was 0.171 g (96%) of a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 9H), 2.69 (s, 3H), 3.45 (m, 1H), 3.65 (m, 1H), 5.04 (d, J=10 Hz, 1H), 5.34 (d, J=17 Hz, 1H), 5.97 (m, 1H), 7.29 (m, 2H), 7.42 (t, J=7 Hz, 1H), 7.78 (d, J=7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6, 24.1, 46.0, 61.8, 113.7, 126.0, 132.7, 133.1, 133.6, 134.1, 138.7, 141.9. IR (cm^{-1}, KBr): ν=3057, 2976, 2930, 1455, 1270, 1216, 1118, 762. Anal. Calcd for $C_{14}H_{21}NOS$: C, 66.89; H, 8.42; N, 5.57; S, 12.76. Found: C, 66.59; H, 8.53; N, 5.57; S, 13.17.

4.2.12. *N*-Allyl-*S*-*tert*-butyl-*S*-(2-methylthiophenyl)sulfoximine (2p). According to the general procedure A from **1g**, the electrophile was Me_2S_2 (0.32 mL, 3.55 mmol). The yield was 0.151 g (90%) of a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 9H), 2.39 (s, 3H), 3.46 (m, 1H), 3.67 (m, 1H), 5.02 (d, J=11 Hz, 1H), 5.33 (d, J=17 Hz, 1H), 5.95 (m, 1H), 7.14 (t, J=7.9 Hz, 1H), 7.26 (d, J=7.9 Hz, 1H), 7.44 (t, J=7.8 Hz, 1H), 7.74 (d, J=7.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 24.6, 46.3, 63.3, 114.1, 123.7, 125.6, 129.1, 131.8, 133.1, 135.1, 144.9. Anal. Calcd for $C_{14}H_{21}NOS_2$: C, 59.32; H, 7.47; N, 4.94; S, 22.62. Found: C, 59.52; H, 7.63; N, 5.07; S, 22.97.

4.2.13. *S*-*tert*-Butyl-*S*-[2-(1-hydroxyethyl)phenyl]-sulfoximine (2r). According to the general procedure A from **1d**, the electrophile was CH_3CHO (large excess). The yield was 0.13 g (76%) of an oil consisting in an unseparable mixture of two diastereoisomers, de=50%. Minor diastereoisomer: ^{1}H NMR (200 MHz, $CDCl_3$): 1.35 (s, 9H), 1.52 (d, J=7 Hz, 3H), 5.80 (q, J=7 Hz, 1H), 7.35 (t, J=8 Hz, 1H), 7.56 (t, J=8 Hz, 1H), 7.69 (d, J=8 Hz, 1H), 7.97 (d, J=7.7 Hz, 1H). Major diastereoisomer: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.31 (s, 9H), 1.52 (d, J=7 Hz, 3H), 5.69 (q, J=7 Hz, 1H), 7.38 (t, J=8 Hz, 1H), 7.57 (t, J=8 Hz, 1H), 7.72 (d, J=8 Hz, 1H), 7.98 (d, J=7.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4, 136.0, 133.8 (3), 133.7, 133.3, 127.8, 127.6, 127.5, 127.4, 65.3, 65.1, 62.9, 61.7, 24.2, 22.8. IR (cm^{-1}, KBr): ν=3459, 3310, 2974, 2931, 1466, 1206, 1184, 979, 782, 770. HRMS (IE, *m*/*z*): calcd for $C_{12}H_{19}NO_2S$: 241.1136. Found: 241.1134.

4.2.14. *S*-*tert*-Butyl-*S*-[2-(1-hydroxybenzyl)phenyl]-sulfoximine (2s). According to the general procedure A from **1d**, the solvent was toluene and TMEDA (129 μL, 0.85 mmol) was added. *sec*-BuLi was used instead of *n*-BuLi. The electrophile was benzaldehyde (0.172 mL, 1.7 mmol). The yield was 0.13 g (60%) of an oil consisting in a mixture of two diastereoisomers (de=50%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.49 (s, 9H), 6.75 (s, 1H), 7.12 (d, J=13 Hz, 1H), 7.43 (m, 7H), 8.10 (d, J=13 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 141.8, 133.9, 133.8, 133.3, 130.8, 128.3, 127.7, 127.3, 126.8, 71.2, 63.9, 24.4. IR (cm^{-1}, KBr): ν=3273, 2972, 1451, 1205, 1176, 986, 755, 707. HRMS (IE, *m*/*z*): calcd for $C_{17}H_{21}NO_2S$: 303.1293. Found: 303.1298 and ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.52 (s, 9H), 4.03 (m, 1H), 6.84 (s, 1H), 7.17 (d, J=13 Hz, 1H), 7.36 (m, 7H), 8.07 (d, J=13 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 141.9, 134.0, 133.7, 133.1, 130.9, 128.4, 128.0, 127.5, 126.9, 71.3, 61.9, 24.3. IR (cm^{-1}, KBr): ν=3271, 2972, 1447, 1206, 980, 759, 707. HRMS (IE, *m*/*z*): calcd for $C_{17}H_{21}NO_2S$: 303.1293. Found: 303.1289.

4.2.15. *S*-*tert*-Butyl-*S*-[2-(1-hydroxy-2,2-dimethyl-propyl)phenyl]sulfoximine (2t). According to the general procedure A from **1d**, the electrophile was pivaldehyde (0.19 mL, 1.7 mmol). The yield was 0.143 g (71%) of an oil consisting in a mixture of two diastereoisomers (de=67%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.99 (s, 9H), 1.32 (s, 9H), 6.02 (s, 1H), 7.42 (t, J=11 Hz, 1H), 7.53 (t, J=11 Hz, 1H), 7.78 (d, J=11 Hz, 1H), 8.10 (d, J=11 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.1, 26.4, 27.0, 36.7, 62.1, 127.1, 129.9, 132.5, 133.5, 135.7, 144.7. IR (cm^{-1}, KBr): ν=3413, 3140, 2955, 1480, 1202, 1180, 1100, 976, 736. HRMS (IE, *m*/*z*):

calcd for $C_{15}H_{25}NO_2S$: 283.1606. Found: 283.1606. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.97 (s, 9H), 1.33 (s, 9H), 5.86 (s, 1H), 7.43 (t, J=11 Hz, 1H), 7.61 (t, J=11 Hz, 1H), 7.79 (d, J=11 Hz, 1H), 8.11 (d, J=11 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.1, 26.5, 27.0, 36.6, 61.6, 127.0, 129.6, 132.5, 133.3, 135.9, 145.3. IR (cm^{-1}, KBr): ν=3333, 2955, 2871, 1480, 1364, 1211, 1183, 1097, 978, 760. HRMS (IE, *m/z*): calcd for $C_{15}H_{25}NO_2S$: 283.1606. Found: 283.1605.

4.3. De-*tert*-butylation reaction

4.3.1. *N*-Methylbenzenesulfinamide ((*S*)-3c). To a solution of sodium borohydride (0.225 g, 5.94 mmol) in anhydrous THF (5 mL) was added at 0 °C a solution of iodine[16] (0.603 g, 2.36 mmol) in anhydrous THF (10 mL). The sulfoximine (*S*)-**1e** (0.25 g, 1.18 mmol) was dissolved in anhydrous THF (5 mL) and the previously prepared BH_3 solution was added. The mixture was stirred for 1 h at 0 and 20 °C overnight. The excess of BH_3 was cautiously destroyed with MeOH (10 mL). After 30 min, a 20% aqueous solution of potassium hydroxide (10 mL) was added and the mixture was stirred for 4 h. The product was extracted with CH_2Cl_2 (3×10 mL) and the organic layers were dried on $MgSO_4$. After removing of the solvents under reduced pressure, the residue was purified on silica gel (AcOEt/cyclohexane 1:1). The yield was 0.14 g (76%). RMN ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.53 (d, J=6 Hz, 3H), 4.07 (q, J=6 Hz, 1H), 7.47 (m, 3H), 7.67 (d, J=9 Hz, 2H). IR (cm^{-1}, KBr): 3224, 1444, 1086, 1051. MS (IC$^+$, isobutane, *m/z*): M+H$^+$=156. HRMS (IE, *m/z*): calcd for C_7H_9NOS: 155.0405. Found: 155.0405. Separation of the enantiomers was achieved on a CHIRALPAK AD. Eluent: heptane/isopropanol: 95:5. Temperature: 18 °C. λ=230 nm, flow rate: 1 mL min^{-1}. Retention times: 10.6 and 12 min. Enantiomeric excess=80%.

4.3.2. *N*-*tert*-Butylcarbonylbenzenesulfinamide (3g). To a solution of *S*-phenyl-*S*-*tert*-butylsulfoximine (**1c**) (2.0 g, 10.1 mmol) in CH_2Cl_2 (20 mL) was added a solution of Na_2CO_3 (0.53 g, 5.0 mmol) in water (15 mL). The mixture was cooled at 10 °C and pivaloyl chloride (1.25 mL, 10.1 mmol) was added. The mixture was stirred for 2 h at 20 °C. The organic layer was dried on $MgSO_4$, filtered and the solvent was removed under reduced pressure. Flash chromatography on silica gel (AcOEt/ cyclohexane 1:2) afforded **3g** as a white solid (1.0 g, 45%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 9H), 7.52 (m, 3H), 7.65 (m, 2H), 7.90 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.4, 40.1, 125.1, 129.8, 132.2, 144.4, 179.2. IR (cm^{-1}, KBr): 3205, 1686. MS (IC$^+$, isobutane, *m/z*): M+H$^+$=226. Anal. Calcd for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.71; N, 6.22; S, 14.23. Found: C, 58.59; H, 6.51; N, 6.15; S, 14.28.

4.4. General procedure B for the sequence metalation/de-*tert*-butylation of sulfoximines 1d,e

To a solution of the corresponding sulfoximine **1d**,**e** (0.95 mmol) in anhydrous THF (10 mL) under a nitrogen atmosphere at −78 °C, a 2.5 M solution of *n*-BuLi in hexanes (0.57 mL, 1.42 mmol) was slowly added. The mixture was stirred for 10 min and the electrophile was added. The solution was stirred for a further 2 h at 0 °C or at −78 °C for aldehydes. Hydrolysis was carried out with a saturated aqueous solution of NH_4Cl (10 mL) and the mixture was extracted with CH_2Cl_2 (3×10 mL). The collected organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dissolved in anhydrous THF (10 mL) under a nitrogen atmosphere. Magnesium perchlorate (0.212 g, 0.95 mmol) was then added and the solution was stirred for 24 h. Hydrolysis was again achieved with a saturated aqueous solution of NH_4Cl (10 mL) and the mixture was extracted with CH_2Cl_2 (3×10 mL). The organic layers were dried ($MgSO_4$), concentrated and the residue was purified by flash chromatography on silica gel.

4.4.1. *S*-(2-Iodophenyl)-*N*-methylbenzenesulfinamide (3a). The starting sulfoximine was **1e**. According to the general procedure B, the electrophile was I_2 (0.96 g, 3.78 mmol). Hydrolysis was carried out with an aqueous saturated solution of $Na_2S_2O_3$. The eluent for purification was AcOEt/cyclohexane 1:1. The yield was 0.213 g (80%) of an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.50 (d, J=5.3 Hz, 3H), 4.14 (br s, 1H), 7.14 (m, 1H), 7.84 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.5, 94.4, 127.6, 128.7, 132.7, 140.5, 145.0. IR (cm^{-1}, KBr): 3228, 1443, 1088, 1059. HRMS (IE, *m/z*): calcd for C_7H_8INOS: 281.9450. Found: 281.9453.

4.4.2. *S*-(2-Chlorophenyl)-*N*-methylbenzenesulfinamide (3b). The starting sulfoximine was **1e**. According to the general procedure B, the electrophile was C_2Cl_6 (0.43 mL, 3.8 mmol). Eluent: AcOEt/cyclohexane 1:1. The yield was 0.147 g (82%) of an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.50 (d, J=5.6 Hz, 3H), 4.17 (br s, 1H), 7.38 (m, 3H), 7.92 (d, J=6.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3, 127.4, 127.5, 130.7, 132.3, 132.7, 140.9. IR (cm^{-1}, KBr): 3229, 2925, 1450, 1066, 1029. HRMS (IE, *m/z*): calcd for C_7H_8ClNOS: 189.0015. Found: 189.0020.

4.4.3. *S*-(2-Trimethylsilylphenyl)benzenesulfinamide (3d). According to the general procedure B, the starting sulfoximine was **1d**. Migration of the trimethylsilyl group occurred while stirring the solution at 0 °C. Eluent for purification: AcOEt. The yield was 0.143 g (71%) of a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.36 (s, 9H), 4.16 (br s, 2H), 7.50 (m, 3H), 8.11 (d, J=7.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.0, 121.0, 128.9, 129.2, 134.1, 137.3, 152.4. IR (cm^{-1}, KBr): 2954, 1474, 1250, 1108, 1051.

4.4.4. *N*-Methyl-*S*-(2-methylthiophenyl)benzenesulfinamide (3f). The starting sulfoximine was **1e**. According to the general procedure B, the electrophile was Me_2S_2 (0.34 mL, 3.78 mmol). Eluent for purification: AcOEt/cyclohexane 1:1. The yield was 0.125 g (66%) of an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H), 2.48 (d, J=5.3 Hz, 3H), 4.15 (d, J=4.9 Hz, 1H), 7.25 (m, 3H), 7.83 (d, J=7.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.9, 26.4, 125.5, 127.3, 129.2, 131.7, 137.8, 141.3. IR (cm^{-1}, KBr): 3226, 1434, 1097, 1066, 1032. HRMS (IE, *m/z*): calcd for $C_8H_{11}NOS_2$: 201.0282. Found: 201.0280.

4.4.5. 3-Methyl-3*H*-2,1-benzoxathiol-1-oxide (4a). The starting sulfoximine was **1e**. According to the general procedure B, the electrophile was acetaldehyde (0.265 mL, 4.74 mmol). Eluent for purification: AcOEt/CH_2Cl_2 1:1. The yield was 0.092 g (58%) of an oil consisting in a

mixture of two diastereoisomers (de=13%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65 (d, J=6.4 Hz, 1.8H), 1.81 (d, J=6.4 Hz, 1.2H), 5.80 (q, J=6.6 Hz, 0.4H), 6.23 (q, J=6.6 Hz, 0.6H), 7.36 (t, J=7.5 Hz, 1H), 7.55 (m, 2H), 7.72 (d, J=7.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 24.0, 87.1, 90.1, 122.5, 122.6, 123.7, 124.0, 129.7, 129.8, 132.6, 132.7, 142.6, 143.0, 146.6, 147.4. IR (cm^{-1}, KBr): 2972, 2926, 1734, 1083, 1044. HRMS (IE, *m/z*): calcd for $C_8H_8O_2S$: 168.0245. Found: 168.0241.

4.4.6. 3-Phenyl-3*H*-2,1-benzoxathiol-1-oxide (4b). The starting sulfoximine was **1e**. According to the general procedure B, the electrophile was benzaldehyde (0.192 mL, 1.89 mmol). The Lewis acid was $Mg(ClO_4)_2$ followed by $MgBr_2$ (0.175 g, 0.95 mmol) in $CHCl_3$. Eluent for purification: cyclohexane/CH_2Cl_2 1:1. The yield was 0.098 g (45%) of an oil containing a mixture of two diastereoisomers. 1st diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (s, 1H), 7.09 (m, 1H), 7.21 (m, 2H), 7.32 (m, 3H), 7.46 (m, 2H), 7.73 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 95.7, 123.9, 124.0, 128.4, 129.3, 129.5, 130.0, 133.0, 138.4, 141.6, 146.6. 2nd diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54 (s, 1H), 7.24 (m, 1H), 7.26 (m, 2H), 7.30 (m, 3H), 7.45 (m, 2H), 7.71 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 92.7, 95.8, 123.7, 123.9, 128.5, 129.4, 132.9, 136.9, 141.6, 147.9. IR (cm^{-1}, KBr): 1456, 1116. HRMS (IE, *m/z*): calcd for $C_{13}H_{10}O_2S$: 230.0402. Found: 230.0400.

4.4.7. 3-*tert*-Butyl-3*H*-2,1-benzoxathiol-1-oxide (4c). The starting sulfoximine was **1e**. According to the general procedure B, the electrophile was pivaldehyde (0.233 mL, 1.89 mmol). The Lewis acid was $Mg(ClO_4)_2$ followed by $MgBr_2$ (0.175 g, 0.95 mmol) in $CHCl_3$. The eluent for purification on silica gel was cyclohexane/CH_2Cl_2 1:1. An other flash chromatography was performed on basic alumina with cyclohexane/CH_2Cl_2 gradient from 3:1 to 1:3. The yield was 0.079 g (40%, de>95%) of a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 9H), 5.41 (s, 1H), 7.51 (d, J=7.5 Hz, 3H), 7.72 (d, J=6.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.6, 36.1, 102.2, 124.4, 129.7, 132.0, 139.8, 146.9. IR (cm^{-1}, KBr): 2958, 1468, 1109. HRMS (IC^+, isobutane, *m/z*): calcd for $C_{11}H_{14}O_2S$: 211.0793. Found: 211.0789.

4.4.8. 3-Isobutyl-3*H*-2,1-benzoxathiol-1-oxide (4d). The starting sulfoximine was **1e**. According to the general procedure B, the electrophile was 3-methylbutyraldehyde (0.204 mL, 1.89 mmol). The Lewis acid was $Mg(ClO_4)_2$ followed by $MgBr_2$ (0.175 g, 0.95 mmol) in $CHCl_3$. The eluent for purification was cyclohexane/CH_2Cl_2 1:1. The yield was 0.069 g (35%) of an oil consisting in a mixture of two diastereoisomers (de=48%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (m, 6H), 1.50–2.10 (m, 3H), 5.66 (d, J=10.2 Hz, 0.4H), 6.12 (d, J=9.8 Hz, 0.6H), 7.29 (m, 1H), 7.40 (m, 2H), 7.64 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 22.2, 23.9, 24.1, 25.7, 25.8, 38.3, 49.1, 89.4, 92.4, 122.6, 122.8, 124.0, 123.8, 130.5, 132.5, 142.1, 142.6, 146.9, 147.4. IR (cm^{-1}, KBr): 2958, 1467, 1126. HRMS (IE, *m/z*): calcd for $C_{11}H_{14}O_2S$: 210.0715. Found: 210.0721.

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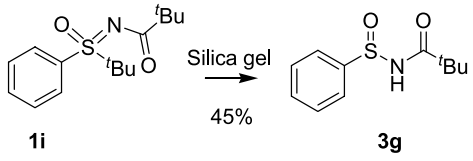
6. During purification on silica gel, sulfinamide **3g** was obtained in 45% yield resulting from a de-*tert*-butylation reaction of **1i**.



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Experimental and theoretical FMO interaction studies of the Diels–Alder reaction of 5-acetyl-3-methythio-1,2,4-triazine with cyclic enamines☆

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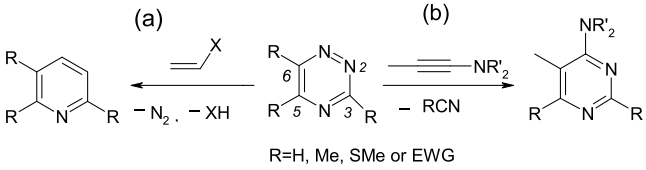
Abstract—Diels–Alder reaction of 5-acetyl-3-methylthio-1,2,4-triazine with five cyclic enamines has been reinvestigated in its preparative and theoretical aspects. Its regioselectivity has been developed practically, which is in agreement with theoretical consideration of the FMO interactions, including secondary orbital interactions in the transition state. Since the energetic demands are similar for all five pairs, it has been indicated that their reactivity differences can be explained by an influence of steric hindrance in the considered transition state. In result, the synthesis of the 3-acetyl-1-methylthiocycloalka[*c*]pyridines, as synthons for preparation of sempervirine and its analogues has been optimized. The subsequent side reaction has been detected as a serious problem, especially in the case of the six-membered enamine, which reacts with the acetyl group of the final product formed in the reaction mixture.

1. Introduction

In recent years aza-Diels–Alder reactions have been important methods for the synthesis and transformation of heterocyclic compounds.[2] Many chemists have developed applications of 1,2,4-triazines as azadienes in inverse electron demand cycloadditions [4+2],[3] both inter-[4] and intramolecular,[5] for the synthesis of many functionalized polyheterocyclic systems. The 1,2,4-triazine ring is known to undergo two different sequences consisting in Diels–Alder–*retro*-Diels–Alder reactions (DA–*r*DA).[6] The sequence that begins with cycloaddition of an electron-rich dienophile across C3–C6 of a 1,2,4-triazine moiety is more common. Then follows the loss of N_2 (*r*DA) and elimination of a small molecule HX (HNR_2 or HOR), which gives the pyridine ring as shown in Scheme 1a. Reactions of the 1,2,4-triazine ring itself[7] and its derivatives[2a,7b,8] with cyclic enamines lead to the synthesis of 3,4-annulated pyridines, important ring systems in pharmacologically interesting molecules.[8c,9] The ynamine dienophiles usually interact in the second sequence: cycloaddition across N2–C5 with subsequent loss of nitrile (*r*DA) and formation of the pyrimidine ring,[3b,4a,8a,10] (see Scheme 1b). In many cases, the two modes of the reaction can run with the formation of a mixture of products.[3b,4a]



Scheme 1. Scheme showing the two main ways in which the 1,2,4-triazine ring can undergo Diels–Alder reaction.

Many reactions with different combinations of substituted 1,2,4-triazine-azadiene with an electron-rich dienophile have been described recently.[11] However, their frontier molecular orbital (FMO) interactions, which can indicate the route of reaction, its regioselectivity and relationship between structure of reactants and the rate of reaction have not been investigated.

In our earlier investigation of the Diels–Alder reaction between 3-substituted 5-acyl-1,2,4-triazine and enamines, we demonstrated the synthetic usefulness of the replacement of –N=N– fragment of 1,2,4-triazine by –C=C– of enamines for the preparation of alkyl-heteroaryl ketones.[12] Then we applied reactions between pairs **1** and **2a–d** for obtaining 3-acetyl-1-(methylthio)cycloalka[*c*]pyridines **3a–d**, the key intermediates in the total synthesis of

☆ See Ref. 1.

Keywords: Aza Diels–Alder reaction; 1,2,4-Triazines; Frontier molecular orbitals interactions; Secondary FMOs interplay in transition state; 3-(Acetyl)-cycloalka[*c*]pyridines.
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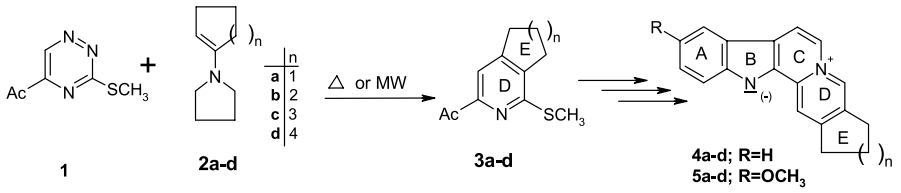


Scheme 2. Synthesis of the 3-acetyl-1-methylthiocycloalkene[*c*]pyridines **3a–d**, as synthons of the sempervirine type alkaloids, via cascade transformation of 5-acetyl-3-methylthio-1,2,4-triazine **1** with cyclic enamines.

pentacyclic indolo[2,3-*a*]quinolizine alkaloids; sempervirine **4b** (R=H, $n=2$),[13] its analogues with different E rings **4a**, **4c**,**d** (R=H, $n=1$, 3, 4)[14] and next, their methoxy derivatives **5a–d** (R=OCH_3, $n=1$–4)[15] (see Scheme 2). This paper presents the correlation of the experimental data and theoretical study of frontier molecular orbital interactions of **1** and **2a–d** in the Diels–Alder reaction in the aspect of optimization of the synthesis of the final products **3a–d**.

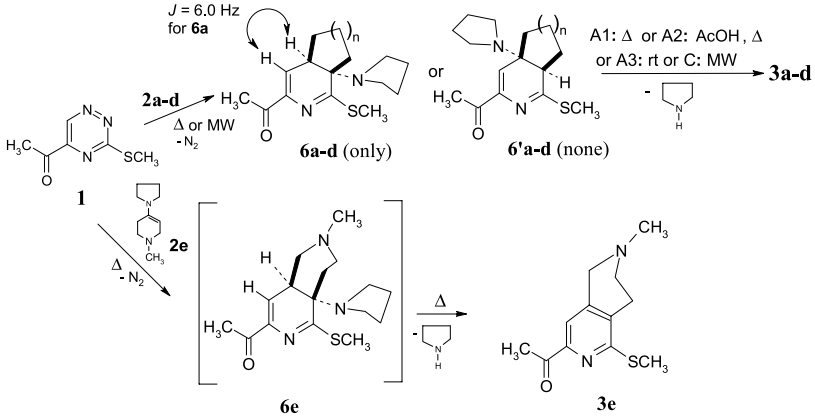
2. Results and discussion

Differences in the course of the Diels–Alder reaction between azadiene **1** and five–eight-membered cyclic enamines **2a–d** as dienophiles were observed during optimization of these processes and, in result, the yields of products **3a–d** varied. The present paper contains the proof of the correlation of the experimental data and the study of the frontier molecular orbital (FMO) interactions in this reaction. Because of the fact that the products **3a–d** are formed only in the first type of reaction (Scheme 1a), the yields should depend on regioselectivity and the rate of three-process cascade: cycloaddition of the enamines **2a–d** across C3–C6 positions of **1** (as the termini of azadiene), *retro*-Diels–Alder reaction (involves the loss of N_2) and cis-elimination (XH=pyrrolidine) towards rearomatization of the heterocyclic ring. These processes can be considered as depending on the frontier molecular orbital (FMO) interactions of reactants with the assumption that a concerted transition state exists in the first stage of a cascade reaction, and that emergence and disappearance of steric hindrance in the course of the first and further rearrangements play the most important role.

Recently, density functional theory (DFT) has been applied for full, quantitative consideration and optimization of the transition states of reactions.[16] We believe, however, that in the case of our investigated process, the basic study of the FMO interactions is fundamental[17] together with considering the possibility of emergence of the secondary (non-bonding) interaction in the course of transition state formation[18] and it gives very interesting and satisfying results.

2.1. Preparative results

2.1.1. Experimental regioselectivity of the Diels–Alder reaction of 1 with cyclic enamines 2a–e and structure elucidation of products 3a–e. In our experiments directed to the synthesis of condensed pyridines **3a–d** in the Diels–Alder reaction between 5-acetyl-3-methylthio-1,2,4-triazine **1** and enamines **2a–d** it was visible (TLC plates) that the consumption of the starting material was in all cases accompanied by the extrusion of nitrogen. This indicated that the first cycloaddition stage ran simultaneously with the *retro*-Diels–Alder reaction, causing emergence and disappearance of steric hindrance. In result, the two regioisomeric dihydropyridine systems **6a–d** or **6′a–d** (Scheme 3) can be formed as intermediates in this step, due to the two possible interaction of cyclic enamines. The second step consists of elimination of pyrrolidine and formation of the final products **3a–d**, in which the structures are independent of the regiochemistry of the dihydro-intermediates. We observed, however, that the two visible steps had different rates for enamines **2a–d**. With the increase of the enamine ring size, the rate of the first stage decreased and the rate of the second one increased. Since the reaction between **1** and the enamine with a small ring (**2a**) proceeded quickly towards a dihydropyridine-intermediate, which transformed slowly into **3a**, this intermediate compound could be isolated from the cooled reaction mixture by preparative



Scheme 3. Cascade reaction between **1** and **2a–e**.

thin-layer chromatography and its structure determined. In the ^{1}H NMR spectrum of this compound the signal of the dihydropyridine proton appears at 6.68 ppm as a doublet (J=6.0 Hz), which indicates structure **6a** (one enantiomer is shown on the Scheme 3), but not **6′a**. We observed (by TLC and ^{1}H NMR spectra) the slow rearrangement of **6a** into **3a** in solvents during isolation and measurement at room temperature. During GC/MS analysis, two substances were also observed on the chromatogram with t_R=11.9 and t_R=13.8 in ratio 12:88, which gave mass spectra with molecular peaks for **3a** (m/z=207) and **6a** (m/z=278).

We performed the reaction of **1** with 1,2,5,6-tetrahydro-*N*-methyl-4-(1-pyrrolidino)pyridine **2e** as dienophile (see Scheme 3) for the purpose of an additional regioselectivity investigation, because the structure of final product of cascade reaction in this case is influenced by regioselectivity of the first stage. From the X-ray structure of the product **3e** (Fig. 1) as 3-acetyl-6-methyl-1-methylthio-5,6,7,8-tetrahydro-2,6-naphthyridine (not 2,7-naphthyridine derivative, the second possible regioisomer), we deduced regioselectivity of the dihydrointermediate **6e**. This is in agreement with our earlier investigations of 5,6,7,8-tetrahydro-2,6-naphthyridine, which is substituted in the same way as **3e**, where in the ^{1}H NMR spectrum the NOE-effect in the resonance of *H*C4 (δ 7.44) and H_2C5 (δ 3.54) was observed.

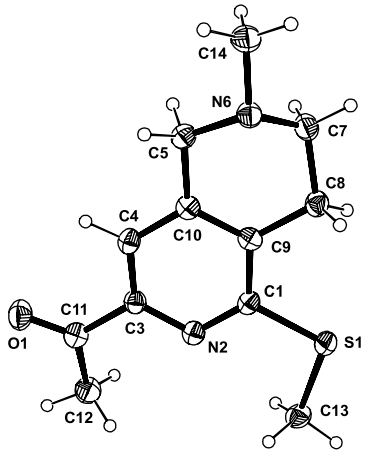
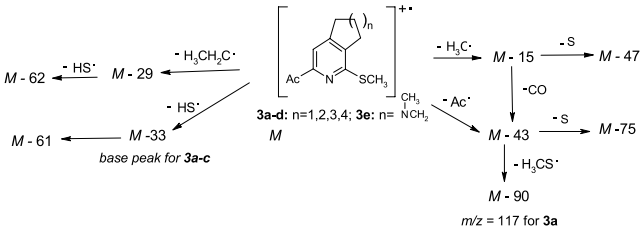


Figure 1. Molecular structure **3e** with thermal ellipsoids drawn at 50% probability level.

The two experiments discussed above show that in the reaction of 5-acetyl-3-methylthio-1,2,4-triazine **1** with all cyclic enamines **2a–e**, interactions occur between the C1′ of dienophiles **2a–e** and the C3 of the 1,2,4-triazine ring-diene **1**, and the C2′ of enamines with C6 of the azadiene, leading to formation of **6a–e** as intermediates in DA–*r*DA reaction sequences only (Scheme 3). These results are in agreement with the theoretical FMO interaction study, which is also described in this paper.

The structure of all products **3a–e** was determined by spectroscopic methods. A sharp absorption at a region 1686–1701 cm^{-1} in the IR spectra was assigned to the C=O bond. The ^{1}H NMR spectra of the **3a–e** showed only a single peak at a low field: 7.44–7.65 ppm, which indicated one aromatic proton *H*C3. In the aliphatic region of the spectra of **3a–d**, two three-proton singlets were presented for H_3CO and H_3CS and two two-proton triplets or multiplets for methylene groups bonded with pyridine ring. Other methylene groups gave multiplets in the high-field region. In this range the ^{1}H NMR spectrum of **3e** was different and corresponded to its structure. The resonance for *C*=O and H*C*3 of **3a–e** was observed in the ^{13}C NMR spectra at regions 200.0–201.0 and 113.0–118.0 ppm, accordingly. The peak for H_3*C*CO appeared at 25.8–26.2 ppm and for H_3*C*S at 12.4–13.8 ppm. The molecular ion peaks were noticeable in the electron-impact mass spectra of all products **3a–e**. The base peaks (100%) were assigned to the extrusion of ˙SH (M-33) from the molecules **3a–c**, ˙CH_3 (M-15) from the **3d** and of ˙NC_2H_6 (M-44) from the molecule **3e**. The main fragmentation paths of the molecules **3a–e** could be defined thanks to investigation of the MS spectra of these five molecules (see Scheme 4). In the mass spectrum of **3a** a three-peak sequence existed at m/z=118, 117 (M-90), 116, which indicated the existence of the naked ring skeleton of this molecule. Interestingly enough, in the spectra of **3b–e**, these peaks were also present (partial fragmentation of the aliphatic rings). In effect, the mass spectra for all products **3a–e** were identical in the region below m/z=116.



Scheme 4.

With the above mentioned results in hand, we started investigating the conditions and limitations of our method for the transformation of **1** into **3a–e**.

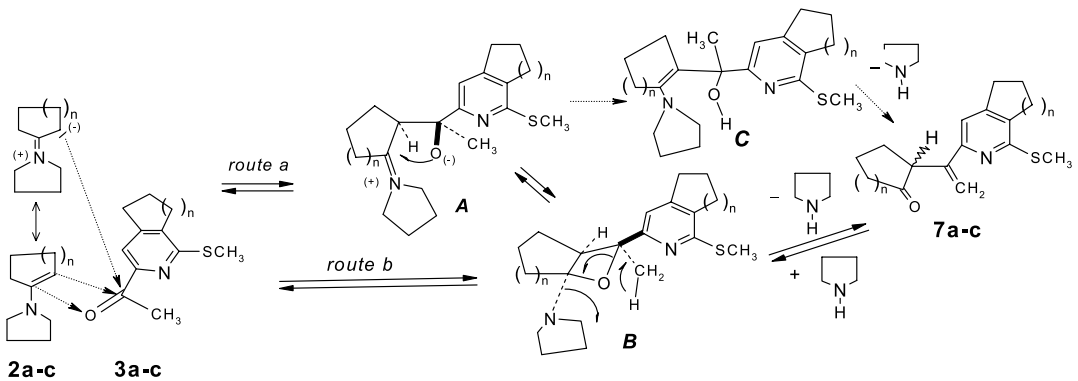
2.1.2. Optimization of the reaction conditions. We tested many solvents for the reactions of 5-acetyl-3-methylthio-1,2,4-triazine **1** with enamines **2a–e**. Some conditions and yields are shown in Table 1. It was clear that for the reactions of **1** with enamines **2a–d** the best conditions were in boiling ethanol. Reactivity of these dienophiles towards products **2a–d** was decreased when the large ring in the dienophile molecules was increased. For the reaction with enamine **2e**, that has different properties, the best conditions were in boiling dioxane. The courses of reactions were observed on TLC plates. Thus, it seemed that in the reaction of **1** with an equimolar amount of enamine **2a** in boiling solvents, complete consumption of substrate occurred within 15–20 min. When heating was stopped, the dihydro-intermediate could be isolated and its structure was established as **6a**. For complete rearrangement to compounds **3a** prolonged heating was necessary over 4–5 h (method **A1**) or the reaction mixture had to be left at room temperature for a longer period (method **A3**). The process of the pyrrolidine elimination was faster (only 15–30 min) when heating was continued in the presence of catalytic amount (10%) of acetic acid (method **A2**). There were smaller difficulties in elimination of pyrrolidine in the case

Table 1. Optimization of the synthesis of **3a–e** in the experimental scale 1 mmol of **1** in conventional heating in method **A**[a,b,c] (substrate **1** concentration 0.2 mol/dm^3), and under microwave irradiation in method **B**[d]

Entry	Enamine	Solvent	Molar ratio of **2a–e** to **1**	Reaction time		Product	Yield (%)
				For consumption of **1** in refluxing solvent	For complete transformation of the dihydrointermediate **6a–e** into final product		
1	**2a**	Benzene	1	20 min	method **A1**[a]:5 h	**3a**	50
2	**2a**	Benzene	1	20 min	method **A2**[b]:20 min	**3a**	65
3	**2a**	Benzene	1	20 min	method **A3**[c]:15 h	**3a**	52
4	**2a**	Ethanol	1	15 min	method **A1**:4 h	**3a**	65
5	**2a**	Ethanol	1	15 min	method **A2**:20 min	**3a**	75
6	**2a**	Ethanol	1	15 min	method **A3**:25 h	**3a**	57
7	**2b**	Benzene	0.95	4 h	method **A1**:5 h	**3b**	65
8	**2b**	Benzene	0.95	4 h	method **A2**:10 min	**3b**	55
9	**2b**	Toluene	0.95	2 h	—	**3b**	60
10	**2b**	Ethanol	0.95	1.5 h	method **A1**:1.5 h	**3n**	75
11	**2b**	Ethanol	0.95	1.5 h	method **A2**:10 min	**3b**	70
12	**2b**	Ethanol	0.95	1.5 h	method **A3**:15 h	**3b**	55
13	**2c**	Toluene	1.1	3 h	—	**3c**	28
14	**2c**	Ethanol	1.1	2.5 h	—	**3c**	54
15	**2c**	Chlorobenzene	1.1	method **B**[d]; 2.5 min	—	**3c**	40
16	**2d**	Toluene	2	5 h	—	**3d**	25
17	**2d**	Ethanol	2	15 h	—	**3d**	30
18	**2d**	Ethanol	2+1+1	25 h[e]	—	**3d**	23
19	**2d**	Chlorobenzene	3	method **B**[d]; 2.5 min	—	**3d**	45
20	**2e**	Ethanol	1.5	2 h	—	**3e**	25
21	**2e**	Toluene	1.5	7 h	—	**3e**	35
22	**2e**	Dioxane	1.5	5 h	—	**3e**	55

[a] Method **A1**: continuation of reflux in the same solvent.
[b] Method **A2**: refluxing in the presence of acetic acid.
[c] Method **A3**: left at room temperature.
[d] Method **B**: fast microwave heating of the high concentration reaction mixture in chlorobenzene at temperature 110 °C.
[e] Reaction without heating (room temperature 22 °C).

of **1** and **2b**, and these problems were absent in cases of **1** and **2c–e**, where new rings were larger. Products **3c–e** were formed simultaneously with disappearance of substrate **1** in reaction with the appropriate enamine. Reaction between **1** and 1-pyrrolidine-1-cyclooctene **2d** was very slow and gave a low yield using conventional heating. It turned out that the cascade process in this case was efficient when a high-concentration reaction mixture in chlorobenzene (with excess of enamine **2d**) was heated by microwave irradiation (1.5 min at 110 °C; method **B**). It means that in this case, the first step of reaction, cycloadduct [2+4] formation, had to run via the densely packed and hindered stage. In general, the speed of the first step diminished together with increasing the ring size of the enamines **2a–e** ring, which caused larger steric hindrances. However, the *retro*-Diels–Alder reactions, with N_2 extrusion, and then pyrrolidine elimination, were faster for larger rings. All reactions did not proceed cleanly. Different side products were noticed in the reaction mixture (on TLC plates), especially when the regime of process; the molar ratio of reactants and their concentration, was not respected. For enamines **2a–c**, the concentration **1** in solvent had to be no higher than 0.2 mol/dm^3. It is noteworthy than the high reactivity of enamines **2a**,**b** (and to a small degree **2c**) towards products **3a–b** was observed also as a tendency towards the formation of side products in the cases when excess of the enamines was used, and/or concentration of both reactants in solvent increased. One kind of the side-product possessing the lowest polarity (the highest R_f) was isolated from the reaction mixtures. After determination of the structure of the representative compound **7b** (see Scheme 5), it became clear that they were formed in reaction between products **3a–c** and excess



Scheme 5. Proposed mechanism of the consecutive reaction between products **3a–c** and appropriate enamine.

appropriate enamine **2a–c**, which existed in the reaction mixture. In Table 1 the optimal ratios of **2a–e** to **1** for minimization of this subsequent reaction are shown.

The best reaction conditions were established in entry 5 for **3a**, in entry 10 for **3a**, in entry 14 for **3c**, in entry 19 (under microwaves) for **3d** and in entry 22 for **3e**.

It is interesting that the strongest tendency to consecutive reaction was observed for **1** and **2b**, while it was not observed for **1** and **2d**. The side product **7b** was formed during synthesis of **3b** in all investigated methods and solvents. The best yield of **3b** (only a trace of **7b**) was obtained when **1** reacted with a deficiency of enamine **2b** and the concentration of reactants in solvents was no larger than 0.2 mol/dm^3. We noticed that in extreme conditions (*B* in experimental), when **1** reacted with double the amount of **2b** without solvent in room temperature, an exothermic reaction was observed and compound **7b** was isolated as a major product (30%), together with only 20% of **3b** and many other side products more polar than these two.

The mechanism of formation of **7a–c** in reaction of **3a–b** with the appropriate enamine is under investigation (Scheme 5). In the first stage, oxetane formation is a rational way for oxygen migration from the acetyl group to cycloalkane ring, in anhydrous reaction medium, and it can be formed in two ways. The first (route a) is preferred in polar solvents and starts with the enamine carbanion addition to acetyl group, as in the aldol type condensation. The subsequent step is the intramolecular nucleophilic attack of the oxygen on the imine carbon in the intermediate **A**, which leads to oxetane **B**. Its formation in the second possible way (route b) involves [2+2] photocyclization, like in the Paterno-Büchi reaction, and is preferred in non-polar solvents in presence of light. However, both mechanisms can take place as concurrently. The stereochemistry of oxetane **B** (one enantiomer is shown on the Scheme 5) can be determined in route a (intramolecular nucleophilic addition), as well as in route b (concerted cycloaddition). The second stage, oxetane rearrangement, is, in summary, the cis-1,4-elimination of pyrrolidine. This process can run as synchronous in six-membered transition state, where three changes are simultaneous: formation of methylene group, establishment of carbonyl group in cycloalkane from the oxetane oxygen and elimination of pyrrolidine via the intramolecular (or intermolecular) accepting proton by nitrogen from the methyl group. It seems that in the proposed mechanism, in the case of the six-membered enamine **2b**, steric hindrance does not exist, and this reaction can run more easily than for **3a**,**c** with appropriate enamine **2a**,**c**. An alternative mechanism via cycloadduct **C**, which gives product **7b** after dehydration and enamine hydrolysis, is less probable because the presence of an acidic reagent is necessary in this case. However, intermediate oxetane **B** and hydroxyenamine **C** have not been isolated so far.

We deduced the mechanism discussed above from the fact of isolation of **7b** and its structure. In order to further research the method of formation of the products **7a–c**, consisting in addition of enamine **2a–c** to acetyl group in the final products **3a–c** (Scheme 5), we have recently carried out experiments, where pure **3a–c** was reacted with appropriate enamine **2a–c** in refluxing ethanol (*C* in the experimental) or toluene. We have noticed that the equilibrium was established, when only trace concentration of compounds **7a–c** existed. This balance remained in the presence of light, but it moved towards the compounds **7a–c** after pyrrolidine was added. We have also detected in the reaction mixture other isomeric products in trace quantities. They will be investigated further. We aim at confirmation of existence of the oxetanes **B** and at the general application of the reaction of the heteroaromatic acetyl derivatives with cyclic enamines.

2.2. Study of the frontier molecular orbitals (FMOs) interactions

We studied the frontier molecular orbitals (FMOs) of the 5-acetyl-3-methylsulfanyl-1,2,4-triazine **1** as azadiene and cyclic enamines **2a–e** as dienophiles and considered their interactions in a concerted Diels–Alder reaction as a first step of a cascade rearrangement to the condensed pyridines **3a–e**. The FMOs model seemed capable of explaining the observed regioselectivity and reactivity differences.[17] Therefore, attempts were made to correlate the energies and coefficients of the FMOs for these reactants using the semi empirical MOPAC-AM1 methodology.[19] The graphs of calculated energy of the HOMOs and LUMOs of **1** (exactly) and **2a–e** (approximately) are shown in Figure 2. Their p_z coefficient pictures and values also are shown. The calculation suggests that the most efficient interaction, leading to product formation, occurs between the LUMO of the azadiene **1** ($LUMO_1$) and the HOMOs of dienophiles **2a–e** ($HOMO_{2a-e}$), not $HOMO_1$ and $LUMO_{2a-e}$. This means, it must be an inverse electron demand cycloaddition. From the picture of the p_z coefficients of $LUMO_1$ it is visible that either C3–C6 or N2–C5 positions can be the termini of diene in molecule **1**, which is in agreement with the two known reactivity sequences of 1,2,4-triazines in Diels–Alder reaction.

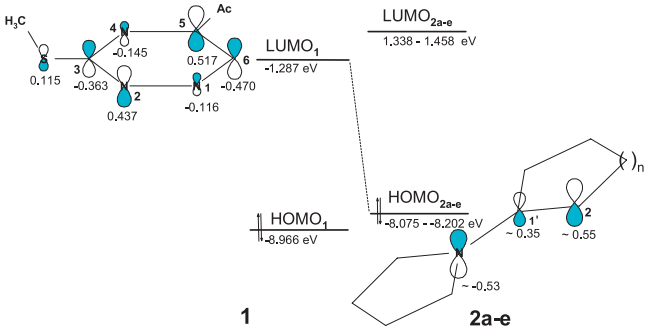


Figure 2. Calculated energy and the pictures (LCAO) of the FMOs (with p_z coefficients and their values) of **1** and **2a–e**, which interact in inverse electron demand [4+2] cycloaddition.

If one takes into consideration the fact that the larger coefficients of the FMOs of both reactants and the smaller coefficients of both reactants combine, an asynchronous transition state should be formed to predict the regioselectivity of cycloadduct. It turns out that there must be two possibilities interactions in these two directions. They are shown on the Figure 3, together with the calculated values

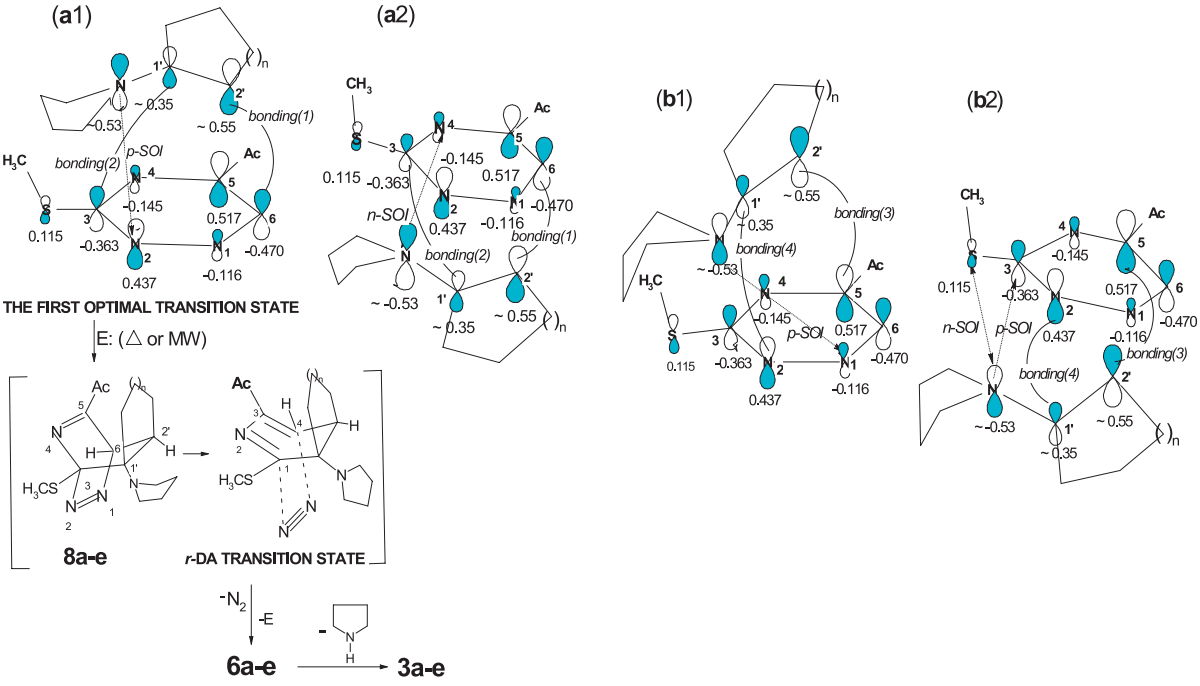


Figure 3. The study of the four possibilities of interaction of the FMOs in Diels–Alder reaction between **1** and **2a–e**: (a) two interaction ways of the enamines with the positions C3–C6 of azadiene **1**; (b) two interaction ways of the enamines with the positions N2–C5 of azadiene; (p-SOI, positive secondary orbitals interaction; n-SOI, negative secondary orbitals interaction) shows the tendency to form mainly by the (**a**1) way of the sensitive **8a–e** cycloadducts, which can limit the cascade rearrangement.

of p_z coefficients of the $LUMO_1$ and with the approximately values of p_z coefficients of the $HOMOs_{2a-e}$. The full values of the latter are given in Table 2. The energy gaps between the reactive frontier molecular orbitals are similar for all pairs **1** and **2a–e** (see Table 2, $\Delta E = E(LUMO_1) - E(HOMO_{2a-e})$) and they give no reason for different course of these reactions. Therefore, in search of a solution, we considered precisely all four possible ways of formation of the hypothetical transition state (see Fig. 3).

On Figure 3 it is visible that, when planar cyclic molecule **1** interacts with cyclic enamines **2a–e** to form (**a**1), (**a**2), (**b**1), (**b**2) possible transition states towards cycloaddition [4+2], we must take into consideration the possibility of bonding interactions between p_z coefficients (1,2,3,4), which appear at the ends of the azadiene and the dienophile molecules. In addition, other than bonding, molecular interplay can exist. Thus, it can be either beneficial and disadvantageous for transition state secondary orbital interactions (SOI). In the (**a**) cases the main interactions appear between C6 of azadiene **1** and C2′ of enamine **2a–e** (bonding (1), with larger p_z coefficients) and between C3 of **1** and C1′ of enamine (bonding (2), with smaller p_z coefficients). The first bonds are formed faster and are shorter than the second in the (**a**1) and (**a**2) transition states. Thus, there are concerted but asynchronous transition states. However, when these two ways of interaction are considered, it is visible that in the case of (**a**1), *exo*-regiochemistry of the Diels–Alder reactants, additional strong p_z-bonding interaction between N2 of azadiene and pyrrolidine nitrogen of enamine may occur. This secondary orbital interaction (SOI) is beneficial for the (**a**1) transition state stabilization (p-SOI: positive SOI). In the (**a**2) case (*endo*-regiochemistry), a small SOI between the pyrrolidine nitrogen and N4 of **1** has an adverse effect on the course of reaction (n-SOI: negative SOI). In the (**b**) situations the bonding interaction are as follows: the first between C5 of azadiene **1** and C2′ of dienophiles **2a–e** (bonding (3)), with larger p_z coefficients and the second between N2 of **1** and C1′ of **2a–e** (bonding (4), with smaller p_z coefficients). These bonding interactions are stronger than in case of the (**a**) combination because p_z(N2) and p_z(C5) coefficients are larger and their overlap with p_z coefficients of dienophiles **2a–e** are bigger, than with p_z(C3) and p_z(C6) coefficients in the (**a**) case. Aside from these, in case of the (**b**1) *exo*-regiochemistry, there is only a weak bonding interaction (p-SOI) between N1 of azadiene **1** and pyrrolidine nitrogen. In the case of (**b**2) *endo*-combination the reactants in the [4+2] cycloaddition, the p_z coefficients of pyrrolidine nitrogen must interact in transition state with two p_z coefficients: C3 and sulfur atom. The first of them has a bonding nature (p-SOI), but the second one is anti-bonding (n-SOI). In result, the reactants are, in both (**b**) cases, at a disadvantage in the transition states. In Table 2 it is shown that the differences between p_z coefficients for bonding interactions in the (**a**) and (**b**) directions (Δp_z) are similar and do not play a decisive role in the course of transition state formation and regioselectivity determination of the cascade reaction.

To sum up the above considerations, we have come to conclusion that the best situation for transition state formation is in the case (**a1**). This *exo*-combination of the azadiene moiety: C3–N4–C5–C6 and pyrrolidine nitrogen as dienophile substituent results from the secondary orbitals interaction, which can exist on the outside of the [4+2] electronic system. This is the optimal starting point for cascade transformation of compounds **1** in reaction with cyclic enamines **2a–e**. We can consider an increase in the

Table 2. The FMO energy of enamines **2a–e** with the values of p_z of their HOMOs, energy gaps between $LUMO_1$ and $HOMO_{2a-e}$ (ΔE), and differences between p_z coefficients (Δp_z) for bonding interactions in (**a**) and (**b**) directions (see Fig. 3)

No	Enamine				$\Delta E = E(LUMO_1) - E(HOMO_{2a-e}) = (-1.287) - E(HOMO_{2a-e})$ (eV)	Δp_z For bonding interaction			
	LUMO energy (eV)	HOMO				(a)		(b)	
		Energy (eV)	p_z (C1′)	p_z (C2′)	p_z (N)	(1) p_z(C6)–p_z(C2′)	(2) p_z(C3)–p_z(C1′)	(3) p_z (C5)–p_z(C2′)	(4) p_z(N2)–p_z(C1′)
2a	1.451	−8.075	0.352	0.552	0.510	6.788	−0.082	0.011	−0.035	0.085
2b	1.452	−8.144	0.377	0.575	0.549	6.857	−0.105	0.014	−0.058	0.060
2c	1.458	−8.112	0.348	0.530	0.533	6.825	−0.060	−0.015	−0.013	0.089
2d	1.434	−8.148	0.348	0.572	0.560	6.861	−0.098	−0.015	−0.055	0.089
2e	1.338	−8.202	0.348	0.557	0.550	6.915	−0.087	−0.015	−0.040	0.089

overlap of the orbitals forming the bonds as progress along the reaction path. It means that the Diels–Alder cycloadducts can have the **8a–e** structure. They can be considered as derivatives with the highest energy, which is necessary to overcome the activation barrier. The strained transition structures **8a–e** must react quickly (exothermic process) to give intermediates **6a–e** after nitrogen extrusion (*r*DA). Our considerations can be expanded in the situation when the starting formation of the first transition state and the second one run simultaneously. Then, after pyrrolidine elimination, products **2a–e** are formed. Steric hindrance increases in course of the formation of the first transition state and in the structure of cycloadducts **8a–e** for enamines with larger rings. This is the reason why the reactivity of hepta- and octa-membered enamines is smaller than penta- and hexa-membered, whereas the energetic demands are similar in all these cases. The structure of the sensitive Diels–Alder cycloadduct theoretically considered as **8a–e** is compatible with the experimentally established structure of the intermediate **6a** (^{1}H NMR) and the final product **3e** (X-ray).

3. Conclusion

In conclusion, this work contains correlations of the experimental data towards optimization and the theoretical calculations of the Diels–Alder reactions between 5-acetyl-3-methylthio-1,2,4-triazine **1** and cyclic enamines **2a–e**. We have demonstrated that the observed regioselectivity is in agreement with the theoretical considerations of the frontier molecular orbital interaction study, including secondary interplay in the course of transition state formation. Different reactivity of pairs of reactants, which have similar energetic demands, can also be explained as the influence of steric crowding of the considered transition state. In result, we have developed the synthetic strategy for the preparation of varied cycloalka[*c*]pyridines **3a–e**. The synthesized compounds contain the acetyl group in the C3 position, which opens access to further transformations, such as the Fischer indole synthesis or aldol type condensation.

4. Experimental

4.1. General

5-Acetyl-3-methylthio-1,2,4-triazine **1**[13,20] was prepared from 3-methylthio1,2,4-triazine,[21] via a two-step procedure described previously.[13] All reactions were performed under calcium chloride tube, in anhydrous solvents, which were dried in standard procedures[22] prior to use. Enamines **2a–e** were synthesized from commercial ketones and pyrrolidine (Aldrich) by Kuehne method.[23] Microwave reactor Synthewave 402 (Prolabo, 300 W, focused microwaves, open, rotating system of reaction vessel) with software (feedback temperature monitoring) was used. The course of reactions was monitored by thin-layer chromatography (TLC), which was carried out on 0.25 mm Merck silica gel plates ($60F_{254}$). Column chromatography was performed on Merck silica gel 60 (230–400 mesh). Melting points were determined on Boëtius microscopic plate and are uncorrected. All new

compounds were determined to be >95% pure by ^{1}H NMR. IR spectra (KBr pellets) were recorded on FT-IR Magna 760 (Nicolet) apparatus. Mass spectra and high-resolution measurements were obtained with an AMD 604 (Intectra, GmbH, Germany) spectrometer. GC/MS experiments were recorded on GC gas chromatograph-MS-QP550 mass detector (Shimadzu) with Zebron ZB-5, 30 M×0.25 mm ID×0.10 μM column. ^{1}H and ^{13}C NMR spectra were recorded with Varian Gemini (200 MHz) and Mercury 400BB (400 MHz) spectrometers. Elemental analyses were obtained with Perkin-Elmer 2400-CHN analyzer. The AM1 method[19a] from the MOPAC,[19b] CAChe 5.0 Fujitsu software[19c] was employed for semi empirical calculations.

4.2. General procedures for Diels–Alder reaction between 1 and 2a–e

Method **A**. To a solution of **1** (1 mmol) in ethanol or other solvent listed in the Table 1 (5 mL) was added an enamine **2a** (1 mmol) or **2b** (0.95 mmol) or **2c** (1.1 mmol) or **2d** (2 mmol) or **2e** (1.5 mmol). The reaction mixture was refluxed under calcium chloride tube for the moment substrate **1** disappearing (monitored by TLC).

In the case of reaction between **1** and **2a**, and **1** and **2b**, an intermediate existed in the reaction mixture. Their complete transformation into products **3a** or **3b** was carried out with three ways: **A1**: continuation of reflux in the same solvent; **A2**: acetic acid (0.10 mmol) was added to the reaction mixture, which was refluxed for 20 min in the case of **3a** and 10 min in the case of **3b**; **A3**: the reaction mixture was stirred at room temperature.

Products **3c–e** were formed simultaneously with slow disappearance of substrate **1** in reaction with an excess of appropriate enamine **2c–e** in refluxing solvent.

In all reactions the solvent was removed under reduced pressure and product was isolated by silica gel column chromatography (eluent: 1:1 hexane/dichloromethane for **3a–d** and dichloromethane to 10:1 dichloromethane/acetone for **3e**).

Method **B**. To a solution of **1** (1 mmol) in chlorobenzene (0.5 mL) placed in a Pyrex cylindrical vessel was added enamine **2c** (1.1 mmol) or **2d** (2 mmol). The reaction mixture was irradiated in the Synthewave 402 microwave reactor. The temperature setpoint was programmed at 110 °C. Irradiation was stopped after 3.0 min from the moment the temperature began to rapidly increase. The reaction mixture was left to chill to 90 °C then was cooled to room temperature. Product **3c** or **3d** was isolated by silica gel column chromatography (1:1 dichloromethane/hexane).

4.2.1. 1-(1-Methylthio-6,7-dihydro-5*H*-[2]pyrindin-3-yl)-ethanone (3a). Colorless crystals with mp 68.5–69.5 °C (from dichloromethane/hexane); R_f=0.43 (dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.15 (2H, quintet, J=7.6 Hz), 2.64 (3H, s), 2.70 (3H, s), 2.82 (2H, t, J=7.6 Hz), 2.94 (2H, t, J=7.6 Hz), 7.64 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.41 (S*C*H$_3$), 24.00 (*C*H$_2$), 26.02 (H$_3$*C*CO), 30.23 (*C*H$_2$), 32.64 (*C*H$_2$), 113.74 (*C*H), 141.01 (*C*), 151.73 (*C*), 153.38 (*C*), 154.16 (*C*), 200.09 (*C*O); IR (KBr): 3072, 2956, 2928, 2835, 1686, 1574, 1556, 1426, 1281, 1251, 1170, 923, 905, 581 cm^{-1}; EI-MS *m*/*z* (%): 207 (M$^+$, 50), 192 (10), 174 (100), 164 (8), 156 (9), 149 (12), 132 (8), 118 (5), 117 (4), 116 (5), 105 (4) 91 (3), 77 (7), 65 (7), 51 (8), 43 (10); HRMS (EI, M$^+$) calcd for $C_{11}H_{13}NOS$ 207.0718, found 207.0717. Anal. Calcd for $C_{11}H_{13}NOS$: C, 63.76; H, 6.28; N, 6.76; Found: C, 64.04; H, 6.40; N, 6.75.

4.2.2. 1-(1-Methylthio-5,6,7,8-tetrahydro-isoquinolin-3-yl)-ethanone (3b). Colorless crystals with mp 68–69 °C (from dichloromethane/hexane), described in our previous paper.[24] mp 62–63 °C (after sublimation). The new data; R_f=0.45 (dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.74–1.82 (2H, m), 1.84–1.92 (2H, m), 2.60 (2H, t, J=6.6 Hz), 2.61 (3H, s),2.70 (3H, s), 2.76 (2H, t, J=6.1 Hz), 7.48 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.99 (S*C*H$_3$), 21.87(*C*H$_2$), 22.87 (*C*H$_2$), 25.32 (*C*H$_2$), 25.83 (H$_3$*C*CO), 29.27 (*C*H$_2$), 117.96 (*C*H), 134.40 (*C*), 145.81 (*C*), 149.75 (*C*), 158.28 (*C*), 200.56 (*C*O); IR (KBr): 3064, 2933, 2920, 2866, 1691, 1579, 1549, 1415, 1394, 1357, 1287, 1240, 1174, 967, 951, 843, 819, 589 cm^{-1}; EI-MS *m*/*z* (%): 221 (M$^+$, 51), 206 (20), 188 (100), 170 (13), 160 (5), 146 (7), 130 (10), 117 (6), 103 (6), 91 (7), 77 (13), 65 (5), 51 (13), 43 (25).

4.2.3. 1-(1-Methylthio-6,7,8,9-tetrahydro-5*H*-cyclohepta-[*c*]pyridin-3-yl)-ethanone (3c). Colorless crystals with mp 56–57 °C, (from dichloromethane/hexane); R_f=049 (dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.59–1.67 (4H, m), 1.83–1.92 (2H, m), 2.58 (3H, s), 2.69 (3H, s), 2.77–2.83 (2H, m), 2.87–2.92 (2H, m), 7.50 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.85 (S*C*H$_3$), 25.80 (H$_3$*C*CO), 26.06 (*C*H$_2$), 26.88 (*C*H$_2$), 30.00 (*C*H$_2$), 32.28 (*C*H$_2$), 35.72 (*C*H$_2$), 118.17 (*C*H), 140.08 (*C*), 150.62 (*C*), 152.26 (*C*), 156.76 (*C*), 200.34 (*C*O); IR (KBr): 3066, 2945, 2921, 2849, 1701, 1574, 1545, 1445, 1417, 1393, 1350, 1350, 1291, 1261, 1194, 1149, 956, 920, 881, 843, 591 cm^{-1}; EI-MS *m*/*z* (%): 235 (70, M$^+$), 220 (65), 206 (25), 202 (100), 192 (20), 174 (65), 160 (18), 144 (9), 130 (7), 118 (9), 117 (8), 116 (8), 105 (5), 91 (10), 77 (10), 65 (6), 51 (11), 43 (12). Anal. Calcd for $C_{13}H_{17}NOS$*:* C, 66.34; H, 7.28; N,5.95; Found: C, 66.20; H, 7.35; N,5.85.

4.2.4. 1-(1-Methylthio-5,6,7,8,9,10-hexahydro-cycloocta-[*c*]pyridin-3-yl)-ethanone (3d). Colorless crystals with mp 101–102 °C, (from dichloromethane/hexane); R_f=0.52 (dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24–1.42 (4H, m), 1.62–1.84 (4H, m), 2.62 (3H, s), 2.71 (3H, s), 2.75–2.81 (2H, m), 2.88–2.94 (2H, m), 7.54 (1H, s); ^{13}C NMR 100 MHz, $CDCl_3$: δ 13.51 (S*C*H$_3$), 25.82 (H$_3$*C*CO), 25.86 (*C*H$_2$), 26.01 (*C*H$_2$), 27.03 (*C*H$_2$), 28.10 (*C*H$_2$), 31.46 (*C*H$_2$), 32.37 (*C*H$_2$), 118.25 (*C*H), 137.72 (*C*), 150.36 (*C*), 150.75 (*C*), 157.40 (C), 200.52 (*C*O); IR (KBr): 3064, 2955, 2918, 2845, 1694, 1573, 1547, 1386, 1350, 1295, 1264, 1195, 1159, 1082, 1014, 899, 839, 598 cm^{-1}; EI-MS *m*/*z* (%): 249 (60, M+), 234 (100), 220 (25), 216 (32), 206 (31), 202 (28), 188 (25), 174 (12), 162 (5), 144 (4), 130 (9), 118 (9), 117 (8), 116 (9), 105 (6), 91 (10), 77 (12), 65 (9), 51 (12), 43 (20); HRMS (EI, M+) calcd for $C_{14}H_{19}NOS$ 249.1184, found 249.1192.

4.2.5. 1-(1-(Methylthio)-5,6,7,8-tetrahydro-2,6-naphthyridin-3-yl)-ethanone (3e). Yellow crystals with mp

102.5–103 °C, (from dichloromethane/diethyl ether, anhydrous); R_f=0.31 (3:1 dichloromethane/acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45 (3H, s), 2.62 (3H, s), 2.70 (3H, s), 2.74 (4H, s), 3.54 (2H, s), 7.44 (1H, s); NMR (100 MHz, $CDCl_3$): δ 12.85 (S*C*H$_3$), 25.79 (H$_3$*C*CO), 25.88 (N*C*H$_3$), 45.71 (*C*H$_2$), 51.89 (*C*H$_2$), 57.07 (*C*H$_2$), 115.21 (*C*H), 131.56 (*C*), 143.52 (*C*), 150.22 (*C*), 158.24 (*C*), 200.20 (*C*O); IR (KBr): 3066, 2966, 2920, 2837, 2774, 1690, 1580, 1555, 1415, 1367, 1348, 1291, 1247, 1177, 1126, 1061, 951, 902, 858, 809, 590 cm^{-1}; EI-MS *m*/*z* (%): 236 (70, M$^+$), 221 (54), 203 (33), 193 (37), 192 (100), 189 (8), 178 (4), 174 (15), 160 (4), 150 (11), 136 (4), 118 (4), 117 (3), 104 (3), 91 (3), 77 (4), 65 (4), 51 (6), 43 (7); HRMS (EI, M$^+$) calcd for $C_{12}H_{16}N_2OS$ 236.0983, found 236.0980. The X-ray structure is shown (Fig. 1) and its data are listed below.

4.3. Isolation and structure determination of intermediate of 6a

The mixture of 5-acetyl-3-methylthio-1,2,4-triazine **1** (42 mg, 0.25 mmol) and 1-(1-cyclopenen-1-yl)-pyrrolidine **2a** (0.25 mmol) in ethanol (2 mL) was refluxed for 15 min and cooled to 0 °C. TLC monitoring (50:1 dichloromethane/acetone) showed that the substrate **1** (R_f=0.65) disappeared but only a trace of product **3a** (R_f=0.75) existed in the reaction mixture besides predominantly the most polar compounds (R_f=0.28). The latter was isolated by preparative thin-layer chromatography using 50/1 dichloromethane/acetone as mobile phase. A white substance (53 mg, ~75%) was obtained, which was stored below 0 °C. In GC/MS measurements of this substance were observed two compounds: **3a** and **6a** on the chromatogram in ratio 12:88 with retention times t_R=11.9 and t_R=13.8, respectively, which gave MS spectra: for **3a** *m*/*z* (%): 207 (M$^+$, 40), 192 (6), 174 (100), 164 (5), 156 (8), 149 (5), 132 (8), 118 (5), 117 (4), 116 (5), 105 (4), 91 (8), 77 (8), 65 (7), 51 (9), 43 (80); for **6a** *m*/*z* (%): 278 (M$^+$, 9), 263 (57), 231 (97), 209 (6), 203 (13), 188 (15), 174 (10), 162 (10), 148 (7), 136 (100), 118 (11), 96 (9), 91 (16), 70 (47), 55 (39), 43 (85). The ^{1}H NMR spectrum also showed the presence of two compounds in the ratio 9:1, which was calculated from the integration ratio of peaks: 6.68 ppm (1H, d, J=6 Hz, for **6a** *H*C4) and 7.64 ppm (1H, s, *H*C4 for **3a**). This spectrum also showed two singlets at 2.43 and 2.48 ppm for resonance of two methyl groups of **6a**. Other aliphatic protons (15H) of this substance gave wide-ranging multiplets in 2.9–1.5 ppm region.

4.4. Isolation and structure determination of side product 7b

A. Reaction between **1** and **2b** *in molar ratio 1:2 in ethanol*. To a solution of 5-acetyl-3-methylthio-1,2,4-triazine **1** (169 mg, 1 mmol) in ethanol (5 mL) was added 1-(1-cyclohexen-1-yl)-pyrrolidine **2b** (2 mmol). The reaction mixture was refluxed for 5 h and cooled to room temperature. TLC monitoring (50:1 dichloromethane/acetone) showed that substrate **1** (R_f=0.65) disappeared but besides the product **3b** (R_f=0.77) the less polar compound **7b** (R_f=0.90) existed in the reaction mixture. After removing solvent under reduced pressure, careful isolation of products was achieved by column chromatography using dichloromethane/hexane 1:2 to 1:1 as eluent. Pure compound **7b** was obtained (60 mg, 20%) and then pure **3b** (44 mg, 20%). The purity of products were analyzed by TLC (dichloromethane; R_f for **1**, **3b**, **7b** was measured as 0.11, 0.45 and 0.70), GC/MS and ^{1}H NMR.

B. Reaction between **1** and **2b** *in molar ratio 1:2 without solvent*. To pure **1** (169 mg, 1 mmol) under argon was added dropwise **2b** (2 mmol) at room temperature during 5 min. Vigorous nitrogen extrusion and temperature increase to 40 °C occurred. Complete consumption of substrate **1** was observed (TLC monitoring using dichloromethane) after stirring for 30 min. The reaction mixture was resolved by column chromatography using dichloromethane/hexane 1:2 to 1:1 as eluent. Compound **7b** (90 mg, 30%) with R_f=0.70 (dichloromethane) and t_R=15.8 min (base peak *m*/*z*=301) was first isolated and then an intermediate fraction (35 mg, 12%), which contained **7b** and a trace of compound isomeric to **7b** with R_f=0.62 (dichloromethane) and t_R=16.2 min (base peak *m*/*z*=301) and next pure **3b** (44 mg, 20%).

C. Reaction between **3b** and **2b** *in ethanol*. To the solution of **3b** (110 mg, 0.5 mmol) in ethanol (2.5 mL) was added 1-(1-cyclohexen-1-yl)-pyrrolidine **2b** (0.5 mmol). The reaction mixture was refluxed under nitrogen for 3 h. It was observed (TLC monitoring, dichloromethane) that only trace concentration of **7b** was present in the reaction mixture besides starting material **3b**. Next, pyrrolidine (0.5 mmol) was added to the reaction mixture and reflux was continued for 3 h. After cooling, the solvent was evaporated under reduced pressure. The residue was resolved by column chromatography to afford: **7b** (39 mg, 26%), then an intermediate fraction (28 mg, 10%), which contained **7b** and its isomer in the molar ratio 1:2.5 (by GC/MS) and **3b** (17 mg, 15%). The purity of products were analysed by TLC (dichloromethane), GC/MS and ^{1}H NMR.

4.4.1. 2-[1-(1-Methylthio-5,6,7,8-tetrahydro-isoquinolin-3-yl)-vinyl]-cyclohexanone (7b). Colorless crystals with mp 52–53 °C, (from dichloromethane/hexane); R_f=0.70 (dichloromethane); GC/MS: 97/3 mixture of **7b**/its isomer was observed on the chromatogram with retention times t_R=15.8 (95%) and t_R=16.2 (3% *m*/*z*=301). MS spectrum for **7b** *m*/*z* (%): 301 (M$^+$, 67), 286 (95), 284 (45), 272 (78), 258 (60), 244 (45), 240 (61), 231 (77), 226 (40), 212 (10), 206 (13), 198 (11), 193 (28), 178 (100), 163 (12), 150 (12), 144 (16), 130 (30), 117 (18), 103 (22), 91 (26), 77 (33), 53 (31), 41 (91); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52–1.68 (4H, m), 1.72–1.82 (2H, m), 1.83–1.91 (2H, m), 1.98–2.05 (4H, m), 2.61 (2H, t, J=6.5 Hz), 2.62 (3H, s), 2.76 (2H, t, J=5.6 Hz), 3.85 (2H, s), 5.56 (1H, br s), 7.48 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.12 (S*C*H$_3$), 21.88 (*C*H$_2$), 22.11 (*C*H$_2$), 22.41 (*C*H$_2$), 22.86 (*C*H$_2$), 25.41 (*C*H$_2$), 28.54 (*C*H$_2$), 29.29 (*C*H$_2$), 29.68 (*C*H$_2$), 46.06 (*C*H), 118.47 (*C*H), 125.50 (=*C*H$_2$), 132.40 (*C*), 134.38 (*C*), 145.89 (*C*), 149.62 (*C*), 158.14 (*C*), 200.44 (*C*O); IR (KBr): 3068, 2929, 2853, 2830, 1692, 1576, 1548, 1426, 1402, 1390, 1328, 1283, 1224, 1141, 1033, 997, 843, 762, 613; EI-MS *m*/*z* (%): (301 M$^+$, 100), 286 (72), 284 (45), 273 (32), 272 (57), 258 (48), 244 (30), 240 (46), 231 (60), 226 (28), 212 (72), 206 (12), 198 (7), 193 (24), 178 (70), 163 (9), 150 (7), 135 (7), 117 (10), 116 (7), 103 (11), 91 (8), 79 (6), 77 (35), 67 (29), 53

(6), 41 (15); HRMS (EI, M^+) calcd for $C_{18}H_{23}NOS$ 301.15004, found 301.14846.

4.5. Crystal data for 3e

$C_{12}H_{26}N_2O_2S$: $M=262.41$, crystal dimensions $0.60\times0.40\times0.30$ mm^3, monoclinic, space group P 21/c (no. 14), $a=7.9070(3)$ Å, $b=14.7600(7)$ Å, $c=21.5930(8)$ Å, $\beta=110.477(3)°$, $U=2360.82(17)$ Å^3, $Z=4$, $F(000)=295$, $D_c=0.738$ g m^3, $T=100(2)$ K, μ(Mo Kα)$=4.19$ mm^{-1}, Nonius Kappa-CCD diffractometer, $\theta_{max}=24.71°$, 3065 unique reflections, which were used in all calculations. The structure was solved by direct methods using the SHELXS-97 program[24] was refined by full matrix least-squares on F^2 using the program SHELXL-97.[25] H-atoms were included in idealized positions and refined isotropically. Refinement converged at $R1=0.0553$, $wR2=0.0908$ for all data and 295 parameters ($R1=0.0418$, $wR2=0.0849$ for 2569 reflections with $I_o>2\sigma(I_o)$). The goodness-of-fit on F^2 was equal 1.068. A weighting scheme $w=[\sigma^2(F_o^2+(0.0418P)^2+3.1964P)]^{-1}$ where $P=(F_o^2+2F_c^2)/3$ was used in the final stage of refinement. The residual electron density$=0.20/-0.21$ e Å^{-3}. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-264189. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).

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Crowned dendron: ion-responsive flexibility of macromolecules induced by integrated crown ether moieties

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Abstract—Polybenzyl ether type dendrons bearing the crown ether moieties at the periphery, namely, crowned dendrons were synthesized, and the effect of complex formation on their flexibility with metal-ion binding properties was examined. Upon addition of Na^+, ^1H NMR spectra of the crowned dendrons in CD_3CN were significantly broadened, reflecting the flexibility restriction of the crowned dendrons by the complex formation with Na^+. Such a significant flexibility restriction was observed only with Na^+, although ESI-MS studies revealed that the crowned dendrons formed 1:2 complexes (a metal ion:the crown ether moiety) regardless of the kind of metal ions. The flexibility restriction became significant with increasing dendron generation on the basis of ^1H NMR spectra and spin-lattice relaxation time (T_1) measurements. Binding constants of the crowned dendrons with metal ions in CD_3CN decreased with the increase of the dendron generation, reflecting an influence of the charge repulsion as well as a dendrimer effect to cause the steric hindrance. The examination of UV–vis absorption spectra for complexes of the crowned dendron with metal picrates in THF displayed the formation of a loose ion-pair complex with Na^+, namely, a typical sandwich type complex. However, in CH_3CN, all metal picrates were solvated to be in a loose ion-pair even without complex formation. These results suggested that the control of macromolecular flexibility with metal ions is feasible by the integration of crown ether moieties with a dendritic structure.

1. Introduction

In biological systems, the stimulation, recognition, and response are a series of events to produce biological functions, in which specific flexibility and shape persistence of macromolecules are essential factors. The molecular recognition to induce an allosterism through flexibility control of macromolecules has been considered as one of factors to produce biological functions such as non-linear response, switching, self-restoration, and so on. To understand such a biological system and to realize it artificially have been a fascinating work in chemistry.

Our interest is in the manipulation of molecular functions with metal ions in view of the molecular recognition. For example, the combination of a crown ether moiety with a photochromic molecule afforded ion-responsive photochromic materials.[1] These contexts prompted us to study flexibility behavior of macromolecules induced by complex formation of integrated crown ether moieties. Recently, dendrimer is one of the attractive macromolecules to produce various function because of its ordered structure, dendritic structure,[2] and some dendrimers, which have several molecular recognition sites have been reported.[3] Therefore, we set out to synthesize a dendrimer bearing crown ether moieties at the periphery, namely, crowned dendrimer. In this macromolecule, the crown ether moieties are integrated with a dendritic structure, and ion-responsive flexibility induced by the complex formation of the integrated crown ether moieties is expected.

Several crowned dendrimers have already been reported.[4–7] In the case of dendrimers bearing crown ether moieties at the periphery,[4,5] however, any flexibility change by the formation of metal ion complex in solution have not been found.[5] Among dendrimers bearing crown ether moieties at the core,[6,7] the first example of ion-responsive morphology was reported in a mesophase.[7] To the best of our knowledge,

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ion-responsive flexibility of crowned dendrimers in solution has not been reported yet, although there is a report on a dendrimer showing pH-responsive flexibility due to the charge repulsion in solution.[8]

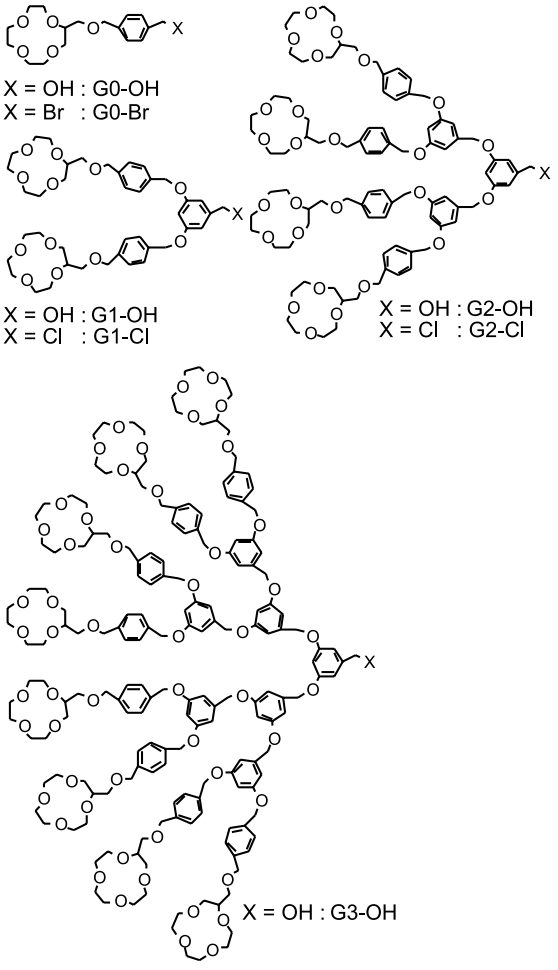
In this paper, we report the synthesis of a new macromolecule bearing crown ether moieties with a dendritic structure, and its ion-responsive flexibility induced by its metal ion binding.

2. Results and discussion

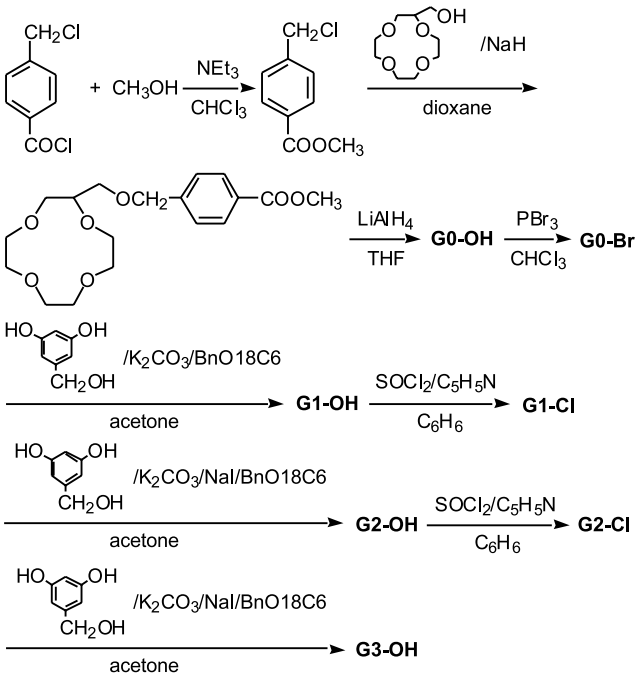
2.1. Synthesis

Crowned dendrons, Gn-X (n=0–3, X=OH, Cl, or Br) listed in Scheme 1 were synthesized according to a convergent approach.[9] We chose 12-crown-4 as a building block for our crowned dendrimer because assembling 12-crown-4 moieties shows marked differences from the single 12-crown-4 moiety not only in the metal-ion binding ability but also in the complex structure; the 12-crown-4 moiety forms 2:1 complexes with Na^+ and 1:1 complexes with Li^+, respectively.[10]

The adopted synthetic procedures for the crowned dendrons are summarized in Scheme 2. At the first step, 12-crown-4



Scheme 1. Synthesized crowned dendrons.



Scheme 2. Synthesis outline. BnO18C6 represents benzyloxymethyl-18-crown-6.

moiety was introduced at the *para* position of benzyl alcohol to afford **G0-OH**. And the generation of the crowned dendron was then increased according to the synthetic procedures for Fréchet type dendrimer in the presence of benzyloxymethyl-18-crown-6 (BnO18C6) as a phase transfer catalyst.[11] The reactivity of benzyl hydroxyl group at the focal position decreased with increasing dendron generation, and finally, attempts to synthesize the fourth generation dendron and the dendrimer with **G3-OH** dendron were not successful. Therefore, we examined the flexibility of maclomolecules with a dendron structure. The structure of **G3-OH** did not seem to be too crowded to hamper the reaction on the basis of the result of molecular mechanics calculation. Some interaction of the crown ether moieties with the reactant may disturb the subsequent reaction.

2.2. Flexibility of G3-OH depending on metal ions

In order to investigate the influence of complex formation on the flexibility of **G3-OH**, ^{1}H NMR spectra were measured in the presence of various alkali and alkaline-earth metal ions in CD_3CN at room temperature. Upon addition of alkali metal perchlorates, a drastic down-field shift in the spectra for protons of the crown ether moieties was observed, which indicated complex formation of the crown ether moieties with metal ions. The spectra of the **G3-OH** protons of the crown ether moieties in the presence of Li^+ and Na^+ are shown in Figure 1. In the case of Na^+, a significant broadening of spectra was induced. This broadening obviously suggests that the flexibility of the crowned dendron was restricted by the Na^+ complex formation in ^{1}H NMR time-scale. On the other hand, such a significant broadening was not observed with other alkali metal ions, although the down-field shift for the protons of the crown ether moieties appeared with all the metal ions.

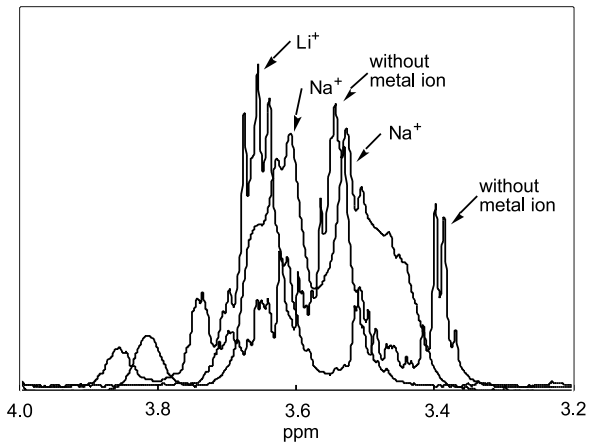


Figure 1. ^{1}H NMR spectra for crown ether protons of **G3-OH** in the presence or absence of metal ions in CD_3CN at room temperature. The concentrations of **G3-OH** and $MClO_4$ were 1×10^{-3} and 1×10^{-2} mol dm^{-3}, respectively.

The spectral change induced by the complex formation was found not only at the protons of the crown ether moieties but also at all the protons of **G3-OH**. Especially, the peaks of the **G3-OH** aromatic protons at the periphery (the protons of the aromatic ring moiety adjacent to the crown ether moiety) showed a very intriguing behavior depending on the kind of metal ions, as depicted in Figure 2. In the presence of Li^+, the shape of the peaks were sharp with a down-field shift indicating the complex formation with Li^+, and such a down-field shift was observed for all the protons in **G3-OH**. To the contrary, the addition of Na^+ induced an up-field shift with a significant broadening in the spectrum, and the up-field shift was observed for all the protons except for the protons of the crown ether moieties. At a higher temperature, 70 °C, the spectrum with Na^+ became sharp with a smaller up-field shift. Therefore, the up-field shift induced by the Na^+ complex formation seemed to reflect diamagnetic anisotropy of aromatic rings[12] caused by the flexibility restriction. In the case of K^+, a slight up-field shift was observed except for the crown ether protons. The behavior of the K^+ complexation is similar to that of the Na^+ complexation, but any broadening was not discernible.

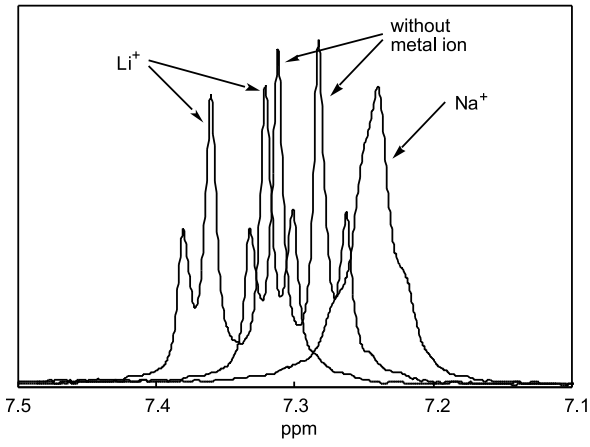


Figure 2. ^{1}H NMR spectra for aromatic protons of **G3-OH** in the presence or absence of metal ions in CD_3CN at room temperature. The concentrations of **G3-OH** and $MClO_4$ were 1×10^{-3} and 1×10^{-2} mol dm^{-3}, respectively.

Furthermore, any spectral change was hardly observed in the presence of Rb^+ and Cs^+ except for the down-field shift of the crown ether protons. In the cases of alkaline-earth metal ions, although a significant down-field shift was observed for the protons of the crown ether moieties, any spectral broadening could not be detected because of the low solubility of the complexes. Those results suggest that the complex formation affects the flexibility of **G3-OH** depending on the kind of metal ions.

In order to investigate the influence of anion on the flexibility of **G3-OH**, lithium and sodium picrates, the picrate anion, of which is known as a large counteranion, were added to **G3-OH** in CD_3CN, and ^{1}H NMR spectra were examined. In the case of sodium picrate, some broadening of ^{1}H NMR spectra was observed in a similar way to the case of $NaClO_4$. With lithium picrate, a down-field shift indicating the complex formation was discernible, but no broadening was detected. This result suggests that the difference of the metal ion size controls the flexibility of **G3-OH** rather than the difference of the anion size.

ESI-MS measurements were carried out to determine how many metal ions were captured by **G3-OH** in CH_3CN. The ESI-MS spectra showed that each **G3-OH** molecule holds four metal ions, where the peaks at *m/z* of 842 with Li^+ and at *m/z* of 858 with Na^+ were observed. Even in the presence of 100-fold excess amount of Li^+ and Na^+, each **G3-OH** molecule was found to hold four metal ions at most. The ESI-MS spectrum with Na^+ is shown in Figure 3. Additionally, the Job plots for ^{1}H NMR titration data gave a maximum close to 0.8 in the molar fraction of Li^+, which is consistent with the ESI-MS result. Therefore, the crown ether moieties tend to form 1:2 complexes (a metal ion:the crown ether moiety) regardless of the kind of metal ions. This result means that the difference between Li^+ and Na^+ complexes of **G3-OH** in ^{1}H NMR spectra was induced by the difference in the metal ion size ($Li^+ = 0.60$ and $Na^+ = 0.98$ Å) but not in the number of the captured metal ions.

In Fréchet type dendrimer, a metal ion could be attached to the benzyl ether oxygens. Upon addition of Li^+, the ^{1}H NMR spectra for **G3-OH** showed a down-field shift induced

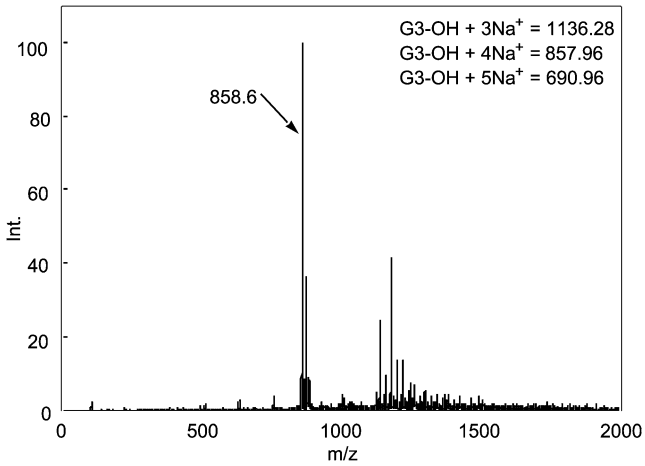


Figure 3. ESI-MS spectra of **G3-OH** in the presence of $NaClO_4$ in CH_3CN. The concentrations of **G3-OH** and $NaClO_4$ were 1×10^{-5} and 1×10^{-3} mol dm^{-3}, respectively.

by complex formation with Li^+ for all protons. The down-field shift for the crown ether protons was about 0.15 ppm but that for the benzyl protons was much smaller being between 0.05 and 0.07 ppm. Furthermore, in the case of Na^+, the down-field shift was observed only for the crown ether protons, and ESI-MS measurements revealed that the **G3-OH** can capture a maximum of four metal ions. Therefore, the metal ion captured by **G3-OH** seems to be located at the crown ether moieties.

Unfortunately, attempts to visualize the difference in flexibility between Li^+ and Na^+ complexes of **G3-OH** by atomic force microscopy (AFM) failed.

2.3. Dendrimer effect on flexibility

In order to evaluate the dendrimer effect, ^{1}H NMR spectra were examined for **G0-OH**, **G1-OH**, and **G2-OH** in the presence of various alkali metal ions in a similar way to **G3-OH**. The ^{1}H NMR spectra of the aromatic protons at the periphery in the presence of Li^+ and Na^+ are shown in Figures 4 and 5, respectively. In Figure 4, Li^+ did not induce any peak broadening in spectra for all the crowned dendrons. However, in the case of Na^+, the ^{1}H NMR spectral peaks became drastically broad with increasing dendron generation (Fig. 5). This result indicates that the flexibility restriction of the crowned dendron by Na^+ complex formation depends strongly on the dendron generation, that is, a dendrimer effect.

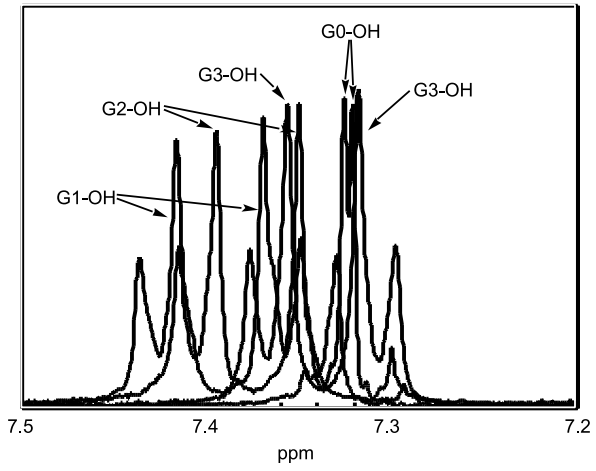


Figure 4. ^{1}H NMR spectra for aromatic protons of **G0∼3-OH** in the presence of $LiClO_4$ in CD_3CN at room temperature. The concentrations of **G0∼3-OH** and $LiClO_4$ were 8, 4, 2, 1×10^{-3}, and 1×10^{-2} mol dm^{-3}, respectively.

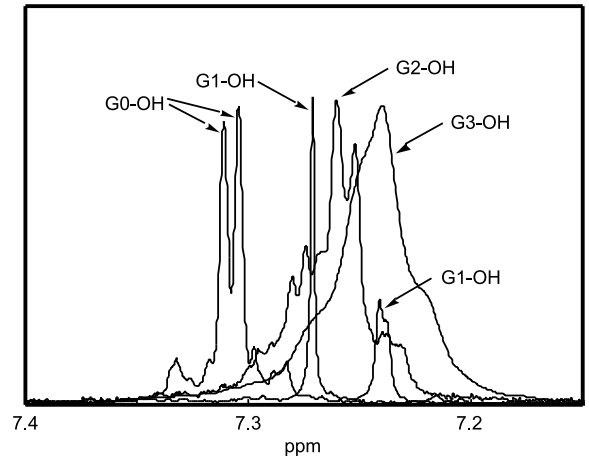


Figure 5. ^{1}H NMR spectra for aromatic protons of **G0∼3-OH** in the presence of $NaClO_4$ in CD_3CN at room temperature. The concentrations of **G0∼3-OH** and $NaClO_4$ were 8, 4, 2, 1×10^{-3} and 1×10^{-2} mol dm^{-3}, respectively.

In Figure 4, the down-field shift induced by the Li^+ complexation is increased with increasing the dendron generation from $\Delta\delta=0.01$ for **G0-OH** to $\Delta\delta=0.04$ for **G3-OH**. On the other hand, the up-field shift caused by the Na^+ complexation showed an opposite tendency. The up-filed shift induced by Na^+ is the most significant for **G1-OH** ($\Delta\delta=-0.12$) and is decreased with the increase of dendron generation, being $\Delta\delta=-0.09$ and -0.06 for **G2-OH** and **G3-OH**, respectively. As anticipated, such an up-field shift was not observed for **G0-OH**. This result again implies that the difference in the metal ion size caused a significant difference in the dendron flexibility.

In order to express the flexibility restriction of the dendron numerically, the spin-lattice relaxation time (T_1) in CD_3CN at room temperature was measured as an indicator for the flexibility restriction of the crowned dendron, where the decrease of intramolecular motion results in the T_1 reduction. It is known that the complex formation of crown ethers with metal ions reduces their T_1 value in the NMR spectra through the reduction of intramolecular motion.[13] The T_1 values of the aromatic protons at the periphery (protons of the aromatic ring moiety adjacent to the crown ether moiety) for **G0∼3-OH** in the absence of metal ions were 3.5, 1.9, 1.5, and 1.3 s, respectively, which indicated the enhancement of flexibility restriction with increasing the dendron generation. When $LiClO_4$ and $NaClO_4$ were added to the **G3-OH** solution, the T_1 value decreased to 1.1 and 0.72 s, respectively. This result clearly indicates that the metal complex formation of **G3-OH** reduces the intramolecular motion, namely, the flexibility, and that Na^+ is more effective in the flexibility restriction than Li^+. This significant flexibility restriction induced by the complex formation of **G3-OH** with Na^+, as shown in the T_1 measurements, is consistent with the result of the ^{1}H NMR studies.

2.4. Metal-ion binding properties

The binding constants for complexes with metal perchlorates in CD_3CN at room temperature were evaluated through the binding isotherms by non-linear least-square regression[14] using the ^{1}H NMR titration data. The tertiary proton of the crown ether moiety was used as an indicator. The binding constants for **G1∼3-OH** were determined as the average value for the binding sites, in which two crown ether moieties captured one metal ion. The obtained data are summarized in Table 1. Although the binding constants for **G0-OH** showed Li^+, Ca^{2+}, and Sr^{2+} selectivity, the selectivity was not remarkable. On the other hand, the binding constants for **G1∼3-OH** indicated a clear selectivity to Na^+ and Ca^{2+}. While the metal-ion binding ability of 12-crown-4 towards Li^+ is well known to form 1:1 complex,[15] bis(12-crown-4) derivatives generally show a high binding ability towards Na^+ by the formation of

Table 1. Binding constants with metal perchlorates in CD_3CN[a]

	Li^+	Na^+	K^+	Rb^+	Cs^+	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
G0-OH	14	7.7	2.3	0.66	0.28	0.34	73	110	24
G1-OH	1.3	110	3.0	1.8	0.79	0.28	460	6.5	—[b]
G2-OH	0.84	96	1.0	0.74	0.64	2.2	330	5.7	—[b]
G3-OH	0.78	90	0.96	(9.8)[c]	(19)[c]	2.1	170	(52)[c]	—[b]

[a] The unit is 10^3 mol^{-1} dm^3.
[b] The values could not be determined.
[c] The values did not reflect conceivable binding constants because of charge repulsion and steric hindrance.

sandwich-type complexes, namely, 1:2 (a metal ion:the crown ether moiety) complex.[16] In the case of polymers carrying a 12-crown-4 moiety at the side chain, high binding abilities towards Na^+ are also attained by the formation of similar sandwich-type complexes.[17] Therefore, this binding ability of **G1～3-OH** to Na^+ is derived from the formation of sandwich-type complexes. However, the binding constants for **G1～3-OH** generally decreased with the increase of dendron generation. The degree of decrease in the binding constants with increasing dendron generation was more significant with Ca^{2+} than with Na^+. This implies that the charge repulsion of divalent Ca^{2+} became more serious than that of monovalent Na^+ with increasing the dendron generation, since the radius of Na^+(0.98 Å) is as large as that of Ca^{2+}(0.99 Å). Thus, the dendrimer effect was also observed in the binding constants reflecting the charge repulsion.[8]

In the cases of Rb^+, Cs^+, and Sr^{2+}, the binding constants for **G3-OH** shown in parenthesis in Table 1 were extraordinary large. To determine the binding constants, **G3-OH** was regarded as a tetradentate ligand, tentatively. However, because of the charge repulsion and steric hindrance with the dendrimer effect, it is likely that **G3-OH** could not act as a tetradentate ligand with those metal ions to yield extraordinarily large binding constants.

2.5. Complexing behavior of G3-OH with metal picrates

Metal picrates are known to show significant changes in the UV–vis absorption spectra depending on the nature of ion-pair. The formation of a sandwich type complex with crown ethers to afford a loose ion-pair complex induces a red-shift in the UV–vis absorption spectra in THF.[18] Therefore, UV–vis absorption spectra with alkali metal picrates were measured in the presence or absence of **G3-OH** to evaluate its complexing behavior. The UV–vis absorption spectra of lithium and sodium picrates are shown in Figure 6. Upon the addition of **G3-OH**, while lithium picrate did not show any meaningful change in the spectrum, sodium picrate indicated a significant spectral change with 7 nm red-shift at the maximal absorption (shift from 352 to 359 nm). It is obvious that this red shift in the spectrum indicates the formation of a sandwich type complex, in which a metal ion is captured by two crown ether moieties effectively, and therefore the formation of a loose ion-pair.[18] Such a significant red-shift was only observed with sodium picrate, and other metal picrates showed only a slight red shift of less than 3 nm.

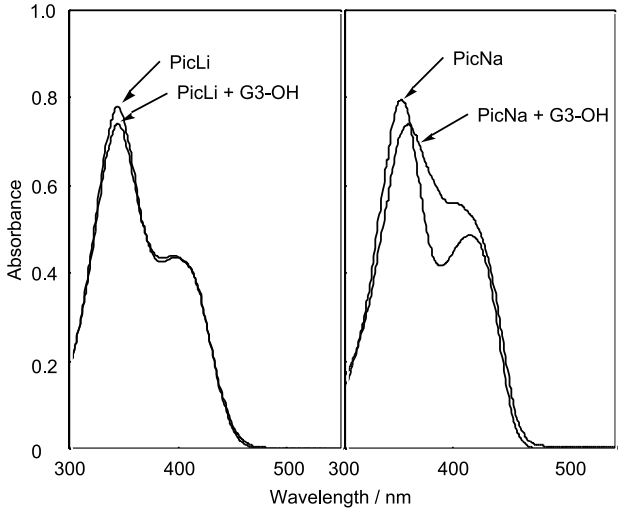


Figure 6. UV–vis absorption spectra of metal picrates in the presence of **G3-OH** in THF at room temperature. The concentrations of **G3-OH** and metal picrates were 5×10^{-5} mol dm^{-3}. PicLi and PicNa represent lithium and sodium picrates, respectively.

In CH_3CN, however, such a spectral change was hardly observed by addition of **G3-OH**, and all the picrates showed the maximal absorption at 375 nm. This tendency shows that all the metal picrates are in a loose ion-pair by solvation with CH_3CN even without complex formation, as the wavelength of the maximal absorption (375 nm) for the metal picrates in CH_3CN was much longer than that (359 nm) for sodium picrate in THF in the presence of **G3-OH**. These observations again support that the metal ion captured by the crown ether moieties is a crucial factor to induce the flexibility restriction of the crowned dendron.

3. Conclusions

The manipulation of macromolecular flexibility by recognition of metal ions was examined with dendrons bearing crown ether moieties at the periphery, crowned dendron, where the crown ether moieties were integrated with their dendron structure. The significant influences of metal complex formation on the flexibility demonstrate that the manipulation of macromolecular flexibility by recognition of metal ions is possible by integration of the crown ether moieties in macromolecules. A study on application of this ion-responsive flexibility of macromolecules for molecular function control to materials chemistry is in progress in due course.

4. Experimental

4.1. General

All chemicals and metal perchlorates were of available

purity and used without further purification. For the UV–vis absorption spectra measurements, THF and CH_3CN of spectroscopic grade were used. Metal picrates were prepared by the reaction of equimolar amounts of aqueous picric acid and metal hydroxide, or carbonate. To avoid the explosion of metal picrates during drying, only a small amount of metal picrates was prepared each time. Gel permeation chromatography (GPC) using chloroform as an eluent was used for purification of the dendrons.

4.2. Synthesis of dendrons

4.2.1. 4-Chloromethylbenzoic acid methyl ester. Methanol (1.60 g, 50 mmol), triethylamine (1.52 g, 15 mmol), and chloroform (100 mL) were put into a three-necked flask at 0 °C. A chloroform solution (20 mL) of 4-chloromethylbenzoyl chloride (1.89 g, 10 mmol) was added dropwise to the mixture. The reaction mixture was allowed to warm at room temperature and stirred for 12 h. The reaction mixture was poured into water, and the organic layer was separated. The crude product (quantitative) obtained as a colorless liquid by solvent evaporation was used for the subsequent synthesis after drying.

4.2.2. 4-(12-Crown-4-methoxymethyl)benzoic acid methyl ester. Hydroxymethyl-12-crown-4 (2.27 g, 11 mmol), sodium hydride (720 mg, 30 mmol), and dioxane (100 mL) were put in a three-necked flask, and the mixture was refluxed. A dioxane solution (20 mL) of crude 4-chloromethylbenzoic acid methyl ester (1.85 g, 10 mmol) was added dropwise and the reaction mixture was then refluxed for 5 h. Methanol was added to the cooled reaction mixture to quench the excess sodium hydride, and the solvent was then evaporated. Aqueous hydrochloric acid (5 wt%) was added to acidify the residue, and the product was extracted with chloroform. The organic layer was separated, and the crude product (quantitative) obtained as a brownish liquid by solvent evaporation was used for the subsequent synthesis after drying.

4.2.3. Compound G0-OH. Lithium aluminum hydride (760 mg, 20 mol) and THF (100 mL) were put in a three-necked flask. A THF solution (20 mL) of crude 4-(12-crown-4-methoxymethyl)benzoic acid methyl ester (3.54 g, 10 mmol) was added dropwise at room temperature, and the reaction mixture was refluxed for 20 h. Concentrated aqueous hydrochloric acid was added dropwise to the cooled reaction mixture to quench the excess lithium aluminum hydride. The solvent was evaporated, and water was poured into the obtained residue. The product was extracted with chloroform twice, and the organic layer was separated. The crude product obtained by solvent evaporation was purified by GPC to afford a colorless liquid product (63%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.4–3.9 (17H, m, OCH_2, OCH═), 4.54 (2H, s, $PhCH_2$), 4.68 (2H, s, $PhCH_2$), 7.31 (2H, d, J=8.4 Hz, ArH), 7.34 (2H, d, J=8.4 Hz, ArH); IR (neat, cm^{-1}): 3019 (CH_2), 1219 (OCH_2); *m/z* 349 (M+ Na^+). Anal. Calcd for $C_{17}H_{26}O_6$: C 62.56, H 8.03, found: C 62.65, H 8.07.

4.2.4. Compound G0-Br. *Compound* **G0-OH** (652 mg, 2 mmol) and chloroform (50 mL) were put in a three-necked flask at room temperature. A chloroform solution (20 mL) of phosphorus tribromide (813 mg, 3 mmol) was added dropwise, and the reaction mixture was stirred for 1 h. The reaction mixture was poured into water, and the organic layer was separated. The crude product obtained by solvent evaporation was purified by GPC to give a colorless liquid product (77%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.4–3.9 (17H, m, OCH_2, OCH═), 4.49 (2H, s, $PhCH_2$), 4.54 (2H, s, $PhCH_2$), 7.30 (2H, d, J=8.0 Hz, ArH), 7.37 (2H, d, J=8.0 Hz, ArH).

4.2.5. Compound G1-OH. Under a nitrogen atmosphere, **G0-Br** (778 mg, 2 mmol), 3,5-dihydroxybenzyl alcohol (133 mg, 0.95 mmol), benzyloxymethyl-18-crown-6 (BnO18C6, 77 mg, 0.2 mmol), potassium carbonate (556 mg, 4 mmol) and acetone (50 mL) were put in a three-necked flask, and the mixture was refluxed for 3 days under nitrogen atmosphere. The solvent was evaporated, and aqueous hydrochloric acid (5 wt%) was poured to acidify the obtained residue. The product was extracted with chloroform, and the organic layer was separated. The crude product obtained by solvent evaporation was purified by GPC to yield a colorless liquid (94%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.4–3.9 (34H, m, OCH_2, OCH═), 4.54 (4H, s, $PhCH_2$), 4.60 (2H, s, PhCH_2OH), 5.01 (4H, s, $PhCH_2$), 6.52 (1H, s, ArH), 6.61 (2H, s, ArH), 7.33 (4H, d, J=7.6 Hz, ArH), 7.38 (4H, d, J=7.6 Hz, ArH); IR (neat, cm^{-1}): 3020 (CH_2), 1215 (OCH_2); *m/z* 756 (M+ Na^+). Anal. Calcd for $C_{41}H_{56}O_{13}$: C, 65.06; H, 7.46. Found: C, 65.18; H, 7.43.

4.2.6. Compound G1-Cl. *Compound* **G1-OH** (724 mg, 1 mmol), pyridine (474 mg, 6 mmol), and benzene (100 mL) were put in a three-necked flask at room temperature. A benzene solution (20 mL) of thionyl chloride (714 mg, 6 mmol) was added dropwise, and the reaction mixture was refluxed for 4 h. Concentrated aqueous hydrochloric acid was added dropwise to the cooled reaction mixture. The reaction mixture was poured into water, and the benzene layer was separated. The crude product obtained by solvent evaporation was purified by GPC to give a colorless liquid product (67%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.4–3.9 (34H, m, OCH_2, OCH═), 4.50 (2H, s, PhCH_2Cl), 4.55 (4H, s, $PhCH_2$), 5.02 (4H, s, $PhCH_2$), 6.55 (1H, s, ArH), 6.63 (2H, s, ArH), 7.34 (4H, d, J=7.6 Hz, ArH), 7.39 (4H, d, J=7.6 Hz, ArH).

4.2.7. Compound G2-OH. Under a nitrogen atmosphere, **G1-Cl** (1.485 g, 2 mmol), 3,5-dihydroxybenzyl alcohol (133 mg, 0.95 mmol), benzyloxymethyl-18-crown-6 (BnO18C6, 77 mg, 0.2 mmol), potassium carbonate (2.76 g, 20 mmol), catalytic amount of sodium iodide, and acetone (50 mL) were put in a three-necked flask, and the mixture was refluxed for 3 days under nitrogen atmosphere. The solvent was evaporated, and aqueous hydrochloric acid (5 wt%) was poured to acidify the obtained residue. The product was extracted with chloroform, and the organic layer was separated. The crude product obtained by solvent evaporation was purified by GPC to afford a pale-yellow liquid (39%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.4–3.9 (68H, m, OCH_2, OCH═), 4.54 (8H, s, $PhCH_2$), 4.60 (2H, s, PhCH_2OH), 4.96 (4H, s, $PhCH_2$), 5.02 (8H, s, $PhCH_2$), 6.51 (1H, s, ArH), 6.55 (2H, s, ArH), 6.58 (2H, s, ArH), 6.66 (4H, s, ArH), 7.33 (8H, d, J=8.0 Hz, ArH), 7.38 (8H, d, J=8.4 Hz, ArH); IR (neat, cm^{-1}): 3017 (CH_2), 1217 (OCH_2);

m/z 1640 (M+ Na^+). Anal. Calcd for $C_{89}H_{116}O_{27}$: C 66.07, H 7.23, found: C 66.00, H 7.13.

4.2.8. Compound G2-Cl. *Compound* **G2-OH** (1.55 g, 1 mmol), pyridine (474 mg, 6 mmol), and benzene (100 mL) were put in a three-necked flask at room temperature. A benzene solution (20 mL) of thionyl chloride (714 mg, 6 mmol) was added dropwise, and the reaction mixture was refluxed for 4 h. Concentrated aqueous hydrochloric acid was added dropwise to the cooled reaction mixture. The reaction mixture was poured into water, and the benzene layer was separated. The crude product obtained by solvent evaporation was purified by GPC to afford a pale-yellow liquid product (74%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.4–3.9 (68H, m, OCH_2, OCH=), 4.51 (2H, s, PhCH_2Cl), 4.55 (8H, s, $PhCH_2$), 4.97 (4H, s, $PhCH_2$), 5.02 (8H, s, $PhCH_2$), 6.5 (3H, m, ArH), 6.62 (2H, s, ArH), 6.67 (4H, s, ArH), 7.34 (8H, d, J=8.0 Hz, ArH), 7.39 (8H, d, J=8.4 Hz, ArH).

4.2.9. Compound G3-OH. Under a nitrogen atmosphere, **G2-Cl** (3.14 g, 2 mmol), 3,5-dihydroxybenzyl alcohol (133 mg, 0.95 mmol), benzyloxymethyl-18-crown-6 (BnO18C6, 77 mg, 0.2 mmol), potassium carbonate (2.76 g, 20 mmol), a catalytic amount of sodium iodide, and acetone (50 mL) were put in a three-necked flask, and the mixture was then refluxed for 3 days under nitrogen atmosphere. The solvent was evaporated, and aqueous hydrochloric acid (5 wt%) was poured to acidify the obtained residue. The product was extracted with chloroform, and the organic layer was separated. The crude product obtained by solvent evaporation was purified by GPC to give a pale-yellow liquid (47%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.4–3.9 (136H, m, OCH_2, OCH=), 4.4–4.6 (18H, m, $PhCH_2$, PhCH_2OH), 4.8–5.0 (28H, m, $PhCH_2$) 6.5–6.7 (21H, m, ArH), 7.32 (16H, d, J=6.4 Hz, ArH), 7.38 (16H, d, J=8.4 Hz, ArH); IR (neat, cm^{-1}): 3015 (CH_2), 1215 (OCH_2); *m/z* 858.6 ((M+4Na^+)/4). Anal. Calcd for $C_{185}H_{236}O_{55}$: C, 66.53; H, 7.12. Found: C, 66.63; H, 7.11.

4.3. NMR spectra measurements

NMR measurement was carried out in the presence or absence of various metal perchlorates or picrates in acetonitrile-d3 at room temperature. The concentrations of $LiClO_4$ and $NaClO_4$ were 1×10^{-2} mol dm^{-3}, and that of **G3-OH** was 1×10^{-3} mol dm^{-3}. Because of the low solubility, the concentrations of $KClO_4$, $RbClO_4$, and $CsClO_4$ were 5×10^{-3} mol dm^{-3} and the concentration of **G3-OH** was 5×10^{-4} mol dm^{-3}. In the cases of alkaline-earth metal perchlorates, a precipitation was formed with **G3-OH** solution (1×10^{-3} mol dm^{-3}), when the concentration of metal ions was more than 1×10^{-4} mol dm^{-3}. For metal picrates, the concentration of **G3-OH** was 5×10^{-4} mol dm^{-3}, and that of lithium and sodium picrates was 2.5×10^{-3} mol dm^{-3}.

In order to examine the dendrimer effect, the concentrations of **G0~3-OH** were 8×10^{-3}, 4×10^{-3}, 2×10^{-3}, and 1×10^{-3} mol dm^{-3}, respectively, and the concentration of lithium and sodium perchlorates was 1×10^{-2} mol dm^{-3}.

In the case of the binding constants determination, the concentrations of **G0~3-OH** were 8×10^{-3}, 4×10^{-3}, 2×10^{-3}, and 1×10^{-3} mol dm^{-3}, respectively, for Li^+ and Na^+. On the other hand, in the cases of K^+, Rb^+, and Cs^+, the concentrations of **G0~3-OH** were 4×10^{-5}, 2×10^{-3}, 1×10^{-3}, and 5×10^{-4} mol dm^{-3}, respectively.

The sum of the concentrations for **G3-OH** and $LiClO_4$ was 1×10^{-2} mol dm^{-3} for Job plots.

For the T_1 measurement, the concentrations of **G0~3-OH** solutions were 8×10^{-3}, 4×10^{-3}, 2×10^{-3}, and 1×10^{-3} mol dm^{-3}, respectively. On the other hand, the concentration of metal ions was 1×10^{-2} mol dm^{-3}. A weighted average was adopted as the T_1 value of coupling peaks.

4.4. ESI-MS spectra measurements

ESI-MS measurement was carried out using acetonitrile as the solvent. The concentration of **G3-OH** was 1×10^{-5} mol dm^{-3}, and that of metal perchlorate was 1×10^{-4} or 1×10^{-3} mol dm^{-3}.

4.5. UV–vis spectra measurements

The concentrations for metal picrates and **G3-OH** were 5×10^{-5} mol dm^{-3}, and THF and CH_3CN of spectroscopic grade were used. For measurements, a quarts cell which has a 10 mm light path length was used.

4.6. AFM measurements

A CH_3CN solution of **G3-OH** whose concentration was 1×10^{-4} mol dm^{-3} was put on graphite plate, and the sample was dried for several hours. Without metal ion, thickness of the **G3-OH** layer was less than 20 nm. In the presence of an equal amount of $NaClO_4$ (1×10^{-4} mol dm^{-3}), however, **G3-OH** formed a particle, the radius, of which was several hundreds nm. The reason for why the addition of $NaClO_4$ to **G3-OH** caused such a significant morphology change of **G3-OH** under dry conditions is not understood yet.

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4-Nitrobenzodifuroxan: a highly reactive nitroolefin in Diels–Alder reactions

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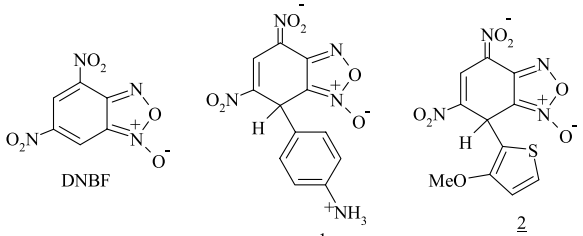
Dedicated to Professor Vladimir Minkin on the occasion of his 70th birthday

Abstract—The reactions of 4-nitrobenzodifuroxan (NBDF) with a series of common dienes are found to proceed very readily to afford stable cycloadducts, which are the result of highly stereoselective normal electron demand (NED) Diels–Alder reactions. Due to the additional activation provided by the two adjacent furoxan rings, the nitroolefinic double bond of NBDF is also prone to undergo NED reactions with less reactive dienic structures such as the enol form of ethoxymethyleneacetylacetone and the in situ generated 2-ethoxy-4-(2-furfuryl)buta-1,3-diene. A number of X-ray structures could be obtained, which leave no doubt as to the stereochemistry of the resulting cycloadducts. A rationalization of the reactions in terms of the electrophilicity parameter ω defined by Parr suggests that all cycloadditions proceed with a notable polar character.

1. Introduction

Much evidence has been accumulated that nitro-substituted 2,1,3-benzoxadiazoles and related 1-oxides, commonly referred to as nitrobenzofurazans and nitrobenzofuroxans, respectively, are 10-π electron heteroaromatic substrates, which exhibit an extremely high electrophilic character.[1–3] As a stronger electrophile than the 4-nitrobenzenediazonium cation, 4,6-dinitrobenzofuroxan (DNBF)—the reference compound in the series—has been used as a probe to assess the reactivity of such weak carbon nucleophiles as benzenoid aromatics (phenols, anilines…) or π-excessive heteroaromatics (indoles, pyrroles, thiophenes, furans…) whose carbon basicities are associated with large negative pK_a values, for example, 1,3-dimethoxybenzene (p$K_a=-9$), aniline (p$K_a=-6$) or 3-methoxythiophene (p$K_a=-6.50$). In all of these reactions, covalent addition of the nucleophile takes place at C-7 of the carbocyclic ring of DNBF to give very stable σ-adducts of type **1** or **2**.[4–12] Also illustrative of the superelectrophilic behaviour of nitrobenzoxadiazole structures is the high tendency of the halogen atom of 7-halo-4-nitro- and 7-halo-4,6-dinitro-benzofurazans and -benzofuroxans to depart in nucleophilic aromatic substitutions, leading to numerous synthetic, analytical and biological applications.[13–15]



It has been recently emphasized that the exceptional electrophilic reactivity of DNBF and related heterocycles is largely the reflection of the low aromatic character of the benzofuroxan and benzofurazan structures.[16] Strong evidence for this relationship has come from the finding that nitrobenzoxadiazoles also behave as very versatile Diels–Alder reagents, contributing to Normal (NED) and Inverse (IED) Electron Demand cycloadditions, which generally proceed with high regio and stereoselectivity.[17–19] An illustrative example is given in Scheme 1, which shows that the reaction of DNBF with cyclopentadiene affords initially a mixture of the two NED and IED monoadducts **3**

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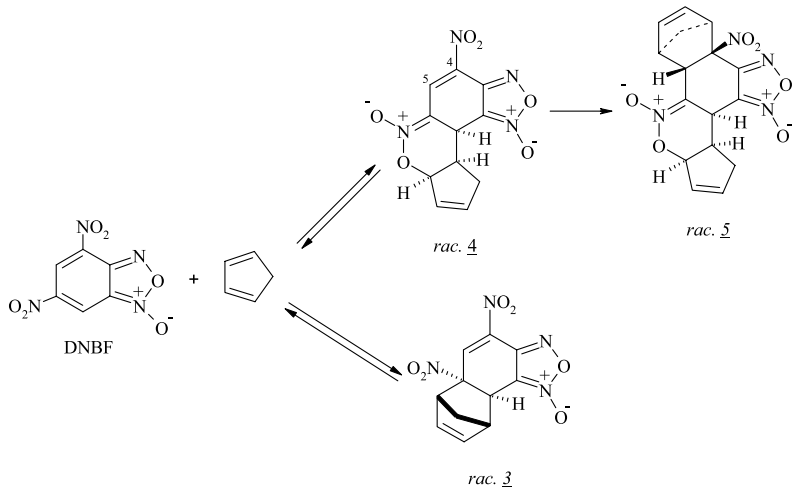
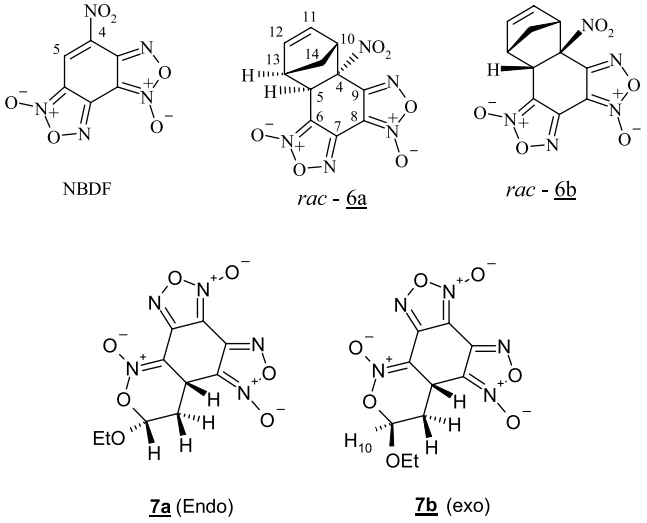


Scheme 1.

and **4** in their racemic forms. Then, a second and highly stereoselective NED process takes place at the remaining and now purely olefinic nitro-activated C_4–C_5 fragment of **4**, leading to an essentially quantitative formation of the highly functionalized diadduct **5** in its racemic form.[19a] A theoretical study by Domingo et al. has confirmed the mechanistic and stereochemical features of this interaction.[20]

The evidence from the above results is that the pericyclic behaviour of DNBF is reminiscent of that of nitroolefins.[21,22] This encouraged us to look at the potential reactivity of the single nitro-activated C_4–C_5 double bond of the related 4-nitrobenzodifuroxan (NBDF) structure. In fact, we reported recently in a communication that this peculiar nitrolefin behaves as an ambident Diels–Alder reagent, reacting readily with cyclopentadiene to give exclusively the NED monoadduct **6a** (in its racemic form) and with ethyl vinyl ether to afford a 95:5 mixture of the *endo* and *exo* IED adducts **7a** and **7b**.[23] In this paper, we report a detailed investigation of the dienophilic character of NBDF, showing that this compound is so reactive that it undergoes NED reactions with a large variety of dienes, including such poorly reactive structures as the enolic forms of some β-dicarbonyl compounds, for example, ethoxymethylacetylacetone, and related enol ethers. Also reported are the X-ray structures of NBDF and the cyclopentadiene adduct **6a**, which complement our preliminary report and usefully add to the understanding of the reactions.



2. Results

2.1. The X-ray structure of NBDF

The ORTEP view in Figure 1 shows that the C_4–C_5 double bond of NBDF has a length of 1.339 Å. This is typical of a nitro-olefinic fragment and in contrast with the situation reported for DNBF where values of 1.37 and 1.40 Å have been measured for the two potentially reactive nitro-activated C_6–C_7 and C_4–C_5 double bonds, respectively.[24] In accord with these data, the least aromatic C_6–C_7 fragment is the one preferentially involved in Diels–Alder interactions, accounting for the regioselectivity observed in the formation of all DNBF monoadducts so far reported.

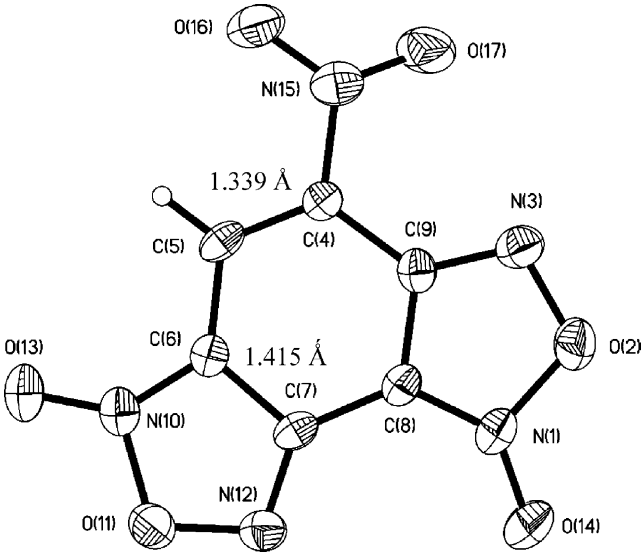
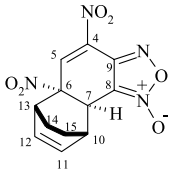


Figure 1. ORTEP view of NBDF.

A most interesting feature, however, is that the cycloadditions involving the C_6–C_7 double bond go along with a strong shortening of the C_4–C_5 double bond of the carbocyclic moiety of DNBF. Values of 1.322, 1.336 and 1.328 Å have thus been measured for this bond in the DNBF–cyclohexadiene adduct **8** and the two related structures **9** and **10**, respectively.[19,25,26] This corresponds to the recovery of a strong olefinic character of this fragment, marking it comparable to the C_4–C_5 bond of NBDF. On this basis, it would be more appropriate to relate the reactivity of NBDF to that of the DNBF monoadducts rather than to the parent molecule.



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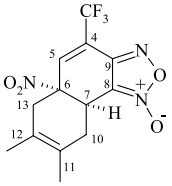

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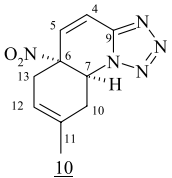
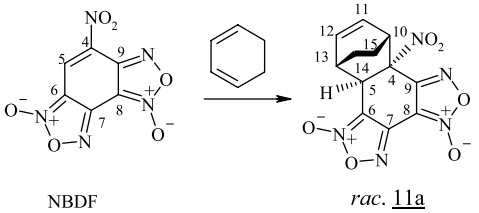


10

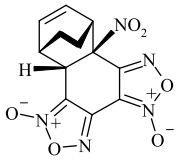
2.2. Reactions of NBDF with cyclopentadiene and cyclohexadiene

The ORTEP view of Figure 2 shows the structure of the single product, namely the NED adduct **6a**, which we previously isolated in its racemic form upon treatment of NBDF with excess cyclopentadiene in chloroform or dichloromethane for 2 h at room temperature (76% yield).[23] Interestingly, the stereochemistry of **6a** in the crystal agrees well with the structural information provided by a detailed analysis of the ^1H and ^{13}C NMR spectra recorded in Me_2SO-d_6 solution via COSY and HETCOR, as well as NOE and *J*-modulation experiments. In particular, NOE experiments agreed with the space proximity of the H_5 and H_{13} protons in **6a**. Other major diagnostic features of the reaction process are the disappearance of the low field proton typical of the olefinic moiety of NBDF and the strong deshielding of the sp^3 carbon C_4 in the resulting adduct. This carbon is subject to the strong electron-withdrawing inductive effects exerted by both the NO_2 group and the adjacent furoxan ring.[18,19,26,27]



NBDF *rac*. 11a

or



rac. 11b (1)

As found for the cyclopentadiene system, the addition of excess cyclohexadiene to NBDF in $CHCl_3$ solution afforded only one product, which was isolated as white crystals in 65% yield (Eq. 1). In as much as the key ^1H and ^{13}C NMR resonances pertaining to this product (e.g., $\delta H_5 = 4.19$; $\delta H_{13} = 3.50$; $\delta C_5 = 39.66$; $\delta C_4 = 89.62$) compare remarkably

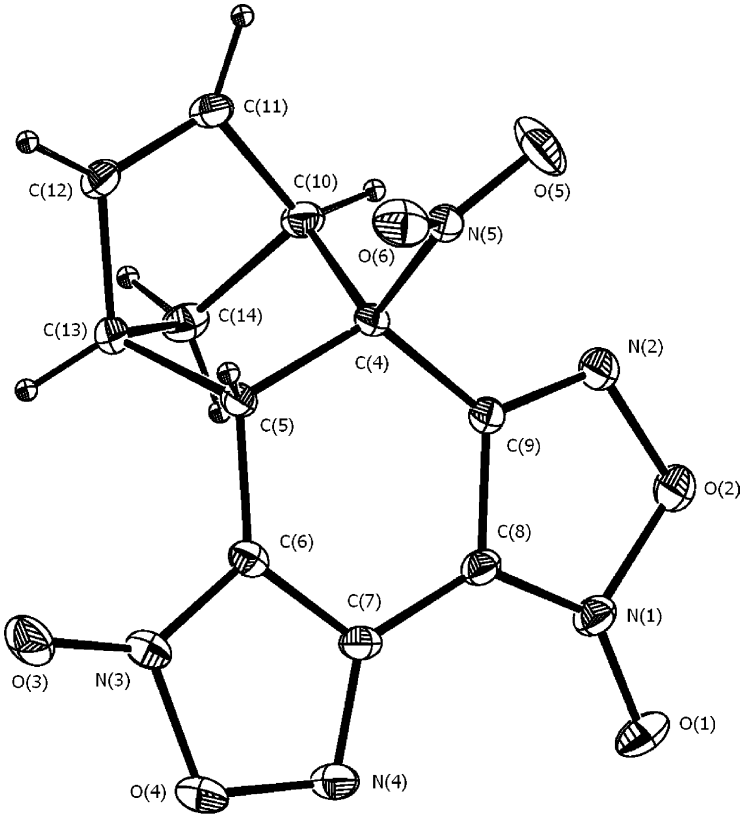


Figure 2. ORTEP view of **6a**.

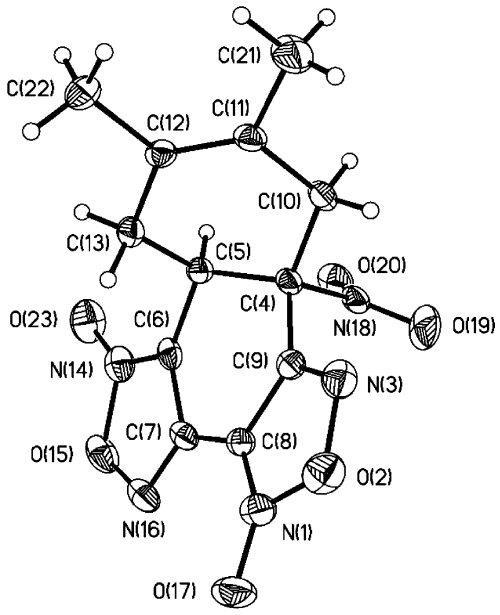


Figure 3. ORTPE view of **12a**.

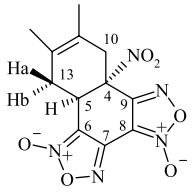
well with those for **6a** (e.g., $\delta H_5 = 4.04$; $\delta H_{13} = 3.48$; $C_5 = 37.12$; $\delta C_4 = 88.92$), there is little doubt as to its identity as the diastereomer **11a** rather than **11b**.

That the interactions of NBDF with cyclopentadiene and cyclohexadiene proceed through highly diastereoselective NED processes to afford exclusively the *endo*-adducts **6a** and **11a** rather than the *exo* isomers **6b** and **11b** is noteworthy. However, the configuration of **6a** and **11a** with the 4-NO_2 group and H_5 being in a trans arrangement to the C_{13}–C_{14}–C_{10} or the C_{13}–C_{14}–C_{15}–C_{10} bridges is reminiscent of that established for the corresponding DNBF-cyclopentadiene and cyclohexadiene mono-adducts **3** and **8**. In the latter system, firm evidence for the proposed stereochemistry was obtained through an X-ray structure.[19a]

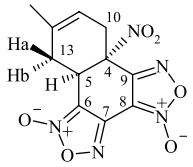
2.3. Reactions of NBDF with isoprene, 2,3-dimethylbutadiene and 1-acetoxybutadiene

Each of the reactions of NBDF with the three above dienes under the same experimental conditions as those used in the cyclopentadiene and cyclohexadiene systems produced a white solid, which was isolated in good yield (65–70%). The ORTEP view in Figure 3 shows that the product isolated in the 2,3-dimethylbutadiene system is a NED adduct, which is formed as the diastereomer **12a** in its racemic form. The resonances of the various protons and carbons of **12a** were unambiguously assigned by 2D and NOE experiments. Of particular significance is the H_5 resonance, which appears as a doublet of doublet due to the non equivalence of the two adjacent methylene protons H_{13a} and H_{13b}. As found for the adducts **6a** and **11a**, the ^{13}C NMR spectra also show a low field signal characteristic of the nitro-substituted quaternary sp^3 carbon C_4.

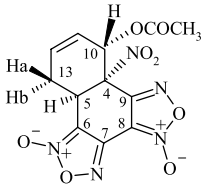
On grounds of analogy with **12a**, structures **13a** and **14a** are assigned to the isoprene-and acetoxybutadiene- NBDF products. As expected, the ^1H and ^{13}C parameters associated to the C_4–C_5–C_{13} fragment of the three adducts are closely similar (see Table 1). On the other hand, the configuration proposed for the carbon C_{10} bearing the acetoxy group of **14a** is the one derived from an *endo* reaction process. Arguments supporting this stereochemistry are given below.



rac. 12a



rac. 13a



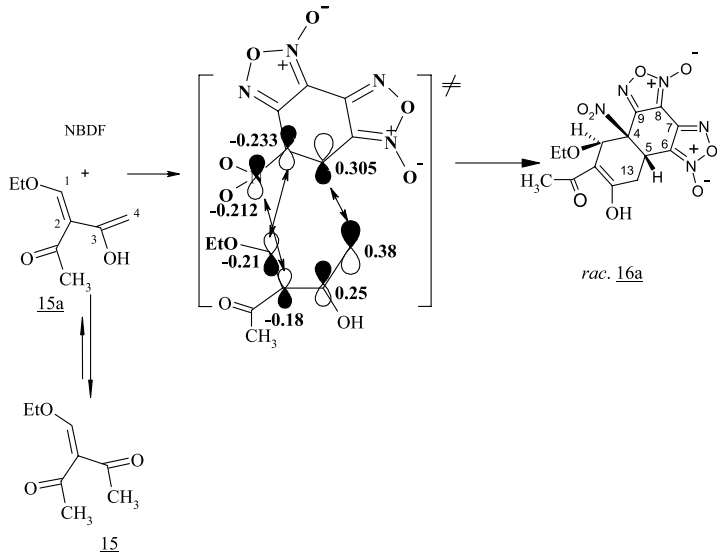
rac. 14a

2.4. Reaction of NBDF with ethoxymethyleneacetylacetone

Scheme 2 shows that the treatment of NBDF with an excess of ethoxymethylene–acetylacetone **15** leads to a single adduct, which we have formulated as the diastereomer **16a** in its racemic form on the basis of the X-ray structure given in Figure 4. In addition to the presence of the 4-NO_2 group and H_5 on the same side of the two carbocyclic rings, Figure 4 reveals that the ethoxy group at C_{10} is located in space proximity with the NO_2 group. This implies that the reaction proceeds with a high *endo* selectivity. As depicted in Scheme 2, there is a possible stabilization of the related transition state, but not of the *exo* counterpart, by a secondary orbital interaction involving the nitrogen atom of the 4-NO_2 group of NBDF and the carbon C_2 of the reactive form of **15**, that is, the enol tautomer **15a**. Obviously a similar stabilizing contribution can operate in the transition state of the NBDF–acetoxybutadiene system,

Table 1. Key NMR data for cycloadducts **12**–**14a**, **16a** and **20a** recorded in acetone d_6

Adduct	δC_4	δC_5	δC_{13}	δH_5	δH_{13a}	δH_{13b}	$J_{H5-H13a}$	$J_{H5-H13b}$	$J_{H13a-H13b}$
12a	88.28	36.51	33.99	4.53	2.37	2.74	10.5	7.5	17.7
13a	85.34	34.41	29.03	4.37	2.15	2.69	10.8	7.0	18.0
14a	88.20	30.85	28.80	4.59	2.50	3.15	10.3	7.7	19.1
16a	89.42	34.22	30.11	4.89	2.58	3.41	10.4	5.8	19.1
20a	90.01	38.85	30.72	4.71	1.91	3.08	10.3	8.5	17.6



Scheme 2.

accounting for our assignment of structure **14a** to the resulting NED adduct.

Even though it proceeds rather slowly, producing **16a** in 28% yield after 3 days at room temperature, the reaction depicted in Scheme 2 is of great significance since the formation of this adduct can only be envisioned as deriving from a NED process involving the enol tautomer **15a** as the diene contributor. Taking into account that this tautomer has a low equilibrium concentration—no detection of **15a** is possible by ^{1}H NMR in $CDCl_3$ or CD_2Cl_2 solution—its contribution to the observed reaction is very illustrative of the high dienophilic reactivity of the nitroolefinic fragment of NBDF.

2.5. Reaction of NBDF with an in situ generated diene

Addition of a mixture of furfurylidene acetone **17** and triethylformate **18** to a $CHCl_3$ solution of NBDF resulted in the slow formation of a product, which we could isolate in 36% yield after 3 weeks at room temperature. In accord with the high susceptibility of the first reaction of Scheme 3 to H^+ catalysis,[28] the same product was obtained more rapidly (3 days) in 80% yield in the presence of a catalytic amount of *p*-toluenesulfonic acid (TsOH). The ORTEP view in Figure 5 reveals that this compound is the adduct **20a**, resulting from a diastereoselective NED process involving the in situ generated enol ether **19** as the diene contributor (Scheme 3). With the furan ring at C_{10} being spatially close to the 4-NO_2 group, the *endo* stereochemistry of **20a** resembles that firmly established above for the adduct **16a**, adding to the evidence that the *endo* approach must also prevail in the formation of related adducts such as **14a**.

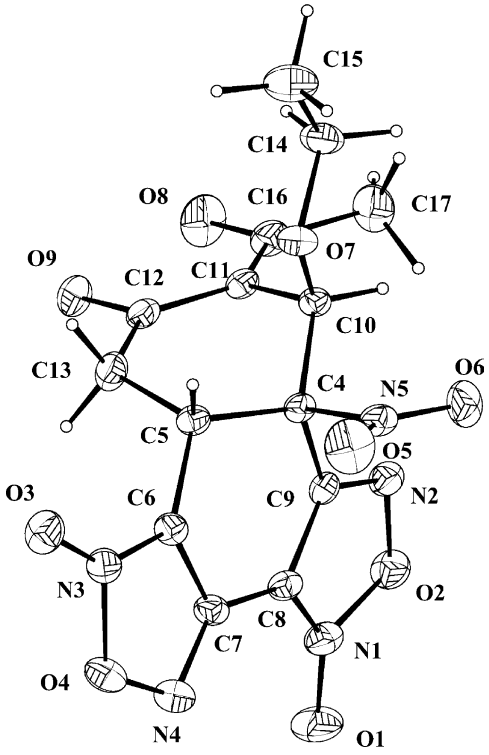
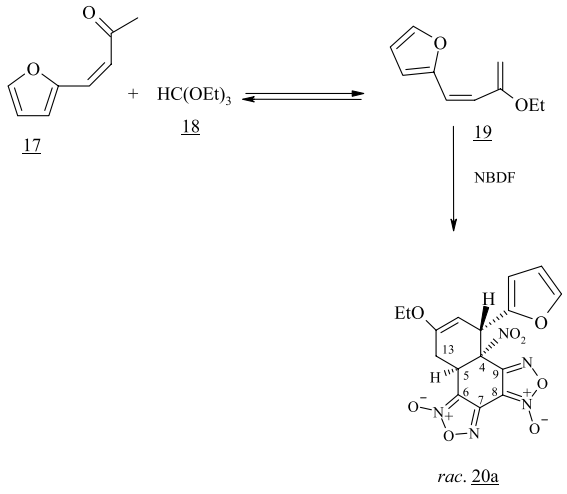


Figure 4. ORTEP view of **16a**.



Scheme 3.

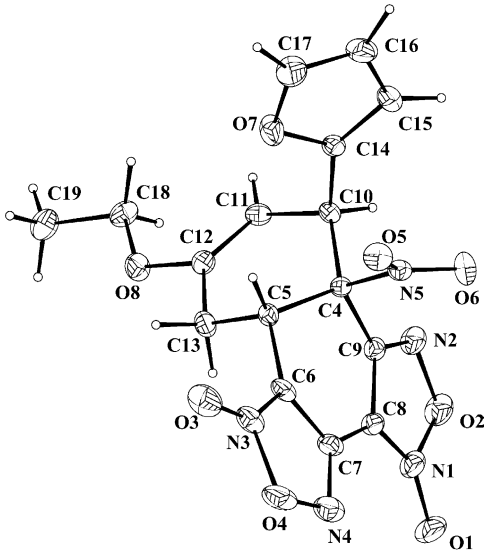


Figure 5. ORTEP view of **20a**.

3. Discussion

3.1. DNBF/NBDF/Nitroethylene reactivity

Recent density functional theory (DFT) studies devoted to Diels–Alder reactions have shown that the classification of the diene/dienophilic pairs on a unique electrophilicity scale is a very nice entry for predicting the feasibility and the more or less polar character of the cycloaddition processes. The question has been especially addressed by Domingo et al.,[20,29,30] using the global electrophilicity index, ω, introduced by Parr and defined by Eq. 2.[31] In this equation, the electronic chemical potential μ and the chemical hardness η of a substrate are two parameters, which were evaluated in terms of the one-electron energies of the frontier molecular orbitals (FMO) HOMO and LUMO at the ground state of the molecules.[31–33] Another index used by Domingo et al. is the so called ΔN_{max} parameter, defined by Eq. 3, which is a measure of the maximum amount of electronic charge that the electrophilic partner can accept.[31] According to the model, the polar character of a DA interaction can be assessed from the difference, $\Delta\omega$, in the global electrophilicities of the two reagents as well as the ΔN_{max} values for the system at hand.[20,29,30] Thus, it can be anticipated that reactions involving a diene and a dienophile located at the ends of the ω scale will proceed with an especially strong polar character. In turn, reactions associated with small $\Delta\omega$ values should be prototypes of non polar processes.

$$\omega = \frac{\mu^2}{2\eta} \tag{2}$$

$$\Delta N_{max} = -\frac{\mu}{\eta} \tag{3}$$

$$\omega_k = \omega f_k^+ \tag{4}$$

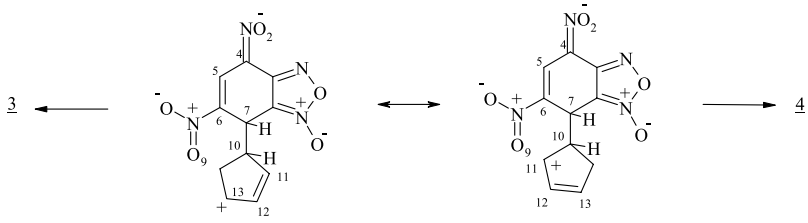
Also important is the local electrophilicity index (ω_k) defined by Eq. 4, which shows that the electrophilic character of a molecule will develop to the greatest extent at the site where the Fukui function for nucleophilic attacks (f_k^+) displays its maximum value, that is, at the most reactive site of the electrophile.[20,29b] Consideration of these ω_k parameters has proved to be useful to account for the regioselectivity in DA reactions exhibiting a polar character.

In Table 2 are collected the various parameters required to compare the DA reactivity of NBDF with that of DNBF and nitroethylene. Focusing first on DNBF, it is a significant result that both the observed regioselectivity and stereospecificity of this compound with cyclopentadiene (Scheme 1) have been perfectly accounted for by Domingo et al. in terms of Eqs. 2–4.[31] With high ω (5.46 eV) and ΔN_{max} (1.84) values, DNBF falls in the range of very strong electrophiles so that its reaction with cyclopentadiene (ω= 0.83 eV)[29a] is characterized by a large $\Delta\omega$ value of 4.63 eV. This leaves no doubt that the two reagents will be involved in a cycloaddition reaction with a large polar character. As a matter of fact, DFT calculations have revealed that the reactions proceed preferentially via the *endo* mode with the initial formation of a zwitterionic intermediate resulting from the nucleophilic attack of cyclopentadiene to the C-7 position of DNBF.[20] Cylization takes place in a second step, either through formation of the C_6–C_{13} bond or the C_{11}–O_9

Table 2. Global properties and global electrophilicity scale for dienophiles and dienes involved in DA reactions of this work[a]

Diene	HOMO	LUMO	μ	η	ω	ΔN_{max}
Cyclopentadiene[b]	−0.2116	−0.0098	−0.1106	0.2016	0.83	0.549
Isoprene[b]	−0.2272	−0.0152	−0.1212	0.2120	0.94	0.572
19[c]	−0.1905	−0.0372	−0.1138	0.1532	1.15	0.743
2,3-Dimethylbutadiene[d]	−0.2248	−0.0174	−0.1211	0.2074	0.97	0.584
15a[d]	−0.2028	−0.0379	−0.1204	0.1648	1.20	0.730
Cyclohexadiene[d]	−0.2083	−0.0188	−0.1136	0.1895	0.90	0.590
1-Acetoxy-1,3-butadiene[b]	−0.2237	−0.0280	−0.1259	0.1957	1.10	0.643
Nitroethylene[b,c]	−0.2958	−0.0957	−0.1958	0.2001	2.61	0.979
Nitroethylene/BH_3[c]	−0.2704	−0.1388	−0.2046	0.1316	4.33	1.554
DNBF[c]	−0.2768	−0.1587	−0.2177	0.1180	5.46	1.845
DNBF/adduct **4**[c]	−0.2511	−0.1297	−0.1904	0.1214	4.06	1.56
DNBF/adduct **3**[c]	−0.2641	−0.1275	−0.1934	0.1366	3.72	0.978
NBDF[d]	−0.2795	−0.1493	−0.2144	−0.1300	4.80	1.65

[a] HOMO and LUMO energies, electronic chemical potential μ and chemical hardness η in atomic units; global electrophilicities ω in eV; ΔN_{max} in electron units.
[b] Ref. 29a.
[c] Ref. 20.
[d] Calculated in this work.



Scheme 4.

bond, to afford a mixture of the NED and IED monoadducts **3** and **4** (Scheme 4).

On the other hand, the observed regioselectivity of the two competitive cycloadditions is consistent with the much greater local electrophilicity at the C-7 than at the C-5 carbon of DNBF: ω_κ (C-7)=1.20 eV; ω_κ (C-5)=0.40 eV.[20] Importantly, the global electrophilicity of the two resulting cycloadducts remains very high, being somewhat greater for **4** (ω=4.06 eV) than for **3** (ω=3.72 eV).[20] In agreement with this trend, the nitroolefin fragment of **4** is the preferred site for a second and equally polar addition of cyclopentadiene to give the diadduct **5**.[20]

Going to NBDF, a ω value of 4.80 eV can be derived from Parr's treatment. This shows that the activation by the two adjacent furoxan ring adds considerably to the electrophilic character of the related nitroolefinic fragment as compared with the situation in the two DNBF monoadducts **3** and **4**. Also, it is very informative for the understanding of the Diels–Alder reactivity of these peculiar nitroolefins that the calculated ω values for NBDF, **3** and **4** are all much higher than for nitroethylene (ω=2.61 eV).[29a] In the presence of a Lewis catalyst, this latter olefin is known to contribute to strongly polar Diels–Alder reactions,[29] in agreement with the finding that it becomes associated with a high ω value, for example, ω=4.33 eV for the nitroethylene/BH_3 complex,[29a] comparable in fact with those for NBDF or **4** in the absence of catalyst.

Table 2 shows that the global electrophilicities of the various dienic structures opposed to NBDF are covering a relatively narrow range of ω values, that is, from 0.82 eV for cyclopentadiene to 1.20 eV for the enol ether **19**. As a result and because of the high ω value of NBDF (4.80 eV), all the cycloadditions depicted in this work are associated with rather high $\Delta\omega$ values. On this basis, it can be reasonably anticipated that these reactions take place with a notable polar character. Whether they occur via a two-step process involving a zwitterionic intermediate or they proceed via a highly asynchronous concerted process cannot be decided at this stage.

In accord with the similarity of the ω values of these dienes, the reactions of NBDF with cyclopentadiene, cyclohexadiene, isoprene, 2,3-dimethylbutadiene and 1-acetoxybutadiene are found to proceed roughly with the same efficiency under the experimental conditions at hand. In contrast, and despite similar ω values, the reactions of NBDF with ethoxymethyleneacetylacetone **15** (Scheme 2) and the enol ether **19** (Scheme 3) occur much more slowly. In these instances, however, the reactive dienic species are at a given time present in very low concentrations in the reaction mixture, being continuously in situ generated through displacement of the equilibria depicted in Schemes 2 and 3. It is this feature, which accounts for the less favourable formation of the cycloadducts **16** and **20a** (in the absence of TsOH as acid catalyst).

4. Experimental

4.1. General

Melting points were determined on a Reichert-type microscope and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 MHz spectrometer. Chemical shifts are reported in ppm (J values in Hertz) relative to internal Me_4Si. Electronic Impact mass spectra (EI, 70 eV) were obtained using a HEWLETT PACKARD 5989B and a NERMAG R10-10C spectrometer equipped with a quadrupole. Elemental analyses were determined by the Microanalytical laboratory of the University Paris VI, France. The crystal structures (Figs. 1–5) have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition numbers CCDC-268687, CCDC-267386, CCDC-268688, CCDC-266344 and CCDC-266345 for NBDF, **6a**, **12a**, **16a** and **20a**, respectively.

4.2. Materials

4-Nitrobenzodifuroxan was prepared as described by Bailey and Case [34] (mp: 158 °C; lit.[34] 158 °C). Commercial 2,3-dimethylbutadiene, isoprene, 1-acetoxybutadiene and cyclohexadiene were used without further purification. Cyclopentadiene, obtained from the heating of bicyclopentadiene, was used without further purification. Ethoxymethylene–acetylacetone was prepared according to Dorofeenko et al.[35]

4.3. Preparation of the Diels–Alder adducts 6a, 11a–14a and 16a. General procedure

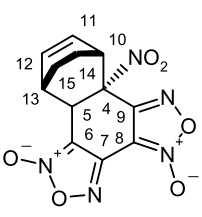
To a solution of 4-nitrobenzodifuroxan (0.2 g, 0.83 mmol) in CH_2Cl_2 or in $CHCl_3$ (10 ml) at room temperature was added an excess (10 equiv) of diene. The solution turned rapidly to orange and the reaction mixture was stirred at room temperature for a few hours. Addition of pentane resulted in the immediate formation of a precipitate, which was collected by filtration and dried under vacuum and then purified by column chromatography, using pentane–ethylacetate mixtures or pentane–CH_2Cl_2 mixtures as eluents.

Crystallographic data for **NBDF**. $C_6HN_5O_6$, FW=239.12 g mol^{-1}, orthorhombic, *Pna*2, a=6.9358 Å, b=

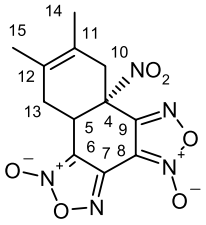
19.161 Å, $c=6.4957$ Å, $\beta=90°$, $V=863.3$ Å^3, Dc$=$ 1.840 mg cm^{-3}, $Z=4$.

Crystallographic data for **6a**. $C_{11}H_7N_5O_6$, FW$=$ 305.22 g mol^{-1}, Triclinic, *P*-1, $a=7.3592$ Å, $b=$ 8.1394 Å, $c=11.141$ Å, $\beta=98.09°$, $V=603.2$ Å^3, Dc$=$ 1.681 mg cm^{-3}, $Z=2$.

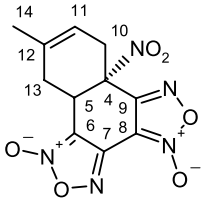
See Ref. 23 for elemental analysis, ^{1}H and ^{13}C NMR as well as mass spectroscopy data.



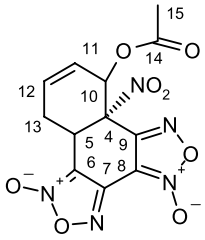
11a



12a



13a



14a

4.3.1. Compound 11a. White solid; yield 65%; mp: 196 °C (dec); MS (EI): *m/z* 319 $[M]^{+\cdot}$, 273 $[M-NO_2]^+$. Anal. Calcd for $C_{12}H_9N_5O_6$ (%): C. 45.15; H. 2.84; N. 21.94; found (%), C. 45.58; H. 2.85; N. 21.60. ^{1}H NMR (300 MHz, acetone-d_6) δ 1.20–1.85 (m, 4H, $2CH_2$), 3.50 (m, 1H, H-13), 4.13 (m, 1H, H-10), 4.19 (m, 1H, H-5), 6.51 (dd, $J=7.6$, 6.6 Hz, 1H, H-12), 6.68 (ddd, $J=7.8$, 6.9, 1.0 Hz, 1H, H-11); ^{13}C NMR (75 MHz, acetone-d_6) δ 18.82, C-15; 20.91, C-14; 29.74, C-13; 39.15, C-10; 39.66, C-5; 89.62, C-4; 105.30, C-8; 110.42, C-6; 113.47, C-12; 136.21, C-11; 142.57, C-7; 152.30, C-9.

4.3.2. Compound 12a. White solid; yield 62%; mp: 171 °C (dec); MS (EI): *m/z* 321 $[M]^{+\cdot}$, 275 $[M-NO_2]^+$. Anal. Calcd for $C_{12}H_{11}N_5O_6$ (%): C. 44.87; H. 3.45; N. 21.80; found (%), C. 44.92; H. 3.59; N. 21.83. ^{1}H NMR (300 MHz, acetone-d_6) δ 1.67 (s, 3H, CH_3-15), 1.83 (s, 3H, CH_3-14), 2.37 (dd, $J=18.1$, 10.5 Hz, 1H, H-13), 2.74 (dd, $J=17.7$, 7.5 Hz, 1H, H-13), 3.27 (d, $J=17.1$ Hz, 1H, H-10), 3.57 (d, $J=17.4$ Hz, 1H, H-10), 4.53 (dd, $J=10.5$, 7.5 Hz, 1H, H-5); ^{13}C NMR (75 MHz, acetone-d_6) δ 19.06, C-15; 19.53, C-14; 33.99, C-13; 36.51, C-5; 36.84, C-10; 88.28, C-4; 104.80, C-8; 112.29, C-6; 122.96, C-12; 125.51, C-11; 142.54, C-7; 152.14, C-9.

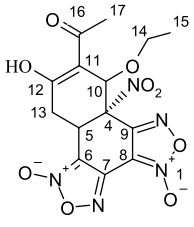
Crystallographic data for **12a**. $C_{12}H_{11}N_5O_6$, FW$=$ 321.26 g mol^{-1}, Monoclinic, *Cc*, $a=12.0520$ Å, $b=$ 18.0076 Å, $c=6.5433$ Å, $\beta=99.70°$, $V=1399.77$ Å^3, Dc$=1.524$ mg cm^{-3}, $Z=4$.

4.3.3. Compound 13a. Yellow solid; yield 73%; mp: 162 °C (dec); MS (EI): *m/z* 307 $[M]^{+\cdot}$, 261 $[M-NO_2]^+$. Anal. Calcd for $C_{11}H_9N_5O_6$ (%): C. 43.01; H. 2.95; N. 22.80; found (%), C. 43.06; H. 3.05; N. 22.85. ^{1}H NMR (300 MHz, acetone-d_6) δ 1.69 (s, 3H, CH_3), 2.15 (dd, $J=$ 18.0, 10.8 Hz, 1H, H-13), 2.69 (dd, $J=18.0$, 7.0 Hz, 1H, H-13), 3.18 (d, $J=17.7$ Hz, 1H, H-10), 3.64 (dd, $J=17.7$, 4.9 Hz, 1H, H-10), 4.37 (dd, $J=10.8$, 7.0 Hz, 1H, H-5) 5.54 (m, 1H, H-11); ^{13}C NMR (75 MHz, acetone-d_6) δ 21.15, C-14; 29.03, C-13; 30.85, C-10; 34.41, C-5; 85.34, C-4; 101.72, C-8; 109.16, C-6; 115.04, C-11; 130.90, C-12; 139.35, C-7;148.83, C-9.

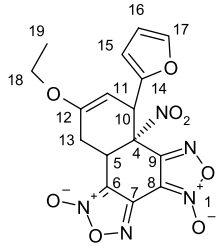
4.3.4. Compound 14a. Yellow solid; yield 66%; mp: 167 °C (dec); MS (EI): *m/z* 351 $[M]^+$. Anal. Calcd for $C_{12}H_9N_5O_8$ (%): C. 41.04; H. 2.95; N. 22.80; found (%), C. 41.06; H. 2.56; N. 21.98. ^{1}H NMR (300 MHz, acetone-d_6) δ 2.07 (s, 3H, CH_3), 2.50 (dddd, $J=19.1$, 10.3, 2.2, 0.7 Hz, 1H, H-13), 3.15 (dddd, $J=19.1$, 7.7, 4.0, 1.5 Hz, 1H, H-13), 4.59 (dd, $J=10.3$, 7.7 Hz, 1H, H-5), 6.07–6.22 (m, 2H, H-11, H-12), 6.51 (d, $J=5.5$ Hz, 1H, H-10); ^{13}C NMR (75 MHz, acetone-d_6) δ 20.28, C-15; 28.80, C-13; 30.85, C-5; 64.93, C-10; 88.20, C-4; 103.74, C-8; 111.65, C-6; 121.12, C-12; 132.32, C-11; 141.26, C-7; 148.36, C-9; 169.13, C-14.

4.3.5. Compound 16a. White solid; yield 30%; mp: 211 °C; MS (EI): *m/z* 395 $[M]^+$. ^{1}H NMR (300 MHz, CD_3CN) δ 1.02 (t, $J=7.6$ Hz, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.58 (dd, $J=19.1$, 5.8 Hz, 1H, H-13), 3.40 (dd, $J=19.1$, 10.4 Hz, 1H, H-13), 3.51 (m, 2H, OCH_2), 4.8 (dd, $J=10.4$, 5.8 Hz, 1H, H-5), 5.77 (s, 1H, H-10), 16.22 (s, 1H, OH); ^{13}C NMR (75 MHz, acetone-d_6) δ 15.52, C-15; 22.28, C-17; 30.11, C-13; 34.22, C-5; 64.91, C-14; 74.71, C-10; 89.42, C-4; 103.77, C-8; 105.3, C-11; 111.99, C-6; 141.22, C-7; 148.26, C-9; 190.00 and 192.95, C-12, C-16.

Crystallographic data for **16a**. $C_{14}H_{13}N_5O_9$, FW$=$ 395.22 g mol^{-1}, Monoclinic, *P*21/*a*, $a=9.698$ Å, $b=$ 14.250 Å, $c=12.123$ Å, $\beta=97.50°$, $V=1661.1$ Å^3, Dc$=$ 1.581 mg cm^{-3}, $Z=4$.



16a



20a

4.4. Preparation of the Diels–Alder adduct 20a

To a suspension of 0.2 g (0.84 mmol) of NBDF in $CHCl_3$ (10 ml) at room temperature were added an excess of furfurylidenelacetone (3 equiv, 2.5 mmol) and triethylorthoformiate (10 equiv, 8.5 mmol) and a catalytic amount of APTS (0.05 equiv). After 3 days at room temperature, the

reaction mixture was evaporated and purified to give compound **20a** in a 80% yield.

4.4.1. Compound 20a. White solid; yield 80%; mp: 201 °C; MS (EI): *m/z* 403 $[M]^+$. HRMS calcd for $C_{16}H_{13}N_5O_8$: 403.0764 $[M]^+$, found *m/z* 403.0768. ^{1}H NMR (300 MHz, acetone-d_6) δ 1.09 (t, J=7.6 Hz, 3H, CH_3), 2.31 (dd, J=17.6, 10.3 Hz, 1H, H-13), 2.94 (dd, J=17.6, 8.5 Hz, 1H, H-13), 3.70 (m, 2H, OCH_2), 4.58 (dd, J=10.3, 8.5 Hz, 1H, H5), 4.87 (d, J=6.2 Hz, 1H, H-10), 5.14 (d, J=6.2 Hz, 1H, H-11), 6.30 (dd, J=3.3, 1.9 Hz, 1H, H-16), 6.40 (d, J=3.3 Hz, 1H, H-15), 7.45 (dd, J=1.9, 0.8 Hz, 1H, H-17); ^{13}C NMR (75 MHz, acetone-d_6) δ 14.60, C-19; 30.72, C-13; 32.28, C-10; 38.85, C-5; 63.91, C-18; 90.01, C-4; 91.73, C-11; 111.33, C-8; 111.77, C-15; 112.04, C-16; 112.22, C-6; 141.48, C-7; 145.12, C-17; 150.0, C-9; 150.57, C-14; 153.20, C-12.

Crystallographic data for **20a**. $C_{16}H_{13}N_5O_8$, FW=403.12 g mol^{-1}, *P*-1, a=8.857 Å, b=9.9944 Å, c=10.9743 Å, β=99.61°.

4.5. Computational information

Full geometry optimizations for the whole series of dienes and dienophiles have been performed at B3LYP/6-31G* level of theory,[36,37] which is implemented in the Gaussian 03 package of programs.[38] The global electrophilicity power (ω) was evaluated by means of Eq. 2. The electronic chemical potential (μ) and chemical hardness (η) values were approximated in terms of the one-electron energies of the frontier molecule orbitals (FMO), ε_H and ε_L, respectively, using $\mu=(\varepsilon_H+\varepsilon_L)/2$ and $\eta=\varepsilon_H-\varepsilon_L$,[32] respectively, at the ground state (GS) of the molecules. The global maximum charge transfer toward the electrophile was evaluated using Eq. 3.

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Synthesis and cation complexation properties of new macrolides

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Abstract—The *cis*-2-alkyl-3-oxy-tetrahydropyran unit as a novel structure for the design and synthesis of a new type of ionophores with C_2-symmetry is reported. The synthesis of seven different macrolides and a crown ether and their cation complexation properties were investigated. The X-ray crystal structure of some of the receptors provides valuable information on the preferred conformation of tetrahydropyrans in the solid state that can be related to the cation complexation properties in solution. The kinetic template effect has been proved to be a useful tool to improve the yield and selectivity in the synthesis of macrodiolide **3**.

1. Introduction

A wide range of biological processes such as the generation and propagation of the electrical impulse in the nervous system, muscular contraction, the production and storage of energy and cellular communication require the interactions of proteins and enzymes with cations. Therefore, the search for simple models that allow us the molecular understanding of these phenomena is of particular importance. Cation receptors have been used in selective complexation, as detectors, in selective transport, catalysis, etc. Over the last 30 years, a great number of functional groups have been incorporated into the design of new cation receptors. Tetrahydropyrans are widespread in nature[1,2,3] and synthetic ionophores.[4,5] This structural unit confers more rigidity and new properties to the systems in which it is present, and it is for that reason that tetrahydropyrans have been used as building blocks in cation recognition. Thus, mention can be made of chorand-type cyclooligolides designed and synthesized by Okada[6] and Burke.[7] On the other hand, Still et al. designed and synthesized a podand-type system of linked tetrahydropyran rings whose conformation is controlled by the presence of methyl groups at C-3.[8] However, all these receptors have in common the use of tetrahydropyran rings linked through positions C-2 and C-6, where the tetrahydropyran oxygen participates in the recognition process.

We have recently, reported that *cis*-2-alkyl-3-oxy-tetrahydropyran can be used as a privileged structural unit for the design of new C_2-symmetry macrodiolides with cation complexation properties.[9] In this article, we report full details of this design concept employed in the synthesis of seven macrolides and a crown ether. In addition, the evaluation of their complexation properties is fully discussed.

The 2-alkyl-3-oxy-tetrahydropyran unit is widely displayed in polyether toxins of marine origin, and is usually found in trans disposition. This configuration directs the two oxygens toward the opposed faces, generating a practically flat system, which may not be well adapted for cation recognition (Fig. 1).[10] Alternatively, the cis configuration can preferredly be found in two conformations, one with the 3-oxy group axial (A), with both oxygens located on the same face, and the other one equatorial (B), forcing both oxygens to be located on opposite faces, the first of these

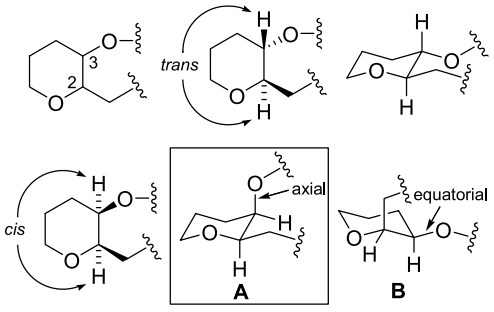

Figure 1. *Trans*- and *cis*-2-alkyl-3-oxy-tetrahydropyran units and main conformers.

Keywords: Macrolides; Ionophores; Template effect.
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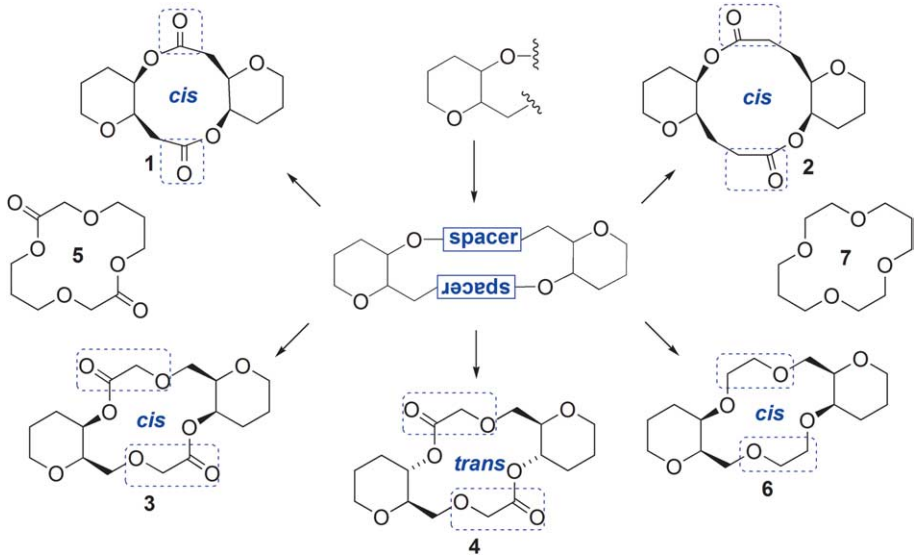


Figure 2. Design and structures of macrodiolides **1**, **2**, **3** and **4** and crown ether **6** based on 2-alkyl-3-oxy-tetrahydropyran units.

being the one that may generate the suitable curvature, such that both oxygens can participate in the recognition.

On the other hand, it is well known that the best and easiest way to maintain the chirality of a unit is by transforming this into a molecule with C_2 symmetry. To accomplish this, we linked the oxy group of a unit with the alkyl group of the other, using identical spacers (Fig. 2). A desirable property for such spacers is that they must be reasonably flexible to allow the participation of the tetrahydropyran oxygen in the recognition. Also, they must allow the easy synthesis of the receptor. Moreover, the existence of additional heteroatoms, susceptible to acting as ligands, may also be positive. Finally, the presence in nature of a great number of bioactive macrodiolides, such as the fattiviracins,[11] cyclovaricins,[12] nactins,[13] or pamamycin-607[14] was considered. With these ideas in mind, a series of macrodiolides of different sizes and different degrees of oxygenation, having different carbon-based spacers, were synthesized. Thus, we designed the tricyclic diolides **1**, **2**, **3**, structurally characterized by the presence of two *cis*-2-alkyl-3-oxy-tetrahydropyran units, linked by two carbonyl, two oxomethylene and two 2-oxy-acetyl groups as spacers, forming a 10-, 12-, and 14-membered macrodiolide, respectively. Using the same design, and in order to check the importance of the configuration of the 2-alkyl-3-oxy-tetrahydropyran moieties, we decided to synthesize compound **4**, which displays the trans fusion. In addition, we prepared the crown ether **6**, to verify the influence of the carbonyl groups in cation recognition.

In principle, these structures could be considered formally to be bibracchial lariat ethers (BiBLE), where the central macroring is a formal crown ether and the tetrahydropyran rings are the side-arms that confer greater conformational rigidity and whose oxygens could participate in the complexation. From modelling,[15] it can be predicted that the cis fusion could create a hydrophilic concave face where

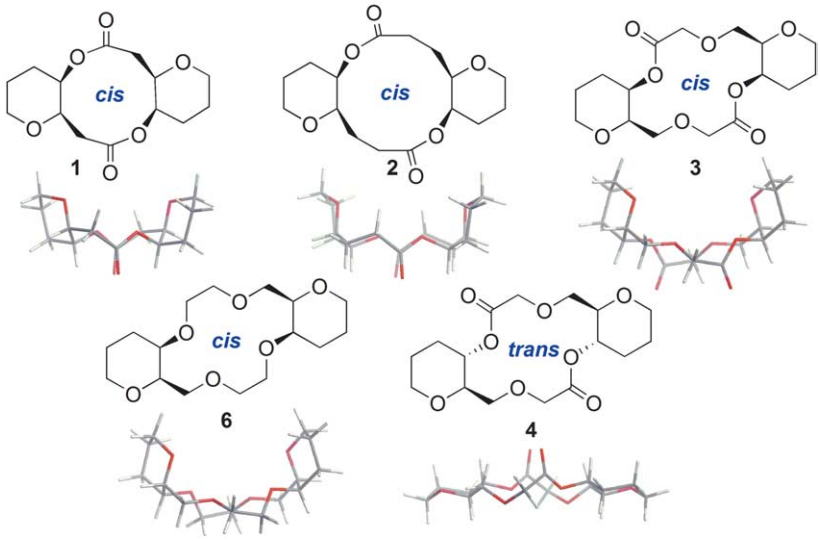
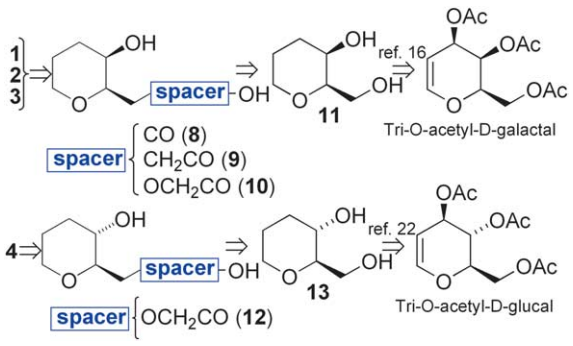
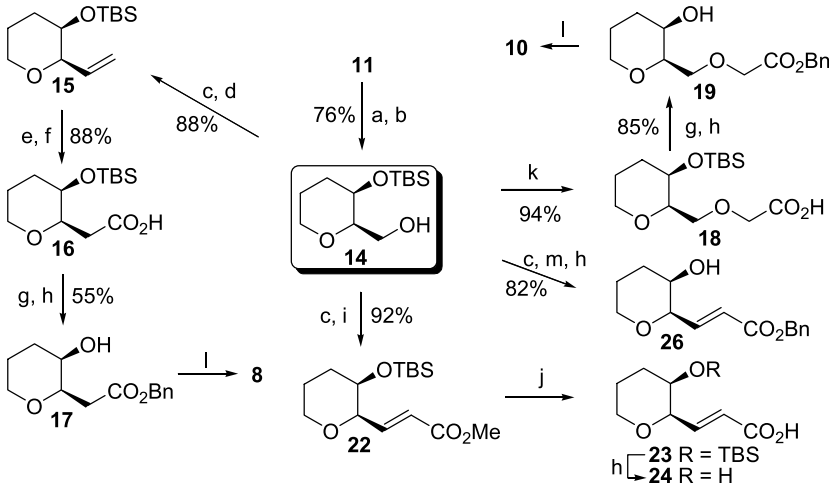


Figure 3. Molecules **1**, **2**, **3** and **6** in the suitable conformation such that cation recognition may take place (U-shaped) and low-energy conformation of *trans*-macrodiolide **4**.



Scheme 1. Retrosynthetic analysis for macrodiolides **1**, **2**, **3** and **4**.

(Scheme 2), the diol **11**[16] was protected, as the bis-silyl ethers, followed by selective deprotection of the silyl ether of the primary alcohol to afford the *cis*-alcohol **14**, which can be considered the key piece in the synthesis of the receptors. Thus, to obtain the precursor of compound **1**, one-carbon homologation of the *cis*-alcohol **14** to the carboxylic acid **16** was performed by a simple four-step sequence: oxidation to aldehyde by Swern reaction, Wittig methylenation ($Ph_3P{=}CH_2$) to afford alkene **15**, hydroboration with 9-BBNH in THF, and oxidative cleavage of the alkyl borane, yielding the primary alcohol, which was oxidated to the corresponding carboxylic acid **16**. Esterification of the carboxylic acid **16** with benzyl alcohol and further



Scheme 2. Reagents and conditions: (a) TBSCl, imidazole, CH_2Cl_2; (b) TFA:THF:H_2O (1:1:1); (c) $(COCl)_2$, DMSO, CH_2Cl_2, then Et_3N; (d) $Ph_3P{=}CH_2$, THF; (e) (i) 9-BBN, THF; (ii) H_2O_2, NaOH; (f) $NaIO_4$, $RuCl_3$ (cat.), CH_3CN: CCl_4: H_2O (2:2:3); (g) BnOH, DMAP, CSA, DCC, CH_2Cl_2; (h) HF, CH_3CN; (i) $Ph_3PCHCO_2CH_3$, C_6H_6; (j) LiOH, THF, H_2O, Δ; (k) NaH, ICH_2CO_2Na, THF; (l) H_2, $Pd(OH)_2$, AcOEt; (m) $(CH_3O)_2POCH_2CO_2Bn$, NaH, C_6H_6.

the oxygen atoms act as ligands wrapping the cation guest, and a hydrophobic convex face where the carbon skeleton is oriented to the outer surface. On the other hand, the trans fusion shows a practically flat structure (Fig. 3).

Additionally, we synthesized the central 14-membered macrodiolide **5** and 14-crown-4(**7**) to verify that metal complexation in the macrodiolides **3** and **4** and crown ether **6** does not take place in the macrocyclic plane.

Macrodiolides **1**, **2**, and **3** were envisioned as being synthesized from two units of a suitable *cis*-hydroxy-acid, where the spacers are: carbonyl (**8**), oxo-methylene (**9**) and 2-oxy-acetyl (**10**) groups, respectively, by an intermolecular esterification followed by macrolactonization (Scheme 1). Tetrahydropyrans **8**, **9** and **10** could be obtained from commercially available tri-*O*-acetyl-D-galactal. Similar retrosynthetic analysis for the *trans*-macrodiolide **4** leads to the use of commercially available tri-*O*-acetyl-D-glucal as starting material.

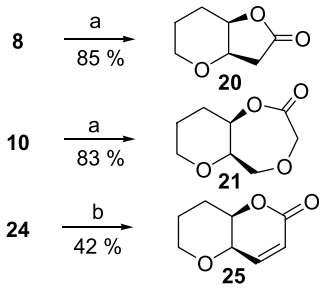
2. Results and discussion

2.1. Synthesis of macrolides

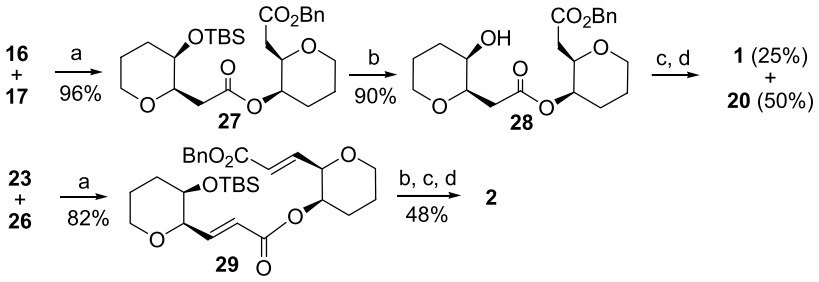
To carry out the synthesis of the hydroxy acids **8** and **10** deprotection of the *tert*-butyl-dimethylsilyl (TBS) ether afforded the hydroxy ester **17**.

The synthesis of the precursor of the macrodiolide **3** was carried out from alcohol **14** by alkylation with sodium iodoacetate to provide the carboxylic acid **18**, then applying the same sequence of reactions as before to obtain compound **17**, afforded the hydroxy ester **19**. The synthesis of free hydroxy-acids **8** and **10** was performed by a simple catalytic hydrogenation of the benzyl esters **17** and **19**, respectively.

Disappointingly, the direct dimerization approach, under all assayed conditions, of the hydroxy acids **8** and **10**, is



Scheme 3. Reagents and conditions: (a) 2-chloro-1,3-dimethylimidazolinium chloride, NaH or KH, DMAP in CH_2Cl_2, 0 °C→rt; (b) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, CH_2Cl_2 (0.1 M).

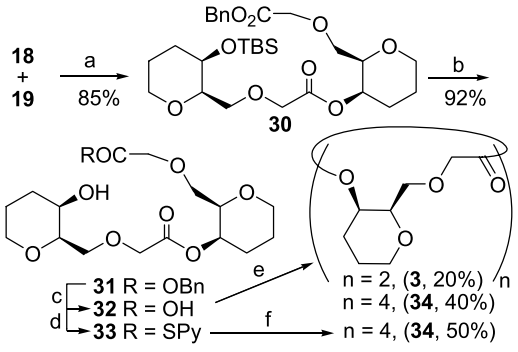


Scheme 4. Reagents and conditions: (a) DMAP, CSA, DCC, CH_2Cl_2; (b) HF, CH_3CN; (c) H_2, $Pd(OH)_2$, AcOEt; (d) PySSPy, Ph_3P, toluene, Δ; (e) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, CH_2Cl_2.

entropically unfavourable, affording the lactonization product **20**[17] and **21**, respectively, even using conditions that have been described as excellent to obtain macrodiolides, such as 2-chloro-1,3-dimethylimidazolinium chloride in the presence of DMAP and NaH or KH in CH_2Cl_2 (Scheme 3).[18]

To overcome this difficulty, alternative synthetic strategies were developed. Thus, in the case of the macrodiolide **2**, a trans double bond could be placed at the α,β position of the acid group in **9**, with which, we avoided the first intramolecular lactonization taking place, only the intermolecular esterification being allowed, followed by a macrolactonization in the same process.

To perform the synthesis of the precursor of compound **2**, two-carbon homologation of the *cis*-alcohol **14** was achieved (Scheme 2), using a Swern oxidation and a Wittig reaction of the aldehyde with the stabilized phosphorane $Ph_3P{=}CHCO_2Me$ in benzene, affording the methyl (*E*)-α,β-unsaturated ester **22**, which was converted into the (*E*)-α,β-unsaturated acid **24**, by saponification of the methyl ester and deprotection of the TBS group. Unfortunately, all attempts (DCC, DMAP; 2-chloro-1,3-dimethylimidazolinium chloride, NaH, DMAP) to carry out the synthesis of the macrodiolide **2** via dimerization of the (*E*)-α,β-unsaturated acid **24** and further catalytic hydrogenation were unfruitful. Surprisingly, when the (*E*)-α,β-unsaturated acid **24** was treated under modified Yamaguchi conditions[19] the (*Z*)-α,β-unsaturated δ-lactone **25** was the only observed product as the result of concomitant isomerization of the double bond and lactonization (Scheme 3).

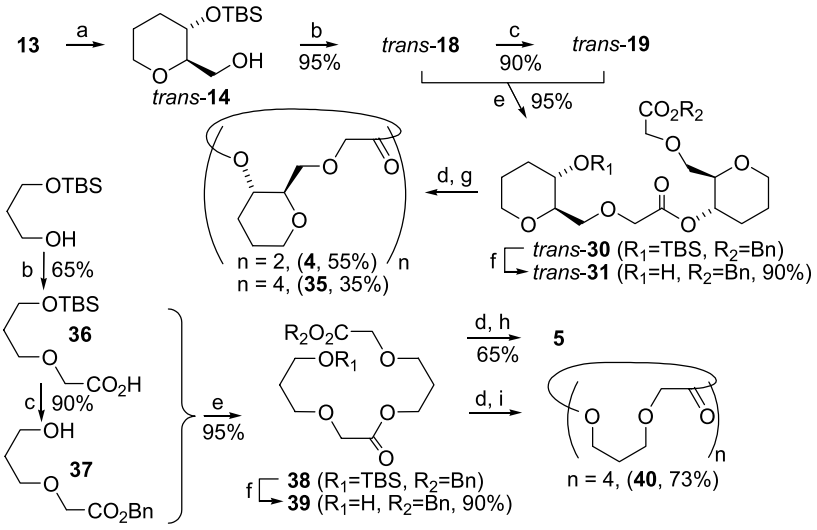


Scheme 5. Reagents and conditions: (a) DMAP, CSA, DCC, CH_2Cl_2; (b) HF, CH_3CN, 0 °C; (c) H_2, $Pd(OH)_2$, AcOEt; (d) PySSPy, Ph_3P, CH_2Cl_2; (e) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, THF (0.01 M)→toluene (0.001 M), Δ; (f) toluene (0.001 M), Δ.

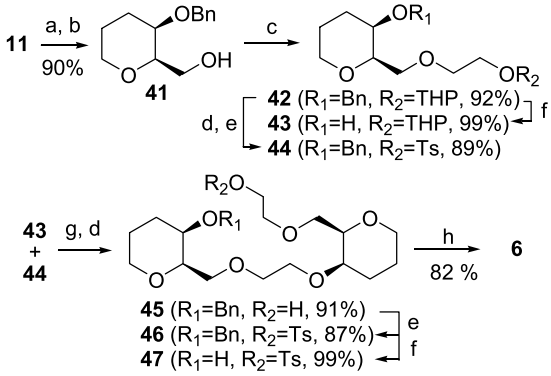
Finally, for the synthesis of macrodiolides **1**, **2** and **3** a convergent strategy was applied: iterative esterification couplings of two suitably functionalized tetrahydropyran units, carboxylic acid **16** and alcohol **17** for macrodiolide **1**, carboxylic acid **23** and alcohol **26** for macrodiolide **2** or carboxylic acid **18** and alcohol **19** for macrodiolide **3**, followed by macrolactonization of the resulting hydroxy-acid. Therefore, to carry out the synthesis of compound **1**, a coupling of the carboxylic acid **16** with the hydroxy ester **17** was achieved affording pseudodimer **27** (Scheme 4). Then, cleavage of the alcohol protecting group gave the hydroxy ester **28**. Catalytic hydrogenation of the benzyl ester **28** provided the hydroxy-acid, which was transformed into the phenylthioester and submitted to Corey macrolactonization conditions,[20] affording the γ-lactone **20** along with the macrodiolide **1**, in 2:1 proportion, respectively. To perform the synthesis of compound **2**, the same sequence of reaction used to obtain macrodiolide **1** was applied, using the (*E*)-α,β-unsaturated acid **23** and the alcohol **26** (Scheme 4), this last compound being prepared from alcohol **14** by a simple three-step sequence: Swern oxidation to the aldehyde, treated with the sodium salt of benzyl dimethylphosphonoacetate and deprotection of the silyl ether (Scheme 2).

To achieve the synthesis of compound **3**, the same sequence of reactions used to obtain **27** was applied, using the carboxylic acid **18** and alcohol **19**, obtaining the hydroxy ester **31** (Scheme 5). Catalytic hydrogenation of **31** afforded the hydroxy-acid **32**, which was transformed into the thioester **33**. Unfortunately, **33** under Corey macrolactonization conditions gave exclusively the macrotetraolide **34**. However, when compound **32** was treated under Yamaguchi conditions, the macrodiolide **3** was obtained in 20% yield along with macrotetraolide **34** in 40% yield.[21] However, the kinetic template effect improved selectivity and yield in the macrolactonization (vide infra).

Using the diol **13**[22] and applying the same sequence of reactions described above, under Yamaguchi conditions in the cyclization step, we obtained the macrodiolide **4** and the macrotetraolide **35** (trans-isomer of **34**) (Scheme 6), in 55 and 35% yields, respectively. The same strategy was applied to obtain compound **5**, using as starting material 3-{[*tert*-butyl(dimethyl)silyl]oxy}-1-propanol. Nevertheless, in this case, when we used Yamaguchi conditions in the macrolactonization step, we obtained exclusively macrotetrolide **40**. Fortunately, using Corey conditions, macrodiolide **5** was the only formed compound.



Scheme 6. Reagents and conditions: (a) (i) TBSCl, imidazole, CH_2Cl_2; (ii) TFA: THF: H_2O (1:1:1); (b) NaH, ICH_2CO_2Na, THF; (c) (i) BnOH, DCC, DMAP, CSA, CH_2Cl_2; (ii) HF, MeCN; (d) H_2, $Pd(OH)_2$, AcOEt; (e) DCC, DMAP, CSA, CH_2Cl_2; (f) HF, MeCN; (g) Et_3N, 2,4,6-trichlorobenzoyl chloride, THF (0.01 M)→toluene (0.001 M), DMAP, Δ; (h) PySSPy, Ph_3P, THF (0.3 M)→toluene (0.01 M), Δ; (i) Et_3N, 2,4,6-trichlorobenzoyl chloride, THF (0.02 M)→toluene (0.002 M), DMAP.



Scheme 7. Reagents and conditions: (a) $PhCH(OCH_3)_2$, CSA (cat.), CH_2Cl_2; (b) DIBAL-H, CH_2Cl_2; (c) $ClCH_2CH_2OTHP$, Bu_4NHSO_4, NaOH(aqueous), 65 °C; (d) HCl (cat.), MeOH; (e) TsCl, KOH(aqueous), THF; (f) H_2, $Pd(OH)_2$, AcOEt; (g) NaH, THF, 0 °C→Δ; (h) NaH, THF, rt.

The crown ether **6** was synthesized by a divergent–convergent strategy, using the diol **11** that was protected as the benzylidene acetal and subsequently submitted to reductive cleavage, affording the benzyl ether **41** in good yield (Scheme 7). The O-alkylation of the primary alcohol of **40** with 2-chloroethyl tetrahydro-2*H*-pyran-2-yl ether yielded compound **42**,[23] which was used as a common precursor. With **42** in hand we prepared the secondary alcohol **43** by cleavage of the benzyl protecting group under hydrogenation conditions. In parallel, compound **42** was transformed to tosylate **44**, by cleavage of the tetrahydropyranyl group under acid conditions and subsequent reaction with tosyl chloride under basic conditions.[24] We next turned our attention to the critical convergent coupling step of the two fragments **43** and **44**, which was achieved with sodium hydride in refluxing THF and further deprotection of the tetrahydropyranyl group under acid conditions, affording compound **45** in excellent yield. The alcohol **45** was converted into the tosylate **46**, which under hydrogenation conditions provided the secondary alcohol **47**. Finally, the intramolecular ether formation was carried out with sodium hydride in THF at rt to afford the crown ether **6**, in good yield. In this case we did not observe the formation of cyclic ethers having a larger ring size, probably due to a Na^+ kinetic template effect.

The 14-crown-4(**7**) was synthesized in accordance with the literature method.[25] The structures of the macrodiolides **1**, **2**, **3**, **4** and **5**, the crown ether **6** and the macrotetrolides **34** and

Table 1. Association constants K_a (M^{-1}) with different cations[a]

Entry	Host	Li^+	Na^+	K^+	NH_4^+	Cs^+
1	**1**	—[b]	—[b]	—[b]	—[b]	—[b]
2	**2**	—[b]	—[b]	—[b]	—[b]	—[b]
3	**3**	4.6×10^3	2.5×10^4	1.6×10^4	2.0×10^3	2.0×10^3
4	**4**	—[b]	—[b]	—[b]	—[b]	—[b]
5	**5**	—[b]	—[b]	—[b]	—[b]	—[b]
6	**34**	—[b]	—[b]	—[b]	—[b]	—[b]
7	**35**	—[b]	—[b]	2.3×10^3	—[b]	—[b]
8	**6**	2.3×10^3	7.1×10^3	6.2×10^3	9.6×10^2	1.1×10^3
9	14-crown-4(**7**)	3.1×10^5	6.7×10^3	4.7×10^2	2.4×10^2	2.8×10^2

[a] These values are the average of three independent measurements.
[b] — means that these values were smaller than 10^2.

35 were unambiguously determined by NMR spectroscopy (^{1}H and ^{13}C) and FAB mass spectrometry.[26]

2.2. Cation complexation studies

The association constants (K_a) of the macrodiolides **1**, **2**, **3**, **4** and **5**, the macrotetraolides **34**, **35** and the ethers **6** and **7** in $CHCl_3$ saturated with water at 23–25 °C were determined by measurements from the $CHCl_3$ layer using Cram's picrate extraction method (Table 1).[27,28] The absorption maxima in $CHCl_3$ ($352 < \lambda_{max} < 359$ nm) of the picrate salts are indicative of 1:1 complexes between metal picrate and the host.[29] The results of Table 1 show that the substrates **3** and **6** display moderate association constants (entries 3 and 8), and the macrodiolide **3** is slightly specific for Na^+ and K^+ ($Na^+/Li^+ = 5.4$, $K^+/Li^+ = 3.5$).

It should be emphasized that the 2,3 relative configuration of the tetrahydropyrans is critical to achieve cation recognition, since the trans-isomer (macrodiolide **4**) is completely ineffective in the extraction process (entry 4). This observation implies that the *cis*-tetrahydropyran oxygen participates in the recognition process and this along with the null complexation observed by macrodiolide **5** (entry 5) allows us to conclude that the complexation in **3** takes place out of the macrodiolide plane, like a clamp-type rather than a chorand-type ionophore, despite the fact that **3** is a macrocycle. This is in agreement with the association constant values and with the minimized structures shown in Figure 3. Host **3** wraps the metal cation and can change the cavity size according to the metal cation size, such that it shows comparable binding ability to all alkali metal cations. Interestingly, in macrotetrolides the result is reversed, trans being better than cis, perhaps as a result of folding of compound **35** over the K^+.

In addition, we observed that the conformation of the tetrahydropyrans of compound **3** is the same before and after the complexation. In the free receptor, the NOE effects ($CDCl_3$) indicate that a large number of molecules have the tetrahydropyran rings in the A conformation (Fig. 1), implying a partially pre-organized system. Thus, when one deals with potassium thiocyanate and ultrasound, to form the complex $\mathbf{3}\cdot\mathbf{K}^+$ ($CDCl_3$),[30] the NOE effects continue as before, although changes take place in the chemical shift of the signals in the proton and carbon NMR spectra.[26] This, along with the value of the association constant, allows us to conclude that almost all the molecules adopt the U-shaped conformation in the complex (Fig. 3), and that the change in the chemical shift must be mainly due to the change in conformation of the flexible part of the molecule, that is to say, the 14-membered macrocycle.

Considering the great difference in the values of the association constants between macrodiolide **5** and the 14-crown-4(**7**) (entry 9, Table 1), we expected that crown

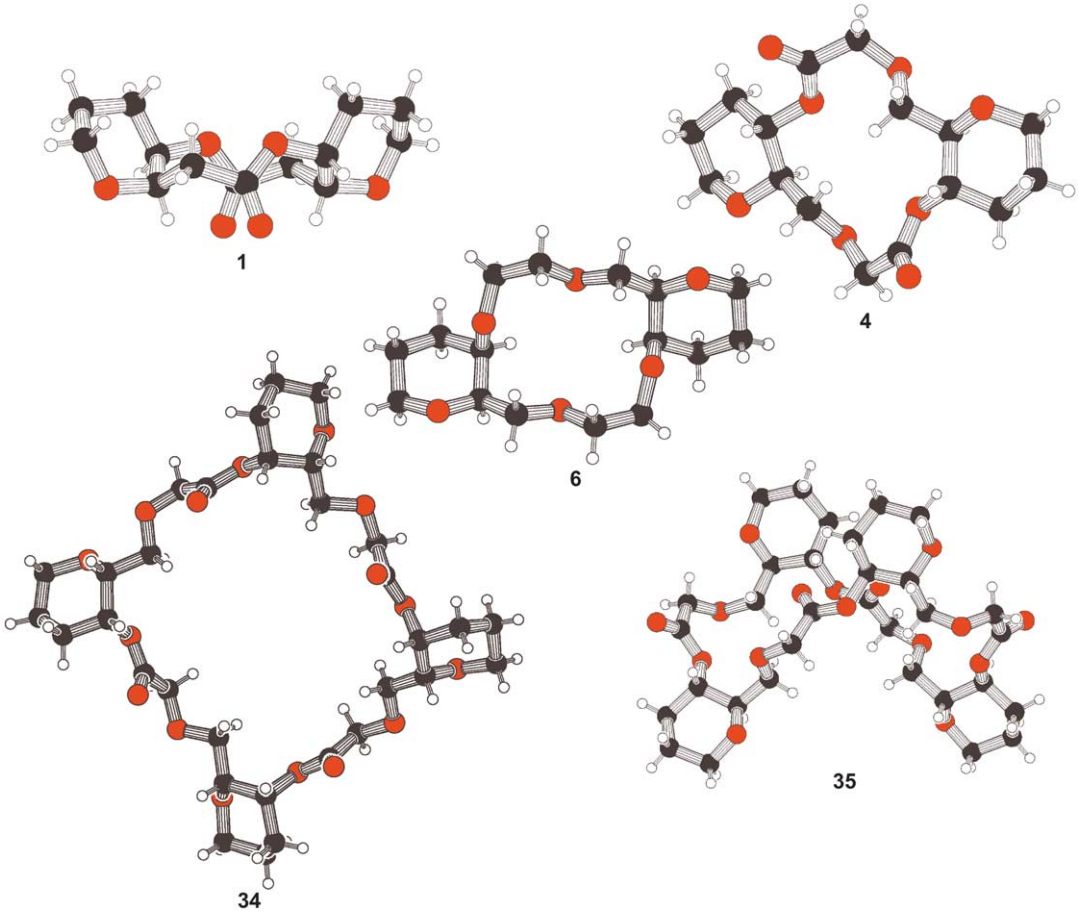


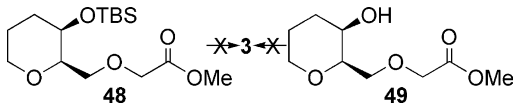
Figure 4. Crystal structures of compounds **1**, **4**, **6**, **34** and **35**.

ether **6** would show better association constants than macrodiolide **3**, since when eliminating the carbonyl groups, which withdraw electronic density from esters oxygen, these oxygens would have a greater contribution in the cations complexation. Surprisingly, we observed a decrease in the association constants (entry 8, Table 1). This fact leads us to believe that although those carbonyl groups produce an unfavourable electronic factor, they confer greater rigidity to the molecule, favouring the suitable conformation for the complexation process. Furthermore, the crystal structure of **6** (Fig. 4) revealed that the tetrahydropyrans have the right conformation for complexation (conformation A, Fig. 1), but the absence of the carbonyl groups causes the central part of this molecule to be quite flexible, preventing good cation recognition.[31]

In contrast, it was observed that the association constants of the small macrodiolides **1** and **2** were smaller (entries 1 and 2, Table 1). A possible explanation may be that the absence of additional oxygens is critical for the complexation. Also, it is possible that the conformation of the tetrahydropyrans is not suitable. Thus, in solid phase, the crystal structure of **1** (Fig. 4)[32] has an inadequate B type conformation (Fig. 1) for the complexation, whereas, in $CDCl_3$ solution, NOE experiments demonstrate that a mixture of conformers exists. Probably, the experimental result reflects the combination of both facts and the deficiency of ligands makes the conversion more expensive towards the A conformation, perhaps because of an insufficient enthalpy change. In contrast, the crystal structure of the macrotetrolide **34** (Fig. 4) revealed a molecule with a pseudo-quaternary symmetry, where the tetrahydropyran rings are in the right conformation for the complexation process. Although the association constants were poor (entry 6, Table 1) as a result of the large cavity that this compound displays. As predicted, the crystal structure of **4** (Fig. 4) practically shows a flat molecule, unsuitable for the cation recognition. Nevertheless, the crystal structure of the *trans*-macrotetrolide **35** (Fig. 4) revealed a folded molecule with a C_2 symmetry that could recognize small cations, despite the enormous size of the macrocycle (28 members). This fact could explain the association constant observed with K^+ (entry 7, Table 1).

2.3. Template effect studies

In light of the low yields obtained in the macrolactonization process in the synthesis of macrodiolide **3**, and considering the association constants observed for **3** and **34**, we decided to explore the possible template effect that could be exerted by metallic cations in the cyclization step. In our first attempt we explored the possibility to perform a covalent self-assembly[33] using the methyl ester **48**,[34] under similar conditions to those employed by Sanders and co-workers (Scheme 8).[35] We even tried to perform a thermodynamic templated synthesis, using the methyl ester **49**[36] with MeONa or MeOK. However, all attempts were unfruitful, affording only the lactone **21** and traces of macrotetraolide **34**.



Scheme 8.

Next, we explored a kinetic template effect, using 2-chloro-1,3-dimethylimidazolinium chloride in the presence of DMAP and Et_3N or NaH or KH in CH_2Cl_2 (entries 1–3, Table 2), affording, in moderate yield, the macrotetraolide **34**.

Having in mind that using the standard Yamaguchi conditions we were able to obtain compound **3** (entry 4, Table 2), albeit with low selectivity, the following step was the addition of an alkali metal cation under such conditions. Since this did not improve yield and selectivity, we

Table 2. Template effect study in the cyclization of **32** and **33**

Entry	Substrate	Reagents[a]	Solvent (M)	Additive (equiv)	Temp. (°C)	Time	Yield[b] (%)	**3**:**34**
1	**32**	Et_3N, DCIC, DMAP	CH_2Cl_2 (0.01)	—	rt	16 h	55	0:100
2	**32**	NaH, DCIC, DMAP	CH_2Cl_2 (0.01)	—	rt	16 h	47	0:100
3	**32**	KH, DCIC, DMAP	CH_2Cl_2 (0.01)	—	rt	16 h	43	0:100
4	**32**	Et_3N, TCBC, DMAP[c]	Toluene (0.001)	—	reflux	6 h	60	33:67
5	**32**	NaH, TCBC, DMAP	THF (0.01)	—	rt	12 h	48	0:100
6	**32**	NaH, TCBC, DMAP	CH_2Cl_2 (0.01)	—	rt	12 h	50	40:60
7	**32**	Et_3N, TCBC[d]	CH_2Cl_2 (0.002)	K_2CO_3 (20)	rt	22 h	65	87:13
8	**33**	PPh_3, PySSPy	Toluene (0.001)	—	reflux	1 day	50	0:100
9	**33**	PPh_3, PySSPy	CH_2Cl_2 (0.002)	—	reflux	7 days	—	—
10	**33**	PPh_3, PySSPy	CH_2Cl_2 (0.002)	Et_3N (2)	reflux	1d	—	—
11	**33**	PPh_3, PySSPy	CH_2Cl_2 (0.002)	DMAP (2)	rt	1 h	65	0:100
12	**33**	PPh_3, PySSPy	CH_2Cl_2 (0.002)	Li_2CO_3 (20)	reflux	9 days	50	50:50
13	**33**	PPh_3, PySSPy	CH_2Cl_2 (0.002)	Na_2CO_3 (20)	reflux	9 days	55	65:35
14	**33**	PPh_3, PySSPy	CH_2Cl_2 (0.002)	K_2CO_3 (20)	reflux	7 days	95	87:13
15	**33**	PPh_3, PySSPy	CH_2Cl_2 (0.002)	Cs_2CO_3 (20)	reflux	12 h	—	—
16	**33**	PPh_3, PySSPy	THF (0.002)	K_2CO_3 (20)	rt	1 day	25	0:100
17	**33**	PPh_3, PySSPy	CH_2Cl_2 (0.002)	KI (20)	reflux	1 day	—	—

[a] DCIC, 2-chloro-1,3-dimethylimidazolinium chloride; TCBC, 2,4,6-trichlorobenzoyl chloride; PySSPy, 2,2′-dipyridyl disulfide.
[b] Yields corresponding to compounds **3**+**34**.
[c] Et_3N (2 equiv), 2,4,6-trichlorobenzoyl chloride (1.3 equiv) in THF (0.01 M), then was diluted with toluene (0.001 M) and poured over DMAP (10 equiv) in boiling toluene.
[d] Et_3N (2 equiv), 2,4,6-trichlorobenzoyl chloride (1.3 equiv) in CH_2Cl_2 (0.01 M), then was diluted with CH_2Cl_2 (0.002 M) and K_2CO_3 (20 equiv) was added and the mixture was warmed up to reflux.

pondered the influence of the solvent. Thus, although using NaH in THF afforded only compound **34** (entry 5, Table 2), in dichloromethane selectivity was slightly improved (entry 6, Table 2). The use of K_2CO_3 enhanced selectivity, but in these conditions the reaction was difficult to reproduce (entry 7, Table 2). Then we decided to explore the macrolactonization using a stable intermediate, thioester **33**, allowing the cyclization step to proceed slowly and in consequence increasing the template effect. Corey conditions (in toluene) afforded macrotetrolide **34** (entry 8, Table 2). When using boiling dichloromethane as solvent, it is noteworthy that no cyclization product was detected (entry 9, Table 2). It seems that, due to the low boiling point of dichloromethane, the addition of a base becomes necessary. Nevertheless, the presence of triethylamine to activate the attack of the hydroxyl group was unfruitful (entry 10, Table 2). On the contrary, the presence of DMAP increased the rate of the reaction, but, unfortunately, toward the formation of macrotetrolide **34** (entry 11, Table 2). After several trials (entries 12–17, Table 2), we found that better selectivity and yields of compound **3** versus **34** were achieved in boiling dichloromethane with potassium carbonate, where the K^+ acts as a template (entry 14, Table 2), pre-organizing the cyclization precursor for macrolactonization (Fig. 5), favouring the formation of **3** (95% yield, **3/34**=6.7).

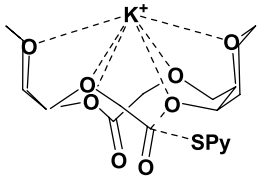


Figure 5. Template effect in the macrolactonization step.

To the best of our knowledge, this is the first time that the Corey macrolactonization reaction is used under alkali metal cation template effect. It should be emphasized that the best guest (Na^+) for host **3** is not the best template for its formation. This may be due to the fact that the cavity size of the transition state leading to compound **3** is slightly larger than the cavity of the final product.

3. Conclusions

We have used the *cis*-2-alkyl-3-oxy-tetrahydropyran as a new structural unit for the design of ionophores. Hosts **3** and **6** behave like a clamp-type ionophore, where the recognition takes place out of the macrocyclic plane, with assistance of the *cis*-tetrahydrofuran oxygen. The carbonyl groups in the macrodiolide **3** help to confer a greater rigidity to the molecule, favouring the suitable conformation for the complexation process. The X-ray crystal structure of compounds **1**, **4**, **6**, **34** and **35** provides valuable information in the solid state that supports their cation complexation properties in solution. The template effect has been proven to be a useful tool to improve the yield and selectivity in the synthesis of macrodiolide **3**. In addition, this structural unit can be used to obtain new receptors, by simply changing the design or nature and length of the spacers.

4. Experimental

4.1. Materials and methods

^1H NMR spectra were recorded at 400 and 300 MHz, ^{13}C NMR spectra were recorded at 75 MHz, and chemical shifts are reported relative to internal Me_4Si. Optical rotations were determined for solutions in chloroform. Column chromatography was performed on silica gel, 60 Å and 0.2–0.5 mm. Compounds were visualized by use of UV light, 2.5% phosphomolybdic acid in ethanol or vanillin with acetic and sulfuric acid in ethanol with heating. All solvents were purified by standard techniques.[37] Reactions requiring anhydrous conditions were performed under nitrogen. Anhydrous magnesium sulfate was used for drying solutions.

4.1.1. Preparation of [(2*R*,3*R*)-3-(*tert*-butyldimethylsilyloxy)-tetrahydro-2*H*-pyran-2-yl]methanol (14). *tert*-Butylchlorodiphenylsilane (12.9 g, 85.3 mmol) was added in one portion to a cold (0 °C) and stirred solution of diol **11** (4.5 g, 34.1 mmol) and imidazole (5.8 g, 85.3 mmol) in dry CH_2Cl_2 (70 mL, 0.5 M) under nitrogen atmosphere. The reaction mixture was stirred at reflux for 20 h before dilution with MeOH and Et_2O. The mixture was washed with an aqueous saturated NH_4Cl solution, water and brine and then dried, filtered and concentrated to yield the crude bis-silyl ether as an oil which was used without further purification.

Trifluoroacetic acid (35 mL) was added dropwise to a solution of the crude bis-silyl ether in THF (35 mL) and water (35 mL) at 0 °C. After stirring for 5 min, the reaction mixture was quenched with ($NaHCO_3$, 25 g), diluted with ether, washed with water and brine and then dried. The solvent was removed by vacuum and the residue was purified by chromatography on silica gel to give alcohol **14** (7.15 g, 85% yield) as an oil: $[\alpha]_D^{25}$ −2.9 (*c* 2.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.06 (s, 6H), 0.89 (s, 9H), 1.34 (d, J= 13.3 Hz, 1H), 1.62 (dddd, J=2.7, 2.7, 13.3, 13.3 Hz, 1H), 1.80 (ddd, J=1.8, 1.8, 13.6 Hz, 1H), 1.90–2.10 (m, 1H), 2.25 (br s, 1H), 3.39–3.56 (m, 3H), 3.77 (dd, J=8.5, 11.2 Hz, 2H), 3.98 (dddd, J=2.1, 2.1, 11.3, 11.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −5.0 (q), −4.6 (q), 18.0 (s), 20.6 (t), 25.7 (q), 31.1 (t), 63.8 (t), 66.5 (d), 67.6 (t), 79.9 (d); IR ($CHCl_3$) (cm^{-1}) 3427, 2951, 2886, 2856, 1463, 1254, 1101; MS *m*/*z* (relative intensity) 247 $(M+H)^+$ (100), 189 $(M-Bu\text{-}t)^+$ (7), 137 (46). HRMS calcd for $C_{12}H_{27}O_3Si$ $(M+H)^+$: 247.1729, found: 247.1732.

4.1.2. Preparation of *tert*-butyl(dimethyl)silyl(2*R*,3*R*)-2-vinyltetrahydro-2*H*-pyran-3-yl ether (15). To a solution of the oxalyl chloride (0.79 mL, 9 mmol) in dry CH_2Cl_2 (30 mL) under argon at −78 °C was added DMSO (0.86 mL, 12 mmol). After 15 min of stirring, a solution of **14** (1.5 g, 6 mmol) in dry CH_2Cl_2 (3 mL) was added. After 1 h, Et_3N (3.35 mL, 24 mmol) was added and the reaction was allowed to warm to rt. The reaction was diluted with CH_2Cl_2 and washed with a HCl aqueous solution (5% w/v), a saturated aqueous solution of $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. The crude obtained was filtered through a pad of silica gel and the aldehyde was used in the next reaction.

A solution of *n*-BuLi (4.1 mL of a 1.75 M solution in hexane, 7.2 mmol) was added dropwise via syringe to a stirred and ice-cooled suspension of methyltriphenylphosphonium bromide (2.79 g, 7.8 mmol) in anhydrous THF (45 mL) under argon. After 15 min, the crude aldehyde dissolved in THF (5 mL) was added. The resulting mixture was stirred for 2 h and then quenched with a saturated aqueous solution of NH_4Cl and diluted with Et_2O. The aqueous layer was extracted with Et_2O and the combined organic layers were dried ($MgSO_4$), filtered, concentrated and purified by silica gel flash-chromatography, yielding **15** (1.28 g, 88% yield) as an oil: $[\alpha]_D^{25}+1.1$ (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.04 (s, 6H), 0.90 (s, 9H), 1.35 (ddd, $J=$ 2.7, 2.7, 13.2 Hz, 1H), 1.63–1.70 (m, 1H), 1.78–1.84 (m, 1H), 1.92–2.08 (m, 1H), 3.49 (ddd, $J=2.5$, 11.3, 11.3 Hz, 1H), 3.73 (s, 1H), 3.83 (d, $J=6.2$ Hz, 1H), 3.99 (d, $J=$ 11.3 Hz, 1H), 5.17 (dd, $J=1.3$, 10.6 Hz, 1H), 5.25 (dd, $J=$ 1.3, 17.2 Hz, 1H), 5.91 (ddd, $J=6.3$, 10.6, 17.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) $\delta-5.0$ (q), -4.6 (q), 18.2 (s), 20.7 (t), 25.9 (q), 31.1 (t), 67.1 (t), 68.6 (d), 81.1 (d), 116.2 (t), 137.0 (d); IR (film) (cm^{-1}) 3019, 2927, 2855, 1216; MS *m/z* (relative intensity) 185 $(M-Bu\text{-}t)^+$(13), 97 (19), 85 (50), 71 (73), 57 (100). HRMS calcd for $C_9H_{17}O_2Si$ $(M-Bu\text{-}t)^+$: 185.0998, found: 185.1000.

4.1.3. Preparation of 2-[(2*R*,3*R*)-3-(*tert*-butyldimethylsilyloxy)-tetrahydro-2*H*-pyran-2-yl]acetic acid (16). To a stirred solution of **15** (1.28 g, 5.3 mmol) in dry THF (50 mL, 0.1 M) under argon at 0 °C was added dropwise the 9-borabicyclo[3.3.1]nonane (15.9 mL, 7.9 mmol). The reaction was allowed to warm slowly to rt and stirred additionally for 12 h until TLC showed the end of the reaction. The reaction mixture was cooled to 0 °C and H_2O_2 (30% w/v, 2.8 mL), NaOH (3 M, 1.2 mL) and H_2O (1.2 mL) were added sequentially with stirring. The mixture was allowed to warm to rt and stirred. After 0.5 h the mixture was extracted with ether and the combined organic solutions were washed with brine, dried, evaporated in vacuo and the residue was used without further purification.

To a solution of the crude in CH_3CN (14 mL), CCl_4 (14 mL), H_2O (21 mL) were added $NaIO_4$ (4.5 g, 21.2 mmol) and a catalytic amount of $RuCl_3\cdot xH_2O$. The reaction mixture was vigorously stirred until TLC showed complete conversion to the acid **16**. The reaction was diluted with Et_2O, $MgSO_4$ was added and the mixture was filtered through a pad of Celite and concentrated. Silica gel column chromatography of the residue gave acid **16** (1.28 g, 88% yield) as a white solid: mp 73–76 °C: $[\alpha]_D^{25}+3.2$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.06 (s, 6H), 0.91 (s, 9H), 1.35 (d, $J=13.4$ Hz, 1H), 1.66 (dd, $J=13.6$, 13.6 Hz, 1H), 1.81–1.87 (m, 1H), 1.90–2.08 (m, 1H), 2.49 (dd, $J=5.0$, 16 Hz, 1H), 2.67 (dd, $J=8.1$, 16 Hz, 1H), 3.49 (dd, $J=11.4$, 11.4 Hz, 1H), 3.73 (s, 1H), 3.79 (dd, $J=5.0$, 8.0 Hz, 1H), 3.96 (d, $J=11.3$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 5.0 (q), -4.6 (q), 18.1 (s), 20.2 (t), 25.8 (q), 30.7 (t), 36.9 (t), 67.0 (d), 67.7 (t), 76.1 (d), 176.2 (s); IR (film) (cm^{-1}) 3020, 2929, 2856, 1216; MS *m/z* (relative intensity) 217 $(M-Bu\text{-}t)^+$ (30), 97 (39), 83 (49), 75 (100). HRMS calcd for $C_9H_{17}O_4Si$ $(M-Bu\text{-}t)^+$: 217.0896, found: 217.0925.

4.1.4. Preparation of benzyl 2-((2*R*,3*R*)-3-hydroxy-tetrahydro-2*H*-pyran-2-yl)acetate (17). To a stirred solution of the acid **16** (0.6 g, 2.2 mmol) in dry CH_2Cl_2 (22 mL) under argon were added sequentially with stirring DMAP (0.35 g, 2.9 mmol), benzyl alcohol (0.27 mL, 2.6 mmol) and camphorsulfonic acid (151 mg, 0.7 mmol) at rt. The mixture was stirred for 15 min, and DCC (0.59 g, 2.9 mmol) was slowly added. The reaction mixture was additionally stirred for 3 h, then, it was diluted in CH_2Cl_2 (10 mL), filtered through a pad of Celite and washed with a 5% (w/v) HC1 aqueous solution, a saturated aqueous solution of $NaHCO_3$ and saturated brine. The organic phase was dried over $MgSO_4$, concentrated, and purified by chromatography on silica gel, to afford the benzyl ester (650 mg, 85% yield) as an oil: $[\alpha]_D^{25}+1.3$ (*c* 1.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.018 (s, 3H), 0.048 (s, 3H), 0.91 (s, 9H), 1.32 (d, $J=13.2$ Hz, 1H), 1.601.72 (m, 1H), 1.80–1.86 (m, 1H), 1.90–2.08 (m, 1H), 2.52 (dd, $J=5.6$, 16.0 Hz, 1H), 2.67 (dd, $J=7.7$, 16.0 Hz, 1H), 3.47 (ddd, $J=2.3$, 11.4, 11.4 Hz, 1H), 3.75 (s, 1H), 3.84 (dd, $J=4.2$, 4.2 Hz, 1H), 3.92 (dd, $J=1.9$, 9.5 Hz, 1H), 5.13 (dd, $J=12.4$, 16 Hz, 2H), 7.30–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) $\delta-5.0$ (q), -4.6 (q), 18.1 (s), 20.4 (t), 25.8 (q), 30.9 (t), 37.0 (t), 66.2 (t), 66.9 (d), 67.6 (t), 76.3 (d), 128.1 (d), 128.2 (d), 128.5 (d), 136.0 (s), 171.6 (s); IR (film) (cm^{-1}) 3034, 2952, 2856, 1737; MS *m/z* (relative intensity) 307 $(M-Bu\text{-}t)^+$(40), 101 (10), 91 (100), 73 (13). HRMS calcd for $C_{16}H_{23}O_4Si$ $(M-Bu\text{-}t)^+$: 307.1366, found: 307.1351.

To a solution of the benzyl ester (646 mg, 1.8 mmol) in CH_3CN (17 mL) at 0 °C was added HF (48%, 0.9 mL) and the reaction was stirred for 1 h. Then, the mixture was diluted with Et_2O (15 mL) and washed with saturated $NaHCO_3$ (aqueous). The aqueous layer was extracted with Et_2O and the combined organic layers were dried ($MgSO_4$), filtered and concentrated. Silica gel column chromatography of the residue gave alcohol **17** (290 mg, 65% yield) as a white solid: mp 67–68 °C: $[\alpha]_D^{25}+1.6$ (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.41 (d, $J=12.8$ Hz, 1H), 1.63–1.69 (m, 1H), 1.83–1.90 (m, 2H), 2.60 (dd, $J=5.6$, 15.8 Hz, 1H), 2.70 (dd, $J=7.8$, 15.9 Hz, 1H), 3.49 (ddd, $J=1.3$, 11.8, 11.8 Hz, 1H), 3.68 (s, 1H), 3.85 (dd, $J=5.9$, 7.0 Hz, 1H), 3.96 (dd, $J=3.0$, 11.5 Hz, 1H), 5.14 (dd, $J=12.4$, 15.7 Hz, 2H), 7.26–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 19.8 (t), 30.4 (t), 37.3 (t), 66.3 (d), 66.3 (t), 68.3 (t), 76.4 (d), 128.0 (d), 128.1 (d), 128.5 (d), 135.9 (s), 171.4 (s); IR (film) (cm^{-1}) 3450, 2943, 2854, 1734; MS *m/z* (relative intensity) 250 $(M)^+$ (0.25), 232 (4), 143 (5), 91 (43), 71 (100). HRMS calcd for $C_{14}H_{18}O_4$ $(M)^+$: 250.1205, found: 250.1195.

4.1.5. Preparation of 2-{[(2*R*,3*R*)-3-(*tert*-butyldimethylsilyloxy)-tetrahydro-2*H*-pyran-2-yl]methoxy}acetic acid (18). To a solution of alcohol **14** (2 g, 8.1 mmol) in dry THF (81 mL) and under nitrogen were added sodium iodoacetate (1.69 g, 8.1 mmol) and NaH (715 mg, 17.9 mmol, 60% oil dispersion) at 0 °C. The reaction was allowed to warm to rt and stirred overnight. The reaction was diluted with water and the pH was adjusted to 4 with a HCl aqueous solution (5% w/v). The aqueous layer was saturated with solid NaCl and extracted with EtOAc. The extracts were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography over silica gel using 1:9 MeOH: CH_2Cl_2 to yield acid **18** (2.33 g, 94% yield) as an oil: $[\alpha]_D^{25}-3.2$ (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.02 (s, 3H), 0.05 (s, 3H), 0.89 (s, 9H), 1.35 (d, $J=13.6$ Hz, 1H),

1.61–1.66 (m, 1H), 1.79–1.80 (m, 1H), 1.95–2.08 (m, 1H), 3.44 (ddd, $J=1.9$, 10.1, 10.1 Hz, 1H), 3.60–3.63 (m, 2H), 3.69–3.71 (m, 1H), 3.75 (s, 1H), 4.03 (ddd, $J=2.4$, 2.4, 11.6 Hz, 1H), 4.09 (d, $J=16.4$ Hz, 1H), 4.17 (d, $J=16.4$ Hz, 1H), 7.41 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ −5.1 (q), −4.6 (q), 18.1 (s), 20.2 (t), 25.7 (q), 30.9 (t), 65.7 (d), 67.7 (t), 69.1 (t), 73.6 (t), 78.6 (d), 173.3 (s); IR (film) (cm^{-1}) 3422, 2925, 2855, 1733, 1090; MS *m/z* (relative intensity) 305 $(M+H)^+$ (0.3), 247 $(M-Bu\text{-}t)^+$ (4), 189 (39), 171 (16), 133 (96), 105 (41), 97 (100), 75 (80). HRMS calcd for $C_{24}H_{29}O_5Si$ $(M+H)^+$: 305.1784, found: 305.1778.

4.1.6. Preparation of benzyl 2-{[(2*R*,3*R*)-3-hydroxytetrahydro-2*H*-pyran-2-yl]methoxy}acetate (19). To a stirred solution of the acid **18** (1.5 g, 4.9 mmol) in dry CH_2Cl_2 (49 mL) under argon were sequentially added with stirring DMAP (787 mg, 6.4 mmol), benzyl alcohol (664 mg, 6.4 mmol) and camphorsulfonic acid (344 mg, 1.5 mmol) at rt. The mixture was stirred for 15 min, and DCC (1.32 g, 6.4 mmol) was slowly added and the mixture was additionally stirred for 3 h, and diluted in CH_2Cl_2, filtered through a pad of Celite and washed with a 5% (w/v) HC1 aqueous solution, a saturated aqueous solution of $NaHCO_3$ and saturated brine. The organic phase was dried over $MgSO_4$, concentrated, and purified by chromatography on silica gel, to afford the benzyl ester (1.85 g, 95% yield): $[\alpha]_D^{25}$ −14.6 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.02 (s, 3H), 0.05 (s, 3H), 0.89 (s, 9H), 1.31 (d, $J=13$ Hz, 1H), 1.55–1.66 (m, 1H), 1.78–1.83 (m, 1H), 1.97–2.05 (m, 1H), 3.44 (ddd, $J=2.2$, 11.6, 11.6 Hz, 1H), 3.58–3.65 (m, 3H), 3.78 (s, 1H), 3.96 (ddd, $J=2.1$, 2.1, 11.3 Hz, 1H), 4.12 (d, $J=16.5$ Hz, 1H), 4.21 (d, $J=16.5$ Hz, 1H), 5.18 (s, 2H), 7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −5.0 (q), −4.6 (q), 18.1 (s), 20.4 (t), 25.8 (q), 31.0 (t), 65.9 (d), 66.4 (t), 67.6 (t), 72.5 (t), 78.8 (d), 128.3 (d), 128.6 (d), 170.3 (s); IR (film) (cm^{-1}) 2951, 2855, 2362, 1758, 1135; MS *m/z* (relative intensity) 417 $(M+Na)^+$ (17), 395 $(M+H)^+$(34), 337 $(M-Bu\text{-}t)^+$ (18), 227 (8), 136 (9), 91 (100), 73 (27). HRMS calcd for $C_{21}H_{34}O_5Na_1Si$ $(M+Na)^+$: 417.2073, found: 417.2094.

To a solution of the benzyl ester (995 mg, 2.5 mmol) in CH_3CN (25 mL) at 0 °C, was added HF (48%, 1.3 mL) and the reaction was stirred for 3–4 h. Then, the mixture was diluted with Et_2O and washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with Et_2O and the combined organic layers were dried ($MgSO_4$), filtered and concentrated. Silica gel column chromatography of the residue gave alcohol **19** (692 mg, 98% yield) as an oil: $[\alpha]_D^{25}$ −14.9 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.35–1.40 (m, 1H), 1.55–1.70 (m,1H), 1.93–2.05 (m, 2H), 3.50–3.55 (m, 1H), 3.68 (dd, $J=2.4$, 5.6 Hz, 2H), 3.87 (s, 1H), 3.99 (ddd, $J=2.3$, 2.3, 11.2 Hz, 1H), 4.11 (d, $J=16.8$ Hz, 1H), 4.15 (d, $J=16.8$ Hz, 1H), 5.18 (dd, $J=12.5$ Hz, 2H), 7.31–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.1 (t), 30.0 (t), 65.3 (d), 66.8 (t), 68.4 (t), 68.5 (t), 72.1 (t), 78.0 (d), 128.5 (d), 128.5 (d), 128.6 (d), 170.7 (s); IR (film) (cm^{-1}) 3479, 2944, 2853, 1752, 1213, 1132; MS *m/z* (relative intensity) 303 $(M+Na)^+$(7), 281 $(M+H)^+$(44), 91 (100). HRMS calcd for $C_{15}H_{20}O_5Na_1$ $(M+Na)^+$: 303.1208, found: 303.1242.

4.1.7. Preparation of methyl (2*E*)-3-((2*R*,3*R*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}tetrahydro-2*H*-pyran-2-yl)-2-propenoate (22). The same procedure used above to obtain compound **15** was applied to **14** on a 554 mg (2.3 mmol) scale, using in the Wittig step methyl (triphenylphosphoranylidene) acetate in dry benzene, yielding **22** (625 mg, 92% yield) as a colourless oil: $[\alpha]_D^{25}$ +1.1 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.003 (s, 3H), 0.04 (s, 3H), 0.87 (s, 9H), 1.38 (d, $J=13.4$ Hz, 1H), 1.69–1.73 (m, 1H), 1.79–1.85 (m, 1H) 1.96–2.04 (m, 1H), 3.50 (ddd, $J=2.6$, 11.1, 11.1 Hz, 1H), 3.73 (s, 3H), 3.82–3.84 (m, 1H), 3.97–4.05 (m, 2H), 6.06 (dd, $J=1.8$, 15.8 Hz, 1H), 6.90 (dd, $J=4.4$, 15.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −5.0 (q), −4.5 (q), 18.1 (s), 20.7 (t), 25.7 (q), 31.1 (t), 51.4 (q), 67.0 (t), 67.8 (d), 78.7 (d), 121.3 (d), 146.6 (d), 166.8 (s); IR (film) (cm^{-1}) 2956, 2857, 1726, 1305, 1262; MS *m/z* (relative intensity) 299 $(M-H)^+$(8), 243 (31), 187 (60), 113 (65), 75 (100). HRMS calcd for $C_{15}H_{27}O_4Si$ $(M-H)^+$: 299.1678, found: 299.1665.

4.1.8. Preparation of (2*E*)-3-[(3*S*,2*R*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}tetrahydro-2*H*-pyran-2-yl)prop-2-enoic acid (23). To a solution of the methyl ester **22** (625 mg, 2.1 mmol) in THF (3 mL) and H_2O (1.8 mL) was added $LiOH\cdot H_2O$ (251 mg, 6.3 mmol) and the mixture was stirred at reflux for 5 h, after which time TLC showed that the starting material had disappeared. Then a 3 M solution of HCl was added at 0 °C until pH≈5 was reached. The reaction mixture was diluted with Et_2O and washed with H_2O and brine. The organic phase was dried over $MgSO_4$, concentrated, and the residue was purified by chromatography on silica gel, to afford the acid **23** (560 mg, 94% yield) as a white solid: mp 101–104 °C: $[\alpha]_D^{25}$ +1.9 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.01 (s, 3H), 0.04 (s, 3H), 0.87 (s, 9H), 1.38 (m, 1H), 1.69–1.85 (m, 2H), 1.95–2.05 (m, 1H), 3.51 (ddd, $J=2.5$, 11.1, 11.1 Hz, 1H), 3.85 (s, 1H), 3.99–4.13 (m, 2H), 6.07 (dd, $J=1.6$, 15.8 Hz, 1H), 6.99 (dd, $J=4.1$, 15.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −4.9 (q), −4.7 (q), 18.1 (s), 20.6 (t), 25.7 (q), 31.2 (t), 67.1 (t), 67.7 (d), 78.7 (d), 121.0 (d), 149.0 (d), 171.4 (s); IR (film) (cm^{-1}) 2953, 2857, 1699, 1257, 1023; MS *m/z* (relative intensity) 229 $(M-Bu\text{-}t)^+$ (92), 211 (37), 185 (35), 137 (38), 75 (100). HRMS calcd for $C_{10}H_{17}O_4Si$ $(M-Bu\text{-}t)^+$: 229.0896, found: 229.0892.

4.1.9. Preparation of unsaturated δ-lactone 25. To a solution of the acid **23** (120 mg, 0.4 mmol) in CH_3CN (3.8 mL) at 0 °C was added HF (48%, 0.4 mL) and the reaction was stirred for 5 h. Then, the mixture was diluted with Et_2O, $MgSO_4$ was added, the mixture was filtered and concentrated and the crude residue was used without further purification.

To a solution of the hydroxy acid in dry CH_2Cl_2 (4.2 mL, 0.1 M) at 0 °C under nitrogen atmosphere were added Et_3N (87 μL, 0.6 mmol) and DMAP (103 mg, 4.2 mmol). The mixture was stirred for 10 min at 0 °C and 2,4,6-trichlorobenzoyl chloride (98 μL, 0.6 mmol) was added and the reaction was allowed to warm to rt. The reaction mixture was diluted in CH_2Cl_2, washed with a 5% (w/v) HC1 aqueous solution, a saturated aqueous solution of $NaHCO_3$ and saturated brine. The organic phase was dried over $MgSO_4$, concentrated, and purified by chromatography on silica gel, to afford the unsaturated δ-lactone **25** (27 mg, 42% overall yield) as a white solid: mp 48–49 °C: $[\alpha]_D^{25}$ −77.7 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.46–1.51 (m, 2H),

1.77–1.88 (m, 2H), 1.93–2.04 (m, 2H) 2.20–2.27 (m, 2H), 3.50 (ddd, $J=2.2$, 11.6, 11.6 Hz, 2H), 3.90–4.07 (m, 4H), 4.34 (s, 2H), 6.17 (d, $J=9.6$ Hz, 2H), 6.87 (dd, $J=5.9$, 9.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 19.9 (t), 27.2 (t), 66.6 (d), 67.4 (t), 73.1 (d), 124.6 (d), 141.7 (d), 163.9 (s); IR (film) (cm^{-1}) 2930, 1715, 1252, 1090; MS (FAB) *m/z* (relative intensity) 155 $(M+H)^+$(100), 154 $(M)^+$(23), 95 (24), 69 (52), 54 (56).

4.1.10. Preparation of benzyl (2*E*)-3-[(2*R*,3*R*)-tetrahydro-3-hydroxy-2*H*-pyran-2-yl]-2-propenoate (26). The same procedure used above to obtain compound **22** was applied to **14** on a 600 mg (2.4 mmol) scale, using in the Wittig–Horner step the sodium salt of benzyl dimethylphosphonoacetate in dry benzene and followed by deprotection of the silyl ether with HF in CH_3CN, yielding **26** (525 mg, 82% yield) as a white solid: mp 114–117 °C: $[\alpha]_D^{25}-19.6$ (*c* 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.42 (m, 1H), 1.73 (m, 1H), 1.89–2.04 (m, 2H), 3.52 (ddd, $J=2.3$, 11.9, 11.9 Hz, 1H), 3.83 (s, 1H), 4.02–4.08 (m, 2H), 5.18 (s, 2H), 6.17 (dd, $J=2.0$, 15.7 Hz, 1H), 6.92 (dd, $J=2.0$, 15.7 Hz, 1H), 7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 19.8 (t), 30.2 (t), 66.3 (t), 66.5 (d), 68.3 (t), 78.6 (d), 122.0 (d), 128.1 (d), 128.2 (d), 128.5 (d), 136.0 (q), 145.7 (d), 166.0 (s); MS *m/z* (relative intensity) 171 $(M-Bn)^+$ (6), 146 (18), 88 (39), 71 (54), 57 (100). HRMS calcd for $C_8H_{11}O_4$ $(M-Bn)^+$: 171.0657, found: 171.0658.

4.1.11. Preparation of (2*R*,3*R*)-2-[2-(benzyloxy)-2-oxoethyl]tetrahydro-2*H*-pyran-3-yl ((2*R*,3*R*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}tetrahydro-2*H*-pyran-2-yl) acetate (27). To a stirred solution of the acid **16** (150 mg, 0.6 mmol) in dry CH_2Cl_2 (3 mL) under argon were added sequentially with stirring DMAP (87 mg, 0.7 mmol), alcohol **17** (137 mg, 0.6 mmol) and camphorsulfonic acid (38 mg, 0.2 mmol) at rt. The mixture was stirred for 15 min, and DCC (147 mg, 0.7 mmol) was slowly added. The reaction mixture was additionally stirred for 5 h and diluted in CH_2Cl_2, filtered through a pad of Celite and washed with a 5% (w/v) HC1 aqueous solution, a saturated aqueous solution of $NaHCO_3$ and saturated brine. The organic phase was dried over $MgSO_4$, concentrated, and purified by chromatography on silica gel, to afford the benzyl ester **27** (266 mg, 96% yield): $[\alpha]_D^{25}-1.4$ (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 3H), 0.05 (s, 3H), 0.90 (s, 9H), 1.28–1.42 (m, 2H), 1.65–1.98 (m, 6H), 2.44 (dd, $J=4.5$, 15.9 Hz, 2H), 2.59–2.71 (m, 2H), 3.48 (ddddd, $J=2.0$, 11.6, 11.6, 11.6, 11.6 Hz, 2H), 3.70 (s, 1H), 3.83–3.94 (m, 2H), 3.94–3.98 (m, 2H), 4.93 (s, 1H), 5.10 (d, $J=12.4$ Hz, 1H), 5.12 (d, $J=12.4$ Hz, 2H), 7.28–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) $\delta-4.8$ (q), -4.5 (q), 18.1 (s), 20.4 (t), 25.9 (q), 27.8 (t), 30.9 (t), 37.3 (t), 66.4 (t), 67.2 (d), 67.4 (t), 68.1 (t), 68.6 (d), 74.7 (d), 76.3 (d), 128.1 (d), 128.5 (d), 135.8 (s), 170.8 (s), 171.2 (s); IR (film) (cm^{-1}) 2952, 2930, 2856, 1737; MS *m/z* (relative intensity) 449 $(M-Bu\text{-}t)^+$ (0.89), 307 (7), 233 (26), 187 (14), 91 (100). HRMS calcd for $C_{23}H_{33}O_7Si$ $(M-Bu\text{-}t)^+$: 449.1996, found: 449.1979.

4.1.12. Preparation of (2*R*,3*R*)-2-[2-(benzyloxy)-2-oxoethyl]tetrahydro-2*H*-pyran-3-yl [(2*R*,3*R*)-3-hydroxy-tetrahydro-2*H*-pyran-2-yl]acetate (28). To a solution of the benzyl ester **27** (266 mg, 0.5 mmol) in CH_3CN (5.3 mL) at 0 °C, was added HF (48%, 0.6 mL) and the reaction was stirred for 3–4 h. Then, the mixture was diluted with Et_2O and washed with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with Et_2O and the combined organic layers were dried ($MgSO_4$), filtered and concentrated. Silica gel column chromatography of the residue gave benzyl ester **28** (200 mg, 96% yield) as an oil: $[\alpha]_D^{25}-7.4$ (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.36–1.39 (m, 2H), 1.70–2.00 (m, 6H), 2.44 (dd, $J=5.0$, 15.9 Hz, 1H), 2.52–2.71 (m, 3H), 3.47 (dd, $J=2.0$, 11.6, 11.6, 11.6, 11.6 Hz, 2H), 3.62 (s, 1H), 3.80–3.83 (m, 1H), 3.91–3.99 (m, 3H), 4.90 (s, 1H), 5.07 (d, $J=12.4$ Hz, 1H), 5.12 (d, $J=12.4$ Hz, 2H), 7.27–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 19.7 (t), 20.3 (t), 27.7 (t), 30.3 (t), 37.1 (t), 37.5 (t), 66.2 (d), 66.3 (t), 68.0 (t), 68.2 (t), 68.6 (d), 74.6 (d), 76.4 (d), 128.0 (d), 128.1 (d), 128.4 (d), 137.7 (s), 170.7 (s), 170.8 (s); IR (film) (cm^{-1}) 3452, 2950, 2855, 1734; MS (FAB) *m/z* (relative intensity) 393 $(M+H)^+$ (8), 307 (7), 154 (47), 136 (37), 91 (100). HRMS (FAB) calcd for $C_{21}H_{29}O_7$ $(M+H)^+$: 393.1913, found: 393.1891.

4.1.13. Preparation of macrolide 1. A mixture of the benzyl ester **28** (200 mg, 0.5 mmol) and $Pd(OH)_2$ (10 mg) in EtOAc (5.1 mL) was placed under H_2 atmosphere. The reaction mixture was vigorously stirred until TLC showed complete conversion to the hydroxyl acid. The mixture was filtered through a pad of Celite. The solvent was removed under reduced pressure and the residue was used without further purification.

To a mixture of hydroxyl acid and 2,2′-dipyridyl disulfide (145 mg, 0.7 mmol) in dry toluene (1.8 mL) at rt was added triphenylphosphine (175 mg, 0.7 mmol) in one portion. The reaction mixture was stirred for 6 h prior to diluting with dry toluene (55 mL, 0.01 M) and then the mixture was refluxed overnight. The solvent was removed under vacuum and the residue was purified by chromatography on silica gel, to yield macrodiolide **1** (36 mg, 25% yield) and γ-lactone **20** (36 mg, 50% yield). Macrodiolide **1**: white solid: mp 130–133 °C: $[\alpha]_D^{25}+9.2$ (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.51–1.53 (m, 2H), 1.82–1.96 (m, 6H), 2.66 (dd, $J=5.3$, 13.3 Hz, 2H), 2.82 (dd, $J=8.2$, 13.3 Hz, 2H), 3.50–3.55 (m, 2H), 3.79–3.84 (m, 2H), 4.05–4.09 (m, 2H), 4.86–4.89 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.7 (t), 26.6 (t), 37.7 (t), 65.9 (t), 69.5 (d), 73.8 (d), 171.1 (s); IR (film) (cm^{-1}) 2952, 2856, 1735; MS (FAB) *m/z* (relative intensity) 285 (M+H) (100), 225 (12), 220 (10). HRMS (FAB) calcd for $C_{14}H_{21}O_6$ (M+H): 285.1338, found: 285.1332.

4.1.14. Preparation of (2*R*,3*R*)-2-{(1*E*)-2-[benzyloxycarbonyl]vinyl}-tetrahydro-2*H*-pyran-3-yl 3-[(3*S*,2*R*)-3-(*tert*-butyldimethylsilyloxy)-(tetrahydro-2*H*-pyran-2-yl)]prop-2-(2*E*)-enoate (29). The same procedure used above to obtain compound **27** was applied to the acid **23** on a 350 mg (1.2 mmol) scale and alcohol **26** (320 mg, 1.2 mmol), yielding **29** (532 mg, 82% yield) as a colourless oil: $[\alpha]_D^{25}-9.8$ (*c* 1.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 3H), 0.01 (s, 3H), 0.84 (s, 9H), 1.30–1.44 (m, 2H), 1.65–2.04 (m, 6H), 3.50 (m, 2H), 3.79 (s, 1H), 3.97–4.13 (m, 3H), 4.16 (s, 1H), 5.05 (s, 1H), 5.14 (s, 2H), 6.05 (d, $J=17.6$ Hz, 1H), 6.11 (d, $J=17.6$ Hz, 1H), 6.85 (m, 2H), 7.26–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 4.8 (q), 18.1 (s), 20.5 (t), 25.7 (q), 27.8 (t), 31.2 (t), 37.3 (t), 66.0 (t), 67.2 (t), 67.6 (d), 67.7 (t), 68.2 (d), 77.0 (d), 78.8 (d), 121.6 (d), 121.9 (d), 128.0 (d),

128.1 (d), 128.4 (d), 128.5 (d), 136.0 (s), 144.7 (d), 146.9 (d), 165.4 (s), 165.8 (s); Anal. Calcd for $C_{29}H_{42}O_7Si$: C, 65.63; H, 7.98. Found: C, 65.65; H, 7.68.

4.1.15. Preparation of macrodiolide 2. To a solution of the benzyl ester **29** (320 mg, 0.6 mmol) in CH_3CN (5.4 mL) at 0 °C, was added HF (48%, 0.6 mL) and the reaction was stirred for 3–4 h. Then, the mixture was diluted with Et_2O and washed with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with Et_2O and the combined organic layers were dried ($MgSO_4$), filtered and concentrated. Silica gel column chromatography of the residue gave the alcohol as an oil. Then, the same procedure used above to obtain compound **1** was applied to the alcohol, yielding macrodiolide **2** (90 mg, 48% overall yield) as a colourless oil: $[\alpha]_D^{25}+19.3$ (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.39–1.44 (m, 2H), 1.69–1.79 (m, 2H), 1.85–2.10 (m, 6H) 2.15 (m, 2H), 2.47 (ddd, $J=3.4$, 7.1, 18.0 Hz, 2H), 2.70 (ddd, $J=3.4$, 11.1, 18.1 Hz, 2H), 3.53 (ddd, $J=2.1$, 12.3, 12.3 Hz, 2H), 3.66 (ddd, $J=1.4$, 3.4, 3.4 Hz, 2H), 3.99 (ddd, $J=2.3$, 2.3, 11.4 Hz, 2H), 4.33 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 19.9 (t), 25.6 (t), 26.1 (t), 28.7 (t), 68.1 (t), 69.7 (d), 75.9 (d), 171.8 (s); IR (film) (cm^{-1}) 2928, 2853, 1730, 1246, 1024; MS (FAB) *m/z* (relative intensity) 313 $(M+H)^+$ (19), 175 (6), 157 (100), 55 (56). HRMS (FAB) calcd for $C_{16}H_{25}O_6$ $(M+H)^+$: 313.1651, found: 313.1661.

4.1.16. Preparation of (2*R*,3*R*)-2-{[(benzyloxycarbonyl) methoxy]methyl}-tetrahydro-2*H*-pyran-3-yl 2-{[(2*R*, 3*R*)-3-(*tert*-butyldimethylsilyloxy)-tetrahydro-2*H*-pyran-2-yl]methoxy}acetate (30). The same procedure used above to obtain compound **27** was applied to the acid **18** on a 500 mg (1.6 mmol) scale and alcohol **19** (460 mg, 1.6 mmol), to afford the benzyl ester **30** (791 mg, 85% yield): $[\alpha]_D^{25}-19.6$ (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.03 (s, 3H), 0.05 (s, 3H), 0.89 (s, 9H), 1.25–1.43 (m, 2H), 1.60–2.07 (m, 6H), 3.45–3.65 (m, 7H), 3.72 (dd, $J=1.4$, 4.6 Hz, 1H), 3.79 (s, 1H), 3.94–4.05 (m, 2H), 4.10–4.17 (m, 4H), 5.00 (s, 1H), 5.16 (s, 2H), 7.31–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −5.0 (q), −4.6 (q), 18.1 (s), 20.4 (t), 20.6 (t), 25.8 (q), 27.6 (t), 31.0 (t), 65.9 (d), 66.5 (t), 67.6 (t), 67.9 (t), 68.0 (d), 68.7 (t), 68.7 (t), 71.7 (t), 72.5 (t), 77.2 (d), 78.8 (d), 128.4 (d), 128.6 (d), 135.4 (s), 170.0 (s); IR (film) (cm^{-1}) 2952, 2854, 1755, 1462, 1132, 1098; MS *m/z* (relative intensity) 566 $(M)^+$(0.12), 509 $(M-Bu\text{-}t)^+$ (0.91), 387 (0.45), 263 (27), 187 (18), 91 (100). HRMS calcd for $C_{29}H_{46}O_9Si$ $(M)^+$: 566.2911, found: 566.2918.

4.1.17. Preparation of benzyl-2-{[(2*R*,3*R*)-3-(2-{[(2*R*,3*R*)-3-hydroxy-tetrahydro-2*H*-pyran-2-yl]methoxy}acetoxy)-tetrahydro-2*H*-pyran-2-yl]methoxy}acetate (31). The same procedure used above to obtain compound **28** was applied to the benzyl ester **30** on a 805 mg (1.4 mmol) scale, yielding alcohol **31** (590 mg, 92% yield) as an oil: $[\alpha]_D^{25}-32.3$ (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.40 (dd, $J=12.4$, 12.4 Hz, 2H), 1.63–2.05 (m, 6H), 3.44–3.73 (m, 8H), 3.88 (s, 1H), 3.95–4.20 (m, 6H), 5.03 (s, 1H), 5.15 (s, 2H), 7.30–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.2 (t), 20.5 (t), 27.5 (t), 30.0 (t), 65.1 (d), 66.5 (t), 68.0 (t), 68.2 (d), 68.5 (t), 68.6 (t), 71.2 (t), 72.0 (t), 77.0 (d), 78.0 (d), 128.4 (d), 128.6 (d), 135.4 (s), 170.0 (s), 170.5 (s); IR (film) (cm^{-1}) 3489, 2949, 2854, 2361, 1751, 1437, 1201, 1130, 1093; MS (FAB) *m/z* (relative intensity) 475 $(M+Na)^+$ (82), 453 $(M+H)^+$ (52), 307 (13), 263 (10). HRMS (FAB) calcd for $C_{23}H_{33}O_9$ $(M+H)^+$: 453.2125, found: 453.2087.

4.1.18. Preparation of the macrodiolide (3) and macrotetraolide (34). A mixture of the alcohol **31** (580 mg, 1.28 mmol) and $Pd(OH)_2$ (10 mg) in EtOAc (13 mL) was placed under H_2 atmosphere. The reaction mixture was vigorously stirred until TLC showed complete conversion to the hydroxyl acid **32**. The mixture was filtered through a pad of Celite. The solvent was removed under reduced pressure and the residue was used without further purification.

For macrolactonization two methods were carried out.

Method A. To a solution of the hydroxy acid **32** (27 mg, 0.07 mmol) in dry THF (6.13 mL, 0.012 M) at rt, were added Et_3N (20 μL, 0.15 mmol) and 2,4,6-trichlorobenzoyl chloride (15 μL, 0.1 mmol). After 2 h, the mixture was diluted with dry toluene (61 mL, 0.0012 M) and added slowly over DMAP (90 mg, 0.7 mmol) in boiling toluene (12 mL). The mixture was stirred at reflux for 1 h. The solvent was evaporated and the residue purified by size exclusion chromatography (Sephadex LH-20 and MeOH as the mobile phase) to yield the macrodiolide (**3**) (5.1 mg, 20% yield) as an oil, and the macrotetraolide (**34**) (10.1 mg, 40% yield) as a white solid and oligomers (10 mg).

Method B. To a mixture of hydroxy acid **32** (50 mg, 0.14 mmol) and 2,2′-dipyridyl disulfide (46 mg, 0.2 mmol) in dry CH_2Cl_2 (2.75 mL, 0.05 M) at rt, was added triphenylphosphine (55 mg, 0.2 mmol) in one portion. The reaction mixture was stirred for 6 h prior to diluting with dry CH_2Cl_2 (67 mL, 0.002 M) and subsequent addition of K_2CO_3 (381 mg, 2.8 mmol), then the mixture was refluxed for 6 days. The reaction was poured into saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under vacuum. The residue was purified by size exclusion chromatography (Sephadex LH-20 and MeOH as the mobile phase) to yield the macrodiolide (**3**) (39 mg, 82% yield) and the macrotetraolide (**34**) (6 mg, 13% yield). Macrodiolide (**3**): $[\alpha]_D^{25}-31.2$ (*c* 0.33, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.41 (d, $J=12.6$ Hz, 2H), 1.68–1.77 (m, 2H), 1.85–1.97 (m, 2H), 2.10 (d, $J=14.2$ Hz, 2H), 3.50 (ddd, $J=1.8$, 1.8, 11.8 Hz, 2H), 3.62 (dd, $J=5.4$, 5.4 Hz, 2H), 3.67–3.77 (m, 4H), 4.05 (d, $J=14.2$ Hz, 4H), 4.16 (d, $J=14.3$ Hz, 2H), 5.08 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 20.6 (t), 27.2 (t), 68.1 (t), 68.2 (d), 70.4 (t), 70.8 (t), 76.2 (d), 169.4 (s); IR (film) (cm^{-1}): 2928, 2854, 1736, 1217, 1095; MS (FAB) *m/z* (relative intensity): 367 $(M+Na)^+$ (19), 135 (8), 81 (51), 69 (100). HRMS (FAB) calcd for $C_{16}H_{24}O_8Na$ $(M+Na)^+$: 367.1369, found: 367.1387. Macrotetraolide (**34**): mp 135–139 °C: $[\alpha]_D^{25}-42.7$ (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.40 (d, $J=13.0$ Hz, 4H), 1.57–1.92 (m, 8H), 2.06 (d, $J=13.4$ Hz, 4H), 3.32–3.68 (m, 12H), 3.99 (m, 4H), 4.05 (d, $J=16.8$ Hz, 4H), 4.21 (d, $J=16.8$ Hz, 4H), 5.01 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 20.5 (t), 27.6 (t), 68.0 (d), 68.2 (t), 71.4 (t), 77.2 (d), 169.8 (s); IR (film) (cm^{-1}): 2954, 2855, 2362, 1751, 1437, 1202, 1132, 1094; MS (FAB) *m/z* (relative intensity): 711 $(M+Na)^+$ (8), 367 (5), 173 (16), 97 (100), 69 (17). HRMS (FAB) calcd for $C_{32}H_{48}O_{16}Na$ $(M+Na)^+$: 711.2840, found: 711.2793.

4.1.19. Preparation of [(2*R*,3*R*)-3-(phenylmethoxy)-tetrahydro-2*H*-pyran-2-yl]methan-1-ol (41). To a stirred solution of diol **11** (2 g, 15.1 mmol) in dry CH_2Cl_2 (50 mL) were sequentially added a catalytic amount of CSA (175 mg, 0.8 mmol) and benzaldehydedimethyl acetal (3.4 mL, 22.7 mmol) at rt. The reaction mixture was stirred for 2 h, after which time TLC showed complete conversion to the benzylidene derivative. Then Et_3N was added until pH≈7, and the mixture was stirred for 5 min, evaporated under reduced pressure and purified by silica gel flash-chromatography.

To a stirred solution of the benzylidene derivative in dry CH_2Cl_2 (150 mL) at 0 °C was added dropwise DIBAL-H (76 mL, 1 M in hexane, 76 mmol). The reaction mixture was stirred for 30 min and then quenched with water (3 mL) and allowed to warm to rt. The mixture was stirred for 30 min, dried over $MgSO_4$ and filtered through a pad of Celite. The solvent was evaporated and the residue was purified by silica gel flash-chromatography, yielding **41** (3.03 g, 90% overall yield) as an oil: $[\alpha]_D^{25}$ −58.9 (*c* 2.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.35–1.49 (m, 2H), 1.96–2.15 (m, 2H), 2.34 (br s, 1H), 3.40–3.45 (m, 1H), 3.49 (s, 1H), 3.55 (dd, *J*=4.2, 11.5 Hz, 1H), 3.84 (dd, *J*=7.1, 11.5 Hz, 1H), 4.03 (m, 1H), 4.37 (d, *J*=12.0 Hz, 1H), 4.65 (d, *J*=12.0 Hz, 1H), 7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.7 (t), 25.8 (t), 63.5 (t), 68.0 (t), 70.6 (t), 71.9 (d), 79.5 (d), 127.7 (d), 127.9 (d), 128.4 (d), 138.2 (s), 170.1 (s); IR (film) (cm^{-1}) 3431, 2932, 2945, 2852, 1455, 1209, 1099; MS (FAB) *m/z* (relative intensity): 245 $(M+Na)^+$(16), 223 $(M+H)^+$(43), 91 (100). HRMS (FAB) calcd for $C_{13}H_{18}O_3Na$ $(M+Na)^+$: 245.1154, found: 245.1150.

4.1.20. Preparation of [2-(tetrahydro-2*H*-pyran-2-yloxy) ethoxy][(2*R*,3*R*)-3-(phenylmethoxy)(tetrahydro-2*H*-pyran-2-yl)]methane (42). To a solution of alcohol **41** (2 g, 9.0 mmol), $THPOCH_2CH_2Cl$ (4.0 mL, 27.0 mmol), and tetrabutylammonium hydrogen sulphate (138 mg, 0.4 mmol) was added dropwise aqueous 50% NaOH (90.1 mmol), and the two-phase mixture was stirred vigorously and maintained at 65 °C for 1 day under nitrogen. The reaction mixture was taken up into CH_2Cl_2 and washed with water. The organic layer was dried ($MgSO_4$) and filtered through a layer of silica gel with EtOAc as eluent. The solvent was evaporated and the residue was purified by silica gel flash-chromatography, yielding **42** (2.9 g, 92% overall yield) as an oil; ^{1}H NMR ($CDCl_3$) δ 1.25–1.90 (m, 16H), 1.92–2.08 (m, 4H), 3.49–3.70 (m, 18H), 3.85 (m, 4H), 4.05 (m, 2H), 4.44 (d, *J*=12.1 Hz, 2H), 4.64 (m, 4H), 7.31 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 19.4 (t), 19.5 (t), 25.4 (t), 26.0 (t), 26.0 (t), 30.5 (t), 62.1 (t), 62.2 (t), 66.5 (t), 66.6 (t), 68.0 (t), 70.5 (t), 70.7 (t), 70.7 (t), 70.9 (t), 70.9 (t), 71.4 (d), 71.5 (d), 71.5 (t), 78.4 (d), 78.5 (d), 98.8 (d), 98.9 (d), 127.5 (d), 127.9 (d), 128.2 (d), 138.6 (s); IR (film) (cm^{-1}) 3437, 2944, 2869, 1717, 1273, 1124, 1035; MS *m/z* (relative intensity): 265 $(M-C_5H_9O)^+$ (15), 159 (11), 105 (36), 91 (100); Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.11; H, 8.97.

4.1.21. Preparation of (2*R*,3*R*)-2-{[2-(tetrahydro-2*H*-pyran-2-yloxy)ethoxy]methyl}-tetrahydro-2*H*-pyran-3-ol (43). A mixture of the benzyl ether **42** (1 g, 2.9 mmol) and $Pd(OH)_2$ (20 mg) in EtOAc (28 mL) was placed under H_2 atmosphere. The reaction mixture was vigorously stirred until TLC showed complete conversion. The mixture was filtered through a pad of Celite. The solvent was removed under reduced pressure and the residue was purified by silica gel flash-chromatography affording **43** (735 mg, 99% overall yield) as an oil; ^{1}H NMR ($CDCl_3$) δ 1.31 (m, 2H), 1.36–1.82 (m, 14H), 1.85–2.07 (m, 4H), 2.97 (d, *J*=5.1 Hz, 1H), 3.09 (d, *J*=5.1 Hz, 1H), 3.42–3.50 (m, 6H), 3.52–3.72 (m, 10H), 3.85 (m, 6H), 4.02 (m, 2H), 4.59 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 19.4 (t), 20.0 (t), 20.1 (t), 25.3 (t), 30.2 (t), 30.5 (t), 62.2 (t), 62.3 (t), 65.9 (d), 66.1 (d), 66.3 (d), 66.4 (t), 68.6 (t), 68.7 (t), 70.8 (t), 70.9 (t), 72.4 (t), 72.6 (t), 77.9 (d), 78.0 (d), 98.9 (d), 99.0 (d); IR (film) (cm^{-1}) 3464, 2942, 2869, 1441, 1126, 1035; Anal. Calcd for $C_{13}H_{24}O_5$: C, 59.98; H, 9.29. Found: C, 59.89; H, 9.22.

4.1.22. Preparation of 2-{[(2*R*,3*R*)-3-(benzyloxy)-tetrahydro-2*H*-pyran-2-yl]methoxy}ethyl 4-methylbenzenesulfonate (44). To a stirred solution of the tetrahydropyranyl ether **42** (1.2 g, 3.43 mmol) in dry MeOH (34 mL) were added a few drops of HCl (concentrated) at rt. The reaction mixture was stirred for 1 h, after which time TLC showed complete conversion. Then Et_3N was added until pH≈7, and the mixture was stirred for 5 min and evaporated under reduced pressure and subjected to silica gel flash chromatography yielding the alcohol (903 mg, 99% yield) as an oil: $[\alpha]_D^{25}$ −19.8 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.35–1.52 (m, 2H), 1.91–2.15 (m, 2H), 2.37 (s, 1H), 3.44–3.70 (m, 9H), 4.03 (m, 1H), 4.38 (d, *J*=12.1 Hz, 1H), 4.65 (d, *J*=12.1 Hz, 1H), 7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.7 (t), 25.8 (t), 61.6 (t), 68.0 (t), 70.7 (t), 71.3 (d), 71.7 (t), 72.6 (t), 78.5 (d), 127.6 (d), 127.9 (d), 128.3 (d), 138.4 (s); IR (film) (cm^{-1}) 3408, 2949, 2858, 1716, 1451, 1274, 1091; MS *m/z* (relative intensity): 267 $(M+H)^+$(0.9), 205 (22), 105 (30), 91 (100).

A solution of alcohol (900 mg, 3.4 mmol) and *p*-toluenesulfonyl chloride (1.61 g, 8.5 mmol) in THF (6.8 mL) was cooled with an ice-water bath, and a solution of KOH (570 mg, 10.1 mmol) in water (0.6 mL) was added slowly over 1 h. The ice-water bath was removed, and the system was stirred for an additional 7 h. The resulting suspension was poured into a mixture of CH_2Cl_2 and ice-water, and the aqueous layer was extracted with CH_2Cl_2. The combined organic solutions were washed three times with distilled water, dried over $MgSO_4$, and filtered and the solvent was evaporated, after which the residue was purified by silica gel flash-chromatography, yielding **44** (1.28 g, 90% yield) as an oil: $[\alpha]_D^{25}$ −12.8 (*c* 1.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.33–1.52 (m, 2H), 1.89–2.18 (m, 2H), 2.41 (s, 1H), 3.41–3.65 (m, 7H), 3.96 (m, 1H), 4.08–4.16 (m, 2H), 4.36 (d, *J*=12.1 Hz, 1H), 4.61 (d, *J*=12.1 Hz, 1H), 7.30 (m, 5H), 7.76 (d, *J*=8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 20.6 (t), 21.6 (q), 25.9 (t), 68.0 (t), 68.8 (t), 69.0 (t), 69.1 (t), 70.8 (t), 71.2 (d), 71.6 (t), 78.3 (d), 127.6 (d), 127.9 (d), 127.9 (d), 128.3 (d), 129.8 (d), 133.1 (s), 138.4 (s), 144.7 (s); IR (film) (cm^{-1}) 2949, 2860, 1716, 1356, 1176, 922; Anal. Calcd for $C_{22}H_{28}O_6S$: C, 62.84; H, 6.71; S, 7.63. Found: C, 62.86; H, 7.19; S, 6.90.

4.1.23. Preparation of 2-{[(2*R*,3*R*)-3-(2-{[(2*R*,3*R*)-3-(benzyloxy)-tetrahydro-2*H*-pyran-2-yl]methoxy}-ethoxy)-tetrahydro-2*H*-pyran-2-yl]methoxy}ethanol

(45). To a solution of alcohol **43** (416 mg, 1.6 mmol) and tosylate **44** (672 mg, 1.6 mmol) in dry THF (16 mL) under nitrogen was added NaH (77 mg, 1.92 mmol, 60% oil dispersion) at 0 °C. The reaction mixture was stirred at reflux for 16 h before dilution with Et_2O. The mixture was washed with aqueous saturated NH_4Cl solution and then dried, filtered, concentrated and purified by chromatography on silica gel to yield the benzyl ether as an oil. Removal of the THP-ether group using the acid conditions described above afforded alcohol **45** (616 mg, 91% overall yield) as an oil: $[\alpha]_D^{25}-28.5$ (*c* 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.24–1.52 (m, 4H), 1.84–2.13 (m, 4H), 3.43–3.70 (m, 18H), 3.99 (m, 2H), 4.39 (d, $J=12.0$ Hz, 1H), 4.63 (d, $J=12.0$ Hz, 1H), 7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.5 (t), 20.6 (t), 25.9 (t), 26.0 (t), 61.5 (t), 67.9 (t), 68.1 (t), 70.7 (t), 70.8 (t), 71.1 (t), 71.5 (d), 71.6 (t), 72.6 (t), 72.7 (d), 78.3 (d), 78.5 (d), 127.5 (d), 127.8 (d), 128.2 (d), 138.4 (s); IR (film) (cm^{-1}) 3439, 2945, 2860, 1716, 1452, 1274, 1093; MS *m/z* (relative intensity): 423 $(M-H)^+$ (0.4), 159 (8), 105 (71), 91 (100). HRMS calcd for $C_{23}H_{35}O_7$ $(M-H)^+$: 423.2383, found: 423.2364.

4.1.24. Preparation of 2-{[(2*R*,3*R*)-3-(2-{[(3*S*,2*R*)-3-(phenylmethoxy)(tetrahydro-2*H*-pyran-2-yl)]methoxy}-ethoxy)-tetrahydro-2*H*-pyran-2-yl]methoxy}ethyl 4-methylbenzenesulfonate (46). The same procedure used above to obtain compound **44** was applied to **45** on a 560 mg (1.3 mmol) scale, yielding tosylate **46** (662 mg, 87% yield) as an oil: $[\alpha]_D^{25}-23.7$ (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.26–1.48 (m, 4H), 1.79–2.09 (m, 4H), 2.42 (s, 3H), 3.33–3.69 (m, 16H), 3.91–4.02 (m, 2H), 4.12 (m, 2H), 4.40 (d, $J=12.1$ Hz, 1H), 4.64 (d, $J=12.1$ Hz, 1H), 7.29 (m, 7H), 7.77 (d, $J=8.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 20.6 (t), 20.7 (t), 21.6 (q), 26.0 (t), 26.1 (t), 67.9 (t), 68.0 (t), 68.3 (t), 68.8 (t), 69.2 (t), 70.8 (t), 71.6 (d), 71.7 (t), 72.8 (d), 78.3 (d), 78.6 (d), 127.5 (d), 127.8 (d), 127.9 (d), 128.2 (d), 129.8 (d), 133.1 (s), 138.6 (s), 144.7 (s); IR (film) (cm^{-1}) 2946, 2863, 1716, 1356, 1176, 922; Anal. Calcd for $C_{30}H_{42}O_9S$: C, 62.26; H, 7.32; S, 5.54. Found: C, 61.93; H, 7.74; S, 5.67.

4.1.25. Preparation of 2-[((2*R*,3*R*)-3-{2-[((2*R*,3*R*)-3-hydroxy(tetrahydro-2*H*-pyran-2-yl))methoxy]ethoxy}-tetrahydro-2*H*-pyran-2-yl)methoxy]ethyl 4-methylbenzenesulfonate (47). The same procedure used above to obtain compound **43** was applied to **46** on a 600 mg (1.04 mmol) scale, yielding alcohol **47** (502 mg, 99% yield) as an oil: $[\alpha]_D^{25}-16.9$ (*c* 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.22–1.48 (m, 3H), 1.61 (m, 1H), 1.79–2.09 (m, 4H), 2.43 (s, 3H), 2.98 (br s, 1H), 3.37 (s, 1H), 3.43–3.70 (m, 14H), 3.85 (s, 1H), 3.96 (m, 2H), 4.13 (m, 2H), 7.32 (d, $J=8.3$ Hz, 2H), 7.77 (d, $J=8.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 20.0 (t), 20.5 (t), 21.5 (q), 26.0 (t), 30.2 (t), 66.1 (d), 67.9 (t), 68.3 (t), 68.6 (t), 68.8 (t), 69.1 (t), 71.1 (t), 71.4 (t), 72.7 (d), 72.8 (t), 78.0 (d), 78.1 (d), 127.9 (d), 129.7 (d), 133.0 (s), 144.7 (s); IR (film) (cm^{-1}) 3461, 2927, 2858, 1448, 1356, 1176, 1094; MS *m/z* (relative intensity): 470 $(M-H_2O)^+$ (6), 199 (27), 159 (28), 115 (24), 97 (100); Anal. Calcd for $C_{23}H_{36}O_9S$: C, 56.54; H, 7.43; S, 6.56. Found: C, 56.34; H, 7.94; S, 6.42.

4.1.26. Preparation of the crown ether 6. To a solution of alcohol **47** (60 mg, 0.12 mmol) in dry THF (12 mL) under nitrogen was added NaH (6.4 mg, 0.16 mmol, 60% oil dispersion) at 0 °C. The reaction mixture was stirred at rt until TLC showed complete conversion (6 h). The mixture was concentrated and purified by flash chromatography over silica gel using 0.5:0.95 $MeOH/CH_2Cl_2$ to yield the crown ether **6** (32 mg, 82% yield) as a white solid: mp 134–136 °C: $[\alpha]_D^{25}-69.9$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.32 (d, $J=14.4$ Hz, 2H), 1.41 (ddd, $J=1.9$, 13.9, 13.9 Hz, 2H), 1.92 (m, 2H), 2.10 (d, $J=13.7$ Hz, 2H), 3.31 (dd, $J=4.3$, 8.0 Hz, 2H), 3.46 (m, 4H), 3.58 (m, 6H), 3.78 (m, 6H), 3.96 (dd, $J=4.3$, 11.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 20.5 (t), 25.4 (t), 67.4 (t), 68.3 (t), 69.8 (t), 71.1 (d), 73.4 (t), 78.0 (d); IR (film) (cm^{-1}) 2928, 2854, 1447, 1138, 1097; MS (FAB) *m/z* (relative intensity): 355 $(M+K)^+$ (5), 339 $(M+Na)^+$ (95), 317 $(M+H)^+$ (15), 307 (30), 154 (100), 136 (65). HRMS (FAB) calcd for $C_{16}H_{28}O_6Na$ $(M+Na)^+$: 339.1784, found: 339.1798.

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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.2005.06.034. X-ray data for compounds **1**, **4**, **6**, **34** and **35**. Experimental details for the preparation of compounds **20**, **21**, *trans*-**18**, *trans*-**19**, *trans*-**30**, *trans*-**31**, **4**, **35**, **36**, **37**, **38**, **39**, **5**, **40**. ^1H and ^{13}C NMR spectra for compounds **1**, **2**, **3**, $\mathbf{3}\cdot\mathbf{K}^+$, **4**, **5**, **6**, **7**, **20**, **21**, **25**, **34**, **35**. FAB spectra for compounds **1**, **2**, **3**, $\mathbf{3}\cdot\mathbf{K}^+$, **4**, **5**, **6**, **34** and **35**; COSY, HSQC, NOEs spectra for compounds **1**, **3** and $\mathbf{3}\cdot\mathbf{K}^+$.

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Synthesis, characterization and photochromic studies in film of heterocycle-containing spirooxazines

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Abstract—A series of novel heterocycle-containing spirooxazines have been designed and synthesized, and their photochromic properties were investigated under flash photolysis and continuous irradiation in particular regard to the fatigue resistance, the lifetime of the colored merocyanine form in various solutions and polymers. Especially, the characteristics of two UV-sensitive spirooxazines dispersed polymethylmethacrylate thin-films were extensively studied. Detailed studies showed that general significant shifts in the λ_{max} of the absorption spectra of the open forms, interesting fatigue resistances and emission fluorescene properties were observed.

1. Introduction

Photochromic compounds are of interest due to their applications in science and technology.[1,2] In addition to their potential applications utilizing their different absorption properties, the changes in electron delocalization have also been employed for the design of photoswitchable nonlinear optical devices, luminescent devices,[3] host–guest systems[4–7] and enzymatic systems.[8–11] Spirooxazines are one of the most popular classes of photochromic materials, and have shown to possess high fatigue resistance and excellent photostability.[12] The photochromism of spirooxazines is attributable to the photochemical cleavage of the spiro-C–O bond, which results in the extension of π-conjugation in the colored photomerocyanine conformer and thus shifts the absorption to the visible region.[13,14] Although the requirements for each application may differ, the common one is the durability. In our previous report,[15,16] we have found that the introduction of an electron-rich heteroaromatic group into the indoline nitrogen and phosphorylation of 9′-OH of spirooxazine as a pendant increased their fatigue resistance.

As a further approach to improve the fatigue resistance of photochromic spiro compounds, we reported here the synthesis of a series of novel spirooxazines **1–10** with nitrogen-containing heterocyclic substituents at 6′-position and the study on their photochromic behaviors in various media including organic solvents and polymethyl methacrylate (PMMA). These compounds were found to be stable for long term usage without decaying the color. In addition, the fluorescene properties of the titled compounds were also studied in solid and solutions.

2. Results and discussion

2.1. Synthesis

As shown in Scheme 1, spirooxazine-containing nitrogen heterocycles **1–10** were synthesized by a thermal condensation reaction of the corresponding alkylidene heterocycle or its conjugate acid with *ortho*-hydroxynitroso aromatic derivatives. They formed readily in most polar organic solvents under heating and could be purified by recrystallization or column chromatography. In addition, 2-methylidene-indoline derivates were not stable in the air at room temperature, so they must be purified by vacuum distillation before use. The syntheses of spirooxazine derivatives were carried out under nitrogen atmosphere. Spirooxazine-containing nitrogen heterocycles **1–10** were obtained in low to moderate yields.

2.2. Photochromic properties in solutions

The photochromic behavior of the synthesized compounds was observed in solutions and polymers. Ultraviolet irradiation of the series of compounds **1–10** at λ_{ex} 365 nm led to an increase in absorption intensity in the visible region of the band at 523–677 nm, corresponding to the

Keywords: Photochromism; Spirooxazines; Nitrogen heterocycles; Fatigue resistance; Fluorescene.
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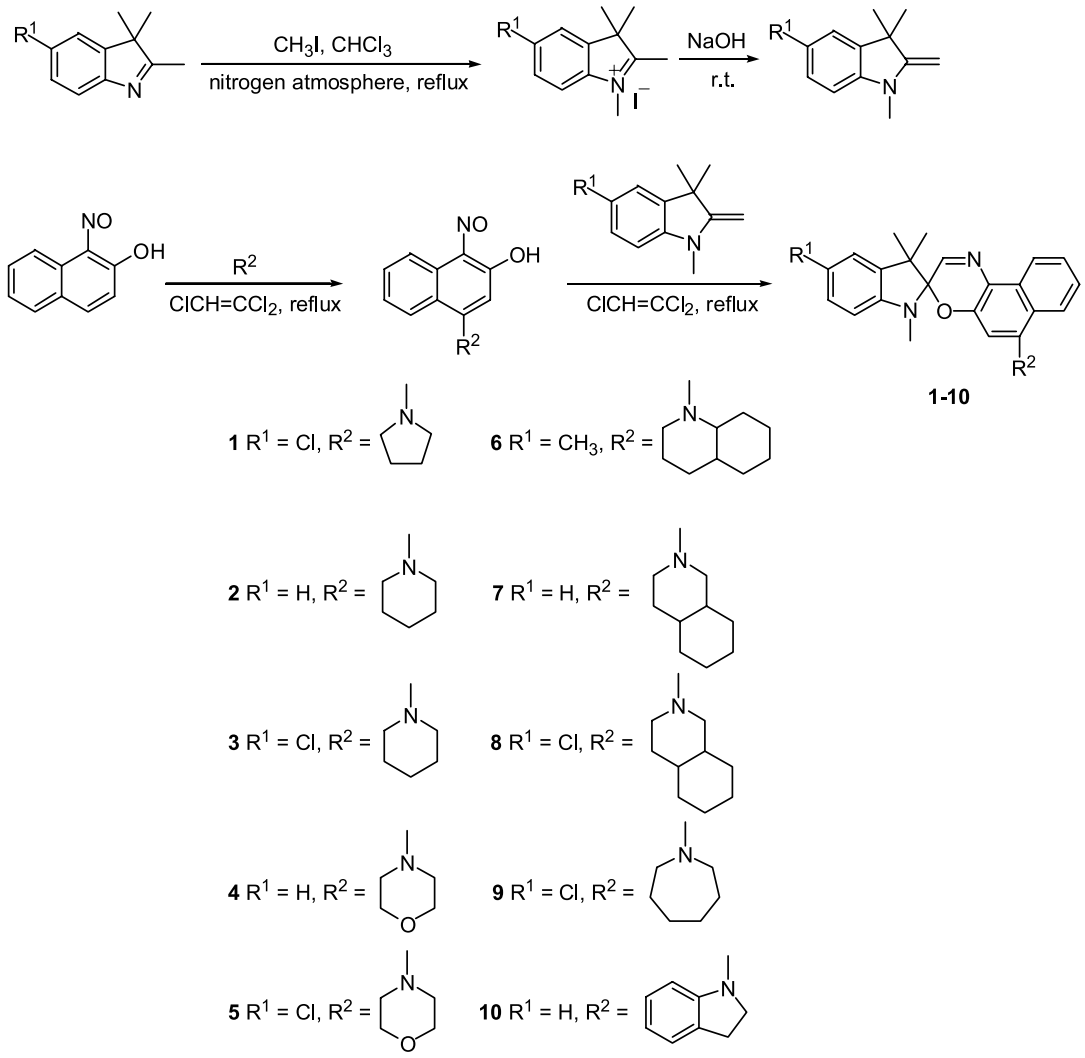

Scheme 1.

generation of the photomerocyanine form (Table 1). The open form generated was thermally unstable and readily underwent thermal bleaching, which followed the first order kinetics, to the closed form. Photochromic properties of compounds **1**–**10**, after excitation at 365 nm, were investigated in different solutions. It was shown that the new compounds had good photochromic properties in methanol, acetone, trichloromethane, dichloromethane and cyclohexane. Moreover, on gradual increase in polarity of the solvent, the maximum absorbance of **1**–**10** underwent a bathochromic shift. In the strong polar solvents, it was even more beneficial to the ring-opened form. The longer conjugate system in the ring-opened form resulted in the bathochromic effects. Figure 1 showed the UV–vis

Table 1. The maximum absorption wavelength of **1**–**10** after irradiation at 365 nm with a 12 W ultraviolet lamp in various solvents

Compound	The maximum absorption wavelength λ_{max} (nm)		
	Trichloromethane	Dichloromethane	Cyclohexane
1	632	545	534
2	640.5	568	545.5
3	646	581.5	545.5
4	632	547.5	532.5
5	642	559.5	523
6	630	620.5	554.5
7	638	631	565
8	648	642	575.5
9	641	637.5	565.5
10	677	581.5	560.5

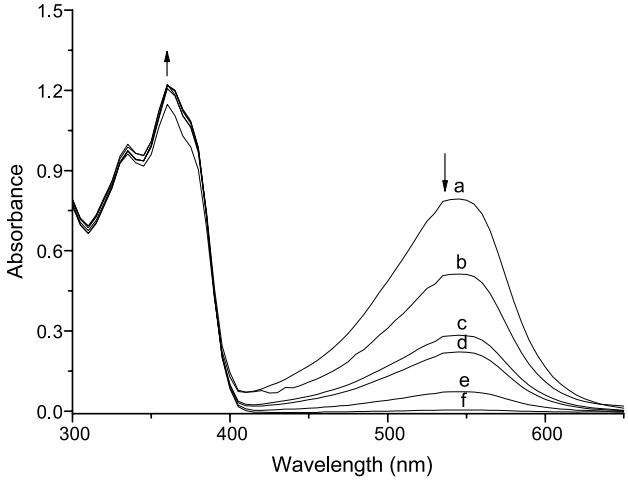

Figure 1. UV–vis absorption spectra of uncolored (f) and colored species (a→e) of **2** in cyclohexane solutions during the decoloration process at room temperature with a 12 W ultraviolet lamp.

decoloring absorption spectra of **2** in cyclohexane solution. Upon excitation at 365 nm, compound **2** exhibited photochromism, with a growth in intensity of the band at 546 nm, corresponding to the generation of the open form. The open form generated was thermally unstable and readily underwent thermal bleaching, which followed the first order kinetics, to the closed form.

2.3. Photochromic properties in polymers

2.3.1. The absorption spectra of compound 2 with different concentrations and irradiation times in PMMA films. After irradiation at 365 nm, the absorption spectra of compound **2** in PMMA films exhibited a new absorption band with a maximum absorption at 573 nm, which demonstrated that **2** had excellent photochromic properties. As shown in Figure 2, on gradual increase in the concentration of photochromic compound, the intensity of absorption band at 573 nm increased gradually. The concentrations of **2** in PMMA film were different, so their chroma was also different after irradiation. And it was possible that the absorbance changes were different from 1.0 to 1.5 to 2.0% loadings of **2** in PMMA film compared with 0.5–1.0 or 3.0–4.0%. In addition, the UV–vis absorption spectra of 0.5% **2** in PMMA films, registered after 0, 0.5, 1.0, 1.5, 2.0, 2.5 min of irradiation, were depicted in Figure 3. Upon excitation at 365 nm, the intensity of absorption band at 360 nm decreased gradually, and a new absorption band appeared with a maximum absorption at 574 nm, which further demonstrated that **2** possessed excellent photochromic properties. The color change of **2** in PMMA films could be attributed to the appearance of the new band in the visible region of the absorption spectrum. It was shown that the absorbance was dependent on the concentration of **2** in PMMA films and the irradiation time.

2.3.2. The decoloration process of the colored merocyanine form of spirooxazines 2 and 10 in PMMA films. Films of **2** and **10** (5 wt% loading) in PMMA were prepared. The absorbance of each film at its λ_{max} was recorded immediately after 30 s irradiation at 365 nm with a 12 W ultraviolet lamp. The thermal reversion processes of **2** or **10** in PMMA films were studied by plotting absorbances at the same λ_{max} for a given compound in different time. Typical examples of the plot made for compounds **2** and **10** were illustrated in Figure 4. The decoloration process of spirooxazines in PMMA films was similar to the decoloration in solutions. After irradiation at 365 nm, the absorption spectra of **10** in PMMA films exhibited a new absorption band appeared with a maximum absorption at 592 nm (insert in Fig. 4), which demonstrated that they exhibited excellent photochromic properties. Moreover, the intensity of absorption band at its λ_{max} decreased gradually during the decoloration process.

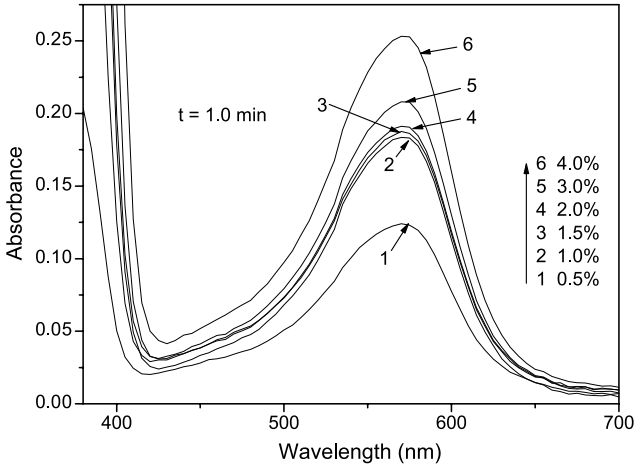

Figure 2. UV–vis absorption spectra of **2** in PMMA films; successive spectra taken after (1) 0.5%; (2) 1.0%; (3) 1.5%; (4) 2.0%; (5) 3.0%; (6) 4.0% (wt% loading) of **2** in PMMA films; spectra taken after 1.0 min of irradiation at 365 nm with a 12 W ultraviolet lamp.

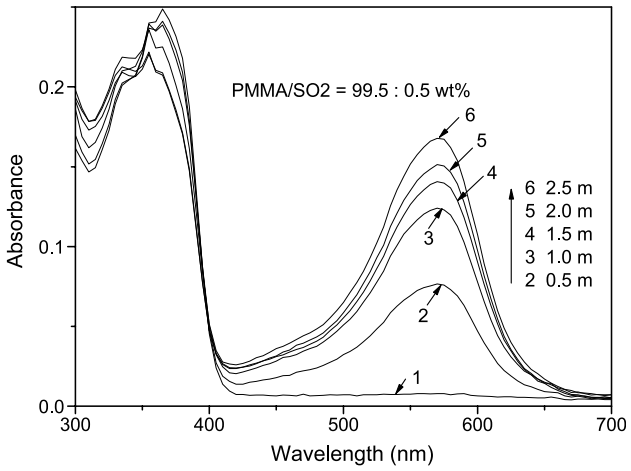

Figure 3. UV–vis absorption spectra of 0.5% (wt% loading) **2** in PMMA films; successive spectra taken after (1) 0 min; (2) 0.5 min; (3) 1.0 min; (4) 1.5 min; (5) 2.0 min; (6) 2.5 min of irradiation at 365 nm with a 12 W ultraviolet lamp.

2.3.3. The parameter $t_{A_0/2}$ for the fatigue resistance of 1–10 in the colored merocyanine form in PMMA. Fifteen slices of thin-films of **2** and **10** (5 wt% loading) in PMMA were prepared. All films were irradiated at the same time with a 400 W high-pressure mercury lamp. The absorbances at λ_{max} of a given compound in different irradiation time

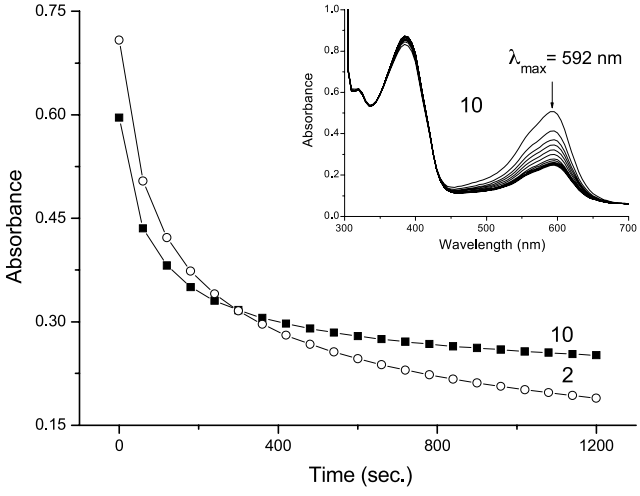

Figure 4. The absorbance change at the λ_{max} of **2** plotted with ○ and **10** plotted with ■ in PMMA films during the decoloration process at room temperature after excitation at 365 nm. The insert showed the overlaid UV–vis absorption spectra of **10** at different decay times at the absorption maximum at 592 nm.

were recorded on a spectrophotometer immediately after irradiation. A plot of the absorbance against the irradiation time was made as shown in Figure 5. The parameter $t_{A_0/2}$ obtained from the plot was defined as the time in minute required decreasing the initial absorbance (A_0) at the λ_{max} of the merocyanine form to the half value ($A_0/2$). The $t_{A_0/2}$ of **2** was calculated to be 170 min; the $t_{A_0/2}$ of **10** was 160 min.[16]

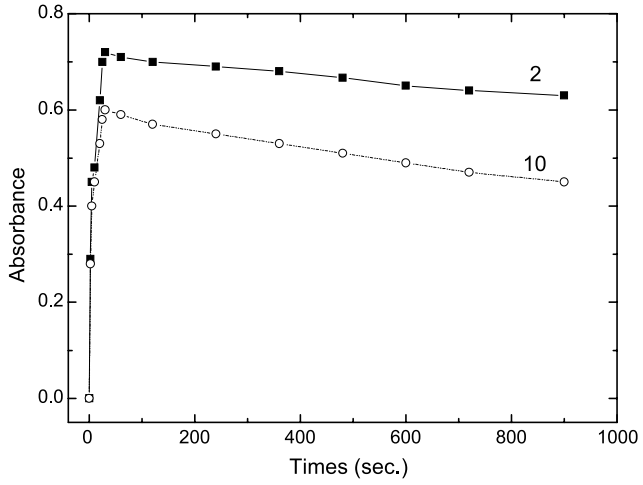

Figure 5. The absorbance change at the λ_{max} of **2** (λ_{max}=573 nm, 5 wt% loading) and **10** (λ_{max}=594 nm, 5 wt% loading) in PMMA under continuous UV irradiation.

2.3.4. Evaluation of the fatigue resistance of spirooxazines in PMMA. The fatigue resistance was examined after 200-cycle irradiation of UV and visible lights. The fatigue resistance of **2** was examined and shown in Figure 6. After 280-cycle irradiation, the absorbance was kept in 99.3%. As it was analogized, the absorbance of the 1000-cycle would be kept in 96.6% ($A=A_0(1-X)^n$, n: cycle times; A_0: the initial absorption intensity; X: the variational absorption intensity). It was shown that spirooxazines containing nitrogen heterocycles exhibited excellent stability. The useful lifetime of the photochromic films is of utmost importance to its commercial success.

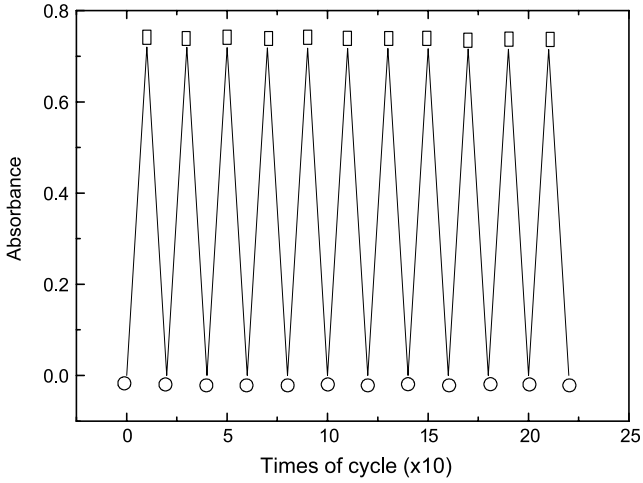

Figure 6. Photoinduced absorption changes for **2** in PMMA film; photoirradiation started at each point of ○ for visible light and then finished at the point of □ for UV light.

2.4. Fluorescent emission properties

Excitation of **10** in $CHCl_3$ and CH_2Cl_2 solutions at λ_{ex}= 400 nm at room temperature produced strong fluorescene (Fig. 7), with the emission band at 497 nm in $CHCl_3$ and one at 514 nm in CH_2Cl_2, respectively. However, excitation of **2** resulted in weak fluorescene at λ_{ex}=404 nm, with one emission band at 500 nm only in $CHCl_3$ solution at room temperature (Fig. 8). The substituent group in compound **10** on 6′-position is dihydro-indoline; whereas it is piperidine in compound **2**. Thus compound **10** has bigger conjugate system than compound **2**, which strengthens the fluorescene intensity.

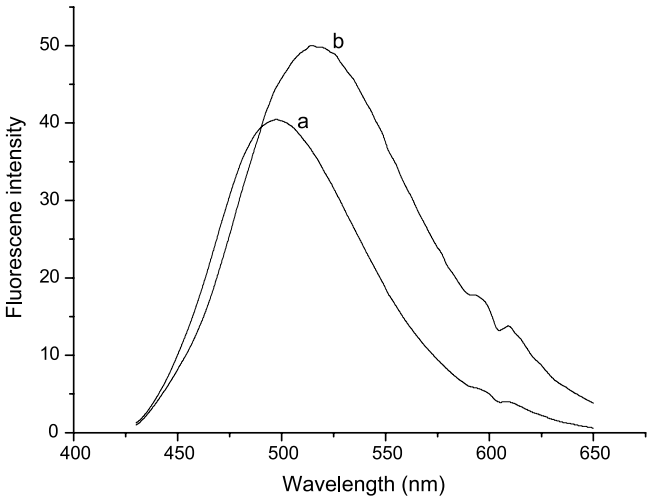

Figure 7. Fluorescene spectra of **10** (1.0×10^{-4} mol dm^{-3}) in chloroform: (a), λ_{ex}=400 nm and dichloromethane (b), λ_{ex}=400 nm.

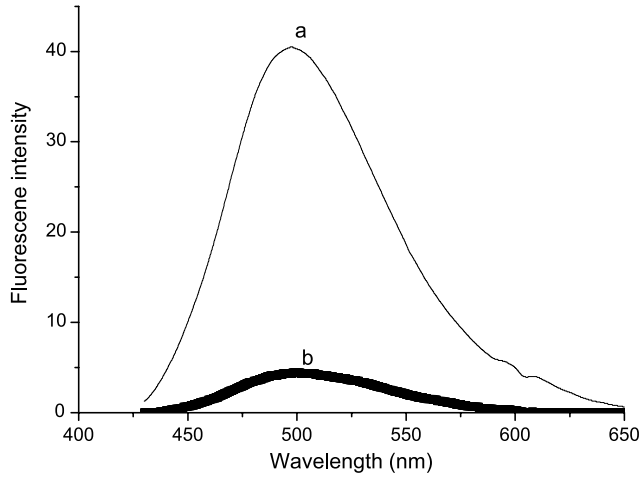

Figure 8. Fluorescene spectra of **10** (1.0×10^{-4} mol dm^{-3}): (a), λ_{ex}= 400 nm and **2** (b), λ_{ex}=404 nm in chloroform at room temperature.

In addition, excitation of **10** in solid state at both λ_{ex}=479 and 400.5 nm at room temperature produced strong fluorescene, with the emission band at 473 and 549 nm, respectively (Fig. 9). In Figure 9, the fluorescene spectra of **10** in solid state had two different peaks corresponding to different excitation wavelengths. When the emission wavelength was set at λ_{ex}=450–530 nm, the highest

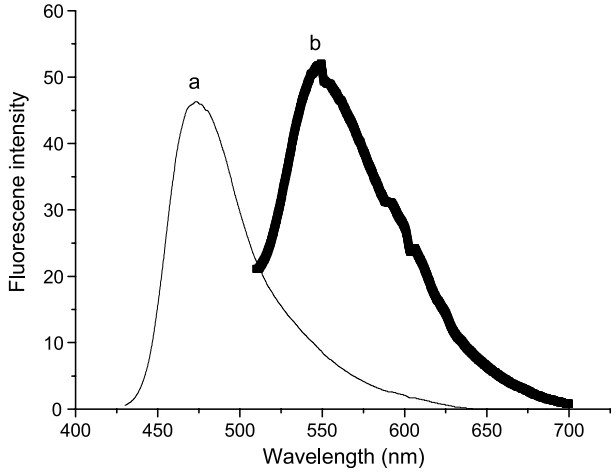

Figure 9. Fluorescene spectra of **10** in solid at room temperature (a), $\lambda_{ex}=$ 400.5 nm and (b), $\lambda_{ex}=479$ nm.

intensity excitation wavelength was $\lambda_{ex}=479$ nm, and the emission band at 549 nm showed strong fluorescene; when the emission wavelength was set at $\lambda_{ex}=330$–450 nm, another excitation wavelength was $\lambda_{ex}=400.5$ nm, and the emission band at 473 nm showed strong fluorescene, too.

Figures 7–9 showed that the fluorescene might arise from the locally excited (LE) state and the formation of merocyanine-type in equilibrium, respectively. Especially, the emission at 473–549 nm of **10** was probably due to the photochemical cleavage of the spiro-C–O bond, which resulted in the extension of π-conjugation in the colored photomerocyanine isomer.

3. Conclusion

A series of spirooxazines containing nitrogen heterocycles have been successfully synthesized and incorporated into PMMA. The formation of the C_{sp^3}–O bonds in the synthesis of title compounds was achieved by a simple and generally applicable method, affording the products in low to moderate yields. The novel photochromic spirooxazines containing nitrogen heterocycle exhibited a remarkable fatigue resistance and substantial bathochromic shifts in the absorption spectra of the open forms in both solutions and polymers. It was shown that the new compounds had good photochromic properties in different solutions. Moreover, on gradual increase in polarity of solvents, it caused a red shift in the maximum absorbance of **1**–**10**. Especially, spirooxazines containing nitrogen heterocycles showed high fatigue resistance and excellent photostability. In addition, the fluorescene properties were studied in solid state and different solutions. These evidences show that spirooxazines containing nitrogen heterocycles may find their potential applications.

4. Experimental

4.1. General remarks

All solvents and polymers were used as received. The spectrophotometric grade solvents were used in the spectrophotometric measurements. Spectral measurements were performed in the dark. UV–vis spectra were measured on a Shimadzu UV-2101PC spectrophotometer. Fluorescene spectra were recorded on a WGY-10 fluorescene spectrophotometer in solid and solutions. IR spectra were recorded on a Bio-Rad FTS 135 spectrophotometer using KBr disks and wavenumbers were given in cm^{-1}. ^1H NMR spectra were recorded on a Bruker AC-P200 instrument at 200 MHz in $CDCl_3$. Mass spectra were measured on a 7070E-HE spectrometer. Melting points were uncorrected. Elemental analysis was performed on a YANACO CHN CORDER MT-3 apparatus.

4.2. Spectral measurements

4.2.1. Preparation of thin polymer films. To 60 mL of toluene, 10 g of the polymer was added and stirred until completely dissolved into transparent liquid by heating. Then a specified amount (wt% of loading) of spirooxazine was added to the polymer solution and stirred well to mix. This solution was poured into a Petri dish and kept in a dark room. After the complete evaporation of the solvent, the dish was baked in an oven at 60 °C for 20 min. The film was then peeled off from the dish. The resulting films were kept in a dark room.

4.2.2. UV–vis spectrophotometric measurements. The solutions of **1**–**10** in chloroform and dichloromethane with the concentration of 1×10^{-4} mol dm^{-3} were prepared. The UV–vis absorption spectra were measured at room temperature in different solutions and PMMA using a Shimadzu UV-2101PC spectrophotometer. The samples were irradiated with a 400 W high-pressure mercury lamp and a 12 W ultraviolet lamp at 365 nm. The fatigue resistance was examined after 200-cycle irradiation of UV and visible lights.

4.2.3. Fluorescene measurements. The solutions of **10** and **2** in chloroform and dichloromethane with the concentration of 1×10^{-4} mol dm^{-3} were prepared. Upon excitation at 400 or 404 nm in solutions and at 400.5 and 479 nm in solid state, the fluorescene were examined.

4.3. General method for synthesis of spirooxazines containing nitrogen heterocycle (entries 1–10)

1-Nitroso-2-naphthol (1.73 g, 0.01 mol) and heterocycle containing nitrogen (0.02 mol) were added to trichloroethylene (50 mL). The resulting mixture was stirred for 30 min at reflux. 2-Methylidene-indoline derivate (1.73 g, 0.01 mol) in trichloroethylene (10 mL) was then added to the solution at reflux within 30 min. The resulting solution was then stirred under nitrogen atmosphere for 3 h at reflux. After removal of the solvent, the residue was purified by recrystallization or column chromatography on silica gel with petroleum ether/ethyl ether (2:1 v/v) as the eluent. Spirooxazines containing nitrogen heterocycle **1**–**10** were obtained in low to modest yields.

4.3.1. 5-Chloro-1,3,3-trimethyl-6′-tetrahydro-azole-spiro[2,3′-[3*H*]-naphtho[2,1-*b*][1,4]oxazine], 1. Yellow solid. Yield 9%. Mp 213–215 °C. IR: 3057, 1670, 1589,

1556, 1509, 1457, 1322, 1260, 1240, 1164, 1040, 963, 747, 673, 610. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.61–6.75 (9H, m, ArH, H-2′), 3.03–3.00 (4H, m, CH_2), 2.77–2.72 (4H, m, CH_2), 1.64–1.55 (9H, m, CH_3). MS (ESI) *m/z*: 431.4 (M^+). $C_{26}H_{26}ON_3Cl$ (431.95). Anal. Calcd for $C_{26}H_{26}ON_3Cl$: C, 72.29; H, 6.07. Found: C, 72.35; H, 6.13%.

4.3.2. 1,3,3-Trimethyl-6′-piperidine-spiro[2,3′-[3*H*]-naphtho[2,1-*b*][1,4]oxazine], 2. White solid. Yield 37%. Mp 226–228 °C. IR: 3069, 1660, 1586, 1486, 1450, 1362, 1305, 1276, 1241, 1165, 1030, 967. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.54–6.56 (10H, m, ArH, H-2′), 3.01–3.00 (4H, m, CH_2), 2.75 (3H, s, CH_3), 1.83–1.80 (4H, m, CH_2), 1.83–1.56 (2H, m, CH_2), 1.35 (6H, s, CH_3). MS (ESI) *m/z*: 411.0 (M^+). $C_{27}H_{29}ON_3$ (411.53). Anal. Calcd for $C_{27}H_{29}ON_3$: C, 78.80; H, 7.10. Found: C, 78.83; H, 7.13%.

4.3.3. 5-Chloro-1,3,3-trimethyl-6′-piperidine-spiro[2,3′-[3*H*]-naphtha[2,1-*b*][1,4]oxazine], 3. Colorless prism. Yield 34%. Mp 230–231 °C. IR: 3030, 1660, 1586, 1566, 1484, 1352, 1241, 1167, 1040, 950, 764, 705, 657. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.52–6.43 (9H, m, ArH, H-2′), 3.00–2.98 (2H, m, CH_2), 2.70 (3H, s, CH_3), 1.81–1.76 (4H, m, CH_2), 1.63–1.56 (4H, m, CH_3), 1.32 (6H, s, CH_3). MS (ESI) *m/z*: 445.4 (M^+). $C_{27}H_{28}ON_3Cl$ (445.97). Anal. Calcd for $C_{27}H_{28}ON_3Cl$: C, 72.71; H, 6.33. Found: C, 72.75; H, 6.35%.

4.3.4. 1,3,3-Trimethyl-6′-morpholine-spiro[2,3′-[3*H*]-naphtho[2,1-*b*][1,4]oxazine], 4. Colorless prism. Yield 40%. Mp 181–183 °C. IR: 3069, 1650, 1588, 1570, 1507, 1486, 1453, 1364, 1300, 1285, 1270, 1240, 1162, 967. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.57–6.54 (10H, m, ArH, H-2′), 3.95–3.91 (4H, m, CH_2), 3.06–3.02 (4H, m, CH_2), 2.74 (3H, s, CH_3), 1.34 (6H, s, CH_3). MS (ESI) *m/z*: 414.2 ($M^+ + 1$). $C_{26}H_{27}O_2N_3$ (413.51). Anal. Calcd for $C_{26}H_{27}O_2N_3$: C, 75.52; H, 6.58. Found: C, 75.57; H, 6.63%.

4.3.5. 5-Chloro-1,3,3-trimethyl-6′-morpholine-spiro[2,3′-[3*H*]-naphtho[2,1-*b*][1,4]oxazine], 5. Colorless plate. Yield 16%. Mp 204–206 °C. IR: 3072, 1670, 1588, 1569, 1508, 1484, 1417, 1300, 1240, 1162, 1031, 950, 764, 706, 653, 635, 615. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.55–6.43 (9H, m, ArH, H-2′), 3.95–3.91 (4H, m, CH_2), 3.08–3.03 (4H, m, CH_2), 2.71 (3H, s, CH_3), 1.33 (6H, s, CH_3). MS (ESI) *m/z*: 448.1 (M^+). $C_{26}H_{26}O_2N_3Cl$ (447.95). Anal. Calcd for $C_{26}H_{26}O_2N_3Cl$: C, 69.71; H, 5.85. Found: C, 69.75; H, 5.89%.

4.3.6. 1,3,3,5-Tetramethyl-6′-decahydro-quinoline-spiro[2,3′-[3*H*]-naphtho[2,1-*b*][1,4]oxazine], 6. White solid. Yield 21%. Mp 184–185 °C. IR: 3354, 3150, 2930, 2853, 2807, 1670, 1586, 1508, 1485, 1455, 1302, 1272, 1244, 1163, 1036, 969. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.48–6.48 (9H, m, ArH, H-2′), 2.94 (3H, s, CH_3), 2.72 (3H, s, CH_3), 1.74–1.57 (12H, m, CH_2), 1.30 (6H, s, CH_3), 1.18–1.16 (3H, m, CH_2, CH), 0.86–0.81 (1H, m, CH). MS (ESI) *m/z*: 480.5 ($M^+ + 1$). $C_{32}H_{37}ON_3$ (479.65). Anal. Calcd for $C_{32}H_{37}ON_3$: C, 80.13; H, 7.77. Found: C, 80.16; H, 7.82%.

4.3.7. 1,3,3-Trimethyl-6′-decahydro-isoquinoline-spiro-[2,3′-[3*H*]-naphtho[2,1-*b*][1,4]oxazine], 7. Colorless plate. Yield 20%. Mp 202–204 °C. IR: 3300, 3051, 1660, 1587, 1508, 1485, 1455, 1302, 1272, 1244, 1163, 1035, 970. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.53–6.53 (10H, m, ArH, H-2′), 3.95–3.93 (2H, m, CH_2), 3.75–3.65 (1H, m, CH), 2.73 (3H, s, CH_3), 2.15–1.57 (12H, m, CH_2), 1.34 (6H, s, CH_3), 1.24–1.20 (1H, m, CH). MS (ESI) *m/z*: 466.33 ($M^+ + 1$). $C_{31}H_{35}ON_3$ (465.62). Anal. Calcd for $C_{31}H_{35}ON_3$: C, 79.96; H, 7.58. Found: C, 79.99; H, 7.61%.

4.3.8. 5-Chloro-1,3,3-trimethyl-6′-decahydro-isoquinoline-spiro[2,3′-[3*H*]-naphtho[2,1-*b*][1,4]oxazine], 8. White solid. Yield 10%. Mp 192–193 °C. IR: 3310, 3030, 1670, 1587, 1571, 1508, 1381, 1358, 1292, 1241, 1164, 1036, 970, 766, 717, 691, 652. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.52–6.42 (9H, m, ArH, H-2′), 3.18–3.12 (2H, m, CH_2), 2.83–2.76 (2H, m, CH), 2.70 (3H, CH_3), 2.15–1.55 (12H, m, CH_2), 1.32 (6H, s, CH_3). MS (ESI) *m/z*: 500.3 (M^+). $C_{31}H_{34}ON_3Cl$ (500.06). Anal. Calcd for $C_{31}H_{34}ON_3Cl$: C, 74.46; H, 6.85. Found: C, 74.50; H, 6.88%.

4.3.9. 5-Chloro-1,3,3-trimethyl-6′-hexmethylene-tertamino-spiro[2,3′-[3*H*]-naphtho[2,1-*b*][1,4]oxazine], 9. White solid. Yield 19%. Mp 226–228 °C. IR: 3030, 1670, 1587, 1571, 1508, 1386, 1281, 1163, 1033, 968, 766, 703, 682, 655, 630. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.52–6.42 (9H, m, ArH, H-2′), 3.25–3.20 (4H, m, CH_2), 2.70 (3H, s, CH_3), 1.85–1.72 (8H, m, CH_2), 1.32 (6H, s, CH_3). MS (ESI) *m/z*: 460.2 (M^+). $C_{28}H_{30}ON_3Cl$ (460). Anal. Calcd for $C_{28}H_{30}ON_3Cl$: C, 73.11; H, 6.57. Found: C, 73.19; H, 6.65%.

4.3.10. 1,3,3-Trimethyl-6′-dihydro-indolinyl-spiro[2,3′-[3*H*]-naphtho[2,1-*b*][1,4]oxazine], 10. Yellow solid. Yield 29%. Mp 232–234 °C. IR: 3747, 3030, 1670, 1588, 1483, 1363, 1301, 1258, 1164, 1021, 959, 746, 703, 655. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.62–6.27 (14H, m, ArH, H-2′), 3.96–3.91 (2H, m, CH_2), 3.18–3.16 (2H, m, CH_2), 2.77 (3H, s, CH_3), 1.36 (6H, s, CH_3). MS (ESI) *m/z*: 445.2 (M^+). $C_{30}H_{27}ON_3$ (445.55). Anal. Calcd for $C_{30}H_{27}ON_3$: C, 80.87; H, 6.11. Found: C, 80.89; H, 6.14%.

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Synthesis of pyrrolo[3,4-*c*]quinolines by 1,5-electrocyclisation of non-stabilised azomethine ylides

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Abstract—A new route to the pyrrolo[3,4-*c*]quinoline ring system has been developed via the 1,5-dipolar electrocyclisation reactions of azomethine ylides derived from easily available 3-formylquinoline derivatives. The intermediacy of azomethine ylides was shown by the trapping of the proposed dipoles with *N*-phenylmaleimide.

1. Introduction

Quinolines and their derivatives are very important in medicinal chemistry because of their wide occurrence in natural products[1] and drugs.[2] Among the quinolines 2-chloro-3-formyl-quinolines occupy a prominent position as they are key intermediates for further [*b*]-annelation of a wide variety of rings and for various functional group interconversions.[3] The applications of these methodologies have yielded beside the huge number of new quinoline derivatives new synthetic approaches for alkaloids such as camptothecin,[4] luotonin A,[5] 22-hydroxyacuminatine[6] or nothapodytine[7] (Fig. 1).

In this paper, we describe[8] the first [*c*]-annelation of this type of quinoline by 1,5-electrocyclisation of azomethine ylides.[9] This conversion gives a direct route to the otherwise hardly accessible pyrrolo[3,4-*c*]quinoline ring system.[10]

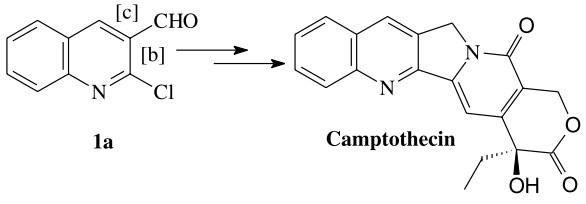

Figure 1.

The starting quinolines (**1a–c**) were prepared by the method described by Meth-Cohn from the corresponding acetanilides by the treatment with the Vilsmeier reagent in a single step.[11] The non-stabilized azomethine ylides **2** were generated from these aldehydes **1a–c** using the decarboxylation method.[12] The reaction of 2-chloro-3-formylquinolines **1a–c** with sarcosine in refluxing xylene gave 2-methyl-2,4,5,9*b*-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinolin-4-ones **4a–c** in acceptable yields via the expected 1,5-electrocyclisation reaction accompanied by hydrolysis of the chlorine function under the applied reaction conditions in the presence of the water formed in the first step (Scheme 1).

The intermediacy of azomethine ylides **2** was shown by trapping the proposed dipoles with *N*-phenylmaleimide to give the two isomeric cycloadducts **5** and **6** (*endo–exo* ratio ≈ 1:1) in quantitative yield (Scheme 1).

After the successful 1,5-electrocyclisation of non-stabilised azomethine ylides, we studied the reactivity of the analogous ester-stabilised system generated from the corresponding Schiff-base **7** by thermal 1,2-prototropy.[13] In contrast, in these cases, no 1,5-electrocyclisation was observed, the **7** imine remained unchanged even after a prolonged reaction time in refluxing xylene (Scheme 2). This result is in good agreement with our earlier observations on the reactivity of azomethine ylides in electrocyclisation reactions.[14]

We performed the next series of experiments with conjugated azomethine ylides derived from 2-phenyl-3-formylquinolines **10a–c**. In these dipoles **11** there is a

Keywords: Azomethine ylide; Cycloaddition; Electrocyclisation; Pyrroles.
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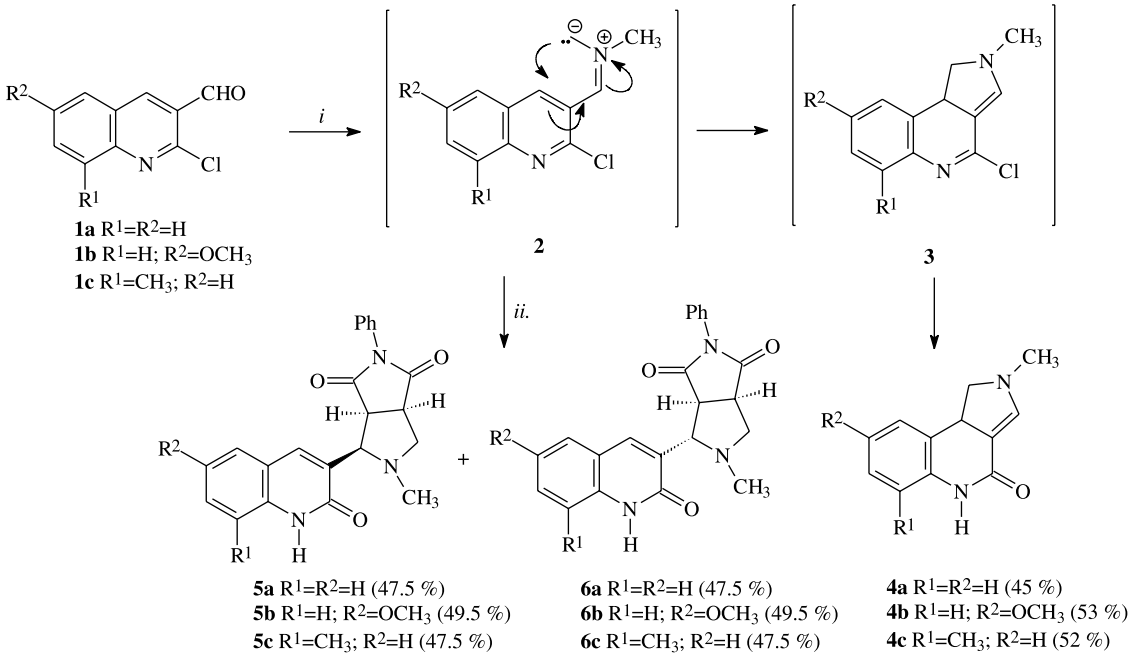


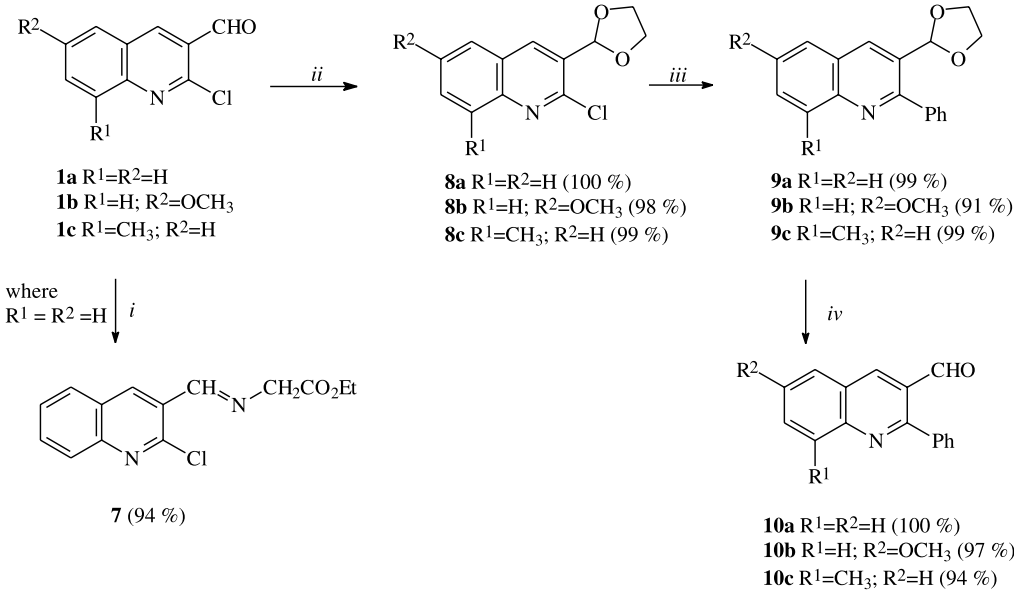
Scheme 1. (i) Sarcosine (2 equiv), xylene, 140 °C; (ii) *N*-phenylmaleimide (1 equiv).

possibility—besides the 1,5-electrocyclisation-of a 1,7-electrocyclic ring closure onto the phenyl group.[15] The starting material was prepared in three simple steps from the 2-chloro-3-formyl-quinolines including a palladium catalysed Suzuki coupling with phenylboronic acid (Scheme 2).

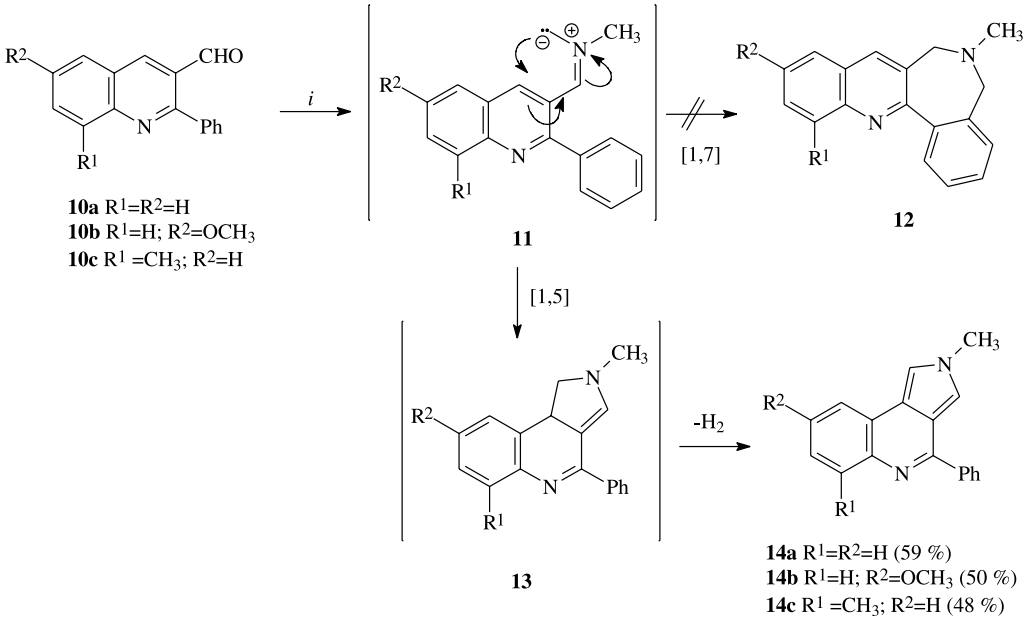
The reaction of the resultant quinolines **10a–c** with sarcosine in refluxing xylene, gave 2-methyl-4-phenyl-1*H*-pyrrolo[3,4-*c*]quinolines **14a–c** as products in moderate yields (Scheme 3). The 1,5-electrocyclisations in these cases were followed by full aromatisation to the tetrahydro-1*H* pyrrolo[3,4-*c*]quinoline **13** ring system. This slightly different result compared to the transformation **1**⇒**4**, may be explained by the delocalisation energy difference between the lactam products **4** and compounds **14** having a more extended conjugation.

The intermediacy of azomethine ylides **11** was again shown by the trapping the dipole with *N*-phenylmaleimide to give the two isomeric cycloadducts **15** and **16** (ratio≈1:5) in good yield. The stereochemistry of the major isomer (**16**) was proved by NOE experiments (Scheme 4).

In conclusion, we have developed a new, one-step route from simple starting materials to the challenging pyrrolo[3,4-*c*]quinoline ring system via the 1,5-dipolar electrocyclisation reaction of non-stabilised azomethine ylides.



Scheme 2. (i) $EtO_2CCH_2NH_2 \cdot HCl$, Et_3N, CH_2Cl_2, rt; (ii) $HOCH_2CH_2OH$, PTSA, benzene, reflux; (iii) $PhB(OH)_2$, $Pd(OAc)_2$ (cat.), K_2CO_3, DME, H_2O; (iv) 5% HCl, THF, 80 °C.

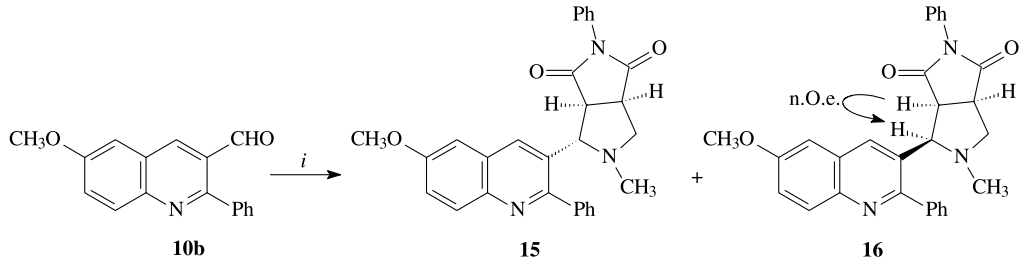


10a $R^1=R^2=H$
10b $R^1=H$; $R^2=OCH_3$
10c $R^1=CH_3$; $R^2=H$

11 **12** **13**

14a $R^1=R^2=H$ (59 %)
14b $R^1=H$; $R^2=OCH_3$ (50 %)
14c $R^1=CH_3$; $R^2=H$ (48 %)

Scheme 3. (i) Sarcosine (2 equiv), xylene, 140 °C.



10b **15** **16**

Scheme 4. (i) *N*-Phenylmaleimide (1 equiv), sarcosine (2 equiv), xylene, 140 °C.

2. Experimental

Melting points were determined on a Gallenkamp apparatus and are uncorrected. Column chromatography was performed using Merck Kieselgel 60 70–230 mesh, TLC on aluminium sheets coated with Kieselgel 60 F_{254}. Plates were stained with anisaldehyde solution (100 ml glacial acetic acid, 2 ml cc sulphuric acid and 1 ml anisaldehyde) and heated at ca. 150 °C. IR spectra were measured on a NICOLET FT-IR instrument. NMR spectra were obtained on a Brucker 250 instrument. Chemical shifts are given relative to δ_{TMS}. All solvents were purified according to standard procedures and the quinolines **1a–c** were prepared by the method of Meth-Cohn et al.[11]

2.1. The 1,5-electrocyclisation reaction of azomethine ylides 2. General procedure

The corresponding 2-chloro-quinoline-3-carbaldehyde **1a–c** (5.0 mmol), was dissolved in xylene (150 ml) and sarcosine (1.34 g; 15.0 mmol) was added. The reaction mixture was boiled for 4 h. After the reaction was completed all the solvents were removed in vacuo and the residue was purified by column chromatography (eluent: chloroform–methanol 8:1 vol/vol).

2.1.1. 2-Methyl-2,4,5,9*b*-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinolin-4-one (4a).

Pale yellow powder (0.45 g, 45%); mp 145–6 °C; [Found: C, 72.0; H, 5.9; N, 14.0. $C_{12}H_{12}N_2O$ requires C 71.98; H 6.04; N 13.99%]; ^{1}H NMR (250 MHz, DMSO-d_6): 7.79 (s, 1H, H-3), 7.66 (d, 1H, $J=8.0$ Hz, H-9), 7.54 (d, 1H, $J=8.0$ Hz, H-6), 7.44 (t, 1H, $J=8.0$ Hz, H-8), 7.14 (t, 1H, $J=8.0$ Hz, H-7), 5.77 (broad s, 1H, NH), 5.17 (broad s, 1H, H-9*b*), 3.69 (t, 1H, $J=9.0$ Hz, H-1), 3.30 (dd, 1H, $J=2.2$, 9.0 Hz, H-1), 2.99 (s, 3H, *N*CH_3); ^{13}C NMR (62.5 MHz, DMSO-d_6): 160.4 (q), 148.5 (q), 130.8 (CH), 128.9 (q), 128.8 (CH), 128.0 (CH), 125.4 (CH), 123.6 (q), 121.3 (CH), 66.0 (CH), 59.8 (CH_2), 31.2 (CH_3); IR (KBr, cm^{-1}): 2944, 2868, 2790, 1651, 1581, 1541, 1507, 1446, 1408, 1359, 1308, 1286, 1252, 1150, 1106, 1071, 1038, 1002.

2.1.2. 2-Methyl-8-methoxy-2,4,5,9*b*-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinolin-4-one (4b).

Pale yellow powder (0.56 g, 53%); mp 157–8 °C; [Found: C, 67.6; H, 6.0; N, 12.1. $C_{13}H_{14}N_2O_2$ requires C 67.81; H 6.13; N 12.17%]; ^{1}H NMR (250 MHz, DMSO-d_6): 7.75 (s, 1H, H-3), 7.48 (d, 1H, $J=8.8$ Hz, H-6), 7.17 (d, 1H, $J=2.4$ Hz, H-9), 7.11 (dd, 1H, $J=2.4$, 8.8 Hz, H-7), 5.74 (broad s, 1H, NH), 5.16 (broad s, 1H, H-9*b*), 3.79 (s, 3H, *O*CH_3), 3.65 (dd, 1H, $J=7.8$, 10.5 Hz, H-1), 3.25 (dd, 1H, $J=4.0$, 10.5 Hz, H-1), 2.95 (s, 3H, *N*CH_3);^{13}C NMR (62.5 MHz, DMSO-d_6): 159.5 (q), 154.0 (q), 143.5 (q), 130.2 (CH), 129.1 (q), 126.5 (CH), 124.0 (q), 119.2 (CH), 108.1 (CH), 66.2 (CH), 60.0 (CH_2),

55.3 (CH_3), 34.4 (CH_3); IR (KBr, cm^{-1}): 3160, 3062, 2994, 2939, 2831, 1648, 1618, 1582, 1500, 1453, 1430, 1404, 1336, 1292, 1235, 1204, 1166, 1097, 1062, 1038.

2.1.3. 2,6-Dimethyl-2,4,5,9*b*-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinolin-4-one (4c). Pale yellow powder (0.55 g, 52%); mp 151 °C; [Found: C, 72.9; H, 6.4; N, 13.0. $C_{13}H_{14}N_2O$ requires C 72.87; H 6.59; N 13.07%]; ^{1}H NMR (250 MHz, DMSO-d_6): 7.77 (s, 1H, H-3), 7.49 (d, 1H, J=7.5 Hz, H-9), 7.32 (d, 1H, J=7.5 Hz, H-7), 7.04 (t, 1H, J=7.5 Hz, H-8), 5.80 (broad s, 1H, NH), 5.09 (broad s, 1H, H-9*b*), 3.66 (dd, 1H, J=7.7, 10.2 Hz, H-1), 3.29 (dd, 1H, J=3.9, 10.2 Hz, H-1), 3.01 (s, 3H, NCH_3), 2.56 (s, 3H, CH_3); ^{13}C NMR (62.5 MHz, DMSO-d_6): 159.7 (q), 147.1 (q), 132.5 (q), 131.1 (CH), 129.1 (CH), 128.3 (q), 126.0 (CH), 123.1 (q), 120.8 (CH), 66.1 (CH), 59.8 (CH_2), 31.1 (CH_3), 17.8 (CH_3); IR (KBr, cm^{-1}): 2942, 2860, 1653, 1583, 1543, 1511, 1442, 1361, 1318, 1256, 1151, 1111, 1071, 1032, 1012.

2.2. The 1,3-dipolar cycloaddition of azomethine ylides 2 to *N*-phenyl-maleimide. General procedure

The corresponding 2-chloro-quinoline-3-carbaldehyde **1a–c** (1.0 mmol), was dissolved in xylene (50 ml) and *N*-phenyl-maleimide (0.17 g; 1 mmol), sarcosine (0.36 g; 4.0 mmol) was added. The reaction mixture was boiled for 2 h. After the reaction was completed all the solvents were removed in vacuo and the residue was purified by column chromatography (eluent: hexanes–acetone 3:1 vol/vol).

2.2.1. 5-(2-Chloroquinolin-3-yl)-1,4-diaza-2,6-dioxo-4-methyl-1-phenyl-bicyclo[3.3.0]octane (5a and 6a). White powder (0.35 g, 95%); 1:1 mixture of two diastereomers; ^{1}H NMR (250 MHz, $CDCl_3$): 8.27 (s, ½H, Ar-4′H), 8.16 (s, ½H, Ar-4′H), 8.03 (d, ½H, J=8.2 Hz, Ar-5′H), 7.83 (d, ½H, J=8.2 Hz, Ar-5′H), 7.77–7.27 (m, 8H, Ar-6′, 7′ and 8′H, Ph–H), 4.37 (d, ½H, J=6.0 Hz, H-5), 4.09 (d, ½H, J=8.5 Hz, H-5), 3.90 (t, ½H, J=8.5 Hz, H-5*a*), 3.79–3.55 (m, 3½H, H-2*a*, H-5*a*, H-3), 2.29 (s, 1½H, NCH_3), 2.23 (s, 1½H, NCH_3); IR (KBr, cm^{-1}): 3060, 2972, 2940, 2836, 2780, 1708, 1619, 1591, 1560, 1496, 1456, 1388, 1320, 1188, 1172, 1158, 1043, 1010; HRMS: Calcd: 373.1426 for $C_{22}H_{19}N_3O_3$; Found: 373.1434.

2.2.2. 5-(2-Chloro-6-methoxyquinolin-3-yl)-1,4-diaza-2,6-dioxo-4-methyl-1-phenyl-bicyclo[3.3.0]octane (5b and 6b). White powder (0.40 g, 99%); 1:1 mixture of two diastereomers; ^{1}H NMR (250 MHz, $CDCl_3$): 8.17 (s, ½H, Ar-4′H), 8.08 (s, ½H, Ar-4′H), 7.93 (d, ½H, J=8.2 Hz, Ar-8′H), 7.90 (d, ½H, J=8.2 Hz, Ar-8′H), 7.51–7.26 (m, 5H, Ar-6′ and 7′H, Ph–H), 7.17–6.95 (m, 3H, Ar-5′H and Ph–H), 4.35 (d, ½H, J=6.0 Hz, H-5), 4.08 (d, ½H, J=8.5 Hz, H-5), 3.93 (s, 1½H, OCH_3), 3.91 (s, 1½H, OCH_3), 3.87–3.41 (m, 4H, H-2*a*, H-5*a*, H-3), 2.24 (s, 3H, NCH_3); IR (KBr, cm^{-1}): 2964, 2794, 1714, 1621, 1589, 1498, 1453, 1498, 1385, 1326, 1262, 1231, 1183, 1096, 1025; HRMS: Calcd: 403.1532 for $C_{23}H_{21}N_3O_4$; Found: 403.1534.

2.2.3. 5-(2-Chloro-8-methylquinolin-3-yl)-1,4-diaza-2,6-dioxo-4-methyl-1-phenyl-bicyclo[3.3.0]octane (5c and 6c). White powder (0.37 g, 95% 1:1 mixture of two diastereomers); ^{1}H NMR (250 MHz, $CDCl_3$): 8.21 (s, ½H, Ar-4′H), 8.11 (s, ½H, Ar-4′H), 7.55–7.25 (m, 8H, Ar-5′, 6′and 7′H, Ph–H), 4.39 (d, ½H, J=6.0 Hz, H-5), 4.09 (d, ½H, J=8.5 Hz, H-5); 3.89 (t, ½H, J=8.5 Hz, H-5*a*), 3.78–3.39 (m, 3½H, H-2*a*, H-5*a*, H-3), 2.77 (s, 1½H, CH_3), 2.75 (s, 1½H, CH_3), 2.28 (s, 1½H, NCH_3), 2.22 (s, 1½H, NCH_3); IR (KBr, cm^{-1}): 2944, 2846, 1708, 1596, 1497, 1483, 1389, 1323, 1185, 1140, 1089, 1027, 941; HRMS: Calcd: 387.1582 for $C_{23}H_{21}N_3O_3$; Found: 387.1588.

2.2.4. Ethyl-(2-chloroquinolin-3-yl)methyleneamino-acetate (7). The 2-chlorquinoline-3-carbaldehyde **1a** (0.38 g; 2.0 mmol) was dissolved in dry dichloromethane (40 ml). Ethyl glycinate hydrochloride (0.28 g; 2.0 mmol), and triethylamine (0.29 ml, 0.2 g; 2.0 mmol) and approximately 2 g anhydrous magnesium sulfate was added. The reaction mixture was stirred at room temperature overnight. After filtration the reaction mixture was evaporated in vacuo. The resulted solid was suspended in ether and filtered again. The etheral solution was evaporated in vacuo to yield the title product as a pale yellow solid (0.52 g, 94.0%); mp 121–2 °C; ^{1}H NMR (250 MHz, $CDCl_3$): 8.88 (s, 1H, CH=*N*), 8.78 (s, 1H, H-4), 7.99 (d, 1H, J=8.3 Hz, H-5), 7.87 (d, 1H, J=8.3 Hz, H-6), 7.76 (t, 1H, J=8.3 Hz, H-8), 7.56 (t, 1H, J=8.3 Hz, H-7), 4.53 (s, 2H, NCH_2), 4.29 (q, 2H, J=7.8 Hz, OCH_2), 1.33 (t, 2H, J=7.8 Hz, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$): 169.6 (q), 161.1 (CH), 148.4 (q), 137.8 (CH), 131.7 (CH), 130.7 (q), 128.7 (CH), 128.2 (CH), 127.5 (CH), 126.9 (q), 126.6 (q), 62.0 (CH_2), 61.2 (CH_2), 14.1 (CH_3); IR (KBr, cm^{-1}): 2981, 2877, 1743, 1646, 1596, 1488, 1373, 1268, 1187, 1087, 1029; HRMS: Calcd: 276.0665 for $C_{14}H_{13}N_2O_2Cl$; Found: 276.0660.

2.3. Synthesis of 3-[1,3-dioxolane-2-yl]-2-chloroquinolines (8a–c). General procedure

The corresponding 2-chlorquinoline-3-carbaldehyde **1a–c** (60 mmol) was suspended in benzene (600 ml), and ethylene glycol (4.5 ml, 5.0 g; 80.0 mmol) and *p*-toluene-sulphonic acid (0.57 g; 3.0 mmol) was added. The reaction mixture was refluxed for 4 h with the continous removal of the formed water by the aid of a Dean–Stark trap. After the reaction was completed saturated aq sodium hydrogen carbonate solution (150 ml) was added. The organic layer was separated, and washed with water (2×100 ml) and brine (100 ml), dried over magnesium sulfate, and evaporated under reduced pressure to give the title products.

2.3.1. 3-(1,3-Dioxolane-2-yl)-2-chloroquinoline (8a). Pale yellow solid (14.12 g, 100%); mp 59–60 °C; ^{1}H NMR (250 MHz, $CDCl_3$): 8.58 (s, 1H, H-4), 8.26 (d, 1H, J=8.0 Hz, H-5), 7.58–7.41 (m, 2H, H-8 and H-6), 7.17 (t, 1H, J=8.0 Hz, H-7), 6.08 (s, 2H, CH), 4.13–4.06 (m, 4H, OCH_2CH_2O); ^{13}C NMR (62.5 MHz, $CDCl_3$): 148.5 (q), 137.3 (CH), 131.4 (CH), 130.9 (q), 128.8 (CH), 128.0 (CH), 127.1 (CH), 126.5 (q), 126.2 (q), 100.2 (CH), 65.3 (2×CH_2); IR (KBr, cm^{-1}): 2894, 1619, 1599, 1568, 1493, 1456, 1368, 1327, 1138, 1101, 1037; HRMS: Calcd: 235.0400 for $C_{12}H_{10}NO2Cl$; Found: 235.0402.

2.3.2. 3-(1,3-Dioxolane-2-yl)-2-chloro-6-methoxy-quinoline (8b). Pale yellow solid (15.74 g, 98%); mp 79–80 °C; ^{1}H NMR (250 MHz, DMSO-d_6): 8.20 (s, 1H, H-4), 7.81 (d,

1H, J=9.2 Hz, H-8), 7.28 (dd, 1H, J=2.8, 9.2 Hz, H-7), 6.97 (d, 1H, J=2.8 Hz, H-5), 6.12 (s, 1H, CH), 4.11–4.08 (m, 2H, OCH_2), 4.05–4.00 (m, 2H, OCH_2), 3.81 (s, 3H, OCH_3); ^{13}C NMR (62.5 MHz, DMSO-d_6): 159.5 (q), 145.8 (q), 142.7 (q), 135.7 (CH), 129.0 (q), 128.9 (CH), 128.0 (q), 123.5 (CH), 106.3 (CH), 99.7 (CH), 65.0 (2×CH_2), 55.5 (CH_3); IR (KBr, cm^{-1}): 3015, 2960, 2903, 1622, 1596, 1498, 1333, 1225, 1179, 1107, 1043, 1022. HRMS: Calcd: 265.0505 for $C_{13}H_{12}NO_3Cl$; Found: 265.0501.

2.3.3. 3-(1,3-Dioxolane-2-yl)-2-chloro-8-methyl-quinoline (8c). Pale yellow solid (14.80 g, 99%); mp 71–2 °C; ^{1}H NMR (250 MHz, $CDCl_3$): 8.31 (s, 1H, H-4), 7.61 (d, 1H, J=8.0 Hz, H-5), 7.51 (d, 1H, J=8.0 Hz, H-7), 7.38 (t, 1H, J=8.2 Hz, H-6), 6.20 (s, 1H, CH), 4.09 (m, 4H, OCH_2CH_2O), 2.72 (s, 3H, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$): 146.9 (q), 136.8 (CH), 136.4 (q), 131.0 (CH), 129.1 (q), 128.5 (q), 127.7 (q), 126.8 (CH), 125.9 (CH), 100.5 (CH), 65.5 (2×CH_2), 17.8 (CH_3); IR (KBr, cm^{-1}): 2954, 2884, 1615, 1598, 1577, 1490, 1466, 1364, 1331, 1182, 1101, 1074, 1021; HRMS: Calcd: 249.0556 for $C_{13}H_{12}NO_2Cl$; Found: 249.0549.

2.4. Suzuki coupling. General procedure

The corresponding acetal (20 mmol) and phenylboronic acid (2.93 g; 24.0 mmol) was dissolved in DME (75 ml) under argon atmosphere. Potassiom carbonate (8.3 g; 60 mmol) dissolved in water (75 ml) was added followed by palladium(II) acetate (49 mg; 0.2 mmol) and triphenyl phosphine (0.21 g; 0.8 mmol). The reaction mixture was refluxed for 1 h. After the reaction was completed it was filtered through a pad of Celite and washed with ethyl acetate. The organic layer was separated and the aqueous phases was extracted with ethyl acetate (2×50 ml). The combined organic extracts were washed with saturated aq sodium hydrogen carbonate solution (50 ml), water (2×50 ml) and brine (50 ml), dried over magnesium sulfate, and evaporated under reduced pressure to give the crude product, which was purified by flash vacuum chromatography (eluent: hexanes–ethyl acetate 3:1 vol/vol).

2.4.1. 3-(1,3-Dioxolane-2-yl)-2-phenylquinoline (9a). White powder (5.50 g, 99%); mp 88–90 °C; ^{1}H NMR (250 MHz, $CDCl_3$): 8.58 (s, 1H, H-4), 8.21 (d, 1H, J=8.1 Hz, H-5), 7.87 (d, 1H, J=8.1 Hz, H-8), 7.81–7.72 (m, 3H, H-6 and Ph–H), 7.54–7.41 (m, 4H, H-7 and Ph–H), 5.88 (s, 1H, CH), 4.18–4.07 (m, 2H, OCH_2), 4.00–3.90 (m, 2H, OCH_2); ^{13}C NMR (62.5 MHz, $CDCl_3$): 158.8 (q), 147.7 (q), 139.1 (q), 135.5 (CH), 130.2 (CH), 129.5 (2×CH), 129.0 (CH), 128.4 (q), 128.3 (CH), 127.9 (2×CH), 127.7 (CH), 126.7 (q), 126.4 (CH), 100.7 (CH), 65.3 (2×CH_2); IR (KBr, cm^{-1}): 3058, 2953, 2889, 1621, 1599, 1558, 1489, 1442, 1368, 1267, 1169, 1128, 1082, 1018; HRMS: Calcd: 277.1102 for $C_{18}H_{15}NO_2$; Found: 277.1100.

2.4.2. 3-(1,3-Dioxolane-2-yl)-6-methoxy-2-phenylquinoline (9b). White powder (5.60 g, 91%); mp 102–3 °C; ^{1}H NMR (250 MHz, $CDCl_3$): 8.42 (s, 1H, H-4), 8.04 (d, 1H, J=7.6 Hz, H-8), 7.75 (d, 2H, J=7.5 Hz, Ph-2′ and 6′H), 7.41–7.28 (m, H-7 and Ph–H), 7.01 (s, 1H, H-5), 5.81 (s, 1H, CH), 4.02 (m, 2H, OCH_2), 3.82 (m, 2H, OCH_2), 3.70 (s, 3H, OCH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$): 157.7 (q), 156.5 (q), 144.0 (q), 139.4 (q), 134.3 (CH), 130.4 (CH), 129.6 (2×CH), 129.3 (q), 128.3 (CH), 128.0 (2×CH), 123.3 (CH), 115. 5 (q), 104.9 (CH), 100.8 (CH), 65.4 (2×CH_2), 55.3 (OCH_3); IR (KBr, cm^{-1}): 3056, 2999, 2964, 2888, 2861, 1622, 1602, 1492, 1462, 1364, 1223, 1168, 1085, 1029; HRMS: Calcd: 307.1208 for $C_{19}H_{17}NO_3$; Found: 307.1212.

2.4.3. 3-(1,3-Dioxolane-2-yl)-8-methyl-2-phenylquinoline (9c). White powder (5.79 g, 99%); mp 98–9 °C; ^{1}H NMR (250 MHz, $CDCl_3$): 8.51 (s, 1H, H-4), 7.84 (d, 2H, J=7.8 Hz, Ph-2′ and 6′H), 7.69 (d, 1H, J=8.1 Hz, H-9), 7.53–7.35 (m, 6H, H-8, H-7 and Ph–H), 5.90 (s, 1H, CH), 4.16 (m, 2H, OCH_2), 3.95 (m, 2H, OCH_2), 2.81 (s, 3H, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$): 157.3 (q), 147.0 (q), 139.8 (q), 137.3 (q), 135.7 (CH), 130.1 (CH), 130.0 (2×CH), 128.3 (q), 128.2 (CH), 127.9 (2×CH), 126.7 (q), 126.2 (CH), 125.8 (CH), 101.0 (CH), 65.5 (2×CH_2), 17.8 (CH_3); IR (KBr, cm^{-1}): 2953, 2892, 1615, 1599, 1568, 1481, 1463, 1365, 1170, 1084, 1072, 1062, 1009; HRMS: Calcd: 291.1259 for $C_{19}H_{17}NO_2$; Found: 291.1265.

2.5. Hydrolysis of ketal 9a–c—General procedure

The corresponding ketal **9a–c** (20 mmol) was dissolved in tetrahydofuran (300 ml), water (50 ml) and concentrated hydrochloric acid (10 ml) was added. The reaction mixture was refluxed for an hour under argon atmosphere. After the reaction was completed saturated aq sodium hydrocarbonate solution (150 ml) was added. The tetrahydrofurane was removed in vacuo and the residue was extracted with ethyl acetate (3×50 ml). The combined organic extracts were washed with water (2×50 ml), brine (50 ml), dried over magnesium sulfate, and evaporated under reduced pressure to give the product.

2.5.1. 2-Phenyl-quinoline-3-carbaldehyde (10a). White powder (3.50 g, 100%); mp 105–6 °C; [Found: C, 82.5; H, 4.8; N, 6.0. $C_{16}H_{11}NO$ requires C 82.38; H 4.75; N 6.00%]; ^{1}H NMR (250 MHz, $CDCl_3$): 10.15 (s, 1H, CHO), 8.79 (s, 1H, H-4), 8.19 (d, 1H, J=8.2 Hz, H-8), 7.96 (d, 1H, J=8.2 Hz, H-5); 7.83 (t, 1H, J=8.2 Hz, H-7), 7.68 (m, 2H, Ph–H), 7.52 (m, 4H, H-6 and Ph–H); ^{13}C NMR (62.5 MHz, $CDCl_3$): 191.3 (CH), 160.1 (q), 149.4 (q), 138.0 (CH), 137.5 (q), 132.5 (CH), 130.1 (2×CH), 129.4 (CH), 129.3 (CH), 129.25 (CH), 128.6 (2×CH), 127.5 (q), 127.3 (CH), 126.2 (q); IR (KBr, cm^{-1}): 2861, 1693, 1614, 1584, 1552, 1485, 1370, 1156, 1121, 1075, 1008.

2.5.2. 6-Methoxy-2-phenylquinoline-3-carbaldehyde (10b). White powder (3.82 g, 97%); mp 125–6 °C; [Found: C, 77.3; H, 4.8; N, 5.2. $C_{17}H_{13}NO_2$ requires C 77.55; H 4.98; N 5.32%]; ^{1}H NMR (250 MHz, $CDCl_3$): 10.14 (s, 1H, CHO), 8.66 (s, 1H, H-4), 8.15 (d, 1H, J=8.3 Hz, H-8), 7.64 (m, 2H, Ph–H), 7.51 (m, 4H, H-7 and Ph–H), 7.16 (d, 1H, J=1.8 Hz, H-5), 3.93 (s, 3H, OCH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$): 191.7 (CH), 158.3 (q), 158.0 (q), 145.9 (q), 137.8 (q), 136.4 (CH), 130.9 (CH), 130.3 (2×CH), 129.4 (CH), 128.7 (2×CH), 127.7 (q), 127.4 (q), 125.8 (CH), 125.9 (CH), 55.6 (OCH_3); IR (KBr, cm^{-1}): 3452, 3057, 2955, 2855, 1686, 1618, 1585, 1563, 1492, 1446, 1416, 1367, 1349, 1226, 1169, 1130, 1027.

2.5.3. 8-Methyl-2-phenylquinoline-3-carbaldehyde (10c).

White powder (3.48 g, 94%); mp 109–11 °C; [Found: C, 82.7; H, 5.4; N, 5.7. $C_{17}H_{13}NO$ requires C 82.57; H 5.30; N 5.66%]; ^{1}H NMR (250 MHz, $CDCl_3$): 10.16 (s, 1H, CHO), 8.71 (s, 1H, H-4), 7.76–7.40 (m, 8H, Ar-H), 2.81 (s, 3H, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$): 191.7 (CH), 158.5 (q), 148.5 (q), 138.2 (CH), 137.7 (q), 132.4 (CH), 132.3 (q), 130.6 (2×CH), 129.2 (CH), 128.5 (2×CH), 128.4 (q), 127.2 (CH), 127.1 (CH), 126.1 (q), 17.8 (CH_3); IR (KBr, cm^{-1}): 2861, 2844, 1692, 1611, 1580, 1555, 1485, 1371, 1152, 1119, 1075, 1011.

2.6. 1,5-Electrocyclization reactions of azomethine ylides 11 generated from 2-phenyl-quinoline-3-carbaldehydes 10a–c. General procedure

The corresponding 2-phenyl-quinoline-3-carbaldehyde **10a–c** (3.0 mmol) was dissolved in xylene (50 ml) and sarcosine (0.54 g; 6.0 mmol) was added. The reaction mixture was refluxed until the starting aldehyde completely disappeared (judged by TLC). All the solvent was removed in vacuo and the residue purified by flash chromatography (eluent: petroleum ether–acetone 3:1) to give the crystalline product.

2.6.1. 2-Methyl-4-phenyl-pyrrolo[3,4-*c*]quinoline (14a). White powder (0.46 g, 59%); mp 182–3 °C; ^{1}H NMR (250 MHz, $CDCl_3$): 8.10 (dd, 1H, J=1.9, 7.9 Hz, H-9), 7.97 (dd, 2H, J=2.0, 8.1 Hz, Ph-2′ and 6′H), 7.92 (dd, 1H, J=1.9, 7.9 Hz, H-6), 7.53–7.38 (m, 5H, H-7, H-8 and Ph–H), 7.27 (d, 1H, J=1.8 Hz, H-3), 7.20 (d, 1H, J=1.8 Hz, H-1), 3.77 (s, 3H, NCH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$): 155.6 (q), 142.8 (q), 140.3 (q), 129.7 (CH), 129.0 (CH), 128.5 (2×CH), 128.4 (2×CH), 126.0 (CH), 125.8 (CH), 122.9 (q), 122.2 (CH), 121.9 (q), 117.6 (CH), 117.5 (q), 112.8 (CH), 37.4 (CH_3); IR (KBr, cm^{-1}): 3139, 2942, 1572, 1538, 1521, 1481, 1467, 1454, 1443, 1413, 1357, 1332, 1234, 1220, 1192, 1143, 1078, 1028; HRMS: Calcd: 258.1156 for $C_{18}H_{14}N_2$; Found: 258.1156.

2.6.2. 8-Methoxy-2-methyl-4-phenyl-pyrrolo[3,4-*c*]quinoline (14b). White powder (0.43 g, 50%); mp 188 °C; ^{1}H NMR (250 MHz, $CDCl_3$): 8.01 (d, 1H, J=9.0 Hz, H-6), 7.96 (m, 2H, Ar-H), 7.49 (m, 3H, Ar-H), 7.30 (m, 2H, Ar-H), 7.22 (d, 1H, J=1.8 Hz, H-1), 7.09 (dd, 1H, J=2.5, 9.0 Hz, H-7), 3.88 (s, 3H, OCH_3), 3.83 (s, 3H, NCH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$): 157.6 (q), 157.5 (q), 153.2 (q), 140.3 (q), 137.5 (q), 131.0 (CH), 128.8 (CH), 128.4 (2×CH), 128.3 (2×CH), 122.9 (q), 122.7 (q), 117.4 (CH), 114.9 (CH), 112.8 (CH), 103.8 (CH), 55.4 (OCH_3), 37.4 (NCH_3); IR (KBr, cm^{-1}): 3142, 3058, 2933, 2832, 1706, 1616, 1531, 1485, 1474, 1452, 1434, 1369, 1250, 1210, 1165, 1141, 1104, 1030; HRMS: Calcd: 288.1262 for $C_{19}H_{16}N_2O$; Found: 288.1263.

2.6.3. 2,6-Dimethyl-4-phenyl-pyrrolo[3,4-*c*]quinoline (14c). White powder (0.39 g, 48%); mp 176–7 °C; ^{1}H NMR (250 MHz, $CDCl_3$): 8.10 (d, 2H, J=7.7 Hz, Ph-2′ and 6′H), 7.81 (dd, 1H, J=2.3, 6.7 Hz, H-9), 7.54–7.25 (m, 7H, Ar-H), 3.92 (s, 3H, NCH_3), 2.82 (s, 3H, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$): 152.4 (q), 140.2 (q), 139.8 (q), 136.4 (q), 128.2 (CH), 127.7 (2×CH), 127.6 (2×CH), 126.1 (CH), 124.6 (CH), 122.6 (q), 120.7 (q), 119.3 (CH), 116.5 (CH), 116.1 (q), 112.2 (CH), 36.7 (NCH_3), 17.8 (CH_3); IR (KBr, cm^{-1}): 3025, 2951, 1528, 1473, 1446, 1428, 1356, 1329, 1216, 1140, 1089, 1073, 1059, 1020; HRMS: Calcd: 272.1313 for $C_{19}H_{16}N_2$; Found: 272.1313.

2.6.4. 5-(2-Phenyl-6-methoxy-quinolin-3-yl)-1,4-diaza-2,6-dioxo-4-methyl-1-phenyl-bicyclo[3.3.0]octane (16). 2-(6-Methoxyphenyl)-quinoline-3-carbaldehyde **10b** (0.26 g; 1 mmol) was dissolved in xylene (50 ml) and *N*-phenylmaleimide (0.17 g; 1.0 mmol) and sarcosine (0.36 g; 4.0 mmol) was added. The reaction mixture was refluxed for 1 h. On cooling the solvent was removed in vacuo and the residue was purified by flash chromatography (eluent: petroleum ether–acetone 3:1) to give the main isomer as a crystalline product as a white powder (0.30 g, 65%); mp 172–3 °C; ^{1}H NMR (250 MHz, DMSO-d_6): 8.32 (s, 1H, Ar-4′H), 8.06 (d, 1H, J=9 Hz, Ar-8′H), 7.52–7.37 (m, 9H, Ar-H, Ph–H), 7.10 (m, 3H, Ar-H, Ph–H), 3.93 (s, 3H, OCH_3), 3.84 (d, 1H, J=7.3 Hz, H-5), 3.65–3.50 (m, 4H, H-2*a*, H-3, H-5*a*), 2.07 (s, 3H, *N*Me); ^{13}C NMR (63 MHz, DMSO-d_6): 176.2 (q), 175.5 (q), 158.4 (q), 157.9 (q), 143.4 (q), 139.9 (q), 134.7 (CH), 131.4 (q), 131.0 (q), 130.8 (CH), 129.8 (2×CH), 129.1 (2×CH), 128.6 (CH), 128.1 (2×CH), 127.9 (CH), 127.8 (q), 126.4 (2×CH), 123.1 (CH), 104.5 (CH), 68.0 (CH), 57.3 (CH_2), 55.5 (CH_3), 54.8 (CH), 44.2 (CH), 38.6 (CH_3). HRMS: Calcd: 463.1895 for $C_{29}H_{25}N_3O_3$; Found: 463.1898.

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Structural revision of clusianone and 7-*epi*-clusianone and anti-HIV activity of polyisoprenylated benzophenones

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Abstract—For the first time, the tautomeric pairs of clusianone and 7-*epi*-clusianone were isolated from the same source, *Clusia torresii* fruits. An extensive NMR spectroscopic study is described to establish ^{1}H and ^{13}C chemical shift assignments and the C-7 relative configuration of these epimers and to clarify contradictory NMR spectroscopic data previously reported. Quantum mechanical computations than pointed out the relationship between indirect coupling constants and the equilibrium between the B-ring chair and twist-boat forms of the bicyclo-[3.3.1.]-nonane system. Clusianone, 7-*epi*-clusianone and polyisoprenylated benzophenones 18,19-dihydroxyclusianone, propolone A and nemorosone were screened for their activity against HIV infection in C8166 cells. All compounds inhibited infection with selectivity index values ranging from 2.25 to 15.6. Only clusianone derivatives inhibited infection by binding to viral protein gp120 and prevented its interaction with cellular receptor CD4 as detected by ELISA using recombinant proteins.

1. Introduction

Guttiferae (Clusiaceae) is a family almost exclusively tropical in distribution and comprises about 40 genera and 1200 species most of which are woody. A large number of polyisoprenylated benzophenone derivatives with a bicyclo-[3.3.1]-nonane-2,4,9-trione system have been isolated from this family. This ring system requires that the substituents at C-1 and C-5 be equatorial, whereas, prenyl group at C-7 has been observed both axial and equatorial. Clusianone (**1**) and 7-*epi*-clusianone (**2**) are polyisoprenylated benzophenones with a bicyclo-nonane ring system, which differ in the orientation of this C-7 prenyl group. Clusianone was first isolated in 1976 from the roots of *Clusia congestiflora* and was identified by X-ray diffraction analysis, which firmly established the equatorial orientation of the 3-methyl-2-butenyl group at C-7.[1] In 1991, clusianone was isolated from fruits of *Clusia sandinensis* and its NMR spectroscopic data reported for the first time,[2] but the stereochemistry at C-7 was not investigated. Finally, in 1996, clusianone was isolated from floral resin of *Clusia spiritu-santensis* after treatment with diazomethane and spectroscopic data of the methyl derivative were reported.[3] However, these two studies reported contradictory NMR data for clusianone. Santos et al. isolated 7-*epi*-clusianone from *Rheedia gardneriana* and identified it by NMR and X-ray diffraction analysis, which indicated an axial orientation of 3-methyl-2-butenyl group at C-7.[4,5] They suggested that the compound reported in 1991 might have been 7-*epi*-clusianone.

As a part of our survey of the Caribbean plants of the Guttiferae family, we investigated the fruits of *Clusia torresii*, an endemic tree of Costa Rica, and isolated the tautomeric pairs of clusianone (**1a** and **1b**) and 7-*epi*-clusianone (**2a** and **2b**) without any previous treatment with diazomethane. The results obtained by application of 1D and 2D NMR spectroscopic methods were used to establish the ^{1}H and ^{13}C chemical shift assignments of these isomers (**1a** and **1b** and **2a** and **2b**), and to clarify the structures of the two epimers. We believe that the NMR data for clusianone (**1**) are reported herein for the first time.

Keywords: Clusia torresii; Clusianone and 7-*epi*-clusianone; NMR; Quantum mechanical calculations; Anti-HIV.
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An interpretation of the measured coupling constants in terms of equilibrium between chair and twist-boat forms of the B-ring is then given on the grounds of extensive quantum mechanical calculations.

Compounds **1** and **2** and the previously isolated poly-isoprenylated benzophenone 18,19-dihydroxyclusianone (**3**),[6] propolone A (**4**)[7] and nemorosone (**5**)[8] were tested for their HIV-inhibitory activity in infected C8166 human T lymphoblastoid cells.

2. Results and discussion

2.1. Extraction and isolation

The fresh fruits of *C. torresii* were extracted with *n*-hexane. A yellow solid was obtained after concentration under reduced pressure and this was purified by RP-HPLC using MeOH/H_2O 9:1 as the eluent to yield clusianone **1** and 7-*epi*-clusianone **2**.

2.2. NMR structure elucidation and conformational study

The molecular formulas $C_{33}H_{42}O_4$ of compounds **1** and **2** were deduced using MS, ^{13}C NMR and ^{13}C DEPT NMR analyses. Both compounds were present in $CDCl_3$ solution as a tautomeric pair in a 3:5 ratio, as evidenced by two sets of NMR signals, the consequence of the presence of the enolizable 1,3-diketone system. Analysis of the 1D and 2D NMR spectra in $CDCl_3$ with homo- and hetero-nuclear direct and long-range correlations allowed assignment of ^1H and ^{13}C NMR signals for the tautomeric forms clusianone (**1a** and **1b**) and 7-*epi*-clusianone (**2a** and **2b**) (Table 1). The bicyclo-[3.3.1]-nonane-2,4,9-trione structures of **1** and **2** and the location of the functionalities and ligands were deduced from NMR data as described previously for 18,19-dihydroxy clusianone.[6]

^{13}C NMR and HMBC data analysis allowed us to differentiate the two tautomers **1a** and **1b** and **2a** and **2b**. The carbon resonances of C-1 and C-4 in tautomers **1a** and **2a** were downfield with respect to those in tautomers **1b** and

Table 1. ^1H and ^{13}C NMR (600 MHz) data for tautomeric pairs clusianone (**1a** and **1b**) and 7-*epi*-clusianone (**2a** and **2b**) in $CDCl_3$[a]

Positions	**1a**		**1b**		**2a**		**2b**	
	δ ^{13}C	δ ^1H (J_{H-H} in Hz)	δ ^{13}C	δ ^1H (J_{H-H} in Hz)	δ ^{13}C	δ ^1H (J_{H-H} in Hz)	δ ^{13}C	δ ^1H (J_{H-H} in Hz)
1	71.0	—	67.3	—	68.6	—	65.5	—
2	192.6	—	194.6	—	193.7	—	196.7	—
3[b]	116.8	—	116.1	—	115.9	—	115.5	—
4	195.5	—	193.9	—	196.6	—	193.6	—
5	59.6	—	64.7	—	58.4	—	63.2	—
6ax	41.5	1.62 (t, 12.4)	42.9	1.38 (t, 12.4)	39.0	2.22 (dd, 14.4, 7.0)	40.3	2.01 (dd, 14.4, 7.0)
6eq		2.17 (m)		2.00 (dd, 12.4, 3.9)		2.26 (dd, 14.4, 1.8)		2.11 (dd, 14.4, 2.8)
7	42.3	1.60 overlapped	43.0	1.51 overlapped	46.3	1.44 overlapped	46.6	1.44 overlapped
8	47.7	—	48.6	—	48.3	—	48.8	—
9	207.3	—	207.3	—	208.1	—	208.3	—
10	25.5	2.69 (m)	24.9	2.74 (m)	26.2	2.47 (m)	25.9	2.72 (m)
11	119.1	4.82 (m)	119.1	4.82 (m)	120.1	5.12 (m)	118.6	4.8 (m)
12	134.5	—	134.5	—	134.8	—	134.8	—
13	18.0	1.72 (s)	18.0	1.70 (s)	18.1	1.70 (s)	18.0	1.68 (s)
14	25.7	1.64 (s)	25.7	1.61 (s)	26.0	1.66 (s)	25.8	1.61 (s)
15[b]	197.7	—	197.5	—	197.5	—	197.2	—
16	137.2	—	137.2	—	136.8	—	136.8	—
17,21[b]	128.9	7.50 (d, 7.6)	128.9	7.53 (d, 7.6)	129.0	7.52 (d, 7.6)	128.9	7.55 (d, 7.6)
18,20[b]	127.8	7.37 (t, 7.6)	127.8	7.40 (t, 7.6)	127.8	7.38 (t, 7.6)	127.8	7.40 (t, 7.6)
19[b]	132.5	7.49 (t, 7.6)	132.5	7.52 (t, 7.6)	132.6	7.53 (t, 7.6)	132.6	7.53 (t, 7.6)
22	29.9	2.63 (m)	30.6	2.43 (m) 2.53 (m)	30.5	2.62 (m)	30.7	2.44 (m) 2.52 (m)
23	120.4	5.03 (m)	119.9	5.16 (m)	118.9	5.15 (m)	119.7	5.24 (m)
24	134.5	—	134.5	—	134.7	—	134.6	—
25	18.1	1.65 (s)	18.1	1.65 (s)	18.1	1.67 (s)	18.2	1.66 (s)
26	26.1	1. 78 (s)	26.1	1.76 (s)	26.0	1.80 (s)	26.1	1.76 (s)
27	28.2	1.64 overlapped 2.12 (m)	28.6	1.67 overlapped 2.13 (m)	28.9	2.05 overlapped 2.16 overlapped	28.9	1.88 (m) 2.00 overlapped
28	122.2	4.92 (m)	122.3	4.96 (m)	123.5	4.85 (m)	124.0	4.87 (m)
29	133.3	—	133.3	—	132.9	—	133.0	—
30	18.1	1.55 (s)	17.9	1.53 (s)	17.7	1.43 (s)	17.8	1.50 (s)
31	26.0	1.62 (s)	26.0	1.70 (s)	25.7	1.58 (s)	25.7	1.64 (s)
32	16.2	0.73 (s)	16.4	0.84 (s)	27.0	0.97 (s)	26.9	1.06 (s)
33	22.6	1.05 (s)	23.7	1.23 (s)	22.5	1.13 (s)	22.8	1.30 (s)

[a] Chemical shift values are in ppm from TMS, and values in Hz are presented in parentheses. All signals were assigned by DQF-COSY, HSQC, and HMBC experiments.
[b] No distinction can be made between the two tautomers.

2b ($\Delta\delta_{C\text{-}1}=+3.7$ and $+3.1$ ppm and $\Delta\delta_{C\text{-}4}=+1.6$ and $+3.0$ ppm in **1** and **2**, respectively), while the resonances of C-2 and C-5 in **1a** and **2a** were upfield with respect to those in **1b** and **2b** ($\Delta\delta_{C\text{-}2}=-2.0$ and -3.0 ppm, and $\Delta\delta_{C\text{-}5}=-5.1$ and -4.8 ppm in **1** and **2**, respectively). Chemical shift differences observed were in agreement with the presence of a keto-enolic equilibrium in the structures (C-2 and C-4) and with the deshielding effects that the carbonyl group exerted on C-1 and C-5. HMBC spectra of **1a** and **2a** showed cross-peaks between the enol carbon C-4 (δ 195.5 and 196.6 in **1a** and **2a**, respectively), and H_2-6 and H_2-22, while the carbonyl group at C-2 (δ 192.6 and 193.7 in **1a** and **2a**, respectively), showed correlations only to the C-10 protons. On the other hand, the carbonyl carbon C-4 in tautomers **1b** (δ 193.9) and **2b** (δ 193.6) showed correlations with H_2-6 and H_2-22, while the enol carbon C-2 (δ 194.6 and 196.7 in **1b** and **2b**, respectively), only with the C-10 protons. On the basis of these considerations, tautomers **a** and **b** were assigned the 2-keto and 4-keto form, respectively, (Fig. 1).

The NMR data of **1** and **2** indicated an epimeric relationship at the C-7 position in these compounds. Observation of NMR data for a series of prenylated benzophenones with different configuration at C-7[8–9] revealed several features useful in establishing the relative stereochemistry at C-7:

- The H-6 protons both resonate above 2.0 ppm and the H-6ax shows a $^3J_{H6ax-H7}=7$–8 Hz when the C-7 substituent is in axial position, while the H-6ax resonates at ca. 1.5 ppm and has a $^3J_{H6ax-H7}=10$–13 Hz when the C-7 substituent is equatorial;
- The *gem*-methyl group at C-8 shows two ranges of ^{13}C chemical shifts: if the C-7 substituent is axial ranges will be δ 26–28 for Me-32ax and δ 22–25 for Me-33eq, while if the C-7 substituent is equatorial ranges will be δ 15–17 for Me-32ax and δ 22–24 for Me-33eq. The upfield shift of the C-32ax signal results from steric compression of a γ-gauche interaction between this carbon and the CH_2-27 of the equatorial isopentenyl group on C-7;
- The C-7 carbons are upfield shifted when their substituents are equatorial (δ 40–44 vs δ 46–48);
- Bicyclo-[3.3.1]-nonanes with an equatorial C-7 substituent show NOE effects between H-6eq, H-7 and Me-33eq, while those of bicyclo-[3.3.1]-nonanes with an axial C-7 substituent exhibit correlations between H-6ax, H-7 and Me-32ax.

Taking account of these observations, a comparative study was performed on compounds **1** and **2**. Clusianone (**1**) showed a coupling constant between H-6ax and H-7 (12.4 Hz), carbon resonances of C-7 (δ 42.3 and 43.0 in **1a** and **1b**), Me-32ax (δ 16.2 and 16.4 in **1a** and **1b**) and Me-33eq (δ 22.6 and 23.7 in **1a** and **1b**) and NOE effects (H-6ax/Me-32ax and H-6eq/H-7/Me-33eq) that indicated an equatorial orientation of the isopentenyl group at C-7. In contrast, 7-*epi*-clusianone (**2**) showed a coupling constant between H-6ax and H-7 (7.0 Hz), carbon resonances of C-7 (δ 46.3 and 46.6 in **2a** and **2b**), Me-32ax and Me-33eq (δ 27.0 and 26.9 and δ 22.5 and 22.8, in **2a** and **2b**, respectively), and NOE effects (H-6ax/H-7 and Me-32ax/H-6eq/Me-33eq) characteristic of an axial orientation. Thus, compounds **1** and **2** corresponded to structures determined by X-ray diffraction of clusianone and 7-*epi*-clusianone,

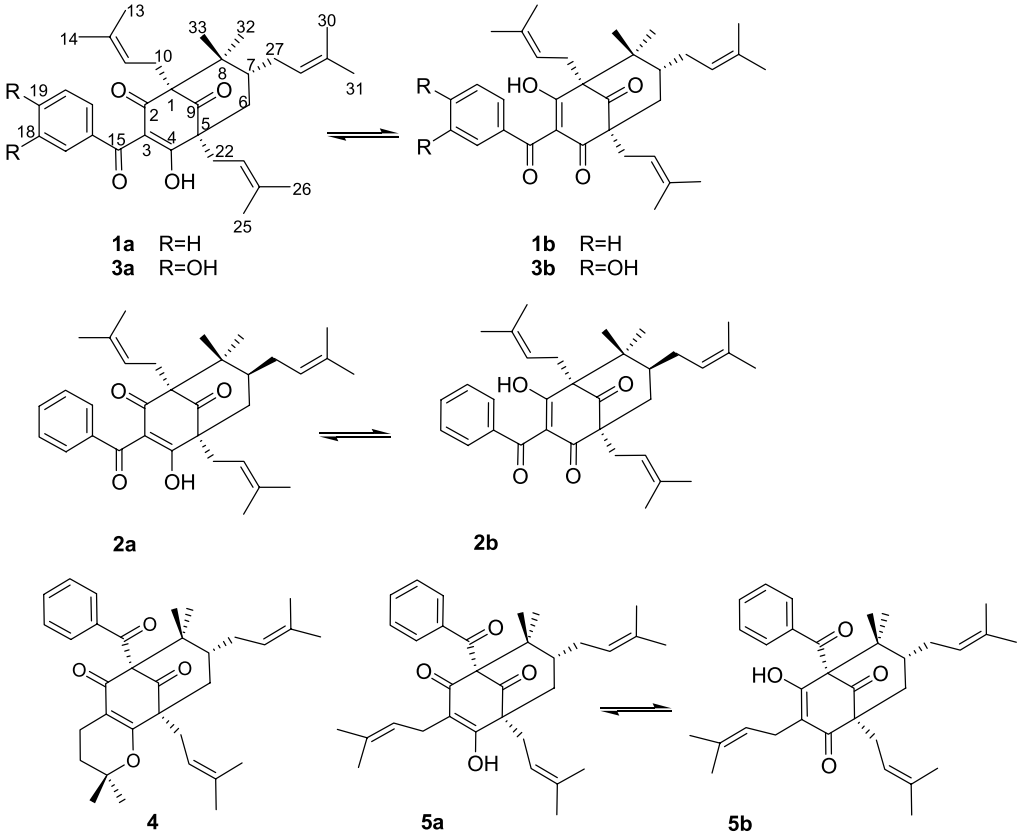

Figure 1. Polyisoprenylated benzophenones **1–5**.

respectively.[1,5] From this spectroscopic evidence, we confirm that clusianone isolated in 1991 was 7-*epi*-clusianone[2] and NMR data for clusianone as it is in nature, without methylation as reported before, are reported herein for the first time.

In the case of clusianone (**1**), the B-ring of the bicyclo-[3.3.1]-nonane system exists a chair conformation, confirming the high value of the vicinal coupling constant (12.4 Hz). In 7-*epi*-clusianone (**2**), the vicinal coupling constant between H-6ax and H-7 has a value of 7.0 Hz. From a conformational point of view, in the case of bicyclo-[3.3.1]-nonane derivatives, one recognizes that each tautomer has two possible conformers: chair and twist-boat. Thus, the conformational situation in clusianone and 7-*epi*-clusianone is very similar. However, 7-*epi*-clusianone and related compounds of the C-27 axial type contain 1,3 diaxial interactions of higher energy. In 7-*epi*-clusianone, the lower stability of the chair conformation, due to steric interactions, seems to be the explanation for the perhaps unexpected high chemical shifts and uncommon coupling constant value observed in C-32ax (δ 26.9 and 27.0) and between H-6ax and H-7 (7.0 Hz), respectively. In conclusion, the molar fraction of twist-boat conformation in 7-*epi*-clusianone and related compounds of the C-27 axial type is increased with respect to that in clusianone and its related compounds. This fact should also explain the differences of NMR data between these two compounds.

In order to further elucidate this point, we performed a quantum-mechanical (QM) characterization of compound **2**. The starting configuration of the chair conformer was taken from crystal structure data,[5] whereas the twist-boat conformer coordinates were obtained from the chair conformer structure by modifying the bicycle dihedral angle.

The 7-*epi*-clusianone chair and twist-boat structures were optimized employing the ONIOM multi-layer method.[10] Within this computational procedure, the theoretical description of the real system is improved by a more accurate treatment of a localized region, referred to as a model system. In our case, the model system consists of the bicycle that is involved in the chair twist-boat equilibrium, while the real system consists of the rest of the molecule. For the real system, we employed the Hartree–Fock (HF)[11] level of theory combined with a 3-21G basis set,[12] whereas the model system calculations were carried out within the density functional theory (DFT), employing the B3LYP hybrid HF-DFT scheme[13] combined to a polarized split-valence basis set augmented by diffuse functions, 6-31+G(d,p).[14] The total energies of the fully optimized chair and twist-boat structures differ by less than 1 kcal/mol, the twist-boat form being slightly more stable. The model system bicycles at their optimized structures are depicted in Figure 2.

Next, we computed the spin–spin coupling constants for these model systems, by the GIAO/B3LYP/6-31+G(d,p) method,[15] taking into account the solvent medium ($CDCl_3$) by means of an implicit solvation model, the polarizable continuum model (PCM).[16] Table 2 lists the $^3J_{H6ax-H7}$ data and the relative energies (the minimum was set to zero) corresponding to the chair and twist-boat conformers. Considering a Boltzmann-weighted average at a temperature of 298.15 K, we obtained for the $^3J_{H6ax-H7}$ coupling a value of 6.8 Hz that is in close agreement with the experimental one (7.0 Hz).

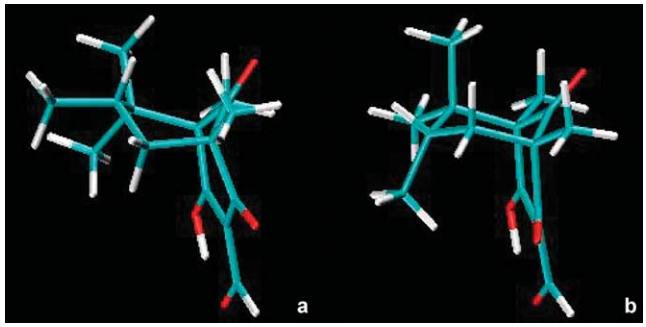

Figure 2. Optimized structures of bicycles in twist-boat (a) and chair (b) conformations.

Table 2. $^3J_{H6ax-H7}$ Coupling constant values corresponding to the chair and twist-boat conformers of 7-*epi*-clusianone and relative energies

	$^3J_{H6ax-H7}$ (Hz)	E (kcal/mol)[a]
Chair	1.0	0.25
Twist-boat	11.5	0.00
Boltzmann average	6.8	
Experimental data	7.0	

[a] The minimum was set to zero.

2.3. Anti-HIV activity

The anti-HIV activity and toxicity of clusianone (**1**), 7-*epi*-clusianone (**2**) as well as previously isolated 18,19-dihydroxyclusianone (**3**), propolone A (**4**) and nemorosone (**5**) were tested in C8166 human T lymphoblastoid cells infected with HIV-1_{MN}. We proposed to group prenylated benzophenones derivatives, that present a bicyclo-[3.3.1]-nonane-2,4,9-trione system, in accord with benzoyl moiety position: type A if it is on C-1 and type B if it is on C-3.[8] Propolone A (**4**) and nemorosone (**5**) are derivatives of type A, whereas clusianone (**1**), 7-epiclusianone (**2**) and 18,19-dihydroxyclusianone (**3**) are derivatives of type B (Fig. 1). Compounds **1**–**3** and **5** showed the keto-enolic equilibrium associated to the process of conversion between tautomers as evidenced by two sets of NMR signals, propolone A (**4**) is the sole compound without that possibility. Compounds **1** and **2** were stereoisomers and **3** was the unique phenolic compound employed.

The results of antiviral activities are presented in Table 3. The most promising compound was propolone A (**4**) with an EC_{50} value of 0.32 μM and a therapeutic index of 15.6. Nemorosone (**5**) and 7-*epi*-clusianone (**2**) demonstrated relatively potent anti-HIV activity with an in vitro EC_{50} value of 0.8 and 2.0 μM, respectively, with good selectivity indices of 6.2 and 10. Clusianone (**1**) was active at very low concentration (EC_{50}=0.02 μM) but also showed increased cytotoxicity, hence a reduced therapeutic index. 18, 19-Dihydroxyclusianone (**3**) had the lowest selectivity index with a EC_{50} value of 7.1 μM.

Table 3. Anti-HIV activity of polyisoprenylated benzophenone derivatives **1–5**

Compounds	EC_{50}[a]	TC_{50}[b]	SI[c]	EC_{50} by gp120-CD4 ELISA
1	0.020±0.003	0.1±0.22	5.0±0.063	0.02±0.003
2	2.0±0.07	20.0±1.3	10.0±1.0	2.4±0.05
3	7.1±0.2	16.0±0.21	2.25±0.03	7.5±0.2
4	0.32±0.01	5.0±0.45	15.6±0.9	>5
	0.80±0.04	5.0±0.26	6.25±0.23	>5

The EC_{50} and TC_{50} values were calculated from averages of three independent experiments showing similar results. The concentration that inhibited gp120-CD4 interaction by 50% was taken as EC_{50} by gp120-CD4 ELISA.
[a] EC_{50}=concentration (μM) that reduces by 50% the production of gp120 in infected C8166 cells.
[b] TC_{50}=concentration (μM) that causes 50% cytotoxicity to uninfected C8166 cells.
[c] SI=selectivity index.

A comparison of the anti-HIV activities of polyisoprenylated benzophenone derivatives suggested that the presence of the keto-enolic equilibrium is not essential in the antiviral activity as the most active compound was propolone A. Another very interesting result was the observed difference between the EC_{50} and TC_{50} values of the epimers clusianone (0.02 and 0.1 μM) and 7-*epi*-clusianone (2 and 20 μM), indicating that the C-7 configuration may play an important role in the potency of the action.

A study of the mechanism of action revealed that the benzophenone derivatives of type B (**1–3**) inhibited the gp120-sCD4 interaction, suggesting that they were interfering with the viral attachment to the cellular receptor CD4 and preventing infection. On the other hand, benzophenones derivatives of type A (**4** and **5**) had no effect on gp120-sCD4 interaction (Table 3). Although only 5 compounds were studied, the importance of the relative position of the benzoyl moiety was quite apparent.

Clusianone (**1**) and 7-*epi*-clusianone (**2**), like dextran sulfate, were more effective when added prior to or at the time of the virus infection. They also neutralized virus infectivity by more than 99%, when incubated with the virus at 0.05 and 10 μM, respectively, for 60 min at 37 °C. The compounds were removed by serial dilutions before adding cells for infection. The virus titer was compared with a control without a compound in the same experiment. It suggests that compounds **1–3** may be inhibiting infection by interfering at an early stage of the virus infection, attachment or fusion while the mode of action for compounds **4** and **5** was different. Similar compounds had also been reported previously to be inhibitors of HIV-1 reverse transcriptase and infection.[17–22]

Although only a small number of these closely related compounds were studied, but the differences in the selectivity and modes of action were quite interesting. Therefore, it may prove possible to synthesize new derivatives with better selectivity and specificity. The mode of action of compounds **1–3** makes them suitable candidates for further studies for use in prevention of infection.

3. Experimental

3.1. General methods

Unless specified, solvents were reagent grade. They were purchased from Aldrich or Fluka or Carlo Erba and were used without further purification. Optical rotations were measured on a Perkin-Elmer 192 polarimeter equipped with a sodium lamp (589 nm) and a 1 cm microcell. UV spectra were obtained with a Beckman DU 670 spectrophotometer and IR spectra with a Bruker IFS-48 spectophotometer. A Bruker DRX-600 spectrometer, operating at 599.19 MHz for ^{1}H and 150.858 for ^{13}C, using the UXNMR software package was used for NMR experiments in $CDCl_3$. ^{1}H–^{1}H DQF-COSY (Double Quantum Filtered COSY), ^{1}H–^{13}C HSQC, HMBC and ROESY experiments were obtained using conventional pulse sequences. Electrospray ionization mass spectrometry (ESI-MS) in the positive and negative ion mode was performed using a Finnigan LC-Q Advantage instrument (Termoquest, San Jose, CA) equipped with Excalibur software. HPLC separations were performed on a Waters 590 series pumping system equipped with a Waters R401 refractive index detector and a Waters μ-Bondapak C18 10 μm (300×7.8 mm) column. All the quantum-mechanical calculations were performed using the GAUSSIAN03 program package.[23] The structures of all the considered species were optimized using the two-layer ONIOM (Becke3LYP/6-31+G(d,p):HF/3-21G) method. Spin–spin coupling constants were computed employing the GIAO/B3LYP/6-31+G(d,p) method taking into account the contribution of the solvent medium ($CDCl_3$) by the polarizable continuum model (PCM).

3.2. Plant material

Fruits of *C. torresii* Standl. were collected in Turrialba, Cartago, Costa Rica, in February 1999 and identified by Prof. Mariano Barrios Chica, of the Universidad Nacional de Costa Rica. A voucher specimen (N. H. 90579) is deposited at the Herbario of Museo Nacional, Costa Rica.

3.2.1. Clusianone (1). White crystal: $[\alpha]_D$ +58.3° (*c* 0.7, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 280 (3.95) and 230 (4.22) nm; IR (KBr) ν_{max} 3352, 1782, 1730, 1716, 1646, 1220 cm^{-1}; ^{1}H and ^{13}C NMR data, Table 1; ESI-MS (positive mode) *m/z* 503 $[M+H]^+$, (positive mode) *m/z* 501 $[M-H]^-$.

3.2.2. 7-*epi*-Clusianone (2). White crystal: $[\alpha]_D$ +62.3° (*c* 1.1, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 280 (4.20) and 248 (4.34) nm; IR (KBr) ν_{max} 3350, 1776, 1728, 1715, 1642, 1224, 1150 cm^{-1}; ^{1}H and ^{13}C NMR data, Table 1; ESI-MS (positive mode) *m/z* 503 $[M+H]^+$, (positive mode) *m/z* 501 $[M-H]^-$.

3.3. Antiviral assays

The anti-HIV activity and toxicity of compounds were assessed in C8166 human T lymphoblastoid cells infected with HIV-1_{MN}. The cells were cultured in RPMI 1640 with 10% fetal calf serum. Forty-thousand cells per microtiter plate well were mixed with five-fold dilutions of compounds prior to addition of 10 $CCID_{50}$ units of virus and incubated for 5–6 days. The inhibition of HIV-infection was assessed by examining syncytia, by estimating antigen gp120 by ELISA,[24] and by measuring cell viability of virus-infected cells and uninfected cell controls using the XTT-formazan method.[25]

3.4. Virus infectivity assay

The total progeny virus was titrated in microtiter plates using double dilutions of freshly collected supernatants and C8166 cells. The end point was determined by examining syncytia formation and by the XTT-formazan method. The virus titer ($CCID_{50}$) is expressed as the reciprocal of the dilution that gave a 50% end point. To measure the effects of compounds on virus infectivity, HIV-1_{IIIB} (10^4–10^5 $CCID_{50}$) was incubated with test compound at 37 °C for 1 h, the virus was serially diluted, and the infectivity end-point determined. In each case the compound was diluted to well below the EC_{50} such that residual compound did not interfere with the virus titration.

3.5. Gp120-sCD4 binding assays

Gp120-sCD4 interaction was measured by ELISA,[24] sCD4 was bound to microtiter plate wells at a concentration of 0.05 μg/well. Various dilutions of compounds were mixed with equal volumes of recombinant gp120 (0.04 μg/mL) and added to CD4 coated wells. After incubation at 37 °C for 3–5 h, the binding of gp120 was detected using human anti-HIV serum and anti-human Ig conjugated to horse-radish peroxidase. Using WIACALC (Pharmacia LKB) the percent inhibition was calculated from linear logarithmic plots using three concentrations of gp120 alone as standard.

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Mn(III)-based C–C bond formation: regioselective α′-allylation of various α,β-unsaturated, α and β-alkoxy α,β-unsaturated ketones

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Abstract—The Manganese(III)-based regioselective α′-keto radical generation of unsaturated ketones is a versatile synthetic procedure with broad applicability. The generated α′-keto radical slowly creates a metal enolate in a solvent at reflux. The resultant metal enolate affords the corresponding α′-allylated α,β-unsaturated ketones in good yields. This method is the first example of the metal mediated regioselective α′-allylation of α,β-unsaturated ketones. The ketones that have α or β-alkoxy groups also work efficiently.

1. Introduction

The empirical endeavour on the synthesis of targets with wide complexity has resulted in the development of reactions that emphasize chemo-, regio-, and stereoselectivity. In defining the strategies and reactions to construct complex molecules, regioselectivity is required.[1] Metal-mediated allylation generally has a central position in the synthesis of various complex natural products. A wide variety of allylations are well known in the literature as useful methods for carbon–carbon bond formation, that is, metal-mediated allyl addition to carbonyl,[2,3] and the direct allylation on the α-position of ketones.[4,5] A considerable challenge is to affect a high regioselectivity between carbonyl carbons and the α and α′-positions of α,β-unsaturated ketones.

In the last decade, Mn(III)-based oxidative free-radical reactions have been developed into a versatile protocol for the formation of highly functionalized products from simple precursors.[6] In 1976, Williams and Hunter reported that the $Mn(OAc)_3 \cdot 2H_2O$ oxidation of enones in HOAc at reflux affords α′-acetoxy enones in low yields.[7] In connection with our synthetic studies with manganese(III) acetate,[8] we found that trapping of the α′-keto radicals that were obtained from β-alkoxy α,β-unsaturated ketones with benzene as solvent is much faster than acetoxylation, affording good yields of tandem oxidation products.[8d] These noteworthy results prompted us toward the development of a new method in the field of regioselective direct allylation of α,β-unsaturated ketones. Recently, we reported a complete regioselectivity related to the metal-mediated α′-allylation of enones.[8f] The allylation of enones mediated by Mn(III) shows exclusive selectivity toward the α′-position of α,β-unsaturated ketones. We describe here, the results of the $Mn(OAc)_3$ based allylation of various α,β-unsaturated ketones and α- or β-alkoxy α,β-unsaturated ketones.

2. Results and discussion

As a starting point, we have studied the use of manganese(III) acetate as a potentially useful mediator for the metal-promoted regioselective α′-allylation reaction of various enones. When 3-methyl-cyclopent-2-enone **1c** (entry 3) was stirred with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of allyl bromide in benzene for 8 h at reflux, 81% of 5-allyl-3-methyl-cyclopent-2-enone **2c** was isolated. When 3 equiv of $Mn(OAc)_3 \cdot 2H_2O$ was used, the isolated yield of the allylation product substantially decreased to 53 and 25% of the α′-acetoxylation product[9] that was isolated. Changing the amount of $Mn(OAc)_3 \cdot 2H_2O$ to 1 equiv decreased the yield of the allylation product too (64%), and no α′-acetoxylation product was observed. The stoichiometric amount of manganese(III) acetate appears to be critical.

As a natural extension of this study, we have pursued a complementary investigation aimed at subjecting various α,β-unsaturated cyclic ketones to comparable scrutiny. Subsequently, a variety of cyclopentenones and cyclohexenones were tested with this allylation method (Scheme 1).

Keywords: Enones; Manganese and compounds; Allylation.
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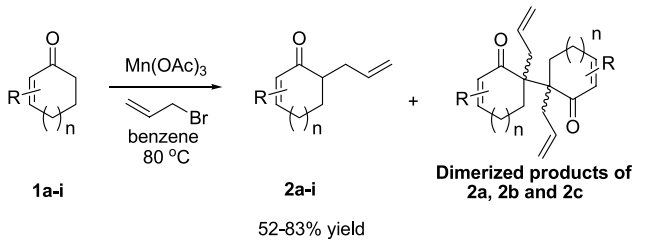


Scheme 1.

Selected examples are shown in Table 1. It was found that various cyclopentenones and cyclohexenones were efficiently allylated. In general, cyclopentenone derivatives afford higher chemical yields than cyclohexenone derivatives. We could not observe any substantial change in the chemical yields related to the substituents on the substrates. In entry 1, 2 and 3, the dimerized allylated products were isolated.[10] These results can strongly support the formation of a radical on the α′-position of enone systems. We attempted to replace benzene with a more innocuous solvent toluene in entries 1–3 and obtained a 5–7% decrease in the yields.[11] Regioselective allylation was also tested with an acyclic substrate mesityl oxide (entry 9) and the allylated acylic product **2i** was obtained in an acceptable yield.

We also examined the allylation reaction of β-alkoxy and α-alkoxy α,β-unsaturated ketones that play an important role in the synthesis of quassinoids and prostaglandines, respectively.

In the first part of that study, 3-ethoxy-5,5-dimethyl-2-cyclohexenone was chosen as a model compound. The reaction of **3e** in benzene with 2 equiv of Mn $(OAc)_3 \cdot 2H_2O$ and 1 equiv of allyl bromide for 8 h at reflux affords 75% of 6-allyl-3-ethoxy-5,5-dimethyl-2-cyclohexenone **4e** (entry 5). Selected examples are shown in Table 2 (Scheme 2).

In order to test the allylation reaction, whether it proceeds by a radical mechanism or by a nucleophilic substitution, 3-ethoxy-5,5-dimethyl-2-cyclohexenone **3e** and 3-methyl-2-cyclohexenone **2e** were reacted with crotyl bromide under the same conditions. Both afforded the nucleophilic substitution products **5a** and **5b** in 49 and 52% yields, respectively, (Scheme 3); the regioselectivity of the allylation implies that the reaction proceeds via an S_N2 mechanism and is not radical in nature.[12]

From these results in particular, with the results of the allylation where it was tested with different allyl side chains, we subsequently proposed a reaction mechanism as is shown in Scheme 4. The reaction presumably proceeds via the formation of Mn(III) enolate **6**, which by way of one electron oxidation, gives the α′-keto radical **7**.[13] The second equiv of $Mn(OAc)_3$ slowly forms the Mn(II) enolate **8**. Alkylation of this metal enolate with allyl bromide yields the α′-allyl α,β-unsaturated cyclic ketone **2**. Vinogradov et al. reported that α′-keto radicals generated by higher ketones would result in secondary radicals, which dimerize or lead to tertiary radicals, which are prone to further oxidation.[14] In accordance with this conclusion, in this current study the dimerization of product **2** was observed for entries 1, 2 and 3 as was mentioned above.

Table 1. α′-Allylation of α,β-unsaturated enones mediated by $Mn(OAc)_3$ in benzene

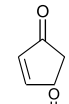
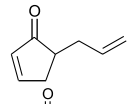
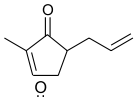
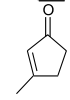
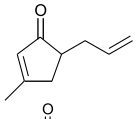
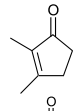
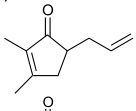
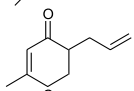
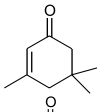
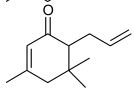
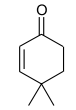
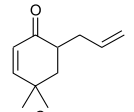
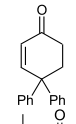
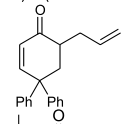
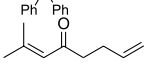
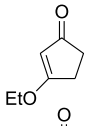
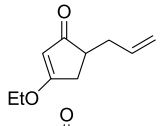
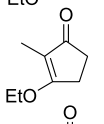
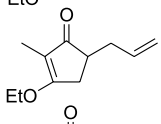
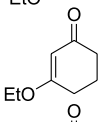
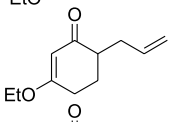
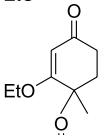
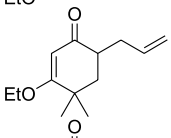
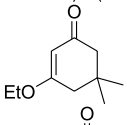
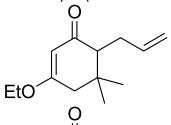
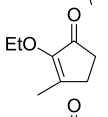
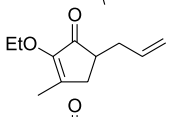
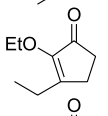
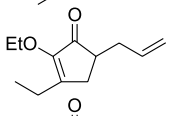
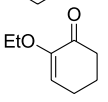
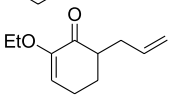
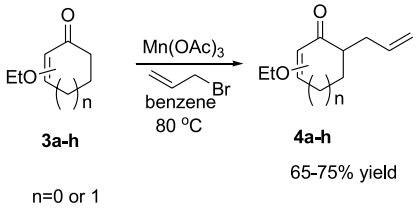
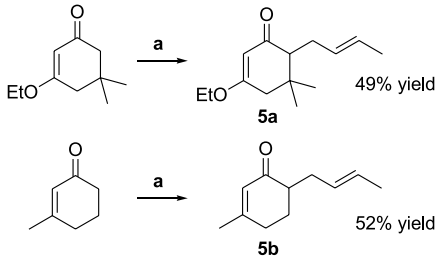
Entry	Reactant **1**	Product	**2**[11]	Yield (%)	Time (h)
1			**2a**	79	8
2			**2b**	80	8
3			**2c**	81	8
4			**2d**	83	10
5			**2e**	78	12
6			**2f**	68	12
7			**2g**	67	10
8			**2h**	72	12
9			**2i**	52	14

Table 2. α'-Allylation of α-alkoxy and β-alkoxy α,β-unsaturated enones mediated with $Mn(OAc)_3$

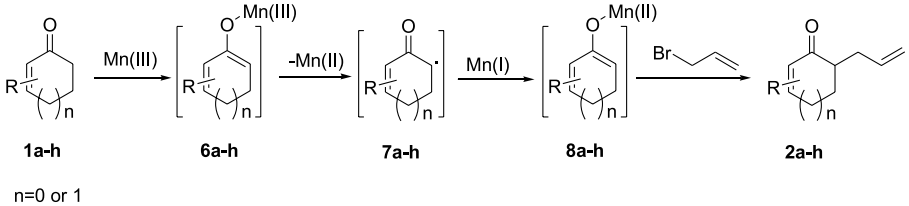
Entry	Reactant **3**	Product	**4**	Yield (%)	Time (h)
1			**4a**	69	7
2			**4b**	72	6
3			**4c**	67	7
4			**4d**	65	5
5			**4e**	75	8
6			**4f**	75	9
7			**4g**	72	12
8			**4h**	65	11



Scheme 2.



Scheme 3.



Scheme 4.

In conclusion, manganese(III) acetate is highly effective for mediating the α'-allylations of α,β-unsaturated cyclic ketones, α-alkoxy and β-alkoxy α,β-unsaturated cyclic ketones. This one-step reaction offers a complete regioselectivity towards the α'-allylation of cyclic enones and opens up a new class of $Mn(OAc)_3$ reactions.

3. Experimental

Nuclear magnetic resonance spectra were acquired on a Bruker Spectrospin Avance DPX 400 spectrometer at 400 MHz for ^1H and 100 MHz for ^{13}C, in $CDCl_3$. Chemical shifts are given in ppm from tetramethylsilane. IR spectra were obtained using a Perkin-Elmer Model 1600 series FT-IR spectrometer and are reported in cm^{-1}. Mass spectra were recorded with a Varian MAT 212. Flash chromatography: Merck silica gel 60 (230–400 mesh).

3.1. General procedure for the $Mn(OAc)_3$ based allylation of α,β-unsaturated ketones 1 and α and β-alkoxy α,β-unsaturated ketones 3

A mixture of $Mn(OAc)_3 \cdot 2H_2O$ (3.25 g, 14.0 mmol) in benzene (150 ml) was heated at reflux for 45 min using a Dean-Stark trap. The mixture was then cooled to room temperature and the α,β-unsaturated ketone (7.0 mmol) and allyl bromide (0.85 g, 7.0 mmol) were added. The mixture was heated to reflux until its dark brown colour disappeared. In addition, it was monitored by TLC. The reaction mixture was diluted with an equal amount of ethyl acetate, and the organic phase was washed with 1 M HCl followed by saturated $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$ and evaporated in vacuo. The crude product was separated by way of flash column chromatography using ethyl acetate/hexane as an eluent to afford the product.

3.1.1. 5-Allyl-cyclopent-2-enone 2a. (0.68 g, 79%) as a colourless oil; ν_{max} (neat) 2960, 2860, 1707, 1590 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.68–7.70 (1H, m, *H*C=CHCO), 6.19 (1H, dd, $J=2.1$, 7.6 Hz, HC=C*H*CO), 5.70–5.81 (1H, m, CH_2=C*H*CH_2), 5.08 (1H, d, $J=19.3$ Hz, C*H*$_a$H$_b$=CH), 5.04 (1H, d, $J=11.1$ Hz, CH_a*H*$_b$=CH), 2.80–2.86 (1H, m, CH_2C*H*CO), 2.52–2.57 (1H, m, C*H*$_a$H$_b$), 2.39–2.44 (2H, m, C*H*$_2$), 2.08–2.18 (1H, m, CH_a*H*$_b$); δ_C (100.6 MHz, $CDCl_3$) 212.0, 164.1, 135.6, 134.2, 117.2, 44.4, 35.6, 35.2; HRMS (EI): M^+, found 122.0737. $C_8H_{10}O$ requires 122.0732.

3.1.2. 5-Allyl-2-methyl-cyclopent-2-enone 2b. (0.76 g, 80%) as a colourless oil; ν_{max} (neat) 2910, 1682, 1615, 1431 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.28 (1H, d, $J=2.1$ Hz, *H*C=CMeCO), 5.70–5.80 (1H, m, CH_2C*H*=CH_2), 5.07 (1H, d, $J=17.1$ Hz, C*H*$_a$H$_b$=CH), 5.02 (1H, d, $J=10.7$ Hz, CH_a*H*$_b$=CH), 2.65–2.71 (1H, m, C*H*CO), 2.53–2.58 (1H, m, C*Ha* Hb), 2.42–2.45 (1H, m, CH_a*H*$_b$), 2.23–2.29 (1H, m, C*H*$_a$H$_b$), 2.10–2.15 (1H, m, CH_a*H*$_b$), 1.78 (3H, s, *Me*CCO); δ_C (100.6 MHz, $CDCl_3$) 211.7, 157.4, 141.6, 135.9, 117.0, 44.6, 35.9, 33.0, 10.6; HRMS (EI): M^+, found 136.0890. $C_9H_{12}O$ requires 136.0888.

3.1.3. 5-Allyl-3-methyl-cyclopent-2-enone 2c. (0.77 g, 81%) as a colourless oil; ν_{max} (neat) 3066, 2973, 1690, 1648 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.92 (1H, s, =C*H*CO), 5.70–5.79 (1H, m, CH_2C*H*=CH_2), 5.07 (1H, d, $J=17.3$ Hz, C*H*$_a$H$_b$=CH), 5.03 (1H, d, $J=10.5$ Hz, CH_a*H*$_b$=CH), 2.69 (1H, dd, $J=6.3$, 18.1 Hz, C*H*CO), 2.49–2.63 (2H, m, C*H*$_2$C=), 2.29 (1H, d, $J=18.1$ Hz, C*H*$_a$H$_b$CHCO), 2.13–2.14 (1H, m, CH_a*H*$_b$CHCO), 2.12 (3H, s); δ_C (100.6 MHz, $CDCl_3$) 211.4, 178.0, 135.7, 130.2, 117.0, 46.1, 39.2, 35.9, 19.7; HRMS (EI): M^+, found 136.0893. $C_9H_{12}O$ requires 136.0888.

3.1.4. 5-Allyl-2,3-dimethyl-cyclopent-2-enone 2d. (0.87 g, 83%) as a colourless oil; ν_{max} (neat) 3066, 2973, 2914, 1690, 1648 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.69–5.80 (1H, m, CH_2C*H*=CH_2), 5.06 (1H, d, $J=17.1$ Hz, C*H*$_a$H$_b$=CH), 5.01 (1H, d, $J=9.5$ Hz, CH_a*H*$_b$=CH), 2.64 (1H, dd, $J=5.8$, 19.3 Hz, C*H*CO), 2.52–2.62 (1H, m, C*H*$_a$H$_b$CH=CH_2), 2.42–2.44 (1H, m, CH_a*H*$_b$CH=CH_2), 2.05–2.10 (1H, m, C*H*$_a$H$_b$CHCO), 2.21 (1H, d, $J=19.3$ Hz, CH_a*H*$_b$CHCO), 2.04 (3H, s, *Me*CCO), 1.69 (3H, s, *Me*C=CMeCO); δ_C (100.6 MHz, $CDCl_3$) 211.1, 169.1, 136.0, 135.8, 116.8, 44.5, 38.1, 36.0, 17.4, 9.8; HRMS (EI): M^+, found 150.1040. $C_{10}H_{14}O$ requires 150.1045.

3.1.5. 6-Allyl-3-methyl-cyclohex-2-enone 2e. (0.82 g, 78%) as a colourless oil; ν_{max} (neat) 3024, 2923, 2855, 2357, 1659 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.78 (1H, s, =C*H*CO), 5.65–5.76 (1H, m, CH_2C*H*=CH_2), 5.09 (1H, d, $J=18.2$ Hz, C*H*$_a$H$_b$=CH), 4.96 (1H, d, $J=9.2$ Hz, CH_a*H*$_b$=CH), 2.53–2.56 (1H, m, C*H*CO), 2.15–2.23 (3H, m, C*H*$_2$CH=CH_2), 1.98–2.09 (2H, m, C*H*$_a$H$_b$CHCO), 1.87 (3H, s, *Me*), 1.58–1.70 (1H, m, CH_a*H*$_b$CHCO); δ_C (100.6 MHz, $CDCl_3$) 201.2, 162.3, 136.7, 126.7, 117.0, 45.4, 34.1, 30.7, 27.6, 24.6; HRMS (EI): M^+, found 150.1044. $C_{10}H_{14}O$ requires 150.1045.

3.1.6. 6-Allyl-3,5,5-trimethyl-cyclohex-2-enone 2f. (0.85 g, 68%) as a colourless oil; ν_{max} (neat) 2956, 1665, 1445, 1370 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.79–5.93 (2H, m, =C*H*CO and C*H*=CH_2), 5.04 (1H, d, $J=15.2$ Hz, C*H*$_a$H$_b$=CH), 4.96 (1H, d, $J=11.3$ Hz, CH_a*H*$_b$=CH), 2.15–2.31 (4H, m, C*H*$_2$CH and C*H*$_2$CMe_2), 2.08–2.12 (1H, m, C*H*CO), 1.91 (3H, s, *Me*C=), 1.05 (3H, s, *Me*$_2$C), 0.96 (3H, s, *Me*$_2$C); δ_C (100.6 MHz, $CDCl_3$) 202.1, 158.5, 138.0, 125.3, 115.7, 57.5, 45.1, 36.7, 30.7, 29.1, 24.6, 24.5; HRMS (EI): M^+, found 178.1355. $C_{12}H_{18}O$ requires 178.1358.

3.1.7. 6-Allyl-4,4-dimethyl-cyclohex-2-enone 2g. (0.77 g, 67%) as a colourless oil; ν_{max} (neat) 3211, 2892, 1715, 1665, 1515, 1289 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.40 (1H, d, $J=10.0$ Hz, C*H*=CHCO), 5.63 (1H, d, $J=10.0$ Hz, CH=C*H*CO), 5.59–5.62 (1H, m, C*H*=CH_2), 4.87 (1H, d, $J=17.1$ Hz, C*H*$_a$H$_b$=CH), 4.84 (1H, d, $J=9.1$ Hz, CH_a*H*$_b$=CH), 2.47–2.53 (1H, m, C*H*CO), 2.26–2.34 (1H, m, C*H*$_a$H$_b$CH=), 1.85–1.92 (1H, m, CH_a*H*$_b$CH=), 1.66 (1H, dd, $J=4.6$, 13.4 Hz, C*H*$_a$H$_b$CHCO), 1.41 (1H, t, $J=13.4$ Hz, CH_a*H*$_b$CHCO), 0.98 (3H, s, *Me*$_2$C), 0.95 (3H, s, *Me*$_2$C); δ_C (100.6 MHz, $CDCl_3$) 200.9, 159.2, 136.6, 127.0, 117.0, 57.3, 42.5, 42.0, 34.0, 30.9, 25.8; HRMS (EI): M^+, found 164.1207. $C_{11}H_{16}O$ requires 164.1202.

3.1.8. 6-Allyl-4,4-diphenyl-cyclohex-2-enone 2h. (1.45 g, 72%) as a colourless oil; ν_{max} (neat) 3024, 2931, 2885, 1665, 1589, 1437 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.20–7.47 (10H, m, *Ph*$_2$C), 7.15 (1H, d, $J=10.1$ Hz, C*H*=CHCO); 6.21 (1H, d, $J=10.1$ Hz, CH=*CH*CO), 5.67–5.77 (1H, m, C*H*=CH_2), 5.02–5.05 (2H, m, CH=C*H*$_2$), 2.67–2.75 (2H, m, C*H*$_2$CH=), 2.32–2.42 (2H, m, C*H*$_2$CHCO), 2.04–2.17 (1H, m, C*H*CO); δ_C (100.6 MHz, $CDCl_3$) 199.8, 155.2, 148.0, 143.1, 135.6, 129.1, 128.8, 128.7, 128.6, 128.5, 128.0, 127.9, 127.8, 127.2, 127.0, 126.7, 117.1, 49.9, 42.7, 41.2, 33.2; HRMS (EI): M^+, found 288.1519. $C_{21}H_{20}O$ requires 288.1514.

3.1.9. 2-Methyl octa-2,7-dien-4-one 2i. (0.5 g, 52%) as a colourless oil; ν_{max} (neat) 3079, 1595, 1692, 981, 882 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.00 (1H, s, Me_2C=C*H*CO), 5.71–5.82 (1H, m, CH_2=C*H*), 4.96 (1H, d, $J=15.2$ Hz, C*H*$_a$H$_b$=CH), 4.90 (1H, d, $J=8.9$ Hz, CH_a*H*$_b$=CH), 2.43 (2H, t, $J=7.0$ Hz, COC*H*$_2$CH$_2$), 2.25–2.30 (2H, m, COCH$_2$C*H*$_2$), 2.08 (3H, s, *Me*$_2$C=), 1.82 (3H, s, *Me*$_2$C=); δ_C (100.6 MHz, $CDCl_3$) 200.5, 155.6, 137.9, 124.1, 115.3, 43.6, 28.5, 28.0,

21.1; HRMS (EI): MH^+, found 139.1116. $C_9H_{14}O$ requires 139.1123.

3.1.10. 5-Allyl-3-ethoxy-cyclopent-2-enone 4a. (0.72 g, 69%) as a colourless oil; ν_{max} (neat) 2950, 1125, 1700, 1560 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.65–5.74 (2H, m, =C*H*CO and C*H*=CH_2), 5.02 (1H, d, J=18.9 Hz, CH_a-H_b=CH), 4.98 (1H, d, J=11.0 Hz, CH_aH_b=CH), 3.97 (2H, q, J=7.1 Hz, MeCH_2O), 2.63 (1H, dd, J=6.8, 17.6 Hz, C*H*CO), 2.47–2.53 (2H, m, CH_2), 2.27 (1H, dd, J=1.7, 17.6 Hz, CH_aH_bCH=CH_2), 2.00–2.14 (1H, m, CH_aH_bCH=CH_2), 1.34 (3H, t, J=7.1 Hz, *Me*CH_2O); δ_C (100.6 MHz, $CDCl_3$) 207.8, 189.4, 135.7, 113.2, 104.3, 68.0, 44.7, 35.9, 34.5, 14.5; HRMS (EI): M^+, found 166.0991. $C_{10}H_{14}O_2$ requires 166.0994.

3.1.11. 5-Allyl-3-ethoxy-2-methyl-cyclopent-2-enone 4b. (0.9 g, 72%) as a colourless oil; ν_{max} (neat) 2900, 1675, 1400, 1120 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.64–5.74 (1H, m, C*H*=CH_2), 5.02 (1H, d, J=18.8 Hz, CH_aH_b=CH), 4.98 (1H, d, J=10.5 Hz, CH_aH_b=CH), 4.15–4.32 (2H, m, MeCH_2O), 3.07 (1H, dd, J=6.6, 18.9 Hz, CH_aH_bCHCO), 2.99 (1H, dd, J=6.7, 18.5 Hz, C*H*CO), 2.79 (1H, d, J=18.9 Hz, CH_aH_bCHCO), 1.47–2.56 (1H, m, CH_2=CHCH_aH_b), 1.98–2.11 (1H, m, CH_2=CHCH_aH_b), 1.71 (3H, s, *Me*C=), 1.37 (3H, t, J=7.0 Hz, *Me*CH_2O); δ_C (100.6 MHz, $CDCl_3$) 201.0, 178.8, 136.0, 119.1, 117.1, 66.2, 45.7, 45.2, 40.1, 15.7, 7.5; HRMS (EI): M^+, found 180.1156. $C_{11}H_{16}O_2$ requires 180.1150.

3.1.12. 6-Allyl-3-ethoxy-cyclohex-2-enone 4c. (0.74 g, 67%) as a colourless oil; ν_{max} (neat) 3020, 2915, 2852, 1650, 1110 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.75–5.86 (1H, m, C*H*=CH_2), 5.35 (1H, s, =C*H*CO), 5.08 (1H, d, J=15.2 Hz, CH_aH_b=CH), 5.05 (1H, d, J=5.1 Hz, CH_a-H_b=CH), 3.88–3.94 (2H, m, MeCH_2O), 2.64–2.68 (1H, m, C*H*CO), 2.43 (2H, t, J=5.3 Hz, CH_2CH=CH_2), 2.25–2.28 (1H, m, C$H_aH_b$$CH_2$CHCO), 2.05–2.19 (2H, m, CH_2CHO), 1.71–1.75 (1H, m, $CH_aH_b$$CH_2$CHCO), 1.38 (3H, t, J=7.0 Hz, *Me*CH_2); δ_C (100.6 MHz, $CDCl_3$) 200.5, 182.6, 137.0, 116.8, 101.3, 64.6, 41.8, 34.2, 27.4, 25.3, 14.4; HRMS (EI): M^+, found 180.1142. $C_{11}H_{16}O_2$ requires 180.1150.

3.1.13. 6-Allyl-3-ethoxy-4,4-dimethyl-cyclohex-2-enone 4d. (0.95 g, 65%) as a colourless oil; ν_{max} (neat) 3210, 2890, 1710, 1662, 1115 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.66–5.76 (1H, m, C*H*=CH_2), 5.16 (1H, s, =C*H*CO), 4.99 (1H, dd, J=15.1 Hz, CH_aH_b=CH), 4.96 (1H, d, J=7.7 Hz, CH_aH_b=CH), 3.72–3.89 (2H, m, MeCH_2O), 2.64–2.70 (1H, m, C*H*CO), 2.31–2.39 (1H, m, CH_aH_bCH=CH_2), 1.97–2.12 (1H, m, CH_aH_bCH=CH_2), 1.70 (1H, dd, J=4.8, 13.3 Hz, CH_aH_bCHCO), 1.54 (1H, t, J=13.5 Hz, CH_aH_bCHCO), 1.28 (3H, t, J=7.0 Hz, *Me*CH_2), 1.16 (3H, s, *Me*$_2$C), 1.09 (3H, s, *Me*$_2$C); δ_C (100.6 MHz, $CDCl_3$) 192.9, 174.8, 171.0, 100.8, 80.3, 77.9, 65.1, 43.7, 36.8, 27.5, 21.1, 20.5, 14.5; HRMS (EI): M^+, found 208.2967. $C_{13}H_{20}O_2$ requires 208.1464.

3.1.14. 6-Allyl-3-ethoxy-5,5-dimethyl-cyclohex-2-enone 4e. (1.24 g, 75%) as a colourless oil; ν_{max} (neat) 3019, 2960, 1740, 1640, 1598, 1456, 1372 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.76–5.87 (1H, m, C*H*=CH_2), 5.21 (1H, s, =C*H*CO), 4.94 (1H, d, J=17.2 Hz, CH_aH_b=CH), 4.90 (1H, d, J=10.3 Hz, CH_aH_b=CH), 3.82 (2H, q, J=7.1 Hz, MeCH_2O), 2.55 (1H, d, J=17.6 Hz, C*H*CO), 2.24–2.31 (2H, m, CH_aH_bCH=CH_2 and C$H_aH_b$$CMe_2$), 2.15 (1H, d, J=17.6 Hz, CH_aH_bCH=CH_2), 1.99–2.03 (1H, m, $CH_aH_b$$CMe_2$), 1.29 (3H, t, J=7.1 Hz, *Me*CH_2), 1.02 (3H, s, *Me*CH_2), 0.93 (3H, s, *Me*CH_2); δ_C (100.6 MHz, $CDCl_3$) 201.6, 174.6, 138.1, 115.5, 101.1, 64.4, 61.8, 57.3, 42.4, 35.5, 31.2, 14.5, 14.4; HRMS (EI): M^+, found 208.1463. $C_{13}H_{20}O_2$ requires 208.1464.

3.1.15. 5-Allyl-2-ethoxy-3-methyl-cyclopent-2-enone 4f. (0.95 g, 75%) as a colourless oil; ν_{max} (neat) 3060, 2970, 1680, 1645, 1115 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.63–5.77 (1H, m, C*H*=CH_2), 5.01 (1H, d, J=18.6 Hz, CH_aH_b=CH), 4.99 (1H, d, J=10.4 Hz, CH_aH_b=CH), 4.04–4.18 (2H, m, MeCH_2O), 2.49 (1H, dd, J=6.4, 16.8 Hz, C*H*CO), 2.48 (1H, dd, J=6.4, 17.9 Hz, CH_aH_bCH=CH_2), 2.32–2.35 (1H, m, CH_aH_bCH=CH_2), 2.02–2.10 (2H, m, CH_2CHCO), 1.90 (3H, s, *Me*C=), 1.19 (3H, t, J=7.0 Hz, *Me*CH_2); δ_C (100.6 MHz, $CDCl_3$) 205.2, 154.5, 151.6, 135.5, 117.2, 66.4, 43.0, 20.7, 33.9, 16.0, 15.2; HRMS (EI): M^+, found 180.1153. $C_{11}H_{16}O_2$ requires 180.1150.

3.1.16. 5-Allyl-2-ethoxy-3-ethyl-cyclopent-2-enone 4g. (0.9 g, 72%) as a colourless oil; ν_{max} (neat) 3055, 2842, 1674, 1145, 1209 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.58–5.78 (1H, m, C*H*=CH_2), 5.02 (1H, d, J=17.1 Hz, CH_aH_b=CH), 4.97 (1H, d, J=10.7 Hz, CH_aH_b=CH), 4.03–4.18 (2H, m, MeCH_2O), 2.50 (1H, dd, J=6.4, 18.1 Hz, C*H*CO), 2.44–2.49 (1H, m, CH_aH_bCH=CH_2), 2.34 (2H, q, J=7.6 Hz, MeCH_2C=), 1.96–2.10 (3H, m, CH_aH_bCH=CH_2 and CH_2CHCO), 1.18 (3H, t, J=7.0 Hz, *Me*CH_2O), 1.04 (3H, t, J=7.6 Hz, *Me*CH_2C=); δ_C (100.6 MHz, $CDCl_3$) 205.6, 160.0, 135.5, 117.2, 114.7, 66.5, 42.9, 36.0, 31.1, 22.3, 16.0, 11.9; HRMS (EI): M^+, found 194.1311. $C_{12}H_{18}O_2$ requires 194.1307.

3.1.17. 6-Allyl-2-ethoxy-cyclohex-2-enone 4h. (0.82 g, 65%) as a colourless oil; ν_{max} (neat) 3015, 2920, 2850, 1690, 1090 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.75 (1H, t, J=4.1 Hz, C*H*=COEt), 5.66–5.76 (1H, m, C*H*=CH_2), 5.00 (1H, d, J=14.9 Hz, CH_aH_b=CH), 4.97 (1H, d, J=8.3 Hz, CH_aH_b=CH), 3.68 (2H, q, J=7.0 Hz, MeCH_2O), 2.54–2.60 (1H, m, C*H*CO), 2.33–2.39 (3H, m, CH_2CH= and CH_aH_bCH=COEt), 2.10–2.14 (1H, m, CH_aH_bCH=COEt), 1.94–2.01 (1H, m, CH_aH_bCHCO), 1.61–1.69 (1H, m, CH_aH_bCHCO), 1.17 (3H, t, J=7.0 Hz, *Me*CH_2O); δ_C (100.6 MHz, $CDCl_3$) 196.2, 150.8, 136.4, 117.2, 116.7, 47.3, 35.4, 34.2, 27.8, 23.4, 14.8; HRMS (EI): M^+, found 180.1154. $C_{11}H_{16}O_2$ requires 180.1150.

3.1.18. 6-((*E*)-but-2-enyl)-3-ethoxy-5,5-dimethylcyclohex-2-enone 5a. (0.76 g, 49%) as a colourless oil; ν_{max} (neat) 3020, 2942, 1735, 1632, 1592, 1453, 1112 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.30–5.60 (2H, m, MeC*H*=C*H*), 5.19 (1H, s, =C*H*CO), 3.81 (2H, q, J=7.1 Hz, MeCH_2O), 2.29 (1H, dd, J=4.6, 17.6 Hz, C*H*CO), 2.14–2.17 (2H, m, =CHCH_2CHCO), 2.11 (1H, d, J=3.5 Hz, C$H_aH_b$$CMe_2$), 1.93–2.03 (1H, m, $CH_aH_b$$CMe_2$), 1.53–1.64 (3H, m, *Me*CH=), 1.29 (3H, t, J=7.0 Hz, *Me*CH_2O), 1.02 (3H, s, *Me*$_2$C), 0.91 (3H, s, *Me*$_2$C); δ_C (100.6 MHz, $CDCl_3$) 202.2, 174.6, 130.4, 126.2, 101.2, 64.4, 57.8, 42.3, 35.5, 30.1, 29.2,

24.9, 18.3, 14.5; HRMS (EI): MH^+, found 223.1703. $C_{14}H_{22}O_2$ requires 223.1698.

3.1.19. 6-((*E*)-but-2-enyl)-3-methyl-cyclohex-2-enone 5b. (0.59 g, 52%) as a colourless oil; ν_{max} (neat) 3022, 2913, 2852, 2255, 1654, 1525 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.78 (1H, s, =C*H*CO), 5.28–5.43 (2H, m, MeC*H*=C*H*), 2.44–2.52 (1H, m, C*H*CO), 2.21–2.22 (2H, m, CH_2CHCO), 2.11–2.16 (1H, m, CH_aH_bCH$_2$), 1.96–2.01 (2H, m, CH_2CHCO), 1.87 (3H, s, *Me*C=), 1.60–1.66 (1H, m, CH$_a$*H*$_b$CH$_2$), 1.59 (3H, d, J=6.0 Hz, *Me*CH=); δ_C (100.6 MHz, $CDCl_3$) 201.5, 161.9, 129.0, 127.6, 126.8, 45.8, 32.8, 30.7, 27.5, 24.6, 18.3; HRMS (EI): M^+, found 164.1205. $C_{11}H_{16}O$ requires 164.1202.

3.2. Byproducts of the reaction

3.2.1. Dimerized product of 2a 1,1′-diallyl-bicyclopentyl-3,3′-diene-2,2′-dione. As a colourless oil; ν_{max} (neat) 2990, 2973, 1707, 1690, 1589, 1437 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.62 (2H, ddd, J=6.7, 7.3, 10.2 Hz, 2×C*H*=CHCO), 6.27 (2H, d, J=10.2 Hz, 2×=C*H*CO), 5.67–5.77 (2H, m, 2×C*H*=CH$_2$), 5.20 (2H, d, J=17.2 Hz, 2×CH_aH$_b$=CH), 5.19 (2H, d, J=10.9 Hz, 2×CH$_a$*H*$_b$=CH), 3.19 (4H, t, J=2.4 Hz, 2×=CHCH_2), 2.82 (2H, dd, J=7.3, 14.2 Hz, 2×CH_aH$_b$CCO), 2.64 (2H, dd, J=6.7, 14.2 Hz, 2×CH$_a$*H*$_b$CCO); δ_C (100.6 MHz, $CDCl_3$) 203.7, 160.5, 132.5, 131.1, 120.5, 58.5, 45.5, 43.5; HRMS (EI): M^+, found 242.1318. $C_{16}H_{18}O_2$ requires 242.1307.

3.2.2. Dimerized product of 2b 1,1′-diallyl-3,3′-dimethyl-bicyclopentyl-3,3′-diene-2,2′-dione. As a colourless oil; ν_{max} (neat) 3066, 2914, 2873, 1707, 1640 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.21 (2H, dd, J=6.8, 7.3 Hz, 2×=C*H*CO), 5.66–5.76 (2H, m, 2×C*H*=CH$_2$), 5.19 (2H, d, J=16.6 Hz, 2×CH_aH$_b$=CH), 5.17 (2H, d, J=10.9 Hz, 2×CH$_a$*H*$_b$=CH), 3.05 (4H, t, J=2.2 Hz, 2×=CHCH_2), 2.82 (2H, dd, J=7.3, 14.2 Hz, 2×CH_aH$_b$CCO), 2.62 (2H, dd, J=6.8, 14.2 Hz, 2×CH$_a$*H*$_b$CCO), 1.86 (6H, s, 2×*Me*C=); δ_C (100.6 MHz, $CDCl_3$) 203.8, 153.8, 139.1, 132.7, 120.3, 59.3, 43.8, 43.6, 11.1; HRMS (EI): M^+, found 270.1611. $C_{18}H_{22}O_2$ requires 270.1620.

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9. For spectroscopic data of 5-acetoxy-3-methyl-2-cyclopentenone, see reference 8g.
10. The dimerized allylated products of **2a**, **2b** and **2c** were isolated in 7, 5 and 7% yields, respectively. For the dimerized product of **2c**, see Ref. 8f. The structure elucidation of dimerized products **2a** and **2b** is given in Section 3.
11. We repeated the experiments for entries 1–3 with toluene under the same conditions and obtained **2a**, **2b** and **2c** with 5, 7 and 5% decrease of the yield, respectively.
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New and efficient synthesis of bi- and trisubstituted indazoles

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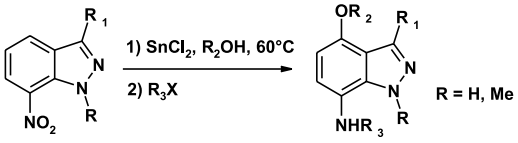
Abstract—In this paper, the synthesis of bi- and trisubstituted indazoles was described. 4-Alkoxy-7-aminoprotected-indazole or 7-aminoprotected-indazole derivatives were prepared selectively using $SnCl_2$ in alcohol or $SnCl_2$ in ethyl acetate, respectively. The effects of the halogen atom in position 3 and of the *N*-alkylation in *N*-1 position of 7-nitroindazoles were investigated.

1. Introduction

Recently, considerable importance has been attached to synthetic methods leading to indazole derivatives because of their biological activities.[1–9] Various indazole derivatives, such as 3-substituted indazoles obtained via different cross-coupling reactions,[10–15] are common components of drugs and are generally found to be of pharmaceutical interest in a variety of therapeutic areas.[16]

One of our research targets is to develop simple and inexpensive synthetic procedures for heterocyclic compounds that are of interest for medical purpose. Here, we present the simple and efficient synthetic procedures developed to obtain 4- and 7-bisubstituted indazole derivatives. During the synthesis of sulfonamides from 7-nitroindazoles, we noticed that the conversion of the nitro group into a corresponding amino group with $SnCl_2$ in the presence of ethanol gave a product functionalized in the 4-position. Afterward we generalized this sequence by using other alcohols as solvent followed by a coupling reaction of amines achieved with various protecting groups (Scheme 1), in order to prepare new bi-and trisubstituted indazoles.



Scheme 1.

Keywords: Indazoles; Cross-coupling reaction; Alcohols; Nucleophilic addition.
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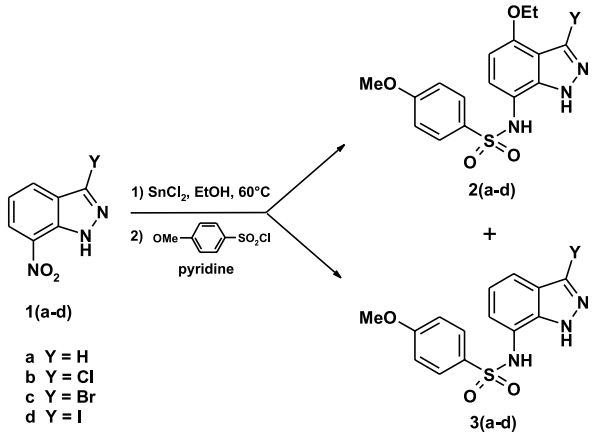
2. Results and discussion

One of the simplest ways to prepare 7-aminoindazole derivatives consists of the reduction of 7-nitroindazole derivatives with $SnCl_2$ in alcoholic solution. However, we observed that reduction of the compounds **1**(**a**–**d**) with $SnCl_2$ in ethanol as solvent gave two different compounds, that is, the desired amine and the amine substituted with ethoxy group in the 4-position, according to ^1H NMR of crude product. It is noteworthy that significant degradation of aromatic primary amine was observed. Consequently, we immediately protected this amine by using 4-methoxybenzenesulfonyl chloride in pyridine. This reaction afforded a mixture of *N*-(3-substituted-7-indazolyl)-benzenesulfonamides **3**(**a**–**d**) with the corresponding 4-ethoxysubstituted derivatives **2**(**a**–**d**) (Scheme 2).



Scheme 2.

The structure of the *N*-(4-ethoxy-3-iodo-7-indazolyl)-4-methoxybenzenesulfonamide **2d**, was unambiguously established by X-ray crystallography (Fig. 1). Indeed, the ethoxy group is bound to the C-4 of the aromatic ring. Moreover, a chelate was found between N(1) bound to H(1) and O(16) with N(1)–O(16)=2.994(5) Å and the angle N(1)–H(1)···O(16)=114.8°, inducing a bent shape for **2**. On the other hand, bond lengths and angles do not show surprising features.

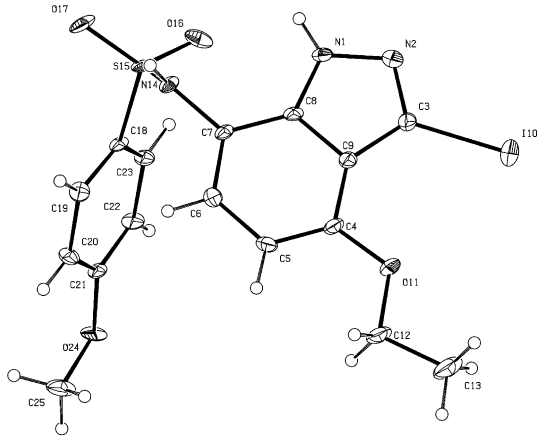


Figure 1. X-ray crystal structure of **2d**.

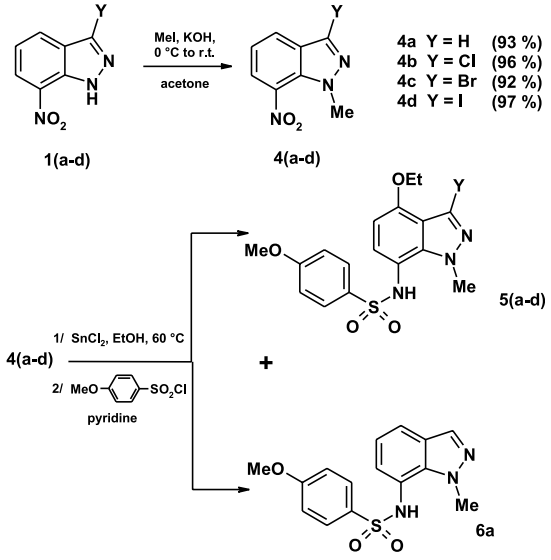
As it was noticed in Table 1, the nature of the substituent in the 3-position on the indazolyl ring in **1** led to different ratios of *N*-(4-ethoxy-1*H*-7-indazolyl)benzenesulfonamides **2**(**a**–**d**) and of corresponding 4-unsubstituted derivatives **3**(**a**–**d**). From the iodine-substituted **1d**, only the *N*-(4-ethoxy-1*H*-7-indazolyl)benzenesulfonamide **2d** was isolated, whereas **1a**, **1b** and **1c** afforded a mixture of compounds **2**(**a**–**c**) and **3**(**a**–**c**) (Table 1).

In the case of palladium-catalyzed reactions achieved with indazole, it was demonstrated the necessity of a protecting group in the *N*-1 position.[12,13] In order to optimize this sequence and considering that the presence of the NH group in 3-substituted-7-nitroindazoles **1**(**a**–**d**) could be the limiting factor, we decided to investigate the reactivity of the *N*-methyl-3-substituted-7-nitroindazoles **4**(**a**–**d**). Hence, the preliminary protection of compounds **1**(**a**–**d**) by iodomethane gave the corresponding 1-methyl-3-substituted-7-nitroindazoles **4**(**a**–**d**).[17,18] Then, compounds **4**(**a**–**d**) were reduced as previously described, and subsequent coupling was achieved with 4-methoxybenzenesulfonyl chloride. We noticed that **4**(**b**-**d**) afforded only the *N*-(4-ethoxy-3-halogeno-1-methyl-7-indazolyl)benzene-sulfonamides **5**(**b**–**d**) functionalized in position 4 (Table 2). Conversely, **4a** gave a mixture of the compound **5a** with the C(4)-nonsubstituted indazole (**6a**) (Scheme 3). In this last case, by comparing the **2/3** and **5/6** ratios, it is clear that S_NH is improved by *N*-alkylation of the *N*-1 position (see Tables 1 and 2).

Table 2. Effect of atom nature in 3-position on the synthesis of *N*-(4-ethoxy-1*H*-1-methyl-7-indazolyl)benzenesulfonamides **5** and C(4) nonsubstituted indazole **6**

Y	Time of reduction	Ratio **5/6**[a]	Yield of **5**[b]
H	4 h	67/33[c]	—
Cl	2 h	100/0	76%
Br	2 h 15 min	100/0	78%
I	1 h 50 min	100/0	80%

[a] Ratio determined by ^{1}H NMR spectroscopy of the reaction mixture.
[b] Compounds **5**(**b**–**d**) were isolated by flash chromatography.
[c] Compounds **5a** and **6a** were not separable by flash chromatography, global yield: 76%.



Scheme 3.

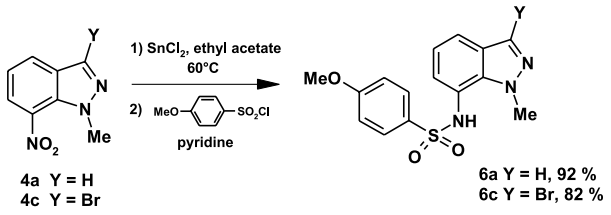
Finally, the reduction-protection of 7-nitro-indazole **4a** and 3-bromo-1-methyl-7-nitro-1*H*-indazole (**4c**) was performed with $SnCl_2$ by using ethyl acetate as solvent. As expected, we obtained exclusively the corresponding amines **6a** and **6c** in 92 and 82% yields, respectively. No trace of S_NH substitution was observed (Scheme 4).

These results could be related to the important role played by nitro groups of 7-nitro-indazole with regards to the introduction of the substituent in 4-position. Due to its

Table 1. Influence of the atom nature in the 3-position in **1**(**a**–**d**) on the synthesis of *N*-(4-ethoxy-1H-7-indazolyl)benzenesulfonamides **2**(**a**–**d**) and 4-unsubstituted derivatives **3**(**a**–**d**)

Y	Time of reduction (h)	Ratio **2/3**[a]	Yield of **2**[b]	Yield of **3**[b]	Yield of **2**+**3**[c] (%)
H	4	52/48	[c]	[c]	72
Cl	5	44/56	28%	37%	65
Br	9	63/37	56%	22%	78
I	2	100/0	76%	0%	76

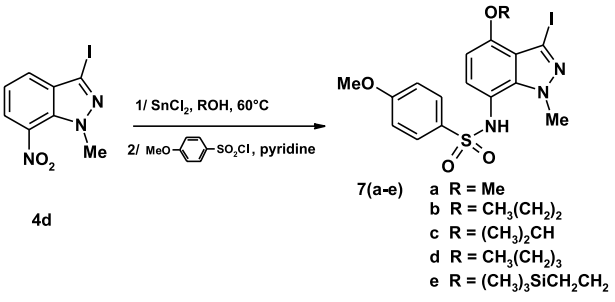
[a] Ratio determined by ^{1}H NMR spectroscopy of the reaction mixture.
[b] Yields of isolated products after flash chromatography.
[c] Compounds **2a** and **3a** were not separable by flash chromatography.



Scheme 4.

electron-withdrawing effect the nitro group in nitroarene activates in *ortho* and *para* for addition of nucleophilic agents.[19–23] Thus, the formation of the compound substituted by an ethoxy group in 4-position could be explained by the presence of the $C_2H_5O^-$ anion in the reaction mixture, followed by the S_NH on 7-nitroindazole. To study this hypothesis we performed reactions between compounds **1a** or **4a** and $C_2H_5O^-$ in ethanol at 60 °C. Unfortunately, no reaction was observed, and we isolated only the starting substances **1a** or **4a** in 92 and 95%, respectively. In addition to the mechanism proposed, we can supposed that the introduction of ethoxy group proceeds on the intermediate stage in reduction of NO_2 namely protonated hydroxylamine compound. Introduction of nucleophilic substituents via reactions of protonated arylhydroxylamines is a well known process.[24]

The reduction of the 3-iodo-7-nitroindazole **4d** was achieved with $SnCl_2$ in different alcohols, in order to introduce various alkoxy groups in the 4-position. In all cases, only compounds **7**(**a**–**e**) were obtained in good yields, illustrating the ability to introduce various alkoxy groups (Scheme 5). The results are collected in Table 3.



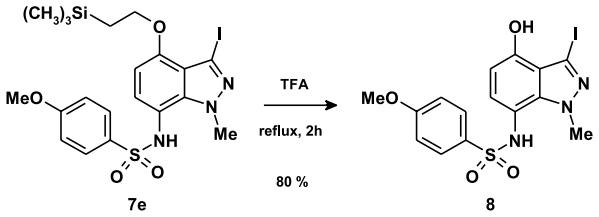
Scheme 5.

Table 3. Synthesis of *N*-(4-alkoxy-3-iodo-1-methyl-7-indazolyl)benzenesulfonamides **7**(**a**–**e**)

R	Time of reduction	Yield (%)[a]
CH_3	3 h	67
$CH_3(CH_2)_2$	1 h 30 min	77
$(CH_3)_2CH$	1 h	79
$CH_3(CH_2)_3$	1 h	75
$(CH_3)_3SiCH_2CH_2$	45 min	78

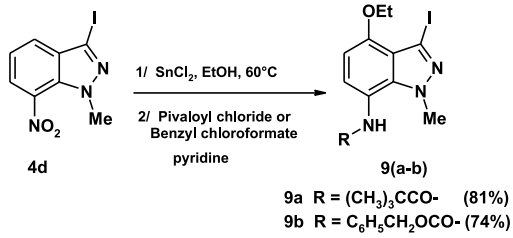
[a] Yields of isolated products after flash chromatography.

Moreover, it is noteworthy that the method developed here, permits, after simple transformation, to obtain other types of functionalization, which presents a potential utility for further developments in medicinal chemistry. For example, after a simple treatment in refluxing TFA, the ether function of compound **7e** was transformed into the corresponding phenol group (product **8**) in good yield (Scheme 6).



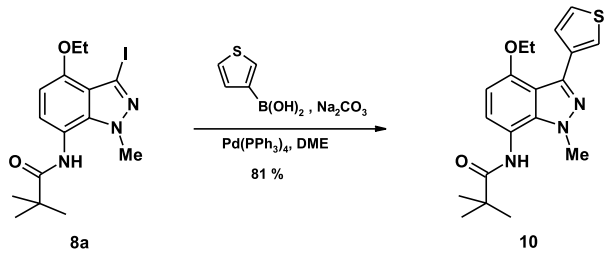
Scheme 6.

In order to use other secondary amine protecting groups, we also studied the coupling reaction with pivaloyl chloride or benzyl chloroformate achieved in pyridine, with **4d** as an example. The desired products **9**(**a**–**b**) were obtained in good yields (Scheme 7).



Scheme 7.

For deep investigations, we used the *N*-(4-ethoxy-3-iodo-1-methyl-1*H*-indazol-7-yl)-2,2-dimethyl-propionamide **9a** for Suzuki cross-coupling reaction with 3-thiopheneboronic acid in presence of catalytic amount of tetrakis(triphenylphosphine)palladium(0). As expected, the sequence gave the *N*-(4-ethoxy-1-methyl-3-thiophen-3-yl-1*H*-indazol-7-yl)-2,2-dimethylpropionamide **10** in a very good yield (Scheme 8).



Scheme 8.

In conclusion, we present simple and efficient synthetic procedures of reduction-protection reaction developed to obtain bi- and tri-bisubstituted indazole derivatives. We determined experimental conditions to generate selectively 4-alkoxy-7-aminoprotected-indazoles by using various alcohols as solvent and different reactants in presence of $SnCl_2$. A selective way to 3-, 4-, 7-trisubstituted indazoles was developed through *N*-alkylation of *N*-1 position and by substitution of hydrogen in the 3-position by various halogens.

The reduction-protection conducted with ethyl acetate as solvent allowed us to generate exclusively 7-aminoprotected-indazoles. No trace of S_NH substitution was observed. Finally, potentiality of the functionalization ability in the

3-position of 3-iodoindazolylbenzenamide by a Suzuki cross-coupling reaction with various aromatic derivatives was established. This appears to be a general method to prepare new building blocks of interest in medicinal chemistry.

3. Experimental

3.1. General

Melting points were determined with Büchi SMP-20 melting point apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker Avance DPX250 spectrometer (250.19 MHz ^{1}H, 62.89 MHz ^{13}C) using tetramethylsilane as the internal standard, multiplicities were determined by the DEPT 135 sequence. Chemical shifts were reported in parts per million (ppm, δ units). Coupling constants were reported in units of hertz (Hz). Splitting patterns were designated as s, singlet; d, doublet, t, triplet. IR spectra were obtained on Perkin-Elmer Paragon 1000 PC FT-IR. Infrared spectra were recorded using NaCl film or KBr pellets. Low-resolution mass spectra (MS) were recorded on a Perkin-Elmer SCIEX API 3000 spectrometer. All commercial solvents were used without further purification. The following solvents and reagents have been abbreviated: dimethylformamide (DMF), dimethyl sulfoxide (DMSO), ethyl acetate (EtOAc), methanol (MeOH), trifluoroacetic acid (TFA), ethylene glycol dimethyl ether (DME) and petroleum ether (EP). Thin layer chromatography (TLC) was carried out on Merck silica gel 60F$_{254}$ precoated plates. Visualization was made with ultraviolet light.

3.2. Crystal structure analysis of 2d

The crystal structure of compound **2d** has been determined by single-crystal X-ray diffraction techniques and refined by full-matrix least-squares procedures, to give a final R value of 0.0479. The crystals are triclinic, space group P-1, with $a=7.924(1)$ Å, $b=9.130(2)$ Å, $c=12.3056(1)$ Å, $\alpha=90.23(2)°$, $\beta=92.89(1)°$, $\gamma=96.71(2)°$, and $Z=2$. A crystal $0.25\times0.10\times0.05$ mm was chosen. The data were collected on a CAD4 Enraf-Nonius diffractometer with graphite monochromatized Cu Kα radiation. Full crystallographic results have been deposited at the Cambridge Crystallographic Data Centre (CCDC), UK, as Supplementary Materials.[25a] The position of non-H atoms were determined by the program SHELXS[25b] and the position of the H atoms were deduced from coordinates of the non-H atoms and confirmed by Fourier synthesis. H atoms were included for structure factor calculations but not refined.

3.2.1. 7-Nitro-1*H*-indazole (1a). This compound was prepared according to method described in the lit.[26] (65% yield): mp 185–186 °C (lit.[26] mp 186 °C). IR (KBr, cm^{-1}): 3180 (NH), 1620 (CN), 1500, 1290 (NO$_2$). ^{1}H NMR (DMSO-d_6) δ 7.32 (t, $J=7.8$ Hz, 1H), 8.32 (d, $J=7.8$ Hz, 1H), 8.35 (d, $J=7.8$ Hz, 1H), 8.41 (s, 1H), 13.94 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 120.2, 123.5, 129.9, 135.6 (4CH), 127.1, 131.9, 132.1 (3C). MS $m/z=164$ [M+1]$^+$.

3.2.2. 3-Chloro-7-nitro-1*H*-indazole (1b). 7-Nitroindazole (1 g, 6.13 mmol) was dissolved in 25 mL of MeOH and 2 N aqueous sodium hydroxide (20 mL), and then sodium hypochlorite (6 mL, 98.2 mmol) was added to the solution. The mixture was refluxed for 1 h. After cooling, the solution acidified with acetic acid. The solid was filtered, washed with water and dried in vacuo to give a yellow solid (98% yield): mp 167–168 °C (lit.[23] mp 166–168 °C). IR (KBr, cm^{-1}): 3210 (NH), 1610 (CN), 1520, 1310 (NO$_2$). ^{1}H NMR (DMSO-d_6) δ 7.45 (t, $J=7.8$ Hz, 1H), 8.20 (d, $J=7.8$ Hz, 1H), 8.44 (d, $J=7.8$ Hz, 1H), 14.13 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 121.3, 125.1, 127.8 (3CH), 123.4, 132.5, 133.2, 134.7 (4C). MS $m/z=198$ (^{35}Cl) [M+1]$^+$, 200 (^{37}Cl) [M+3]$^+$.

3.2.3. 3-Bromo-7-nitro-1*H*-indazole (1c). To a solution of 7-nitroindazole (1 g, 6.13 mmol), (1.2 g, 6.74 mmol) of *N*-bromosuccinimide in acetonitrile was heated at reflux for 30 min. The solvent was removed in vacuo and the residue was taken up in 50 mL of ethyl acetate, washed with 2× 100 ml of water, 100 mL of 10% sodium thiosulfate, brine and then dried. The solvent was removed in vacuo and the residue was purified by flash chromatography on silica gel eluting with EtOAc/hexane to provide 1.3 g (90%) of **3** as a yellow solid: mp 175–176 °C (lit.[18] mp 176–178 °C). IR (KBr, cm^{-1}): 3180 (NH), 1620 (CN), 1500, 1310 (NO$_2$). ^{1}H NMR (DMSO-d_6) δ 7.46 (t, $J=7.9$ Hz, 1H); 8.13 (d, $J=7.9$ Hz, 1H); 8.45 (d, $J=7.9$ Hz, 1H), 14.25 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 121.3, 124.9, 128.3, (3CH), 123.1, 126.1, 133.3, 133.1 (4C). MS $m/z=242$ (^{79}Br) [M+1]$^+$, 244 (^{81}Br) [M+3]$^+$.

3.2.4. 3-Iodo-7-nitro-1*H*-indazole (1d). Iodine (3.1 g, 12.26 mmol) and potassium hydroxide pellets (1.28 g, 23 mmol) were successively added into a DMF solution (60 mL) of 7-nitroindazole (1 g, 6.13 mmol) at room temperature under stirring. After 1 h, the reaction mixture was poured into 10% aqueous NaHSO$_3$ (200 mL) and extracted with Et$_2$O (2×150 mL). The combined organic layers were washed with water and brine, dried over MgSO$_4$ and the solvent evaporated to give a light yellow solid (95% yield): mp 188–189 °C. IR (KBr, cm^{-1}): 3110 (NH), 1600 (CN), 1520, 1300 (NO$_2$). ^{1}H NMR (DMSO-d_6) δ 7.44 (t, $J=7.8$ Hz, 1H), 8.00 (d, $J=7.8$ Hz, 1H), 8.46 (d, $J=7.8$ Hz, 1H), 14.32 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 120.9, 124.6, 130.8 (3CH), 96.8, 130.8, 132.1, 132.6 (4C). MS $m/z=290$ [M+1]$^+$. Anal. Calcd for C$_7$H$_4$IN$_3$O$_2$; C, 29.09; H, 1.39; I, 43.91; N, 14.54. Found: C, 29.16; H, 1.53; I, 44.08; N, 14.46.

3.3. General method for alkylation of 7-nitroindazole derivatives

To a solution of 7-nitroindazole derivatives (6.13 mmol) in acetone (15 mL) cooled at 0 °C was added potassium hydroxide (9.2 mmol). After 15 mn at 0 °C, iodomethane (6.13 mmol) was added dropwise. Upon disappearance of the starting material as indicated by TLC, the resulting mixture was evaporated. The crude material was dissolved with EtOAc (50 mL), washed with water and brine, dried over MgSO$_4$ and the solvent removed in vacuo to give the corresponding compounds. Spectral data for representative compounds are as follows:

3.3.1. 1-Methyl-7-nitro-1*H*-indazole (4a). Chromatography using EtOAc/hexane give a yellow solid (93% yield): mp 99–100 °C (lit.[26] mp 98 °C). IR (KBr, cm^{-1}): 1620 (CN), 1510, 1290 (NO_2). ^1H NMR (DMSO-d_6) δ 4.16 (s, 3H, CH_3), 7.40 (t, $J=7.7$ Hz, 1H), 7.90 (d, $J=7.7$ Hz, 1H), 8.29 (d, $J=7.7$ Hz, 1H), 8.32 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 40.3 (NCH_3), 120.1, 124.5, 128.6, 134.3 (4CH), 125.4, 128.4, 130.4 (3C). MS $m/z=178$ $[M+1]^+$.

3.3.2. 3-Chloro-1-methyl-7-nitro-1*H*-indazole (4b). This compound was similarly prepared from 3-chloro-7-nitroindazole in 96% yield as a yellow solid: mp 150–151 °C (lit.[18] mp 148–150 °C). IR (KBr, cm^{-1}): 1615 (CN), 1490, 1300 (NO_2). ^1H NMR (DMSO-d_6) δ 4.11 (s, 3H, CH_3), 7.42 (t, $J=7.8$ Hz, 1H), 8.11 (d, $J=7.8$ Hz, 1H), 8.28 (d, $J=7.8$ Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 40.9 (NCH_3), 121.2, 126.1, 126.5 (3CH), 124.6, 132.0, 132.8, 135.1 (4C). MS $m/z=212$ (^{35}Cl) $[M+1]^+$, 214 (^{37}Cl) $[M+3]^+$.

3.3.3. 3-Bromo-1-methyl-7-nitro-1*H*-indazole (4c). This compound was similarly prepared from 3-bromo-7-nitroindazole in 92% yield as a yellow solid: mp 158–159 °C (lit.[18] mp 160–162 °C). IR (KBr, cm^{-1}): 1610 (CN), 1520, 1310 (NO_2). ^1H NMR (DMSO-d_6) δ 4.22 (s, 3H, CH_3), 7.45 (t, $J=7.8$ Hz, 1H), 8.02 (d, $J=7.8$ Hz, 1H), 8.27 (d, $J=7.8$ Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 41.4 (NCH_3), 121.8, 126.6, 126.7 (3CH), 122.0, 127.8, 128.8, 130.1 (4C). MS $m/z=256$ (^{79}Br) $[M+1]^+$, 258 (^{81}Br) $[M+3]^+$.

3.3.4. 3-Iodo-1-methyl-7-nitro-1*H*-indazole (4d). This compound was similarly prepared from 3-iodo-7-nitroindazole in 97% as a yellow solid: mp 171–172 °C. IR (KBr, cm^{-1}): 1610 (CN), 1530, 1300 (NO_2). ^1H NMR (DMSO-d_6) δ 4.16 (s, 3H, CH_3), 7.40 (t, $J=7.7$ Hz, 1H), 7.9 (d, $J=7.7$ Hz, 1H), 8.29 (d, $J=7.7$ Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 40.8 (NCH_3), 120.8, 125.7, 128.6 (3CH), 95.1, 131.4, 132.1, 134.7 (4C). MS $m/z=304$ $[M+1]^+$. Anal. Calcd for $C_8H_6IN_3O_2$; C, 31.71; H, 2.00; I, 41.87; N, 13.87. Found: C, 31.80; H, 2.13; I, 41.77; N, 13.72.

3.4. Synthesis of compounds 2(a–d) and 3(a–d)

General method. A mixture of 3-halogeno-7-nitroindazole **1**(**a**–**d**) (0.66 mmol) and anhydrous $SnCl_2$ (0.62 g, 3.3 mmol) in 25 mL of absolute ethanol is heated at 60 °C. After reduction, the starting material has disappeared and the solution is allowed to cool down. The pH is made slightly basic (pH 7–8) by addition of 5% aqueous potassium bicarbonate before being extracted with ethyl acetate. The organic phase is washed with brine and dried over magnesium sulfate. The solvent was removed to afford the amine, which was immediately dissolved in pyridine (5 mL) and then reacted with 4-methoxybenzenesulfonyl chloride (0.15 g, 0.72 mmol) at room temperature overnight. After the reaction mixture was concentrated in vacuo, the resulting residue was purified by flash chromatography (eluted with EtOAc/EP).

3.4.1. *N*-(3-Chloro-4-ethoxy-1*H*-7-indazolyl)-4-methoxybenzenesulfonamide (2b). Rose solid, yield 28%: mp 104–105 °C. IR (KBr, cm^{-1}): 3342, 3229 (NH), 1596 (CN), 1341, 1160 (SO_2), 1244, 1025 (ArOCH). ^1H NMR (acetone-d_6) δ 1.43 (t, $J=6.9$ Hz, 3H, CH_3), 3.84 (s, 3H, OCH_3), 4.12 (q, 2H, $J=6.9$ Hz, CH_2O), 6.38 (d, $J=8.1$ Hz, 1H), 6.76 (d, $J=8.1$ Hz, 1H), 7.00 (d, $J=8.9$ Hz, 2H), 7.62 (d, $J=8.9$ Hz, 2H), 8.52 (s, 1H, NH), 12.08 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ 14.8 (CH_3), 56.0 (OCH_3), 64.7 (CH_2O), 101.7, 114.8, 126.5, 130.3 (4CH), 113.1, 114.3, 131.8, 133.4, 141.2, 152.6, 163.9 (7C). MS $m/z=382$ (^{35}Cl) $[M+1]^+$, 384 (^{37}Cl) $[M+3]^+$. Anal. Calcd for $C_{16}H_{16}ClN_3O_4S$; C, 50.33; H, 4.22; Cl, 9.29; N, 11.00, S, 8.40. Found: C, 50.30; H, 4.16; Cl, 9.45; N, 11.17, S, 8.49.

3.4.2. *N*-(3-Bromo-4-ethoxy-1*H*-7-indazolyl)-4-methoxybenzenesulfonamide (2c). Violet solid, yield 56%: mp 114–115 °C. IR (KBr, cm^{-1}): 3342, 3142 (NH), 1596 (CN), 1342, 1160 (SO_2), 1258, 1018 (ArOCH). ^1H NMR (acetone-d_6) δ 1.44 (t, $J=7.2$ Hz, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.12 (q, $J=7.2$ Hz, 2H, CH_2O), 6.38 (d, $J=8.1$ Hz, 1H), 6.76 (d, $J=8.1$ Hz, 1H), 6.99 (d, $J=9.1$ Hz, 2H), 7.61 (d, $J=9.1$ Hz, 2H), 8.53 (s, 1H, NH), 12.25 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ 14.8 (CH_3), 56.0 (OCH_3), 64.7 (CH_2O), 101.8, 114.8, 126.4, 130.3 (4CH), 109.7, 114.2, 131.8, 152.5, 153.0, 154.8, 164.0 (7C). MS $m/z=426$ (^{79}Br) $[M+1]^+$, 428 (^{81}Br) $[M+3]^+$. Anal. Calcd for $C_{16}H_{16}BrN_3O_4S$; C, 45.08; H, 3.78; Br, 18.74; N, 9.86, S, 7.52. Found: C, 45.20; H, 3.70; Br, 18.60; N, 10.09, S, 7.66.

3.4.3. *N*-(3-Chloro-1*H*-7-indazolyl)-4-methoxybenzenesulfonamide (3b). Colorless solid, yield 37%: mp 201–202 °C. IR (KBr, cm^{-1}): 3338, 3242 (NH), 1596 (CN), 1337, 1170 (SO_2), 1254, 1017 (ArOCH). ^1H NMR (DMSO-d_6) δ 3.78 (s, 3H, OCH_3), 6.95 (d, $J=7.5$ Hz, 1H), 7.01 (dd, $J=7.5$, 7.8 Hz, 1H), 7.07 (d, $J=8.7$ Hz, 2H), 7.24 (d, $J=7.8$ Hz, 1H), 7.67 (d, $J=8.7$ Hz, 2H), 10.02 (s, 1H, NH), 13.00 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 55.6 (OCH_3), 114.3, 115.7, 120.0, 121.8, 129.2 (5CH), 120.1, 121.5, 130.5, 132.5, 136.2, 162.6 (6C). MS $m/z=338$ (^{35}Cl) $[M+1]^+$, 340 (^{37}Cl) $[M+3]^+$. Anal. Calcd for $C_{14}H_{12}ClN_3O_3S$; C, 49.78; H, 3.58; Cl, 10.50; N, 12.44; S, 9.49. Found: C, 49.86; H, 3.44; Cl, 10.75; N, 12.40; S, 9.39.

3.4.4. *N*-(3-Bromo-1*H*-7-indazolyl)-4-methoxybenzenesulfonamide (3c). Colorless solid, yield 22%: mp 193–194 °C. IR (KBr, cm^{-1}): 3317, 3228 (NH), 1596 (CN), 1340, 1146 (SO_2), 1252, 1002 (ArOCH). ^1H NMR (acetone-d_6) δ 3.83 (s, 3H, OCH_3), 7.01 (d, $J=9.1$ Hz, 2H), 7.10 (d, $J=7.2$ Hz, 1H), 7.43 (dd, $J=7.2$, 8.8 Hz, 1H), 7.53 (d, $J=8.8$ Hz, 1H), 7.66 (d, $J=9.1$ Hz, 2H), 8.90 (s, 1H, NH), 12.33 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ 56.0 (OCH_3), 115.0, 118.1, 122.7, 122.8, 130.3 (5CH), 114.4, 122.2, 125.4, 126.7, 131.6, 164.1 (6C). MS $m/z=382$ (^{79}Br) $[M+1]^+$, 384 (^{81}Br) $[M+3]^+$. Anal. Calcd for $C_{14}H_{12}BrN_3O_3S$; C, 43.99; H, 3.16; Br, 20.90; N, 10.99; S, 8.39. Found: C, 43.90; H, 3.25; Br, 20.85; N, 11.18; S, 8.21.

3.4.5. *N*-(4-Ethoxy-3-iodo-1*H*-7-indazolyl)-4-methoxybenzenesulfonamide (2d). Violet solid, yield 76%: mp 171–172 °C. IR (KBr, cm^{-1}): 3304, 3260 (NH), 1600 (CN), 1338, 1156 (SO_2), 1270, 1024 (ArOCH). ^1H NMR (acetone-d_6) δ 1.38 (t, $J=6.9$ Hz, 3H, CH_3), 3.79 (s, 3H, OCH_3), 4.05 (q, $J=6.9$ Hz, 2H, OCH_2), 6.33 (d, $J=8.4$ Hz, 1H), 6.58 (d, $J=8.4$ Hz, 1H), 7.03 (d, $J=8.7$ Hz, 2H), 7.60 (d, $J=8.7$ Hz, 2H), 9.56 (s, 1H, NH), 13.20 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ 14.3 (CH_3), 55.6 (OCH_3), 63.5 (CH_2O), 100.8, 114.1, 123.8, 129.1 (4CH), 88.2, 112.9, 116.9, 130.8,

138.9, 150.4, 162.3 (7C). MS $m/z=474$ $[M+1]^+$. Anal. Calcd for $C_{16}H_{16}IN_3O_4S$; C, 40.60; H, 3.41; I, 26.81; N, 8.88; S, 6.77. Found C, 40.42; H, 3.66; I, 26.76; N, 8.94; S, 6.59.

3.5. Synthesis of 5(a–d) and 6a

These compounds were prepared from 3-halogeno-1-methyl-7-nitroindazole **4**(**a**–**d**) by using the same procedure applied to **1**(**a**–**d**).

3.5.1. *N*-(3-Chloro-4-ethoxy-1-methyl-1*H*-7-indazolyl)-4-methoxybenzenesulfonamide (5b). Colorless solid, yield 76%: mp 168–169 °C. IR (KBr, cm^{-1}): 3261 (NH), 1590 (CN), 1340, 1154 (SO_2), 1260, 1054 (ArOCH). ^1H NMR (acetone-d_6) δ 1.39 (t, $J=6.9$ Hz, 3H, CH_3), 3.87 (s, 3H, OCH_3), 4.08 (q, $J=6.9$ Hz, 2H, CH_2O), 4.20 (s, 3H, NCH_3), 6.28 (d, $J=8.1$ Hz, 1H), 6.43 (d, $J=8.1$ Hz, 1H), 7.04 (d, $J=9.1$ Hz, 2H), 7.59 (d, $J=9.1$ Hz, 2H), 8.39 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ 14.7 (CH_3), 39.2 (NCH_3), 56.1 (OCH_3), 64.8 (CH_2O), 101.4, 114.9, 130.5, 130.6 (4CH), 113.8, 114.3, 126.7, 132.2, 141.1, 153.6, 164.1 (7C). MS $m/z=396$ (^{35}Cl) $[M+1]^+$, 398 (^{37}Cl) $[M+3]^+$. Anal. Calcd for $C_{17}H_{18}ClN_3O_4S$; C, 51.58; H, 4.58; Cl, 8.96; N, 10.61; S, 8.10. Found: C, 51.66; H, 4.48; Cl, 9.11; N, 10.51; S, 8.23.

3.5.2. *N*-(3-Bromo-4-ethoxy-1-methyl-1*H*-7-indazolyl)-4-methoxybenzenesulfonamide (5c). Colorless solid, yield 78%: mp 158–159 °C. IR (KBr, cm^{-1}): 3240 (NH), 1590 (CN), 1332, 1146 (SO_2), 1254, 1060 (ArOCH). ^1H NMR (acetone-d_6) δ 1.40 (t, $J=6.9$ Hz, 3H, CH_3), 3.86 (s, 3H, OCH_3), 4.08 (q, $J=6.9$ Hz, 2H, CH_2O), 4.23 (s, 3H, NCH_3), 6.28 (d, $J=8.1$ Hz, 1H), 6.43, (d, $J=8.1$ Hz, 1H), 7.04 (d, $J=9.1$ Hz, 2H), 7.60 (d, $J=9.1$ Hz, 2H), 8.38 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ 14.7 (CH_3), 39.3 (NCH_3), 56.1 (OCH_3), 64.8 (CH_2O), 101.5 114.9, 130.3, 130.6 (4CH), 113.6, 116.4, 117.3, 132.1, 141.0, 153.5, 164.0 (7C). MS $m/z=440$ (^{79}Br) $[M+1]^+$, 442 (^{81}Br) $[M+3]^+$. Anal. Calcd for $C_{17}H_{18}BrN_3O_4S$; C, 46.37; H, 4.12; Br, 18.15; N, 9.54; S, 7.28. Found: C, 46.44; H, 4.03; Br, 18.32; N, 9.59; S, 7.40.

3.5.3. *N*-(4-Ethoxy-3-iodo-1-methyl-1*H*-7-indazolyl)-4-methoxybenzenesulfonamide (5d). Colorless solid, yield 80%: mp 183–184 °C. IR (KBr, cm^{-1}): 3290 (NH), 1590 (CN), 1332, 1154 (SO_2), 1260, 1018 (ArOCH). ^1H NMR (acetone-d_6) δ 1.47 (t, $J=7.2$ Hz, 3H, CH_3), 3.90 (s, 3H, OCH_3), 4.12 (q, $J=7.2$ Hz, 2H, CH_2O), 4.30 (s, 3H, NCH_3), 6.30 (d, $J=8.1$ Hz, 1H), 6.44 (d, $J=8.1$ Hz, 1H), 7.07 (d, $J=8.7$ Hz, 2H), 7.62 (d, $J=8.7$ Hz, 2H), 8.42 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ 14.7 (CH_3), 39.3 (NCH_3), 56.1 (OCH_3), 64.8 (CH_2O), 101.4, 114.9, 130.0, 130.6 (4CH), 85.5, 113.4, 126.7, 132.2, 143.2, 153.2, 164.0 (7C). MS $m/z=488$ $[M+1]^+$. Anal. Calcd for $C_{17}H_{18}IN_3O_4S$; C, 41.90; H, 3.72; I, 26.04; N, 8.62; S, 6.58. Found: C, 41.96; H, 3.88; I, 26.00; N, 8.49; S, 6.43.

3.6. General procedure for the preparation of compounds 6a and 6c

A mixture of 3-halogeno-7-nitroindazole **4a**, **c** (0.66 mmol) and anhydrous $SnCl_2$ (0.62 g, 3.3 mmol) in 25 mL of ethyl acetate is heated at 60 °C. After reduction, the starting material has disappeared and the solution is allowed to cool down. The pH is made slightly basic (pH 7–8) by addition of 5% aqueous potassium bicarbonate before being extracted with ethyl acetate. The organic phase is washed with brine and dried over magnesium sulfate. The solvent was removed to afford the amine, which was immediately dissolved in pyridine (5 mL) and then reacted with 4-methoxybenzenesulfonyl chloride (0.15 g, 0.72 mmol) at room temperature overnight. After the reaction mixture was concentrated in vacuo, the resulting residue was purified by flash chromatography (eluted with EtOAc/EP).

3.6.1. 4-Methoxy-*N*-(1-methyl-1*H*-7-indazolyl)-benzenesulfonamide (6a). Colorless solid, yield 92%: mp 163–164 °C. IR (KBr, cm^{-1}): 3274 (NH), 1598 (CN), 1304, 1160 (SO_2), 1258, 1023 (ArOCH). ^1H NMR (DMSO-d_6) δ 3.48 (s, 3H, OCH_3), 4.23 (s, 3H, NCH_3), 6.43 (d, $J=7.5$ Hz, 1H), 6.90 (dd, $J=7.5$, 7.9 Hz, 1H), 7.10 (d, $J=8.5$ Hz, 2H), 7.59 (d, $J=8.5$ Hz, 2H), 7.65 (d, $J=7.9$ Hz, 1H), 8.06 (s, 1H), 9.83 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 38.7, (NCH_3) 55.7 (OCH_3), 114.0, 114.3, 120.2, 120.6, 123.1, 125.4, 127.6, 129.6, 133.7, 137.8, 162.8. MS $m/z=318$ $[M+1]^+$. Anal. Calcd for $C_{15}H_{15}N_3O_3S$; C, 56.77; H, 4.76; N, 13.24; S, 10.10. Found: C, 56.58; H, 4.93; N, 13.36; S, 9.96.

3.6.2. *N*-(3-Bromo-1-methyl-1*H*-7-indazolyl)-4-methoxybenzenesulfonamide (6c). Colorless solid, yield 82%: mp 184–185 °C. IR (KBr, cm^{-1}): 3440, 3232 (NH), 1644 (CN), 1318, 1154 (SO_2), 1278, 1076 (ArOCH). ^1H NMR (acetone-d_6) δ 3.90 (s, 3H, OCH_3), 4.33 (3H, NCH_3), 6.66 (dd, $J=1.6$, 7.2 Hz, 1H), 6.99–7.09 (m, 3H), 7.52 (dd, $J=1.6$, 7.2 Hz, 1H), 7.62 (d, $J=9.1$ Hz, 2H), 8.71 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ 39.6 (NCH_3), 56.2 (OCH_3), 115.0, 119.8, 120.5, 121.7, 122.2 (5CH), 126.8, 130.7, 131.9, 139.4, 164.2 (5C). MS $m/z=396$ (^{79}Br) $[M+1]^+$, 398 (^{81}Br) $[M+1]^+$. Anal. Calcd for $C_{15}H_{14}BrN_3O_3S$; C, 45.47; H, 3.56; Br, 20.16; N, 10.60; S, 8.09. Found: C, 45.38; H, 3.69; Br, 20.04; N, 10.77; S, 8.23.

3.7. Synthesis of 7(a–e)

These compounds were synthesized as described for **1**(**a**–**d**) by using the appropriate alcohol.

3.7.1. *N*-(3-Iodo-4-methoxy-1-methyl-1*H*-7-indazolyl)-4-methoxybenzenesulfonamide (7a). Green solid, yield 67%: mp 203–204 °C. IR (KBr, cm^{-1}): 3276 (NH), 1590 (CN), 1326, 1154 (SO_2), 1254, 1060 (ArOCH). ^1H NMR (acetone-d_6) δ 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.19 (s, 3H, NCH_3), 6.33 (d, $J=8.5$ Hz, 1H), 6.37 (d, $J=8.5$ Hz, 1H), 7.19 (d, $J=8.7$ Hz, 2H), 7.58 (d, $J=8.7$ Hz, 2H), 9.56 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ 35.9 (NCH_3), 55.6, 55.7 (2OCH_3), 100.4, 114.3, 128.4, 129.2 (4CH), 86.4, 112.7, 118.7, 131.1, 139.1, 152.1, 162.4 (7C). MS $m/z=474$ $[M+1]^+$. Anal. Calcd for $C_{16}H_{16}IN_3O_4S$; C, 40.60; H, 3.41; I, 26.81; N, 8.88; S, 6.77. Found: C, 40.54; H, 3.61; I, 26.92; N, 8.70; S, 6.50.

3.7.2. *N*-(3-Iodo-4-propoxy-1-methyl-1*H*-7-indazolyl)-4-methoxybenzenesulfonamide (7b). Colorless solid, yield 77%: mp 139–140 °C. IR (KBr, cm^{-1}): 3226 (NH), 1582

(CN), 1326, 1146 (SO_2), 1254, 1026 (ArOCH). ^{1}H NMR (acetone-d_6) δ 1.10 (t, J=7.5 Hz, 3H, CH_3), 1.75–1.81 (m, 2H, CH_2); 3.84 (s, 3H, OCH_3), 3.97 (t, J=6.3 Hz, 2H, CH_2O), 4.18 (s, 3H, NCH_3), 6.29 (d, J=7.9 Hz, 1H), 6.34 (d, J=7.9 Hz, 1H), 7.10 (d, J=8.8 Hz, 2H), 7.58 (d, J=8.8 Hz, 2H), 9.60 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ 10.8 (CH_3), 38.4 (NCH_3), 21.8 (CH_2), 55.6 (OCH_3), 69.4 (CH_2O), 112.2, 114.4, 128.6, 129.2 (4CH), 86.6, 100.7, 114.7, 118.5, 131.0, 151.7, 162.4 (7C). MS m/z=502 $[M+1]^+$. Anal. Calcd for $C_{18}H_{20}IN_3O_4S$; C, 43.12; H, 4.02; I, 25.31; N, 8.38; S, 6.40. Found: C, 43.01; H, 4.23; I, 25.55; N, 8.19; S, 6.56.

3.7.3. *N*-(3-Iodo-4-isopropoxy-1-methyl-1*H*-7-indazolyl)-4-methoxybenzenesulfonamide (7c). Colorless solid, yield 79%: mp 101–102 °C. IR (KBr, cm^{-1}): 3018 (NH), 1582 (CN), 1326, 1154 (SO_2), 1218, 1082 (ArOCH). ^{1}H NMR (acetone-d_6) δ 1.37 (d, J=6.0 Hz, 6H, $2CH_3$), 3.90 (s, 3H, OCH_3), 4.29 (s, 3H, NCH_3), 4.69–4.78 (m, 1H, $(CH_3)_2CH$–O), 6.33 (d, J=8.3 Hz, 1H), 6.44 (d, J=8.3 Hz, 1H), 7.08 (d, J=8.9 Hz, 2H), 7.63 (d, J=8.9 Hz, 2H), 8.41 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ 21.5, 22.1 ($2CH_3$), 39.3 (NCH_3), 56.1 (OCH_3), 71.5 (CHO), 102.5, 114.9, 126.7, 130.0, 130.6 (5CH), 85.7, 113.0, 120.4, 132.3, 140.6, 152.1, 164.0 (7C). MS m/z=502 $[M+1]^+$. Anal. Calcd for $C_{18}H_{20}IN_3O_4S$; C, 43.12; H, 4.02; I, 25.31; N, 8.38; S, 6.40. Found: C, 43.01; H, 4.23; I, 25.55; N, 8.19; S, 6.56.

3.7.4. *N*-(4-Butoxy-3-iodo-1-methyl-1*H*-7-indazolyl)-4-methoxybenzenesulfonamide (7d). Colorless solid, yield 75%: mp 91–92 °C. IR (KBr, cm^{-1}): 3228 (NH), 1590 (CN), 1332, 1146 (SO_2), 1234, 1060 (ArOCH). ^{1}H NMR (acetone-d_6) δ 0.94 (t, J=7.2 Hz, 3H, CH_3), 1.52–1.61 (m, 2H, CH_2), 1.73–1.77 (m, 2H, CH_2), 3.84 (s, 3H, OCH_3), 4.01 (t, J=6.6 Hz, 2H, CH_2O), 4.18 (s, 3H, NCH_3), 6.31 (d, J=8.3 Hz, 1H), 6.35 (d, J=8.3 Hz, 1H), 7.10 (d, J=8.8 Hz, 2H), 7.58 (d, J=8.8 Hz, 2H), 9.60 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ 13.7 (CH_3), 38.4 (NCH_3), 18.8, 30.5 ($2CH_2$), 55.6 (OCH_3), 67.5 (CH_2O), 100.7, 112.2, 114.2, 129.2 (4CH), 119.5, 125.4, 128.6, 131.1, 139.0, 151.6, 162.4 (7C). MS m/z=516 $[M+1]^+$. Anal. Calcd for $C_{19}H_{22}IN_3O_4S$; C, 44.28; H, 4.30; I, 24.62; N, 8.15; S, 6.22. Found: C, 44.45; H, 4.21; I, 24.43; N, 8.38; S, 6.41.

3.7.5. *N*-(3-Iodo-4-(2-trimethylsilanyl-ethoxy)-1-methyl-1*H*-7-indazolyl)-4-methoxybenzene sulfonamide (7e). Colorless solid yield 78%: mp 172–173 °C. IR (KBr, cm^{-1}): 3254 (NH), 1590 (CN), 1334, 1146 (SO_2), 1246, 1040 (ArOCH). ^{1}H NMR (acetone-d_6) δ 0.10 (s, 9H, CH_3), 1.29 (t, J=8.5 Hz, 2H, CH_2), 3.91 (s, 3H, OCH_3), 4.19 (t, J=8.5 Hz, 2H, CH_2), 4.29 (s, 3H, NCH_3), 6.33 (d, J=8.1 Hz, 1H), 6.44 (d, J=8.1 Hz, 1H), 7.08 (d, J=8.9 Hz, 2H), 7.63 (d, J=8.9 Hz, 2H), 8.41 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ −1.3 ($3CH_3$), 18.0 (CH_2), 39.3 (NCH_3), 56.1 (OCH_3), 66.8 (CH_2O), 101.6, 114.9, 130.0, 130.6 (4CH), 85.5, 113.2, 119.8, 132.2, 140.4, 153.2, 164.0 (7C). MS m/z=560 $[M+1]^+$. Anal. Calcd for $C_{20}H_{26}IN_3O_4SSi$; C, 42.94; H, 4.68; I, 22.68; N, 7.51; S, 5.73, Si, 5.02. Found: C, 42.77; H, 4.51; I, 22.59; N, 7.73; S, 5.90, Si, 4.96.

3.7.6. *N*-(4-Hydroxy-3-iodo-1-methyl-1*H*-7-indazolyl)-4-methoxy-benzenesulfonamide (8). Compound **7e** (100 mg, 0.18 mmol) was dissolved in 5 mL of trifluoroacetic acid. The mixture was refluxed for 2 h. After cooling, solvent was removed. The crude material was dissolved with EtOAc, washed with sodium hydrogen carbonate and brine, dried over $MgSO_4$ and the solvent removed in vacuo. The residue was purified by flash chromatography on silica gel eluting with EtOAc/EP to provide 80% of **8** as colorless solid: mp 227–228 °C. IR (KBr, cm^{-1}): 3310 (OH), 3246 (NH), 1602 (CN), 1344, 1143 (SO_2). ^{1}H NMR (acetone-d_6) δ 3.89 (s, 3H, OCH_3), 4.30 (s, 3H, NCH_3), 6.24 (d, J=7.9 Hz, 1H), 6.35 (d, J=7.9 Hz, 1H), 7.06 (d, J=8.9 Hz, 2H), 7.62 (d, J=8.9 Hz, 2H), 8.34 (s, 1H, NH), 9.26 (s, 1H, OH). ^{13}C NMR (acetone-d_6) δ 39.2 (NCH_3), 56.1 (OCH_3), 104.9, 114.8, 130.0, 130.6 (4CH), 85.5, 112.4, 119.7, 132.2, 140.9, 151.9, 163.9 (7C). SM: m/z=460 $[M+1]^+$. Anal. Calcd for $C_{15}H_{14}IN_3O_4S$; C, 39.23; H, 3.07; I, 27.63; N, 9.15; S, 6.98. Found: C, 39.36; H, 3.28; I, 27.43; N, 9.05; S, 6.84.

3.8. General procedure for the preparation of compounds 9(a,b)

A mixture of 3-halogeno-7-nitroindazole **1**(**a**–**d**) (0.66 mmol) and anhydrous $SnCl_2$ (0.62 g, 3.3 mmol) in 25 mL of absolute ethanol is heated at 60 °C. After reduction, the starting material has disappeared and the solution is allowed to cool down. The pH is made slightly basic (pH 7–8) by addition of 5% aqueous potassium bicarbonate before being extracted with ethyl acetate. The organic phase is washed with brine and dried over magnesium sulfate. The solvent was removed to afford the amine, which was immediately dissolved in CH_2Cl_2 (5 mL) and then Et_3N (1.5 equiv) and trimethylacethyl chloride(1.1 equiv) or benzyl chloroformate (1.1 equiv) were added. The reaction mixture was stirred at room temperature overnight. After the reaction mixture was concentrated in vacuo, the resulting residue was purified by flash chromatography (eluted with EtOAc/EP).

3.8.1. *N*-(4-Ethoxy-3-iodo-1-methyl-1*H*-7-indazolyl)-2,2-dimethyl-propionamide (9a). Colorless solid, yield 81%: mp 161–162 °C. IR (KBr, cm^{-1}): 3268 (NH), 1640 (CO), 1602 (CN), 1246, 1016 (ArOCH). ^{1}H NMR (acetone-d_6) δ 1.28 (s, 9H, $3CH_3$), 1.45 (t, J=6.9 Hz, 3H, CH_3), 4.04 (s, 3H, NCH_3), 4.12 (q, J=6.9 Hz, 2H, OCH_2), 6.40 (d, J=8.1 Hz, 1H), 6.92 (d, J=8.1 Hz, 1H), 8.57 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ 14.8 (CH_3), 27.8 ($3CH_3$), 38.3 (NCH_3), 39.5 ($C(CH_3)_3$), 64.6 (OCH_2), 101.6, 128.6 (2CH), 85.1, 115.5, 119.6, 139.8, 152.1 (5C), 179.2 (CO). SM m/z=402 $[M+1]^+$. Anal. Calcd for $C_{15}H_{20}IN_3O_2$; C, 44.90; H, 5.02; I, 31.63; N, 10.47. Found: C, 44.97; H, 4.89; I, 31.44; N, 10.56.

3.8.2. (4-Ethoxy-3-iodo-1-methyl-1*H*-7-indazolyl)-carbamic acid benzyl ester (9b). Colorless solid, yield 74%: mp 167–168 °C. IR (KBr, cm^{-1}): 3254 (NH), 1682 (CO), 1604 (CN), 1240, 1054 (ArOCH). ^{1}H NMR (acetone-d_6) δ 1.45 (t, J=7.2 Hz, 3H, CH_3), 4.03 (s, 3H, NCH_3), 4.14 (q, J=7.2 Hz, 2H, OCH_2), 5.14 (s, 2H, CH_2), 6.44 (d, J=8.1 Hz, 1H), 7.08 (d, J=8.1 Hz, 1H), 7.34 (m, 5H), 8.25 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ 14.8 (CH_3), 38.1 (NCH_3), 64.7 (OCH_2), 67.2 (OCH_2), 101.7, 114.9, 121.4, 128.8, 129.2 (5CH), 85.4, 119.8, 138.0, 139.7, 152.4, 158.6 (6C), 177.1 (CO). SM m/z=452 $[M+1]^+$. Anal. Calcd for $C_{18}H_{18}IN_3O_3$; C, 47.91; H, 4.02; I, 28.12; N, 9.31. Found: C, 47.86; H, 3.92; I, 28.30; N, 9.15.

3.8.3. *N*-(4-Ethoxy-1-methyl-3-thiophen-3-yl-1*H*-7-indazolyl)-2,2-dimethyl-propionamide (10). Under argon atmosphere, a mixture of **9a** (100 mg, 0.24 mmol) and 3-thiopheneboronic acid ($m=40$ mg, 0.28 mmol) in DME (8 mL), sodium carbonate (80 mg, 0.72 mmol) in H_2O (4 mL) was added followed by the addition of $Pd(PPh_3)_4$ (30 mg, 0.043 mmol). The reaction mixture was refluxed with vigorous stirring for 2 h. It was then evaporated to dryness under reduced pressure. Ethyl acetate (5 mL) was added; the organic phase was washed with a saturated solution of sodium chloride (10 mL), dried over $MgSO_4$ and the solvent removed in vacuo. The residue was purified by flash chromatography (EtOAc/EP) yielding 72 mg (81%) of **10** as a colorless solid: mp 132–133 °C. IR (KBr, cm^{-1}): 3320 (NH), 1644 (CO), 1602 (CN), 1258, 1048 (ArOCH). ^1H NMR (acetone-d_6) δ 1.36 (s, 9H, $3CH_3$), 1.48 (t, $J=7.2$ Hz, 3H, CH_3), 4.13 (s, 3H, NCH_3), 4.20 (q, $J=7.2$ Hz, 2H, CH_2O), 6.98 (d, $J=8.1$ Hz, 1H), 7.22 (d, $J=8.1$ Hz, 1H), 7.58 (dd, $J=6.2$, 4.0 Hz, 1H), 7.90 (d, $J=6.2$ Hz, 1H), 8.34 (d, $J=4.0$ Hz, 1H), 8.60 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ 14.8 (CH_3), 27.9 ($3CH_3$), 38.2 (NCH_3), 39.6 ($C(CH_3)_3$) 64.7 (OCH_2), 101.2, 124.7, 126.7, 128.1, 129.7 (5CH), 114.7, 115.9, 135.8, 141.1, 153.0 (5C), 179.1 (CO). SM $m/z=358$ $[M+1]^+$. Anal. Calcd for $C_{19}H_{23}IN_3O_2S$; C, 63.84; H, 6.49; N, 11.75, S, 8.97. Found: C, 63.78; H, 6.30; N, 11.96, S, 9.18.

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Annulation of pyrrole: application to the synthesis of indolizidine alkaloids

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Abstract—The nucleophilicity of pyrrole has been exploited to rapidly assemble the bicyclic skeleton of the indolizidine alkaloids. The key sequence is the annulation of a second ring onto pyrrole from a γ-lactone and has been exploited in the synthesis of the natural products (±)-monomorine and (±)-indolizidine 209D.

1. Introduction

Indolizidine alkaloids such as those derived from amphibians and ants have proved popular targets for total synthesis for both conformation of structure and investigation of the potent biological activity that many of these possess.[1] They have also been exploited to highlight new synthetic methods.[1] Many of the alkaloids isolated possess alkyl substituents around the bicyclic core such as the 5-alkyl substituted derivative assigned as indolizidine 209D[2] and the Pharaoh's ant trail pheromone (+)-monomorine,[3] which is a 3,5-dialkyl indolizidine (Fig. 1).

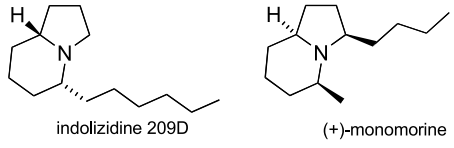
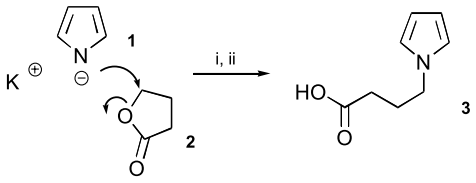


Figure 1.

The synthesis of bicyclic alkaloids from pyrrole derivatives has been reported to be an effective method for the synthesis of indolizidine alkaloids.[4] The pyrrole unit provides a template not only to form a second ring but also to reveal the saturated heterocycle by hydrogenation. One of the most efficient methods for the formation of the indolizidine skeleton was reported by Jefford[5] and Taylor,[6] who have shown that the activation of the carboxylate group of a γ-pyrrolic ester with boron tribromide promoted cyclisation onto the nucleophilic pyrrole ring. By developing a short synthesis of the appropriately substituted γ-pyrrolic esters, a rapid synthesis of the indolizidine skeleton of targeted alkaloids could be developed (Scheme 1).



Scheme 1. Reagents: (i) 160 °C; (ii) H_3O^+(90%).

Recently, the unusual S_N2 type ring opening of γ-butyrolactone (**2**) with the potassium salt of pyrrole (**1**), as reported by Li and Snyder,[7] has been exploited on a multi-gram scale to give the γ-pyrrolic acid **3** as a key intermediate in the synthesis of the naturally occurring alkaloid rhazinal, which posseses anti-mitotic properties.[8] Therefore, we set about investigating the extension of the lactone ring opening to substituted γ-pyrrolic acid derivatives, particularly those bearing a substituent at the γ-position of the lactone. This could be exploited to introduce a substituent at C-5 of an indolizidine simply by the choice of lactone. The reaction of substituted lactones has not been reported and it would be expected that the size of the substituent at the γ-position may inhibit the reaction if the process is truly an S_N2 type substitution. Subsequent conversion of the γ-pyrrolic acids to an ester, and Lewis acid mediated intramolecular acylation onto the nucleophilic pyrrole would yield the bicyclic structure. The availability and low cost of numerous substituted lactones that could be used to target indolizidine alkaloids warranted investigation into a rapid synthesis of these natural products via γ-pyrrolic esters.

Keywords: Pyrrole; Indolizidines; Alkaloids; γ-Lactones.
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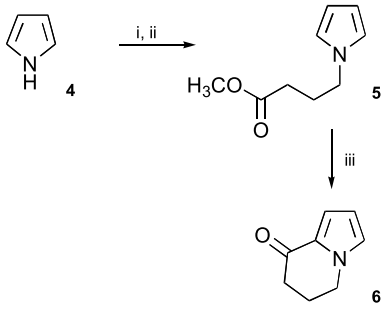
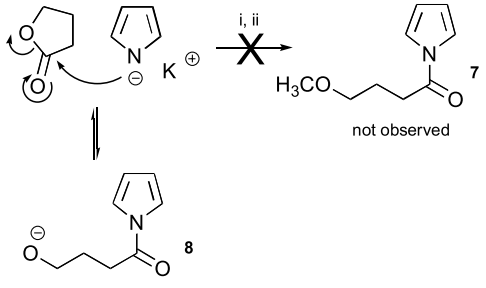
2. Results and discussion

Initial studies were carried out on the ring opening of γ-butyrolactone to form the unsubstituted indolizidine **6**. While the original reaction was carried out under solventless conditions, we investigated the use of a solvent to facilitate the formation of the desired ester directly from the crude reaction mixture. We found that reaction of the potassium salt of pyrrole with γ-butyrolactone at 160 °C in DMF affected the desired ring opening and addition of methyl iodide to the cooled mixture alkylated the intermediate carboxylate salt (Scheme 2).



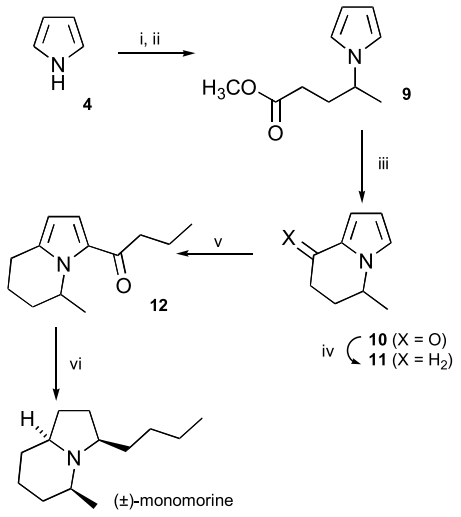
Scheme 2. Reagents: (i) KH, DMF, 0 °C then γ-butyrolactone, 160 °C, 4 h; (ii) CH_3I (excess) 18 °C (61%); (iii) BBr_3 (1.1 equiv) CH_2Cl_2, 0 °C (91%).

It was interesting to note that no acyl pyrrole **7** was observed on the treatment of the reaction mixture with methyl iodide as might have been expected by trapping the, presumably kinetically favoured, acyl nucleophilic ring opened product (**8**) of the lactone. (Scheme 3) This indicates that the equilibrium favours the starting materials and results in the thermodynamically favoured γ-pyrrolic ester as the only observed product. This gave the methyl ester **5** in 61% yield in one step, making it a viable method for the synthesis of this type of compound. The γ-pyrrolic ester was then cyclised by treatment with boron tribromide[5] to yield the indolizidine **6** as indicated by desymmetrisation of the pyrrole ring in the ^1H NMR spectrum and a shift of the carbonyl stretch in the IR spectrum to 1651 cm^{-1}. Therefore, in two short steps we have achieved the annulation of pyrrole to form the indolizidine skeleton in 56% overall yield. As a result, we then investigated the application of this reaction to substituted lactones.



Scheme 3. Reagents: (i) DMF, 160 °C, 4 h; (ii) CH_3I (excess) 18 °C.

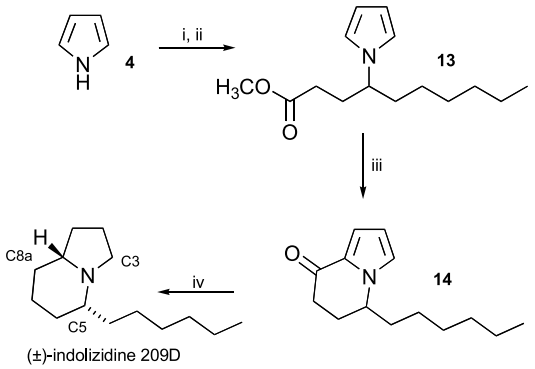
The reaction of the potassium salt of pyrrole with (±)-γ-valerolactone, which bears a methyl substituent at C-5 of the lactone, under the reaction conditions reported above yielded the γ-pyrrolic ester **9**[9] in low yield. Not surprisingly, the extra bulk at the γ-position of the lactone hindered the reaction and reduced the yield dramatically giving support for the S_N2 mechanism. To overcome this, the reaction was repeated under the conditions of Li and Snyder[7] to give the intermediate acid, which was then converted directly to the ester **9** in 48% over two steps. Clearly the substituted lactones require more forcing conditions but the γ-pyrrolic esters can be formed in reasonable yields and this has been carried out on a multi-gram scale. Cyclisation of the ester **9** gave the 5-substituted indolizidine **10** as expected in high yield (Scheme 4).



Scheme 4. Reagents: (i) KH, 0 °C; and then γ-valerolactone, 160 °C, 4 h (60%); (ii) K_2CO_3, DMF, CH_3I (excess) 18 °C (80%); (iii) BBr_3 (1.1 equiv) CH_2Cl_2, 0 °C (90%); (iv) $NaBH_3CN$, ZnI_2, CH_2Cl_2, 45 °C (73%); (v) butyryl chloride, AgOTf, CH_2Cl_2, 0 °C (20%); (vi) Ref. 9: Pd/C, H_2 (55 psi), CH_3OH, catalytic H_2SO_4.

To exploit this method for the synthesis of natural products, we targeted the Pharaoh's ant pheromone monomorine that bears a methyl substituent at C-5. To achieve this synthesis, the carbonyl group adjacent to the pyrrole was removed by reduction with $ZnI_2/NaBH_3CN$[10] to activate C-3 of the indolizidine (**11**) to introduce a butyl substituent. Initially, we investigated Vilsmeier–Haack formylation and Wittig olefination to introduce the butyl chain required, however, formylation was low yielding and not regioselective occurring equally at C-2 and C-3. This was surprising as we expected formylation to occur exclusively at C-3 based upon a similar reaction for the synthesis of rhazinal,[8] consequently the methyl group at C-5 must hinder attack at this position. Surprisingly, the activation of an acid chloride, butyryl chloride, by typical Lewis acids such as $AlCl_3$ and $ZnCl_2$ proved unsuccessful. However, the use of silver triflate promoted the reaction to give the desired acylated product **12** in 20% yield (40% based upon starting material consumed). The selective acylation at C-3 of the indolizidine was indicated by the coupling constant of 4.2 Hz for the two protons of the pyrrole moiety. The ketone **12** has previously been hydrogenated stereoselectively by Muchowski[9] to yield monomorine. Thus, in five short steps we have accomplished the formal synthesis of this 3,5-dialkyl indolizidine (Scheme 5).

We then investigated the formation of the 5-hexyl



Scheme 5. Reagents: (i) KH, 0 °C; and then γ-decanolactone, 160 °C, 4 h; (ii) K_2CO_3, DMF, CH_3I (excess) 18 °C (30% over two steps); (iii) BBr_3 (1.1 equiv) CH_2Cl_2, 0 °C (90%); (iv) Pd/C, H_2 (40 psi) CH_3CO_2H (90%).

substituted derivative 209D from the commercially available (±)-γ-decanolactone. The yield for the formation of the ester **13** in this instance was reduced further to 30% over two steps. The cause is most likely attributed to the increasing bulk of the C-4 substituent on the lactone therefore suggesting a limit to the size of the substituent at this position. Cyclisation of the ester **13** proceeded in high yield to give the 5-hexyl indolizidine **14**, which was then hydrogenated with palladium on carbon,[11] with high diastereoselectively, to yield (±)-indolizidine 209D. The assignment was confirmed by comparison of the ^{13}C NMR spectrum with that of both possible diastereomers.[12] (Table 1). In particular, the resonances of the three carbon atoms attached to nitrogen, (C3, C5 and C8a) resonating at 50.7, 63.9 and 65.4 ppm, respectively, are diagnostic for the formation of the desired diastereomer. The chemical shifts of these carbon atoms in the other possible isomer are 48.8, 55.1 and 55.5 ppm, respectively.[12b] Therefore, the racemic alkaloid was formed in 24% yield over four steps from commercial starting materials. The low yield of the lactone ring opening is offset by low cost of the reagents and the fact that the reaction can be carried out on a significant scale to enable the total synthesis of the targeted alkaloids in a few short steps. One downfall is that enantio-pure lactones are extremely expensive therefore limiting the method to the formation of racemic products at the present time. We are currently engaged in overcoming this problem to develop an asymmetric synthesis of γ-pyrrolic esters.

Table 1. ^{13}C NMR comparison of synthetic (±)-indolizidine 209D[a]

Smith et al.	Polniaszek et al.[12b]
65.4	65.1
63.9	63.9
50.7	51.6
33.8	34.7
31.8	31.9
30.0	31.1
29.8	30.9
29.7	30.6
29.5	29.8
25.9	25.9
24.3	24.8
22.6	22.7
20.2	20.5
14.1	14.2

[a] ^{13}C NMR δ (75 MHz, $CDCl_3$).

3. Conclusions

In conclusion, we have performed a rapid annulation of lactones onto pyrrole to yield 5-substituted indolizidines via γ-pyrrolic esters in only a few sequential synthetic steps. While the yields are not consistently high for the proposed S_N2 ring opening of the substituted lactones, the low cost and availability of the starting substrates makes this a viable entry into γ-pyrrolic esters as the reactions can be readily carried out on a multi-gram scale. These derivatives have been manipulated to complete a formal synthesis of (±)-monomorine and the total synthesis of (±)-indolizidine 209D.

4. Experimental

4.1. General experimental

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Mercury Plus spectrometer operating at 300 and 75 MHz, respectively. Infrared spectroscopy was recorded on a Perkin–Elmer, paragon 1000 FT-IR as neat films on sodium chloride plates unless otherwise stated. High resolution and Low resolution mass spectroscopy was performed on a Kratos Concept ISQ mass instrument. Melting points were carried out on a Yanagimoto micro melting point apparatus and are uncorrected. Chemicals and reagents were purchased from Aldrich and used as received unless otherwise stated. Solvents were purified by standard literature methods before use.[13] Organic extracts were dried with anhydrous magnesium sulfate unless otherwise stated. Column chromatography was carried out using Merck Silica gel (40–63 μm).

4.2. General procedure for the *N*-alkylation of pyrrole

Method A. Pyrrole (0.200 g, 2.99 mmol) was added dropwise to a suspension of potassium hydride (0.120 g, 2.99 mmol) in anhydrous DMF (2 mL) under an atmosphere of nitrogen at 0 °C. The solution was stirred at room temperature for 10 min, γ-butyrolactone (0.256 g, 2.99 mmol) added and the mixture heated on an oil bath at 160 °C for 4 h. The solution was cooled to room temperature, methyl iodide (0.053 mL, excess) added and the mixture stirred overnight at room temperature. Water (10 mL) was added and the product extracted with 1:1 ethyl acetate/hexanes (3×10 mL). The organic extract was dried and evaporated to give the crude product, which was purified by flash chromatography on silica (eluent: ethyl acetate/hexanes, 1:9) to give **5** as a colourless oil in 61% yield. ν_{max}(neat)/cm^{-1} 1737; ^1H NMR spectrum (300 MHz, $CDCl_3$): 2.05–2.15 (m, 2H), 2.30 (t, J=6.9 Hz, 2H), 3.70 (s, 3H), 3.96 (t, J=6.9 Hz, 2H), 6.17 (apparent t, 2H), 6.66 (apparent t, 2H); ^{13}C NMR spectrum (75 MHz, $CDCl_3$): 27.0, 31.0, 48.7, 51.9, 108.5, 120.7, 173.5.

Method B. Pyrrole (3.30 g, 49 mmol) was added dropwise to solid potassium hydride (1.96 g, 49 mmol) under a nitrogen atmosphere and the mixture stirred at room temperature for 1 h. γ-Valerolactone (4.90 g, 62 mmol) was added and the mixture heated on an oil bath at 160 °C for 4 h. $NaHCO_3$ (5%) solution (50 mL) was added carefully and extracted

with dichloromethane (3×20 mL). The aqueous layer was retained, acidified with 2 M HCl and extracted with dichloromethane (3×20 mL). The organic extract was dried and evaporated to give the crude acid that was dissolved in DMF (20 mL), potassium carbonate (excess) and methyl iodide (4 equiv) added and stirred overnight at room temperature. The reaction mixture was worked up the same as for method A to yield the methyl ester as a colourless oil **9**[9] in 48% yield. ν_{max}(neat) 1733 cm^{-1}; ^1H NMR spectrum (300 MHz, $CDCl_3$): 1.45 (d, $J=6.9$ Hz, 3H), 1.94–2.08 (m, 2H), 2.10–2.18 (m, 2H), 3.64 (s, 3H), 4.10 (m, 1H), 6.14 (apparent t, 2H), 6.67 (apparent t, 2H); ^{13}C NMR spectrum (75 MHz, $CDCl_3$): 22.2, 30.5, 33.2, 51.6, 54.5, 107.9, 118.4, 173.5.

4.2.1. 8-Oxo-5,6,7,8-dehydroindolizidine (6). Boron tribromide (0.718 mL, 7.60 mmol) was added dropwise to a solution of **5** (1.16 g, 6.91 mmol) in dichloromethane (20 mL) under an atmosphere of nitrogen at 0 °C. The mixture was stirred at this temperature for 10 min and the reaction quenched by the careful addition of water (10 mL) followed by 2 M Na_2CO_3 (10 mL). The product was extracted with dichloromethane (2×20 mL), the organic extract dried and evaporated to give the crude product, which was purified by passing through a plug of silica gel (eluent: ethyl acetate/hexanes, 1:1) to give the indolizidine **6** in 91% yield as a colourless oil that solidified on storage in the refrigerator. ν_{max}(neat) 1651 cm^{-1}; ^1H NMR spectrum (300 MHz, $CDCl_3$): 2.20–2.29 (m, 2H), 2.56 (t, $J=6.9$ Hz, 2H), 4.09 (t, $J=6.0$ Hz, 2H), 6.22 (dd, $J=3.9$, 2.4 Hz, 2H), 6.83–6.84 (m, 1H), 6.98 (dd, $J=3.9$, 1.2 Hz, 1H); ^{13}C NMR spectrum (75 MHz, $CDCl_3$): 23.4, 36.1, 45.0, 110.2, 113.8, 125.9, 130.2, 187.2.

4.2.2. 5-Methyl-8-oxo-5,6,7,8-dehydroindolizidine (10). The γ-pyrrolic ester **9** was reacted under the same conditions as for **6** to give the product **10**, which was recrystallised from ether/hexanes (10:3) to yield the titled product as a colourless solid in 90% yield: mp=98–100 °C, [Found $M^{\cdot+}$, 149.0837 $C_9H_{11}NO$ requires 149.0840]; ν_{max}(neat) 1644 cm^{-1}; ^1H NMR spectrum (300 MHz, $CDCl_3$): 1.55 (d, $J=6.3$ Hz, 3H), 1.97–2.09 (m, 1H), 2.24–2.34 (m, 1H), 2.46–2.70 (m, 2H), 4.20–4.31 (m, 1H), 6.24 (dd, $J=2.4$, 4.2 Hz, 1H), 6.92–6.93 (m, 1H), 7.00 (dd, $J=2.2$, 4.2 Hz, 1H); ^{13}C NMR spectrum (75 MHz, $CDCl_3$: 20.6, 30.8, 34.5, 50.5, 110.4, 114.1, 124.1, 130.4, 187.2; *m/z* (EI) 149(100%), 134(30), 106(50), 93(40), 80(25), 67(30).

4.2.3. 5-Methyl-5,6,7,8-dehydroindolizidine (11). Sodium cyanoborohydride (0.10 g, 1.59 mmol) was added to a solution of the indolizidine **10** (0.20 g, 1.34 mmol) and zinc iodide (0.41 g, 1.28 mmol) in dichloromethane under an atmosphere of nitrogen (20 mL) and the mixture refluxed for 6 h. Water (10 mL) was added and the product extracted with dichloromethane (2×10 mL), the organic extract dried and evaporated to give the crude product. The indolizidine **11** was purified by flash chromatography on silica gel (eluent: ethyl acetate/hexanes, 1:4) to give the product as a colourless, unstable oil that was used immediately. ^1H NMR spectrum (300 MHz, $CDCl_3$): 1.52 (d, $J=6.3$ Hz, 3H), 1.60–1.80 (m, 2H), 1.91–2.10 (m, 1H), 2.04–2.13 (m, 1H), 2.69–2.80 (m, 2H), 4.04–4.17 (m, 1H), 5.92 (br s, 1H), 6.17 (s, 1H), 6.67 (br s, 1H); ^{13}C NMR spectrum (75 MHz, $CDCl_3$): 19.9, 22.3, 23.6, 32.0, 50.4, 103.7, 107.4, 116.7, 129.5.

4.2.4. 5-Methyl-3-butyryl-5,6,7,8-dehydroindolizidine (12). Butyryl chloride (0.019 mL, 0.17 mmol) was added dropwise to a solution of indolizidine **11** (16 mg, 0.12 mmol) and silver triflate (52 mg, 0.20 mmol) in dichloromethane (1 mL) under an atmosphere of nitrogen and the mixture stirred at room temperature overnight. The reaction was quenched with water (10 mL) and extracted with dichloromethane (3×10 mL). The organic extract was dried and evaporated to give the crude product, which was purified by flash chromatography (eluent: ethyl acetate/hexanes, 1:9) to give unreacted starting material (50%) and **12** as a colourless oil in 20% yield. [Found $M^{\cdot+}$, 205.1471 $C_{13}H_{19}NO$ requires 205.1467]; ν_{max}(neat)/cm^{-1} 1643; ^1H NMR spectrum (300 MHz, $CDCl_3$): 0.96 (t, $J=7.5$ Hz, 3H), 1.33 (d, $J=6.6$ Hz, 3H), 1.60–2.03 (m, 6H), 2.61–2.80 (m, 1H), 2.70 (t, $J=7.5$ Hz, 2H), 2.86–2.97 (m, 1H), 5.26–5.32 (m, 1H), 5.86 (d, $J=4.2$ Hz, 1H), 6.98 (d, $J=4.2$ Hz, 1H); ^{13}C NMR spectrum (75 MHz, $CDCl_3$): 14.0, 15.0, 19.3, 22.0, 23.8, 29.3, 41.1, 49.6, 106.5, 120.5, 189.7, C3 and C8a not observed.

4.2.5. Methyl 4-(pyrrol-1-yl) decanoate (13). The γ-pyrrolic ester **13** was isolated as a colourless oil in 30% overall yield from pyrrole by Method B: [Found $M^{\cdot+}$, 251.1887 $C_{15}H_{25}NO_2$ requires 251.1885]; ν_{max}(neat)/cm^{-1} 1740; ^1H NMR spectrum (300 MHz, $CDCl_3$) 0.85 (m, 3H), 1.14–1.36 (m, 8H), 1.70–1.78 (m, 2H), 1.89–2.14 (m, 4H), 3.64 (s, 3H), 3.79–3.88 (m, 1H), 6.14 (apparent t, 2H), 6.62 (apparent t, 2H); ^{13}C NMR spectrum (75 MHz, $CDCl_3$): 14.0, 22.6, 26.2, 29.0, 30.5, 31.6, 31.7, 36.7, 51.6, 59.6, 107.8, 118.8, 173.7; *m/z* (EI) 251(50%), 220(25), 164(100), 134(15), 106(35), 94(70), 81(50), 67(40).

4.2.6. 5-Hexyl-8-oxo-5,6,7,8-dehydroindolizidine (14). The product was formed by the same conditions as reported for compound **6**. Indolizidine **14** was isolated as a colourless oil in 90% yield: [Found $M^{\cdot+}$, 219.1617 $C_{14}H_{21}NO$ requires 219.1622]; ν_{max}(neat)/cm^{-1} 1662; ^1H NMR spectrum (300 MHz, $CDCl_3$): 1.51 (d, $J=6.3$ Hz, 3H), 1.69–1.83 (m, 8H), 1.84–1.97 (m, 1H), 2.06–2.16 (m, 1H), 2.30–2.42 (m, 1H), 2.51 (ddd, $J=17.7$, 9.3, 4.3 Hz, 1H), 2.67 (ddd, $J=17.7$, 10.2, 4.3 Hz, 1H), 4.15 (m, 1H), 6.24 (dd, $J=3.9$, 2.4 Hz, 1H), 6.91 (dd, $J=2.4$, 1.5 Hz, 1H), 7.01 (dd, $J=3.9$, 1.5 Hz, 1H); ^{13}C NMR spectrum (75 MHz, $CDCl_3$): 14.0, 22.5, 26.0, 27.7, 29.1, 31.6, 33.3, 34.3, 54.8, 110.1, 114.3, 125.0, 130.2, 187.2 *m/z* (EI) 219(30%), 191(20), 148(65), 134(95), 106(100), 93(60), 67(30).

4.2.7. Indolizidine 209D. The indolizidine **14** (27 mg, 0.12 mmol) was dissolved in acetic acid (10 mL), Pd/carbon (20 mg of 5%) added and hydrogenated at 40 psi on a Parr shaker hydrogenator for 10 h. The catalyst was removed by filtration through Celite and the solvent removed. The residue was dissolved in 2 M Na_2CO_3 (10 mL) and extracted with dichloromethane (3×10 mL). The organic extracts were dried (Na_2SO_4), evaporated and the product purified by flash chromatography (eluent: dichloromethane/methanol/ammonia, 95:4.75:0.25) to give indolizidine 209D as a colourless oil in 90% yield; ^1H NMR spectrum (300 MHz, $CDCl_3$): 0.86 (t, $J=6.9$ Hz, 3H), 1.16–1.46 (m,

13H), 1.50–1.96 (m, 8H), 2.02–2.20 (m, 2H), 3.37 (td, $J=$ 9.3, 2.1 Hz, 1H); ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 14.1, 20.2, 22.6, 24.3, 25.9, 29.5, 29.7, 29.8, 30.0, 31.8, 33.8, 50.7, 63.9, 65.4.

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Regio- and stereochemical aspects in synthesis of 2-allyl derivatives of glycolic, mandelic and lactic acids and their iodocyclisations to 3-hydroxy-3,4-dihydrofuran-2(5*H*)-ones

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Abstract—Glyoxalic, phenylglyoxalic and pyruvic acids **1a–c** undergo regio- and diastereoselective indium mediated allylations with allyl and cinnamyl bromides and ethyl 4-bromocrotonate to provide respective 2-allyl-, 2-(1-phenylallyl)- and 2-[(1-ethoxycarbonyl)allyl]-derivatives of glycolic, mandelic and lactic acids **3–11**. The reactions follow Cram's chelation model for allylation and give *syn* addition products as the major or the only products. Diastereoselective iodocyclisations of **3–8** and **10** provide 3-hydroxy-3,4-dihydrofuran-2(5*H*)-ones (**15–21**), the stereochemical outcome, of which depends on the nature and position of the substituents on the substrate, choice of solvent and base. The relative stereochemistries have been ascertained by X-ray structure and NOE experiments and coupling constants in the ^{1}H NMR spectra.

1. Introduction

2(5*H*)-Furanones have attained considerable significance as the synthetic targets due to their wide-spread biological activity, occurrence in nature and their use as synthetic intermediates.[1] Approaches towards stereoselective synthesis are therefore a continued challenge in their synthesis. The electrophile induced intramolecular cyclisation of an appropriately substituted alkene ester constitutes one practical approach for their synthesis.[2]

The availability of the appropriate alkene esters or acid moieties constitutes the key step in the synthesis of target furanones. The allylation of 2-oxocarboxylic acids could be a simple and general approach for the synthesis of functionalized alkene acids.[3–5] However, the earlier reported procedures for the allylation under Grignard type conditions with allyl boronates[3] and allyl trichloromethyl silane[4] or under Barbier type conditions by using mixed metal combinations $BiCl_3$–Mg(0)/$BiCl_3$–Zn(0)[5] suffer from pre-synthesis of the reagents and non-availability of substituted allyl organometallic reagents. In recent years, indium mediated allylations have provided simple synthetic procedures for the aqueous media allylation of carbonyl compounds even in the presence of proton donor functionalities.[6] The presence of hydroxy-, alkoxy or amino moieties at α- or β- to carbonyl group has led to considerable π-facial discrimination through participation of Cram's chelation model.[7–9] However, the participation of COOH coordination in indium mediated allylation is not known.

Now we report that 2-oxocarboxylic acids **1a–1c** undergo regio- and stereoselective indium mediated allylations with allyl and cinnamyl bromides and ethy 4-bromoccrotonate to provide respective 2-allyl-, 2-(1-phenylallyl)- and 2-[(1-ethoxycarbonyl)allyl]- derivatives of glycolic, mandelic and lactic acids **3–11**.[10] These allylation reactions, in general, follow Cram's cyclic model to provide *syn* addition products as the only or the major products. 2-Hydroxypent-4-en-1-oic acids **3–8** and **10**, depending on the nature and position of the substituents on the substrate, choice of solvent and base undergo diastereoselective iodocyclisations to provide a general procedure for 3-hydroxy-3,4-dihydrofuran-2(5*H*)-ones **15–21**. It has been observed that the balance of steric factors on C-2 and C-3 position of respective alkenoic acids significantly affects the outcome of stereoselectivities in 3-hydroxy-3,4-dihydrofuran-2(5*H*)-ones.

2. Results and discussion

2.1. Allylation of 2-oxocarboxylic acids

A solution of glyoxalic acid **1a**, allyl bromide **2a** and indium

Keywords: Indium allylation; Diastereoselective; Iodocyclisations; Furan-2-ones.
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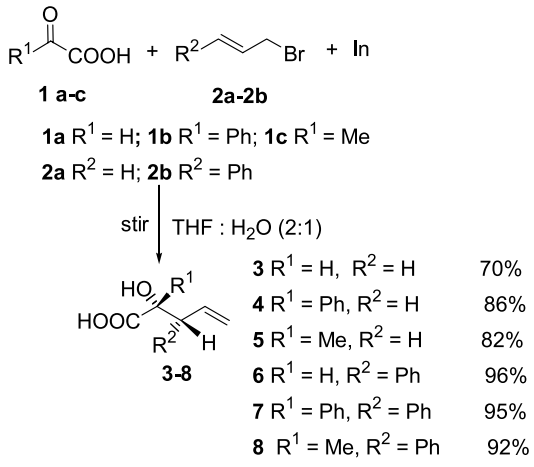


Scheme 1.

metal (suspension) (1:1.5:1) in THF–H_2O (2:1) on stirring at 0 °C, following usual work-up and chromatography gave 2-allyl glycolic acid **3**, as a pale yellow liquid (70%), M^+ *m/z* 116 (Scheme 1). Similarly, phenylglyoxalic acid **1b** and pyruvic acid **1c** underwent indium mediated allylation with allyl bromide to give respective 2-allyl- mandelic and lactic acids **4** and **5** (82–86%).

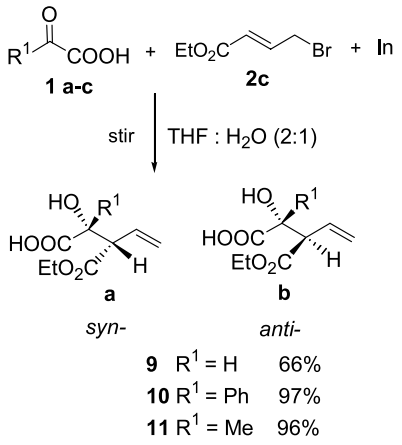
In order to extend the scope of this reaction to achieve a diasteroselective allylation, the reactions of **1a–c** have been performed with cinnamyl bromide and ethyl 4-bromocrotonate. Glyoxalic acid **1a** on indium mediated allylation with cinnamyl bromide **2b** gave 2-(1-phenylallyl) glycolic acid **6**, pale yellow liquid (96%), M^+ *m/z* 192, 116 ($M^+ - C_6H_5$) (Scheme 1). In its ^1H NMR spectrum, the presence of 1H double doublet at δ 3.86 due to C*H*Ph and lack of CH_2 signals in the region δ 2.0–3.5 confirmed the formation of γ- addition product. The presence of only one set of signals in both ^1H and ^{13}C NMR spectra points to a single diastereomer being formed.

Similarly, indium mediated allylation of **1b** and **1c** with cinnamyl bromide gave the respective 2-(1-phenylallyl)-mandelic and pyruvic acids **7** and **8** (Table 1). Therefore, 2-oxocarboxylic acids **1a–c** undergo indium mediated highly γ-regio- and diastereoselective Barbier type allylation with cinnamyl bromide. The stereochemistries as *syn* addition products to 2-allyl carboxylic acids **6–8** have been assigned on the basis of the X-ray crystal structure of iodocyclised products **19a** and **19b** and coupling constant and NOE experiments on the ^1H NMR spectra of **18–20** (Scheme 1).

Table 1. Reactions of 2-oxocarboxylic acids **1a–c** with **2b** and **2c**

S.no.	R^1	R^2	Product	Yield (%)	dr (*syn*: *anti*)
1	H	C_6H_5	**6**	96	>99:1
2	C_6H_5	C_6H_5	**7**	95	>99:1
3	CH_3	C_6H_5	**8**	92	>99:1
4	H	$CO_2C_2H_5$	**9**	66	86:14
5	C_6H_5	$CO_2C_2H_5$	**10**	97	90:10[a]
6	CH_3	$CO_2C_2H_5$	**11**	96	86:14

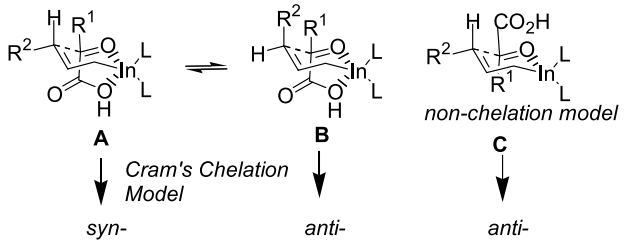
[a] After single crystallization increases to >98:2.



Scheme 2.

Similarly, **1b** and **1c** underwent indium mediated allylation with **2c** to provide respective 2-[(1-ethoxy carbonyl)allyl] mandelic and lactic acids **10** and **11** (Scheme 2). Both **10** and **11** have been formed as a mixture of *syn* and *anti* diastereomers, the *syn* diastereomer being the major product (Table 1). In the case of **10**, the diastereomeric ratio could be increased to >98:2 by single crystallization. Therefore, allylation of **1a–c** with ethyl 4-bromocrotonate leads to lower diastero-selectivities than those found with cinnamyl bromide.

The formation of *syn* addition products as the only, or major products, in allylation of **1a–c** with **2b** and **2c** could be explained by the participation of Cram's chelation model A (Scheme 3) where the conformation of 2-oxocarboxylic acid is locked by complexation with allylindium reagent and allylic anion adds from the sterically less hindered face. In case of ethyl 4-bromocrotonate, the lower diastereoselectivities, could be due to partial participation of transition state B or non-chelation model C (Scheme 3).[11,12]

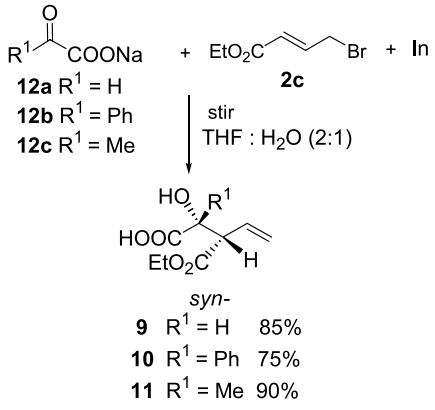


Scheme 3.

We envisioned that the increased ease of participation of carboxylic acid moiety in forming cyclic transition state with allylindium reagent could increase the participation of Cram's chelation model and thus the diastereoselectivity. The conversion of carboxylic acid to carboxylate anion (**12a–c**), due to the presence of negative charge, would facilitate chelation during the allyl transfer process. Alternatively, the conversion of acid to amide **13**, due to delocalisation of the nitrogen lone pair of electrons with carbonyl, is expected to increase the participation of amide oxygen towards complexation with indium and thus higher diastereoselectivities.

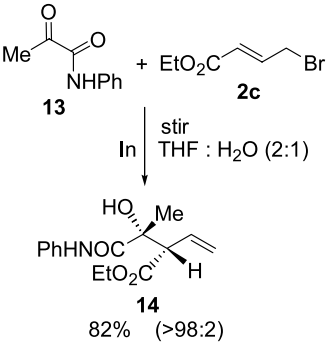
However, sodium pyruvate **12c** did not undergo allylation with ethyl 4-bromocrotonate in THF–H_2O. On performing

the reaction at pH 4.7±0.2, the allylation proceeded quite smoothly and in a highly diastereoselective manner to provide **11** (dr>98:2), but the yield of **11** was lowered to 50%. On using 2 equiv of indium metal and 3 equiv of **2c**, the yield of **11** could be increased to 90%. During the reaction, the pH of the solution was maintained by adding 4 N NaOH solution from time to time. Similarly, **12a** and **12b** underwent diastereoselective allylation with **2c** at pH 4.7±0.2 to provide **9** and **10**, respectively, in dr> 98:2 (Scheme 4). The allylation of **12a–c** was completed in shorter times (4–6 h) than the time taken for the reactions of respective 2-oxocarboxylic acids **1a–c** (18–24 h). Both higher diastereoselectivities and shorter reaction time for allylation at pH 4.7±0.2 could be assigned to better participation of the carboxylate anion in chelation than the carboxylic acid moiety. In an alternative approach, the pH of the solution of **1a–c** in THF–H_2O (2:1) was adjusted to 6±0.2 by adding NaOH solution and then ethyl 4-bromocrotonate and indium was added and the stirring was continued. The reactions were completed in 4–6 h and **9–11** were formed with diastereoselectivities >98:2.



Scheme 4.

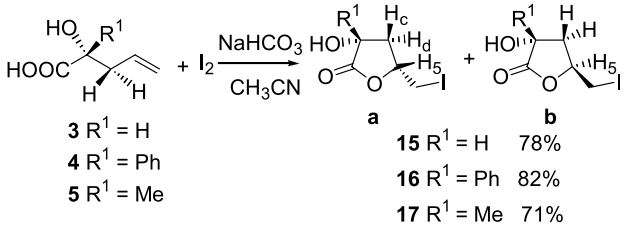
Similarly, indium mediated allylation of **13**, with ethyl 4-bromocrotonate in THF–H_2O proceeded quite smoothly (4–5 h) and in a highly diastereoselective manner (dr> 98:2) to provide **14** (Scheme 5). Both higher diastereoselectivities and shorter reaction time for allylation point to the increased participation of amide oxygen towards complexation with indium.



Scheme 5.

2.2. Synthesis of 3-hydroxy-3,4-dihydrofuran-2(5*H*)-ones (15–21)

A solution of **3** in dry CH_3CN containing I_2 and suspended $NaHCO_3$ (3 equiv) on stirring at 0 °C after work-up gave **15a**, mp 69 °C, M^+ *m/z* 242 in diastereomeric ratio >99:1 (Scheme 6). The ^1H NMR spectrum of **15a** exhibits five 1H signals with well defined multiplicities and one 1H signal as multiplet and shows that each proton is magnetically non-equivalent. The decoupling of 1H multiplet at δ 4.41–4.45 coverts dt at δ 1.98 to triplet, and ddd's at δ 2.89 to double doublet, two dd's at δ 3.31 and 3.45 to doublets and has been assigned the 5-H proton. The decoupling of the dd at δ 4.62 (H_3) modulates dt at δ 1.98, and doublet of dd at δ 2.89 and confirms the signals at δ 1.98 and 2.89 due to ring CH_2 protons. The higher coupling constants (J=10.4 Hz) between H-c, and H-5 with signal at δ 1.98 and lower coupling constants (J=5.4/8.6 Hz) with signal at δ 2.89 support the stereochemistries defined in Figure 1. The positive NOE of signal H_c (δ 2.89) with H_3 and H_5 signals and lack of NOE of H_d with these protons conspicuously assigns these stereochemistries. Therefore **3** undergoes highly diastereoselective iodocyclisation to provide (3*R**,5*R**)-3-hydroxy-5-iodomethylfuran-2(5*H*)-one (**15a**).



Scheme 6.

2-Allylmandelic acid **4** on iodocyclisation (I_2–CH_3CN–$NaHCO_3$) provided the crude reaction mixture, which in its ^1H NMR spectrum shows two multiplets at δ 4.33–4.41 (1H) and 4.68–4.79 (1H) due to CH in 66:34 ratio and pointed it to be a mixture of two diastereomeric furan-2(5*H*)-ones **16a** and **16b**. However, even on repeated chromatography and crystallization, the two components could not be separated. Since the diastereoselectivity in iodocyclisation reactions is significantly affected by the choice of solvent and base, the iodocyclisation of **4** was attempted under various conditions by using solvents of varied polarities and Na^+/RNH_4^+ carboxylates in place of COOH (Table 2).

On performing the reaction of **4** in dry THF, the dr **16a/16b** was increased to 80:20, which was further increased to 91:9 on carrying out the reaction in dry DMF. The sodium salt of

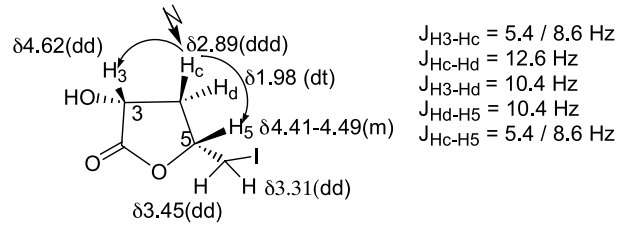


Figure 1. The relative stereochemistries in **15a** from NOE and coupling constant experiments.

Table 2. Disatereoselectivities in iodocyclisations of **4**

S. no.	Base	Solvent	Time (h)	dr	Yield %
Effect of solvent					
1	$NaHCO_3$	CH_3CN	72	66:34	82
2	$NaHCO_3$	THF	6	80:20	83
3	$NaHCO_3$	DMF	1–2	91:9	56
Effect of base					
4	Benzyl amine	THF	3–5	86:14	63
5	[a]	THF	3–5	89:11	90
6	[a]	DMF	1–2	93:7	56
7	[b]	THF	3–5	91: 9	82
8	[b]	DMF	1–2	95: 5	70
9	Pyrrolidine	THF	3–5	90:10	62

[a] Phenylethylamine.
[b] Diisopropylamine.

4 in dry DMF also gave **16a** and **16b** in 91:9 ratio but failed to react in THF or CH_3CN, probably due to its poor solubility in latter solvents. It seems that on moving from THF and CH_3CN, to DMF, the nature of the nucleophile shifts from carboxylic acid to carboxylate ion. Since ammonium salts find more solubility in non-polar solvents, the reactions of **4** were performed in the presence of various amines. The iodocyclisation of **4** in I_2-benzylamine/phenyl ethyl amine by using THF as solvent gave **16a/16b** in dr 86:14–89:11 (Table 2, s. no. 4,5), which was further increased to 90:10–91:9 by using secondary alkyl amines as base (s. no. 7, 9). On performing iodocyclisation of **4** in the presence of primary and secondary amines and by using DMF as solvent, the dr **16a/16b** was enhanced to 93:7 and 95:5 (s. no. 6, 8), respectively. The 95:5 mixture of **16a/16b** on crystallization gave pure **16a**, mp 70 °C, M^+ *m/z* 318.

Compound **16a**. in its ^1H NMR spectrum shows four 1H double doublets and one 1H multiplet along with aromatic (5*H*) protons. The decoupling of multiplet at δ 4.33–4.41 converts all the four double doublets to doublets and unambiguously assigns H-5 proton to this multiplet. In its ^1H-^{13}C COSY spectrum, the correlation of most up-field negative carbon (CH_2I) signal at δ 5.13 (due to iodine effect) with two double doublets at δ 3.34 and 3.47 assigns them to be CH_2I protons. The irradiation of 1H multiplet at δ 4.33–4.41 (H-5) enhances the signals for H_c (δ 2.87) and phenyl protons by 7.6 and 13.6%, respectively, (Fig. 2) and points to the presence of H-5, H_c and 3-Ph moieties on the same face of furan-2(5*H*)-one ring. The higher coupling constant between H-5 and H_d ($J=10$ Hz) than between H-5 and H_c ($J=5.4$ Hz) (Fig. 2) also supports the presence of H_d proton trans to H-5 proton. This data confirms the structure (3*S**,5*R**)-3-hydroxy-3-phenyl-5-iodomethylfuran-2(5*H*)-one (**16a**) to this compound.

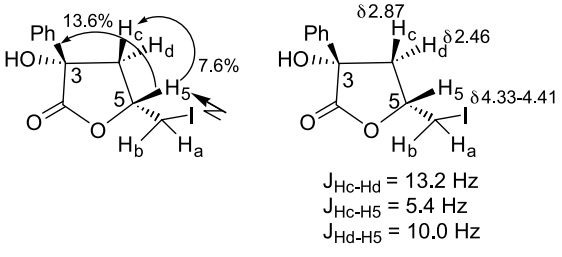
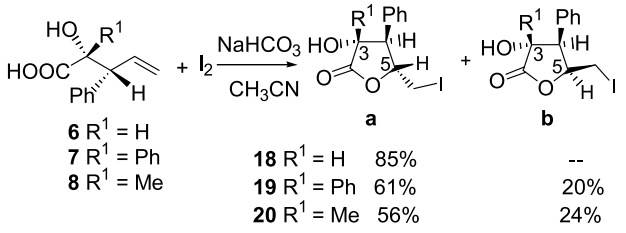


Figure 2. The relative stereochemistries in **16a** from NOE and coupling constant experiments.

The signals for the minor component **16b** were picked from the 2:1 mixture of **16a** and **16b**. The irradiation of H-5 signal at δ 4.68–4.79 does not show NOE with the phenyl protons and has been assigned the structure **16b**.

2-Allyl lactic acid **5** on iodocyclisation provided 80:20 mixture of two diastereomers, which on column chromatography followed by repeated crystallization resulted in isolation of major diastereomer **17a**. The assignment of the signals to each proton and carbon has been made on the basis of ^1H, ^{13}C NMR, decoupling experiments and ^1H–^{13}C COSY spectra. The relative stereochemistries at C-3 and C-5 carbons have been ascertained from NOE experiment. The irradiation of H-5 multiplet at δ 4.44–4.49 shows positive NOE for CH_3 (12.6%) and H_c (δ 2.54) (5.2%). These observations show that H-4, CH_3 and H-5 are on the same side of furan-2(5*H*)-one ring and have been assigned the structure (3*R**,5*R**)-3-hydroxy-3-methyl-5-iodomethyl-furan-2(5*H*)-one (**17a**).

2-(1-Phenylallyl)glycolic acid **6** on iodocyclisation gave only one diastereomer **18a** (85%), mp 84 °C, M^+ *m/z* 318 (Scheme 7). The $J=10.2$ Hz coupling constant between H-5 (δ 4.25–4.31) and H-4 (δ 3.42) and $J=10.2$ Hz coupling constant between H-3 (δ 4.77) and H-4 (δ 3.42) assign *trans*, *trans* stereochemistry between H-3, H-4 and H-5. The irradiation of H-3 doublet at δ 4.77 shows NOE enhancement of H-5 (3.7%) and Ph (6.1%) protons and irradiation of H-5 multiplet (δ 4.25–4.31) shows NOE enhancement of H-3 (2.2%) and Ph (5.7%) protons and confirms the structure (3*R**,4*R**,5*R**)-3-hydroxy-4-phenyl-5-iodomethyl-furan-2 (5*H*)-one (**18a**) for this compound.



Scheme 7.

2-(1-Phenylallyl)mandelic acid **7** on iodocyclisation in CH_3CN–$NaHCO_3$ gave 75:25 mixture of two diastereomers **19a** (61%) and **19b** (20%). On using DMF–$NaHCO_3$ the diastereoselectivity decreased to 50:50. In ^1H NMR spectrum of major component $J_{H\text{-}4,\ H\text{-}5}=10.4$ Hz shows the presence of H-4 and H-5 on the opposite side of furan-2(5*H*)-one ring (**19a**). The minor component in its ^1H NMR spectrum exhibits $J_{H\text{-}4,\ H\text{-}5}=5.4$ Hz and points to the presence of H-4 and H-5 protons on the same side of furan-2(5*H*)-one ring (**19b**). However, the relative stereochemsitries at C-3 and C-4 in **19a** and **19b** could not be assigned on the basis of NMR or NOE experiments and have been confirmed by X-ray structure analysis.

The X-ray crystal structures of both **19a** (Fig. 3) and **19b** (Fig. 4), show the presence of two aryl rings on the same face of furan-2(5*H*)-one ring and confirm the formation of *syn* homoallylic alcohol **7**. In **19a**, the CH_2I and OH

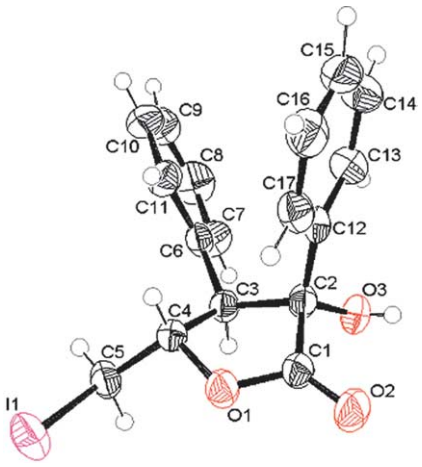


Figure 3. The ORTEP view (50% ellipsoide) of **19a**.

moieties are on the same face. This results in placement of H-3 and H-4 protons on the opposite face of furan-2(5*H*)-one ring and is in agreement with $J_{H\text{-}4,\,5}=10.4$ Hz observed in its ^{1}H NMR spectrum. Similarly, in the case of **19b**, $J_{H\text{-}4,5}=5.4$ Hz is in agreement with placement of H-3 and H-4 protons on the same side of furan-2(5*H*)-one ring as confimed by X-ray structure. In both **19a** and **19b** C(4)–O(1)–C(1)–C(2) make one mean plane (Tables 3 and 4) and C-3 carbon moves out of plane by an angle of $23\pm1°$. The two phenyl rings on C-2 and C-3 carbons are placed at dihedral angle of 44.6(3)° in **19a** and 39.2(3)° in **19b**. The placement of CH_2I unit in two different orientations in **19a** and **19b** controls the placement of C-2 and C-3 phenyl rings. In the case of **19a**, 3-phenyl ring is placed at equatorial position [C(6)–C(3)–C(4)–O(1) –163.5(2)°] and 2-phenyl is placed at axial position [O(1)–C(1)–C(2)–C(12) 97.3(3)°]. But in the case of **19b**, 2-phenyl ring is placed at equatorial position [O(1)–C(1)–C(2)–C(12) −151.4(2)°] and 3-phenyl is placed at axial position [C(6)–C(3)–C(4)–O(1) 86.9(3)°].

Iodine mediated intramolecular cyclisation of **8** in CH_3CN provided 70:30 mixture of **20a** and **20b**. In the case of **20a** the irradiation of H-5 multiplet (δ 4.57–4.64) shows NOE enhancement of CH_3 (22.6%) and phenyl (21.8%) protons. Therefore, H-5, CH_3 and phenyl are on the same side of furan-2(5*H*)-one ring and confirms the structure (3*R**,4*R**,5*R**)-3-hydroxy-3-methyl-4-phenyl-5-iodo methyl-furan-2(5*H*)-one (**20a**). In the case of **20b**,

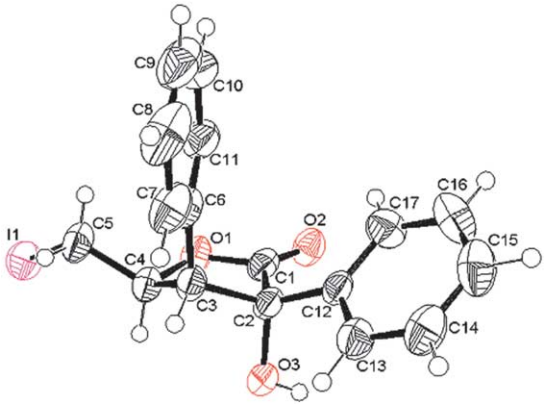
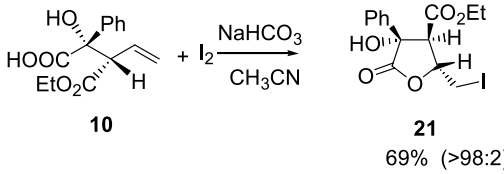


Figure 4. The ORTEP view (50% ellipsoide) of **19b**.

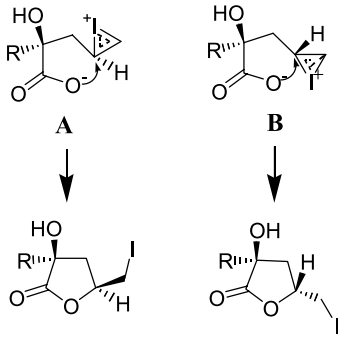
$J_{H4,5}=4.8$ Hz shows the presence of H-4 and H-5 protons on the same side of furan-2(5*H*)-one ring and lack of NOE of H-5 with phenyl and methyl protons points the placement of methyl and phenyl groups on the opposite face than H-5 and confirms structure (3*R**,4*R**,5*S**)-3-methyl-4-phenyl-3-hydroxy-5-idomethyl-furan-2(5*H*)-one (**20b**) to the minor product.

Compound **10** underwent diastereoselective iodocyclisation to provide **21** in dr>98:2 (Scheme 8). The assignment of signals has been made on the basis of ^{1}H NMR and ^{1}H decoupling experiments. The coupling constant $J=9$ Hz between H-4 (d, δ 3.62) and H-5 (m, δ 4.64–4.69), shows the presence of H-4 and H-5 protons on the opposite side of furan-2(5*H*)-one ring. The irradiation of H-5 multiplet shows positive NOE for phenyl ring multiplet (5.0%) and $COOCH_2$ multiplet (7.67%) and points to the presence of phenyl ring, COOEt and H-5 moieties on the same side of furan-2(5*H*)-one ring. Therefore, iodine mediated cyclisation of **10** gives only (3*S**,4*S**, 5*R**)-3-hydroxy-4-ethoxycarbonyl-5-iodomethylfuran-2(5*H*)-one **21**.



Scheme 8.

The formation of two diastereomers of furan-2(5*H*)-ones could be visualized to proceed through intermediates **A** and **B** (Scheme 9) formed by the addition of iodine on either of the two faces of double bond. Iodonium ion intermediate **A** would result in the formation of 3,5-substituted product with OH and CH_2I groups placed *syn* to each other, while iodonium ion intermediate **B** would result in formation of product with OH and CH_2I groups on the opposite faces of furane ring. The present iodine mediated intramolecular cyclisations of 2-hydroxy-4-pentene-1-oic acid and its derivatives result in formation of the products with OH and CH_2I moieties present on same side either exclusively or predominantly and involve the preferential participation of intermediate **A**. This preference arises probably due to stabilisation of iodonium ion intermediate by its electrostatic interactions with lone pair of oxygen in intermediate **A**. Such participation of oxygen lone pairs in the



Scheme 9.

stabilization of iodonium ion has earlier been suggested in iodocyclizations of 4-hydroxy-pentenoic acids.[13]

3. Conclusions

Thus, 2-oxocarboxylic acids undergo facile indium mediated allylation in aqueous media with allyl bromide, cinnamyl bromide and ethyl 4-bromocrotonate to provide the corresponding 2-allyl derivatives of glycolic, mandelic and lactic acids. In the case of reactions with cinnamyl bromide and ethyl 4-bromocrotonate, the allylation reactions proceed with high γ-regio- and diastereoselectivities. The formation of *syn* addition products confirms possible chelation of carboxylic acid moiety with indium during allyl transfer process. The iodine mediated intramolecular cyclizations of **3–8** and **10** provide furan-2(5*H*)-one derivatives with OH and CH_2I moieties placed *syn* to each other as the major or the only product.

4. Experimental

4.1. General details

Melting points were determined in capillaries and are uncorrected. ^{1}H NMR spectra were recorded on JEOL Al 300 MHz instrument using $CDCl_3$ solution containing tetramethylsilane as an internal standard. The chemical shifts are reported in δ values relative to TMS and coupling constants (J) are expressed in Hz. ^{13}C NMR spectra were recorded at 75 MHz and values are reported relative to $CDCl_3$ signal at δ 77.0. Chromatography was performed with silica 100–200 mesh and the reactions were monitored by thin-layer chromatography (TLC) with glass plates coated with silca gel HF-254.

4.2. General procedure

Procedure A. The 2-oxocarboxylic acid **1** (5 mmol), allyl bromide (7.5 mmol) and indium metal (fine flakes) (5 mmol) were taken in THF–H_2O (2:1) mixture and the reaction mixture was stirred in an ice bath until the indium metal dissolved (18–24 h). The turbid reaction mixture was treated with 4 N HCl and extracted with $CHCl_3$. The organic solvent was distilled off and the residue was column chromatographed (silica gel, 60–120 mesh) to isolate the allyl addition product.

Procedure B. The sodium salt of 2-oxocarboxylic acid **1** (5 mmol), **2c** (15 mmol) and indium metal (fine falkes) (10 mmol) were taken in THF–H_2O (2:1) mixture. The pH 4.7 of the reaction was controlled initially by addition of acetic acid. The reaction mixture was stirred in an ice bath until the indium metal dissolved. During the course of reaction the pH was controlled 4.7 ± 0.2 by the addition of aqueous NaOH (4 N). After completion of the reaction, the turbid reaction mixture was treated with 4 N HCl and extracted with $CHCl_3$.The organic solvent was distilled off and the residue was column chromatographed (silica gel, 60–120 mesh) to isolate the allyl addition product.

4.2.1. 2-Allylglycolic acid (3). *Procedure A*. 406 mg, 70%; pale yellow liquid; FAB mass M^+ *m/z* 116 (M^+); ^{1}H NMR ($CDCl_3$): δ 2.34–2.63 (m, 2H, CH_2), 4.22–4.32 (m, 1H, CH), 4.60–4.92 (b, 1H, OH, exchanges with D_2O), 5.04–5.17 (m, 2H, $=CH_2$), 5.62–5.85 (m, 1H, =CH), 6.24–6.55 (bs, 1H, OH, exchanges with D_2O); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 38.47 (−ve, CH_2), 69.65 (+ve, CH), 118.07 (+ve, CH), 132.93 (−ve, CH_2), 176.23 (ab, C); IR ν_{max} (neat): 1722 (C=O), 3440 (OH) cm^{-1}. (For Na salt: mp > 300 °C. Found: C, 43.2; H, 5.1. $C_5H_7O_3Na$ requires C, 43.48; H, 5.07%).

4.2.2. 2-Allylmandelic acid (4). *Procedure A*. White solid 825 mg, 86%; mp 110 °C ($CHCl_3$); FAB mass M^+ *m/z* 192 (M^+); ^{1}H NMR ($CDCl_3$): δ 1.87 (s, 1H, OH, exchanges with D_2O), 2.71 (dd, $J_1=13.8$ Hz, $J_2=6.8$ Hz, 1H of CH_2), 2.96 (dd $J_1=13.8$ Hz, $J_2=6.8$ Hz, 1H of CH_2), 5.11–5.22 (m, 2H, $=CH_2$), 5.69–5.89 (m, 1H, =CH), 7.19–7.64 (m, 5*H*, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 44.32 (−ve, CH_2), 78.08 (ab, C), 119.72 (−ve, CH_2), 125.67 (+ve, CH), 127.89 (+ve, CH), 128.45 (+ve, CH), 133.78 (+ve, CH), 140.85 (ab, C), 178.79 (ab, C); IR ν_{max} (neat): 1720 (C=O), 3442 (OH) cm^{-1}. Found C, 61.4; H, 5.3%. $C_{11}H_{11}O_3Na$ requires C, 61.68; H, 5.14%.

4.2.3. 2-Allyllactic acid (5). *Procedure A*. 533 mg, 82%; colourless liquid; FAB mass M^+ *m/z* 130 (M^+), 111 (M^+ − allyl); ^{1}H NMR ($CDCl_3$): δ 1.49 (s, 3H, CH_3), 2.41 (dd, 1H, $J_1=10$ Hz, $J_2=6$ Hz, 1H of CH_2), 2.57 (dd, 1H, $J_1=10$ Hz, $J_2=6$ Hz, 1H of CH_2), 5.16–5.29 (m, 2H, $=CH_2$), 5.74–5.87 (m, 1H, =CH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 25.22 (−ve, CH_2), 44.51 (+ve, CH_3), 74.41 (ab, C), 119.33 (+ve, CH), 131.79 (−ve, CH_2), 180.18 (ab, C); IR ν_{max} (neat): 1724 (C=O), 3446 (OH) cm^{-1}. (For Na salt: mp > 300 °C. Found: C, 47.3; H, 5.7. $C_6H_{10}O_3Na$ requires C, 47.36; H, 5.92%).

4.2.4. (2*R,3*R**)-2-(1-Phenylallyl)-glycolic acid (6).** *Procedure A*. 920 mg, 96%; light yellow liquid; FAB mass M^+ *m/z* 192 (M^+), 116 ($M^+ - C_6H_5$); ^{1}H NMR ($CDCl_3$): δ 2.18 (s, 1H, OH, exchanges with D_2O), 3.86 (dd, $J_1=7.6$ Hz, $J_2=4$ Hz, 1H, CH), 4.59 (d, $J=4$ Hz, 1H, CH), 5.20–5.29 (m, 2H, $=CH_2$), 6.25 (ddd, $J_1=17.4$ Hz, $J_2=10$ Hz, $J_3=7.4$ Hz, 1H, =CH), 7.22–7.37 (m, 5*H*, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 52.82 (+ve, CH), 73.74 (+ve, CH), 117.29 (−ve, CH_2), 127.37 (+ve, CH), 128.46 (+ve, CH), 128.74 (+ve, CH), 137.72 (ab, C), 136.88 (+ve, CH), 177.72 (ab, C); IR ν_{max} (neat): 1687 (C=O), 3521 (OH) cm^{-1}. (For Na salt: mp > 300 °C. Found C, 61.4; H, 5.3%. $C_{11}H_{11}O_3Na$ requires C, 61.68; H, 5.14%).

4.2.5. (2*R,3*R**)-2-(1-Phenylallyl)-mandelic acid (7).** *Procedure A*. White solid 206 g, 95%; mp 168 °C (CH_2Cl_2); FAB mass M^+ *m/z* 269 ($M^+ + 1$); ^{1}H NMR ($CDCl_3$): δ 4.39 (s, 1H, OH, exchanges with D_2O), 4.40 (d, $J=9.6$ Hz, 1H, CH), 4.79–4.99 (m, 2H, $=CH_2$), 5.96 (ddd, $J_1=17.4$ Hz, $J_2=9.6$ Hz, $J_3=8.1$ Hz, 1H, =CH), 7.19–7.41 (m, 8H, ArH), 7.72–7.73 (m, 2H, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 57.13 (+ve, CH), 80.75 (ab, C), 118.49 (−ve, CH_2), 126.42 (+ve, CH), 127.26 (+ve, CH), 127.89 (+ve, CH), 128.12 (+ve, CH), 128.21(+ve, CH), 129.43 (+ve, CH), 135.29 (+ve, CH), 138.93 (ab, C), 139.17 (ab, C), 177.75 (ab, C); IR ν_{max}

(KBr): 1685 (C=O), 3519 (OH) cm^{-1}. (Found C, 76.3; H, 5.9. $C_{17}H_{16}O_3$ requires C, 76.12; H, 5.97%).

4.2.6. (2*R,3*R**)-2-(1-Phenylallyl)-lactic acid (8).** *Procedure A*. 948 mg, 92%; light yellow liquid; FAB mass M^+ *m/z* 206 (M^+); ^1H NMR ($CDCl_3$): δ 1.49 (s,3H, CH_3), 3.55 (d, $J=9.6$ Hz, 1H, CH), 5.16–5.31 (m, 2H, $=CH_2$), 6.26 (dt, $J_1=16.8$ Hz, $J_2=9.6$ Hz, 1H, =CH), 7.24–7.29 (m, 5*H*, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 24.42 (+ve, CH_3), 57.61 (+ve, CH), 76.77 (ab, C), 118.80 (−ve, CH_2), 127.19 (+ve, CH), 128.38 (+ve, CH), 128.53 (+ve, CH), 135.39 (+ve, CH), 139.39 (ab, C), 180.41 (ab, C); IR ν_{max} (neat): 1728 (C=O), 3481 (OH) cm^{-1}. (For Na salt: mp > 300 °C. Found C, 63.1; H, 6.1. $C_{12}H_{13}O_3Na$ requires C, 63.16; H, 5.70%).

4.2.7. (2*R,3*S**)-2-[(1-Ethoxy carbonyl)allyl] glycolic acid (9).** *Procedure B*. 798 mg, 85%; light yellow liquid; FAB mass M^+ *m/z* 188 (M^+), 143 (M^+-COOH); ^1H NMR ($CDCl_3$): δ 1.31 (t, $J=7$ Hz, 3H, CH_3), 2.09 (s, 1H,OH, exchanges with D_2O), 3.62 (dd, $J_1=8.4$ Hz, $J_2=3.6$ Hz, 1H, CH), 4.20 (s, 1H, OH, exchanges with D_2O), 4.22 (q, $J=7$ Hz, 2H, OCH_2), 4.47 (d, $J=3.6$ Hz,1H, CH), 5.26–5.38 (m, 2H, $=CH_2$), 5.92 (dt, $J_1=17.4$ Hz, $J_2=8.4$ Hz, 1H, =CH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 14.21 (+ve, CH_3), 50.21 (+ve, CH), 60.32 (−ve, CH_2), 71.20 (+ve, CH), 121.23 (−ve, CH_2), 136.13 (+ve, CH), 173.22 (ab, C), 175.59 (ab, C); IR ν_{max} (neat): 1728 (C=O), 3481 (OH) cm^{-1}. (For Na salt: mp > 300 °C. Found C, 45.4; H, 4.9. $C_8H_{11}O_5Na$ requires C, 45.71; H, 5.24%).

4.2.8. (2*S,3*S**)-2-[(1-Ethoxy carbonyl)allyl] mandelic acid (10).** *Procedure B*. White solid 991 mg, 75%; mp 97–98 °C (CH_2Cl_2); FAB mass M^+ *m/z* 219 (M^+-COOH); ^1H NMR ($CDCl_3$): δ 1.29 (t, $J=7.2$ Hz, 3H, CH_3), 2.20 (s, 1H, OH, exchanges with D_2O), 4.14 (d, $J=8.2$ Hz, 1H, CH), 4.22 (q, $J=7.2$ Hz, 2H, OCH_2), 5.02–5.17 (m, 2H, $=CH_2$), 5.56–5.62 (ddd, $J_1=17.4$ Hz, $J_2=7.2$ Hz, $J_3=6.4$ Hz, 1H, =CH), 7.29–7.42 (m, 8H, ArH), 7.58–7.63 (m, 2H, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 13.90 (+ve, CH_3), 56.88 (+ve, CH), 61.31 (−ve, CH_2), 78.73 (ab, C), 120.64(−ve, CH_2), 125.66 (+ve, CH), 127.66 (+ve, CH), 128.01 (+ve, CH), 130.23 (+ve, CH), 138.51 (ab, C), 173.22 (ab, C), 175.63 (ab, C); IR ν_{max} (KBr): 1706 (C=O), 1730 (C=O), 3504 (OH) cm^{-1}. (Found: C, 63.3; H, 6.0. $C_{14}H_{16}O_5$ requires C, 63.63; H, 6.06%).

4.2.9. (2*R,3*S**)-2-[(1-Ethoxy carbonyl)allyl] lactic acids (11).** *Procedure B*. 909 mg, 90%; light yellow liquid; FAB mass M^+ *m/z* 202 (M^+); ^1H NMR ($CDCl_3$): δ 1.33 (t, $J=8$ Hz, 3H, CH_3), 1.39 (s, 3H, CH_3), 2.84 (br s, 1H, OH, exchanges with D_2O), 4.17 (dd, $J_1=8.4$ Hz, $J_2=3.6$ Hz, 1H, CH), 4.20 (s, 1H, OH, exchanges with D_2O), 4.22 (q, $J=7$ Hz, 2H, OCH_2), 5.31–5.44 (m, 2H, $=CH_2$), 5.89 (ddd, $J_1=17$ Hz, $J_2=9$ Hz, $J_3=8.4$ Hz, 1H, =CH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 12.91 (+ve, CH_3), 22.87 (+ve, CH_3), 55.96 (+ve, CH), 59.54 (−ve, CH_2), 73.18 (ab, C), 119.46 (−ve, CH_2), 130.59 (+ve, CH), 176.96 (ab, C), 176.23 (ab, C); IR ν_{max}: 1730 (C=O), 1785 (C=O), 3558 (OH) cm^{-1}. (For Na salt of **11**: mp > 300 °C. Found: C, 48.0; H, 6.1. $C_9H_{13}NaO_5$ requires C, 48.21; H, 5.8%).

4.3. Synthesis of 2-oxo-*N*-phenyl-propionamide (13)

The mixture of ethyl lactate (1 mmol, 2 g) and aniline (1 mmol, 1.6 g) was heated without solvent for 5–6 h on water bath. The progress of the reaction was monitored by TLC. On completion of reaction (TLC) the reaction mixture was diluted with 10 ml of water and extracted with $CHCl_3$ (3×20 ml). The organic phase was washed with water and dried over sodium sulphate. The removal of solvent provided yellow liquid. The crude reaction mixture was column chramotaographed over silica gel to isolate pure 2-hydroxy-*N*-phenylpropionamide (2.23 g, 80%). It was treated with Jones reagent. On completion the reaction mixture was diluted with 10 ml of water and extracted with $CHCl_3$ (3×20 ml). The organic phase was washed with water and dried over sodium sulphate. The crude reaction mixture was column chromatographed over silica gel to isolate pure (**13**) (1.14 g, 52%);white solid, mp 62 °C ($CHCl_3$); FAB mass M^+ *m/z* 163 (M^+); ^1H NMR ($CDCl_3$): δ 2.55 (s, 3H, CH_3), 7.16 (t, $J=7.4$ Hz, 1H, ArH), 7.35 (t, $J=7.4$ Hz, 2H, ArH), 7.62 (d, $J=9$ Hz, 2H, ArH), 8.70 (br s, 1H, NH, exchanges with D_2O); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 24.40 (+ve, CH_3), 119.68 (+ve, CH), 125.26 (+ve, CH), 129.20 (+ve, CH), 136.21 (ab, C), 162.56 (ab, C), 197.29 (ab, C); IR ν_{max} (KBr): 1674 (C=O), 1710 (C=O), 3321 (NH) cm^{-1}. (Found: C, 66.2; H, 5.3; N, 8.3. $C_9H_9NO_2$ requires C, 66.3; H, 5.52; N, 8.59%).

4.3.1. (2*R,3*S**)-2-[(1-Ethoxy carbonyl)allyl]-*N*-phenyl-propionamide (14).** *Procedure A*. White solid 1.135 g, 82%; mp 71 °C ($CHCl_3$); FAB mass M^+ *m/z* 277 (M^+); ^1H NMR ($CDCl_3$): δ 1.23 (t, $J=7.2$ Hz, 3H, CH_3), 1.37 (s, 3H, CH_3), 3.83 (d, $J=9.2$ Hz, 1H, CH), 4.09–4.22 (m, 2H, OCH_2), 4.95 (s, 1H, OH, exchanges with D_2O), 5.35–5.44 (m, 2H, $=CH_2$), 5.90 (ddd, $J_1=17.2$ Hz, $J_2=10.8$ Hz, $J_3=9.2$ Hz, 1H, =CH) 7.13 (t, $J=7.2$ Hz, 1H, ArH), 7.35 (t, $J=7.5$ Hz, 2H, ArH), 7.55 (d, $J=9$ Hz, 2H, ArH), 8.73 (br s, 1H, NH, exchanges with D_2O); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 14.03 (+ve, CH_3), 24.01 (+ve, CH_3), 54.20 (+ve, CH), 61.65 (−ve, CH_2), 76.73 (ab, C), 119.59 (+ve, CH), 122.16 (−ve, CH_2), 124.36 (+ve, CH), 128.95 (+ve, CH), 130.15 (+ve, CH), 137.11 (ab, C), 173.81 (ab, C), 175.13 (ab, C); IR ν_{max} (KBr): 1668 (C=O), 1701 (C=O), 3355 (NH), 3421 (OH) cm^{-1}. (Found: C, 64.8; H, 7.1; N, 4.9. $C_{15}H_{19}NO_4$ requires C, 64.98; H, 6.86; N, 5.05%).

4.4. Iodine mediated cyclization of homoallylic alcohols

Procedure C. Sodium hydrogen carbonate (0.009 mol) was added to an ice cold solution of homoallylic alcohol (0.003 mol) in dry acetonitrile and resulting suspension was stirred for 15 min at 0 °C. Iodine (0.009 mol) 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 furan-2(5*H*)-one derivatives.

Procedure D. Di-isopropylamine (0.009 mol) was added to an ice cold solution of homoallylic alcohol (0.003 mol) in

dry DMF and resulting solution was stirred for 15 min at 0 °C. Iodine (0.009 mol) was added and stirring was continued for 24 h at 0 °C in dark (TLC monitoring). The reaction mixture was diluted with water and extracted with ether. 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 furan-2(5*H*)-one derivatives.

4.4.1. (3*R,5*R**)-3-Hydroxy-5-iodomethylfuran-2(5*H*)-one (15a).** *Procedure C*. White solid 566 mg, 78%; mp 69 °C (benzene); FAB mass M^+ *m/z* 242 (M^+); ^{1}H NMR ($CDCl_3$): δ 1.98 (dt, $J_1=12.6$ Hz, $J_2=10.4$ Hz, 1H of CH_2 [H_d]), 2.89 (ddd, $J_1=12.6$ Hz, $J_2=8.6$ Hz, $J_3=5.4$ Hz, 1H, 1H of CH_2 [H_c]), 3.31 (dd, $J_1=10.4$ Hz, $J_2=7.5$ Hz, 1H, 1H of ICH_2), 3.45 (dd, $J_1=10.4$ Hz, $J_2=5.4$ Hz, 1H, 1H of ICH_2), 3.82 (br s, 1H, OH, exchanges with D_2O), 4.41–4.45 (m, 1H, H_5), 4.62 (dd, $J_1=10.4$ Hz, $J_2=8.6$ Hz, 1H, H_3); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 5.41(−ve, CH_2I), 37.41 (−ve, CH_2-4), 68.84 (+ve, CH-3), 75.52 (+ve, CH-5), 176.53 (ab, C=O); IR ν_{max} (KBr): 1772 (C=O), 3361 (OH) cm^{-1}. (Found: C, 25.2; H, 2.9. $C_5H_7IO_3$ requires C, 24.79; H, 2.89%).

4.4.2. (3*S,5*R**)-3-Hydroxy-3-phenyl-5-iodomethylfuran-2(5*H*)-one(16a).** Procedure *D*. White solid 562 mg, 59%; mp 70 °C (benzene); FAB mass M^+ *m/z* 318 (M^+); ^{1}H NMR ($CDCl_3$): δ 2.46 (dd, $J_1=13.2$ Hz, $J_2=10$ Hz,1H, 1H of CH_2 [H_d]), 2.87 (dd, $J_1=13.2$ Hz, $J_2=5.4$ Hz, 1H of CH_2 [H_c]), 3.11 (br s, 1H, OH, exchanges with D_2O), 3.34 (dd, $J_1=10.5$ Hz, $J_2=7.8$ Hz,1H, 1H of CH_2i), 3.47 (dd, $J_1=10.5$ Hz, $J_2=5.4$ Hz,1H, 1H of CH_2i), 4.33–4.41 (m,1H, H_5), 7.23–7.46 (m, 5*H*,Arh); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 5.13 (−ve, CH_2I), 44.64 (−ve, CH_2-4), 75.53 (+ve, CH-5), 79.12 (ab, C-3), 125.16 (+ve, CH), 129.09 (+ve, CH), 129.13 (+ve, CH), 139.55 (ab, C), 176.99 (ab, C=O); IR ν_{max} (KBr): 1778 (C=O), 3429 (OH) cm^{-1}. (Found: C, 41.8; H, 3.3. $C_{11}H_{11}IO_3$ requires C, 41.51; H, 3.46%).

4.4.3. (3*S,5*S**)-3-Hydroxy-3-phenyl-5-iodomethylfuran-2(5*H*)-one (16b).** From the spectrum of 1:2 mixture of **16a** and **16b** the lower concentration signals have been chosen. ^{1}H NMR ($CDCl_3$): δ 2.21 (dd, $J_1=18$ Hz, $J_2=8.2$ Hz, 1H, 1H of ring CH_2), 2. 83 (dd, $J_1=18$ Hz, $J_2=6$ Hz, 1H, 1H of ring CH_2), 3.29 (dd, $J_1=10$ Hz, $J_2=1.8$ Hz, 1H, 1H of CH_2I) and 3.45 (dd, $J_1=10$ Hz, $J_2=4.4$ Hz, 1H, 1H of CH_2I), 4.68–4.79 (m, 1H, H_5), 7.23–7.46 (m, 5*H*, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 7.78 (−ve, CH_2), 45.87 (−ve, CH_2), 76.11 (+ve, CH), 78.79 (ab, C), 125.55 (+ve, CH), 128.46 (+ve, CH), 139.65 (ab, C), 176.21 (ab, C).

4.4.4. (3*R,5*R**)-3-Hydroxy-3-methyl-5-iodomethylfuran-2(5*H*)-one (17a).** *Procedure C*. White solid 430 mg, 56%; mp 95 °C (benzene); FAB mass M^+ *m/z* 256 (M^+); ^{1}H NMR ($CDCl_3$): δ 1.52 (s, 3H, CH_3), 2.18 (dd, $J_1=13.2$ Hz, $J_2=8.4$ Hz, 1H, 1H of CH_2 [H_d]), 2.54 (dd, $J_1=13.2$ Hz, $J_2=10.8$ Hz, 1H, 1H of CH_2 [H_c]), 2.61 (br s, 1H, OH, exchanges with D_2O), 3.32 (dd, $J_1=10.4$ Hz, $J_2=8.1$ Hz, 1H, 1H of CH_2i), 3.46 (dd, $J_1=10.4$ Hz, $J_2=4.8$ Hz, 1H, 1H of CH_2i), 4.44–4.49 (m, 1H, H_5); Decoupling: the decoupling of H_5 multiplet at δ 4.44–4.49, converts two dd δ 3.32 and δ 3.46 (CH_2I) and at δ 2.18 (H_d) and 2.54 (H_c) into doublets NOE experiments: the irradiation of H_5 multiplet at δ 4.44–4.49 shows positive NOE for CH_3 (12.6%) and H_c (δ 2.54) (5.2%); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 5.65 (−ve, CH_2I), 24.647 (+ve, CH_3), 42.82 (−ve, CH_2-4), 73.93 (ab, C-3), 75.82 (+ve, CH-5), 178.44 (ab, C=O); IR ν_{max} (KBr): 1762 (C=O), 3442 (OH) cm^{-1}. (Found: C, 28.4; H, 3.6. $C_6H_9IO_3$ requires C, 28.13; H, 3.52%).

4.4.5. (3*R,4*R**,5*R**)-3-Hydroxy-4-phenyl-5-iodomethylfuran-2(5*H*)-one (18a).** *Procedure C*. White solid 810 mg, 85%; mp 84 °C (benzene); FAB mass M^+ *m/z* 318 (M^+); ^{1}H NMR ($CDCl_3$): δ 2.04 (br s, 1H, OH, exchanges with D_2O), 3.27 (dd, $J_1=11.4$ Hz, $J_2=5.4$ Hz, 1H, 1H of CH_2I), 3.42 (t, $J=10.4$ Hz, 1H, H_4), 3.52 (dd, $J_1=11.4$ Hz, $J_2=3.3$ Hz, 1H, 1H of CH_2i), 4.25–4.31 (m, 1H, H_5), 4.77 (d, $J=10.4$ Hz, 1H, H_3), 7.28–7.45 (m, 5*H*, Arh); Decoupling of 1H multiplet at δ 4.25–4.31 changes two double doublets at δ 3.27, 3.52 into doublets and triplet at δ 3.42 into doublet; ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 4.77(−ve, CH_2I), 55.65 (+ve, CH), 74.16 (+ve, CH), 79.75 (+ve, CH), 127.72 (+ve, CH), 128.52 (+ve, CH), 129.33 (+ve, CH), 134.48 (ab, C), 175.02 (ab, C); IR ν_{max} (KBr): 1791 (C=O), 3384 (OH) cm^{-1}. (Found: C, 41.2; H, 3.6. $C_{11}H_{11}IO_3$ requires C, 41.51; H, 3.46%).

4.4.6. (3*S,4*R**,5*R**)-3-Hydroxy-3-phenyl-4-phenyl-5-iodomethyl-furan-2(5*H*)-one (19a).** *Procedure C*. White solid 721 mg, 61%; mp 203 °C; FAB mass M^+ *m/z* 394 (M^+); ^{1}H NMR ($CDCl_3$): δ 1.71 (br s, 1H, OH, exchanges with D_2O), 3.27 (dd, $J_1=12.0$ Hz, $J_2=6.0$ Hz, 1H, 1H of CH_2I), 3.53 (dd, $J_1=12.0$ Hz, $J_2=4.0$ Hz, 1H, 1H of CH_2i), 3.79 (d, $J=10.6$ Hz, H_4), 4.40–4.49 (m, 1H, H_5), 6.66–6.71 (m, 2H, Arh), 6.71–6.95 (m, 2H, Arh), 7.13–7.26 (m, 2H, Arh); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 4.43 (−ve, CH_2), 59.96 (+ve, CH), 77.42 (+ve, CH), 82.17 (absent, C), 127.13 (+ve, CH), 127.71 (+ve, CH), 127.77 (+ve, CH), 128.21 (+ve, CH), 128.37 (+ve, CH), 129.47 (+ve, CH), 131.94 (ab, C), 136.17 (ab, C),176.62 (ab, C); IR ν_{max} (KBr): 1760 (C=O), 3377 (OH) cm^{-1}. (Found: C, 51.5; H, 3.6%. $C_{17}H_{15}IO_3$ requires C, 51.78; H, 3.81%).

4.4.7. (3*S,4*R**,5*S*)-3-Hydroxy-3-phenyl-4-phenyl-5-iodomethyl-furan-2(5*H*)-one (19b).** *Procedure C*. White solid 235 mg, 20%; mp 257 °C (benzene); FAB mass M^+ *m/z* 394 (M^+); ^{1}H NMR ($CDCl_3$): δ 2.91 (t, $J=9.6$ Hz, 1H of CH_2I), 3.51 (br s, 1H, OH, exchanges with D_2O), 3.38 (dd, $J_1=9.6$ Hz, $J_2=6.3$ Hz, 1H, 1H of CH_2i), 3.90 (d, $J=5.4$ Hz, H_4), 5.41–5.47 (m, 1H, H_5), 6.90–7.92 (m, 2H, Arh), 7.02–7.11 (m, 2H, Arh), 7.34–7.36 (m, 6H, Arh); Decoupling: the decoupling of H_5 multiplet at δ 5.41–5.47, converts triplet at δ 2.91, dd at δ 3.55 into doublet and doublet at δ 3.61 into singlet; ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 0.79 (−ve, CH_2), 57.24 (+ve, CH), 58.92 (+ve, CH), 80.82 (+ve, CH), 81.83 (ab, C), 127.12 (+ve, CH), 127.77 (+ve, CH), 128.21 (+ve, CH), 128.37 (+ve, CH), 129.47 (+ve, CH), 132.32 (ab, C), 132.65 (ab, C), 176.58 (ab, C); IR ν_{max} (KBr): 1775 (C=O), 3438 (OH) cm^{-1}. (Found: C, 52.1; H, 3.6. $C_{17}H_{15}IO_3$ requires C, 51.78; H, 3.81%).

4.4.8. (3*R,4*R**,5*R**)-3-Hydroxy-3-methyl-4-phenyl-5-iodomethyl-furan-2(5*H*)-one (20a).** *Procedure C*. White

solid 558 mg, 56%; mp 134 °C (benzene); FAB mass M^+ *m/z* 332 (M^+); ^{1}H NMR ($CDCl_3$): δ 1.59 (s, 3H, CH_3), 2.82 (s, 1H, OH, exchanges with D_2O), 3.34 (dd, $J_1=11.4$ Hz, $J_2=6.0$ Hz, 1H, 1H of CH_2I), 3.53–3.66 (m, 2H, 1H of CH_2i and H_4), 4.57–4.64 (m, 1H, H_5), 7.22–7.26 (m, 2H, Arh), 7.33–7.44 (m, 3H, Arh); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 4.80 (−ve, CH_2I), 21.06 (+ve, CH_3), 57.62 (+ve, CH-4), 78.08 (+ve, CH-5), 81.12 (ab, C), 128.271 (+ve, CH), 128.38 (+ve, CH), 128.99 (+ve, CH), 129.05 (+ve, CH), 129.29 (+ve, CH),132.91 (ab, C), 177.47 (ab, C); IR ν_{max} (KBr): 1764 (C═O), 3365 (OH) cm^{-1}. (Found: C, 43.7; H, 4.2. $C_{12}H_{13}IO_3$ requires C, 43.37; H, 3.92%).

4.4.9. (3*R,4*R**,5*S**)-3-Hydroxy-3-methyl-4-phenyl-5-iodomethyl-furan-2(5*H*)-one (20b).** *Procedure C*. White solid 231 mg, 24%; mp 145 °C (benzene); FAB mass M^+ *m/z* 322 (M^+); ^{1}H NMR ($CDCl_3$): δ 1.20 (s, 3H, CH_3), 2.37 (br s, 1H, OH, exchanges with D_2O), 2.82 (t, $J=9.6$ Hz, 1H, 1H of CH_2I), 3.33 (dd, $J_1=9.6$ Hz, $J_2=6.0$ Hz, 1H, 1H of CH_2i), 3.61 (d, $J=4.8$ Hz, 1H, H_4), 5.29–5.36 (m, 1H, H_5), 7.07–7.12 (m, 2H, Arh), 7.31–7.76 (m, 3H, ArH); *Decoupling*: the decoupling of H_5 multiplet at δ 5.29–5.34, converts two dd's at δ 2.82, δ 3.55 into doublet and doublet at δ 3.61 into singlet; ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 0.77 (−ve, CH_2I), 19.48 (+ve, CH_3), 57.24 (+ve, CH-4), 80.10 (+ve, CH-5), 76.87 (absent, C-3), 127.23 (+ve, CH), 128.16 (+ve, CH), 128.56 (+ve, CH), 135.16 (absent, C), 176.58 (absent, C═O); IR ν_{max} (KBr): 1772 (C═O), 3404 (OH) cm^{-1}. (Found: C, 43.5; H, 4.1. $C_{12}H_{13}IO_3$ requires C, 43.37; H, 3.92%).

4.4.10. (3*S,4*S**,5*R**)-3-Hydroxy-3-phenyl-4-ethoxycarbonyl-5-iodomethyl-furan-2(5*H*)-one (21).** *Procedure C*. 807 mg, 69%; light yellow liquid; FAB mass M^+ *m/z* 390 (M^+); ^{1}H NMR ($CDCl_3$): δ 1.05 (t, $J=7.2$ Hz, 3H, CH_3), 1.67 (br s, 1H, OH, exchanges with D_2O), 3.45 (dd, $J_1=11.4$ Hz, $J_2=4.8$ Hz, 1H, 1H of CH_2I), 3.62 (d, $J=9$ Hz, 1H, CH), 3.66 (dd, $J_1=11.4$ Hz, $J_2=4.8$ Hz, 1H, 1H of CH_2i), 3.88–3.93 (m, 2H, OCH_2), 4.64–4.69 (m,1H, CH), 7.28–7.45 (m, 5*H*, Arh); *Decoupling*: the decoupling of 1H multiplet (δ 4.64–4.69) converts double doublet at δ 3.45 and δ 3.66 into doublet and doublet at δ 3.62 into singlet; ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 5.83 (−ve, CH_2I), 13.77 (+ve, CH_3), 59.04 (+ve, CH), 61.77 (−ve, CH_2), 75.62 (+ve, CH), 80.16 (ab, C), 125.12 (+ve, CH), 128.79 (+ve, CH), 129.48 (+ve, CH), 136.34 (ab, C), 167.16 (ab, C), 175.02 (ab, C). IR ν_{max} (neat): 1726 (C═O), 1787 (C═O), 3614 (OH) cm^{-1}. (Found: C, 43.2; H, 3.9. $C_{14}H_{15}IO_5$ requires C, 43.10; H, 3.87%).

4.5. X-ray crystal data collection for 19a and 19b

X-ray crystal data was measured by using θ–2θ scan mode. The structures were solved by using direct method SHELX-97.

4.5.1. Compound 19a. CCDC 261510, Mol. formulae $C_{17}H_{15}IO_3$; triclinic space group *P*-1, $a=8.039$ Å, $b=10.102$ Å, $c=10.590$ Å, $\alpha=88.40(13)°$, $\beta=80.13(13)°$, $\gamma=70.17(15)°$, $V=796.6(2)$ Å^3, $z=2$, dc = 1.643 mg/m^3, Mo Kα = 0.70930 Å, θ range for data collection 1.95–24.97°. The structure solution is based on 3021 reflections, which converged to $R=0.037$. Refinement method: full-matrix least squares on *F*2, goodness of fit = 1.105.

4.5.2. Compound 19b. CCDC 261098, Mol. formulae $C_{17}H_{15}IO_3$; triclinic space group *P*-1, $a=8.3040(14)$ Å, $b=9.6450(15)$ Å, $c=10.6990(17)$ Å, $\alpha=76.422(13)°$, $\beta=89.511(13)°$, $\gamma=70.592(15)°$, $v=783.4(2)$ Å^3 , $z=2$, dc = 1.671 mg/m^3, Mo Kα = 0.70930 Å, θ range for data collection 1.96–24.93°. The structure solution is based on 2636 reflections, which converged to $R=0.023$. Refinement method: full-matrix least squares on *F*2, goodness of fit = 1.069.

Acknowledgements

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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.2005.06.045

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Synthesis of 4-substituted 3-(indol-3-yl)maleimides and azepines with annelated indole and maleimide nuclei

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Abstract—A series of 4-substituted 3-(indole-3-yl)maleimides has been synthesized. Upon the action of CH_3SO_3H in TFA, the 3-(indole-3-yl)-4-(arylalkylamino)-maleimides undergo cyclization to give 12b,13-dihydro-4b*H*-indolo[3,2-*d*]pyrrolo[3,4-*b*][1]benzazepine-5,7(6*H*, 8*H*)-dione derivatives.

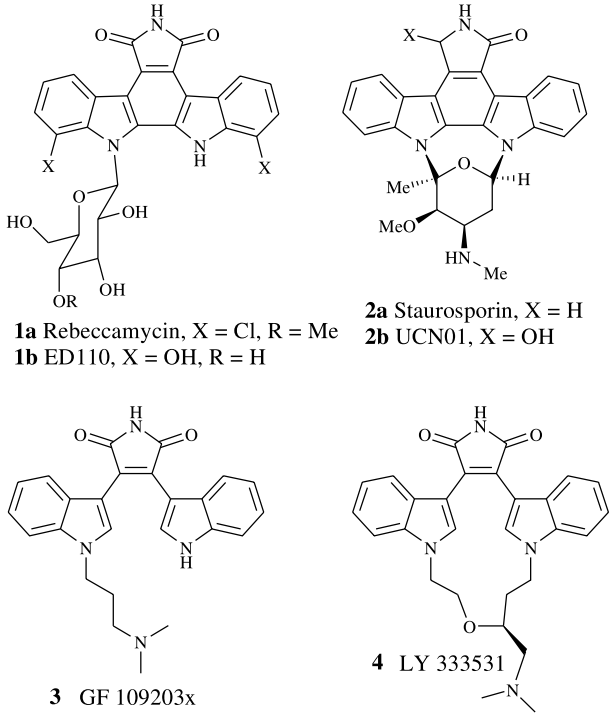
1. Introduction

Bisindolylmaleimide derivatives, their analogues, and related polycondensed compounds are known to have valuable biological properties. Some of them are inhibitors of topoisomerase I (e.g., rebeccamycin **1a** and ED110 **1b**) and the enzymes of proteinkinase C family (staurosporin **2a**, UCN01 **2b**, and some bis(indol-3-yl)maleimides, for example, **3** and **4**) as well as other types of protein kinases[1] (Scheme 1).

Under the action of protic acids, bis(indol-3-yl)maleimides **5** undergo 2,2′-cyclization accompanied by the opening of one of the indole rings to form aminophenylcarbazoles **7**.[2] However, in the presence of an oxidant (e.g., DDQ) they are transformed into indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazol-5,7-diones **8**.[3] Previously, we showed that bis(indol-1-yl)maleimides **9** and 3-dialkyl-(3-arylalkyl-)amino-4-(indol-1-yl)maleimides **11** under the action of protic acids form diazepine[1,4] derivatives **10** and **12** (Scheme 2).[4]

The transformation of **11** into **12** proceeds with a hydride shift followed by an intramolecular electrophilic substitution reaction (Scheme 3).[5]

In this work, the synthesis of 4-substituted 3-(indole-3-yl) maleimides and new polycondensed heterocyclic systems derived from them are described.



Scheme 1.

2. Results and discussion

1-Methyl-3-bromo-4-(indol-3-yl)maleimide and its *N*-Boc-derivative were obtained as previously described.[6] However, the bromine atoms in these bromomaleimides were inert to nucleophilic substitution by primary or secondary amines in contrast to the easy substitution of bromine atoms

Keywords: Indoles; Bisindolylmaleimides; Cyclization.
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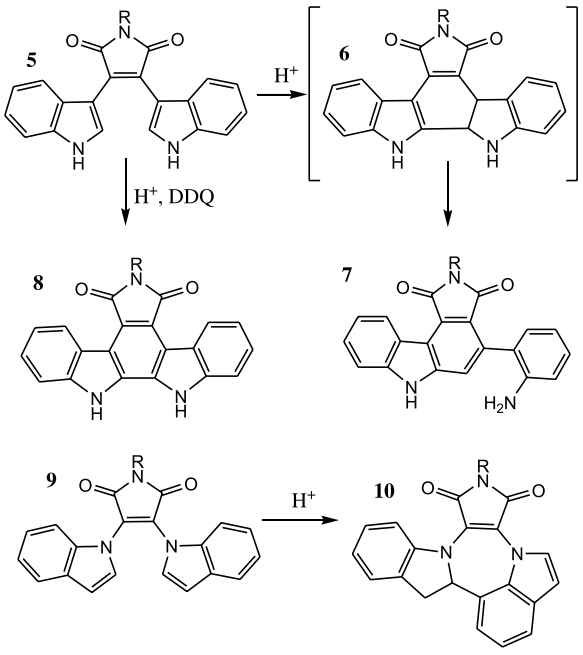
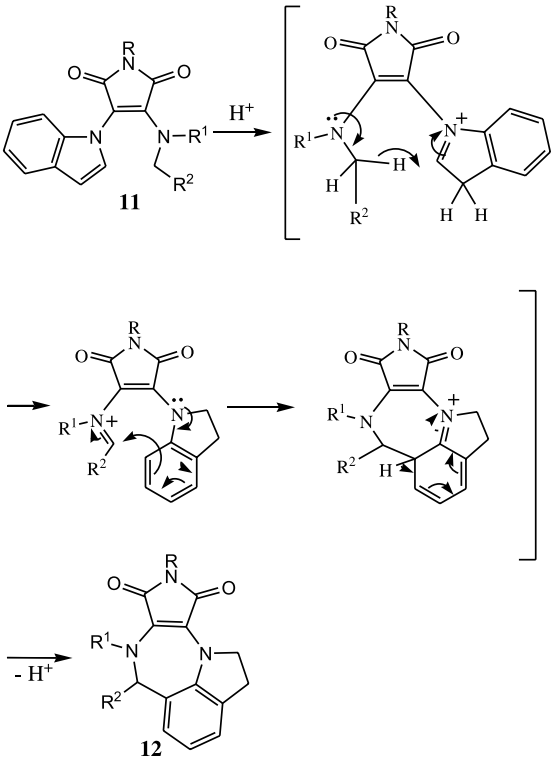


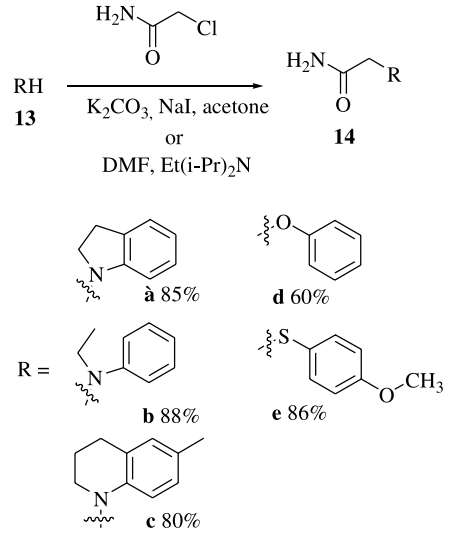
Scheme 2.

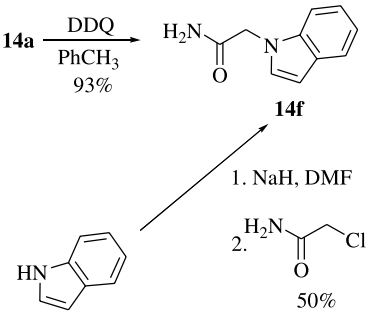


Scheme 3.

by primary or secondary amines in 3-bromo-4-(indol-1-yl)maleimides.[4] Another known method for the synthesis of bis(aryl)maleimides is based on condensation of methyl arylglyoxylates with acetamides using KO^{t}Bu.[7]

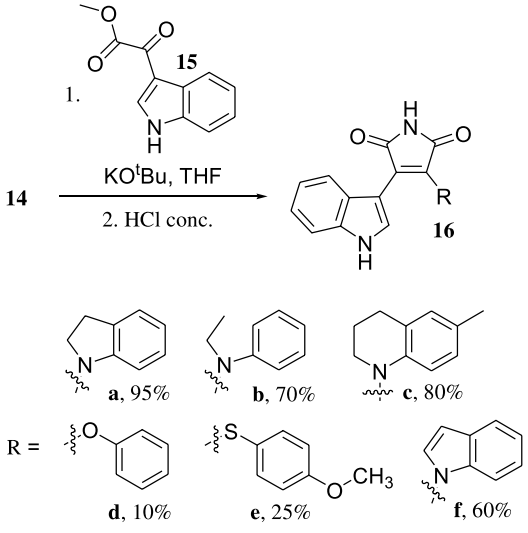
2-Substituted acetamides **14** were obtained in a good yield from the corresponding amines **13a–c**, phenol **13d** and 4-methoxythiophenole **13e** and 2-chloroacetamide in acetone in the presence of anhydrous K_2CO_3 or in DMF in the presence of Hünig's base (Scheme 4). Indol-1-ylacetamide **14f** was prepared by dehydrogenation of **14a** with DDQ in boiling toluene. It was also prepared in lower yield by alkylation of indolyl sodium with 2-chloroacetamide.



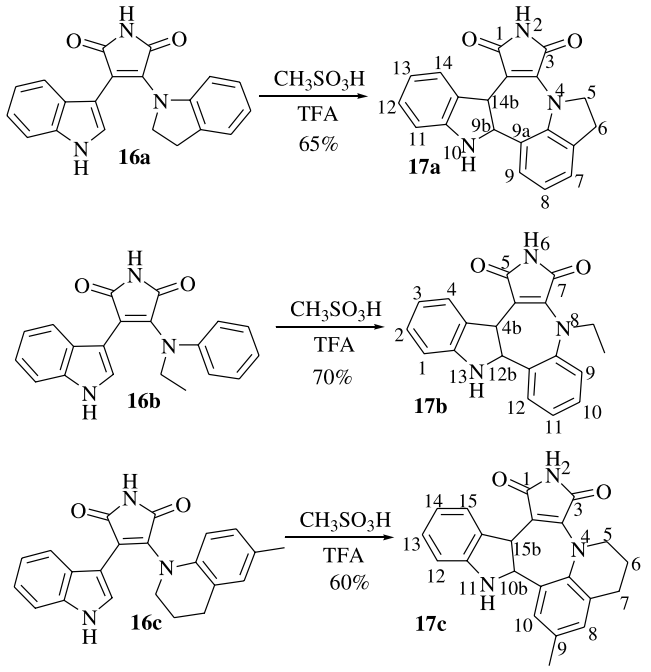


Scheme 4.

Compounds **14a–f** were condensed with methyl indole-3-glyoxylate **15** to give the corresponding 4-substituted 3-(indol-3-yl)maleimides **16** (Scheme 5).



Scheme 5.



Scheme 6.

Maleimides **16a–c** were treated with TFA in CH_2Cl_2. Although the color of the reaction mixture changed from red to dark violet, starting materials were recovered after stirring for 2 h followed by neutralization of the acid by aq $NaHCO_3$. These compounds were also stable in neat TFA. However, after treatment with the mixture of TFA/CH_3SO_3H (5:1) for ~2 h the cyclization products **17a–c** were isolated and purified by crystallization or column chromatography. The analysis of the NMR spectra of **17a–c** indicated that intramolecular electrophilic substitution occurred to form azepine derivatives with indoline and maleimide nuclei annelated (Scheme 6). In the ^1H NMR spectra of cyclization products **17a–c** two 1H signals coupled with each other were present corresponding to the hydrogens at the positions 2 and 3 of 2,3-disubstituted indoline subfragment. One of them was coupled with 1H doublet, in the area δ 5–6 ppm, corresponding to the indoline NH hydrogen. The signals corresponding to four hydrogens at the positions 4–7 of 2,3-disubstituted indoline subfragment (two doublets and two triplets) and one hydrogen singlet of NH imide hydrogen were present in the low field area of the spectrum. It differs from the earlier described[4] cyclization of 3-dialkyl-(3-arylalkyl-)amino-4-(indol-1-yl)maleimides **11** (Scheme 3), proceeding with hydride shift and transfer of electrophilic center from indole nucleus to alkylamino moiety. In the case of 3-aryl-alkylamino-4-(indol-3-yl)maleimides **16a–c**, the hydride shift was not observed.

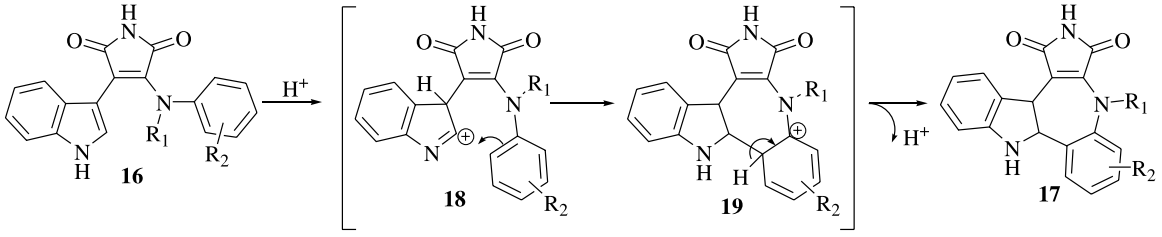
The mechanism of this transformation apparently consists of the following steps: (1) protonation of the indole nucleus to form the iminium electrophilic center at position-2 (**18**) and (2) attack of the electrophile on the position adjacent (*ortho*) to the alkylamino substituent in the benzene ring leading to the formation of azepine ring (**19**) (Scheme 7).

We failed to obtain a product of the cyclization of 3-(indol-3-yl)-4-phenoxymaleimide **16d** upon the action of CH_3SO_3H in TFA. 3-(Indol-3-yl)-4-(4-methoxythiophenyl)maleimide **16e** under the same conditions gave a complex mixture.

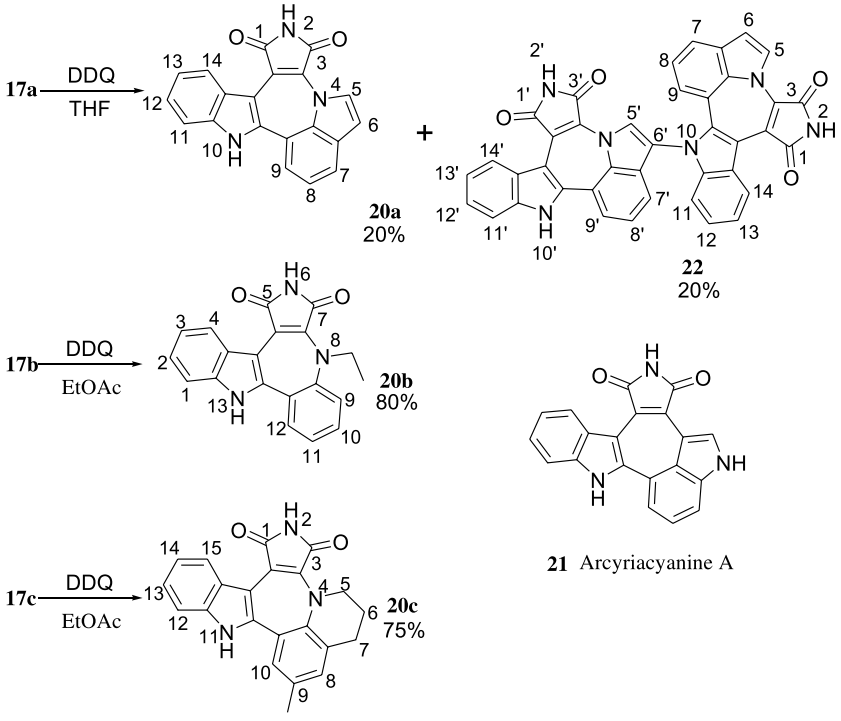
Dehydrogenation of **17a** with an excess of DDQ in THF led to the corresponding aromatic derivative **20a** in 20% yield, isomeric to the natural antibiotic arcyriacyanine A **21**.[2] From the reaction mixture, the dimer **22** of **20a** was also isolated in 20% yield (Scheme 8). When 2 equiv of DDQ were used, a mixture of starting **17a**, and the reaction products **20a** and **22** was formed. In the ^1H NMR spectrum of **22** two broad singlets corresponding to two imide hydrogens (N2–H and N2′–H) at δ 11.2 and δ 11.14 and only one singlet corresponding to the indole NH hydrogen (N10′–H) at δ 11.7 were present. Also present were one singlet signal for C5′–H δ 8.06 and two doublet signals coupled with each other corresponding to C5–H and C6–H. The signals corresponding to the hydrogens of the benzene moieties of four indole subfragments (four doublets and four triplets of C11–H, C12–H, C13–H, C14–H, and C11′–H, C12′–H, C13′–H, C14′–H, as well as four doublets and two triplets of C7–H, C8–H, C9–H, and C7′–H, C8′–H, C9′–H) were seen. The structure of the dimer **22** was supported by HRMS and EI MS data. The dehydrogenation of **17a** by Pd/C in boiling toluene proceeded slowly, however, the dimer **22** was not formed. It suggests that the dimerization was induced by the presence of dichlorodicyanohydroquinone formed from DDQ in the process of the reaction. The dehydrogenation of indoline derivatives **17b**,**c** with 1 equiv of DDQ in EtOAc gave the corresponding indoloazepines **20b**,**c** in good yield (Scheme 8).

Bisindolylmaleimide **16f** was obtained by the dehydrogenation of **16a** with DDQ in 80% yield or by condensation of methyl (indol-3-yl)glyoxylate **15** with acetamide **14f** in 60% yield.

Upon the action of the excess of CH_3SO_3H in TFA, bisindolylmaleimide **16f** afforded 8b,9-dihydroindolo[4′,3′:3,4,5]pyrrolo[3′,4′:6,7]azepino[1,2-*a*]indol-



Scheme 7.



Scheme 8.

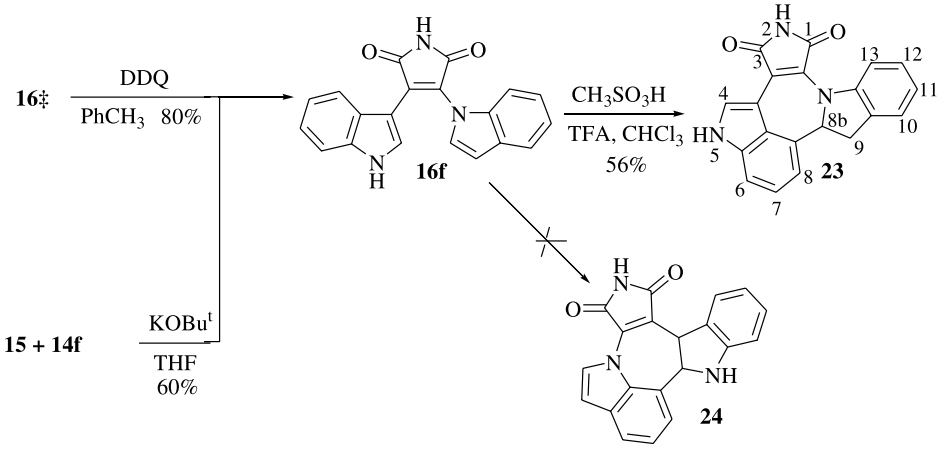
1,3(2*H*,5*H*)dione **23** in 56% yield. In the ^{1}H NMR-spectrum of **23**, the signals corresponding to the hydrogen atoms of 3,4-disubstituted indole and 1,2-disubstituted indoline fragments are present. It is interesting to note the difference in reactivity between 1- and 3-subsituted indole fragments of the bisindolylmaleimide **16f**, as the formation of the azepine derivative **24** isomeric to **23** was not observed (Scheme 9).

3. Conclusion

3-(Indol-3-yl)maleimides containing an *N*-alkylaryl substituent (including *N*-tetrahydroquinolinyl or *N*-indolinyl moiety) in position 4 of the maleimide ring produced azepines annelated with maleimide, indoline, and arylamine (including indoline or tetrahydroquinoline) nuclei under acid treatment. Subsequent dehydrogenation led to the corresponding azepines annelated with maleimide and indole nuclei.

4. Experimental

Mps were determined on a Buchi SMP-20 apparatus. NMR spectra were recorded with Varian VXR-400 instrument at 400 MHz (^{1}H NMR) or at 75 MHz (^{13}C NMR) with internal reference. Chemical shifts are given in ppm and coupling constants in Hz. Assignment of signals was based on the decoupling experiments for ^{1}H NMR and APT-experiments for ^{13}C NMR spectra, signals corresponding to the quaternary carbon atoms are marked (q). Electron impact mass-spectra (EI-MS) were obtained on a SAQ 710 Finnigan instrument at 70 eV (direct introduction, ion source temperature 150 °C). HRMS mass spectra were registered on a MAT 8430 Finnigan instrument with data



Scheme 9.

operating system SS-300 (EI, 70 eV, direct introduction, ion source temperature 250 °C). Infrared spectra were recorded with Nicolet Avatar 330 FTIR spectrometer using KBr discs. UV–vis spectra were recorded using Hitachi U-2000 spectrophotometer using THF as a solvent. Analytical TLC was performed on Silica Gel F254 plates (Merck) and column chromatography on Silica Gel Merck 60. Extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Solvents and reagents were obtained from commercial suppliers unless otherwise specified.

4.1. Acetamides 14

(A) Compound **13** (70 mmol) and an excess of anhydrous K_2CO_3 were added to the solution of 2-chloroacetamide (3 g, 32.2 mmol) in acetone (200 mL). The reaction mixture was refluxed with intensive stirring for 3 h. After cooling to rt the reaction mixture was filtered and the filtrate evaporated. The residue was dissolved in EtOAc (200 mL), the solution was washed with 1 N HCl (2× 50 mL), 0.5 N Na_2CO_3 solution (2×50 mL), water (2× 50 mL), dried, and evaporated. The residue was recrystallized from an appropriate solvent.

(B) Compound **13** (70 mmol) and Et(^{i}Pr)$_2$N (4.5 g, 35 mmol) were added to the solution of 2-chloroacetamide (3 g, 32.2 mmol) in dry DMF (40 mL). The reaction mixture was left to stir overnight at 60 °C. After cooling to rt the reaction mixture was poured into 1 N HCl (100 mL) and extracted with EtOAc (2×100 mL). The organic layer was washed with 1 N HCl (100 mL), water (50 mL), dried, and evaporated. The residue was recrystallized from an appropriate solvent.

4.1.1. 2-(2,3-Dihydroindol-1-yl)acetamide (14a). Compound **14a** was obtained by method A as colorless crystals (from EtOAc) (4.8 g, 27.4 mmol, 85%); mp 146–147 °C (EtOAc); [Found: C, 68.26; H, 7.97; N, 15.75. $C_{10}H_{12}N_2O$ requires C, 68.16; H, 7.86; N, 15.90%]; R_f 0.61 ($CHCl_3$–MeOH 10:1); ν_{max}: 1242, 1305, 1335, 1385, 1398, 1458, 1473, 1489, 1605, 1653, 2842, 2897, 3185, 3377 cm^{-1}; δ_H (d_6-DMSO) 2.92 (2H, t, J=8.3 Hz), 3.41 (2H, t, J=8.3 Hz), 3.61 (2H, s), 6.44 (1H, d, J=7.6 Hz), 6.60 (1H, t, J= 7.4 Hz), 6.98 (1H, t, J=7.4 Hz), 7.04 (1H, d, J=7.1 Hz), 7.16 (1H, s), 7.44 (1H, s); δ_C (d_6-DMSO) 28.1, 52.1, 53.6, 106.5, 117.3, 124.1, 127.0, 129.4 (q), 152.0 (q), 171.4 (C=O); *m/z* (EI-MS) M$^+$176 (35), 132 M$^+$ −CONH$_2$ (100%).

4.1.2. 2-(*N*-Ethylphenylamino)acetamide (14b). Compound **14b** was obtained by method B as colorless crystals (from ^{i}PrOH) (5.05 g, 28.3 mmol, 88%); mp 104–106 °C (^{i}PrOH); [Found: C, 67.26; H, 7.97; N, 15.78. $C_{10}H_{14}N_2O$ requires C, 67.39; H, 7.92; N, 15.72%]; R_f 0.62 ($CHCl_3$–MeOH 25:1); ν_{max}: 1239, 1257, 1340, 1405, 1502, 1654, 2976, 3182, 3417 cm^{-1}; δ_H (d_6-DMSO) 1.10 (3H, m, –CH$_2$C*H*$_3$), 3.42 (2H, m, –C*H*$_2$CH$_3$), 3.78 (2H, s, –C*H*$_2$C(O)NH$_2$), 6.59–6.64 (3H, m), 7.13 (1H, s, N*H*), 7.15–7.19 (2H, m), 7.32 (1H, s, N*H*); δ_C (d_6-DMSO) 11.8, 45.4, 53.5, 111.7, 115.8, 147.9 (q), 172.3 (C=O); *m/z* (EI-MS) M$^+$178 (55), 134 M$^+$ −CONH$_2$ (100%).

4.1.3. 2-(6-Methyl-3,4-dihydroquinolin-1-yl)acetamide (14c). Compound **14c** was obtained by method B as colorless crystals (from ^{i}PrOH) (5.3 g, 25.8 mmol, 80%); mp 175–177 °C (^{i}PrOH); [Found: C, 70.43; H, 8.03; N, 13.79. $C_{12}H_{16}N_2O$ requires C, 70.56; H, 7.90; N, 13.71%]; R_f 0.6 ($CHCl_3$–MeOH 25:1); ν_{max}: 1209, 1243, 1331, 1387, 1403, 1512, 1619, 1655, 2837, 2886, 2924, 3169, 3345 cm^{-1}; δ_H (d_6-DMSO) 1.9 (2H, m, –NCH$_2$C*H*$_2$CH$_2$), 2.14 (3H, s, PhC*H*$_3$), 2.67 (2H, t, J=6.4 Hz, –NCH$_2$CH$_2$C*H*$_2$), 3.30 (2H, t, J=6.2 Hz, –NC*H*$_2$CH$_2$CH$_2$), 3.69 (2H, s, –C*H*$_2$-C(O)NH$_2$), 6.26 (1H, d, J=8.1 Hz, C8–*H*), 6.72 (1H, d, J=1.9 Hz, C5–*H*), 6.76 (1H, dd, J=8.2, 1.9 Hz, C7–*H*), 7.18 (1H,s, N*H*), 7.26 (1H, s, N*H*); δ_C (d_6-DMSO) 20.0, 21.9, 27.4, 50.3, 55.0, 110.6, 122.1 (q), 124.3 (q), 127.1, 129.4, 143.1 (q), 172.3 (C=O); *m/z* (EI-MS) M$^+$204 (100), 160 M$^+$ −CONH$_2$ (33%).

4.1.4. 2-Phenoxyacetamide (14d). Compound **14d** was obtained by method A as colorless crystals (from ^{i}PrOH) (3 g, 19.4 mmol, 60%); mp 96–98 °C (^{i}PrOH); [Found: C, 63.65; H, 6.10; N, 9.39. $C_8H_9NO_2$ requires C, 63.56; H, 6.00; N, 9.27%]; R_f 0.56 ($CHCl_3$–MeOH 10:1); ν_{max}: 1243, 1292, 1354, 1415, 1458, 1497, 1586, 1679, 2923, 3062, 3141, 3457 cm^{-1}; δ_H ($CDCl_3$) 4.52 (2H, s), 6.65 (2H, br s), 6.96 (2H, d, J=7.8 Hz), 7.06 (1H, t, J=7.3 Hz), 7.35 (2H, m); δ_C ($CDCl_3$) 67.0, 114.5, 122.0, 129.7, 157.0 (q), 171.3 (C=O); *m/z* (EI-MS) M$^+$151 (100), 107 M$^+$ −CONH$_2$ (75%).

4.1.5. 2-(4-Methoxythiophenyl)acetamide (14e). Compound **14e** was obtained by method A as yellowish crystals (from ^{i}PrOH) (5.4 g, 27.6 mmol, 86%); mp 100–102 °C (^{i}PrOH); [Found: C, 54.85; H, 5.72; N, 7.18. $C_9H_{11}NO_2S$ requires C, 54.80; H, 5.62; N, 7.10%]; R_f 0.4 ($CHCl_3$–MeOH 10:1); ν_{max}: 1237, 1288, 1383, 1420, 1456, 1496, 1573, 1626, 2919, 2961, 3199, 3383 cm^{-1}; δ_H (d_6-DMSO) 3.49 (2H, s), 3.74 (3H, s), 6.92 (2H, d), 7.11 (1H, br s), 7.36 (2H, d), 7.48 (1H, br s); δ_C (d_6-DMSO) 38.3, 55.2, 114.7 (2C), 126.0 (q), 131.7 (2C), 158.4 (q), 170.1 (C=O); *m/z* (EI-MS) M$^+$197 (100), 153 M$^+$ −CONH$_2$ (55), 139 M$^+$ − CH$_2$CONH$_2$ (20%).

4.1.6. Indol-1-ylacetamide (14f). (A) The solution of **14a** (500 mg, 2.8 mmol) in the mixture of toluene and THF (2:1, 150 mL) was treated with DDQ (770 mg, 3.4 mmol), and the reaction mixture was refluxed for 2 h. The cooled to rt reaction mixture was diluted with EtOAc (50 mL), washed with aq $NaHSO_3$ (2×30 mL), aq Na_2CO_3 (2×30 mL), water (50 mL), brine (30 mL), dried and evaporated. The residue was purified by flash chromatography ($CHCl_3$). The product was obtained as a grey colored solid (453 mg, 2.6 mmol, 93%); mp 158–160 °C ($CHCl_3$); [Found: C, 69.06; H, 5.84; N, 16.19. $C_{10}H_{10}N_2O$ requires C, 68.95; H, 5.79; N, 16.08%]; R_f 0.51 ($CHCl_3$–MeOH 10:1); ν_{max}: 1311, 1325, 1405, 1466, 1484, 1515, 1626, 1668, 3183, 3382 cm^{-1}; δ_H (d_6-acetone) 4.87 (2H, s), 6.50 (1H, d, J=3.1 Hz, C3–*H*), 6.63 (2H, br s), 7.06 (1H, t, J=7.5 Hz), 7.17 (1H, t, J= 7.6 Hz), 7.31 (1H, d, J=3.1 Hz), 7.39 (1H, d, J=8.2 Hz), 7.59 (1H, d, J=7.9 Hz); δ_C (d_6-acetone) 49.6, 102.3, 110.3, 120.2, 121.4, 122.2, 129.7 (q), 130.0, 137.5 (q), 170.4 (C=O); *m/z* (EI-MS) M$^+$174 (90), M$^+$ −CONH$_2$ 130 (100%).

(B) A solution of indole (580 mg, 5 mmol) in DMF (3 mL) was added to the stirred suspension of NaH (60% in mineral oil, 200 mg, 5 mmol) in DMF (4 mL), the mixture was left

to stir at rt for 30 min. The reaction mixture was then treated with the solution of 2-chloroacetamide (470 mg, 5 mmol) in DMF (5 mL) and left to stir overnight. The reaction mixture was poured into ice and extracted with EtOAc (2×50 mL). The organic layer was washed with water (3×30 mL), dried and evaporated. The residue was purified by flash chromatography ($CHCl_3$) to give **14f** (435 mg, 50%). The obtained product was identical to **14f**, obtained by method A according to TLC and NMR data.

4.2. 4-Substituted 3-(indol-3-yl)maleimides 16

The stirred solution or suspension of acetamide **14** (200–500 mg) and equimolar amount of methyl (indol-3-yl)glyoxylate **15** in THF (20 mL) was treated with KO^{t}Bu (1.5 equiv). The reaction mixture was left to stir for 2.5–3 h at 50 °C, cooled to 0 °C, and concd HCl (3 equiv) was added. The mixture was stirred for 15 min, diluted with water (50 mL), and extracted with EtOAc (2×50 mL). The organic layer was separated, washed with water up to neutral pH, dried, and evaporated. The residue was worked up as indicated below.

4.2.1. 3-(2,3-Dihydroindol-1-yl)-4-(indol-3-yl)maleimide (16a). Compound **16a** was obtained from **14a** (240 mg, 1.4 mmol) and **15** (280 mg, 1.4 mmol) as a red colored oil, that crystallized upon storage to give dark violet crystals (440 mg, 1.3 mmol. 95%); mp 198–200 °C (EtOH); [Found: C, 73.04; H, 4.51; N, 12.80. $C_{20}H_{15}N_3O_2$ requires C, 72.94; H, 4.59; N, 12.76%]; R_f 0.61 ($CHCl_3$–MeOH 10:1); ν_{max}: 1214, 1239, 1320, 1340, 1429, 1461, 1486, 1517, 1599, 1634, 1680, 1754, 3051, 3356 cm^{-1}; δ_H (d_6-DMSO) 3.10 (2H, t, J=8.2 Hz, indoline C3–*H*), 4.16 (2H, t, J=8.2 Hz, indoline C2–*H*), 6.21 (1H, dd, J=8.2 Hz, indoline C4–*H*), 6.59–6.63 (2H, two triplets, indoline C5–*H* and C6–*H*), 6.84 (1H, t, J=7.4 Hz, indole C6–*H* or C5–*H*), 7.00 (1H, t, J=8.1 Hz, indole C6–*H* or C5–*H*), 7.07 (1H, dd, J=8.3 Hz, indoline C7–*H*), 7.31 (1H, d, J=8.0 Hz, indole C4–*H* or C7–*H*), 7.33 (1H, d, J=8.2 Hz, indole C4–*H* or C7–*H*), 7.42 (1H, d, J=2.6 Hz, indole C2–*H*), 10.72 (1H, s, imide N*H*), 11.49 (1H, br d, J=2.5 Hz, indole N*H*); δ_C (d_6-DMSO) 28.7 (indoline C3), 52.2 (indoline C2), 104.7 (q), 111.59, 111.61 (q), 112.0, 119.4, 120.1, 120.6, 121.4, 124.1, 125.8, 126.8 (q), 127.6, 131.1 (q), 134.3 (q), 135.5 (q), 143.7 (q), 169.6 (C═O), 171.8 (C═O); EI HRMS calcd M^+ for $C_{20}H_{15}N_3O_2$ 329.1164, found 329.1177 (100), $M^+-(CO)_2NH$ 285 (13%).

4.2.2. 3-(Indol-3-yl)-4-(*N*-ethylanilino)maleimide (16b). Compound **16b** was obtained from **14b** (200 mg, 1.12 mmol) and **15** (230 mg, 1.12 mmol) as dark red crystals (300 mg, 0.78 mmol, 70%); mp 248–250 °C (EtOH); [Found: C, 72.80; H, 5.39; N, 12.72. $C_{20}H_{17}N_3O_2$ requires C, 72.49; H, 5.17; N, 12.68%]; R_f 0.29 ($CHCl_3$–MeOH 25:1); ν_{max}: 1223, 1239, 1262, 1311, 1340, 1398, 1435, 1499, 1509, 1594, 1615, 1625, 1694, 1756, 3040, 3223, 3377 cm^{-1}; δ_H (d_6-DMSO) 1.05 (3H, m, ethyl C*H*$_3$), 3.55 (2H, m, ethyl C*H*$_2$), 6.87 (1H, t, J=7.2 Hz, Ph), 6.91 (1H, t, J=7.9 Hz, Ph), 6.99 (2H, d, J=7.9 Hz, Ph, C2–*H* and C6–*H*), 7.09 (1H, t, J=7.6 Hz, indole), 7.17–7.20 (2H, t and t, indole and Ph C4–*H*), 7.28 (1H, d, J=8.0 Hz, indole), 7.42 (1H, d, J=8.0 Hz, indole), 7.96 (1H, d, J=2.8 Hz, indole C2–*H*), 10.74 (1H, s, imide N*H*), 11.70 (1H, d, J=2.8 Hz, indole N*H*); δ_C (d_6-DMSO) 13.5 (ethyl *C*H$_3$), 44.7 (ethyl *C*H$_2$), 104.1 (q), 112.0, 118.1 (2C, Ph), 119.2 (q), 120.0, 120.4, 120.8, 121.7, 126.3 (q), 128.4, 128.7 (2C, Ph), 135.7 (q), 136.0 (q), 145.1 (q), 169.7 (C═O), 171.6 (C═O); *m*/*z* (EI-MS) M^+ 331 (100) M^+- NH 316 (20%).

4.2.3. 3-(1*H*-Indol-3-yl)-4-(3,4-dihydro-6-methylquinolin-1-yl)maleimide (16c). Compound **16c** was obtained from **14c** (220 mg, 1.08 mmol) and **15** (220 mg, 1.08 mmol) as dark red crystals (308 mg, 0.86 mmol, 80%); mp 260–262 °C (EtOH); [Found: C, 73.81; H, 5.49; N, 11.87. $C_{22}H_{19}N_3O_2$ requires C, 73.93; H, 5.36; N, 11.76]; R_f 0.36 ($CHCl_3$–MeOH 20:1); ν_{max}: 1243, 1299, 1329, 1398, 1433, 1502, 1522, 1613, 1630, 1674, 1760, 2920, 3186, 3342 cm^{-1}; δ_H (d_6-DMSO) 1.73 (2H, m, $CH_2CH_2CH_2$), 2.18 (3H, s, PhC*H*$_3$), 2.67 (2H, t, J=6.2 Hz, PhC*H*$_2$CH$_2$–), 3.25 (2H, t, J=5.9 Hz, NC*H*$_2$CH$_2$), 6.70 (1H, d, J=8.2 Hz, Ph C6–*H*), 6.77 (1H, dd, J=8.2, 1.5 Hz, Ph C5–*H*), 6.82 (1H, d, J=1.5 Hz, Ph C3–*H*), 6.91 (1H, t, J=7.6 Hz, indole), 7.10 (1H, t, J=7.6 Hz, indole), 7.32 (1H, d, J=8.2 Hz, indole), 7.45 (1H, d, J=8.2 Hz, indole), 7.70 (1H, d, J=2.8 Hz, indole C2–*H*), 10.64 (1H, s, imide N*H*), 11.7 (1H, br s, indole N1–*H*); δ_C (d_6-DMSO) 20.2, 21.9, 26.4, 48.6, 104.2 (q), 112.0, 118.5 (q), 119.6 (q), 119.9, 120.4, 121.8, 124.8 (q), 126.1 (q), 126.8, 128.3, 128.9 (q), 129.4, 136.1 (q), 136.4 (q), 138.3 (q), 169.2 (C═O), 171.6 (C═O); *m*/*z* (EI-MS) M^+ 357 (100) M^+- C(O)NHC(O) 286 (15%).

4.2.4. 3-(Indol-3-yl)-4-phenyloxymaleimide (16d). The residue after solvent evaporation was chromatographed ($CHCl_3$–MeOH 20:1), the fractions containing **16d** were pooled and evaporated, the residue was purified by the preparative TLC ($CHCl_3$–MeOH 20:1), to give **16d** as a yellow solid (52 mg, 0.17 mmol, 10% from **14d**, 250 mg, 1.7 mmol); R_f 0.5 ($CHCl_3$–MeOH 10:1), EI HRMS, found M^+ 304.0837 (100%). $C_{18}H_{12}N_2O_3$ requires 304.0848; ν_{max}: 1221, 1251, 1318, 1353, 1379, 1444, 1488, 1590, 1642, 1671, 1716, 2925, 3170, 3359 cm^{-1}; δ_H (d_6-DMSO) 6.99 (2H, d, J=8.5 Hz), 7.1 (1H, t J=7.6 Hz), 7.15 (1H, t, J=7.6 Hz), 7.19 (1H, m), 7.28–7.32 (2H, m), 7.46 (1H, d, J=8.0 Hz), 7.9 (1H, d, J=8.2 Hz), 8.13 (1H, d, J=2.9 Hz), 11.0 (1H, s), 11.92 (1H, br d).

4.2.5. 3-(Indol-3-yl)-4-[(4-methoxyphenyl)thio]maleimide (16e). Compound **16e** was obtained from **14e** (300 mg, 1.5 mmol) and **15** (305 mg, 1.5 mmol). The residue after solvent evaporation was chromatographed ($CHCl_3$) and left to crystallize. **22e** crystallized from $CHCl_3$ as orange crystals as a solvate with $CHCl_3$ (178 mg, 0.38 mmol, 25%); mp 185–186 °C ($CHCl_3$); [Found: C, 51.43; H, 3.21; N, 6.06. $C_{20}H_{15}Cl_3N_2O_3S$ requires C, 51.13; H, 3.22; N, 5.96%]; R_f 0.46 ($CHCl_3$–MeOH 10:1); ν_{max}: 1231, 1292, 1303, 1338, 1425, 1489, 1579, 1701, 1762, 3251, 3374, 3539, 3635 cm^{-1}; δ_H (d_6-DMSO) 3.7 (3H, s), 6.81 (2H, d, J=8.8 Hz), 7.11 (1H, dt, ^4J=1.1, 7.9 Hz), 7.18 (1H, dt, ^4J=1.1, 8.2 Hz), 7.21 (C*H*Cl$_3$), 7.26 (2H, d, J=8.8 Hz), 7.46 (1H, d, J=8.1 Hz), 7.85 (1H, d, J=2.9 Hz, indole C2–*H*), 7.88 (1H, d, J=8.0 Hz), 11.09 (1H, s), 11.97 (1H, br d, J=2.9 Hz); δ_C (d_6-DMSO) 55.2 (O*C*H$_3$), 79.2 (*C*HCl$_3$), 104.8 (q), 112.0, 114.6 (2C), 120.1, 122.1, 122.3, 122.8 (q), 125.0 (q), 126.0 (q), 131.1, 131.6 (2C), 136.4 (q), 137.9 (q), 158.7 (q), 169.2 (*C*═O), 170.4 (*C*═O); *m*/*z* (EI-MS) M^+ 350 (100), M^+-C(O)NHC(O) 279 (10%).

4.2.6. 3-(Indol-1-yl)-4-(indol-3-yl)maleimide (16f). (A) To the solution of **16a** (100 mg, 0.3 mmol) in toluene (50 mL) was added the solution of DDQ (76 mg, 0.33 mmol) in toluene (3 mL). The reaction mixture was refluxed for 3 h. After cooling to rt it was diluted with EtOAc (50 mL), washed with saturated aq $NaHSO_3$ (30 mL), aq $NaHCO_3$ (2×30 mL), water (30 mL), brine (30 mL), dried and evaporated. The product was isolated by flash chromatography ($CHCl_3$) as a red solid (78 mg, 0.24 mmol, 80%); mp 160–161 °C (EtOH–$CHCl_3$); [Found: C, 73.45; H, 4.10; N, 12.96. $C_{20}H_{13}N_3O_2$ requires C, 73.38; H, 4.00; N, 12.84%]; EI HRMS, found M^+ 327.1016 (100), $M^+ - (CO)_2NH$ 256 (30%). $C_{20}H_{13}N_3O_2$ requires 327.1008; R_f 0.5 ($CHCl_3$–MeOH 10:1); ν_{max}: 1207, 1238, 1329, 1420, 1457, 1513, 1616, 1712, 1761, 2925, 3342 cm^{-1}; δ_H (d_6-DMSO) 6.05 (1H, d, J=8.2 Hz), 6.49 (1H, t, J=7.6 Hz), 6.76 (1H, d, J=3.3 Hz), 6.86 (1H, t, J=8.2 Hz), 6.93 (1H, t, J=8.1 Hz), 6.95–7.00 (2H, t and d), 7.34 (1H, d, J=8.2 Hz), 7.56 (1H, d, J=3.3 Hz), 7.57 (1H, d, J=7.7 Hz), 8.06 (1H, d, J=3.0 Hz), 11.23 (1H, s), 11.97 (1H, br s); δ_C (d_6-DMSO) 103.8 (q), 105.1, 111.8, 112.0, 119.7, 120.3, 120.6, 120.7, 122.1, 122.2, 125.3 (q), 126.0 (q), 126.4 (q), 128.1 (q), 128.4, 131.1, 136.6 (q), 136.1 (q), 169.3 (C=O), 171.0 (C=O).

(B) Bisindolylmaleimide **16f** was also obtained by condensation of (indol-1-yl)acetamide **14f** and **15** by the action of $KOBu^t$ in 60% yield after column chromatography ($CHCl_3$). It was identical to **16f** obtained by method A according to TLC and NMR data.

4.3. Transformation of 4-substituted 3-(indol-3-yl)maleimides 16 upon the action of CH_3SO_3H

To the solution of **16** (200–300 mg) in TFA (5 mL) was added CH_3SO_3H (1 mL) and the reaction mixture was stirred for 3 h at rt and then was poured into aq $NaHCO_3$/EtOAc (1:1, 100 mL), $NaHCO_3$ was added up to neutral pH. The organic layer was separated, washed with water (50 mL), dried, and worked up as indicated below.

4.3.1. 5,6,10,14b-Tetrahydro[1′,7′:1,2,3]pyrrolo[3′,4′:6,7]azepino[4,5-*b*]indol-1,3(2*H*,9b*H*)-dione (17a). The solution was concentrated and left to crystallize at 0 °C. The precipitate was filtered, washed with EtOAc (2×5 mL) and dried to give **23a** as a dark yellow solid (130 mg, 0.4 mmol, 65%, from **22a** 200 mg, 0.61 mmol); mp 254–255 °C (EtOAc, decomp.); EI HRMS, found 329.1173 (100), $M^+ - CO$ 301 (13), $M^+ - (CO)_2NH$ 258 (40%). $C_{20}H_{15}N_3O_2$ requires M^+ 329.1164; R_f 0.7 ($CHCl_3$–MeOH 10:1); ν_{max}: 1245, 1303, 1334, 1355, 1415, 1462, 1586, 1623, 1679, 1757, 2877, 3044, 3249, 3359 cm^{-1}; λ_{max}: 243 nm (ε 13,337 $cm^{-1}\,M^{-1}$), 293 (4225), 413 (8464); δ_H (d_6-DMSO) 3.09–3.13 (2H, m, C6–H), 4.42–4.49 (3H, m), 4.66 (1H, d, J=6.6 Hz, C14b–*H*), 6.48 (1H, br s, N10–*H*), 6.52 (1H, t, J=7.5 Hz), 6.55 (1H, d, J=7.3 Hz), 6.91 (1H, t, J=7.6 Hz), 6.98 (1H, t, J=7.6 Hz), 7.00 (1H, d, J=7.1 Hz), 7.17 (1H, d, J=7.1 Hz), 7.42 (1H, d, J=7.8 Hz, C14–*H*), 10.63 (1H, s, N2–*H*); δ_C (d_6-DMSO) 27.5, 42.5, 49.6, 62.6, 103.1 (q), 108.9, 117.2, 122.8, 124.1, 124.2, 127.4, 129.6, 131.6 (q), 133.0 (q), 138.1 (q), 142.1 (q), 149.5 (q), 168.3 (*C*=O), 171.9 (*C*=O).

4.3.2. 8-Ethyl-12b,13-dihydro-4b*H*-indolo[3,2-*d*]pyrrolo[3,4-*b*][1]benzazepine-5,7(6*H*,8*H*)-dione (17b). The extract was evaporated and the residue was chromatographed ($CHCl_3$) to give **17b** as a yellow crystals (140 mg, 0.42 mmol, 70%, from **16b**, 200 mg, 0.6 mmol); mp 209–210 °C ($CHCl_3$); [Found: C, 72.42; H, 5.31; N, 12.40. $C_{20}H_{17}N_3O_2$ requires C, 72.49; H, 5.17; N, 12.68%]; R_f 0.27 ($CHCl_3$); ν_{max}: 1249, 1279, 1348, 1409, 1481, 1492, 1598, 1650, 1701, 1755, 2924, 2972, 3350, 3380 cm^{-1}; λ_{max}: 240 nm (ε 19,332 $cm^{-1}\,M^{-1}$), 276 (8254), 404 (4934); δ_H (d_6-DMSO) 1.10 (3H, m, CH_2CH_3), 4.03 (2H, m, CH_2CH_3), 4.25 (1H, d, J=7.1 Hz C4b–*H*), 4.94 (1H, dd, J_{12b-4b}=7.3 Hz, J_{12b-13}=2.6 Hz, C12b–*H*), 6.12 (1H, d, J_{13-12b}=2.6 Hz, N13–*H*), 6.54 (1H, dt, J=7.5, 1.0 Hz, C3–*H*), 6.57 (1H, d, J=6.8 Hz, C1–*H*), 6.95 (1H, dt, J=7.6, 1.3 Hz, C2–*H*), 7.08–7.12 (1H, m), 7.19 (1H, d, J=7.3 Hz, C4–*H*), 7.31–7.39 (3H, m), 10.5 (1H, s, N6–*H*); δ_C (d_6-DMSO) 14.3 (CH_2CH_3), 41.6 (*C*4b), 44.7 (N–CH_2–), 64.9 (*C*12b), 108.6, 113.1 (q), 116.8, 122.4, 123.5, 124.4, 127.4, 130.5 (q), 131.4 (q), 131.5, 141.1 (q), 145.6 (q), 150.9 (q), 169.0 (C=O), 171.4 (C=O); *m/z* (EI-MS) M^+ 331 (100) $M^+ - C(O)NH$ 288 (15), $M^+ - C(O)NHC(O)$ 260 (20%).

4.3.3. 9-Methyl-6,7,11,15b-tetrahydro-5*H*-indolo[2′,3′:4,5]pyrrolo[3′,4′:6,7]azepino[3,2,1-*ij*]quinoline-1,3(2*H*,10b*H*)-dione (17c). Compound **17c** was obtained from **16c** (200 mg, 0.56 mmol) as described for **17b** as a yellow solid (120 mg, 0.42 mmol, 60%,); EI HRMS, found M^+ 357.1489 (100%). $C_{22}H_{19}N_3O_2$ requires 357.1477; R_f 0.27 ($CHCl_3$); ν_{max}: 1263, 1337, 1405, 1437, 1454, 1477, 1606, 1637, 1706, 1753, 2729, 2926, 3424 cm^{-1}; λ_{max}: 245 nm (ε 13,059 $cm^{-1}\,M^{-1}$), 294 (4515), 408 (3253); δ_H (d_6-DMSO) 1.93 (1H, m, C6–*H*), 2.08 (1H, m, C6–*H*), 2.26 (3H, s, $PhCH_3$), 2.81–2.89 (2H, m, C7–*H*), 3.32–3.40 (1H, m, C5–*H*), 4.48 (1H, dt, J=13.0, 4.0 Hz, C5–*H*), 4.85 (1H, d, J=7.3 Hz, C10b–*H*), 6.01 (1H, br s, N11–*H*), 6.52–6.57 (2H, t and d, C14–*H* and C12–*H*), 6.93 (1H, d, J=1.9 Hz, C8–*H* or C10–*H*), 6.95 (1H, dt, J_{13-15}=1.4, 7.7 Hz, C13–*H*), 7.19 (1H, d, J=7.22 Hz, C15–*H*), 10.45 (1H, s, N2–*H*); δ_C (d_6-DMSO) 20.1 (CH_3), 22.7, 26.5, 42.0 (*C*15b), 46.8 (*C*5), 65.8 (*C*10b), 109.4, 110.8 (q), 117.4, 124.9, 127.8, 129.8, 129.9 (q), 130.3 (q), 130.4, 131.7 (q), 132.3 (q), 140.5 (q), 141.5 (q), 151.2 (q), 168.7 (C=O), 171.8 (C=O); *m/z* (EI-MS) M^+ 357 (100), $M^+ - C(O)NHC(O)$ 286 (23%).

4.3.4. Indolo[1′,7′:1,2,3]pyrrolo[3′,4′:6,7]azepino[4,5-*b*]indol-1,3(2*H*,10*H*)-dione (20a) and its dimer (22). The solution of **17a** (200 mg, 0.61 mmol) in THF (100 mL) was treated with DDQ (300 mg, 1.3 mmol) in THF (2 mL). The reaction mixture was stirred at 60 °C for 3 h, concentrated to the volume 5 mL, and the residue was dissolved in EtOAc (150 mL). The solution was washed with aq $NaHSO_3$ (2×30 mL), aq $NaHCO_3$ (2×30 mL), water (50 mL), dried and evaporated. The residue was chromatographed ($PhCH_3$–acetone 20:1) to give **20a** as a dark blue solid (40 mg, 0.12 mmol, 20%); mp 248–250 °C (EtOH); EI HRMS, found M^+ 325.0857 (100), $M^+ - (CO)_2NH$ 254 (16%). $C_{20}H_{11}N_3O_2$ requires 325.0851; R_f 0.57 ($CHCl_3$–MeOH 10:1); ν_{max}: 1208, 1232, 1283, 1359, 1419, 1449, 1523, 1587, 1649, 1704, 1757, 2974, 3057, 3165, 3414 cm^{-1}; λ_{max}: 245 nm (ε 27,191 $cm^{-1}\,M^{-1}$), 350 (23,491), 586 (1933); δ_H (d_6-DMSO) 6.5 (1H, d, J=3.6 Hz, C6–H), 6.91 (1H, t, J=7.7 Hz, C8–H), 6.99 (1H, t, J=7.1 Hz), 7.07 (1H, t, J=7.1 Hz), 7.11 (1H, d, J=7.5 Hz), 7.15 (1H, d, J=

8.1 Hz), 8.01 (1H, d, J=8.1 Hz), 8.12 (1H, d, J=3.6 Hz, C5–H); δ_C (d_6-DMSO) 104.3 (q), 106.2, 118.1, 118.8 (q), 121.09, 121.14 (q), 121.4, 123.0, 123.5, 123.8, 125.8, 126.0 (q), 130.5 (q), 132.7 (q), 137.2 (q), 138.2 (q), 141.8 (q), 166.8 (C=O), 169.6 (C=O); and **22** as a green solid (80 mg, 0.12 mmol, 20%); mp>330 °C ($PhCH_3$/acetone); EI HRMS, found M^+ 648.1555 (100%). $C_{40}H_{20}N_6O_4$ requires 648.1546; R_f 0.25 ($CHCl_3$–MeOH 10:1); ν_{max}: 1214, 1231, 1313, 1360, 1431, 1578, 1618, 1646, 1707, 2870, 2956, 3386, 3641 cm^{-1}; λ_{max}: 246 nm (ε 23,257 cm^{-1} M^{-1}), 301–368 (24,561–23,307), 602 (1950); δ_H (d_6-DMSO) 5.93 (1H, d, J=8.1 Hz), 6.65 (1H, t, J=7.9 Hz), 6.92 (1H, td, J=7.7, 1.1 Hz), 6.92 (1H, d, J=3.8 Hz), 6.97 (1H, d, J=7.5 Hz), 7.01 (1H, td, J=7.0, 1.0 Hz), 7.21 (1H, d, J=7.8 Hz), 7.24 (1H, td, J=7.5, 0.9 Hz), 7.33 (1H, t, J=7.7 Hz), 7.70 (1H, d, J=7.3 Hz), 7.76 (1H, d, J=7.1 Hz), 7.79 (1H, d, J=7.1 Hz), 7.95 (2H, two doublets, J=7.7 Hz), 8.06 (1H, s), 8.41 (1H, d, J=3.7 Hz); δ_C (d_6-DMSO) 104.1 (q), 109.0, 109.2 (q), 111.6, 114.3 (q), 117.9, 118.4, 119.2 (q), 119.3 (q), 120.4, 121.1, 121.4 (q), 123.1, 123.3, 123.4, 124.0, 124.6, 124.8, 124.9, 125.0, 125.6 (q), 125.8 (q), 128.0, 129.0, 129.2, 130.1 (q), 131.0 (q), 131.6 (q), 136.6 (q), 136.7 (q), 138.1 (q), 142.8 (q), 154.9 (q), 166.1 (C=O), 166.4 (C=O), 168.9 (C=O), 169.3 (C=O); *m/z* (EI-MS) M^+ 648 (100), $M^+ - (CO)_2NH$ 577 (10), $M^+ - ((CO)_2NH)_2$ 508 (10), $M^+/2$ 324 (20%).

4.3.5. 8-Ethyl-8,13-dihydro-5*H*-indolo[3,2-*d*]pyrrolo[3,4-*b*][1]benzazepine-5,7(6*H*)-dione (20b). To the solution of **17b** (200 mg, 0.6 mmol) in EtOAc (50 mL) was added DDQ (140 mg (0.62 mmol) and the reaction mixture was left with stirring at rt for 3 h. The reaction mixture was diluted with EtOAc (50 mL), washed with aq $NaHSO_3$ (30 mL), aq $NaHCO_3$ (2×30 mL), water (50 mL), dried and evaporated. The residue was chromatographed ($CHCl_3$–MeOH 50:1) to give **20b** as dark blue crystals (160 mg, 0.48 mmol, 80%); mp>330 °C (^{i}PrOH); [Found: C, 72.91; H, 4.77; N, 12.72. $C_{20}H_{15}N_3O_2$ requires C, 72.94; H, 4.59; N, 12.76%]; R_f 0.58 ($CHCl_3$–MeOH 20:1); ν_{max}: 1201, 1227, 1241, 1313, 1347, 1439, 1504, 1633, 1696, 1753, 2975, 3056, 3252 cm^{-1}; λ_{max}: 244 nm (ε 25,465 cm^{-1} M^{-1}), 331 (15,850), 500 (2163); δ_H (d_6-DMSO) 1.12 (3H, m, CH_2CH_3), 3.86 (2H, m, CH_2CH_3), 7.07 (1H, d, J=7.9 Hz), 7.09 (1H, t, J=7.9 Hz, C3–*H*), 7.16 (1H, t, J=7.4 Hz), 7.20 (1H, t, J=7.3 Hz, C2–*H*), 7.39 (1H, t, J=7.5 Hz), 7.44 (2H, d+d, J=7.6 Hz, C1–*H* and Ph-*H*), 7.97 (1H, d, C4–*H*), 10.75 (1H, s, N6–*H*), 11.96 (1H, s, N13–*H*); δ_C (d_6-DMSO) 14.4, 44.3, 106.2 (q), 111.6, 120.3, 121.6, 122.1, 123.0, 124.5, 124.9 (q), 126.1 (q), 127.9 (q), 128.6, 130.8, 137.0 (q), 140.0 (q), 142.6 (q), 150.4 (q), 167.6 (C=O), 170.0 (C=O); *m/z* (EI-MS) M^+ 329 (78), $M^+ - CH_2CH_3$ 300 (100), $M^+ - CH_2CH_3$–$(CO)_2NH$ 229 (27%).

4.3.6. 9-Methyl-6,7-dihydro-5*H*-indolo[2′,3′:4,5]pyrrolo[3′,4′:6,7]azepino[3,2,1-*ij*]quinoline-1,3(2*H*,11*H*)-dione (20c). Compound **20c** was obtained from **17c** (250 mg, 0.7 mmol) as described for **20b** as dark blue crystals (186 mg, 0.53 mmol, 75%); mp>330 °C (^{i}PrOH); [Found: C, 74.33; H, 4.78; N, 11.71. $C_{22}H_{17}N_3O_2$ requires C, 74.35; H, 4.82; N, 11.82]; R_f 0.67 ($CHCl_3$–MeOH 20:1); ν_{max}: 1207, 1240, 1318, 1335, 1362, 1435, 1497, 1538, 1638, 1690, 1745, 2878, 2915, 3054, 3234, 3303, 3344 cm^{-1}; λ_{max}: 245 nm (ε 21,199 cm^{-1} M^{-1}), 340 (15,347); δ_H (d_6-DMSO) 2.01 (2H, m, C6–H_2), 2.69 (2H, t, J=2.0 Hz, C7–H_2), 3.55 (2H, m, C5–H_2), 6.83 (1H, d, J=1.3 Hz, C10–*H* or C8–*H*), 6.94 (1H, d, J=1.3 Hz, C10–*H* or C8–*H*), 6.99 (1H, dt, J=1.0, 8.1 Hz, C14–*H*), 7.10 (1H, dt, J=1.0, 8.0 Hz, C13–*H*), 7.34 (1H, d, J=8.2 Hz, C12–*H*), 7.84 (1H, d, J=8.1 Hz, C15–*H*), 10.62 (1H, s, N2–*H*), 11.65 (1H, s, N11–*H*); δ_C (d_6-DMSO) 20.0, 49.5, 51.2, 45.3, 106.1 (q), 111.5, 120.2, 122.1, 122.5 (q), 122.6, 125.1 (q), 126.7 (q), 127.0, 129.8 (q), 132.0, 133.2 (q), 137.3 (q), 139.7 (q), 145.0 (q), 146.6 (q), 166.9 (C=O), 1701.0 (C=O); *m/z* (EI-MS) M^+ 355 (100), $M^+ - CH_3$ 340 (20), M^+ 284–$(CO)_2NH$ (21%).

4.3.7. 8b,9-Dihydroindolo[4′,3′:3,4,5]pyrrolo[3′,4′:6,7]azepino[1,2-*a*]indole-1,3(2*H*,5*H*)-dione (23). The solution of **16f** (100 mg, 0.31 mmol) in $CHCl_3$ (5 mL) was treated with CH_3SO_3H (0.2 mL) and TFA (1 mL). The reaction mixture was left with stirring for 2 h and then poured into the mixture of saturated aq $NaHCO_3$/EtOAc (1:1, 150 mL). The organic layer was separated, washed with water (2× 50 mL), dried and evaporated. The residue was chromatographed (toluene–acetone 15:1), the fractions containing **23** were pooled and left for crystallization at rt for 24 h. The dark violet crystals were filtered off, washed with toluene and dried in vacuo to give pure **23** (56 mg, 0.17 mmol, 56%); mp>330 °C; [Found: C, 73.44; H, 3.84; N, 12.28. $C_{20}H_{13}N_3O_2$ requires C 73.38; H, 4.00; N, 12.84%]; R_f 0.41 ($PhCH_3$–acetone 5:2); ν_{max}: 1249, 1264, 1350, 1412, 1480, 1518, 1603, 1613, 1639, 1694, 1752, 2922, 3051, 3165, 3300 cm^{-1}; λ_{max}: 246 nm (ε 17,157 cm^{-1} M^{-1}), 337 (5417), 502 (6693); δ_H (d_6-DMSO) 3.66 (1H, dd, J_{gem}= 16.3 Hz, J_{9-8b}=10.0 Hz), 3.94 (1H, dd, J_{gem}=16.3 Hz, J_{9-8b}=2.8 Hz), 5.12 (1H, dd, J_{8b-9}=10.3, 2.5 Hz), 6.79–6.81 (2H, triplet and doublet), 7.00 (1H, t, J=7.8 Hz), 7.17–7.21 (2H, m), 7.28 (1H, d, J=7.5 Hz), 7.46 (1H, d, J= 7.7 Hz), 7.99 (1H, d, J=2.8 Hz, C4–H), 10.52 (1H, s), 11.85 (1H, br d, J=2.0 Hz, $N^{ind}H$); δ_C (d_6-DMSO) 30.2 (C9), 64.5 (C8b), 106.9 (q), 111.9, 112.0, 115.8, 117.5 (q), 120.2, 122.1, 124.0, 124.5 (q), 125.0, 126.8 (q), 128.4, 133.3 (q), 133.4 (q), 136.3 (q), 144.2 (q), 176.3 (C=O), 170.9 (C=O).

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Thienylpyrrole azo dyes: synthesis, solvatochromic and electrochemical properties

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Abstract—The synthesis and the evaluation of solvatochromic and electrochemical properties of new donor–acceptor-substituted thienylpyrrole azo dyes **3** are described. These derivatives exhibit dramatic changes in both their electronic and redox properties in comparison with thienylpyrroles **1**. In agreement with the solvatochromic and electrochemical studies of push–pull derivatives **3** the new compounds prepared, may find application in the manufacture of new materials with notable non-linear optical properties.

1. Introduction

The design and synthesis of organic chromophores as non-linear optical (NLO) materials have attracted much attention in recent years.[1,2] They have great potential especially for use in optical communication, information processing, frequency doubling and integrated optics.[3] Organic NLO materials have many advantages over inorganic materials, including large non-linear optical coefficients, greater ease of synthetic design, easy preparation and lower cost.[4,5] It has been shown that the second order hyperpolarizabilities (β) of heterocyclic chromophores are often higher than their benzene analogues.[6,7] Recently, we have also demonstrated that donor–acceptor substituted bithiophenes and terthiophenes have many favourable features as NLO materials.[8–11]

Use of conjugated thiophene and pyrrole derivatives as donors combined with substituted acceptor groups are promising candidates among such D–A systems due to their numerous applications. Unlike the thiophene or furan analogues, the pyrrole ring can be further substituted at the nitrogen atom so that the electron density of the chromophore can be changed. In addition, replacing the N–H group of the pyrrole ring with another substituent would eliminate some intramolecular hydrogen bondings, which might also affect their macroscopic structures and NLO properties.[12–21]

Azo dyes with heterocyclic diazo components have been intensively investigated to produce bright and strong colour shades ranging from red to greenish blue on synthetic fabrics. These results led to the development of commercial products, which replaced the conventional azobenzene disperse dyes.[22]

A renewed interest in aryl(heteroaryl)-azo dyes has been sparked by efforts to find organic second-order non-linear optical (NLO) materials suitable for applications such as harmonic generation and optical switching. Azo dyes are of particular interest because they can be readily prepared with a wide range of donor and acceptor groups and also because the planarity of the azo bridge versus the non-planarity of stilbenes or other systems should contribute to larger π electron transmission effects and lead to higher optical activity.[22–25]

These previous studies prompted us to the synthesis and the characterization of new thienylpyrrole azo dyes as suitable candidates for potential use in optical data storage devices.

As part of our continuing interest in non-linear optical material[8–11,26,27] we report in this paper the synthesis, the solvatochromic and the electrochemical properties of new 1-alkyl(aryl)-2-(2′-thienyl)-5-phenylazopyrrole derivatives **3**, which have *para* CO_2Me, CN, NO_2 and *ortho–para* NO_2 groups as the electron-withdrawing groups on the phenylazo

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moiety and the conjugated 1-alkyl(aryl)-2-(2′-thienyl)pyrrole, as strong π-electron donor moieties.

2. Results and discussion

2.1. Synthesis

Recently, we have reported the synthesis of thienylpyrroles **1** through a combination of Friedel–Crafts and Lawesson reactions.[28] Compounds **1** have proved to be versatile substrates in diazo coupling reactions, allowing the preparation of several new donor–acceptor substituted thienylpyrroles.

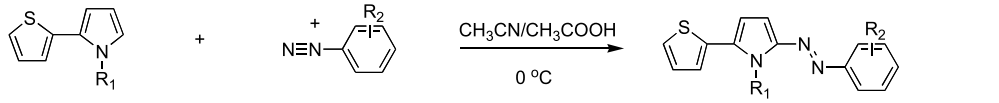
The synthesis of thienylpyrrole azo dyes **3** is outlined in Scheme 1. The coupling reaction of aryldiazonium salts **2a–d**, with 1-alkyl(aryl)-2-(2′-thienyl)pyrroles **1A–H** gave rise to the formation of 1-alkyl(aryl)-2-(2′-thienyl)-5-phenylazopyrrole derivatives **3**. This functionalization was made by reacting 1-alkyl(aryl)-2-(2′-thienyl)pyrroles **1A–H** with aryldiazonium salts **2a–d** in acetonitrile/acetic acid for 2 h at 0 °C.

Diazo coupling was accomplished selectively at the 5-position[29,30] of pyrrole ring to give compounds **3** in moderate to excellent yields (31–90%) (Scheme 1, Table 1). These results are in accordance with the greater nucleophilicity of the pyrrole ring versus the thiophene ring as has been shown earlier in the case of formylation and tricyanovinylation of thienylpyrroles.[31–34]

The structures of the thienylpyrrole azo dyes **3** were unambiguously confirmed by their analytical and spectral data.

2.2. UV–vis and solvatochromic studies of thienylpyrrole azo dyes

Electronic absorption spectra of compounds **3** show an intense lowest energy charge-transfer absorption band in the UV–vis region. Dramatic differences in energy occur upon arylazo substitution of thienylpyrroles **1**. For example, 1-aryl-2-(2′-thienyl)pyrrole **1D** (λ_{max} = 290.0 nm) is shifted 241.0 nm upon arylazo substitution (thienylpyrrole azo dye **3Dd**, λ_{max} = 531.0 nm) (Table 1). The influence of the strength of the acceptor group is demonstrated by comparison of the absorption maxima of compounds **3Da** and **3Dd** as the longest wavelength transition is shifted from 473.0 nm in 1-(4″-methoxyphenyl)-2-(2′-thienyl)-5-(4‴-carbomethoxyphenylazo)pyrrole **3Da** (Table 1, entry 1) to 531.0 nm for 1-(4″-methoxyphenyl)-2-(2′-thienyl)-5-(2‴,4‴-dinitrophenylazo)pyrrole **3Dd** (Table 1, entry 11). This effect has been attributed to the stabilization of LUMO by the electron-withdrawing groups.[35] A distinct spectral effect is also caused by the substituent at the nitrogen atom of the pyrrole ring. The influence of the substituent on the nitrogen atom of the pyrrole ring is demonstrated by comparison of the absorption maxima of compounds **3Ac** and **3Ec** as the longest wavelength transition is shifted from 488.0 nm in 1-(*n*-propyl)-2-(2′-thienyl)-5-(4″-nitrophenylazo)pyrrole **3Ac** (Table 1, entry 3) to 507.0 nm for 1-(2″,4″-dimethoxyphenyl)-2-(2′-thienyl)-5-(4‴-nitrophenylazo)-pyrrole **3Ec** (Table 1, entry 7).



1A R_1 = *n*–propyl
1B R_1 = phenyl
1C R_1 = naphthyl
1D R_1 = 4–methoxyphenyl
1E R_1 = 2,4–dimethoxyphenyl
1F R_1 = 3,4,5–trimethoxyphenyl
1G R_1 = 4–fluorophenyl
1H R_1 = 4–bromophenyl

2a R_2 = 4–CO_2Me
2b R_2 = 4–CN
2c R_2 = 4–NO_2
2d R_2 = 2,4–diNO_2

3Da R_1 = 4–methoxyphenyl, R_2 = 4–CO_2Me
3Db R_1 = 4–methoxyphenyl, R_2 = 4–CN
3Ac R_1 = *n*–propyl, R_2 = 4–NO_2
3Bc R_1 = phenyl, R_2 = 4–NO_2
3Cc R_1 = naphthyl, R_2 = 4–NO_2
3Dc R_1 = 4–methoxyphenyl, R_2 = 4–NO_2
3Ec R_1 = 2,4–dimethoxyphenyl, R_2 = 4–NO_2
3Fc R_1 = 3,4,5–trimethoxyphenyl, R_2 = 4–NO_2
3Gc R_1 = 4–fluorophenyl, R_2 = 4–NO_2
3Hc R_1 = 4–bromophenyl, R_2 = 4–NO_2
3Dd R_1 = 4–methoxyphenyl, R_2 = 2,4–diNO_2

Scheme 1.

Table 1. Yields and UV–vis absorption spectra of 1-alkyl(aryl)-2-(2′-thienyl)-5-(phenylazo)pyrroles **3** and thienylpyrroles **1**

Entry	R_1	R_2	Compound	λ_{max}[a] (nm) (ε)	Compound	Yield (%)	λ_{max}[a] (nm) (ε)
1	4-Methoxyphenyl	4-CO_2Me	—	—	**3Da**	85	473.0 (31,700)
2	4-Methoxyphenyl	4-CN	—	—	**3Db**	84	479.0 (37,640)
3	*n*-Propyl	4-NO_2	**1A**	291.0 (1800)	**3Ac**	63	488.0 (25,100)
4	Phenyl	4-NO_2	**1B**	294.5 (9208)	**3Bc**	70	497.0 (33,480)
5	Naphthyl	4-NO_2	**1C**	288.5 (15,638)	**3Cc**	34	498.0 (33,840)
6	4-Methoxyphenyl	4-NO_2	**1D**	290.0 (11,410)	**3Dc**	81	500.0 (37,580)
7	2,4-Dimethoxyphenyl	4-NO_2	**1E**	286.5 (10,093)	**3Ec**	84	507.0 (33,640)
8	3,4,5-Trimethoxyphenyl	4-NO_2	**1F**	281.5 (8477)	**3Fc**	88	499.0 (33,520)
9	4-Fluoro	4-NO_2	**1G**	293.0 (8505)	**3Gc**	90	496.0 (33,580)
10	4-Bromo	4-NO_2	**1H**	289.5 (7939)	**3Hc**	31	492.0 (22,080)
11	4-Methoxyphenyl	2,4-diNO_2	—	—	**3Dd**	47	531.0 (38,420)

[a] All the UV–vis spectra were recorded in ethanol.

To evaluate the intermolecular forces between solvents and solute molecules and in order to determine the best indicator dye, we carried out a preliminary study of the absorption spectra for compounds **3** in selected solvents of different solvatation character (diethyl ether, ethanol and DMF). We found that compound **3Dc** shows the greatest shift in wavenumber maxima ($\Delta\upsilon_{max}=801\ cm^{-1}$). Therefore, **3Dc** was submitted to a full solvatochromic study involving 15 solvents (Table 2). With respect to the influence of the solvent on the absorption properties of the compounds studied, a bathochromic shift of the longest wavelength bands is generally observed as a result of an increase in the solvent polarity (positive solvatochromism; $\Delta\upsilon=+2088\ cm^{-1}$ for **3Dc**). Because of its pronounced solvatochromism, good correlation with π^* values by Kamlet and Taft[36,37] for the solvents investigated and long wavelength absorption in the visible range, **3Dc** seemed to be a very appropriate solvent polarity indicating dye (Table 2).

Colour chemistry studies have demonstrated that the replacement of a benzene ring by a less aromatic heterocycle in typical donor–acceptor chromogens, such as azo and stilbene dyes, results in a significant bathochromic shift of the visible absorption spectra. This red shift, obtained, for example, with thiophene, furan, pyrrole and thiazole rings suggests an increase of molecular hyperpolarizability, accordingly to theoretical NLO studies. Experimental data confirmed this positive effect, in particular, for thiophene ring. In accordance with other solvatochromic studies for heteroaryl-azo dyes, the increase of the electron-withdrawing strength on the substituent of the diazo component and/or the increase of the electron-donating strength of the coupling moiety was found to cause pronounced bathochromism. In general, red shifts in absorption were accompanied by positive solvatochromic shifts.[39–46]

Table 2. Solvatochromic data [λ_{max} (nm) and υ_{max} (cm^{-1}) of the charge-transfer band] for **3Dc**, in 15 solvents in comparison with π^* values by Kamlet and Taft[36]

Solvents	π^*[a]	Compound **3Dc**	
		λ_{max}	υ_{max}
n-Hexane	−0.008	478.0	20,920
Cyclohexane	0.00	485.0	20,618
Diethyl ether	0.27	490.0	20,408
Dioxane	0.55	496.0	20,161
Ethyl acetate	0.55	496.0	20,161
Tetrahydrofuran	0.58	500.0	20,000
Acetone	0.71	500.0	20,000
Acetonitrile	0.75	508.0	19,685
Dimethylformamide	0.88	510.0	19,607
Dimethylsulfoxide	1.00	516.0	19,379
Ethanol	0.54	500.0	20,000
Methanol	0.60	500.0	20,000
Chloroform	0.58/0.76[37]	531.0	18,832
Dichloromethane	0.82	528.0	18,939
Toluene	0.54	497.0	20,120

[a] The correlation coefficient *r* obtained for the linear solvatation energy relationship with π^* values by Kamlet and Taft for aliphatic and dipolar aprotic solvents was $r=0.9750$. This value was obtained without the alcohols, aromatic and chlorinated solvents,[9,38] which deviate slightly from the regression line.

2.3. Electrochemistry of thienylpyrrole precursors 1 and thienylpyrrole azo dyes 3

To obtain a deeper insight into the ground state properties and more specifically the mutual donor–acceptor electronic influence, we studied the redox properties of the thienylpyrroles **1** and thienypyrrole azo dyes **3** by cyclic voltammetry. These results are presented in Table 3.

Upon diazo coupling, the thienylpyrrole azo dyes **3** display oxidations at more positive potentials as a consequence of the destabilizing effect of the electron-withdrawing group on the phenylazo moiety. For example, thienylpyrrole azo dye **3Dd** displays an oxidation at $^1E_{pa}=0.68$ V, an anodic shift of 0.20 V with respect to the unsubstituted thienylpyrrole **1D**.

Compounds **3Da** and **3Db** exhibit three redox processes, two oxidations and one reduction. The pyrroles azo dyes **3Ac–Hc** and **3Dd** exhibit four redox processes, two oxidation and two reductions. In the anodic scan, the first of these processes is associated with the irreversible oxidation of the pyrrole moiety. These results are consistent with previous electrochemical studies of other pyrrole and thiophene derivatives.[17,47,48] The second anodic feature is assigned to the irreversible oxidation of the azobenzene moiety.[47]

A variation of the peak potential for oxidation of the pyrrole moiety reflect the magnitude of the electronic influence exerted upon the pyrrole ring system by the terminal electron-withdrawing substituent of the azoaryl group, for example, 1-(4″-methoxyphenyl)-2-(2′-thienyl)-5-(4‴-carbomethoxyphenylazo)pyrrole **3Da** display a first oxidation at $^1E_{pa}=0.57$ V and 1-(4″-methoxyphenyl)-2-(2′-thienyl)-5-(2‴,4‴-dinitrophenylazo)pyrrole **3Dd** display an oxidation at $^1E_{pa}=0.68$ V.

Cyclic voltammetry of all the compounds **3** shows a reversible reduction attributed to the azobenzene moieties.[47] The cathodic regime in the voltammetry of the pyrroles azo dyes, **3Ac–3Hc** and **3Dd**, studied revealed two reversible couples. These correspond to the one electron reduction of the nitro ($^1E_{1/2}$) and azobenzene moieties ($^2E_{1/2}$), respectively. Compounds **3Da** and **3Db** shows only one reversible reduction due to the azobenzene moiety.

The extent of the interaction between the electron donating and accepting termini is dependent on the substituent group at the nitrogen atom on the pyrrole ring. For example, 1-(*n*-propyl)-2-(2′-thienyl)-5-(4‴-nitrophenylazo)pyrrole **3Ac** display a second reduction at $^2E_{1/2}=-1.70$ V and 1-(4″-methoxyphenyl)-2-(2′-thienyl)-5-(4‴-nitrophenylazo)pyrrole **3Dc** display a reduction at $^2E_{1/2}=-1.83$ V (Fig. 1).

In summary, we have achieved the first synthesis of a series of thienylpyrrole azo dyes **3** in moderate to excellent yields. By comparing the several derivatives synthesized, it can be shown that the withdrawing group on the phenylazo moiety and the type of substituent on the nitrogen atom of the pyrrole ring have significant influence on the solvatochromic and electrochemical properties of these compounds. These derivatives exhibit dramatic changes in both their

Table 3. Electrochemical data for thienylpyrroles **1** and thienylpyrrole azo dyes **3**

Thienylpyrroles **1**		Thienylpyrrole azo dyes **3**				
	Oxidation[a]		Reduction[a]		Oxidation[a]	
Compound	E_{pa}/V	Compound	$-{}^1E_{1/2}$/V	$-{}^2E_{1/2}$/V	${}^1E_{pa}$/V	${}^2E_{pa}$/V
—	—	**3Da**	1.71	—	0.57	0.87
—	—	**3Db**	1.74	—	0.59	0.88
1A	0.57	**3Ac**	1.23	1.70	0.78	0.96
1B	0.53	**3Bc**	1.29	1.76	0.72	0.93
1C	0.54	**3Cc**	1.31	1.80	0.72	0.92
1D	0.48	**3Dc**	1.35	1.83	0.62	0.90
1E	0.45	**3Ec**	1.36	1.77	0.61	0.90
1F	0.46	**3Fc**	1.35	1.81	0.63	0.91
1G	0.55	**3Gc**	1.27	1.73	0.80	0.96
1H	0.54	**3Hc**	1.25	1.72	0.79	0.97
—	—	**3Dd**	1.40	1.76	0.68	0.93

[a] Measurements were carried out in *N*,*N*-dimethylformamide containing 0.1 mol dm^{-3} [NBu_4][BF_4] as base electrolyte at a carbon working electrode with a scan rate of 0.1 V s^{-1}. Ferrocene was added as an internal standard at the end of each measurement, and all *E* values are quoted in volts versus the ferrocinium/ferrocene-couple.

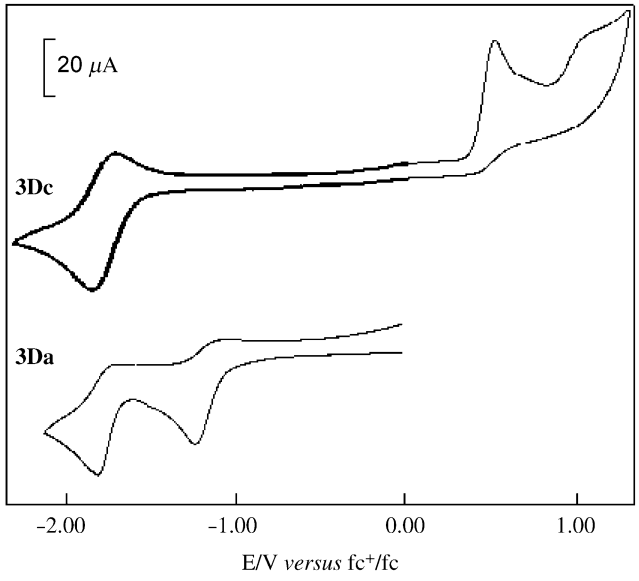


Figure 1. Cyclic voltammograms of **3Da** and **3Dc**, recorded in *N*,*N*-dimethylformamide containing 0.1 mol dm^{-3} [NBu_4][BF_4] at a vitreous carbon electrode (area = 0.049 cm^2). Scan rate = 0.1 V s^{-1}.

electronic and redox properties in comparison to thienylpyrroles **1**.

The study of the non-linear optical properties of the new donor–acceptor systems is currently underway.

3. Experimental

3.1. General

^{1}H NMR spectra were obtained on a Varian Unity Plus Spectrometer at 300 MHz and ^{13}C NMR spectra were determined on a Varian Unity Plus Spectrometer at 75. 4 MHz using the solvent peak as internal reference. The solvents are indicated in parenthesis before the chemical shift values (δ relative to TMS). Mps were determined on a Gallenkamp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1600 FTIR spectrophotometer. UV–vis absorption spectra were obtained using a Shimadzu UV/2501PC spectrophotometer. EI mass spectra EI (70 eV) and HRMS were run on a Unicam GC–MS 120. Elemental analysis was carried out on a Leco CHNS-932. Voltammetric measurements were performed using a potentiostat/galvanostat (AUTOLAB /PSTAT 12) with the low current module ECD from ECO-CHEMIE and the data analysis processed by the general purpose electrochemical system software package also from ECO-CHEMIE. Three electrode-two compartment cells equipped with vitreous carbon-disc working electrodes, a platinum-wire secondary electrode and a silver-wire pseudo-reference electrode were employed for cyclic voltammetric measurements. The concentration of the compounds were typically 1–2 mmol dm^{-3} and 0.2 mol dm^{-3} [NBu_4][BF_4] was used as the supporting electrolyte in *N*,*N*-dimethylformamide solvent. The potential is measured with respect to ferrocinium/ferrocene as an internal standard. Column chromatography was performed on Merck silica gel 60 (Art 9385). Light petroleum refers to solvent boiling in the range 40–60 °C.

4-Nitroaniline, 4-cyanoaniline, 4-carbomethoxyaniline and 2,4-dinitroaniline used as precursors for the synthesis of aryldiazonium salts **2a–d** were purchased from Aldrich and Fluka and used as received.

The synthesis of thienylpyrroles **1A–H** has been described elsewere.[28]

3.2. General procedure for diazo coupling of thienylpyrroles 1A–H with 4-carbomethoxy-, 4-cyano- and 4-nitro-substituted aryldiazonium salts 2a–c

(*i*) *Diazotisation of 4-carbomethoxy-, 4-cyano- and 4-nitroaniline*. Aniline (4.0 mmol) was pasted with $NaNO_2$ (4.0 mmol) and water (10 ml) to a smooth slurry and it was added to a well-stirred mixture of HCl (d = 1.18; 3 ml) and ice (3 g) at 0–5 °C. The reaction mixture was stirred for 30 min.

(*ii*) *Coupling reaction with thienylpyrroles* **1A–H**. The diazonium salt solution previously prepared (4.0 mmol) was added drop wise to the solution of thienylpyrroles **1** (4.0 mmol) in acetonitrile (50 ml) and some drops of acetic acid. The combined solution was maintained at 0 °C for 2 h

with stirring. After this time the resulting mixture was diluted with petrol ether (20 ml) and water (40 ml) and the product formed was isolated by filtration. The organic layer was diluted with chloroform, washed with water and dried with anhydrous $MgSO_4$. The dried solution was evaporated and the remaining 1-alkyl(aryl)-2-(2′-thienyl)-5-(phenylazo)pyrroles **3** were purified by column chromatography on silica with increasing amounts of ether in light petroleum as eluent.

3.2.1. 1-(4″-Methoxyphenyl)-2-(2′-thienyl)-5-(4‴-carbomethoxyphenylazo)pyrrole 3Da. Dark grey solid with metallic luster (85%). Mp: 193.8–194.2 °C. Recrystallization from acetone gave a gray solid mp: 195.5–197.0 °C. UV (EtOH): λ_{max} nm (ε/M^{-1} cm^{-1}) 473.0 (31,700), 260.0 (10,080), 227.0 (19,520). IV (Nujol) ν 1711 (C═O), 1603, 1536, 1512, 1424, 1363, 1326, 1278, 1226, 1191, 1166, 1110, 981, 836, 767, 692, 591 cm^{-1}. ^{1}H NMR (Acetone-d_6) δ 3.90 (s, 3H, OCH_3), 3.99 (s, 3H, COO*Me*), 7.14 (m, 3H, 4′-H and 2″ and 6″-H or 3″ and 5″-H), 7.29 (m, 3H, 3-H, 3″ and 5″-H or 2″ and 6″-H), 7.64 (dd, 1H, J=3.9, 1.2 Hz, 3′-H), 7.69 (dd, 1H, J=5.1, 1.2 Hz, 5′-H), 7.80 (d, 2H, J=8.7 Hz, 2‴ and 6‴-H), 7.99 (d, 2H, J=9.0 Hz, 3‴ and 5‴-H), 9.37 (d, 1H, J=5.4 Hz, 4-H). ^{13}C NMR ($CDCl_3$) δ 52.19, 55.76, 115.32, 118.28, 121.61, 123.27, 125.73, 128.82, 128.93, 130.09, 130.13, 130.97, 134.63, 135.86, 145.43, 145.54, 151.10, 161.67, 166.19. MS (EI) *m*/*z* (%): 417 (M^+, 100), 416 (10), 402 (6), 358 (7), 254 (20), 121 (33). Anal. Calcd for $C_{23}H_{19}N_3O_3S$: C, 66.14; H, 4.55; N, 10.06; S, 7.68. Found: C, 66.30; H, 4.70; N, 10.35; S, 7.85. HRMS: *m*/*z* (EI) for $C_{23}H_{19}N_3O_3S$; calcd 417.1147; found: 417.1142.

3.2.2. 1-(4″-Methoxyphenyl)-2-(2′-thienyl)-5-(4‴-cyanophenylazo)pyrrole 3Db. Dark red solid with metallic luster (84%). Mp: 196.4–197.2 °C. Recrystallization from acetone gave a dark red solid with metallic luster 198.0–199.5 °C. UV (EtOH): λ_{max} nm (ε/M^{-1} cm^{-1}) 479.0 (37,640), 259.0 (11,700), 228.0 (22,200). IV (Nujol) ν 2223 (CN), 1600, 1538, 1496, 1462, 1442, 1426, 1384, 1361, 1326, 1285, 1229, 1192, 1167, 1148, 1107, 1092, 1015, 980, 914, 838, 801, 729, 645, 619, 510 cm^{-1}. ^{1}H NMR (Acetone-d_6) δ 3.99 (s, 3H, OCH_3), 7.25 (m, 3H, 4′-H, 2″ and 6″-H or 3″ and 5″-H), 7.45 (d, 1H, J=5.1 Hz, 3-H), 7.58 (d, 2H, J=9.0 Hz, 2″ and 6″-H or 3″ and 5″-H), 7.71 (dd, 1H, J=3.9, 1.2 Hz, 3′-H), 7.78–7.84 (m, 5H, 5′-H, 2‴, 3‴, 5‴ and 6‴-H), 8.27 (br d, 1H, J=5.1 Hz, 4-H). ^{13}C NMR (Acetone-d_6) δ 55.94, 104.28, 112.19, 113.76, 115.16, 119.29, 122.80, 128.09, 128.36, 128.63, 129.52, 129.83, 131.47, 131.59, 134.06, 134.06, 134.46, 150.43, 161.37. MS (EI) *m*/*z* (%): 384 (M^+, 100), 254 (19), 223 (10), 192 (8), 121 (36), 77 (5). Anal. Calcd for $C_{22}H_{16}N_4OS$: C, 68.74; H, 4.16; N, 14.58; S, 8.35. Found: C, 68.90; H, 4.05; N, 14.75; S, 8.60. HRMS: *m*/*z* (EI) for $C_{22}H_{16}N_4OS$; calcd 384.1045; found: 384.1043.

3.2.3. 1-(*n*-Propyl)-2-(2′-thienyl)-5-(4‴-nitrophenylazo)pyrrole 3Ac. Green solid with metallic luster (63%). Mp: 148.0–149.0 °C. Recrystallization from acetone gave a green solid with metallic luster 150.0–151.0 °C. UV (EtOH): λ_{max} nm (ε/M^{-1} cm^{-1}) 488.0 (25,100), 289.0 (7900), 218.0 sh(11,600). IR (Nujol) ν 1615, 1550, 1488, 1417, 1330, 1283, 1260, 1137, 851, 748, 533, 509 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 0.87 (t, 3H, J=7.2 Hz, $CH_2CH_2CH_3$), 1.77–1.83 (m, 2H, $CH_2CH_2CH_3$), 4.50–4.60 (m, 2H, $CH_2CH_2CH_3$), 6.80 (d, 1H, J=4.5 Hz, 3-H), 6.96 (d, 1H, J=4.5 Hz, 4-H), 7.24–7.28 (m, 1H, 4′-H), 7.54 (dd, 1H, J=3.6, 1.2 Hz, 3′-H), 7.80 (dd, 1H, J=5.1, 1.2 Hz, 5′-H), 7.94 (d, 2H, J=9.3 Hz, 2″ and 6″-H), 8.34 (d, 2H, J=9.3 Hz, 3″ and 5″-H). ^{13}C NMR (DMSO-d_6) 10.99, 24.26, 45.18, 103.35, 114.35, 122.13, 125.14, 127.83, 128.38, 128.57, 131.94, 135.38, 146.56, 147.65, 156.87. MS (EI) *m*/*z* (%): 340 (M^+, 100), 203 (98), 179 (65), 162 (70), 121 (58). Anal. Calcd for $C_{17}H_{16}N_4O_2S$: C, 60.00; H, 4.70; N, 16.47; S, 9.43. Found: C, 60.25; H, 4.85; N, 16.63; S, 9.72. HRMS: *m*/*z* (EI) for $C_{17}H_{16}N_4O_2S$; calcd 340.0994; found: 340.0998.

3.2.4. 1-Phenyl-2-(2′-thienyl)-5-(4‴-nitrophenylazo)pyrrole 3Bc. Green solid with metallic luster (70%). Mp: 158.9–159.2 °C. Recrystallization from acetone gave a green solid with metallic luster 161.0–163.0 °C. UV (EtOH): λ_{max} nm (ε/M^{-1} cm^{-1}) 497.0 (33,480), 297.0 (9400), 257.0 (9140), 230.0 (17,820). IR (Nujol) ν 1583, 1513, 1455, 1379, 1350, 1333, 1318, 1239, 1226, 1193, 1147, 1102, 1040, 914, 887, 859, 848, 766, 753, 721, 693, 642, 593, 573, 506 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 7.00–7.05 (m, 1H, 4′-H), 7.06–7.10 (m, 2H, 3-H and 4″-H), 7.16 (dd, 1H, J=3.8, 1.2 Hz, 3′-H), 7.49–7.64 (m, 8H, 4-H, 5′-H, 2″, 3″, 5″, 6″ and 2‴, 6‴-H), 8.25 (d, 2H, J=9.0 Hz, 3‴ and 5‴-H). ^{13}C NMR (DMSO-d_6) 103.14, 113.05, 121.50, 125.04, 127.35, 127.66, 128.22, 129.33, 129.52, 129.69, 132.18, 135.99, 136.49, 146.58, 149.44, 156.87. MS (EI) *m*/*z* (%): 374 (M^+, 100), 373 (10), 224 (13), 121 (14), 77 (14). Anal. Calcd for $C_{20}H_{14}N_4O_2S$: C, 64.16; H, 3.74; N, 14.97; S, 8.57. Found: C, 64.33; H, 3.92; N, 15.26; S, 8.73. HRMS: *m*/*z* (EI) for $C_{20}H_{14}N_4O_2S$; calcd 374.0837; found: 374.0836.

3.2.5. 1-Naphthyl-2-(2′-thienyl)-5-(4‴-nitrophenylazo)pyrrole 3Cc. Dark red solid with metallic luster (91%). Mp: 156.7–157.3 °C. Recrystallization from acetone gave a dark red solid with metallic luster 159.0–161.0 °C. UV (EtOH): λ_{max} nm (ε/M^{-1} cm^{-1}) 498.0 (33,840), 282.0 (14,260). IR (Nujol) ν 1548, 1510, 1330, 1307, 1259, 1099, 850 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 6.90–6.94 (m, 1H, 4′-H), 7.12 (br d, 1H, J=8.4 Hz, Naphthyl-*H*), 7.19–7.39 (m, 6H, 3, 3′, 5′-H, Naphthyl-*H*, 2‴ and 6‴-H), 7.42–7.50 (m, 1H, Naphthyl-*H*), 7.52–7.58 (m, 1H, Naphthyl-*H*), 7.74 (t, 1H, J=8.1 Hz, Naphthyl-*H*), 7.83 (br d, 1H, J=8.1 Hz, Naphthyl-*H*), 8.08 (m, 3H, 4-H and 3‴ and 5‴-*H*), 8.24 (br d, 1H, J=8.4 Hz, Naphthyl-*H*). ^{13}C NMR (DMSO-d_6) δ 103.98, 112.80, 121.68, 121.79, 124.96, 125.69, 126.83, 127.17, 127.41, 127.92, 128.20, 128.28, 128.42, 130.36, 131.28, 131.76, 132.59, 133.64, 137.41, 146.49, 149.83, 156.65. MS (EI) *m*/*z* (%): 424 (M^+, 100), 274 (29), 273 (17), 241 (14), 217 (7), 127 (11), 121 (22). Anal. Calcd for $C_{24}H_{16}N_4O_2S$: C, 67.91; H, 3.77; N, 13.20; S, 7.56. Found: C, 68.20; H, 3.92; N, 13.37; S, 7.80. HRMS: *m*/*z* (EI) for $C_{24}H_{16}N_4O_2S$; calcd 424.0994; found: 424.0986.

3.2.6. 1-(4″-Methoxyphenyl)-2-(2′-thienyl)-5-(4‴-nitrophenylazo)pyrrole 3Dc. Violet solid with gold luster (81%). Mp: 176.0–179.0 °C. Recrystallization from acetone gave a violet solid with gold luster 181.0–183.0 °C. UV (EtOH): λ_{max} nm (ε/M^{-1} cm^{-1}) 500.0 (37,580), 264.0 (9900), 228.0 (22,820). IR (Nujol) ν 3051, 2568, 1569, 1546, 1509, 1490, 1436, 1429, 1421, 1366, 1338, 1326, 1308, 1291, 1253, 1243, 1233, 1196, 1166, 1109, 1149,

1091, 1041, 1018, 982, 963, 850, 815, 771, 748, 734 cm^{-1}. ^1H NMR (Acetone-d_6) δ 3.95 (s, 3H, OCH_3), 6.97 (d, 1H, $J=4.5$ Hz, 3-H), 7.02–7.06 (m, 1H, 4′-H), 7.08 (d, 1H, $J=4.5$ Hz, 4-H), 7.13 (dd, 1H, $J=3.9$, 1.2 Hz, 3′-H), 7.16 (d, 2H, $J=9.0$ Hz, 2″ and 6″-H or 3″ and 5″-H), 7.45 (d, 2H, $J=9.0$ Hz, 3″ and 5″-H or 2″ and 6″-H), 7.48 (dd, 1H, $J=5.1$, 1.2 Hz, 5′-H), 7.71 (d, 2H, $J=9.2$ Hz, 2‴ and 6‴-H), 8.29 (d, 2H, $J=9.2$ Hz, 3‴ and 5‴-H). ^{13}C NMR (DMSO-d_6) δ 55.55, 103.51, 113.12, 114.53, 121.88, 125.16, 127.70 (2 overlapped signals), 128.32, 128.68, 130.73, 132.24, 137.31, 146.49, 149.66, 156.79, 159.96. Anal. Calcd for $C_{21}H_{16}N_4O_3S$: C, 62.38; H, 4.06; N, 13.60; S, 7.92. Found: C, 62.37; H, 3.96; N, 13.86; S, 7.93.

3.2.7. 1-(2″,4″-Dimethoxyphenyl)-2-(2′-thienyl)-5-(4‴-nitrophenylazo)pyrrole 3Ec. Dark violet solid with gold luster (84%). Mp: 185.0–187.0 °C. Recrystallization from acetone gave a violet solid with gold luster 191.0–193.0 °C. UV (EtOH): λ_{max} nm ($\varepsilon/M^{-1}\,cm^{-1}$) 507.0 (37,640), 279.0 (10,940), 223.0 sh(10,000). IR (Nujol) ν 1614, 1569, 1552, 1513, 1488, 1338, 1325, 1267, 1194, 1152, 1129, 1091, 1032, 1016, 977, 917, 855, 801, 747, 728, 686, 644, 621 cm^{-1}. ^1H NMR (Acetone-d_6) 3.72 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.75 (dd, 1H, $J=8.4$, 2.4 Hz, 5″-H), 6.80 (d, 1H, $J=2.4$ Hz, 3″-H), 7.00 (d, 1H, $J=4.5$ Hz, 3-H), 7.03–7.07 (m, 1H, 4′-H), 7.08 (d, 1H, $J=4.5$ Hz, 4-H), 7.25 (dd, 1H, $J=3.9$, 1.2 Hz, 3′-H), 7.36 (d, 1H, $J=8.4$ Hz, 6″-H), 7.45 (dd, 1H, $J=5.1$, 1.2 Hz, 5′-H), 7.68 (d, 2H, $J=9.3$ Hz, 2‴ and 6‴-H), 8.27 (d, 2H, $J=9.3$ Hz, 3‴ and 5‴-H). ^{13}C NMR ($CDCl_3$) δ 55.98, 55.64, 99.64, 105.48 (2 overlapped signals), 113.77, 116.84, 121.15, 127.68, 128.16, 129.49, 131.33, 131.98, 139.03, 128.16, 146.15, 148.82, 156.06, 156.90, 161.85. Anal. Calcd for $C_{22}H_{18}N_4O_4S$: C, 60.82; H, 4.15; N, 12.90; S, 7.39. Found: C, 60.50; H, 4.27; N, 12.70; S, 7.38.

3.2.8. 1-(3″,4″,5″-Trimethoxyphenyl)-2-(2′-thienyl)-5-(4‴-nitrophenylazo)pyrrole 3Fc. Green solid with metallic luster (88%). Mp: 208.4–209.3 °C. Recrystallization from acetone gave a green solid with metallic luster 210.0–212.0 °C. UV (EtOH): λ_{max} nm ($\varepsilon/M^{-1}\,cm^{-1}$) 499.0 (33,520), 300.0 sh(5000). IR (Nujol) ν 1595, 1567, 1528, 1419, 1362, 1332, 1303, 1275, 1156, 1058, s1016, 985, 919, 873, 854, 805, 746, 716, 687, 633, 569, 524 cm^{-1}. ^1H NMR (Acetone-d_6) δ 3.89 (s, 6H, 2×OCH_3), 3.96 (s, 3H, OCH_3), 7.11 (s, 2H, 2″ and 6″-H), 7.30–7.35 (m, 1H, 4′-H), 7.63 (d, 1H, $J=5.1$ Hz, 3-H), 7.91 (d, 2H, $J=9.0$ Hz, 2‴ and 6‴-H), 7.95 (br d, 1H, $J=3.3$ Hz, 3′-H), 7.98 (dd, 1H, $J=5.1$, 1.2 Hz, 5′-H), 8.32 (d, 2H, $J=9.0$ Hz, 3‴ and 5‴-H), 8.60 (d, 1H, $J=5.1$ Hz, 4-H). ^{13}C NMR (DMSO-d_6) δ 56.38, 60.49, 104.87, 107.55, 109.27, 114.01, 121.43, 125.17, 127.71, 128.63, 129.77, 130.98, 131.91, 138.56, 146.25, 149.17, 153.13, 156.03. MS (EI) m/z (%): 464 (M^+, 100), 449 (28), 303 (13), 121 (26). Anal. Calcd for $C_{23}H_{20}N_4O_5S$: C, 59.47; H, 4.30; N, 12.07; S, 6.91. Found: C, 59.65; H, 4.15; N, 11.85; S, 6.70. HRMS: m/z (EI) for $C_{23}H_{20}N_4O_5S$; calcd 464.1154; found: 464.1154.

3.2.9. 1-(4″-Fluorophenyl)-2-(2′-thienyl)-5-(4‴-nitrophenylazo)pyrrole 3Gc. Brown solid with metallic luster (90%). Mp: 184.0–185.0 °C. Recrystallization from acetone gave a brown solid with metallic luster 187.0–188.0 °C. UV (EtOH): λ_{max} nm ($\varepsilon/M^{-1}\,cm^{-1}$) 496.0 (33,580), 295.0 (9080), 261.0 (8580). IR (Nujol) ν 1615, 1553, 1513, 1434, 1354, 1327, 1287, 1234, 1193, 1106, 1042, 1023, 979, 852, 816, 803, 747, 708, 643, 629, 593, 570 cm^{-1}. ^1H NMR (Acetone-d_6) δ 7.00 (d, 1H, $J=4.2$ Hz, 3-H), 7.06–7.10 (m, 1H, 4′-H), 7.13 (d, 1H, $J=4.5$ Hz, 4-H), 7.14 (dd, 1H, $J=3.9$, 1.2 Hz, 3′-H), 7.44 (t, 2H, $J=8.7$ Hz, 3″ and 5″-H), 7.53 (dd, 1H, $J=5.2$, 1.2 Hz, 5′-H), 7.64 (dd, 2H, $J=9.1$, 4.8 Hz, 2″ and 6″-H), 7.74 (d, 2H, $J=9.0$ Hz, 2‴ and 6‴-H), 8.32 (d, 2H, $J=9.0$ Hz, 3‴ and 5‴-H). ^{13}C NMR (DMSO-d_6) δ 104.51, 113.83, 116.37 and 116.22 (d, $J=23$ Hz, C3″, C5″), 121.68, 125.12, 127.83, 128.32, 129.19, 131.74 and 131.86 (d, $J=9.2$ Hz, C2″, C6″), 131.13 and 132.09 (d, $J=3.2$ Hz, C1″), 137.79, 146.47, 149.28, 156.24, 160.86 and 164.13 (d, $J=245$ Hz, C4″). MS (EI) m/z (%): 392 (M^+, 100), 242 (3), 231 (6), 204 (5), 121 (78), 95 (5). Anal. Calcd for $C_{20}H_{13}FN_4O_2S$: C, 61.21; H, 3.32; N, 14.28; S, 8.18. Found: C, 61.13; H, 3.15; N, 14.50; S, 8.37. HRMS: m/z (EI) for $C_{20}H_{13}FN_4O_2S$; calcd 392.0743; found: 392.0734.

3.2.10. 1-(4″-Bromophenyl)-2-(2′-thienyl)-5-(4‴-nitrophenylazo)pyrrole 3Hc. Dark brown solid with metallic luster (74%). Mp: 192.2–196.6 °C. Recrystallization from acetone gave a brown solid with metallic luster 198.0–199.0 °C. UV (EtOH): λ_{max} nm ($\varepsilon/M^{-1}\,cm^{-1}$) 492.0 (22,080), 292.0 (8980), sh(227.0), (19,100). IR (Nujol) ν 1512, 1488, 1462, 1428, 1380, 1241, 1228, 1195, 1149, 1102, 1068, 1040, 1023, 1006, 977, 844, 824, 803, 791, 747, 705, 690, 596, 506 cm^{-1}. ^1H NMR (Acetone-d_6) δ 7.14–7.17 (m, 1H, 4′-H), 7.20 (d, 1H, $J=4.8$ Hz, 3-H), 7.38 (br d, 1H, 3′-H), 7.61 (2 overlapped doublets, 3H, $J=8.7$ Hz, 2″, 6″-H and 4-H), 7.69 (dd, 1H, $J=4.8$, 1.2 Hz, 5′-H), 7.80 (d, 2H, $J=9.3$ Hz, 3″ and 5″-H), 7.89 (d, 2H, $J=8.7$ Hz, 2‴ and 6‴-H), 8.32 (d, 2H, $J=9.3$ Hz, 3‴ and 5‴-H). ^{13}C NMR (DMSO-d_6) δ 103.48, 113.38, 121.99, 122.83, 125.09, 127.73, 127.75, 128.54, 131.66, 131.85, 132.31, 135.29, 136.47, 146.65, 149.23, 156.69. MS (IE) m/z (%): 453 (M^{+81}Br, 79), 451 (M^{+79}Br, 80), 380 (4), 304 (5), 237 (7), 223 (7), 157 (6), 121 (100), 76 (5). Anal. Calcd for $C_{20}H_{13}BrN_4O_2S$: C, 52.98; H, 2.87; N, 12.36; S, 7.08. Found: C, 53.20; H, 2.75; N, 12.50; S, 7.33. HRMS: m/z (EI) for $C_{20}H_{13}^{79}BrN_4O_2S$; calcd 451.9943; found: 451.9942.

3.3. Diazo coupling of thienylpyrrole 1D with 2,4-dinitro-substituted aryldiazonium salt 2d

(*i*) *Diazotisation of 2,4-dinitroaniline*. $NaNO_2$ (4.0 mmol) was added gradually to concentrated sulfuric acid (5 ml) and the mixture was heated to 70 °C. The resultant solution was allowed to cool to 35 °C before 2,4-dinitroaniline (4.0 mmol) was added, then stirred to room temperature for 1.5 h, and poured onto crushed ice (7 g). The aqueous solution (containing 4.0 mmol of diazonium salt) was filtered before use in coupling experiments.

(*ii*) *Coupling with thienylpyrrole* **1D**. The diazonium salt solution previously prepared (4.0 mmol) was added drop wise to the solution of thienylpyrrole **1D** (4.0 mmol) in acetonitrile (50 ml) and acetic acid (15 ml) and the combined solution maintained at 0 °C for 3 h with stirring. After this time the resulting mixture was diluted with petrol ether (20 ml) and water (40 ml) and the product formed was isolated by filtration. The organic layer was diluted with chloroform, washed with water and dried with anhydrous

$MgSO_4$. The dried solution was evaporated and the remaining 1-aryl-2-(2′-thienyl)-5-(2‴,4‴-dinitrophenylazo)pyrrole **3Dd** was purified by column chromatography on silica with increasing amounts of ether in light petroleum as eluent.

3.3.1. 1-(4″-Methoxyphenyl)-2-(2′-thienyl)-5-(2‴,4‴-dinitrophenylazo)pyrrole 3Dd. Dark violet solid (47%). Mp: 145.0–146.0 °C. Recrystallization from acetone gave a dark violet with metallic luster 148.0–149.0 °C. UV (EtOH): λ_{max} nm (ε/M^{-1} cm^{-1}) 531.0 (38,420), 298.0 (7480), 226.0 (24,860). IR (Nujol) ν 1593, 1515, 1455, 1417, 1378, 1345, 1322, 1257, 1187, 1167, 1133, 1017, 998, 919, 895, 842, 809, 776, 741, 708 cm^{-1}. ^{1}H NMR (Acetone-d_6) δ 3.99 (s, 3H, OCH_3), 7.10–7.14 (m, 1H, 4′-H), 7.13 (d, 1H, J=4.8 Hz, 3-H), 7.17 (d, 1H, J=4.8 Hz, 4-H), 7.20 (d, 2H, J=9.0 Hz, 3″ and 5″-H, or 2″ and 6″-H), 7.33 (dd, 1H, J=3.6, 1.2 Hz, 3′-H), 7.50 (d, 2H, J=9.0 Hz, 3″ and 5″-H, or 2″ and 6″-H), 7.59 (dd, 1H, J=5.1, 1.2 Hz, 5′-H), 7.63 (d, 2H, J=9.0 Hz, 6‴-H), 8.44 (dd, 1H, J=9.3, 2.7 Hz, 5‴-H), 8.71 (d, 1H, J=2.7 Hz, 3‴-H). ^{13}C NMR ($CDCl_3$) δ 55.97, 114.48, 115.36, 119.45, 119.69, 120.49, 127.86, 128.49, 128.99, 129.33, 129.63, 129.94, 131.41, 132.26, 133.19, 140.61, 146.46, 150.19, 161.61. MS (EI) m/z (%): 449 (M^+100), 403 (42), 281 (17), 254 (25), 121 (56). Anal. Calcd for $C_{21}H_{15}N_5O_5S$: C, 56.10; H, 3.34; N, 15.59; S, 7.14. Found: C, 56.23; H, 3.14; N, 15.80; S, 7.32. HRMS: m/z (EI) for $C_{21}H_{15}N_5O_5S$; calcd 449.0794; found: 449.0783.

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Gas-phase thermolysis of benzotriazole derivatives. Part 3: Kinetic and mechanistic evidence for biradical intermediates in pyrolysis of aroylbenzotriazoles and related compounds

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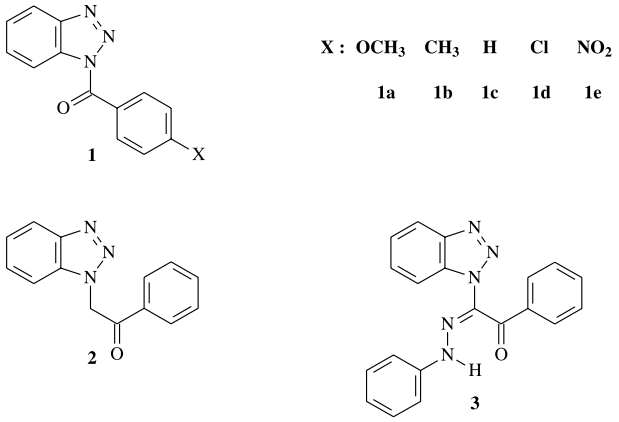
Abstract—Gas-phase pyrolysis (static and FVP) of 1-aroylbenzotriazoles gave the corresponding substituted benzoxazole, benzimidazole, benzamide, *N*-phenylbenzamide, phenanthridin-6(5*H*)-one derivatives and 1-cyanocyclopentadiene. The present kinetic and mechanistic findings also provide further evidence of the involvement of biradical or carbene reactive intermediates in the reaction pathway of gas-phase pyrolysis of benzotriazoles.

1. Introduction

The results reported in earlier papers[1,2] in this series have combined mechanistic and kinetic investigations to probe the gas-phase pyrolytic reactions of a range of benzotriazole (BT) heterocycles. Besides, the reactions provided an environmentally friendly and facile alternative for the synthesis of several novel condensed heterocycles.[1,2] Much research has recently been directed towards the study of the products of gas-phase pyrolysis, including flash vacuum pyrolysis (FVP), of numerous BT compounds.[3–7] In these reactions, thermolysis of the benzotriazoles appears to involve formation of reactive biradical intermediates, loss of molecular nitrogen, and intramolecular cyclization leading to interesting condensed heterocycles. This investigation is now extended to include the gas-phase thermolysis of 1-aroylbenzotriazoles **1a–e**, and the present results are compared with our earlier findings on related BT derivatives; their homologue 1-phenyl-2-(benzotriazol-1-yl)ethanone **2** with analogue 2-(benzotriazol-1-yl)-1-phenyl-2-(2-phenylhydrazono)ethanone **3** (Scheme 1). Previous work, further showed that pyrolysis of a number of 1-acylbenzotriazoles under different thermolytic conditions including FVP gives the corresponding benzoxazole derivatives in ca. 10–40% yield alongside other products depending on the nature of the substituents on the acyl moiety.[8–14] An important feature of our kinetic analysis of these reactions concerns the magnitude of rate enhancement attributed to extended π-conjugative interactions involving the biradical system and the substituents at the α-*N*(1) radical centre.[1,2]



Scheme 1. Aroylbenzotriazoles **1a–e**, homologue **2**, and analogue **3**.

Keywords: Aroylbenzotriazoles; Pyrolysis; Biradical intermediates; Kinetics; Mechanism.
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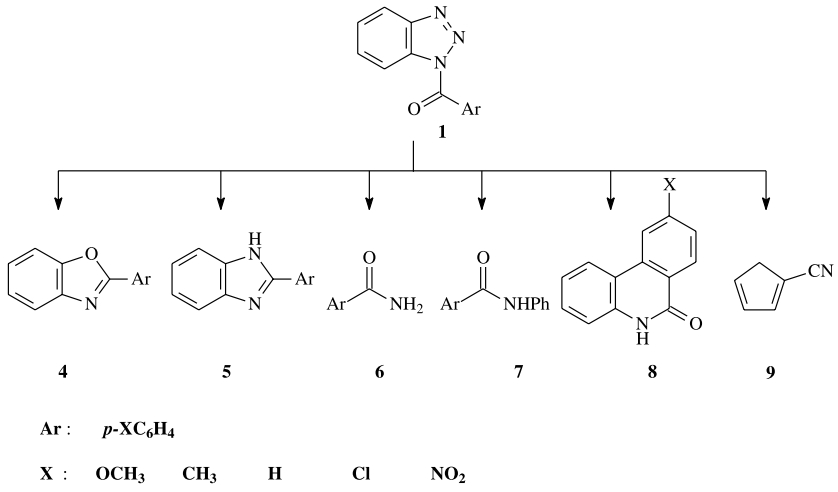


Scheme 2. Pyrolysates from thermolysis of **1a–e**.

2. Results and discussion

2.1. Pyrolysate composition and reaction pathway

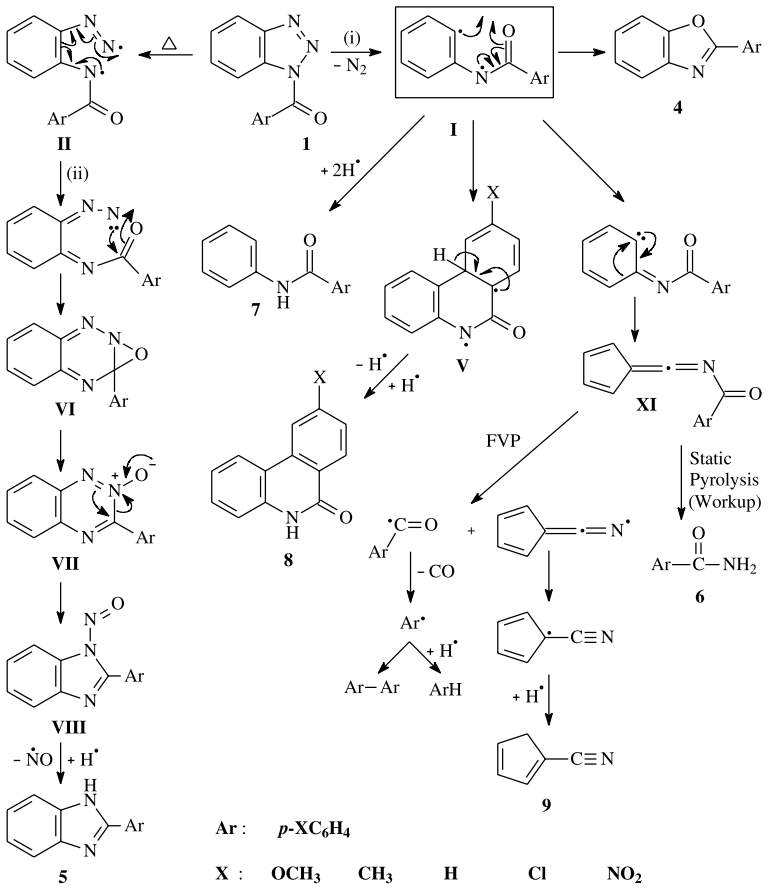
Reaction products from complete static pyrolysis of **1a–e** (Scheme 2) were obtained at optimal reactor conditions of temperature (300–340 °C), pressure (6×10^{-2} mbar) and substrate residence time compatible with $\geq$98% reaction established from kinetic runs. These products were separated by preparative HPLC and characterized as the corresponding arylbenzoxazole **4**, arylbenzimidazole **5**, substituted benzamide **6**, *N*-phenylbenzamide **7**, phenanthridin-6(5*H*)-one derivatives **8** and 1-cyanocyclopentadiene **9**. On the other hand, compounds **4**, **8** and **9** were the only characterized products upon FVP of **1a–e** at 600 °C and 0.2 Torr. Towards this end, the pyrolysates were qualitatively and quantitatively analysed by HPLC (these yields were also calculated by ^{1}H NMR), and the results are recorded in Table 1. The structures of the pyrolysis products were established using GC–MS, LCMS, ^{1}H and ^{13}C NMR, and FT-IR spectroscopy, and compared with authentic samples. Scheme 3 illustrates possible mechanistic routes to the formation of **4–9** obtained in the present pyrolytic studies of substrates **1a–e**. The first route (i) involves extrusion of N_2 to give the biradical intermediate **I**, which either cyclizes to give benzoxazole derivatives **4**, or phenanthradinone derivatives **8** or rearranges to the *N*-aroylcyclopentadienylketeneimines **XI** through the carbene intermediate as reported.[11] Further fragmentation of **XI** under FVP leads to the formation of 1-cyanocyclopentadiene **9**, benzene and biphenyl derivatives as reported earlier.[11] Addition of two hydrogen atoms to **I** explains the formation of *N*-phenylamides **7**. The second route (ii), which explains the formation of 2-arylbenzimidazoles **5** involves N–N bond cleavage of the benzotriazole ring to give biradical **II**, which rearranges into the 3-aryl-1,2,4-benzotriazine-2-oxides **VII** through the intermediacy of **VI**. Conversion of some 1-substituted benzotriazoles into benzotriazine derivatives were reported.[5] Rearrangement of **VII** into **VIII** followed by loss of (NO) radical and capture of (H) gives **5**. It is to be noted that conversion of benzotriazin-2-oxide into benzimidazole derivatives has been documented.[15] The isolated benzamide derivatives has only been proved after HPLC separation and most probably were produced by hydrolysis of the *N*-aroylcyclopentadienylketeneimines **XI**.

2.2. Kinetic data and comparative molecular reactivity

The rates of gas-phase thermolysis of the 1-aroylbenzotriazoles **1a–e** were measured over the temperature range 400–505 K with an average range of 54 K per substrate, in order to ensure reliable activation parameters for the first-order gas-phase elimination process of these compounds.[16] The kinetic data is given in Table 2. Each rate constant recorded is an average from at least three independent evaluations of the rate at each reaction temperature, and which are in agreement to within $\pm$2% rate spread. The Arrhenius parameters were obtained from strictly linear correlations over >85% reaction. A typical Arrhenius plot is given in Figure 1 for compound **1a** (with a correlation

Table 1. Pyrolysis products of **5–10(a–e)** (% yield from Static/FVP)

Substrate **1a–e**	Pyrolysis	Pyrolysis products (% Yields)					
		4a–e	**5a–e**	**6a–e**	**7a–e**	**8a–e**	**9**
1a, X=OCH$_3$	Static	21	—	24	5	—	—
	FVP	15	—	—	—	—	5
1b, X=CH$_3$	Static	4	14	22	15	3	—
	FVP	16	—	—	—	2	1
1c, X=H	Static	3	11	5	23	7	—
	FVP	13	—	—	—	3	5
1d, X=Cl	Static	5	5	22	6	5	—
	FVP	14	—	—	—	—	3
1e, X=NO$_2$	Static	20	4	18	6	4	—
	FVP	18, 15 (**4c**)	—	—	—	—	4



Scheme 3. Pathways of gas-phase pyrolysis of aroylbenzotriazoles **1a–e**.

Table 2. Rate coeffecients (k/s^{-1}), Arrhenius parameters and rate constants (k/s^{-1}) at 500 K of compounds **1a–e**

Compound	*T*/K	10^4 k/s^{-1}	log A/s^{-1}	E_a/kJ mol^{-1}	$k_{500\ K}/s^{-1}$	k_{rel}
1a	450.50	2.309	8.013±0.07	100.49±0.66	3.29×10^{-3}	0.14
	457.30	3.440				
	466.05	5.567				
	477.75	10.81				
	489.75	20.14				
	501.95	35.52				
1b	445.40	0.585	8.773±0.30	110.52±2.68	1.70×10^{-3}	0.07
	454.30	1.072				
	462.30	2.058				
	474.65	3.999				
	484.25	6.764				
	494.75	12.89				
	504.65	21.94				
1c	405.25	2.344	6.942±0.42	82.175±3.38	2.29×10^{-2}	1.00
	415.15	3.658				
	425.20	6.997				
	435.25	12.63				
	445.25	19.58				
1d	400.55	0.958	7.633±0.32	89.120±2.60	2.11×10^{-2}	0.92
	410.65	1.975				
	420.35	3.955				
	430.35	7.243				
	440.35	11.73				
	449.75	16.92				
	459.65	32.86				
1e	400.15	1.310	8.083±0.40	91.709±3.31	3.19×10^{-2}	1.39
	410.25	2.625				
	420.15	6.100				
	430.1	7.886				
	440.2	16.37				
	449.95	29.00				
	460.55	51.26				

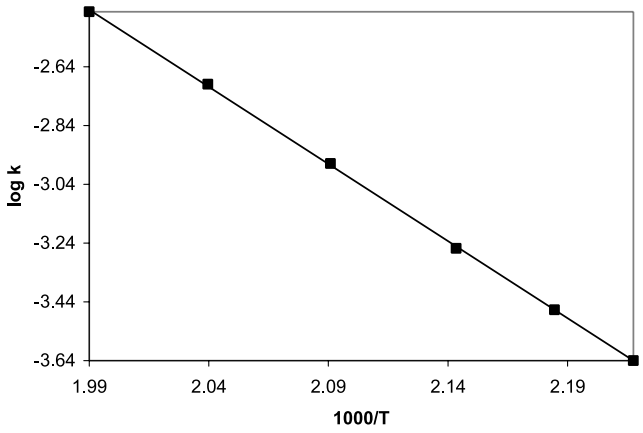


Figure 1. Arrhenius plot for pyrolysis of benzotriazol-1-yl 4-methoxyphenyl ketone **1a**.

coefficient of 1.000), and the correlation coefficients for the five substrates under study averaged 0.998 ± 0.002. The value of the $\log A/s^{-1}$ and E_a/kJ mol^{-1} are in the range expected for homogeneous, unimolecular gas-phase elimination processes.[17] The Arrhenius parameters and rate constants (k/s^{-1}) calculated at 500 K for substrates **1a–e** are summarized in Table 2. To facilitate comparison of molecular reactivities, the rate constants are also tabulated in Figure 2 together with the rate data of related BT compounds reported in earlier publications.[1,2] The reaction mechanism (Scheme 3) and the kinetic data (Fig. 2) allow the following conclusions and structure/reactivity correlations to be made.

1. The 1,3-biradical intermediate **I** proposed in this study (Scheme 3), has earlier been suggested to account for the results of gas-phase pyrolysis of α-*N*-benzotriazolyl ketones and their arylhydrazono derivatives.[1,2] The reaction pathways of the present aroylbenzotriazoles **1a–e** (Scheme 3) also include 1,5-biradical intermediate **II**. Formally, loss of a stable (N_2) molecule by **II** results in the formation of **I**. However, both reactive intermediates are subject to stabilizing resonance effects. It has further been suggested that, the BT 1,3-biradical intermediate **I** might exist as a canonical form in resonance with a carbene resonance structure.[18] It is of particular interest to note that although the biradical mechanism has been used in many investigations to explain the course of numerous gas-phase pyrolysis of BT compounds,[1,2,18] the present investigation and its predecessors represent the first kinetic study in support of the proposed mechanism of pyrolysis.
2. The half-life of biradicals generated photochemically was found to be longest for radicals conjugated to unsaturated moieties. This structural effect was rationalized in terms of resonance stabilization extended by conjugation.[19] The results of the kinetic study reported here, and in the earlier two papers in the series confirm this structural relation, and provide a kinetic rationale for the proposed biradical mechanism and the effect of structure and substituents on both rate and reaction product.
3. The aroylbenzotriazoles **1** are ca. 2×10^2–3×10^3-fold more reactive than their homologue **2**. This large decrease in reactivity is the direct result of loss of conjugation consequent to the intervention of a methylene unit between the radical centre and the unsaturated substituent moiety, and hence, loss of extended resonance stabilization of the biradical intermediate. Conjugative resonance stabilization also accounts for the relatively high rate of pyrolysis of 1-cyanobenzotriazole[1] **10**, which is of a magnitude ($k = 2.00\times10^{-2}$ s^{-1}) comparable to the rates of reaction of the aroylbenzotriazoles **1a–e**.
4. A comparison of the relative rate coefficients (k_{rel}) for pyrolysis at 500 K of compounds **1a–e** recorded in Table 2 indicates little variation in rates, and there is no Hammet type correlation of substituent effects from the aryl moiety.
5. Compound **3** offers an interesting example of how structural factors moderate molecular reactivities. This molecule has an unsaturated moiety, which is in direct conjugation with the radical centre of the proposed biradical reaction intermediate. However, this moiety is also cross-conjugated with the remaining part of the molecule, a structural factor, which limits the effectiveness of direct conjugation between the radical centre and the unsaturated moiety and, hence, reduces resonance stabilization of the intermediate. This structure/reactivity relation is borne out by the observed relative reactivities (Fig. 2). Thus, the reactivity of substrate **3** lies inbetween that of the aroylbenzotriazoles **1**, which

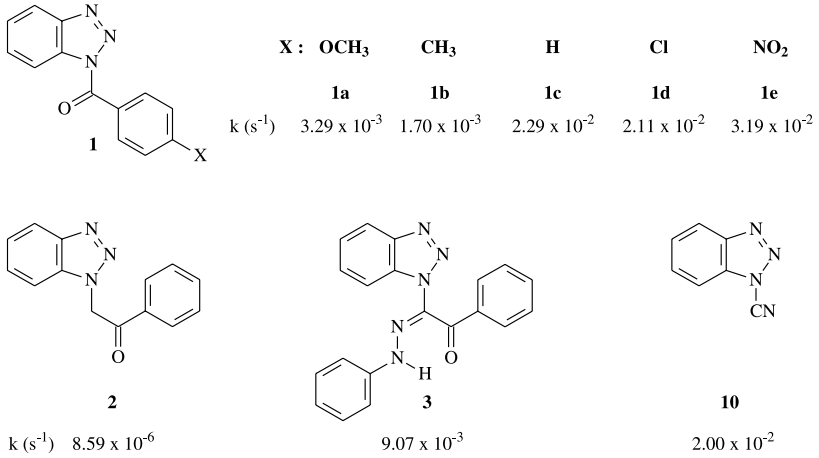


Figure 2. Rate constants (k/s^{-1}) at 500 K of aroylbenzotriazoles and related compounds.

exhibit direct conjugation and effective resonance stabilization, and their homologue **2**, which altogether lacks this stabilizing effect. The variation in reactivity between each two of the three sets of substrates [**1**, **2** and **3**] involves two orders of magnitude difference in rate of reaction.

3. Experimental

3.1. Synthesis. General procedure for synthesis of *N*-aroylbenzotriazoles 1a–e

Benzotriazole (5.95 g, 0.05 mol) in dichloromethane (100 mL) was cooled to 0 °C and triethylamine (9 mL, 0.06 mol) was added from a syringe, followed by addition of the aroyl chloride (0.055 mol). The mixture was stirred at room temperature for 30 min, and then HCl (2 M, 100 mL) was added to the mixture. The organic solution was washed twice with water and dried over anhydrous Na_2SO_4. The solvent was then evaporated and the product was recrystallized from ethanol to give the corresponding **1a–e**.

3.1.1. 1-*p*-Methoxybenzoylbenzotriazole (1a). White crystals from ethanol, yield 95%, mp 115–116 °C (lit.[20] 108–109 °C).

3.1.2. 1-*p*-Methylbenzoylbenzotriazole (1b). White crystals from ethanol, yield 90%, mp 127–128 °C (lit.[20,21] 123–24 °C).

3.1.3. 1-Benzoylbenzotriazole (1c). White crystals from petroleum ether (60–80), yield 95%, mp 115–116 °C (lit.[20,22] 112 °C).

3.1.4. 1-*p*-Chlorobenzoylbenzotriazole (1d). White crystals from petroleum ether (60–80), yield 98%, mp 138–139 °C (lit.[22] 138–139 °C).

3.1.5. 1-*p*-Nitrobenzoylbenzotriazole (1e). White crystals from ethanol, yield 96%, mp 196–198 °C (lit.[22,23] 193–194 °C).

3.2. Pyrolysis. General procedure for pyrolysis

(*a*) *Static pyrolysis*. Each of the substrates **1a–e** (0.2 g) was introduced into the reaction tube (1.5×12 cm Pyrex), cooled in liquid nitrogen, sealed under vacuum (0.06 mbar) and then placed in the pyrolyzer for 15 min at 330, 340, 310, 300, 300 °C for **1a–e**, respectively. The pyrolysate was then separated by preparative HPLC using ABZ^+ column and an eluent of suitable composition (acetonitrile and water). The collected solutions of the pyrolysate fractions were evaporated and each fraction was subjected to ^{1}H NMR and GC–MS and LCMS analysis.

(*b*) *Flash vacuum pyrolysis (FVP)*. The apparatus used was similar to the one, which has been described in our recent publications.[24,25] The sample was volatilized from a tube in a Büchi Kugelrohr oven through a 30×2.5 cm horizontal fused quartz tube. This was heated externally by a Carbolite Eurotherm tube furnace MTF-12/38A to a temperature of 600 °C, the temperature being monitored by a Pt/Pt-13%Rh thermocouple situated at the centre of the furnace. The products were collected in a U-shaped trap cooled in liquid nitrogen. The whole system was maintained at a pressure of 10^{-2} Torr by an Edwards Model E2M5 high capacity rotary oil pump, the pressure being measured by a Pirani gauge situated between the cold trap and the pump. Under these conditions the contact time in the hot zone was estimated to be ≅10 ms. The different zones of the products collected in the U-shaped trap were analyzed by ^{1}H NMR, LCMS and GC–MS. Relative and percent yields were determined from ^{1}H NMR. Identity of compounds obtained were confirmed by comparison of their ^{1}H NMR with data of products separated from preparative HPLC.

3.3. Reaction products from complete gas-phase pyrolysis of substrates 1a–e

3.3.1. 2-(4-Methoxyphenyl)benzoxazole (4a). White crystals, mp 99–100 °C (lit.[26,27] 98–99 °C). LCMS: *m/z*=266 (M+1). ^{1}H NMR ($CDCl_3$): δ 3.89 (s, 3H, OCH_3), 7.03 (d, 2H, *J*=9.0 Hz), 7.30–7.35 (m, 2H), 7.55 (m, 1H), 7.74 (m, 1H), 8.20 (d, 2H, *J*=9.0 Hz).

3.3.2. 2-*p*-Tolylbenzoxazole (4b). White crystals, mp 112–113 °C (lit.[26,28] 113–114 °C). LCMS: *m/z*=210 (M+1). ^{1}H NMR ($CDCl_3$): δ 2.42 (s, 3H, CH_3), 7.31–7.34 (m, 4H), 7.56 (m, 1H), 7.76 (m, 1H), 8.14 (d, 2H, *J*=8.2 Hz).

3.3.3. 2-Phenylbenzoxazole (4c). White crystals, mp 101–102 °C (lit.[26,28,29]102–103 °C). LCMS: *m/z*=196 (M+1). ^{1}H NMR ($CDCl_3$): δ 7.33–7.37 (m, 2H), 7.51–7.54 (m, 3H), 7.56–7.59 (m, 1H), 7.80 (m, 1H), 8.29 (m, 2H).

3.3.4. 2-(4-Chlorophenyl)benzoxazole (4d). White crystals, mp 146–147 °C (lit.[26,28] 148–149 °C). LCMS: *m/z*=232 (M+3), 230 (M+1). ^{1}H NMR ($CDCl_3$): δ 7.34–7.40 (m, 2H), 7.53 (d, 2H, *J*=8.4 Hz), 7.61 (m, 1H), 7.79 (m, 1H), 8.22 (d, 2H, *J*=8.4 Hz).

3.3.5. 2-(4-Nitrophenyl)benzoxazole (4e). White crystals, mp 264–265 °C (lit.[26] 263–264 °C). LCMS: *m/z*=240 (M+1). ^{1}H NMR ($CDCl_3$): δ 7.48–7.54 (m, 6H), 8.44 (d, 2H, *J*=8.2 Hz).

3.3.6. 2-(4-Methoxyphenyl)-1*H*-benzimidazole (5a). White crystals, mp 223–224 °C (lit.[30] 222–225 °C). LCMS: *m/z*=225 (M+1). ^{1}H NMR ($CDCl_3$): δ 3.84 (s, 3H, OCH_3), 7.24 (d, 2H, *J*=8.8 Hz), 7.48 (m, 2H), 7.74 (m, 2H), 8.08 (d, 2H, *J*=8.8 Hz), 12.80 (br, 1H, NH).

3.3.7. 2-*p*-Tolyl-1*H*-benzimidazole (5b). Colorless crystals, mp 269–270 °C (lit.[30] 270–272 °C). LCMS: *m/z*=209 (M+1). ^{1}H NMR (DMSO-d_6): δ 2.33 (s, 3H, CH_3), 7.16 (m, 2H), 7.32 (d, 2H, *J*=8.0 Hz), 7.56 (m, 2H), 8.05 (d, 2H, *J*=8.0 Hz), 12.80 (br, 1H, NH).

3.3.8. 2-Phenyl-1*H*-benzimidazole (5c). White crystals, mp 289–290 °C (lit.[31a,32] 286–289 °C). LCMS: *m/z*=266 (M+1). ^{1}H NMR ($CDCl_3$): δ 7.29 (m, 3H), 7.45 (m, 3H), 7.68 (m, 2H), 8.12 (m, 2H).

3.3.9. 2-(4-Chlorophenyl)-1*H*-benzimidazole (5d). White crystals, mp 289–290 °C (lit.[30] 290–292 °C). LCMS: $m/z=$ 231 (M+3), 229 (M+1). ^{1}H NMR (DMSO-d_6): δ 7.19 (m, 2H), 7.57 (m, 2H), 7.58 (d, 2H, $J=8.4$ Hz), 8.18 (d, 2H, $J=$ 8.4 Hz), 12.98 (br, 1H, NH).

3.3.10. 2-(4-Nitrophenyl)-1*H*-benzimidazole (5e). White crystals, mp 297–298 °C (lit.[32] 297–299 °C). LCMS: $m/z=$ 239 (M+1). ^{1}H NMR (DMSO-d_6): δ 6.80–7.74 (m, 5H), 8.25–8.57 (m, 4H).

3.3.11. 4-Methoxybenzamide (6a). LCMS: $m/z=152$ (M+1). ^{1}H NMR ($CDCl_3$): δ 3.45 (s, 3H, CH_3), 5.88 (br d, 2H, NH_2), 6.93 (d, 2H, $J=8.5$ Hz), 7.56 (d, 2H, $J=$ 8.5 Hz).[31b]

3.3.12. 4-Methylbenzamide (6b). LCMS: $m/z=136$ (M+ 1). ^{1}H NMR ($CDCl_3$): δ 2.42 (s, 3H, CH_3), 5.80 (br d, 2H, NH_2), 7.27 (d, 2H, $J=7.9$ Hz), 7.73 (d, 2H, $J=7.9$ Hz).[31c]

3.3.13. Benzamide (6c). LCMS: $m/z=122$ (M+1). ^{1}H NMR ($CDCl_3$): δ 5.80 (br d, 2H, NH_2), 7.48 (t, 2H, $J=$ 7.3 Hz), 7.57 (t, 1H, $J=7.3$ Hz), 7.76 (d, 2H, $J=7.3$ Hz).[31d]

3.3.14. 4-Chlorobenzamide (6d). LCMS: $m/z=158$ (M+ 3), 156 (M+1). ^{1}H NMR ($CDCl_3$): δ 5.90 (br d, 2H, NH_2), 7.45 (d, 2H, $J=8.3$ Hz), 7.78 (d, 2H, $J=8.5$ Hz).[33]

3.3.15. 4-Nitrobenzamide (6e). LCMS: $m/z=167$ (M+1). ^{1}H NMR ($CDCl_3$): δ 5.72, 6.11 (br d, 2H, NH_2), 8.0 (d, 2H, $J=8.4$ Hz), 8.34 (d, 2H, $J=7.4$ Hz).[31e]

3.3.16. 4-Methoxy-*N*-phenylbenzamide (7a). White crystals, mp 170–171 °C (lit.[34] 169–170 °C). LCMS: $m/z=228$ (M+1). ^{1}H NMR ($CDCl_3$): δ 3.88 (s, 3H), 6.68 (d, 2H, $J=8.6$ Hz), 7.15 (t, 1H, $J=7.8$ Hz), 7.43 (t, 2H, $J=$ 8.0 Hz), 7.58 (d, 2H, $J=7.6$ Hz), 7.82 (d, 2H, $J=8.6$ Hz), 7.89 (br, 1H, NH).

3.3.17. 4-Methyl-*N*-phenylbenzamide (7b). White crystals, mp 149–150 °C (lit.[34] 150 °C). LCMS: $m/z=212$ (M+1). ^{1}H NMR ($CDCl_3$): δ 2.44 (s, 3H), 7.17 (t, 1H, $J=$ 7.3 Hz), 7.29 (d, 2H, $J=8.0$ Hz), 7.39 (t, 2H, $J=8.0$ Hz), 7.66 (d, 2H, $J=7.8$ Hz), 7.79 (d, 2H, $J=8.0$ Hz), 7.88 (br, 1H, NH).

3.3.18. *N*-Phenylbenzamide (7c). White crystals, mp 159–160 °C (lit.[35] 159–161 °C). LCMS: $m/z=198$ (M+1). ^{1}H NMR ($CDCl_3$): δ 7.11 (t, 1H, $J=7.3$ Hz), 7.36 (t, 2H, $J=$ 7.6 Hz), 7.53 (t, 2H, $J=7.0$ Hz), 7.60 (t, 1H, $J=7.2$ Hz), 7.80 (d, 2H, $J=8.2$ Hz), 7.97 (d, 2H, $J=7.4$ Hz), 10.3 (br, 1H, NH).

3.3.19. 4-Chloro-*N*-phenylbenzamide (7d). Colorless crystals, mp 195–196 °C (lit.[36] 195–196 °C). LCMS: $m/z=234$ (M+3), 232 (M+1). ^{1}H NMR (DMSO-d_6): δ 7.12 (t, 1H, $J=7.3$ Hz), 7.34 (t, 2H, $J=7.8$ Hz), 7.60 (d, 2H, $J=8.4$ Hz), 7.75 (d, 2H, $J=8.0$ Hz), 7.98 (d, 2H, $J=$ 8.4 Hz), 10.30 (br, 1H, NH).

3.3.20. 4-Nitro-*N*-phenylbenzamide (7e). Colorless crystals, mp 217–218 °C (lit.[37] 217–218.5 °C). LCMS: $m/z=244$ (M+1). ^{1}H NMR ($CDCl_3$): δ 7.21 (m, 1H), 7.41 (m, 2H), 7.63 (m, 2H), 7.79 (br, 1H, NH), 8.04 (m, 2H), 8.35 (m, 2H).

3.3.21. 9-Methoxyphenanthridin-6(5*H*)-one (8a). Colorless crystals, mp 235 °C (lit.[38] 235–236 °C). LCMS: $m/z=$ 226 (M+1).

3.3.22. 9-Methylphenanthridin-6(5*H*)-one (8b). LCMS: $m/z=210$ (M+1).

3.3.23. Phenanthridin-6(5*H*)-one (8c). White crystals, mp 290–292 °C (lit.[39] 293–294 °C). LCMS: $m/z=195$ (M+1). ^{1}H NMR (DMSO-d_6): δ 7.26 (t, 1H, $J=7.8$ Hz), 7.36 (t, 1H, $J=8.0$ Hz), 7.49 (t, 1H, $J=8.0$ Hz), 7.65 (t, 1H, $J=7.5$ Hz), 7.84 (t, 1H, $J=8.0$ Hz), 8.32 (d, 1H, $J=8.0$ Hz), 8.37 (d, 1H, $J=8.0$ Hz), 8.51 (d, 1H, $J=8.0$ Hz), 11.70 (br, 1H, NH).

3.3.24. 9-Chlorophenanthridin-6(5*H*)-one (8d). White crystals from hexane, LCMS: $m/z=232$ (M+3), 230 (M+1). ^{1}H NMR ($CDCl_3$): δ 7.36 (t, 1H, $J=7.8$ Hz), 7.46 (d, 1H, $J=8.4$ Hz), 7.60 (t, 1H, $J=8.0$ Hz), 7.82 (t, 1H, $J=7.8$ Hz), 8.10 (d, 1H, $J=8.0$ Hz), 8.22 (d, 1H, $J=$ 8.0 Hz), 8.41 (d, 1H, $J=8.0$ Hz), 10.28 (br, 1H, NH).[40]

3.3.25. 9-Nitrophenanthridin-6(5*H*)-one (8e). LCMS: $m/z=241$ (M+1). ^{1}H NMR ($CDCl_3$): δ 7.36 (t, 1H, $J=$ 7.8 Hz), 7.46 (m, 1H), 7.64 (m, 1H), 7.78 (t, 1H, $J=7.8$ Hz), 7.95 (d, 1H, $J=8.0$ Hz), 8.38 (d, 1H, $J=8.0$ Hz), 8.51 (d, 1H, $J=8.0$ Hz), 10.25 (br, 1H, NH).[40]

3.3.26. Cyanocyclopentadiene (9). MS: $m/z=91$ (M^+, 10%), ^{1}H NMR ($CDCl_3$): δ 3.26 (m, 2H), 6.65 (m, 2H), 7.25 (m, 1H).[41]

3.4. Kinetic runs and data analysis

Stock solution (7 mL) is prepared by dissolving 6–10 mg of the substrate in acetonitrile as solvent to give a concentration of 1000–2000 ppm. Internal standard is then added, the amount of, which is adjusted to give the desired peak area ratio of substrate to standard (2.5:1). The solvent and the internal standard are selected because both are stable under the conditions of pyrolysis, and because they do not react with either substrate or product. The internal standard used in this study, is chlorobenzene. Each solution is filtered to ensure that a homogeneous solution is obtained.

The weight ratio of the substrate with respect to the internal standard is calculated from the ratio of the substrate peak area to the peak area of the internal standard. The kinetic rate was obtained by tracing the rate of disappearance of the substrate with respect to the internal standard as follows:

An aliquot part (0.2 mL) of each solution containing the substrate and the internal standard is pipetted into the reaction tube, which is then placed in the pyrolyzer for 6 min under non-thermal conditions. A sample is then analyzed using the HPLC probe with the UV detector at wavelength of 256 nm, and the standardization value (A_o) is then calculated. Several HPLC measurements are obtained with an accuracy of $\geq 2\%$. The temperature of the pyrolysis block is then raised until approximately 10% pyrolysis is

deemed to occur over 900 s. This process is repeated after each 10–15 °C rise in the temperature of the pyrolyzer until >85% pyrolysis takes place. The relative ratios of the integration values of the sample and the internal standard (*A*) at the pyrolysis temperature are then calculated. A minimum of three kinetic runs are carried out at each reaction temperature following each 10–15 °C rise in the temperature of the pyrolyzer to ensure reproducible values of (*A*). Treatment of the kinetic data has been detailed elswere.[17,42–43]

Acknowledgements

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Model studies in the lepadin series: synthesis of enantiopure decahydroquinolines by aminocyclization of 2-(3-aminoalkyl)cyclohexenones

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Abstract—Syntheses of enantiopure 3-acetoxy-2-methyldecahydroquinolines are accomplished by coupling cyclohexenyllithium **3** with α-amino epoxides and an aminocyclization of 2-(3-aminoalkyl)cyclohexenones (i.e., **5** and **9**) as the key steps. The procedure allows the incorporation of alkyl substituents at C(5) to give enantiopure 2,3,5-trisubstitued decahydroquinolines.

1. Introduction

Lepadin alkaloids are structurally characterized by the presence of a 2,3,5-trisubstituted *cis*-fused decahydroquinoline ring. The substitution pattern, which has a methyl group at C(2), a hydroxyl group, free or acylated, at C(3), and an eight carbon side chain at C(5), shows a variety of stereochemical arrangements, as shown in Figure 1. Eight lepadins (A–H) have been isolated from marine sources since 1991,[1–4] of which lepadins A–C have been found to possess significant in vitro cytotoxicity against several human cancer cell lines, whereas lepadins D–F have shown low cytotoxicity but significant and selective antiplasmodial and antitrypanosomal activity.

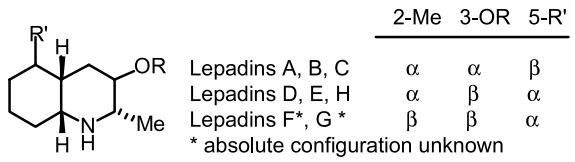

Figure 1.

Total enantioselective syntheses of lepadins A,[5] B,[5–7] C,[5] D–E,[7] and H,[7] as well as a formal route to *rac*-lepadin B[8] have been reported. The strategies described for the construction of 5-substituted 3-hydroxy-2-methyldecahydroquinolines in these synthetic approaches involve the elaboration of a polyfunctionalized piperidine followed by carbocyclic ring closure through aldol processes[5,6] or the construction of the piperidine ring from cyclohexanone derivatives either by an intramolecular enamine alkylation[7] or using a xanthate-mediated radical cyclization[8] (Scheme 1).

In this work, we report our studies on a new synthetic entry to the azabicyclic core of lepadins, either those that show a *cis* or *trans* relationship between the respective methyl and hydroxyl substituents at C(2) and C(3) of the decahydroquinoline ring (see Fig. 1). In our approach, we envisaged enantiopure cyclohexenones of type **I** (R′=H) as potential intermediates as they would bring about ring closure by forming the N–C(8a) bond. Here, we present the synthesis of these building blocks and the results obtained by their aminocyclization, either when R′=H or R′=alkyl.

2. Results and discussion

2.1. Synthetic aspects

The required starting materials are 2-bromocyclohex-2-enone ethylene acetal (**1**) and the (*S*) and (*R*) isomers of [(*S*)-1′-(dibenzylamino)ethyl]oxirane (**2a** and **2b**). The cyclohexenone derivative **1**, reported by Smith,[9] is a precursor of the α-ketovinyl anion equivalent **3**, often used in the formation of C–C bonds, for example, in reactions with alkyl halides,[9,10] ketones,[11] ethyl chloroformate,[9] and DMF.[12] Moreover, this vinyllithium derivative has been

Keywords: Lepadin alkaloids; Decahydroquinolines; Epoxides; Organolithiums; Nitrogen heterocycles.
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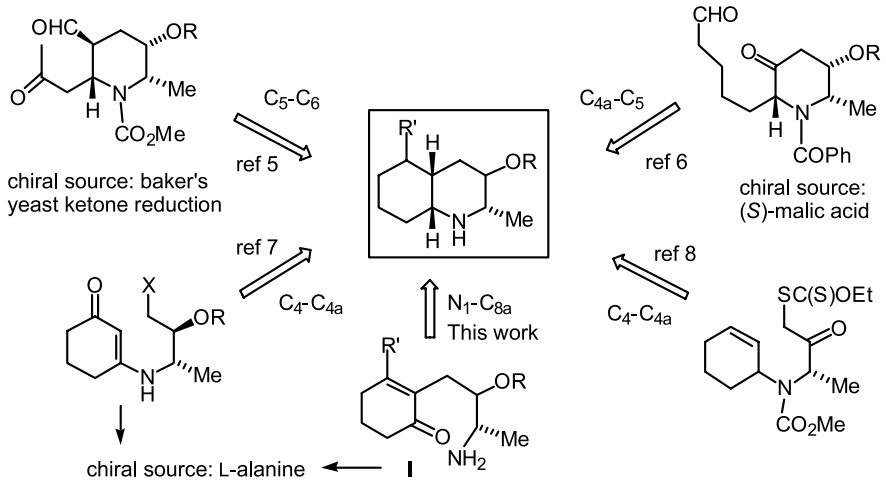
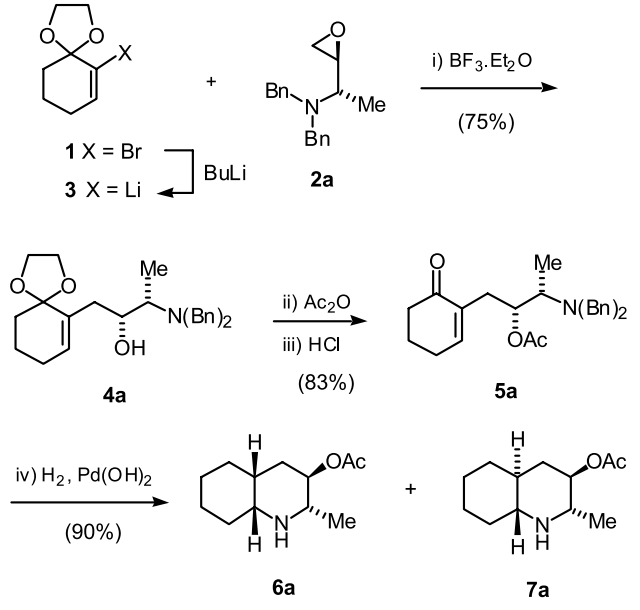


Scheme 1. Synthetic approaches to lepadin alkaloids.

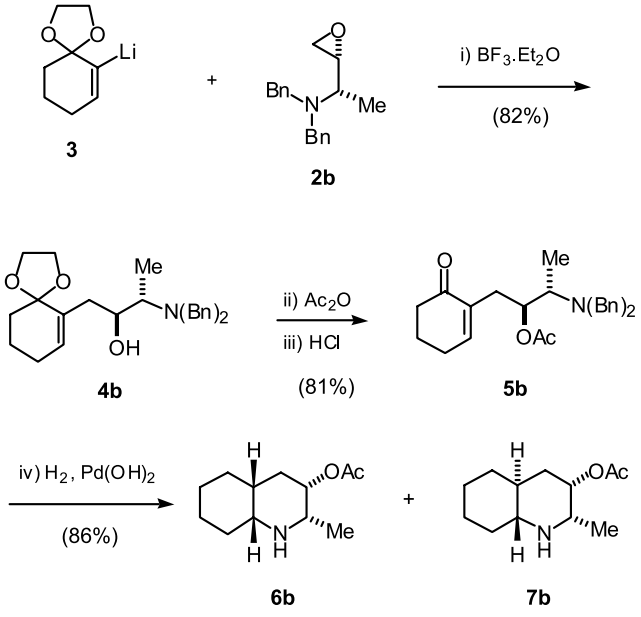
transmetallated with copper,[13] tin,[14] and palladium[15] reagents and then used in coupling processes. Finally, the lithium compound **3** reacts with TMSCl[16] and sulfinates to give vinylsilane and vinylsulfoxide[17] derivatives, respectively. To our knowledge, this versatile lithium derivative has not been used in reactions with epoxides, such as described in the present work. On the other hand, epoxides **2**[18] have been described by Reetz,[19] Barluenga and Concellón[20] and Beaulieu,[21] but there are no examples of their reactions with organolithium derivatives.[22]

The vinyllithium **3** formed on treatment of bromoacetal **1** with *n*-BuLi in THF reacted with epoxide **2a**[20] in presence of $BF_3 \cdot Et_2O$ (Ganem's conditions)[23,24] to give enantiopure alcohol **4a** (Scheme 2). After protection of the hydroxyl group as an acetate and subsequent deprotection of the acetal, the resulting cyclohexenone **5a** was submitted to a hydrogenation reaction, which involves a reduction of the double bond, a double debenzylation of the tertiary amine and an intramolecular reductive amination, to give the decahydroquinoline ring. In this process, in which two new



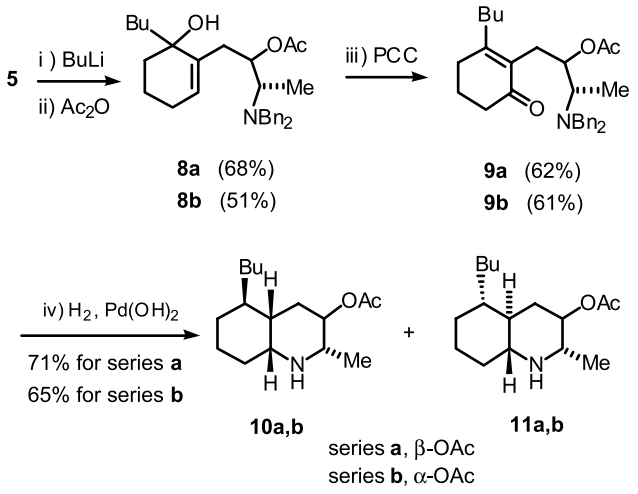
Scheme 2.

stereogenic centers are formed, the bicyclic compounds **6a** and **7a** were isolated in a 2:1 ratio. We then carried out the same sequence of reactions but starting from epoxide **2b**[20] (Scheme 3). In this series, the aminocyclization step starting from cyclohexenone **5b** gave a nearly equimolecular mixture of decahydroquinolines **6b** and **7b**. Thus, 5-dealkyllepadin derivatives with the same absolute configuration as lepadins D, E, and H (i.e., compound **6a**), and lepadins A, B, and C (i.e., compound **6b**) were achieved.



Scheme 3.

At this point, we explored the usefulness of cyclohexenones **5** as precursors of 5-alkylsubstituted decahydroquinolines (Scheme 4). Treatment of **5a** with *n*-BuLi gave a tertiary alcohol as an epimeric mixture, which was reacetylated upon the hydroxyl of the side chain, and the resulting **8a** was oxidized[25] to give the rearranged enone **9a**. The multi-step tranformation of **9a** under a hydrogen atmosphere (hydrogenation, debenzylation, and reductive aminocyclization) gave a mixture of trisubstituted decahydroquinolines **10a**



Scheme 4.

and **11a** in a nearly equimolecular ratio (71% overall yield), in which three new stereogenic centers were formed. Working with the epimeric epoxide **5b**, and following the same reaction sequence, decahydroquinolines **10b** and **11b** were formed in a 1:4 ratio (65% overall yield).

In all the cyclization processes (**5**→**6**+**7** and **9**→**10**+**11**), both in series **a** (3*R* configuration) and series **b** (3*S* configuration), the isolated decahydroquinolines show an *R* configuration at C(8a) (see Fig. 2). The configuration at C(4a) is controlled by the configuration of C(3) as well as by the presence or absence of a substituent at C(5). From the β-unsubstituted cyclohexenones (i.e., compounds **5**), the aminocyclization takes place with some diastereoselection if the acetoxy substituent can adopt a pseudo-equatorial disposition in the transition state leading to the reduced product, as occurs in **6a**, whereas in the epimeric series no stereocontrol was observed in the formation of the C(4a) stereocenter. Since it has not been established if the course of the reaction follows a pathway through an enimine intermediate or if there is a reduction of the double bond prior to the cyclization step, a clear understanding of the stereochemical course is not possible at this stage. More intriguing is the pathway of the aminocyclization leading to 2,3,5-trisubstituted decahydroquinolines **10** and **11**. The configuration at C(4a) and C(5) in all cases showed a trans relationship between the hydrogen atoms of these stereocenters suggesting that the double bond underwent a trans hydrogenation, as has been reported in some tetrasubstituted alkenes,[26] or, after a cis hydrogenation and formation of the subsequent imine, an epimerization took place at C(4a) through an enamine intermediate. Again, as occured in the 5-unsubstituted series, the ratio of trans decahydroquinolines (i.e., **11b**) to the cis epimers was higher in compounds with a 3*S* rather than 3*R* configuration.

2.2. NMR studies of decahydroquinolines 6, 7, 10, and 11 (series a and b)

The cis (**6** and **10**) and trans decahydroquinolines (**7** and **11**) are clearly differentiated by two NMR features: (i) the ^{1}H NMR chemical shift of H-8a, which appears more deshieled (δ 2.95) in the *cis*-than in the trans-derivatives (δ 2.20); (ii) the ^{13}C chemical shift of C(7) is more deshielded (~4–5 ppm) in the trans than in the cis derivatives.[27] In all cases, the preferred conformation of the cis decahydroquinolines has the H-8a axial with respect to the *N*-containing ring (*N-endo* conformer).

The absolute configuration of **6a** was deduced considering that: (a) the coupling constants for H-2 (dq, J=10, 6.5 Hz) and H-3 (td, J=10.5, 4.8 Hz) determined their axial location and hence, fixed the methyl at C(2) and the acetoxy at C(3) to an equatorial disposition; (b) the multiplicity of H-8a (br s) implied an equatorial relationship with respect to the cyclohexane ring, which discarded not only a trans junction of the decaline ring but also, taking into account the preferred conformation, implied an *R* configuration for C(8a). The ^{13}C chemical shifts also agree with this elucidation since the value of δ 20.3 for C(7) is diagnostic of a cis decahydroquinoline in a *N-endo* conformation. For trans compound **7a**, the axial proton H-8a is strongly coupled to two adjacent axial protons and one equatorial proton. Hence, its resonance signal appears as a deceptively simple triplet (J=10.4 Hz) of doublets (J=3.2 Hz) centered at δ 2.19. The NMR data for compounds **6b** and **7b** follow the same pattern of signals as that of their corresponding epimers at C(3), the major differences being in the chemical shift for H-3, which is now more deshielded since it is located in an equatorial arrangement, and in C-3 and C-4a, which resonate at a lower field, due to the axially

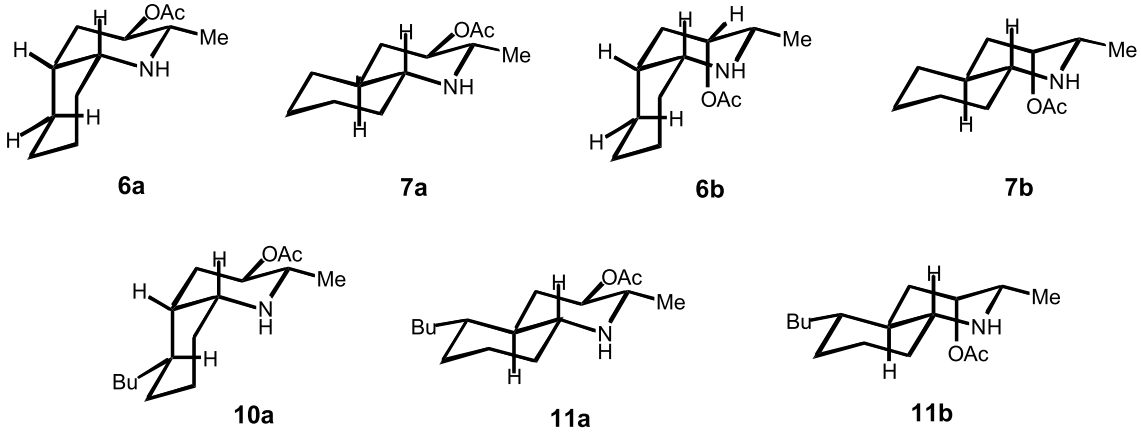


Figure 2. Preferred conformation of decahydroquinolines **6**, **7**, **10**, and **11**.

Table 1. ^{13}C NMR data for decahydroquinolines **6**, **7**, **10**, and **11**

	C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	C-9	C-1′	C-2′	C-3′	C-4′	OAc
6a	56.5	73.0	36.4	36.8	26.5	26.1	20.3	31.9	54.3	18.9	—	—	—	—	170.6/21.3
6b	55.0	70.3	35.0	33.5	27.5	26.8	20.8	32.6	54.6	18.2	—	—	—	—	170.8/21.4
7a	55.7	75.7	37.5	41.6	31.8	25.6	25.3	32.6	60.9	18.5	—	—	—	—	170.4/21.2
7b	54.0	71.6	36.6	36.9	31.9	26.0	25.5	33.2	61.4	18.3	—	—	—	—	171.0/21.3
10a	56.5	72.7	32.5	41.8	33.0	29.7	21.3	32.7	55.5	18.8	31.9	28.1	23.1	14.1	170.5/21.1
11a	55.4	76.4	34.4	46.3	40.8	31.3	24.7	33.1	60.8	18.7	32.1	28.5	23.1	14.1	170.5/21.3
11b	53.7	71.6	33.5	40.9	40.7	31.9	24.9	33.4	61.1	18.2	31.7	28.4	23.1	14.1	171.0/21.3

All spectra were recorded at 100 MHz in $CDCl_3$ and the assignments were aided by HSQC experiments.

located acetoxy group (Table 1). For trisubstituted cis decahydroquinoline **10a**, the butyl substituent at C(5) controls the preferred conformation of the bicyclic ring, which agrees with the conformation showed for lepadins where the substituent at C(5) is always equatorially located. The stereochemistry at C(5) for the butyl substituted products (**10** and **11**) was determined considering that the equatorially located butyl side chain exerts a steric crowding on H-4*eq*, due to their 1,3-synperiplanar relationship, which is reflected in the ^{13}C and ^{1}H NMR spectra by an upfield chemical shift (~3 ppm) for C(4) and a downfield chemical shift (δ 2.25±0.05) for H-4*eq* as compared to the NMR data for compounds **6** and **7**.

In summary, a new synthetic entry to enantiopure polysubstituted decahydroquinolines has been reported. Although the observed stereoselectivity does not allow lepadin-type stereochemistries to be achieved, further studies in aminocyclization processes, starting from cyclohexenones of type **5**, are in progress with the aim of achieving the required stereochemistry of lepadin derivatives. Interestingly, the reported methodology could be applied to the synthesis of another type of natural decahydroquinolines, such as *trans*-195A,[28] 5-*epi*-*trans*-243A,[29] and related alkaloids isolated from dendrobatid frogs,[27c] which show the same pattern of relative configuration as compounds **11a** and **11b** in their four stereocenters.

3. Experimental

3.1. General

All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions. Analytical TLC was performed on SiO_2 (silica gel $60F_{254}$, Merck) or Al_2O_3 (ALOX N/UV_{254}, Polygram), and the spots were located with iodoplatinate reagent (compounds **4**, **5**, **8**, and **9**) or 1% aqueous $KMnO_4$ (compounds **6**, **7**, **10**, and **11**). Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230–240 mesh ASTM) or Al_2O_3 (aluminium oxide 90, Merck). Drying of organic extracts during workup of reactions was performed over anhydrous Na_2SO_4. Optical rotations were recorded with a Perkin-Elmer 241 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Gemini 200 or 300, or a Varian Mercury 400 instrument. Chemical shifts are reported in ppm downfield (δ) from Me_4Si. All new compounds were determined to be >95% pure by ^{1}H NMR spectroscopy.

3.1.1. 2-[(2*R*,3*S*)-3-Dibenzylamino-2-hydroxybutyl] cyclohex-2-enone ethylene acetal (4a). A solution of 6-bromo-1,4-dioxaspiro[4.5]dec-6-ene (**1**, 1.04 g, 4.75 mmol) in THF (3 mL) was added to a solution of *n*-BuLi (1.6 M in hexanes, 3.2 mL, 5.11 mmol) in THF (7 mL) at −78 °C. The reaction mixture was stirred for 90 min, treated with a solution of (2*S*)-[1′(*S*)-(dibenzylamino)ethyl]oxirane (**2a**, 489 mg, 1.83 mmol) in THF (6 mL) and $BF_3\cdot Et_2O$ (0.64 mL, 5.11 mmol), and continuously stirred at −78 °C for 2 h prior to being quenched with saturated $NaHCO_3$ solution (10 mL) and warmed to rt. The

product was extracted with Et_2O (3×20 mL), the combined organic layers were dried, concentrated, and the residue was chromatographed (SiO_2, elution with 9:1 hexane/EtOAc) to give 560 mg (75%) of **4a** as a colorless oil: R_f=0.31 (SiO_2, 8:2 hexane/EtOAc); $[\alpha]_D^{20}$ +10.0 (*c* 1.2 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 1.15 (d, *J*=6.3 Hz, 3H), 1.60–1.80 (m, 5H), 1.95–2.05 (br, 2H), 2.52–2.61 (m, 1H), 2.85 (dm, *J*=14 Hz, 1H), 3.25 (br, 1H), 3.45 (d, *J*=13.8 Hz, 2H), 3.66–3.73 (m, 1H), 3.77 (d, *J*=13.8 Hz, 2H), 3.84–3.90 (m, 2H), 3.91–3.97 (m, 2H), 5.76 (t, *J*=3 Hz, 1H), 7.18–7.40 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) 8.4 (CH_3), 20.6 (CH_2), 25.4 (CH_2), 33.2 (CH_2), 36.2 (CH_2), 54.3 (CH_2), 57.7 (CH), 64.6 (CH_2), 64.7 (CH_2), 74.1 (CH), 107.5 (C), 126.7 (CH), 128.1 (CH), 128.7 (CH), 133.6 (CH), 140.3 (C). HRFABMS calcd for $C_{26}H_{34}NO_3$ (M^++1) 408.2539, found 408.2516.

3.1.2. 2-[(2*S*,3*S*)-3-Dibenzylamino-2-hydroxybutyl] cyclohex-2-enone ethylene acetal (4b). Operating as above, starting from 881 mg (4.02 mmol) of **1** and using (2*R*)-[1′(*S*)-(dibenzylamino)ethyl]oxirane (**2b**, 414 mg, 1.55 mmol), and after chromatography (SiO_2, 9:1 hexane/EtOAc) **4b** (518 mg, 82%) was isolated as an oil: R_f=0.28 (SiO_2, 9:1 hexane/EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) 1.05 (d, *J*=6.6 Hz, 3H), 1.62–1.72 (m, 5H), 1.95–2.05 (br, 2H), 2.17–2.25 (m, 1H), 2.52–2.62 (m, 1H), 3.33 (d, *J*=13.6 Hz, 2H), 3.64–3.76 (m, 1H), 3.88 (d, *J*=13.6 Hz, 2H), 3.90–3.98 (m, 4H), 5.93 (t, *J*=2 Hz, 1H), 7.16–7.40 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) 8.6 (CH_3), 20.6 (CH_2), 25.3 (CH_2), 33.6 (CH_2), 34.3 (CH_2), 53.6 (CH_2), 58.2 (CH), 64.7 (CH_2), 64.8 (CH_2), 70.8 (CH), 107.8 (C), 127.0 (CH), 128.3 (CH), 128.9 (CH), 131.5 (CH), 139.2 (C).

3.1.3. 2-[(2*R*,3*S*)-2-Acetoxy-3-(dibenzylamino)butyl] cyclohex-2-enone (5a). To a solution of **4a** (101 mg, 0.25 mmol) in pyridine (0.8 mL) and Ac_2O (0.24 mL, 2.5 mmol) was added DMAP (5 mg, 0.04 mmol). The reaction mixture was stirred overnight at rt. A saturated $NaHCO_3$ solution (15 mL) was added and the mixture was extracted with CH_2Cl_2 (3×10 mL). The dried organic extracts were concentrated to give the corresponding acetate, which was used directly in the following acetal hydrolysis step. The above crude acetal was dissolved in 1:1 H_2O/THF (4 mL) and stirred at rt for 1 h. The reaction mixture was basified with saturated aqueous $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (3×10 mL), and the resulting organic extracts were dried and concentrated. The residue was purified by chromatography (SiO_2, hexane/EtOAc 8:2) to give **5a** as an oil (80 mg, 83%): R_f=0.27 (SiO_2, 8:2 hexane/EtOAc); $[\alpha]_D^{20}$ +7.8 (*c* 0.7 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 1.08 (d, *J*=6.6 Hz, 3H), 1.75–1.83 (m, 1H), 1.83–1.93 (m, 2H), 1.94 (s, 3H), 2.16–2.28 (m, 2H), 2.31–2.38 (m, 2H), 2.75 (quint, *J*=6 Hz, 1H), 3.18 (dm, *J*=14 Hz, 1H), 3.41 (d, *J*=13.6 Hz, 2H), 3.78 (d, *J*=13.6 Hz, 2H), 5.17 (ddd, *J*=9.6, 7.6, 3.4 Hz, 1H), 6.53 (t, *J*=4 Hz, 1H), 7.17–7.41 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) 8.8 (CH_3), 21.2 (CH_3), 22.9 (CH_2), 26.2 (CH_2), 33.2 (CH_2), 38.2 (CH_2), 53.9 (CH_2), 55.1 (CH), 74.3 (CH), 126.7 (CH), 128.1 (CH), 129.0 (CH), 136.4 (C), 139.9 (C), 146.4 (CH), 170.4 (C), 198.7 (C). Anal. Calcd for $C_{26}H_{31}NO_3$: C, 77.00; H, 7.70; N, 3.45. Found C, 76.75; H, 7.85; N, 3.39.

3.1.4. 2-[(2*S*,3*S*)-2-Acetoxy-3-(dibenzylamino)butyl] cyclohex-2-enone ethylene acetal (5b). Operating as above, starting from 263 mg (0.64 mmol) of alcohol **4b**, and after chromatography (SiO_2, 8:2 hexane/EtOAc), acetate **5b** (196 mg, 81%) was isolated as an oil: R_f=0.25 (SiO_2, hexane/EtOAc, 8:2); $[\alpha]_D^{20}$ −32 (*c* 1.8 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 1.09 (d, *J*=7.2 Hz, 3H), 1.86–1.94 (m, 3H), 2.01 (s, 3H), 2.16–2.30 (m, 3H), 2.33–2.40 (m, 1H), 2.60 (dm, *J*=14 Hz, 1H), 2.89 (quint, *J*=7 Hz, 1H), 3.37 (d, *J*=13.8 Hz, 2H), 3.87 (d, *J*=13.8 Hz, 2H), 5.06 (ddd, *J*=10.2, 6.2, 2.6 Hz, 1H), 6.60 (t, *J*=4.2 Hz, 1H), 7.18–7.40 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): 9.7 (CH_3), 21.2 (CH_3), 22.9 (CH_2), 26.1 (CH_2), 33.0 (CH_2), 38.2 (CH_2), 54.3 (CH_2), 55.4 (CH), 74.7 (CH), 126.6 (CH), 128.1 (CH), 128.8 (CH), 136.3 (C), 140.3 (C), 146.3 (CH), 170.3 (C), 198.8 (C). HRFABMS calcd for $C_{26}H_{32}NO_3$ (M^++1) 406.2382, found 406.2339.

3.1.5. Aminocyclization of 5a. A suspension of enone **5a** (50 mg, 0.12 mmol) and activated[30] $Pd(OH)_2$ in EtOH (2 mL) was stirred overnight under hydrogen. The catalyst was removed by filtration through Celite, and the solvent was evaporated to give a residue, which was purified by chromatography (Al_2O_3, 9:1 hexane/EtOAc) to give **6a** (13 mg, 54%) and **7a** (9 mg, 36%), both as oils.

(2*S*,3*R*,4a*R*,8a*R*)-3-Acetoxy-2-methyldecahydroquinoline (**6a**). R_f=0.51 (Al_2O_3, 8:2 hexane/EtOAc); $[\alpha]_D^{20}$ −20.7 (*c* 1.3 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, COSY) 1.08 (d, *J*=6.4 Hz, 3H, Me), 1.20 (m, H-5*ax*), 1.40 (m, 3H, H-6*ax* and H-7), 1.45 (m, H-4*ax*), 1.55 (m, H-8), 1.70 (m, H-8), 1.74 (m, 3H, H-4a, H-5*eq*, H-6*eq*), 1.87 (ddd, *J*=11.0, 3.6, 1.2 Hz, H-4*eq*), 2.05 (s, 3H, OAc), 2.70 (dq, *J*=10.0, 6.5 Hz, H-2*ax*), 2.95 (br s, H-8a), 4.58 (td, *J*=10.5, 4.8 Hz, H-3*ax*); ^{13}C NMR see Table 1. HRFABMS calcd for $C_{12}H_{22}NO_2$ (M^++1) 212.1651, found 212.1646.

(2*S*,3*R*,4a*S*,8a*R*)-3-Acetoxy-2-methyldecahydroquinoline (**7a**). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) 1.02 (qd, *J*=10.4, 3.2 Hz, H-5*ax*), 1.10 (masked, H-4*ax*), 1.12 (d, *J*=6.4 Hz, 3H, Me), 1.20–1.30 (m, 2H, H-8*ax* and H-4a), 1.35 (m, 2H, H-6*ax* and H-7*ax*), 1.65 (m, 2H, H-7*eq* and H-5*eq*), 1.8 (m, 2H, H-8*eq* and H-6*eq*), 2.04 (s, 3H, OAc), 2.05 (masked, H-4*eq*), 2.19 (td, *J*=10.4, 3.2 Hz, H-8a), 2.76 (dq, *J*=10, 6.4 Hz, H-2*ax*), 4.45 (td, *J*=10.4, 4.4 Hz, H-3*ax*); ^{13}C NMR see Table 1.

3.1.6. Aminocyclization of 5b. Operating as above, starting from 49 mg (0.12 mmol) of enone **5b**, and after chromatography (Al_2O_3, from 9:1 to 7:3 hexane/EtOAc), 11 mg (43%) of **6b** and 11 mg (43%) of **7b**, both as colorless oils, were isolated.

(2*S*,3*S*,4a*R*,8a*R*)-3-Acetoxy-2-methyldecahydroquinoline (**6b**). R_f=0.30 (Al_2O_3, 8:2 hexane/EtOAc); $[\alpha]_D^{20}$ +10.8 (*c* 0.8 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, COSY) 1.08 (d, *J*=6.6 Hz, 3H, Me), 1.20 (m, H-5*ax*), 1.40 (m, 3H, H-6*ax*, H-7), 1.50 (m, 2H, H-8*ax*, H-4*ax*), 1.72 (m, 4H, H-4a, H-5*eq*, H-6*eq*, H-8*eq*), 1.87 (ddd, *J*=12, 3.6, 1.5 Hz, H-4*eq*), 2.09 (s, 3H, OAc), 2.90 (qd, *J*=6.8, 2 Hz, H-2*ax*), 2.92 (br, H-8a), 4.75 (ddd, *J*=3.2, 3.2, 1.6 Hz, H-3*eq*); ^{13}C NMR see Table 1. HRFABMS calcd for $C_{12}H_{22}NO_2$ (M^++1) 212.1651, found 212.1648.

(2*S*,3*S*,4a*S*,8a*R*)-3-Acetoxy-2-methyldecahydroquinoline

(**7b**). R_f=0.23 (Al_2O_3, 8:2 hexane/EtOAc); $[\alpha]_D^{20}$ +28.6 (*c* 0.8 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, COSY) 0.94 (qd, *J*=12, 3 Hz, H-5*ax*), 1.06 (dd, *J*=6.8 Hz, 3H, Me), 1.21–1.34 (m, 5H, H-4*ax*, H-4a, H-6*ax*, H-7*ax*, H-8*ax*), 1.54 (dm, *J*=12 Hz, H-5*eq*), 1.69 (dm, *J*=12 Hz, H-6*eq*), 1.77 (dm, 2H, *J*=12 Hz, H-7*eq*, H-8*eq*), 1.88 (dd, *J*=10.8, 3.2 Hz, H-4*eq*), 2.12 (s, 3H, OAc), 2.22 (td, *J*=10, 3.2 Hz, H-8a), 2.92 (qd, *J*=6.4, 1.6 Hz, H-2*ax*), 4.88 (ddd, *J*=3.2, 3.2, 1.6 Hz, H-3*eq*); ^{13}C NMR see Table 1. HRFABMS calcd for $C_{12}H_{22}NO_2$ (M^++1) 212.1651, found 212.1648.

3.1.7. 2-[(2*R*,3*S*)-2-Acetoxy-3-(dibenzylamino)butyl]-1-butylcyclohex-2-en-1-ol (8a). To a cooled (−78 °C) solution of **5a** (105 mg, 0.258 mmol) in THF (3 mL) was added *n*-BuLi (1.6 M in hexanes, 0.8 mL, 1.29 mmol) and the reaction mixture was stirred for 4 h, the temperature slowly rising to rt. The reaction was quenched by addition of saturated aqueous NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3×20 mL). The dried organic extracts were concentrated and the residue was dissolved in pyridine (1 mL) and treated with Ac_2O (0.25 mL, 2.58 mmol) and DMAP (5 mg, 0.04 mmol). The reaction mixture was stirred overnight at rt, saturated aqueous $NaHCO_3$ (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3× 15 mL). The dried organic extract was concentrated and purified by chromatography (SiO_2, hexane/EtOAc 8:2) to give the epimeric alcohols **8a** and 1-*epi*-**8a** (81 mg, 68%), in a 1:1 ratio according to the NMR spectrum, which were used directly in the next step.*Compound* **8a**. R_f=0.82 (SiO_2, 8:2 hexane/EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) 0.92 (t, *J*=6.8 Hz, 3H), 1.11 (d, *J*=7.0 Hz, 3H), 1.18–1.38 (m, 4H), 1.49–1.80 (m, 7H), 1.82–1.93 (m, 2H), 1.98 (s, 3H), 2.75 (quint, *J*=7 Hz, 1H), 2.95 (dm, *J*=12 Hz, 1H), 3.44 (d, *J*=13.6 Hz, 2H), 3.75 (d, *J*=13.6 Hz, 2H), 5.29–5.40 (m, 2H), 7.18–7.40 (m, 10H). *Compound* 1-*epi*-**8a**. R_f=0.64 (SiO_2, 8:2 hexane/EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) 0.89 (t, *J*=6.6 Hz, 3H), 1.06 (d, *J*=6.6 Hz, 3H), 1.18–1.38 (m, 4H), 1.40–1.70 (m, 7H), 1.74–1.88 (m, 2H), 2.00 (s, 3H), 2.44–2.54 (m, 1H), 2.85 (quint, *J*=7 Hz, 1H), 3.48 (d, *J*=13.6 Hz, 2H), 3.73 (d, *J*=13.6 Hz, 2H), 5.30 (m, 1H), 5.39 (t, *J*=3.9 Hz, 1H), 7.18–7.40 (m, 10H).

3.1.8. 2-[(2*S*,3*S*)-2-Acetoxy-3-(dibenzylamino)butyl]-1-butylcyclohex-2-enol (8b). Operating as above, starting from 147 mg (0.36 mmol) of cyclohexenone **5b**, and after chromatography (SiO_2, hexane/EtOAc 8:2), 85 mg (51%) of **8b** was obtained: R_f=0.58 (SiO_2, 8:2 hexane/EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) 0.91 (t, *J*=6.8 Hz, 3H), 1.09 (d, *J*=7 Hz, 3H), 1.20–1.40 (m, 5H), 1.42–1.78 (m, 6H), 1.84–1.96 (m, 2H), 2.05 (s, 3H), 2.18–2.28 (m, 1H), 2.85 (quint, *J*=7 Hz, 1H), 3.37 (d, *J*=13.5 Hz, 2H), 3.90 (d, *J*=13.5 Hz, 2H), 5.13–5.22 (m, 1H), 5.45 (t, *J*=3.7 Hz, 1H), 7.18–7.40 (m, 10H).

3.1.9. 2-[(2*R*,3*S*)-2-Acetoxy-3-(dibenzylamino)butyl]-3-butylcyclohex-2-enone (9a). To a solution of epimeric alcohols **8a** (81 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) were added PCC (57 mg, 0.26 mmol) and SiO_2 (57 mg), and the mixture was stirred overnight at rt. The residue obtained after evaporation of the solvent was purified by chromatography (SiO_2, hexane/EtOAc 9:1) to give **9a** as a viscous oil (50 mg, 62%): R_f=0.36 (SiO_2, 8:2 hexane/EtOAc); $[\alpha]_D^{20}$ −5.3 (*c* 0.3 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 0.91 (t, *J*=6.8 Hz, 3H), 1.11 (d, *J*=6.4 Hz, 3H), 1.20–1.50 (m, 4H), 1.70–1.8 (m, 2H), 1.92 (s, 3H), 1.98–2.33 (m, 6H), 2.34–2.42 (m, 1H), 2.71 (quint, *J*=6.8 Hz, 1H), 3.08 (dd, *J*=13.6, 4.4 Hz, 1H), 3.45 (d, *J*=13.6 Hz, 2H), 3.75 (d, *J*=13.6 Hz, 2H), 5.20 (ddd, *J*=8.8, 6.8, 5.2 Hz, 1H), 7.18–7.40 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$, HSQC) 8.9 (CH_3), 14.1 (CH_3), 21.2 (CH_3), 22.4 (CH_2), 22.9 (CH_2), 28.3 (CH_2), 30.1 (CH_2), 30.8 (CH_2), 34.7 (CH_2), 37.7 (CH_2), 54.0 (CH_2), 55.2 (CH), 75.0 (CH), 126.7 (CH), 128.1 (CH), 128.9 (CH), 131.3 (C), 140.1 (C), 160.9 (C), 170.4 (C), 198.7 (C). Anal. Calcd for $C_{30}H_{39}NO_3\cdot H_2O$: C, 75.12; H, 8.62; N, 2.92. Found C, 75.48; H, 9.02; N, 2.58.

3.1.10. 2-[(2*S*,3*S*)-2-Acetoxy-3-(dibenzylamino)butyl]-3-butylcyclohex-2-enone (9b). Operating as above, starting from 71 mg (0.15 mmol) of alcohol **8b** and after chromatography (SiO_2, 9:1 hexane/EtOAc), enone **9b** (41 mg, 61%) was isolated as a viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$) 0.89 (t, *J*=7.2 Hz, 3H), 1.10 (d, *J*=6.8 Hz, 3H), 1.20–1.32 (m, 2H), 1.32–1.44 (m, 2H), 1.81–1.88 (m, 2H), 1.96 (s, 3H), 1.96–2.03 (m, 2H), 2.16–2.42 (m, 6H), 2.34–2.42 (m, 1H), 2.68 (dd, *J*=13.8, 11.0 Hz), 2.89–2.96 (m, 1H), 3.39 (d, *J*=13.6 Hz), 3.90 (d, *J*=13.6 Hz), 5.08 (ddd, *J*=11.0, 5.8, 2.4 Hz, 1H), 7.18–7.40 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$, HSQC) 9.7 (CH_3), 14.1 (CH_3), 21.1 (CH_3), 22.4 (CH_2), 23.0 (CH_2), 28.4 (CH_2), 30.1 (CH_2), 30.9 (CH_2), 34.8 (CH_2), 37.8 (CH_2), 54.5 (CH_2), 55.8 (CH), 75.9 (CH), 126.7 (CH), 128.1 (CH), 128.7 (CH), 131.7 (C), 140.22 (C), 160.1 (C), 170.1 (C), 198.8 (C).

3.1.11. Aminocyclization of 9a. Following the above procedure for the aminocyclization of **5a** using enone **9a** (38 mg, 0.08 mmol) and carrying out the hydrogenation process for 36 h, the crude product was purified by chromatography (Al_2O_3, from 9:1 to 7:3 hexane/EtOAc) to give 7 mg (33%) of **10a** and 8 mg (38%) of **11a**, both as colorless oils.

(2*S*,3*R*,4a*S*,5*R*,8a*R*)-3-Acetoxy-5-butyl-2-methyldecahydroquinoline (**10a**). R_f=0.59 (Al_2O_3, 8:2 hexane/EtOAc); $[\alpha]_D^{20}$ −34.5 (*c* 0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, COSY) 0.90 (m, 1H, H-1′), 0.90 (t, *J*=6.8 Hz, 3H, H-4′), 1.10 (d, *J*=6.4 Hz, Me), 1.12 (masked, H-8*ax*), 1.20 (m, 4H, H-6 and H-2′), 1.25 (m, 2H, H-3′), 1.30 (m, H-4*ax*), 1.40 (m, H-4a), 1.48 (m, 2H, H-7), 1.5 (m, H-8*eq*), 1.70 (m, 2H, H-5*ax*, H-1′), 2.04 (s, 3H, OAc), 2.27 (ddd, *J*=12.4, 3.6, 2.8 Hz, H-4*eq*), 2.76 (dq, *J*=10, 6.5 Hz, H-2*ax*), 2.97 (br s, H-8a), 4.49 (td, *J*=10.4, 4.4 Hz, H-3*ax*); ^{13}C NMR see Table 1. HRFABMS calcd for $C_{16}H_{30}NO_2$ (M^++1) 268.2198, found 268.2202.

(2*S*,3*R*,4a*R*,5*S*,8a*R*)-3-Acetoxy-5-butyl-2-methyldecahydroquinoline (**11a**). R_f=0.28 (Al_2O_3, 8:2 hexane/EtOAc); $[\alpha]_D^{20}$ −4.3 (*c* 0.3 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, COSY) 0.88 (t, *J*=6.8 Hz, 3H, H-4′), 0.90 (masked, 1H, H-6*ax*), 0.94 (m, 2H, H-4*ax*, H-4a), 1.05 (masked, 2H, H-5 and H-1′), 1.07 (d, *J*=6.4 Hz, 3H, Me), 1.15 (m, 1H, H-8*ax*), 1.25 (m, 4H, H-2′, H-3′), 1.30 (m, 1H, H-7*ax*), 1.45 (m, 1H, H-1′), 1.75 (m, 3H, H-6, H-7, H-8), 2.05 (s, 3H, OAc), 2.20 (ddd, *J*=11, 9, 3 Hz, H-8a), 2.29 (dm, *J*=12 Hz, H-4*eq*), 2.70 (dq, *J*=10.4, 6.4 Hz, H-2*ax*), 4.41 (td, *J*=10.4, 4.8 Hz, H-3*ax*); ^{13}C NMR see Table 1.

HRFABMS calcd for $C_{16}H_{30}NO_2$ ($M^+ + 1$) 268.2198, found 268.2203.

3.1.12. Aminocyclization of 9b. Operating as in the cyclization of **9a**, from enone **11** (22 mg, 0.05 mmol) was obtained **11b** as an oil (6 mg, 52%) after chromatography (Al_2O_3, from 9:1 to 7:3 hexane/EtOAc).[31]

(2*S*,3*S*,4a*R*,5*S*,8a*R*)-3-Acetoxy-5-butyl-2-methyldecahydroquinoline (**11b**). R_f=0.13 (Al_2O_3, 8:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, COSY) 0.87 (t, J=6.8 Hz, 3H, H′-4), 0.98 (m, 4H, H-4a, H-5, H-6, H-1′), 1.06 (d, J=6.8 Hz, 3H, Me), 1.15 (m, 2H, H-4*ax*, H-8*ax*), 1.25 (m, 4H, H-2′ and H-3′), 1.30 (m, H-7*ax*), 1.45 (m, 1H, H-1′), 1.77 (m, 3H, H-8*eq*, H-7*eq*, H-6*eq*), 2.11 (s, 3H, OAc), 2.20 (dt, J=10, 3.2 Hz, H-4*eq*), 2.27 (td, J=10, 3 Hz, H-8a), 2.90 (qd, J=6.4, 1.6 Hz, H-2*ax*), 4.91 (ddd, J=3.2, 3.2, 1.6 Hz, H-3*eq*); ^{13}C NMR see Table 1. HRFABMS calcd for $C_{16}H_{30}NO_2$ ($M^+ + 1$) 268.2198, found 268.2194.

Acknowledgements

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31. Minor signals (approximately in a 1:3 ratio with respect to the major compound isolated **11b**) in the NMR of the crude reaction mixture at δ 4.76 (ddd, J=3.2, 3.2, 1.6 Hz, H-3*eq*), 2.96 (m, H-8a), 2.66 (qd, J=6.4, 3.2 Hz, H-2*ax*), and 2.16 (dm, J=12 Hz, H-4*eq*) were observed. They could be attributed to the isomer **10b**, which cannot be isolated in pure form. The isolated decahydroquinoline **11b** remains partially contaminated by this compound even after repeating the chromatography.

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Stereocontrolled palladium(0)-catalyzed preparation of unsaturated azidosugars: an easy access to 2- and 4-aminoglycosides

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Abstract—The palladium-catalyzed substitution of alkyl 4,6-di-*O*-acetyl-α-D-*erythro*-hex-2-eno-pyranosides using NaN_3 as the nucleophile gave predominantly the corresponding alkyl 2-azido-2,3,4-trideoxy-α-D-*threo*-hex-2-enopyranosides in the presence of $Pd(PPh_3)_4$. However, alkyl 6-*O*-acetyl-4-azido-2,3,4-trideoxy-α-D-*erythro*-hex-2-enopyranosides were obtained as the major products using $Pd(PPh_3)_4$ as the catalyst in the presence of dppb as the added ligand. Conversely, alkyl 6-*O*-(*tert*-butyldimethylsilyl)-4-*O*-methoxycarbonyl-2,3-dideoxy-α-D-hex-2-enopyranosides gave exclusively alkyl 4-azido-6-*O*-(*tert*-butyldimethylsilyl)-2,3,4-trideoxy-α-D-*erythro*-hex-2-enopyranosides in the presence of $Pd_2(dba)_3/PPh_3$ as the catalyst and Me_3SiN_3 as the nucleophile. The bis-hydroxylation followed by hydrogenation of ethyl 4-azido-2,3,4-trideoxy-α-D-*erythro*-hex-2-enopyranoside afforded the corresponding 4-amino-α-D-mannopyranoside, when propyl 2-azido-2,3,4-trideoxy-α-D-*threo*-hex-3-enopyranoside gave the 2-amino-α-D-altropyranoside under the same conditions.

1. Introduction

Various aminosugars are present in nature.[1,2] They also represent an important class of carbohydrate units, some of them being found in numerous oligosaccharides and glycoconjugates.[3–14] For instance 4-aminosugars are major structural elements in some compounds exhibiting very important biological properties such as pyranmycin,[15,16] acarbose,[17–20] apramycin,[21] apicamycin,[22] aebramycin,[21,23,24] and trehalosamine derivatives.[25–28]

Due to the very large spectrum of their possible applications in chemistry, biochemistry, medicine, as well as pharmaceutical fields,[3,15,16,29–34] extensive studies have thus been performed towards the synthesis of these aminosugars.

One of the most convenient routes to aminosugars is the introduction on the appropriate carbohydrate of a nitrogen substituent via the use of a tethered nitrogen nucleophile.[35] The amino group was most often introduced and masked via a nucleophilic displacement of halides or sulfonates as an azido group, which was finally converted into the amino group at the end of the synthesis.[15,16,36–43]

In connection with our interest on the valorisation of unsaturated carbohydrates as starting materials for the synthesis of biologically active compounds, and particularly the metal-catalyzed functionalization of these unsaturated compounds,[44–55] we expected that the azido group could be introduced stereospecifically at position 4 of 2,3-unsaturated substrates under very mild conditions using a palladium-catalyzed reaction. Secondary and tertiary amines have already been introduced on this position under palladium-catalysis.[56,57] Palladium-catalyzed azidation of allylic esters has also been investigated using sodium azide[58,59] or trimethylsilyl azide as the nucleophile.[60–62] These unsaturated 4-azido-2,3-dideoxyhexopyranosides would be valuable starting materials for the synthesis of 4-amino-2,3-dideoxyhexopyranosides or various 4-aminohexopyranosides.

In this paper, we described the methodologies used for the introduction of the azido function at C-4 and C-2 on 2,3-dideoxyhex-2-enopyranosides and the transformation of the latter to some aminosugars.

2. Results and discussion

The starting alkyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosides **1a–c** were prepared via a Ferrier reaction of 3,4,6-tri-*O*-acetyl-D-glucal with the corresponding alcohol (Scheme 1).[63,64] Deacetylation of unsaturated carbohydrates

Keywords: Palladium catalyst; Azidation; Alkyl azidohexenopyranoside; Amino carbohydrate.
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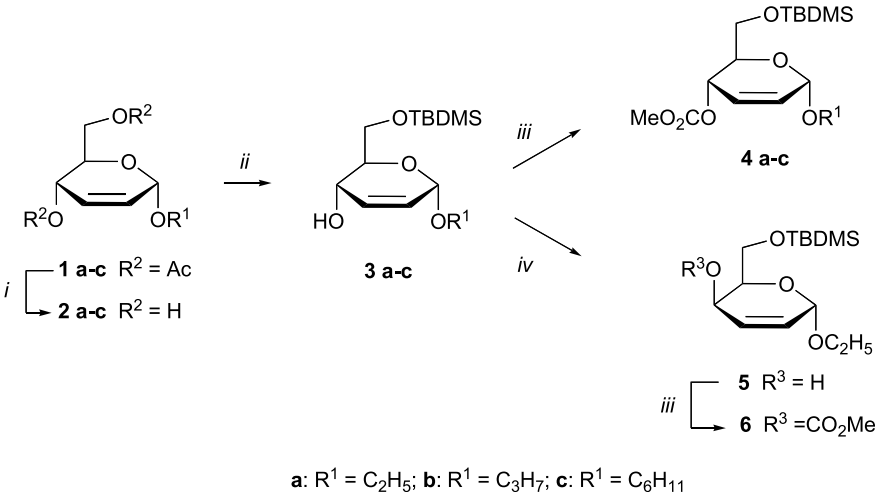
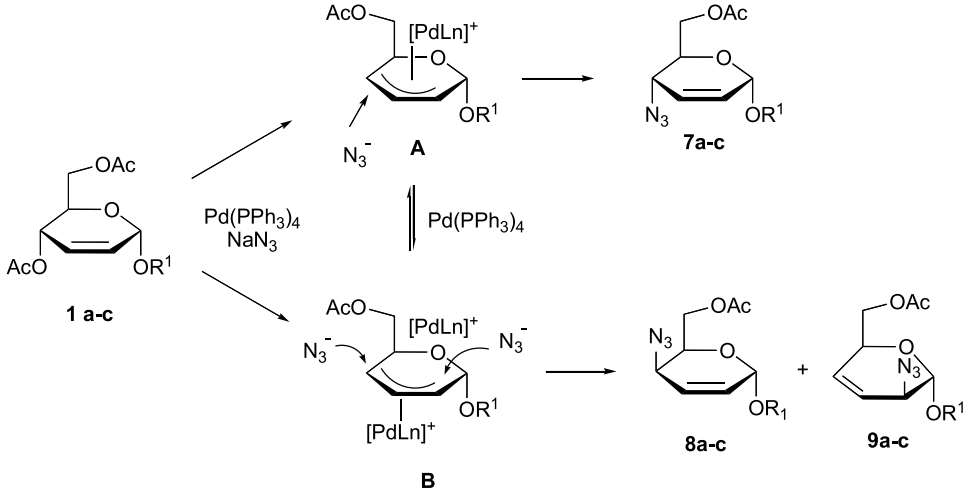


Scheme 1. Reagents and conditions: i: cat. MeONa, MeOH; ii: *tert*-$BuMe_2SiCl$, imidazole, DMF, 0 °C; iii: CH_3OCOCl, pyridine, DMAP, CH_2Cl_2, 0 °C; iv: PPh_3, $ClCH_2CO_2H$, diethyl azodicarboxylate, toluene, then cat. MeONa, MeOH.

1a–c with sodium methoxide in methanol (Zemplèn procedure[65]) afforded quantitatively the corresponding unsaturated diols **2a–c**. The regioselective monoprotection of the primary hydroxyl function of compounds **2a–c** with TBDMSCl gave the corresponding monosilylated unsaturated derivatives **3a–c** in quite good yields (Scheme 1). Reaction of compounds **3a–c** with methyl chloroformate in the presence of pyridine afforded the corresponding unsaturated carbonates **4a–c**. The *threo* derivative **6** was obtained from the *erythro* derivative **3a** in a two-step sequence, involving an inversion of configuration at C-4 via a Mitsunobu reaction using chloroacetic acid in presence of triphenylphosphine and diethyl azodicarboxylate, followed by saponification with sodium methoxide in methyl alcohol, and subsequent treatment with methylchloroformate in the presence of pyridine.

The azidation of unsaturated carbohydrates **1a–c** was first examined in detail using $Pd(PPh_3)_4$ as the catalyst and sodium azide as the nucleophile as a typical example (Scheme 2), the reaction being performed in a THF/H_2O mixture at 50 °C. The results summarized in Table 1 showed that azidation occurred in 72–78% yields after column chromatography, affording a mixture of three unsaturated azides **7–9 a–c** in a quite similar ratio whatever the aglycon present; however, the expected 4-azido compound **7** was the minor one and 2-azido compound **9** was the major product (Table 1, entries 1–3). Even performing the azidation reaction in the presence of $Pd(PPh_3)_4$ and 5 equiv of PPh_3 gave practically the same results (Table 1, entries 4 and 5). Fortunately, substitution of PPh_3 by the chelating bidentate ligand dppb [or 1,4-bis(diphenylphosphino)butane] (2 equiv of ligand per palladium) resulted in a very highly regio- and stereoselectivity, the expected unsaturated azide **7** being obtained with chemical yields up to 92%, the two other allylic azides **8** and **9** being observed as traces (Table 1, entries 6–8). It is noteworthy that adding more dppb (Table 1, entry 9) gave the same ratio of isomers **7c–9c**, although the catalyst seemed more sluggish. The same behaviour was observed using $Pd_2(dba)_3$ and 4 dppb as the catalyst (Table 1, entry 10).

The formation of these three isomers could be rationalized



Scheme 2.

Table 1. Palladium-catalyzed azidation of carbohydrates **1a–c** using NaN_3 as the nucleophile

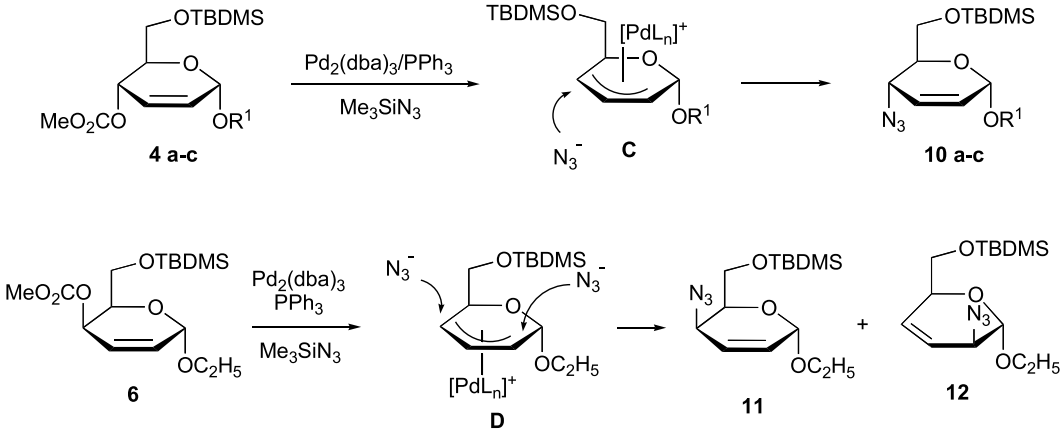
Entry	Carbohydrate	Catalyst	Time (h)	Yield (%)[a]	Ratio **7**:**8**:**9**[b]
1	**1a**	$Pd(PPh_3)_4$	1	76	14:32:54
2	**1b**	$Pd(PPh_3)_4$	1	72	15:32:53
3	**1c**	$Pd(PPh_3)_4$	1	78	14:36:50
4	**1a**	$Pd(PPh_3)_4$+5 PPh_3	2	69	14:30:56
5	**1b**	$Pd(PPh_3)_4$+5 PPh_3	2	68	19:29:52
6	**1a**	$Pd(PPh_3)_4$+2 dppb	1	70	91:2:7
7	**1b**	$Pd(PPh_3)_4$+2 dppb	1	69	92:4:4
8	**1c**	$Pd(PPh_3)_4$+2 dppb	1	72	86:8:6
9	**1c**	$Pd(PPh_3)_4$+4 dppb	1	46	76:13:11
10	**1a**	$Pd_2(dba)_3$+4 dppb	2	45	84:11:5

[a] Calculated on the mixture of compounds **7–9** after column chromatography.
[b] Determined by ^1H NMR on the mixture.

according to Scheme 2. The first step is the oxidative addition of the unsaturated carbohydrate **1** to Pd(0) species giving the (π-allyl)palladium intermediate **A** with inversion of configuration at the allylic carbon. The attack of N_3^- occurs *trans* to the palladium on the π-allyl complex **A** at C-4 only, the C-2 position being crowded by the aglycon moiety, affording allylic azide **7**. However, this π-allyl palladium complex **A** could be in equilibrium with the π-allyl palladium complex **B** formed by the attack of the palladium species on complex **A**. The attack of the azide ion on complex **B** afforded the two unsaturated azides **8** and **9** with inversion of configuration; the formation of azide **9** as the major product is probably due also to steric hindrance at C-4, the position at C-2 being less crowded. Another possibility is the isomerization of the allylic azides in the presence of $Pd(PPh_3)_4$. In order to underline this isomerization, the three allylic azides **7a**, **8a**, and **9a** were treated separately under similar reaction conditions (THF/H_2O) in the presence of $Pd(PPh_3)_4$ at 50 °C for 1 h. Compound **7a** gave a 94:3:3 mixture of **7a**, **8a**, and **9a**, compound **8a** a 11:67:22 mixture of **7a**, **8a**, and **9a**, and compound **9a** a 18:30:52 mixture of **7a**, **8a**, and **9a**. Isomerization effectively occurred, but it seems that this reaction is slow. It is to be noticed that the thermal isomerization of allylic azide **9a** under the same conditions but without added $Pd(PPh_3)_4$ does not occur, only 3% of compound **8a** being formed; however, heating the mixture at 70 °C for 14 h increased the amount of **8a** to 26%. The difference observed using PPh_3 or dppb as the ligand, quite similar to the results of Murahashi and coll.[58] could be related to the bulkiness of the palladium catalyst, which prevents the attack of the free palladium complex on the π-allyl palladium intermediate **A**.

We then examined the azidation of alkyl 6-*O*-(*tert*-butyldimethylsilyl)-4-*O*-methoxycarbonyl-2,3-dideoxy-α-D-hex-2-enopyranosides (**4a–c**) using Me_3SiN_3 as the nucleophile in the presence of Pd_2dba_3 or tris(dibenzylideneacetone)dipalladium and PPh_3 in THF at 50 °C (Scheme 3). Starting from unsaturated carbohydrate **4a**, the highest conversion and chemical yield were obtained using 10% Pd and a ratio [PPh_3]/[Pd]=4, with a chemical yield up to 73% for **10a** after column chromatography (Table 2, entries 1–3). Using these optimised conditions, the unsaturated carbohydrates **4b** and **4c** gave the corresponding unsaturated azides **10b** and **10c** in 69 and 71% chemical yields, respectively. It is to be noticed that the sole formation of the azide **10** was observed under these conditions; this could be due probably to the use of the more reactive allylic carbonate instead of the acetate, avoiding the presence of any palladium(0) complex in solution.[66] The retention of configuration resulted from an *exo* attack of the nucleophile at the C-4 of the π-allyl palladium complex **C**.

The structures of compounds **7–10** were assigned on the basis of their ^1H and ^{13}C NMR spectral analysis. The vicinal coupling constants $J_{4,5}$=9.4–10.0 Hz observed for the hydrogen atom H-4 for compounds **7a–c** and **10a–c**



Scheme 3.

Table 2. Palladium-catalyzed azidation of carbohydrates **4a–c** using Me_3SiN_3 as the nucleophile

Entry	Carbohydrate	% Pd	$[PPh_3]/[Pd]$	Time (h)	Conversion of **4** (%)[a]	Yield of **10** (%)[b]
1	**4a**	5	2/1	24	40	15
2	**4a**	5	4/1	5	80	54
3	**4a**	10	4/1	2	100	73
4	**4b**	10	4/1	2	100	69
5	**4c**	10	4/1	2	100	71

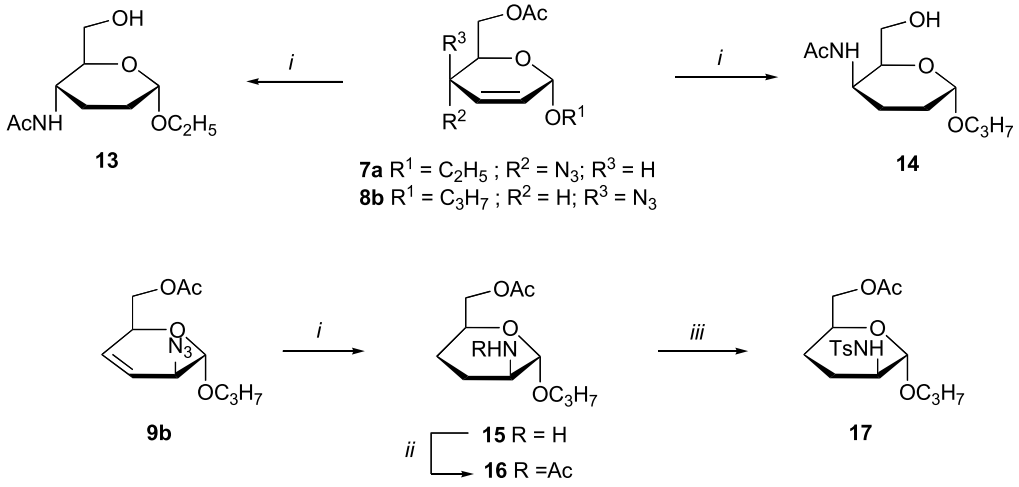
[a] Determined by ^{1}H NMR on the crude product.
[b] Chemical yield of pure product **10** after column chromatography.

indicated a *trans* diaxial relationship between H-4 and H-5, proving the *erythro* configuration. Conversely, the signal for the same proton H-4 in compounds **8a–c** appeared at $\delta = 3.35$–3.36 ppm, with a coupling constant $J_{4,5} = 1.5$–2.3 Hz, characteristic for a *cis* relationship between H-4 and H-5, and therefore, a *threo* configuration for **8**. We noticed also that the H-4 signal for *erythro* compounds **7a–c** and **10a–c** appeared at higher δ values than that of the analogous hydrogen atom for *threo* compounds **8a–b** ($\Delta\delta = 0.53$ ppm), owing to the respective axial and equatorial orientation of H-4. The ^{13}C NMR spectra, and particularly the chemical shift of the anomeric carbon, also gave some informations. These signals appeared at δ 99.2, 99.3 and 97.3 ppm for compounds **9a**, **9b**, **9c**, respectively, compared to 94.2, 94.4 and 92.8 ppm for compounds **8a**, **8b**, and **8c**; this is characteristic for a 3,4-insaturation versus a 2,3-insaturation in enopyranose chemistry.[56] In addition, a very weak $J_{1,2}$ coupling constant observed for compounds **8a–c** is also in agreement with 2,3-enopyranosides having the α-D-*threo* configuration.[56] Further, spectral data for compounds **8** and **9** are in agreement with those published for quite similar structures.[42]

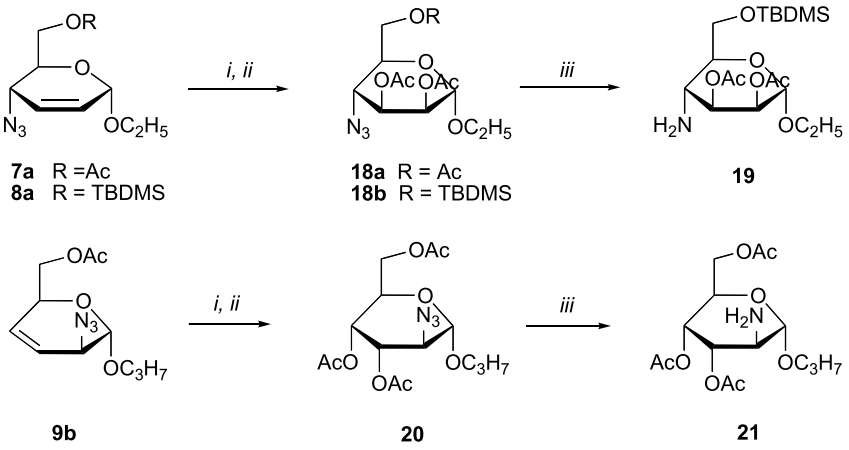
In order to confirm unambiguously the assigned configurations, azidocarbohydrates **7a**, **8b**, and **9b**, were transformed to the corresponding saturated amines **13**, **14**, and **15** (Scheme 4). Reduction of 4-azido-α-D-hex-2-enopyranosides **7a** and **8b**, having, respectively, the *erythro* and *threo* configuration, with hydrogen in the presence of palladium on charcoal gave the corresponding saturated compounds **13** and **14** bearing a 4-acetamido group in quite good chemical yields. Such $O \rightarrow N$ migration of an acetate during hydrogenation in carbohydrate chemistry has already been observed.[67] The ^{1}H an ^{13}C NMR spectra are in good agreement with the proposed structures. Coupling constants $J_{5,4} = 9.8$ and 1.4 Hz are observed for compounds **13** and **14**, respectively, characteristic of a *trans* and a *cis* relationship for H-4 and H-5. The IR spectra showed two amide bands (1640, 1570 cm^{-1}) next to C=O vibration (1730 cm^{-1}), as well as a OH band (3300 cm^{-1}). Furthermore, the ^{1}H NMR spectra showed only one proton for the N*H*Ac signal as a doublet (δ 5.48 and 6.27 ppm for **13** and **14**, respectively).

Reduction of unsaturated 2-azido-3,4-dideoxy-α-D-*threo*-pyranoside **9b** gave quantitatively the 2-amino-2,3,4-α-D-*threo*-pyranoside **15** that was transformed into the acetamido and toluenesulfonamido derivatives **16** and **17** (Scheme 3). The configuration of toluenesulfonamido derivative **17** was confirmed by NMR. The H-2 signal appeared as a dd with coupling constants $J_{2,3eq} = J_{2,3ax} = 3.0$ Hz, and $J_{2,1} = 0$ Hz, suggesting that H-2 is equatorial. Moreover, the relation between H-2 and NH was clearly showed using a H,H COSY spectrum, when a H,H NOESY experiment showed a NOE contact due to a *syn* relationship, between NH and H-1, H-3$_{eq}$ and H-4$_{ax}$.

We finally, turned our attention to the palladium-catalyzed reaction of ethyl 6-*O*-(*tert*-butyldimethylsilyl)-4-*O*-methoxycarbonyl-2,3-dideoxy-α-D-*threo*-hex-2-enopyranoside (**6**) with Me_3SiN_3 under the above optimized conditions (Scheme 3). A 40:60 mixture of 4-azido-2,3,4-trideoxy-α-D-*threo*-hex-2-enopyranoside **11** and 2-azido-2,3,4-trideoxy-α-D-*threo*-hex-2-enopyranoside **12** was obtained in 76% chemical yield. The structures of compounds **11** and **12** were assigned from the ^{1}H and ^{13}C NMR spectra of the mixture, which showed some similarities with the spectra of



Scheme 4. Reagents and conditions: i: H_2 (1 bar), Pd/C, CH_3OH; ii: Ac_2O, pyridine, 0 °C; iii: TsCl, pyridine, CH_2Cl_2, 0 °C.



Scheme 5. Reagents and conditions: i: cat. OsO4, NMO, acetone/water, rt; ii: Ac_2O, pyridine; iii: H_2, Pd/C, CH_3CO_2Et.

compounds **8a** and **9a**, respectively. However, since these two compounds **11** and **12** could not be separated, the mixture was desilylated using *n*-$Bu_4NF\cdot 3H_20$ in THF, and the resulting mixture was acetylated using $(CH_3CO)_2O$ in C_5H_5N to give in 77% global yield a mixture of two compounds, whose characteristics, after separation, are similar to those of compounds **8a** and **9a**. The formation of these two regioisomers having the *threo* configuration resulted from the attack of the nucleophile at the two termini C-4 and C-2 of the π-allyl complex **D**; such behaviour has already been observed in palladium-catalyzed alkylation starting from the *threo* derivative.[49]

Ethyl 4-azido-α-D-*erythro*-hex-2-enopyranosides **7a** and **10a** were subjected to the bis-hydroxylation reaction in the presence of a catalytic amount of OsO_4, followed by acetylation of the obtained mixture (Scheme 5). As expected ethyl 4-azido-4-deoxy-α-D-mannopyranosides **18a** and **18b** were obtained in 91 and 85% chemical yield, respectively, as the unique products. These compounds resulted from the bishydroxylation on the less hindered side of the double bond, as expected from preceding results in this field.[68,69] The assigned configurations are mainly based on the coupling constant $J_{4,5}=10.3$, 10.6 Hz, and $J_{3,4}=9.9$, 10.6 Hz (δ 3.82 and 3.88 ppm, respectively, for H-4) for **18a** and **18b**, characteristics of an axial–axial disposition for H-3, H-4 and H-5. Moreover reduction of the azido derivative **18b** with molecular hydrogen in the presence of Pd/C afforded ethyl 4-amino-4-deoxy-α-D-mannopyranoside **19** in 87% yield, characterized again by the axial–axial couplings $J_{4,5}=J_{3,4}=10.5$ Hz.

Bis-hydroxylation of propyl 2-azido-2,3,4-trideoxy-α-D-*threo*-hex-3-enopyranoside **9b** under the same conditions gave, after acetylation, the unique propyl 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-altropyranoside (**20**) in 77% yield, which was reduced in 80% yield to the corresponding triacetylated 2-aminoaltropyranoside **21** (Scheme 5). The bis-hydroxylation occurred again on the less hindered side of the double bond of the azido carbohydrate **9b**. The altrose configuration is consistent with the NMR data. The coupling constant $J_{4,5}=8.1$ Hz for H-4 at δ 5.24 ppm is in agreement with an axial–axial disposition of H-4 and H-5. Moreover, a H,H NOESY experiment showed no NOE contact between H-5 and H-3, which should be expected if the bis-hydroxylation occurred on the other side of the double bond.

3. Conclusion

In conclusion, the palladium-catalyzed substitution of allylic acetate or carbonate derivatives of alkyl α-D-*erythro*-hex-2-enopyranosides is a useful methodology for the preparation of unsaturated 4-azido or 2-azidopyranosides. The selectivity of the palladium-catalyzed substitution is dependent on the nature of the catalyst used and the leaving group at C-4 of the carbohydrate. Alkyl 4,6-di-*O*-acetyl-α-D-*erythro*-hex-2-eno-pyranosides gave predominantly alkyl 2-azido-2,3,4-trideoxy-α-D*threo*-hex-2-enopyranosides in the presence of $Pd(PPh_3)_4$, when alkyl 6-*O*-acetyl-4-azido-2,3,4-trideoxy-α-D-*erythro*-hex-2-enopyranosides were obtained as the major products in the presence of dppb as the added ligand. Conversely, alkyl 6-*O*-(*tert*-butyldimethylsilyl)-4-*O*-methoxycarbonyl-2,3-dideoxy-α-D-hex-2-enopyranosides gave exclusively alkyl 4-azido-6-*O*-(*tert*-butyldimethylsilyl)-2,3,4-trideoxy-α-D-*erythro*-hex-2-enopyranosides in the presence of Pd(0)/PPh_3 as the catalyst. These readily accessible 2- or 4-azido unsaturated carbohydrates are key intermediates for the preparation of aminocarbohydrates. For example, the bishydroxylation of ethyl 4-azido-2,3,4-trideoxy-α-D-*erythro*-hex-2-enopyranoside **10a** afforded 4-amino-α-D-mannopyranoside **19**, when propyl 2-azido-2,3,4-trideoxy-α-D-*threo*-hex-3-enopyranoside **9b** gave the corresponding 2-amino-α-D-altropyranoside **21** under the same conditions.

4. Experimental

Melting points were determined on a Buchi melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin Elmer Model 241 polarimeter. The IR spectra were obtained on a Perkin Elmer Model 681. ^1H (300 MHz) and ^{13}C NMR (75.5 MHz) spectra were recorded on a Brucker AM 300 spectrometer; chemical shifts are reported with reference to $SiMe_4$ or $CDCl_3$ as an internal standard. Exact mass spectra were recorded on a Finnigan Mat 95 XL spectrometer. Thin layer chromatography (TLC) was carried out on plates coated with silica

gel (60 F-254), and column chromatography on Silica gel 60 or Silica Florisil Merck, the ratio of solvents being measured in volume.

Alkyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosides (**1a–c**) and alkyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosides (**2a–c**) have been prepared according to literature procedures.[53,64,70,71]

4.1. General procedure for the preparation of alkyl 6-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosides (3a–c)

To a solution of unsaturated carbohydrate **2** (1 mmol) and imidazole (75 mg, 1.1 mmol) in DMF (4 mL) maintained at 0 °C was slowly added *tert*-butyldimethylsilyl chloride (166 mg, 1.1 mmol). The solution was stirred at rt until TLC showed no more starting material. After addition of water (15 mL), and extraction with ether (3× 15 mL), the organic layer was dried. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography using petroleum ether/EtOAc (9:1) as the eluent to give the corresponding alkyl 6-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside **3**.

4.1.1. Ethyl 6-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (3a). Yield 83%; oil; R_f=0.4 ($CHCl_3$); $[\alpha]_D^{20}$ +23 (*c* 1.0, CH_2Cl_2) [lit.[72] +22.1 (*c* 1.0, CH_2Cl_2)]; the ^1H and ^{13}C NMR data are in agreement with the literature.[72]

4.1.2. Propyl 6-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (3b). Yield 84%; oil; R_f=0.4 ($CHCl_3$); $[\alpha]_D^{20}$ +25 (*c* 1.5 CH_2Cl_2). IR: 3500, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$):δ −0.01 (s, 6H, $SiMe_2$), 0.80 (s, 9H, CMe_3), 1.51 (m, 2H, CH_2CH_3), 2.80 (d, 1H, OH, *J*=4.3 Hz), 3.33 (dt, 1H, OCH_2CH_2, *J*=9.4, 6.6 Hz), 3.55–3.72 (m, 3H, OCH_2CH_2, H-5, H-6), 3.79 (dd, 1H, H-6′, *J*=9.8, 5.1 Hz), 4.04 (ddd, 1H, H-4, *J*=6.3, 4.3, 2.0 Hz), 4.82 (br s, 1H, H-1), 5.59 (ddd, 1H, H-2, *J*=10.2, 2.5, 2.0 Hz), 5.80 (br d, 1H, H-3, *J*=10.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −5.1, 10.9, 18.5, 23.2, 26.2, 64.5, 65.6, 70.4, 71.6, 94.3, 126.2, 133.5. Anal. Calcd for $C_{15}H_{30}O_4Si$: C, 59.56; H, 10.0. Found: C, 59.15; H, 10.39.

4.1.3. Cyclohexyl 6-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (3c). Yield 80%; oil; R_f=0.5 ($CHCl_3$); $[\alpha]_D^{20}$ +31 (*c* 1.0, $CHCl_3$); IR: 3450, 1060 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ −0.1 (s, 6H, $SiMe_2$), 0.81 (s, 9H, CMe_3), 1.27–1.80 (m, 10H, 5× CH_2), 2.70 (d, 1H, OH, *J*=4.3 Hz), 3.50 (m, 1H, $C_5H_{10}CHO$), 3.65–3.78 (m, 3H, H-5, H-6, H-6′), 4.01 (m, 1H, H-5), 4.98 (br s, 1H, H-1), 5.60 (ddd, 1H, H-2, *J*=10.2, 2.6, 2.2 Hz), 5.80 (br d, 1H, H-3, *J*=10.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −5.1, 18.6, 24.0, 24.6, 26.0, 26.2, 34.1, 34.3, 65.7, 67.4, 70.5, 76.5, 92.8, 127.0, 132.8. Anal. Calcd for $C_{18}H_{34}O_4Si$: C, 63.11; H, 10.00. Found: C, 62.93; H, 10.02.

4.2. General procedure for the preparation of alkyl 6-*O*-(*tert*-butyldimethylsilyl)-4-*O*-methoxycarbonyl-2,3-dideoxy-α-D-hex-2-enopyranoside (4a–c)

To a solution of unsaturated carbohydrate **3** (1.2 mmol) in CH_2Cl_2 (10 mL) maintained at 0 °C was added pyridine, (200 mg, 2.4 mmol), DMAP (50 mg), and methyl chloroformate (227 mg, 2.4 mmol). After being stirred at rt for 24 h, the solution was diluted with water (5 mL) and extracted with CH_2Cl_2 (3×15 mL). Evaporation of the solvent followed by column chromatography gave the corresponding carbonate **4** as an oil.

4.2.1. Ethyl 6-*O*-(*tert*-butyldimethylsilyl)-4-*O*-methoxycarbonyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (4a). Yield 74%; oil; R_f=0.8 ($CHCl_3$); $[\alpha]_D^{20}$ +91 (*c* 1.1, CH_2Cl_2); IR: 1750, 1270 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.01 (s, 6H, $SiMe_2$), 0.8 (s, 9H, CMe_3), 1.12 (t, 3H, CH_3CH_2, *J*=7.2 Hz), 3.49 (dq, 1H, OCH_2CH_3, *J*=9.7, 7.0 Hz), 3.73 (s, 3H, CH_3O), 3.68–3.75 (m, 2H, H-6, H-6′), 3.79 (dq, 1H, OCH_2CH_3, *J*=9.4, 7.1 Hz), 3.89 (ddd, 1H, H-5, *J*=9.7, 4.3, 3.0 Hz), 4.96 (br s, 1H, H-1), 5.10 (br dd, 1H, H-4, *J*=9.4, 1.4 Hz), 5.77 (ddd, 1H, H-2, *J*=10.2, 2.6, 2.6 Hz), 5.89 (br d, 1H, H-3, *J*=10.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −5.1, 15.6, 18.8, 26.3, 55.3, 63.0, 64.4, 69.5, 94.4, 128.7, 129.1, 155.6. Anal. Calcd for $C_{16}H_{30}O_6Si$: C, 55.46; H, 8.73. Found: C, 55.68; H, 8.56.

4.2.2. Propyl 6-*O*-(*tert*-butyldimethylsilyl)-4-*O*-methoxycarbonyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (4b). Yield 79%; oil; R_f=0.7 ($CHCl_3$); $[\alpha]_D^{20}$ +92 (*c* 1.0, CH_2Cl_2); IR: 1750, 1270 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ −0.01 (s, 6H, $SiMe_2$), 0.84 (s, 9H, CMe_3), 1.16 (t, 3H, CH_2CH_3, *J*=7.1 Hz), 1.55 (m, 2H, CH_2CH_3), 3.38 (dt, 1H, OCH_2CH_2, *J*=13.1, 6.6 Hz), 3.48 (dt, 1H, OCH_2CH_2, *J*=13.1, 7.0 Hz), 3.71 (s, 3H, OCH_3), 3.62–3.82 (m, 2H, H-6, H-6′), 3.88 (m, 1H, H-5), 4.94 (br s, 1H, H-1), 5.08 (br d, 1H, H-4, *J*=9.4 Hz), 5.75 (ddd, 1H, H-2, *J*=10.2, 2.6, 2.3 Hz), 5.87 (br d, 1H, H-3, *J*=10.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −5.2, 10.9, 18.6, 23.2, 26.2, 55.0, 62.9, 64.1, 69.3, 69.4, 94.2, 128.6, 128.9, 155.4. Anal. Calcd for $C_{17}H_{32}O_6Si$: C, 56.64; H, 8.95. Found: C, 57.00; H, 9.28.

4.2.3. Cyclohexyl 6-*O*-(*tert*-butyldimethylsilyl)-4-*O*-methoxycarbonyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (4c). Yield 69%; oil; R_f=0.7 ($CHCl_3$); $[\alpha]_D^{20}$ +88 (*c* 1.0, CH_2Cl_2); IR: 1750, 1270 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ −0.1 (s, 6H, $SiMe_2$), 0.91 (s, 9H, CMe_3), 1.20–1.90 (m, 10H, 5×CH_2), 3.80 (s, 3H, OCH_3), 3.60–3.90 (m, 3H, $C_5H_{10}CHO$, H-6, H-6′), 4.02 (ddd, 1H, H-5, *J*=9.4, 4.3, 3.2 Hz), 5.16 (dd, 1H, H-4, *J*=9.4, 1.7 Hz), 5.19 (br s, 1H, H-1), 5.82 (ddd, 1H, H-2, *J*=10.1, 2.5, 1.7 Hz), 5.95 (br d, 1H, H-3, *J*=10.1 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −5.1, 18.8, 24.6, 24.8, 26.0, 26.3, 32.3, 34.1, 55.3, 63.2, 69.4, 69.6, 76.3, 92.6, 128.8, 129.3, 155.6. Anal. Calcd for $C_{20}H_{36}O_6Si$: C, 59.97; H, 9.06. Found: C, 60.31; H, 9.49.

4.2.4. Ethyl 6-*O*-(*tert*-butyldimethylsilyl)-4-*O*-methoxycarbonyl-2,3-dideoxy-α-D-*threo*-hex-2-enopyranoside (6). To a solution of unsaturated carbohydrate **3a** (1.3 g, 4.8 mmol) in toluene (2.5 mL) was added triphenylphosphine (2.5 g,

9.6 mmol) and chloroacetic acid (0.9 g, 9.6 mmol). After being stirred for 30 min at rt, diethyl azodicarboxylate (1.7 g, 9.6 mmol) was added and the solution was stirred for 24 h. The solution was filtered, then washed with hexane (10×5 mL) and concentrated. The resulting oil was dissolved in methanol (30 mL) and treated with a catalytic amount of sodium methanolate. After 2 h, the solution was concentrated, the oil was dissolved in CH_2Cl_2 (30 mL) and the solution washed with a 0.1 N aqueous solution of ammonium chloride (10 mL). Evaporation of the solvent under reduced pressure gave the *threo* derivative **5** (950 mg, 73% yield) as an oil, whose characteristics were in agreement with the literature.[13] Following the procedure described for **4**, the carbonate **6** was obtained (750 mg, 48% from **3a**) as an oil. R_f=0.6 (eluent hexane/ethyl acetate 9:1); $[\alpha]_D^{20}$ −148 (*c* 1, CH_2Cl_2); IR: 1750, 1270 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ −0.06 (s, 3H, SiMe), −0.01 (s, 3H, SiMe), 0.82 (s, 9H, CMe_3), 1.17 (t, 3H, CH_3CH_2, J=7.2 Hz), 3.48 (dq,1H, OCH_2CH_3, J=9.6, 7.2 Hz), 3.65–3.75 (m, 2H, H-6, H-6′), 3.71 (s, 3H, OCH_3), 3.79 (dq,1H, OCH_2CH_3, J=9.6, 7.2 Hz), 4.13 (ddd, 1H, H-5, J=6.9, 6.6, 2.3 Hz), 4.82 (dd, 1H, H-4, J=5.5, 2.3 Hz), 4.98 (d, 1H, H-1, J=3.0 Hz), 5.97 (dd, 1H, H-2, J=10.0, 3.0 Hz), 6.13 (dd, 1H, H-3, J=10.0, 5.5 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −5.3, −5.1, 15.6, 18.5, 26.1, 55.1, 61.9, 64.2, 66.6, 69.5, 94.0, 125.3, 131.8, 155.8. Anal. Calcd for $C_{16}H_{30}O_6Si$: C, 55.46; H, 8.73. Found: C, 55.23; H, 8.75.

4.3. Palladium-catalyzed azidation using sodium azide. General procedure

The catalytic system was prepared by stirring for 1 h in a Schlenk tube under argon the palladium complex (3%) and the corresponding ligand in tetrahydrofuran (3 mL). This solution was added under argon to a Schlenk tube containing the unsaturated carbohydrate **1** (1 mmol) and sodium azide (72 mg, 1.1 mmol) in a mixture THF/water (3 mL/2 mL). The mixture was stirred at 50 °C for 1 h, and then extracted with ether (3×10 mL), and the combined extracts were washed successively with 1 M HCl (30 mL), saturated $NaHCO_3$ (30 mL) and brine (30 mL). The organic layer was dried over Na_2SO_4. Removal of the solvent under reduced pressure gave a residue that was submitted to column chromatography on silica gel using petroleum ether/EtOAc as the eluent to afford the pure corresponding allyl azide **7**, **8** and **9**.

4.3.1. Ethyl 6-*O*-acetyl-4-azido-2,3,4-trideoxy-α-D-*erythro*-hex-2-enopyranoside (7a). Oil; R_f=0.6 (petroleum ether/EtOAc 4:1); $[\alpha]_D^{20}$ +219 (*c* 1.0, CH_2Cl_2); IR: 2100, 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, 3H, CH_3CH_2, J=7.2 Hz), 2.11 (s, 3H, CH_3CO), 3.58 (dq, 1H, OCH_2CH_3, J=9.6, 7.0 Hz), 3.80 (dq, 1H, OCH_2CH_3, J=9.6, 7.2 Hz), 3.89 (br d, 1H, H-4, J=10.0 Hz), 3.94 (ddd, 1H, H-5, J=10.0, 4.4, 2.4 Hz), 4.28 (dd, 1H, H-6′, J=11.9, 4.4 Hz), 4.35 (dd, 1H, H-6, J=11.9, 2.4 Hz), 5.03 (d, 1H, H-1, J=2.3 Hz), 5.94 (ddd, 1H, H-2, J=10.3, 2.3, 1.7 Hz), 6.00 (br d, 1H, H-3, J=10.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.6, 21.1, 54.8, 63.8, 64.6, 68.0, 94.4, 128.0, 129.3, 171.0. Anal. Calcd for $C_{10}H_{15}O_4N_3$: C, 49.79; H, 6.27. Found: C, 49.99; H, 6.37.

4.3.2. Ethyl 6-*O*-acetyl-4-azido-2,3,4-trideoxy-α-D-*threo*-hex-2-enopyranoside (8a). Oil; R_f=0.6 (petroleum ether/EtOAc 4:2); $[\alpha]_D^{20}$ −255 (*c* 2.0, CH_2Cl_2); IR: 2100, 1745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, 3H, CH_3CH_2, J=7.0 Hz), 2.09 (s, 3H, CH_3CO), 3.36 (dd, 1H, H-4, J=5.2, 1.5 Hz), 3.59 (dq, 1H, OCH_2CH_3, J=9.8, 7.0 Hz), 3.84 (dq, 1H, OCH_2CH_3, J=9.8, 7.0 Hz), 4.25–4.34 (m, 3H, H-5, H-6, H-6′), 5.07 (d, 1H, H-1, J=2.8 Hz), 6.09 (dd, 1H, H-3, J=10.1, 5.2 Hz), 6.16 (dd, 1H, H-2, J=10.1, 2.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.6, 21.1, 52.8, 64.2, 64.4, 68.4, 94.2, 124.4, 131.4, 171.0. HRMS: Calcd for $C_{10}H_{16}O_4N_3$ $[M+H-N_2]^+$: 214.1079. Found: 214.1080.

4.3.3. Ethyl 6-*O*-acetyl-2-azido-2,3,4-trideoxy-α-D-*threo*-hex-3-enopyranoside (9a). Oil; R_f=0.7 (petroleum ether/EtOAc 4:1); $[\alpha]_D^{20}$ +370 (*c* 0.7, $CHCl_3$); IR: 2100, 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, 3H, CH_3CH_2, J=7.2 Hz), 2.09 (s, 3H, CH_3CO), 3.35 (br d, 1H, H-2, J=4.0 Hz), 3.62 (dq, 1H, OCH_2CH_3, J=9.8, 7.2 Hz), 3.82 (dq, 1H, OCH_2CH_3, J=9.8, 7.0 Hz), 4.2 (d, 2H, H-6, H-6′, J=5.1 Hz), 4.42 (m, 1H, H-5), 5.00 (br s, 1H, H-1), 5.90 (dddd, 1H, H-3, J=10.5, 5.1, 2.1, 1.1 Hz), 6.1 (br d, 1H, H-4, J=10.5 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.0, 21.2, 55.0, 64.7, 65.6, 66.9, 99.2, 121.1, 131.3, 171.0. HRMS: Calcd for $C_{10}H_{16}O_4N_3$ $[M+H]^+$: 242.1141. Found: 242.1142.

4.3.4. Propyl 6-*O*-acetyl-4-azido-2,3,4-trideoxy-α-D-*erythro*-hex-2-enopyranoside (7b). Oil; R_f=0.7 (petroleum ether/EtOAc 4:1); $[\alpha]_D^{20}$ +145 (*c* 1.0, CH_2Cl_2); IR: 2100, 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.94 (t, 3H, CH_3CH_2, J=7.4 Hz), 1.62 (m, 2H, CH_2CH_3), 2.11 (s, 3H, CH_3CO), 3.48 (dt, 1H, OCH_2CH_2, J=9.4, 6.4 Hz), 3.71 (dt, 1H, OCH_2CH_2, J=9.4, 6.8 Hz), 3.88 (br d, 1H, H-4, J=9.9 Hz), 3.94 (ddd, 1H, H-5, J=9.9, 4.7, 2.3 Hz), 4.28 (dd, 1H, H-6′, J=12.1, 4.7 Hz), 4.35 (dd, 1H, H-6, J=12.1, 2.3 Hz), 5.01 (br d, 1H, H-1, J=1.5 Hz), 5.9 (ddd, 1H, H-2, J=10.3, 1.8, 1.8 Hz), 6.00 (br d, 1H, H-3, J=10.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 11.1, 21.2, 23.3, 54.8, 63.9, 71.0, 68.1, 94.5, 128.0, 129.3, 171.1. HRMS: Calcd for $C_{11}H_{18}O_4N_3$ $[M+H]^+$: 256.1297. Found: 256.1299.

4.3.5. Propyl 6-*O*-acetyl-4-azido-2,3,4-trideoxy-α-D-*threo*-hex-2-enopyranoside (8b). Oil; R_f=0.6 (petroleum ether/EtOAc 8:2); $[\alpha]_D^{20}$ −273 (*c* 0.6, CH_2Cl_2); IR: 2100, 1735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.94 (t, 3H, CH_3CH_2, J=7.4 Hz), 1.64 (m, 2H, CH_2CH_3), 2.09 (s, 3H, CH_3CO), 3.35 (dd, 1H, H-4, J=5.4, 1.7 Hz), 3.50 (dt, 1H, OCH_2CH_2, J=9.1, 6.4 Hz), 3.73 (dt, 1H, OCH_2CH_2, J=9.1, 6.7 Hz), 4.25–4.35 (m, 3H, H-5, H-6, H-6′), 5.06 (d, 1H, H-1, J=2.7 Hz), 6.07 (dd, 1H, H-3, J=10.2, 5.4 Hz), 6.17 (dd, 1H, H-2, J=10.2, 2.7 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 11.0, 21.1, 23.3, 52.8, 64.2, 70.6, 68.5, 94.4, 124.3, 131.4, 170.9. HRMS: Calcd for $C_{11}H_{18}O_4N_3$ $[M+H]^+$: 256.1297. Found: 256.1291.

4.3.6. Propyl 6-*O*-acetyl-2-azido-2,3,4-trideoxy-α-D-*threo*-hex-3-enopyranoside (9b). Oil; R_f=0.7 (petroleum ether/EtOAc 4:1); $[\alpha]_D^{20}$ +421 (*c* 1.0, CH_2Cl_2); IR: 2100, 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.92 (t, 3H, CH_3CH_2), J=7.2 Hz), 1.60 (m, 2H, CH_2CH_3), 2.09 (s, 3H, CH_3CO), 3.35 (br d, 1H, H-2, J=4.0 Hz), 3.50 (dt, 1H,

OCH_2CH$_2$, J=9.6, 6.6 Hz), 3.70 (dt, 1H, OCH_2CH$_2$, J=9.6, 6.8 Hz), 4.24 (m, 2H, H-6, H-6′), 4.42 (m, 1H, H-5), 4.98 (br s, 1H, H-1), 5.91 (dddd, 1H, H-3, J=10.4, 4.5, 2.1, 1.1 Hz), 6.11 (br d, 1H, H-4, J=10.4 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 10.9, 21.2, 23.1, 55.0, 65.6, 69.9, 70.8, 99.3, 121.1, 131.3, 171.3. Anal. Calcd for $C_{11}H_{17}O_4N_3$: C, 51.76; H, 6.71. Found: C, 51.70; H, 6.85.

4.3.7. Cyclohexyl 6-*O*-acetyl-4-azido-2,3,4-trideoxy-α-D-*erythro*-hex-2-enopyranoside (7c). Oil; R_f=0.7 (petroleum ether/EtOAc 4:1); $[\alpha]_D^{20}$ +139 (c 1.5, CH_2Cl_2); IR: 2100, 1740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10–1.90 (m, 10H, 5×CH_2), 2.11 (s, 3H, CH_3CO), 3.63 (m, 1H, $C_5H_{10}CHO$), 3.87 (dd, 1H, H-4, J=9.9, 1.4 Hz), 3.98 (ddd, 1H, H-5, J=9.9, 5.3, 2.6 Hz), 4.29 (dd, 1H, H-6′, J=12.1, 5.3 Hz), 4.32 (dd, 1H, H-6, $J_{6,5}$=12.1, 2.6 Hz), 5.15 (br s, 1H, H-1), 5.90 (ddd, 1H, H-2, J=10.2, 2.4, 2.0 Hz), 5.98 (br d, 1H, H-3, J=10.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.2, 24.6, 24.8, 25.9, 32.5, 34.1, 54.9, 64.0, 68.0, 77.0, 93.0, 127.8, 129.9, 171.1. Anal. Calcd for $C_{14}H_{21}O_4N_3$: C, 56.94; H, 7.17. Found: C, 57.41; H, 7.61.

4.3.8. Cyclohexyl 6-*O*-acetyl-4-azido-2,3,4-trideoxy-α-D-*theo*-hex-2-enopyranoside (8c). Oil; R_f=0.6 (petroleum ether/EtOAc 4:1); $[\alpha]_D^{20}$ −207 (c 2.4, CH_2Cl_2); IR: 2100, 1740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.3–1.9 (m, 10H, 5×CH_2), 2.08 (s, 3H, CH_3CO), 3.35 (dd, 1H, H-4, J=5.3, 2.3 Hz), 3.67 (m, 1H, $C_5H_{10}CHO$), 4.29 (d, 2H, H-6, H-6′, J=5.8 Hz), 4.38 (dt, 1H, H-5, J=5.8, 2.3 Hz), 5.21 (d, 1H, H-1, J=2.7 Hz), 6.06 (dd, 1H, H-3, J=10.0, 5.3 Hz), 6.15 (dd, 1H, H-2, J=10.0, 2.7 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.1, 24.5, 24.8, 25.9, 32.5, 34.1, 52.9, 64.3, 68.4, 76.8, 92.8, 124.1, 131.9, 170.9. HRMS: Calcd for $C_{14}H_{22}O_4N_3$ $[M+H]^+$: 296.1610. Found: 296.1608.

4.3.9. Cyclohexyl 6-*O*-acetyl-2-azido-2,3,4-trideoxy-α-D-*threo*-hex-3-enopyranoside (9c). Oil; R_f=0.7 (petroleum ether/EtOAc 4:1); $[\alpha]_D^{20}$ +231 (c 2.3, CH_2Cl_2); IR: 2100, 1740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.11–1.91 (m, 10H, 5×CH_2), 2.09 (s, 3H, CH_3CO), 3.32 (d, 1H, H-2, J=5.1 Hz), 3.64 (m, 1H, $C_5H_{10}CHO$), 4.24 (d, 2H, H-6, H-6′, J=4.9 Hz), 4.46 (m, 1H, H-5), 5.12 (br s, 1H, H-1), 5.89 (dddd, 1H, H-3, J=10.3, 5.1, 2.3, 1.0 Hz), 6.10 (br d, 1H, H-4, J=10.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.2, 24.3, 24.6, 25.9, 32.0, 33.7, 55.5, 65.7, 67.1, 76.5, 97.3, 121.3, 131.3, 171.3. HRMS: Calcd for $C_{140}H_{22}O_4N_3$ $[M+H]^+$: 296.1610. Found: 296.1611.

4.4. Palladium-catalyzed azidation using trimethylsilyl azide. General procedure

To a mixture of $Pd_2(dba)_3$ (45 mg, 0.05 mmol), PPh_3 5% (104 mg, 0.4 mmol), and the unsaturated carbohydrate **4** (0.1 mmol) in THF (2.5 mL) was added $TMSN_3$ (172 mg, 1.5 mmol). The solution was stirred at 50 °C for 2 h. Evaporation of the solvent under reduced pressure gave a residue that was purified by column chromatography on silica using petroleum ether/EtOAc (95:5) as the eluent to give the corresponding allylic azides **10a–c**.

4.4.1. Ethyl 4-azido-6-*O*-(*tert*-butyldimethylsilyl)-2,3,4-trideoxy-α-D-*erythro*-hex-2-enopyranoside (10a). Yield 73%; oil; R_f=0.6 (petroleum ether/EtOAc 49:1); $[\alpha]_D^{20}$ +129 (c 1.1, CH_2Cl_2); IR: 2100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.00 (s, 6H, $SiMe_2$), 0.81 (s, 9H, CMe_3), 1.13 (t, 3H, CH_3CH$_2$), J=7.2 Hz), 3.45 (dq, 1H, OCH_2CH$_3$, J=9.6, 7.0 Hz), 3.64 (dq, 1H, OCH_2CH$_3$,, J=9.6, 3.4 Hz), 3.72–3.78 (m, 3H, H-5, H-6, H-6′), 3.86 (br d, 1H, H-4, J=9.6 Hz), 4.91 (br s, 1H, H-1), 5.80 (ddd, 1H, H-2, J=10.3, 2.4, 2.3 Hz), 5.88 (br d, 1H, H-3, J=10.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −5.0, 15.6, 18.8, 26.3, 54.4, 63.3, 64.3, 70.7, 94.2, 128.7, 129.1. Anal. Calcd for $C_{14}H_{27}O_3N_3Si$: C, 53.64; H, 8.68. Found: C, 53.49; H, 8.58.

4.4.2. Propyl 4-azido-6-*O*-(*tert*-butyldimethylsilyl)-2,3,4-trideoxy-α-D-*erythro*-hex-2-enopyranoside (10b). Yield 69%; oil; R_f=0.7 (petroleum ether/EtOAc 49:1); $[\alpha]_D^{20}$ +117 (c 1.5, CH_2Cl_2); IR: 2100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.00 (s, 6H, Me_2Si), 0.80 (t, 3H, CH_3CH$_2$, J=7.2 Hz), 0.82 (s, 9H, CMe_3), 1.52 (m, 2H, CH$_3$CH_2), 3.34 (dt, 1H, OCH_2CH$_2$, J=9.4, 6.6 Hz), 3.57–3.71 (m, 2H, OCH_2CH$_2$, H-5), 3.75 (d, 2H, H-6, H-6′, J=4.0 Hz), 3.85 (br d, 1H, H-4, J=9.7 Hz), 4.89 (br s, 1H, H-1), 5.80 (ddd, 1H, H-2, J=10.2, 2.3, 2.3 Hz), 5.87 (br d, 1H, H-3, J=10.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −5.0, 11.0, 18.8, 23.3, 26.3, 54.5, 63.3, 70.6, 70.7, 94.4, 128.6, 129.1. Anal. Calcd for $C_{15}H_{29}O_3N_3Si$: C, 55.01; H, 8.93. Found: C, 55.28; H, 9.14.

4.4.3. Cyclohexyl 4-azido-6-*O*-(*tert*-butyldimethylsilyl)-2,3,4-trideoxy-α-D-*erythro*-hex-2-enopyranoside (10c). Yield 71%; oil; R_f=0.8 (petroleum ether/EtOAc 49:1); $[\alpha]_D^{20}$ +105 (c 1.0, CH_2Cl_2); IR: 2100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.01 (s, 6H, $SiMe_2$), 0.82 (s, 9H, CMe_3), 1.10–1.80 (m, 10H, 5×CH_2), 3.30–3.75 (m, 4H, $C_5H_{10}CHO$, H-5, H-6, H-6′), 3.82 (br d, 1H, H-4, J=9.4 Hz), 5.04 (br s, 1H, H-1), 5.77 (ddd, 1H, H-2, J=10.0, 2.6, 2.1 Hz), 5.86 (br d, 1H, H-3, J=10.0 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −5.0, 18.9, 24.6, 24.8, 26.0, 32.4, 34.2, 26.3, 54.5, 63.5, 70.6, 76.5, 92.5, 128.3, 129.7. Anal. Calcd for $C_{18}H_{33}O_3N_3Si$: C, 58.82; H, 9.05. Found: C, 58.39; H, 9.32.

4.4.4. Ethyl 4-azido-6-*O*-(*tert*-butyldimethylsilyl)-2,3,4-trideoxy-α-D-*threo*-hex-2-enopyranoside (11) and ethyl 2-azido-6-*O*-(*tert*-butyldimethylsilyl)-2,3,4-trideoxy-α-D-*threo*-hex-3-enopyranoside (12). The title compounds were obtained as described before using Me_3SiN_3 as the azido nucleophile starting from carbonate **6** (500 mg 1.4 mmol). Purification by silica gel chromatography using petroleum ether/ethyl acetate (95:5) as the eluent gave the regioisomeric azides **11** and **12** as a 40:60 inseparable mixture (340 mg, 76% yield), which gave, however, distinct signals patterns in the ^{1}H and ^{13}C NMR spectra. Colourless oil; R_f=0.8 (petroleum ether/EtOAc 9:1). Anal. Calcd for $C_{14}H_{27}O_3N_3Si$: C, 53.64; H, 8.68. Found: C, 53.96; H, 8.89.

4.4.5. Ethyl 4-azido-6-*O*-(*tert*-butyldimethylsilyl)-2,3,4-trideoxy-α-D-*threo*-hex-2-enopyranoside (11). ^{1}H NMR (300 MHz, $CDCl_3$): δ −0.01 (s, 3H, SiMe), 0.01 (s, 3H, SiMe), 0.82 (s, 9H, CMe_3), 1.15 (t, 3H, CH_3CH$_2$, J=7.2 Hz), 3.33 (dd, 1H, H-4, J=4.8, 2.1 Hz), 3.50–3.65 (m, 1H, OCH_2CH$_3$), 3.76–3.88 (m, 3H, OCH_2CH$_3$, H-6, H-6′),

4.16 (ddd, 1H, J=9.0, 6.8, 2.4 Hz, H-5), 4.96 (br s, 1H, H-1), 6.08 (dm, 1H, H-3, J=10.0 Hz), 6.13 (dd, 1H, H-2, J=10.0, 2.4 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −5.0, 15.6, 18.7, 26.2, 52.7, 63.0, 64.4, 70.9, 94.2, 125.0, 131.2.

4.4.6. Ethyl 2-azido-6-*O*-(*tert*-butyldimethylsilyl)-2,3,4-trideoxy-α-D-*threo*-hex-3-enopyranoside (12). ^{1}H NMR (300 MHz, $CDCl_3$): δ −0.01 (s, 3H, SiMe), 0.01 (s, 3H, SiMe), 0.82 (s, 9H, CMe_3), 1.15 (t, 3H, CH_3CH_2, J=7.2 Hz), 3.27 (br d, 1H, H-2, J=4.3 Hz), 3.50–3.65 (m, 2H, OCH_2CH_3), 3.76–3.88 (m, 2H, H-6, H-6′), 4.22 (m, 1H, H-5), 4.87 (br s, 1H, H-1), 5.74 (br dd, 1H, H-3, J=10.4, 4.3 Hz), 6.17 (br d, 1H, H-4, J=10.4 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −5.0, 15.6, 18.7, 26.2, 0.82, 15.0, 21.2, 55.6, 64.1, 66.1, 69.3, 98.9, 119.3, 133.1.

4.4.7. Ethyl 4-acetylamino-2,3,4-trideoxy-α-D-*erythro*-hexopyranoside (13). A solution of azide **7a** (100 mg, 0.4 mmol) in methanol (10 mL) was stirred under H_2 (2 bar) for 17 h in the presence of 10% Pd–C (20 mg). The catalyst was removed by filtration and evaporation of the solvent under reduced pressure afforded the amino sugar **13** (79 mg, 90% yield) as a solid; mp=119–121 °C; R_f=0.3 (petroleum ether/EtOAc/methanol 6:3:1); $[\alpha]_D^{20}$ +108 (c 0.5, CH_2Cl_2); IR: 3400, 1730, 1640, 1540 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (t, 3H, CH_3CH_2, J=7.0 Hz), 1.83 (br s, 4H, 2×CH_2), 2.04 (s, 3H, CH_3CO), 3.39 (br d, 1H, H-5, J=9.8 Hz), 3.48 (dq, 1H, OCH_2CH_3, J=9.8, 6.8 Hz), 3.58 (dd, 1H, H-6, J=13.0, 1.7 Hz), 3.67 (dd, 1H, H-6′, J=13.0, 2.7 Hz), 3.73 (m, 1H, OCH_2CH_3), 3.95 (m, 1H, H-4), 4.89 (br s, 1H, H-1), 5.48 (d, 1H, NH, J=7.4 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 16.6, 24.6, 26.2, 30.9, 46.7, 63.5, 63.9, 70.4, 97.5, 172.9. Anal. Calcd for $C_{10}H_{19}O_4N$: C, 55.28; H, 8.81. Found: C, 54.79; H, 8.74.

4.4.8. Propyl 4-acetylamino-2,3,4-trideoxy-α-D-*threo*-hexopyranoside (14). Reduction of **8b** following the procedure already described for the preparation of **13** gave compound **14** in 94% yield as a solid; mp=45–47 °C; R_f=0.2 (petroleum ether/EtOAc/methanol 6:3:1); $[\alpha]_D^{20}$ +36 (c 0.5, CH_2Cl_2); IR: 3400, 1700, 1570, 1480 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, 3H, CH_3CH_2, J=7.4 Hz), 1.50–1.80 (m, 6H, 3×CH_2), 2.07 (s, 3H, CH_3CO), 3.05 (br s, 1H, OH), 3.33 (dd, 1H, H-6, J=11.7, 8.5 Hz), 3.35 (dt, 1H, OCH_2CH_2, J=13.4, 6.6 Hz), 3.52 (dd, 1H, H-6′, J=11.7, 5.7 Hz), 3.58 (dt, 1H, OCH_2CH_2, J=13.4, 7.0 Hz), 4.01 (ddd, 1H, H-5, J=8.2, 5.9, 1.4 Hz), 4.15 (dm, 1H, H-4, J=7.1 Hz), 4.81 (br s, 1H, H-1), 6.27 (d, 1H, NH, J=7.1 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 11.0, 23.1, 23.2, 23.6, 25.2, 44.2, 62.0, 69.4, 69.4, 96.9, 171.9. HRMS: Calcd for $C_{11}H_{22}O_4N$ $[M+H]^+$: 232.1549. Found: 232.1543.

4.4.9. Propyl 6-*O*-acetyl-2-amino-2,3,4-trideoxy-α-D-*threo*-hexopyranoside (15). Reduction of **9b** following the procedure already described for the preparation of **13** gave compound **15** in 97% yield; R_f=0.1 (petroleum ether/EtOAc/methanol 6:3:1); $[\alpha]_D^{20}$ +24 (c 0.3, CH_2Cl_2); IR: 3400, 1740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (t, 3H, CH_3CH_2, J=7.4 Hz), 1.45–1.70 (m, 8H, 3×CH_2, NH_2), 2.09 (s, 3H, CH_3CO), 2.84 (br s, 1H, H-2), 3.39 (dt, 1H, OCH_2CH_2, J=9.6, 6.4 Hz), 3.64 (dt, 1H, OCH_2CH_2, J=9.6, 7.0 Hz), 3.94–4.12 (m, 3H, H-6, H-6′, H-5), 4.58 (br s, 1H, H-1); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 11.1, 21.3, 21.5, 23.2, 25.8, 47.9, 67.1, 67.2, 69.4, 102.0, 171.3. HRMS: Calcd for $C_{11}H_{22}O_4N$ $[M+H]^+$: 232.1548. Found: 232.1548.

4.4.10. Propyl 2-acetylamino-6-*O*-acetyl-2,3,4-trideoxy-α-D-*threo*-hexopyranoside (16). To a solution of amino carbohydrate **15** (75 mg, 0.32 mmol) in pyridine (1.5 mL) at 0 °C was added acetic anhydride (1 mL), and the mixture was stirred for 13 h at rt. The solution was concentrated under reduced pressure and the residue was purified by chromatography on Silica Fluorisil using petroleum ether/EtOAc (4:6) as the eluent to give **16** (78 mg, 88% yield) as a solid; mp=60–63 °C; R_f=0.4 (petroleum ether/EtOAc/methanol 6:3:1); $[\alpha]_D^{20}$ +77 (c 1.0, CH_2Cl_2); IR: 3300, 1740, 1650, 1540 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (t, 3H, CH_3CH_2, J=7.4 Hz), 1.42–1.72 (m, 6H, CH_2), 2.01 (s, 3H, CH_3CO), 2.09 (s, 6H, CH_3CO), 3.39 (dt, 1H, OCH_2CH_2, J=9.4, 6.4 Hz), 3.62 (dt, 1H, OCH_2CH_2, J=9.4, 6.6 Hz), 3.97–4.10 (m, 4H, H-6, H-6′, H-5, H-2), 4.61 (br s, 1H, H-1), 6.09 (br d, 1H, NH, J=8.5 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 11.0, 21.1, 23.0, 22.3, 22.7, 23.6, 46.0, 66.7, 67.0, 69.5, 98.9, 170.1, 171.2. Anal. Calcd for $C_{13}H_{23}O_5N$: C, 57.13; H, 8.48. Found: C, 57.11; H, 8.53.

4.4.11. Propyl 6-*O*-acetyl-2-*p*-toluenesulfonylamino-2,3,4-trideoxy-α-D-*threo*-hexopyranoside (17). To a solution of amino carbohydrate **15** (50 mg, 0.21 mmol) in pyridine (1 mL) and CH_2Cl_2 (2 mL) at 0 °C was added *p*-toluenesulfonyl chloride (42 mg, 0.22 mmol), and the mixture was stirred for 16 h at rt. The reaction mixture was then diluted with water (10 mL), and extracted with dichloromethane (2×5 mL). Evaporation of the solvent under reduced pressure gave a residue that was purified by chromatography on Silica Fluorisil using petroleum ether/EtOAc (7:3) as the eluent to give **17** (58 mg, 70% yield) as an oil. R_f=0.7 (petroleum ether/EtOAc/methanol 6:3:1); $[\alpha]_D^{20}$ +38 (c 2.0, CH_2Cl_2); IR: 3300, 1740 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.79 (t, 3H, CH_3CH_2, J=7.4 Hz), 1.41 (m, 1H, H-4_{eq}), 1.49 (m, 1H, H-4_{ax}), 1.52 (m, 2H, CH_2CH_3), 1.57 (m, 1H, H-3_{eq}), 1.98 (m, 1H, H-3_{ax}), 2.00 (s, 3H, CH_3CO), 2.35 (s, 3H, CH_3Ar), 3.18 (dt, 1H, OCH_2CH_2, J=9.6, 6.4 Hz), 3.34 (ddd, 1H, H-2, J=9.6, 3.0, 3.0 Hz), 3.43 (dt, 1H, OCH_2CH_2, J=9.6, 6.8 Hz), 3.93 (m, 1H, H-5), 4.00 (dd, 1H, H-6, J=11.6, 6.5 Hz), 4.04 (dd, 1H, H-6′, J=11.6, 3.6 Hz), 4.27 (br s, 1H, H-1), 5.21 (d, 1H, NH, J=9.6 Hz), 7.23 (d, 2H, Ar, J=8.3 Hz), 7.69 (d, 2H, Ar, J=8.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 11.0, 21.2, 22.9, 21.8, 21.9, 23.7, 50.0, 66.6, 66.9, 69.4, 98.7, 127.3, 127.4, 130.2, 138.3, 143.9, 171.3. Anal. Calcd for $C_{18}H_{27}O_6NS$: C, 56.08; H, 7.06. Found: C, 55.65; H, 7.39.

4.5. General procedure for bis-hydroxylation

The unsaturated azide **7a**, **9b**, or **10a** (1 mmol) was dissolved in a 4:1 mixture of acetone/water (5 mL) in the presence of a catalytic amount of osmium tetroxide (2%) and *N*-methylmorpholine-*N*-oxide (458 mg, 4 mmol). The mixture was stirred overnight at rt, $NaHSO_3$ (500 mg) was then added, and the mixture was stirred for 30 min. A saturated aqueous solution of NaCl (10 mL) was added, and the mixture was extracted with EtOAc (2×10 mL). The organic layer was dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude mixture

obtained was acetylated using Ac_2O/pyridine for 1 day. After removing the solvent under reduced pressure, the residue was purified by column chromatography on silica gel using petroleum ether/EtOAc (8:2) as the eluent to afford the corresponding pure saturated azido carbohydrate.

4.5.1. Ethyl 2,3,6-tri-*O*-acetyl-4-azido-4-deoxy-α-D-mannopyranoside (18a). Yield 91%; oil; R_f=0.3 (petroleum ether/EtOAc 4:1); $[\alpha]_D^{20}$ +101 (*c* 1.7, CH_2Cl_2); IR: 1750, 2100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.23 (t, 3H, CH_3CH_2), *J*=7.0 Hz), 2.08 (s, 3H, CH_3CO), 2.14 (s, 3H, CH_3CO), 2.15 (s, 3H, CH_3CO), 3.52 (dq, 1H, OCH_2CH_3, *J*=9.8, 7.1 Hz), 3.72 (dq, 1H, OCH_2CH_3, *J*=9.8, 7.1 Hz), 3.82 (dd, 1H, H-4, *J*=10.3, 9.9 Hz), 3.70–3.80 (m, 1H, H-5), 4.31 (dd, 1H, H-6′, *J*=12.1, 4.1 Hz), 4.37 (dd, 1H, H-6, *J*=12.1, 2.1 Hz), 4.81 (d, 1H, H-1, *J*=1.7 Hz), 5.21 (dd, 1H, H-2, *J*=3.2, 1.7 Hz), 5.30 (dd, 1H, H-3, *J*=9.9, 3.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.2, 21.1, 21.1, 21.2, 57.5, 63.7, 64.4, 69.0, 69.4, 70.9, 97.8, 169.9, 170.3, 171.0. Anal. Calcd for $C_{14}H_{21}O_8N_3$: C, 46.80; H, 5.89. Found: C, 46.30; H, 5.92.

4.5.2. Ethyl 2,3-di-*O*-acetyl-4-azido-6-O-(*tert*-butyldimethylsilyl)-4-deoxy-α-D-mannopyranoside (18b). Yield 85%; oil; R_f=0.6 (petroleum ether/EtOAc 9:1); $[\alpha]_D^{20}$ +108 (*c* 0.5, CH_2Cl_2); IR: 1750, 2100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.00 (s, 6H, $SiMe_2$), 0.83 (s, 9H, CMe_3), 1.09 (t, 3H, CH_3CH_2, *J*=7.0 Hz), 1.98 (s, 3H, CH_3CO), 2.01 (s, 3H, CH_3CO), 3.38 (dq, 1H, OCH_2CH_3, *J*=9.8, 7.0 Hz), 3.44 (ddd, 1H, H-5, *J*=10.6, 3.4, 1.7 Hz), 3.6 (dq, 1H, OCH_2CH_3, *J*=9.8, 7.1 Hz), 3.71 (dd, 1H, H-6′, *J*=11.5, 1.7 Hz), 3.81 (dd, 1H, H-6, *J*=11.5, 3.4 Hz), 3.88 (dd, 1H, H-4, *J*=10.6, 10.6 Hz), 4.68 (d, 1H, H-1, *J*=1.7 Hz), 5.06 (dd, 1H, H-2, *J*=3.3, 1.8 Hz), 5.17 (dd, 1H, H-3, *J*=10.6, 3.4 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −5.0, 15.2, 18.7, 21.2, 26.2, 57.0, 62.6, 63.9, 69.6, 70.9, 71.8, 97.6, 170.4, 170.1. Anal. Calcd for $C_{18}H_{33}O_7N_3Si$: C, 50.10; H, 7.71. Found: C, 49.80; H, 7.69. HRMS: Calcd for $C_{18}H_{34}O_7N_3Si$ $[M+H]^+$: 432.2166. Found: 432.2165.

4.5.3. Propyl 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-altropyranoside (20). Yield 77%; oil; R_f=0.4 (petroleum ether/EtOAc 4:1); $[\alpha]_D^{20}$ +148 (*c* 2.3, CH_2Cl_2); IR: 1740, 2100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.97 (t, 3H, CH_3CH_2, *J*=7.4 Hz), 1.64 (m, 2H, CH_3CH_2), 2.08 (s, 3H, CH_3CO), 2.09 (s, 3H, CH_3CO), 2.11 (s, 3H, CH_3CO), 3.45 (dt, 1H, OCH_2CH_2, *J*=9.4, 6.3 Hz), 3.71 (dt, 1H, OCH_2CH_2, *J*=9.4, 6.7 Hz), 3.83 (dd, 1H, H-2, *J*=6.6, 3.5 Hz), 4.15 (dd, 1H, H-6′, *J*=11.8, 2.9 Hz), 4.25 (ddd, 1H, H-5, *J*=7.0, 5.6, 2.9 Hz), 4.35 (dd, 1H, H-6, *J*=11.8, 5.6 Hz), 4.76 (d, 1H, H-1, *J*=3.5 Hz), 5.12 (dd, 1H, H-3, *J*=6.6, 3.6 Hz), 5.19 (dd, 1H, H-4, *J*=7.0, 3.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 11.0, 21.1, 23.1, 60.6, 62.8, 70.8, 66.0, 68.3, 68.8, 99.1, 170.0, 170.3, 170.9. Anal. Calcd for $C_{15}H_{23}O_8N_3$: C, 48.25; H, 6.21. Found: C, 48.41; H, 6.40.

4.6. General procedure for the synthesis of amino sugars 19 and 21.

A solution of unsaturated azido carbohydrate **18b** or **20** (1 mmol) in ethyl acetate (5 mL) was stirred under H_2 atmosphere (1 atm) for 16 h in the presence of 10% Pd–C (10% w/w of azido sugar). The catalyst was then removed by filtration and the solvent was evaporated under reduced pressure. The obtained residue was purified by chromatography on Silica Florisil using 4% MeOH in CH_2Cl_2 as the eluent affording the corresponding amino sugar **19** and **21**, respectively.

4.6.1. Ethyl 2,3-di-*O*-acetyl-4-amino-6-*O*-(*tert*-butyldimethylsilyl)-4-deoxy-α-D-mannopyranoside (19). Yield 87%; oil; R_f=0.6 (CH_2Cl_2/MeOH 19:1); $[\alpha]_D^{20}$ +96 (*c* 1, CH_2Cl_2); IR: 3400, 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ −0.01 (s, 6H, $SiMe_2$), 0.82 (s, 9H, CMe_3), 1.11 (t, 3H, CH_3CH_2, *J*=7.0 Hz), 1.28 (br s, 2H, NH_2), 1.97 (s, 3H, CH_3CO), 1.99 (s, 3H, CH_3CO), 3.13 (dd, 1H, H-4, *J*=10.5, 10.5 Hz), 3.32–3.48 (m, 2H, OCH_2CH_3, H-5), 3.63 (dq, 1H, OCH_2CH_3, *J*=9.6, 7.1 Hz), 3.77 (dd, 1H, H-6, *J*=11.3, 3.2 Hz), 3.83 (dd, 1H, H-6′, *J*=11.3, 4.3 Hz), 4.67 (d, 1H, H-1, *J*=1.3 Hz), 4.98 (dd, 1H, H-3, *J*=10.5, 3.2 Hz), 5.05 (dd, 1H, H-2, *J*=3.2, 1.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −4.9, 15.3, 18.7, 21.2, 21.3, 26.3, 48.7, 63.6, 63.9, 69.7, 73.2, 74.4, 97.7, 170.6, 170.9. Anal. Calcd for $C_{18}H_{35}O_7NSi$: C, 53.31; H, 8.70. Found: C, 53.99; H, 8.80.

4.6.2. Propyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-altropyranoside (21). Yield 80%; oil; R_f=0.5 (CH_2Cl_2/MeOH 19:1); $[\alpha]_D^{20}$ +78 (*c* 1.5, CH_2Cl_2); IR: 3400, 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.97 (t, 3H, CH_3CH_2, *J*=7.5 Hz), 1.55–1.68 (m, 4H, NH_2, CH_3CH_2), 2.05 (s, 3H, CH_3CO), 2.08 (s, 3H, CH_3CO), 2.10 (s, 3H, CH_3CO), 3.24 (dd, 1H, H-2, *J*=5.5, 2.8 Hz), 3.40 (dt, 1H, OCH_2CH_2, *J*=9.4, 6.2 Hz), 3.68 (dt, 1H, OCH_2CH_2, *J*=9.4, 6.8 Hz), 4.15 (dd, 1H, H-6′, *J*=11.3, 2.1 Hz), 4.27–4.40 (m, 2H, H-5, H-6), 4.66 (d, 1H, H-1, *J*=2.8 Hz), 5.04 (1H, H-3, *J*=5.5, 3.6 Hz), 5.24 (dd, 1H, H-4, *J*=8.1, 3.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 11.1, 21.1, 21.2, 21.3, 23.2, 54.5, 63.1, 70.4, 66.0, 68.3, 68.8, 101.9, 170.2, 170.8, 171.1. Anal. Calcd for $C_{15}H_{25}O_8N$: C, 51.87; H, 7.25. Found: C, 52.05; H, 7.58.

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Synthesis of new 8-arylisoquinoline derivatives by application of palladium-catalyzed Suzuki cross-coupling reactions

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Abstract—New 8-(*het*)aryltetrahydroisoquinolines (**10**–**14**), 8-aryltetrahydroisoquinolin-4-ols (**15**,**16**), and 8-phenylisoquinolin-4-ol (**17**), flexible analogues of aporphine, were synthesized in good yields using palladium-catalyzed Suzuki cross-coupling reactions from 8-bromotetrahydroisoquinolin-4-one (**6**) as a common intermediate. We also describe the synthesis of this novel intermediate through an easy and efficient method, which involved intramolecular Friedel–Crafts cyclization.

1. Introduction

For many years, isoquinoline alkaloids have been an interesting structural class of compounds, which have found many uses in the field of medicinal chemistry.

(*R*)-Apomorphine[1] as well as many natural[2] and synthetic[3] aporphines (Fig. 1) have been extensively studied for their interaction with the receptors of the central nervous system.[4]

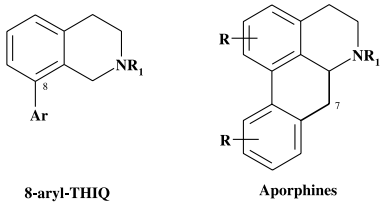

Figure 1. Structures of isoquinolines.

In this medicinal chemistry context, we have decided to focus on the preparation of new 8-arylisoquinoline derivatives (8-arylIQ), first, because only few studies have been realized on this type of structure and second because no efficient method of preparation has been reported. From a pharmacological point of view, we can consider 8-arylisoquinoline derivatives as flexible structural analogues of aporphines without any C-7 methylene bridge (Fig. 1).

Although many methods such as Bischler–Napieralski (this cyclization requires an electron-donating group to direct the cyclization to its *para* position), Pictet–Spengler and Pomeranz–Fritsch reactions are available for the synthesis of IQ, none is satisfactory for the one of 8-arylIQ derivatives. To our knowledge, in the synthesis of 8-arylTHIQ derivatives, only a small number of approaches have been reported.[5] Ellefson accomplished two different routes following multi-step sequences and using an aryloxazoline as key intermediate.[5a,b] Hara prepared tetrahydroisoquinoline dimers from *p*-quinol acetate.[5c] McKenna et al. prepared a mixture of 6- and 8-arylTHIQ isomers by Suzuki–Miyaura cross-coupling reactions of triflates.[5d] The latter method is complex, and requires the preparation of a bromo intermediate in order to block the 6-position, so as to avoid a mixture of cyclization products. An alternative method to prepare 8-arylTHIQ through catalytic hydrogenation of the parent 8-arylIQ has been reported without specifying what yield was obtained in the reduction reaction.[5e] The 8-arylIQ parents were prepared using dichloro[1,3-bis(diphenylphosphino)propane]-nickel(II) as catalyst in the coupling reaction between organomagnesium halides and haloisoquinolines. However, this procedure has some limitations. Indeed, on the one hand, the availability of many haloisoquinolines, notably of 8-haloisoquinolines is restricted, and on the other hand,

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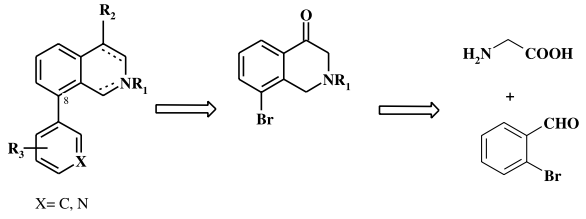
many substituents are not compatible with the hydrogenation step. None of these methods can actually be applied to produce a library of various 8-arylIQ.

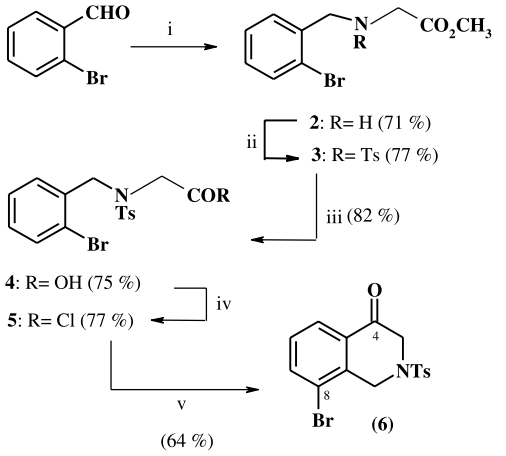
Herein, in order to construct the structurally flexible aporphine analogues, we describe an efficient pathway to the preparation of 8-arylIQ derivatives from the new 8-bromotetrahydroisoquinolin-4-one as a common intermediate. Nevertheless, the synthesis of 8-halogenoIQ is rarely reported in the literature and often involves tedious approaches under drastic conditions and in moderate yields.[6] Indeed, 8-bromoTHIQ was synthesized by Pictet–Spengler reaction from phenylethylamine in low yield because this reaction requires an electron-donating group on the aromatic ring.[7] It is the reason why, in the first part of this study, we present a new route for the synthesis of 8-bromoIQ and 8-bromoTHIQ intermediates followed by the results of their use as partners of palladium-catalyzed Suzuki cross-coupling reaction with various arylboronic acids as depicted in the retrosynthetic pathway (Scheme 1).



Scheme 1. Retrosynthetic pathway.

2. Results and discussion

We first aimed at synthesizing the new 8-bromotetrahydroisoquinolin-4-one in a six-step pathway, thanks to an easy and efficient method based on Nichols et al.[8] methodology, which we used to prepare 8-methylTHIQ-4-one. The key step of this methodology a very mild low controlled temperature intramolecular Friedel–Crafts type cyclization. The synthesis of 8-bromoTHIQ-4-one (**6**) was started with the standard reductive amination[9] of 2-bromobenzaldehyde and glycine methyl ester[10] (**1**) to give the secondary amine **2**. *N*-protection of the amine **2** with a *p*-toluenesulfonyl group, hydrolysis of the ester function and the subsequent activation into its acid chloride allowed the required precursor **5** to cyclization (see Scheme 2).

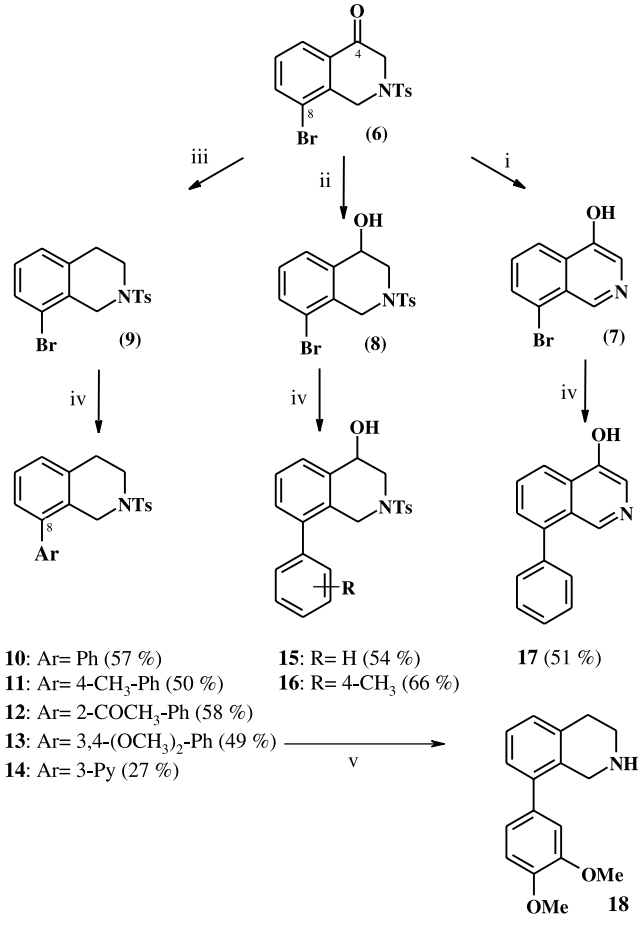


Scheme 2. Synthesis of 8-bromoTHIQ-4-one. Reagents and conditions: (i) methylglycinate, Et_3N/EtOH, $MgSO_4$, rt, 2 h, followed by $NaBH_4$, rt, overnight; (ii) PTSCl, 4-DMAP/Et_3N, CH_2Cl_2, 0 °C to rt, 6 h; (iii) 15% aq NaOH, reflux, 3 h; (iv) $SOCl_2$, CH_2Cl_2, reflux, 5 h; (v) $AlCl_3$, CH_2Cl_2, −78 to −10 °C, 4 h.

The treatment of **5** with $AlCl_3$ in CH_2Cl_2 at −78 °C leads to 8-bromoTHIQ-4-one **6** in a 64% yield showing thus that this cyclization could be achieved in the presence of an electron-withdrawing substituent. To obtain a clean and good yield reaction, it was essential to keep the temperature below −10 °C (Scheme 2).

Then starting from this 8-bromoTHIQ-4-one (**6**) all our attempts to perform palladium catalyzed Suzuki cross-coupling reactions with arylboronic acids in standard conditions failed, since it always led to the aromatized 8-bromoIQ-4-ol (**7**).

Studying the elimination of the tosyl group we demonstrated that the aromatization of **6** occurred in mild alkaline medium such as sodium hydrogen carbonate solution. To overcome this problem, the ketone **6** was reduced by using the combination of a 0.07% catalytic amount of $InCl_3$ and



Scheme 3. Synthesis of 8-aryl(TH)IQ. Reagents and conditions; yields refer to isolated products after column chromatography on silica gel: (i) aq satd $NaHCO_3$, EtOH; reflux, 77%; (ii) $NaBH_4$, EtOH, rt. 3 h, 95%; (iii) 0.07% $InCl_3$, Me_2SiHCl, CH_2Cl_2, reflux, 78%; (iv) 1 equiv 8-BrIQ, 1.3 equiv $RB(OH)_2$, base (3 equiv 2 M Na_2CO_3 or 2 equiv NaOH), toluene/EtOH 20:1, 5% $Pd(PPh_3)_4$, 27–66%; (v) Na/NH_3 (liq.), THF, 62%.

Me_2SiHCl (4.7 equiv) in CH_2Cl_2 at reflux[11] to give the 8-Br-THIQ (**9**). Only partial reduction to the alcohol was found using other Lewis acid reagents such as $AlCl_3$ in combination with $NaBH_4$ or $AlLiH_4$. Furthermore, when we used the hydrogenation standard methods (e.g., H_2/Pd–C) the results were not very satisfactory because of the debromination or partial cleavage of the *N*-tosyl group leading to unusable mixtures. Finally we prepared 8-bromo-THIQ-4-ol (**8**) using $NaBH_4$ in ethanol (Scheme 3).

To achieve our goal we submitted the three key intermediates **7**, **8**, **9** to palladium catalyzed Suzuki cross-coupling reactions. In all cases and in standard conditions the results were satisfactory producing 8-(*het*)arylTHIQ (**10**–**14**), 8-arylTHIQ-4-ol (**15**,**16**) and 8-phenylIQ-4-ol **17** in 27–66% yield. *N*-Tosyl protecting group can be removed under standard conditions[12] (sodium in ammonia), for example, *N*-tosyl derivative (**13**) gave the corresponding deprotected 8-(3,4-dimethoxyphenyl)THIQ[5e] (**18**) in good yield (Scheme 3).

These palladium-catalyzed Suzuki cross-coupling reactions, enabled us to gain access to 8-arylisoquinoline derivatives, which would have been difficult to prepare via other methods.

In conclusion, this study demonstrates that, thanks to our efficient and new method of synthesis, 8-arylIQ derivatives can be obtained by a straightforward route. Moreover, it also shows that 8-bromoTHIQ-4-one opens the way to a valuable medicinal chemistry scaffolding.

3. Experimental

3.1. General instrumentation

Commercial reagents were used without additional purification. Melting points were taken on a Wagner and Heizbank system Kofler type WME. IR spectra were run on a Perkin–Elmer BX FT-IR spectrometer using KBr pellets. EIMS and HREIMS were recorded on a JEOL JMS GCMate spectrometer. Liquid chromatography with mass spectrometry detection (LC–MS) with ESI (electrospray ionization) in positive mode was determined on a HPLC–MS Waters 2695. ^{1}H NMR and ^{13}C NMR were recorded on a JEOL Lambda 400 Spectrometer at 400 and 100 MHz, respectively. Coupling constants (*J*) are reported in Hz. NMR chemical shifts are reported in ppm downfield from an internal solvent peak. All reactions were monitored by analytical TLC. The residues were purified through silica gel 60 (0.063–0.2 mm) (Merck). Elemental analyses for new compounds were performed at the 'Institut de Recherche en Chimie Organique Fine' (Rouen-France).

3.2. General procedure for synthesis of isoquinolines 7, 8, 9

3.2.1. Methyl *N*-(2-bromobenzyl)glycinate (2). Prepared from glycine methyl ester[10] (**1**, 72 g, 0.8 mol) and 2-bromobenzaldehyde (98 g, 0.53 mol) by standard procedure.[9] The residue was purified by silica gel column chromatography (cyclohexane/EtOAc, 80:20) to yield **2** (148 g, 0.57 mol, 71%). Mp: 84–86 °C. IR: 3340, 2942, 1743, 1466, 1438, 1202, 1026, 752 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 (d, 1H, J=8.0 Hz), 7.36 (d, 1H, J=7.7 Hz), 7.20 (t, 1H, J=7.5 Hz), 7.10 (t, 1H, J=7.5 Hz), 3.81 (s, 2H), 3.70 (s, 3H), 3.42 (s, 2H), 2.10 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.0, 138.0, 132.2, 129.6, 128.5, 127.0, 123.5, 52.4, 52.1, 49.3. EIMS *m*/*z* (%) 257 $[M]^+$(3), 198 (73), 184 (28), 169 (100). Anal. Calcd for $C_{10}H_{12}NO_2Br$: C, 46.53; H, 4.69; N, 5.43. Found: C, 46.61; H, 4.73; N, 5.63.

3.2.2. Methyl *N*-(2-bromobenzyl)-*N*-[(4-methylphenyl)-sulfonyl]glycinate (3). The *p*-toluenesulfonyl chloride (42.51 g, 0.22 mol) was added to a stirred solution of amine (**2**, 57.42 g, 0.22 mol) 4-DMAP (1.36 g, 0.011 mol) and Et_3N (62.68 mL, 0.45 mol) in CH_2Cl_2 (400 mL) at 0 °C. The reaction mixture was stirred at room temperature for 6 h, and then quenched by addition of 2 N HCl. The layers were separated and the organic layer was washed with H_2O, brine, dried over $MgSO_4$ and concentrated to provide a white residue, which crystallized from CH_2Cl_2/EtOAc giving the compound **3** as colourless crystals (70.7 g, 0.17 mol, 77%). Mp: 104–106 °C. IR: 3483, 2952, 1751, 1597, 1430, 1311, 1210, 1118, 1095, 768, 548 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75 (d, 2H, J=8.2 Hz), 7.47–7.53 (m, 2H), 7.26–7.35 (m, 3H), 7.17 (t, 1H, J=7.6 Hz), 4.62 (s, 2H), 3.99 (s, 2H), 3.56 (s, 3H), 2.45 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.0, 143.6, 136.5, 134.5, 132.8, 130.3, 129.5, 129.4, 127.8, 127.4, 123.7, 52.0, 51.1, 47.5, 21.5. LC–MS (ES positive mode) *m*/*z* 258 $[M+1-Ts]^+$ EIMS *m*/*z* (%) 353 $[M-COOCH_3]^+$(35), 257 (70), 198 (10), 169 (100), 91 (80). Anal. Calcd for $C_{17}H_{18}NO_4BrS$: C, 49.52; H, 4.40; N, 3.40. Found: C, 49.57; H, 4.63; N, 3.28.

3.2.3. *N*-(2-Bromobenzyl)-*N*-[(4-methylphenyl)sulfonyl)]-glycine (4). The acetic acid methyl ester **3** (64.2 g, 0.16 mol) was treated with a 15% aq NaOH solution (400 mL) and refluxed for 3 h. The mixture was cooled in an ice-bath, diluted with H_2O and washed with CH_2Cl_2, and then the aqueous layer was acidified with 1 M HCl, and extracted with AcOEt. The combined organic layers were washed with H_2O, brine and evaporated under reduced pressure. The residue was crystallized from CH_2Cl_2/EtOAc to give the acid **4** as white crystals (47.64 g, 0.12 mol, 75%). IR: 3430, 3055, 2972, 1728, 1597, 1440, 1345, 1167, 1095, 950, 756, 546 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.49 (br s, 1H), 7.73 (d, 2H, J=8.2 Hz,), 7.51 (d, 1H, J=8.0 Hz), 7.45 (d, 1H, J=7.7 Hz), 7.26–7.30 (m, 3H), 7.16 (t, 1H, J=7.8 Hz), 4.61 (s, 2H), 4.01 (s, 2H), 2.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.2, 143.7, 136.2, 134.1, 132.7, 130.3, 129.5, 127.7, 127,2, 123.7, 51.2, 47.4, 21.4. LC–MS (ES positive mode) *m*/*z* 398 $[M+1]^+$. EIMS *m*/*z* (%) 354 $[M-COO]^+$(14), 242 (36), 198 (13), 169 (83), 91 (100). Anal. Calcd for $C_{16}H_{16}NO_4BrS$: C, 48.25; H, 4.05; N, 3.52. Found: C, 48.43; H, 3.98; N, 3.71.

3.2.4. *N*-(2-Bromobenzyl)-*N*-[(4-methylphenyl)sulfonyl)]-glycyl chloride (5). Under argon, a solution of the acid **4** (46 g, 0.116 mol) in CH_2Cl_2 (350 mL) was treated with $SOCl_2$ (25.4 mL, 0.348 mol) and refluxed for 5 h. The solvent and the excess of $SOCl_2$ were distilled off under vacuum. The residue was used directly in the following

reaction without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73 (d, 2H, J=8.4 Hz), 7.51 (d, 1H, J=8.0, 1.2 Hz), 7.45 (dd, 1H, J=7.8, 1.6 Hz), 7.29–7.34 (m, 3H), 7.18 (td, 1H, J=7.7, 1.6 Hz), 4.58 (s, 2H), 4.40 (s, 2H), 2.43 (s, 3H).

3.2.5. 8-Bromo-2-[(4-methylphenyl)sulfonyl]-2,3-dihydro-1*H*-isoquinolin-4-one (6). $AlCl_3$ (560 mg, 4.20 mmol) was added in portions with stirring to a solution of the acid chloride **5** (500 mg) in anhydrous CH_2Cl_2 (15 mL) previously pre-cooled to −78 °C and under N_2 atmosphere. The reaction mixture was allowed to warm to −10 °C over 4 h. Then, a 10% aq HCl solution–ice mixture was added dropwise at −10 °C and stirred for 30 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, washed with H_2O, brine, dried over $MgSO_4$, filtered, evaporated and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (cycloxenane/EtOAc, 90:10) to give 8-bromoTHIQ-4-one **6** as a white solid (291 mg, 64%). IR: 3387, 2926, 2863, 1706, 1586, 1431, 1349, 1286, 1162, 1091, 1028, 961, 860, 814, 699, 544 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, 1H, J=7.8 Hz), 7.71 (d, 1H, J=7.9 Hz), 7.60 (d, 2H, J=8.2 Hz), 7.19–7.24 (m, 3H), 4.57 (s, 2H), 4.04 (s, 2H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.7, 144.2, 137.8, 137.6, 132.9, 131.7, 129.8, 129.4, 128.7, 125.9, 121.5, 53.3, 48.0, 21.3. EIMS *m/z* (%) 379 $[M]^+$(5), 224 (100), 148 (23), 105 (54), 91 (49). HRMS (EI) (M^+) calcd for $C_{16}H_{14}NO_3SBr$ 378.9877, found 378.9888. Anal. Calcd for $C_{16}H_{14}NO_3SBr$: C, 50.54; H, 3.71; N, 3.68. Found: C, 50.45; H, 3.68; N, 3.70.

3.2.6. 8-Bromoisoquinolin-4-ol (7). A solution of 8-bromo-THIQ-4-one **6** (770 mg, 2.03 mmol) and satd aq $NaHCO_3$ solution (50 mL) in EtOH (10 mL) was refluxed overnight. The solvent was partially evaporated and the mixture was extracted with EtOAc. The organic layer was washed with H_2O, brine, dried over $MgSO_4$, filtered, evaporated and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (cyclohexane/EtOAc, 80:20) to yield **7** as a brown powder (350 mg, 1.56 mmol, 77%). Mp: 230 °C. IR: 3438, 2925, 2854, 1585, 1458, 1402, 1364, 1304, 1145, 850, 802 cm^{-1}. ^{1}H NMR (DMSO, 400 MHz) δ 10.78 (br s, 1H), 8.95 (s, 1H), 8.17 (s, 1H), 8.15 (d, 1H, J=8.2 Hz), 7.96 (d, 1H, J=7.6 Hz), 7.61 (t, 1H, J=7.9 Hz). ^{13}C NMR (DMSO, 100 MHz) δ 148.1, 141.1, 131.7, 129.7, 128.0, 126.8, 126.5, 121.3, 120.5. EIMS *m/z* (%) 223 $[M]^+$(33), 184 (34), 116 (59), 91 (100).). HRMS (EI) (M^+) calcd for C_9H_6NOBr 222.9632, found 222.9617. Anal. Calcd for C_9H_6NOBr: C, 48.25; H, 2.70; N, 6.25. Found: C, 48.37; H, 2.64; N, 6.33.

3.2.7. 8-Bromo-2-[(4-methylphenyl)sulfonyl]-1,2,3,4-tetrahydroisoquinolin-4-ol (8). Over an ice-bath, $NaBH_4$ (600 mg, 15.79 mmol) was added to a solution of 8-bromo-THIQ-4-one **6** (2 g, 5.27 mmol) in EtOH (50 mL). The reaction mixture was stirred at room temperature for 3 h. After this time, the suspension was basified with saturated $NaHCO_3$ saturated and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc, 70:30) to afford the compound **8** as a white solid (1.9 g, 4.98 mmol, 95%). Mp: 124–126 °C. IR: 3410, 2921, 2360, 1596, 1432, 1327, 1159, 1091, 967, 814, 666 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, 2H, J=8.3 Hz), 7.47 (d, 1H, J=7.8 Hz), 7.41 (d, 1H, J=7.8 Hz), 7.37 (d, 2H, J=8.3 Hz), 7.15 (t, 1H, J=7.8 Hz), 4.75 (m, 1H), 4.48 (d, 1H, J=15.8 Hz), 3.83 (d, 1H, J=15.8 Hz), 3.66 (dd, 1H, J=3.2, 11.9 Hz), 3.09 (dd, 1H, J=3.2, 11.9 Hz), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.2, 138.2, 132.9, 132.2, 131.3, 130.0, 128.7, 128.3, 128.0, 127.1, 121.8, 66.1, 50.8, 50.1, 21.5. EIMS *m/z* (%) 381 $[M]^+$(5), 226 (53), 198 (51), 184 (100), 155 (94), 91 (62). Anal. Calcd for $C_{16}H_{16}NO_3SBr$: C, 50.27; H, 4.22; N, 3.66. Found: C, 50.38; H, 4.17; N, 3.58.

3.2.8. 8-Bromo-2-[(4-methylphenyl)sulfonyl]-1,2,3,4-tetrahydroisoquinoline (9). A mixture of 0.07% $InCl_3$ (82 mg, 0.37 mmol) and Me_2SiHCl (2.34 g, 24.8 mmol) in anhydrous CH_2Cl_2 (6 mL) at room temperature was treated with 8-BrTHIQ-4-one (**6**, 2.0 g, 5.27 mmol) in anhydrous CH_2Cl_2 (10 mL). The reaction mixture was stirred and refluxed overnight, cooled at room temperature, diluted with H_2O and extracted with CH_2Cl_2. The organic layers were washed with 5% aq HCl, satd $NaHCO_3$, brine, dried over $MgSO_4$, partially evaporated and precipitated with MeOH to obtain a white solid (**8**, 1.5 g, 4.11 mmol, 78%). Mp: 112–114 °C. IR: 2963, 2361, 1598, 1261, 1093, 1024, 800 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.62 (d, J=8.3 Hz, 2H), 7.23 (m, 3H), 6.93–6.98 (m, 2H), 4.12 (s, 2H), 3.26 (t, J=5.7 Hz, 2H), 2.87 (t, J=5.7 Hz, 2H), 2.36 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.8, 135.9, 133.3, 131.3, 130.4, 129.8, 128.0, 127.9, 122.5, 48.5, 43.2, 29.3, 21.5. EIMS *m/z* (%) 365 $[M]^+$(10), 210 (100), 184 (24), 130 (15), 91 (40).). HRMS (EI) (M^+) calcd for $C_{16}H_{16}NO_2SBr$ 365.0085, found 365.0145. Anal. Calcd for $C_{16}H_{16}NO_2SBr$: C, 52.47; H, 4.40; N, 3.82. Found: C, 52.29; H, 4.31; N, 3.91.

3.3. General procedure for the synthesis of 8-(*Het*)-aryltetrahydroisoquinolines 10–16

A degassed (Ar) solution of 8-BrTHIQ (**9**), (350 mg, 0.96 mmol) or 8-BrTHIQ-4-ol (**8**, 350 mg, 0.92 mmol) in a mixture of toluene/EtOH (20:1, v/v), (42 mL) and 0.05% $Pd(PPh_3)_4$ (80 mg, 0.07 mmol) was treated with the aryllboronic acid (1.5 equiv), and 2 M Na_2CO_3 (3 equiv). The reaction mixture was refluxed overnight under nitrogen. The mixture was then hydrolysed with H_2O and extracted with EtOAc. The organic layers were washed with brine and water, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude material was purified through silica gel column chromatography yielding the 8-(*Het*)aryltetrahydroisoquinolines **10**–**16**.

3.3.1. 8-Phenyl-2-[(4-methylphenyl)sulfonyl]-1,2,3,4-tetrahydroisoquinoline (10). Column chromatography (petroleum ether/EtOAc, 96:4) yielded a white solid (**10**, 199 mg, 0.55 mmol, 57%). Mp: 150–152 °C. IR: 3428, 2920, 2360, 2326, 1597, 1495, 1452, 1338, 1165, 1090, 954, 814, 705 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48 (d, 2H, J=8.3 Hz), 7.34–7.29 (m, 3H), 7.17 (d, 2H, J=8.3 Hz), 7.12–7.10 (m, 3H), 7.0–6.95 (m, 2H), 4.01 (s, 2H), 3.28 (t, 2H, J=5.9 Hz), 2.91 (t, 2H, J=5.9 Hz), 2.32 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.5, 140.6, 140.0, 133.6,

133.5, 129.6, 129.4, 128.8, 128.4, 127.9, 127.6, 127.5, 126.6, 46.6, 43.5, 29.2, 21.4. EIMS *m/z* (%) 363 $[M]^+$(17), 208 (100), 165 (32), 133 (25), 91 (56). HRMS (EI) (M^+) calcd for $C_{22}H_{21}NO_2S$ 363.1293, found 363.1273. Anal. Calcd for $C_{22}H_{21}NO_2S$: C, 72.70; H, 5.82; N, 3.85. Found: C, 72.83; H, 5.77; N, 3.87.

3.3.2. 8-(4-Methylphenyl)-2-[(4-methylphenyl)sulfonyl]-1,2,3,4-tetrahydroisoquinoline (11). Column chromatography (petroleum ether/EtOAc, 96:4) yielded a white solid (180 mg, 0.48 mmol, 50%). Mp: 178–180 °C. IR: 3424, 2919, 2855, 2360, 1592, 1515, 1458, 1358, 1338, 1168, 952, 940, 789, 750 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.57 (d, 2H, $J=8.3$ Hz), 7.27 (d, 2H, $J=8.0$ Hz), 7.23–7.16 (m, 3H), 7.08 (d, 2H, $J=8.0$ Hz), 7.06–7.02 (m, 2H), 4.12 (s, 2H), 3.35 (t, 2H, $J=6.0$ Hz), 2.97 (t, 2H, $J=6.0$ Hz), 2.42 (s, 3H), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.5, 140.6, 137.1, 137.0, 133.6, 133.5, 129.6, 129.5, 129.1, 128.6, 128.0, 127.7, 127.6, 126.5, 46.7, 43.6, 29.2, 21.5, 21.2. EIMS *m/z* (%) 377 $[M]^+$(10), 221 (74), 178 (37), 132 (66), 104 (51), 91 (100), 77 (37). HRMS (EI) (M^+) calcd for $C_{23}H_{23}NO_2S$ 377.1449, found 377.1391. Anal. Calcd for $C_{23}H_{23}NO_2S$: C, 73.18; H, 6.14; N, 3.71. Found: C, 73.09; H, 6.22; N, 3.84.

3.3.3. 8-(2-Acetylphenyl)-2-[(4-methylphenyl)sulfonyl]-1,2,3,4-tetrahydroisoquinoline (12). Column chromatography (cyclohexane/EtOAc, 80:20) yielded a beige syrup (225 mg, 0.56 mmol, 58%). Mp: <50 °C. IR: 3430, 2920, 2840, 2360, 2342, 1684, 1596, 1457, 1337, 1164, 1090, 953, 815, 668 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.63 (d, 1H, $J=7.3$ Hz), 7.46–7.37 (m, 4H), 7.16 (d, 2H, $J=7.8$ Hz), 7.05 (dd, 2H, $J=7.3$, 1.2 Hz), 6.99 (d, 1H, $J=7.6$ Hz), 6.79 (d, 1H, $J=7.3$ Hz), 3.96 (d, 1H, $J=15.6$ Hz), 3.72 (d, 1H, $J=15.6$ Hz), 3.30 (m, 1H), 3.17 (m, 1H), 2.86 (m, 2H), 2.28 (s, 3H), 1.97 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.4, 143.5, 139.3, 139.2, 138.5, 133.5, 131.3, 130.4, 129.5, 129.4, 128.6, 128.3 127.9, 127.4, 127.3, 126.4, 46.3, 43.3, 29.3, 28.9, 21.3. LC–MS (ES positive mode) *m/z* 405 $[M+1]^+$. EIMS *m/z* (%) 250 (100), 91 (26). HRMS (EI) (M^+) calcd for $C_{24}H_{23}NO_3S$ 405.1398, found 405.1352. Anal. Calcd for $C_{24}H_{23}NO_3S$: C, 71.09; H, 5.72; N, 3.45. Found: C, 70.88; H, 5.64; N, 3.39.

3.3.4. 8-(3,4-Dimethoxyphenyl)-2-[(4methylphenyl)-sulfonyl]-1,2,3,4-tetrahydroisoquinoline (13). Column chromatography (cyclohexane/EtOAc, 80:20) yielded a brown syrup (200 mg, 0.47 mmol, 49%). Mp: <50 °C. IR: 3433, 2923, 2832, 2357, 2255, 1598, 1516, 1464, 1337, 1164, 1025, 952, 814, 749, 660 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.44 (d, 2H, $J=8.2$ Hz), 7.12 (d, 2H, $J=8.2$ Hz), 7.03 (t, 1H, $J=7.4$ Hz), 6.92 (m, 2H), 6.78 (d, 1H, $J=8.1$ Hz), 6.62 (dd, 1H, $J=8.1$, 1.9 Hz), 6.57 (d, 1H, $J=1.9$ Hz), 3.97 (s, 2H), 3.80 (s, 3H), 3.72 (s, 3H), 3.21 (t, 2H, $J=6.1$ Hz), 2.84 (t, 2H, $J=6.1$ Hz), 2.25 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.4, 148.1, 140.0, 134.0, 133.1, 132.4, 129.3, 127.7, 127.5, 127.3, 126.3, 120.8, 111.8, 111.0, 55.6, 55.5, 46.4, 43.3, 28.9, 21.1. EIMS *m/z* (%) 423 $[M]^+$(12), 274 (100), 268 (44), 149 (28), 137 (18), 106 (59), 98 (11). HRMS (EI) (M^+) calcd for $C_{24}H_{25}NO_4S$ 423.1504, found 423.1504. Anal. Calcd for $C_{24}H_{25}NO_4S$: C, 68.06; H, 5.95; N, 3.31. Found: C, 68.04; H, 5.91; N, 3.28.

3.3.5. 8-(Pyridin-3-yl)-2-[(4-methylphenyl)sulfonyl]-1,2,3,4-tetrahydroisoquinoline (14). Column chromatography (cyclohexane/EtOAc, 80:20) yielded a beige solid (95 mg, 0.26 mmol, 27%). Mp: 104–106 °C. IR: 3457, 2924, 2850, 2360, 1597, 1457, 1338, 1163, 1019, 950, 815, 785, 751, 661 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.68 (br s, 1H), 8.50 (br s, 1H), 7.57 (d, 2H, $J=8.0$ Hz), 7.30–7.23 (m, 5H), 7.14 (d, 1H, $J=7.6$ Hz), 7.03 (d, 1H, $J=7.6$ Hz), 4.07 (s, 2H), 3.37 (t, 2H, $J=5.9$ Hz), 3.03 (t, 2H, $J=5.9$ Hz), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.5, 149.0, 143.7, 136.7, 136.3, 134.0, 133.3, 129.7, 128.9, 128.2, 127.6, 126.9, 46.6, 43.5, 29.2, 21.5. EIMS *m/z* (%) 364.$[M]^+$(36), 209 (100), 180 (49), 155 (23), 91 (73). HRMS (EI) (M^+) calcd for $C_{21}H_{20}N_2O_2S$ 364.1245, found 364.1221. Anal. Calcd for $C_{21}H_{20}N_2O_2S$: C, 69.21; H, 5.53; N, 7.69. Found: C, 69.44; H, 5.58; N, 7.73.

3.3.6. 8-Phenyl-2-[(4-methylphenyl)sulfonyl]-1,2,3,4-tetrahydroisoquinolin-4-ol (15). Column chromatography (petroleum ether/CH_2Cl_2/EtOAc, 90:4:6) yielded a white solid (188 mg, 0.50 mmol, 54%). Mp: 122–124 °C. IR: 3517, 3065, 3029, 2920, 2855, 1595, 1497, 1458, 1340, 1252, 1219, 1161, 1089, 952, 811, 762, 703 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.57 (d, 2H, $J=8.3$ Hz), 7.43–7.36 (m, 4H), 7.29–7.26 (m, 3H), 7.18–7.16 (m, 2H), 7.12–7.10 (m, 1H), 4.80 (br s, 1H), 4.26 (d, 1H, $J=15.5$ Hz), 3.83 (d, 1H, $J=15.5$ Hz), 3.58 (dd, 1H, $J=12.0$, 3.8 Hz), 3.16 (dd, 1H, $J=12.0$, 3.8 Hz), 3.10 (br s, 1H), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.0, 140.3, 139.7, 135.8, 133.0, 133.5, 129.9, 129.8, 129.3, 128.7, 128.6, 128.5, 127.7, 127.3, 66.4, 50.8, 47.1, 21.5. EIMS *m/z* (%) 379 $[M]^+$(8), 224 (48), 206 (34), 196 (100), 167 (57), 155 (24), 91 (38). HRMS (EI) (M^+) calcd for $C_{22}H_{21}NO_3S$ 379.1242, found 379.1266. Anal. Calcd for $C_{22}H_{21}NO_3S$: C, 69.63; H, 5.58; N, 3.69. Found: C, 69.57; H, 5.52; N, 3.81.

3.3.7. 8-(4-Methylphenyl)-2-[(4-methylphenyl)sulfonyl]-1,2,3,4-tetrahydroisoquinolin-4-ol (16). Column chromatography (petroleum ether/EtOAc/CH_2Cl_2, 90:4:6) yielded a yellow solid (240 mg, 0.61 mmol, 66%). Mp: 190–192 °C. IR: 3550, 3025, 2894, 2361, 2319, 1594, 1514, 1448, 1352, 1336, 1168, 955, 815, 730, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.61 (d, 2H, $J=8.2$ Hz), 7.43 (d, 1H, $J=7.6$ Hz), 7.33–7.30 (m, 3H), 7.23 (d, 2H, $J=7.8$ Hz), 7.15 (d, 1H, $J=7.6$ Hz), 7.08 (d, 2H, $J=7.8$ Hz), 4.80 (br s, 1H), 4.36 (d, 1H, $J=15.4$ Hz), 3.75 (m, 2H), 3.06 (dd, 1H, $J=12.0$, 2.9 Hz), 2.70 (br s, 1H), 2.43 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.9, 140.3, 137.4, 136.6, 135.7, 132.9, 129.0, 129.7, 129.3, 129.2, 128.5, 128.3, 127.7, 127.3, 66.4, 50.8, 47.1, 21.5, 21.2. EIMS *m/z* (%) 393 $[M]^+$(9), 238 (31), 210 (77), 165 (41), 91 (100). HRMS (EI) (M^+) calcd for $C_{23}H_{23}NO_3S$ 393.1398, found 393.1386. Anal. Calcd for $C_{23}H_{23}NO_3S$: C, 70.20; H, 5.89; N, 3.56. Found: C, 70.01; H, 5.97; N, 3.44.

3.3.8. Synthesis of 8-phenylisoquinolin-4-ol (17). The synthesis was done using the same procedure as for compounds **10**–**14**, using the corresponding starting material, 8-BrIQ-4-ol (**7**, 250 mg, 1.12 mmol). After usual workup the crude material was purified through silica gel column chromatography (cyclohexane/EtOAc, 70:30) yielded a brown solid (127 mg, 0.57 mmol, 51%). Mp: 174–176 °C. IR: 3438, 2360, 2326, 1613, 1577, 1409, 1297,

1280, 1133, 1069, 860, 819, 760, 700 cm^{-1}. ^1H NMR ($CDCl_3$ + three drops CD_3OD, 400 MHz) δ 10.60 (br s, 1H) 8.71 (br s, 1H), 8.28 (d, 1H, J=8.0 Hz), 7.99 (br s, 1H), 7.74 (t, 1H, J=8.0 Hz), 7.50 (br s, 6H). ^{13}C NMR ($CDCl_3$ + three drops CD_3OD, 100 MHz) δ 149.5, 140.9, 140.3, 138.9, 129.8, 128.8, 128.6, 128.2, 127.6, 125.0, 120.7. EIMS *m/z* (%) 221 $[M]^+$(100), 165 (82), 139 (14), 84 (32). HRMS (EI) (M^+) calcd for $C_{15}H_{11}NO$ 221.0841, found 221.0826. Anal. Calcd for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.31; H, 4.87; N, 6.21.

3.4. Deprotection of *N*-tosyl group

3.4.1. 8-(3,4-Dimethoxyphenyl)-1,2,3,4-tetrahydro-isoquinoline[5e] (18). The *N*-tosyl group was removed according to the literature[12], from 8-(3,4-dimethoxy-phenyl)-2-[(4-methyl-phenyl)sulphonyl]-1,2,3,4 THIQ (**13**, 140 mg, 0.33 mmol) with sodium (31 mg, 1.33 mmol) in liquid ammonia (15 mL). After usual workup, the crude of the reaction was purified through silica gel column chromatography (CH_2Cl_2/MeOH, 90:10) to yield the deprotected tetrahydro-isoquinoline **18** (55 mg, 0.2 mmol, 62%). ^1H NMR (CD_3OD, 400 MHz) δ 7.35 (m, 2H), 7.27 (d, 1H, J=7.8 Hz), 7.16 (d, 1H, J=7.3 Hz), 6.85 (m, 2H), 4.18 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.49 (t, 2H, J=6.0 Hz), 3.20 (t, 2H, J=6.0 Hz), 2.79 (br s, 1H). ^{13}C NMR (CD_3OD, 100 MHz) δ 161.3, 142.1, 133.3, 130.9, 129.4, 129.3, 122.2, 115.7, 114.3, 56.7, 56.6, 44.9, 42.5, 26.4. EIMS *m/z* (%) 269 $[M]^+$(9), 268 (64), 238 (100), 195 (30), 131 (35), 91 (19).

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Synthesis of novel 1,3,4-benzotriazepine derivatives from 4-oxo-3,1-benzoxazine and 3,1-benzothiazine-2-carbonitriles

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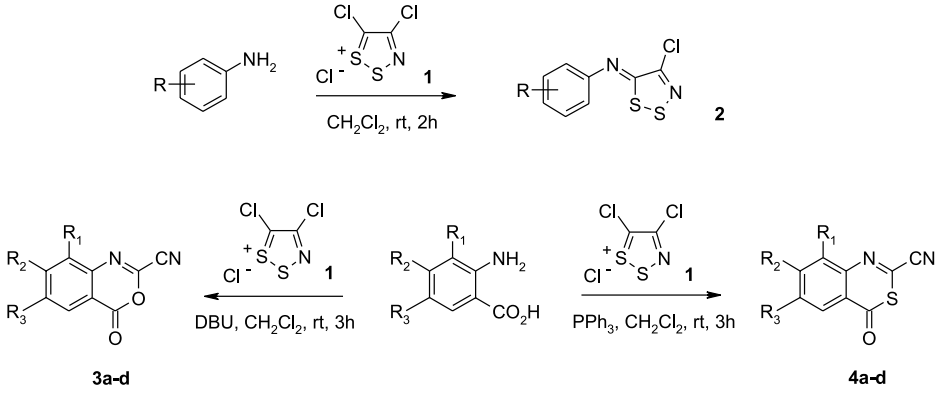
Abstract—Synthesis of novel oxygen and sulfur containing 1,3,4-benzotriazepine derivatives was performed via 3,1-benz-oxazine and 3,1-benzothiazine intermediates obtained from Appel's salt chemistry. We observed that the sulfur containing precursors reacted differently than their oxygenated congeners and, after rearrangement, afforded novel heterocyclic compounds (e.g., benzoxazin-4-thione and 2-cyano-1,3,4-triazepine).

1. Introduction

4*H*-3,1-Benzoxazin-4-ones have been known for more than a century[1] and compounds possessing this ring system are found in nature.[2] Some derivatives have been used as linking-units in thermally stable polymers[3] and have been shown to possess biological activity. They are potent inactivators of C1r serine protease[4] as well as inhibitors of human leukocyte elastase[5] and HSV-1 protease.[6]

By far the most popular and versatile route to the 3,1-benzoxazin-4-one moiety relies on anthranilic acid or its derivatives as a convenient starting material. As part of our main research program on the chemistry of 4,5-dichloro-1,2,3-dithiazolium chloride (Appel's salt)[7,8] **1**, we described that primary aromatic amines can be condensed with the salt **1** in dichloromethane at room temperature, followed by addition of pyridine, to give the stable crystalline imino-1,2,3-dithiazoles **2** (Scheme 1).



3a-d **4a-d**

Scheme 1. Synthesis of 3,1-benzoxazin-4-ones **3a–d** and 3,1-benzothiazin-4-ones **4a–d** from anthranilic acids (for yields see Table 1).

Keywords: 1,3,4-Triazepines; 3,1-Benzoxazines; 3,1-Benzothiazines; 4,5-Dichloro-1,2,3-dithiazolium chloride (Appel's salt).
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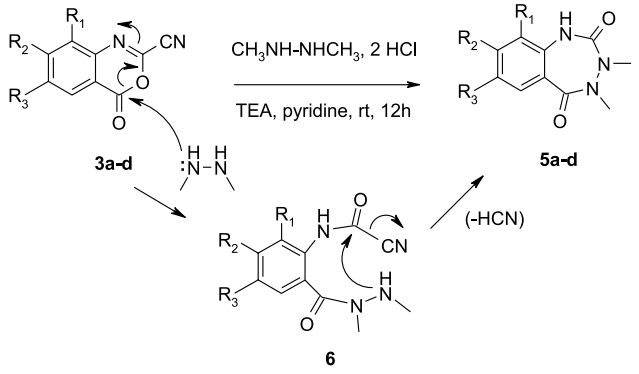
We observed that anthranilic acid and its benzo-substituted derivatives (e.g., 4-chloro and 4,5-dimethoxy-anthranilic acid) behave differently to all the anilines investigated and did not give the analogous imines **2** but rather 2-cyano-3,1-benzoxazin-4-ones derivatives **3**, and, with triphenylphosphine, it gave the novel 2-cyano-3,1-benzothiazin-4-ones **4**.[9] The chemistry of the 2-cyano-3,1-benzoxazin-4-ones derivatives **3** have been widely studied[1] but, to the best of our knowledge, the chemical behaviour of their sulfur containing counterparts **4** has rarely been reported.[10] Owing to our interest for access to novel heterocyclic compounds with potential pharmaceutical value, we decided to re-investigate the synthesis of the 2-cyano derivatives **3** and **4**. We extended the nature of the substituents present on the benzenic part of the molecule and, inspired by a preliminary example of diamine condensations on 3,1-benzoxazin-4-ones,[10] we studied the chemical transformation of these two rings in the presence of hydrazine derivatives.

In this paper, we describe the synthesis of substituted 1,3,4-triazepine-2,5-diones **5** (Scheme 2) from the starting 3,1-benzoxazin-4-ones **3** whilst condensation of 1,2-dimethylhydrazine on 4-oxo-3,1-benzothiazine-2-carbonitriles involves the synthesis of various unexpected products. Traditional thionation (P_2S_5) of the oxygenated congeners was also explored to afford novel 1,3,4-benzotriazepin-5-thiones **10** and 1,3,4-benzotriazepine-2,5-dithiones **11** in good yields (Scheme 5, Table 4).



Scheme 2. Synthesis of 1,3,4-benzotriazepine-2,5-diones **5** from benzoxazin-4-ones **3** (for yields see Table 2).

2. Results and discussion

2.1. Synthesis of 3,1-benzoxazin-4-one and 3,1-benzothiazin-4-one precursors

Compounds **3** and **4** were synthesised using a one-pot procedure via Appel's salt **1** chemistry.[8] It is now well known that the salt **1** reacts with primary aromatic amines to allow access to *N*-arylimino-1,2,3-dithiazoles **2**, which have proved to be versatile synthetic intermediates in organic synthesis and can be converted into 2-cyano derivatives of various heterocyclic skeletons.[8–10] We decided to re-investigate our preliminary work and we observed that reaction of anthranilic acids with Appel's salt **1** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), in methylene chloride and at room temperature, allows the synthesis of 4-oxo-4*H*-3,1-benzoxazine-2-carbonitriles **3a–d** (Scheme 1 and Table 1). Two novel methoxy substituted congeners were then obtained (**3a** and **3b**), together with a small amount (less than 10%) of their benzothiazine analogues **4a** and **4b**. Using triphenylphosphine, instead of DBU, the reaction led to 4*H*-3,1-benzothiazin-4-one-2-carbonitriles **4a–d** in good yields (e.g., 67 and 55% for the novel derivatives **4a** and **4b**, respectively) (Scheme 1 and Table 1).

Table 1

Compound	R_1	R_2	R_3	Yield (%)
3a	H	OCH_3	OCH_3	31
3b	OCH_3	OCH_3	OCH_3	43
3c	H	H	H	26
3d	H	H	CH_3	20
4a	H	OCH_3	OCH_3	67
4b	OCH_3	OCH_3	OCH_3	55
4c	H	H	H	28
4d	H	H	CH_3	38

2.2. Synthesis of 1,3,4-benzotriazepine-2,5-diones

The second part of our work consisted to investigate the possible reaction of 3,1-benzoxazines **3** and benzothiazines **4** with diamines. We were inspired by previous works showing that reaction of 4-oxo-3,1-benzoxazine-2-carbonitrile with amines may lead to the corresponding quinazolin-4-ones.[1,11] In our study, we suggested that the presence of the cyano group may involve different ways. Although, preliminary experiments with hydrazine or ethylenediamine were unfruitful and led to complex mixtures, we observed that treatment of 3,1-benzoxazin-4-ones **3a–d** with 1,2-dimethylhydrazine dihydrochloride allowed the convenient access to novel substituted 1,3,4-benzotriazepine-2,5-diones **5a–d** (Scheme 2 and Table 2). The mechanism described in Scheme 2 suggests that 1,3,4-benzotriazepine-2,5-diones **5a–d** would be obtained through the intermediate compounds **6** themselves obtained by nucleophilic attack of 1,2-dimethylhydrazine on position 4 of the benzoxazin-4-one ring. Cyclisation and elimination of hydrogen cyanide may lead to products **5a–d**, which are stable white or pale yellow solids.

Table 2

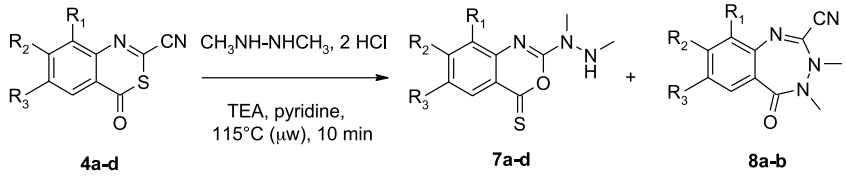
Compound	R_1	R_2	R_3	Yield (%)
5a	H	OCH_3	OCH_3	65
5b	OCH_3	OCH_3	OCH_3	65
5c	H	H	H	77
5d	H	H	CH_3	67

Considering our one-pot synthesis of the benzoxazin-4-one ring **3a–d** (via Appel's salt chemistry), the method presented here constitutes a short and efficient access to the rarely described 1,3,4-benzotriazepine-2,5-dione skeleton. The novel derivatives obtained can be considered as interesting intermediates for the preparation of novel rings.

2.3. Synthesis of sulfur containing 1,3,4-benzotriazepines

The following part of our study was focused on the chemical behaviour of the 4-oxo-benzothiazine-2-carbonitriles **4**.

According to the results obtained above, we decided to



Scheme 3. Nucleophilic attack of 1,2-dimethylhydrazine on the 3,1-benzothiazin-4-one skeleton (for yields see Table 3).

study the condensation of 1,2-dimethylhydrazine with various starting benzothiazines **4a–d**. Using the procedures described for the oxygenated partners **3a–d**, we observed that treatment of the precursors **4a–d** with 1,2-dimethylhydrazine dihydrochloride led to various products. In this case, an interesting improvement of the procedure was observed (short reaction time and better yields) under microwave irradiation.[12] Condensation of 1,2-dimethylhydrazine with the two compounds **4a** and **4b** afforded two different products (**7a–b** and **8a–b**), whilst starting from compounds **4c** and **4d** gave only one product identified as the *N*-substituted benzoxazine-4-thiones **7c** and **7d**, respectively. In the two experiments from **4a** and **4b**, the 3,1-benzoxazin-4-thiones **7a** and **7b** were also mainly generated, together with a small amount of the cyclised 5-oxo-benzo[1,3,4]benzotriazepine-2-carbonitriles **8a** and **8b** (Scheme 3 and Table 3).

Table 3

Starting compound	R_1	R_2	R_3	Yield of **7** (%)	Yield of **8** (%)
4a	H	OCH_3	OCH_3	40	36
4b	OCH_3	OCH_3	OCH_3	36	27
4c	H	H	H	55	—
4d	H	H	CH_3	70	—

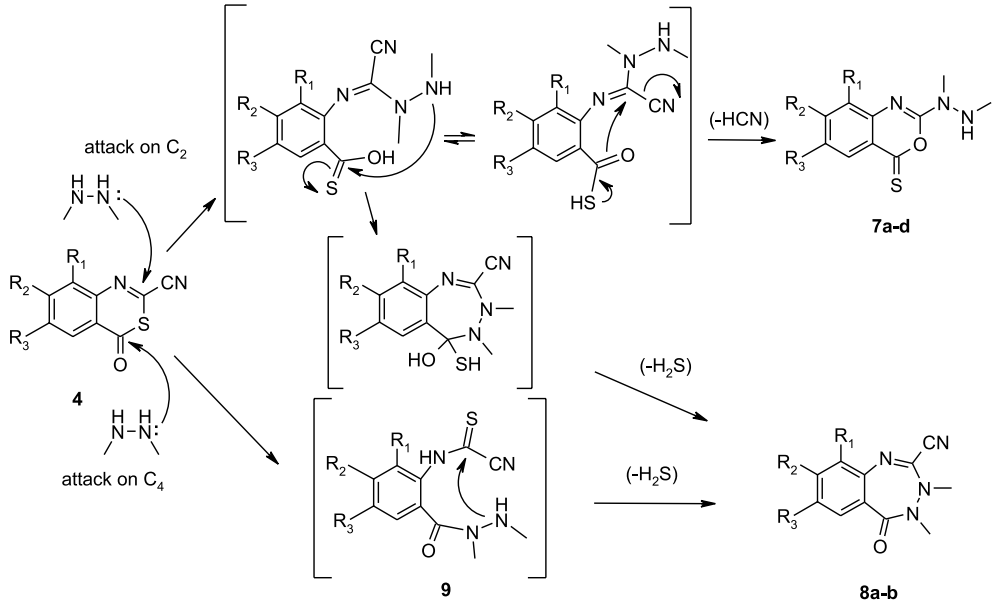
Table 4

Starting compound	R_1	R_2	R_3	Yield of **10** (%)	Yield of **11** (%)
5a	H	OCH_3	OCH_3	64	19
5b	OCH_3	OCH_3	OCH_3	74	18
5c	H	H	H	66	13
5d	H	H	CH_3	56	24

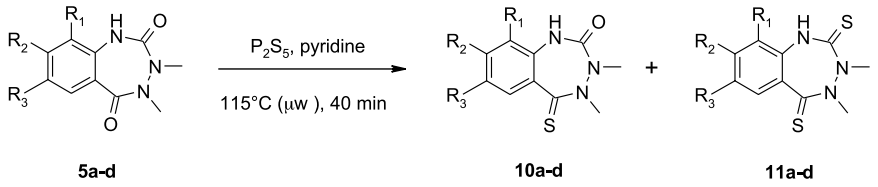
The mechanism suggested before for the benzo[1,3,4]triazepine-2,5-diones **5** may explain formation of **8a** and **8b** by a preliminary attack of the hydrazine on carbon 4 of the 3,1-benzothiazin-4-one skeleton (**4a** and **4b**), cyclisation of the intermediate cyanothioformamide **9** by nucleophilic attack on the thione carbon and ejection of sulfur hydrogen. In contrast, synthesis of the benzoxazine-4-thiones **7a–d** may suggest a first attack of hydrazine on carbon 2 of **4** and cyclisation of the opened intermediate, accompanied by elimination of hydrogen cyanide. In this route, a nucleophilic attack of a nitrogen atom on the carbon of the thioacid may also be suggested for the synthesis of **8** accompanied, here again, by elimination of sulfur hydrogen (Scheme 4).

In the preceding experiments, no trace of expected thioxo-benzo[1,3,4]triazepinones was detected. Synthesis of such compounds was successfully realised by heating the dioxygenated precursors **5a–d** in the presence of phosphorus pentasulfide, in pyridine.[13] The 5-thioxo-benzo-[1,3,4]triazepin-2-ones **10a–d** were obtained as the major products, with a small amount of the corresponding dithiones **11** (Scheme 5 and Table 4).

The 3D structure of **10a** was unambigously established by X-ray crystallography and confirmed the 5-thioxo-benzotriazepin-2-one structure in the solid state (Fig. 1).[14] Indeed, the C(11)–S(16) bond in **10a** was found at 1.662(2) Å, as



Scheme 4. Supposed mechanisms for the formation of compounds **7** and **8** from **4**.



Scheme 5. Synthesis of 2-thioxo-benzo[1,3,4]triazepin-5-ones **10a–d** and benzo[1,3,4]triazepin-2,5-dithiones **11a–d** from benzo[1,3,4]triazepine-2,5-diones **5a–d** (for yields see Table 4).

typically observed for the C=S double bonds,[15] while the C(14)–O(19) double bond was logically noticed at 1.227(3) Å.

3. Conclusion

In conclusion, during the study of chemistry of 3,1-benzoxazine-2-carbonitriles **3a–d** and their sulfur containing analogues **4a–d**, we observed that condensation of 1,2-dimethylhydrazine with the oxygenated derivatives gave convenient yields of novel 1,3,4-benzotriazepine-2,5-diones **5a–d**, whilst, in the same conditions, the behaviour of the 3,1-benzothiazin-4-ones was different, affording novel heterocyclic compounds. The chemical and biological interest of the 2-(1,2-dimethylhydrazino-4*H*-3,1-benzoxazine-4-thiones **7a–d** mainly obtained in these experiments are under investigation.

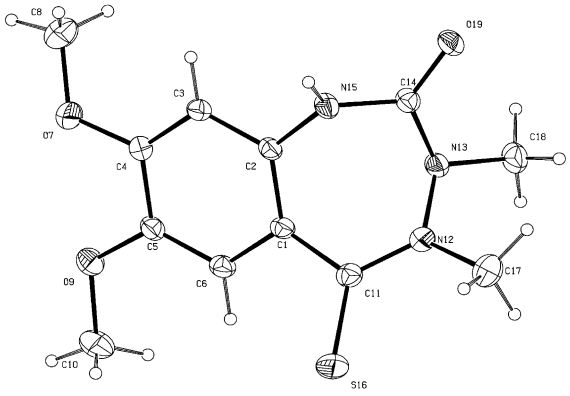


Figure 1. ORTEP view of **10a** with our numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

4. Experimental

4.1. Chemistry

Commercial reagents were used further without additional purification. Melting points were measured using a Kofler melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Paragon 1000PC FT-IR instrument. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded with a JEOL JNM LA400 spectrometer. Chemical shifts (δ values) are expressed in parts per million downfield from tetramethylsilane as an internal standard and coupling constants (J) are expressed in Hertz. Mass spectra were recorded on Spectrometer simple quad platform LC micromass, electrospray. Thin-layered chromatography (TLC), was performed on 0.2 mm precoated plates of silica gel 60F-264 (Merk). Visualisation was made with ultraviolet light. Column chromatography was performed by using Merck silica gel (70–230 mesh). High-resolution mass measurements were performed on a Varian MAT 311, at a ionizing potential of 70 eV, in the Centre Régional de Mesures Physiques de l'Ouest (CRMPO, Université de Rennes).

Microwave experiments were carried out at atmospheric pressure using a focused microwave reactor (CEM Discover™). The instrument consists of a continuous focused microwave power output from 0 to 300 W. Reactions were performed in a glass vessel prolonged by a condenser; it is also possible to work under dry atmosphere, in vacuo, or under pressure (0–20 bar, tubes of 10 mL, sealed with a septum) if necessary. The temperature content of a vessel is monitored using calibrated infrared sensor mounted under the vessel. All the experiments were performed using stirring option whereby the contents of a vessel are stirred by means of a rotating plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel. In all experiments a target temperature was selected together with a power. The target temperature was reached with a ramp of 2 min and the chosen microwave power stay constant to hold the mixture at this temperature. The time of the reaction does not include the ramp period.

4.2. Substituted-4-oxo-4*H*-3,1-benzoxazine-2-carbonitriles (3): general procedure

4,5-Dichloro-1,2,3-dithiazolium chloride **1** (16.6 mmol) was added to a solution of anthranilic acid derivative (15.0 mmol) in dichloromethane (CH_2Cl_2, 25 mL). The reaction mixture was stirred at room temperature for 1 h. After cooling at 0 °C (ice bath), DBU (2.5 mL, 16.6 mmol) was added dropwise. The reaction was stirred again at room temperature for 2 h, then filtered through a short pad of silica gel and washed with DCM. The solvents were removed under reduced pressure and the residue was purified by chromatography on silica gel (Heptane/DCM, 6:4) to produce product **3** as a white solid.

Compounds **3a** and **3c** were previously described in Ref. 8.

4.2.1. 6,7,8-Trimethoxy-4-oxo-4*H*-3,1-benzoxazine-2-carbonitrile (3b). White solid, mp 133 °C (Heptane/CH_2Cl_2); IR (KBr) ν 3086, 2952, 2246, 1758, 1348, 1091, 946, 746 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.00 (s, 3H), 4.06 (s, 3H), 4.11 (s, 3H), 7.44 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 56.7, 61.6, 63.1, 104.7, 110.4, 114.2, 132.1, 133.5, 148.8, 149.7, 156.1, 156.1; MS (ESI, EI^{+}) m/z=263 (MH^{+}). HRMS: calcd for $C_{12}H_{10}N_2O_5$, 262.0590; found, 262.0567.

4.2.2. 6-Methyl-4-oxo-4*H*-3,1-benzoxazine-2-carbonitrile (3d). White solid, mp 148 °C (Heptane/CH_2Cl_2); IR (KBr) ν 3064, 2930, 2246, 1792, 1610, 1036 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.55 (s, 3H), 7.65 (dd, $J=8.4$, 2.0 Hz, 1H), 7.75 (d, $J=8.4$ Hz), 8.07 (d, $J=2.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.7, 110.2, 118.4, 128.2, 129.0, 133.9, 138.6, 142.2, 143.0, 156.1; MS (ESI, El^+) $m/z=187$ (MH^+). HRMS: calcd for $C_{10}H_6N_2O_2$, 186.0429; found, 186.0438.

4.3. Substituted-4-oxo-4*H*-3,1-benzothiazine-2-carbonitriles (4): general procedure

4,5-Dichloro-1,2,3-dithiazolium chloride **1** (2.2 mmol) was added to a solution of anthranilic acid (2 mmol) in CH_2Cl_2 (75 mL). The reaction mixture was stirred at room temperature for 2 h and triphenylphosphine (4.4 mmol) was added. The reaction mixture was allowed to stir at room temperature for another 1 h. The solvents were removed under reduced pressure and the residue was purified by chromatography on silica gel (Heptane/CH_2Cl_2, 6:4) to furnish product **4** as a white solid.

Compounds **4a** and **4c** were previously described in Ref. 8.

4.3.1. 6,7,8-Trimethoxy-4-oxo-4*H*-3,1-benzothiazine-2-carbonitrile (4b). Yellow solid, mp 148 °C (CH_2Cl_2); IR (KBr) ν 3086, 2952, 2230, 1660, 1489, 1348, 1093, 944, 756, 711 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.03 (s, 3H), 4.08 (s, 3H), 4.09 (s, 3H), 7.53 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 56.6, 61.5, 63.2, 101.1, 113.4, 117.5, 132.3, 137.2, 149.3, 150.8, 156.3, 178.7; MS (ESI, El^+) $m/z=279$ (MH^+). HRMS: calcd for $C_{12}H_{10}N_2O_4S$, 278.0361; found, 278.0352.

4.3.2. 6-Methyl-4-oxo-4*H*-3,1-benzothiazine-2-carbonitrile (4d). Pale yellow solid, mp 154 °C (Heptane/CH_2Cl_2); IR (KBr) ν 3031, 2950, 2238, 1672, 1072, 852, 711 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.56 (s, 3H), 7.77 (dd, $J=8.4$, 2.0 Hz), 7.86 (d, $J=8.4$ Hz), 8.11 (d, $J=2.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.7, 113.0, 120.8, 124.9, 132.4, 134.8, 137.5, 143.6, 144.9, 179.3; MS (ESI, El^+) $m/z=203$ (MH^+). HRMS: calcd for $C_{10}H_6N_2OS$, 202.0201; found, 202.0200.

4.4. Substituted-3,4-dimethyl-3,4-dihydro-1*H*-1,3,4-benzotriazepine-2,5-diones (5): general procedure

A mixture of 4-oxo-4*H*-3,1-benzoxazine-2-carbonitrile **3** (4.0 mmol), 1,2-dimethylhydrazine dihydrochloride (4.4 mmol) and triethylamine (8.8 mmol) in pyridine (30 mL) was stirred 12 h at room temperature. Pyridine was evaporated under reduced pressure and the residue was dissolved in $CHCl_3$. The organic phase was washed several times with water and dried ($MgSO_4$). After evaporation of the solvent under reduced pressure, the residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc, 9:1 then 8:2) to furnish the attempted product **5**.

4.4.1. 7,8-Dimethoxy-3,4-dimethyl-3,4-dihydro-1*H*-1,3,4-benzotriazepine-2,5-dione (5a). Pale yellow solid, mp 203 °C (EtOAc); IR (KBr) ν 3318, 2930, 1708, 1616, 1446, 1256, 1214, 1009 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.07 (s, 3H), 3.31 (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 6.37 (s, 1H), 6.85 (br s, 1H), 7.33 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 32.7, 33.9, 56.1, 56.2, 102.3, 112.0, 116.1, 135.1, 145.9, 152.7, 164.4, 169.1; MS (ESI, El^+) $m/z=266$ (MH^+). HRMS: calcd for $C_{12}H_{15}N_3O_4$, 265.1063; found, 265.1065.

4.4.2. 7,8,9-Trimethoxy-3,4-dimethyl-3,4-dihydro-1*H*-1,3,4-benzotriazepine-2,5-dione (5b). Pale yellow solid, mp 161 °C (CH_2Cl_2/EtOAc); IR (KBr) ν 3234, 2930, 1707, 1658, 1453, 1376, 1108, 860, 768 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.07 (s, 3H), 3.31 (s, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 3.93 (s, 3H), 7.08 (br s, 1H), 7.15 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 32.8, 34.0, 56.1, 61.0, 61.6, 107.4, 118.8, 128.9, 141.7, 145.2, 149.6, 164.0, 168.9; MS (ESI, El^+) $m/z=296$ (MH^+). HRMS: calcd for $C_{13}H_{17}N_3O_5$, 295.1168; found, 295.1167.

4.4.3. 3,4-Dimethyl-3,4-dihydro-1*H*-1,3,4-benzotriazepine-2,5-dione (5c). White solid, mp 188–189 °C (CH_2Cl_2/EtOAc) (Lit. mp 188–189 °C);[11] ^1H NMR ($CDCl_3$) δ 3.08 (s, 3H), 3.35 (s, 3H), 6.97 (d, $J=8.0$ Hz, 1H), 7.19 (t, $J=7.6$ Hz, 1H), 7.42 (t, $J=7.6$ Hz, 1H), 7.65 (br s, 1H), 7.91 (d, $J=8.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 32.6, 33.9, 119.4, 124.0, 124.5, 130.9, 132.6, 140.6, 164.5, 169.2; MS (ESI, El^+) $m/z=206$ (MH^+). HRMS: calcd for $C_{10}H_{11}N_3O_2$, 205.0851; found, 205.0849.

4.4.4. 3,4,7-Trimethyl-3,4-dihydro-1*H*-1,3,4-benzotriazepine-2,5-dione (5d). White solid, mp 185 °C (CH_2Cl_2/EtOAc); IR (KBr) ν 3262, 2930, 1708, 1644, 1496, 1354, 1228, 804 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.35 (s, 3H), 3.06 (s, 3H), 3.33 (s, 3H), 6.83 (d, $J=8.4$ Hz, 1H), 7.22 (d, $J=8.4$ Hz, 1H), 7.49 (br s, 1H), 7.69 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.5, 32.6, 33.9, 119.3, 124.3, 130.9, 133.5, 133.8, 138.1, 164.6, 169.3; MS (ESI, El^+) $m/z=220$ (MH^+). HRMS: calcd for $C_{11}H_{13}N_3O_2$, 219.1008; found, 219.1015.

4.5. Reaction of 4-oxo-4*H*-3,1-benzothiazine-2-carbonitriles (4) with 1,2-dimethylhydrazine: general procedure

A solution of 4-oxo-4*H*-3,1-benzothizazine-2-carbonitrile **4** (1.0 mmol), 1,2-dimethylhydrazine dihydrochloride (1.1 mmol) and Et_3N (2.2 mmol) in pyridine (10 mL) was either irradiated at 115 °C (power input: 80 W) until completion (TLC monitoring, 10 min) or stirred at room temperature 1 h. The solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (CH_2Cl_2 then CH_2Cl_2/EtOAc, 9:1) to furnish **7** and **8** as yellow solids.

4.5.1. 2-(1,2-Dimethylhydrazino)-6,7-dimethoxy-4*H*-3,1-benzoxazine-4-thione (7a). Yellow solid, mp 94 °C (CH_2Cl_2/EtOAc); IR (KBr) ν 3248, 2983, 2852, 1736, 1652, 1502, 1262, 1108, 845, 599 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.30 (s, 3H), 3.33 (s, 3H), 3.88 (s, 3H), 3.92 (s, 3H), 6.46 (s, 1H), 7.35 (s, 1H), 8.32 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 32.5, 39.2, 56.19, 56.22, 102.1, 111.8, 116.9, 135.5, 146.5, 152.6, 169.1, 194.5; MS (ESI, El^+) $m/z=282$ (MH^+). HRMS: calcd for $C_{12}H_{15}N_3O_3S$, 281.0834; found, 281.0841.

4.5.2. 2-(1,2-Dimethylhydrazino)-6,7,8-trimethoxy-4*H*-3,1-benzoxazine-4-thione (7b). Yellow solid, mp 90 °C (CH_2Cl_2/EtOAc); IR (KBr) ν 3250, 2980, 2850, 1640, 1570,

1270, 1108, 846, 600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.30 (s, 3H), 3.35 (s, 3H), 3.90 (s, 3H), 3.93 (s, 3H), 3.96 (s, 3H), 7.16 (s, 1H), 8.41 (br s, 1H); MS (ESI, El^+) $m/z=312$ (MH^+). HRMS: calcd for $C_{13}H_{17}N_3O_4S$, 311.0940; found, 311.0930.

4.5.3. 2-(1,2-Dimethylhydrazino)-4*H*-3,1-benzoxazine-4-thione (7c). Yellow solid, mp 230 °C (decomp.) (CH_2Cl_2/EtOAc); IR (KBr) ν 3258, 2970, 1636, 1520, 1360, 1273, 1122, 774 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.33 (s, 3H), 3.34 (s, 3H), 6.94 (d, $J=8.0$ Hz, 1H), 7.25 (td, $J=8.0$, 1.6 Hz, 1H), 7.45 (td, $J=8.0$, 1.6 Hz, 1H), 7.94 (dd, $J=8.0$, 1.6 Hz, 1H), 8.19 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 32.5, 39.4, 119.2, 125.10, 125.13, 131.2, 132.9, 140.5, 169.1, 194.7; MS (ESI, El^+) $m/z=222$ (MH^+). HRMS: calcd for $C_{10}H_{11}N_3OS$, 221.0623; found, 221.0621.

4.5.4. 2-(1,2-Dimethylhydrazino)-6-methyl-4*H*-3,1-benzoxazine-4-thione (7d). Yellow solid, mp 217 °C (CH_2Cl_2/EtOAc); IR (KBr) ν 3256, 2930, 1644, 1454, 1270, 1128, 817 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.36 (s, 3H), 3.31 (s, 6H), 6.84 (d, $J=8.0$ Hz, 1H), 7.25 (d, $J=8.0$ Hz, 1H), 7.72 (s, 1H), 8.22 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.6, 34.4, 39.3, 119.1, 125.0, 128.6, 131.1, 133.7, 135.1, 138.4, 169.3, 194.8. MS (ESI, El^+) $m/z=236$ (MH^+). HRMS: calcd for $C_{11}H_{13}N_3OS$, 235.0779; found, 235.0776.

4.5.5. 7,8-Dimethoxy-3,4-dimethyl-5-oxo-4,5-dihydro-3*H*-1,3,4-benzotriazepine-2-carbonitrile (8a). Yellow solid, mp 202 °C (CH_2Cl_2/EtOAc); IR (KBr) ν 2984, 2944, 2230, 1744, 1658, 1446, 1221, 994, 874 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.17 (s, 3H), 3.31 (s, 3H), 3.94 (s, 3H), 3.98 (s, 3H), 6.85 (s, 1H), 7.44 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 32.1, 36.0, 56.2, 56.3, 110.8, 110.8, 112.1, 112.2, 123.4, 137.1, 138.5, 149.5, 168.6; MS (ESI, El^+) $m/z=275$ (MH^+). HRMS: calcd for $C_{13}H_{14}N_4O_3$, 274.1066; found, 274.1078.

4.5.6. 7,8,9-Trimethoxy-3,4-dimethyl-5-oxo-4,5-dihydro-3*H*-1,3,4-benzotriazepine-2-carbonitrile (8b). Yellow solid, mp 101 °C (CH_2Cl_2/EtOAc); IR (KBr) ν 3000, 2840, 2216, 1620, 1573, 1420, 1336, 1089, 765, 737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.15 (s, 3H), 3.32 (s, 3H), 3.94 (s, 3H), 3.96 (br s, 6H), 7.27 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 31.9, 36.0, 56.2, 61.2, 62.2, 108.3, 112.1, 126.7, 132.0, 136.3, 145.4, 149.1, 153.9, 168.2; MS (ESI, El^+) $m/z=305$ (MH^+). HRMS: calcd for $C_{14}H_{16}N_4O_4$, 304.1172; found, 304.1166.

4.6. Substituted-3,4-dimethyl-5-thioxo-1,2,3,4-tetrahydro-5*H*-1,3,4-benzotriazepin-2-ones (10) and substituted 3,4-dimethyl-3,4-dihydro-1*H*-1,3,4-benzotriazepine-2,5-dithiones (11): general procedure

A solution of 3,4-dimethyl-3,4-dihydro-1*H*-1,3,4-benzotriazepine-2,5-dione (2 mmol) and P_2S_5 (3 mmol) in pyridine (7 mL) was irradiated at 115 °C (power input: 80 W) until completion (TLC monitoring, 40 min). After cooling, the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (CH_2Cl_2 then CH_2Cl_2/EtOAc, 8:2) to furnish **10** and **11** as yellow solids.

4.6.1. 7,8-Dimethoxy-3,4-dimethyl-5-thioxo-1,2,3,4-tetrahydro-5*H*-1,3,4-benzotriazepin-2-one (10a). Yellow solid, mp 196 °C (CH_2Cl_2/EtOAc); IR (KBr) ν 3233, 3141, 2938, 1716, 1448, 1382, 1262 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.08 (s, 3H), 3.76 (s, 3H), 3.88 (s, 3H), 3.93 (s, 3H), 6.51 (s, 1H), 7.40 (br s, 1H), 7.64 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 34.0, 40.2, 56.1, 56.1, 101.9, 114.6, 124.3, 132.0, 145.8, 152.7, 165.0, 196.9; MS (ESI, El^+) $m/z=282$ (MH^+). HRMS: calcd for $C_{12}H_{15}N_3O_3S$, 281.0834; found, 281.0814.

4.6.2. 7,8,9-Trimethoxy-3,4-dimethyl-5-thioxo-1,2,3,4-tetrahydro-5*H*-1,3,4-benzotriazepin-2-one (10b). Yellow solid, mp 145 °C (CH_2Cl_2); IR (KBr) ν 3256, 2952, 1700, 1488, 1362, 784 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.09 (s, 3H), 3.76 (s, 3H), 3.90–3.92 (m, 9H), 7.15 (br s, 1H), 7.44 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 34.0, 40.4, 56.0, 61.0, 61.5, 110.0, 125.9, 126.6, 141.3, 145.0, 149.4, 164.5, 197.0; MS (ESI, El^+) $m/z=312$ (MH^+). HRMS: calcd for $C_{13}H_{17}N_3O_4S$, 311.0940; found, 311.0912.

4.6.3. 3,4-Dimethyl-5-thioxo-1,2,3,4-tetrahydro-5*H*-1,3,4-benzotriazepin-2-one (10c). Yellow solid, mp 187 °C (CH_2Cl_2/EtOAc); IR (KBr) ν 3290, 3172, 2922, 1670, 1640, 1396, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.09 (s, 3H), 3.77 (s, 3H), 6.87 (dd, $J=8.0$, 1.2 Hz, 1H), 7.17 (m, 1H), 7.37 (m, 1H), 7.68 (br s, 1H), 8.15 (dd, $J=8.0$, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 34.0, 40.3, 119.3, 124.3, 132.2, 133.2, 137.4, 164.7, 197.5; MS (ESI, El^+) $m/z=222$ (MH^+). HRMS: calcd for $C_{10}H_{11}N_3OS$, 221.0623; found, 221.0621.

4.6.4. 3,4,7-Trimethyl-5-thioxo-1,2,3,4-tetrahydro-5*H*-1,3,4-benzotriazepin-2-one (10d). Yellow solid, mp 193 °C (CH_2Cl_2/EtOAc); IR (KBr) ν 3234, 3150, 3016, 2930, 1921, 1702, 1574, 1488, 1362, 818 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.35 (s, 3H), 3.07 (s, 3H), 3.77 (s, 3H), 6.77 (d, $J=8.4$ Hz, 1H), 7.18 (d, $J=8.4$ Hz, 1H), 7.57 (br s, 1H), 7.93 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.6, 34.0, 40.2, 119.3, 131.9, 133.1, 133.2, 134.0, 135.1, 164.9, 197.6; MS (ESI, El^+) $m/z=236$ (MH^+). HRMS: calcd for $C_{11}H_{13}N_3OS$, 235.0779; found, 235.0776.

4.6.5. 7,8-Dimethoxy-3,4-dimethyl-3,4-dihydro-1*H*-1,3,4-benzotriazepine-2,5-dithione (11a). Yellow solid, mp 200 °C (CH_2Cl_2/EtOAc); IR (KBr) ν 3206, 2938, 2832, 1609, 1502, 1534, 1170, 1093 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.29 (s, 3H), 3.71 (s, 3H), 3.90 (s, 3H), 3.94 (s, 3H), 6.32 (s, 1H), 7.65 (s, 1H), 8.04 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 38.7, 39.6, 56.2, 56.4, 101.5, 114.7, 125.3, 132.4, 146.6, 152.7, 195.8, 197.6; MS (ESI, El^+) $m/z=298$ (MH^+). HRMS: calcd for $C_{12}H_{15}N_3O_2S_2$, 297.0606; found, 297.0598.

4.6.6. 7,8,9-Trimethoxy-3,4-dimethyl-3,4-dihydro-1*H*-1,3,4-benzotriazepine-2,5-dithione (11b). Yellow solid, mp 124 °C (CH_2Cl_2); IR (KBr) ν 3312, 2958, 2930, 2846, 1912, 1744, 1734, 1658, 1581, 1466, 1354, 1122 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.30 (s, 3H), 3.71 (s, 3H), 3.92 (s, 3H), 3.93 (s, 3H), 3.95 (s, 3H), 7.45 (s, 1H), 8.46 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 38.9, 39.8, 56.1, 61.1, 62.3, 110.2, 126.8, 127.4, 141.3, 145.0, 150.2, 196.0, 197.9; MS (ESI, El^+) $m/z=328$ (MH^+). HRMS: calcd for $C_{13}H_{17}N_3O_3S_2$, 327.0711; found, 327.0707.

4.6.7. 3,4-Dimethyl-3,4-dihydro-1*H*-1,3,4-benzotriazepine-2,5-dithione (11c). Yellow solid, mp 199 °C

(CH_2Cl_2/EtOAc); IR (KBr) ν 3226, 2983, 1600, 1739, 1600, 1517, 1366, 1260, 1238, 1103, 763, 673, 596, 503 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.29 (s, 3H), 3.73 (s, 3H), 6.86 (d, J= 7.2 Hz, 1H), 7.22 (t, J=7.2 Hz, 1H), 7.40 (t, J=7.2 Hz, 1H), 8.17 (dd, J=7.2, 1.2 Hz, 1H), 8.20 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 38.9, 39.6, 118.9, 125.3, 132.3, 132.9, 133.4, 137.6, 195.8, 198.0; MS (ESI, El^+) m/z=238 (MH^+). HRMS: calcd for $C_{10}H_{11}N_3S_2$, 237.0394; found, 237.0383.

4.6.8. 3,4,7-Trimethyl-3,4-dihydro-1*H*-1,3,4-benzotriazepine-2,5-dithione (11d). Yellow solid, mp 189 °C (CH_2Cl_2/EtOAc); IR (KBr) ν 3242, 3064, 2972, 2930, 1912, 1694, 1588, 1518, 1100, 810 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.37 (s, 3H), 3.27 (s, 3H), 3.72 (s, 3H), 6.75 (d, J=8.0 Hz, 1H), 7.20 (d, J=8.0 Hz, 1H), 7.96 (s, 1H), 8.12 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 20.7, 38.8, 39.5, 118.9, 132.7, 133.2, 133.4, 135.3, 135.5, 195.8, 198.1; MS (ESI, El^+) m/z=252 (MH^+). HRMS: calcd for $C_{11}H_{13}N_3S_2$, 251.0551; found, 251.0546.

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Dde-protected PNA monomers, orthogonal to Fmoc, for the synthesis of PNA–peptide conjugates

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Abstract—Peptide nucleic acids have become, arguably, one of the most interesting of DNA mimics. Herein the efficient solution phase synthesis of four novel 1-(4,4-dimethyl-2,6-dioxacyclohexylidene)ethyl/4-methoxytrityl (Dde/Mmt) protected PNA monomers is reported which were then used to synthesise PNA–peptide conjugates through a mild Dde deprotection strategy, which was fully orthogonal to Fmoc chemistry, allowing at will Fmoc peptide and Dde–PNA synthesis.

1. Introduction

Peptide Nucleic Acids (PNAs) were first reported in 1991 as a DNA mimic[1] and since this time, a vast number of studies have been reported covering their synthesis, properties and potential applications.[2] In PNAs, the sugar–phosphate backbone present in DNA has been replaced by a repeating polyamide chain of *N*-(2-aminoethyl)glycine monomer units, yet despite this major modification PNA still hybridises efficiently to complementary DNA and RNA sequences according standard base pairing rules (Fig. 1); indeed, due to the lack of electrostatic repulsion in PNA/DNA complexes present in DNA/DNA or DNA/RNA double strands, the binding affinity and selectivity of PNA towards DNA, RNA and PNA is higher than for its DNA counterparts under physiological conditions. Moreover, PNA is resistant to biological degradation by nucleases or proteases, properties which make PNA an ideal tool in a

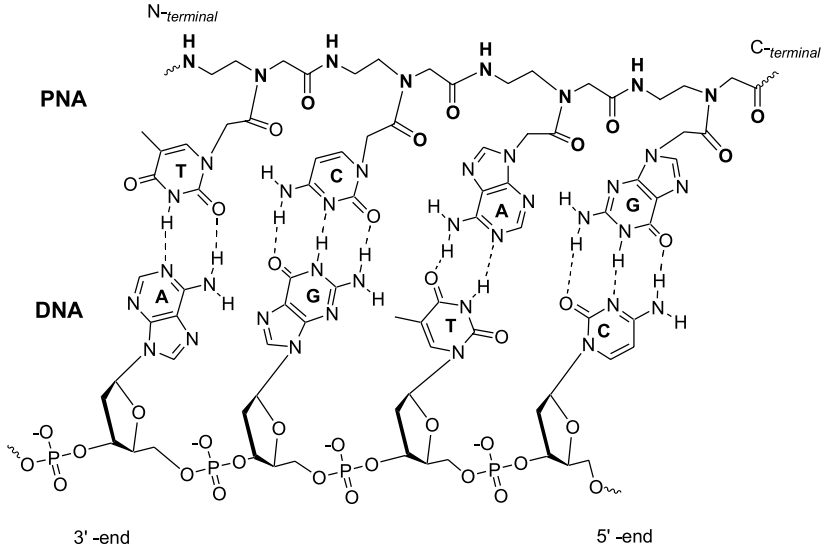

Figure 1. General structure of a PNA/DNA duplex.

Keywords: PNA; Dde; Fmoc; Orthogonality; Conjugate; Peptide.
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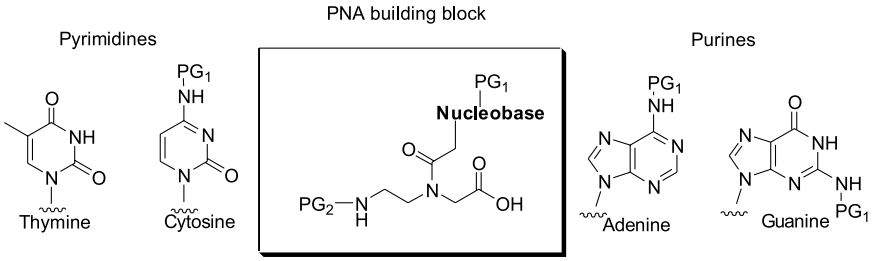


Figure 2. General structure of the four PNA building blocks.

number of different areas of research such as gene therapy, SNP analysis and mRNA profiling.[3] A further advantage of PNA over other DNA mimetics stems from its pseudo-peptidic structure which allows PNA synthesis to be carried out by straightforward and traditional solid phase peptide chemistry based methods (SPPS). However PNA does suffer from a number of drawbacks and disadvantages, such as issues relating to its cellular delivery and uptake, the inability to enzymatically extend PNA primers and the complexities of PNA synthesis, which to date has made concurrent peptide/PNA synthesis and PNA/DNA synthesis very inefficient. However, the conjugation of PNA to peptides can be used to enable the properties of the PNA to be highly modulated, for example, by allowing membrane permeability which then opens up a host of opportunities for new applications of PNA and better exploitation of its full potential. Therefore, methods to allow the efficient preparation of peptide–PNA conjugates in which the peptide and PNA strands can be prepared at will would have huge potential.[4]

To allow the construction of peptide–PNA conjugates, monomeric building blocks protected with two orthogonal protecting groups (one for the N terminus and one for the nucleobase) are required, and during the past decade PNA monomers with a range of compatible protecting groups have been developed with Fmoc/Bhoc[5] and Boc/Cbz[6] being the most frequently used but other combinations such as Fmoc/Mmt[7] or Fmoc/Cbz[8] have also been used. While these monomers are useful for the synthesis of standard PNA oligomers, their utility in the synthesis of PNA–peptide conjugates is limited as they do not allow orthogonal synthesis with commercially available amino acid monomers (the most frequently used being the N-terminal Fmoc protected amino acids with acid labile side-chain protecting groups).

In the quest for alternative N-terminal protecting groups for PNA monomers which would allow the desired degree of orthogonality, 1-(4,4-dimethyl-2,6-dioxacyclohexylidene) ethyl (Dde) was identified, as a protecting group which has been used for primary amines and one that is classically removed with hydrazine.

Here, we describe the synthesis of novel Dde/Mmt PNA monomers and the development of new deprotection conditions for the Dde group which were robust and fully orthogonal to other commonly used protecting groups in peptide chemistry, such as Fmoc, Boc, Mmt, ^{t}Bu, MeO, etc. We further demonstrate the application of these monomers to a highly versatile synthesis of various PNA–peptide conjugates.

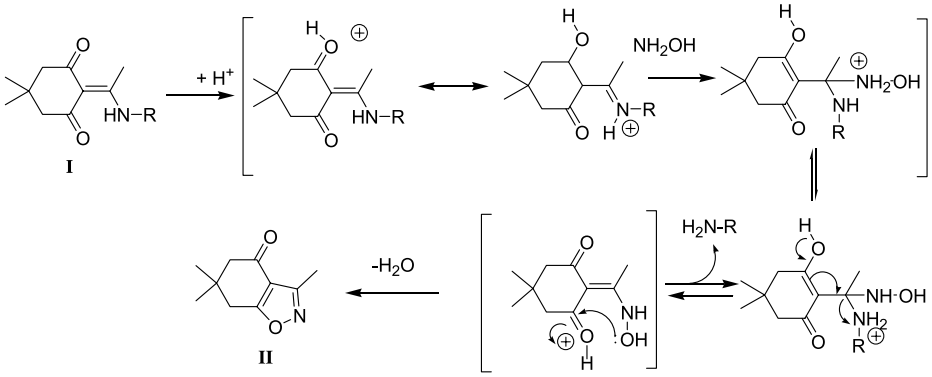
2. Results and discussion

In order to carry out solid phase PNA oligomers synthesis, PNA monomeric building blocks protected on the amino group of the *N*-(2-aminoethyl)glycine backbone as well as the nucleobases (Fig. 2), had to be prepared.

It was desired that the PNA and the peptide moieties should be elongated in a truly orthogonal fashion, thus imposing no restrictions on the design of these conjugates, but protecting groups on the nucleobases (PG_1) and the amino acids should be cleaved together under the final acidic cleavage conditions. The use of an acid labile linker such as the Rink amide linker[9] would also enable deprotection to be performed during the final cleavage of the conjugate from the solid-support. For this purpose, the mono-methoxytrityl (Mmt) group was chosen for the nucleobase protecting group (PG_1). The correct choice of PG_2-which had to be orthogonal to the Fmoc group and the acid-labile side-chain protecting groups on peptides proved more challenging, as none of the PNA monomers reported to date met these criteria.

As a possible solution, the allyloxycarbonyl (Aloc) group, which can be cleaved by palladium catalysts under essentially neutral conditions,[10] was examined. Although the Aloc group can be deprotected without affecting the Fmoc group, the use of Aloc-protected PNA monomers, synthesized in our group, proved to be unsuccessful in chain extension with the expected products obtained in very low yield and purities. Moreover, the length of the PNA oligomers was severely affected as during Aloc deprotection, Pd(0) species become trapped within the solid supports (generating black beads) causing premature and random Aloc deprotection. Thus synthesis on solid support using Aloc protected monomers in a coupling–deprotection strategy was fundamentally flawed.

Hence, after unsuccessful attempts to use Aloc-PNA monomers for the oligomerization process, another protecting group was identified, 1-(4,4-dimethyl-2,6-dioxacyclohexylidene)ethyl (Dde). While hydrazine, the usual reagent to deprotect the Dde group, also deprotects the Fmoc group, we reasoned that the Dde group should be deprotected by hydroxylamine (mixture of $NH_2OH{\cdot}HCl$ and imidazole) under slightly acidic conditions which would be fully orthogonal to the Fmoc group.[11] The principle of the orthogonality being based on the different mechanisms involved for both deprotections. While Fmoc protected amines are deprotected through an E1cb elimination generating dibenzofulvene, the Dde group is cleaved by



Scheme 1. Possible Dde deprotection mechanism using $NH_2OH \cdot HCl$/imidazole.

nucleophiles through a transenamination or Michael type mechanism followed by ring closure yielding an isoxazole **II** (Scheme 1, Fig. 3).

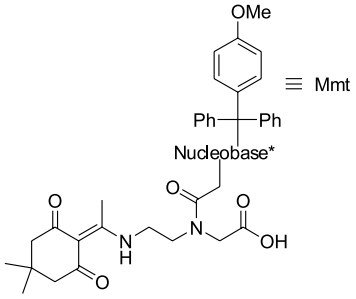


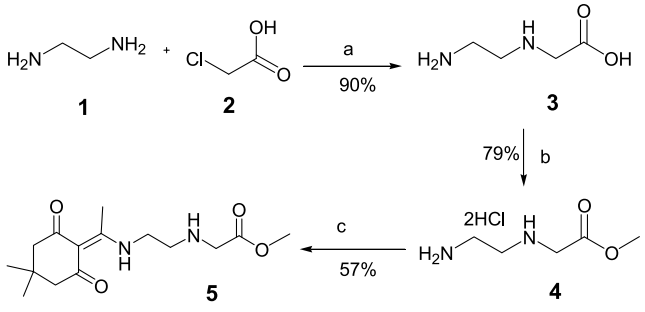
Figure 3. Novel Dde/Mmt PNA monomers. *Thymidine monomers do not require nucleobase protection.

2.1. Synthesis of Dde/Mmt PNA monomers

The synthesis of the PNA monomers containing the four nucleobases was carried out in solution. Retro-synthetically, the monomers can be disconnected into two synthons, a backbone and the derivatised nucleobase and this allows the straightforward synthesis of all four desired PNA monomers.

2.2. Synthesis of the Dde-protected backbone

The synthesis of the Dde-protected backbone **5** is depicted in Scheme 2. Thus, chloroacetic acid was alkylated with an excess of ethylendiamine **1**, which following precipitation with DMSO gave 2-aminoethylglycine **3** in quantitative yield.[12] Following esterification of **3**, Dde protection was carried out using Dde-OH previously prepared from dimedone and acetic acid,[13] yielding the PNA backbone ethyl 2-*N*-Dde-aminoethylglycinate **5** in an overall yield of 40% (Scheme 2).

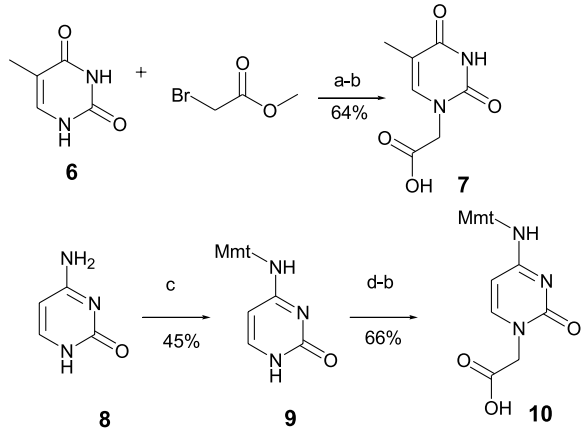


Scheme 2. Dde backbone synthesis: (a) room temperature, 16 h; (b) 10 equiv SO_2Cl, MeOH, reflux, 16 h.; (c) 2 equiv DIPEA, 1 equiv Dde-OH; CH_2Cl_2/EtOH (1/1), room temperature, 16 h.

2.3. Derivatization of the nucleobases

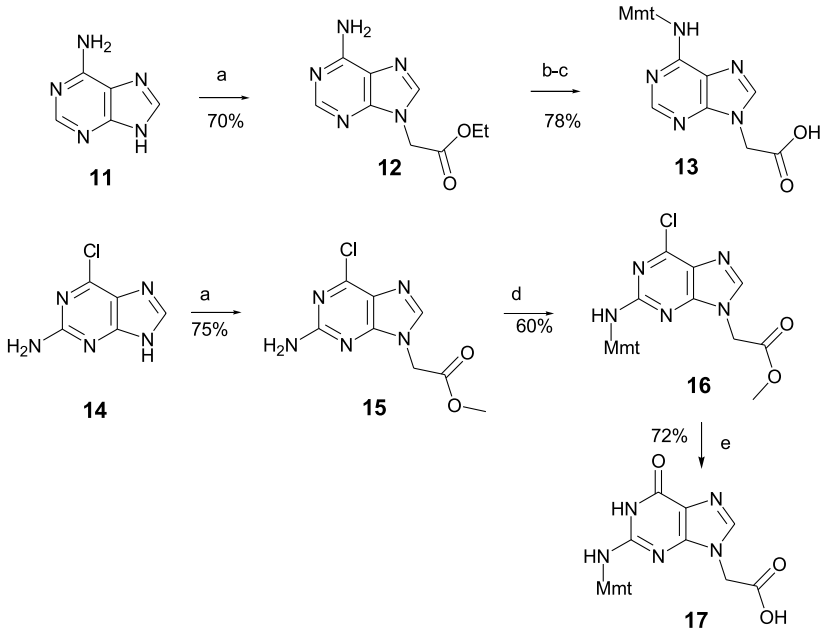
The nucleobases were derivatized through alkylation and protection of the exocyclic amino group, if necessary, with the monomethoxytritryl group (Mmt) following a procedure reported by Breihpol.[7]

Thymine **6** was thus alkylated following the procedure by Buchardt,[6] by treatment of commercially available thymine with methyl bromoacetate using K_2CO_3 as base, followed by saponification of the resulting compound with NaOH yielding thymin-1-yl acetic acid **7**. Cytosine, was first protected with Mmt-Cl in pyridine and then alkylated using a similar procedure as described for **7** (Scheme 3).



Scheme 3. Pyrimidine nucleobases derivatizion: (a) 1 equiv K_2CO_3, DMF under N_2, 16 h; (b) 10% NaOH (aq), reflux, 10 min; (c) 1.5 equiv Mmt-Cl, 1 equiv NEM, Pyr, 40 °C, overnight; (d) 1 equiv K_2CO_3, 1 equiv methyl 2-bromoacetate, DMF, under N_2, 16 h.

In order to obtain selective N^9 over N^7 alkylation, purine nucleobases were first alkylated followed by exocyclic amino protection. Following deprotonation of adenine with sodium hydride, alkylation was carried out using ethyl bromoacetate to give **12**. Amino protection using Mmt chloride in pyridine and subsequent saponification yielded [N^6-(Mmt)-adenin-9yl]-acetic acid **13** (Scheme 4).



Scheme 4. Purine nucleobases derivatization: (a) 1.1 equiv NaH, 1 equiv methyl 2-bromoacetate, DMF, under N_2, 4 h; (b) 1.5 equiv Mmt-Cl, 1 equiv NEM, CH_2Cl_2, 40 °C, 3 h, then 25 °C, 16 h; (c) 1 N aqueous NaOH, reflux, 2 h; (d) 1.5 equiv Mmt-Cl, 1 equiv DIPEA, THF, overnight; (e) 10% NaOH (aq.), reflux, 2 h.

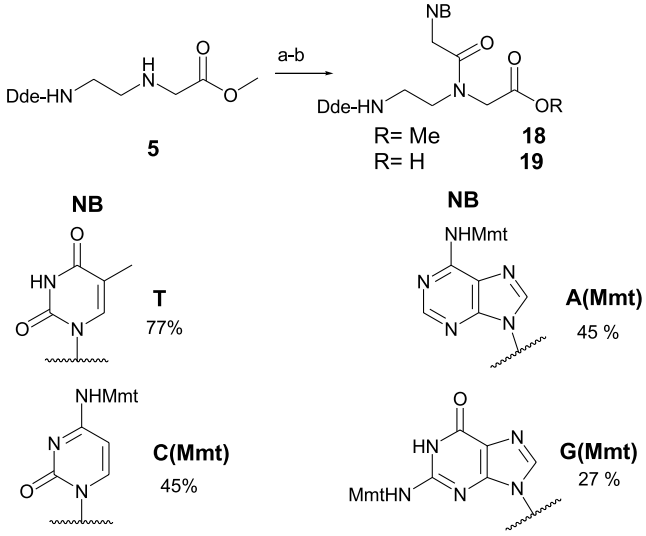
2-Amino-6-chloropurine **14** was used as precursor of the guanine nucleobase. This was due to the poor solubility of guanine, the lack of reactivity of its exocyclic amino group and the difficulty in obtaining selectively the N^9 alkyl derivatives. Alkylation and Mmt protection were carried out as for adenine, however dry CH_2Cl_2 instead of pyridine was used in the Mmt protection step. The use of pyridine as solvent led to the formation of the 6-pyridinium derivative as a side product. In the last step, basic hydrolysis of the ester moiety as well as the C-6 chlorine substituent provided [N^2-(Mmt)-guanin-9-yl]-acetic acid **16** (Scheme 4).

2.4. Monomer synthesis

Two steps remained for the synthesis of the monomers: coupling of the protected backbone **5** and the derivatised nucleobases **7**, **10**, **13**, and **16**, and hydrolysis of the ester moiety. Amide formation with the secondary amine moiety in **5** proved to be sluggish. Protected nucleobases-acetic acid derivatives, **10**, **13** and **17** (mainly purine), are known to be difficult substrates for amide formation and therefore various different coupling reagents were screened.

Couplings of pyrimidine nucleobase derivatives **7** and **10** to the backbone **5** were achieved using different coupling reagents such as 1-propylphosphonic acid cyclic,[14] PyBroP and DCC/DhbtOH[6] with similar efficiencies. Esters **18T** and **18C**(**Mmt**) were obtained with average yields of 60%. PyBroP proved to be the most efficient coupling agent (according to HPLC analysis) with complete conversion however, with this coupling reagent, the purification process was challenging, especially on a large scale. In fact removal of *tris*-(pyrrolidin-1-yl)-phosphoramide was best performed after ester hydrolysis by repeated precipitation (see Section 4).

The second step involved basic hydrolysis of the ester group. Among the conditions tested (LiOH in THF, LiOH in MeOH/H_2O, NaOH in MeOH/H_2O, KOH in H_2O, Na_2CO_3 in MeOH/H_2O, K_2CO_3 in MeOH/H_2O), a 1 M solution of cesium carbonate in MeOH/H_2O (1:1) gave the best results (**19a**–**d**). The lack of Dde deprotection during saponification is a major advantage compared to the preparation of Fmoc protected PNA monomers, where an extra Fmoc re-protection step is often required following ester hydrolysis.[7] Another major advantage of the synthesis of Dde-protected monomers is that no chromatographic separations were needed, with only extraction and precipitation procedures used. The final products were obtained as pure materials (as determined by HPLC and NMR), allowing multi-gram quantities of the monomers to be



Scheme 5. Dde protected PNA monomers: (a) T-CH_2COOH, 50% 1-propylphosphonic acid cyclic in DMF, NEM, 16 h (**18T**); C(Mmt)CH_2-COOH or A(Mmt)CH_2COOH or G(Mmt)CH_2COOH, PyBroP, DIPEA, DMF, 2.5–15 h (**18C**(**Mmt**)-**18A**(**Mmt**)–**18G**(**Mmt**)); (b) 1 M Cs_2CO_3 MeOH/H_2O 1/1, 1.5 h. NB = Nucleobases.

easily synthesized following our protocols, indeed we have prepared up to 5 g of monomers using this synthetic route (Scheme 5).

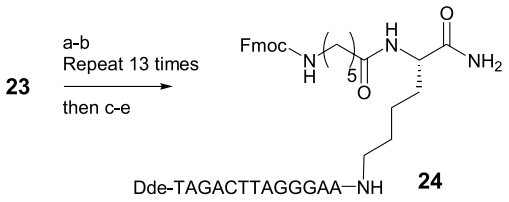
2.5. PNA–peptide conjugates

The Dde PNA monomers open up new opportunities for the flexible synthesis of PNA conjugates. In a previous communication, our group reported the orthogonality between Dde and Fmoc protecting groups.[11] Furthermore the Dde deprotection protocol was completely compatible with the Mmt protecting group and the nucleobases. To demonstrate this robustness we embarked on the synthesis of various different conjugates.

Fmoc-Lys(Dde)-OH **21** was used as core of these conjugates (Scheme 6)[15] which was coupled to commercially available Rink amino PEGA resin, using PyBOP, to give **22**. Three possible strategies are realizable for the construction of PNA–peptide conjugates: (a) building up first the PNA arm (using Dde monomers **19**), and then the peptide arm (using Fmoc monomers); (b) or vice versa; (c) or alternating PNA elongation and peptide elongation steps.

The synthesis of the PNA oligo arm was firstly investigated. Initially three different resin types were tested: PS, Tentagel and PEGA but in terms of Dde deprotection, PEGA showed the fastest cleavage kinetics (complete deprotection after 1 h); while the other resins required longer times (up to 3 h).[11] PEGA was thus considered most suited for the purpose of PNA synthesis with Dde PNA monomers and after selective Dde deprotection with a solution of $NH_2OH \cdot HCl$/imidazol (1/0.75 equiv) in NMP/DMF (5/1) for one hour resin **23** (as the salt) was obtained.

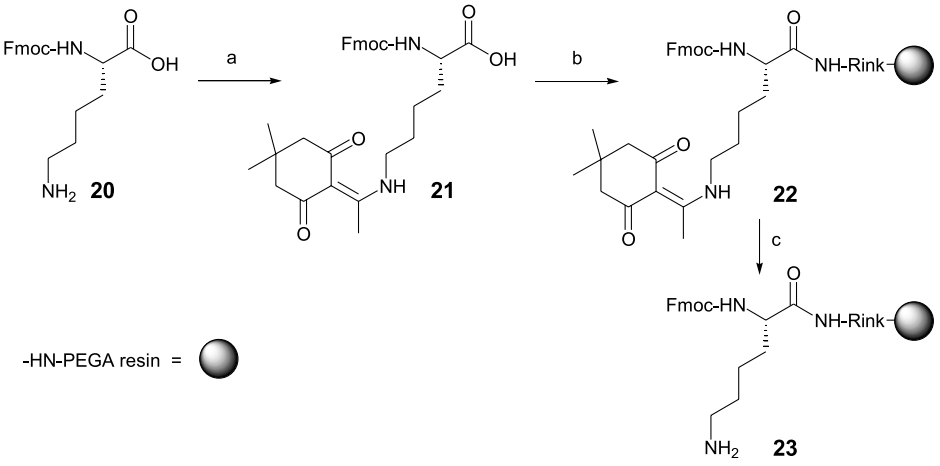
A 13mer PNA oligo containing the four natural nucleobases was synthesised starting from **23** (Scheme 7) with PNA monomer couplings achieved with PyBOP/NEM in DMF using 5.5 equiv of monomer (0.11 M) for 3 h while Dde deprotection was achieved using the protocol described above. After elaboration of the PNA arm, Fmoc deprotection was carried using 20% piperidine in DMF and after coupling of Fmoc–aminohexanoic acid the PNA intermediate **24** was cleaved with a mixture of TFA/TIS/CH_2Cl_2 (90/5/5) for 1 h. After precipitation from TFA–diethyl ether, the purity and identity of the crude material was determined by HPLC and MALDI-TOF, where no loss of the Fmoc group could be detected. Thus, the new monomers were demonstrated to be valid building blocks for PNA oligomerization.



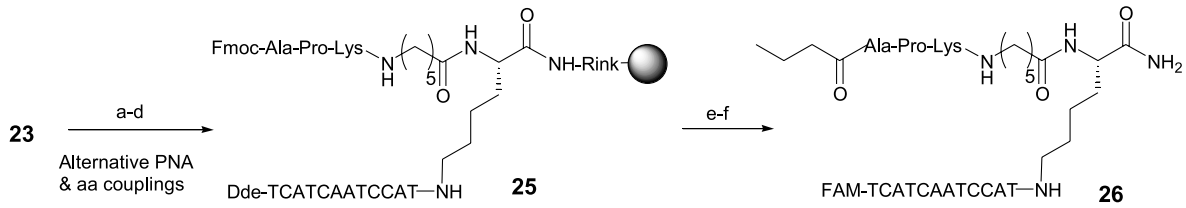
Scheme 7. Synthesis of a 13 mer PNA oligo using Dde protected PNA monomers: (a) Dde-PNA-OH (5.5 equiv), PyBOP (5 equiv 0.1 M), NEM (11 equiv) in DMF, 3 h; (b) $NH_2OH \cdot HCl$/imidazole in NMP/DMF; repeat (a) and (b) as necessary; (c) excess 20% piperidine in DMF; (d) Fmoc-Ahx-OH (5.5 equiv), PyBOP (5 equiv, 0.1 M), DIPEA (11 equiv) in DMF, 3 h; (e) excess TFA/TIS/CH_2Cl_2 (90/5/5), 1 h.

Traditionally, peptides have been conjugated to PNA using either traditional solid phase chemistry by coupling amino acids followed by PNA monomers or vice versa[16–18] using disulfide linkage[19] or ligation through disulfide bonds.[20] However, the method reported here allows a much more flexible strategy which involves elongation of either PNA or peptide parts at any stage of the synthesis (see above). To demonstrate this flexibility, a conjugate was synthesised by alternating PNA coupling and amino acids coupling steps (Scheme 8). PNA monomer couplings were performed as for compound **24** and amino acid couplings were carried out using PyBOP/DIPEA in DMF with HOBt for 3 h. Fmoc deprotection was carried out using 20% piperidine in DMF for two cycles of 6 min. No Dde cleavage was observed under these conditions.

Once the construct **25** was prepared the peptide arm was capped using butyric acid and the conjugate was labelled with 5(6)-carboxyfluorescein on the PNA arm, to yield **26**. Following cleavage from the resin with TFA/TIS/CH_2Cl_2



Scheme 6. Fmoc-Lys-Rink-PEGA 23 synthesis: (a) Dde-OH (2 equiv, 26 mM), TFA (0.1 equiv) in EtOH, reflux, 2 days;[15] (b) **21** (5.5 equiv), PyBOP (5 equiv, 0.1 M), amino-Rink-PEGA resin, DIPEA (11 equiv) in DMF, 3 h; (c) 20% $NH_2OH.HCl$/imidazole (1/0.75 equiv) in NMP/DMF (5/1).



Scheme 8. Synthesis of **26** using alternative PNA and amino acid couplings: (a) Dde-PNA-OH (5.5 equiv), PyBOP (5 equiv), NEM (11 equiv) in DMF, 3 h; (b) 20% piperidine in DMF; (c) Fmoc-AA-OH or butyric acid (last step) (5.5 equiv), PyBOP (5 equiv, 0.08 M), DIPEA (16 equiv), HOBt (5.5 equiv) in DMF, 3 h; (d) $NH_2OH.HCl$/imidazole; repeat a–d as necessary; (e) 5(6)-carboxyfluorescein (22 equiv), PyBOP (22 equiv, 0.08 M), NEM (44 equiv), in DMF, 15 h; (f) TFA/TIS/CH_2Cl_2 (90/5/5), 1 h. FAM = 5(6)-carboxyfluorescein.

(90/5/5) and precipitation, HPLC and MALDI-TOF analysis was undertaken to give the data shown in Figure 4.

3. Conclusion

The solution phase synthesis of a new class of PNA monomers and their application to PNA oligomerization is presented. These monomers present an alternative to Fmoc protected PNA monomers, and the Dde monomers show distinct advantages, especially in the context of PNA–peptide conjugates giving the possibility of a more flexible strategy to obtain PNA–peptide conjugates, such as the possibility of a truly orthogonal synthesis of PNA and peptide when using commercially available Fmoc amino acids. This strategy is routinely used in our group for the synthesis of split and mix PNA encoded peptide libraries which require alternative coupling steps for amino acid and PNA monomers. Further possible applications beyond the synthesis of PNA–peptide conjugates include the synthesis of PNA molecular beacons (i.e., the complementary PNA arm constructed with Fmoc protected PNA monomers). However, it should be noted that PNA poly-T sequences (more than four Ts in a row) cannot be synthesized with this method, due to the strong interactions of polythymidine chains within the beads.

4. Experimental

4.1. General

NMR spectra were recorded using a Bruker AC300 spectrometer operating at 300 MHz for ^1H and 75 MHz

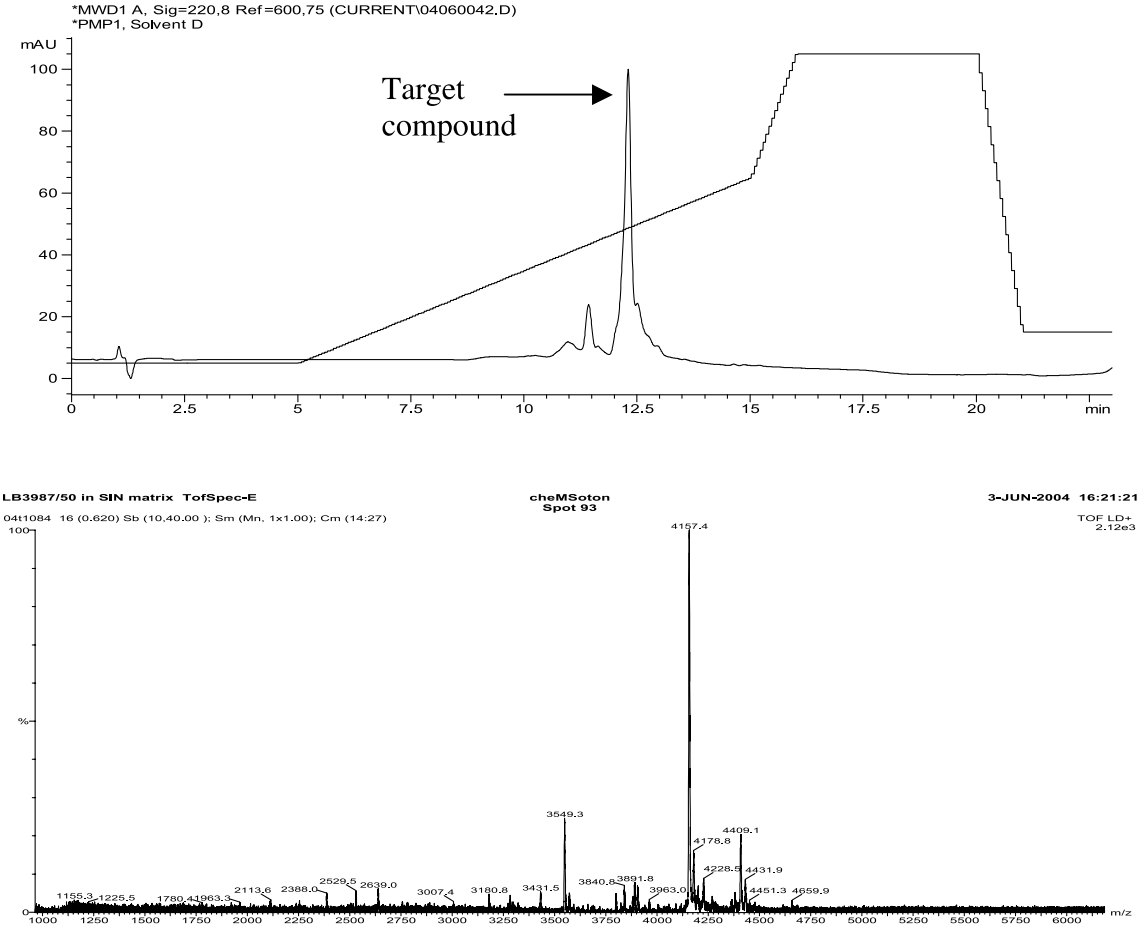


Figure 4. HPLC (acetonitrile gradient is shown, $\lambda = 220$ nm) and MALDI-TOF of crude compound **26**.

for ^{13}C and a Bruker AC400 spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. All coupling constants (J values) were measured in Hz. ES mass spectra were recorded using a VG Platform Quadrupole Electrospray Ionisation mass spectrometer. Reverse phase analytical HPLC (RP HPLC) was performed using a Hewlett Packard HP1100 Chemstation, using a Phenomenex C_{18} prodigy 5 μm (150 mm×3.0 mm i.d.) column. The following methods were used: solvent A=H_2O/CH_3CN/TFA 90/10/0.1 to solvent B=H_2O/CH_3CN/TFA 10/90/0.1, solvent C=H_2O/CH_3CN/TFA 100/0/0.1, solvent D=H_2O/CH_3CN/TFA 0/100/0.1.

Method 1 (flow rate 0.5 mL/min). 100% A to 100% B over 10 min, followed by 100% B for 5 min. Method 2 (flow rate 1 mL/min) 100% A H_2O to 100% B over 3 min followed by 100% B for 1 min. Method 3 (flow rate 0.5 mL/min); 100% C over 5 min, then 100% C to 40% C/60% D over 10 min then to 100% D followed by 100% D over 4 min).

Retention time (R_t). Thin layer chromatography (TLC) was performed using Alugram SIL G/UV/254 precoated plates. Visualisation was achieved by UV radiation.

PyBOP (benzotriazole-1-yl-oxy-tris-pyrrolidinio-phosphonium hexafluorophosphate) and PyBroP (bromo-tris-pyrrolidinio-phosphonium hexafluorophophate) were purchased from Novabiochem (Merck Bioscience, UK). PEGA resin (acrylolated *O*,*O*-bis(aminoproplyl)polyethylene glycol resin) 0.4 mmol/g 150–300 μm was purchased from Polymer Labs (UK), DIPEA (*N*,*N*-di*iso*propyl-*N*-ethylamine), NEM (*N*-ethylmorpholine).

4.1.1. Methyl *N*-{2-[1-(4,4-dimethyl-2,6-dioxo-cyclohexyliden)-ethylamino]-ethyl}-glycinate (5). To a stirred solution of diamine salt **4**[12] (41.6 g, 203 mmol) and DIPEA (71 mL, 406 mmol) in CH_2Cl_2/MeOH (1/1 500 mL) was added Dde-OH (37 g, 203 mmol). The solution was stirred at room temperature for 16 h before evaporating the solvent in vacuo. The crude material was taken up in EtOAc (400 mL) and extracted with 1 M $KHSO_4$ (4×100 mL), which was brought to pH 9 with $NaHCO_3$ before extraction with further EtOAc (4×100 mL). The organic phases were combined, washed with brine (1×100 mL), dried over $MgSO_4$ and concentrated in vacuo to give ester **5** as a brown oil. (34.2 g, 57%). R_f=0.34 (EtOAc); HPLC (method 2) R_t=2.5 min; mp 37 °C; HRMS (ES+): m/z calcd for $C_{15}H_{24}N_2O_4$ [M+H^+] 297.1808, found 297.1807; ^{1}H NMR (400 MHz, $CDCl_3$): δ=13.42 (s, 1H, NH-Dde), 3.66 (s, 3H, OCH_3), 3.43–3.48 (m, 4H, CH_2), 2.87 (t, ^{3}J(H,H)=6.2 Hz, 2H, CH_2), 2.50 (s, 3H, CCH_3), 2.29 (s, 4H, CH_2-Dde), 1.96 (s, 1H, NH), 0.95 (s, 6H, (CH_3-Dde) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=198.1 (CO-Dde), 173.4 (*C*CH_3), 172.7 (*C*$OOCH_3$), 107.9 (Dde-*C*=C), 52.8 (CH_2-Dde), 51.8 (OCH_3), 50.2 (NH*C*H_2CO), 47.6 (DdeNHCH_2*C*H_2NH), 44.0 (DdeNH*C*H_2CH_2NH), 30.0 ((CH_2)$_2$*C*(CH_3)$_2$), 28.2 (CH_3-Dde), 18.1 (C–*C*H_3).

4.1.2. [N^4-(4-Methoxytrityl)-cytosin-1-yl]-acetic acid (10). NaH (1.04 g, 60% in mineral oil, 26 mmol) was added to a stirred suspension of pyrimidine **9**[7] (10 g, 26 mmol) in DMF (100 mL). After stirring for 1 h at room temperature the mixture was cooled to 0 °C and methyl 2-bromoacetate (3.43 mL, 31.3 mmol) was added dropwise. The reaction was stirred at room temperature for 16 h before evaporating the solvent in vacuo. The resulting oil was precipitated with H_2O and removed by filtration, and washed with H_2O to give a white solid which was dried over P_2O_5 in vacuo. R_f=0.32 (EtOAc); HPLC (method 2) R_t=3.43; mp>200 °C min; HRMS (ES+): m/z calcd for $C_{27}H_{25}NaN_3O_4$ [M+Na^+] 478.1737, found 478.1741; ^{1}H NMR (300 MHz, d_6-DMSO): δ=12.8 (br s, 1H, COOH), 8.4 (br s, 1H, NH), 7.45 (d, ^{3}J(H,H)=7.7 Hz, 1H, CH_{Cyt}) 7.4–7.1 (m, 12H, CH_{Mmt}), 6.81 (d, ^{3}J(H,H)=8.8 Hz, 2H, CH_{Mmt}), 6.18 (d, ^{3}J(H,H)=7.7 Hz, 1H, CH_{Cyt}), 4.25 (s, 2H, CH_2), 3.70 (s, 3H, H_3CO–Ar), 3.60 (s, 3H, $COOCH_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.4 (COOH), 166.0 (=C_{Cyt}), 158.8 (*C*OCH_3), 155.7 (CO), 145.2 (CH_{Mmt}), 144.2 (C_{Mmt}), 135.9 (C_{Mmt}), 130.0 (CH_{Cyt}), 129.0 (CH_{Mmt}), 128.6 (CH_{Mmt}), 127.8 (CH_{Mmt}), 113.6 (CH_{Mmt}), 94.9 (CH_{Cyt}), 70.6 (C_{Mmt}), 55.2 (OCH_3), 52.6 ($COOCH_3$), 50.1 (CH_2).

Methyl [N^4-(4-methoxytrityl)-cytosin-1-yl]-acetate[7,21] (31.1 g, 67 mmol) was suspended in 2 N aqueous NaOH (200 mL) and the mixture was stirred for 2 h at reflux. The reaction was cooled to room temperature, washed with CH_2Cl_2 (3×50 mL) and acidified with 2 N aqueous HCl until pH 2. The precipitated was collected by filtration, washed with small portions of water until the filtrate was neutral (pH=7) and dried in vacuo for 12 h to give acid **10** (11.4 g, 66% over two steps) as a white solid.; R_f=HPLC (method 2); R_t=3.33 min; mp 210 °C; HRMS (ES^+) m/z calcd for $C_{26}H_{24}N_3O_4$ [M+H^+] 442.1762; found 442.1770; ^{1}H NMR (400 MHz, d_6-DMSO): 8.31 (s, 1H, NH_{Mmt}), 7.44 (d, ^{3}J(H,H)=6.5 Hz, 1H, CH_{Cyt}), 7.27–7.16 (m, 12H, CH_{Mmt}), 6.82 (d, ^{3}J(H,H)=5.5 Hz, 2H, C*H*$COCH_3$), 6.17 (d, ^{3}J(H,H)=5.8 Hz, 1H, CH_{Cyt}), 4.24 (s, 2H, CH_2), 3.72 (s, 3H, H_3CO–Ar) ppm; ^{13}C NMR (100 MHz, d_6-DMSO): 169.9 (COOH), 164.1 (C_{Cyt}), 158.6 (*C*–OCH_3), 157.5 (CO), 144.9 (CH_{Mmt}), 144.2 (C_{Mmt}), 135.1 (C_{Mmt}), 129.9 (CH_{Cyt}), 128.6 (CH_{Cyt}), 127.4 (CH_{Cyt}), 126.1 (CH_{Mmt}), 112.8 (CH_{Mmt}), 95.5 (CH_{Cyt}), 69.7 ($C(Ar)_3$), 55.0 (O–CH_3), 49.7 (*C*H_2COOH) ppm.

4.1.3. [N^6-(4-Methoxytrityl)-adenin-9-yl]-acetic acid (13). A mixture of ester **12**[6] (7.21 g, 32.3 mmol), NEM (4.1 mL, 32.3 mmol) and 4-monomethoxytrityl chloride (15.0 g, 48.5 mmol) in pyridine (100 mL) and dichloromethane (100 mL) was heated at 40 °C for 3 h, then at 25 °C for 16 h. After evaporation of the solvent in vacuo, the residue was re-dissolved in EtOAc (400 mL), washed with 1 N aqueous $KHSO_4$ (100 mL), 10% aqueous $NaHCO_3$ (100 mL), brine (100 mL) and dried over $MgSO_4$. After evaporation of the solvent in vacuo, the residue was washed with petroleum ether to give a yellowish solid which was refluxed for 2 h in 1 N aqueous NaOH (200 mL) and stirred at 25 °C for 2 h. The solution was cooled to 0 °C. Following addition of 1 N aqueous $KHSO_4$ (250 mL), the mixture was stirred at 0 °C for 30 min, giving rise to the precipitation of acid **13**. After filtration, the residue was washed with small portions of water until the filtrate was neutral (pH=7) and dried in vacuo for 12 h to give acid **13** (14.8 g, 78% over two steps) as a white solid.

R_f=0.28 (CH_2Cl_2/MeOH/HOAc 100/10/1); HPLC R_t

(method 1) = 8.79 min; mp 111–120 °C; HRMS (ES^+): *m/z* calcd for $C_{27}H_{24}N_5O_3$ [M + H^+] 466.1874, found 466.1871; ^1H (300 MHz, d_6-DMSO): δ = 8.15 (s, 1H, CH_{pur}), 7.88 (s, 1H, CH_{pur}), 7.30–7.20 (m, 12H, CH_{Mmt}), 6.85 (d, 2H, ^3J(H,H) = 8.9 Hz, C*H*$COCH_3$), 4.80 (s, 2H, CH_2COO) 3.72 (s, 3H, H_3CO–Ar) ppm; ^{13}C NMR (75 MHz, d_6-DMSO): δ = 169.2 (CO), 157.7 (C), 153.3 (C), 151.0 (CH_{Pur}), 148.9 (C), 145.2 (C), 142.3 (CH_{Pur}), 137.1 (C), 129.8 (CH_{Mmt}), 128.4 (CH_{Mmt}), 127.7 (CH_{Mmt}), 126.5 (CH_{Mmt}), 119.9 (C), 113.0 (CH_{Mmt}), 69.9 ($C(Ar)_3$), 55.0 (CH_3O), 45.0 (CH_2).

4.1.4. Methyl N^2-(4-methoxytrityl)-amino-6-chloro-purin-9-yl acetate (16). To a solution of ester **15**[7] (5 g, 20 mmol) and 4-methoxytrityl chloride (9.58 g, 30 mmol) in dry THF (135 mL) was added DIPEA (3.6 mL, 20 mmol) and the mixture was stirred under a N_2 atmosphere for 12 h. Following evaporation of the solvent, the mixture was taken up in Et_2O (150 mL) and washed with 1 M $KHSO_4$ (3×25 mL); 10% aqueous $NaHCO_3$ (3×25 mL) and brine (1×25 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give oil which was triturated with petroleum ether 40–60 °C to give ester **16** as a yellowish solid (6.2 g, 60%). R_f = 0.5 (EtOAc); HPLC (method 1) R_t = 10.00 min; mp 55 °C; MS (ES+): *m/z* calcd for $C_{28}H_{25}ClN_5O_3$ [M + H^+] 514.16 found 514.2 [^{35}Cl]; 516.2 [^{37}Cl] ^1H NMR (400 MHz, $CDCl_3$): δ = 7.67 (s, 1H, CH_{pur}), 7.35–7.24 (m, 12H, CH_{Mmt}), 6.81 (d, 2H, ^3J(H,H) = 8.6 Hz, C*H*$COCH_3$), 6.65 (s, 1H, NH-Mmt), 4.37 (s, 2H, CH_2), 3.81 (s, 3H, H_3CO–Ar), 3.67 (s, 3H, $COOCH_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8 (CO), 158.2 (C), 157.6 (C), 152.7 (C), 150.5 (C), 145.0 (C), 141.5 (CH_{pur}), 137.1 (C), 130.2 (CH_{Mmt}); 128.9 (CH_{Mmt}), 127.6 (CH_{Mmt}), 126.5 (CH_{Mmt}), 124.0 (C), 112.9 (CH_{Mmt}), 70.8 ($C(Ar)_3$), 55.3 (H_3CO–Ar), 52.9 ($COOCH_3$), 43.8 (CH_2) ppm.

4.1.5. [N^2-(4-Methoxytrityl)-guanin-9-yl]-acetic acid (17). Ester **16** (6.2 g, 12 mmol) was suspended in 2 N aqueous NaOH (150 mL) and the mixture was stirred for 4 h at reflux. The reaction was cooled to room temperature and acidified with 2 N aqueous HCl (pH = 2). The precipitated was collected by filtration, washed with water and dried, in vacuo overnight giving a solid which was washed with di*iso*propyl ether to give acid **17** (4.2 g, 72%) as a yellowish solid.; R_f = 0.12 (CH_2Cl_2/MeOH 7/3); HPLC (method 1) R_t = 7.50 min; mp >200 °C; HRMS (ES^+) calcd for $C_{27}H_{24}N_5O_4$ [M + H^+] 482.1828; found 482.1831; ^1H NMR (400 MHz, d_6-DMSO): δ = 11.18 (s, 1H, NH_{pur}), 8.06 (s, 1H, NH-Mmt), 8.04 (s, 1H, CH_{pur}), 7.27–7.16 (m, 12H, CH_{Mmt}), 6.81 (d, 2H, ^3J(H,H) = 8.6 Hz, C*H*$COCH_3$), 4.28 (s, 2H, CH_2), 3.72 (s, 3H, H_3CO–Ar) ppm; ^{13}C NMR (100 MHz, d_6-DMSO): δ = 168.5 (CO), 168.0 (CO), 157.7 (C), 155.2 (C), 151.6 (C), 149.1 (C), 148.0 (C) 144.6 (C), 138.0 (CH_{pur}), 136.6 (C); 129.8 (CH_{Mmt}), 128.3 (CH_{Mmt}), 127.4 (CH_{Mmt}), 126.4 (CH_{Mmt}), 112.8 (CH_{Mmt}), 69.9 ($C(Ar)_3$), 55.0 (H_3CO–Ar), 43.8 (CH_2) ppm.

4.1.6. Methyl *N*-{2-[N'^6-(4-methoxytrityl)-adenin-9-yl] acetyl}-*N*-{2-[1-(4,4-dimethyl-2,6-dioxo-cyclohexyliden) ethylamino]ethyl}glycinate (18A(Mmt)). To a solution of acid **13** (5.10 g, 10.9 mmol) and amine **5** (3.38 g, 10.9 mmol) in DMF (25 mL) at 0 °C was added PyBroP (5.07 g, 10.9 mmol) and DIPEA (3.7 mL, 21.8 mmol) at 0 °C, and the reaction was stirred under N_2 at 25 °C for 2 h. The solvent was removed in vacuo, the residue was re-dissolved in CH_2Cl_2 (300 mL), washed with 1 M $KHSO_4$ (100 mL), 10% aqueous $NaHCO_3$ (100 mL) and brine (100 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo to give ester **18A(Mmt)** as a brown solid which was used in the next step without purification. An analytical sample was obtained by chromatography.

R_f = 0.62 (CH_2Cl_2/MeOH 5/1); HPLC (method 1) R_t = 9.60 min; mp 125–135 °C; HRMS (ES^+): *m/z* calcd for $C_{42}H_{46}N_7O_6$ [M + H^+] 744.3504, found 744.3510; ^1H (300 MHz, d_6-DMSO) two rotamers: δ = 13.28 and 13.17 (s, 1H, Dde-NH), 8.09 and 8.08 (s, 1H, CH_{pur}), 7.88 (s, 1H, CH_{pur}), 7.31–7.22 (m, 12H, CH_{Mmt}), 6.85 (d, 2H, ^3J(H,H) = 8.5 Hz, CH_{Mmt}), 5.26 and 5.09 (s, 2H, CH_2COO), 4.52 and 4.13 (s, 2H, CH_2CO), 3.79 (m, 2H, CH_2N), 3.74 (s, 3H, CH_3O), 3.72 (s, 3H, CH_3O), 3.57 (m, 2H, CH_2N), 2.57 and 2.46 (s, 3H, CH_3C), 2.30 and 2.27 (s, 4H, CH_2-Dde), 0.94 (s, 6H, CH_3-Dde) ppm; ^{13}C NMR (75 MHz, d_6-DMSO) two rotamers: δ = 196.6 and 196.4 (CO), 173.2 (CO), 169.8 (CO), 169.3 (CO), 167.7 and 167.1 (C), 157.7 (C), 153.4 (C), 151.1 (CH), 149.0 (C), 145.2 (C), 142.3 and 142.1 (CH), 137.1 (C), 129.8 (CH), 128.4 (CH), 127.7 (CH), 126.5 (CH), 119.7 (C), 113.0 (CH), 107.4 and 107.2 (C), 69.9 ($C(Ar)_3$), 55.0 (CH_3), 52.4 (CH_2), 51.8 (CH_3), 49.0 and 48.1 (CH_2), 45.8 (CH_2), 43.7 (CH_2), 41.0 (CH_2), 29.7 (C), 27.8 (CH_3), 17.3 and 17.1 (CH_3) ppm.

4.1.7. Methyl *N*-{2-[N'^4-(4-methoxytrityl)-cytosin-1-yl]-acetyl}-*N*-{2-[1-(4,4-dimethyl-2,6-dioxo-cyclohexyliden) ethylamino]ethyl}-glycinate (18C(Mmt)). This compound was synthesized in analogy to ester **18A(Mmt)**.

R_f = 0.21 (EtOAc); HPLC (method 2) R_t = 3.63 min; mp 135 °C; HRMS (ES+): *m/z* calcd for $C_{41}H_{46}N_5O_7$ [M + H^+] 720.3397, found 720.3402; ^1H NMR (400 MHz, $CDCl_3$): two rotamers δ = 13.50 and 13.37 (br s, 1H, Dde-NH), 7.23–7.05 (m, 12 H, CH_{Mmt}, ^1H CH_{Cyt}), 6.76 (d, ^3J(H,H) = 9.0 Hz, 2H, CH_{Mmt}), 4.99 (d, ^3J(H,H) = 7.8 Hz, 1H, CH_{Cyt}), 4.53 and 4.36 (s, 2H, CH_2COO), 4.27 and 4.02 (s, 2H, CH_2CO), 3.72–3.63 (m, 3H, CH_3O, 4H, CH_2N), 3.52 (CH_3O), 2.51 and 2.47 (s, 3H, CH_3C), 2.25 and 2.24 (s, 4H, CH_2-Dde), 0.95 and 0.93 (s, 6H, CH_3-Dde); ^{13}C NMR (100 MHz, $CDCl_3$) two rotamers: 199.0 and 198.6 (CO), 175.7 (CNH), 170.8 and 170.4 (CO), 168.8 and 168.0 (CO), 163.8 (C), 159.8 (C), 153.0 (CO), 148.2 and 147.2 (CH), 145.1 (C), 136.7 (C), 130.2 (CH), 129.6 (CH), 129.8 (CH), 128.8 (CH), 128.6 (CH), 114.7 and 114.2 (CH), 95.9 (CH), 71.8 ($C(Ar)_3$), 56.3 (H_3C), 53.9 and 53.5 (CH_2), 51.9 and 51.3 (CH_2), 49.9 and 49.5 (CH_2), 47.4 and 47.3 (CH_2), 42.6 and 41.8 (CH_2), 31.0 (C), 29.2 (CH_3), 18.9 and 18.7 (CH_3).

4.1.8. Methyl *N*-[N'^2-(4-methoxytrityl)-guanin-9-yl]-*N*-[2-[1-(4,4-dimethyl-2,6-dioxacyclohexylidene) ethyl-amino]ethyl]glycinate (18G(Mmt)). This compound was synthesized in analogy to ester **18A(Mmt)**.

18 G(Mmt) was obtained as a brown solid (48%) R_f = 0.31 (CH_2Cl_2/MeOH 5/1); HPLC (method 1) R_t = 8.42 min; mp 142–145 °C; HRMS (ES^+) *m/z* calcd for $C_{42}H_{46}N_7O_7$ 760.3459 found 760.3460 [M + H^+] ^1H NMR (400 MHz,

d_6-DMSO) two rotamers $\delta=13.16$ and 13.12 (br s, 1H, Dde-NH), 10.58 and 10.55 (br s, 1H, NH_{pur}), 7.58 and 7.55 (s, 1H, NH-Mmt), 7.44 and 7.42 (s, 1H, CH_{pur}), 7.28–7.12 (m, 12H, CH_{Mmt}), 6.83 (d, ^3J(H,H)=8.5 Hz, 2H, CH_{Mmt}), 4.43 and 4.24 (s, 2H, CH_2COO), 4.10 and 4.05 (s, 2H, CH_2CO), 3.72–3.67 (m, 4H, N–CH_2CH_2-N), 3.66 and 3.61 (s, 3H, CH_3O), 3.43 (s, 3H, CH_3O), 2.49 and 2.47 (s, 4H, CH_2-Dde), 2.30 and 2.26 (s, 3H, CH_3C), 0.95 and 0.94 (s, 6H, CH_3-Dde); ^{13}C NMR (100 MHz, d_6-DMSO): $\delta=196.4$ and 196.2 (CO), 173.0 and 172.7 (CO), 169.4 and 169.2 (CO), 166.9 (CO), 166.3 (C), 157.5 (C), 156.4 (C), 150.8 and 150.7 (C), 149.9 (C), 144.8 (C), 136.7 (CH_{pur}), 129.7 and 129.6 (CH); 128.8 (CH), 127.6 and 127.4 (CH), 126.3 and 126.3 (CH), 116.1 and 116.0 (C), 112.7 (CH), 107.2 (C), 69.7 and 69.6 ($C(Ar)_3$), 54.8 (CH_3), 52.2 (CH_2), 51.7 (CH_3), 48.8 (CH_2), 48.1 (CH_2), 46.5 (CH_2), 40.7 (CH_2), 29.6 (C) 27.7 (CH_3), 17.2 and 17.0 (CH_3) ppm.

4.1.9. *N*-{2-[*N′*^{6}-(4-Methoxytrityl)-adenin-9-yl]-acetyl}-*N*-{2-[1-(4,4-dimethyl-2,6-dioxo-cyclohexyliden)-ethyl-amino]-ethyl}-glycine (19A(Mmt)). Crude ester **18A**(**Mmt**) was suspended in a 1:1 (v/v) mixture of MeOH and 2 M Cs_2CO_3 (60 mL) and stirred for 1.5 h. MeOH was evaporated in vacuo. The remaining solution was diluted with 200 mL water, washed with EtOAc (100 mL), acidified with 1 M aqueous $KHSO_4$, extracted with CH_2Cl_2 (3×200 mL). The organic extracts were washed with brine (100 mL) and the solvent was evaporated in vacuo. The residue was dissolved in a minimum amount of EtOAc. After addition of an excess of hexane, the precipitated solid was collected and dried in vacuo. This precipitate was dissolved in a minimum amount of MeOH. After addition of excess of water, the precipitated solid was collected and dried in vacuo to give acid **19A**(**Mmt**) (3.55 g, 45%) as an off-white solid.

$R_f=0.24$ (CH_2Cl_2/MeOH/HOAc 100/10/1); HPLC (method 1) $R_t=9.01$ min; mp 180 °C (dc); HRMS (ES^+): *m/z* calcd for $C_{41}H_{44}N_7O_6$ [M+H$^+$] 730.3348, found 730.3346 ^{1}H (300 MHz, d_6-DMSO): $\delta=13.26$ and 13.16 (s, 1H, Dde-NH), 8.09 and 8.08 (s, 1H, CH_{pur}), 7.87 (s, 1H, CH_{pur}), 7.31–7.21 (m, 12H, CH_{Mm}), 6.85 (d, 2H, ^3J(H,H)=8.8 Hz,, CH_{Mmt}), 5.24 and 5.07 (s, 2H, CH_2COO), 4.40 and 4.03 (s, 2H, CH_2CO), 3.77 (s, 2H, CH_2N), 3.72 (s, 3H, CH_3O), 3.53 (m, 2H, CH_2N), 2.56 and 2.46 (s, 3H, CH_3CN), 2.29 and 2.26 (s, 4H, CH_2CO), 0.93 (s, 6H, CH_3) ppm; ^{13}C NMR (75 MHz, d_6-DMSO): $\delta=196.4$ (CO), 173.2 (CO), 170.7 (CO), 170.2 (CO), 167.7 and 166.9 (C), 157.7 (C), 153.4 (C), 151.1 (CH), 149.0 (C), 145.2 (C), 142.4 (CH), 137.1 (C), 129.8 (CH), 128.5 (CH), 127.7 (CH), 126.5 (CH), 119.7 (C), 113.0 (CH), 112.2 (C), 69.9 (C), 55.0 (CH_3), 52.4 (CH_2), 49.2 (CH_2), 48.0 and 46.6 (CH_2), 43.7 (CH_2), 40.9 (CH_2), 29.7 (C), 27.8 (CH_3), 17.3 and 17.1 (CH_3).

4.1.10. *N*-{2-[*N′*^{4}-(4-Methoxytrityl)-cytosin-1-yl]-acetyl}-*N*-{2-[1-(4,4-Dimethyl-2,6-dioxo-cyclohexyliden)-ethyl-amino]-ethyl}-glycine (19C(Mmt)). This compound was synthesized in analogy to acid **19A**(**Mmt**).

$R_f=0.37$ (BuOH/HOAc/MeOH 3/1/1); HPLC (method 2) $R_t=3.52$ min; mp 174 °C; HRMS (ES+): *m/z* calcd for $C_{40}H_{43}N_5O_7$ [M+Na$^+$] 728.3055, found 728.3034^{1}H NMR (400 MHz, CD_3OD)= two rotamers $\delta=7.42$–7.25 (m, 10H, CH_{Mmt}, 1H, CH_{Cyt}), 7.20 (d, 2H ^3J(H,H)=8.5 Hz, CH_{Mmt}), 6.90 (d, ^3J(H,H)=9.0 Hz, 2H, CH_{Mmt}), 5.30 and 5.26 (d, ^3J(H,H)=7.5 Hz, 1H, CH_{Cyt}), 4.71 and 4.57 (s, 2H, CH_2COO), 4.26 and 4.12 (s, 2H, CH_2CO), 3.90–3.66 (m, 3H, CH_3O, 4H, CH_2N), 2.56 and 2.53 (s, 3H, CH_3C), 2.33 and 2.29 (s, 4H, CH_2-Dde), 0.98 and 0.96 (s, 6H, CH_3-Dde) ppm; ^{13}C NMR (100 MHz, CD_3OD) two rotamers: 198.9 and 198.6 (CO), 174.8 (CNH), 171.4 and 171.1 (CO), 168.8 and 1678.0 (CO), 163.8 (C), 159.5 (C), 153.5 (CO), 148.8 (CH), 143.6 (C), 135.1 (C) 129.9 (CH), 128.5 (CH), 128.1 (CH), 127. (CH), 113.2 (CH), 95.1 (CH), 71.6 ($C(Ar)_3$), 56.3 (H_3C), 53.9 (CH_2), 51.2 and 50.9 (CH_2), 50.0 (CH_2), 49.2 and 49.0 (CH_2), 42.9 and 42.7 (CH_2), 29.9 (C), 27.4 (CH_3), 17.4 and 17.2 (CH_3) ppm.

4.1.11. *N*-[*N′*^{2}-(4-Methoxytrityl)guanin-9-yl]-*N*-[2-[1-(4,4-dimethyl-2,6-dioxacyclohexylidene)ethylamino] ethyl]glycine (19G(Mmt)). To a solution of ester **18G**(**Mmt**) (2.5 g, 3.3 mmol) in methanol (16.5 mL) was added dropwise a 2 M Cs_2CO_3 aqueous solution (16.5 mL). The solution was stirred for 1.30 h. MeOH was evaporated in vacuo and the remaining solution was diluted with water (50 mL) washed with CH_2Cl_2 (3×15 mL). The basic solution was brought to pH 2 using 1 M $KHSO_4$. The precipitate was collected by filtration, washed with water and re-dissolved in a minimum of MeOH. Following addition of an excess of water, the precipitated solid was collected and dried in vacuo to give acid **19G**(**Mmt**) (1.4 g, 57%) as a brown solid $R_f=0.24$ (BuOH/HOAc/H_2O 3/1/1); HPLC (method 1) R*t*=7.072 min; mp 175 °C(dc); HRMS (ES^+) calcd for $C_{41}H_{44}N_5O_4$ [M+H$^+$]746.3297, found 746.3280; ^{1}H NMR (400 MHz, d_6-DMSO): two rotamers $\delta=13.14$ and 13.13 (br s, 1H, Dde-NH), 10.50 (br s, 1H, NH_{pur}), 7.5 and 7.55 (s, 1H, NH-Mmt), 7.46 and 7.44 (s, 1H, CH_{pur}), 7.25–7.13 (m, 12H, CH_{Mmt}), 6.83 (d, ^3J(H,H)= 8.7 Hz, 2H, CH_{Mmt}), 4.45 and 4.22 (s, 1H, CH_2COO), 3.98 and 3.93 (s, 1H, CH_2CO), 3.73–3.70 (m, 4H, NCH_2CH_2N), 3.41 (s, 3H, CH_3O), 2.50 and 2.47 (s, 4H, CH_2-Dde), 2.31 and 2.27 (s, 3H, CH_3C), 0.95 and 0.94 (s, 6H, CH_3-Dde) ^{13}C NMR (100 MHz, d_6-DMSO) two rotamers: $\delta=196.4$ and 196.2 (CO), 172.9 and 172.7 (CO), 170.4 and 170.2 (CO), 167.0 (CO), 166.1 (C), 157.5 (C), 156.4 and 156.4 (C), 150.8 and 150.6 (C), 149.7 (C), 144.8 (C), 138.1 and 137.8 (CH_{pur}), 129.7 and 129.6 (CH); 128.3 and 128.3 (CH), 127.4 (CH), 126.3 (CH), 116.1 and 116.0 (C), 112.7 (CH), 107.2 and 107.1 (C), 69.7 and 69.5 ($C(Ar)_3$), 54.8 (CH_3), 52.3 (CH_2), 49.3 and 49.3 (CH_2), 48.1 (CH_2), 46.6 and 46.5 (CH_2), 42.7 and 42.5 (CH_2), 40.7 (CH_2), 29.6 (C), 27.7 and 27.7 (CH_3), 17.2 and 17.0 (CH_3) ppm.

4.1.12. *N*-[2-(Thymin-1-yl)-acetyl]-*N*-{2-[1-(4,4-dimethyl-2,6-dioxo-cyclohexyliden)-ethylamino]-ethyl}-glycine (19T). To a solution of amine **5** (4.5 g, 15.1 mmol) in EtOAc (17 mL) was added propylphosphonic acid cyclic (50% solution in DMF) (17 mL, 15.7 mmol), acid **7** (2.9 g, 15.7 mmol), and DIPEA (5.57 mL, 32 mmol and the reaction was stirred for 16 h. Then a mixture of ice-cold water (650 mL) and saturated $NaHCO_3$ solution (350 mL) was added and stirred. The mixture was extracted with EtOAc (100 mL ×9). The organic layers were dried over $MgSO_4$ and concentrated to give a crude product which was reprecipitated using EtOAc/diisopropyl ether mixture. The

solid was collected by filtration to give ester **18T** (4.5 g, 65%) as a white solid.

Crude **18T** (4.5 g, 9 mmol) was suspended in a 1:1 (v/v) mixture of MeOH and 2 M Cs_2CO_3 (90 mL) and stirred for 1.5 h. The MeOH was evaporated in vacuo, the aqueous phase was acidified with 4 N HCl (pH=1), the solvents were removed in vacuo. The residue was treated with hot 2-propanol and the hot suspension was filtrated. The filtrate was collected and 2-propanol was removed in vacuo. The residue was sonicated with water (25 mL) and filtrated to give acid **19T** (3.1 g, 77%) as a white solid.

R_f=0.13 (CH_2Cl_2/MeOH/HOAc 100/10/1); HPLC (method 1) Rt=7.59 min; mp 243–247 °C; HRMS (ES^+): *m/z* calcd for $C_{21}H_{28}NaN_4O_7$ [M+Na^+] 471.1850, found 471.1846; ^1H (300 MHz, d_6-DMSO) two rotamers: δ=13.15/13.10 (m, 1H, Dde-NH), 11.30 and 11.27 (s, 1H, COOH), 7.32 and 7.30 (d, 1H, ^4J(H,H)=1.5 Hz, CH), 4.64 and 4.48 (s, 2H, CH_2COO), 4.26 and 3.99 (s, 2H, CH_2CO), 3.60–3.70 (m, 2H, CH_2N), 3.43–3.57 (m, 2H, CH_2N), 2.50 and 2.45 (s, 3H, CH_3C), 2.26 and (s, 4H, CH_2-Dde), 1.72 (s, 6H, CH_3-Dde), 0.91 and 0.90 (s, 6H, CH_3-Dde) ppm; ^{13}C NMR (75 MHz, CD_3COOD): δ=199.7 and 199.5 (CO), 175.8 (CO), 172.7 and 172.5 (CO), 169.2 and 168.5 (CO), 166.2 (C), 151.8 (CO), 142.8 (CH), 110.5 (C), 107.9 (C), 51.6 (CH_2), 51.4 (CH_2), 49.7 (CH_2), 48.4 and 47.7 (CH_2), 41.5 and 41.0 (CH_2), 29.7 (C), 27.1 (CH_3), 17.8 and 17.6 (CH_3), 11.1 (CH_3).

4.1.13. Fmoc-Lys(Dde)-Rink amide PEGA resin (22). Fmoc-Lys(Dde)-OH **21**[15] (851 mg, 1.6 mmol) and HOBt (211 mg, 1.6 mmol) were dissolved in DMF (16 mL) and shaken for 10 min. DIC (0.296 mL, 1.92 mmol) was added to the mixture and stirred for a further 10 min. The resulting solution was added to the PEGA Rink amine resin (10 g of wet resin, loading 0.04 mmol/g) which was pre-swollen in CH_2Cl_2 (3×25 mL). The mixture was shaken overnight and the progress of the reaction was monitored by a qualitative ninhydrin test. The resin was filtered and washed thoroughly with DMF (3×20 mL), CH_2Cl_2 (3×20 mL) and MeOH (3×20 mL). An analytical sample was taken and cleaved using TFA/TIS (95:5) to give Fmoc-Lys(Dde)-NH_2. HPLC (method 1) R_t=9.62 min; MS (ES^+): *m/z* calcd for $C_{31}H_{38}N_3O_5$ [M+H^+] 532.3, found 532.3.

4.1.14. Fmoc-Lys-Rink amide PEGA resin (23). Resin **22** was pre-swollen in DMF (3×25 mL) before adding a 20% solution of imidazole/hydroxylamine hydrochloride (1/0.75 equiv) in NMP/DMF (5/1, 25 mL).[11] The resulting mixture was shaken for 1 h and the resin was filtered and washed thoroughly with DMF (3×20 mL), CH_2Cl_2 (3×20 mL) and MeOH (3×20 mL). An analytical sample was taken and coupled to Fmoc-Gly-OH (see general procedure for amino acids coupling) before cleavage was carried out using TFA/TIS (95:5) to give Fmoc-Lys(Fmoc-Gly)-NH_2. HPLC (method 1) R_t=10.49 min; MS (ES^+): *m/z* calcd for $C_{38}H_{38}NaN_4O_6$ [M+Na^+] 669.2, found 669.22.

4.2. General procedure for PNA monomer couplings

Dde PNA monomer **19** (5.5 equiv) and PyBOP (5 equiv) were dissolved in DMF followed by the addition of NEM (11 equiv). The resulting solution was mixed for 10 sec. before adding to the resin (1 equiv) pre-swollen in DMF and the mixture was then shaken for 3 h. Resins were washed with DMF (3×3 mL), CH_2Cl_2 (3×3 mL) and MeOH (3×3 mL),

4.3. General procedure for amino acids couplings

Fmoc amino acids (5.5 equiv), PyBOP (5 equiv) and HOBt (5 equiv) were dissolved in DMF followed by addition of DIPEA (11 equiv). The resulting solution was mixed for 10 s. before adding to resins (1 equiv) pre-swollen in DMF and the mixture was then shaken for 3 h. Resins were washed with DMF (3×3 mL), CH_2Cl_2 (3×3 mL) and MeOH (3×3 mL),

4.3.1. Conjugate 24. HPLC (method 3) R_t=13.75 min; MALDI-TOF: *m/z* calcd for $C_{21}H_{28}NaN_4O_7$ (average mass) [M+H^+] 4327.21 found 4237.45.

4.3.2. Conjugate 26. HPLC (method 3) R_t=12.26 min; MALDI-TOF: *m/z* calcd for $C_{179}H_{227}N_{72}O_{48}$ (average mass) [M+H^+] 4155.1 found 4157.4.

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References and notes

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