Tetrahedron

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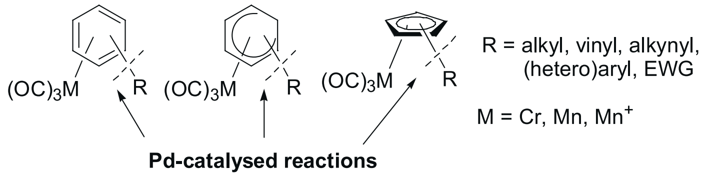

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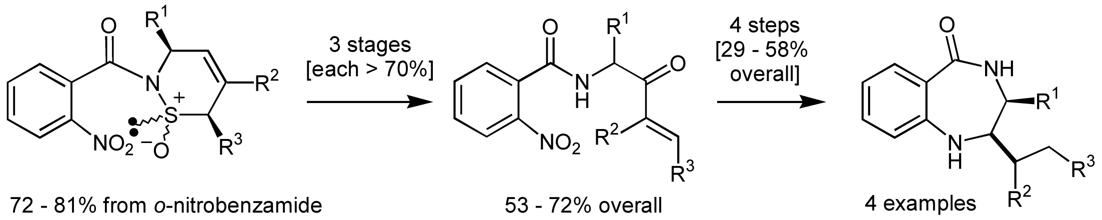
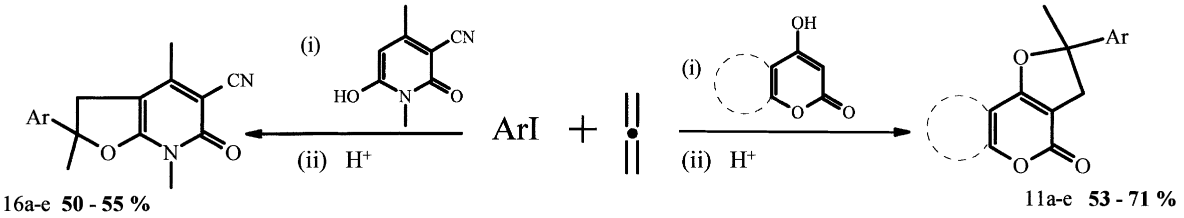
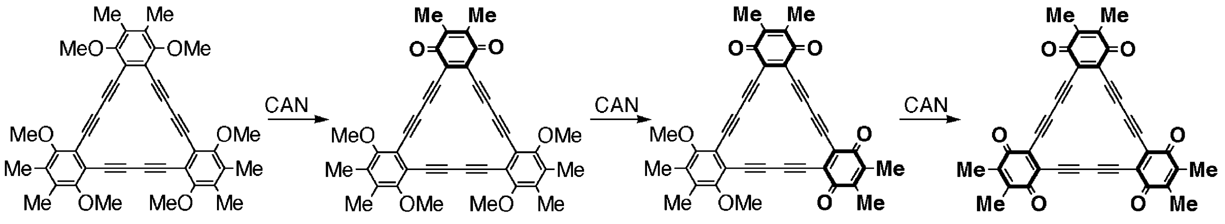


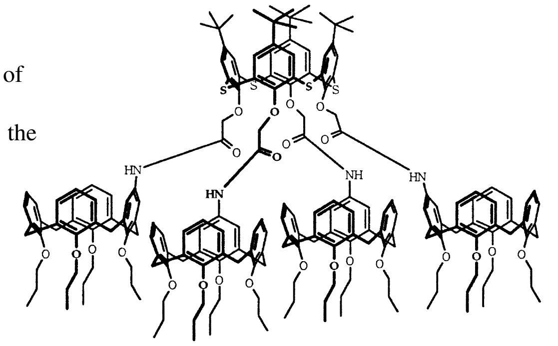


Synthesis and properties of *p*-benzoquinone-fused hexadehydro[18]annulenes **pp 3375–3382**
Tohru Nishinaga, Yasuo Miyata, Nobutake Nodera and Koichi Komatsu*

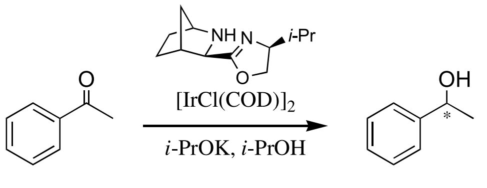


Synthesis of (thia)calix[4]arene oligomers: towards calixarene-based dendrimers **pp 3383–3391**
Václav Štastný, Ivan Stibor, Hana Dvořáková and Pavel Lhoták*

Starting from thiacalix[4]arene-tetraacetates (*cone*, *1,3-alternate*) a novel type of highly preorganised oligo-calixarenes has been prepared. These compounds represent the first example of potential dendrimer-core molecules bearing both the 'classical' calix[4]arene and thiacalix[4]arene moieties.



Development of a new class of (1*S*,3*R*,4*R*)-2-azabicyclo[2.2.1]heptane-oxazoline ligands and their application in asymmetric transfer hydrogenation **pp 3393–3403**
Anna Trifonova, Klas E. Källström and Pher G. Andersson*



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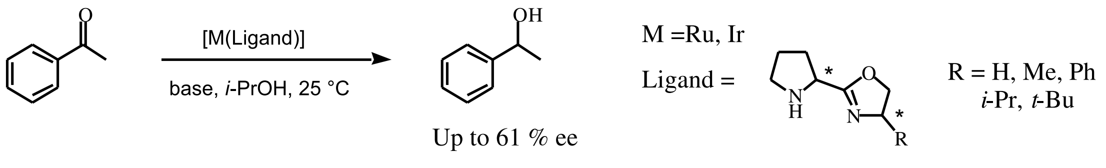
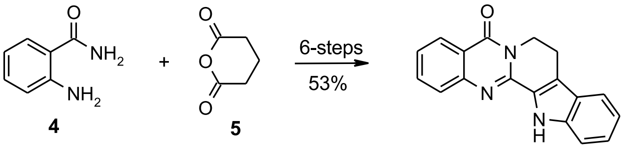
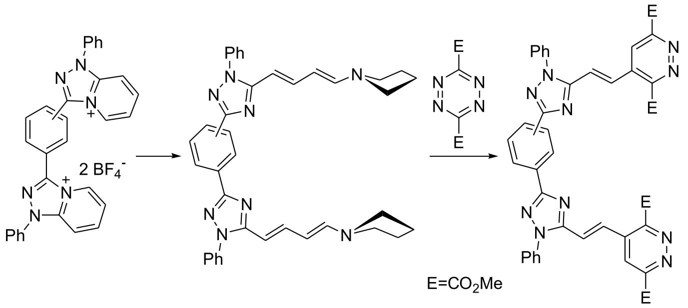
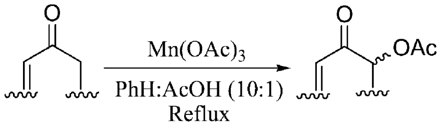
Helen A. McManus, Sarah M. Barry, Pher G. Andersson and Patrick J. Guiry*

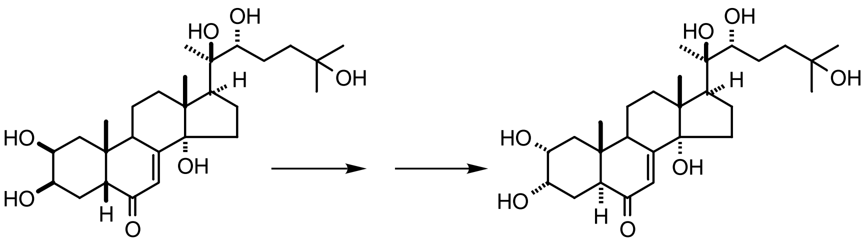


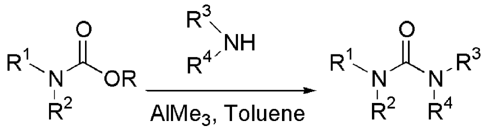


Rutaecarpine (**1a**)

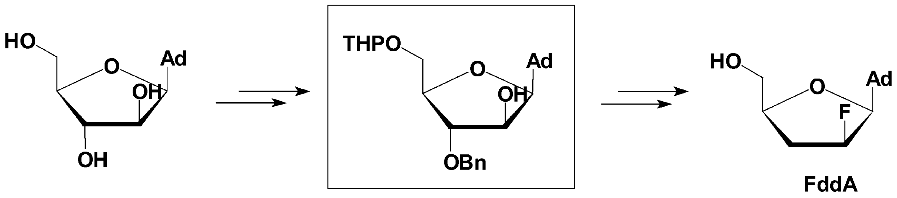




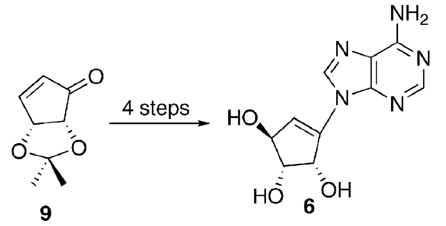




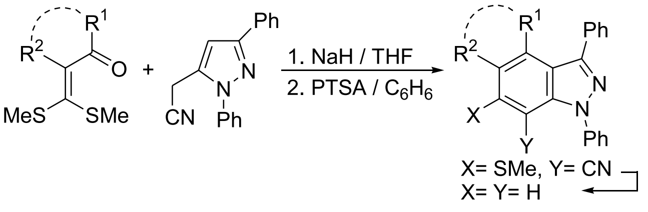
AlMe3, Toluene



HO
Ad
OH
OH
THPO
OBn
F
FddA



4 steps
9
6

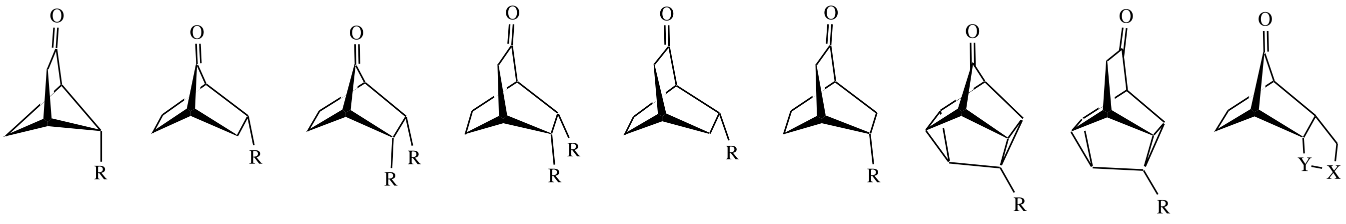


1. NaH / THF
2. PTSA / C6H6
X= SMe, Y= CN
X= Y= H

Development of predictive models of π-facial selectivity; a critical study of nucleophilic addition to sterically unbiased ketones

pp 3465–3472

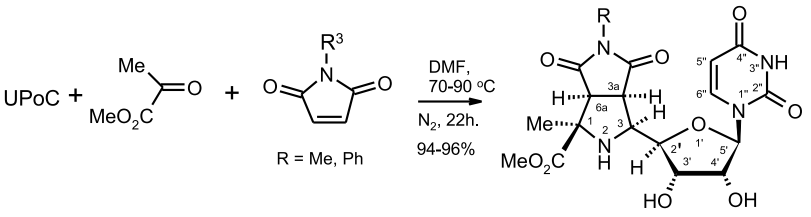
U. Deva Priyakumar, G. Narahari Sastry* and Goverdhan Mehta*



1,3-Dipolar cycloaddition of stabilised and non-stabilised azomethine ylides derived from uracil polyoxin C (UPoC): access to nikkomycin analogues

pp 3473–3485

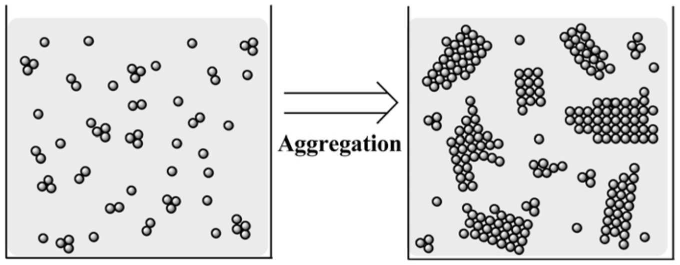
H. Ali Dondas, Colin W. G. Fishwick, Ronald Grigg* and Colin Kilner



Narcissistic aggregation of steroid compounds in diluted solution elucidated by CSI-MS, PFG NMR and X-ray analysis

pp 3487–3492

Kazuaki Shikii, Shigeru Sakamoto, Hiroko Seki, Hiroaki Utsumi and Kentaro Yamaguchi*

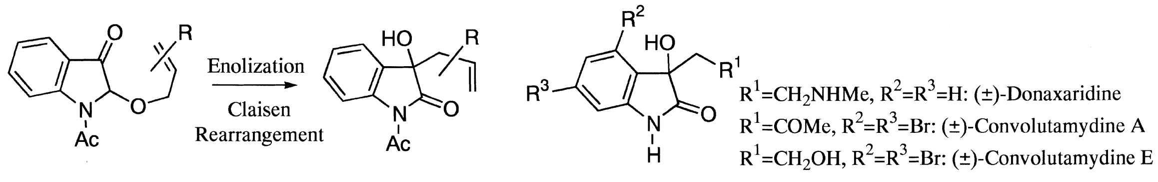


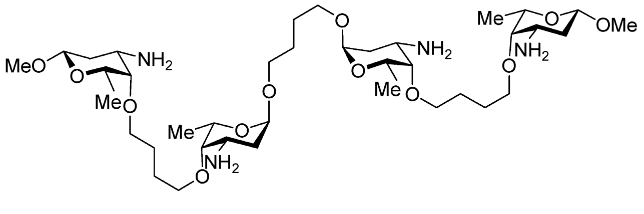
Large-scale aggregated chain structures of progesterone, estrone, cortisone, hydrocortisone and cholic acid were observed in diluted solution by means of cold-spray ionization mass spectrometry (CSI-MS) and pulsed field gradient (PFG) NMR.

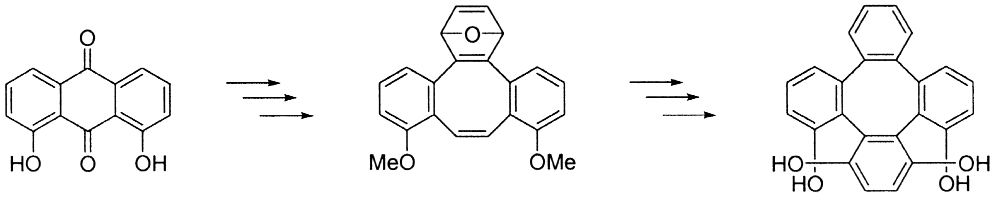
Synthesis of 3-hydroxyindolin-2-one alkaloids, (±)-donaxaridine and (±)-convolutamydines A and E, through enolization–Claisen rearrangement of 2-allyloxyindolin-3-ones

pp 3493–3503

Tomomi Kawasaki,* Miyuki Nagaoka, Tomoko Satoh, Ayako Okamoto, Rie Ukon and Atsuyo Ogawa







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Bimetallic Pd/Cr and Pd/Mn activation of carbon–halide bonds in organochromium and organomanganese complexes

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1. Introduction

Activation of haloarene, halocyclopentadienyl (Cp) or halocyclohexadienyl (Ch) carbon–halide bonds using palladium-catalysed reactions and coordination of the organic ligand to tricarbonyl-chromium or -manganese moieties is now commonly defined as bimetallic Pd/Cr or Pd/Mn activation.[1,2] A combination of the two transition metals greatly expanded the scope of arene–chromium and -manganese chemistry and allowed completion of the reactivity panel of organo-chromium and -manganese complexes.

It is well established that the presence of a tricarbonyl–Cr or -Mn fragment dramatically activates the carbon–halogen bond and opens up the possibilities for nucleophilic attack.[3–7] The very high electrophilicity of these complexes has been exemplified and gave rise to an unprecedented and convenient access to numerous natural products[8–14] and elaborated polymetallic structures with potential applications in materials science.[15–18] Despite intense research, however, the preparation and reactivity of such complexes still lack generality and selective access to vinyl, alkynyl, aryl and electron-withdrawing group (EWG) substituted complexes remains unsolved. Indeed, direct complexation of phenyl-substituted alkynes, alkenes or arenes generally proceeds with low yields and with poor chemo- and regioselectivity. Additionally, the low electronic density of aromatics bearing EWGs prevents direct complexation of the metal.

Keywords: Bimetallic activation; Palladium-catalysed reactions; Organomanganese complexes; Organochromium complexes.

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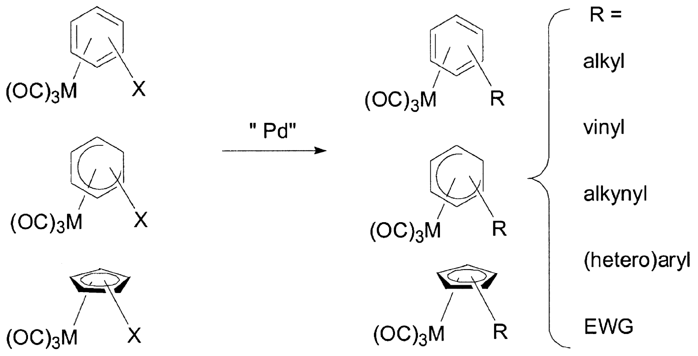


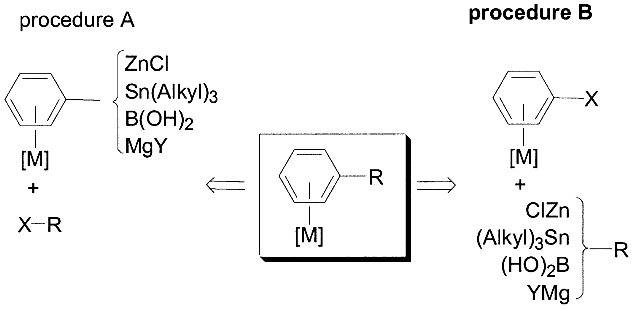
Scheme 1.

In 1985, Villemin[19] first proposed a palladium-catalysed selective and elegant access to phenylalkyne–tricarbonylchromium complexes. Undoubtedly, this pioneering work signalled the early beginnings of a tremendous amount of studies on bimetallic activation of arenes. Since these studies, the scope of bimetallic Cr/Pd activation has not only been applied to the introduction of substituents on arene rings, but has also been employed with Cp and Ch substrates. More recently, the less toxic Mn/Pd combination has been reported to be efficient for the introduction of various substituents on organic ligands. Although a few other bimetallic combinations involving metal carbonyl complexes ($Re(CO)_3$,[20–23] $Mo(CO)_3Me$,[22,23] $W(CO)_3Me$,[22–24] $Fe(CO)_2Me$[22–24] and $Fe(CO)_3$.[25–30]) and palladium are reported in the literature, this article intends to overview palladium-catalysed introduction of sp, sp^2 and sp^3 carbon-based substituents and soft nucleophiles (O-, N-, P- and S-based) on η^6-organochromium complexes and on η^5- and η^6-organomanganese complexes (Scheme 1). The literature is covered up to the begining of 2003.

2. Coupling partners

Palladium-catalysed carbon–carbon bond formation between two partners including an arene–tricarbonylmetal complex can be envisioned owing to two retrosynthetic disconnections: coupling of the (metalloaryl)$M(CO)_3$ with R-halide according to procedure A or coupling of (haloaryl)$M(CO)_3$ with R-metal as illustrated in procedure B (Scheme 2).

Although, in the case of chromium complexes, some type A procedures were successful,[31,32] they mainly afforded the expected coupling product in poor yield or led to demetallation or even no reaction.[33,34] As a consequence, this review will only focus on the type B procedures.

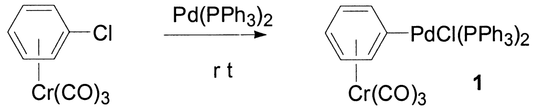


Scheme 2.

3. Pd/Cr Bimetallic activation

3.1. Oxidative addition

The $(\eta^6\text{-}C_6H_5R)Cr(CO)_3$ unit behaves as a strongly EWG.[3–7,35] The withdrawing ability of the $Cr(CO)_3$ moiety being generally comparable to a nitro group.[4] It has been reported that the oxidative addition of the carbon–halogen bond of an aryl halide to palladium(0) is dramatically accelerated by coordination of the highly electrophilic $Cr(CO)_3$ fragment to the arene ring.[36] Indeed, whereas the oxidative addition of chlorobenzene to palladium(0) species requires either elevated temperatures[37] or the use of elaborated basic and bulky phosphine ligands,[38,39] the presence of the $Cr(CO)_3$ fragment allows oxidative addition to take place at room temperature on $(\eta^6\text{-}C_6H_5Cl)Cr(CO)_3$, furnishing complex **1** (Scheme 3).[37]

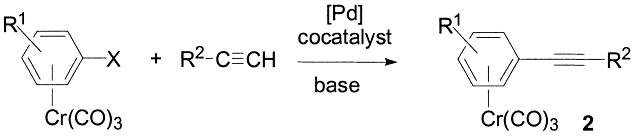


Scheme 3.

Moreover, due to the presence of the $Cr(CO)_3$ fragment, complexed chloroarenes have been shown to react about 15-fold faster than the free iodoarenes in palladium-catalysed carbon–carbon bond formation reactions under very mild experimental conditions.[40]

3.2. Introduction of alkynyl groups

3.2.1. Sonogashira reaction. Alkynylated (η^6-arene)-$Cr(CO)_3$ complexes **2** have received much attention in



Scheme 4.

Table 1. Coupling conditions for the preparation of alkynylated complexes using the Sonogashira procedure

Entry	R^1	X	R^2	Conditions	Yield (%)	Reference
1	H	Cl	H, $SiMe_3$, Ph, CH(OH)Ph, $C(OH)Ph_2$, $(CH_2)_8CO_2H$	$Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$, Et_3N, CuI, 18 h, rt	80–92	18,19,41,42, 46
2	*m*- and *p*-NMe_2, *m*- and *p*-^{t}Bu	I	$SiMe_3$	$Pd(PPh_3)_4$, Et_3N, CuI, 16 h, rt	[a]	46
3	H	Cl	Ph, 4-NO_2Ph, 4-MeOPh, 4-NMe_2Ph, 2-thienyl, 2-furyl, ferrocenyl	$PdCl_2(PPh_3)_2$, Et_3N, THF, CuI, 18 h, rt or reflux	58–91	35
4	H, *o*-, *m*- and *p*-Me	Cl	CH_2OH, $C(OH)Me_2$, $C(OH)Ph_2$,$C(OH)(CH_2)_5$	$PdCl_2(PPh_3)_2$, Et_3N, THF, CuI, 18 h, reflux	69-quant.	43,44
5	*o*-$CH(OMe)_2$	I	$SiMe_3$	$PdCl_2(PPh_3)_2$, Et_3N, THF, CuI, 18 h, reflux	69	45
6	H	Cl	$(\eta^6\text{-}C_6H_5)Cr(CO)_3$	$Pd(PPh_3)_4$, Et_3N, CuI, 24 h, reflux	34	42

[a] Yields not indicated.

recent years, due to their beneficial introduction into building blocks with potential application in materials science.[18,35,41] In this context, most studies were devoted to the palladium-catalysed coupling methodologies, which allow highly chemo- and regioselective alternatives over direct complexation (Scheme 4).

Indeed, classical direct complexation does not tolerate alkyne substituents[42] and thus affords phenylacetylene complexes in low yields (<5%).[19] The Sonogashira procedure appeared to be the most appropriate approach to the regioselective preparation of alkynylated complexes **2** in good to excellent yields (Table 1). The starting arene complexes were usually unsubstituted or substituted by electron-releasing groups and both chloro- and iodoarene complexes were used. Coupling of trimethylsilyl-, aromatic, heteroaromatic and organometallic acetylenes furnished the expected alkynylated complexes. In addition, variously substituted propargylic alcohols were successfully used (entries 1 and 4).[43,44]

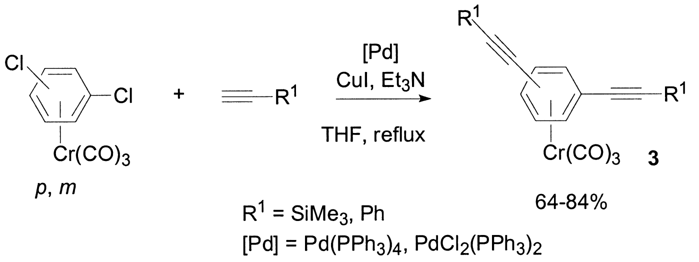
Generally, the catalytic systems are based on Pd(0) or Pd(II) species in combination with CuI as cocatalyst and triethylamine as base in THF. It is noteworthy that some interesting difunctional planar chiral arenes were also obtained using this methodology (entry 5).[45]

Dialkynylated (η^6-arene)$Cr(CO)_3$ complexes **3** were efficiently prepared from 1,3- and 1,4-(dichlorobenzene)$Cr(CO)_3$ complexes through 'one-pot' bis-Sonogashira coupling (Scheme 5).[45] High yields (64–84%) of the dicoupled adducts were obtained using either Pd(0) or Pd(II) precatalysts in classical coupling conditions.

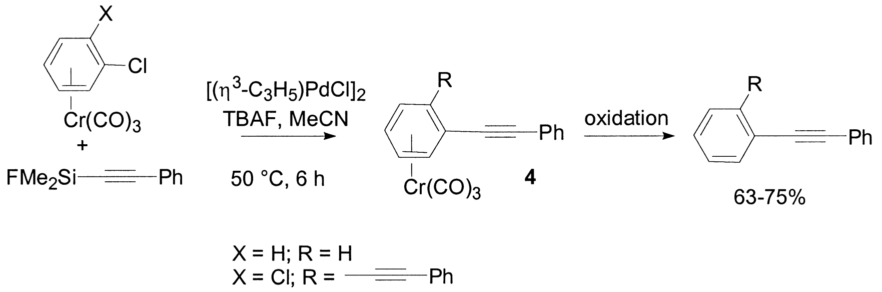
$Cr(CO)_3$-complexed mono- and dichloroarenes were also used in cross-coupling reactions involving organofluorosilanes (Scheme 6).[47] In this case, mono- and di- 'sila type' Sonogashira reactions took place in the presence of $[(\eta^3\text{-}C_3H_5)PdCl]_2$ and TBAF as a fluoride source. The complexed alkynylated adducts **4** were obtained as intermediates, but they immediately reacted with iodine, affording the free acetylenic ligands in 63–75% yield.

Recently, Müller[40] reported the first Sonogashira coupling reaction of the (η^6-chlorobenzene)$Cr(CO)_2PPh_3$ complex **5** with terminal alkynes (Scheme 7). Although replacing the CO residue by a phosphane ligand reduced the electron-withdrawing ability of the metallic fragment, the (η^6-chlorobenzene)$Cr(CO)_2PPh_3$ complexes were found to be efficient coupling partners. Nevertheless, as a consequence of the reduced electron-withdrawing ability, longer reaction times were required to ensure completion of the coupling and formation of the products **6**.

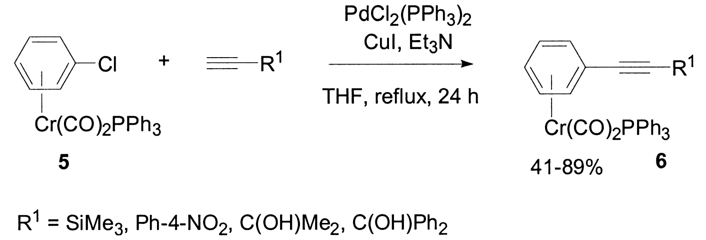
Alkynyl(η^6-arene)$Cr(CO)_3$ complexes **7** obtained using a Sonogashira coupling reaction between (η^6-C_6H_5Cl)$Cr(CO)_3$ and propargylic alcohols have recently been shown to undergo base-catalysed isomerisation into the final enone **9** through an allenol intermediate **8** in a one-pot coupling-isomerisation sequence (Scheme 8).[48] Moreover, starting from the same coupling partners, addition of hydrazine after completion of the coupling-isomerisation sequence allowed



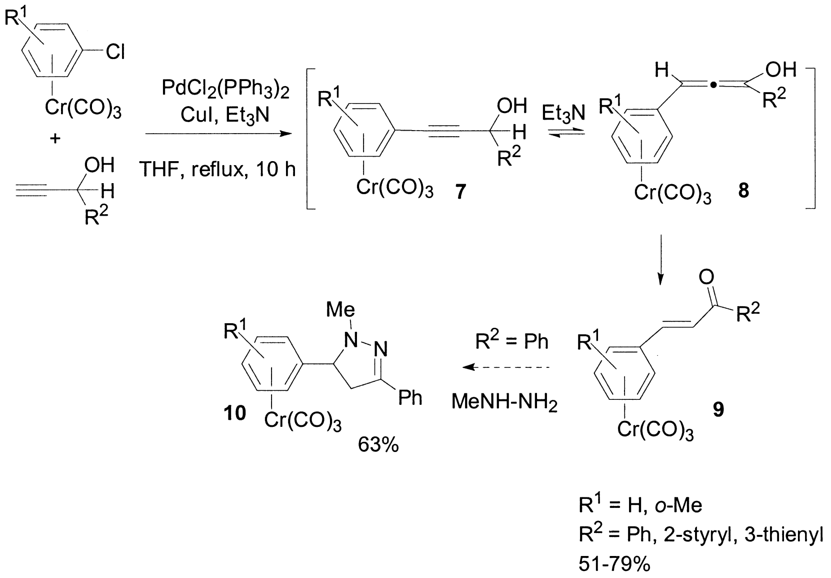
Scheme 5.



Scheme 6.



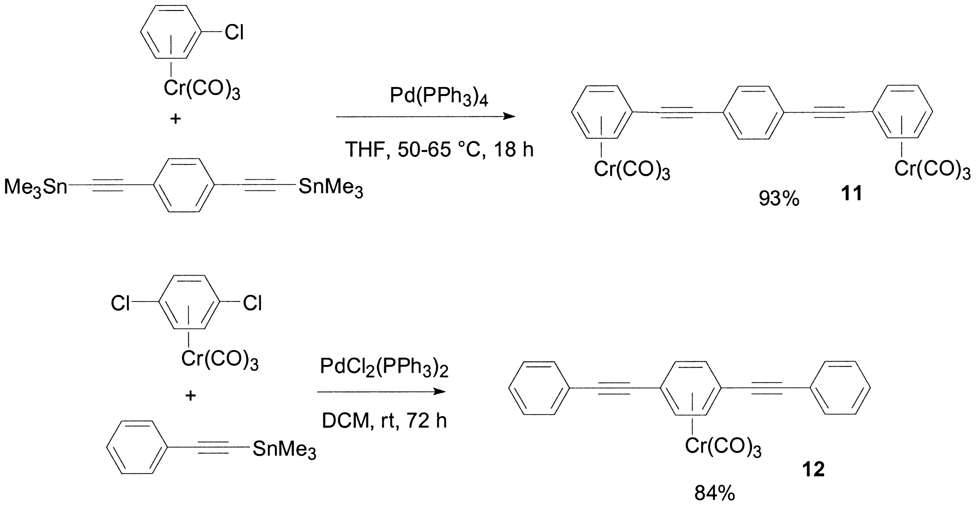
Scheme 7.



Scheme 8.

a one-pot three-component access to the substituted pyrazolines **10**.

3.2.2. Stille reaction. Complementary to the Sonogashira methodology, Stille couplings between trimethylstannylacetylenes and (η^6-C_6H_5Cl)$Cr(CO)_3$ have been used to prepare organometallic-substituted acetylenes (Scheme 9). In one example, two molar equivalents of (η^6-C_6H_5Cl)-$Cr(CO)_3$ were reacted with 1,4-di-(trimethylstannylethynyl)benzene, affording the corresponding dichromium

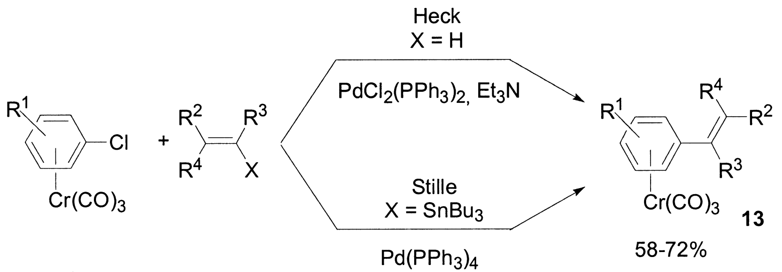


Scheme 9.

complex **11** in 93% yield.[49] Similar couplings using complexed 1,4-dichlorobenzene and trimethylethynylphenylstannane gave the corresponding monochromium complex **12** in 84% yield.[50]

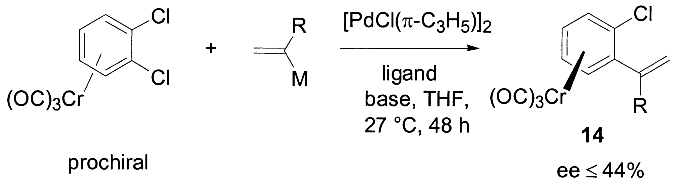
3.3. Introduction of alkenyl groups

Stille reactions and Heck olefinations have been described to introduce vinyl substituents using vinylstannanes and

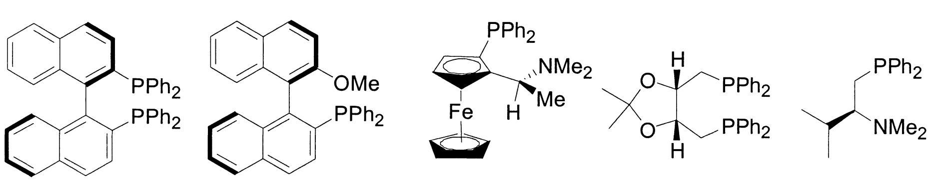


R^1 = *p*-Me, *p*-MeO
R^2 = H, $COCH_3$
R^3 = H, Ph, CH_2OMe, CH(OH)Me, $C(OH)Me_2$
R^4 = H, $SnBu_3$

Scheme 10.



R = H, Me
M = $SnBu_3$, MgBr, ZnCl, $B(OH)_2$
base (Suzuki only) = TlOH 0.4 M
ligand = (*R*)-BINAP, (*R*)-MeO-MOP,
(*S*)-(*R*)-PPFA, (*S*,*S*)-DIOP, (*S*)-Valphos



(*R*)-BINAP (*R*)-MeO-MOP (*S*)-(*R*)-PPFA (*S*,*S*)-DIOP (*S*)-Valphos

Scheme 11.

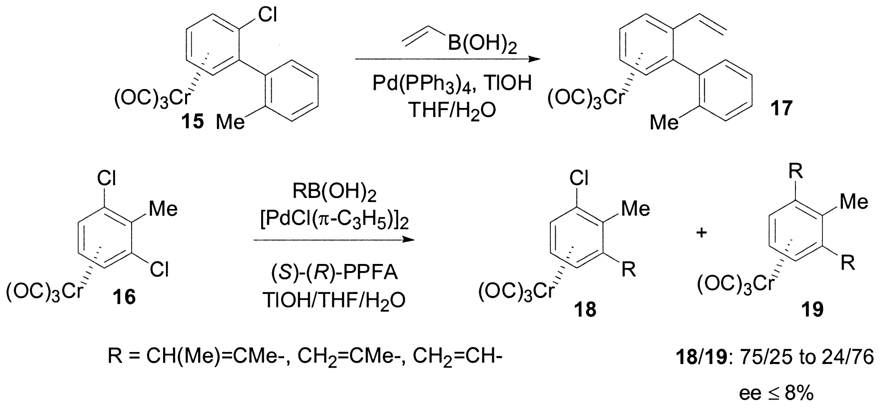
alkenes, respectively. Treatment of methyl vinyl ketone under typical Heck olefination conditions afforded the desired keto complex **13** (Scheme 10; R^2=COMe, R^3=R^4=H, X=H) in 58% yield.[51,52]

Variously substituted styrene complexes **13** could be selectively prepared in high yield by reacting (η^6-C_6H_5Cl)-$Cr(CO)_3$ complexes with vinylstannanes in the presence of Pd(0).[51,53]

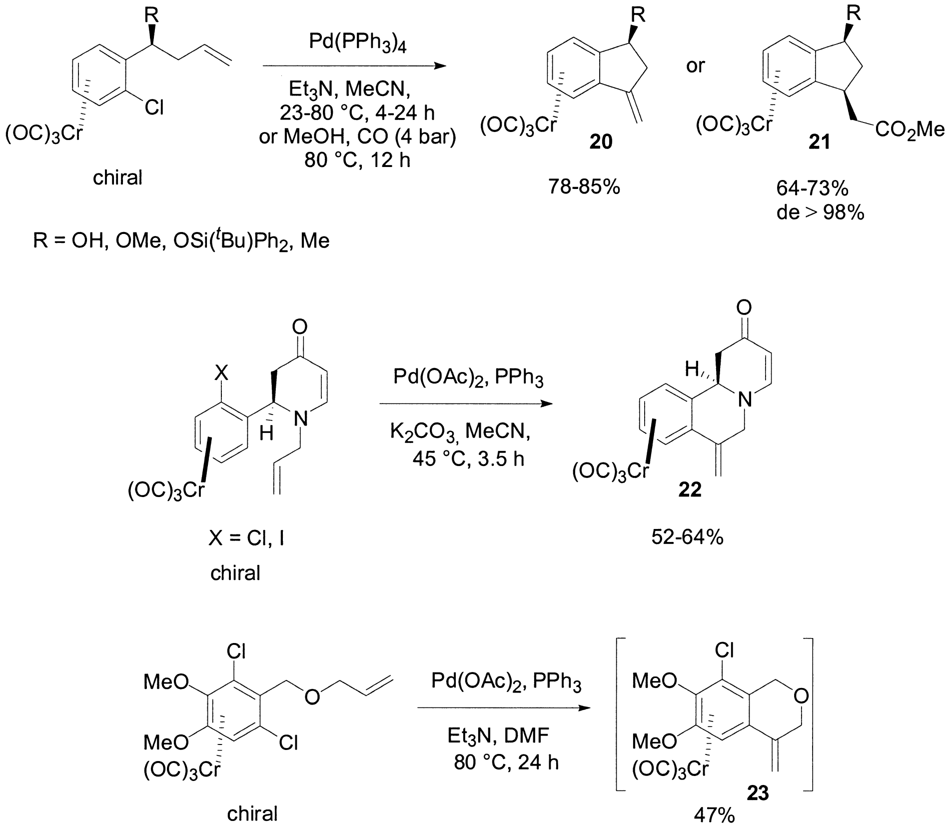
Planar chiral complexes were obtained from prochiral precursors such as (η^6-dichlorobenzene)$Cr(CO)_3$ complex shown in Scheme 11 and the palladium-catalysed monosubstitution of one of the enantiotopic chlorine atoms in this complex affords the optically active complexes **14**. These chiral complexes were obtained in moderate enantioselectivity (up to 44% ee) under Stille (Sn), Corriu-Kumada-Tamao (Mg), Negishi (Zn) or Suzuki (B) conditions, using chiral ligands.[54,55]

Uemura also investigated the couplings between vinylmetals and enantiomerically pure tricarbonylchromium complexes.[56] He particularly exemplified the enantioselective couplings of chloro- **15** or dichlorobenzene **16** tricarbonylchromium complexes with various vinyl boronic acids to afford complexes **17**-**19** (Scheme 12).

An intramolecular version of Heck olefination has only recently attracted much attention and it has been shown that $Cr(CO)_3$ complexes successfully undergo an



Scheme 12.

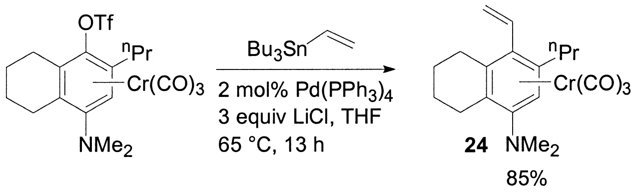


Scheme 13.

intramolecular palladium-catalysed Heck reaction, affording indane, (*iso*)quinolines and benzofuran heterocyclic complexes (Scheme 13).

Kündig first showed that palladium-catalysed intramolecular cyclisations could be performed without decomplexation. Under classical Heck conditions, the methyleneindane complexes **20** were obtained keeping the stereogenic benzylic centre intact.[57,58] Trapping the alkylpalladium species under carbonylative conditions in methanol selectively afforded a single methyl ester diastereomer **21**. The same strategy using the enantiomerically pure chromium complex gave the enantiopure hydro(*iso*)quinolines **22**,[59] whilst the benzofuran skeleton **23** was prepared from the dichloroaryl ether complex in 47% yield under classical Heck conditions.[60]

Another interesting feature of the tricarbonylchromium complexation is illustrated in the preparation of vinyl tricarbonyl complexes from triflates. It is well known that the cross-coupling between electron-rich aryl triflates and stannanes generally requires extreme conditions, but proceeds rather smoothly when a tricarbonyl-chromium moiety is coordinated to the arene. Using this approach, in 1994, Wulff reported that the cross-coupling between a tricarbonylchromium-complexed electron rich arene triflate and a vinylstannane affords compound **24** in excellent yields (Scheme 14).[61]



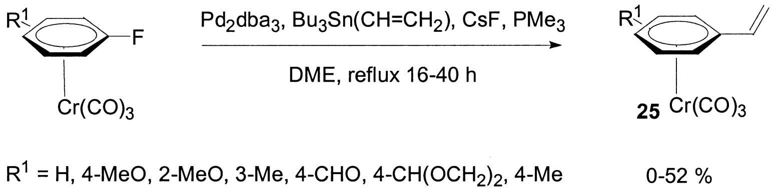
Scheme 14.

Stille olefinations involving (fluoroarene)tricarbonylchromium complexes were also reported by Widdowson (Scheme 15).[62] The coupled adducts **25** were, however, isolated in poor to moderate yields (0–52%). For a general discussion about the use of C–F bonds, see Scheme 32.

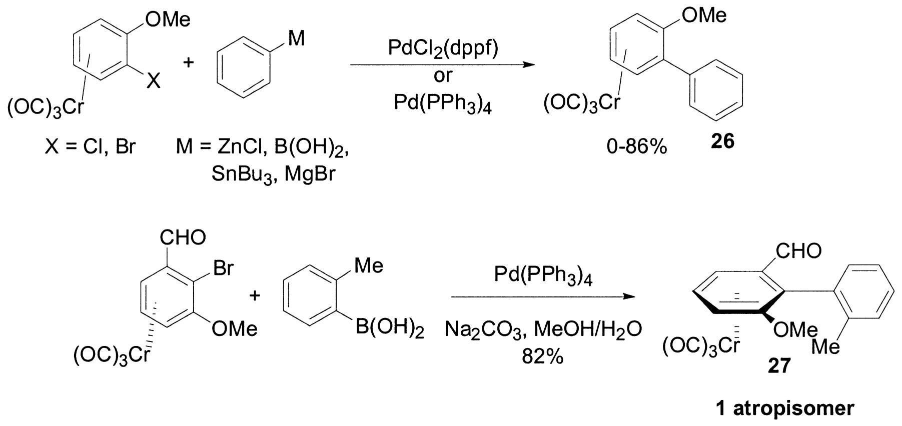
3.4. Introduction of aryl groups

Biphenyl and binaphthyl derivatives are not only attractive compounds as chiral ligands for asymmetric reactions, but are also commonly found in biologically active natural compounds. It has been extensively demonstrated that the presence of a chromium-coordinated arene ligand drastically influences the regioselectivity of chemical reactions on the arene, but also allows unexpected reactions such as aromatic nucleophilic substitutions.[4] Additionally, the coordination of a $Cr(CO)_3$ moiety to a phenyl group differentiates the two prochiral faces of *ortho*- or *meta*-disubstituted arenes and induces a planar chirality. As a consequence, the monochromium complexes of *ortho*- or *meta*-disubstituted biphenyl compounds are expected to exhibit both axial and planar chiralities that could be useful in asymmetric reactions. Since the selective tricarbonylchromium complexation of a biphenyl compound remains elusive and leads to complex mixtures,[63] direct couplings between an arenechromium complex and another arene would provide an elegant route to elaborated biphenyl complexes.

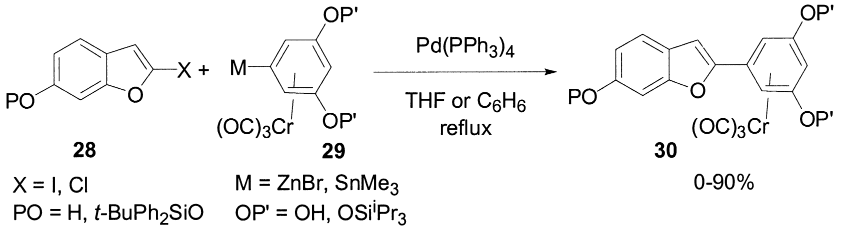
One of the first report describing this approach appeared in 1994 when Uemura et al. described the palladium-catalysed coupling between a haloarene and a metallated (Zn, B, Sn or Mg) species (Scheme 16).[63,64] The expected monochromium biphenyl complex **26** was isolated in poor to excellent yields (up to 86%), along with the dehalogenated or the demetallated arenechromium complex. The best result was obtained by coupling the phenylboronic acid with the



Scheme 15.



Scheme 16.



Scheme 17.

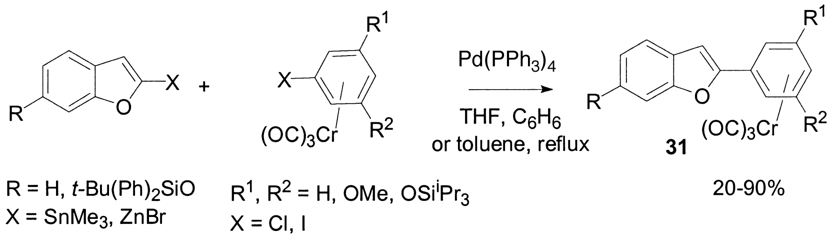
o-bromoanisole chromium complex using $Pd(PPh_3)_4$ as a catalyst in a mixture $MeOH/H_2O$ in the presence of Na_2CO_3.

Interestingly, the stereochemistry of the coupling was investigated for the chiral (3-methoxy-2-bromobenzaldehyde)$Cr(CO)_3$. Using the conditions described above, the expected coupled product **27** was isolated in 82% yield, as a single atropisomer and characterised by X-ray crystallography structure.[63]

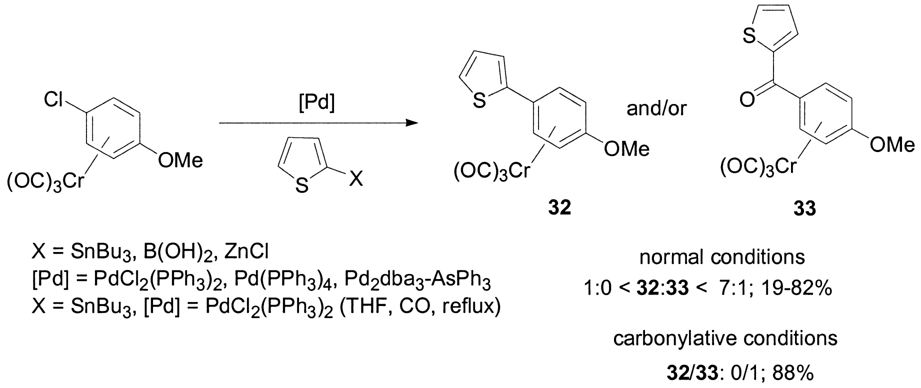
A few years earlier, Widdowson et al. had already investigated the coupling reactions between the halobenzofurans **28** and metallo-resorcinols **29** (Scheme 17).[65] The best conditions were found to involve the triisopropylsilyl-protected iodoresorcinol and a stannylated benzofuran partner. In the presence of $Pd(PPh_3)_4$, the cross-coupling compound **30** was isolated in 90% yield.

Later, the same group investigated further the coupling conditions between 2-trimethylstannyl- or 2-bromozinc-benzofurans with the appropriately functionalised 5-iodo-resorcinols (Scheme 18).[66] The best coupling conditions appeared to involve the trimethylstannylbenzofurans. Using these conditions, the coupled compounds **31** were isolated in moderate to very good yields (20–90%).

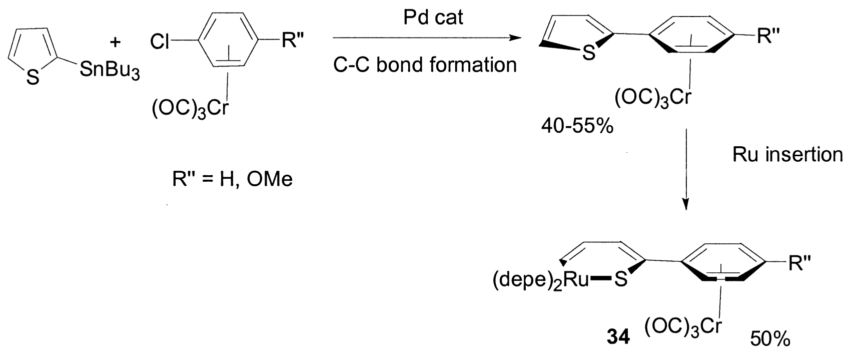
The couplings between heterocycles and tricarbonylchromium complexes have been further studied in recent years. In particular, Rose et al. reported that the couplings between 2-metallated thienyl derivatives (Scheme 19; X=$SnBu_3$, $B(OH)_2$ or ZnCl) and (*p*-chloroanisole)tricarbonylchromium complexes afforded not only the expected tricarbonyl-η^6-[(thiophenyl)arene)] **32**, but also the tricarbonyl-η^6-[(thiophenyl)carbonylarene)] complex **33**, resulting from the insertion of the carbonyl moiety during the coupling (Scheme 19).[67,68] The coupling conditions were investigated and the authors demonstrated that the reaction of stannyl, boronic or zinc derivatives with (*p*-chloroanisole)-chromium complexes generally affords a mixture of the carbonylated and non-carbonylated coupled compounds. The use of the catalytic system $Pd_2(dba)_3$, $AsPh_3$ in DMF at room temperature, however, allowed the exclusive preparation of the expected non-carbonylated species in 82% yield. Additionally, when the reaction was performed under a CO atmosphere in the presence of $PdCl_2(PPh_3)_2$ as the catalyst, only the carbonylated compound was isolated in excellent (88%) yield.



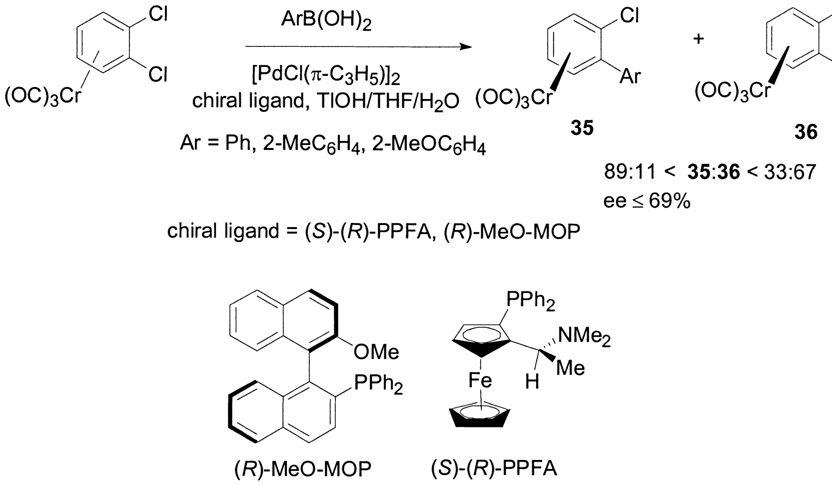
Scheme 18.



Scheme 19.



Scheme 20.

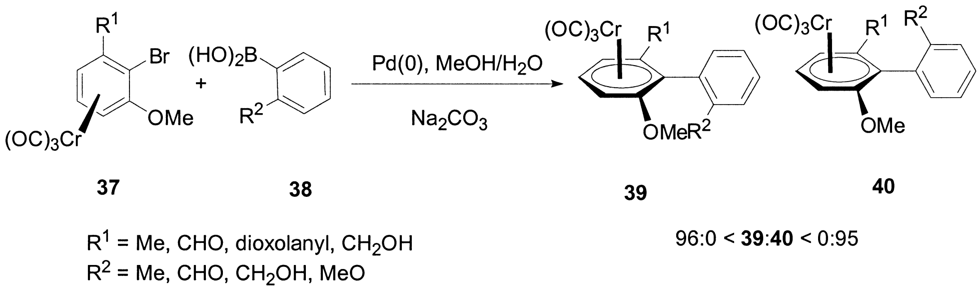


Scheme 21.

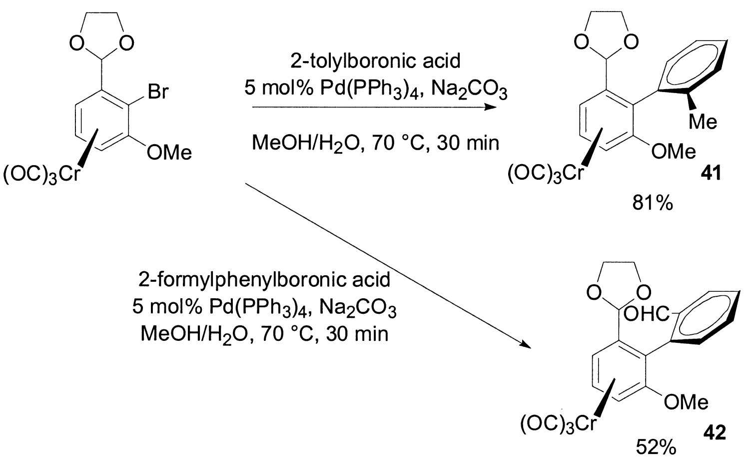
The same group then investigated further the reactivity of the (thienylanisole)chromium complex.[69,70] In particular, the regioselective insertion of ruthenium into the thienyl S–C bond was evidenced (Scheme 20). The arenechromium thiaruthenacycle **34** was isolated in 50% yield and it has been suggested that the regioselectivity of the ruthenium insertion might have been directed by steric factors, as already observed by other workers.[71]

As described earlier, *ortho*- and *meta*-disubstituted arenechromium complexes exist in two enantiomeric forms and can give rise to biaryl complexes with both planar and axial chiralities. This property has been extensively demonstrated over the years. In 1994, Uemura et al. reported the synthesis of the bi- or triphenyl complexes **35** and **36**, starting from the *ortho*-dichlorobenzenechromium complex (Scheme 21).[56] Under palladium catalysis, the expected biaryl structures were isolated in moderate to good yields with enantiomeric excesses up to 69%.

Following a similar approach, chiral biaryl compounds were prepared using Suzuki coupling conditions.[72] These conditions appeared to be rather effective and were applicable to a wide variety of substrates. The disubstituted anisolechromium complexes **37**, bearing either electron-withdrawing or electron-releasing groups, were reacted with the *ortho*-substituted boronic acids **38** under palladium catalysis and afforded the coupled compounds **39** and **40** in reasonable to good yield (Scheme 22). During the couplings, the steroselectivity of the reaction appeared to be controlled by the nature of the *ortho*-substituent of the phenylboronic acid used. It is worth noting, however, that



Scheme 22.



Scheme 23.

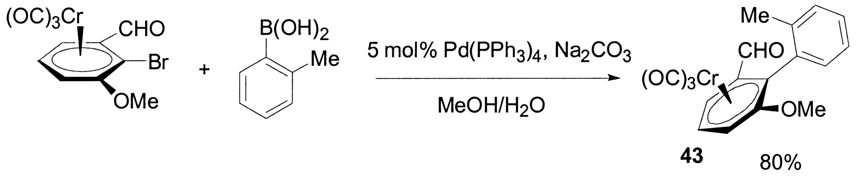
up to 40% of the CO-inserted compound was obtained when R^1=dioxolanyl and R^2=CH_2OH.

This result therefore provides a promising approach for the preparation of the enantiomerically pure biphenyl compounds, with axial chirality, **41** and **42**. The biphenyls obtained using this methodology and depicted in Scheme 23 were recently shown to undergo further selective functionalisation and were isolated as single diastereomers.[73]

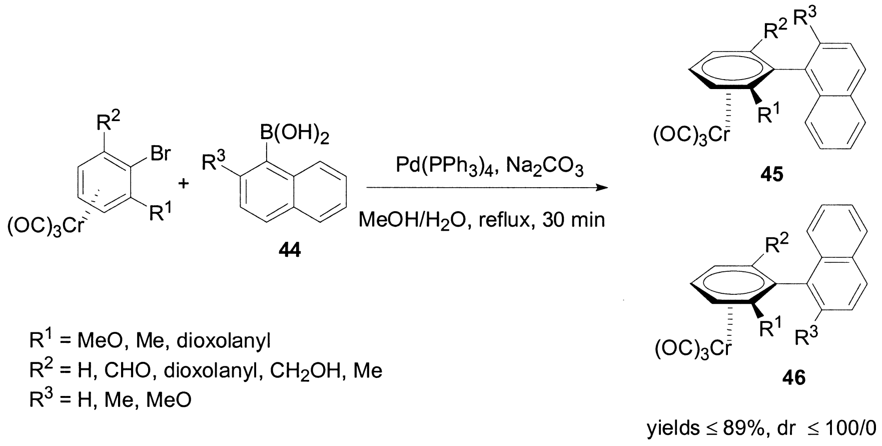
More elaborated structures were prepared using Suzuki cross-coupling[74] and enantiomerically pure (+)-(*R*,*R*)-tricarbonyl[1,2,3,4,5,6-η^6)(2-methoxy-2′-methyl-6-formylbiphenyl]-chromium **43** was synthesised by reacting 2-tolylboronic acid and the enantiomerically pure (−)-(2-bromo-3-methoxybenzaldehyde)chromium complex, under palladium catalysis, in 80% yield (Scheme 24).

The same methodology was successfully applied to the coupling of naphthylboronic acids with substituted arenechromium complexes (Scheme 25).[75] Many natural products including korupensamines or ancistrocladine possess naphthyltetrahydroquinoline substructures in their skeleton. Access to the naphthyl-substituted arenechromium complexes **45** and **46** was successfully achieved by coupling naphthylboronic acids with substituted arenechromium complexes in good to excellent yields. The stereochemistry of the coupling products was also investigated. It appeared that the major coupling compound is the complex **45** (Scheme 25). In this isomer, the naphthalene substituent R^3 lies in the opposite plane with respect to the $Cr(CO)_3$ fragment.

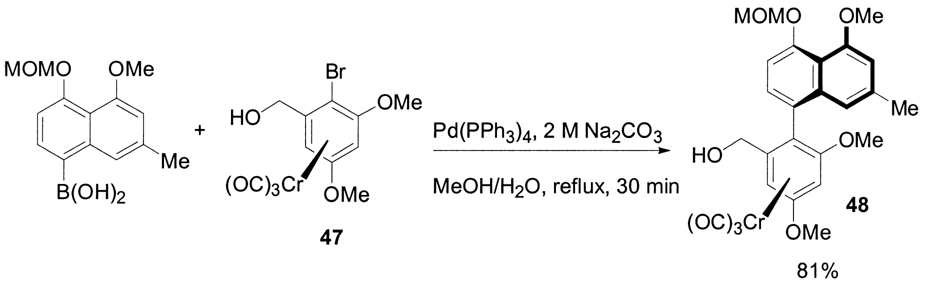
When an enantiomerically pure tricarbonylchromium derivative **47** was used, the coupling compound **48** was



Scheme 24.

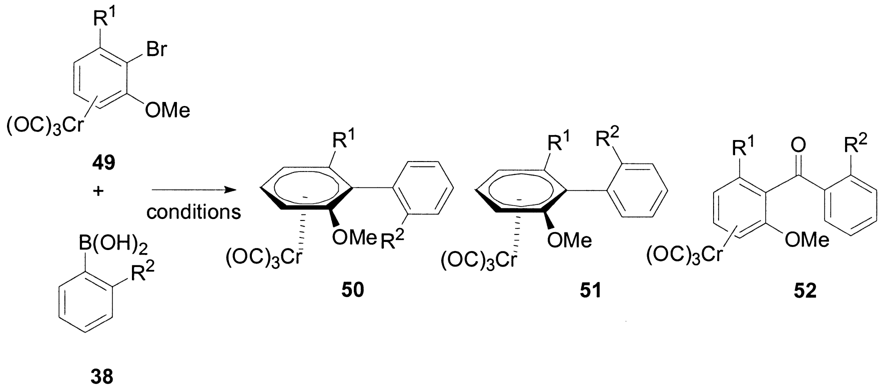


Scheme 25.



Scheme 26.

Table 2. Arylation of arylmetalCr(CO)$_3$ complexes using phenylboronic acids: selected examples



conditions: Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, MeOH/H$_2$O, reflux 30 min

Entry	Complex	Phenylboronic acid	R^1	R^2	Ratio **50/51/52**	Yield (%)
1	**49a**	**38a**	Me	Me	100:0:0	96
2	**49b**	**38a**	CHO	Me	92:0:8	89
3	**49c**	**38a**	$\overline{\text{CHO(CH}_2)_2\text{O}}$	Me	100:0:0	81
4	**49d**	**38a**	CH$_2$OH	Me	100:0:0	77
5	**49a**	**38b**	Me	CHO	0:100:0	95
6	**49b**	**38b**	CHO	CHO	0:100:0	43
7	**49c**	**38b**	$\overline{\text{CHO(CH}_2)_2\text{O}}$	CHO	0:100:0	52
8	**49a**	**38c**	Me	CH$_2$OH	81:0:19	68
9	**49c**	**38c**	$\overline{\text{CHO(CH}_2)_2\text{O}}$	CH$_2$OH	0:0:100	40[68]
10	**49a**	**38d**	Me	OMe	97:3:0	94
11	**49b**	**38d**	CHO	OMe	4:96:0	85
12	**49d**	**38d**	CH$_2$OH	OMe	94:6:0	90

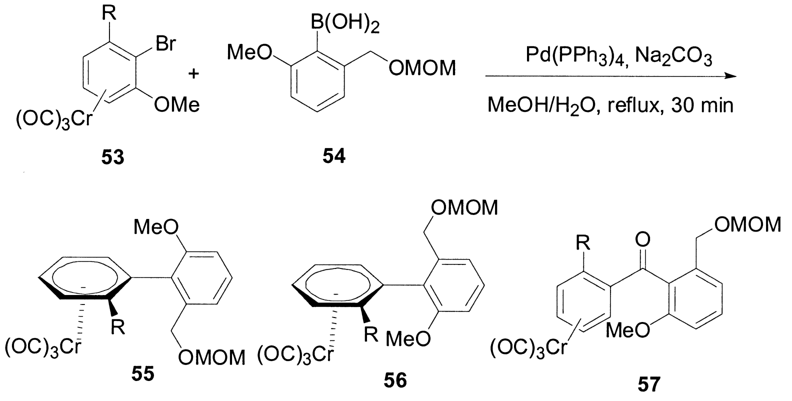
isolated as a single enantiomer without racemisation (Scheme 26).

The use of chiral tricarbonylchromium complexes was then further exemplified. In particular, Uemura et al. reported the stereoselective synthesis of the enantiomers of axially-chiral biaryls using this route.[76] The effects of the different substituents of the coupling partners and the coupling conditions were thoroughly studied (Table 2). As shown in Table 2, Suzuki couplings were proved to be particularly efficient.

The stereoselectivity of the coupling reaction was investigated. From the results gathered in Table 2, it appears that the stereoselectivity of the process is again strictly driven by the bulkiness of the *ortho*-substituents adjacent to the coupling positions. Interestingly, when a 2,6-disubstituted phenylboronic acid **54** was used, the stereochemical differentiation appeared to be lower (Table 3). On the other hand, the reaction of a (2,6-disubstituted aryl halide)Cr(CO)$_3$ **53** with *ortho*-monosubstituted phenylboronic acids proved to be more efficient than the coupling of a monosubstituted aryl halide chromium complex with a disubstituted boronic acid. The authors proposed that the lower yield in the latter coupling reaction could be attributed to the lower propensity for displacement of the palladium intermediate during the transmetallation step.

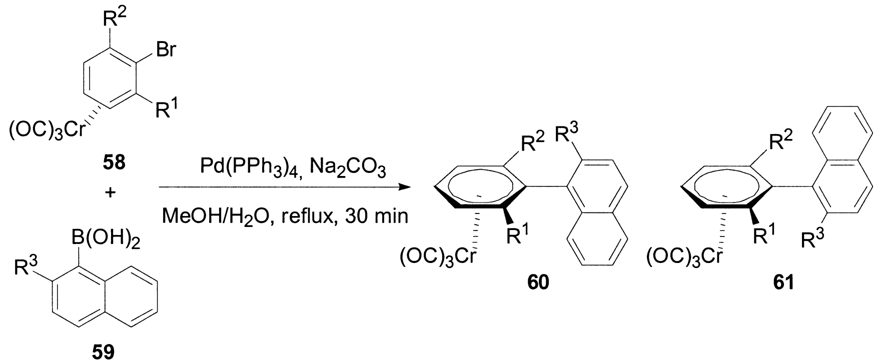
Naphthylboronic intermediates were also investigated in this study (Table 4). As already reported by the same

Table 3. Arylation of arylmetalCr(CO)$_3$ complexes using (2,6-disubstitued)phenylboronic acids

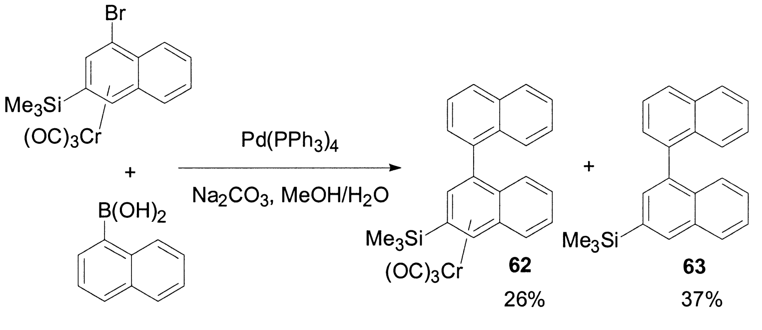


Entry	R	Conditions	Ratio **55/56/57**	Yield (%)
1	Me	$Na_2CO_3/MeOH/H_2O$	94:6:0	77
2	OMe	$Ba(OH)_2$, DME, H_2O	55:22:23	86
3	CHO	$Na_2CO_3/MeOH/H_2O$	0:0:100	40[68]

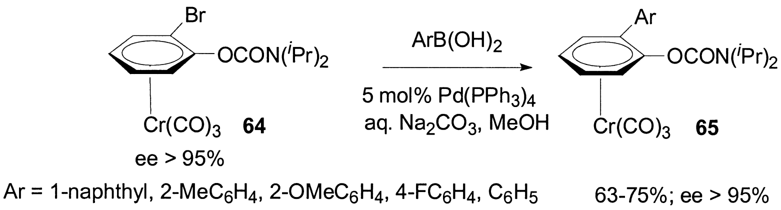
Table 4. Coupling of naphthylboronic acids with arylmetalCr(CO)$_3$ complexes



Entry	Complex **58**	Naphthylboronic acid **59**	Ratio **60/61**	Yield (%)
1	R^1=MeO, R^2=Me	R^3=H	100:0	88
2	R^1=MeO, R^2=CHO	R^3=H	100:0	89
3	R^1=MeO, R^2=CH_2OH	R^3=H	100:0	86
4	R^1=MeO, $R^2 = \overline{\text{CHO(CH}_2\text{)}_2\text{O}}$	R^3=H	100:0	85
5	R^1=Me, R^2=H	R^3=Me	95:5	25
6	R^1=MeO, R^2=H	R^3=Me	71:29	71
7	$R^1 = \overline{\text{CHO(CH}_2\text{)}_2\text{O}}$, R^2=H	R^3=Me	100:0	57
8	R^1=Me, R^2=H	R^3=MeO	97:3	78



Scheme 27.



Scheme 28.

authors in previous studies, the coupling appeared to be really efficient. According to Uemura, the stereochemistry controlled by the bulkiness of the larger fragment near the biaryl axis was determined in a *syn* orientation to the $Cr(CO)_3$ moiety.[77]

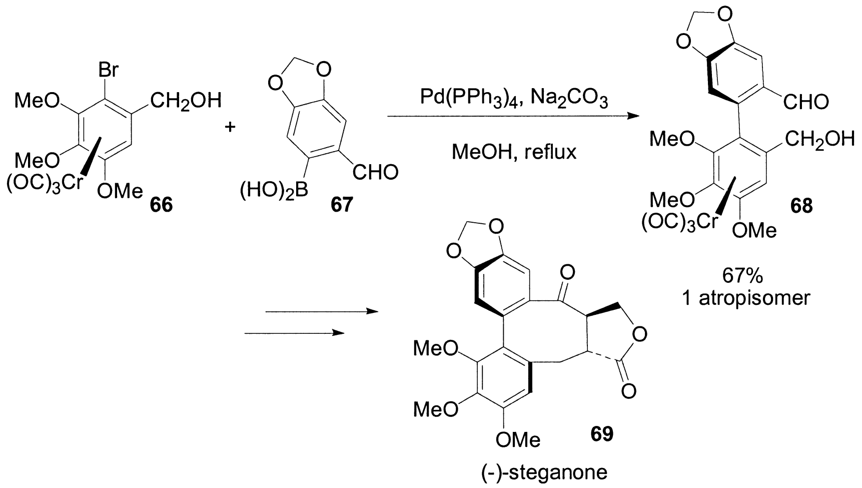
The preparation of binaphthyl derivatives was attempted according to the same procedure (Scheme 27). Unfortunately, the coupling afforded a mixture of the complexed and decomplexed binaphthyl compounds **62** and **63**, respectively, in 26 and 37% yield.

Over the years, Suzuki coupling conditions involving more elaborated partners have appeared in the literature. Nelson reported, in 1999, a Suzuki cross-coupling between an enantiomerically enriched ($95 < ee < 97$) *ortho*-bromo-carbamate–chromium complex **64** and various boronic acids (Scheme 28).[78] In general, the coupled products **65** were isolated in good yields without racemisation.

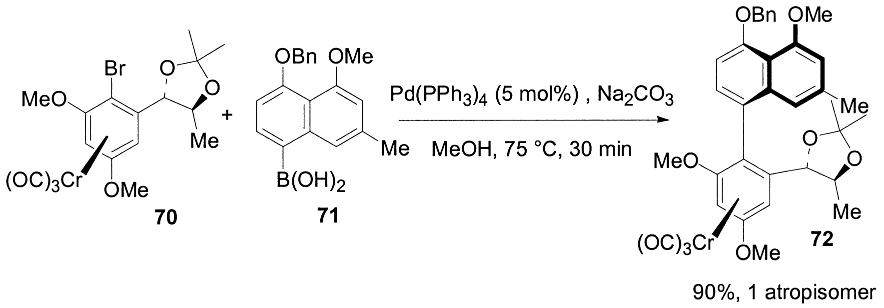
Additionally, the carbamates were shown to be displaced by Ph_2PLi, affording the corresponding diphenylphosphino derivatives in good yield without racemisation.

The versatile character of the cross-couplings involving chiral or non-chiral arenechromium complexes, and the possible preparation of decomplexed products rendered this methodology extremely attractive for the preparation of biologically active compounds. Pioneering work in this area was reported about a decade ago by Uemura et al.,[12] who applied this approach to the synthesis of (−)-steganone.[12] They first prepared the enantiomerically pure pentasubstituted arenechromium complex **66** from the commercially available trimethoxybenzaldehyde. Coupling the halo-arenechromium complex **66** with the boronic acid **67** under palladium catalysis afforded the expected coupling compound **68** in 67% yield, without the formation of the other atropisomer. With this key synthon in hand, the authors were able to access to the (−)-steganone structure **69** in a very elegant manner (Scheme 29).

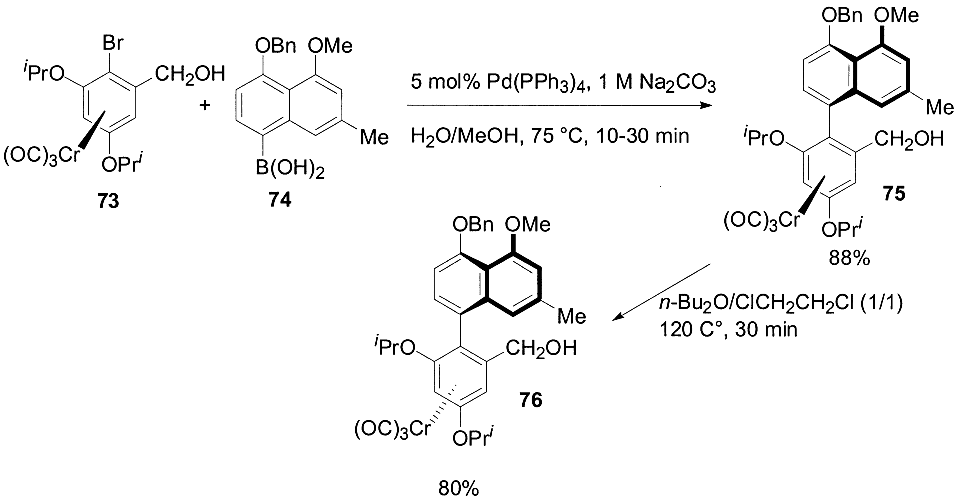
A few years later, the same group used a similar approach



Scheme 29.



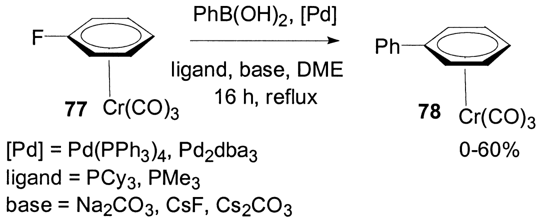
Scheme 30.



Scheme 31.

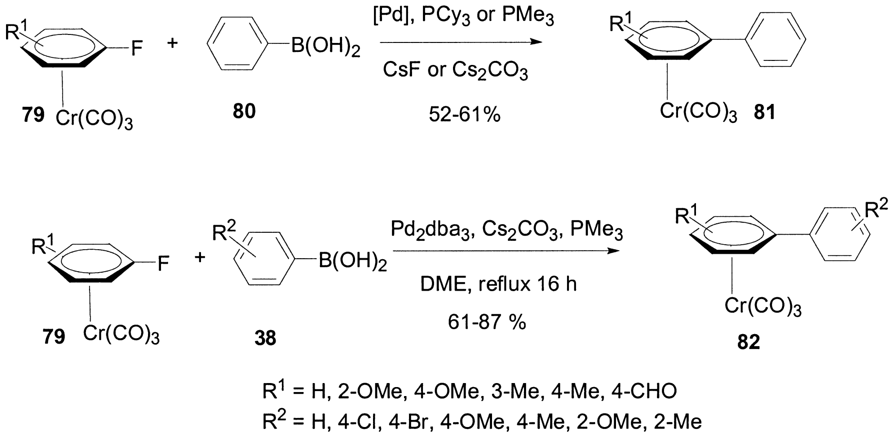
for the preparation of *O*,*O*-dimethylkorupensamine, which is known to exhibit both antimalarial and anti-HIV activities.[79] A key step in the synthesis involved the preparation of a chiral arenechromium-substitued naphthyl complex **72**, a precursor of the naphthyltetrahydroisoquinoline present in the dimethylkorupensamine (Scheme 30). The latter complex was efficiently prepared in a stereoselective manner by coupling the chiral arenechromium complex **70** with the 4-benzyloxy-5-methoxy-6-methylnaphthylboronic acid **71** in the presence of Pd(PPh_3)$_4$ and sodium carbonate in 90% yield.

Key building blocks giving access to the antimalarial korupensamine A and *ent*-korupensamine B were also prepared from chiral planar arenechromium complexes (Scheme 31).[80] Interestingly, the same complex was used in the two parallel syntheses. Both enantiomers of the chiral tricarbonyl(2-bromo-3,5-diisopropoxybenzaldehyde)chromium complex **73**, prepared according to classical organometallic chemistry, were reacted with the naphthylboronic acid derivative **74** under Suzuki coupling conditions. As exemplified, the expected *syn* coupling product **75** was isolated in high yield (88%) as a single diastereomer. The other diastereomer **76** was isolated after a selective atropoisomerisation performed by heating at 120 °C for 30 min.

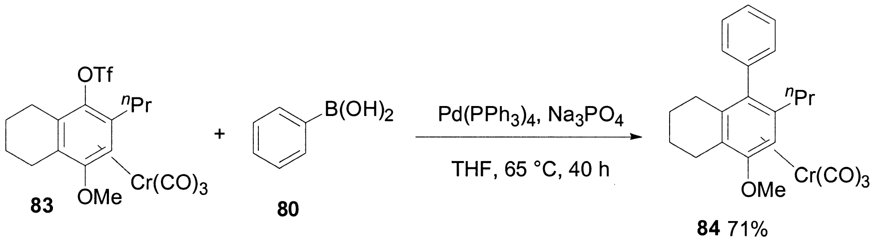


Scheme 32.

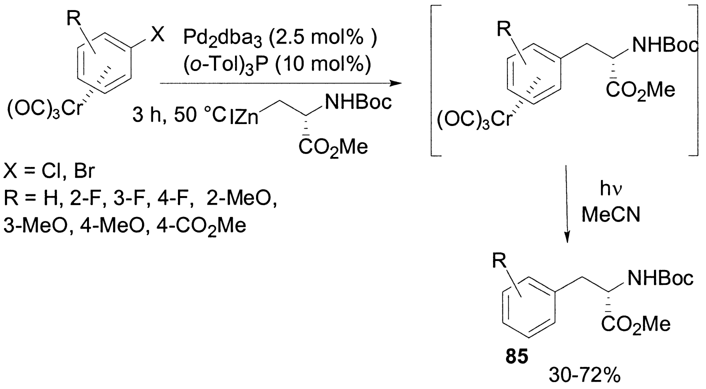
Numerous advantages of arene coordination by a Cr(CO)$_3$ moiety have been listed above. Nevertheless, some other properties of arenechromium complexes remain to be exemplified. In particular, the electronic effects brought about by the coordination of Cr(CO)$_3$ weaken the aromatic bonds and allow remarkable chemical sequences. One of the most striking examples concerns the oxidative addition of palladium involved in aromatic C–F bonds that offers attractive and efficient cross-couplings involving fluoroarenes. Widdowson et al. were among the first chemists to investigate this opportunity and in 1999, they reported Suzuki-type couplings between a phenylboronic acid, and the fluorobenzenetricarbonylchromium complex **77** (Scheme 32).[81] Different coupling conditions were tested. The best results were obtained using Pd_2dba_3 as the



Scheme 33.



Scheme 34.



Scheme 35.

palladium source, PMe_3 as the ligand and Cs_2CO_3 as the base. Under these conditions, the coupling products such as **78** were isolated in about 60% yield (see also Scheme 15).

More recently, the same authors investigated further the potential of this approach with substituted arenechromium complexes and boronic acids.[62,82] In particular, both the catalytic conditions and the effect of substitution on the arenechromium moiety **79** were investigated. Two different sets of catalytic conditions appeared to be the most suitable: Pd_2dba_3–PCy_3, CsF and Pd_2dba_3–PMe_3, Cs_2CO_3. The use of the latter gave an access to monocomplexed biphenyls **81** and **82** (Scheme 33).

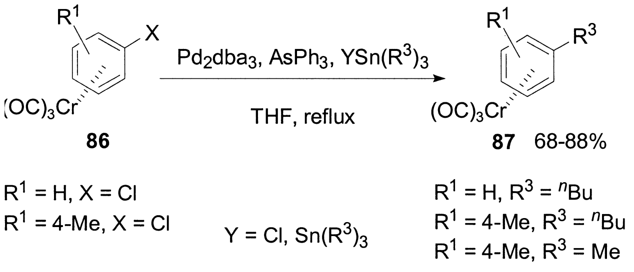
To the best of our knowledge, very few examples of couplings involving arenechromium complexes bearing non-halogenated leaving groups have been reported. It should be mentioned, however, that triflates were found to be good alternative partners for the couplings and, in 1994, Wulff et al. reported the coupling between an arenechromium triflate complex **83** and phenylboronic acid **80** in 71% yield (Scheme 34).[61]

3.5. Introduction of alkyl groups

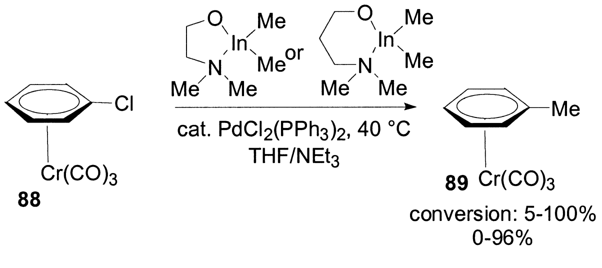
The versatility of the arenechromium chemistry has been extensively exemplified in the former part of this review with the observation of very efficient arene–arene couplings. Another feature of the arene chromium activation by a tricarbonylchromium moiety concerns the coupling of alkyl groups on arenes using palladium catalysis.

To the best of our knowledge, this methodology was first reported in 1996 by Jackson et al. who described the alkylation of halo-arenechromiumtricarbonyl complexes by zinc-activated aminoacid residues. Under classical catalytic conditions (Pd_2dba_3, $(o\text{-Tol})_3P$), the coupling compounds **85** were obtained in 30–72% yield after decomplexation (Scheme 35).[83]

More recently, Rose et al. reported a different arene alkylation involving a very efficient and selective alkyl group migration from the stannylated reactant, $(alkyl)_3SnCl$ or $[(alkyl)_3Sn]_2$, on a chloroarenetricarbonylchromium complex **86** (Scheme 36).[84] In this case, alkyl-substituted complexes **87** were obtained in 68–88% yield.



Scheme 36.

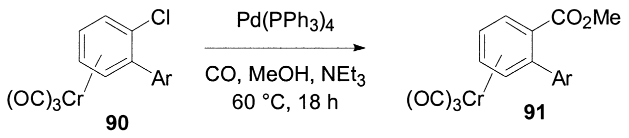


Scheme 37.

Finally, in 2002, Schmaltz et al. reported methyl *ipso* substitutions of the chlorotricarbonylchromium complex **88** using methylindium derivatives and affording complexes **89** (Scheme 37).[85] The reactions took place in good to excellent yields at 40 °C in THF.

3.6. Introduction of carboxylated groups

The association of palladium and arenechromium chemistries has been widely used in the preparation of aromatic esters, amides, aldehydes or α-oxo-amides. In a typical experiment, a haloarenetricarbonylchromium complex is reacted with a nucleophile under palladium catalysis and a carbon monoxide atmosphere. Uemura et al. described a pioneering result in this area in 1994.[56] Using the strategy described above, they reported the preparation of a benzoate methyl ester tricarbonylchromium complex **91**, starting from the corresponding chloroarene derivative **90** (Scheme 38). No yield concerning the reaction was mentioned.



Scheme 38.

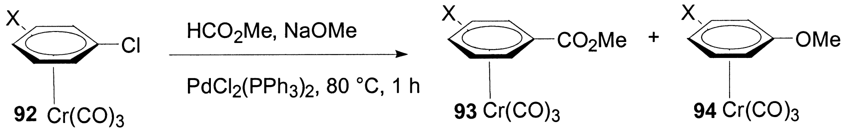
The same year, Carpentier et al. reported a similar approach using substituted chloroarenetricarbonylchromium complexes **92**.[86] Interestingly, the conditions they used not only afforded the expected esters **93**, but also the corresponding anisoles **94** in good combined yields. In the case of chloroarenes substituted by EWGs, the anisoles were isolated as the major compounds (Scheme 39).

Using the same catalytic conditions, this group further investigated the effect of the substituents.[87,88] They observed that the presence of electron-donating groups on the starting chloroarene favoured the formation of the esters **95** and **96** at the expense of the anisole **97** (Scheme 40).

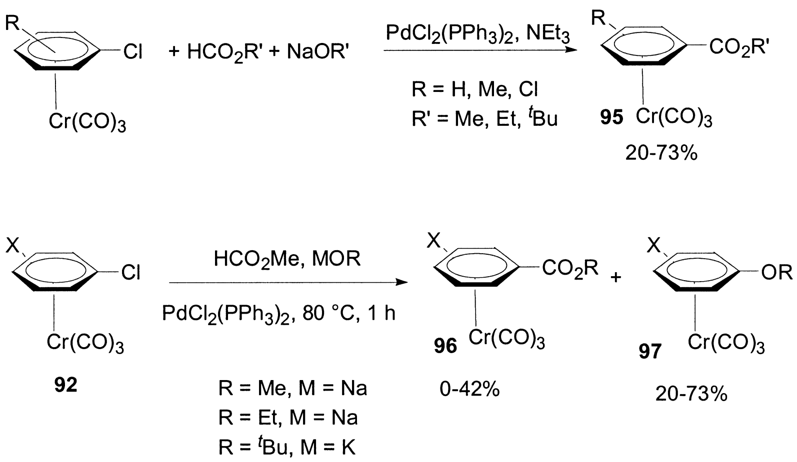
3.7. Introduction of carbonylated groups

Carbonylation of haloarenetricarbonylchromium complexes can additionally be achieved via a similar strategy. The mechanistic insights of the strategy were thoroughly investigated in 1991 by Basset et al.[37] and the first reports appeared in 1993 when Carpentier et al. described the preparation of the benzaldehyde derivatives **98**, starting from substituted chloroarenetricarbonylchromium complexes (Scheme 41).[51]

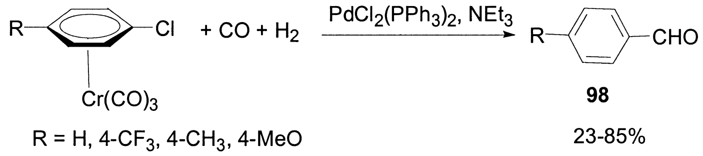
Using a similar strategy, Carpentier et al. reported that the amide **99** and α-oxo-amide **100** could be prepared through an aminocarbonylation sequence (Scheme 42).



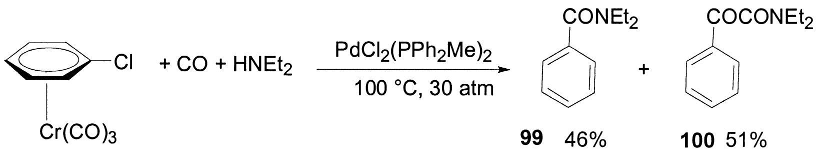
Scheme 39.



Scheme 40.



Scheme 41.



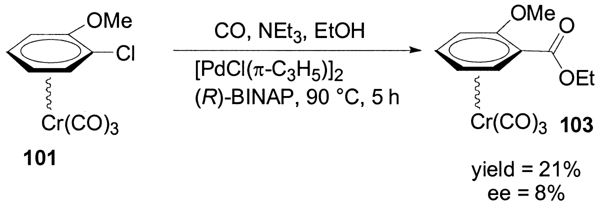
Scheme 42.

Aminocarbonylations were also described by Basset et al. (Scheme 43).[37] These authors pointed out that the ratio between the amide and the α-oxo-amide depends on the carbon monoxide pressure used during the reaction.

Later, they pursued their investigations further and generalised the methodology (Scheme 43).[89]

In 1996, Carpentier et al. developed a chiral version of alkoxycarbonylation for the kinetic resolution of 2(-chloroanisole)tricarbonylchromium complexes such as **101** (Scheme 44).[90] In this approach, they took advantage of the efficiency of esterification reactions of electron-rich chloroarene complexes. In particular, they reported the preparation of diastereomeric esters, for example, **102**, from (*S*)-2-methyl-1-butanol and the (*o*-chloroanisole)chromium complex (Scheme 44) in good yields, but with poor enantiomeric excesses.

In a similar manner, the asymmetric reaction catalysed by the palladium–(*R*)-BINAP complex in ethanol gave the expected ester **103** with an interesting selectivity, but a poor yield (Scheme 45).

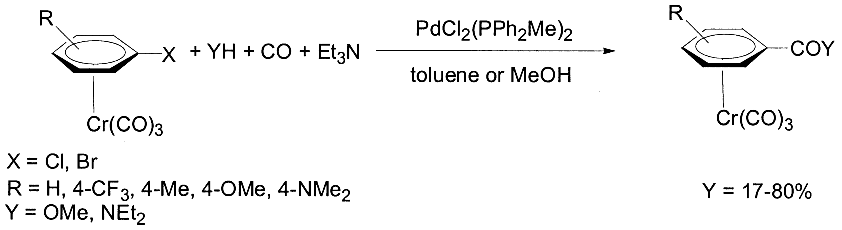


Scheme 45.

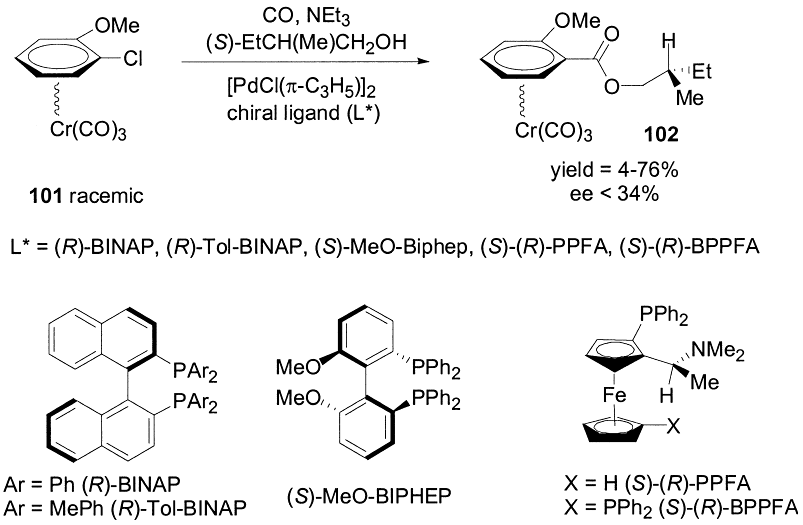
4. Pd/Mn Bimetallic activation

4.1. Introduction

$Mn(CO)_3$ complexes have been known since the early 1970s. $Mn(CO)_3$ or $Mn^+(CO)_3$ fragments have been described as even more electrophilic than the corresponding $Cr(CO)_3$ moiety.[4,91] Palladium-catalysed reactions involving $Mn(CO)_3$ complexes were, however, scarcely described until recently. Taking into account the withdrawing ability of the $Mn(CO)_3$ fragment and by analogy with arene-chromium chemistry, Mn-complexed chloroarenes were expected to undergo oxidative addition from palladium(0)



Scheme 43.

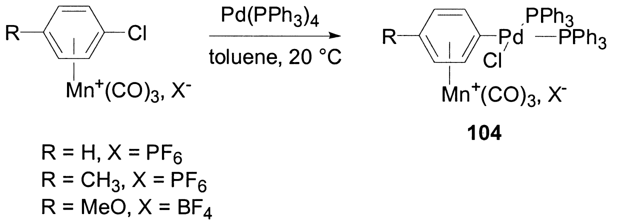


Scheme 44.

species and allow palladium-catalysed reactions. This section is devoted to recent progresses in palladium catalysis using cationic (η^6-chloroarene)Mn(CO)$_3$, (η^5-chloroCp)Mn(CO)$_3$ and (η^5-chloroCh)Mn(CO)$_3$ complexes.

4.2. Cationic (η^6-arene)Mn(CO)$_3$ complexes

As recently described, oxidative addition products are easily obtained from cationic (η^6-chloroarene)Mn(CO)$_3$ and Pd(0) species (Scheme 46).[92] The formation and stability of the *cis*-adducts **104** have been attributed to the X^- ligand bulkiness in the (η^6-arene)Mn^+(CO)$_3$ complex. The first intermediate in the catalytic cycle was easily reached, but no further catalytic transformations could be induced.

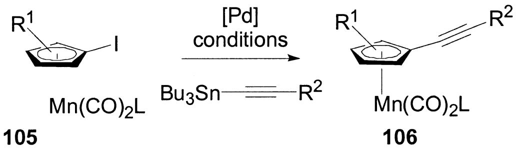


Scheme 46.

These results are in sharp contrast with Espinet's studies[93] that demonstrated that the first-formed *cis*-adduct rapidly isomerises into the more stable *trans* isomer.

4.3. Neutral (η^5-Cp)Mn(CO)$_3$ complexes

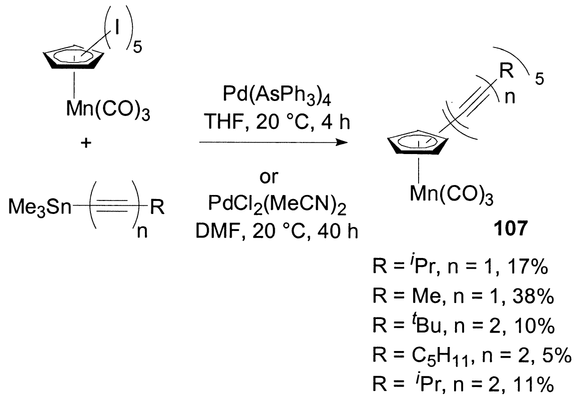
To the best of our knowledge, palladium-catalysed reactions starting from manganese-complexed Cp rings exclusively concern the introduction of alkynyl groups by Stille methodology.



Scheme 47.

The easily accessible (iodoCp)Mn(CO)$_3$ complexes **105** are useful starting material in coupling sequences (Scheme 47). As shown in Table 5, the catalytic systems are based on PdCl$_2$(MeCN)$_2$ or Pd$_2$dba$_3$-AsPh$_3$. A wide range of stannylated alkynes (entries 1–4) and organometallics (entries 5 and 6) have been used as coupling partners, affording disubstituted mono- and bimetallic alkynes **106** in 26–92% yields. Modification of the metal-withdrawing ability by changing from a carbonyl to a phosphane ligand does not influence the palladium-catalysed reactions. Indeed, (iodoCp)Mn(CO)$_2$PPh$_3$ complexes, subjected to classical coupling conditions, afforded the expected alkynylated complex (entry 6).

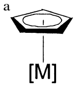
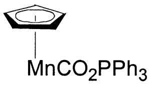
By analogy with hexaethynylbenzene, (pentaethynylCp)-Mn(CO)$_3$ complexes **107** could be prepared in 5–38% yield (Scheme 48). The coupling reactions between (pentaiodoCp)Mn(CO)$_3$ complexes and alkyl-substituted acetylenes and butadiynes using Pd(AsPh$_3$)$_4$ or PdCl$_2$-(MeCN)$_2$ afforded the corresponding star-shaped complexes.[26,95]



Scheme 48.

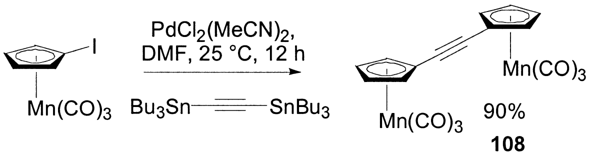
To close this section, the homobimetallic Mn–Mn complex **108**, shown in Scheme 49, was efficiently prepared in 90% yield by the coupling of the (iodoCp)Mn(CO)$_3$ complex and bis(tributylstannyl)acetylene using PdCl$_2$(MeCN)$_2$ as a catalyst in DMF at room temperature.[23]

Table 5. Introduction of alkynyl groups by Stille reaction

Entry	L	R^1	R^2	Conditions	[Pd]	Yield (%)	Reference
1	CO	H	H	DMF, 25 °C, 2 h	PdCl$_2$(MeCN)$_2$	92	22,25,94
2	CO	H	$—\equiv—SiMe_3$	THF, 25 °C, 4 h	Pd$_2$dba$_3$-AsPh$_3$	79	26
3	CO	$2—\equiv—SiMe_3$	SiMe$_3$	DMF, 25 °C, 1 h	PdCl$_2$(MeCN)$_2$	57	26,94
4	CO	$3—\equiv—SiMe_3$	SiMe$_3$	DMF, 25 °C, 1 h	PdCl$_2$(MeCN)$_2$	26	26,94
5	CO	H	[a] 	DMF, 25 °C, 8–12 h	PdCl$_2$(MeCN)$_2$	70–81	22
6	PPh$_3$	H		DMF, 25 °C, 12 h	PdCl$_2$(MeCN)$_2$	[b]	24

[a] [M]=Mn(CO)$_3$, Re(CO)$_3$, W(CO)$_3$Me, Fe(CO)$_2$Me.

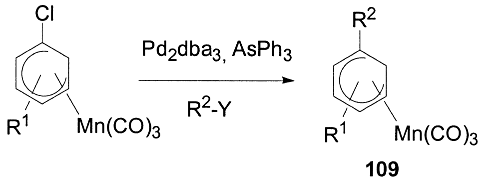
[b] Yield not mentioned.



Scheme 49.

4.4. Neutral (η^5-Ch)Mn(CO)$_3$ complexes

Among the different classes of arenetricarbonylmetal complexes, (η^5-chloroCh)Mn(CO)$_3$ complexes have only recently received much attention. Until the first palladium-catalysed functionalisation was reported,[96] reactions at the π-system were restricted to nucleophilic additions and substi-tutions.[91,97] It has been shown that (η^5-chloro-Ch)Mn(CO)$_3$ complexes can be readily coupled with aryltributylstannanes in Stille reactions (Scheme 50).[96]



R^1 = H, 4-Me, 4-OMe, 2-Me
R^2 = thienyl, phenyl; Y = $SnBu_3$ 45-78%
R^2 = alkenyl; Y = H, $SnBu_3$ 13-32%
R^2 = alkynyl; Y = H, ZnCl, $SnBu_3$ 40-91%

Scheme 50.

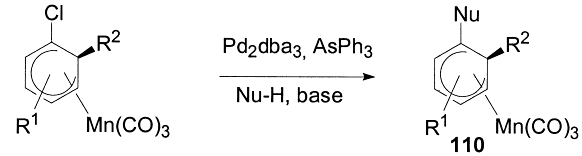
The major outcome of the studies directed towards the determination of effective catalytic systems are listed below:

- The Pd_2dba_3–$AsPh_3$ combination smoothly catalyses coupling reactions, affording the functionalised complexes in high yields. Arsine ligands are already known to accelerate transmetallation steps due to their higher decoordination ability.[98,99]
- The use of various phosphorous-based ligands such as PPh_3, dppf, P^tBu_3 or $P(OEt)_3$ only led to decomplexation of the starting material. A possible interaction between Mn, Pd and the P-based ligand seems to be responsible for the observed decomplexation and lack of efficiency.[91,100]
- When $AsPh_3$ was replaced by $SbPh_3$, high yields of the expected coupling products and shorter reaction times were observed. The reaction was less chemoselective, however, giving rise to the formation of decomplexed and carbonylated side products.[100]

As shown in Scheme 50, Stille arylation afforded good to high yields of the thienyl- and phenyl-substituted (η^5-Ch)Mn(CO)$_3$ complexes **109**, regardless of the starting substitution pattern.

The use of the same catalytic system also allowed the introduction of alkenyl and alkynyl substituents through Stille-, Heck- or Negishi-type reactions.

This methodology was extended to Buchwald–Hartwig-type reactions (Scheme 51).[101] Palladium-catalysed amination, as well as etherification, thioetherification and phosphorylation, were successfully performed. The preparation of the unprecedented N-, O-, S- and P-substituted (η^5-Ch)Mn(CO)$_3$ complexes **110** was achieved in 31–93% yield, using a non-elaborated catalytic system (Pd/As).[102]

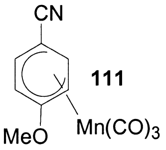


R^1 = H, 4-Me, 4-MeO, 2-MeO
R^2 = H, Ph
Nu-H = morpholine, $HNEt_2$, $NH_2(C_6H_4)OMe$
PhOH, *iso*amylOH, $C_5H_{11}SH$, *p*-tolylSH
$HP(O)(OEt)_2$, $HP(O)(Ph)_2$, $HP(Ph)_2$
base = Cs_2CO_3, NaH

"N" 42-90%
"O" 31-38%
"S" 73-93%
"P" 43-77%

Scheme 51.

Attempts to use carbon nucleophiles such as ketone enolates or malonitrile anions under similar catalytic conditions failed. In contrast, a nitrile function could be introduced using potassium cyanide in the presence of the Pd/As catalytic system and 18-C-6 crown ether affording the expected cyano complex **111** (Scheme 52).[100]



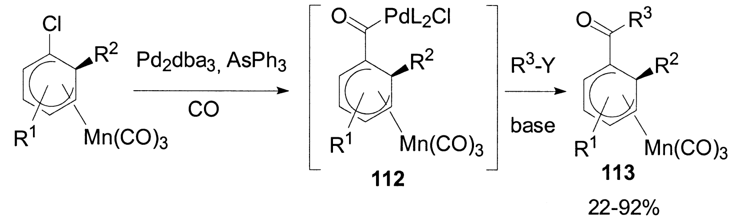
Scheme 52.

Taking advantage of the facile palladium-catalysed *ipso* substitution of the chlorine atom in the (η^5-chloro-Ch)Mn(CO)$_3$ complexes, the same strategy was applied under carbonylative conditions (Scheme 53).[103] The acylpalladate intermediate **112**, generated from (η^5-chloro-Ch)Mn(CO)$_3$ complexes and the Pd/As catalytic system under a CO atmosphere was reacted with various nucleophiles affording EWG-substituted (η^5-Ch)MnCO$_3$ complexes **113**.

Aryl and alkyl ketones, yne- and ene–ones, as well as carboxylic esters, thioesters and amides, were obtained in 22–92% yield. It is worth noting that the palladium-catalysed functionalisation of (η^5-chloroCh)Mn(CO)$_3$ complexes keeps the Ch moiety intact. It is therefore possible to abstract the *exo* hydrogen atom of the sp^3 group. This methodology offers an original approach for the preparation of substituted (η^6-arene)Mn(CO)$_3$ complexes that cannot be synthetised using direct complexation of a Mn(CO)$_3$ entity of the starting organic product.

5. Concluding remarks

This review covers 18 years of intense research in bimetallic Pd/Cr and Pd/Mn activation of the carbon–halide bond in organo-chromium and -manganese complexes from the pioneering work of Villemin until the more recent



R^1 = H, 4-Me, 4-OMeO, 2-Me
R^2 = H, Ph
R^3 = aryl, alkyl, vinyl, alkynyl; Y = $SnBu_3$
OPh, MeO, $N(CH_2CH_2)O$, *p*-tolylS; Y = H; base = NaH, Et_3N, K_2CO_3

Scheme 53.

discoveries. There is no doubt that this expanding area at the frontier of organic and organometallic chemistry will shortly reveal a variety of spectacular applications, ranging from the synthesis of natural compounds to more straightforward accesses to original polymetallic molecules. Considering this potential, the coming years will definitely witness a radical development in this chemistry.

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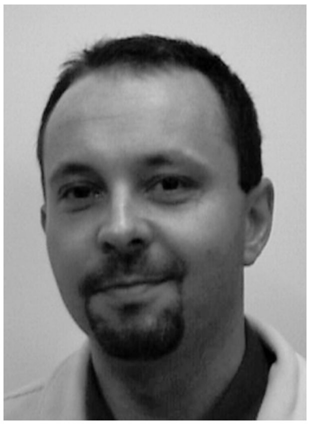
Biographical sketch



Damien Prim received his PhD degree at the University of Metz in 1994. After a postdoctoral period at the University Catholique de Louvain with Professor L. Ghosez, he returned to the University of Metz as Assistant Professor (1995–1999). Then, he moved to the university Pierre et Marie Curie in Paris as CNRS research associate for 2 years and joined the University of Versailles as Assistant Professor in Prof. F. Couty's group. His current research includes organic synthesis in aqueous media and transition metal-assisted catalytic transformations.

Françoise Rose-Munch was born in Metz, France. She entered the CNRS in 1975 and received her PhD degree in 1976 from the University Pierre et Marie Curie, Paris. After a postdoctoral period in 1976 and 1977 at the University of Stanford, California, USA with Prof. Jim Collman, she returned to Paris and was promoted CNRS Research Director. Her research interests concern the organometallic chemistry of Pd, Fe, Cr and Mn complexes and the nucleophilic substitutions of arene–Cr and –Mn complexes, as well as their application in non linear optics.

Bruno Andrioletti was born in Troyes-France in 1968. He studied chemistry at the University of Burgundy (Dijon-France) and received his PhD degree in 1997 under the supervision of Prof. R. Guilard and Dr. B. Boitrel. His PhD focused on the development of new porphyrinic models of the cytochrome c oxidase active centre. Afterwards, for 2 years, he joined Prof. J. L. Sessler's group at the University of Texas at Austin, Austin, Texas for postdoctoral training. There, he studied the chemistry of expanded porphyrins and carried out the development of new anion sensors. In 1999, he was appointed CNRS researcher at the University Pierre et Marie Curie in Paris, France in Dr. E. Rose's group. His current interests mainly concern the development of new porphyrin and other oligopyrrolic macrocycles and their use in asymmetric catalysis and molecular recognition.

Eric Rose was born in Nancy, France. He entered the CNRS in 1970 and obtained his PhD degree in 1975 from the University P. et M. Curie, Paris. After postdoctoral training in 1976 and 1977 at the University of Stanford, California, USA with Prof. Jim Collman, he then moved back to Paris and was promoted to CNRS Research Director in 1985. His research interests are focused on the preparation of models of hemoproteins (Mb, Hb and cyt P450) and of new chiral porphyrins as catalysts for the epoxidation of terminal olefins, as well as nucleophilic substitutions in arene-metal complexes.

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The synthesis of bicyclic 1,2,3,4-tetrahydro-1,4-benzodiazepin-5-ones from 2-(*o*-nitrobenzoyl)-1,2-thiazine-1-oxide precursors

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Abstract—Sulfinylation of *o*-nitrobenzamide and subsequent hetero Diels–Alder reaction gave a series of 2-(*o*-nitrobenzoyl)-1,2-thiazine-1-oxides. The 2-(*o*-nitrobenzoyl)-1,2-thiazine-1-oxides undergo a ring opening reaction with phenyl magnesium bromide to give allylic sulfoxides, which, after [2,3]-sigmatropic rearrangement and desulfurisation, furnish unsaturated vicinal *N*-(*o*-nitrobenzoyl)-1,2-amino alcohols. Oxidation of the alcohol and reductive ring closure gave a series of bicyclic 1,2,3,4-tetrahydro-1,4-benzodiazepin-5-ones, a subset of the 'privileged' 1,4-benzodiazepine structure. A 4-hydroxy-1,2,5-benzothiadiazepin-1,1-dioxide was synthesised by the same route starting from *o*-nitrobenzenesulfonamide.

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1. Introduction

The 1,4-benzodiazepine nucleus occupies a position as a 'privileged' structure within medicinal chemistry.[1] The most well-known sub-sets of this privileged set of structures are the 1,4-benzodiazepin-2-ones[2] and the 1,4-benzodiazepin-2,5-diones,[3] and these continue to attract enormous interest, due to a broad and ever evolving spectrum of biological activities.[2,3] Relatively less well studied are the 1,4-benzodiazepin-5-ones, although interest in the synthesis and biological activity even within this sub-set is considerable. Amongst the 1,4-benzodiazepin-5-ones, most attention has been paid to tricyclic systems, such as the antitumour pyrrolo-1,4-benzodiazepin-5-ones,[4] the biologically active quinazolino-fused circumdatin and asperlicin natural products,[5] the pyrido- and benzo- fused non-nucleosidic reverse transcriptase inhibitors,[6] muscarinic receptor ligands,[7] and the clinically used anti-depressant, cognition enhancing imidazolo-fused flumazenil,[8] and positron emission tomography tracers derived from flumazenil.[9] Bicyclic 1,4-benzodiazepin-5-ones have attracted attention as simplified analogues and precursors of these tricyclic systems,[10–15] are of interest generally as members of the privileged 1,4-benzodiazepine class, and are of specific interest as anti-convulsants, anti-anxiety agents, anti-depressants,[10–13] sedatives, hypnotics, muscle relaxants,[10,11] analgesics,[12] anti-tumour agents[14] and fibrinogenic receptor antagonists.[15]

Synthetic approaches to the bicyclic 1,4-benzodiazepin-5-ones most commonly involve formation of the 1,2 N–C bond as the final step. This can be achieved either via the intramolecular cyclisation of (*o*-aminobenzamido)carbonyls[11a,16a] and acetals/thioacetals,[16b] reductive cyclisation of (*o*-nitrobenzamido)carbonyls and (*o*-nitrobenzamido)-acetals/thioacetals,[14,17] intramolecular cycloadditions of (*o*-azidobenzamido)alkenes and alkynes,[8b,18] aza-Wittig ring closure of [*o*-(iminophosphoranyl)benzamido]carbonyls,[5a,19] intramolecular Michael additions of (*o*-aminobenzamido)enones,[15,20] intramolecular cyclisation of (*o*-aminobenzamido) π-allyl complexes obtained from acylnitroso-derived Diels–Alder cycloadducts,[21] or the cyclisation of α-(*o*-aminobenzamido)nitriles.[22] Construction of the 3,4 C–N bond as the final step is another common approach and can be achieved via cyclodehydrochlorination of *o*-[(2-chloroethyl)amino]benzamides,[12] cyclodehydrobromination of *o*-[(bromoalkyl)amino]aroylhydrazines,[23] and ozonolysis of *o*-(allylamino)benzamides, followed by cyclisation.[24] 1,2 or 3,4 C–N bond formation as the final step also occurs during in the reaction of anthranilamide derivatives with cyanoester epoxides[25] or bromoacetaldehyde acetals,[26] or reaction of methyl anthranilate with aziridines.[27] Other cyclisation methods include 1,7 N–C bond formation as a final step by intramolecular aromatic nucleophilic displacement,[28] 4,5 C–N formation via reduction of *N*-alkylnitrile substituted anthranilates and subsequent ring closure,[29] and 5,6 C–C bond formation via treatment of β-anilino ethylisocyanates with aluminium trichloride.[27] 1,4-Benzodiazepin-5-ones can also be made from hydride reductions of 1,4-benzodiazepin-2,5-diones,[11e,30] Schmidt reaction between the azide anion and 1,2,3,4-tetrahydroquinolin-4-ones,[31] ring expansion reactions of chloromethyl quinazolin-4-ones,[32] photolytic ring

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Keywords: Benzodiazepine; 1,2-Thiazine; Reductive ring closure; Diels–Alder reaction; Sigmatropic rearrangement; Benzothiadiazepine.

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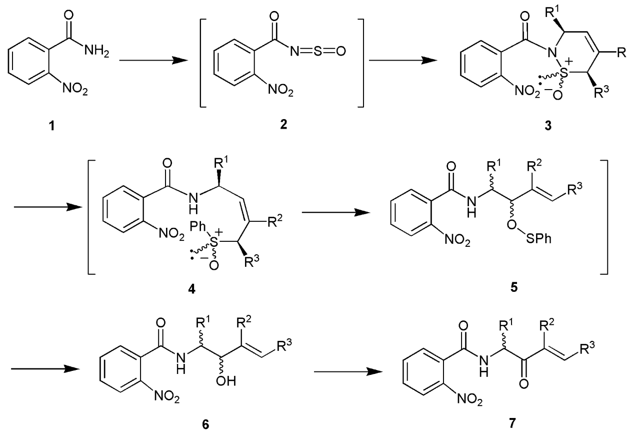
expansions of 4-azidoquinazolines,[33] and ring expansions of benzoxazines with subsequent cyclisation of the intermediate amidine carboxamides.[5b] In this paper we present a new strategy for the synthesis of the bicyclic 1,2,3,4-tetrahydro-1,4-benzodiazepin-5-one nucleus, which relies upon a novel method for the synthesis of (*o*-nitrobenzamido)carbonyl cyclisation precursors for 1,2 N–C bond formation. Reductive cyclisation of these gives the desired 1,4-benzodiazepin-5-one nucleus. The method presented in this paper is advantageous in allowing readily available 1,3-dienes to be used as starting materials for the synthesis of 1,4-benzodiazepin-5-ones, only the second such method to be published,[21] and the first that utilises easily accessible *N*-sulfinyl dienophiles.

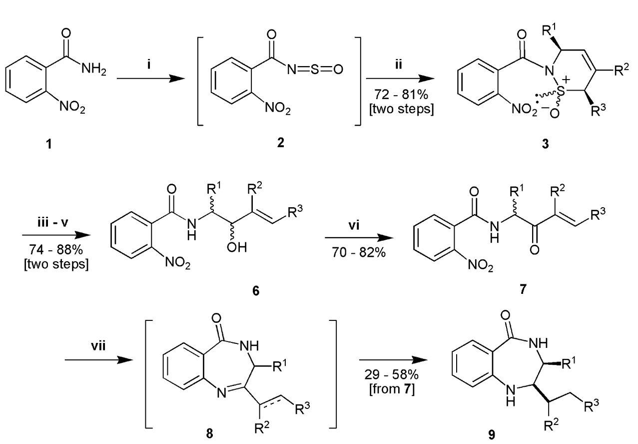
2. Results and discussion

We envisaged (see Scheme 1) that the 2-(*o*-nitroaroyl)-1,2-thiazine-1-oxides **3** would be excellent precursors for the synthesis of the (*o*-nitrobenzamido)carbonyl cyclisation precursors **7** via the intermediate (*o*-nitrobenzamido)-alcohols **6**. The alcohols **6** would be formed from the 1,2-thiazine-1-oxides **3** via ring opening with a Grignard reagent, [2,3]-sigmatropic rearrangement of the resultant sulfoxide **4**, and desulfurisation[34] of the rearranged product, the sulfenate ester **5**. The requisite 2-(*o*-nitroaroyl)-1,2-thiazine-1-oxides **3** would be made available via the hetero-Diels–Alder reaction of the *N*-sulfinyl dienophile **2** with a variety of dienes, where the *N*-sulfinyl compound should easily be formed from the reaction of *o*-nitrobenzamide **1** with thionyl chloride.[35]



Scheme 1. Proposed route to (*o*-nitrobenzamido)ketones **7**.

Thus, as shown in Scheme 2, *o*-nitrobenzamide **1** was reacted under anhydrous conditions with thionyl chloride and pyridine in THF at room temperature for 4 h to give *N*-sulfinyl compound **2**. Compound **2** could not be purified and was extremely unstable, undergoing facile hydrolysis (over 10 to 15 min) in the air to liberate sulfur dioxide and *o*-nitrobenzamide, the products of hydrolysis. However, rapid analysis of the reaction mixture by infrared spectroscopy showed the total disappearance of the sulfonamide $-NH_2$ group after 4–5 h and the appearance of a band (1176 cm^{-1}) characteristic[35] of the $-N{=}S{=}O$ group. At this point, the appropriate diene [(*E*,*E*)-2,4-hexadiene, (*E*)-1,3-pentadiene, isoprene or butadiene] was added into the mixture. Hetero-Diels–Alder reaction proceeded smoothly under anhydrous conditions, after which chromatographic work-up yielded the required 2-(*o*-nitroaroyl)-1,2-thiazine-1-oxides **3** in good to excellent yields for the purified compounds over the two steps (4 examples, see Table 1). Due to the fact that our target ketones **7** have only one chiral centre, we did not need to confirm the stereochemical outcome of the cycloaddition reaction. However, those cycloadducts **3** with more than one chiral centre, i.e. compounds **3a** and **3b** (see Table 1), were formed as single diastereoisomers, an observation in keeping with other *N*-sulfinyl cycloadditions.[34,35]



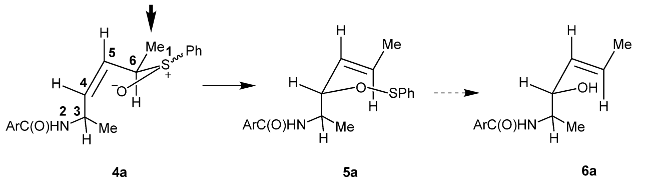
Scheme 2. Synthesis of 1,4-benzodiazepin-5-ones **9** from 1,2-thiazine-1-oxides **3**. Reagents and Conditions: (i) $SOCl_2$, pyridine, THF, room temperature, 4 h. (ii) $R^1HC{=}CH{-}CR^2{=}CHR^3$, THF, room temperature, overnight. (iii) PhMgBr, THF, −40 °C, 3 h. (iv) Sat. NH_4Cl(aq.). (v) MeOH, $P(OMe)_3$, 60 °C, 10–15 h. (vi) Dess–Martin periodinane, CH_2Cl_2, room temperature, 1 h. (vii) H_2, Pd/C, MeOH, room temperature, 16–20 h.

Next, also shown in Scheme 2, the purified 2-(*o*-nitrobenzoyl)-1,2-thiazine-1-oxides **3** were treated with phenylmagnesium bromide in THF at low temperature (−40 °C). Aqueous work-up and treatment of the dried crude product with hot methanolic trimethyl phosphite[34] gave the (*o*-nitrobenzamido)alcohols **6**. The products **6** were consistent with the thiazine **3** having undergone ring opening to give the allylic sulfoxide **4**, shown previously in Scheme 1, followed by a thermally allowed (reversible) [2,3]-sigmatropic rearrangement to give intermediate sulfenate ester **5**, also shown in Scheme 1. Trimethyl phosphite mediated

Table 1. % Yields for pure and isolated compounds **3**, **6**, **7** and **9**

Entry	R^1	R^2	R^3	% Yield of thiazine **3** (from **1**)	% Yield of alcohol **6** (from **3**)	% Yield of ketone **7** (from **6**)	% Yield of benzodiazepine **9** (from **7**)
a	Me	H	Me	77	88	82	47
b	Me	H	H	81	74	75	58
c	H	Me	H	75	85	72	29
d	H	H	H	72	76	70	40

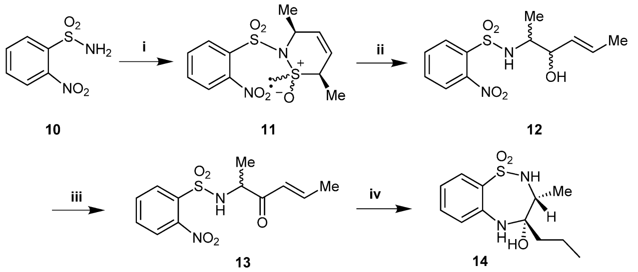
(irreversible) desulfurisation of the intermediate sulfenate esters **5** gave the (*o*-nitrobenzamido)alcohols **6**. We made no attempt to purify or characterise the intermediates **4** or **5** since the overall yields obtained for the purified (*o*-nitrobenzamido)alcohols **6** were consistently excellent for this three-step process (see Table 1). The relative stereochemistry of compounds **6a** and **6b** (R^1=Me) was not determined as, at the next stage, the alcohol chiral center was to be oxidised. It is of interest to note, however, that others have reported that this sequence of reactions proceeds with a high degree of stereoselectivity when performed with other substrates,[34–36] a point reflected by the fact that we found compounds **6a** and **6b** to be single diasteroisomers. In the one case where it is appropriate, i.e. for compound **6a** (R^2=H, R^3=Me), the alkene geometry of compound **6** was found to be (*E*). This can be explained[34] by invoking a 5-membered ring envelope transition state for the [2,3]-sigmatropic rearrangement, in which the methyl group that occupies position 6 (see Scheme 3) is in a pseudo-equatorial position leading to (*E*)-alkene geometry in the sulfenate ester **5a** and, subsequently, in the alcohol **6a**.



Scheme 3. The formation of (*E*)-alkene **6a**.

Oxidation of the purified alcohols **6**, as per Scheme 2, was best achieved with Dess–Martin periodinane, giving the corresponding (*o*-nitrobenzamido)ketones **7** in good yields (Table 1). Exposure of the (*o*-nitrobenzamido)ketones **7** to hydrogenation at atmospheric pressure using 5% palladium over activated carbon resulted in reduction of the nitro group to the amine, ring closure to a cyclic imine followed by reduction of imine bond, and accompanying reduction of the exocyclic olefinic double bond. These four steps gave, as the only isolated products, the 1,2,3,4-tetrahydro-1,4-benzodiazepin-5-ones **9**, as shown in Scheme 2. Where relevant (i.e. for compounds **9a** and **9b**, R^1=Me, R^2=H, R^3=Me/H), a single diastereoisomer was isolated, and the relative stereochemistry of the groups at positions 2 and 3 of the 1,4-benzodiazepin-5-one was assigned *cis*/*syn* on the basis of nOe experiments. Thus, clear signal enhancements were observed between the C3 R^1 methyl protons and the C2-bound CH_2 group (R^2=H), but not between the C3 R^1 methyl and the C2 proton, nor between the C3 proton and the C2-bound CH_2 group. The observed stereochemistry is in line with the expected delivery of hydrogen to the face of the imine bond in intermediate **8** that is opposite to the existing methyl group at C3. The yields (Table 1) were fair considering the four-step nature of the reaction and, furthermore, considering that similar (*o*-nitrobenzamido)-carbonyl reductive cyclisations reported in the literature often give bicyclic 1,4-benzodiazepin-5-one yields in approximately the same range.[4,14,17]

In an attempt to extend the scope of this methodology, we also synthesised the 2-(*o*-nitrobenzenesulfonyl)-1,2-thiazine-1-oxide **11** (60% yield from **10**; single diastereoisomer), as shown in Scheme 4, and subjected it to the same sequence of reactions as was applied to the 2-(*o*-nitroaroyl)-1,2-thiazine-1-oxides **3**. This gave access to the 2-(*o*-nitrobenzenesulfonamido)alcohol **12** in 89% yield from the thiazine **11**. Dess–Martin periodinane oxidation proceeded in 84% yield to give the 2-(*o*-nitrobenzenesulfonamido)ketone **13**. Compound **13** was treated with hydrogen and palladium over activated carbon. Intriguingly, and anomalous to the corresponding (*o*-nitrobenzamido) systems **7a–d**, this gave the carbinolamine 1,2,3,4-tetrahydro-4-hydroxy-1,2,5-benzothiadiazepin-1,1-dioxide **14** in 45% yield. The product was isolated as a single diastereoisomer. The stereochemistry was assigned on the basis of nOe experiments that showed a clear enhancement between the CH proton at position 3 of the 1,2,5-benzothiadiazepine ring and the C4-bound CH_2 group of the C4 *n*-propyl substituent, but not between the methyl group at position 3 and the same CH_2 group.



Scheme 4. Synthesis of 4-hydroxy-1,2,5-benzothiadiazepin-1,1-dioxide **14**. Reagents and conditions: (i) (a) $SOCl_2$, benzene, reflux, 72 h; (b) (*E*,*E*)-2,4-hexadiene, room temperature, 14 h. (ii) (a) PhMgBr, THF, −40 °C, 2 h; (b) Sat. NH_4Cl(aq.); (c) $P(OMe)_3$, MeOH, 60 °C, 5 h. (iii) Dess–Martin periodinane, CH_2Cl_2, room temperature, 30 min. (iv) H_2, Pd/C, MeOH, room temperature, 4 h.

3. Conclusion

In summary, we have shown that 2-(*o*-nitrobenzoyl)-1,2-thiazine-1-oxides, which are readily available from *o*-nitrobenzamide and diene feedstocks, are easily transformed into *o*-nitrobenzamido alkenones that are readily ring closed to give 1,2,3,4-tetrahydro-1,4-benzodiazepin-5-ones in moderate to good yield. This constitutes a new route to this important sub-set of the 'privileged' 1,4-benzodiazepine pharmacophore and adds to the diversity of structures available. The method is also applicable to the synthesis of 1,2,5-benzothiadiazepines, although in this case, ring closure gives the 4-hydroxy compound. We are currently exploring this latter process further, together with other 1,2-thiazine-1-oxide based routes to 1,2,5-benzothiadiazepin-1,1-dioxides and will report our results in due course.

4. Experimental

4.1. General instructions

^1H NMR spectra were recorded on a Bruker AC-250 (250 MHz) or a Bruker Advance DPX-400 (400 MHz) spectrometer using deuterochloroform as solvent with tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded on a Bruker AC-250 (63 MHz) or a Bruker

Advance DPX-400 (100 MHz) spectrometer using deuterochloroform as solvent, referencing to the deuterochloroform lock. Coupling constants (*J*) are reported in Hertz (Hz). Low resolution mass spectra were performed on a Micromass Quattro II triple quadrupole mass spectrometer, and high resolution mass spectra were recorded on a Finnegan MAT 900 XLT instrument operated at the EPSRC National Mass Spectrometry Service Center, Swansea. Flash silica chromatography was performed using Merck Kieselgel 60. Thin layer chromatography was carried out with Camlab 0.25 mm silica gel (F_{254}) coated plastic or aluminium plates, using petroleum ether (40–60°)/ethyl acetate as eluent, and were visualised using ultraviolet light or a vanillin stain. All reagents and reaction solvents were purchased from Sigma-Aldrich and solvents for chromatography were purchased from Merck. Petroleum ether and ethyl acetate were purchased as AR grade and were used as received. Reactions were routinely carried out under an atmosphere of dry, oxygen-free, nitrogen, unless otherwise stated. All new compounds were isolated by flash silica chromatography as one spot pure compounds (TLC) and were single pure compounds (>98% purity) by ^{1}H NMR and ^{13}C NMR spectroscopy.

4.2. Synthesis of 2-(*o*-nitrobenzoyl)-1,2-thiazine-1-oxides 3

A solution of *o*-nitrobenzamide (~9–9.3 mmol, 1.0 equiv.) and anhydrous pyridine (6.0 equiv.) in anhydrous tetrahydrofuran (15 ml), under an atmosphere of dry nitrogen, was prepared. To this solution was added, dropwise with stirring over a period of 3–4 h, a solution of freshly distilled thionyl chloride (1.5 equiv.) in anhydrous tetrahydrofuran (5 ml), to yield the crude *N*-sulfinyl compound. The crude reaction mixture was stirred for 30 min, followed by dropwise addition of the appropriate 1,3-diene (1.6 equiv., except for butadiene where 10 equiv. were condensed into the reaction flask), and the whole was stirred at room temperature for 16 h, whilst being monitored by TLC. After completion of the reaction, the solvent was removed in vacuo and the crude product was purified by flash silica chromatography (eluent PE/EtOAc 1:1). The following products were obtained:

4.2.1. 3,6-Dihydro-3,6-dimethyl-2-(*o*-nitrobenzoyl)-1,2-thiazine-1-oxide 3a. Obtained, after column chromatographic purification (single spot by TLC), as a white solid (2.0335 g, 77%) from *o*-nitrobenzamide (1.5000 g, 9.03 mmol, 1.0 equiv.) and 2,4-hexadiene (d=0.720, 1.65 ml, 14.45 mmol, 1.6 equiv.). Mp: 154–156 °C.

δ_H (250 MHz, $CDCl_3$): 1.30 (d, 3H, J=7.2 Hz, Me), 1.68 (d, 3H, J=6.4 Hz, Me), 3.45 (dquint, 1H, J=7.2, 1.0 Hz, C*H*Me), 4.72 (dquint, 1H, J=5.7, 0.9 Hz, C*H*Me), 5.92 (ddd, 1H, J=10.6, 7.2, 0.6 Hz, C═C*H*), 6.25 (dd, 1H, J=10.6, 4.8 Hz, C═C*H*), 7.61–7.70, (m, 2H, 2×ArH), 7.79 (dt, 1H, J=7.7, 1.2 Hz, 1×ArH), 8.23 (dd, 1H, J=7.3, 1.6 Hz, 1×ArH). δ_C (63 MHz, $CDCl_3$): 15.7 (CH_3), 20.7 (CH_3), 48.9 (CH), 54.4 (CH), 119.6 (CH), 124.6 (CH), 128.1 (quat.), 129.5 (CH), 130.7 (CH), 131.5 (quat.), 132.4 (CH), 134.7 (CH), 145.5 (quat.), 170.4 (quat.). υ_{max} (KBr disc, cm^{-1}): 3019, 1677, 1532, 1350, 1216, 1092, 669. EI mass spectrum (*m*/*z*, %): 295 ($M+H^+$, 1%), 269 (5%), 104 (45%), 150 (95%), 82 (100%), 76 (85%). HRMS (ES+): found MH^+ 295.0755, $C_{13}H_{14}N_2SO_4$ requires MH^+ 295.0753.

4.2.2. 3,6-Dihydro-3-methyl-2-(*o*-nitrobenzoyl)-1,2-thiazine-1-oxide 3b. Obtained, after column chromatographic purification (single spot by TLC), as a pale yellow solid (2.0961 g, 81%) from *o*-nitrobenzamide (1.5163 g, 9.13 mmol, 1.0 equiv.) and 1,3-pentadiene (d=0.683, 1.46 ml, 14.60 mmol, 1.6 equiv.). Mp: 130–132 °C.

δ_H (250 MHz, $CDCl_3$): 1.55 (d, 3H, J=6.5 Hz, Me), 3.49 (dt, 1H, J=3.0, 1.2 Hz, C*H*H), 3.55 (dd, 1H, J=7.4, 1.2 Hz, C*H*H), 4.97 (dquint, 1H, J=6.4, 0.9 Hz, C*H*Me), 5.93 (ddd, 1H, J=10.0, 7.4, 3.2 Hz, C═C*H*), 6.55 (ddd, 1H, J=10.0, 6.2, 2.8 Hz, C═C*H*), 7.58–7.70 (m, 2H, 2×ArH), 7.78 (dt, 1H, J=7.5, 1.2 Hz, 1×ArH), 8.25 (dd, 1H, J=8.3, 1.1 Hz, 1×ArH). δ_C (63 MHz, $CDCl_3$): 18.2 (CH_3), 47.8 (CH_2), 49.6 (CH), 115.0 (CH), 124.6 (CH), 129.5 (CH), 130.8 (CH), 131.5 (quat.), 134.7 (CH), 134.9 (CH), 145.1 (quat.), 168.7 (quat.). υ_{max} (KBr disc, cm^{-1}): 3017, 1654, 1533, 1349, 1317, 1216, 1147, 1099, 859, 668. EI mass spectrum (*m*/*z*, %): 281 ($M+H^+$, 1%), 233 (3%), 215 (20%), 150 (50%), 104 (35%), 82 (30%), 76 (100%). HRMS (ES+): found MH^+ 281.0597, $C_{12}H_{12}N_2SO_4$ requires MH^+ 281.0596.

4.2.3. 3,6-Dihydro-5-methyl-2-(*o*-nitrobenzoyl)-1,2-thiazine-1-oxide 3c. Obtained, after column chromatographic purification (single spot by TLC), as a beige solid (1.9410 g, 75%) from *o*-nitrobenzamide (1.5419 g, 9.28 mmol, 1.0 equiv.) and isoprene (d=0.681, 1.49 ml, 14.85 mmol, 1.6 equiv.). Mp: 128–130 °C.

δ_H (250 MHz, $CDCl_3$): 1.94 (s, 3H, Me), 3.23 (d, 1H, J=15.1 Hz, C*H*H), 3.41 (bd, 1H, J=15.4 Hz, C*H*H), 4.14 (dt, 1H, J=17.6, 1.2 Hz, C*H*H), 4.68 (bd, 1H, J=17.8 Hz, C*H*H), 5.86 (s, 1H, C═C*H*), 7.51 (d, 1H, J=7.5 Hz, 1×ArH), 7.67 (dt, 1H, J=8.2, 1.4 Hz, 1×ArH), 7.77 (dt, 1H, J=7.5, 1.1 Hz, 1×ArH), 8.15 (dd, 1H, J=8.3, 1.1 Hz, 1×ArH). δ_C (63 MHz, $CDCl_3$): 25.0 (CH_3), 38.6 (CH_2), 53.5 (CH_2), 119.0 (CH), 123.0 (quat.), 125.1 (CH), 128.9 (CH), 131.1 (CH), 131.9 (quat.), 135.2 (CH), 145.6 (quat.), 167.5 (quat.). υ_{max} (KBr disc, cm^{-1}): 3018, 1664, 1531, 1347, 1326, 1216, 1105, 1090, 850, 668. EI mass spectrum (*m*/*z*, %): 281 ($M+H^+$, 1%), 233 (2%), 150 (20%), 104 (20%), 82 (30%), 76 (100%). HRMS (ES+): found MH^+ 281.0591, $C_{12}H_{12}N_2SO_4$ requires MH^+ 281.0596.

4.2.4. 3,6-Dihydro-2-(*o*-nitrobenzoyl)-1,2-thiazine-1-oxide 3d. Obtained, after column chromatographic purification (single spot by TLC), as pale yellow prisms (1.7418 g, 72%) from *o*-nitrobenzamide (1.5022 g, 9.04 mmol, 1.0 equiv.) and 1,3-butadiene (4.89 g, 10 equiv.). Mp: 136–138 °C.

δ_H (250 MHz, $CDCl_3$): 3.46–3.52 (m, 2H, 2×C*H*H), 4.15 (dhextet, 1H, J=18.5, 1.8 Hz, C*H*H), 4.84 (bd, 1H, J=18.1 Hz, C*H*H), 5.79–5.89 (m, 1H, C═C*H*), 6.23 (dd, 1H, J=8.1, 1.7 Hz, C═C*H*), 7.40 (d, 1H, J=7.5 Hz, 1×ArH), 7.67 (ddd, 1H, J=8.2, 7.6, 1.5 Hz, 1×ArH), 7.80 (dt, 1H, J=7.5, 1.2 Hz, 1×ArH), 8.24 (dd, 1H, J=8.2, 1.2 Hz, 1×ArH). δ_C (63 MHz, $CDCl_3$): 37.8 (CH_2), 49.3 (CH_2), 114.3 (CH), 124.8 (CH), 125.4 (CH), 128.5 (CH), 130.9 (CH), 131.4 (quat.), 134.8 (CH), 144.9 (quat.), 167.0 (quat.).

υ_{max} (KBr disc, cm^{-1}): 3019, 1682, 1531, 1348, 1311, 1152, 1100, 1095, 669. EI mass spectrum (*m/z*, %): 267 (M+H$^+$, 2%), 219 (25%), 150 (100%), 104 (35%), 82 (30%), 76 (40%). HRMS (ES+): found MH$^+$ 267.0441, $C_{11}H_{10}N_2SO_4$ requires MH$^+$ 267.0439.

4.2.5. 3,6-Dihydro-3,6-dimethyl-2-(*o*-nitrobenzenesulfonyl)-1,2-thiazine-1-oxide 11. *o*-Nitrobenzenesulfonamide (1.0000 g, 4.95 mmol, 1.0 eq) and thionyl chloride (1.5 equiv.) were heated in anhydrous benzene (15 ml) at reflux for 72 h. The mixture was cooled to room temperature and the solvent and excess thionyl chloride were removed in vacuo. The residue was dissolved in freshly distilled anhydrous THF (10 ml). 2,4-Hexadiene (*d*=0.720, 0.90 ml, 7.91 mmol, 1.6 equiv.) was added, and the mixture was stirred at room temperature for 14 h. The crude product was purified by flash silica chromatography (eluent PE/EtOAc 6:5) to give the pure product as a pale yellow solid (0.9830 g, 60%). Mp: 110–112 °C.

δ_H (400 MHz, $CDCl_3$): 1.39 (d, 3H, *J*=7.4 Hz, Me), 1.56 (d, 3H, *J*=7.0 Hz, Me), 3.29–3.41 (m, 1H, C*H*Me), 4.57 (dquint, 1H, *J*=6.8, 3.4 Hz, C*H*Me), 5.45 (ddd, 1H, *J*=11.0, 2.5, 2.0 Hz, C=C*H*), 5.96 (ddd, 1H, *J*=11.0, 3.4, 2.9 Hz, C=C*H*), 7.71–7.91 (m, 3H, 3×ArH), 8.19 (dd, 1H, *J*=8.3, 1.1 Hz, 1×ArH). δ_C (100 MHz, $CDCl_3$): 15.7 (CH_3), 23.5 (CH_3), 51.8 (CH), 53.1 (CH), 119.5 (CH), 124.8 (CH), 129.5 (CH), 131.3 (CH), 132.5 (CH), 133.0 (quat), 134.8 (CH), 147.6 (quat.). υ_{max} (KBr disc, cm^{-1}): 3019, 1531, 1332, 1311, 1156, 1106, 1095, 753, 669. EI mass spectrum (*m/z*, %): 331 (M+H$^+$, 2%), 282 (2%), 229 (35%), 186 (20%), 82 (100%), 67 (85%). HRMS (CI+[NH_3]): found MH$^+$ 331.0419, $C_{12}H_{14}N_2O_5S_2$ requires MH$^+$ 331.0422.

4.3. Synthesis of (*o*-nitrobenzamido)alkenols 6

A solution of phenylmagnesium bromide (3 M solution in ether, 2.0 equiv.) was added with stirring to a solution of the 2-(*o*-nitrobenzoyl)-3,6-dihydro-1,2-thiazine-1-oxide (1.5–3.5 mmol, 1.0 equiv.) in anhydrous tetrahydrofuran (10 ml) at −78 °C under an atmosphere of dry nitrogen. The reaction mixture was kept at low temperature (∼−40 °C) for 3 h, whilst being monitored by TLC. Upon completion of the reaction, the mixture was quenched at −20 °C with saturated ammonium chloride solution (15 ml) and allowed to warm to room temperature. The mixture was extracted with ethyl acetate (2×10 ml) and washed with water (2×10 ml) and brine (10 ml). The organic phase was collected, dried ($MgSO_4$), filtered and the solvent evaporated off to yield the allylic sulfoxide, which was not purified further. To a solution of this crude allylic sulfoxide in anhydrous methanol (10 ml) was added trimethyl phosphite (*d*=1.052, 2.0 equiv.), under an atmosphere of dry nitrogen, and the whole was heated under reflux for a total of 10–15 h, and was monitored by TLC. Upon completion of the reaction, the solvent was removed in vacuo and the crude product was purified by column chromatography (eluent: PE/EtOAc 3:2) to yield the (*o*-nitrobenzamido)alkenols as follows:

4.3.1. (*E*)-5-(*o*-Nitrobenzamido)-hex-2-en-4-ol 6a. Obtained, after column chromatographic purification (single spot by TLC), as a yellow oil (0.7900 g, 88%) from 3,6-dihydro-3,6-dimethyl-2-(*o*-nitrobenzoyl)-1,2-thiazine-1-oxide **3a** (1.0000 g, 3.40 mmol, 1.0 equiv.).

δ_H (400 MHz, $CDCl_3$): 1.30 (d, 3H, *J*=6.6 Hz, Me), 1.74 (dd, 3H, *J*=6.4, 1.1 Hz, Me), 2.27 (bs, 1H, OH), 4.05–4.25 (m, 2H, C*H*Me and C*H*OH), 5.61 (ddd, 1H, *J*=14.6, 6.0, 1.5 Hz, =C*H*CHOH), 5.77 (dq, 1H, *J*=14.8, 6.2 Hz, =C*H*Me), 6.18 (bd, 1H, *J*=8.0 Hz, NH), 7.49 (dd, 1H, *J*=7.3, 1.7 Hz, ArH), 7.56 (dt, 1H, *J*=7.8, 1.6 Hz, ArH), 7.66 (dt, 1H, *J*=7.4, 1.3 Hz, ArH), 8.04 (dd, 1H, *J*=8.1, 1.2 Hz, ArH). δ_C (100 MHz, $CDCl_3$): 17.3 (CH_3), 17.8 (CH_3), 50.2 (CH), 75.2 (CHOH), 124.5 (CH), 128.7 (CH), 129.2 (CH), 130.4 (CH), 130.6 (CH), 133.1 (quat.), 133.6 (CH), 146.5 (quat.), 166.4 (quat.). υ_{max} (NaCl plates, neat, cm^{-1}): 3380 (broad), 3268, 2978, 2932, 1645, 1532, 1450, 1349, 1260, 1146, 1112, 1093, 972, 788, 702. EI mass spectrum (*m/z*, %): 265 (MH$^+$, 1%), 193 (25%), 150 (100%), 121 (25%), 104 (35%), 76 (30%). HRMS (ES+): found MH$^+$ 265.1188, $C_{13}H_{16}N_2O_4$ requires MH$^+$ 265.1188.

4.3.2. 4-(*o*-Nitrobenzamido)-pent-1-en-3-ol 6b. Obtained, after column chromatographic purification (single spot by TLC), as a yellow oil (0.3300 g, 74%) from 3,6-dihydro-3-methyl-2-(*o*-nitrobenzoyl)-1,2-thiazine-1-oxide **3b** (0.5000 g, 1.78 mmol, 1.0 equiv.).

δ_H (400 MHz, $CDCl_3$): 1.36 (d, 3H, *J*=6.6 Hz, Me), 5.26 (dq, 1H, *J*=9.8, 1.5 Hz, C*H*Me), 5.40 (qt, 1H, *J*=8.6, 1.2 Hz, C*H*OH), 5.89 (dd, 1H, *J*=16.0, 5.2 Hz, *H*HC=CHCHOH), 5.97 (ddd, 1H, *J*=15.9, 5.4, 1.1 Hz, =C*H*CHOH), 6.04 (m, 1H, *H*HC=CHCHOH), 6.15 (bs, 1H, NH), 7.51–7.68 (m, 3H, 3×ArH), 8.07 (dd, 1H, *J*=8.1, 1.2 Hz, ArH). δ_C (100 MHz, $CDCl_3$): 17.1 (CH_3), 54.2 (CH), 76.4 (CH), 122.8 (CH), 124.1 (CH), 126.0 (CH), 128.6 (CH), 129.1 (quat.), 130.2 (CH), 132.3 (CH), 142.6 (quat.), 167.4 (quat.). υ_{max} (NaCl plates, neat, cm^{-1}): 3388 (broad), 3318 (broad), 2925, 2870, 1651, 1537, 1454, 1377, 1349, 1261, 1216, 1041, 699. EI mass spectrum (*m/z*, %): 251 (MH$^+$, 1%), 193 (35%), 150 (100%), 104 (15%), 76 (20%). HRMS (ES+): found MH$^+$ 251.1032, $C_{12}H_{14}N_2O_4$ requires MH$^+$ 251.1032.

4.3.3. 2-Methyl-4-(*o*-nitrobenzamido)-but-1-en-3-ol 6c. Obtained, after column chromatographic purification (single spot by TLC), as a yellow oil (0.6050 g, 85%) from 3,6-dihydro-5-methyl-2-(*o*-nitrobenzoyl)-1,2-thiazine-1-oxide **3c** (0.8000 g, 2.85 mmol, 1.0 equiv.).

δ_H (400 MHz, $CDCl_3$): 1.79 (s, 3H, Me), 2.18 (bs, 1H, OH), 3.36 (ddd, 1H, *J*=13.8, 7.6, 4.9 Hz, C*H*H), 3.81 (ddd, 1H, *J*=13.8, 6.8, 3.4 Hz, CH*H*), 4.33 (dd, 1H, *J*=7.5, 3.4 Hz, C*H*OH), 4.97 (s, 1H, C=C*H*$_2$), 5.10 (s, 1H, C=C*H*$_2$), 6.39 (bs, 1H, NH), 7.50–7.64 (m, 2H, 2×ArH), 7.66 (dt, 1H, *J*=7.4, 1.3 Hz, ArH), 8.04 (dd, 1H, *J*=8.0, 1.3 Hz, ArH). δ_C (100 MHz, $CDCl_3$): 18.6 (CH_3), 44.2 (CH_2), 73.8 (CH), 111.9 (CH_2), 124.6 (CH), 128.8 (CH), 130.5 (CH), 132.9 (quat.), 133.7 (CH), 144.8 (quat.), 146.8 (quat.), 167.1 (quat.). υ_{max} (NaCl plates, neat, cm^{-1}): 3396 (broad), 3304 (broad), 3087, 2921, 1654, 1532, 1442, 1350, 1314, 1083, 1055, 907, 858, 789, 699. EI mass spectrum (*m/z*, %): 251(MH$^+$, 1%), 151 (70%), 150 (100%), 121 (45%), 104 (40%), 76 (72%). HRMS (CI+[NH_3]): found MH$^+$ 251.1036, $C_{12}H_{14}N_2O_4$ requires MH$^+$ 251.1032.

4.3.4. 4-(*o*-Nitrobenzamido)-but-1-en-3-ol 6d. Obtained, after column chromatographic purification (single spot by TLC), as a yellow oil (0.3370 g, 76%) from 3,6-dihydro-2-(*o*-nitrobenzoyl)-1,2-thiazine-1-oxide **3d** (0.5000 g, 1.88 mmol, 1.0 equiv.).

δ_H (400 MHz, $CDCl_3$): 2.55 (bs, 1H, OH), 3.31 (ddd, 1H, J=13.8, 7.7, 5.1 Hz, C*H*H), 3.78 (ddd, 1H, J=13.8, 7.6, 3.5 Hz, CH*H*), 4.39–4.46 (m, 1H, C*H*OH), 5.24 (dt, 1H, J=10.5, 1.4 Hz, C=CH_2), 5.38 (dt, 1H, J=17.2, 1.4 Hz, C=CH_2), 5.89 (ddd, 1H, J=17.2, 10.5, 5.5 Hz, H_2C=C*H*CHOH), 6.58 (bs, 1H, NH), 7.54 (dt, 1H, J=7.3, 1.5 Hz, ArH), 7.59–7.70 (m, 2H, 2×ArH), 8.05 (dd, 1H, J=8.0, 1.3 Hz, ArH). δ_C (100 MHz, $CDCl_3$): 45.5 (CH_2), 71.4 (CH), 116.6 (CH), 124.6 (CH), 128.8 (CH), 130.5 (CH), 133.7 (quat.), 133.8 (CH), 137.6 (CH), 146.5 (quat.), 167.2 (quat.). υ_{max} (NaCl plates, neat, cm^{-1}): 3360 (broad), 3309 (broad), 3086, 3013, 2929, 1651, 1530, 1349, 1313, 1048, 930, 857, 788, 698. EI mass spectrum (*m*/*z*, %): 237 (MH^+, 2%), 151 (25%), 152 (65%), 121 (20%), 104 (50%), 76 (100%), 57 (54%). HRMS (ES+): found MH^+ 237.0875, $C_{11}H_{12}N_2O_4$ requires MH^+ 237.0875.

4.3.5. (*E*)-5-(*o*-Nitrobenzenesulfamido)-hex-2-en-4-ol 12. This was obtained by the identical procedure except that, at the trimethyl phosphite stage, the reaction was noted to be complete after 5 h. Chromatographic purification gave the product (single spot by TLC) as a yellow oil (0.8100 g, 89%) from 3,6-dihydro-3,6-dimethyl-2-(*o*-nitrobenzenesulfonyl)-1,2-thiazine-1-oxide **11** (1.0000 g, 3.03 mmol, 1.0 equiv.).

δ_H (400 MHz, $CDCl_3$): 1.15 (d, 3H, J=6.7 Hz, Me), 1.58 (dd, 3H, J=6.4, 1.5 Hz, Me), 1.82 (bs, 1H, OH), 3.49 (dquint, 1H, J=6.7, 5.0 Hz, C*H*Me), 3.95 (dd, 1H, J=7.3, 5.0 Hz, C*H*OH), 5.35 (ddq, 1H, J=15.2, 7.4, 1.6 Hz, *H*C=CHMe), 5.61 (bd, 1H, J=7.9 Hz, NH), 5.70 (qdd, 1H, J=15.2, 6.5, 0.8 Hz, HC=C*H*Me), 7.72–7.78 (m, 2H, 2×ArH), 7.85–7.90 (m, 1H, ArH), 8.13–8.17 (m, 1H, ArH). δ_C (100 MHz, $CDCl_3$): 17.8 (CH_3), 18.2 (CH_3), 55.1 (CH), 75.5 (CH), 125.3 (CH), 129.6 (CH), 130.4 (CH), 130.7 (CH), 132.8 (CH), 133.3 (CH), 134.7 (quat.), 149.0 (quat.). υ_{max} (NaCl plates, neat, cm^{-1}): 3389 (broad), 3327 (broad), 3045, 2996, 1547, 1449, 1346, 1287, 1180, 1108, 1027, 780, 662. EI mass spectrum (*m*/*z*, %): 301 (MH^+, 3%), 229 (33%), 218 (20%), 186 (100%), 109 (55%), 84 (41%), 76 (20%). HRMS (CI+[NH_3]): found MNH_4^+ 318.1129, $C_{12}H_{14}N_2O_5S$ requires MNH_4^+ 318.1125.

4.4. Synthesis of (*o*-nitrobenzamido)alkenones 7

To a solution of Dess–Martin periodinane (1.1 equiv.) in dry dichloromethane (10 ml) was added a solution of the allylic alcohol (1–2 mmol, 1 equiv.) in dry dichloromethane (5 ml) at room temperature. The reaction mixture was stirred at room temperature for 0.5–1 h, whilst being monitored by TLC. The solvent was evaporated off and the crude product was purified by column chromatography (eluent: PE/EtOAc 3:2) to yield the following products:

4.4.1. (*E*)-5-(*o*-Nitrobenzamido)-hex-2-en-4-one 7a. Obtained, after column chromatographic purification (single spot by TLC), as a yellow oil (0.4070 g, 82%) from (*E*)-5-(*o*-nitrobenzamido)-hex-2-en-4-ol **6a** (0.5000 g, 1.89 mmol, 1.0 equiv.).

δ_H (400 MHz, $CDCl_3$): 1.54 (d, 3H, J=7.1 Hz, Me), 1.99 (dd, 3H, J=6.9, 1.5 Hz, Me), 5.05 (quint., 1H, J=7.0 Hz, C*H*Me), 6.26 (dq, 1H, J=15.7, 1.6 Hz, MeHC=C*H*CO), 6.88 (bs, 1H, NH), 7.11 (dq, 1H, J=15.5, 6.9 Hz, Me*H*C=CH), 7.52–7.72 (m, 3H, 3×ArH), 8.10 (d, 1H, J=8.0 Hz, ArH). δ_C (100 MHz, $CDCl_3$): 18.2 (CH_3), 18.6 (CH_3), 52.8 (CH), 124.6 (CH), 127.8 (CH), 128.7 (CH), 130.6 (CH), 132.7 (quat.), 133.7 (CH), 146.3 (quat.), 146.6 (CH), 165.7 (quat.), 197.0 (quat). υ_{max} (NaCl plates, neat, cm^{-1}): 3321 (broad), 3018, 2928, 1654, 1532, 1444, 1349, 1217, 1078, 970, 667. EI mass spectrum (*m*/*z*, %): 263 (MH^+, 2%), 193 (25%), 150 (100%), 104 (15%), 76 (15%), 69 (35%). HRMS (ES+): found MH^+ 263.1030, $C_{13}H_{14}N_2O_4$ requires MH^+ 263.1032.

4.4.2. 4-(*o*-Nitrobenzamido)-pent-1-en-3-one 7b. Obtained, after column chromatographic purification (single spot by TLC), as a yellow oil (0.2225 g, 75%) from 4-(*o*-nitrobenzamido)-pent-1-en-3-ol **6b** (0.3000 g, 1.20 mmol, 1.0 equiv.).

δ_H (400 MHz, $CDCl_3$): 1.56 (d, 3H, J=7.1 Hz, Me), 5.14 (quint., 1H, J=7.1 Hz, CH*Me*), 6.02 (dd, 1H, J=8.1, 3.5 Hz, C=C*H*), 6.49–6.52 (m, 2H, 2×C=C*H*), 6.84 (bs, 1H, NH), 7.52–7.73 (m, 3H, 3×ArH), 8.09 (dd, 1H, J=8.0, 1.3 Hz, ArH). δ_C (100 MHz, $CDCl_3$): 18.0 (CH_3), 52.1 (CH), 124.7 (CH), 128.7 (CH), 130.6 (CH), 131.3 (CH), 132.5 (CH), 133.8 (CH), 134.0 (quat.), 143.3 (quat.), 168.2 (quat.), 197.6 (quat.). υ_{max} (NaCl plates, neat, cm^{-1}): 3324 (broad), 2924, 1650, 1531, 1349, 1075, 852, 789, 699. EI mass spectrum (*m*/*z*, %): 249 (MH^+, 2%), 193 (35%), 150 (100%), 76 (65%), 55 (90%). HRMS (CI+[NH_3]): found MNH_4^+ 266.1140, $C_{12}H_{12}N_2O_4$ requires MNH_4^+ 266.1141.

4.4.3. 2-Methyl-4-(*o*-nitrobenzamido)-but-1-en-3-one 7c. Obtained, after column chromatographic purification (single spot by TLC), as a yellow oil (0.2500 g, 72%) from 2-methyl-4-(*o*-nitrobenzamido)-but-1-en-3-ol **6c** (0.3500 g, 1.40 mmol, 1.0 equiv.).

δ_H (270 MHz, $CDCl_3$): 1.93 (s, 3H, Me), 4.69 (d, 1H, J=4.4 Hz, CH_2), 5.94 (d, 1H, J=1.5 Hz, C=C*H*H), 6.12 (s, 1H, C=CH*H*), 6.91 (bs, 1H, NH), 7.56–7.61 (m, 2H, 2×ArH), 7.68 (dt, 1H, J=7.5, 1.2 Hz, ArH), 8.05 (dd, 1H, J=8.0, 0.8 Hz, ArH). δ_C (63 MHz, $CDCl_3$): 17.2 (CH_3), 46.0 (CH_2), 124.5 (CH), 126.5 (CH_2), 128.7 (CH), 130.6 (CH), 132.4 (quat.), 133.6 (CH), 142.0 (quat.), 146.5 (quat.), 166.3 (quat.), 195.0 (quat.). υ_{max} (NaCl plates, neat, cm^{-1}): 3306 (broad), 2927, 1657, 1532, 1349, 1075, 1052, 857, 789, 699. EI mass spectrum (*m*/*z*, %): 249 (MH^+, 2%), 193 (35%), 150 (100%), 120 (20%), 104 (25%), 76 (65%). HRMS (CI+[NH_3]): found MNH_4^+ 266.1140, $C_{12}H_{12}N_2O_4$ requires MNH_4^+ 266.1141.

4.4.4. 4-(*o*-Nitrobenzamido)-but-1-en-3-one 7d. Obtained, after column chromatographic purification (single spot by TLC), as a yellow oil (0.1736 g, 70%) from 4-(*o*-nitrobenzamido)-but-1-en-3-ol **6d** (0.2500 g, 1.06 mmol, 1.0 equiv.).

δ_H (400 MHz, $CDCl_3$): 4.62 (d, 2H, J=4.4 Hz, CH_2), 6.07 (t, 1H, *J*=3.8 Hz, C=C*H*), 6.46 (d, 2H, *J*=3.8 Hz, 2× C=C*H*), 6.79 (bs, 1H, NH), 7.56–7.65 (m, 2H, 2×ArH), 7.71 (dt, 1H, *J*=7.4, 1.3 Hz, ArH), 8.11 (dd, 1H, *J*=8.1, 1.2 Hz, ArH). δ_C (100 MHz, $CDCl_3$): 47.6 (CH_2), 124.7 (CH_2), 127.1 (quat.), 128.7 (CH), 130.8 (CH), 133.6 (CH), 133.8 (CH), 134.8 (CH), 148.8 (quat.), 166.2 (quat.), 193.8 (quat.). υ_{max} (NaCl plates, neat, cm^{-1}): 3301 (broad), 2925, 1654, 1530, 1349, 1260, 856, 790, 699. EI mass spectrum (*m/z*, %): 235 (MH^+, 3%), 177 (45%), 166 (25%), 150 (30%), 121 (35%), 105 (70%), 91 (97%), 77 (100%). HRMS (CI+[NH_3]): found MNH_4^+ 252.0990, $C_{11}H_{10}N_2O_4$ requires MNH_4^+ 252.0984.

4.4.5. (E)-5-(*o*-Nitrobenzenesulfamido)-hex-2-en-4-one 13. Obtained, after column chromatographic purification (single spot by TLC), as a yellow oil (0.4170 g, 84%) from (*E*)-5-(*o*-nitrobenzenesulfamido)-hex-2-en-4-ol **12** (0.5000 g, 1.67 mmol, 1.0 equiv.).

δ_H (270 MHz, $CDCl_3$): 1.42 (d, 3H, *J*=7.2 Hz, Me), 1.91 (dd, 3H, *J*=6.9, 1.7 Hz, Me), 4.42 (quint., 1H, *J*=7.2 Hz, C*H*Me), 6.15 (dq, 1H, *J*=15.6, 1.6 Hz, *H*C=CHMe), 6.47 (bd, *J*=7.2 Hz, NH), 6.94 (dq, 1H, *J*=15.6, 6.9 Hz, C=C*H*Me), 7.67–7.75 (m, 2H, 2×ArH), 7.87–7.90 (m, 1H, ArH), 8.03–8.07 (m, 1H, ArH). δ_C (63 MHz, $CDCl_3$): 18.6 (CH_3), 19.6 (CH_3), 56.6 (CH), 125.6 (CH), 127.0 (CH), 129.5 (quat.), 130.3 (CH), 132.8 (CH), 133.6 (CH), 134.4 (quat.), 146.3 (CH), 195.8 (quat.). υ_{max} (NaCl plates, neat, cm^{-1}): 3319 (broad), 3021, 2989, 1660, 1552, 1447, 1348, 1318, 1287, 1216, 1180, 1108, 1077, 796, 700, 669. EI mass spectrum (*m/z*, %): 299 (MH^+, 1%), 229 (47%), 186 (95%), 109 (20%), 76 (15%), 69 (100%). HRMS (CI+[NH_3]): found MNH_4^+ 316.0965, $C_{12}H_{14}N_2O_5S$ requires MNH_4^+ 316.0967.

4.5. Synthesis of 1,4-benzodiazepin-5-ones 9

A solution of the allylic ketone (0.3–0.8 mmol) in dry methanol (10 ml) at room temperature was treated with 5% palladium on charcoal (~0.1 g) and a slow stream of hydrogen was allowed to pass from a balloon into the reaction mixture. The reaction was monitored by TLC and was showed to be complete after 16–20 hrs, except for compound **14**, the formation of which was complete after 4 h. The reaction mixture was filtered (celite) to remove the catalyst, the solvent was evaporated off and the residue was purified by column chromatography (PE:EtOAc, 1:2). Thus obtained were the following 1,4-benzodiazepin-5-ones:

4.5.1. 1,2,3,4-Tetrahydro-3-methyl-2-(*n*-propyl)-1,4-benzodiazepin-5-one 9a. Obtained, after column chromatographic purification (single spot by TLC), as a white crystalline solid (0.0782 g, 47%) from (*E*)-5-(*o*-nitrobenzamido)-hex-2-en-4-one **7a** (0.2000 g, 0.7626 mmol). Mp: 193–195 °C.

δ_H (400 MHz, $CDCl_3$): 0.97 (t, 3H, *J*=6.9 Hz, Me), 1.22 (d, 3H, *J*=6.9 Hz, Me), 1.25–1.63 (m, 4H, C$\mathit{H_2}$C$\mathit{H_2}$), 3.39 (dd, 1H, *J*=8.8, 2.5 Hz, C*H*N), 3.70 (quint., 1H, *J*=7.1 Hz, CMe*H*N), 6.29 (bd, 1H, *J*=8.5 Hz, NH), 6.58 (dd, 1H, *J*=8.2, 1.0 Hz, ArH), 6.76 (dt, 1H, *J*=7.3, 1.0 Hz, ArH), 7.23, (dt, 1H, *J*=7.6, 1.6 Hz, ArH), 8.03 (dd, 1H, *J*=8.1, 1.6 Hz, ArH). δ_C (100 MHz, $CDCl_3$): 14.0 (CH_3), 16.8 (CH_3), 19.6 (CH_2), 33.2 (CH_2), 50.6 (CH), 60.6 (CH), 117.5 (CH), 118.0 (CH), 126.1 (quat.), 132.7 (CH), 133.3 (CH), 145.5 (quat.), 169.8 (quat.) υ_{max} (KBr disc, cm^{-1}): 3283, 3126, 2970, 2927, 1628, 1527, 1441, 1260, 1089, 1023, 803. EI mass spectrum (*m/z*, %): 219 (MH^+, 10%), 218 (50%), 203 (10%), 175 (30%), 147 (25%), 133 (60%), 132 (65%), 119 (100%), 105 (35%), 91 (55%), 77 (30%), 65 (25%), 57 (35%), 45 (50%). HRMS (ES+): found MH^+ 219.1498, $C_{13}H_{18}N_2O$ requires MH^+ 219.1497.

4.5.2. 2-Ethyl-1,2,3,4-tetrahydro-3-methyl-1,4-benzodiazepin-5-one 9b. Obtained, after column chromatographic purification (single spot by TLC), as a yellow oil (0.0716 g, 58%) from 4-(*o*-nitrobenzamido)-pent-1-en-3-one **7b** (0.1500 g, 0.6043 mmol).

δ_H (400 MHz, $CDCl_3$): 0.97 (t, 3H, *J*=7.4 Hz, Me), 1.15 (d, 3H, *J*=6.9 Hz, Me), 1.43–1.52 (m, 1H, C$\mathbf{H_2}$), 1.96–2.02 (m, 1H, C$\mathbf{H_2}$), 3.24 (t, 1H, *J*=6.8 Hz, C*H*), 3.65 (quint., 1H, *J*=6.2 Hz, C*H*Me), 4.88 (bs, 1H, NH), 6.53 (d, 1H, *J*=8.17 Hz, ArH), 6.69 (t, 1H, *J*=7.4 Hz, ArH), 7.16 (bs, 1H, NH), 7.40 (t, 1H, *J*=7.0 Hz, ArH), 7.96 (d, 1H, *J*=8.0 Hz, ArH). δ_C (100 MHz, $CDCl_3$): 10.9 (CH_3), 16.7 (CH_3), 24.0 (CH_2), 50.6 (CH), 62.5 (CH), 117.5 (CH), 118.0 (CH), 124.0 (quat.), 132.7 (CH), 133.2 (CH), 145.5 (quat.), 169.5 (quat.). υ_{max} (NaCl plates, neat, cm^{-1}): 3341, 3155, 2960, 2926, 2855, 1626, 1464, 1262, 1216, 1088, 1022, 668. EI mass spectrum (*m/z*, %): 205 (MH^+, 10%), 204 (65%), 189 (15%), 175 (20%), 161 (55%), 147 (30%), 133 (90%), 132 (100%), 118 (30%), 104 (75%), 77 (40%), 57 (35%), 44 (40%). HRMS (ES+): found MH^+ 205.1339, $C_{12}H_{16}N_2O$ requires MH^+ 205.1341.

4.5.3. 1,2,3,4-Tetrahydro-2-isopropyl-1,4-benzodiazepin-5-one 9c. Obtained, after column chromatographic purification (single spot by TLC), as a yellow oil (0.0239 g, 29%) from 2-methyl-4-(*o*-nitrobenzamido)-but-1-en-3-one **7c** (0.1000 g, 0.4028 mmol, 1.0 equiv.).

δ_H (400 MHz, $CDCl_3$): 0.90 (d, 3H, *J*=6.8 Hz, Me), 0.96 (d, 3H, *J*=6.7 Hz, Me), 1.81 (octet, 1H, *J*=6.6 Hz, CHC*H*Me_2), 3.27 (dd, 1H, *J*=5.8, 1.9 Hz, C$\mathit{H_2}$), 3.28–3.36 (m, 2H, C$\mathit{H_2}$ and C*H*CHMe_2), 6.55 (d, 1H, *J*=8.2 Hz, ArH), 6.75 (t, 1H, *J*=7.5 Hz, ArH), 7.16 (dd, 1H, *J*=6.9, 1.6 Hz, ArH), 7.29 (bs, 1H, NH), 7.49 (d, 1H, *J*=7.3 Hz, ArH), 7.79 (dd, 1H, *J*=6.5, 1.5 Hz, ArH), 8.03 (dd, 1H, *J*=7.1, 1.5 Hz, ArH). δ_C (100 MHz, $CDCl_3$): 18.3 (CH_3). 18.9 (CH_3), 29.7 (CH), 42.8 (CH_2), 65.0 (CH), 118.2 (CH), 118.9 (CH), 128.3 (quat.), 132.5 (CH), 132.9 (CH), 145.1 (quat.), 172.1 (quat.). υ_{max} (NaCl plates, neat, cm^{-1}): 3328, 3166, 2963, 2927, 1637, 1609, 1466, 1264, 1098, 1047, 796. EI mass spectrum (*m/z*, %): 205 (MH^+, 5%), 204 (20%), 161 (60%), 133 (45%), 132 (40%), 84 (100%), 104 (20%), 91 (40%), 77 (40%), 57 (45%), 49 (85%). HRMS (ES+): found MH^+ 205.1338, $C_{12}H_{16}N_2O$ requires MH^+ 205.1341.

4.5.4. 2-Ethyl-1,2,3,4-tetrahydro-1,4-benzodiazepin-5-one 9d. Obtained, after column chromatographic purification (single spot by TLC), as a yellow oil (0.0325 g, 40%) from 4-(*o*-nitrobenzamido)-but-1-en-3-one **7d** (0.1000 g, 0.4270 mmol, 1.0 equiv.).

δ_H (400 MHz, $CDCl_3$): 1.10 (t, 3H, *J*=7.4 Hz, Me), 1.60

(hextet, 1H, *J*=7.3 Hz, $\mathrm{CHC}\mathit{H}_2\mathrm{Me}$), 2.00–2.05 (m, 1H, *J*=7.2 Hz, $\mathrm{CHC}\mathit{H}_2\mathrm{Me}$), 3.24–3.35 (m, 1H, C*H*N), 3.40 (dd, 1H, *J*=5.7, 2.3 Hz, $\mathrm{C}\mathit{H}_2\mathrm{N}$), 3.57 (dd, 1H, *J*=6.6, 2.3 Hz, $\mathrm{C}\mathit{H}_2\mathrm{N}$), 4.95 (bs, 1H, NH), 6.60 (d, 1H, *J*=8.2 Hz, NH), 6.81 (t, 1H, *J*=7.5 Hz, ArH), 7.41 (d, 1H, *J*=7.5 Hz, ArH), 7.91 (dd, 1H, *J*=7.8, 1.6 Hz, ArH), 8.10 (dd, 1H, *J*=7.2, 1.3 Hz, ArH). δ_C (100 MHz, $CDCl_3$): 14.1 (CH_3), 22.7 (CH_2), 31.9 (CH_2), 44.9 (CH), 118.7 (CH), 119.3 (CH), 128.1 (CH), 129.7 (quat.), 132.9 (CH), 139.8 (quat.), 161.9 (quat.). v_{max} (NaCl plates, neat, cm^{-1}): 3307, 3149, 2966, 2925, 1633, 1444, 1260, 1096, 1035, 798, 698. EI mass spectrum (*m*/*z*, %): 191 (MH^+, 10%), 190 (75%), 161 (100%), 133 (55%), 132 (80%), 118 (20%), 104 (45%), 77 (35%), 57 (25%). HRMS (ES+): found MH^+ 191.1188, $C_{11}H_{14}N_2O$ requires MH^+ 191.1184.

4.5.5. 2,3,4,5-Tetrahydro-4-hydroxy-3-methyl-4-(*n*-propyl)-1,2,5-benzothiadiazepin-1,1-dioxide 14.

Obtained, as a single spot by TLC, by the identical procedure via column chromatography (eluent PE:EtOAc, 1:1) as a yellow oil (0.0408 g, 45%) from (*E*)-5-(*o*-nitrobenzenesulfamido)-hex-2-en-4-one **13** (0.1000 g, 0.3352 mmol, 1 equiv.).

δ_H (400 MHz, $CDCl_3$): 0.76 (t, 3H, *J*=7.4 Hz, Me), 1.30 (d, 3H, *J*=7.2 Hz, Me), 1.42 (hextet, 2H, *J*=7.4 Hz, $\mathrm{CH_2C}\mathit{H}_2\mathrm{Me}$), 2.18 (dt, 1H, *J*=17.4, 7.1 Hz, $\mathrm{C}\mathit{H}_2\mathrm{CH_2Me}$), 2.37 (dt, 1H, *J*=17.6, 7.0 Hz, $\mathrm{C}\mathit{H}_2\mathrm{CH_2Me}$), 3.88 (quintet, 1H, *J*=7.1 Hz, C*H*Me), 4.89 (bs, 2H, OH and NH), 5.89 (d, 1H, *J*=6.8 Hz, NH), 6.71–6.80 (m, 2H, 2×ArH), 7.30 (t, 1H, *J*=7.4 Hz, ArH), 7.66 (d, 1H, *J*=7.9 Hz, ArH). δ_C (100 MHz, $CDCl_3$): 13.4 (CH_3), 16.8 (CH_3), 19.0 (CH_2), 29.1 (CH), 40.9 (CH_2), 57.0 (quat.), 117.7 (CH), 118.0 (CH), 127.3 (quat.), 127.5 (quat.), 129.3 (CH), 134.3 (CH). v_{max} (NaCl plates, neat, cm^{-1}): 3401, 3377, 3265, 3038, 2960, 1600, 1483, 1455, 1332, 1156, 1024, 753. EI mass spectrum (*m*/*z*, %): 271 (MH^+, 20%), 270 (95%), 199 (80%), 182 (50%), 156 (75%), 108 (35%), 92 (100%), 65 (40%). HRMS (CI+[NH_3]): found MNH_4^+ 288.1379, $C_{12}H_{18}N_2O_3S$ requires 288.1381.

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Tetrahedron

Dihydrofurocoumarin and dihydrofurodihydropyrid-2-one derivatives via palladium catalysed cascades involving aryl/heteroaryl/vinyl iodides and allene followed by acid catalysed cyclisation

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Abstract—Mono 3-(2′-arylallyl) derivatives of 4-hydroxycoumarin **1a**,**b**, 4-hydroxy-6-methyl-pyran-2-one (**3**) and 6-hydroxy-1,4-dimethyl-1,2-dihydropyrid-2-one-3-carbonitrile (**4**) are produced in 3-component cascades involving aryl/heteroaryl/vinyl iodides and allene (1 atm) using $Pd(PPh_3)_4/Cs_2CO_3/MeCN/80$ °C or $Pd_2(dba)_3$/tris(2-furyl)phosphine/K_2CO_3/DMF/80 °C as the catalyst system. 4-Hydroxy-2-quinolone (**2**) afforded a mixture of mono- and bis-allylation products under these conditions. Mono C-allylation products **5a**–**e** and **15a**–**e** undergo facile acid catalysed cyclisation to afford dihydrofurocoumarins **11a**–**e** and dihydrofurodihydropyrid-2-ones **16a**–**e** in good overall yield.

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1. Introduction

π-Allylpalladium (II) species are versatile intermediates for organic synthesis and can be generated from Pd(0) and a wide range of allylic substrates including halides, carbonates, acetates, esters, ethers, alcohols, phosphates, amines, sulfones and nitro compounds.[1,2] The generation of π-allylpalladium (II) species from allenes is also well documented.[3] We[4] and others[5] have generated a wide variety of π-allylpalladium (II) species from allenes and aryl/heteroaryl/vinyl halides or triflates. These versatile intermediates undergo attack by a wide range of nucleophiles[4] of which stabilised carbanions, such as malonate, and heteroatom centred nucleophiles, such as amines, N-deprotonated-amides, sulphonamides, ureas and alkoxides and thiolates, are the most widely employed. Previously we have reported the C-dienylation of active methylene pronucleophiles[6] and the O-dienylation of phenols and hydroxyisoquinoline[7] employing allene as the π-allyl precursor. As part of a search for novel nucleophiles for π-allylpalladium (II) species we have investigated the nucleophilicity of heterocyclic scaffolds having an enolic system. Herein, we report the use of the heterocyclic enols 4-hydroxycoumarins **1a**,**b**, 4-hydroxy-2-quinolone (**2**), 4-hydroxy-6-methyl-pyran-2-one (**3**), and 6-hydroxy-1,4-dimethyl-1,2-dihydropyrid-2-one-3-carbonitrile (**4**) as novel nucleophiles for π-allylpalladium (II) species generated in situ from allene (1 atm) and aryl/heteroaryl/vinyl iodides (Scheme 2).

C-Allyl-4-hydroxycoumarins are important intermediates in the synthesis of dihydrofurocoumarins. This nucleus occurs in a number of natural products[8] and exhibits a range of biological properties including anticoagulant, insecticidal, anthelmintic, hypnotic, antifungal, phytoalexin and HIV protease inhibition.[9] 3,3-Diallylquinolines are also core components of a range of natural products.[10] 3-Allylation of 4-hydroxycoumarin is normally achieved by Claisen rearrangement of *O*-allyl derivatives[11] or by direct base induced allylation with a suitable allyl precursor.[12] A potential problem with the former methodology is the requirement of vigorous reaction conditions, while the latter methodology may lack regioselectivity and thus produce a mixture of *C*-allyl and *O*-allyl products. Both approaches are constrained by the lack of more complex allylating agents. The implementation of Scheme 2 opens up a rich vein of novel allylic species.

Keywords: Allylpalladium; Nucleophiles; Allylation; Hydroxycoumarins; Hydroxyquinolones; Pyrones; Claisen rearrangement; Cyclisation.

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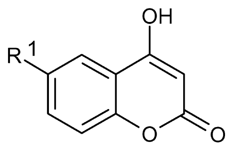
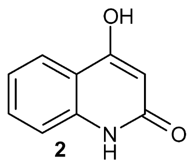


1a R^1=H, **1b** R^1=Me



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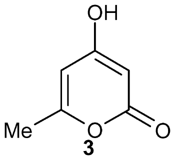

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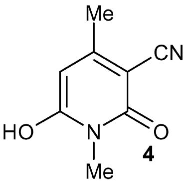

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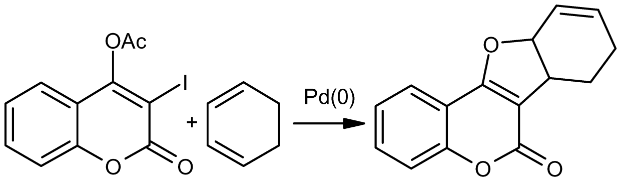
Dihydrofurocoumarins have been synthesised by a number of methods including acid catalysed[11b] and palladium catalysed[11a] cyclisation of 3-allyl-4-hydroxycoumarins, oxidative addition of 4-hydroxycoumarin and alkenes or phenylacetylene in the presence of ceric (IV) ammonium nitrate (CAN),[13] manganese (III) acetate hydrate (MAH),[14] silver (I) carbonate/celite[15] and BF_3.[16] The reaction of 4-hydroxycoumarins with alkenes or alkynes frequently suffer from poor regiselectivity giving mixtures of angular and linear products. In our case (vide infra), only angular products were obtained. Recently dihydrofurocoumarins have been synthesised by palladium catalysed annulation of 1,3-dienes with *o*-iodoacetoxycoumarins (Scheme 1).[17]



Scheme 1.

2. Results and discussion

2.1. 4-Hydroxycoumarins (1a,b), 4-hydroxy-2-quinolone (2) and 4-hydroxy-6-methyl-pyran-2-one (3) as nucleophiles

Initially we surveyed the effect of several combinations of catalyst, base, solvent and concentration on the 3-component cascade using **1a** as substrate (Table 1). This survey identified $Pd(PPh_3)_4$ (5 mol%) and Cs_2CO_3 (2.0 mol equiv.) in MeCN (20 ml/mmol ArI) at 80 °C (Table 1, entry 3) as an efficient combination. The concentration of the reaction mixture has a significant effect on product formation. Thus the use of 20 ml MeCN/mmol ArI gives the mono C-allylation product **5a** (Table 1, entry 3), whilst higher concentrations give rise to a 1:1 mixture of mono- and bis-C-allylation products (Table 1, entry 2), leaving unreacted nucleophile. The mono C-allylation product **5a** could not be isolated as it appears to exist as a mixture of free OH compound and its cesium salt which was insoluble in chloroform. Formation of mono-allyl products was assessed from the ^1H NMR spectra of the reaction mixtures in deuterated dimethyl sulfoxide which exhibit characteristic resonances for olefinic protons at δ 4.8 and 5.3 and for the methylene protons next to olefinic carbon at δ 3.7. Washing the crude reaction mixture with dilute HCl or acetic acid resulted in partial cyclisation to give **11a** which was evidenced in the ^1H NMR spectra ($CDCl_3$) by the appearance of new AB signals for the methylene protons next to the tetrasubstituted carbon (δ 3.35) and a singlet for the methyl group (δ 1.9).

It was convenient to treat the crude product with TFA in $CHCl_3$ at room temperature for 2–3 h to effect complete cyclisation to **11a**. The allylation–cyclisation can be carried out as a one-pot process (TFA, MeCN, 4–5 h), but the isolated yield was lower. The scope and limitations of the 2-step process were then explored employing a range of aryl/heteroaryl/vinyl iodides (Table 2). The presence of an electron withdrawing group in the aryl iodide suppresses cyclisation of **5** to **11** (Scheme 2) by destabilising the intermediate carbocation. This effect, as expected, is general and allows easy isolation of the mono-allylation products (Table 3). A general survey was carried out employing **1a**,**b** and **3** as pronucleophiles and a range of aryl iodides bearing inductive electron withdrawing groups and/or weak mesomeric donors (Table 3). The C-allylation products **5f**–**j**, **6a**–**e** and **12a**–**d** thus obtained did not undergo cyclisation on work-up in aq. acidic solution or even upon treatment with TFA in chloroform which confirms the considerable carbocation character involved in the cyclisation. Under acidic conditions the protonation of the *N*-atom of the pyridyl ring of mono-allyl products **5i** and **6d** (Table 3) has a similar destabilizing effect.

4-Hydroxy-2-quinolone (**2**) afforded a mixture of mono- and bis-C-allylation products **7** and **9**, respectively, under the same reaction conditions applied for the mono-C-allylation

Table 1. Effect of catalyst, base and solvent on the C-allylation of heterocyclic nucleophiles (NuH)[a]

Entry	NuH	Catalyst system[b]	Base	Solvent (ml)	Temperature (°C)	Mono/bis[c]
1	**1a**	$Pd(PPh_3)_4$	Cs_2CO_3	Toluene (20)	110	1:1[d]
2		$Pd(PPh_3)_4$	Cs_2CO_3	MeCN (10)	80	1:1
3		$Pd(PPh_3)_4$	Cs_2CO_3	MeCN (20)	80	100:0
4	**2**	$Pd(PPh_3)_4$	Cs_2CO_3	MeCN (20)	80	1:2
5[e]		$Pd_2(dba)_3$/TFP	K_2CO_3	DMF (10)	60	0:100
6	**3**	$Pd(PPh_3)_4$	Cs_2CO_3	MeCN (20)	80	100:0
7	**4**	$Pd_2(dba)_3$/TFP	K_2CO_3	DMF (10)	80	100:0

[a] All reactions employed *p*-$MeOC_6H_4I$ (1.0 mmol), nucleophiles **1**–**4** (1.2 equiv.), allene (1 atm), base (2.0 mol equiv.) in a Schlenk tube for 20–24 h.

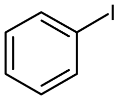
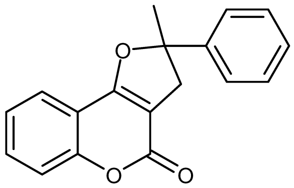
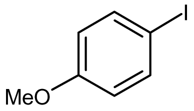
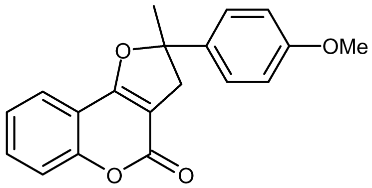
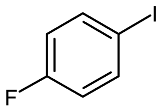
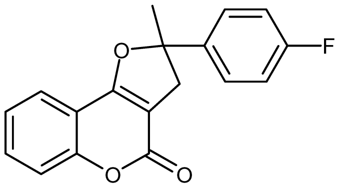
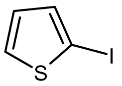
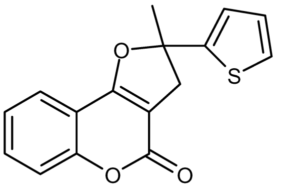
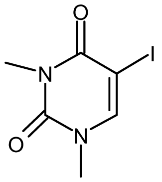
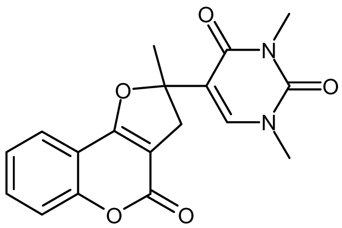
[b] 5 mol% Pd and 10–20 mol% phosphine ligand were used.

[c] Ratio of mono- and bis-allyl products were determined by ^1H NMR.

[d] Conversion was 25%.

[e] 2.1 equiv. Ar–I was used.

Table 2. C-Allylation–cyclisation of 4-hydroxycoumarin[a]

Entry	R–I	Product **11a–e**		Yield(%)[b]
1			**11a**	62
2			**11b**	65
3[c]			**11c**	54
4			**11d**	53
5			**11e**	71

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[a] All reactions employed RI (1.0 mmol), 4-hydroxycoumarin (1.1 equiv.), allene (1 atm) in a Schlenk tube in presence of $Pd(PPh_3)_4$ (5 mol%) and Cs_2CO_3 (2.0 mol equiv.) in MeCN (20 ml) at 80 °C for 20 h. The mixture was then cooled, excess allene released, the mixture filtered and the filtrate evaporated. The residue was suspended in $CHCl_3$, the pH adjusted to 2–3 with TFA and the mixture stirred at room temperature for 2–3 h.

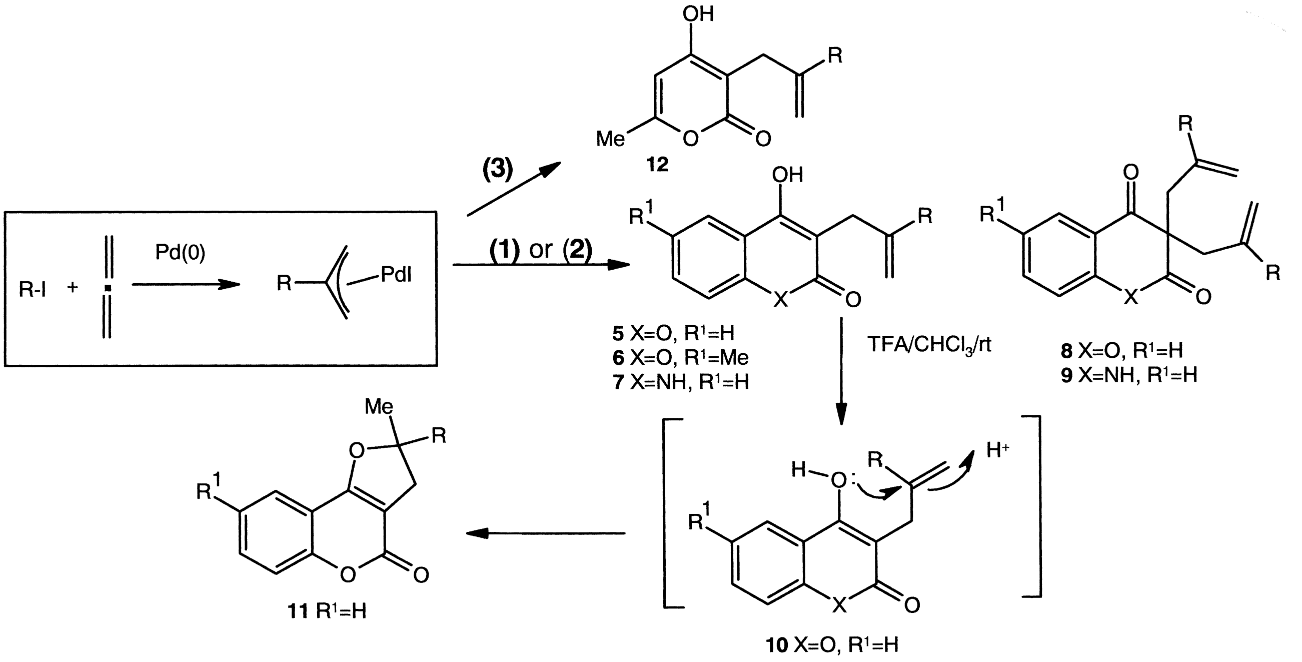
[b] Isolated overall yield for the two steps.

[c] Cyclisation carried out at 50 °C for 2 h.

of 4-hydroxycoumarin (Table 1, entry 4). Using 2.1 equivalent of aryl iodide gave only the bis-C-allylation product (Table 1, entry 5) and several further examples of bis-C-allylation were prepared using $Pd_2(dba)_3$ (2.5 mol%), tris(2-furyl)phosphine (10 mol%), K_2CO_3 (2.0 mol equiv.) in DMF at 60 °C (Table 4). The anomalous behaviour of 4-hydroxy-2-quinolone is not fully understood, but is clearly related to the reactivity of the two anions **13** and **14** generated from the mono-allylation products **5** and **7** (Scheme 3). The negative charge of the anion **13** is delocalised over the adjacent carbonyl groups whilst the analogous anion **14** from **7** is less effectively stabilized since nitrogen is less electronegative than oxygen (Scheme 3) and amide resonance of **14** is also important.

2.2. 6-Hydroxy-1,4-dimethyl-1,2-dihydropyrid-2-one-3-carbonitrile (4) as nucleophile

Construction of the dihydrofuro[2,3-*b*] pyridinone substructure is as important synthetic issue as this unit occurs in cladobotryal,[18] a potent antifungal and antibacterial agent and in psoralene,[19] a drug for the treatment of skin diseases. We therefore focused on the heterocycle **4** as a potential pronucleophile for our π-allyl intermediates. The reaction of aryl/heteroaryl/vinyl iodides (RI), allene (1 bar) and the nucleophile (**4**) (Scheme 4) was studied with a catalyst system comprising $Pd_2(dba)_3$ (2.5 mol%), tris(2-furyl)-phosphine (10 mol%) and K_2CO_3 (2.0 mol equiv.) in DMF at 80 °C for 20 h. The results are shown in Table 5. As encountered before intermediates **15a–e** could not be isolated. Again they appear to exist as a mixture of the free OH compound and the potassium salt and washing the crude product with dilute HCl or acetic acid resulted in a partial cyclisation of the intermediate **15** to **16**. We therefore instituted a second step (TFA, $CHCl_3$, room temperature, 2 h) which gave the cyclised products **16a–e** (Table 5). The cyclisation of the intermediate is also possible as a one-pot process but it requires longer reaction time and results in poor yield. From the mechanistic point of view, the C-allylation of nucleophiles



Scheme 2.

Table 3. *C*-Allylated 4-hydroxycoumarins and 4-hydroxy-6-methyl-pyran-2-one[a]

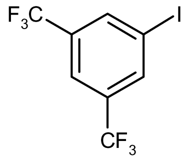
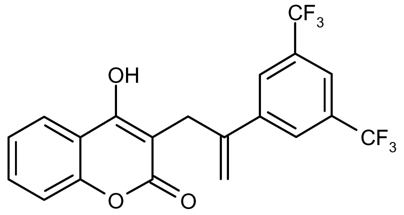
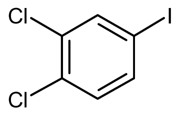
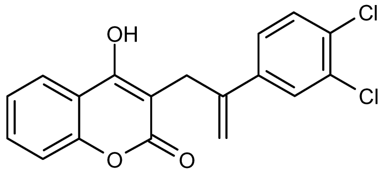
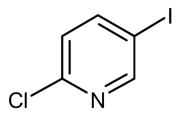
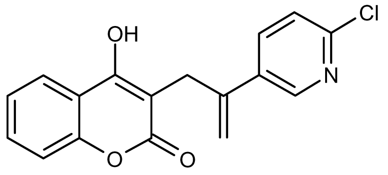
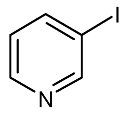
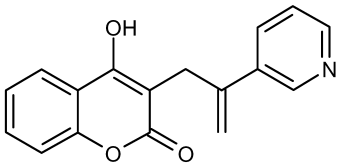
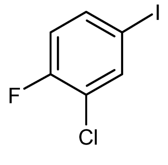
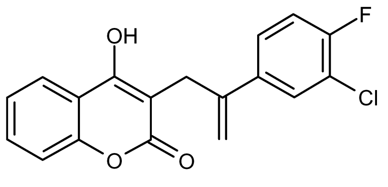
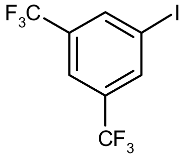
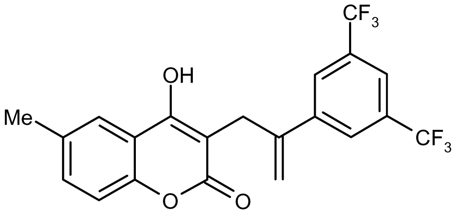
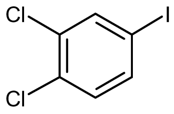
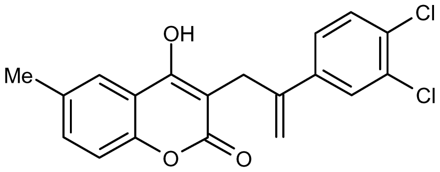
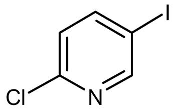
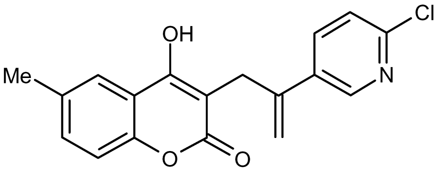
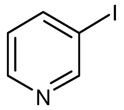
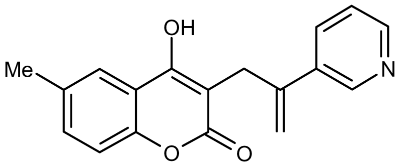
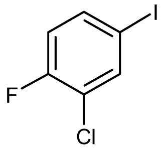
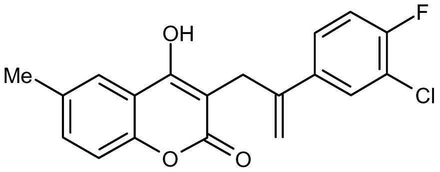
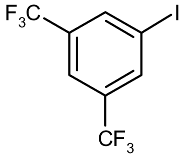
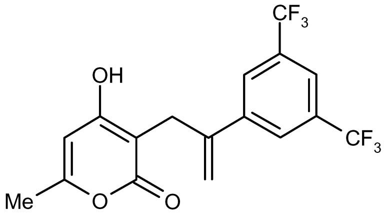
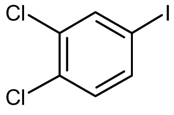
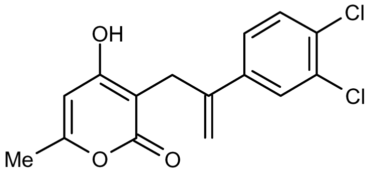
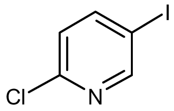
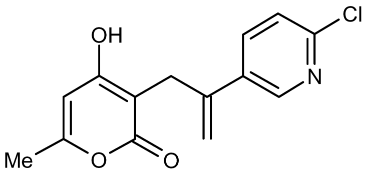
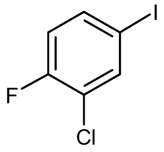
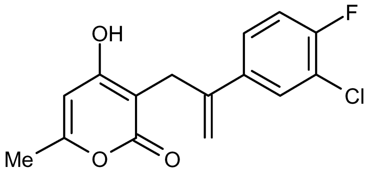
Entry	NuH	Ar–I	Products		Yield (%)[b]
1	**1a**			**5f**	97
2				**5g**	91
3				**5h**	91
4				**5i**	65
5	**1b**			**5j**	92

Table 3 (*continued*)

Entry	NuH	Ar–I	Products		Yield (%)[b]
6				**6a**	69
7				**6b**	75
8				**6c**	94
9				**6d**	66
10				**6e**	62
11	**3**			**12a**	67
12				**12b**	72
13				**12c**	95
14				**12d**	71

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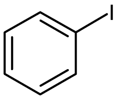
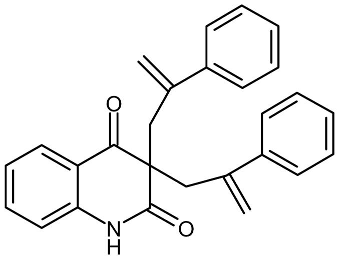
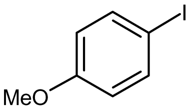
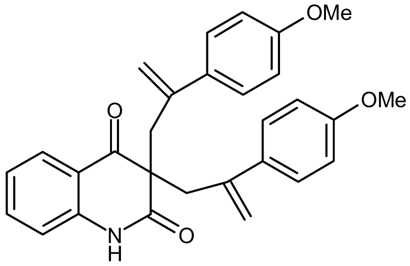
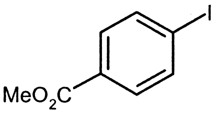
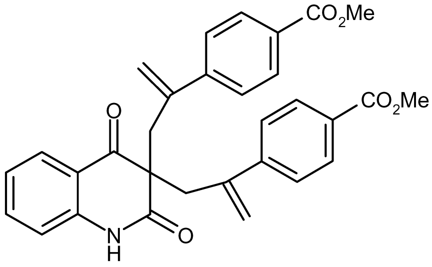
[a] All reactions employed ArI (1.0 mmol), 4-hydroxycoumarins **1a**,**b** or 4-hydroxy-6-methyl-pyran-2-one (**3**) (1.10 equiv.), allene (1 atm) in a Schlenk tube in the presence of $Pd(PPh_3)_4$ (5 mol%) and Cs_2CO_3 (2.0 mol equiv.) in MeCN (20 ml) at 65 °C for 20 h.

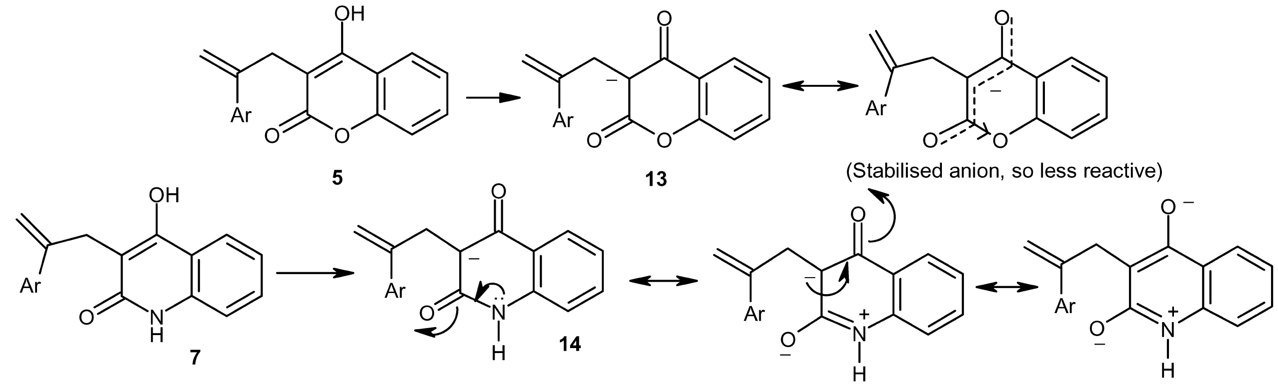
[b] Isolated yield.

Table 4. Bis-*C*-allylated of 4-hydroxy-2-quinolone[a]

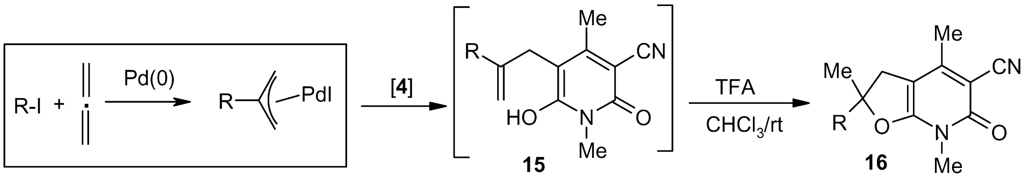
Entry	Ar–I	Products **9a–c**		Yield (%)[b]
1			**9a**	56
2			**9b**	41
3			**9c**	75

[a] All reactions employed Ar–I (2.1 mmol), allene (1 atm) and 4-hydroxy-2-quinolone (**2**) (1.0 equiv.) in the presence of $Pd_2(dba)_3$ (2.5 mol%), tris(2-furyl)phosphine (10 mol%) and K_2CO_3 (2.0 mol equiv.) in DMF (10 ml) at 60 °C for 20 h.

[b] Isolated yield.

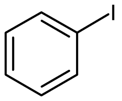
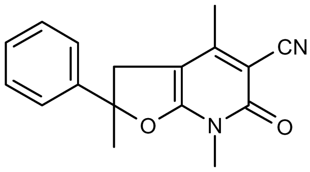
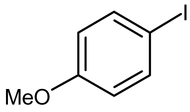
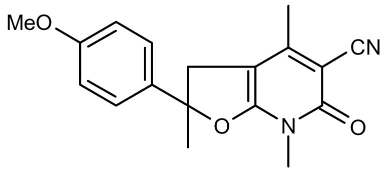
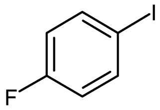
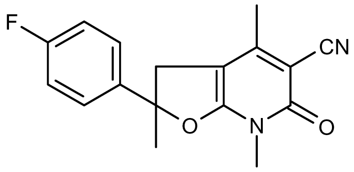
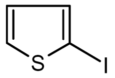
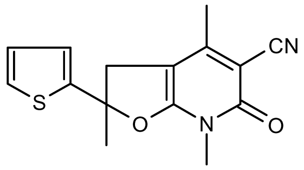
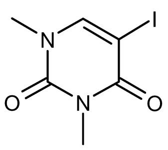
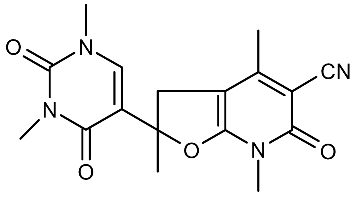


Scheme 3.



Scheme 4.

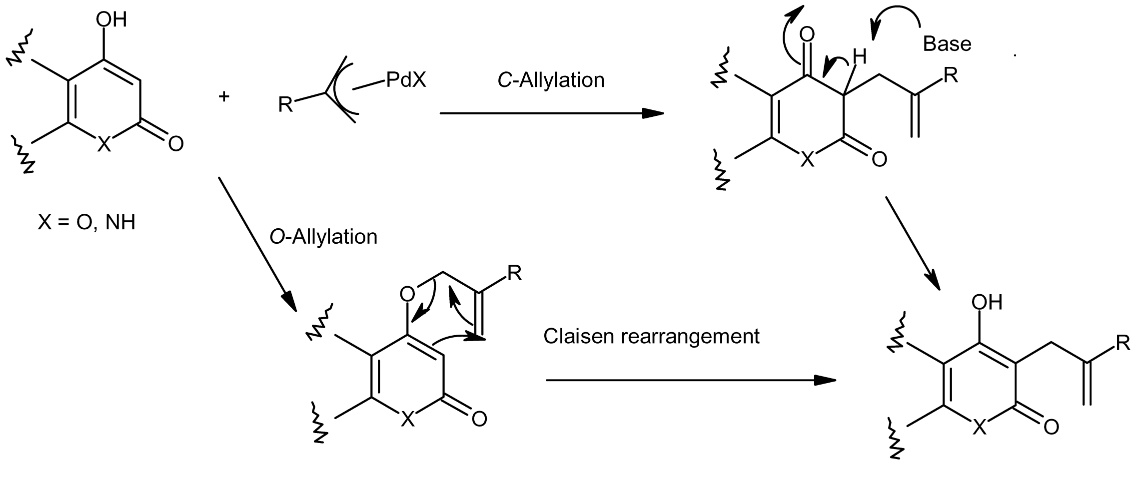
Table 5. C-Allylation–cyclisation of 6-hydroxy-1,4-dimethyl-1,2-dihydropyrid-2-one-3-carbonitrile (**4**)[a]

Entry	RI	Products		Yield (%)[b]
1			**16a**	52
2			**16b**	55
3			**16c**	35
4			**16d**	50
5			**16e**	52

[a] All reactions employed RI (1.0 mmol), pyridone **4** (1.1 equiv.) and allene (1 atm) in presence of $Pd_2(dba)_3$ (2.5 mol%), tris(2-furyl)phosphine (10 mol%) and K_2CO_3 (2.0 mol equiv.) in DMF (10 ml) at 80 °C in a Schlenk tube for 20 h. The crude material was suspended in $CHCl_3$ and treated with TFA (pH=2–3) and left for 2–3 h with stirring.

[b] Isolated yield.

1–4 could arise by direct C-allylation or by O-allylation followed by Claisen rearrangement (Scheme 5). A few examples of the palladium catalysed alkylation of phenols with allyl carbonates, acetates or related π-allylpalladium (II) precursors have been reported.[20] Normally, Claisen rearrangement requires heating above 100 °C but we could not rule out this route as Claisen, and other [3,3]-sigmatropic, rearrangements have been reported to be catalysed by palladium[21,22] under mild conditions.



Scheme 5.

3. Conclusion

4-Hydroxycoumarins **1a**,**b**, 4-hydroxy-2-quinolone (**2**), 4-hydroxy-6-methyl-pyran-2-one (**3**) and pyridone (**4**) have been developed as novel pronucleophiles for palladium-catalysed cascades involving aryl/heteroaryl/vinyl iodides and allene. Mono-C-allylation of **1a**,**b**, **3** and **4** proceeded in the presence of $Pd(PPh_3)_4/Cs_2CO_3$/MeCN (20 ml/mmol RI)/80 °C and $Pd_2(dba)_3$/tris(2-furyl)-phosphine/K_2CO_3/DMF/80 °C respectively. The mono-allylation products **5a–e** and **15a–e** could not be isolated as they comprised mixtures of salts of cesium or potassium and free OH compounds. Treatment of these mixtures with TFA in $CHCl_3$ at room temperature effects cyclisation to afford dihydrofurocoumarin and dihydro-furo-dihydropyrid-2-one derivatives **11a–e** and **16a–e** respectively. Allylation of **2**, under the same conditions as for **1a**,**b** and **3**, gives a 1:2 mixture of mono- and bis-allyl products **7** and **9**, respectively. Bis-allylation products **9a–c** were prepared by employing an excess of aryl iodide (2.1 equiv.).

4. Experimental

4.1. General technical data

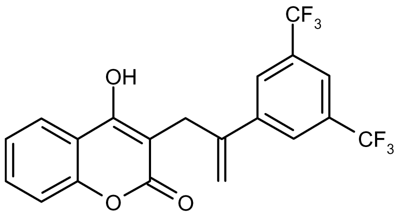
Commercially available reagents were used without further purification but, where appropriate, solvents were purified according to procedures given in *Purification of Laboratory Chemicals*, Perrins, D. D.; Armarego, W. L. F.; Perrin, D. R. Permagon Press, 1980. Nucleophile **4** was a gift from BASF. Flash column chromatography was performed on Merck silica gel 60 (230–400 mesh). R_f values were determined by thin layer chromatography (TLC) on Merck silica gel 60 F_{254} and spots were visualised with UV light (254 nm). The term petroleum ether refers to the fraction with bp 40–60 °C and the term ether refers to diethyl ether. Melting points were determined on a Kofler hot stage apparatus and are uncorrected.

Microanalyses were obtained using a Carlo-Erba Model 1106 instrument. Proton nuclear magnetic resonance (^1H NMR) spectra experiments were determined at 300 MHz on a Bruker DPX300 spectrometer. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as internal standard and coupling constants are given in Hertz (Hz). Except where otherwise stated, spectra were determined in deuteriochloroform. The following abbreviations are used; s=singlet, d=doublet, t=triplet, q=quartet, dd=double doublet, dt=double triplet, td=triple doublet, m=multiplet, br=broad and brs=broad singlet. ^{13}C NMR spectra were recorded with a Bruker DPX300 (75 MHz) and chemical shift values are reported in parts per million (ppm) relative to $CDCl_3$ (δ=77.0). Mass spectra were obtained on a VG Autospec instrument at 70 eV using electron impact (EI) and on a LCT Micromas using electrospray (ES) techniques. Infrared spectra were recorded on a Perkin–Elmer FT-IR spectrometer either by a film technique on sodium chloride discs by spreading DCM solution on the discs or for solids using a Combi pod. The samples for the film technique were prepared by dissolving a small amount of compound in DCM, pipetting the solution on to a sodium chloride plate and allowing the DCM to evaporate.

4.2. General procedure for C-allylation of 4-hydroxycoumarins (1a,b) and 4-hydroxy-6-methylpyran-2-one (3)

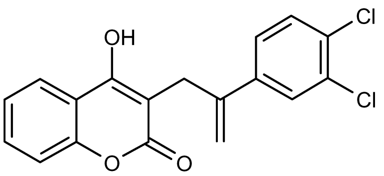
A mixture of aryl/heteroaryl/vinyl iodide (1.0 mmol, 1.0 equiv.), 4-hydroxycoumarin **1a** (0.18 g, 1.10 mmol, 1.10 equiv.), or **1b** (0.21 g, 1.10 mmol, 1.10 equiv.) or 4-hydroxypyrone **3** (0.15 g, 1.10 mmol, 1.10 equiv.), tetrakis(triphenyl)phosphinepalladium (0.06 g, 5.0 mol%) and cesium carbonate (0.65 g, 2.0 mol equiv.) in MeCN (20 ml) was stirred for 15 min in a Schlenk tube. The mixture was then degassed, frozen, evacuated and charged with allene (1 bar). After warming to room temperature it was heated at 65–80 °C in an oil bath for 16 h. The mixture was then cooled to room temperature, excess allene vented, the mixture was treated with 5% (w/v) aq. HCl (15 ml) and the mixture was extracted with chloroform (3×10 ml). The combined organic layer was washed with water (20 ml), dried ($MgSO_4$) and the filtrate concentrated under reduced pressure. The residue was either purified by column chromatography or directly used for cyclisation.

4.2.1. 3-{2-[3,5-Bis(trifluoromethyl)phenyl]prop-2-en-1-yl}-4-hydroxy-2*H*-chromen-2-one (5f).



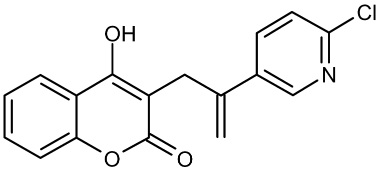
Column chromatography eluting with 7:3 v/v petroleum ether–ethyl acetate gave the product (97%) as a colourless solid, which crystallized from acetone as colourless needles, mp 183–185 °C. (Found: C, 57.60; H, 2.75; $C_{20}H_{12}O_3F_6$ requires C, 57.65; H, 2.95%); δ_H (300 MHz, DMSO-d_6) 3.75 (2H, s, $=C-CH_2$), 5.09 (1H, s, $CH_2=$), 5.62 (1H, s, $CH_2=$), 7.32–7.38 (2H, m, ArH), 7.61 (1H, m, ArH), 7.95 (1H, d, J=7.7 Hz, ArH) 8.01 (1H, s, ArH), 8.2 (2H, s, ArH); δ_C (75 MHz, DMSO-d_6) 29.1 (CH_2), 101.9, 115.7, 116.4, 116.5, 121.3, 123.7, 124.2, 126.9, 123.7 (q, $JC-^{19}F$=272.9 Hz, CF_3), 130.7 (q, $JC-^{19}F$=32.7 Hz, $C-CF_3$), 132.3, 142.2, 143.8, 152.5, 161.6 and 163.0 (CO); m/z (ES) 415 (100%, M^+), 343 (15), 175 (84) and 102 (33); ν_{max}/cm^{-1} (film) 3944, 3691, 3054, 2987, 2685, 2305, 1667, 1633, 1572, 1497, 1421, 1332, 1265, 1169, 1075, 965, 896, 739, 643, and 549.

4.2.2. 3-{2-[3,4-Dichlorophenyl]prop-2-en-1-yl}-4-hydroxy-2*H*-chromen-2-one (5g).



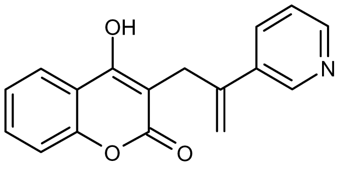
Column chromatography eluting with 1:1 v/v petroleum ether–ethyl acetate gave the product (91%) as a colourless solid, mp 174–176 °C. (Found: C, 62.20; H, 3.65, Cl, 20.35; $C_{18}H_{12}Cl_2O_3$ requires C, 62.25; H, 3.50, Cl, 20.40%) δ_H (500 MHz, DMSO-d_6) 3.66 (2H, s, =C–CH$_2$), 4.93 (1H, s, CH$_2$=), 5.45 (1H, s, CH$_2$=), 7.35–7.39 (2H, m, ArH), 7.55 (1H, d, J=8.2 Hz, ArH), 7.61–7.63 (2H, m, ArH), 7.79 (1H, s, ArH), 7.96 (1H, d, J=7.8 Hz, ArH); δ_C (75 MHz, DMSO-d_6) 29.0 (CH$_2$), 102.1, 113.6, 116.5, 116.6, 123.7, 124.2, 126.5, 128.1, 130.3, 130.7, 131.4, 132.3, 141.8, 142.3, 152.5, 161.5 and 163.0 (CO); m/z (ES) 352 (11%, M$^+$, ^{37}Cl and ^{37}Cl), 350 (66, M$^+$, ^{37}Cl and ^{35}Cl) and 348 (100, M$^+$, ^{35}Cl and ^{35}Cl); ν_{max}/cm^{-1} (film) 3126, 1666, 1630, 1496, 1453, 1398, 1330, 1292, 1202, 1163, 1111, 1070, 1025, 961, 905, 878, 823, 759, 718, 683, 647 and 457.

4.2.3. 3-[2-(6-Chloropyridin-3-yl)prop-2-en-1-yl]-4-hydroxy-2*H*-chromen-2-one (5h).



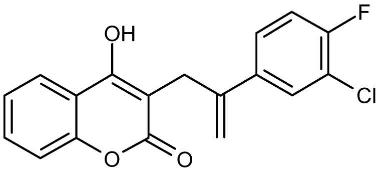
Column chromatography eluting with 3:7 v/v petroleum ether–ethyl acetate afforded the product (91%), as a colourless amorphous solid, mp 170–172 °C. (Found: C, 65.05; H, 4.35; N, 4.40; $C_{17}H_{12}O_3NCl$ requires C, 65.10; H, 4.15; N, 4.45%); δ_H (300 MHz, DMSO-d_6) 3.65 (2H, s, =C–CH$_2$), 4.95 (1H, s, CH$_2$=), 5.5 (1H, s, CH$_2$=), 7.33–7.39, (2H, m, ArH), 7.52 (1H, d, J=8.3 Hz, ArH), 7.6 (1H, t, J=8.2 Hz, ArH), 7.95 (1H, d, J=7.8 Hz, ArH), 8.0 (1H, dd, J=8.3, 2.5 Hz, ArH), 8.6 (1H, d, J=2.5 Hz, ArH); δ_C (75 MHz, DMSO-d_6) 29.0 (CH$_2$), 101.9, 114.1, 116.5, 116.6, 123.7, 124.1, 124.3, 132.3, 136.0, 137.3, 140.7, 147.5, 149.5, 152.5, 161.7 and 163.0 (CO); m/z (ES) 316 (33%, M$^+$, ^{37}Cl) and 314 (100, M$^+$, ^{35}Cl); ν_{max}/cm^{-1} (film) 3189, 1666, 1631, 1573, 1554, 1497, 1474, 1452, 1431, 1399, 1366, 1328, 1291, 1202, 1162, 1148, 1110, 1072, 1017, 915, 824, 685, 516 and 483.

4.2.4. 4-Hydroxy-3-(2-pyridin-3-ylprop-2-en-1-yl)-2*H*-chromen-2-one (5i).



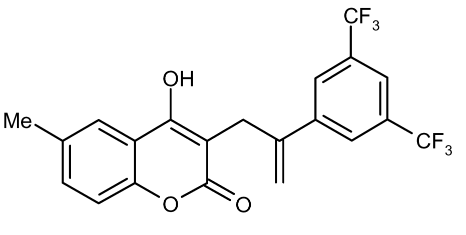
Washed with dichloromethane and crystallised from petroleum ether–ethyl acetate to afford the product (65%) as a colourless amorphous solid, mp 182–184 °C. (HRMS: 280.0959 (M$^+$+H); $C_{17}H_{13}NO_3$ requires 280.0974 (M$^+$+H)); δ_H (300 MHz, DMSO-d_6) 3.69 (2H, s, =C–CH$_2$), 4.94 (1H, s, CH$_2$=), 5.44 (1H, s, CH$_2$=), 7.32–7.42 (3H, m, ArH), 7.61 (1H, t, J=8.3 Hz, ArH), 7.95 (2H, d, J=7.64 Hz, ArH), 8.5 (1H, d, J=4.6 Hz, ArH), 8.75 (1H, s, ArH); δ_C (75 MHz, DMSO-d_6) 29.1 (CH$_2$), 100.8, 113.1, 116.4, 117.7, 123.6, 123.8, 123.9, 131.8, 133.5, 137.5, 142.4, 147.3, 148.8, 152.7, 163.3, and 163.4 (CO); m/z (ES) 280 (100%, M$^+$+H), and 127 (16); ν_{max}/cm^{-1} (film) 3043, 2906, 1691, 1610, 1570, 1495, 1456, 1421, 1333, 1283, 1237, 1193, 1166, 1056, 919, 898, 819, 770, 724, 652, 608, 533 and 486.

4.2.5. 3-{2-[3-Chloro-4-fluorophenyl]prop-2-en-1-yl}-4-hydroxy-2*H*-chromen-2-one (5j).



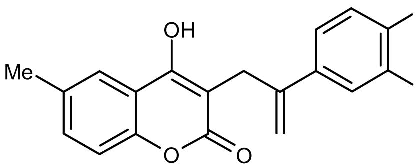
Column chromatography eluting with 1:1 v/v petroleum ether–ether gave the product (92%) as a colourless amorphous solid, mp 175–177 °C. (Found: C, 65.05; H, 3.75; $C_{18}H_{12}O_3F_6$ requires C, 65.35, H, 3.65%); δ_H (300 MHz, DMSO-d_6) 3.65 (2H, s, =C–CH$_2$), 4.86 (1H, s, CH$_2$=), 5.39 (1H, s, CH$_2$=), 7.34–7.44 (3H, m, ArH), 7.56–7.65 (2H, m, ArH), 7.75 (1H, d, J=5.2 Hz, ArH), 7.95 (1H, d, J=7.5 Hz, ArH); δ_C (75 MHz, DMSO-d_6) 29.2 (CH$_2$), 102.2, 113.0 (=CH$_2$), 116.5, 116.6, 116.9, 117.1, 123.7, 124.3, 126.8, 126.9, 128.2, 132.3, 139.0, 142.4, 152.5, 161.5 and 163.0 (CO); m/z (ES) 334 (33%, M$^+$, ^{37}Cl) and 332 (100, M$^+$, ^{35}Cl); ν_{max}/cm^{-1} (film) 3167, 2875, 1714, 1664, 1629, 1498, 1454, 1398, 1330, 1262, 1199, 1162, 1111, 1056, 960, 879, 819, 762, and 645.

4.2.6. 3-{2-[3,5-Bis(trifluoromethyl)phenyl]prop-2-en-1-yl}-4-hydroxy-6-methyl-2*H*-chromen-2-one (6a).



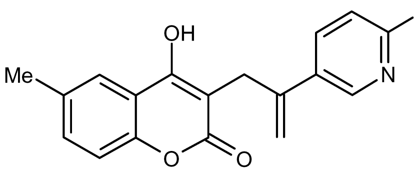
Column chromatography eluting with 1:1 v/v petroleum ether–ethyl acetate afforded the product (67%) as a colourless solid, which crystallized from DCM as colourless needles, mp 165–167 °C. (Found: C, 58.70; H, 3.45; $C_{21}H_{14}O_3F_6$ requires C, 58.9; H, 3.30%); δ_H (300 MHz, DMSO-d_6) 2.36 (3H, s, Me), 3.73 (2H, s, =C–CH$_2$), 5.06 (1H, s, CH$_2$=), 5.62 (1H, s, CH$_2$=), 7.25 (1H, d, J=8.4 Hz, ArH), 7.40 (1H, d, J=8.4 Hz, ArH), 7.75 (1H, s, ArH), 8.0 (1H, s, ArH), 8.15 (2H, s, ArH); δ_C (75 MHz, DMSO-d_6) 20.8 (Me), 29.2 (CH$_2$), 101.7, 115.7, 116.1, 116.3, 123.3, 126.9, 130.6, 123.7 (q, JC–^{19}F=272.9 Hz, CF$_3$), 130.7 (q, JC–^{19}F=32.7 Hz, C–CF$_3$), 133.1, 133.5, 142.3, 143.8, 150.6, 161.6 and 163.1 (CO); m/z (ES) 429 (100%, M$^+$+H), 173 (10), 151 (13) and 103 (26); ν_{max}/cm^{-1} (film) 3084, 1654, 1627, 1579, 1504, 1430, 1316, 1287, 1209, 1181, 1149, 1121, 1075, 1012, 976, 912, 889, 847, 823, 770, 732, 693, 683, 659, 611, 538 and 465.

4.2.7. 3-[2-(3,4-Dichlorophenyl)prop-2-en-1-yl]-4-hydroxy-6-methyl-2*H*-chromen-2-one (6b).



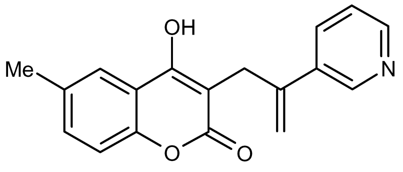
Column chromatography eluting with 1:1 v/v petroleum ether–ethyl acetate afforded the product (75%), which crystallized from dichloromethane as a colourless needles, mp 186–188 °C. (Found: C, 63.25; H, 4.10; Cl, 19.35; $C_{19}H_{14}Cl_2O_3$ requires 63.20; H, 3.90; Cl, 19.60%); δ_H (300 MHz, DMSO-d_6) 2.40 (3H, s, Me), 3.60 (2H, s, =C–CH_2), 4.9 (1H, s, CH_2=), 5.4 (1H, s, CH_2=), 7.28 (1H, d, J=8.5 Hz, ArH), 7.4 (1H, d, J=8.2 Hz, ArH), 7.5 (1H, d, J=8.2 Hz, ArH), 7.6 (1H, d, J=8.5 Hz, ArH), 7.7 (1H, s, ArH), 7.9 (1H, s, ArH); δ_C (75 MHz, DMSO-d_6) 20.8 (Me), 29.0 (CH_2), 102.0, 113.6, 116.1, 116.4, 123.3, 126.5, 128.1, 130.3, 130.7, 131.4, 133.1, 133.5, 141.8, 142.4, 150.6, 161.5 and 163.1 (CO); m/z (ES) 365 (11%, M^+, ^{37}Cl and ^{37}Cl), 363 (66, M^+, ^{37}Cl and ^{35}Cl) and 361 (100, M^+, ^{35}Cl and ^{35}Cl); ν_{max}/cm^{-1} (film) 3282, 2827, 1662, 1627, 1583, 1503, 1421, 1391, 1294, 1202, 1144, 1114, 1065, 1024, 977, 898, 881, 819, 770, 720, 694, 659, 626, 538, 488 and 477.

4.2.8. 3-[2-(6-Chloropyridin-3yl)prop-2-en-1-yl]-4-hydroxy-6-methyl-2*H*-chromen-2-one (6c).



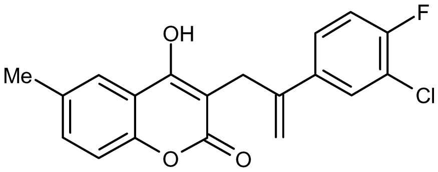
Column chromatography eluting with 3:7 v/v petroleum ether–ethyl acetate afforded the product (94 as a colourless powder, mp 171–173 °C. (Found: C, 65.75; H, 4.8; 4.05; $C_{17}H_{12}ClNO_3$ requires C, 65.95; H, 3.80, N, 4.25%); δ_H (300 MHz, DMSO-d_6) 2.4 (3H, s, Me), 3.65 (2H, s, =C–CH_2), 4.95 (1H, s, CH_2=), 5.5 (1H, s, CH_2=), 7.25 (1H, d, J=8.4 Hz, ArH), 7.4 (1H, d, J=8.0 Hz, ArH), 7.5 (1H, d, J=8.4 Hz, ArH), 7.75 (1H, s, ArH), 8.0 (1H, dd, J=8.0, 2.4 Hz, ArH), 8.6 (1H, d, J=2.4 Hz, ArH); δ_C (75 MHz, DMSO-d_6) 20.8 (Me), 29.0 (CH_2), 101.8, 114.1, 116.1, 116.4, 123.3, 124.1, 133.2, 133.5, 136.0, 137.3, 140.7, 143.5, 147.5, 149.4, 150.6 and 161.5 (CO); m/z (ES) 331 (33% M^++H, ^{37}Cl), 329 (100, M^++H, ^{35}Cl), and 280 (17); ν_{max}/cm^{-1} (film) 3667, 2924, 1666, 1630, 1583, 1555, 1503, 1475, 1430, 1393, 1367, 1295, 1234, 1200, 1143, 1115, 1064, 1017, 979, 913, 884, 813, 785, 818, 694, 663, 630, 546 and 489.

4.2.9. 4-Hydroxy-6-methyl-3-(2-pyridin-3-ylprop-2-en-1-yl)-2*H*-chromen-2-one (6d).



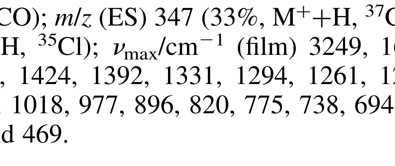
Column chromatography eluting with 1:4 v/v petroleum ether–ethyl acetate afforded the product (63%), which crystallized from ethyl acetate–petroleum ether as a colourless powder, mp 174–176 °C. (HRMS: 294.1123 (M^++H); $C_{18}H_{15}NO_3$ requires 294.1130 (M^++H)); δ_H (300 MHz, DMSO-d_6) 2.4 (3H, s, Me), 3.70 (2H, s, =C–CH_2), 5.0 (1H, s, CH_2=), 5.55 (1H, s, CH_2=), 7.3 (1H, d, J=8.3 Hz, ArH), 7.4 (1H, d, J=8.3 Hz, ArH), 7.7 (1H, dd, J=7.8, 4.7 Hz, ArH), 7.75 (1H, s, ArH), 8.3 (1H, d, J=7.8 Hz, ArH), 8.65 (1H, d, J=4.7 Hz, ArH), 8.9 (1H, s, ArH); δ_C (75 MHz, DMSO-d_6) 20.8 (Me), 28.9 (CH_2), 101.8, 115.0, 116.1, 116.4, 123.3, 125.2, 133.2, 133.5, 137.6, 137.9, 140.8, 144.0, 145.5, 150.6 and 161.7 (CO); m/z (ES) 294 (100%, M^++H); ν_{max}/cm^{-1} (film) 3063, 1694, 1630, 1580, 1539, 1494, 1389, 1323, 1280, 1229, 1180, 1144, 1109, 1049, 939, 902, 808, 713, 666, 620, 478, and 464.

4.2.10. 3-[2-(3-Chloro-4-fluorophenyl)prop-2-en-1-yl]-4-hydroxy-6-methyl-2*H*-chromen-2-one (6e).



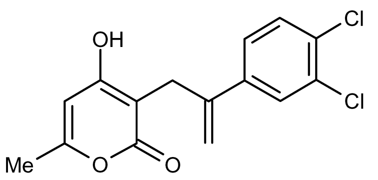
Column chromatography eluting with 3:2 v/v petroleum ether–ethyl acetate afforded the product (62%), which crystallized from acetone as a colourless needles, mp 181–182 °C. (Found: C, 66.0; H, 4.30; Cl, 10.15; $C_{19}H_{14}ClFO_3$ requires C, 66.20; H, 4.10, Cl, 10.30%); δ_H (300 MHz, DMSO-d_6) 2.5 (3H, s, Me), 3.65 (2H, s, =C–CH_2), 4.85 (1H, s, CH_2=), 5.4 (1H, s, CH_2=), 7.25 (1H, d, J=8.4 Hz, ArH), 7.35–7.4 (2H, m, ArH), 7.55 (1H, m, ArH), 7.7–7.75 (2H, m, ArH); δ_C (75 MHz, DMSO-d_6) 20.8 (Me), 29.2 (CH_2), 102.1, 112.9, 116.1, 116.3, 116.8, 117.1, 119.6, 123.3, 126.8, 126.9, 128.2, 133.1, 133.5, 139.0, 142.4, 161.5 and 163.1 (CO); m/z (ES) 347 (33%, M^++H, ^{37}Cl) and 345 (100, M^++H, ^{35}Cl); ν_{max}/cm^{-1} (film) 3249, 1665, 1628, 1583, 1501, 1424, 1392, 1331, 1294, 1261, 1200, 1145, 1116, 1067, 1018, 977, 896, 820, 775, 738, 694, 657, 628, 541, 488 and 469.

4.2.11. 3-{2-[3,5-Bis(trifluoromethyl)phenyl]prop-2-en-1-yl}-4-hydroxy-6-methyl-2*H*-pyran-2-one (12a).



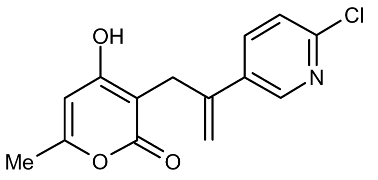
Column chromatography eluting with the solvent petroleum ether–ethyl acetate 1:1 afforded the product (67%) as a colourless solid, which crystallized from dichloromethane as a colourless needles, mp 166–168 °C. (Found: C, 54.0; H, 3.15; $C_{17}H_{12}O_3F_6$ requires C, 54.0; H, 3.20%); δ_H (300 MHz, DMSO-d_6) 2.15 (3H, s, Me), 3.5 (2H, s, =C–CH_2), 5.2 (1H, s, CH_2=), 5.60 (1H, s, CH_2=), 6.0 (1H, s, O–C=CH), 8.0 (1H, s, ArH), 8.15 (2H, s, ArH); δ_C (75 MHz, DMSO-d_6) 19.6 (Me), 28.4 (CH$_2$), 98.1, 100.1, 116.6 (C=CH$_2$), 121.1, 126.8, 123.7 (q, JC–^{19}F=272.7 Hz, CF$_3$), 130.6 (q, JC–^{19}F=32.7 Hz, C–CF$_3$), 142.7, 143.5, 161.1, 164.8 and 166.7; m/z (ES) 380 (100%, M$^+$+H); ν_{max}/cm^{-1} (film) 2617, 1662, 1620, 1560, 1451, 1405, 1378, 1292, 1274, 1180, 1163, 1116, 994, 901, 693, 639, 611, 505 and 466.

4.2.12. 3-[2-(3,4-Dichlorophenyl)prop-2-en-1-yl]-4-hydroxy-6-methyl-2*H*-pyran-2-one (12b).



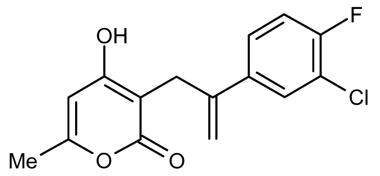
Column chromatography eluting with 1:1 v/v petroleum ether–ethyl acetate afforded the product (73%), which crystallized from ethanol–water as colourless plates, mp 184–186 °C. (HRMS: 311.0240 (M$^+$+H); C$_{15}$H$_{13}$Cl$_2$O$_3$ requires 311.0242 (M$^+$+H)); δ_H (300 MHz, DMSO-d_6) 2.15 (3H, s, Me), 3.4 (2H, s, =C–CH$_2$), 4.95 (1H, s, CH$_2$=), 5.4 (1H, s, CH$_2$=), 6.0 (1H, S, O–C=CH), 7.5 (1H, d, J=8.4 Hz, ArH), 7.6 (1H, d, J=8.4 Hz, ArH), 7.75 (1H, s, ArH); δ_C (75 MHz, DMSO-d_6) 19.7 (Me), 28.3 (CH$_2$), 98.4, 100.1, 114.2, 126.5, 128.1, 130.2, 130.6, 131.3, 141.7, 142.8, 161.0, 164.8 and 166.4 (CO); m/z (ES) 315 (11%, M$^+$, ^{37}Cl and ^{37}Cl), 313 (66, M$^+$, ^{37}Cl and ^{35}Cl) and 311 (100, M$^+$, ^{35}Cl and ^{35}Cl); ν_{max}/cm^{-1} (film) 2886, 2628, 1664, 1621, 1574, 1552, 1478, 1447, 1428, 1398, 1267, 1128, 1025, 995, 918, 898, 871, 844, 822, 737, 684, 638, 614, 545 and 466.

4.2.13. 3-[2-(6-Chloropyridin-3-yl)prop-2-en-1-yl]-4-hydroxy-6-methyl-2*H*-pyran-2-one (12c).



Column chromatography eluting with petroleum ether–ethyl acetate 3:7 (v/v) afforded the product (95%) as a colourless solid, which crystallized from ethanol–water as colourless needles, mp 183–185 °C. (Found: C, 60.3; H, 4.35; N, 4.9, Cl, 12.7; C$_{14}$H$_{12}$O$_3$NCl requires C, 60.55; H, 4.35; N, 5.05, Cl, 12.75%); δ_H (300 MHz, DMSO-d_6) 2.15 (3H, s, Me), 3.40 (2H, s, =C–CH$_2$), 5.0 (1H, s, CH$_2$=), 5.4 (1H, s, CH$_2$=), 6.0 (1H, s, O–C=CH), 7.45 (1H, d, J=8.3 Hz, ArH), 7.95 (1H, dd, J=8.3, 2.5 Hz, ArH), 8.55 (1H, d, J=2.5 Hz, ArH); δ_C (75 MHz, DMSO-d_6) 19.7 (Me), 28.2 (CH$_2$), 98.2, 100.1, 114.7, 124.1, 135.8, 137.3, 141.2, 147.5, 149.3, 161.1, 164.8 and 166.5 (CO); m/z (ES) 281 (33%, M$^+$+H, ^{37}Cl) and 279 (100, M$^+$+H, ^{35}Cl); ν_{max}/cm^{-1} (film) 2628, 2302, 1662, 1626, 1558, 1449, 1404, 1265, 1135, 1108, 1053, 1018, 996, 919, 895, 829, 738, 641, 615, and 526.

4.2.14. 3-[2-(3-Chloro-4-fluorophenyl)prop-2-en-1-yl]-4-hydroxy-6-methyl-2*H*-pyran-2-one (12d).

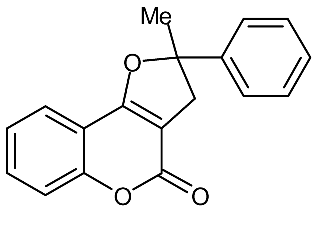


Column chromatography eluting with 1:1 (v/v) petroleum ether–ethyl acetate afforded the product (71%) as a colourless solid, mp 178–180 °C. (Found: C, 60.80; H, 4.50, Cl, 11.75; C$_{15}$H$_{12}$ClFO$_3$ requires C, 61.10; H, 4.10; Cl, 12.00%); δ_H (300 MHz, DMSO-d_6) 2.15 (3H, s, Me), 3.35 (2H, s, =C–CH$_2$), 4.9 (1H, s, CH$_2$=), 5.35 (1H, s, CH$_2$=), 6.0 (1H, s, O–C=CH), 7.35 (1H, t, J=9.0 Hz, ArH) (JH–H≈JH–^{19}F), 7.5 (1H, m, ArH), 7.7 (1H, dd, J=7.2, 2.0 Hz, ArH); δ_C (75 MHz, DMSO-d_6) 19.6, 28.4, 98.4, 100.2, 113.5, 116.7, 119.7, 126.9, 128.1, 138.9, 142.9, 155.2, 158.5, 160.9, 164.9 and 166.7; m/z (ES) 297 (33%, M$^+$+H, ^{37}Cl) and 295 (100, M$^+$+H, ^{35}Cl); ν_{max}/cm^{-1} (film) 2616, 1625, 1558, 1504, 1448, 1423, 1401, 1270, 1133, 1086, 1057, 995, 896, 817, 737, 641, 617, 515 and 462.

4.3. General procedure C-allylation–cylisation

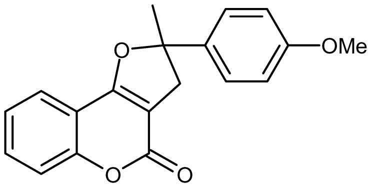
Allylation was carried out as described above in Section 4.2. The mixture was then cooled to room temperature, excess allene vented, the mixture filtered and the filtrate evaporated under reduced pressure. The brown residue was dissolved in chloroform (10 ml) and trifluoroacetic acid was added dropwise with stirring until the pH of the mixture was approximately 3. The mixture was then stirred at room temperature for 3–4 h, diluted with chloroform (10 ml) and washed with water (2×10 ml). The organic layer was dried (MgSO$_4$), filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel.

4.3.1. 2-Methyl-2-phenyl-2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-one (11a).



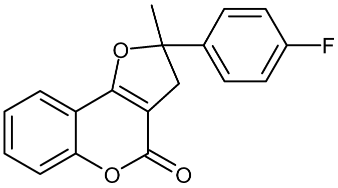
Column chromatography eluting with 4:1 v/v petroleum ether–EtOAc afforded the product (60%) as a colourless oil. (HRMS: 279.1021 (M$^+$+H); C$_{18}$H$_{14}$O$_3$ requires 279.1019 (M$^+$+H); δ_H (300 MHz, CDCl$_3$) 1.9 (3H, s, Me), 3.35 (1H, d, J=15.1 Hz, CH$_2$), 3.45 (1H, d, J=15.1 Hz, CH$_2$), 7.3–7.45 (7H, m, ArH), 7.55 (1H, td, J=7.1, 1.5 Hz, ArH), 7.8 (1H, dd, J=7.8, 1.5 Hz, ArH); δ_C (75 MHz, CDCl$_3$) 29.9 (Me), 42.0 (CH$_2$), 95.2, 101.9, 113.1, 117.4, 123.2, 124.4, 124.6, 125.1, 128.3, 129.1, 132.8, 145.1, 155.5, 161.1 and 165.7 (CO); m/z (ES) 279 (100%, M$^+$+H); ν_{max}/cm^{-1} (film) 3061, 2976, 2923, 2862, 1723, 1646, 1607, 1498, 1446, 1409, 1345, 1279, 1213, 1084, 1028, 961, 887, 766, 751, 729 and 699.

4.3.2. 2-(4-Methoxyphenyl)-2-methyl-2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-one (11b).



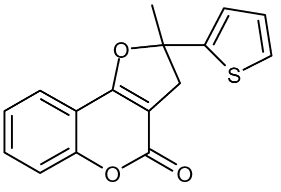
Column chromatography eluting with 4:1 v/v petroleum ether–EtOAc afforded the product (65%) as a colourless oil. (Found: C, 73.7; H, 5.30; $C_{19}H_{16}O_4$ requires C, 74.0; H, 5.20%); δ_H (300 MHz, $CDCl_3$) 1.9 (3H, s, Me), 3.3 (1H, d, J=15.1 Hz, CH_2), 3.4 (1H, d, J=15.1 Hz, CH_2), 3.8 (3H, s, OMe), 6.9 (2H, d, J=8.8 Hz, ArH), 7.3 (1H, t, J=7.1 Hz, ArH), 7.4 (3H, d, J=8.8 Hz, ArH), 7.55 (1H, t, J=7.1 Hz, ArH), 7.75 (1H, d, J=7.8 Hz, ArH); δ_C (75 MHz, $CDCl_3$) 29.6 (Me), 41.9 (CH_2), 55.7 (OMe), 95.1, 101.9, 113.1, 114.4, 117.4, 123.2, 124.4, 124.4, 126.1, 132.8, 137.0, 155.4, 159.6, 161.1 and 165.7 (CO); m/z (ES) 309 (100%, M^++H); ν_{max}/cm^{-1} (film) 3055, 2987, 1719 (CO), 1646, 1516, 1420, 1265, 1032, 896, 737 and 705.

4.3.3. 2-(4-Fluorophenyl)-2-methyl-2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-one (11c).



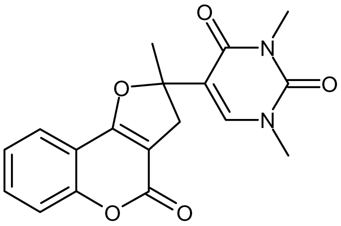
Column chromatography eluting with 4:1 v/v petroleum ether–EtOAc afforded the product (54%) as a colourless oil. (Found: C, 72.7; H, 4.70; $C_{18}H_{13}O_3F$ requires C, 72.9; H, 4.40%); δ_H (300 MHz, $CDCl_3$) 1.9 (3H, s, Me), 3.35 (1H, d, J=15.15 Hz, CH_2), 3.4 (1H, d, J=15.15 Hz, CH_2), 7.1 (2H, t, J=8.7 Hz, ArH), 7.3–7.45 (4H, m, ArH), 7.6 (1H, td, J=7.3, 1.6 Hz, ArH), 7.7 (1H, dd, J=7.8, 1.6 Hz, ArH); δ_C (75 MHz, $CDCl_3$) 29.9 (Me), 42.1 (CH_2), 94.7, 101.8, 113.0, 115.8, 116.1, 117.5, 123.2, 124.4, 126.5, 126.6, 132.9, 140.9, 155.5, 161.0, 164.3 and 165.6 (CO); m/z (ES) 297 (100%, M^++H); ν_{max}/cm^{-1} (film) 3066, 2979, 2931, 2866, 1725 (CO), 1647, 1607, 1559, 1512, 1500, 1410, 1279, 1233, 1162, 1101, 1057, 1029, 962, 888, 836, 752, 730, 555 and 540.

4.3.4. 2-Methyl-2-(2-thienyl)-2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-one (11d).



Column chromatography eluting with 4:1 v/v petroleum ether–EtOAc afforded the product (63%) as a colourless oil. (Found: C, 67.6; H, 4.45; S, 11.0; $C_{16}H_{12}O_3S$ requires C, 67.6; H, 4.25; S, 11.2%); δ_H (300 MHz, $CDCl_3$) 2.0 (3H, s, Me), 3.35 (1H, d, J=15.4 Hz, CH_2), 3.6 (1H, d, J=15.4 Hz, CH_2), 7.0 (1H, dd, J=5.0, 3.6 Hz, thienyl H), 7.12 (1H, dd, J=3.6, 1.2 Hz, thienyl H), 7.25–7.35 (2H, m, ArH), 7.35 (1H, d, J=7.7 Hz, ArH), 7.55 (1H, td, J=7.8, 1.6 Hz, ArH), 7.7 (1H, dd, J=7.8, 1.6 Hz, ArH); δ_C (75 MHz, $CDCl_3$) 29.6 (Me), 42.3 (CH_2), 92.8, 101.7, 113.0, 117.4, 123.3, 124.4, 124.5, 126.2, 127.4, 132.9, 148.0, 155.4, 160.9 and 165.3 (CO); m/z (ES) 285 (100%, M^++H); ν_{max}/cm^{-1} (film) 3429 (br), 2979, 2928, 2868, 1720 (CO), 1646, 1607, 1569, 1498, 1409, 1344, 1280, 1056, 1029, 898, 880, 752, 730 and 705.

4.3.5. 1,3-Dimethyl-5-(2-methyl-4-oxo-2,3-dihydro-4*H*-furo[3,2-*c*]chromen-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (11e).

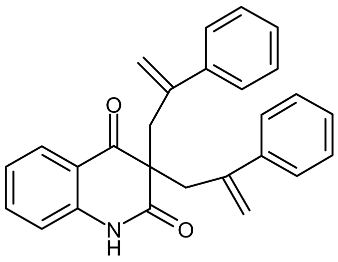


Column chromatography eluting with 4:1 v/v petroleum ether–EtOAc afforded the product (71%) as colourless plates, mp 74–76 °C. (Found: C, 63.5; H, 4.90; N, 8.1; $C_{18}H_{16}N_2O_5$ requires C, 63.5; H, 4.75; N, 8.2%); δ_H (300 MHz, $CDCl_3$) 1.85 (3H, s, Me), 3.25 (1H, d, J=15.9 Hz, CH_2), 3.35 (1H, d, J=15.9 Hz, CH_2), 3.36, 3.45 (2×3H, 2×s, 2×Me), 7.3–7.45 (2H, m, ArH), 7.38 (1H, s, vinyl H), 7.57 (1H, td, J=8.7, 1.5 Hz, ArH), 7.72 (1H, dd, J=7.7, 1.5 Hz, ArH); δ_C (75 MHz, $CDCl_3$) 27.4 (Me), 28.3 (Me), 37.8 (Me), 40.1 (CH_2), 92.0, 103.1, 112.9, 116.0, 117.5, 122.8, 124.4, 132.8, 138.9, 151.8, 155.4, 160.8 (CO), 161.5 (CO) and 164.6 (CO); m/z (ES) 341 (100%, M^++H); ν_{max}/cm^{-1} (film) 3440 (br), 3066, 2983, 2934, 1707 (CO), 1660, 1607, 1500, 1455, 1410, 1366, 1347, 1280, 1254, 1219, 1029, 895, 783, 771, 732 and 700.

4.4. General procedure for bis-C-allylation of 4-hydroxy-2-quinolone (2)

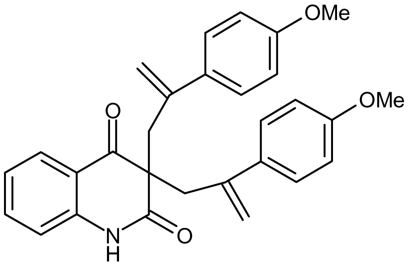
A mixture of aryl iodide (2.1 mmol, 2.1 equiv.), 4-hydroxy-2-quinolone **2** (0.16 g, 1.0 mmol, 1.0 equiv.), tris(dibenzylideneacetone)dipalladium (0.02 g, 2.5 mol%), tris(2-furyl)-phosphine (0.02 g, 10 mol%) and potassium carbonate (0.25 g, 1.8 mol equiv.) in DMF (GPR, 10 ml) was stirred for 15 min in a Schlenk tube. The mixture was then degassed, frozen, evacuated and charged with allene (1 bar). After warming to room temperature it was heated at 60 °C in an oil bath for 16–20 h. The mixture was then cooled to room temperature and excess allene vented. The resulting mixture was diluted with water (10 ml) and extracted with ether (2×20 ml). The combined organic layer was washed with water (2×20 ml), dried ($MgSO_4$), filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel.

4.4.1. 3,3-Bis(2-phenylprop-2-en-1-yl)quinoline-2,4(1*H*,3*H*)-dione-methane(1:1) (9a).



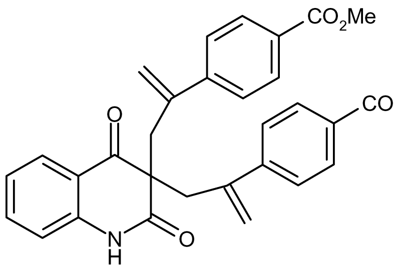
Column chromatography eluting with 4:1 v/v petroleum ether–EtOAc afforded the product (56%) as colourless oil. (HRMS: 394.1808 (M^++H); $C_{27}H_{24}NO_2$ requires 394.1807 (M^++H); δ_H (500 MHz, $CDCl_3$) 3.30 (2H, d, J=14.0 Hz, CH_2), 3.38 (2H, d, J=14.0 Hz, CH_2), 4.88, 5.0 (2×2H, 2×s, 2×C$=$$CH_2$), 6.66 (1H, d, J=7.9 Hz, ArH), 6.85 (1H, t, J=7.2 Hz, ArH), 7.05–7.3 (10H, m, ArH), 7.35–7.37 (2H, m, ArH), 9.45 (1H, s, CONH); δ_C (75 MHz, $CDCl_3$) 46.2 (CH_2), 61.2, 116.4, 116.9 (CH_2), 120.5, 123.4, 127.2, 127.3, 128.0, 128.2, 135.9, 141.0, 141.1, 144.9, 174.5 (CO) and 197 (CONH); *m/z* (EI) 393 (10%, M^+), 275 (35), 262 (40), 115 (80), 103 (30), 91 (100), 77 (60) and 65 (25); ν_{max}/cm^{-1} (film) 3383, 3190, 3055, 2987, 2932, 2305, 1698 (CO), 1661, 1614, 1599, 1486, 1438, 1385, 1265, 1157, 910, 896, 739 and 704.

4.4.2. 3,3-Bis[(2-(4-methoxyphenyl)prop-2-en-1-yl]-quinoline-2,4(1*H*,3*H*)-dione-methane(1:1) (9b).



Column chromatography eluting with 7:3 v/v petroleum ether–EtOAc afforded the product (41%) as colourless needles, mp 139–141 °C. (Found: C, 76.5; H, 5.90; N, 3.1; $C_{29}H_{27}NO_4$ requires C, 76.8; H, 6.00; N, 3.1%); δ_H (300 MHz, $CDCl_3$) 3.25 (2H, d, J=13.9 Hz, CH_2), 3.35 (2H, d, J=13.9 Hz, CH_2), 3.7 (6H, s, 2×OMe), 4.8, 4.95 (2×2H, 2×s, 2×C$=$$CH_2$), 6.6 (4H, d, J=8.6 Hz, ArH), 6.65 (1H, d, J=8.3 Hz, ArH), 6.9 (1H, t, J=7.5 Hz, ArH), 7.0 (4H, d, J=8.6 Hz, ArH), 7.35 (1H, d, J=7.5 Hz, ArH), 7.4 (1H, d, J=7.5 Hz, ArH), 8.75 (1H, s, CONH); δ_C (75 MHz, $CDCl_3$) 46.7 (CH_2), 55.6 (OMe), 61.3, 113.4, 115.7, 116.0, 120.5, 123.2, 127.3, 128.5, 133.5, 135.7, 140.8, 144.3, 159.5, 173.9 (CO) and 197 (CONH); *m/z* (ES) 454 (100%, M^++H); ν_{max}/cm^{-1} (film) 3278 (br, CONH), 3010, 2918, 2836, 1815, 1651 (CO), 1605, 1509, 1378, 1276, 1259, 1180, 1158, 1112, 1029, 949, 906, 837, 805, 764, 748, 696 and 545.

4.4.3. Dimethyl 4,4′-[(2,4-dioxo-1,2,3,4-tetrahydroquinoline-3,3-diyl)diprop-1-ene-3,2-diyl]dibenzoate (9c).

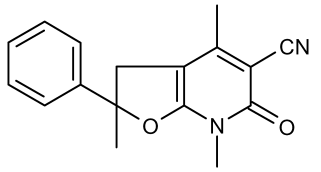


Column chromatography eluting with 7:3 v/v petroleum ether–EtOAc afforded the product (68%) as colourless plates, mp 168–170 °C. (HRMS: 527.2182 (M^++NH_4); $C_{31}H_{27}NO_6$ requires 527.2186 (M^++NH_4); δ_H (300 MHz, $CDCl_3$) 3.3 (2H, d, J=13.9 Hz, CH_2), 3.38 (2H, d, J=13.9 Hz, CH_2), 3.85 (6H, s, 2×CO_2Me), 4.95, 5.1 (2×2H, 2×s, 2×C$=$$CH_2$), 6.65 (1H, d, J=8.0 Hz, ArH), 6.85 (1H, t, J=7.5 Hz, ArH), 7.1 (4H, d, J=8.3 Hz, ArH), 7.25–7.4 (2H, m, ArH), 7.75 (4H, d, J=8.3 Hz, ArH), 9.25 (1H, s, CONH); δ_C (75 MHz, $CDCl_3$) 45.6 (CH_2), 52.5 (CO_2*Me*), 61.3, 116.3, 118.8, 120.3, 123.7, 127.1, 129.5, 129.6, 136.4, 140.8, 144.0, 145.7, 167.2, 173.8 (CO) and 197 (CONH); *m/z* (EI) 509 (7%, M^+), 333 (45), 320 (50), 174 (25), 115 (100), 102 (50), 91 (45), 77 (42) and 59 (42); ν_{max}/cm^{-1} (film) 3288 (br, CONH), 3181, 3082, 3005, 2956, 2912, 2851, 1930, 1830, 1717 (CO), 1690, 1608, 1495, 1437, 1396, 1279, 1198, 1109, 1013, 948, 913, 879, 676, 717 and 669.

4.5. General procedure for C-allylation–cyclisation of 6-hydroxy-1,4-dimethyl-1,2-dihydropyrid-2-one-3-carbonitrile (4)

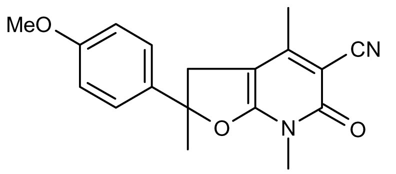
A mixture of aryl iodide (1.0 mmol, 1.0 equiv.), 6-hydroxy-1,4-dimethyl-1,2-dihydropyrid-2-one-3-carbonitrile **3** (1.1 mmol, 1.1 equiv.), tris(dibenzylideneacetone)dipalladium (23 mg, 2.5 mol%), tris(2-furyl)phosphine (23 mg, 10 mol%) and potassium carbonate (0.27 g, 2.0 mol equiv.) in DMF (GPR, 10 ml) was stirred for 15 min in a Schlenk tube. The mixture was then degassed, frozen, evacuated and charged with allene (1 bar). After warming to room temperature, it was heated at 80 °C in an oil bath for 16 h. Upon cooling to room temperature, excess allene was vented, the mixture diluted with ether (20 ml) and washed with dilute aq. trifluoroacetic acid solution. The organic layer was separated and the aqueous layer was further extracted with ether (2×20 ml). The combined organic layer was dried ($MgSO_4$), filtered and the filtrate concentrated under reduced pressure. The brown residue was dissolved in chloroform (10 ml) and trifluoroacetic acid was added dropwise to the stirred solution until pH was approximately 3. Stirring was continued for 3–4 h at room temperature. The reaction mixture was then diluted with chloroform (10 ml) and washed with water (2×10 ml). The organic layer was dried ($MgSO_4$), filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel.

4.5.1. 2,4,7-Trimethyl-6-oxo-2-phenyl-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-5-carbonitrile (16a).



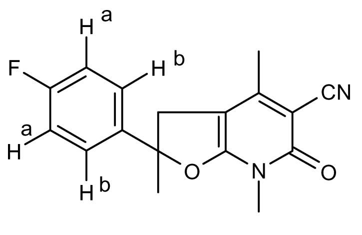
Column chromatography eluting with 9:1 v/v EtOAc–petroleum ether afforded the product (50%) as colourless rods, mp 143–145 °C. (Found: C, 72.6; H, 5.70; N, 10.1; $C_{17}H_{16}N_2O_2$ requires C, 72.8; H, 5.75; N, 10.0%); δ_H (300 MHz, $CDCl_3$) 1.9, 2.3 (2×3H, 2×s, 2×Me), 3.3 (1H, d, J=14.1 Hz, CH_2), 3.35 (1H, d, J=14.1 Hz, CH_2), 3.55 (3H, s, Me), 7.3–7.45 (5H, m, ArH); δ_C (75 MHz, $CDCl_3$) 19.1 (Me), 29.6 (Me), 30.0 (Me), 42.2 (CH_2), 92.3, 95.9, 99.2, 124.3, 128.8, 129.3, 144.0, 155.6, 160.0, 161.2 and 177.1 (CO); m/z (ES) 303 (100%, M^++Na); ν_{max}/cm^{-1} (solid) 3065, 3035, 2989, 2943, 2879, 2206 (CN), 1654 (CO), 1561, 1292, 1211, 1150, 1089, 1059, 1028, 939, 890, 822, 759, 719, 698, 672, 634 and 523.

4.5.2. 2-(4-Methoxyphenyl)-2,4,7-trimethyl-6-oxo-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-5-carbonitrile (16b).



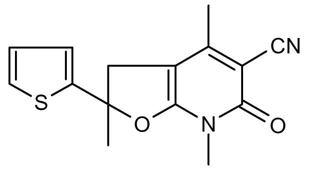
Column chromatography eluting with 4:1 v/v EtOAc–petroleum ether afforded the product (55%) as colourless plates, mp 142–144 °C. (Found: C, 69.5; H, 5.90; N, 9.0; $C_{18}H_{18}N_2O_3$ requires C, 69.6; H, 5.85; N, 9.0%); δ_H (300 MHz, $CDCl_3$) 1.85, 2.3 (2×3H, 2×s, 2×Me), 3.25 (1H, d, J=14.1 Hz, CH_2), 3.35 (1H, d, J=14.1 Hz, CH_2), 3.5, 3.8 (2×3H, 2×s, 2×Me), 6.9 (2H, d, J=9.0 Hz, ArH), 7.3 (2H, d, J=9.0 Hz, ArH); δ_C (75 MHz, $CDCl_3$) 19.1 (Me), 29.5 (Me), 29.7 (Me), 42.1 (CH_2), 55.8 (OMe), 92.0, 96.0, 99.4, 114.5, 117.2, 125.9, 135.8, 155.5, 159.9, 160.1 and 161.2 (CO); m/z (ES) 333 (100%, M^++Na); ν_{max}/cm^{-1} (solid) 3104, 2988, 2210 (CN), 1774 (CO), 1624, 1414, 1276, 1261, 1172, 910, 833, 764, 751, 721 and 638.

4.5.3. 2-(4-Fluorophenyl)-2,4,7-trimethyl-6-oxo-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-5-carbonitrile (16c).



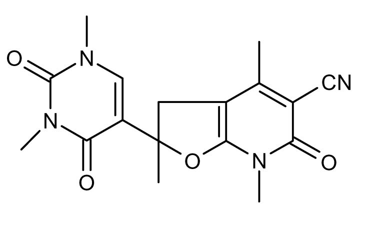
Column chromatography eluting with 4:1 v/v EtOAc–petroleum ether afforded the product (45%) as colourless needles, mp 154–156 °C. (Found: C, 68.1; H, 5.10; N, 9.3; $C_{17}H_{15}N_2O_2F$ requires C, 68.4; H, 5.05; N, 9.4%); δ_H (300 MHz, $CDCl_3$) 1.9, 2.3 (2×3H, 2×s, 2×Me), 3.3, (1H, d, J=14.1 Hz, CH_2), 3.35 (1H, d, J=14.1 Hz, CH_2), 3.5 (3H, s, Me), 7.1 (2H, t, J=8.8 Hz, ArH^a) ($JH^a-H^b \approx JH^a-{}^{19}F$), 7.35 (2H, dd, J=8.8, 5.1 Hz, ArH^b, H^b couples with H^a and F); δ_C (75 MHz, $CDCl_3$) 19.1 (Me), 29.6 (Me), 30.0 (Me), 42.3 (CH_2), 92.4, 95.4, 98.9, 116.1, 116.4, 117.1, 126.3, 126.5, 139.8, 155.7, 159.8, 161.1 and 164.5 (CO); m/z (ES) 321 (100%, M^++Na); ν_{max}/cm^{-1} (solid) 2943, 2205 (CN), 1661 (CO), 1567, 1511, 1420, 1291, 1230, 1164, 1068, 1028, 891, 834, 760, 717, 646 and 520.

4.5.4. 2,4,7-Trimethyl-6-oxo-2-thien-2-yl-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-5-carbonitrile (16d).



Column chromatography eluting with 4:1 v/v EtOAc–petroleum ether afforded the product (55%) as colourless needles, mp 129–131 °C. (HRMS: 309.3415 (M^++Na); $C_{15}H_{14}N_2O_2S$ requires 309.3400 (M^++Na); δ_H (300 MHz, $CDCl_3$) 2.0, 2.3 (2×3H, 2×s, 2×Me), 3.3, (1H, d, J=14.3 Hz, CH_2), 3.45 (3H, s, Me), 3.5 (1H, d, J=14.3 Hz, CH_2), 7.0 (1H, dd, J=5.0, 4.0 Hz, ArH), 7.05 (1H, m, ArH), 7.35 (1H, d, J=4.0 Hz, ArH); δ_C (75 MHz, $CDCl_3$) 19.1 (Me), 29.5 (Me), 29.6 (Me), 42.5 (CH_2), 92.4, 93.5, 99.0, 117.1, 124.9, 126.5, 127.6, 146.7, 155.5, 159.6 and 161.1 (CO); m/z (ES) 309 (100%, M^++Na); ν_{max}/cm^{-1} (solid) 3100, 2984, 2260 (CN), 1656 (CO), 1555, 1469, 1287, 1207, 1128, 1028, 885, 757, 700 and 657.

4.5.5. 2-(1,3-Dimethyl-2,4-dioxo-1,2,3-tetrahydropyrimidin-5-yl)-2,4,7-trimethyl-6-oxo-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-5-carbonitrile (16e).



Column chromatography eluting with 4:1 v/v Et_2O–MeOH afforded the product (52%) as colourless plates, mp 180 °C (dec.). (Found: C, 59.3; H, 5.35; N, 16.1; $C_{17}H_{18}N_4O_4$ requires C, 59.6; H, 5.30; N, 16.3%); δ_H (300 MHz, $CDCl_3$) 1.85, 2.25 (2×3H, 2×s, 2×Me), 3.2, (1H, d, J=14.7 Hz, CH_2), 3.35 (1H, d, J=14.7 Hz, CH_2), 3.35, 3.45, 3.5 (3×3H, 3×s, 3×Me), 7.35 (1H, s, vinyl H); δ_C (75 MHz, $CDCl_3$) 19.0 (Me), 27.4 (Me), 28.3 (Me), 29.7 (Me), 37.9 (Me), 40.2 (CH_2), 91.7, 93.0, 100.4, 114.5, 117.3, 140.0, 151.7, 155.7, 159.5 (CO), 161.1 (CO) and 161.7 (CO); m/z (ES) 365 (100%, M^++Na); ν_{max}/cm^{-1} (solid) 2951, 2211 (CN), 1711 (CO), 1655, 1566, 1452, 1368, 1344, 1273, 1211, 1079, 1022, 764, 754 and 519.

Acknowledgements

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Tetrahedron

Synthesis and properties of *p*-benzoquinone-fused hexadehydro[18]annulenes

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Abstract—A series of hexadehydro[18]annulenes fused with different numbers of *p*-benzoquinone, **4**-**6**, were synthesized by stepwise transformation of the *p*-dimethoxybenzene moiety of the precursor dehydroannulene **3** fused with three 3,6-dimethoxy-4,5-dimethylbenzene units at 1,2-positions into *p*-benzoquinone using ceric ammonium nitrate. The UV–vis spectra of compounds **4** and **5**, which have both electron-donating *p*-dimethoxybenzene unit(s) and electron-accepting *p*-benzoquinone unit(s) in the π-systems, showed the maximum absorption bands bathochromically shifted in comparison with **3** having only *p*-dimethoxybenzene units and 6 having only *p*-benzoquinone units. However, the solvatochromism expected for **4** and **5** was found to be quite weak possibly because the HOMO and LUMO (B3LYP/6-31G(d)) are not localized but rather delocalized over the whole π-systems.

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1. Introduction

There is considerable interest in macrocyclic dehydroannulenes[1] from various viewpoints. For example, the cyclic π-systems containing triple bonds have been shown to be useful precursors for a variety of carbon rich polymeric compounds.[1a,2] Possible application of the macrocycles toward photonic devices has also been studied owing to the unique optical properties of π-conjugated systems.[3,4] In addition, fundamental physical properties such as tropicity of the macrocyclic rings[5] have also been the subject of continued discussion in the dehydroannulene chemistry. In the previous studies, we synthesized a series of dehydroannulenes fused with electron-donating systems such as bicyclo[2.2.2]octene[6] and 1,4-dimethoxynaphthalene (at 2,3-positions),[7] as well as electron-withdrawing system such as tetrafluorobenzene.[8] The electronic effects of these subunits have been shown to significantly affect the properties of the macrocycles as exemplified by the formation of stable complex with Ag(I) ion at the central cavity of tetradehydro[16]annulene when fused with the electron-donating bicyclo[2.2.2]octene systems[6b] and by reduction of the solid-state reactivity of highly strained tetradehydro[12]annulene when fused with electron-withdrawing perfluorobenzene.[8]

As a good π-electron acceptor, *p*-benzoquinone is known to have characteristic electronic properties, and the fusion of such an electron-accepting group to the highly conjugated dehydroannulenes is of interest, since such compounds would constitute a new type of push–pull π-systems when electron-donating moieties are introduced on other site(s) of the macrocyle. In 1993, Youngs and co-workers reported the transformation of *p*-dimethoxybenezene units fused to tridehydro[12]annulene into *p*-benzoquinone using ceric ammonium nitrate (CAN), and they found that only one of three *p*-dimethoxybenezene units in the precursor tridehydro[12]annulene **1** can be transformed into *p*-benzoquinone to give π-conjugated system **2**.[9] However, although the synthesis and NMR, IR, and MS spectral data of **2** were reported, no discussion has been made as to the structural and electronic properties of **2** and/or related compounds. In the present paper, we report the synthesis of hexadehydro[18]annulene fused with 3,6-dimethoxy-4,5-dimethylbenzene units at 1,2-positions **3** and its stepwise transformation into *p*-benzoquinone-fused dehydroannulenes **4**-**6**. Also their electronic properties investigated by means of ^{1}H NMR, electronic spectra, and cyclic voltammetry will be described together with the results of theoretical calculations.

2. Results and discussion

2.1. Synthesis of hexadehydro[18]annulenes 3-6

For the synthesis of dehydroannulene **3** fused with three 3,6-dimethoxy-4,5-dimethylbenzene units at 1,2-positions, which is the precursor of a series of *p*-benzoquinone-fused dehydroannulene **4-6**, the simple copper-mediated coupling

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Keywords: Dehydroannulenes; Benzoquinones; Absorption spectra; Redox potential; DFT calculation.

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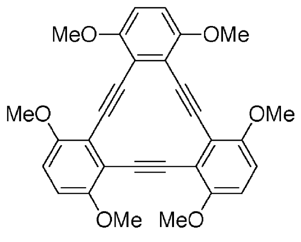

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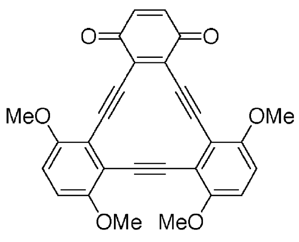

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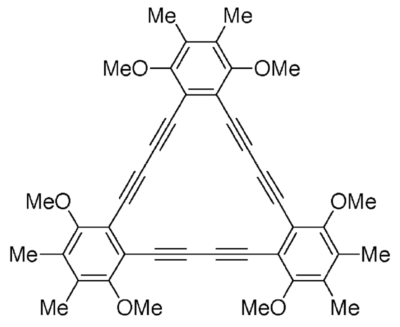

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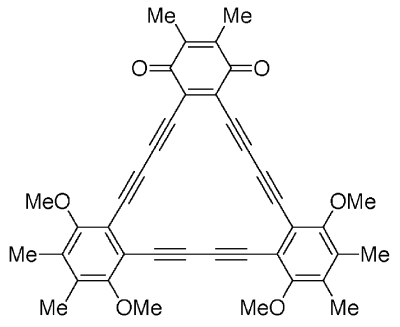

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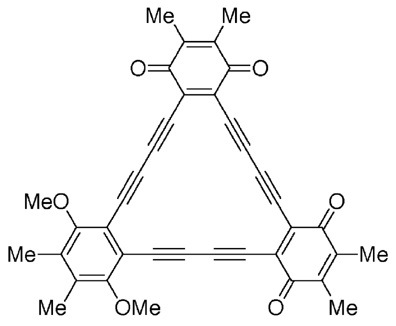

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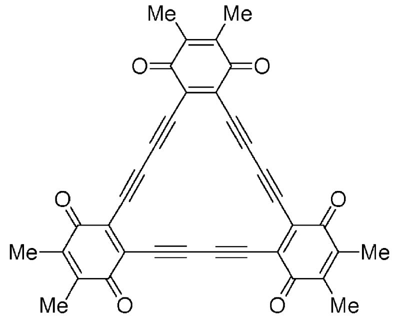

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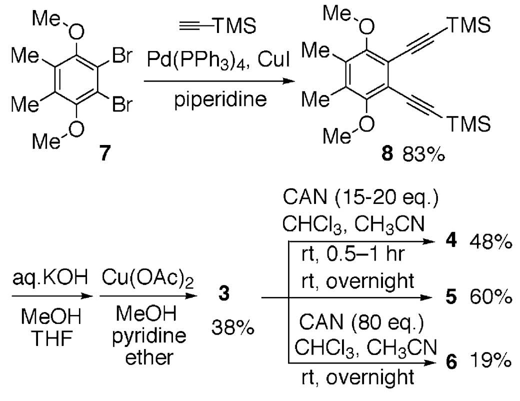
of the corresponding 1,2-diethynylarene was employed. As shown in Scheme 1, the Pd-catalyzed Sonogashira cross-coupling reaction between 1,2-dibromo-3,6-dimethoxy-4,5-dimethylbenzene (**7**)[10] and trimethylsilylacetylene afforded 1,2-bis(trimethylsilylethynyl)-3,6-dimethoxy-4,5-dimethylbenzene (**8**) in 83% yield. After desilylation, the cyclization reaction by the copper-mediated oxidative coupling under Eglinton's condition[11] gave dehydro[18]annulene **3** as yellow solid in 38% yield together with hardly soluble byproducts, which are possibly the higher oligomers.



Scheme 1.

Transformation of the *p*-dimethoxybenzene unit(s) into *p*-benzoquinone unit(s) was conducted by the use of CAN. The reaction was found to proceed stepwise. Thus, when the reaction of **3** was conducted with 15–20 equiv. of CAN in a mixed solvent of $CHCl_3$ and CH_3CN (1:1 by volume) at room temperature for 0.5–1 h, monoquinone **4** was obtained as a main product in 48% yield, while bisquinone **5** was obtained in 60% yield after stirring overnight. For the synthesis of trisquinone **6**, a larger amount, that is, 80 equiv. of CAN was used to complete the reaction by stirring for 24 h at room temperature. For separation of the crude products of annulenes **4-6**, chromatography using either silica gel or alumina was not suitable because of decomposition of the annulenes, and the only applicable method was reprecipitation using chloroform–hexane resulting in rather modest isolated yield (19%) of **6**. All of **4-6** were obtained as red powders.

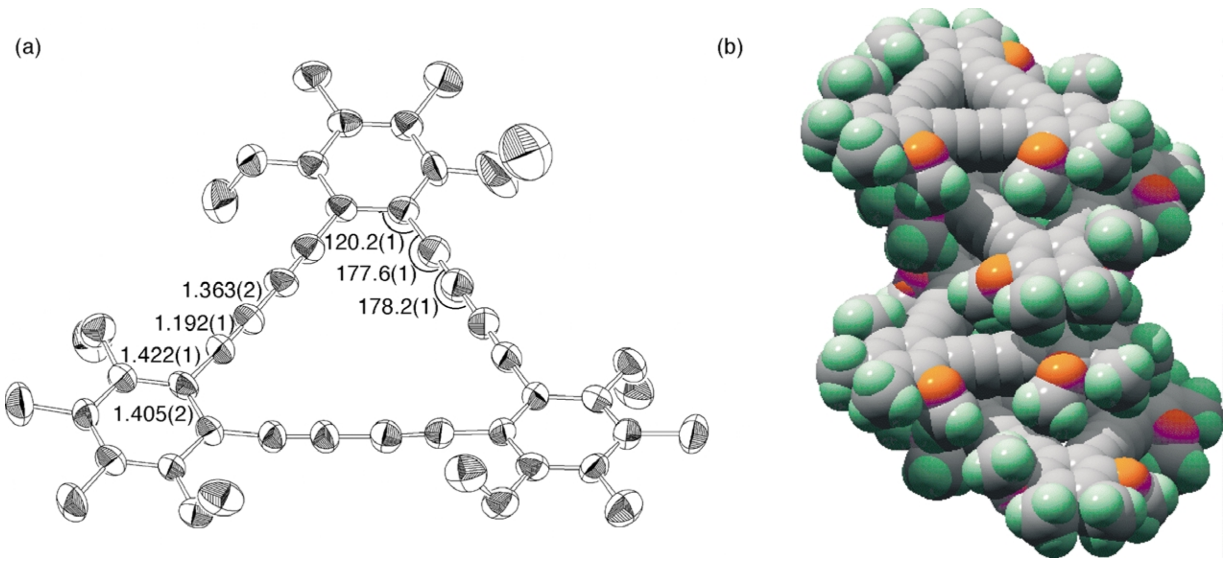


Figure 1. (a) ORTEP drawing (50% probability) showing the X-ray structure of **3** and (b) its crystal packing in a space-filling diagram. The averaged bond lengths (in Å) and angles (in degree) in the [18]annulene core are given with esd's calculated by the following equation; $\sigma(l)=(\sum(1/\sigma_i^2))^{-1/2}$.

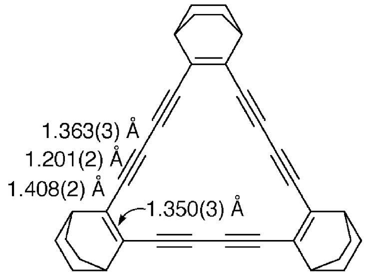


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Figure 2. Structure of **9**. The averaged bond lengths in the [18]annulene core are given with esd's calculated by the following equation; $\sigma(l)=(\sum(1/\sigma_i^2))^{-1/2}$.

2.2. Structures and diatropicity of hexadehydro[18]-annulenes 3-6

Among the newly synthesized four hexadehydro[18]-annulenes **3**-**6**, a single crystal suitable for X-ray structural analysis was obtained only for **3**, and the result is shown in Figure 1. As expected from the structures reported for analogous benzodehydro[18]annulenes,[3] the central 18-membered ring in **3** is essentially planar and the bending of butadiyne moiety is quite small since the averaged angle of C(sp^2)–C(sp^2)–C(sp) (120.2°) is nearly ideal for the formation of the [18]annulene hexagon. In the packing structure (Fig. 1(b)), the nearest intermolecular contact was observed between a hydrogen atom of one of the methoxy groups and an sp carbon (the distance between C(MeO) and C(sp), 3.26 Å) rather than between the sp carbons of the central annulene rings (3.61 Å). Thus, no π stacking structure was observed. Rather, the CH/π interaction between the methoxyl protons and the butadiyne π-system in the central ring is likely to operate in the solid state.

The crystal structure with no π stacking mode of **3** suggests less reactivity and enhanced thermal stability of the hexadehydro[18]annulene π-system in **3** in the solid state. In this respect, for example, unsubstituted hexadehydro[18]annulene turns black at 75 °C and explodes at 85 °C,[12] and the corresponding tribenzo-[13] and tris(tetrafluorobenzo)-[8] derivatives start to decompose at 210 and 193 °C, respectively. A series of other benzodehydro[18]-annulenes with various substituents also undergo exothermic polymerization at the temperature range of 164–240 °C.[3] Among the benzodehydro[18]annulenes so far reported, **3** was found to be most stable against heating: it only turned black at 272 °C. On the other hand, the thermal decomposition took place for **4**-**6** (**4**; 237 °C, **5**; 220 °C, **6**; 208 °C) at the similar decomposing temperatures observed in the other benzodehydro[18]annulenes.

As concerns the bond-length alternation in the [18]annulene

Table 1. Calculated bond lengths (Å)[a] of the [18]annulene core and NICS(1) values (ppm)[b] for **3**-**6**

Compound	Bond length				NICS(1)		
	C(sp^2)–C(sp^2)	C(sp^2)–C(sp)	C(sp)≡C(sp)	C(sp)–C(sp)	[18]Annulene	Benzene	Quinone
3	1.425	1.414	1.223	1.356	0.43	−11.4	—
4	1.384, 1.426	1.401, 1.411, 1.413	1.223, 1.224, 1.225	1.351, 1.355	−0.1	−11.5	0.5
5	1.387, 1.429	1.398, 1.398, 1.408	1.227, 1.227, 1.226	1.346, 1.348	−1.0	−12.0	0.5
6	1.387	1.398	1.227	1.346	−2.6	—	1.0

[a] B3LYP/6-31G(d).

[b] GIAO/HF/6-31+G(d)//B3LYP/6-31G(d).

core, which is one of the indicators for aromaticity, the averaged length (1.422(1) Å) of C(sp^2)–C(sp) single bonds in **3** is slightly longer than that (1.408(2) Å) in the [18]annulene **9** fused with bicyclo[2.2.2]octene units[6a] (Fig. 2), while the C(sp)≡C(sp) triple bond (1.192(1) Å) in **3** is shorter than that (1.201(2) Å) in **9**. Thus, the bond alternation in **3** is larger than that in **9** and, hence, the aromaticity of **3** is considered to be lower than that of **9**. The presence of diamagnetic ring current in **9** has already been proven based on an upfield shift of the bridgehead protons of the bicyclic framework (*δ* 3.41) in comparison with that (*δ* 2.72) of 2,3-diethynylbicyclo[2.2.2]octene.[6a] Apparently, the local ring current in the fused benzene rings of **3** reduces the aromaticity of the central 18-membered ring.

From the same reason, the bond alternation in the [18]annulene core of benzoquinone-fused systems **4-6** is expected to become smaller with the increase in the number of the quinone unit because the aromatic character of the [18]annulene should be enhanced when the dimethoxybenzene units are transformed into non-aromatic benzoquinone units. This supposition is supported by the comparison of the optimized structures for **3-6** at the B3LYP/6-31G(d) level. As shown in Table 1, the C(sp)≡C(sp) triple bond becomes very slightly longer and C(sp^2)–C(sp) and C(sp)–C(sp) single bonds become shorter as the number of the fused-quinone ring increases. The aromaticity for the quinone-fused [18]annulene core is also experimentally supported by the gradual downfield shift of the ^{1}H NMR signals for methoxy and methyl groups in **3**, **4**, **5**, and **6** as shown in Figure 3, reflecting the increasing diamagnetic ring current in this order. In accord with this, the NICS values[14] (HF/6-31+G(d)//B3LYP/6-31G(d)) calculated for a dummy atom at 1 Å above the center of the ring (NICS(1)) in the central core of the [18]annulenes indicate that the diamagnetic ring current become larger, albeit in a minute degree, with increasing number of the quinone units in **4-6**, as shown in Table 1.

The successful transformation of all the three *p*-dimethoxybenzene units in **3** into *p*-benzoquinone units in **6**, albeit in a rather modest yield, may be attributed to the enhanced aromaticity in the dehydro[18]annulene system. This result is in contrast to the case of dehydro[12]annulene **1**, in which only one *p*-dimethoxybenzene unit could be transformed into *p*-benzoquinone[9] possibly due to the antiaromaticity resulting in the dehydro[12]annulene system fused with larger numbers of *p*-benzoquinone units.

2.3. Electronic properties of hexadehydro[18]annulenes 3-6

To compare the electronic properties of **3-6**, UV–vis spectral measurements and cyclic voltammetry (CV) were carried out. As shown in Figure 4, the longest-wavelength absorptions of **4** and **5** showed bathochromic shift in comparison with **3** and **6**, suggesting that the HOMO-LUMO gaps of **4** and **5** are reduced due to the presence of both electron-donating *p*-dimethoxybenzene unit(s) and electron-withdrawing *p*-benzoquinone unit(s) in the same π-conjugated system. On the other hand, the cyclic voltammetry of **4-6** in benzonitrile showed multi-step reversible reduction waves at −0.69 and −1.21 V vs Fc/

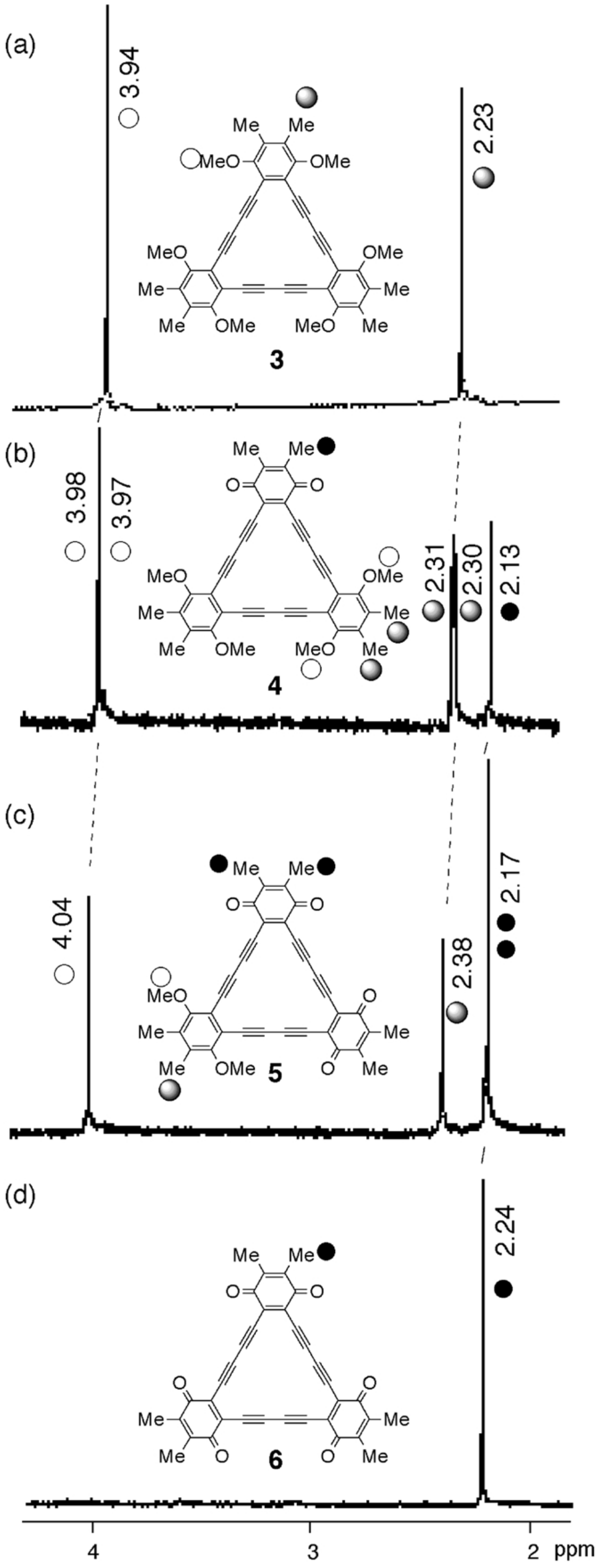

Figure 3. ^{1}H NMR spectra of **3**, **4**, **5**, and **6** in $CDCl_3$.

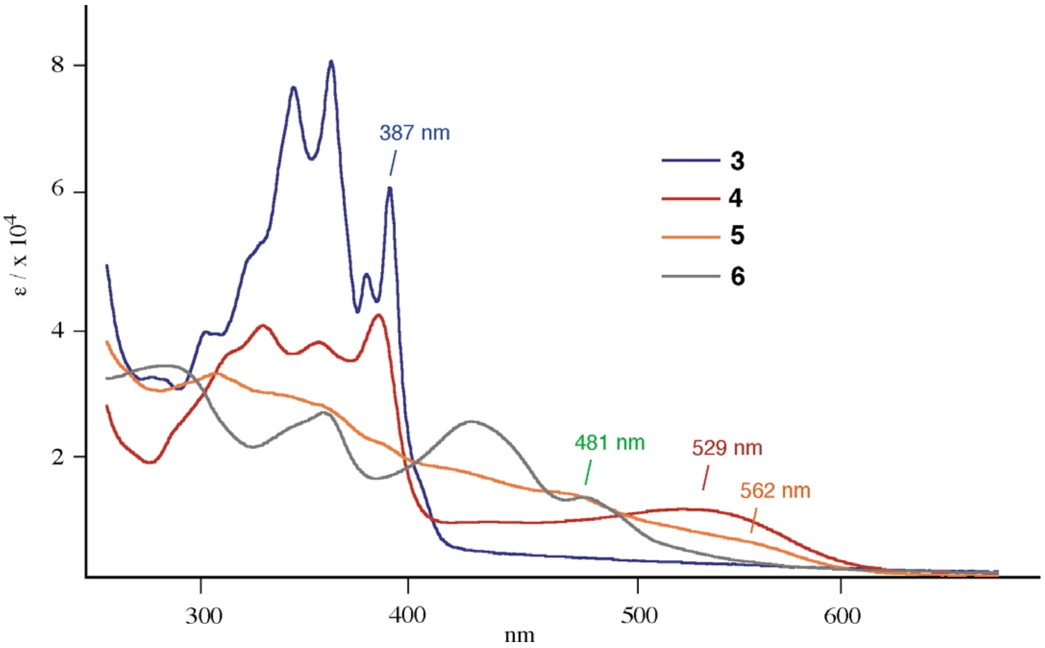

Figure 4. UV–vis spectra of **3**, **4**, **5**, and **6** in $CHCl_3$.

Fc^+ for **4**, −0.60, −0.82, and −1.41 V for **5**, and −0.58, −0.75, −0.97, and −1.50 V for **6**. Each wave corresponded to the transfer of one electron and no further reduction wave was observed for these compounds in the potential range lower than −2.0 V. In contrast, no redox wave was observed in a range from +1.2 to −2.2 V for **3**. Thus, the LUMO levels of **4-6** are shown to be significantly lowered as compared with **3** due to the presence of *p*-benzoquinone unit(s). The negative charge generated upon one-electron reduction is considered not to localize on the *p*-benzoquinone moiety but to delocalize over the whole π-system since the one-electron reduction was found to take place stepwise reflecting the effective electronic interaction between the multiple *p*-benzoquinone units in **5** and **6**. Thus, no more than three electrons are accommodated in **5** and no more than four electrons in **6** under the present experimental conditions.

These experimental observations are in qualitative agreement with the results of DFT calculations (B3LYP/6-31G(d)). As shown in Table 2, the calculated HOMO-LUMO gaps for **4** and **5** are smaller than those of **3** and **6**, causing the bathochromic shifts in **4** and **5** in comparison with **3** and **6**. Also the calculated LUMO level is lowered as the number of quinone unit increases, which is consistent with the gradual lowering of the first reduction potential with increasing number of the quinone unit.

Table 2. The longest-wavelength UV–vis absorptions, first reduction potentials, and Kohn-Sham (KS) HOMO and LUMO levels of **3-6** calculated at B3LYP/6-31G(d)

Compound	λ_{max}[a] (nm)	$E_{1/2}$[b] (V)	HOMO (eV)	LUMO (eV)	Δ[c] (eV)
3	387	—[d]	−5.31	−1.90	3.41
4	529	−0.69	−5.53	−3.31	2.22
5	562	−0.60	−5.82	−3.68	2.14
6	481	−0.58	−6.41	−3.93	2.48

[a] Measured in $CHCl_3$.
[b] Measured in benzonitrile. Electrolyte; 0.1 M TBAP. V vs Fc/Fc^+.
[c] $\Delta = E_{LUMO} - E_{HOMO}$.
[d] No redox wave was observed at the range from +1.2 to −2.2 V.

In many π-conjugated systems containing both donor- and acceptor-substituents, the intramolecular charge-transfer (CT) interaction, which is recognized as an important factor for second-order nonlinear optical properties,[15] has been observed, and such interaction has been proven by observation of the solvatochromism. In the case of **4** and **5**, however, only a small extent of solvatochromism was

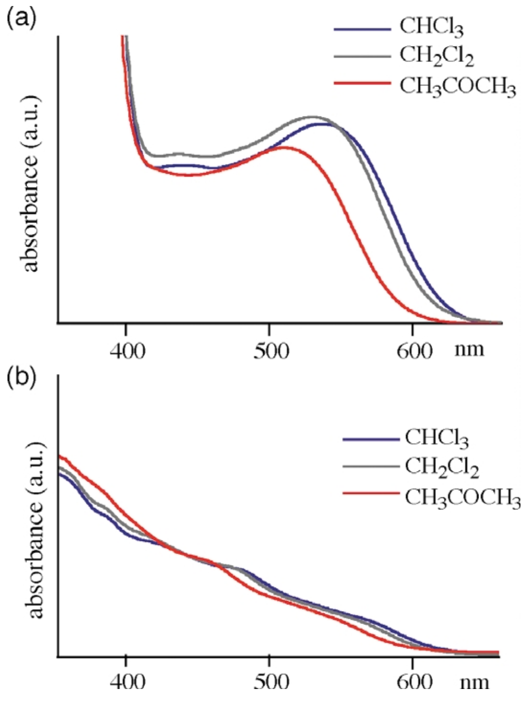

Figure 5. Solvent effects upon the longest-wavelength absorptions of (a) **4** and (b) **5**.

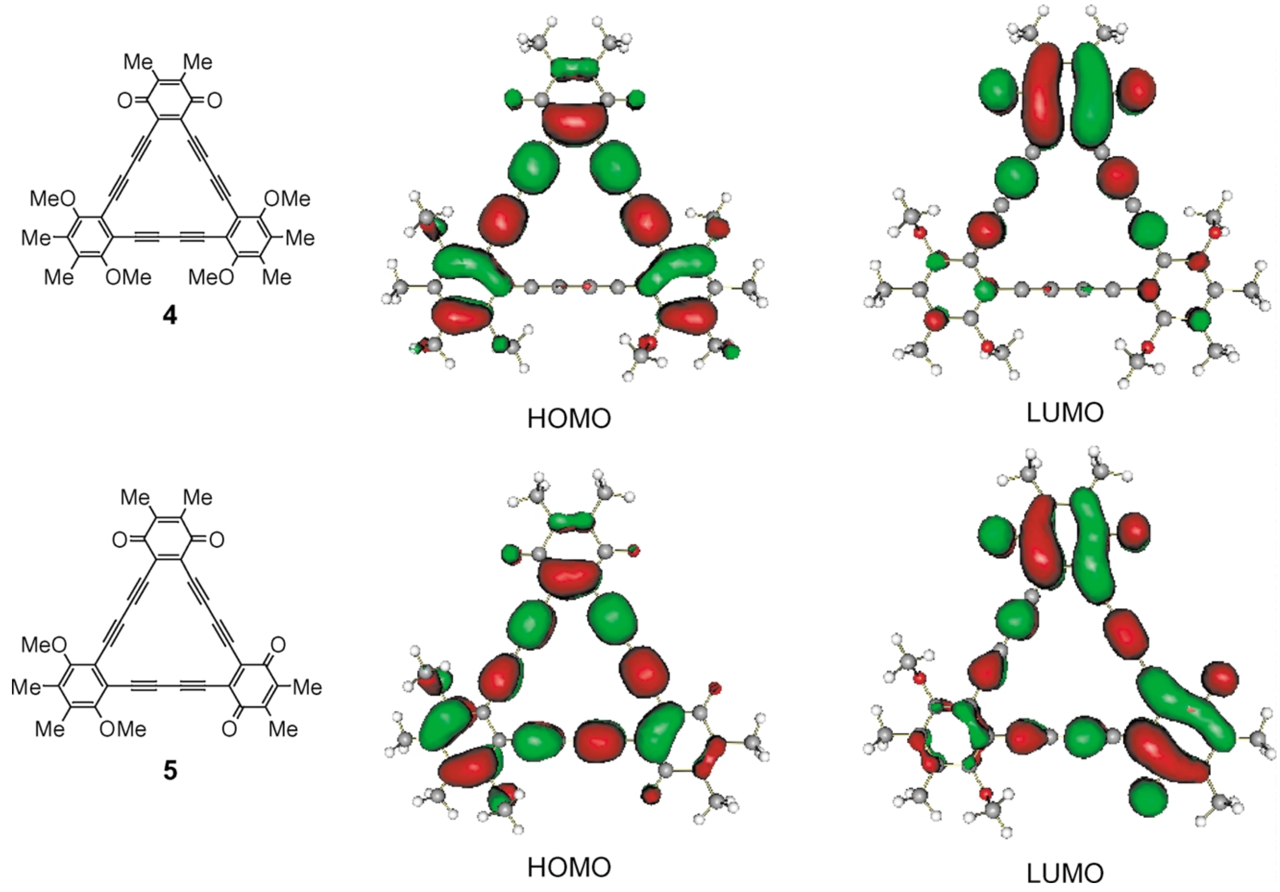

Figure 6. KS HOMOs and LUMOs of **4** and **5** calculated at the B3LYP/6-31G(d) level.

observed, although the examined solvents were quite limited due to the solubility problem (Fig. 5). This result may be rationalized as follows. According to ZINDO calculations, the longest absorption for **4** and **5** can be assigned to the HOMO→LUMO transition (**4**; 531 nm (coefficient 0.66, oscillator strength 0.254), **5**; 562 nm (coefficient 0.61, oscillator strength 0.089)). The HOMO and LUMO are not localized only on the electron donating or accepting moieties, that is, *p*-dimethoxybenzene or *p*-benzoquinone units, but rather delocalized extensively over the whole π-system as shown in Figure 6. Therefore, there would result only a small change in charge distribution, or polarity, upon the HOMO→LUMO transition in the dehydro[18]annulene molecules of **4** and **5**, and hence the extent of solvatochromic shifts becomes small.

3. Conclusion

A series of hexadehydro[18]annulenes **4-6** fused with one, two, and three *p*-benzoquinone unit(s) were synthesized by the stepwise oxidation of *p*-dimethoxybenzene units of tris(3,6-dimethoxy-1,2-benzo)-dehydro[18]annulene **3**. In these annulenes, the diatropicity of the central 18-membered ring was shown to gradually increase with the increasing number of *p*-benzoquinone unit(s) due to the enhanced double bond character at the fused position(s). Although **4** and **5** have both the π-electron donating and accepting groups and can be regarded as novel push–pull type π-systems, the extent of intramolecular charge-transfer is very small, due to the delocalization of both HOMO and LUMO over the whole dehydro[18]annulene π-systems.

4. Experimental

4.1. General

Melting points were measured on a Yanaco MP-500D apparatus and are uncorrected. Elemental analyses were performed at the Microanalysis Division of Institute for Chemical Research, Kyoto University. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury-300 or a JEOL JNM-GX 400 spectrometer. The chemical shifts of NMR are expressed in ppm from TMS as determined with reference to the internal $CHCl_3$ and $CDCl_3$ (δ 7.26 in ^{1}H and δ 77.0 in ^{13}C NMR). UV–vis spectra were taken on a SHIMADZU UV-2100PC spectrometer. Mass spectra were taken on a JEOL JMS 700 spectrometer for EI method and on a Finigan TSQ7000 for APCI method. Preparative gel permeation chromatography (GPC) was performed with a JAI LC-908 chromatograph equipped with JAIGEL 1H and 2H columns.

Ether and THF were distilled from sodium benzophenone ketyl. Methanol was distilled from sodium methoxide. Piperidine, pyridine, chloroform, and acetonitrile were distilled over CaH_2. All other solvents and reagents were used as purchased. Theoretical calculations were performed using the Gaussian 98 program.[16]

4.1.1. 1,2-Bis(trimethylsilylethynyl)-3,6-dimethoxy-4,5-dimethylbenzene (8). To a degassed solution of 1,2-dibromo-3,6-dimethoxy-4,5-dimethylbenzene (**7**)[10] (671 mg, 2.07 mmol), $Pd(PPh_3)_4$ (106 mg, 0.092 mmol), and CuI (37 mg, 0.19 mmol) in dry piperidine (70 mL) was added trimethylsilylacetylene (1.0 mL, 0.70 g, 7.1 mmol), and the reaction mixture was stirred at 100 °C for 13 h under an Ar atmosphere in a sealed tube. After the reaction was quenched with water, the mixture was extracted with ether, and the ethereal solution washed with aqueous NaCl, and dried over $MgSO_4$. After the removal of the solvent and the volatile under reduced pressure, the product was purified by chromatography over silica gel (hexane–EtOAc (20:1)) to give **8** (615 mg, 1.72 mmol, 83%) as a colorless solid: mp 112.7–113.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.82 (s, 6H), 2.16 (s, 6H), 0.28 (s, 18H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.8, 132.4, 117.7, 102.1, 99.5, 60.4, 12.8, 0.0. Anal. Calcd for $C_{20}H_{30}O_2Si_2$: C, 66.98; H, 8.43%. Found: C, 66.70; H, 8.47%.

4.1.2. tris(3,6-Dimethoxy-4,5-dimethyl-1,2-benzo)hexadehydro[18]annulene (3). A solution of KOH (ca. 0.5 g) in distilled water (2 mL) was added in one portion to a solution of **8** (1.39 g, 3.86 mmol) in a mixed solvent of methanol (40 mL) and THF (9 mL). The reaction mixture was vigorously stirred at room temperature for 15 min, diluted quickly with water (10 mL), extracted with ether, and the ethereal solution dried over $MgSO_4$. The volatiles were removed in vacuo and the crude product was separated by flash chromatography over silica gel eluted with hexane–AcOEt (20:1) to give crude 1,2-diethynyl-3,6-dimethoxy-4,5-dimethylbenzene (0.791 g, 3,69 mmol, 95%) as a colorless solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.82 (s, 6H), 3.50 (s, 2H), 2.19 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 156.2, 133.1, 117.1, 84.4, 78.3, 60.8, 12.9. The crude diyne was used for the next step without further purification.

To a solution of $Cu(OAc)_2$ (1.38 g, 7.59 mmol) in a mixed solvent of pyridine (50 mL), methanol (50 mL), and ether (10 mL) was added a solution of 1,2-diethynyl-3,6-dimethoxy-4,5-dimethylbenzene (434 mg, 2.03 mmol) in a mixed solvent of pyridine (20 mL) and methanol (20 mL) over a period of 2 h. The mixture was stirred at 60 °C for 0.5 h and overnight at room temperature under air. The reaction was quenched by 30% aqueous H_2SO_4, and the aqueous layer was extracted with $CHCl_3$. The combined organic solution was washed with 50% aqueous H_2SO_4 and with aqueous $NaHCO_3$, and dried over $MgSO_4$. The organic solution was evaporated and the crude mixture was separated by preparative GPC to give crude **3** (163 mg, 0.256 mmol, 38%). The crude product was recrystallized from $CHCl_3$ to give single crystals of **3** suitable for X-ray analysis.

Compound **3**: mp >300 °C (the color turned to black at 272 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.94 (s, 18H), 2.23 (s, 18H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 156.8, 133.6, 117.2, 81.5, 77.7, 61.4, 13.1; IR (KBr) 2210 (C≡C) cm^{-1}. HRMS (EI) calcd for $C_{42}H_{36}O_6$ 636.2512, found 636.2514.

4.1.3. Transformation of 3 to *p*-benzoquinone-fused dehydro[18]annulenes 4-6. To a stirred solution of **3** (15 mg, 0.023 mmol) in a mixed solvent of CH_3CN (6 mL) and $CHCl_3$ (6 mL) was added dropwise a solution of ceric ammonium nitrate (CAN) (190 mg, 0.35 mmol) in distilled water (0.8 mL) over 5 min. After 25 min of stirring, the reaction was quenched by adding water (ca. 10 mL). The aqueous layer was extracted with $CHCl_3$. The combined organic solution was dried over $MgSO_4$ and evaporated to give a crude mixture containing the mono-benzoquinone derivative **4** as a major component. The mixture was dissolved in $CHCl_3$ (ca. 10 mL), and 10 mL of hexane was slowly diffused into the solution to give pure **4** (7.0 mg, 0.011 mmol, 48%) as a red powder.

Compound **4**: mp >300 °C (the color turned to black at 237 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 (s, 6H), 3.97 (s, 6H), 2.31 (s, 6H), 2.30 (s, 6H), 2.13 (s, 6H); IR (KBr) 2192, 2172, and 2129 (C≡C), 1656 (C=O) cm^{-1}. HRMS (FAB) calcd for $C_{40}H_{30}O_6$ 606.2042, found 606.2029. The poor solubility of **4** hampered the ^{13}C NMR measurement.

In the same way, the reaction of **3** (11 mg, 0.017 mmol) with CAN (200 mg, 0.36 mmol) was conducted by stirring at room temperature overnight. The reaction mixture was treated in exactly the same way as above. Reprecipitation with $CHCl_3$–hexane gave bis-benzoquinone derivative **5** (5.7 mg, 0.10 mmol, 60%) as a red powder.

Compound **5**: mp >300 °C (the color turned to black at 220 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.04 (s, 6H), 2.38 (s, 6H), 2.17 (s, 12H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 181.9, 181.7, 157.6, 142.7, 142.5, 135.6, 133.1, 130.8, 116.3, 94.2, 92.5, 91.1, 85.4, 82.5, 81.9, 78.1, 62.0, 13.5, 13.1; IR (KBr) 2189 (C≡C), 1650 and 1628 (C=O) cm^{-1}; MS (APCI) *m/z* 576 (M^+).

In the same way, the reaction of **3** (25 mg, 0.039 mmol) with CAN (1.86 g, 3.39 mmol) was conducted in a mixed solvent of CH_3CN (10 mL) and $CHCl_3$ (10 mL) at room temperature overnight. The post treatment as described above and the similar reprecipitation afforded tris-benzoquinone derivative **6** (4 mg, 0.007 mmol, 19%) as a red powder.

Compound **6**: mp >300 °C (the color turned to black at 208 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.24(s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 181.5, 143.2, 132.0, 92.5, 83.5, 13.2; IR (KBr) 2178 and 2126 (C≡C), 1655 (C=O) cm^{-1}; MS (APCI) *m/z* 546 (M^+).

4.2. Cyclic voltammetry

Cyclic voltammetry (CV) was performed on a BAS-50W electrochemical analyzer. The CV cell consisted of a glassy carbon working electrode, a Pt wire counter electrode, and a $Ag/AgNO_3$ reference electrode. The measurements were carried out for 1.0 mM solutions of each sample with tetrabutylammonium perchlorate as a supporting electrolyte (0.1 M) in benzonitrile, and the values for oxidation potentials were calibrated with ferrocene as an internal standard.

4.3. X-ray structural determination

Crystal data for **3**: $(C_{42}H_{36}O_6)\cdot CHCl_3$, FW=1392.79, triclinic; space group P-1; a=11.755(5) Å, b=17.474(7) Å, c=20.099(8) Å, α=66.685(9)°, β=84.648(11)°, γ=78.572(9)°, V=3716(3) Å^3, Z=4, D_{calc}=2.488 mg/m^3. Intensity data were collected at 123 K on a Bruker SMART APEX diffractometer with Mo K_α radiation (λ=0.71073 Å) and graphite monochromater. Frames corresponding to an arbitrary hemisphere of data were collected using ω scans of 0.3° counted for a total of 10 s per frame. A total of 21075 reflections were measured and 14161 were independent. The structure was solved by direct methods (SHELXTL) and refined by the full-matrix least-squares on F^2 (SHELXL-93). The presence of a disordered solvent molecule in the lattice was evident, and the SQUEEZE[17] data processed with the program implemented in PLATON-96[18] were used for the further refinement. All non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined isotropically and the refinement converged to R_1=0.0667, wR_2=0.1739 ($I>2\sigma(I)$), and GOF=0.948. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 229724. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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Tetrahedron

Synthesis of (thia)calix[4]arene oligomers: towards calixarene-based dendrimers

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Abstract—Thiacalix[4]arenes bearing two or four carboxylic functions on the lower rim served as starting compounds for the synthesis of novel calixarene oligomers connected by amidic functions. The cone conformers react smoothly with four molecules of 5-amino-calix[4]arene to yield the corresponding pentakis-calixarenes. On the other hand, because steric hindrance, the 1,3-alternate condenses only with two molecules leading thus to *tris*-calixarene, possessing a novel type of inherent chirality based on the 25,26-substitution pattern. The title compounds, which connect together 'classical' calixarene and thiacalixarene building blocks, represent a first step towards calixarene-based dendritic structures.

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1. Introduction

The overall shape of hyperbranched polymers or dendritic structures[1] can be controlled by using an appropriate multivalent core. The geometry of this core determines the direction of branching while the number of its functional groups controls the number of branches. The chemistry of calix[*n*]arenes and thiacalix[n]arenes offers us broad variations in the structural and geometrical features of calixarene derivatives, making the calixarenes ideal candidates for the core moieties of dendrimers. The shape of the core can be changed depending on the conformation used. Particularly, we can control the size (calix[4]arene, calix[6]arene, calix[8]arene), the multiplicity of functionality (e.g., number of hydroxyl groups could be from 4 to 8) and the conformation of molecules (Fig. 1).

Thiacalixarene[2] **1** has appeared recently as a novel member of the well-known calixarene[3] family. The presence of four sulfur atoms results in many novel features[4] compared with 'classical' calixarenes, such as different complexation ability with sulfur contribution, easy chemical modification (oxidation) of bridges, different size and different conformational behaviour of this novel macrocycle. Hence, thiacalix[4]arene exhibits a broad range of interesting functions, which make this compound a good candidate for many applications in supramolecular chemistry.

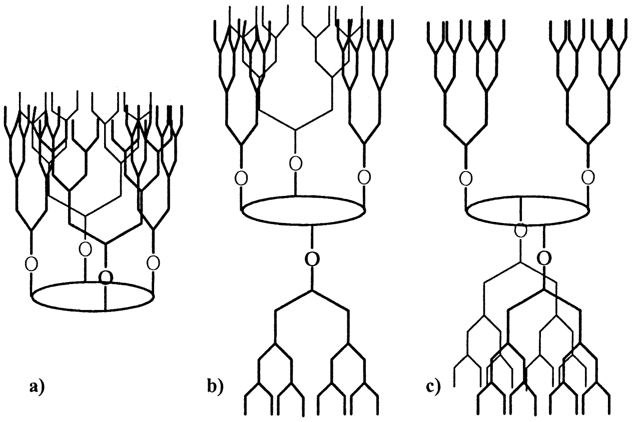

Figure 1. Dendritic structures based on the various calix[4]arene conformations (schematically): (a) *cone*, (b) *partial cone*, (c) *1,3-alternate*.

Tetraalkylation of the phenolic functions (lower rim) is a common procedure for the shaping of the thiacalixarene skeleton.[3] Recently, several groups[5] have studied the conformational preferences during the alkylation reaction of thiacalixarenes **1** and **2** with ethyl bromoacetate in acetone. It was found that thiacalixarenes exhibit a pronounced template effect, and the conformer distribution depends strictly on the reaction conditions used. Thus, using different bases M_2CO_3 (M=Na^+, K^+ and Cs^+), the reaction yields selectively the corresponding tetraacetates in various conformations (cone, partial cone, 1,3-alternate). As the products are readily isolable in multi-gram amounts without chromatographic purification, the tetraacetates represent suitable building blocks for the construction of more sophisticated molecules.

Keywords: Calixarenes; Dendrimers; Conformational analysis.

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In this paper we report on the first example of systems combining both types of building blocks (classical calix[4]-arenes and thiacalix[4]arenes) within one molecule. These oligocalixarenes are preorganised in defined conformations and could be potentially used as the core molecules for the construction of various dendritic[6] structures.

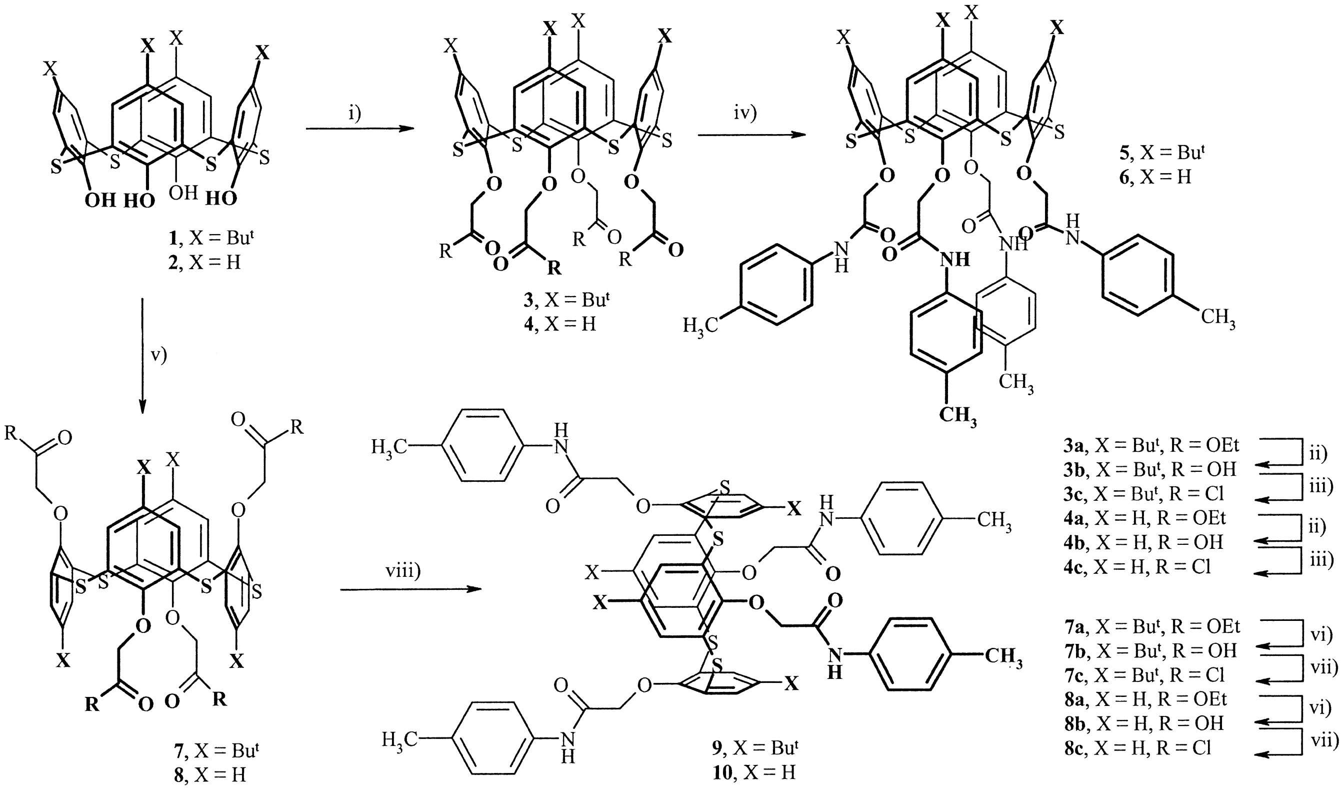
2. Results and discussion

2.1. Synthesis of conjugates

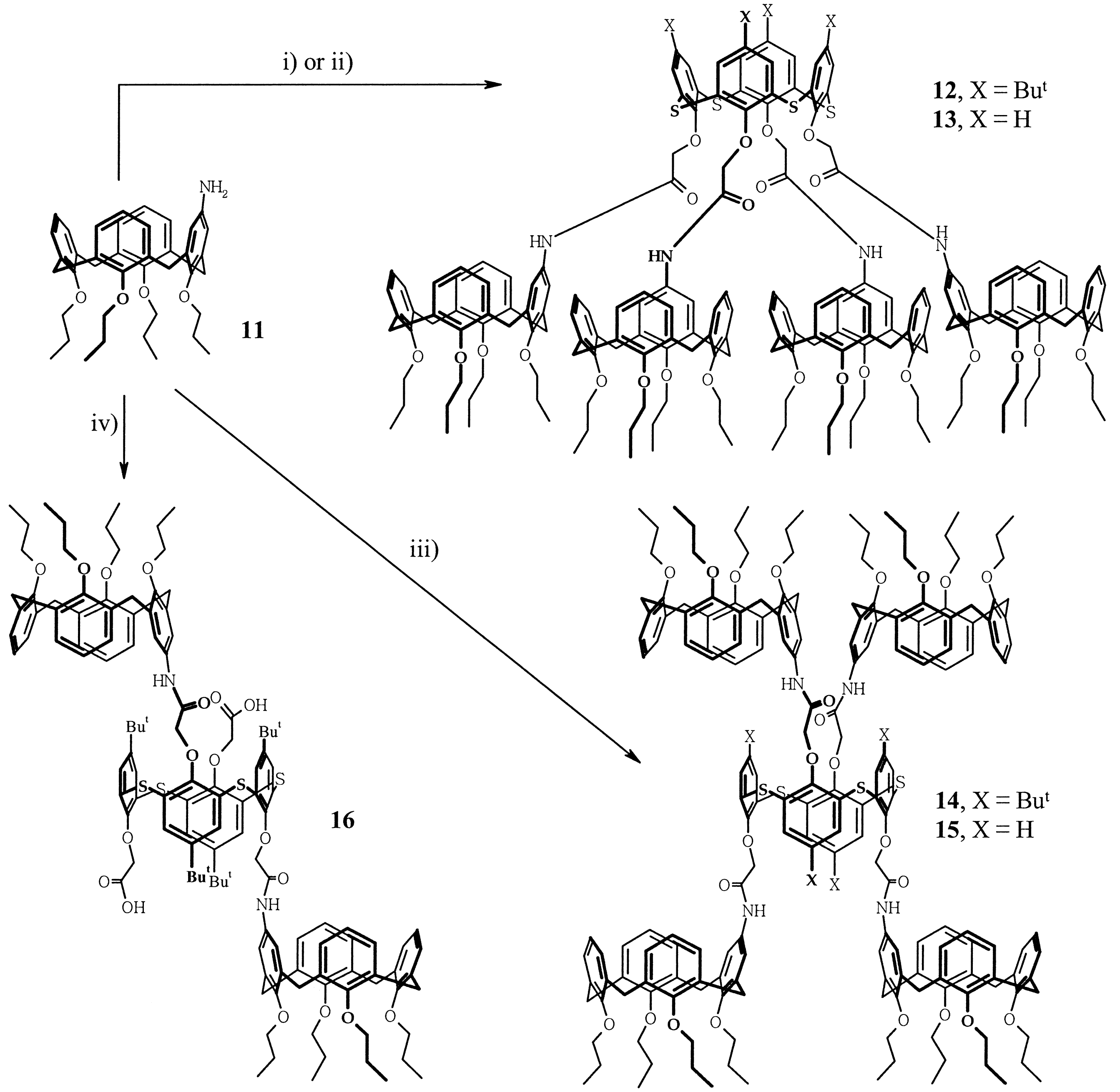
The synthesis started from parent thiacalixarenes **1** and **2**, which were transformed into the corresponding tetraacetates by alkylation with ethyl bromoacetate in refluxing acetone using Na_2CO_3 (**3a**, 75%; **4a**, 55% yield) or Cs_2CO_3 (**7a**, 68%; **8a**, 48% yield) as a base. These esters were hydrolysed with NaOH in aqueous ethanol under reflux to yield tetracarboxylic acids **3b**, **4b**, **7b**, and **8b** in quantitative yields. Before coupling with the corresponding amino-calix[4]arene, we tested the general applicability of the synthetic methods in the thiacalixarene series using a model aromatic amine (4-aminotoluene). Two methods were selected for the screening: (i) a direct reaction of carboxylic acids with 4-aminotoluene using dicyclohexylcarbodiimide as a coupling agent, and (ii) reaction of the corresponding acyl chlorides with 4-aminotoluene (Scheme 1).

The reactions with DCC/4-aminotoluene were carried out in dichloromethane solution. The coupling accomplished with 5 equiv. of DCC led to a complicated mixture of several products corresponding to the incomplete reaction (mixture of mono- to tetra-amides). Surprisingly, using an excess of DCC (10, 20, and 40 equiv.) did not significantly improve the outcome. The plausible explanation could be based on steric reasons: the DCC is too bulky for the activation of all four carboxylic functions at the same time. Hence, we focused on the second method. The preparation of acid chlorides was accomplished by stirring the starting acids with an excess of oxalyl chloride in CCl_4 under reflux. The crude acid chlorides **3c**, **4c**, **7c**, and **8c** were obtained in almost quantitative yield and used without purification in the next step due to their presumed instability. Subsequent condensation with 4-aminotoluene (5 equiv., dichloromethane or THF, rt) in the presence of Et_3N gave the corresponding tetraamides both in the *cone* **5** (88%), **6** (41%), and in the *1,3-alternate* **9** (71%), and **10** (20%) conformations (Scheme 1).

Similar reaction conditions were applied for the synthesis of oligocalixarenes combining within the molecule both common building blocks: 'classical' calixarene and thiacalixarene. Thus, monoamino derivative **11** immobilised in the *cone* conformation, reacted smoothly with central *cone* acid tetrachloride moieties **3c** and **4c** to give the corresponding pentakis-calixarenes **12** and **13** in 25 and 52% yields, respectively. On the other hand, the reaction of chlorides **7c** and **8c** revealed that steric hindrance of the central *1,3-alternate* unit plays a key role in the condensation. While the corresponding pentakis-calixarene **15** was obtained in 11% yield after preparative TLC of a very complicated reaction mixture, the similar product **14** bearing *tert*-butyl groups on the upper rim of the *1,3-alternate* core was not isolated at all. Instead, *tris*-calixarene **16** was obtained in 21% yield



Scheme 1. (i) $BrCH_2COOEt/Na_2CO_3$, acetone, reflux (**3a**, 75%; **4a**, 55%); (ii) NaOH, EtOH/water, reflux (**3b**, 99%; **4b**, 99%); (iii) oxalyl chloride/CCl_4, reflux (**3c**, **4c**, quant.); (iv) 4-aminotoluene/Et_3N/CH_2Cl_2, rt (**5**, 88%; **6**, 41%); (v) $BrCH_2COOEt/Cs_2CO_3$, acetone, reflux (**7a**, 68%; **8a**, 48%); (vi) NaOH, EtOH/water, reflux (**7b**, 99%; **8b**, 99%); (vii) oxalyl chloride/CCl_4, reflux (**7c**, **8c**, quant.); (iv) 4-aminotoluene/Et_3N/CH_2Cl_2, rt (**9**, 71%; **10**, 20%).



Scheme 2. (i) **3c**/Et_3N/CH_2Cl_2, rt (**12**, 25%); (ii) **4c**/Et_3N/CH_2Cl_2, rt (**13**, 52%); (iii) **8c**/Et_3N/CH_2Cl_2, rt (**15**, 11%); (iv) **7c**/Et_3N/CH_2Cl_2, rt (**16**, 21%).

(Scheme 2). It is obvious, that the presence of bulky groups on the upper rim prevents the complete condensation of both acid chlorides at the same side of the molecule. The acid tetrachloride can react only with two amines **11** leading thus to derivative **16** after quenching of the reaction mixture. This compound represents a novel type of inherent[7] chirality in the calixarene family. The symmetry of *1,3-alternate* structure is broken by a 25,26-substitution pattern which gives rise to a chiral derivative never described in calixarene literature.[8] Unfortunately, all our attempts to separate the racemate using chiral HPLC columns (Chiralpack, Wheelk-O) failed.

2.2. Structure assignments and NMR study

The structures of the novel tetraamides were proved using a combination of ^1H NMR spectroscopy and mass spectroscopy (ESI-MS or FAB MS). As the synthesis started from the conformationally immobilised compounds of known structures, proved by one-dimensional DPFGSE-NOE experiments,[9] the conformation assignment of products was not necessary. Thus, the ^1H NMR spectrum of derivative **15** (Fig. 2) reflects several characteristic features of both thiacalix[4]arene and calix[4]arene systems: (i) the presence of two doublets due to the equatorial protons of $Ar-CH_2-Ar$ bridging groups (3.08 and 3.12 ppm) with the geminal coupling constant of 13.2 Hz being clear evidence for a mono-substituted *cone* conformation (coming from amine units); (ii) the presence of two singlets of amidic NH and bridging $-CO-CH_2-$ groups at 8.28 and 4.81 ppm, respectively; (iii) typical doublet of aromatic protons (*meta*) of thiacalixarene part (7.51 ppm, $J=7.7$ Hz), all in accordance with proposed S_4 symmetry of the whole system. The

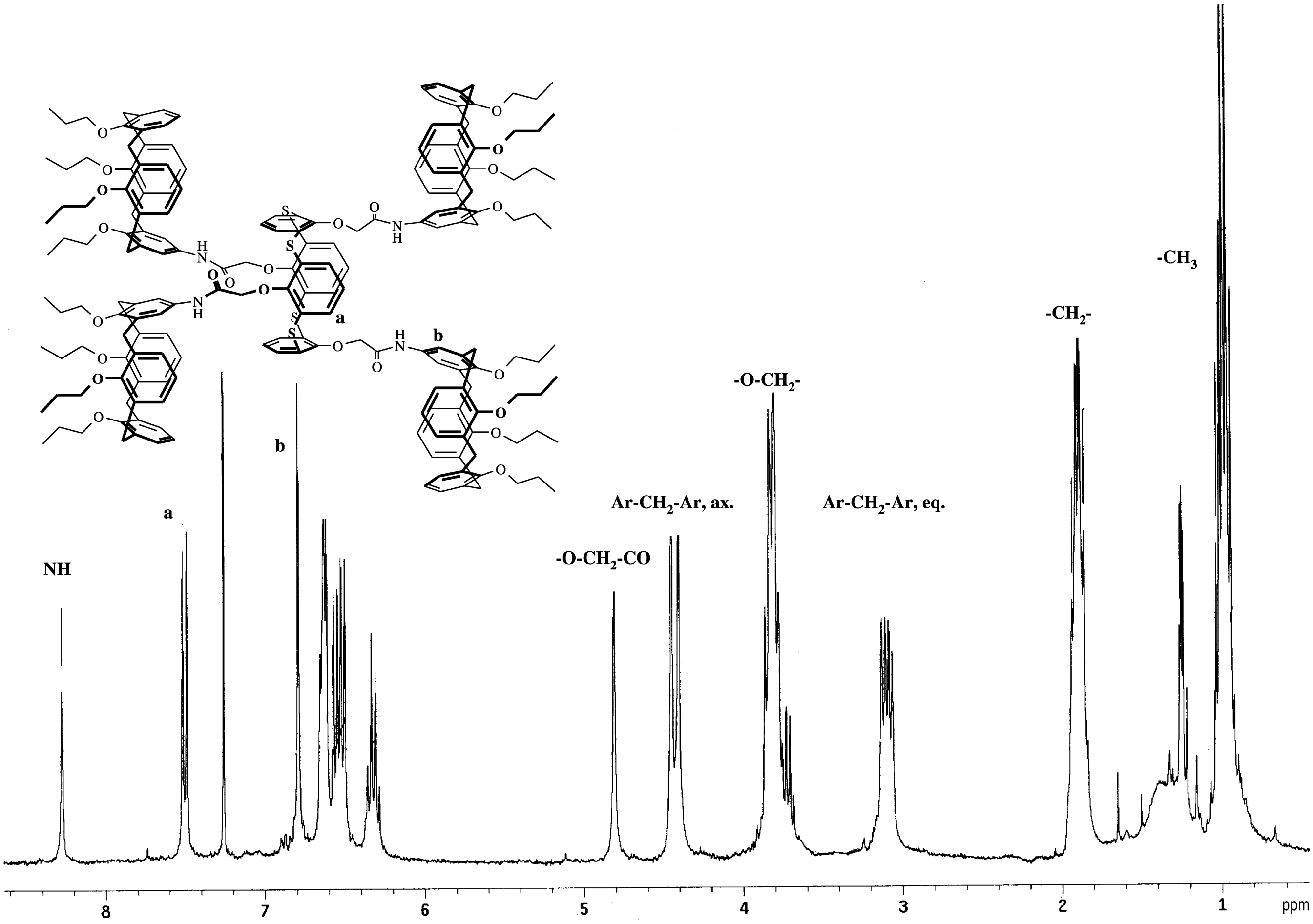


Figure 2. ^{1}H NMR spectrum of pentakis-calixarene **15** (300 MHz, CDCl$_3$, 298 K).

FAB MS spectrum shows the two most intense signals at m/z=3090.7 and 2440.3 corresponding to the molecular peak $[M+1]^+$ and to the fragment without one calix-CO–CH$_2$– moiety, respectively.

Interesting behaviour was found in the case of tetraamides **6** and **13** possessing a central thiacalix[4]arene moiety in the *cone* conformation without *tert*-butyl groups on the upper rim. The ^{1}H NMR spectrum of **6** measured in CDCl$_3$ at room temperature showed duplicate multiplicity with a substantial line broadening indicating a dynamic process ascribed to the *pinched cone–pinched cone* interconversion (Fig. 3). It is known, that the C_{4v} symmetry usually observed in the NMR spectra of classical calix[4]arene *cone* derivatives is a time-averaged signal due to fast chemical exchange between the two conformers with lower C_{2v} symmetry.[3] While the coalescence phenomenon of this interconversion in tetraalkylated classical calix[4]arenes is usually observable only at very low temperatures,[10] the situation in the thiacalixarene series is notably different. As we have shown in our previous study,[11] this phenomenon in

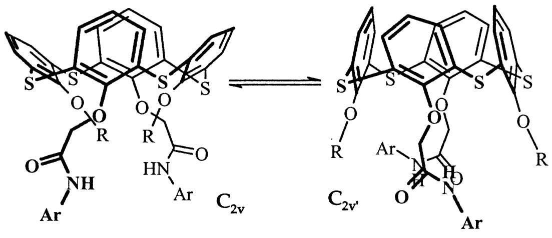


Figure 3. *Pinched cone–pinched cone* interconversion of **6**.

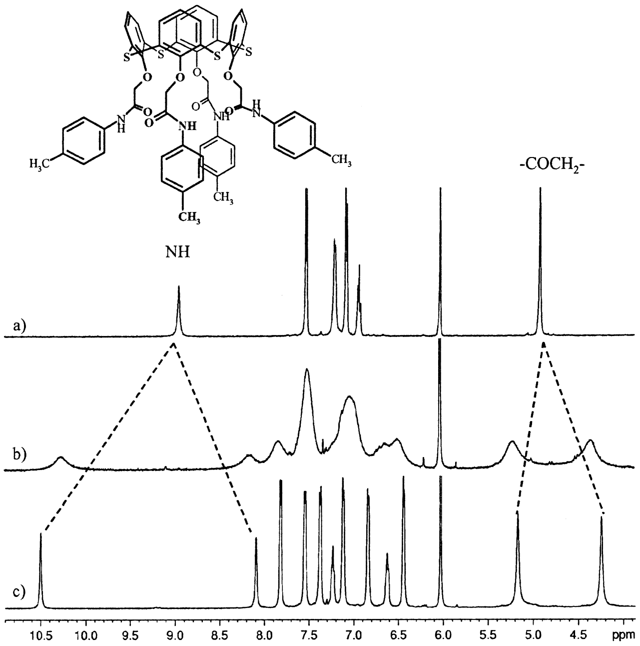


Figure 4. The partial ^{1}H NMR spectra of **6** (500 MHz, CDCl$_2$CDCl$_2$): measured at (a) 398 K; (b) 308 K; (c) 248 K.

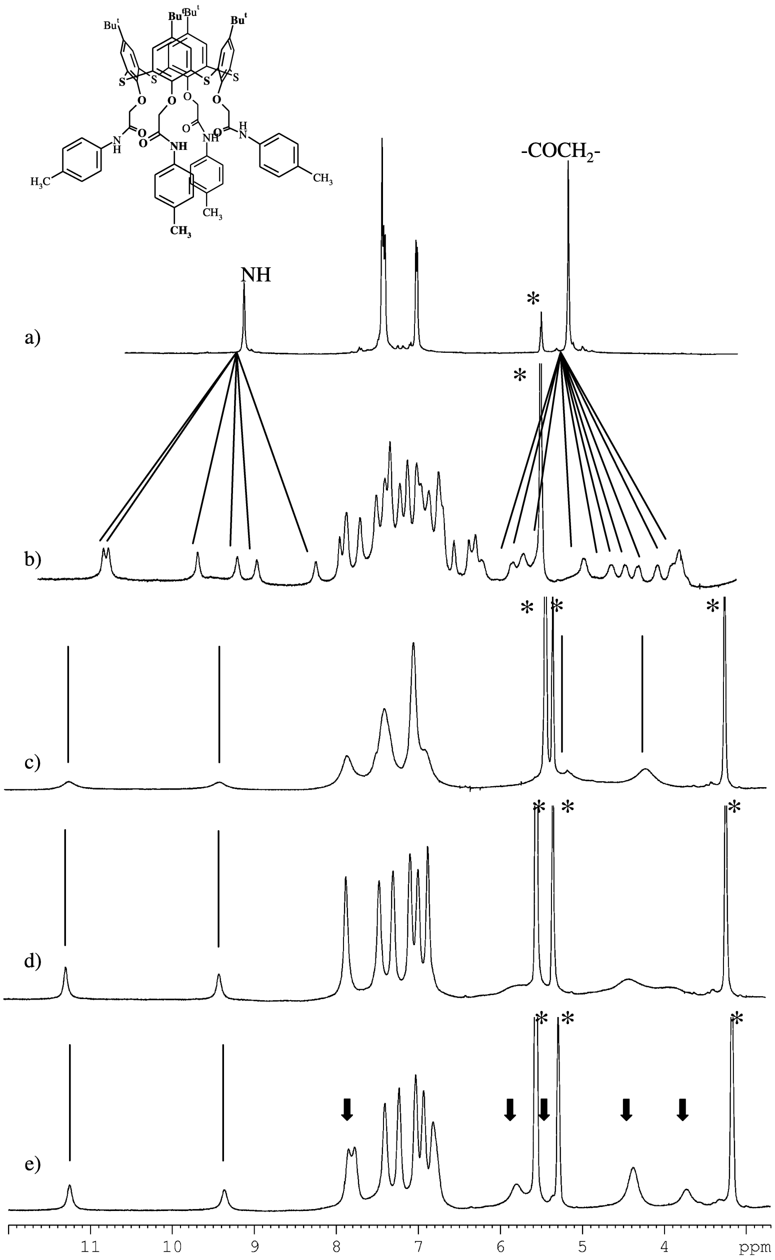


Figure 5. The partial ^{1}H NMR spectra of **5** (500 MHz, a,b=CD_2Cl_2; c,d,e=CD_2Cl_2/CD_3OD=4:1v/v): measured at (a) 298 K; (b) 203 K; (c) 203 K; (d) 183 K; (e) 173 K; *denotes the solvents.

the thiacalix[4]arene series exhibits much higher coalescence temperatures if compared with classical calixarenes.

The conformational behaviour of tetraamide derivative **6** was studied in the range of 213–398 K using $CDCl_2CDCl_2$ as a solvent. As shown in Figure 4, a simple set of signals corresponding to C_{4v} symmetry (e.g., singlets at δ=9.11 ppm (NH) and 4.92 ppm ($-COCH_2-$)) appeared at 398 K because of fast chemical exchange of C_{2v} conformers. Subsequent lowering the temperature led to the appearance of new signals, already well visible at ambient temperature, and corresponding to the presence of two conformers having C_{2v} symmetry (Fig. 4(b)).

The coalescence temperature T_c of the above exchange process was used to calculate the activation free energy of the process by means of the Eq. 1 (where R is the universal gas constant, $\Delta\nu$ is the chemical shift difference of the exchanging signals at zero rate of chemical exchange).

$$\Delta G_0^{\#} = RT_c[22.96 + \ln(T_c/\Delta\nu)] \qquad (1)$$

The activation free energy $\Delta G_0^{\#}$=60.5 kJ mol^{-1} (±1 kJ mol^{-1}) computed from independent signals (Δ_{NH}=1206 Hz, T_c=333 K; Δ_{-COCH_2-}=462 Hz, T_c=323 K) and the corresponding coalescence temperatures are the highest ever observed in the thiacalixarene series. As the coalescence temperature of $-CO-CH_2-$ groups in starting tetraester **4a** (T_c=263 K) is much lower, the substitution pattern on the lower rim obviously plays an important role in the overall energy barrier of this process. On the other hand, the activation free energy $\Delta G_0^{\#}$ of derivative **13** was found to be essentially the same as that of **6**. It indicates that the presence of four calix[4]arene units in the amidic part of the molecule has almost no influence on the dynamics of the whole system.

The temperature-dependent NMR study on derivative **5** revealed a dramatic influence of the *tert*-butyl groups on the dynamic behavior of thiacalixarenes. The spectra measured in $CDCl_2CDCl_2$ corresponded to C_{4v} symmetry in the whole temperature range with considerable line broadening at the lowest temperatures (≈213 K) indicating additional motion. Surprisingly, the low temperature ^{1}H NMR in CD_2Cl_2 reflected unexpected asymmetry of the system. Figure 5(a) and (b) shows the situation where the originally simple spectrum (room temp.) gradually becomes very complicated at 203 K. Obviously, the singlet of the OCH_2- group at 4.95 ppm is split into at least eight new signals at low temperature, and the same tendency is well observable for all other signals. As the exact assignment of spectrum is extremely difficult we can only speculate that this phenomenon corresponds to the formation of asymmetric hydrogen bonding array(s) on the lower rim (amidic functions), probably with simultaneous appearance of the *pinched cone* interconversion. This assumption is further supported by the fact that addition of CD_3OD into the sample leads to the interruption of hydrogen bonds array and to the reappearance of proposed C_2 symmetry at lower temperature (Fig. 5(c)). The coalescence temperature (213 K) corresponds to the activation free energy $\Delta G_0^{\#}=38\pm1$ kJ mol^{-1} as computed from the NH signals. While the NH signals (2 singlets) and the aromatic part of spectrum (6 signals) exactly reflect the proposed C_2 symmetry at −90 °C (Fig. 5(d)), the CH_2 region surprisingly reveals another coalescence phenomenon. This is clearly apparent at −100 °C (Fig. 5(e)) where several novel signals appeared if compared with original C_2 symmetry (designated by arrows).

As the *cone* tetraacetates are known[12] for their complexation ability towards alkali metal cations, we tested the influence of sodium cation on the dynamic behaviour of compounds **5** and **6**. As expected, the addition of 2 equiv. of Kobayashi reagent (tetrakis[3,5-bis(trifluoromethyl)-phenyl]boron sodium) led to the formation of 1:1 complexes with tetraamides **5** and **6**. As a consequence, only the spectra reflecting the C_{4v} symmetry of the complex formed were observable in CD_2Cl_2 with no indications of intra/intermolecular hydrogen bonding or *pinched cone–pinched cone* interconversion down to 40 °C.

In conclusion, we have shown that thiacalix[4]arene tetraacetates can be used as a starting point in the synthesis of multiple calixarenes connecting together 'classical' calixarene and thiacalixarene building blocks. These compounds, representing a first step towards calixarene-based dendritic structures, exhibit interesting dynamic behaviour because of multiple hydrogen bonding interactions.

3. Experimental

3.1. General

Melting points were determined on a Boetius block (Carl Zeiss Jena, Germany) and are not corrected. The IR spectra were measured on an FT-IR spectrometer Nicolet 740 in $CHCl_3$ and/or in KBr. ^{1}H NMR spectra were recorded on a Varian Gemini 300 spectrometer, the temperature dependant spectra were recorded on a Bruker AMX3 400 and Bruker DRX 500 Avance spectrometers using tetramethylsilane as an internal standard. Dichloromethane and CCl_4 used for the reaction were dried with CaH_2 and P_2O_5, respectively, and stored over molecular sieves. The purity of the substances and the courses of reactions were monitored by TLC using TLC aluminium sheets with Silica gel 60 F_{254} (Merck). Preparative TLC chromatography was carried out on 20×20 cm glass plates covered by Silica gel 60 GF_{254} (Merck).

Starting esters **3a**, **4a**, **7a** and **8a** were prepared according to known procedures[12] by the reaction of **1** and **2** with ethyl bromoacetate in boiling acetone in the presence of Na_2CO_3 or Cs_2CO_3.

It is known that the elemental analyses of the calixarene derivatives are sometimes ambiguous.[13] The EA usually resulted in *C* values 1–3% lower than the calculated values. There are two possible and widely accepted explanations: (i) cavity-possessing compounds contain the molecules of solvents/reagents which are extremely difficult to eliminate; (ii) the incomplete combustion of these high-melting compounds under the standardized conditions of the elemental analysis. We believe that the structures of the calixarenes are sufficiently documented by the spectral evidence or by the subsequent chemical transformations.

3.1.1. Synthesis of 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis(carboxymethoxy)-2,8,14,20-tetrathia-calix[4]arene (*cone*) 3b. Tetraester **3a** (2.0 g, 1,88 mmol) was dissolved in 150 ml of EtOH and a solution of NaOH (1.5 g, 37.5 mmol) in 10 ml of distilled water was added. The reaction mixture was stirred for 6 days at reflux. Ethanol was then removed on vacuum evaporator, the residue was dissolved in water and acidified by 1 M HCl. The white precipitate was collected by filtration and dried in vacuum to yield the title compound in quantitative yield. Mp 333–334 °C (lit.[14] mp 293.4–294.8 °C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.40 (s, 8H, H-arom), 5.03 (s, 8H, $-O-CH_2-CO-$), 1.12 (s, 36H, Bu^t). IR (KBr) ν_{max} (cm^{-1}): 1758 (C=O), 3462 (O–H). MS-ESI m/z=975.1 [M+Na]$^+$.

3.1.2. Synthesis of 25,26,27,28-tetrakis(carboxymethoxy)-2,8,14,20-tetrathiacalix[4]arene (*cone*) 4b. The preparation was analogous to that described for **3b**, quantitative yield of white precipitate. Mp 287–288 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 6.93 (bs, 8H, H-arom), 6.84 (t, 4H, H-arom, J=7.14 Hz), 5.04 (s, 8H, $-O-CH_2-CO$). IR (KBr) ν_{max} (cm^{-1}): 1738 (C=O). EA Calcd for $C_{32}H_{24}O_{12}S_4$: C, 52.74; H, 3.32; S, 17.60. Found: C, 52.82; H, 3.52; S, 17.12.

3.1.3. Synthesis of 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-(carboxymethoxy)-2,8,14,20-tetrathia-calix[4]arene (*1,3-alternate*) 7b. The preparation was analogous to that described for **3b**, quantitative yield of white precipitate. Mp 325–326 °C (lit.[15] 325–327 °C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.39 (s, 8H, H-arom), 4.66 (s, 8H, –O–CH_2–CO–), 1.25 (s, 36H, Bu^t). IR (KBr) ν_{max} (cm^{-1}): 1695 (C=O). MS-ESI *m/z*=975.1 $[M+Na]^+$.

3.1.4. Synthesis of 25,26,27,28-tetrakis(carboxymethoxy)-2,8,14,20-tetrathiacalix[4]arene (*1,3-alternate*) 8b. The preparation was analogous to that described for **3b**, quantitative yield of white precipitate. Mp 309–310 °C (lit.[16] 290 °C (decomp.)). ^1H NMR (DMSO-d_6, 300 MHz) δ: 7.60 (d, 8H, H-arom, *J*=7.69 Hz), 6.81 (t, 4H, H-arom, *J*=7.14 Hz), 4.53 (s, 8H, –O–CH_2–CO–). IR (KBr) ν_{max} (cm^{-1}): 1743 (C=O). MS-ESI *m/z*=751.0 $[M+Na]^+$.

3.2. Synthesis of model compounds

3.2.1. Preparation of acid chloride. A mixture of tetraacid (76 μmol) and $(COCl)_2$ (0.13 ml; 1.52 mmol) in 5 ml of anhydrous CCl_4 was stirred under reflux for 3 h (**3c**) to 3 days (**8c**). The end of reaction was indicated by the formation of the clear yellowish solution. The solvent and the residual oxalyl chloride were distilled off, the residue was treated with anhydrous CH_2Cl_2 (5 ml) and the solvent was again evaporated under reduced pressure. The resulting solid was then dried in a vacuum (5 Torr) for 2 h to yield the corresponding acyl chlorides **3c**, **4c**, **7c**, and **8c** in almost quantitative yield. These reactive intermediates were used in the next step without subsequent characterisation and purification.

3.2.2. Synthesis of 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[(4-methylphenyl)carbamoyl-methoxy]-2,8,14,20-tetrathiacalix[4]arene (*cone*) 5. A solution of 4-aminotoluene (0.11 g, 1.05 mmol) in 5 ml of dry DCM was added dropwise at room temperature to a stirred solution of tetrachloride **3c** (0.215 g, 0.21 mmol) and Et_3N (0.3 ml, 2.1 mmol) in 5 ml of dry DCM. The reaction mixture was stirred overnight and the solvent was removed in a reduced pressure. The residue was dissolved in $CHCl_3$ (30 ml) and washed with 1 M HCl and then with water. The separated organic layer was dried over $MgSO_4$. The volume of solution was reduced to 5 ml and product (190 mg, 88%) was obtained by precipitation with methanol as beige solid with mp 272–273 °C ($CHCl_3$–MeOH). ^1H NMR ($CDCl_3$, 300 MHz) δ: 9.28 (s, 4H, –NH), 7.43 (d, 8H, H-arom, *J*=8.2 Hz), 7.38 (s, 8H, H-arom), 6.97 (d, 8H, H-arom, *J*=8.2 Hz), 4.95 (s, 8H, –O–CH_2–CO–), 2.24 (s, 12H, Ar-CH_3), 1.13 (s, 36H, Bu^t). IR ($CHCl_3$) ν_{max} (cm^{-1}): 3307 (N–H), 1678 (C=O). EA Calcd for $C_{76}H_{84}N_4O_8S_4$: C, 69.69; H, 6.46; N, 4.28; S, 9.79. Found: C, 70.41; H, 6.75; N, 4.32; S, 10.23.

3.2.3. Synthesis of 25,26,27,28-tetrakis[(4-methyl-phenyl)-carbamoylmethoxy]-2,8,14,20-tetrathia-calix[4]-arene (*cone*) 6. The reaction was carried out analogously to the procedure described for **5** using tetrachloride **4c** as starting compound. The crude product was purified by preparative TLC chromatography on silica gel using $CHCl_3$–acetone (10:1) mixture to yield derivative **6** (41%) as a white powder with mp 289–290 °C. ^1H NMR ($CDCl_2$–$CDCl_2$, 135 °C, 500 MHz) δ (ppm): 9.11 (s, 4H, –NH), 7.52 (d, 8H, *J*=7.2 Hz, H-arom), 7.20 (brd, 8H, H-arom), 7.07 (d, 8H, *J*=7.3 Hz, H-arom), 6.92 (t, 4H, H-arom), 4.92 (s, 8H, –O–CH_2–CO–), 2.32 (s, 12H, Ar-CH_3). IR ($CHCl_3$) ν_{max} (cm^{-1}): 3409, 3314 (N–H), 1680 (C=O). MS-ESI *m/z*=1107.2 $[M+Na]^+$.

3.2.4. Synthesis of 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[(4-methylphenyl)carbamoyl-methoxy]-2,8,14,20-tetrathiacalix[4]arene (*1,3-alternate*) 9. The reaction was carried out analogously to the procedure described for **5** using tetrachloride **7c** as starting compound. The crude product was purified by precipitation from $CHCl_3$/methanol mixture to yield derivative **9** (71%) as a white powder with mp 295–296 °C ($CHCl_3$–MeOH). ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.45 (s, 4H, –NH), 7.47 (s, 8H, H-arom), 7.40 (d, 8H, *J*=8.2 Hz, H-arom), 7.15 (d, 8H, *J*=8.8 Hz, H-arom), 4.86 (s, 8H, –O–CH_2–CO–), 2.32 (s, 12H, Ar-CH_3), 0.70 (s, 36H, Bu^t). IR ($CHCl_3$) ν_{max} (cm^{-1}): 3394, 3283 (N–H), 1679 (C=O). EA Calcd for $C_{76}H_{84}N_4O_8S_4$: C, 69.69; H, 6.46; N, 4.28; S, 9.79; C, 69.66; H, 6.55; N, 3.78; S, 10.19.

3.2.5. Synthesis of 25,26,27,28-tetrakis[(4-methyl-phenyl)-carbamoylmethoxy]-2,8,14,20-tetrathia-calix[4]-arene (*1,3-alternate*) 10. The reaction was carried out analogously to the procedure described for **5** using tetrachloride **8c** as starting compound. The crude product was purified by preparative TLC chromatography on silica gel using $CHCl_3$ as eluent to yield derivative **10** (20%) as a beige solid with mp 256–257 °C ($CHCl_3$–MeOH). ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.22 (s, 4H, –NH), 7.53 (d, 8H, *J*=7.7 Hz, H-arom), 7.28 (d, 8H, *J*=8.8 Hz, H-arom), 7.17 (d, 8H, *J*=8.2 Hz, H-arom), 6.56 (t, 4H, *J*=7.7 Hz, H-arom), 4.95 (s, 8H, –O–CH_2–CO–), 2.35 (s, 12H, Ar-CH_3). IR ($CHCl_3$) ν_{max} (cm^{-1}): 3388, 3298 (N–H), 1686 (C=O). MS-ESI *m/z*=1107.2 $[M+Na]^+$.

3.2.6. Synthesis of pentakis-calixarene 12. A solution of aminocalixarene **11** (75 mg, 0.123 mmol) in 3 ml of dry CH_2Cl_2 was added at room temperature under a nitrogen atmosphere to a stirred solution of tetrachloride **3c** (24.6 mg, 0.024 mmol) and Et_3N (0.1 ml, 0.72 mmol) in 3 ml of dry CH_2Cl_2. The reaction mixture was stirred for 22 h and the solvent was distilled off. The residue was dissolved in $CHCl_3$ (20 ml) and thoroughly washed with 1 M HCl. The organic layer was separated and the aqueous layer was extracted twice with small amount of $CHCl_3$. The collected organic layers were dried over $MgSO_4$ end evaporated to dryness. The residue was purified by repeated preparative TLC on silica gel using $CHCl_3$–ethyl acetate=250:1 and petroleum-ether–$CHCl_3$=5:1 mixtures as eluents. The title compound was obtained as yellowish powder (20 mg, 25%) with mp 195–196 °C ($CHCl_3$–MeOH). ^1H NMR ($CDCl_3$, 300 MHz) δ: 9.12 (s, 4H, –NH), 7.39 (s, 8H, H-arom), 7.06 (s, 8H, H-arom), 6.66–6.38 (m, 36H, H-arom), 4.98 (s, 8H, –O–CH_2–CO–), 4.41, 4,30 (2d, 16H, *J*=13.5 Hz, Ar-CH_2-Ar ax.), 3.84–3.73 (m, 32H, –O–CH_2–CH_2–), 3.09, 3.01 (2d, 16H, *J*=13.2 Hz, Ar-CH_2-Ar eq.), 1.90–1.80 (m, 32H, –CH_2–CH_3), 1.14 (s, 36H, Bu^t), 1.20–0.90 (m, 48H, –CH_2–CH_3). IR ($CHCl_3$) ν_{max} (cm^{-1}): 3308 (N–H), 1678 (C=O). MS-ESI *m/z*=3335.2 $[M+Na]^+$, 1679,5 $[M+2Na]^{2+}$.

3.2.7. Synthesis of pentakis-calixarene 13. Reaction was carried out analogously to the procedure described for **12** using tetrachloride **4c** as starting compound. The product was obtained as a beige solid (52%) after preparative TLC chromatography on silica gel using $CHCl_3$ as an eluent. Mp 197–199 °C ($CHCl_3$–MeOH). ^{1}H NMR ($CDCl_2$–$CDCl_2$, 135 °C, 500 MHz) δ: 8.58 (s, 4H, –NH), 6.84 (s, 8H, H-arom), 6.24–6.52 (m, 36H, H-arom), 4.68 (s, 8H, –O–$\mathit{CH_2}$–CO–), 4.34, 4.26 (2d, 16H, J=13.5 Hz, Ar-$\mathit{CH_2}$-Ar ax.), 3.71 (m, 32H, O–$\mathit{CH_2}$–CH_2–), 3.00, 2.92 (2d, 16H, J=13.2 Hz, Ar-$\mathit{CH_2}$-Ar eq.), 1.85–1.95 (m, 32H, –$\mathit{CH_2}$–CH_3), 0.80–1.00 (m, 48H, –CH_2–$\mathit{CH_3}$). IR ($CHCl_3$) ν_{max} (cm^{-1}): (N–H), (C═O). MS-ESI (CH_3CN) m/z=3111 [M+Na]$^+$, 1567 [M+2Na]$^{2+}$.

3.2.8. Synthesis of pentakis-calixarene 15. The reaction was carried out analogously to the procedure described for **12** using tetrachloride **8c** as starting compound. The product was obtained as a white solid (11%) after repeated preparative TLC chromatography on silica gel using $CHCl_3$ and then petroleum-ether–ethyl acetate=10:1 as an eluent. Mp 214–216 °C ($CHCl_3$–MeOH). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.28 (s, 4H, –NH), 7,51 (d, 8H, J=7.7 Hz, H-arom), 6.79 (s, 8H, H-arom), 6.65–6.50 and 6.32 (2m, 40H, H-arom), 4.81 (s, 8H, –O–$\mathit{CH_2}$–CO–), 4.43 (d, 16H, J=13.2 Hz, Ar-$\mathit{CH_2}$-Ar ax.), 3.86–3.71 (m, 32H, O–$\mathit{CH_2}$–CH_2–), 3.12, 3.08 (2d, 16H, J=13.2 Hz, Ar-$\mathit{CH_2}$-Ar eq.), 1.90 (m, 32H, –O–CH_2–$\mathit{CH_2}$–), 0.99 (m, 48H, CH_2–$\mathit{CH_3}$). IR ($CHCl_3$) ν_{max} (cm^{-1}): 3399, 3288 (N–H), 1677 (C═O). MS-FAB m/z (int.%)=3090.7 (100%) [MH]$^+$, 2440.3 (98%) [M–(calix-CO–CH_2–)]$^+$.

3.2.9. Synthesis of *tris*-calixarene 16. Reaction was carried out analogously to the procedure described for **12** using tetrachloride **7c** as starting compound. The product was obtained as a white solid (21%) after several times repeated preparative TLC chromatography on silica gel ($CHCl_3$–acetone=50:1, petroleum-ether–ethyl acetate=5:2). Mp 206–208 °C ($CHCl_3$–MeOH). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.60 (s, 2H, –NH), 7.70 (d, 2H, J=2.8 Hz, H-arom), 7.54 (d, 2H, J=2.2 Hz, H-arom), 7.33 (d, 2H, J=2.2 Hz, H-arom), 7.19 (d, 2H, J=2.2 Hz, H-arom), 6.80 (d, 4H, J=7.7 Hz, H-arom), 6.59 (t, 2H, J=7.4 Hz, H-arom), 6.44–6.39 (m, 16H, H-arom), 4.71, 4.58, 4.37, 4.22 (4d, 8H, –O–$\mathit{CH_2}$–CO–), 4.46, 4.42 (2d, 8H, Ar-$\mathit{CH_2}$-Ar), 3,95–3,71 (m, 16H, O–$\mathit{CH_2}$–CH_2–), 3.17, 3.13 (2d, 8H, Ar-$\mathit{CH_2}$-Ar), 1.88 (m, 16H, –$\mathit{CH_2}$–CH_3), 1.20, 1,13 (2s, 36H, Bu^t), 1.09–0.92 (m, 24H, CH_2–$\mathit{CH_3}$). IR ($CHCl_3$) ν_{max} (cm^{-1}): 3451, 3387, 3302 (N–H), 1786 (C═O). MS-FAB m/z=2131.5 [M$^+$].

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Development of a new class of (1*S*,3*R*,4*R*)-2-azabicyclo[2.2.1]heptane-oxazoline ligands and their application in asymmetric transfer hydrogenation

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Abstract—New 2-aza-norbornane-oxazoline compounds were synthesized and evaluated as ligands in the transfer hydrogenation of acetophenone. The best catalyst prepared in situ from [IrCl$_2$(COD)]$_2$ and a ligand afforded 1-(*S*)-phenylethanol in good yields and 79% ee.
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1. Introduction

The development of new chiral ligands for catalytic asymmetric transformations is one of the most important issues in the research of asymmetric synthesis.[1] Among the nitrogen ligands[1c] oxazoline compounds have been used for a long time in different asymmetric catalytic reactions.[2] Chelating atoms could, in addition to the nitrogen in the oxazoline ring, be phosphorus, amino nitrogen, aromatic nitrogen or sulfur atoms present in the molecule.[3] Bis(oxazolines) are widely employed as ligands[4] as well.

Enantioselective transfer hydrogenation represents a very useful method for the preparation of optically active alcohols.[5] Recently Noyori and co-workers[6] showed that the NH function within the ligand molecule is crucial for the asymmetric transformation of prochiral ketones into chiral alcohols. Several C_2 symmetric chiral bis(oxazolinylmethyl)amine ligands[7a] were found to be efficient in the Ru(II) catalyzed asymmetric transfer hydrogenation. Recently the use of ruthenium and iridium complexes with bis(oxazoline) ligands in this asymmetric process was also reported.[7b] However, there are few reports on the use of C_1 symmetric amine-oxazoline ligands in transfer hydrogenation of prochiral ketones. The only example described is the application of chiral 1,2,3,4-tetrahyroquinolinyl-oxazoline ligands in complexes with Ru(II)[7b] (conversion 40–78%, ee 12–83%).

Previously 2-aza-norbornan-3-ylmethanol has been used by our research group[8] as an efficient ligand in Ru(arene)-catalyzed asymmetric transfer hydrogenation. Herein we describe the synthesis of a new class of 2-aza-norbornane-oxazoline ligands. We also show the importance of the bulky aza-bicyclic group in the ligand molecule for asymmetric transfer hydrogenation of acetophenone by comparison of the results obtained using acyclic chiral amine-oxazoline ligand complexes and initial results from a series of aza-bicycle-oxazoline ligand complexes.

2. Results and discussion

The syntheses of bicyclic amine-oxazoline ligands using a Cbz-protecting group for cyclic secondary nitrogen are shown in Scheme 1. The (1*S*,3*R*,4*R*)-2-azabicyclo[2.2.1]-heptane-3-carboxylic acid (**1**) is easily available from a stereoselective aza-Diels Alder reaction.[9] The protection of the amine was performed using benzyl chloroformate[10] to give **2** in 72% yield. The amide coupling[11,12] of **2** with appropriate L- and D-aminoalcohols lead to hydroxylamines **3a**, **3b**, **4a**, **4b**, **5a** and **5b** (yield 64–94%). These compounds were converted into protected oxazolines **6a**, **6b**, **7a**, **7b**, **8a** and **8b** by treatment with mesyl chloride under basic conditions[11] in 65–95% yield after purification. The cleavage of the benzyloxycarbonyl group from the amine was accomplished by hydrogenolysis using palladium on carbon as a catalyst[13] to yield the ligands **9a**, **9b**, **10a**, **10b**, **11a** and **11b** in 55–74%.

The syntheses of bicyclic amine-oxazoline ligands using *p*-nitrobenzyloxycarbonyl protecting group are shown in Scheme 2. First, the compounds having the secondary amine protected by benzyloxycarbonyl were synthesized. It turned out that the deprotection of these oxazolines by

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Keywords: Azabicyclo[2.2.1]heptane; Oxazoline; Chiral ligands; [IrCl$_2$(COD)]$_2$; Acetophenone; Catalysis; Asymmetric transfer hydrogenation.

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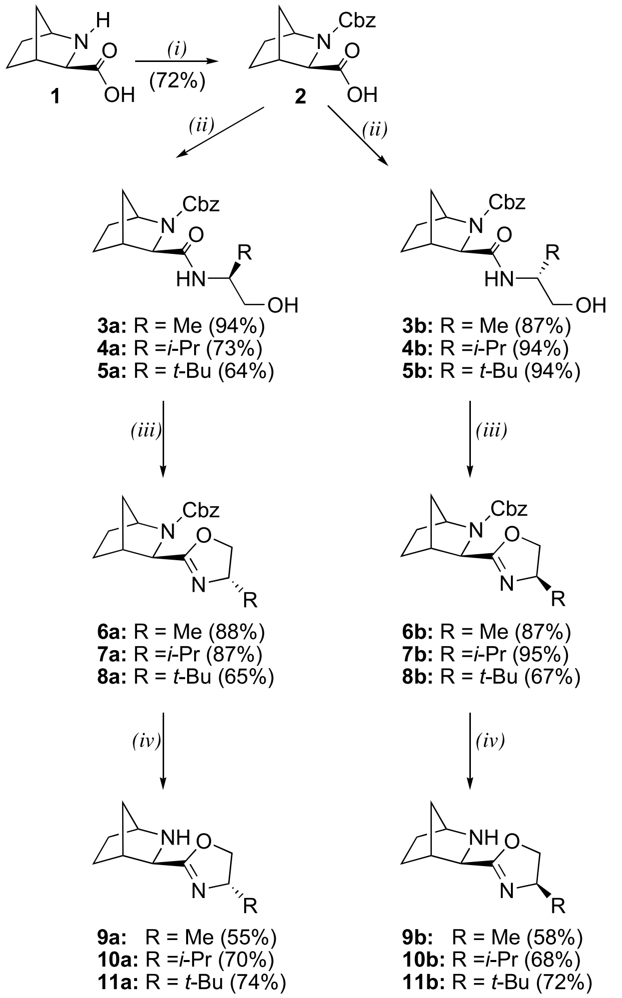


Scheme 1. Synthesis of ligands **9a**, **9b**, **10a**, **10b**, **11a** and **11b**. Conditions and reagents: (i) CbzCl, sat. $NaHCO_3$ in H_2O, rt, 3 h; (ii) EDC, HOBt, aminoalcohol, CH_2Cl_2, rt, overnight; (iii) MsCl, Et_3N, CH_2Cl_2, 0 °C→rt, overnight; (iv) Pd/C (10 wt%), H_2 (1 atm.), EtOH, rt, overnight.

hydrogenolysis using Pd/C as a catalyst resulted in decomposition of the oxazoline ring. We then started a search for a new protecting group, which could be removed under basic conditions (oxazolines are highly unstable under acidic conditions) or is more readily cleaved by catalytic hydrogenation. It was found that a recently reported method[14] for the preparation of oxazolines using a base-labile Fmoc protecting group did not work in the case of bicyclic amine-oxazoline molecules. It was not possible to cleave the Fmoc group by treatment of these compounds with piperidine, diethyl amine or *t*-butyl ammonium fluoride.[15] Instead, *p*-nitrobenzyloxycarbonyl was chosen because of its higher lability under mild catalytic hydrogenation conditions as compared to benzyloxycarbonyl. Alternatively, the deprotection can also be accomplished by treatment of the substrate with sodium dithionite,[16] but it was found, that the oxazolines were not stable under these conditions, even in the presence of a base.

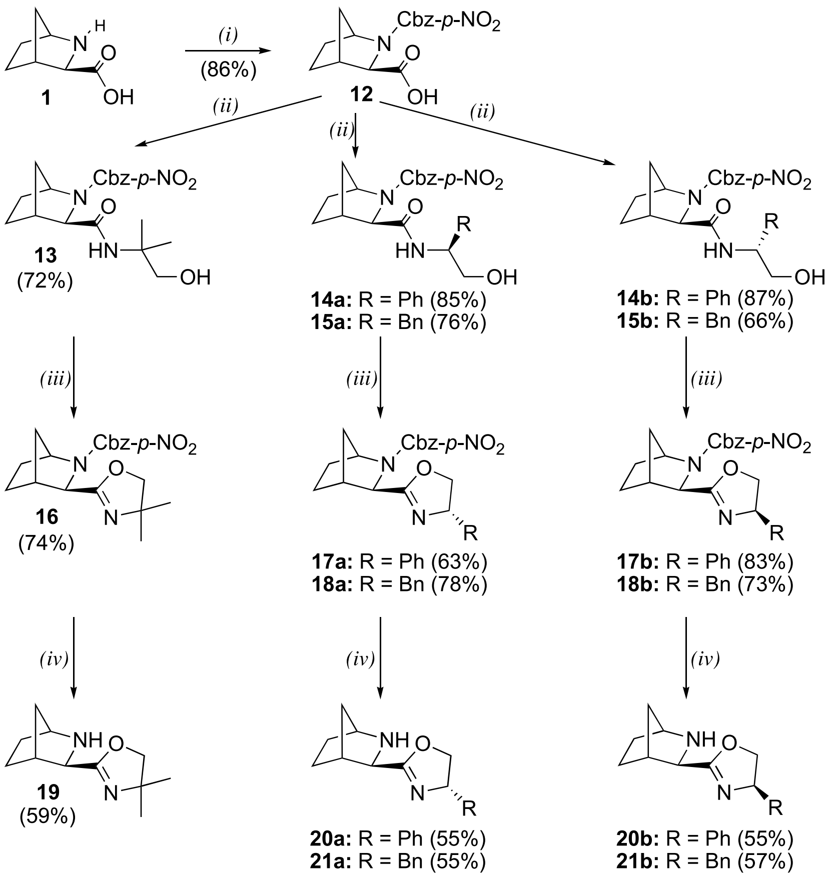
The *p*-nitrobenzyl ester protected amino acid[17] **12** was coupled[11,12] with the appropriate L- and D-aminoalcohols to produce hydroxylamines **13**, **14a**, **14b**, **15a** and **15b** in 66–87% yield. These compounds were cyclized by treatment with mesyl chloride under basic conditions[11] to give protected oxazolines **16**, **17a**, **17b**, **18a** and **18b** in 63–83% yield. The *p*-nitrobenzyloxycarbonyl group was readily cleaved by hydrogenolysis using palladium on carbon as a catalyst[16b] to yield the ligands **19**, **20a**, **20b**, **21a** and **21b** in 55–59% yield. No considerable amounts of oxazoline decomposition products were observed in the ^1H NMR spectra of the crude materials after deprotection.

2.1. Evaluation of the new oxazoline ligands in transfer hydrogenation

As a starting point of our investigation, we screened a number of different metal complexes as precatalysts for transfer hydrogenation using isopropanol as a hydrogen source and *i*-PrOK as a base. The following metal complexes were tested together with ligand **10a**: $[RuCl_2(benzene)]_2$, $RuCl_2(PPh_3)_3$, $[IrCl(COD)]_2$, $RhCl(PPh_3)_3$, $[Rh(COD)Cl]_2$ and $RuCl_2(DMSO)_4$. The results are shown in Table 1. Surprisingly, in our study we found that with the complexes $[RuCl_2(benzene)]_2$, $RuCl_2(PPh_3)_3$ and $RuCl_2(DMSO)_4$, no 1-phenylethanol formation was observed at all.[7] Rh(I) complexes $RhCl(PPh_3)_3$ and $[Rh(COD)Cl]_2$ were also able to catalyze this asymmetric transformation, but the catalyst was not as efficient as the one formed from $[IrCl_2(COD)]_2$ and produced the 1-phenylethanol with lower enantiomeric excess.

The presence of the bulky 2-aza-norbornanyl group in the ligand molecule was found to be crucial. The acyclic amine-oxazoline ligands **22a** and **22b**[18] (Scheme 3) were tested in transfer hydrogenation of acetophenone with $[IrCl_2(COD)]_2$ as the catalyst precursor. These catalysts turned out to be unselective and produced racemic 1-phenylethanol with low conversion (10%).

Next, the influence of the size and configuration of the substituent on the oxazoline part of the ligand was studied (Table 2). First, the Ir-complex was prepared from compound **19**, which has two methyl groups in the oxazoline (entry 1). When we employed this catalyst, acetophenone was reduced to 1-(*R*)-phenylethanol in 73% conversion and moderate ee (53%). To investigate how the configuration of the methyl substituent influences the stereoselectivity, oxazolines **9a** and **9b** were tested. These ligands gave 1-(*R*)-phenylethanol in 41% ee (20% conversion) and 33% ee (40% conversion) respectively (entries 2 and 3). These results show that in the case of ligands with a methyl substituent on the oxazoline ring the configuration of the bicycle is mainly responsible for the stereoselectivity. The diastereomeric pair of ligands **10a** and **10b** (entries 4 and 5) having a larger substituent on the oxazoline ring had higher selectivity. Use of ligand **10a** lead to the formation of 1-(*R*)-phenylethanol with 79% ee (32% conversion), while ligand **10b** resulted in formation of 1-(*S*)-phenylethanol (27% ee, 58% conv.). A further increase of the substituent steric size (*t*-butyl group) made the reaction more sluggish and also decreased the ee significantly (ligands **11a** and **11b**, entries 6 and 7). The ligands **20a** and **20b** prepared from L- and D-phenylglycinol also formed less selective catalysts with $[IrCl_2(COD)]_2$ (entries 8 and 9). This is in accordance with the hypothesis that the steric bulk of the substituent is crucial for asymmetric induction. The best conversion of acetophenone to 1-(*R*)-phenylethanol (83%) was observed

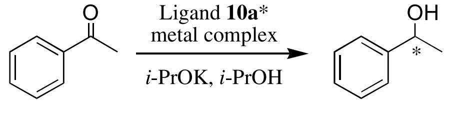


Scheme 2. Synthesis of ligands **19**, **20a**, **20b**, **21a** and **21b**. Conditions and reagents: (i) p-NO_2-CbzCl, 2.0 M NaOH in dioxane/H_2O, rt, overnight; (ii) EDC, HOBt, aminoalcohol, CH_2Cl_2, rt, overnight; (iii) MsCl, Et_3N, CH_2Cl_2, 0 °C→rt, overnight; (iv) Pd/C (10 wt%), H_2 (1 atm.), EtOH, rt, overnight.

when ligand **21a** (entry 10) was employed, but in this case the selectivity was low (28%). The diastereomeric ligand **21b** (entry 11) also afforded 1-(*R*)-phenylethanol (35% ee) but with lower conversion (15%).

These results show that in diastereomeric ligand pairs the configuration of product strongly depends on the configuration of a substituent on the oxazoline ring, except the molecules where steric bulk is missing (ligands **9a**, **9b**, **21a** and **21b**). Use of ligands produced from L-aminoalcohol leads to 1-(*R*)-phenylethanol formation. 1-(*S*)-Phenylethanol is obtained employing the Ir-complex with an oxazoline synthesized from a D-aminoalcohol. It was also noticed, that the rate of the reaction with ligands prepared from D-aminoalcohol is usually higher, but the ee of the product is lower.

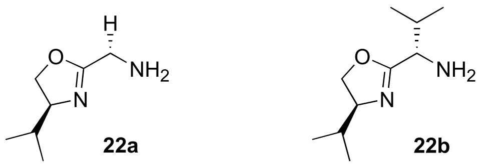
Table 1. Transfer hydrogenation of acetophenone using different metal complexes and ligand **10a**[a]



Entry	Metal complex[b]	Conv., 16 h (%)[c]	ee (%)[c]	Conf. of product
1	$RhCl(PPh_3)_3$	3	25	*R*
2	$[RhCl(COD)]_2$	18	71	*R*
3	$[IrCl(COD)]_2$	32	79	*R*
4	$[RuCl_2(benzene)]_2$	—	—	—
5	$RuCl_2(PPh)_3$	—	—	—
6	$RuCl_2(DMSO)_4$	—	—	—

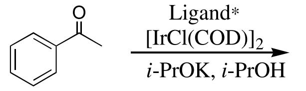
[a] See Section 4.1 for procedure.
[b] Substrate/metal/ligand/base=200:1:2:5.
[c] Determined by chiral GC.

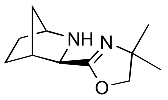
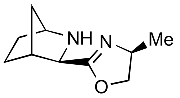
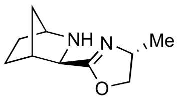
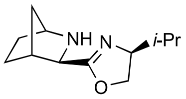
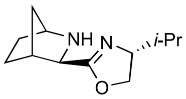
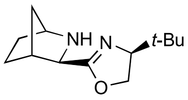
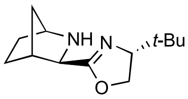
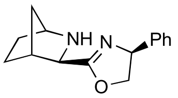
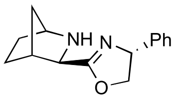
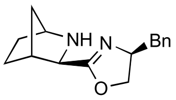
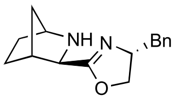
Interestingly, it was found that the enantioselectivity changes during the reaction time (Table 3). For example the Ir-complex prepared from ligand **10a** produced 1-(*R*)-phenylethanol in 38% ee after 1 h. When the product was analyzed after 16 h of reaction time its enantiomeric excess unexpectedly increased up to 79% (entry 1). Compound **10b** gave 1-(*S*)-phenylethanol in 16% ee after 1 h and 27% ee after 16 h (entry 2). Similar behaviour was recorded for the Ir-complex of compound **20b**. Using this ligand acetophenone was reduced to 1-(*S*)-phenylethanol in 14% ee in 1 h and in 24% ee after 16 h (entry 3). In reaction with oxazoline **21b** the enantiomeric excess of 1-(*R*)-phenylethanol significantly decreased during the reaction time (42% ee in 1 h and 28% ee in 16 h, entry 4). In a recently published computational study the mechanisms for transfer hydrogenation reactions of ketones catalyzed by Ru- and Ir-amino alcohol complexes were compared.[19] The calculation suggests that the Ru-catalysis proceeds via a concerted



Scheme 3. Structure of ligands **22a** and **22b**.

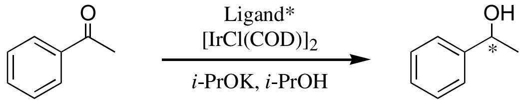
Table 2. Transfer hydrogenation of acetophenone using ligands **9a**, **9b**, **10a**, **10b**, **11a**, **11b**, **19**, **20a**, **20b**, **21a** and **21b**[a]

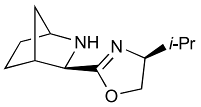
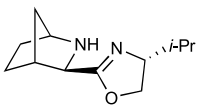
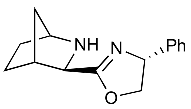
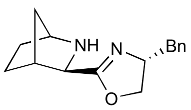


Entry	Ligand[b]	Conv., 16 h (%)[c]	ee (%)[c]	Conf. of product
1	 **19**	73	53	*R*
2	 **9a**	20	41	*R*
3	 **9b**	40	33	*R*
4	 **10a**	32	79	*R*
5	 **10b**	58	27	*S*
6	 **11a**	10	18	*R*
7	 **11b**	43	23	*S*
8	 **20a**	16	48	*R*
9	 **20b**	48	24	*S*
10	 **21a**	15	35	*R*
11	 **21b**	83	28	*R*

[a] See Section 4 for procedure.
[b] Substrate/metal/ligand/base=200:1:2:5.
[c] Determined by chiral GC.

Table 3. Transfer hydrogenation of acetophenone using ligands **10a**, **10b**, **20b** and **21b**[a]



Entry	Ligand[b]	Time (h)	Conv. (%)[c]	ee (%)[c]	Conf. of product
1	 **10a**	1	3	38	*R*
		16	32	79	
2	 **10b**	1	9	16	*S*
		16	58	27	
3	 **20b**	1	14	14	*R*
		16	48	24	
4	 **21b**	1	13	42	*R*
		16	83	28	

[a] See Section 4 for procedure.
[b] Substrate/metal/ligand/base=200:1:2:5.
[c] Determined by chiral GC.

mechanism while the Ir-catalyzed reaction proceeds via direct hydrogen transfer between simultaneously coordinated ketone and alcohol. This difference in reaction mechanisms might explain the change of the enantiomeric excess in Ir-catalyzed transfer hydrogenation.

3. Conclusions

The synthesis of a new class of (1*S*,3*R*,4*R*)-2-azabicyclo[2.2.1]heptane-oxazoline ligands has been developed. This route can be used to prepare various derivatives of these new ligands in enantiomerically pure forms from commercially available starting materials.

The compounds were evaluated in the asymmetric transfer hydrogenation of acetophenone. It was found that [IrCl$_2$(COD)]$_2$ was the best catalyst precursor and use of the oxazoline **10a** as a ligand gave rise to a catalyst of good selectivity, 79% ee. These C$_1$ symmetric oxazolinyl azabicyclic amine ligands are currently under investigation and will be also tested in other asymmetric transformations.

4. Experimental

^{1}H and ^{13}C NMR spectra were recorded in CDCl$_3$ solutions at 399.95/100.57 MHz. The chemical shifts are reported using the residual signal of CDCl$_3$ as the internal reference. Optical rotations were recorded on a thermostated polarimeter using a 1.0 dm cell. GC analysis was performed using the chiral column CP-Chiralsil-Dex CB with N_2 as the carrier gas at 15 psi and using a FID detector. Flash chromatography was performed on silica gel (37–70 μm). The TLCs were performed on 0.25 mm precoated plates, silica gel 60 UV_{254} and spots were visualized using UV light and ethanolic phosphomolybdic acid followed by heating. The chiral starting materials, amines, acids and other reagents were used as received from commercial suppliers. Dichloromethane and isopropanol were dried over CaH_2 and distilled under nitrogen prior to use.

4.1. General procedure for transfer hydrogenation of acetophenone

$[IrCl(COD)]_2$ (3.35 mg, 5.0 μmol), ligand (20.0 μmol) and *i*-PrOH (2 mL) were added to a dry 50 mL Schlenk flask under argon. The solution was stirred for 1 h at 80 °C and then cooled down to room temperature. *i*-PrOH (18 mL) was added followed by acetophenone (235 μL, 2.0 mmol) and 1.0 M *i*-PrOK in *i*-PrOH (50 μL, 50.0 μmol). The reaction mixture was stirred for 16 h at room temperature and quenched by addition of two drops of 1.0 M HCl. Evaporation of solvent and flash chromatography (diethyl ether/pentane) gave the pure 1-phenylethanol. The enantiomeric excess was determined by chiral GC analysis.

4.1.1. (1*S*,3*R*,4*R*)-2-Aza-bicyclo-[2.2.1]-heptane-2,3-dicarboxylic acid 2-benzyl ester (2). Compound **1** (7.0 g, 47.6 mmol) was dissolved in 476 mL of H_2O (10 mL/mmol). A solid $NaHCO_3$ (10.0 g, 119.0 mmol) was added and the mixture was stirred until a clear solution was obtained. Benzyl chloroformate (7.5 mL, 52.4 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 3 h. The water solution was extracted with diethyl ether (2×200 mL), the phases were separated and the aqueous phase was acidified with conc. HCl to pH~4. (A milky white suspension was formed.) The suspension was extracted with diethyl ether (2×300 mL), the organic phase was dried over $MgSO_4$ and evaporated to yield compound **2** (9.4 g, 34.3 mmol, yield 72%) as a colorless oil, which was used in later steps without further purification. (NMR spectra are reported for a mixture of two rotamers.) ^1H NMR ($CDCl_3$) δ 10.24 (brs, 1H); 7.39–7.26 (m, 5H); 5.23–5.08 (m, 2H); 4.44–4.34 (m, 1H); 3.96–3.90 (m, 1H); 2.90–2.79 (m, 1H); 2.00–1.30 (m, 6H) ppm; ^{13}C NMR ($CDCl_3$) δ 175.1, 174.0, 155.5, 153.8, 136.2, 136.0, 128.2, 128.1, 127.8, 127.6, 127.5, 127.1, 67.2, 66.6, 64.45, 63.8, 57.4, 56.9, 42.35, 41.0, 35.4, 34.4, 30.2, 29.8, 27.5, 27.0 ppm; IR (neat) ν_{max} 2952, 1750, 1705, 1666, 1426, 1359, 1130, 1109 cm^{-1}; MS (EI) *m/z* (rel. intensity) 276 (M^++1, 40%), 232 (20), 186 (34), 158 (48), 141 (52), 112 (28), 92 (100), 68 (44); HRMS (FAB^+) ($M+H^+$): calcd for $C_{15}H_{18}NO_4$: 276.1236. Found: 276.1247.

4.1.2. (1*S*,3*R*,4*R*)-2-Aza-bicyclo-[2.2.1]-heptane-2,3-dicarboxylic acid 2-*p*-nitrobenzyl ester (12). Compound **1** (4.1 g, 29.0 mmol) was dissolved in mixture of dioxane (96 mL) and water (68 mL) followed by addition of 2.0 M NaOH (16.6 mL). The solution was stirred for 5 min. Then *p*-nitrobenzylchloroformate (8.1 g, 37.7 mmol) in dioxane (58 mL) and 2.0 M NaOH (19.9 mL) were added simultaneously. The reaction was stirred at room temperature overnight. Water (280 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (2×500 mL). The water phase was acidified with conc. HCl and extracted with EtOAc (2×500 mL). The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using 0–5%MeOH/CH_2Cl_2 as the eluent to give after evaporation the title compound **12** as pale yellow crystals (8.0 g, 24.9 mmol, yield 86%) mp=198–199 °C. (NMR spectra are reported for a mixture of two rotamers.) ^1H NMR ($CDCl_3$) δ 8.32–8.07 (m, 2H), 7.62–7.38 (m, 2H), 5.43–4.18 (m, 2H), 4.52–4.30 (m, 1H), 4.00–3.86 (m, 1H), 2.98–2.76 (m, 1H), 2.00–1.10 (m, 7H) ppm; ^{13}C NMR ($CDCl_3$) δ 176.1, 174.1, 155.3, 153.2, 147.7, 147.4, 144.0, 143.6, 66.05, 65.4, 64.8, 64.0, 57.8, 57.35, 42.7, 41.1, 35.9, 34.7, 30.5, 30.1, 27.8, 27.15 ppm; IR (neat) ν_{max} 3444, 2955, 1700, 1607, 1520, 1436, 1407, 1130, 859, 737 cm^{-1}; MS (EI) *m/z* (rel. intensity) 321 (M^+, 1%), 275 (20), 203 (69), 160 (20), 154 (47), 137 (100), 107 (90); HRMS (FAB^+) ($M+H^+$): calcd for $C_{15}H_{17}N_2O_6$: 321.1087. Found: 321.1084.

4.2. General procedure for preparation of hydroxylamides 3a, 3b, 4a, 4b, 5a, 5b, 13, 14a, 14b, 15a and 15b

A mixture of protected acid **2** or **12** (1 equiv.), EDC (2 equiv.) and HOBt (2 equiv.) was stirred in dry CH_2Cl_2 (4 mL/mmol of acid) at 0 °C for 5 min. The appropriate aminoalcohol (1.5 equiv.) was dissolved in dry CH_2Cl_2 (2 mL/mmol) and added to the reaction mixture. The resulting clear solution was warmed up to room temperature and stirred overnight. The reaction mixture was washed with 1.0 M HCl (aq.) and saturated $NaHCO_3$ (aq.). The organic phase was dried over $MgSO_4$ and evaporated to give the crude hydroxylamide, which was purified by column chromatography using 0–2%MeOH/CH_2Cl_2 as the eluent to yield pure compounds **3a**, **3b**, **4a**, **4b**, **5a**, **5b**, **13**, **14a**, **14b**, **15a** and **15b** after removal of solvents.

4.3. General procedure for preparation of protected oxazolines 6a, 6b, 7a, 7b, 8a, 8b, 16, 17a, 17b, 18a and 18b

The hydroxylamide (1 equiv.) was dissolved in CH_2Cl_2/Et_3N (3/1, v/v, 9 mL/mmol) under nitrogen atmosphere and the solution was cooled to 0 °C. To this solution MsCl (2 equiv.) was slowly added and the reaction mixture was stirred at room temperature overnight. It was washed with water; the organic phase was dried over $MgSO_4$ and evaporated to afford crude protected oxazoline. Purification by column chromatography with 0–2%MeOH/CH_2Cl_2 as the eluent and evaporation of solvents gave protected oxazolines **6a**, **6b**, **7a**, **7b**, **8a**, **8b**, **16**, **17a**, **17b**, **18a** and **18b** as clear colorless oils.

4.4. General deprotection procedure for preparation of oxazolines 9a, 9b, 10a, 10b, 11a, 11b, 19, 20a, 20b, 21a and 21b

The protected oxazoline was dissolved in dry EtOH (10 mL/mmol) and a solution of activated Pd/C in dry EtOH (10 wt% of Pd/C related to oxazoline) was added. The mixture was connected to the H_2 source (1 atm.) and stirred at room temperature overnight. The Pd/C was filtered off and the solvent was evaporated to give crude deprotected oxazoline. The crude compounds were purified on a deactivated silica gel column. The deactivation was done as follows: the column was packed with a suspension of silica gel in 20%Et_3N/CH_2Cl_2 and the silica was washed with 1%Et_3N/CH_2Cl_2. The chromatography was performed using 0–2%MeOH/1%Et_3N/CH_2Cl_2 as the eluent to afford oxazolines **9a**, **9b**, **10a**, **10b**, **11a**, **11b**, **19**, **20a**, **20b**, **21a** and **21b** after evaporation of solvents under reduced pressure.

4.4.1. (1*S*,3*R*,4*R*)-3-(2′-Hydroxy-1′(*S*)-methyl-ethyl-carbomoyl)-2-aza-bicyclo-[2.2.1]-heptane-2-carboxylic acid 2-benzyl ester (3a). (0.92 g, 2.86 mmol, yield 94%) (white crystals) mp=92–95 °C; (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 7.45–7.22 (m, 5H); 6.82–6.68 (m, 0.55H); 6.28–6.18 (m, 0.45H); 5.30–4.93 (m, 2H); 4.34–4.19 (m, 1H); 4.08–3.90 (m, 1H); 3.81–3.72 (m, 1H); 3.64–3.37 (m, 2H); 3.19–2.78 (m, 2H); 1.91–0.86 (m, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 171.1, 156.5, 155.7, 136.1, 135.9, 128.4, 128.1, 127.8, 67.3, 67.0, 66.9, 47.8, 47.5, 42.1, 40.3, 35.9, 34.55, 30.05, 29.0, 27.2, 26.6, 16.6, 16.5 ppm; IR (neat) ν_{max} 3408, 3325, 2947, 2871, 1702, 1650, 1530, 1411, 1352, 1101, 1050 cm^{-1}; MS (EI) *m/z* (rel. intensity) 333 (M^++1, 22%), 302 (24), 230 (32), 186 (84), 158 (82), 92 (100), 65 (20); HRMS (FAB^+) ($M+H^+$): calcd for $C_{18}H_{25}N_2O_4$: 333.1814. Found: 333.1817.

4.4.2. (1*S*,3*R*,4*R*)-3-(2′-Hydroxy-1′(*R*)-methyl-ethyl-carbomoyl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid benzyl ester (3b). (0.96 g, 2.98 mmol, yield 87%) (white crystals) mp=143–145 °C; (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 7.38–7.23 (m, 5H); 6.73–6.63 (m, 0.6H); 6.38–6.31 (m, 0.4H); 5.27–4.93 (m, 2H); 4.30–4.19 (m, 1H); 4.04–3.89 (m, 1H); 3.81–3.73 (m, 1H); 3.68–3.16 (m, 2.6H); 2.94–2.63 (m, 1.4H); 1.82–0.98 (m, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 170.6, 156.5, 155.0, 136.0, 128.4, 128.05, 127.8, 67.3, 66.9, 66.2, 66.05, 57.9, 47.4, 47.1, 42.0, 40.2, 35.9, 34.5, 29.9, 29.0, 27.2, 26.7, 16.7 ppm; IR (neat) ν_{max} 3408, 3330, 2952, 2874, 1691, 1661, 1536, 1414, 1354, 1167, 1102, 1050 cm^{-1}; MS (EI) *m/z* (rel. intensity) 333 (M^++1, 42%), 302 (14), 230 (30), 186 (90), 158 (80), 92 (100), 65 (16); HRMS (FAB^+) ($M+H^+$): calcd for $C_{18}H_{25}N_2O_4$: 333.1814. Found: 333.1820.

4.4.3. (1*S*,3*R*,4*R*)-3-(2′-Hydroxy-1′(*S*)-isopropyl-ethyl-carbomoyl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid benzyl ester (4a). (1.10 g, 3.32 mmol, yield 73%) (light-yellow oil) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 7.38–7.23 (m, 5H); 6.80–6.71 (m, 0.55H); 6.42–6.34 (m, 0.45H); 5.20–5.02 (m, 2H); 4.30–4.14 (m, 1H); 3.80–3.20 (m, 5H); 2.94–2.72 (m, 1H); 1.92–1.09 (m, 7H); 0.98–0.59 (m, 6H) ppm; ^{13}C NMR ($CDCl_3$) δ 171.0, 170.8, 156.2, 155.3, 136.0, 135.8, 128.3, 128.2, 128.0, 127.9, 127.7, 127.6, 67.1, 67.0, 66.7, 63.3, 62.8, 57.8, 56.8, 56.4, 42.0, 40.4, 35.6, 34.3, 29.9, 28.9, 28.5, 28.2, 27.0, 26.6, 19.4, 19.2, 18.3, 18.0 ppm; IR (neat) ν_{max} 3411, 2959, 2875, 1700, 1530, 1409, 1354, 1299, 1168, 1101, 1049, 912 cm^{-1}; MS (EI) *m/z* (rel. intensity) 361 (M^++1, 18%), 344 (6), 159 (11), 92 (100); HRMS (FAB^+) ($M+H^+$): calcd for $C_{20}H_{29}N_2O_4$: 361.2127. Found: 361.2125.

4.4.4. (1*S*,3*R*,4*R*)-3-(2′-Hydroxy-1′(*R*)-isopropyl-ethyl-carbomoyl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid benzyl ester (4b). (1.68 g, 4.69 mmol, yield 94%) (white crystals) mp=129–132 °C; (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 7.41–7.26 (m, 5H); 6.77–6.65 (m, 0.6H); 6.33–6.23 (m, 0.4H); 5.30–4.97 (m, 2H); 4.34–4.25 (m, 1H); 3.86–3.35 (m, 4H); 2.96–2.81 (m, 1H); 1.79–1.30 (m, 7H); 0.94–0.78 (m, 6H) ppm; ^{13}C NMR ($CDCl_3$) δ 171.1, 171.0, 156.7, 155.6, 136.1, 136.0, 128.4, 128.15, 127.8, 67.4, 67.2, 63.7, 63.3, 58.0, 57.3, 56.7, 42.05, 40.1, 36.1, 34.7, 30.0, 28.8, 28.7, 27.3, 26.7, 19.4, 18.6, 18.5 ppm; IR (neat) ν_{max} 3408, 2960, 2873, 1687, 1530, 1414, 1353, 1301, 1167, 1100 cm^{-1}; MS (EI) *m/z* (rel. intensity) 361 (M^++1, 40%), 329 (33), 275 (20), 230 (26), 186 (100), 158 (70), 92 (88), 65 (18); HRMS (FAB^+) ($M+H^+$): calcd for $C_{20}H_{29}N_2O_4$: 361.2127. Found: 361.2125.

4.4.5. (1*S*,3*R*,4*R*)-3-(2′-Hydroxy-1′(*S*)-*tert*-butyl-ethyl-carbomoyl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid benzyl ester (5a). (0.68 g, 1.87 mmol, yield 64%) (white crystals) mp=120–122 °C; (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 7.42–7.20 (m, 5H); 6.98–6.78 (m, 0.6H); 6.36–6.19 (m, 0.4H); 5.27–5.02 (m, 2H); 4.39–4.09 (m, 1H); 3.93–3.65 (m, 3H); 3.35–3.52 (m, 1H); 3.01–2.81 (m, 1H); 2.72–2.57 (m, 0.6H); 2.21–2.38 (m, 0.4H); 1.93–1.18 (m, 6H); 0.53–1.01 (m, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 171.8, 170.9, 156.65, 156.62, 136.4, 136.3, 128.4, 128.1, 127.8, 67.3, 66.9, 63.3, 62.7, 60.1, 59.3, 58.0, 42.3, 40.2, 36.1, 34.55, 33.2, 30.1, 29.0, 27.1, 26.6 ppm; IR (neat) ν_{max} 3412, 3331, 2959, 2871, 1704, 1653, 1528, 1399, 1352, 1300, 1167, 1097, 1050 cm^{-1}; MS (EI) *m/z* (rel. intensity) 375 (M^++1, 5%), 343 (50), 255 (20), 230 (22), 186 (82), 158 (62), 91 (100), 65 (20); HRMS (FAB^+) ($M+H^+$): calcd for $C_{21}H_{31}N_2O_4$: 375.2284. Found: 375.2282.

4.4.6. (1*S*,3*R*,4*R*)-3-(2′-Hydroxy-1′(*R*)-*tert*-butyl-ethyl-carbomoyl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid benzyl ester (5b). (1.55 g, 4.15 mmol, yield 94%) (light-yellow oil) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 7.41–7.25 (m, 5H); 6.78–6.65 (m, 0.7H); 6.38–6.27 (m, 0.3H); 5.30–4.97 (m, 2H); 4.37–4.18 (m, 1H); 3.86–3.27 (m, 4H); 3.02–2.77 (m, 1.7H); 2.53–1.98 (m, 0.3H); 1.88–1.23 (m, 6H); 0.83 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 171.1, 156.6, 155.3, 136.05, 135.9, 128.4, 128.0, 127.7, 67.3, 67.1, 62.4, 59.7, 58.9, 57.9, 42.0, 39.9, 36.2, 34.7, 33.0, 29.9, 28.95, 26.6 ppm; IR (neat) ν_{max} 3332, 2960, 2874, 1685, 1540, 1414, 1355, 1302, 1169, 1100, 1050 cm^{-1}; MS (EI) *m/z* (rel. intensity) 375 (M^++1, 9%), 186 (24), 158 (22), 91 (100), 68 (19); HRMS (FAB^+) ($M+H^+$): calcd for $C_{21}H_{31}N_2O_4$: 375.2284. Found: 375.2279.

4.4.7. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*S*)-methyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid benzyl ester (6a). (0.45 g, 1.42 mmol, yield 88%) (light-yellow oil) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 7.35–7.25 (m, 5H); 5.24 (d, *J*=12.7 Hz, 0.45H); 5.21 (d, *J*=12.7 Hz, 0.55H); 5.01 (d, *J*=13.1 Hz, 0.55H); 4.98 (d, *J*=13.1 Hz, 0.45H); 4.39–3.99 (m, 4H); 3.81–3.79 (m, 0.55H); 3.62–3.57 (m, 0.45H); 2.70–2.62 (m, 1H); 2.08–2.03 (m, 1H); 1.80–1.42

(m, 4H); 1.33–1.10 (m, 4H) ppm; ^{13}C NMR (CDCl$_3$) δ 165.8, 165.6, 155.0, 153.9, 136.7, 136.6, 129.3, 128.15, 127.75, 127.73, 127.5, 127.3, 74.2, 74.05, 66.8, 66.3, 61.35, 61.30, 60.6, 60.3, 57.4, 56.9, 42.9, 41.6, 35.3, 34.7, 30.4, 29.9, 27.5, 27.1, 21.3, 21.05 ppm; IR (neat) $\nu_{\max}$ 3330, 2966, 2871, 1705, 1670, 1415, 1355, 1190, 1166, 1101 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 314 (M$^+$, 16%), 208 (18), 179 (30), 164 (16), 91 (100), 65 (24); HRMS (FAB$^+$) (M+H$^+$): calcd for $C_{18}H_{23}N_2O_3$: 315.1709. Found: 315.1711.

4.4.8. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*R*)-methyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid benzyl ester (6b). (0.82 g, 2.61 mmol, yield 87%) (light-yellow oil) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR (CDCl$_3$) δ 7.37–7.26 (m, 5H); 5.25 (d, J=12.6 Hz, 0.45H); 5.20 (d, J=12.6 Hz, 0.55H); 5.06 (d, J=12.6 Hz, 0.55H); 4.97 (d, J=12.6 Hz, 0.45H); 4.40–3.96 (m, 4H); 3.85–3.69 (m, 1H); 2.68–2.62 (m, 1H); 2.08–2.02 (m, 1H); 1.82–1.45 (m, 4H); 1.33–1.11 (m, 4H) ppm; ^{13}C NMR (CDCl$_3$) δ 165.5, 165.4, 156.7, 155.6, 136.8, 136.6, 128.3, 128.2, 127.77, 127.75, 127.5, 127.3, 74.2, 74.1, 66.8, 66.3, 61.3, 61.2, 60.7, 60.3, 57.4, 56.9, 42.7, 41.9, 35.5, 34.7, 30.5, 29.9, 27.5, 27.2, 21.3, 21.2 ppm; IR (neat) $\nu_{\max}$ 3336, 2967, 1705, 1671, 1416, 1356, 1190, 1164, 1101 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 315 (M$^+$+1, 90%), 230 (12), 208 (24), 186 (50), 158 (44), 112 (18), 93 (100), 65 (18); HRMS (FAB$^+$) (M+H$^+$): calcd for $C_{18}H_{23}N_2O_3$: 315.1709. Found: 315.1709.

4.4.9. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*S*)-isopropyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid benzyl ester (7a). (0.99 g, 2.89 mmol, yield 87%) (light-yellow oil) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR (CDCl$_3$) δ 7.36–7.25 (m, 5H); 5.21 (d, J=12.6 Hz, 0.55H); 5.19 (d, J=12.6 Hz, 0.45H); 5.04 (d, J=12.4 Hz, 0.55H); 5.02 (d, J=12.4 Hz, 0.44H); 4.40–4.22 (m, 2H); 4.08–3.97 (m, 2H); 3.87–3.77 (m, 1H); 2.65–2.59 (m, 1H); 2.17–2.08 (m, 1H); 1.90–1.45 (m, 5H); 1.38–1.28 (m, 1H); 0.93–0.76 (m, 6H) ppm; ^{13}C NMR (CDCl$_3$) δ 165.7, 165.4, 154.85, 153.9, 136.7, 136.6, 128.4, 128.25, 128.1, 127.9, 127.7, 127.5, 127.3, 71.9, 71.6, 70.0, 69.6, 60.6, 60.3, 57.35, 56.9, 43.2, 42.0, 35.4, 34.8, 32.2, 31.9, 30.4, 29.9, 27.5, 27.2, 18.63, 18.59, 17.8, 17.2 ppm; IR (neat) $\nu_{\max}$ 3350, 2959, 2871, 1703, 1661, 1414, 1354, 1300, 1166, 1102 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 343 (M$^+$+1, 22%), 275 (15), 230 (30), 207 (16), 186 (96), 158 (72), 92 (100), 68 (20); HRMS (FAB$^+$) (M+H$^+$): calcd for $C_{20}H_{27}N_2O_3$: 343.2022. Found: 343.2018.

4.4.10. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*R*)-isopropyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid benzyl ester (7b). (1.36 g, 3.97 mmol, yield 95%) (light-yellow oil) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR (CDCl$_3$) δ 7.40–7.25 (m, 5H); 5.22–4.99 (m, 2H); 4.40–3.81 (m, 5H); 2.71–2.61 (m, 1H); 2.07–1.99 (m, 1H); 1.90–1.45 (m, 5H); 1.34–1.23 (m, 1H); 0.94–0.73 (m, 6H) ppm; ^{13}C NMR (CDCl$_3$) δ 165.5, 165.3, 154.7, 153.9, 136.71, 136.66, 128.2, 128.1, 127.6, 127.5, 127.3, 71.5, 71.4, 69.7, 69.5, 66.6, 66.2, 60.6, 60.4, 57.4, 57.0, 43.1, 42.1, 35.5, 34.7, 32.0, 31.9, 30.4, 29.9, 27.4, 27.1, 18.34, 18.28, 17.4, 17.1 ppm; IR (neat) $\nu_{\max}$ 3411, 3331, 3012, 2961, 2875, 1700, 1416, 1356, 1191, 1103 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 342 (M$^+$, 100%), 255 (30), 236 (52), 208 (58), 192 (32), 158 (30); HRMS (FAB$^+$) (M+H$^+$): calcd for $C_{20}H_{27}N_2O_3$: 343.2022. Found: 343.2025.

4.4.11. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*S*)-*tert*-butyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid benzyl ester (8a). (0.43 g, 1.22 mmol, yield 65%) (yellow oil) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR (CDCl$_3$) δ 7.37–7.26 (m, 5H); 5.21–5.04 (m, 2H); 4.38–3.76 (m, 5H); 2.63–2.59 (m, 1H); 2.21–2.13 (m, 1H); 1.76–1.25 (m, 5H); 0.90–0.73 (m, 9H) ppm; ^{13}C NMR (CDCl$_3$) δ 165.7, 165.4, 154.1, 154.0, 136.8, 136.7, 128.3, 128.15, 127.72, 127.70, 127.5, 127.3, 75.63, 75.54, 68.73, 68.68, 60.6, 60.3, 57.3, 57.0, 43.3, 42.3, 35.5, 34.8, 33.7, 33.4, 30.5, 29.9, 27.5, 27.3, 25.7, 25.6 ppm; IR (neat) $\nu_{\max}$ 2952, 1707, 1414, 1356, 1190, 1102 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 357 (M$^+$+1, 32%), 255 (30), 186 (16), 158 (18), 91 (100), 65 (26); HRMS (FAB$^+$) (M+H$^+$): calcd for $C_{21}H_{29}N_2O_3$: 357.2178. Found: 357.2175.

4.4.12. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*R*)-*tert*-butyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid benzyl ester (8b). (0.46 g, 1.25 mmol, yield 67%) (yellow oil) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR (CDCl$_3$) δ 7.37–7.24 (m, 5H); 5.20–4.98 (m, 2H); 4.38–4.30 (m, 1H); 4.18–3.7 (m, 4H); 2.70–2.60 (m, 1H); 2.01–1.96 (m, 1H); 1.78–1.21 (m, 5H); 0.93–0.73 (m, 9H) ppm; ^{13}C NMR (CDCl$_3$) δ 165.5, 165.2, 154.6, 153.9, 136.6, 128.1, 128.0, 127.6, 127.5, 127.4, 127.3, 75.2, 68.7, 68.5, 66.5, 66.2, 60.6, 60.4, 57.3, 56.9, 43.2, 42.2, 35.5, 34.7, 33.6, 33.4, 30.4, 29.8, 27.3, 27.0, 25.4, 25.3 ppm; IR (neat) $\nu_{\max}$ 2953, 2871, 1706, 1415, 1357, 1305, 1190, 1164, 1128, 1102, 1050, 998 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 357 (M$^+$+1, 100%), 255 (25), 91 (70); HRMS (FAB$^+$) (M+H$^+$): calcd for $C_{21}H_{29}N_2O_3$: 357.2178. Found: 357.2179.

4.4.13. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*S*)-methyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane (9a). (140 mg, 0.78 mmol, yield 55%) (yellow oil) $[\alpha]_D^{23}=-63$ (*c*=0.55 in CDCl$_3$); ^{1}H NMR (CDCl$_3$) δ 4.37 (dd, J=8.0, 9.4 Hz, 1H); 4.17–4.11 (m, 1H); 3.82–3.78 (m, 1H); 3.56–3.49 (m, 1H); 3.41–3.36 (m, 1H); 2.60–2.53 (m, 1H); 1.82 (brs, 1H); 1.65–1.57 (m, 3H); 1.48–1.43 (m, 2H); 1.45–1.23 (m, 4H) ppm; ^{13}C NMR (CDCl$_3$) δ 168.55, 74.4, 60.95, 58.8, 55.9, 40.9, 35.4, 31.4, 28.2, 21.3 ppm; IR (neat) $\nu_{\max}$ 3304, 2968, 2871, 1665, 1360, 1203, 1055, 1033, 1002, 853 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 181 (M$^+$+1, 100%), 151 (26), 94 (22); HRMS (FAB$^+$) (M+H$^+$): calcd for $C_{10}H_{17}N_2O$: 181.1341. Found: 181.1343.

4.4.14. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*R*)-methyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane (9b). (272 mg, 1.51 mmol, yield 58%) (yellow oil) $[\alpha]_D^{23}=+48$ (*c*=0.62 in CDCl$_3$); ^{1}H NMR (CDCl$_3$) δ 4.36 (dd, J=8.0, 9.3 Hz, 1H); 4.18–4.10 (m, 1H); 3.84–3.80 (m, 1H); 3.53–3.48 (m, 1H); 3.40–3.35 (m, 1H); 2.57–2.52 (m, 1H); 1.90 (brs, 1H); 1.63–1.58 (m, 3H); 1.47–1.42 (m, 2H); 1.26–1.21 (m, 4H) ppm; ^{13}C NMR (CDCl$_3$) δ 168.5, 74.3, 60.9, 58.8, 55.8, 40.95, 35.4, 31.3, 28.2, 21.2 ppm; IR (neat) $\nu_{\max}$ 3305, 2968, 1664, 1357, 1199, 1054, 1033, 1002 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 181

(M^++1, 100%), 151 (52), 94 (38); HRMS (FAB$^+$) (M+H$^+$): calcd for $C_{10}H_{17}N_2O$: 181.1341. Found: 181.1343.

4.4.15. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*S*)-isopropyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane (10a). (420 mg, 2.02 mmol, yield 70%) (oily white crystals, melts at rt) $[\alpha]_D^{23}=-61$ (c=1.00 in CDCl$_3$); ^{1}H NMR (CDCl$_3$) δ 4.23 (dd, J=8.15, 9.6 Hz, 1H); 3.99–3.95 (m, 1H); 3.92–3.85 (m, 1H); 3.51–3.49 (m, 1H); 3.38–3.34 (m, 1H); 2.53–2.49 (m, 1H); 2.24 (brs, 1H); 1.79–1.69 (m, 1H); 1.61–1.55 (m, 3H); 1.47–1.39 (m, 2H); 1.23–1.20 (m, 1H); 0.90 (d, J=6.75 Hz, 3H); 0.84 (d, J=6.75 Hz, 3H) ppm; ^{13}C NMR (CDCl$_3$) δ 168.55, 71.3, 70.2, 58.9, 55.9, 41.15, 35.5, 32.2, 31.3, 28.3, 18.5, 17.7 ppm; IR (neat) ν_{max} 3306, 2963, 2872, 1667, 1468, 1363, 1208, 1146, 1055, 1032, 945, 854 cm^{-1}; MS (EI) *m/z* (rel. intensity) 208 (M^+, 24%), 179 (100), 94 (22), 68 (20); HRMS (FAB$^+$) (M+H$^+$): calcd for $C_{12}H_{21}N_2O$: 209.1654. Found: 209.1651.

4.4.16. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*R*)-isopropyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane (10b). (562 mg, 2.70 mmol, yield 68%) (yellow oil) $[\alpha]_D^{23}=+42$ (c=1.07 in CDCl$_3$); ^{1}H NMR (CDCl$_3$) δ 4.23 (dd, J=9.9, 8.5 Hz, 1H); 3.99 (dd, J=7.5, 8.5 Hz, 1H); 3.89–3.83 (m, 1H); 3.51–3.47 (m, 1H); 3.40–3.36 (m, 1H); 2.56–2.51 (m, 1H); 2.26 (brs, 1H); 1.78–1.65 (m, 1H); 1.62–1.53 (m, 3H); 1.50–1.39 (m, 2H); 1.24–1.21 (m, 1H); 0.91 (d, J=6.75 Hz, 3H); 0.83 (d, J=6.35 Hz, 3H) ppm; ^{13}C NMR (CDCl$_3$) δ 168.4, 71.3, 70.4, 58.95, 55.9, 41.1, 35.5, 32.3, 31.2, 28.3, 18.4, 17.7 ppm; IR (neat) ν_{max} 3387, 2961, 2872, 1666, 1471, 1361, 1203, 1055, 1033, 946, 853 cm^{-1}; MS (EI) *m/z* (rel. intensity) 209 (M^++1, 100%), 179 (94), 96 (38), 68 (55); HRMS (FAB$^+$) (M+H$^+$): calcd for $C_{12}H_{21}N_2O$: 209.1654. Found: 209.1650.

4.4.17. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*S*)-*tert*-butyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane (11a). (200 mg, 0.90 mmol, yield 74%) (white crystals) mp=105–108 °C; $[\alpha]_D^{23}=-54$ (c=0.61 in CDCl$_3$); ^{1}H NMR (CDCl$_3$) δ 4.21 (dd, J=8.75, 10.05 Hz, 1H); 4.08 (dd, J=7.7, 8.75 Hz, 1H); 3.83 (ddd, J=1.65, 7.7, 10.05 Hz, 1H); 3.55–3.48 (m, 1H); 3.41–3.33 (m, 1H); 2.55–2.47 (m, 1H); 2.09 (brs, 1H); 1.66–1.42 (m, 5H); 1.30–1.23 (m, 1H); 0.88 (s, 9H) ppm; ^{13}C NMR (CDCl$_3$) δ 168.5, 75.2, 69.15, 59.1, 55.95, 41.3, 35.6, 33.5, 31.2, 28.4, 25.7 ppm; IR (neat) ν_{max} 3256, 2954, 2900, 2869, 1656, 1361, 1346, 1248, 1218, 985 cm^{-1}; MS (EI) *m/z* (rel. intensity) 223 (M^++1, 100%), 193 (40), 100 (26), 68 (16); HRMS (FAB$^+$) (M+H$^+$): calcd for $C_{13}H_{23}N_2O$: 223.1810. Found: 223.1805.

4.4.18. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*R*)-*tert*-butyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane (11b). (200 mg, 0.90 mmol, yield 72%) (white crystals) mp=45–47 °C; $[\alpha]_D^{23}=+45$ (c=1.03 in CDCl$_3$); ^{1}H NMR (CDCl$_3$) δ 4.17 (dd, J=10.0, 8.7 Hz, 1H); 4.09 (dd, J=7.6, 8.7 Hz, 1H); 3.78 (ddd, J=0.9, 7.6, 10.0 Hz, 1H); 3.52–3.47 (m, 1H); 3.42–3.37 (m, 1H); 2.58–2.52 (m, 1H); 2.31 (brs, 1H); 1.62–1.52 (m, 3H); 1.48–1.40 (m, 2H); 1.25–1.20 (m, 1H); 0.85 (s, 9H) ppm; ^{13}C NMR (CDCl$_3$) δ 168.35, 75.0, 69.15, 59.05, 55.9, 41.2, 35.6, 33.5, 31.2, 28.3, 25.5 ppm; IR (neat) ν_{max} 3306, 2955, 2904, 2870, 1669, 1479, 1359, 1199, 1055, 1027, 1004, 945, 853 cm^{-1}; MS (EI) *m/z* (rel. intensity) 223 (M^++1, 100%); HRMS (FAB$^+$) (M+H$^+$): calcd for $C_{13}H_{23}N_2O$: 223.1810. Found: 223.1803.

4.4.19. (1*S*,3*R*,4*R*)-3-(2′-Hydroxy-1′,1′-dimethyl-ethyl-carbomoyl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid *p*-nitrobenzyl ester (13). (0.62 g, 2.25 mmol, yield 72%) (yellow oil) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR (CDCl$_3$) δ 8.21–8.08 (m, 2H), 7.49–7.38 (m, 2H), 6.69 and 6.15 (2 brs, 1H) 5.34–5.14 and 5.10–4.98 (m, 2H), 4.69–4.38 (m, 1H), 4.28–4.18 (m, 1H), 3.69 (*s*, 1H) 3.55–3.39 (m, 1H), 2.88–2.69 (m, 1H), 1.86–1.05 (m, 12H) ppm; ^{13}C NMR (CDCl$_3$) δ 170.7, 155.9, 147.5, 143.5, 128.0, 123.6, 69.8, 67.2, 65.8, 65.6, 65.5, 59.2, 58.0, 55.7, 53.3, 42.4, 40.2, 39.0, 36.0, 34.5, 30.1, 29.5, 29.0, 27.4, 26.6, 24.3, 24.1, 22.8 ppm; IR (neat) ν_{max} 3383, 2973, 2872, 1707, 1607, 1522, 1403, 1344, 1165, 1107, 857, 736, 668 cm^{-1}; MS (EI) *m/z* (rel. intensity) 392 (M^++1, 5%), 360 (30), 275 (79), 203 (100), 140 (32), 136 (36), 106 (32), 89 (42), 78 (78), 68 (40); HRMS (FAB$^+$) (M+H$^+$): calcd for $C_{19}H_{26}N_3O_6$: 392.1822. Found: 392.1821.

4.4.20. (1*S*,3*R*,4*R*)-3-(2′-Hydroxy-1′(*S*)-phenyl-ethyl-carbomoyl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid *p*-nitrobenzyl ester (14a). (0.82 g, 2.66 mmol, yield 85%) (pale yellow semicrystals) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR (CDCl$_3$) δ 8.30–8.06 (m, 2H), 7.58–7.40 (m, 2H), 7.39–7.12 (m, 5H), 6.80 (brs, 1H), 5.40–4.96 (m, 3H), 4.38–4.16 (m, 1H), 4.00–3.66 (m, 3H), 3.06–2.22 (m, 1H), 1.89–1.18 (m, 7H) ppm; ^{13}C NMR (CDCl$_3$) δ 170.5, 143.4, 138.7, 128.8, 128.2, 127.8, 127.7, 126.6, 123.8, 67.2, 66.3, 66.0, 65.8, 58.3, 55.7, 40.2, 36.3, 30.2, 29.6, 26.7 ppm; IR (neat) ν_{max} 3401, 2952, 1703, 1606, 1521, 1400, 1106, 458, 700 cm^{-1}; MS (EI) *m/z* (rel. intensity) 441 (M^++1, 5%), 408 (50), 276 (61), 259 (100), 203 (40), 91(47), 77 (53), 68 (44); HRMS (FAB$^+$) (M+H$^+$): calcd for $C_{23}H_{26}N_3O_6$: 440.1822. Found: 440.1819.

4.4.21. (1*S*,3*R*,4*R*)-3-(2′-Hydroxy-1′(*R*)-phenyl-ethyl-carbomoyl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid *p*-nitrobenzyl ester (14b). (0.85 g, 2.72 mmol, yield 87%) (pale yellow semicrystals) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR (CDCl$_3$) δ 8.25–7.98 (m, 2H), 7.57–7.47 (m, 1H), 7.39–7.10 (m, 6H), 6.70 (brs, 1H), 5.40–4.96 (m, 4H), 4.40–4.22 (m, 1H), 3.94–3.68 (m, 3H), 3.03–2.87 (m, 1H), 2.39–2.08 (m, 1H), 2.00–1.16 (m, 7H) ppm; ^{13}C NMR (CDCl$_3$) δ 170.6, 165.2, 154.9, 147.6, 143.6, 143.0, 138.5, 128.8, 128.1, 127.8, 126.5, 123.8, 67.4, 67.1, 66.5, 66.3, 66.0, 58.2, 55.6, 55.4, 55.3, 42.5, 40.4, 36.2, 34.8, 30.3, 29.7, 29.2, 27.5, 26.7 ppm; IR (neat) ν_{max} 3372, 2943, 1692, 1519, 1402, 1344, 1106, 747, 668 cm^{-1}; MS (EI) *m/z* (rel. intensity) 441 (M^++1, 3%), 408 (47), 275 (72), 259 (100), 203 (60), 91(41), 77 (50), 68 (45); HRMS (FAB$^+$) (M+H$^+$): calcd for $C_{23}H_{26}N_3O_6$: 440.1822. Found: 440.1835.

4.4.22. (1*S*,3*R*,4*R*)-3-(2′-Hydroxy-1′(*S*)-benzyl-ethyl-carbomoyl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid *p*-nitrobenzyl ester (15a). (0.75 g, 2.38 mmol, yield 76%) (yellow foam) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR (CDCl$_3$) δ 8.29–8.17 (m, 2H), 7.59–7.43 (m, 2H), 7.34–7.11 (m, 5H), 6.63 (brs, 0.6H), 6.20 (brs, 0.4H), 5.31–5.05 (m, 2H), 4.26–4.11 (m, 1H), 3.81–3.44 (m, 2H), 2.98–2.30 (m, 5H), 1.82–1.06 (m, 7H) ppm; ^{13}C NMR ($CDCl_3$) δ 170.3, 170.1, 155.6, 154.4, 147.2, 143.4, 137.5, 132.1, 131.8, 131.7, 131.6, 131.1, 128.8, 128.3, 128.2, 128.0, 127.8, 127.6, 126.1, 123.4, 66.8, 65.6, 65.3, 63.2, 63.0, 58.8, 57.8, 57.6, 53.3, 52.1, 52.0, 42.1, 40.3, 36.6, 35.4, 33.9, 29.9, 29.3, 29.0, 27.1, 26.5 ppm; IR (neat) ν_{max} 3396, 2952, 1703, 1656, 1606, 1521, 1401, 1344, 1107, 756, 747 cm^{-1}; MS (EI) *m/z* (rel. intensity) 454 (M$^+$, 5%), 362 (10), 273 (100), 203 (34), 91 (29), 78 (19), 68 (12); HRMS (FAB$^+$) (M+H$^+$): calcd for $C_{24}H_{28}N_3O_6$: 454.1978. Found: 454.1972.

4.4.23. (1*S*,3*R*,4*R*)-3-(2′-Hydroxy-1′(*R*)-benzyl-ethyl-carbomoyl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid *p*-nitrobenzyl ester (15b). (0.63 g, 2.07 mmol, yield 66%) (pale yellow crystals) mp=57–60 °C; (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 8.16–8.01 (m, 1H), 7.60–7.53 (m, 1H), 7.51–7.33 (m, 2H), 7.20–7.05 (m, 5H), 6.75 (brs, 0.7H), 6.66 (brs, 0.3H), 5.24–4.95 (m, 2H), 4.27–4.08 (m, 2H), 4.00–3.68 (m, 2H), 3.64–3.42 (m, 2H), 2.92–2.65 (m, 1H), 2.58 (brs, 1H), 1.73–1.00 (m, 7H) ppm; ^{13}C NMR ($CDCl_3$) δ 170.5, 170.2, 155.8, 154.5, 147.3, 143.4, 137.5, 128.9, 128.1, 127.9, 127.7, 126.2, 123.5, 66.9, 65.7, 65.4, 63.4, 57.9, 57.7, 52.2, 42.1, 40.3, 36.6, 35.4, 34.0, 30.0, 29.3, 29.0, 27.1, 26.5 ppm; IR (neat) ν_{max} 3366, 2943, 1700, 1651, 1521, 1400, 1344, 1106, 756, 668 cm^{-1}; MS (EI) *m/z* (rel. intensity) 274 (M$^+$−*p*-Cbz-NO$_2$, 19%), 273 (100), 203 (46), 91 (42), 78 (20), 68 (12); HRMS (FAB$^+$) (M+H$^+$): calcd for $C_{24}H_{28}N_3O_6$: 454.1978. Found: 454.1990.

4.4.24. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′,5′-dimethyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid *p*-nitrobenzyl ester (16). (0.41 g, 1.09 mmol, yield 74%) (yellow oil) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 8.27–8.09 (m, 2H), 7.56–7.43 (m, 2H), 5.42–4.48 (m, 2H), 4.42–4.30 (m, 1H), 4.03–3.80 (m, 3H), 2.71–2.62 (m, 1H), 2.14–2.01 (m, 1H), 1.87–1.09 (m, 11H) ppm; ^{13}C NMR ($CDCl_3$) δ 164.4, 164.2, 154.6, 153.9, 147.6, 144.7, 144.6, 138.4, 127.8, 124.0, 123.8, 79.64, 79.61, 67.5, 65.7, 65.3, 61.1, 60.9, 58.0, 57.6, 43.1, 42.1, 35.7, 35.0, 30.9, 30.1, 28.5, 28.4, 27.8, 27.5 ppm; IR (neat) ν_{max} 2969, 1709, 1667, 1522, 1402, 1345, 1103, 736, 668 cm^{-1}; MS (EI) *m/z* (rel. intensity) 374 (M$^+$, 24%), 373 (36), 344 (25), 305 (27), 203 (18), 178 (100), 150 (26), 136 (25), 89 (38), 78 (68); HRMS (FAB$^+$) (M+H$^+$): calcd for $C_{19}H_{24}N_3O_5$: 374.1716. Found: 374.1720.

4.4.25. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*S*)-phenyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid *p*-nitrobenzyl ester (17a). (0.45 g, 1.08 mmol, yield 63%) (white semicrystals) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 8.14–7.95 (m, 2H), 7.50–7.32 (m, 2H), 7.30–7.03 (m, 5H), 5.34–4.97 (m, 3H), 4.63–4.51 (m, 1H), 4.37–4.27 (m, 1H), 4.14–3.90 (m, 2H), 2.77–2.65 (m, 1H), 3.20–2.05 (m, 1H), 1.86–1.13 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$) δ 166.6, 166.3, 153.9, 153.1, 147.1, 146.9, 144.0, 143.9, 141.9, 141.5, 128.2, 128.1, 127.7, 127.2, 127.1, 126.2, 126.0, 123.3, 123.1, 74.9, 74.7, 69.3, 69.21, 69.20, 65.1, 54.8, 60.5, 60.2, 57.3, 57.0, 42.8, 41.6, 35.2, 34.6, 30.4, 29.7, 27.2, 27.0 ppm; IR (neat) ν_{max} 3400, 2952, 1708, 1519, 1402, 1344, 1104, 755 cm^{-1}; MS (EI) *m/z* (rel. intensity) 286 (M$^+$−*p*-NO$_2$-C$_7$H$_7$, 2%), 285 (90), 275 (23), 241 (28), 226 (66), 225 (89), 203 (36), 106 (49), 91 (72), 78 (100); HRMS (FAB$^+$) (M+H$^+$): calcd for $C_{23}H_{24}N_3O_5$: 422.1716. Found: 422.1720.

4.4.26. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*R*)-phenyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid *p*-nitrobenzyl ester (17b). (0.48 g, 1.13 mmol, yield 83%) (white semicrystals) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 8.21–7.98 (m, 2H), 7.54–7.36 (m, 2H), 7.34–6.70 (m, 5H), 5.36–5.06 (m, 3H), 4.65–4.51 (m, 1H), 4.42–4.35 (m, 1H), 4.17–4.06 (m, 2H), 2.81–2.72 (m, 1H), 2.27–2.04 (m, 1H), 1.89–1.16 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$) δ 166.6, 166.5, 153.8, 153.3, 147.1, 156.9, 144.0, 144.0, 142.0, 141.7, 128.3, 128.2, 127.7, 127.3, 127.8, 127.0, 126.3, 126.2, 126.0, 123.3, 123.2, 69.2, 65.1, 64.8, 60.4, 60.3, 57.3, 57.1, 42.6, 41.7, 35.3, 34.5, 30.5, 29.3, 27.3, 27.1 ppm; IR (neat) ν_{max} 3305, 2947, 1708, 1666, 1519, 1403, 1344, 1103, 747, 668 cm^{-1}; MS (EI) *m/z* (rel. intensity) 423 (M$^+$+1, 5%), 421 (23), 285 (83), 226 (60), 225 (24), 106 (26), 104 (48), 91 (58), 78 (100); HRMS (FAB$^+$) (M+H$^+$): calcd for $C_{23}H_{24}N_3O_5$: 422.1716. Found: 422.1714.

4.4.27. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*S*)-benzyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid *p*-nitrobenzyl ester (18a). (0.45 g, 1.03 mmol, yield 78%) (colorless oil) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 8.22–8.03 (m, 2H), 7.51–7.38 (m, 2H), 7.28–7.03 (m, 5H), 5.37–4.93 (m, 2H), 4.47–4.25 (m, 2H), 4.23–4.08 (m, 1H), 4.05–3.80 (m, 2H), 3.12–2.87 (m, 1H), 2.69–2.47 (m, 2H), 2.14–2.02 (m, 1H), 1.82–1.14 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$) δ 165.9, 165.7, 154.1, 153.2, 147.2, 147.1, 144.3, 143.9, 137.4, 137.2, 129.0, 128.9, 128.4, 128.21, 128.2, 127.8, 127.2, 126.3, 126.2, 123.4, 123.3, 71.8, 71.7, 69.3, 66.99, 66.96, 65.2, 64.7, 60.5, 60.2, 57.4, 57.0, 53.3, 49.5, 42.6, 41.5, 41.2, 41.1, 35.3, 34.6, 30.4, 29.8, 29.4, 27.3, 27.0 ppm; IR (neat) ν_{max} 3400, 2952, 1707, 1606, 1521, 1404, 1345, 1188, 1105, 747, 668 cm^{-1}; MS (EI) *m/z* (rel. intensity) 435 (M$^+$, 5%), 344 (82), 299 (19), 203 (32), 191 (100), 148 (30), 117 (25), 91 (80), 78 (49); HRMS (FAB$^+$) (M+H$^+$): calcd for $C_{24}H_{26}N_3O_5$: 436.1872. Found: 436.1869.

4.4.28. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*R*)-benzyl-1′,3′-oxazol-2′yl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid *p*-nitrobenzyl ester (18b). (0.42 g, 0.96 mmol, yield 73%) (colorless oil) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 8.21–8.05 (m, 2H), 7.54–7.41 (m, 2H), 7.29–7.05 (m, 5H), 5.35–5.00 (m, 2H), 4.45–4.25 (m, 2H), 4.17–3.89 (m, 3H), 3.11–2.94 (m, 1H), 2.69–2.41 (m, 2H), 2.03–1.90 (m, 1H), 1.85–1.15 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$) δ 157.0, 156.7, 154.0, 153.3, 147.3, 147.2, 144.2, 144.1, 137.5, 137.2, 129.1, 128.9, 128.3, 128.2, 127.8, 127.3, 126.3, 126.2, 123.5, 123.3, 71.7, 66.9, 65.2, 64.9, 60.7, 60.4, 57.5, 57.1, 42.7, 41.7, 41.3, 41.2, 35.4, 34.7, 30.5, 29.8, 29.4, 27.3, 27.1 ppm; IR (neat) ν_{max} 3400, 2923, 1708, 1605, 1521, 1403, 1345, 1106, 756, 668 cm^{-1}; MS (EI) *m/z* (rel. intensity) 436 (M$^+$+1, 4%) 344 (52), 299 (6), 203 (23), 191 (63), 117 (19), 91 (100), 78 (64); HRMS (FAB$^+$) (M+H$^+$): calcd for $C_{24}H_{26}N_3O_5$: 436.1872. Found: 436.1881.

4.4.29. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′,5′-dimethyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane (19). (32 mg, 0.17 mmol, yield 59%) (yellow oil) $[\alpha]_D^{20}=0$ (*c* 4.25 in $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.90 (d, J=8.1 Hz, 1H), 3.87 (d, J=8.1 Hz, 1H), 3.48–3.43 (m, 1H), 3.30–3.29 (m, 1H), 2.53–2.48 (m, 1H), 2.08 (brs, 1H), 1.61–1.50 (m, 3H), 1.42–1.34 (m, 2H), 1.24–1.14 (m, 7H) ppm; ^{13}C NMR ($CDCl_3$) δ 167.2, 79.5, 66.6, 58.9, 55.9, 41.1, 35.4, 31.5, 28.31, 28.3, 28.1 ppm; IR (neat) ν_{max} 3305, 2968, 2926, 2872, 1663, 1191, 1004, 909, 732, 642 cm^{-1}; MS (EI) *m/z* (rel. intensity) 195 (M^++1, 98%), 194 (41), 165 (100), 94 (37), 72 (64), 68 (45); HRMS (FAB^+) ($M+H^+$): calcd for $C_{11}H_{19}N_2O$: 195.1497. Found: 195.1501.

4.4.30. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*S*)-phenyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane (20a). (64 mg, 0.26 mmol, yield 55%) (yellow oil) $[\alpha]_D^{20}=+2$ (c=5.0 in $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.39–7.14 (m, 5H), 5.19–5.09 (m, 1H) 4.66 (dd, J=8.4, 1.7 Hz, 1H), 4.15–4.06 (m, 1H), 3.55–3.50 (m, 1H), 3.49–3.44 (m, 1H), 2.69–2.62 (m, 1H), 2.29 (brs, 1H), 1.73–1.57 (m, 3H), 1.54–1.40 (m, 2H), 1.33–1.11 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 170.2, 142.2, 128.6, 127.5, 126.5, 76.7, 75.4, 69.2, 59.1, 56.1, 41.3, 35.7, 31.4, 28.4 ppm; IR (neat) ν_{max} 3305, 2967, 1661, 1360, 1191, 1055, 1031, 755, 700 cm^{-1}; MS (EI) *m/z* (rel. intensity) 242 (M^+, 37%), 213 (70), 120 (100), 94 (52), 91 (23); HRMS (FAB^+) ($M+H^+$): calcd for $C_{15}H_{19}N_2O$: 243.1497. Found: 243.1498.

4.4.31. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*R*)-phenyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane (20b). (63 mg, 0.26 mmol, yield 55%) (yellow oil) $[\alpha]_D^{20}=-5$ (c=4.7 in $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.39–7.18 (m, 5H), 5.23–5.12 (m, 1H), 4.66 (dd, J=8.3, 1.8 Hz, 1H), 4.19–4.10 (m, 1H), 3.57–3.50 (m, 2H), 2.68–2.63 (m, 1H), 2.26 (brs, 1H), 1.74–1.60 (m, 3H), 1.54–1.44 (m, 2H), 1.36–1.23 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 170.2, 142.1, 128.6, 127.5, 126.5, 69.1, 59.2, 56.1, 41.4, 35.7, 31.5, 28.5 ppm; IR (neat) ν_{max} 3304, 2967, 1661, 1453, 1358, 1189, 1054, 1033 cm^{-1}; MS (EI) *m/z* (rel. intensity) 242 (M^+ 40%), 213 (86), 120 (100), 94 (60), 91 (26); HRMS (FAB^+) ($M+H^+$): calcd for $C_{15}H_{19}N_2O$: 243.1497. Found: 243.1486.

4.4.32. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*S*)-benzyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane (21a). (65 mg, 0.25 mmol, yield 55%) (yellow oil) $[\alpha]_D^{20}=-2$ (c=7.62 in $CDCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.35–7.15 (m, 5H), 4.43–4.32 (m, 1H), 4.25–4.20 (m, 1H), 4.02 (dd, J=13.7, 7.3 Hz, 1H), 3.56–3.52 (m, 1H), 3.40–3.36 (m, 1H), 3.10 (dd, J=13.7, 5.1 Hz, 1H), 2.64 (dd, J=13.7, 8.5 Hz, 1H), 2.56–2.52 (m, 1H), 2.16 (brs, 1H), 1.68–1.59 (m, 3H), 1.51–1.40 (m, 2H), 1.30–1.23 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 169.3, 137.5, 129.2, 128.5, 126.5, 66.8, 58.9, 56.0, 41.6, 41.1, 35.6, 31.5, 29.6, 28.4 ppm; IR (neat) ν_{max} 3300, 2967, 2871, 1663, 1493, 1452, 1360, 1202, 1055, 1028, 946, 849, 757 cm^{-1}; MS (EI) *m/z* (rel. intensity) 256 (M^+ 30%), 227 (100), 117 (60), 94 (22), 91 (30), 68 (28); HRMS (FAB^+) ($M+H^+$): calcd for $C_{16}H_{21}N_2O$: 257.1654. Found: 257.1650.

4.4.33. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*R*)-benzyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane (21b). (67 mg, 0.26 mmol, yield 57%) (yellow oil) $[\alpha]_D^{20}=+1$ (c=7.66 in $CDCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.34–7.17 (m, 5H), 4.43–4.32 (m, 1H), 4.22 (dd, J=9.3, 8.5 Hz, 1H), 4.01 (dd, J=9.4, 8.4 Hz, 1H), 3.55–3.51 (m, 1H), 3.40–3.37 (m, 1H), 3.08 (dd, J=8.4, 7.0 Hz, 1H), 2.65 (dd, J=13.6, 8.4 Hz, 1H), 2.57–2.53 (m, 1H), 2.15 (brs, 1H), 1.65–1.56 (m, 3H), 1.50–1.42 (m, 2H), 1.29–1.23 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 169.6, 137.7, 129.3, 128.5, 126.5, 66.8, 59.1, 56.0, 41.6, 41.2, 35.6, 31.5, 28.4 ppm; IR (neat) ν_{max} 3300, 2967, 2871, 1663, 1493, 1452, 1361, 1198, 1054, 1028, 946, 771, 701 cm^{-1}; MS (EI) *m/z* (rel. intensity) 257 (M^++1, 48%). 256 (44), 227 (100), 117 (49), 94 (22), 91 (12), 69 (27); HRMS (FAB^+) ($M+H^+$): calcd for $C_{16}H_{21}N_2O$: 257.1654. Found: 257.1658.

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Preparation of pyrrolidine–oxazoline containing ligands and their application in asymmetric transfer hydrogenation

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Abstract—Nine members of a new ligand class incorporating both an oxazoline ring and a pyrrolidine unit were prepared in an efficient four-step synthesis starting from readily available chiral amino alcohols and proline. A study of these ligands in the asymmetric transfer hydrogenation of acetophenone showed that the catalysts formed from [Ir(cod)Cl]$_2$ were the most active while those derived from [Ru(*p*-cymene)Cl$_2$]$_2$ gave the highest enantioselectivities (up to 61% ee).
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1. Introduction

The preparation of enantiopure secondary alcohols by the catalytic enantioselective reduction of prochiral ketones is an important transformation in organic synthesis.[1] In recent years, extensive research has been carried out in this area with the development of asymmetric transfer hydrogenation.[2] This process offers an attractive alternative and/or complement to the use of molecular hydrogen and hydride reduction due to its operational simplicity and use of a safe, inexpensive and easy to handle hydrogen source.

Rhodium,[3,4c] iridium[4] and ruthenium[5] are the most commonly used metals for transfer hydrogenation with 2-propanol being the hydrogen source of choice. Ruthenium(arene) complexes bearing chiral 1,2-amino alcohol,[6] monotosylated diamine[7] and 1,2-diamine ligands[8,7c] are some of the most effective catalysts for asymmetric transfer hydrogenation of aromatic ketones in terms of both enantioselectivity and catalytic activity. It is thought that the NH group in these ligands plays a crucial role in achieving high enantioselectivity via a six-membered cyclic transition state brought about by hydrogen bonding between it and the ketone substrate.[9]

Chiral oxazoline-containing ligands have also been successful in asymmetric transfer hydrogenation using 2-propanol as the hydrogen donor.[10] For example, Zhang's tridentate bis(oxazolinylmethyl)amine ligand **1** gives up to 97% ee for the ruthenium-catalysed reduction of a variety of aromatic ketones with excellent conversions.[11] The catalyst formed from [Ru(*p*-cymene)Cl$_2$]$_2$ and the chiral 1,2,3,4-tetrahydroquinolinyl-oxazoline ligand **2** gave 83% ee for the reduction of acetophenone at −20 °C using 5 mol% ruthenium in moderate yield (46% after 21 h).[12]

α-Amino acids and their derivatives have also attracted attention as ligands for asymmetric transfer hydrogenation because they are relatively cheap and easily accessible.[13] Proline-derived ligands have recently been investigated and [Ru(*p*-cymene)Cl$_2$]$_2$ complexes of prolinamide **3** with a 4 mol% catalyst loading gave enantioselectivities in the range of 60–93% ee at −24 °C for a variety of ketone substrates.[14] (*S*)-2-Anilinomethylpyrrolidine **4** and (*S*)-2-naphthylaminomethyl-pyrrolidine **5** form highly active complexes with [Ru(*p*-cymene)Cl$_2$]$_2$ giving high enantioselectivities (74–96% ee) for the reduction of aromatic ketones in good to excellent yields (59–99%) with a catalyst loading of 0.2–0.5 mol% ruthenium.[15]

Encouraged by the results obtained by the use of both proline-derived and oxazoline-containing ligands, we have designed and prepared a new class of ligands **6a**-**i** for asymmetric transfer hydrogenation, which incorporate both of these structural units. These ligands contain the important NH moiety thought to be crucial for high enantioselectivities and the 1,2 arrangement of coordinating nitrogen atoms present in ligands **1** and **3**-**5**. In this paper, we describe the synthesis of nine members of this new class of ligands and discuss the results obtained in the reduction of acetophenone. As these ligands contain two chiral

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Keywords: Pyrrolidine–oxazoline; Hydrogenation; Proline-derived ligands.

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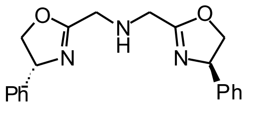

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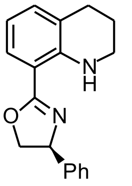

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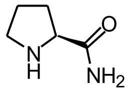

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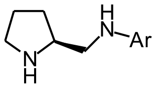
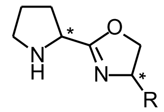


4 Ar = phenyl
5 Ar = naphthyl



6

	pyr.[a]	R		pyr.[a]	R
6a	(*S*)	H	**6f**	(*S*)	(*S*)-^{t}Bu
6b	(*S*)	(*S*)-^{i}Pr	**6g**	(*R*)	(*S*)-^{t}Bu
6c	(*S*)	(*R*)-^{i}Pr	**6h**	(*S*)	(*S*)-Me
6d	(*S*)	(*S*)-Ph	**6i**	(*S*)	(*S*)- Bn
6e	(*S*)	(*R*)-Ph			

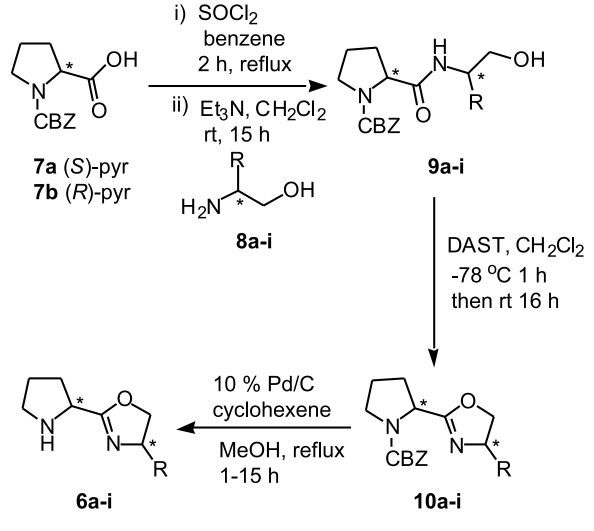
[a] Configuration of the pyrrolidine chiral centre

centres, diastereomeric ligand pairs (**6b** and **6c**, **6d** and **6e** and **6f** and **6g**) were investigated in order to determine the role of each chiral centre in enantioselection.

2. Results and discussion

2.1. Ligand synthesis

We envisaged that ligands **6a**-**i** could be prepared by means of a four-step synthesis starting from readily available chiral amino alcohols and proline (Scheme 1, Table 1). First, *N*-carbobenzyloxy(CBZ)-protected proline **7a**-**b** was chlorinated with thionyl chloride[16] and then reacted without purification with a chiral amino alcohol **8a**-**i** in the presence of triethylamine to give β-hydroxyamides **9a**-**i** in moderate to good yields (57–92%). We have recently reported that diethylaminosulfur triflouride (DAST) is a useful reagent for the cyclisation of β-hydroxyamides to oxazolines giving better results compared to the usual protocol of chlorination followed by base-induced cyclisation.[17] Cyclodehydration of **9a**-**i** by treatment with DAST afforded excellent yields (75–98%) of the CBZ-protected pyrrolidine–oxazolines **10a**-**i**, which were then deprotected in a transfer hydrogenolysis reaction using Pd/C and cyclohexene[18] yielding the required pyrrolidine–oxazoline ligands **6a**-**i** in moderate yields (40–89%). It was found that both **10a**-**i** and the final ligands were subject to ring-opening to the corresponding β-hydroxyamide after prolonged storage at room temperature. However, these compounds can be stored under nitrogen without significant decomposition at −6 °C.



Scheme 1. Synthesis of pyrrolidine–oxazoline ligands **6a**-**i**.

Table 1. Yields obtained for the reaction steps in the synthesis of ligands **6a**-**i**[a]

R	Hydroxyamide formation		Cyclisation		Deprotection	
	9	Yield (%)	10	Yield (%)	6	Yield (%)
H	**9a**	87	**10a**	86	**6a**	49
(*S*)-^{i}Pr	**9b**	92	**10b**	92	**6b**	89
(*R*)-^{i}Pr	**9c**	86	**10c**	87	**6c**	67
(*S*)-Ph	**9d**	57	**10d**	81	**6d**	46
(*R*)-Ph	**9e**	57	**10e**	94	**6e**	40
(*S*)-^{t}Bu	**9f**	81	**10f**	88	**6f**	48
(*S*)-^{t}Bu	**9g**[b]	82	**10g**[b]	75	**6g**[b]	55
(*S*)-Me	**9h**	60	**10h**	93	**6h**	55
(*S*)-Bn	**9i**	87	**10i**	98	**6i**	68

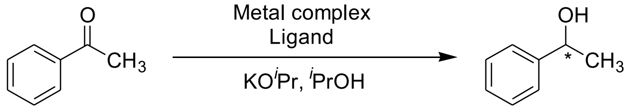
[a] (*S*)-Configuration of the pyrrolidine chiral centre.
[b] (*R*)-Configuration of the pyrrolidine chiral centre.

Because the pyrrolidine–oxazoline ligands have two chiral centres, it was necessary to prepare diastereomers to examine the effect of match and mismatch chiral centres on enantioselection. Initially, five ligands **6b**,**d**,**f**,**h**,**i** were prepared from (*S*)-proline **7a** and the corresponding naturally occurring (*S*)-amino alcohol. Using (*R*)-amino alcohols, diastereomers **6c** and **6e** of the *iso*-propyl- and phenyl-substituted ligands **6b** and **6d**, respectively, were synthesised. Since (*R*)-*tert*-leucinol is more expensive than its enantiomer, a diastereomer **6g** of the *tert*-butyl substituted ligand **6f** was accessed using (*S*)-*tert*-leucinol and (*R*)-proline **7b**. In total, nine members of this new ligand class **6a**-**i**, including three diastereomeric pairs were prepared in good overall yield for application in asymmetric transfer hydrogenation.

2.2. Metal screening and reaction optimisation

Using Chemspeed® ASW 2000 equipment, ligands **6a**-**i** were evaluated in the asymmetric transfer hydrogenation of

Table 2. Optimisation of reaction conditions for transfer hydrogenation of acetophenone[a]



Entry	Metal complex	Ligand	Lig/Met	Conv. (%)[b]		ee (%)[b]		Conf.[c]
				1 h	10 h	1 h	10 h	
1	[Ru(p-cymene)Cl$_2$]$_2$	**6b**	2.0		2		62	*R*
2	[Ir(cod)Cl]$_2$	**6b**	1.2	10	79	36	43	*R*
3	[Ir(cod)Cl]$_2$	**6b**	2.0	13	80	44	43	*R*
4	[Ir(cod)Cl]$_2$	**6b**	3.0	13	78	43	42	*R*
5	[Ir(cod)Cl]$_2$	**6b**	4.0	17	84	41	42	*R*
6[d]	[Ir(cod)Cl]$_2$	**6b**	2.0		65		41	*R*
7	[Ir(cod)Cl]$_2$	**6c**	2.0	9	63	45	42	*S*
8[e]	[Ir(cod)Cl]$_2$	**6c**	2.0	5	19	45	49	*S*
9[f]	[Ir(cod)Cl]$_2$	**6c**	2.0	18	88	43	41	*S*

[a] Acetophenone:KO^{i}Pr:Metal=200:5:1.

[b] Determined by GC analysis on a CP-Chirasil-Dex CB column (25 m, 0.25 (diam.), 0.25 μm).

[c] Determined by reference to literature values.[20]

[d] Acetophenone:KO^{i}Pr:Metal=20:5:1, reaction conducted at 0 °C.

[e] Acetophenone:KO^{i}Pr:Metal=200:2.5:1.

[f] Acetophenone:KO^{i}Pr:Metal=100:5:1.

acetophenone (Table 2). Six metal complexes of rhodium, iridium and ruthenium were screened with ligand **6b** in an attempt to find the optimal metal for transfer hydrogenation. Ruthenium [RuCl$_2$(PPh$_3$)$_3$ and RuCl$_2$(DMSO)$_4$] and rhodium [RhCl(PPh$_3$)$_3$ and [Rh(cod)Cl]$_2$] complexes showed no catalytic activity when tested with ligand **6b**. [Ru(p-cymene)Cl$_2$]$_2$ gave a slight conversion (2%) accompanied by a moderate ee of 62% (entry 1). The best results were achieved with the catalyst formed from ligand **6b** and [Ir(cod)Cl]$_2$ which afforded moderate enantioselectivity (43% ee) and good conversion (79%) after 10 h at room temperature (entry 2). The reaction was optimised by varying the reaction temperature, catalyst loading of the [Ir(cod)Cl]$_2$ pre-catalyst and the equivalents of ligand and base used. Changing the number of equivalents of ligand **6b** used (up to 4 equiv. lig/metal) had very little effect on both conversion and enantioselectivity (entries 2–5). In an attempt to increase enantioselectivities, the reaction was carried out at 0 °C using the iridium source and ligand **6b**. At this temperature, the reaction was sluggish affording 65% conversion after 10 h with a ten-fold increase in catalyst loading (5 mol%) but the enenatioselectivity did not change (entry 6). With the diastereomeric (*S*)-proline-(*R*)-*iso*-propyl ligand **6c**, the enantioselectivity increased (49% vs. 42%) when the amount of base used was halved, however this was accompanied by a significant decrease in catalytic activity (19% vs. 63% conversion after 10 h) (entries 7–8). Not surprisingly, increasing the catalyst loading by a factor of 2–1 mol% iridium resulted in increased conversion but little change in enantioselectivity (entry 9).

Table 3. Transfer hydrogenation of acetophenone using [Ir(cod)Cl]$_2$ and ligands **6a-i**[a]

Entry	Ligand	R	Conv. (%)[b]		ee (%)[b]		Conf.[c]
			1 h	15 h	1 h	15 h	
1	**6a**	H	42	94	Rac.	Rac.	—
2	**6b**	^{i}Pr	30	91	38	37	*R*
3	**6c**	^{i}Pr	32	81	39	38	*S*
4	**6d**	Ph	40	79	33	32	*R*
5	**6e**	Ph	21	55	41	34	*S*
6	**6f**	^{t}Bu	96	97	20	17	*R*
7	**6g**	^{t}Bu	60	86	16	16	*R*
8	**6h**	Me	27	79	10	13	*S*
9	**6i**	Bn	19	74	29	32	*S*

[a] Acetophenone:KO^{i}Pr:ligand:Ir=200:5:2:1, reactions conducted at room temperature.

[b] Determined by GC analysis on a Supelco β-Dex 120 column (30 m, 0.25 mm (diam.), 0.25 μm).

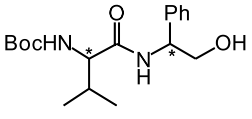
[c] Determined by reference to literature values.[20]

2.3. Iridium catalysed asymmetric transfer hydrogenation

Having determined the optimal reaction conditions ([Ir(cod)Cl]$_2$ (0.25 mol%), 5 equiv. KO^{i}Pr/Ir, 2 equiv. lig/Ir, room temp.), isolated experiments were carried out to evaluate the pyrrolidine–oxazoline ligands **6a-i** in transfer hydrogenation (Table 3). Firstly, all catalysts formed from [Ir(cod)Cl]$_2$ and ligands **6a-i** demonstrated high catalytic activity in the reaction giving up to 94% conversion after 15 h. Of these the (*S*)-proline-(*S*)-*tert*-butyl-substituted ligand **6f** proved particularly active affording 96% conversion after just 1 h. However, the enantioselctivity obtained using this ligand was poor (20% ee after 1 h) (entry 6). Similar levels of enantioselectivity were afforded using the *tert*-butyl diastereomer **6g** and the methyl-substituted ligand **6h** (entries 7–8). The *iso*-propyl- (**6b** and **6c**), phenyl- (**6d** and **6e**) and benzyl- (**6i**) substituted ligands gave the best levels of enantioselection but these were modest at best (32–38% ee) (entries 2–5 and 9).

Examining the results obtained using the three diastereomeric ligand pairs (**6b** and **6c**, **6d** and **6e** and **6f** and **6g**) reveals an interesting trend. In the case of the *iso*-propyl- and phenyl-substituted ligands, changing the configuration of the chiral centre at the oxazoline ring results in very similar levels of enantioselectivity but different enantiomers of the 1-phenylethanol product (entries 2–5). The *tert*-butyl-substituted diastereomers (**6f** and **6g**) with the same chiral centre at the oxazoline ring but with opposite configurations of the pyrrolidine chiral centre both gave (*R*)-1-phenylethanol with almost identical enantioselectivities after 15 h (entries 6 and 7). These results suggest that only the chiral centre on the oxazoline ring is important in controlling the stereochemical outcome of the reaction. This was confirmed by the racemic product obtained when ligand **6a**, which comprises of an unsubstituted oxazoline ring, was used (entry 1).

Conversely, the chiral centre of the pyrrolidine ring, appears to play some part in determining catalyst activity. This is evident by examining the conversions obtained by the catalysts formed from the diastereomeric ligand pairs. In all three cases, the ligand derived from (*S*)-proline and the (*S*)-amino alcohol gave higher conversions than those obtained with their respective diastereomers. This is best seen with the *tert*-butyl-substituted ligands, where the (*S*)-pyrrolidine-(*S*)-*tert*-butyl ligand **6d** gives (*R*)-1-phenylethanol in 96% conversion after 1 h while its diastereomer **6g** afforded product in only 60% conversion (entries 6 vs 7). Also, ligand **6a** which contains only the pyrrolidine chiral centre gives high conversions (94% after 15 h). This effect where one chiral centre, of the two in the ligand, dictates the stereochemistry of the product has been previously reported by Adolfsson in his study of transfer hydrogenation employing ligands of type **11**.[19]



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2.4. Ruthenium-catalysed asymmetric transfer hydrogenation

As shown in Table 2 (entry 1), when ligand **6b** was screened with [Ru(*p*-cymene)Cl_2]$_2$ (0.25 mol%), slight catalytic activity was observed. It has been reported in the literature, that quite high catalyst loadings (4–5 mol% Ru) were used for ruthenium-catalysed transfer hydrogenation with some oxazoline and pyrrolidine containing ligands.[12,14] Encouraged by this and in an attempt to increase the enantioselectivites obtained with this ligand class, we tested ligands **6a-i** in the transfer hydrogenation of acetophenone using a ten-fold increase in catalyst loading (2.5 mol% of [Ru(*p*-cymene)Cl_2]$_2$). Gratifyingly, for the majority of ligands tested moderate catalytic activity was recorded accompanied by improved enantioselectivity in some cases (Table 4). The best results were obtained using the *iso*-propyl-substituted ligands **6b** and **6c**, giving much improved enantioselectivities (51 (*R*) and 61 (*S*)% ee, respectively) compared to those afforded by iridium catalysis (37 (*R*) and 38 (*S*)% ee, respectively). The catalysts formed from these ligands and [Ru(*p*-cymene)Cl_2]$_2$ were also the most active giving 73–76% conversion after 15 h (entries 3 and 4). A much increased catalytic activity was obtained when the reaction was conducted at reflux temperature (98% conversion after 2 h) but the enantioselectivity decreased dramatically (16% ee) using **6b** as the ligand (entry 2). The remaining ligands afforded poor to moderate conversions (8–51% after 15 h) and enantioselectivites (4–25% ee) which were no better and in some cases lower than those obtained in the Ir-catalysed reaction. By comparing the results obtained with the diastereomeric ligand pairs (entries 3–8), it can be seen that the sense of asymmetric induction achieved was similar to that observed with iridium, i.e. the chiral centre on the oxazoline was dominant.

Table 4. Transfer hydrogenation of acetophenone using [Ru(*p*-cymene)Cl_2]$_2$ and ligands **6-8**[a]

Entry	Ligand	R	Conv. (%)[b]		ee (%)[b]		
			1 h	15 h	1 h	15 h	Conf.[c]
1	**6a**	H	6	8	7	4	*R*
2	**6b**[d]	^{i}Pr	98[e]		16[e]		*R*
3	**6b**	^{i}Pr	8	76	52	51	*R*
4	**6c**	^{i}Pr	8	73	63	61	*S*
5	**6d**	Ph	3	30	14	15	*R*
6	**6e**	Ph	1	24	10	14	*S*
7	**6f**	^{t}Bu	5	43	25	20	*R*
8	**6g**	^{t}Bu	5	37	34	25	*R*
9	**6h**	Me	2	51	14	16	*R*
10	**6i**	Bn	5	40	18	17	*R*

[a] Acetophenone:KO^{i}Pr:ligand:Ru=20:5:2:1, reactions conducted at room temperature.
[b] Determined by GC ananlysis on a Supelco chiral β-dex column.
[c] Determined by reference to literature values.[20]
[d] Reaction carried out at 82 °C.
[e] Results after 2 h.

3. Conclusions

A new class of ligands **6a-i**, comprising chiral pyrrolidine and oxazoline rings, was prepared in four steps starting from readily available enantiopure proline and chiral amino alcohols. These were screened with a number of metal complexes and it was found that only those catalysts derived from [Ir(cod)Cl]$_2$ and [Ru(*p*-cymene)Cl_2]$_2$ were successful. The catalysts formed from ligands **6a-i** and [Ir(cod)Cl]$_2$ (0.25 mol%) proved to be very active in this reaction (up to 96% conversion after 1 h at room temperature) but gave only modest enantioselectivities (up to 38% ee). Much improved enantioselectivities (61% ee with ligand **6c**) were achieved using [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol%) as the pre-catalyst. The results obtained using diastereomeric ligand pairs revealed that the stereochemical outcome of the reaction was controlled only by the oxazoline chiral centre.

4. Experimental

4.1. General

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian Oxford 300 spectrometer at room temperature in $CDCl_3$ or d^6-DMSO using tetramethylsilane as an internal standard. Chemical shifts (δ) are given in parts per million and coupling constants are given as absolute values expressed in Hertz. Low resolution electron-impact MS spectra were measured at an ionization potential of 70 eV. Isomers were assumed to have the same response factors. Electro-spray mass spectrometric analysis was performed on a Waters Micromass Quattro Ultima mass spectrometer. Elemental analyses were performed by Ms Anne Connolly, Department of Chemistry, University College Dublin. Infra-red spectra were recorded on a Perkin–Elmer Infra-red FT spectrometer. Optical rotation values were measured on a Perkin–Elmer 343 polarimeter. Melting points were determined in open capillary tubes in a Gallenkamp melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was carried out on plastic sheets pre-coated with silica gel 60 F_{254} (Merck). Column chromatography separations were performed using Merck Kieselgel 60 (0.040–0.063 mm). GC analysis was performed using (a) a Varian 3400 instrument equipped with a CP-Chirasil-Dex CB column (25 m, 0.25 mm (diam.), 0.25 μm) with nitrogen as a carrier gas at 15 psi and a flame-ionizing detector or (b) a Shimadzu GC-17A gas chromatograph equipped with a Shimadzu C-R3A chromatopac integrator and a Supelco β-Dex 120 chiral capillary column (30 m, 0.25 mm (diam.)×0.25 μm) with helium as a carrier gas at 1.0 mL/min and a flame-ionizing detector. Solvents were dried immediately before use by distillation from standard drying agents. Amino alcohols were prepared from their corresponding amino acids using a standard reduction procedure.[21] *N*-Carbobenzyloxy-(*S*)-proline and *N*-carbobenzyloxy-(*R*)-proline were prepared from the corresponding amino acids following the procedure reported by Corey.[22] It should be noted that for the majority of compounds prepared, the ^{1}H NMR and ^{13}C NMR spectra obtained showed two signals for most protons and carbons and such signals are given in square brackets.

4.2. Synthesis of hydroxyamides

Thionyl chloride (2.6 mL, 35.64 mmol) was added dropwise to a solution of carbobenzyloxy-(*S*)-proline (5.00 g, 20.06 mmol) in dry benzene (40 mL). The resulting clear solution was heated at reflux for 2 h. After cooling to room temperature, the yellow reaction mixture was concentrated in vacuo to give the acid chloride as a yellow oil. Yield: 99% (5.37 g), IR (neat): ν=1783 cm^{-1} (COCl) (lit.[16] 1780 cm^{-1}), 1709 cm^{-1} (CBZ).

The acid chloride (5.370 g, 20.05 mmol) was dissolved in dry CH_2Cl_2 (160 mL) in an oven-dried Schlenk tube and the resulting solution was cooled to 0 °C in an ice/water bath. To this was added dropwise a solution of the amino alcohol (22.06 mmol) and triethylamine (22.06 mmol) in dry CH_2Cl_2 (30 mL). A cloudy reaction mixture was obtained and this was allowed to stir at room temperature overnight (15 h) under an atmosphere of nitrogen. The reaction mixture was reduced in volume to approx. 50 mL, washed successively with aq. NH_4Cl (3×50 mL) and water (2×50 mL), dried over anhyd. sodium sulfate and concentrated in vacuo to give an off-white solid. The crude product was then purified by recrystallisation from CH_2Cl_2/pet. ether (40/60 °C).

4.2.1. (2*S*)-2-(2-Hydroxy-ethylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester (9a). Yield: 5.11 g, 87%. White solid; mp: 106–108 °C; $[\alpha]_D$=−39.1 (*c* 0.45, EtOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.80–1.92 (br m, 3H, pyr-H_2C(4), pyr-H_2C(3)), 2.05–2.24 (br m, 1H, pyr-H_2C(3)), 3.10–3.24 (br m, 2H, CH_2N), 3.43–3.51 (br m, 4H, pyr-H_2C(5), CH_2O, O*H*), 4.19–4.26 (m, 1H, pyr-*H*C(2)), 4.68 (app t, *J*=5.3 Hz, 1H, CH_2O), 5.01–5.18 (m, 2H, CH_2Ph(CBZ)), 7.36–7.44 (m, 5H, Ar-*H*C(CBZ)), 7.93–7.97 (m, 1H, N*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ [23.8, 24.6] (pyr-H_2*C*(4)), [30.9, 32.0] (pyr-H_2*C*(3)), 42.1 (*C*H_2N), [47.2, 47.8] (pyr-H_2*C*(5)), [60.3, 60.8] (pyr-H*C*(2)), 60.5 (*C*H_2O), [66.4, 66.6] (*C*H_2Ph(CBZ)), [127.7, 128.5], [128.16, 128.23], [128.9, 129.1] (Ar-H*C*(CBZ)), 137.7 (*ipso*-Ph(CBZ)), [154.6, 154.8] (*C*=O(CBZ)), [172.6, 172.9] (*C*ONH)); IR (KBr): ν 3428, 3292, 1689, 1646, 1548, 1431, 1363, 1138, 1093, 735 cm^{-1}; MS-ES$^+$ (CH_3CN): *m/z* 293 (M+H$^+$, 100%). Anal. Calcd for $C_{15}H_{20}N_2O_4$: C, 61.61; H, 6.89; N, 9.62. Found: C, 61.25; H, 6.88; N, 9.50.

4.2.2. (2*S*)-2-((1*S*)-1-Hydroxymethyl-2-methyl-propylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester (9b). Yield: 6.17 g, 92%. White solid; mp: 114–116 °C; $[\alpha]_D$=−61.0 (*c* 0.46, EtOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ[0.73 (d, *J*=6.7 Hz), 0.77 (d, *J*=6.7 Hz) and 0.84 (app t, *J*=7.1 Hz)] (6H, CH(CH_3)$_2$, ratio 1.3:1.0), 1.73–1.90 (m, 4H, C*H*(CH_3)$_2$, pyr-H_2C(4), pyr-H_2C(3)), 2.07–2.15 (m, 1H, pyr-H_2C(3)), 3.37–3.46 (m, 3H, pyr-H_2C(5), CH_2O), 3.51–3.58 (m, 1H, C*H*N), [4.23 (dd, *J*=8.8, 2.7 Hz) and 4.29 (dd, *J*=8.8, 2.5 Hz)] (1H, pyr-*H*C(2), ratio 1.0:1.4), 4.47–4.54 (m, 1H, CH_2O), [4.95 (d, *J*=12.8 Hz), 5.04 (d, *J*=12.8 Hz) and 5.07 (d, *J*=10.3 Hz), 5.11 (d, *J*=10.3 Hz)] (2H, CH_2Ph(CBZ), ratio 1.3:1.0), 7.28–7.38 (m, 5H, Ar-*H*C(CBZ)), 7.52 (app t, *J*=9.0 Hz, 1H, CON*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ [18.7, 18.8] (CH(*C*H_3)$_2$), [20.2, 20.4] (CH(*C*H_3)$_2$), [23.7, 24.6] (pyr-H_2*C*(4)), [28.8, 29.0] (*C*H(CH_3)$_2$), [30.8, 32.2] (pyr-H_2*C*(3)), [47.3, 47.9] (pyr-H_2*C*(5)), 56.3 (*C*HN), [60.0, 60.6] (pyr-H*C*(2)), [62.0, 62.1] (*C*H_2O), 66.4 (*C*H_2Ph(CBZ)), [127.8, 128.4], [128.15, 128.2], [128.9, 129.1] (Ar-H*C*(CBZ)), 137.7 (*ipso*-Ph(CBZ)), [154.6, 154.7] (*C*=O(CBZ)), [172.4, 172.7] (*C*ONH); IR (KBr): ν 3455, 3299, 1666, 1656, 1544, 1441, 1357, 1171, 1119, 699, 668 cm^{-1}; MS-ES$^+$ (CH_3CN): *m/z* 335 (M+H$^+$, 100%). Anal. Calcd for $C_{18}H_{26}N_2O_4$: C, 64.63; H, 7.83; N, 8.41. Found: C, 64.28; H, 7.83; N, 8.27.

4.2.3. (2*S*)-2-((1*R*)-1-Hydroxymethyl-2-methyl-propylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester (9c). Yield: 5.84 g, 86%. White solid; mp: 118–122 °C; $[\alpha]_D$=−21.6 (*c* 0.61, EtOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.77–0.86 (m, 6H, CH(CH_3)$_2$), 1.82–1.84 (br m, 4H, C*H*(CH_3)$_2$, pyr-H_2C(4), pyr-H_2C(3)), 2.09–2.22 (br m, 1H, pyr-H_2C(3)), 3.25–3.46 (m, 3H, pyr-H_2C(5), CH_2O), 3.57–3.59 (br m, 1H, C*H*N), 4.22–4.30 (m, 1H, pyr-*H*C(2)), 4.47–4.53 (m, 1H, CH_2O), 4.97–5.11 (m, 2H, CH_2Ph(CBZ)), 7.29–7.37 (m, 5H, Ar-*H*C(CBZ)), [7.48 (d, *J*=9.2 Hz) and 7.52 (d, *J*=9.2 Hz)] (1H, CON*H*, ratio 1.0:1.2); ^{13}C NMR (75 MHz, DMSO-d_6): δ [18.4, 18.5] (CH(*C*H_3)$_2$), 20.4 (CH(*C*H_3)$_2$), [23.7, 24.6] (pyr-H_2*C*(4)), [26.7, 28.8] (*C*H(CH_3)$_2$), [31.1, 32.4] (pyr-H_2*C*(3)), [47.2, 47.8] (pyr-H_2*C*(5)), 55.9 (*C*HN), [60.2, 60.8] (pyr-H*C*(2)), 62.0 (*C*H_2O), 66.5 (*C*H_2(CBZ)), [127.8, 128.5], [128.1, 128.2], [128.9, 129.1] (Ar-H*C*(CBZ)), 137.7 (*ipso*-Ph(CBZ)), 154.6 (*C*=O(CBZ)), [172.3 172.6] (*C*ONH); IR (KBr): ν 3455, 3303, 2970, 1673, 1655, 1551, 1441, 1353, 1178, 1129, 695, 624 cm^{-1}; MS-ES$^+$ (CH_3CN): *m/z* 335 (M+H$^+$, 100%). Anal. Calcd for $C_{18}H_{26}N_2O_4$: C, 64.63; H, 7.83; N, 8.41. Found: C, 64.35; H, 7.76; N, 8.35.

4.2.4. (2*S*)-2-(2-Hydroxy-(1*S*)-1-phenyl-ethylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester (9d). Yield: 4.21 g, 57%. White solid; mp: 151–154 °C; [α]$_D$=+29.8 (*c* 0.58, EtOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.77–1.90 (m, 3H, pyr-H_2C(4), pyr-H_2C(3)), 2.09–2.23 (m, 1H, pyr-H_2C(3)), 3.39–3.50 (m, 2H, pyr-H_2C(5)), 3.52–3.63 (m, 2H, CH_2O), [4.30–4.33 (m) and 4.36 (dd, *J*=8.0, 2.3 Hz)] (1H, pyr-*H*C(2)), 4.82–4.88 (m, 2H, C*H*N, CH_2Ph(CBZ)), [5.03 (d, *J*=12.9 Hz) and 5.09 (d, *J*=12.9 Hz)] (1H, CH_2Ph(CBZ)), 7.17–7.38 (m, 10H, Ar-*H*C(Ph), Ar-*H*C(CBZ)), [8.25 (d, *J*=8.2 Hz), and 8.33 (d, *J*=8.2 Hz)] (1H, N*H*, ratio 1.0:1.3); ^{13}C NMR (75 MHz, DMSO-d_6): δ [23.8, 24.7] (pyr-H$_2$*C*(4)), [30.9, 32.2] (pyr-H$_2$*C*(3)), [47.2, 47.9] (pyr-H$_2$*C*(5)), 55.6 (*C*HN), [60.1, 60.6] (pyr-H*C*(2)), [65.3, 65.4] (*C*H$_2$O), [66.4, 66.6] (*C*H$_2$-Ph(CBZ)), [127.3, 128.5], 127.6, 127.7, [128.1, 128.2], 128.6, [128.9, 129.1] (Ar-H*C*(Ph), Ar-H*C*(CBZ)), 137.7 (*ipso*-Ph(CBZ)), [141.7, 141.8] (*ipso*-Ph), [154.5, 154.8] (*C*═O (CBZ)), [172.3, 172.6] (*C*ONH); IR (KBr): ν 3405, 3318, 2891, 1665, 1542, 1456, 1361, 1259, 1174, 1126, 1078, 771, 698 cm^{-1}; MS-ES$^+$ (CH$_3$CN): *m/z* 369 (M+H$^+$, 100%). Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.44; H, 6.56; N, 7.63. Found: C, 68.11; H, 6.49; N, 7.58.

4.2.5. (2*S*)-2-(2-Hydroxy-(1*R*)-1-phenyl-ethylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester (9e). Yield: 4.21 g, 57%. White solid; mp: 133–136 °C; [α]$_D$=−108.7 (*c* 0.55, EtOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.77–1.80 (br m, 3H, pyr-H_2C(4), pyr-H_2C(3)), 2.09–2.18 (br m, 1H, pyr-H_2C(3)), 3.40–3.47 (m, 2H, pyr-H_2C(5)), 3.51–3.59 (m, 2H, CH_2O, O*H*), 4.28–4.34 (br m, 1H, pyr-*H*C(2)), 4.81–4.88 (m, 2H, C*H*N, CH_2O), 4.99–5.10 (m, 2H, CH_2Ph(CBZ)), 7.21–7.40 (m, 10H, Ar-*H*C(CBZ), Ar-*H*C(Ph)), 8.25–8.31 (m, 1H, N*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ [23.7, 24.5] (pyr-H$_2$*C*(4)), [30.8, 31.9] (pyr-H$_2$*C*(3)), [47.3, 47.8] (pyr-H$_2$*C*(5)), 55.5 (*C*HN), [60.2, 60.7] (pyr-H*C*(2)), [65.1, 65.4] (*C*H$_2$O), 66.6 (*C*H$_2$Ph(CBZ)), 127.4, 127.5, [127.8, 128.5], [128.15, 128.25], 128.7, [129.0, 129.1] (Ar-H*C*(Ph), Ar-H*C*(CBZ)), [137.6, 137.8] (*ipso*-Ph(CBZ)), 142.0 (*ipso*-Ph), [154.7, 154.8] (*C*═O(CBZ)), [172.1, 172.3] (*C*ONH); IR (KBr): ν 3473, 3265, 3066, 1705, 1654, 1559, 1421, 1355, 1169, 1089, 699 cm^{-1}; MS-ES$^+$ (CH$_3$CN): *m/z* 369 (M+H$^+$, 100%). Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.44; H, 6.56; N, 7.63. Found: C, 68.00; H, 6.52; N, 7.59.

4.2.6. (2*S*)-2-((1*S*)-1-Hydroxymethyl-2,2-dimethyl-propylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester (9f). Yield: 5.50 g, 81%. White solid; mp: 136–138 °C; [α]$_D$=−42.0 (*c* 0.49, EtOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ [0.77 (s) and 0.85 (s)] (9H, C(CH_3)$_3$, ratio 1.2:1.0), 1.76–1.93 (br m, 3H, pyr-H_2C(4), pyr-H_2C(3)), 2.04–2.19 (br m, 1H, pyr-H_2C(3)), 3.24–3.33 (br m, 1H, CH_2O), 3.38–3.46 (br m, 2H, pyr-H_2C(5)), 3.54–3.58 (br m, 2H, C*H*N, O*H*), 4.25–4.38 (br m, 2H, pyr-*H*C(2), CH_2O), [4.90 (app d, *J*=13.1 Hz, 1H) and 5.04 (d, *J*=12.6 Hz), 5.10 (d, *J*=12.6 Hz)] (2H, CH_2Ph (CBZ)), 7.27–7.38 (m, 5H, Ar-*H*C(CBZ)), 7.44–7.49 (m, 1H, N*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ [23.6, 24.6] (pyr-H$_2$*C*(4)), [27.5, 27.6] (C(*C*H$_3$)$_3$), [30.7, 32.2] (pyr-H$_2$*C*(3)), [34.2, 34.4] (*C*(CH$_3$)$_3$), [47.2, 47.9] (pyr-H$_2$*C*(5)), 59.3 (*C*HN), [60.1, 60.6] (pyr-H*C*(2)), 61.3 (*C*H$_2$O), 66.4 (*C*H$_2$-Ph(CBZ)), [127.9, 128.4], 128.2, [128.9, 129.1] (Ar-H*C*(CBZ)), [137.7, 137.8] (*ipso*-Ph(CBZ)), 154.6 (*C*═O(CBZ)), [172.6, 173.0] (*C*ONH)); IR (KBr): ν 3395, 3322, 2966, 1672, 1661, 1555, 1428, 1356, 1113 cm^{-1}; MS-ES$^+$ (CH$_3$CN): *m/z* 349 (M+H$^+$, 100%). Anal. Calcd for $C_{19}H_{28}N_2O_4$: C, 65.47; H, 8.10; N, 8.07. Found: C, 65.73; H, 8.00; N, 8.15.

4.2.7. (2*R*)-2-((1*S*)-1-Hydroxymethyl-2,2-dimethyl-propylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester (9g). Yield: 5.57 g, 82%. White solid; mp: 100–102 °C. [α]$_D$=+47.4 (*c* 0.49, EtOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.85 (s, 9H, C(CH_3)$_3$), 1.83–1.87 (br m, 3H, pyr-H_2C(4), pyr-H_2C(3)), 2.11–2.16 (br m, 1H, pyr-H_2C(3)), 3.39–3.59 (m, 4H, CH_2O, pyr-H_2C(5), O*H*), 3.62–3.66 (m, 1H, C*H*N), 4.21–4.35 (m, 2H, pyr-*H*C(2), CH_2O), 4.95–5.15 (m, 2H, CH_2Ph(CBZ)), 7.22–7.37 (m, 5H, Ar-*H*C(CBZ)), 7.44 (d, *J*=9.5 Hz, 1H, N*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ [23.7, 24.6] (pyr-H$_2$*C*(4)), 27.6 (C(*C*H$_3$)$_3$), [31.0, 32.3] (pyr-H$_2$*C*(3)), 34.7 (*C*(CH$_3$)$_3$), [47.3, 47.8] (pyr-H$_2$*C*(5)), [58.8. 58.9] (*C*HN), [60.4, 60.9] (pyr-H*C*(2)), 61.5 (*C*H$_2$O), 66.5 (*C*H$_2$Ph(CBZ)), [128.0, 128.5], 128.2, [128.9, 129.1] (Ar-H*C*(CBZ)), 137.7 (*ipso*-Ph(CBZ)), 154.8 (*C*═O(CBZ)), [172.3, 172.5] (*C*ONH)); IR (KBr): ν 3239, 3089, 2968, 1708, 1651, 1581, 1419, 1342, 1082, 697 cm^{-1}; MS-ES$^+$ (CH$_3$CN): *m/z* 349 (M+H$^+$, 100%). Anal. Calcd for $C_{19}H_{28}N_2O_4$: C, 65.47; H, 8.10; N, 8.07. Found: C, 65.24; H, 7.98; N, 7.98.

4.2.8. (2*S*)-2-((2-Hydroxy-(1*S*)-1-methyl-ethylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester (9h). Yield: 3.69 g, 60%. White solid; mp: 116–118 °C. [α]$_D$=−36.7 (*c* 0.46, EtOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ [0.99 (d, *J*=6.6 Hz) and 1.08 (d, *J*=6.6 Hz)] (3H, CH_3, ratio 1.5:1.0), 1.84–1.96 (br m, 3H, pyr-H_2C(4), pyr-H_2C(3)), 2.09–2.22 (br m, 1H, pyr-H_2C(3)), 3.22–3.27 (m, 1H, CH_2O), 3.34–3.54 (m, 3H, pyr-H_2C(5), O*H*), 3.75–3.84 (m, 1H, C*H*N), [4.20 (d, *J*=6.0 Hz) and 4.24 (dd, *J*=8.4, 2.9 Hz)] (1H, pyr-*H*C(2)), 4.66–4.73 (m, 1H, CH_2O), [5.02 (d, *J*=12.9 Hz), 5.09 (d. *J*=12.9 Hz), 5.12 (d, *J*=12.8 Hz), 5.15 (d, *J*=12.8 Hz)] (2H, CH_2Ph(CBZ)), 7.32–7.43 (m, 5H, Ar-*H*C(CBZ)), [7.68 (d, *J*=8.1 Hz) and 7.73 (d, *J*=8.1 Hz)] (1H, N*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ [17.7, 17.8) (pyr-H$_2$*C*(4)), [23.8, 24.6] (CH$_3$), [31.0, 32.1] (pyr-H$_2$*C*(3)), [47.1, 47.2] (pyr-H$_2$*C*(5)), 47.8 (CHN), [60.1, 60.6] (pyr-H*C*(2)), 65.1 (*C*H$_2$O), 66.4 (*C*H$_2$Ph(CBZ)), [127.7, 128.5], [128.1, 128.2], [128.9, 129.1] (Ar-H*C*(CBZ)), 137.7 (*ipso*-Ph(CBZ)), 154.6 (*C*═O(CBZ)), [172.0, 172.3] (*C*ONH); IR (KBr): ν 3427, 3307, 2958, 2890, 1698, 1548, 1432, 1362, 769, 736 cm^{-1}; MS-ES$^+$ (CH$_3$CN): *m/z* 307 (M+H$^+$, 100%). Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.70; H, 7.23; N, 9.18. Found: C, 62.52; H, 7.20; N, 8.93.

4.2.9. (2*S*)-2-((1*S*)-1-Benzyl-2-hydroxy-ethylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester (9i). Yield: 6.68 g, 87%. White solid; mp: 138–140 °C; [α]$_D$=−68.7 (*c* 0.52, EtOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.65–1.72 (m, 3H, pyr-H_2C(4), pyr-H_2C(3)), 1.95–2.09 (m, 1H, pyr-H_2C(3)), 2.60–2.72 (m, 1H, CH_2Ph), 2.77–2.88 (m, 1H, CH_2Ph), 3.23–3.38 (m, 2H, pyr-H_2C(5)), 3.40–3.47 (m, 1H, CH_2O), 3.90–3.94 (m, 1H, C*H*N), 4.15–4.18 (m, 1H, CH_2O), 4.71–4.78 (m, 1H, pyr-*H*C(2)), [4.95 (d, *J*=13.0 Hz), 5.01 (d, *J*=13.0 Hz) and 5.07–5.15 (m)] (2H, CH_2Ph(CBZ), ratio 1.9:1.0), 7.12–7.40 (m, 10H, Ar-*H*C(Bn), Ar-*H*C(CBZ)), [7.65 (d, *J*=8.2 Hz) and 7.73 (d, *J*=8.4 Hz)] (1H, N*H*, ratio 1.0:1.2); ^{13}C NMR (75 MHz, DMSO-d_6): δ [23.5, 24.4] (pyr-H$_2$*C*(4)), [30.6, 31.9] (pyr-H$_2$*C*(3)), 37.0 (*C*H$_2$Ph), [47.2, 47.8] (pyr-H$_2$*C*(5)), 52.9 (*C*HN), [60.4, 60.8] (pyr-H*C*(2)), 63.1 (*C*H$_2$O), [66.3, 66.6] (*C*H$_2$Ph(CBZ)), 126.5, 127.7, 128.2 (Ar-H*C*(Bn), Ar-H*C*(CBZ)), 128.5 (*ipso*-Ph(Bn), [128.7, 128.9], 129.1, [129.7, 129.9] (Ar-H*C*(Bn), Ar-H*C*(CBZ)), [137.8, 139.9] (*ipso*-Ph(CBZ)), [154.6, 154.9] (*C*=O(CBZ)), [172.1, 172.4] (*C*ONH); IR (KBr): ν 3367, 3321, 2875, 1679, 1643, 1541, 1430, 1364, 741, 698, 624 cm^{-1}; MS-ES$^+$ (CH$_3$CN): *m*/*z* 383 (M+H$^+$, 100%). Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.07; H, 6.85; N, 7.35. Found: C, 68.88; H, 6.74; N, 7.28.

4.3. Synthesis of the oxazolines

The hydroxyamide (13.68 mmol) was dissolved in dry CH$_2$Cl$_2$ (120 mL) in an oven-dried Schlenk tube under an atmosphere of nitrogen and was cooled to −78 °C in a dry ice/acetone bath. DAST (15.05 mmol) was added dropwise via syringe and the resulting yellow solution was stirred at −78 °C for 1 h and then at room temperature overnight (16 h). The reaction mixture was poured slowly onto sat. aq. NaHCO$_3$ (150 mL), the two layers were separated and the organic layer was washed with water (2×50 mL). All the aqueous layers were then combined and extracted with CH$_2$Cl$_2$ (3×100 mL). The combined organic layers were dried over anhyd. sodium sulfate and concentrated in vacuo to give a brown oil. This crude oil was then purified by flash column chromatography on silica gel (4×40 cm) using 10% MeOH/AcOEt as the eluent.

4.3.1. (2*S*)-2-(4,5-Dihydro-oxazol-2-yl)-pyrrolidine-1-carboxylic acid benzyl ester (10a). Yield: 3.22 g, 86%. Colourless oil; $[\alpha]_D$=−68.4 (*c* 0.54, EtOH); ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.89–1.97 (br m, 1H, pyr-*H*$_2$C(4)), 2.01–2.09 (br m, 2H, pyr-*H*$_2$C(4), pyr-*H*$_2$C(3)), 2.12–2.23 (br m, 1H, pyr-*H*$_2$C(3)), 3.45–3.65 (m, 2H, pyr-*H*$_2$C(5)), 3.71 (app t, *J*=9.5 Hz, 1H, C*H*$_2$N/C*H*$_2$O), 3.86 (app t, *J*=9.5 Hz, 1H, C*H*$_2$N/C*H*$_2$O), 4.02 (app q, *J*=9.0 Hz, 0.5H, C*H*$_2$N/C*H*$_2$O), 4.14 (app q, *J*=9.0 Hz, 0.5H, C*H*$_2$N/C*H*$_2$O), 4.24–4.35 (m, 1H, C*H*$_2$N/C*H*$_2$O), 4.57 (br dd, *J*=13.2, 7.8 Hz, 1H, pyr-*H*C(2)), [5.00 (d, *J*=12.6 Hz), 5.08 (d, *J*=12.4 Hz), 5.21 (d, *J*=12.4 Hz), 5.28 (d, *J*=12.6 Hz)] (2H, C*H*$_2$Ph(CBZ)), 7.28–7.34 (m, 5H, Ar-*H*C(CBZ)); ^{13}C NMR (75 MHz, CDCl$_3$): δ [23.7, 24.4] (pyr-H$_2$*C*(4)), [30.4, 31.6] (pyr-H$_2$*C*(3)), [46.6, 47.1] (pyr-H$_2$*C*(5)), [54.5, 54.6] (*C*H$_2$N), [54.7, 55.1] (pyr-H*C*(2)), [66.9, 67.2] (*C*H$_2$-Ph(CBZ)), [68.0, 68.2] (*C*H$_2$O), 127.96, 128.04, 128.1, 128.4, 128.57, 128.64, 128.8 (Ar-H*C*(CBZ)) [137.0, 137.2] (*ipso*-Ph(CBZ)), [154.7, 155.0] (*C*=O(CBZ)), [168.3, 168.6] (*C*=N); IR (neat): ν 2964, 2882, 1709, 1673, 1416, 1358, 1160, 1118 cm^{-1}; MS-ES$^+$ (CH$_3$CN): *m*/*z* 275 (M+H$^+$, 100%). Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.32; H, 6.54; N, 9.91.

4.3.2. (2*S*)-2-((4*S*)-4-Isopropyl-4,5-dihydro-oxazol-2-yl)-pyrrolidine-1-carboxylic acid benzyl ester (10b). Yield: 3.98 g, 92%. Colourless oil; $[\alpha]_D$=−113.6 (*c* 0.39, EtOH); ^{1}H NMR (300 MHz, CDCl$_3$): δ [0.80 (d, *J*=6.8 Hz), 0.86 (d, *J*=6.8 Hz), 0.87 (d, *J*=6.8 Hz), 9.06 (d, *J*=6.8 Hz)] (6H, CH(C*H*$_3$)$_2$), [1.62–1.73 and 1.76–1.83] (m, 1H, C*H*(CH$_3$)$_2$), 1.86–1.95 (m, 1H, pyr-*H*$_2$C(4)), 1.98–2.05 (m, 2H, pyr-*H*$_2$C(4), pyr-*H*$_2$C(3)), 2.12–2.28 (m, 1H, pyr-*H*$_2$C(3)), 3.42–3.64 (m, 2H, pyr-*H*$_2$C(5)), 3.76–3.83 (m, 0.6H, C*H*N), 3.89 (app t, *J*=7.9 Hz, 0.6H, C*H*$_2$O), 3.95–4.05 (m, 1.4H, CH$_2$O(1H), C*H*N), 4.21 (app t, *J*=7.9 Hz, 0.4H, C*H*$_2$O), 4.54–4.60 (m, 1H, pyr-*H*C(2)), 5.04–5.23 (m, 2H, C*H*$_2$Ph(CBZ)), 7.27–7.34 (m, 5H, Ar-*H*C(CBZ)); ^{13}C NMR (75 MHz, CDCl$_3$): δ [17.5, 17.7) (CH(*C*H$_3$)$_2$), 18.4 (CH(*C*H$_3$)$_2$), [23.5, 24.3] (pyr-H$_2$*C*(4)), [30.6, 31.7] (pyr-H$_2$*C*(3)), 32.2 (*C*H(CH$_3$)$_2$,), [46.4, 47.0] (pyr-H$_2$*C*(5)), [54.7, 55.0] (pyr-H*C*(2)), [66.7, 66.8] (*C*H$_2$Ph(CBZ)), 70.1 (*C*H$_2$O), [71.6, 71.7] (*C*HN), 127.8, 128.3, 128.4 (Ar-H*C*(CBZ)), 136.9 (*ipso*-ph(CBZ)), [152.3, 154.5] (*C*=O(CBZ)), [166.9, 167.1] (*C*=N); IR (neat): ν 2960, 2878, 1709, 1673, 1413, 1357, 1171, 1117, 982, 770, 697 cm^{-1}; MS (70 eV, EI): *m*/*z*(%) 316 (M$^+$, 10), 225 (15), 199 (5), 164 (23), 140 (100), 127 (18). Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 67.95; H, 7.62; N, 8.76.

4.3.3. (2*S*)-2-((4*R*)-4-Isopropyl-4,5-dihydro-oxazol-2-yl)-pyrrolidine-1-carboxylic acid benzyl ester (10c). Yield: 3.77 g, 87%. Colourless oil; $[\alpha]_D$=−30.8 (*c* 0.37, EtOH); ^{1}H NMR (300 MHz, CDCl$_3$): δ [0.78 (d, *J*=6.7 Hz), 0.87 (app t, *J*=7.2 Hz), 0.93 (d, *J*=6.7 Hz)] (6H, CH(C*H*$_3$)$_2$), 1.51–1.62 (m, 0.5H, C*H*(CH$_3$)$_2$), 1.79–1.91 (m, 1.5H, pyr-*H*$_2$C(4)(1H), C*H*(CH$_3$)$_2$), 1.98–2.11 (m, 2H, pyr-*H*$_2$C(4), pyr-*H*$_2$C(3)), 2.14–2.28 (m, 1H, pyr-*H*$_2$C(3)), 3.42–3.65 (m, 2H, pyr-*H*$_2$C(5)), [3.75–3.84 and 3.93–4.02] (m, 2H, C*H*N, C*H*$_2$O), 4.11–4.29 (m, 1H, C*H*$_2$O), 4.56–4.59 (m, 1H, pyr-*H*C(2)), 5.06–5.21 (m, 2H, C*H*$_2$Ph(CBZ)), 7.28–7.34 (m, 5H, Ar-*H*C(CBZ)); ^{13}C NMR (75 MHz, CDCl$_3$): δ [17.8, 18.3] (CH(*C*H$_3$)$_2$), 19.1 (CH(*C*H$_3$)$_2$), [23.7, 24.4] (pyr-H$_2$*C*(4)), [30.8, 31.9] (pyr-H$_2$*C*(3)), [32.5, 32.7] (*C*H(CH$_3$)$_2$), [46.7, 47.2] (pyr-H$_2$*C*(5)), [54.8, 55.2] (pyr-H*C*(2)), [66.97, 67.08] (*C*H$_2$Ph(CBZ)), [70.3, 70.6] (*C*H$_2$O), [72.1, 72.4] (*C*HN), [128.0, 128.1], [128.4, 128.6], 128.8 (Ar-H*C*(CBZ)), 137.1 (*ipso*-Ph), 154.8 (*C*=O(CBZ)), [167.1, 167.5] (*C*=N); IR (neat): ν 2958, 2881, 1708, 1673, 1414, 1356, 1186, 1118, 980, 696 cm^{-1}; MS (70 eV, EI): *m*/*z* (%) 316 (M$^+$, 14), 225 (16), 199 (5), 164 (25), 140 (100), 127 (19). Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 67.99; H, 7.52; N, 8.72.

4.3.4. (2*S*)-2-((4*S*)-4-Phenyl-4,5-dihydro-oxazol-2-yl)-pyrrolidine-1-carboxylic acid benzyl ester (10d). Yield: 3.88 g, 81%. Yellow oil; $[\alpha]_D$=−85.1 (*c* 0.26, EtOH); ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.92–2.05 (br m, 1H, pyr-*H*$_2$C(4)), 2.08–2.19 (br m, 2H, pyr-*H*$_2$C(4), pyr-*H*$_2$C(3)), 2.23–2.35 (br m, 1H, pyr-*H*$_2$C(3)), 3.45–3.62 (br m, 1H, pyr-*H*$_2$C(5)), 3.64–3.70 (m, 1H, pyr-*H*$_2$C(5)), [4.02 (app t, *J*=8.0 Hz,) and 4.12 (app t, *J*=8.0 Hz)] (1H, C*H*$_2$O/C*H*N, ratio 1.0:1.0), 4.40 (app t, *J*=9.1 Hz, 0.5H, C*H*$_2$O/C*H*N), 4.60–4.68 (m, 1.5H, pyr-*H*C(2), C*H*$_2$O/C*H*N(0.5H)), 5.05 (app t, *J*=9.1 Hz, 0.5H, C*H*$_2$O/C*H*N), 5.11–5.24 (m, 2.5H, C*H*$_2$Ph(CBZ), C*H*$_2$O/C*H*N (0.5H))), 7.12–7.27 (m, 1H, Ar-*H*C(Ph)), 7.30–7.39 (m, 9H, Ar-*H*C(Ph), Ar-*H*C(CBZ)); ^{13}C NMR (75 MHz, CDCl$_3$): δ [23.6, 24.4] (pyr-H$_2$*C*(4)), [30.6, 31.7] (pyr-H$_2$*C*(3)), [46.5, 47.0] (pyr-H$_2$*C*(5)), [54.7, 55.0] (pyr-H*C*(2)), [66.9, 67.0] (*C*H$_2$Ph(CBZ)), [69.4, 69.6] (*C*HN), [75.2, 75.5] (*C*H$_2$O), 126.5, 126.7, 127.4, 127.6, 127.85, 127.93, 128.5, 128.7 (Ar-H*C*(Ph), Ar-H*C*(CBZ)), 136.9 (*ipso*-Ph(CBZ)), 142.5 (*ipso*-Ph), 154.8 (*C*=O(CBZ)), 168.7 (*C*=N); IR (neat): ν 3031, 2957, 2893, 1703, 1668, 1416, 1358, 1170, 985, 761, 703 cm^{-1}; MS (70 eV, EI): *m/z* (%) 350 (M$^+$, 11), 259 (9), 215 (15), 198 (14), 174 (100), 161 (28), 132 (8), 104 (84). Anal. Calcd for C$_{21}$H$_{22}$N$_2$O$_3$: C, 71.98; H, 6.33; N, 7.99. Found: C, 71.80; H, 6.34; N, 7.98.

4.3.5. (2*S*)-2-((4*R*)-4-Phenyl-4,5-dihydro-oxazol-2-yl)-pyrrolidine-1-carboxylic acid benzyl ester (10e). Yield: 4.51 g, 94%. Yellow oil; $[\alpha]_D=-16.9$ (*c* 0.46, EtOH); ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.91–2.01 (br m, 1H, pyr-*H*$_2$C(4)), 2.06–2.14 (br m, 2H, pyr-*H*$_2$C(4), pyr-*H*$_2$C(3)), 2.21–2.34 (br m, 1H, pyr-*H*$_2$C(3)), 3.48–3.58 (br m, 1H, pyr-*H*$_2$C(5)), 3.60–3.69 (br m, 1H, pyr-*H*$_2$C(5)), [3.94 (app t, *J*=8.3 Hz) and 4.08 (app t, *J*=7.9 Hz)] (1H, C*H*$_2$O/C*H*N, ratio 1.0:1.0), 4.54 (app t, *J*=8.8 Hz, 0.5H, C*H*$_2$O/C*H*N), 4.63–4.69 (m, 1.5H, pyr-*H*C(2), C*H*$_2$O/C*H*N(0.5H)), 5.05–5.24 (m, 3H, C*H*$_2$Ph(CBZ), C*H*$_2$O/C*H*N), 7.11–7.13 (br m, 1H, Ar-*H*C(Ph)), 7.24–7.36 (m, 9H, Ar-*H*C(Ph), Ar-*H*C(CBZ)); ^{13}C NMR (75 MHz, CDCl$_3$): δ [23.6, 24.4] (pyr-H$_2$*C*(4)), [30.6, 31.9] (pyr-H$_2$*C*(3)), [46.5, 47.1] (pyr-H$_2$*C*(5)), [54.6, 55.0] (pyr-H*C*(2)), [66.9, 67.0] (*C*H$_2$-Ph(CBZ)), [69.6, 69.7] (*C*HN), [75.1, 75.5] (*C*H$_2$O), 126.6, 126.7, 127.4, 127.6, 127.8, 127.9, 128.5, 128.7 (Ar-H*C*(Ph), Ar-H*C*(CBZ)), 136.9 (*ipso*-Ph(CBZ)), [142.1, 142.5] (*ipso*-Ph), 154.6 (*C*=O(CBZ)), [168.6, 168.9] (*C*=N); IR (neat): ν 3029, 2956, 2892, 1704, 1667, 1454, 1416, 1358, 1170, 1116, 984, 770, 699 cm^{-1}; MS (70 eV, EI): *m/z* (%) 350 (M$^+$, 16), 259 (13), 215 (15), 198 (58), 174 (100), 161 (29), 132 (9), 104 (76). Anal. Calcd for C$_{21}$H$_{22}$N$_2$O$_3$: C, 71.98; H, 6.33; N, 7.99. Found: C, 71.72; H, 6.44; N, 7.81.

4.3.6. (2*S*)-2-((4*S*)-4-*tert*-Butyl-4,5-dihydro-oxazol-2-yl)-pyrrolidine-1-carboxylic acid benzyl ester (10f). Yield: 3.98 g, 88%. Colourless oil; $[\alpha]_D=-120.3$ (*c* 0.30, EtOH); ^{1}H NMR (300 MHz, CDCl$_3$): δ [0.82 (s) and 0.87 (s)] (9H, C(C*H*$_3$)$_3$, ratio 1.5:1), 1.85–1.94 (br m, 1H, pyr-*H*$_2$C(4)), 1.96–2.04 (br m, 2H, pyr-*H*$_2$C(4), pyr-*H*$_2$C(3)), 2.10–2.26 (br m, 1H, Pyr-*H*$_2$C(3)), 3.42–3.62 (m, 2H, pyr-*H*$_2$C(5)), 3.70 (app t, *J*=7.7 Hz, 0.5H, C*H*$_2$O/C*H*N), 3.83–4.00 (m, 1.5H, C*H*$_2$O/C*H*N), 4.07–4.20 (m, 1H, C*H*$_2$O/C*H*N), 4.56–4.60 (m, 1H, pyr-*H*C(2)), 5.04–5.23 (m, 2H, C*H*$_2$Ph(CBZ)), 7.27–7.34 (m, 5H, Ar-*H*C(CBZ)); ^{13}C NMR (75 MHz, CDCl$_3$): δ [23.6, 24.3] (pyr-H$_2$*C*(4)), 25.7 (C(*C*H$_3$)$_3$), [30.7, 31.8] (pyr-H$_2$*C*(3)), 33.6 (*C*(CH$_3$)$_3$), [46.5, 47.0] (pyr-H$_2$*C*(5)), [54.7, 55.1] (pyr-H*C*(2)), 66.7 (*C*H$_2$Ph(CBZ)), [68.9, 69.1] (*C*H$_2$O), 75.7 (*C*HN), 127.4, 127.9, 128.4 (Ar-H*C*(CBZ)), 136.9 (*ipso*-Ph(CBZ)), 154.6 (*C*=O(CBZ)), [166.8, 167.1] (*C*=N); IR (neat): ν 2954, 2892, 1709, 1674, 1413, 1356, 1172, 1117, 982, 769 cm^{-1}; MS (70 eV, EI): *m/z* (%) 330 (M$^+$, 45), 273 (15), 229 (34), 195 (22), 154 (100), 141 (17), 114 (6). Anal. Calcd for C$_{19}$H$_{26}$N$_2$O$_3$: C, 69.06; H, 7.93; N, 8.48. Found: C, 68.69; H, 7.81; N, 8.26.

4.3.7. (2*R*)-2-((4*S*)-4-*tert*-Butyl-4,5-dihydro-oxazol-2-yl)-pyrrolidine-1-carboxylic acid benzyl ester (10g). Yield: 3.39 g, 75%. Colourless oil; $[\alpha]_D=+36.8$ (*c* 0.13, EtOH); ^{1}H NMR (300 MHz, CDCl$_3$): δ [0.80(s) and 0.89 (s)] (9H, C(C*H*$_3$)$_3$, ratio 1.1:1), 1.87–1.93 (br m, 1H, pyr-*H*$_2$C(4)), 1.96–2.23 (br m, 3H, pyr-*H*$_2$C(4), pyr-*H*$_2$C(3)), 3.45–3.64 (m, 2H, pyr-*H*$_2$C(5)), [3.74–3.89 (m, 1.2H), 3.97 (app t, *J*=8.1 Hz, 0.5H), 4.04–4.22 (m, 1.2H)] (3H, C*H*N, C*H*$_2$O), 4.60 (br d, *J*=8.1 Hz, 1H, pyr-*H*C(2)), 5.06–5.19 (m, 2H, C*H*$_2$Ph(CBZ)), 7.27–7.34 (m, 5H, Ar-*H*C(CBZ)); ^{13}C NMR (75 MHz, CDCl$_3$): δ [23.7, 24.4] (pyr-H$_2$*C*(4)), [26.0, 27.0] (C(*C*H$_3$)$_3$) [30.8, 32.0] (pyr-H$_2$*C*(3)), [33.7, 34.0] (*C*(CH$_3$)$_3$), [46.6, 47.2] (pyr-H$_2$*C*(5)), [54.8. 55.2] (pyr-H*C*(2)), [63.1, 67.0] (*C*H$_2$Ph(CBZ)), 69.2 (*C*H$_2$O), 75.9 (*C*HN), 127.9, 128.0, 128.4, 128.6, 128.8 (Ar-H*C*(CBZ)), 137.1 (*ipso*-Ph), 154.9 (*C*=O(CBZ)), 167.4 (*C*=N)); IR (neat): ν 2956, 2879, 1709, 1675, 1414, 1358, 1194, 1116, 979, 789, 698 cm^{-1}; MS-ES$^+$ (CH$_3$CN): *m/z* 331 (M+H$^+$, 100%). Anal. Calcd for C$_{19}$H$_{26}$N$_2$O$_3$: C, 69.06; H, 7.93; N, 8.48. Found: C, 68.78; H, 7.99; N, 8.34.

4.3.8. (2*S*)-2-((4*S*)-4-Methyl-4,5-dihydro-oxazol-2-yl)-pyrrolidine-1-carboxylic acid benzyl ester (10h). Yield: 3.67 g, 93%. Colourless oil; $[\alpha]_D=-112.4$ (*c* 1.09, EtOH); ^{1}H NMR (300 MHz, CDCl$_3$): δ [1.12 (d, *J*=6.2 Hz) and 1.23 (d, *J*=6.4 Hz)] (3H, C*H*$_3$, ratio 1.2:1), 1.87–1.93 (br m, 1H, pyr-*H*$_2$C(4)), 1.96–2.10 (br m, 2H, pyr-*H*$_2$C(4), pyr-*H*$_2$C(3)), 2.12–2.23 (br m, 1H, pyr-*H*$_2$C(3)), 3.42–3.53 (m, 1H, pyr-*H*$_2$C(5)), 3.55–3.65 (m, 1H, pyr-*H*$_2$C(5)), [3.69 (app t, *J*=6.6 Hz) and 3.82 (app t, *J*=7.4 Hz)] (1*H*, C*H*$_2$O, ratio 1.2:1), 3.98–4.22 (m, 1.5H, C*H*N, C*H*$_2$O), 4.33 (app t, *J*=8.3 Hz, 0.5H, C*H*$_2$O), 4.50–4.58 (m, 1H, pyr-*H*C(2)), 5.02 (d, *J*=12.6 Hz), 5.10 (d, *J*=12.6 Hz), 5.18 (d, *J*=12.6 Hz), 5.25 (d, *J*=12.6 Hz)] (2H, C*H*$_2$Ph(CBZ)), 7.30–7.34 (m, 5H, Ar-*H*C(CBZ)); ^{13}C NMR (75 MHz, CDCl$_3$): δ [21.6, 21.7] (*C*H$_3$), [23.7, 24.5] (pyr-H$_2$*C*(4)), [30.6, 31.6] (pyr-H$_2$*C*(3)), [46.7, 47.2] (pyr-H$_2$*C*(5)), [54.7 55.2] (pyr-H*C*(2)), 61.6 (*C*HN), [66.9, 67.1] (*C*H$_2$Ph(CBZ)), [74.5, 74.6] (*C*H$_2$O), 127.9, 128.0, 128.1, 128.55, 128.60 (Ar-H*C*(CBZ)), 137.1 (*ipso*-Ph(CBZ)), [154.7, 154.9] (C=O(CBZ)), [167.1, 167.3] (C=N); IR (neat): 2971, 2890, 1708, 1671, 1449, 1416, 1356, 1172, 1106, 977, 769, 701 cm^{-1}; MS-ES$^+$ (CH$_3$CN): *m/z* 289 (M+H$^+$, 100%). Anal. Calcd for C$_{16}$H$_{20}$N$_2$O$_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.41; H, 6.86; N, 9.73.

4.3.9. (2*S*)-2-((4*S*)-4-Benzyl-4,5-dihydro-oxazol-2-yl)-pyrrolidine-1-carboxylic acid benzyl ester (10i). Yield: 4.89 g, 98%. Colourless oil; $[\alpha]_D=-101.7$ (*c* 0.39, EtOH); ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.83–2.01 (m, 3H, pyr-*H*$_2$C(4), pyr-*H*$_2$C(3)), 2.07–2.25 (m, 1H, pyr-*H*$_2$C(3)), [2.46 (dd, *J*=13.8, 8.5 Hz) and 2.65 (dd, *J*=13.8, 8.5 Hz)] (1H, C*H*$_2$Ph, ratio 1.2:1.0), [2.96 (dd, *J*=13.8, 4.8 Hz) and 3.08 (dd, *J*=13.8, 4.8 Hz)] (1H, C*H*$_2$Ph, ratio 1.2:1.0), 3.41–3.62 (m, 2H, pyr-*H*$_2$C(5)), 3.81–3.96 (m, 1.5H, C*H*$_2$O), 4.03 (app t, *J*=7.9 Hz, 0.5H, C*H*$_2$O), [4.19–4.29 (m) and 4.36–4.46 (m)] (1H, C*H*N, ratio 1.2:1.0), 4.51–4.59 (m, 1H, pyr-*H*C(2)), [5.02 (d, *J*=12.6 Hz), 5.12 (d, *J*=12.6 Hz), 5.19 (d, *J*=12.6 Hz) and 5.26 (d, *J*=12.6 Hz)] (2H, C*H*$_2$Ph(CBZ)), 7.10–7.34 (m, 10H, Ar-*H*C(Ph), Ar-*H*C(CBZ)); ^{13}C NMR (75 MHz, CDCl$_3$): δ [23.7, 24.5] (pyr-H$_2$*C*(4)), [30.6, 31.6] (pyr-H$_2$*C*(3)), [41.6, 41.7] (*C*H$_2$Ph), [46.7, 47.2] (pyr-H$_2$*C*(5)), [54.8, 55.2] (pyr-H*C*(2)), [67.0, 67.1] (*C*H$_2$-Ph(CBZ)), [67.2, 67.3] (*C*HN), [72.1, 72.2] (*C*H$_2$O), 126.7, 128.1, 128.6, 128.7, 129.55, 129.64 (Ar-H*C*(Ph), Ar-H*C*(CBZ)), 137.1 (*ipso*-Ph(CBZ)), [137.9, 138.1] (*ipso*-Ph), 154.7 (*C*=O(CBZ)), 168.1 (*C*=N); IR (neat): ν 2959, 2896, 1709, 1670, 1415, 1357, 1168, 1117, 980, 699, 624 cm^{-1}; MS-ES$^+$ (CH$_3$CN): *m/z* 365 (M+H$^+$, 100%). Anal. Calcd for C$_{22}$H$_{24}$N$_2$O$_3$: C, 72.50; H, 6.64; N, 7.69. Found: C, 72.40; H, 6.79; N, 7.52.

4.4. Deprotection of the CBZ-oxazolines

An oven-dried Schlenk tube was charged with 10% Pd/C (0.810 g) and to this was added cyclohexene (14.2 mL, 140 mmol). A solution of the protected oxazoline (10.13 mmol) in 10 mL of dry MeOH was added via syringe and the resulting black suspension was heated at reflux under a nitrogen atmosphere until TLC (10% MeOH in AcOEt) showed complete reaction (1–15 h). After cooling to room temperature, the reaction mixture was filtered through a pad of celite, washed thoroughly with MeOH and the filtrate was concentrated in vacuo to give product. The crude product was then purified by flash column chromatography on silica gel (3x30 cm) using 20% pet. ether(40–60 °C)/MeOH or 20% MeOH/AcOEt as the eluent.

4.4.1. 2-Pyrrolidin-(2*S*)-2-yl-4,5-dihydro-oxazole (6a). Yield: 0.70 g, 49%. Yellow oil; $[\alpha]_D=-5.2$ (*c* 1.8, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.72–1.95 (m, 3H, pyr-H_2C(4), pyr-H_2C(3)), 2.00–2.13 (m, 1H, pyr-H_2C(3)), 2.43 (br s, 1H, N*H*), 2.88–2.95 (m, 1H, pyr-H_2C(5)), 3.05–3.13 (m, 1H, pyr-H_2C(5)), 3.80–3.87 (m, 3H, CH_2O/CH_2N, pyr-*H*C(2)), 4.29 (app t, *J*=9.3 Hz, 2H, CH_2N/CH_2O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.6 (pyr-H_2*C*(4)), 30.1 (pyr-H_2*C*(3)), 46.9 (pyr-H_2*C*(5)), 54.1 (*C*H_2N), 55.3 (pyr-H*C*(2)), 67.9 (*C*H_2O), 170.4 (*C*═N); IR (neat): ν 3317, 2938, 1649, 1569, 1406, 1350, 1072 cm^{-1}; MS-ES$^+$ (MeOH): *m*/*z* 141 (M+H$^+$, 100%); HRMS (ES$^+$) calcd. for $C_7H_{12}N_2O$ [M+H]$^+$: 141.1028, found: 141.1023.

4.4.2. (4*S*)-4-Isopropyl-2-pyrrolidin-(2*S*)-2-yl-4,5-dihydro-oxazole (6b). Yield: 1.64 g, 89%. Yellow oil; $[\alpha]_D=-91.0$ (*c* 0.48, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (app d, *J*=6.7 Hz, 3H, CH(CH_3)$_2$), [0.94 (d, *J*=6.9 Hz) and 0.95 (d, *J*=6.7 Hz)] (3H, CH(CH_3)$_3$), 1.69–1.93 (m, 4H, pyr-H_2C(4), pyr-H_2C(3), C*H*(CH$_3$)$_2$), 2.03–2.13 (m, 1H, pyr-H_2C(3)), 2.22 (br s, 1H, N*H*), 2.87–2.95(m, 1H, pyr-H_2C(5)), 3.08–3.14 (m, 1H, pyr-H_2C(5)), 3.82–3.94 (m, 2H, C*H*N, pyr-*H*C(2)), [3.99 (app t, *J*=7.8 Hz,) and 4.00 (app t, *J*=7.8 Hz)] (1H, CH_2O), 4.26 (dd, *J*=9.5, 8.2 Hz, 1H, CH_2O); ^{13}C NMR (75 MHz, $CDCl_3$): δ [18.0, 18.1] (CH(*C*H$_3$)$_2$), 18.8 (CH(*C*H$_3$)$_2$), [25.6, 25.8] (pyr-H$_2$*C*(4)), 30.5 (pyr-H$_2$*C*(3)), [32.5, 32.6] (*C*H(CH$_3$)$_2$), [47.07, 47.10] (pyr-H$_2$*C*(5)), [55.46, 55.50] (pyr-H*C*(2)), [70.4, 70.5] (*C*H$_2$O), [71.7, 71.9] (*C*HN), [169.2, 169.3] (*C*═N); IR (neat): ν 3344, 2962, 2873, 1667, 1479, 1363, 1203, 1105, 985, 946 cm^{-1}; MS (70 eV, EI): *m*/*z* (%) 182 (M$^+$, 35), 153 (15), 140 (100), 127 (62), 111 (41), 84 (30), 70 (81); HRMS (ES$^+$) calcd. for $C_{10}H_{19}N_2O$ [M+H]$^+$: 183.1497, found: 183.1488.

4.4.3. (4*R*)-4-Isopropyl-2-pyrrolidin-(2*S*)-2-yl-4,5-dihydro-oxazole (6c). Yield: 1.24 g, 67%. Yellow oil; $[\alpha]_D=+51.9$ (*c* 0.16, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (d, *J*=6.7 Hz, 3H, CH(CH_3)$_2$), [0.94 (d, *J*=6.7 Hz) and 0.95 (d, *J*=6.7 Hz)] (3H, CH(CH_3)$_2$), 1.71–1.99 (m, 4H, pyr-H_2C(4), Pyr-H_2C(3), C*H*(CH$_3$)$_2$), 2.01–2.13 (br m, 2H, N*H*, pyr-H_2C(3)), 2.86–2.95 (m, 1H, pyr-H_2C(5)), 3.08–3.15 (m, 1H, pyr-H_2C(5)), 3.82–3.88 (m, 1H, pyr-*H*C(2)), 3.88–3.95 (m, 1H, C*H*N), [3.99 (app t, *J*=7.8 Hz) and 4.00 (app t, *J*=7.8 Hz)] (1H, CH_2O), 4.26 (dd, *J*=9.4, 8.2 Hz, 1H, CH_2O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.1 (CH(*C*H$_3$)$_2$), 18.9 (CH(*C*H$_3$)$_2$), 25.8 (pyr-H$_2$*C*(4)), 30.6 (pyr-H$_2$*C*(3)), 32.6 (*C*H(CH$_3$)$_2$), 47.2 (pyr-H$_2$*C*(5)), 55.6 (pyr-H*C*(2)), 70.5 (*C*H$_2$O), 71.8 (*C*HN), 169.4 (*C*═N); IR (neat): ν 3340, 2962, 2873, 1667, 1465, 1367, 1204, 1190, 1098, 988, 946, 789 cm^{-1}; MS-ES$^+$ (CH_3CN): *m*/*z* (183 (M+H$^+$, 80%); HRMS (ES$^+$) calcd. for $C_{10}H_{19}N_2O$ [M+H]$^+$: 183.1497, found: 183.1490.

4.4.4. (4*S*)-4-Phenyl-2-pyrrolidin-(2*S*)-2-yl-4,5-dihydro-oxazole (6d). Yield: 1.01 g, 46%. Yellow oil; $[\alpha]_D=+37.6$ (*c* 0.25, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.72 (br s, 1H, N*H*), 1.78–1.90 (m, 2H, pyr-H_2C(4)), 1.92–2.04 (m, 1H, pyr-H_2C(3)), 2.09–2.19 (m, 1H, pyr-H_2C(3)), 2.91–2.99 (m, 1H, pyr-H_2C(5)), 3.10–3.19 (m, 1H, pyr-H_2C(5)), 3.93–4.00 (m, 1H, pyr-*H*C(2)), [4.137 (app t, *J*=8.2 Hz) and 4.144 (app t, *J*=8.2 Hz)] (1H, CH_2O/C*H*N), [4.65 (dd, *J*=8.3, 1.3 Hz) and 4.68 (dd, *J*=8.3, 1.3 Hz)] (1H, CH_2O/C*H*N), 5.18 (app t, *J*=8.3 Hz, 1H, CH_2O/C*H*N), 7.21–7.38 (m, 5H, Ar-*H*C(Ph)); ^{13}C NMR (75 MHz, $CDCl_3$): 25.9 (pyr-H$_2$*C*(4)), [30.6, 30.8] (pyr-H$_2$*C*(3)), 47.2 (pyr-H$_2$*C*(5)), 55.6 (pyr-H*C*(2)), [69.46, 69.52] (*C*HN), 75.5 (*C*H$_2$O), [126.77, 126.80], 127.8, [128.96, 128.98] (Ar-H*C*(Ph)) [142.40, 142.48] (*ipso*-Ph), [171.01, 171.07] (*C*═N); IR (neat): ν 3324, 2959, 2874, 1661, 699 cm^{-1}; MS (70 eV, EI): *m*/*z* (%) 216 (M$^+$, 4), 174 (28), 161(4), 120 (76), 104 (100); HRMS (ES$^+$) calcd. for $C_{13}H_{17}N_2O$ [M+H]$^+$: 217.1341, found: 217.1347.

4.4.5. (4*R*)-4-Phenyl-2-pyrrolidin-(2*S*)-2-yl-4,5-dihydro-oxazole (6e). Yield: 0.88 g, 40%. Yellow oil; $[\alpha]_D=+132.9$ (*c* 0.24, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.64 (br s, 1H, N*H*), 1.79–1.90 (m, 2H, pyr-H_2*C*(4)), 1.93–2.04 (m, 1H, pyr-H_2C(3)), 2.09–2.21 (m, 1H, pyr-H_2C(3)), 2.91–2.99 (m, 1H, pyr-H_2C(5)), 3.10–3.19 (m, 1H, pyr-H_2C(5)), 3.93–4.00 (m, 1H, pyr-*H*C(2)), [4.137 (app t, *J*=8.2 Hz) and 4.144 (app t, *J*=8.2 Hz)] (1H, CH_2O/C*H*N), [4.65 (dd, *J*=8.5, 1.5 Hz) and 4.68 (dd, *J*=8.5, 1.6 Hz)] (1H, CH_2O/C*H*N), 5.18 (app t, *J*=8.5 Hz, 1H, CH_2O/C*H*N), 7.21–7.37 (m, 5H, Ar-*H*C(Ph)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.9 (pyr-H$_2$*C*(4)), [30.6, 30.7] (pyr-H$_2$*C*(3)), 47.2 (pyr-H$_2$*C*(5)), 55.6 (pyr-H*C*(2)), [69.46, 69.52] (*C*HN), 75.5 (*C*H$_2$O), [126.76, 126.80], 127.8, [128.96, 128.97] (Ar-H*C*(Ph)), [142.42, 142.49] (*ipso*-Ph), [171.02, 171.07] (*C*═N); IR (neat): ν 3321, 2969, 1661, 1174, 987, 700 cm^{-1}; MS (70 eV, EI): *m*/*z* (%) 216 (M$^+$, 11), 198 (21), 174 (45), 161 (50), 132 (6), 120 (96), 104 (100); HRMS (ES$^+$) calcd. for $C_{13}H_{17}N_2O$ [M+H]$^+$: 217.1341, found: 217.1338.

4.4.6. (4*S*)-4-*tert*-Butyl-2-pyrrolidin-(2*S*)-2-yl-4,5-dihydro-oxazole (6f). Yield: 0.95 g, 48%. Yellow oil; $[\alpha]_D=-150.2$ (*c* 0.26, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (s, 9H, C(CH_3)$_3$), 1.69–1.92 (m, 3H, pyr-H_2C(4), pyr-H_2C(3)), 2.01–2.12 (m, 1H, pyr-H_2C(3), 2.27 (br s, 1H, N*H*), 2.86–2.93 (m, 1H, pyr-H_2C(5)), 3.04–3.16 (m, 1H, pyr-H_2C(5)), 3.80–3.87 (m, 2H, pyr-*H*C(2), C*H*N), 4.09 (app t, *J*=8.6 Hz, 1H, CH_2O), 4.20 (dd, *J*=9.9, 8.6 Hz, 1H, CH_2O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.9 (C(*C*H$_3$)$_3$), 26.0 (pyr-H$_2$*C*(4), 30.7 (pyr-H$_2$*C*(3)), 33.8 (*C*(CH$_3$)$_3$), 47.3 (pyr-H$_2$*C*(5)), 55.7 (pyr-H*C*(2)), 69.3 (*C*H$_2$O), 75.6 (*C*HN), 169.3 (*C*═N); IR (neat): ν 3378, 2960, 2871, 1668, 1364 cm^{-1}; MS (70 eV, EI): *m*/*z* (%) 196 (M$^+$, 18), 195 (22), 168 (25), 154 (100), 141 (100), 122 (23), 111 (96);

HRMS (ES$^+$) calcd. for $C_{11}H_{21}N_2O$ [M+H]$^+$: 197.1654, found: 197.1651.

4.4.7. (4*S*)-4-*tert*-Butyl-2-pyrrolidin-(2*R*)-2-yl-4,5-dihydro-oxazole (6g). Yield: 1.09 g, 55%. Yellow oil; $[\alpha]_D=-40.1$ (*c* 0.44, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (s, 9H, (C(CH_3)$_3$), 1.73–1.90 (m, 3H, pyr-H_2C(4), pyr-H_2C(3)), 1.99–2.10 (m, 1H, pyr-H_2C(3)), 2.38 (br s, 1H, NH), 2.87–2.94 (m, 1H, pyr-H_2C(5)), 3.09–3.16 (m, 1H, pyr-H_2C(5)), 3.80–3.86 (m, 2H, CHN, pyr-HC(2)), 4.09 (app t, J=8.6 Hz, 1H, CH_2O), 4.2 (dd, J=9.8, 8.6 Hz, 1H, CH_2O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.7 (pyr-H$_2$$C$(4)), 26.0 (C($CH_3$)$_3$), 30.7 (pyr-H$_2$$C$(3)), 33.9 ($C$(CH$_3$)$_3$), 47.2 (pyr-H$_2$$C$(5)), 55.6 (pyr-H$C$(2)), 69.3 ($CH_2$O), 75.5 ($C$HN), 169.3 ($C$=N); IR (neat): ν 3312, 2959, 2908, 2860, 1669, 1478, 1364, 1207, 1176, 1105, 983, 943 cm^{-1}; MS-ES$^+$ (CH_3CN): *m/z* 197 (M+H$^+$, 88%); HRMS (ES$^+$) calcd. for $C_{11}H_{21}N_2O$ [M+H]$^+$: 197.1654, found: 197.1661.

4.4.8. (4*S*)-4-Methyl-2-pyrrolidin-(2*S*)-2-yl-4,5-dihydro-oxazole (6h). Yield: 0.86 g, 55%. Yellow oil; $[\alpha]_D=-90.6$ (*c* 0.32, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ [1.25 (d, J=6.6 Hz) and 1.25 (d, J=6.6 Hz)] (3H, CH_3), 1.74–1.93 (m, 3H, pyr-H_2C(4), pyr-H_2C(3)), 2.01–2.39 (m, 2H, NH, pyr-H_2C(3)), 2.87–2.95 (m, 1H, pyr-H_2C(5)), 3.06–3.14 (m, 1H, pyr-H_2C(5)), 3.78–3.85 (m, 2H, CH_2O, pyr-HC(2)), 4.12–4.19 (m, 1H, CHN), [4.371 (app t, J=9.2 Hz) and 4.374 (app t, J=9.2 Hz)] (1H, CH_2O); ^{13}C NMR (75 MHz, $CDCl_3$): δ [21.57, 21.61] (CH$_3$), [25.80, 25.83] (pyr-H$_2$$C$(4)), 30.4 (pyr-H$_2$$C$(3)), 47.2 (pyr-H$_2$$C$(5)), 55.5 (pyr-H$C$(2)), 61.4 ($C$HN), [74.59, 74.63] ($CH_2$O), [169.4, 169.5] ($C$=N); IR (neat): ν 3318, 2971, 2889, 1664, 1450, 1363, 1287, 1203, 1178, 1106, 1068, 985, 949 cm^{-1}; MS-ES$^+$ (CH_3CN): *m/z* 155 (M+H$^+$, 100%); HRMS (ES$^+$) calcd. for $C_8H_{15}N_2O$ [M+H]$^+$: 155.1184, found: 155.1188.

4.4.9. (4*S*)-4-Benzyl-2-pyrrolidin-(2*S*)-2-yl-4,5-dihydro-oxazole (6i). Yield: 1.58 g, 68%. Yellow oil; $[\alpha]_D=-37.4$ (*c* 0.77, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 1.71–1.90 (m, 3H, pyr-H_2C(4), pyr-H_2C(3)), 2.00–2.11 (m, 1H, pyr-H_2C(3)), 2.17 (br s, 1H, NH), [2.64 (dd, J=8.5, 4.4 Hz) and 2.69 (dd, J=8.5, 4.4 Hz)] (1H, CH_2Ph), 2.87–2.95 (m, 1H, pyr-H_2C(5)), 3.05–3.14 (m, 2H, CH_2Ph, pyr-H_2C(5)), 3.80–3.84 (m, 1H, pyr-HC(2)), 4.01 (app t, J=7.5 Hz, 1H, CH_2O), 4.18–4.24 (m, 1H, CH_2O), 4.32–4.44 (m, 1H, CHN), 7.18–7.32 (m, 5H, Ar-HC(Ph)); ^{13}C NMR (75 MHz, $CDCl_3$): δ [25.8, 25.9] (pyr-H$_2$$C$(4)), [30.3, 30.4] (pyr-H$_2$$C$(3)), [41.7, 41.9] ($CH_2$Ph), 47.2 (pyr-H$_2$$C$(5)), [55.4, 55.5] (pyr-HC(2)), [67.0, 67.2] (CHN), [72.3, 72.4] (CH$_2$O), 126.7, [128.68, 128.72], [129.52, 129.59] (Ar-HC(Ph), [137.9, 138.0] (*ipso*-Ph), 170.1 (C=N); IR (neat): ν 3326, 2964, 2881, 1664, 1496, 1463, 1365, 1203, 1777, 1105, 985, 949, 754, 700 cm^{-1}; MS-ES$^+$ (CH_3CN): *m/z* 231 (M+H$^+$, 30%); HRMS (ES$^+$) calcd. for $C_{14}H_{19}N_2O$ [M+H]$^+$: 231.1497, found: 231.1489.

4.5. General procedure for metal screening and optimisation:

All reactions were carried out using Chemspeed® ASW 2000 apparatus equipped with two reaction blocks under a nitrogen atmosphere. Reaction tubes containing the metal pre-catalyst (5.00 μmol metal) were placed in one reaction block and to these were added ligand (as a solution in ^{i}PrOH (approx. 300 μL) and dry ^{i}PrOH (approx. 2700 μL to bring the total volume to 3000 μL). The resulting mixtures were then heated at reflux for 30 min. After cooling to 25 °C, catalyst solution (1500 μL, 2.50 μmol) from each of the reaction vessels was transferred to the corresponding reaction tube in the second reaction block to which acetophenone (59 μL, 0.50 mmol) and dry ^{i}PrOH (3428 μL) had previously been added. The reactions were initiated by the addition of KO^{i}Pr (12.5 μL of a 1 M ^{i}PrOH solution, 12.5 μmol) to each reaction tube. The reactions were monitored by taking samples after 1 h and 10 h and were analysed by GC using a CP-Chirasil-Dex CB column (25 m, 0.25 mm (diam.), 25 μm). GC conditions: 100–130 °C (1.3 °C min^{-1}) then 130–180 °C (30 °C min^{-1}). Retention times: (*R*)-1-phenylethanol 12.34 min, (*S*)-1-phenylethanol 13.14 min.

4.6. General procedure for transfer hydrogenation using [Ir(cod)Cl]$_2$

An oven-dried schlenk tube was charged with [Ir(cod)Cl]$_2$ (1.7 mg, 2.53×10^{-3}mmol). To this was added a solution of the ligand (1.01×10^{-3}mmol, 2.0 equiv./Ir) in dry ^{i}PrOH (0.5 mL) and dry ^{i}PrOH (4.5 mL). The resulting suspension was heated at reflux under a nitrogen atmosphere for 30 min to give a yellow solution. After cooling to room temperature, dry ^{i}PrOH (5 mL) and acetophenone (117 μL, 1 mmol) were added and the reaction was started by the addition of KO^{i}Pr (25 μL of a 1 M solution in ^{i}PrOH). The reaction was allowed to stir at room temp. under an atmosphere of nitrogen and was monitored at time intervals by quenching aliquots of the reaction mixture with a 10% acetic acid/^{i}PrOH solution. The aliquots were filtered through a pad of silica and the conversion and enantioselectivity of the sample were determined by chiral GC analysis using a Supelco β-Dex 120 chiral capillary column (30 m, 0.25 mm (diam.), 0.25 μm). Retention times: 120 °C, (*R*)-1-phenylethanol 19.93 min, (*S*)-1-phenylethanol 21.15 min.

4.7. General procedure for transfer hydrogenation using [Ru(*p*-cymene)Cl$_2$]$_2$

An oven-dried schlenk tube was charged with [Ru(*p*-cymene)Cl$_2$]$_2$ (7.7 mg, 1.25×10^{-2} mmol). To this was added a solution of the ligand (0.05 mmol, 2.0 equiv./Ru) in dry ^{i}PrOH (0.5 mL) and dry ^{i}PrOH (2.0 mL). The resulting suspension was heated at reflux under a nitrogen atmosphere for 30 min to give an orange/brown solution. After cooling to room temperature, dry ^{i}PrOH (2.5 mL) and acetophenone (59 μL, 0.5 mmol) were added and the reaction was started by the addition of KO^{i}Pr (125 μL of a 1 M solution in ^{i}PrOH) which resulted in an instantaneous red reaction mixture. The reaction was allowed to stir at room temp. under an atmosphere of nitrogen and was monitored at time intervals by quenching aliquots of the reaction mixture with a 10% acetic acid/^{i}PrOH solution. The aliquots were filtered through a pad of silica and the conversion and enantioselectivity of the sample were determined by chiral GC analysis using a Supelco β-Dex 120 chiral capillary column (30 m, 0.25 mm (diam.), 0.25 μm). Retention times: 120 °C, (*R*)-1-phenylethanol 19.93 min, (*S*)-1-phenylethanol 21.15 min.

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Facile zeolite induced Fischer-indole synthesis: a new approach to bioactive natural product rutaecarpine☆

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Dedicated to Dr. B. G. Hazra, OCS, NCL, Pune

Abstract—Starting from glutaric anhydride (**5**) we have demonstrated an elegant six-step practical synthesis of bioactive natural product rutaecarpine (**1a**) via *o*-amidoglutaranilic acid formation, esterification, chemoselective ester reduction, intramolecular dehydrative cyclizations, hydrazone formation and zeolite induced Fischer-indole synthesis with 53% overall yield. The conditions employed in the present synthesis are mild, efficient and general.
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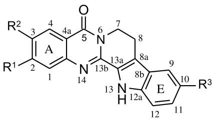
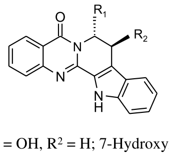
1. Introduction

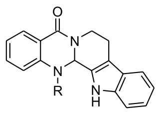
Large numbers of quinazolinone alkaloids have been isolated from a number of plants, animals and microorganisms and synthesized in view of their well established pharmacological activities.[1] Development of new, elegant synthetic routes to these bioactive quinazolinone alkaloids and their precursors is a challenging task of current interest.[2] The dried fruits of *Evodia rutaecarpa* have been used in traditional Chinese medicine under the name Wu-Chu-ru[3] and Shih-Hu[4] as a remedy for headache, dysentery, cholera, worm infections and postpartum.[5] The drug extract contains quinazolinocarboline alkaloids rutaecarpine (**1a**) and evodiamine (**3b**).[6] Recently, callus tissue cultured from the stem of *Phellodendron amurense* has been shown to produce **1a**, along with a variety of other alkaloids[7] (Fig. 1). In recent literature, **1a** and its derivatives have been reported to possess strong analgesic,[8] antiemetic,[8] astringent,[8] antihypertensive,[8] uterotonic,[9] TCDD-receptor,[10] atinociceptive,[11] anti-inflammatory[11] and cycloxygenase (COX-2) inhibitory[8] activities. The rutaecarpine (**1a**) was also found to suppress platelet plug formation in mesenteric venules and increase intracellular Ca^{2+} in endothelial cells.[12] The first total synthesis of this important bioactive natural product **1a** was reported[13] by Robinson et al. in 1927 and since then several routes to **1a** and its derivatives have been developed.[14] In our on-going studies on the synthesis of bioactive natural products using cyclic anhydrides as a potential precursors,[15] we became interested in total synthesis of rutaecarpine (**1a**). We felt that it would be possible to design the five carbon six-membered ring C



1a: $R^1 = R^2 = R^3 = H$; Rutaecarpine ($C_{18}H_{13}N_3O$, 287.32)
1b: $R^1 = R^2 = R^3 = H$; Carbon-carbon double bond between 7 and 8 position; Dehydrorutaecarpine ($C_{18}H_{11}N_3O$, 285.31)
1c: $R^1 = R^2 = H$, $R^3 = OMe$; Hortiacine ($C_{19}H_{15}N_3O_2$, 317.35)
1d: $R^1 = R^2 =$ -O-CH$_2$-O-, $R^3 = H$; Euxylophoricine ($C_{19}H_{13}N_3O_3$, 331.33)
1e: $R^1 = R^2 = OMe$, $R^3 = H$; Euxylophoricine A ($C_{20}H_{17}N_3O_3$, 347.37)
1f: $R^1 = R^2 = R^3 = OMe$; Euxylophoricine D ($C_{21}H_{19}N_3O_4$, 377.4)



2a: $R^1 = OH$, $R^2 = H$; 7-Hydroxyrutaecarpine ($C_{18}H_{13}N_3O_2$, 303.32)
2b: $R^1 = R^2 = OH$; 7,8-Dihydroxyrutaecarpine ($C_{18}H_{13}N_3O_3$, 319.32)



3a: R = H; (13*b*,14)-Dihydrorutaecarpine ($C_{18}H_{15}N_3O$, 289.34)
3b: R = Me; Evodiamine ($C_{19}H_{17}N_3O$, 303.36)
3c: R = CHO; 14-Formyl-13*b*,14-dehydrorutaecarpine ($C_{19}H_{15}N_3O_2$, 317.35)

Figure 1. Naturally occurring bioactive rutaecarpines and analogs.

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Keywords: Glutaric anhydride; Mackinazolinone; Zeolite; Fischer indole synthesis; Rutaecarpine.

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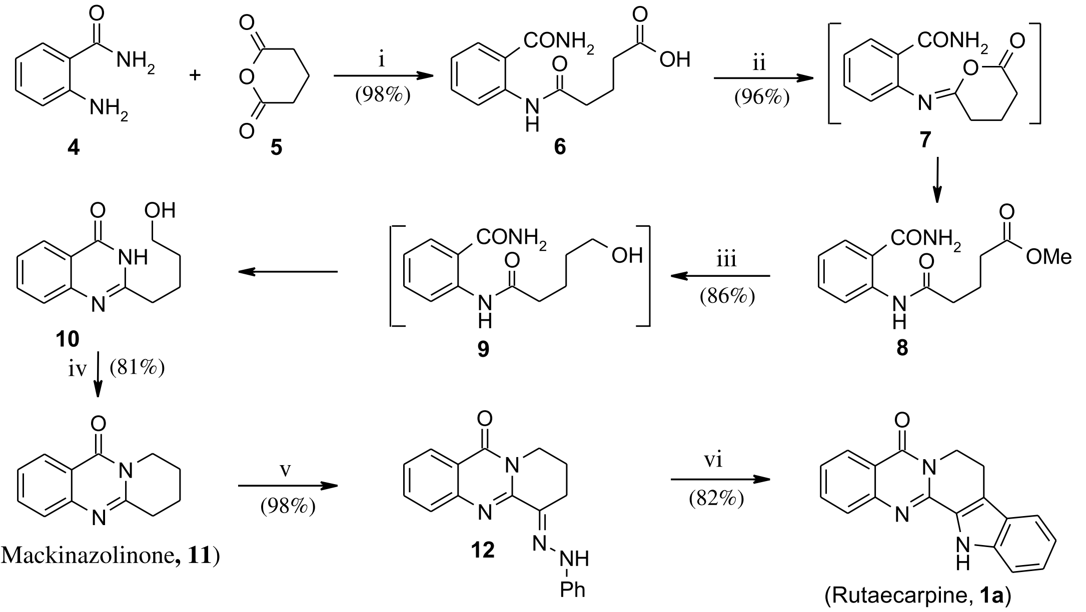

Scheme 1. Reagents, conditions and yields: (i) C_6H_6, 1,4-dioxane (2:1), room temperature, 2 h (98%); (ii) MeOH, H_2SO_4 (cat.), room temperature, 8 h (96%); (iii) $NaBH_4$, THF, reflux, 3 h, aqueous workup (86%); (iv) NaH, *p*-TsCl, THF, room temperature, 30 min (81%); (v) aniline, 30% HCl, $NaNO_2$, AcOH, −5 to 5 °C, 8 h (98%); (vi) zeolite (H-Mordenite), AcOH, reflux, 5 h (82%).

in **1a** from glutaric anhydride (**5**) and we herein report a facile six-step synthesis of **1a** (Scheme 1).

2. Results and discussion

The reaction of anthranilamide (**4**) with glutaric anhydride (**5**) in benzene/1,4-dioxane (2:1) at room temperature furnished the corresponding *o*-amidoglutaranilic acid (**6**) in quantitative yield. The glutaranilic acid **6**, on treatment with methanol and catalytic amount of sulfuric acid at room temperature, gave the corresponding methyl ester **8** in 96% yield. We feel that the present esterification at room temperature is plausibly taking place via the corresponding isoimide **7**. The ester **8** underwent smooth chemoselective sodium borohydride reduction to yield intermediate alcohol **9** which, during the aqueous work-up, underwent an in situ NaOH-catalyzed dehydrative ring closure to yield quinazolinone **10** in 86% yield. The quinazolinone **10**, on treatment with *p*-TsCl and sodium hydride in THF at room temperature, underwent a facile intramolecular dehydrative cyclization and furnished the bioactive natural product mackinazolinone (**11**) [From *Mackinalaya* species][16] in 81% yield. The analytical and spectral data obtained for **11** was in complete agreement with reported data.[16] Although several routes to **11** are known,[13,14,16] this is the first approach starting from glutaric anhydride and has several advantages. The mackinazolinone, on reaction with in situ generated diazonium salt of aniline at −5 to 5 °C, gave the corresponding hydrazone **12** in 98% yield.[14i,j] The hydrazone **12** on zeolite (H-Mordenite) induced Fischer-indole synthesis[17] in refluxing glacial acetic acid yielded the bioactive natural product rutaecarpine (**1a**) in 82% yield. The analytical and spectral data obtained for **1a** was in complete agreement with reported data.[14f,m] The overall yield of **1a** in six-steps was 53%. The rutaecarpine (**1a**) on DDQ-oxidation is known to give dehydrorutaecarpine (**1b**) in 77% yield.[14f]

3. Conclusion

In summary, starting from glutaric anhydride, we have demonstrated an elegant six-step total synthesis of bioactive natural product rutaecarpine with 53% overall yield via zeolite induced Fischer-indole synthesis. The present zeolite induced Fischer-indole synthesis conditions are mild and efficient compared to earlier known conditions and will be useful to design several naturally occurring indole skeletons. The present practical approach to quinazolinone alkaloid **1a** is efficient, general, noteworthy and can be used to design libraries of rutaecarpine analogs and derivatives.

4. Experimental

4.1. General

Melting points are uncorrected. Column chromatographic separations were carried out on ACME silica gel (60–120 mesh). Anthranilamide, glutaric anhydride, sodium borohydride, sodium hydride, *p*-toluenesulfonyl chloride and aniline were obtained from Aldrich Chemical Co. Zeolite H-Mordenite was obtained from PQ Zeolites (Netherlands) and was heated at 500 °C for 6 h before using.

4.1.1. *o*-Amidoglutaranilic acid (6). To a solution of glutaric anhydride (**5**, 2.28 g, 20 mmol) in benzene (50 mL) was added a solution of anthranilamide (**4**, 2.72 g, 20 mmol) in 1,4-dioxane (25 mL), in a dropwise fashion with constant stirring at room temperature. Reaction mixture was further stirred for 2 h and the formed precipitate was filtered in vacuo and washed with benzene (2×25 mL). The obtained compound **6** was used for the next step without any further purification. Analytically pure **6** was obtained by recrystallization from ethyl acetate.

Compound **6**. 4.90 g (98% yield); crystalline solid; mp 131–133 °C (ethyl acetate); ^{1}H NMR (CD_3OD, 300 MHz) δ 2.01 (quintet, J=9 Hz, 2H), 2.42 (t, J=9 Hz, 2H), 2.49 (t, J=9 Hz, 2H), 7.16 (t, J=9 Hz, 1H), 7.50 (t, J=9 Hz, 1H), 7.75 (d, J=9 Hz, 1H), 8.41 (d, J=9 Hz, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 21.9, 34.1, 37.9, 122.2, 122.6, 124.4, 129.4, 133.4, 140.2, 173.5, 173.6, 176.7; IR (Nujol) ν_{max} 3449, 3317, 3260, 2700–2500, 1688, 1680, 1634 cm^{-1}. Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.72; H, 5.81; N, 11.03.

4.1.2. Methyl *o*-amidoglutaranilate (8). To a solution of acid **6** (4.50 g, 18 mmol) in methanol (50 mL) was added two drops of H_2SO_4 and the reaction mixture was stirred at room temperature for 8 h. The reaction mixture was concentrated in vacuo. The residue was dissolved in ethyl acetate and washed with aqueous sodium bicarbonate solution, water, brine and the organic layer was dried over Na_2SO_4. The organic layer was concentrated in vacuo to obtain ester **8**. The obtained ester **8** was used for the next step without any further purification. Analytically pure **8** was obtained by recrystallization from benzene.

Compound **8**. 4.56 g (96% yield); crystalline solid; mp 98–100 °C (C_6H_6); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.06 (quintet, J=10 Hz, 2H), 2.43 (t, J=10 Hz, 2H), 2.47 (t, J=10 Hz, 2H), 3.68 (s, 3H), 6.15 (bs, 1H), 6.48 (bs, 1H), 7.06 (t, J=10 Hz, 1H), 7.48 (t, J=10 Hz, 1H), 7.55 (d, J=10 Hz, 1H), 8.61 (d, J=10 Hz, 1H), 11.24 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.5, 33.0, 37.1, 51.5, 118.7, 121.3, 122.5, 127.4, 133.0, 139.9, 171.0, 171.6, 173.5; IR (Nujol) ν_{max} 3337, 3273, 3179, 1740, 1680, 1678, 1616 cm^{-1}. Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 58.97; H, 6.18; N, 10.69.

4.1.3. 2-(4-Hydroxybutyl)quinazolin-4(1*H*)-one (10). To a solution of ester **8** (4.00 g, 15 mmol) in THF (50 mL) was added $NaBH_4$ (2.88 g, 76 mmol) and the reaction mixture was refluxed for 3 h under an argon atmosphere. The reaction mixture was allowed to cool to room temperature and slowly quenched with water (50 mL). The reaction mixture was further stirred for 1 h at room temperature and then acidified with acetic acid. The reaction mixture was then concentrated and dried in vacuo. The residue was stirred with THF (100 mL) for 1 h and the organic layer was filtered through celite®, dried over Na_2SO_4 and concentrated in vacuo. The obtained crude product was purified by silica gel column chromatography using a mixture of ethyl acetate and methanol (99:1) to furnish **10**.

Compound **10**. 2.84 g (86% yield); crystalline solid; mp 175–177 °C (ethyl acetate); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.66 (quintet, J=10 Hz, 2H), 1.90 (quintet, J=10 Hz, 2H), 2.73 (t, J= 10 Hz, 2H), 3.63 (t, J=10 Hz, 2H), 7.50 (t, J=10 Hz, 1H), 7.65 (d, J=10 Hz, 1H), 7.80 (t, J=10 Hz, 1H), 8.19 (d, J=10 Hz, 1H); ^{13}C NMR (CD_3OD, 125 MHz) δ 25.3, 33.0, 35.9, 62.4, 121.9, 127.2, 127.3, 127.6, 135.9, 150.1, 159.6, 164.5; IR (Nujol) ν_{max} 3398, 3173, 1686, 1614, 1468 cm^{-1}. Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.83. Found: C, 66.11; H, 6.54; N, 12.98.

4.1.4. 6,7,8,9-Tetrahydropyrido[2,1-*b*]quinazolin-11-one (mackinazolinone, 11). To a stirred slurry of NaH (607 mg, 25.3 mmol) in THF (10 mL) was added a solution of alcohol **10** (2.5 g, 11.5 mmol) in THF (20 mL). To the above reaction mixture, a solution of *p*-toluenesulfonyl chloride (2.63 g, 14 mmol) in THF (10 mL) was added in a dropwise fashion over a period of 15 min and the reaction mixture was further stirred at room temperature for 30 min. Reaction was quenched with water (10 mL), concentrated in vacuo and extracted with ethyl acetate (100 mL). The organic layer was washed with aqueous sodium bicarbonate solution, water and brine. The organic layer was dried over Na_2SO_4 concentrated and dried in vacuo. The crude product was purified by silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (1:1) to furnish **11**.

Compound **11**. 1.86 g (81% yield); crystalline solid; mp 99–101 °C (hexane) (lit.[16] mp 98.5–99.5 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.96 (quintet, J=10 Hz, 2H), 2.02 (quintet, J=10 Hz, 2H), 3.00 (t, J=10 Hz, 2H), 4.08 (t, J=10 Hz, 2H), 7.42 (t, J=10 Hz, 1H), 7.60 (d, J=10 Hz, 1H), 7.71 (t, J=10 Hz, 1H), 8.26 (d, J=10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.2, 22.0, 31.7, 42.2, 120.3, 125.9, 126.2, 126.5, 134.0, 147.2, 154.8, 162.0; IR (Nujol) ν_{max} 1657, 1612, 1587, 1566, 1462 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.08; H, 6.19; N, 14.12.

4.1.5. 6-Phenylhydrazono-6,7,8,9-tetrahydro-11*H*-pyrido-[2,1-*b*]quinazolin-11-one (12). Phenyldiazonium chloride was prepared from aniline (512 mg, 5.5 mmol) in 20% hydrochloric acid (5 mL) at 0 °C using a solution of sodium nitrite (380 mg, 5.5 mmol) in water (5 mL). The reaction mixture was diluted with acetic acid (5 mL) and then was adjusted to pH 4 using sodium acetate. To this solution of phenyldiazonium chloride was added dropwise a solution of the quinazolinone **11** (1.00 g, 5.0 mmol) in 50% acetic acid (10 mL) at 0 °C over a period of 15 min. The reaction mixture was further stirred at 0 °C for 3 h and then allowed to stand overnight in a refrigerator. The precipitated crystalline compound was filtered off, washed with water, dried in vacuo to obtain pure **12**.

Compound **12**. 1.50 g (98% yield); yellow crystalline solid; mp 184–186 (PrOH) (lit.[14j] mp 182–184 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.06 (quintet, J=10 Hz, 2H), 2.79 (t, J=10 Hz, 2H), 4.02 (t, J=5 Hz, 2H), 6.89 (t, J=10 Hz, 1H), 7.20 (d, J=10 Hz, 2H), 7.25 (t, J=10 Hz, 2H), 7.39 (t, J=10 Hz, 1H), 7.57 (d, J=10 Hz, 1H), 7.68 (t, J=10 Hz, 1H), 8.20 (d, J=10 Hz, 1H), 14.56 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.3, 31.0, 43.0, 113.5, 120.2, 121.6, 124.0, 126.3, 126.6, 126.9, 129.2, 134.1, 143.7, 145.5, 147.3, 161.3; IR ($CHCl_3$) ν_{max} 3018, 1670, 1607 cm^{-1}. Anal. Calcd for $C_{18}H_{16}N_4O$: C, 71.03; H, 5.30; N, 18.41. Found: C, 70.89; H, 5.41; N, 18.66.

4.1.6. 8,13-Dihydroindolo[2′,3′:3,4]pyrido[2,1-*b*]quinazolin-5(7*H*)-one (rutaecarpine, 1a). To a solution of hydrazone **12** (500 mg, 1.65 mmol) in freshly distilled glacial acetic acid (10 mL) was added zeolite H-Mordenite (2 g) and the stirred reaction mixture was refluxed for 5 h under argon atmosphere. Acetic acid was distilled off in vacuo and the residue was dried to the pump and then stirred with THF (50 mL) for 1 h. The above reaction mixture was filtered and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the obtained crude product was purified by silica gel column chromatography using a mixture of ethyl acetate and methanol (98:2) to furnish **1a**.

Compound **1a**. 387 mg (82% yield); crystalline solid; mp 257–259 °C (ethyl acetate) (lit.[14j] mp 258 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.15 (t, J=10 Hz, 2H), 4.51 (t, J=10 Hz, 2H), 7.09 (t, J=10 Hz, 1H), 7.17–7.28 (m, 2H), 7.34 (t, J=10 Hz, 1H), 7.52–7.64 (m, 3H), 8.25 (d, J=10 Hz, 1H), 9.62 (bs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.7, 41.2, 112.1, 118.5, 120.1, 120.6, 121.2, 125.6 (2-carbons), 126.2, 126.5, 127.1, 127.3, 134.3, 138.4, 145.1, 147.4, 161.5; IR ($CHCl_3$) ν_{max} 3416, 1670, 1651, 1630, 1599 cm^{-1}. Anal. Calcd for $C_{18}H_{13}N_3O$: C, 75.25; H, 4.56; N, 14.63. Found: C, 75.31; H, 4.67; N, 14.72.

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The 'inverse electron-demand' Diels–Alder reaction in polymer synthesis. Part 5: Preparation and model reactions of some electron-rich bis-dienamines☆

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Dedicated to Professor Károly Lempert on the occasion of his 80th birthday

Abstract—The *m*- and *p*-phenylene-bridged bis-azolopyridinium salts have been synthesized and converted into the corresponding bis-dienamines by reaction with pyrrolidine. These dienamines react readily with dimethyl 1,2,4,5-tetrazine-dicarboxylate to yield the bis-azolylvinyl-pyridazines.

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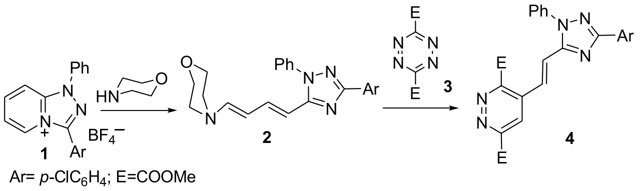
1. Introduction

As part of our investigation into the synthesis of 'high-performance' aromatic and heteroaromatic polymers, we have developed an interest in the 'inverse electron-demand' Diels–Alder reactions of bifunctional substrates. To this end synthetic routes to bis-alkynes,[2] bis-(1,2,4-triazines)[3] and bis-(1,2,4,5-tetrazines)[1] have been established; however the bis-alkynes have proved insufficiently reactive towards the above bis-azadienes, and the search for more electron-rich bis-dienophiles has therefore been further extended.

It has been reported[4,5] that dienamines, formed by the ring opening of condensed azolopyridinium salts, react smoothly with tetrazines to give azolylvinylpyridazines in good yield. Thus the triazolyl-dienamine **2**, formed by the reaction of morpholine with the triazolopyridinium salt **1**, reacts readily with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate **3** to form the triazolylvinylpyridazine **4** (Scheme 1). The reaction takes place selectively on the sterically less hindered 3,4-double bond of the diene, and the geometry of the 1,2-double bond in **2** is retained in most cases during the process.[6]



Scheme 1.

We have aimed to exploit this exceptional reactivity of dienamines towards electron-deficient dienes by extending the synthetic route to bis-dienamines. A potential benefit of polymers arising from bis-dienamines and bis-azadienes is that they also incorporate double bonds which can then easily be functionalised, allowing for the subsequent modification of the polymer chain, or else can provide sites where cross linking can occur.

2. Results and discussion

To overcome the difficulties which regularly arise in the synthesis of bis-functionalised molecules (mono-functionalisation, separation of products, etc.) we had to choose as targets such bis-salts where the synthesis appeared to be straightforward and the interference of a second functionality in the molecule could be minimized during the preparation. Both the [1,2,4]triazolo[4,3-*a*]pyridinium and the [1,2,3]triazolo[1,5-*a*]pyridinium systems were promising candidates, as the preparation of these heterocycles utilizes selective ring closure procedures.[6,7] Another advantage of these ring syntheses is that the central phenylene linking units are not only stable but are ultimately

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☆ See Ref. 1.

Keywords: Tetrazines; Dienamines; Diels–Alder reaction; Ring opening.

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derivable from commonly available starting materials, namely isophthaloyl and terephthaloyl chloride.

To prepare the bis-[1,2,4]triazolopyridinium salts, 1-phenyl-1-(2-pyridyl)hydrazine **6**[8] was acylated with isophthaloyl and terephthaloyl chloride **5a–b**. These reactions yielded the bis-hydrazides **7a–b** as the sole products. Compounds **7a** and **7b** were converted into the bis-[1,2,4]triazolo[4,3-*a*]pyridinium salts **8a–b** by heating with phosphoryl chloride and workup with tetrafluoroboric acid (Scheme 2). Under these conditions no partially cyclised products were observed.

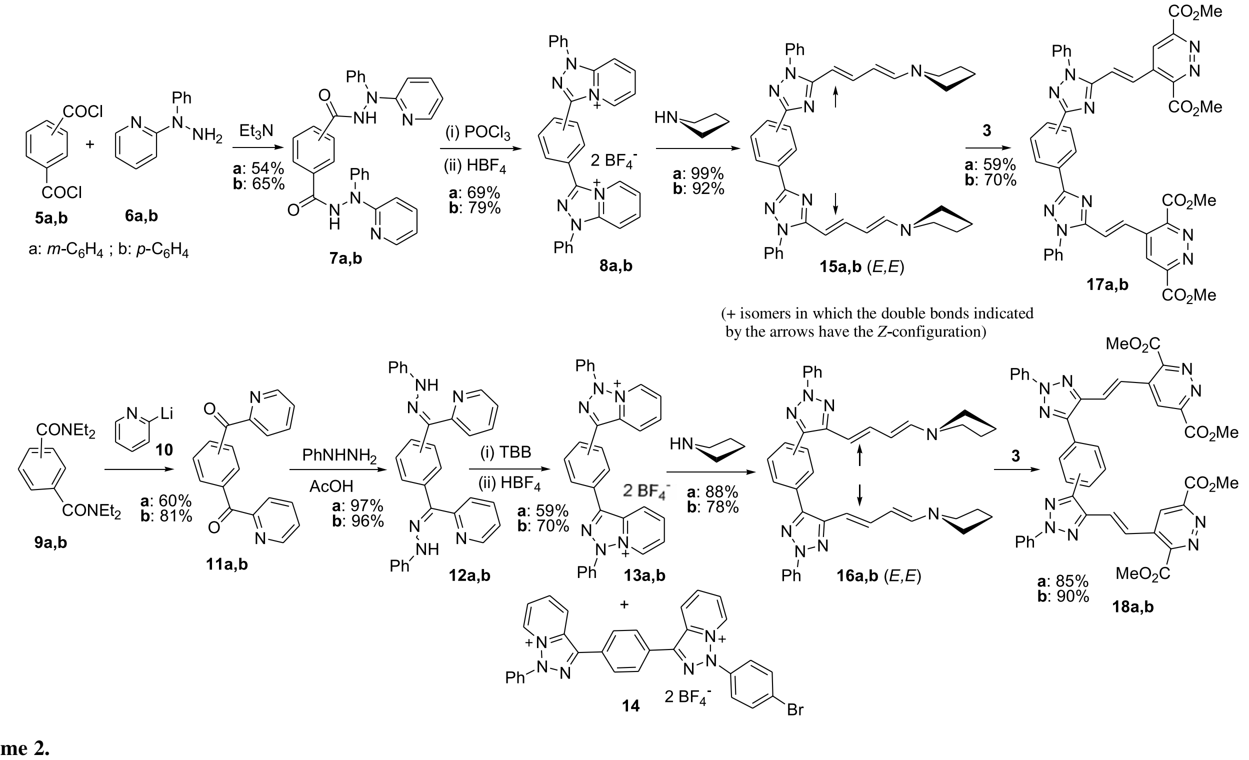
The synthesis of the [1,2,3]triazolo analogues of **8** started from iso- and terephthaloyl bis-diethylamides **9a–b**. The bis-amides were reacted with 2-lithiopyridine **10**—prepared in situ from 2-bromopyridine and *n*-butyllithium[10]—to give the 2-pyridoylbenzenes **11a–b** in moderate to high yield. The bis-ketones **11a–b** were converted into their phenylhydrazones **12a–b** using phenylhydrazine in acetic acid. The ^{1}H NMR spectra of **12a** and **12b** show the presence of all three possible *syn–anti* isomers. After the separation of the three isomers by preparative TLC, the ^{1}H NMR spectrum of each fraction shows the same complex pattern again, which suggests the fast equilibration of the three forms in solution. The crude hydrazones **12a–b** were oxidized to the bis-[1,2,3]triazolo[1,5-*a*]pyridinium salts **13a–b** by 2,4,4,6-tetrabromocyclohexa-2,5-dienone (‘tribromophenol-bromine’, TBB)[11] in good yield (Scheme 2). In the case of **12b**, a by-product of this oxidation is the mono-(*p*-bromophenyl) analogue **14**: this was detected by ^{1}H, ^{13}C and ^{15}N NMR as a minor component of the unpurified reaction product.

To test the applicability of the bis-triazolopyridinium salts as precursors for bis-dienamines, compounds **8a–b** and **13a–b** were reacted with pyrrolidine. The reactions proceeded readily in each case and the bis-dienamines **15a–b** and **16a–b** were formed in good yield. In accordance with earlier findings[4] for mono-dienamines, all of these bis-dienamines consisted of a mixture of the *E*,*E* and *Z*,*E* side-chain isomers. The preliminary product of the ring opening reaction has a *Z*,*E* geometry, but the dienamines are capable of isomerisation to the preferred *E*,*E* isomer in solution under the applied conditions.[12]

For the above reasons the separation of dienamine isomers is very tedious—if indeed it is possible at all—and the use of mixtures of *Z*,*E* and *E*,*E* isomers could lead in principle to isomeric products. To overcome this undesired result we carried out the inverse electron-demand Diels–Alder reaction of the bis-dienamines with tetrazinedicarboxylic ester **3** in a solvent, where the isomerisation of the intermediates formed in the cycloaddition might occur.[5] The bis-triazolyldienamines **15a–b** and **16a–b** were reacted with the tetrazine **3** at room temperature in dichloromethane, and only the *E*-bis-triazolylvinyl-pyridazines **17a–b** and **18a–b** were isolated from the reaction mixtures, in nearly quantitative yield.

3. Conclusion

In summary we demonstrated that bis-azolopyridinium salts might be prepared in good yield utilizing easily available starting materials and a straightforward synthetic strategy. Analogously to the simple azolopyridinium salts the bis-salts undergo facile ring opening with secondary amines to give bis-dienamines. The formed bis-dienamines are promising building blocks for heterocyclic polymers as they react readily with electron deficient azadienes. The simple and high yielding reactions make this approach



Scheme 2.

attractive for the synthesis of new polymers utilizing the inverse electron-demand Diels–Alder approach. This is currently under investigation.

4. Experimental

4.1. General

Melting points were determined on a hot-stage microscope and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 spectrometer in $CDCl_3$ and CD_3SOCD_3 and chemical shifts are given in ppm. For NMR spectra the residual peak of $CHCl_3$ (7.26 ppm) and the central peaks of DMSO (δ_H 2.50 ppm), $CDCl_3$ (δ_C 77.0) and DMSO-d_6 (δ_H 39.43) were used as the internal reference. In this paper DMSO-d_6 was used as the solvent unless otherwise indicated. Direct C–H correlations were obtained in each case by 2D-HMQC spectra. Since direct measurement of the nitrogen resonances was impossible in CD_3CN, ^{15}N NMR signals were indirectly obtained with the same instrument by detection of protons (2D-HMBC); the chemical shifts are given upfield from nitromethane (δ_N=0) as external reference. The 2D-HMQC and 2D-HMBC spectra were obtained by using the standard Bruker pulse programs INV4GS and INV4GSLPLRND respectively.

4.1.1. Iso- and terephthaloyl bis-[2-phenyl-2-(2-pyridyl)]hydrazide (7a–b). A mixture of *N*-phenyl-*N*-(2-pyridyl)-hydrazine[8] **6** (3.70 g, 20 mmol) and isophthaloyl or terephthaloyl chloride (2.03 g, 10 mmol) was heated under reflux in pyridine (20 ml) for 3 h, then stirred at ambient temperature overnight and poured into water. The bis-hydrazide was filtered off and recrystallised from dimethylformamide–water.

7a: Yield: 2.72 g (54%), white solid, mp: 279–280 °C; IR 3238, 1671, 1588, 1432, 1324, 1279, 697 cm^{-1}; ^{1}H NMR: 11.46 (s, 2H), 8.56 (s, 1H), 8.19 (d, 2H, *J*=7.4 Hz), 8.16 (br s, 2H), 7.72 (t, 1H, *J*=7.4 Hz), 7.64 (t, 2H, *J*=7.1 Hz), 7.48 (d, 4H, *J*=7.2 Hz), 7.37 (br t, 4H), 7.14 (t, 2H, *J*=6.8 Hz), 6.92 (d, 2H, *J*=8.3 Hz), 6.86 (t, 2H, *J*=5.3 Hz); ^{13}C NMR: 166.26, 157.76, 148.25, 144.77, 138.90, 133.75, 131.82, 129.95, 129.57, 127.90, 125.27, 124.00, 116.88, 109.71; Anal. Calcd For $C_{30}H_{24}N_6O_2$: C, 71.99; H, 4.83; N, 16.79; found C, 72.13; H, 4.79; N, 17.11%.

7b: Yield: 3.25 g (65%), white solid, mp: >290 °C; IR 3239, 1660, 1589, 1432, 1324, 1283, 697 cm^{-1}; ^{1}H NMR: 11.44 (s, 2H), 8.16 (d, 2H, *J*=7.3 Hz), 8.11 (s, 4H), 7.64 (t, 2H, *J*=7.1 Hz), 7.48 (d, 4H, *J*=7.8 Hz), 7.37 (t, 4H, *J*=7.5 Hz), 7.14 (t, 2H, *J*=7.3 Hz), 6.91 (d, 2H, *J*=8.5 Hz), 6.88 (t, 2H, *J*=6.3 Hz); ^{13}C NMR: 166.13, 157.71, 148.28, 144.72, 138.93, 136.30, 129.59, 128.73, 125.28, 123.95, 116.92, 109.71; Anal. Calcd For $C_{30}H_{24}N_6O_2$: C, 71.99; H, 4.83; N, 16.79; found C, 72.24; H, 5.01; N, 17.06%.

4.1.2. 3,3′-*m*-, and 3,3′-*p*-Phenylenebis(1-phenyl-[1,2,4]triazolo[4,3-*a*]pyridinium) bis-tetrafluoroborates 8a and 8b. A mixture of the appropriate hydrazide **7a** or **7b** (2.00 g, 4 mmol) and phosphoryl chloride (15 ml) was heated under reflux for 2 h. The resulting mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The residue was dissolved in boiling water (30 ml), the mixture filtered, and the filtrate treated with 40% tetrafluoroboric acid (3 ml) and cooled to 0 °C. The resulting precipitate was filtered off, washed with water, dried and recrystallised from butan-1-ol.

8a: Yield: 1.77 g (69%), white solid, mp: >290 °C; IR 1646, 1513, 1341, 1059, 756 cm^{-1}; ^{1}H NMR: 9.16 (d, 2H, *J*=7.0 Hz), 8.61 (s, 1H), 8.46–8.44 (m, 4H), 8.40 (t, 2H, *J*=7.8 Hz), 8.20 (t, 1H, *J*=7.8 Hz), 7.94 (d, 4H, *J*=7.5 Hz), 7.83–7.79 (m, 6H), 7.75 (t, 2H, *J*=7.4 Hz); ^{13}C NMR: 146.40, 143.82, 140.73, 135.60, 134.31, 132.22, 131.93, 131.68, 131.39, 128.27, 125.21, 124.66, 120.63, 112.21; Anal. Calcd For $C_{30}H_{22}N_6B_2F_8$: C, 56.29; H, 3.46; N, 13.13; found C, 56.44; H, 3.49; N, 12.82%.

8b: Yield: 2.03 g (79%), white solid, mp: >290 °C; IR 1644, 1522, 1341, 1083, 764 cm^{-1}; ^{1}H NMR: 9.21 (d, 2H, *J*=6.8 Hz), 8.46 (d, 2H, *J*=9.1 Hz), 8.42–8.39 (m, 6H), 7.96 (d, 4H, *J*=7.9 Hz), 7.85–7.81 (m, 6H), 7.76 (t, 2H, *J*=7.4 Hz); ^{13}C NMR: 146.50, 144.05, 140.77, 135.70, 131.85, 131.75, 131.45, 128.34, 126.83, 125.31, 120.75, 112.34; Anal. Calcd For $C_{30}H_{22}N_6B_2F_8$: C, 56.29; H, 3.46; N, 13.13; found C, 56.47; H, 3.39; N, 12.82%.

4.1.3. 1,3- and 1,4-Bis(2-pyridoyl)benzene (11a and 11b). A solution of 2-lithiopyridine **10**, prepared from 2-bromopyridine (2.24 g, 14.2 mmol) and *n*-butyllithium (9.0 ml, 1.6 M in hexanes) in dry ether (10 ml) at −78 °C, was added dropwise at the same temperature to the slurry of isophthaloyl or terephthaloyl bis(diethylamide)[9] **9a** or **9b** (1.93 g, 7 mmol) in dry ether (20 ml). The mixture was left to warm to room temperature, stirred overnight, then treated with saturated aqueous ammonium chloride solution and extracted with dichloromethane. The combined organic phases were dried and the solvent evaporated, and the crude product was recrystallised from ethanol.

11a: 1.47 g (60%), white solid, mp: 128–130 °C; IR 1668, 1594, 1303, 1121, 1013, 696 cm^{-1}; ^{1}H NMR: 8.75 (d, 2H, *J*=4.5 Hz), 8.61 (s, 1H), 8.28 (d, 2H, *J*=7.8 Hz), 8.12–8.07 (m, 4H), 7.75–7.69 (m, 3H); ^{13}C NMR: 193.23, 155.10, 149.00, 137.48, 136.66, 135.37, 134.31, 128.47, 126.77, 125.08; Anal. Calcd For $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20; N, 9.72; found C, 75.11; H, 4.25; N, 9.61%.

11b: 1.63 g (81%), white solid, mp: 184–6 °C; IR 1667, 1580, 1310, 936 cm^{-1}; ^{1}H NMR: 8.74 (d, 2H, *J*=4.5 Hz), 8.10–8.07 (m, 4H), 8.06 (s, 4H), 7.70 (dd, 2H, *J*=7.6, 4.5, 1.7 Hz); ^{13}C NMR: 193.67, 154.31, 149.19, 139.77, 138.24, 130.51, 127.61, 124.70; Anal. Calcd For $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20; N, 9.72; found C, 74.67; H, 4.26; N, 9.52%.

4.1.4. 1,3- and 1,4-Bis(2-pyridoyl)benzene bis-phenylhydrazones (12a and 12b). A mixture of the appropriate bis-(2-pyridoyl)benzene **11a** or **11b** (0.59 g, 2 mmol), phenylhydrazine (0.45 g, 4.2 mmol), acetic acid (3 ml) and 48% hydrobromic acid (1 drop) was stirred at ambient temperature overnight to give a red solution which was poured into cold water. The resulting precipitate was filtered off, washed with cold water and dried. The crude products, which consist in each case of a mixture of three isomers (*syn*,*syn*; *syn*,*anti*; *anti*,*anti*) were used in the subsequent step without further purification.

12a: Yield: 0.91 g (97%), yellow solid; **12b**: Yield: 0.90 g (96%), yellow solid.

4.1.5. 1,1′-*m*-, and 1,1′-*p*-Phenylenebis(3-phenyl-[1,2,3]triazolo[1,5-*a*]pyridinium) bis-fluoroborate 13a and 13b. Solutions of 2,4,4,6-tetrabromocyclohexa-2,5-dienone[13] (1.05 g, 2.5 mmol) in dichloromethane (3 ml) and of the appropriate hydrazone **12a** or **12b** (0.20 g, 0.4 mmol) in dichloromethane (2 ml) were mixed and stirred at ambient temperature for 30 min. Ether was added to the resulting mixture and the precipitate was filtered off, dissolved in nitromethane and the solution treated with cyclohexene (1 ml). Ether was then added to the solution, and the resulting precipitate was filtered off; the crude bromide salt was converted into the tetrafluoroborate by addition of acetonitrile (3 ml) followed by 40% tetrafluoroboric acid (4 drops). The resulting solution was diluted with water and extracted with nitromethane. The combined organic extracts were dried, the solvent evaporated and the crude product recrystallised from dimethylformamide–water.

13a: Yield: 0.15 g (59%), white solid, mp: 268–269 °C (dec); IR 1624, 1492, 1124, 1084, 1039, 694 cm^{-1}; ^{1}H NMR: 9.40 (d, 2H, *J*=7.0 Hz), 9.04 (d, 2H, *J*=8.8 Hz), 8.70 (br s, 1H), 8.47 (d, 2H, *J*=7.7 Hz), 8.41 (br t, 2H, *J*=7.6 Hz), 8.09–8.01 (m, 7H), 7.89–7.86 (m, 6H), 7.75; ^{13}C NMR: 141.47, 136.21, 134.58, 134.13, 133.72, 131.70, 131.08, 130.31, 129.18, 128.11, 127.63, 126.20, 124.79, 121.55; Anal. Calcd For $C_{30}H_{22}N_6B_2F_8$: C, 56.29; H, 3.46; N, 13.13; found C, 55.90; H, 3.55; N, 13.40%.

13b: 0.18 g (70%), white solid, mp: >290 °C; IR 1627, 1494, 1427, 1126, 1060, 850, 742 cm^{-1}; ^{1}H NMR: 9.38 (d, 2H, *J*=7.0 Hz), 9.05 (d, 2H, *J*=8.7 Hz), 8.46 (s, 4H), 8.40 (dd, 2H, *J*=8.9, 7.0 Hz), 8.13–7.98 (m, 8H), 7.91–7.87 (m, 4H); ^{13}C NMR: 141.27, 136.20, 134.80, 134.56, 134.14, 133.75, 131.70, 130.29, 128.10, 126.24, 124.79, 121.55; Anal. Calcd For $C_{30}H_{22}N_6B_2F_8$: C, 56.29; H, 3.46; N, 13.13; found C, 56.44; H, 3.32; N, 12.91%.

4.1.6. General procedure for the ring opening of the bis-triazolopyridinium salts (8a–b, 13a–b) with pyrrolidine. The synthesis of bis-dienamines. Pyrrolidine (0.7 ml) was added to a slurry of the appropriate bis-salt (0.32 g, 0.5 mmol) in acetonitrile (5 ml) and the resulting mixture was stirred at room temperature for 3 days. The precipitate which formed was filtered off, washed, and dried to give the crude dienamine, which was used without further purification in the subsequent step.

15a: Yield: 0.30 g (99%), yellow solid, a 70:30 mixture of *E*,*E*–*E*,*E* and *Z*,*E*–*E*,*E* isomers; ^{1}H NMR (CDCl$_3$): (*E*,*E*–*E*,*E*) 9.01 (s, 1H), 8.22 (d, 2H, *J*=7.7 Hz), 7.59–7.40 (m, 13H), 6.86 (d, 2H, *J*=12.1 Hz), 5.93 (d, 2H, *J*=14.7 Hz), 5.07 (t, 2H, *J*=11.9 Hz), 3.25–3.20 (m, 8H), 1.92–1.87 (m, 8H); (*Z*,*E*–*E*,*E*) 9.09 (s, 1H), 8.26 (d, 2H, *J*=7.7 Hz), 7.59–7.40 (m, 12 H), 6.90 (t, 1H, *J*=11.7 Hz), 6.86 (d, 1H, *J*=12.1 Hz), 6.84 (t, 1H, *J*=12.0 Hz), 6.45 (t, 1H, *J*=9.0 Hz), 5.93 (d, 1H, *J*=14.7 Hz), 5.56 (d, 1H, *J*=9.0 Hz), 5.07 (t, 1H, *J*=11.9 Hz), 3.24–3.20 (m, 4H), 3.38–3.34 (m, 4H), 1.91–1.87 (m, 4H), 1.84–1.80 (m, 4H).

15b: Yield: 0.28 g (92%), yellow solid, a 40:60 mixture of *E*,*E*–*E*,*E* and *Z*,*E*–*E*,*E* isomers; ^{1}H NMR (CDCl$_3$): (*E*,*E*–*E*,*E*) 8.28 (s, 4H), 7.57–7.38 (m, 12H), 6.87 (d, 2H, overlapping signals), 5.91 (d, 2H, *J*=14.8 Hz), 5.06 (t, 2H, *J*=12.1 Hz), 3.25–3.21 (m, 8H), 1.90–1.84 (m, 8H); (*Z*,*E*–*E*,*E*) 8.32 (d, 2H, *J*=4.8 Hz), 8.27 (d, 2H, *J*=5.1 Hz), 7.59–7.40 (m, 11 H), 6.87–6.84 (m, 3H), 6.46 (dd, 1H, *J*=11.0, 10.2 Hz), 5.91 (d, 1H, *J*=14.8 Hz), 5.53 (d, 1H, *J*=11.0 Hz), 5.06 (dd, 1H, *J*=14.8, 10.2 Hz), 3.39–3.35 (m, 4H), 3.23–3.20 (m, 4H), 1.98–1.93 (m, 4H), 1.89–1.84 (m, 4H).

16a: Yield: 0.265 g (88%), yellow solid, a 90:10 mixture of *E*,*E*–*E*,*E* and *Z*,*E*–*E*,*E* isomers; ^{1}H NMR (CDCl$_3$): (*E*,*E*–*E*,*E*) 8.10 (1H, t, *J*=1.5 Hz), 8.07 (4H, d, *J*=7.7 Hz), 7.71 (2H, dd, 7.7, *J*=1.5 Hz), 7.49 (1H, t, *J*=7.7 Hz), 7.39 (4H, t, *J*=7.7 Hz), 7.22 (2H, t, *J*=7.7 Hz), 7.16 (2H, dd, *J*=15.2, 10.9 Hz), 6.65 (2H, d, *J*=13.2 Hz), 6.18 (2H, d, *J*=15.2 Hz), 5.09 (2H, dd, *J*=13.2, 10.9 Hz), 3.12 (8H, t, *J*=6.8 Hz), 1.81 (8H, t, *J*=6.8 Hz); ^{13}C NMR (CDCl$_3$): 146.60, 145.30, 142.10, 140.40, 135.90, 132.30, 129.50, 129.30, 128.40, 128.35, 127.00, 118.90, 106.00, 99.30, 49.30, 25.70.

16b: Yield: 0.235 g (78%), yellow solid, a 85:15 mixture of *E*,*E*–*E*,*E* and *Z*,*E*–*E*,*E* isomers; ^{1}H NMR (CDCl$_3$): (*E*,*E*–*E*,*E*) 8.17 (4H, d, *J*=7.7 Hz), 7.91 (4H, s), 7.50 (4H, t, *J*=7.7 Hz), 7.33 (2H, t, *J*=7.7 Hz), 7.26 (2H, dd, *J*=15.3, 12.7 Hz), 6.78 (2H, d, *J*=12.9 Hz), 6.27 (2H, d, *J*=15.3 Hz), 5.19 (2H, t, *J*=12.7 Hz), 3.25 (8H, t, *J*=6.2 Hz), 1.94 (8H, t, *J*=6.2 Hz); ^{13}C NMR (CDCl$_3$): 146.6, 145.2, 142.1, 140.4, 135.9, 131.6, 129.5, 128.8, 127.0, 118.9, 106.0, 99.1, 49.3, 25.7.

4.1.7. General procedure for the inverse electron-demand Diels–Alder reaction of bis-dienamines (14a–b, 15a–b) with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (3). The tetrazine diester **3**[14] (0.070 g, 0.35 mmol) was added in one portion to the slurry of the appropriate bis-dienamine **15a–b** or **16a–b** (0.097 g, 0.16 mmol) in dichloromethane (5 ml) and the mixture was stirred for 6 h. After evaporation of the solvent the residue was washed with ether and the crude product recrystallised from aqueous dimethylformamide.

17a: Yield: 0.15 g (59%), white solid, mp: 215–216 °C (dec.); IR 1730, 1499, 1264, 1137, 772, 693 cm^{-1}; ^{1}H NMR: 8.86 (s, 1H), 8.48 (s, 2H), 8.22 (d, 2H, *J*=8.3 Hz), 8.06 (d, 2H, *J*=16.1 Hz), 7.73–7.61 (m, 11H), 7.37 (d, 2H, *J*=16.1 Hz), 4.00 (s, 6H), 3.98 (s, 6H); ^{13}C NMR: 165.46, 164.92, 164.50, 161.64, 153.10, 153.00, 152.15, 135.79, 130.67, 130.46, 130.21, 128.25, 126.39, 126.29, 124.50, 124.07, 122.91, 54.23, 54.09; Anal. Calcd For $C_{42}H_{32}N_{10}O_8$: C, 62.68; H, 4.01; N, 17.40; found C, 62.34; H, 4.16; N, 17.32%.

17b: Yield: 0.18 g (70%), white solid, mp: >290 °C (dec.

starting around 240 °C); IR 1726, 1500, 1265, 1138, 775, 692 cm^{-1}; ^{1}H NMR: 8.53 (s, 2H), 8.28 (s, 4H), 8.08 (d, 2H, J=15.6 Hz), 7.72–7.61 (m, 10H), 7.44 (d, 2H, J=15.6 Hz), 4.02 (s, 6H), 3.99 (s, 6H); Anal. Calcd For $C_{42}H_{32}N_{10}O_8$: C, 62.68; H, 4.01; N, 17.40; found C, 62.41; H, 4.10; N, 17.28%; ^{13}C NMR not recorded on account of low solubility, even on heating.

18a: Yield: 0.109 g (85%), white solid, mp: 120–124 °C (dec.); IR 1732, 1502, 1269, 1134, 774, 696 cm^{-1}; ^{1}H NMR: 8.63 (2H, s), 8.24 (1H, br s), 8.08 (4H, d, J=7.9 Hz), 7.98 (2H, dd, J=7.5, 1.5 Hz), 7.87 (2H, d, J=16.0 Hz), 7.80 (2H, d, J=16.0 Hz), 7.75 (1H, t, J=7.5 Hz), 7.58 (4H, t, J=7.8 Hz), 7.48 (2H, t, J=7.9 Hz), 3.97 (6H, s), 3.92 (6H, s); ^{13}C NMR: 165.5, 164.5, 152.7, 151.9, 147.8, 143.4, 139.5, 136.1, 133.6, 130.9, 130.6, 129.4, 128.8, 126.9, 125.6, 125.2, 121.5, 119.6, 54.2, 54.0; Anal. Calcd For $C_{42}H_{32}N_{10}O_8$: C, 62.68; H, 4.01; N, 17.40; found C, 62.55; H, 3.95; N, 17.76%.

18b: Yield: 0.116 g (90%), white solid, mp: 174–176 °C (dec.); IR 1729, 1505, 1262, 1141, 777, 695 cm^{-1}; ^{1}H NMR: 8.38 (2H, s), 8.14 (4H, d, J=7.7 Hz), 8.00 (2H, d, J=16.2 Hz), 7.85 (4H, s), 7.50 (2H, d, J=16.2 Hz), 7.47 (4H, t, J=7.7 Hz), 7.35 (2H, t, J=7.7 Hz), 4.02 (6H, s), 4.01 (6H, s); ^{13}C NMR: 165.3, 164.9, 152.4, 151.9, 147.2, 142.7, 139.8, 136.7, 131.2, 129.8, 129.6, 128.7, 126.4, 125.3, 124.4, 119.6, 54.1, 54.0; Anal. Calcd For $C_{42}H_{32}N_{10}O_8$: C, 62.68; H, 4.01; N, 17.40; found C, 62.80; H, 4.09; N, 17.01%.

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Reinvestigation of the synthetic and mechanistic aspects of Mn(III) acetate mediated oxidation of enones

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Abstract—$Mn(OAc)_3$ mediated α′-acetoxylation of α,β-unsaturated enones is reinvestigated from a synthetic and mechanistic point of view and an improved procedure based on the use of acetic acid as a co-solvent is presented. Excellent results were obtained for a variety of structurally diverse and synthetically important enones under the optimized conditions.
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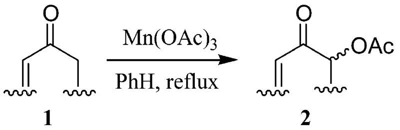
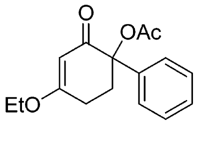
1. Introduction

Selective α′-acetoxylation of α,β-unsaturated ketones **1** provides key precursors for pharmaceutically important compounds and useful chiral ligands.[1] As Williams and Hunter reported that the $Mn(OAc)_3$ oxidation of enones in AcOH produces α′-acetoxy enones, with low yields when compared to more commonly used lead(IV) acetate, the utility of this reagent was diminished.[2] Watt and co-workers greatly improved the yields by using excess dried $Mn(OAc)_3$ in refluxing benzene.[3] Today, $Mn(OAc)_3$ mediated acetoxylation is one of the most useful methods for the synthesis of α′-acetoxy α,β-unsaturated ketones **2** (Scheme 1).



Scheme 1.

Although successful α′-acetoxylation of a great variety of substrates have been reported so far by us and others (Table 1), there are some problems associated with the use of $Mn(OAc)_3$. A brief list of them is as follows: (1) excess $Mn(OAc)_3$ (4–6 equiv.) is generally used for acceptable yields and reaction times; (2) many contradictory results can be seen when literature reports are closely inspected. These include, the amount of $Mn(OAc)_3$ which was employed to carry out the desired conversion, and irreproducible yields/reaction times were observed under the same set of conditions. A representative example of this is the α′-acetoxylation of 1-indanone (**1a**) to 2-acetoxy-1-indanone (**2a**) that is a key precursor of the HIV protease inhibitor indinavir. Hiyama[4] reported a 53% yield as compared to the 82% previously reported by Demir.[5a] Possibly, the most striking contradictory observation is the different chemoselectivity observed for the same substrate under seemingly identical reaction conditions. For example, $Mn(OAc)_3$ mediated oxidation of β-ethoxy cyclohexenone **1c** was recently reported to be giving tandem α′-acetoxylation, and α′-phenylation product **3** in a 56% yield together with a 35% acetoxylation product **2c**. This observation was shown to be general for a variety of β-alkoxy cyclohexenone and cyclopentenone derivatives.[6] The presence of the arylation product was explained on the basis of fast trapping of the α′-keto radical by the solvent benzene. We reported the acetoxylation of β-methoxy cyclohexenone in a 79–83% yield and only a trace amount of unidentified arylated products were detected in crude ^{1}H NMR spectra.[7]



3

These inconsistencies and the use of an undesirable amount of $Mn(OAc)_3$ reduced the value of the method. This indirectly indicates that the mechanism and the factors governing the outcome of this reaction are not so clear. Considering that there are not many simple methods for the direct acetoxylation of enones, optimization of $Mn(OAc)_3$

Keywords: Enones; Oxidation; $Mn(OAc)_3$; Alkenes.
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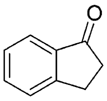
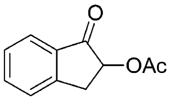
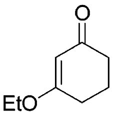
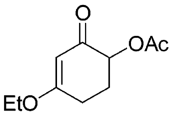
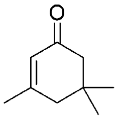
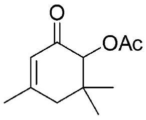
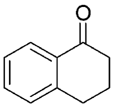
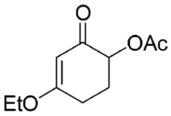
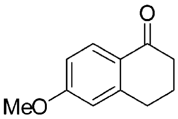
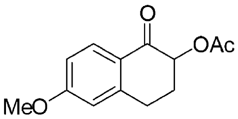
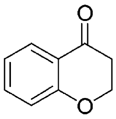
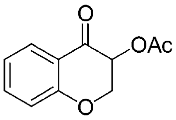
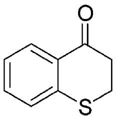
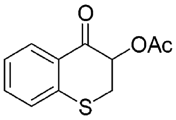
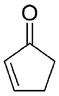
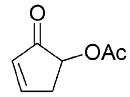
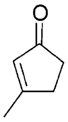
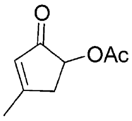
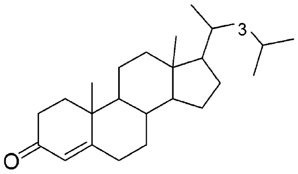
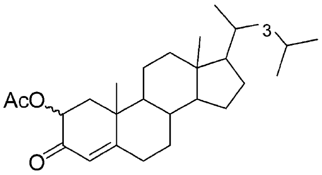
Table 1. Yields and structures of α′-acetoxy α,β-unsaturated ketones[a]

Entry	Enone **1**		Acetoxy enone **2**	Yield (%)[b]	Time (h)	Yield (%)[c]
1		**1a**		98	1	53, A[4] 82, A[5a]
2		**1b**		97	7	81,[d] A[7] 35, A[6]
3		**1c**		99	7	78, B[10]
4		**1d**		98	5	59, B[11] 86, A[5a]
5		**1e**		97	5	82, A[5b]
6		**1f**		96	5	82[12]
7		**1g**		96	5	89[12]
8		**1h**		75	2	65, A[13]
9		**1i**		83	2	81, A[13]
10[e]		**1j**		98	11	20, B[14]

[a] 1 mmol enone and 1.25 mmol $Mn(OAc)_3$ in 11 mL benzene–AcOH (10:1) was stirred under reflux; although 1.25 equiv. of $Mn(OAc)_3$ was used for full conversion, the addition of 0.25 equiv. of $Mn(OAc)_3$ towards the end of the reaction greatly shortens the reaction times.

[b] Isolated yields.

[c] Yields of previously reported acetoxylations mediated by Mn(III) acetate (Method A) or lead(IV) acetate (Method B).

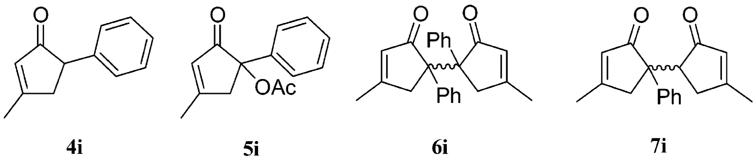
[d] For methoxy derivative.

[e] 1:6 mixture of easily separable isomers was obtained.

mediated α′-acetoxylation of enones and reaching its maximum potential has a great importance from a synthetic and economical point of view. Herein we report our investigation towards understanding the nature of this reaction together with increasing its efficiency and reproducibility.

2. Results and discussion

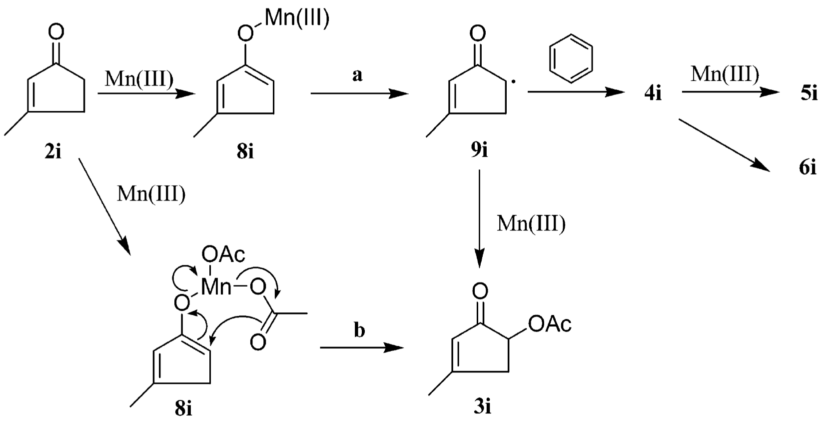
We started our investigations with the synthesis of $Mn(OAc)_3{\cdot}2H_2O$ from $Mn(OAc)_2{\cdot}4H_2O$ and $KMnO_4$ according to well established methods[8] in order to provide consistency for the source of $Mn(OAc)_3$ because Bush and



Scheme 2.

Finkbeiner[9] showed that the reactivity of $Mn(OAc)_3$ may change with the way it is synthesized. Next, we chose 1-indanone **1a** as the model substrate for our experiments and investigated its reaction with 4 equiv. $Mn(OAc)_3$. We first directed our attention to the reactivity of $Mn(OAc)_3$ and conversion times. According to the optimized procedure by Watt,[3] $Mn(OAc)_3$ was dried over P_2O_5 under high vacuum to remove water and was then reacted with **1a** in refluxing benzene monitored by TLC and GC–MS. Although a smooth reaction was observed, conversion was slow, therefore $Mn(OAc)_3$ was further dried in a heating gun (refluxing xylene) under high vacuum to obtain a dark brown colored $Mn(OAc)_3$. Reaction with this extensively dried $Mn(OAc)_3$ provided only a trace amount of product. An interesting property of this dry $Mn(OAc)_3$ was the lack of AcOH odor that is typical for any $Mn(OAc)_3$ either from a commercial source or synthesized from $Mn(OAc)_2 \cdot 4H_2O$ and $KMnO_4$. Considering that the absence of AcOH might be responsible for the slow conversions, we carried out the reaction in a AcOH–benzene (1:100) mixture. Reaction under this condition was quite successful with increased conversion rates. A careful monitoring revealed that increasing the AcOH content shortened the reaction time and full conversion was observed after 15 min at 1:10 AcOH–benzene affording **2a** in >99% yield (GC–MS). This is quite an improvement when compared to previous reports in terms of its yield, reaction time and reproducibility. $Mn(OAc)_3$ from a commercial source provided similar results as long as it was extensively dried. Although benzene is the most frequently used solvent after the report by Watt, we found that cyclohexane and MeCN can also be used instead of benzene and α'-acetoxylation was the only detectable product in a GC–MS analysis despite slower conversion rates. Reactions in THF and DMF were too slow to be useful for α'-acetoxylation. It is worth mentioning that acetic anhydride as a co-solvent instead of acetic acid shows a similar rate enhancement whereas the latter is more effective. Another optimization was made for the determination of the amount of $Mn(OAc)_3$ required for full conversion. Based on the largely accepted radical mechanism, a minimum 2 equiv. of $Mn(OAc)_3$ was necessary. After a series of reactions, we have found that 1 equiv. of $Mn(OAc)_3$ is sufficient for this conversion. A slight excess (1.25 equiv.) of the $Mn(OAc)_3$ was used to ensure complete conversion. Several structurally diverse enones were tested under optimized conditions for **1a** and where possible a comparison was made with previously reported results as shown in Table 1.

Although conditions were not optimized for any particular enone type, excellent results were obtained for a variety of enones. As can be seen in Table 1, these are the best available yields for the specified conversion except the fact that highly toxic reagent thallium(III) triflate (not shown in table) provides **2a** in a 99% yield.[15] Considering many high yield (>90%) hydrolysis methods for α-acetoxy groups that were developed thus far, this optimized protocol can also be considered as one of the most useful ways to obtain α'-hydroxy α,β-unsaturated ketones.[16] Generally, no product other than acetoxylation was detected in the ^1H NMR spectrum of crude products and they were pure enough for further synthetic manipulations. An apparent exception was observed for the cyclopentenones **1h** and **1i** in which a small amount of side products were detected in crude mixtures by NMR and GC–MS. These products were identified for **1i** and found to be an α'-phenylation product **4i**, α'-phenylation and α'-acetoxylation product **5i** and a dimerization product **6i**. Products **4i**, **5i** and **6i** (two isomers were separated providing a 1:2.5 ratio) were isolated in an approximate ratio of 1:2.5:2 accounting for ~15% of the starting material. These seem to be pointing out the intermediacy of **4i**, which is acetoxylated at the benzylic position or dimerized in an alternative pathway (Scheme 2). Thus, phenylation instead of acetoxylation is a minor alternative route, resulting in aromatic signals in NMR spectra of crude products of $Mn(OAc)_3$ mediated



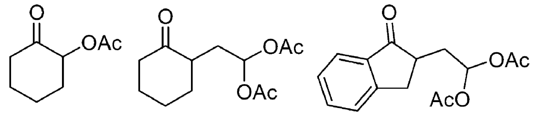
Scheme 3.

acetoxylation reactions. In a previous report, the formation of products **6i** and **7i** was reported, but not **4i** and **5i**.[13] Although these products do not have any importance from a synthetic point of view, they would be useful towards understanding the nature of the reaction as discussed below.

It is hard to justify the role of acetic acid, but it could be related to an increased solubility of $Mn(OAc)_3$ in the reaction mixture. Although the structure of $Mn(OAc)_3$ has been shown to be an oxo-centered triangle of Mn(III) with bridging acetates,[17] the prevalent form in benzene and a benzene–acetic acid mixture can be quite different resulting in different conversion rates and isolated yields.

For the mechanism of the reaction, both radical mechanism (route **a**) and ligand transfer via metal-enolate intermediate (route **b**, proposed based on $Pb(OAc)_4$ mediated acetoxylation of carbonyl compounds) have been proposed (Scheme 3).[2] Since $Mn(OAc)_3$ is a single electron oxidant and a vast majority of the reactions mediated by it have been shown to be taking place via a radical mechanism, route **a** is widely accepted.[17]

Although discrimination between the mechanisms is not a trivial question at this stage, we wish to underline a few points and address the questions to be clarified to improve our understanding of these types of processes. First, we carried out preliminary reactions to compare the behavior of enones with saturated ketones in the presence or absence of vinyl acetate. Oxidation of cyclohexanone afforded acetoxylation product **10**[18] together with side products in an unoptimized reaction (GC–MS). Same reaction in the presence of vinyl acetate mainly afforded product **11** along with little acetoxylation. Oxidation of **1a** in the presence of vinyl acetate afforded acetoxylation together with small amount (~15%) of alkene addition product **12** in benzene (Scheme 4). Different behavior of enones and saturated ketones might be the indication of different mechanisms (routes **a** and **b** in Scheme 3) depending on the types of substrates and solvents.[19] The structure and the amount of $Mn(OAc)_3$ employed in this study, possible presence of homolysis labile organomanganese[20] or manganese bound radical[21] intermediates should be clarified to elucidate the preferred mechanistic pathways and widen the scope of the reaction, a subject already under investigation.



10 **11** **12**

Scheme 4.

In conclusion, we have presented an improved procedure based on the use of acetic acid as a co-solvent. From a synthetic point of view, excellent results were obtained for a variety of structurally diverse and synthetically important enones under optimized conditions. From an economical point of view, as low as 1.25 equiv. $Mn(OAc)_3$ can be used as compared to the previously used 4–6 equiv. Moreover, MeCN and cyclohexane can also be used instead of benzene and acetic anhydride instead of acetic acid even though the presented conditions seem to be the best choice. However, combinations of these possibilities may prove to be more useful for different substrates and applications. We have also shown in unoptimized reactions that saturated ketones can be substrates of the $Mn(OAc)_3$ mediated acetoxylation.[18] Besides, these optimized conditions can be useful for the intermolecular addition of ketones to alkenes previously reported to be a low yield process that generally requires the use of an excess amount of carbonyl compound. Applicability and generality of these reactions together with the kinetic and mechanistic investigations in this context will be reported in due course. As a result, this report will be helpful by providing not only reliable and reproducible results for the $Mn(OAc)_3$ mediated acetoxylation of enones, but also a better understanding of the reaction for other applications utilizing $Mn(OAc)_3$.

3. Experimental

NMR spectra were recorded on a Bruker DPX 400. Chemical shifts δ are reported in ppm relative to $CHCl_3$ (^1H: δ=7.26) and $CDCl_3$ (^{13}C: δ=77.0) as an internal standard. Column chromatography was conducted on silica gel 60 (mesh size 40–63 μm). IR spectra were obtained from a Perkin–Elmer Model 1600 series FT-IR spectrometer and are reported in cm^{-1}. TLC was carried out on aluminum sheets precoated with silica gel $60F_{254}$ (Merck), and the spots were visualized with UV light (λ=254 nm). GC–MS spectra were determined using a ThermoQuest (TSP) TraceGC-2000 Series equipped with Phenomenex Zebron ZB-5 capillary column. All known compounds have data in agreement with the previously published values; **2a**, **d**,[5a] **2b**,[6] **2c**,[10] **2e**,[5b] **2f**, **g**,[12] **2h**, **i**,[13] **4i**,[22] **6i**, **7i**,[13] **10**,[18] $Mn(OAc)_3.2H_2O$ was prepared as reported previously (Ref. 8, p 308). As reported by Bush and Finkbeiner,[9] increasing the amount of water at the end of the reaction yields $Mn(OAc)_3$ that results in much slower conversions and slightly reduced yields, possibly related to longer reaction times.

3.1. General procedure for the α′-acetoxylation of α,β-unsaturated ketones

A solution of 1 mmol α,β-unsaturated ketone and 1.25 mmol $Mn(OAc)_3$ in 11 mL benzene–AcOH (10:1) was stirred under reflux (Dean–Stark apparatus) during which the dark brown color of $Mn(OAc)_3$ disappeared by time which was also monitored by GC–MS and TLC. After all starting material was consumed, the reaction mixture was diluted with ether and washed with brine. Resulting organic phase was dried over $MgSO_4$ and concentrated under vacuum. If necessary, crude products were purified by column chromatography using EtOAc–hexane as eluent. In some cases, direct filtering of the reaction mixture through a pad of silica provided pure acetoxy enones. Reactions with 5–10 mmol substrates worked equally well.

For the oxidation of cyclohexanone and alkene addition reactions, the same procedure was applied according to the following points; 2 equiv. of alkene with respect to carbonyl compound was used for addition reactions. Due to the high volatility of vinyl acetate, Dean–Stark apparatus was removed after refluxing the $Mn(OAc)_3$ solution for 15 min and substrates were added on to the resulting mixture.

3.1.1. 2-Acetoxy-4-cholesten-3-one (2j).[14] *Major isomer*. White solid, mp 102–104 °C (EtOAc–hexane); IR ($CHCl_3$, cm^{-1}) 1683, 1739, 2867, 2948; ^1H NMR ($CDCl_3$) δ 0.63 (3H, s), 0.79 (6H, d, J=5.5 Hz), 0.83 (3H, d, J=6.5 Hz), 0.9–1.1 (9H, m), 1.12 (3H, s), 1.15–1.6 (10H, m), 1.7–2.0 (4H, m), 2.07 (3H, s), 2.14–2.23 (2H, m), 2.37–2.47 (1H, m), 5.25 (1H, dd, J=12.5, 4.9 Hz), 5.7 (1H, s); ^{13}C NMR ($CDCl_3$) δ 12.4, 18.9, 21.3, 22.6, 22.9, 23.2, 24.2, 24.5, 28.3, 28.6, 33.3, 35.0, 36.1, 36.4, 37.8, 39.8, 39.9, 41.4, 43.2, 51.0, 56.1, 56.4, 70.9, 120.8, 129.4, 170.6, 173.8, 194.0. Anal. Calcd for $C_{29}H_{46}O_3$: C, 78.68; H 10.47 found C, 78.85; H, 10.66

Minor isomer. White solid, mp 121–123 °C (EtOAc–hexane); IR ($CHCl_3$, cm^{-1}) 1686, 1742, 2868, 2944; ^1H NMR ($CDCl_3$) 0.63 (3H, s), 0.79 (6H, d, J=6.5 Hz), 0.84 (3H, d, J=6.4 Hz), 0.85–2.35 [22H(1.24, CH_3 and 2.10, CH_3), m], 5.38 (1H, dd, J=15, 5.3 Hz); 5.67 (1H, s); ^{13}C NMR ($CDCl_3$) δ 12.3, 18.5, 19.0, 21.2, 21.3, 22.9, 23.2, 24.1, 24.4, 28.4, 28.5, 32.3, 32.9, 35.4, 36.1, 36.5, 39.84, 39.88, 41.0, 41.8, 42.7, 54.7, 56.1, 56.4, 71.7, 122.0, 170.7, 171.6, 194.1. Anal. Calcd for $C_{29}H_{46}O_3$: C, 78.68; H 10.47 found C, 78.75; H, 10.57.

3.1.2. 5-Acetoxy-3-methyl-5-phenyl-2-cyclopentenone (5i). Colorless oil, IR ($CHCl_3$, cm^{-1}) 1624, 1719, 3020; ^1H NMR ($CDCl_3$) δ 2.09 (3H, s), 2.16 (3H, d, J=1 Hz), 3.05 (1H, d, J=18.3 Hz), 3.24 (1H, d, J=18.3 Hz), 5.99 (1H, d, J=1 Hz), 7.2–7.3 (5H, m); ^{13}C NMR ($CDCl_3$) δ 19.9, 21.5, 47.2, 84.9, 124.9, 128.51, 128.54, 128.7, 138.2, 170.1, 174.2, 202.4; MS (EI), m/z 230 ($M^{+\cdot}$, 7), 187 (33), 170 (15), 141 (10), 128 (9), 105 (100), 76 (29). Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H 6.13 found C, 73.15; H, 6.24.

3.1.3. 4,4′-Dimethyl-1,1′-diphenyl-bicyclopentyl-3,3′-diene-2,2′-dione (6i).[13] Separation of isomers provided a 2.5:1 ratio.

Major isomer. White solid, mp >165 °C (decompose); IR ($CHCl_3$, cm^{-1}) 1629, 1683; ^1H NMR ($CDCl_3$) δ 1.71 (6H, s), 2.94 (2H, d, J=19.6 Hz), 3.95 (2H, d, J=19.6 Hz), 5.47 (2H, s), 7.05–7.2 (6H, m), 7.57 (4H, d, J=7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 19.1, 45.9, 60.7, 127.4, 128.1, 129.9, 130.6, 138.9, 177.8, 209.7

Minor isomer. White semi-solid; IR ($CHCl_3$, cm^{-1}) 1630, 1689; ^1H NMR ($CDCl_3$) δ 2.0 (6H, s), 2.51 (2H, d, J=18 Hz), 3.9 (2H, d, J=18 Hz), 5.74 (2H, s), 7.05 (4H, m), 7.1–7.2 (6H, m); ^{13}C NMR ($CDCl_3$) δ 19.7, 46.0, 60.1, 127.6, 127.7, 129.1, 129.7, 139.7, 177.0, 209.3.

3.1.4. 2-(2,2-Diacetoxy-1-ethyl) cyclohexanone (11). Colorless liquid, IR ($CHCl_3$, cm^{-1}) 1709, 1757, 2863, 2938; ^1H NMR ($CDCl_3$) δ; 1.34 (1H, m), 1.47 (1H, m), 1.60 (1H, m), 1.81 (1H, m), 1.98 (3H, s), 2.0 (3H, s), 2.16–2.38 (6H, m); 6.70 (1H, dd, J=5.7, 5.3 Hz); ^{13}C NMR ($CDCl_3$) δ 21.0, 25.5, 28.3, 33.3, 34.8, 42.1, 46.0, 89.7, 168.7, 168.8, 210.3. Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H 7.49 found C, 59.65; H, 7.54.

3.1.5. 2-(2,2-Diacetoxy-1-ethyl) indanone (12). Colorless viscous oil, IR ($CHCl_3$, cm^{-1}) 1712, 1759; ^1H NMR ($CDCl_3$) δ 1.78 (1H, m), 1.97 (3H, s), 2.03 (3H, s), 2.48 (1H, m), 2.66 (1H, m), 2.89 (1H, dd, J=17.1, 4.5 Hz), 3.35 (1H, dd, J=8.1, 17.1 Hz), 6.88 (1H, dd, J=4.6, 6.6 Hz), 7.3 (1H, m), 7.6 (1H, d, J=7.3 Hz), 7.52 (1H, m), 7.6 (1H, d, J=7.7 Hz); ^{13}C NMR ($CDCl_3$) δ 21.1, 33.4, 35.0, 43.2, 89.7, 124.4, 126.7, 127.8, 135.1, 136.6, 153.4, 168.6, 168.7, 206.1. Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H 5.84 found C, 65.31; H, 5.97.

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Stereoselective synthesis and moulting activity of 2,3-*diepi*-20-hydroxyecdysone and 2,3-*diepi*-5α-20-hydroxyecdysone

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Abstract—The ecdysteroid analogues 2,3-*diepi*-20-hydroxyecdysone and 2,3-*diepi*-5α-20-hydroxyecdysone have been synthesized from the readily available ecdysteroid, 20-hydroxyecdysone, and moulting activity has been determined using the *Musca* bioassay. As expected, the 2,3-*diepi*-analogue was less active than the parent ecdysteroid, 20-hydroxyecdysone. However, the 2,3-*diepi*-5α-analogue, which was expected to be inactive in the assay, exhibited moulting activity though it was approximately 1.5-fold less active than its 5β-analogue. The activity of the 5α-analogue could possibly result from the ability of this compound to bind to the ecdysteroid receptor. Alternatively, a possible in vivo C-5 epimerization of the 2,3-*diepi*-5α-analogue to the corresponding 5β-analogue could account for its activity.
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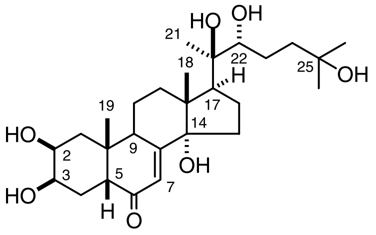
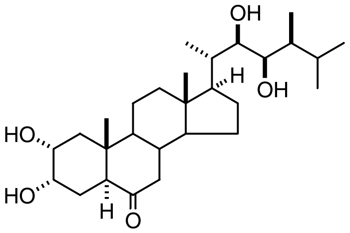
1. Introduction

Ecdysteroids are arthropod moulting hormones found in invertebrates and plant species and 20-hydroxyecdysone (**1**) is a representative of this class of compounds.[1–3] The physiological functions in invertebrates including insects are to control moulting and metamorphosis processes and are involved in the control of reproduction. Essential features contributing to high moulting activity include a *cis*-A/B ring junction, a 6-keto-7-ene system, a full sterol side chain and a free 14α-hydroxyl group.[4] The number, location and stereochemistry of the hydroxyl groups in the molecule are also responsible for the high activity of ecdysteroids. Many works indicated that the 3β-hydroxyl group is required for high activity of ecdysteroids and that the 2-hydroxyl group is not essential to such activity.[4–6] Previous works have shown that moulting activity of ecdysteroids decreased in going from the 3β-hydroxyl to the corresponding 3α-hydroxyl analogues.[4] All active ecdysteroids have a *cis*-fused A/B ring junction, whereas the 5α-epimers are inactive.[4,7] 5α-Ecdysteroid analogues, which have a *trans*-A/B ring junction, have an approximately planar ring structure while ecdysteroids (5β) are non-planar in the region of the A ring with C-2, C-3 and C-4 lying below the plane of the other rings.



1
12 2-Deoxy-5α-analogue of **1**



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It was found that the brassinosteroid castasterone (**2**), the 7,8-dihydro analogue of ecdysteroid with the 2α,3α-dihydroxyl groups and 5α-orientation, inhibited ecdysteroid activity and the effects could be explained by competitive displacement of ecdysteroids, for example, compound **1**.[8] By comparing molecular models of **1** and **2** it was found that the 3β-hydroxyl group of **1** and the 3α-hydroxyl group of **2**

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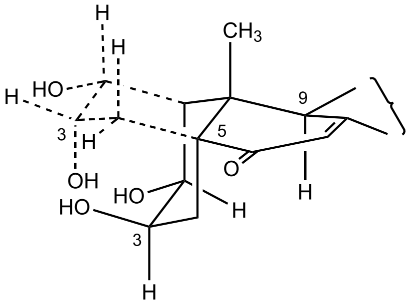
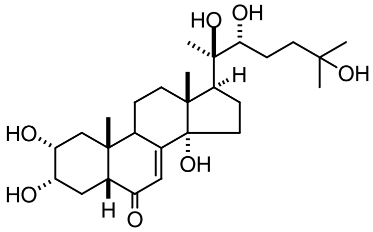


Figure 1. The A-ring geometry of the ecdysteroid **1** (solid line) and brassinosteroid **2** (broken line) and the near spatial coincidence of the 3β-hydroxyl group in **1** with the 3α-hydroxyl group in **2**. Some hydrogens are omitted in the structure for clarity.

occupied the same space (Fig. 1) and this might lead to effective competition in binding the ecdysteroid receptor of **2**. It was therefore of interest to study moulting activity of a 2,3-*diepi*-5α-ecdysteroid and, for comparison, the activity of a 2,3-*diepi*-ecdysteroid should also be evaluated. The present work deals with the stereoselective synthesis of 2,3-*diepi*-20-hydroxyecdysone (**3**) and 2,3-*diepi*-5α-20-hydroxyecdysone (**4**) from the readily available ecdysteroid **1** and evaluation of moulting activity of these two ecdysteroid analogues. Compound **4** possesses a structural framework in the A-ring region comparable to that of the brassinosteroid **2**.



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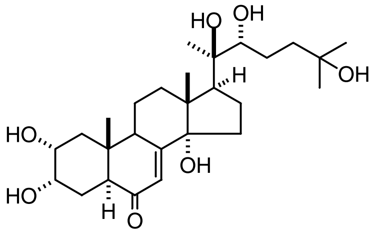

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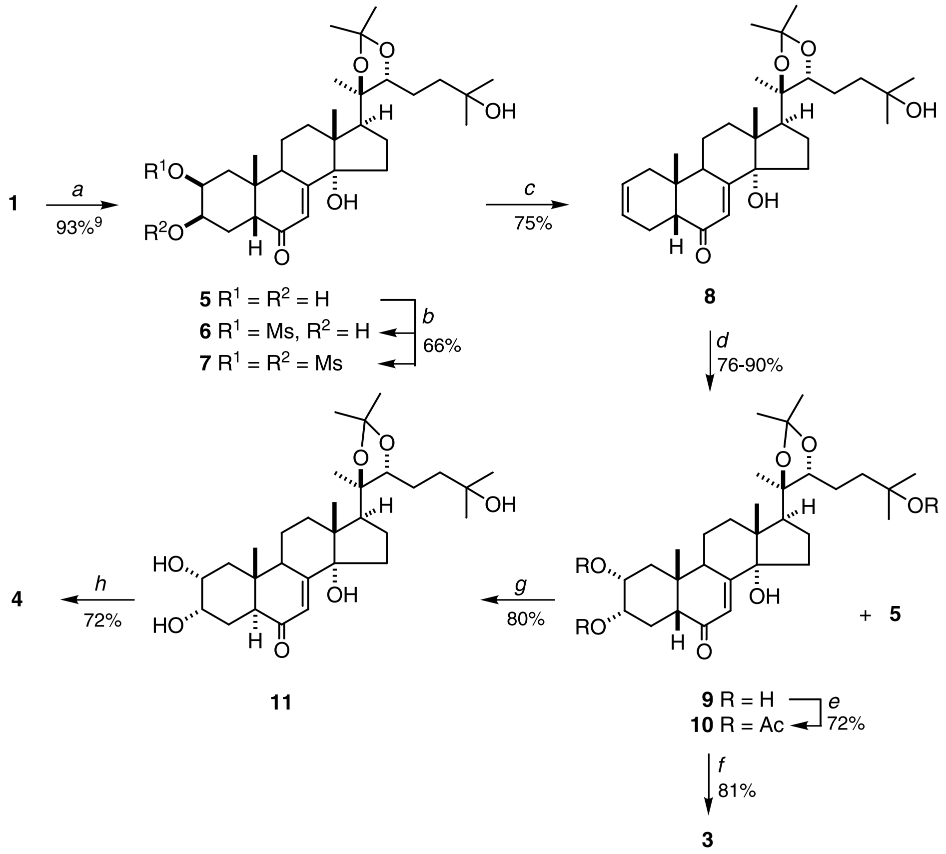
2. Results and discussion

The first ecdysteroid analogue we planned to synthesize was the 2,3-*diepi*-ecdysteroid **3**. It was then expected that this compound would be transformed into the corresponding C-5 epimer, 2,3-*diepi*-5α-ecdysteroid **4**, by base-catalyzed epimerization. Starting from **1**, the 20,22-acetonide **5** was prepared by the literature procedure.[9] Mesylation of **5** with mesyl chloride in pyridine yielded the corresponding 2-mesylate **6**[10] and 2,3-dimesylate **7** in 30 and 66% yields, respectively. The former could be recycled in the mesylation step. Prolonged reaction time gave only the dimesylate **7**, but it was usually accompanied by a less polar side product. The presence of the mesylate groups at the 2- and 3-positions in **7** was evident from a 1.13 and 1.11 ppm downfield shifts of H-2 and H-3 as compared with that of the starting acetonide **5** and the presence of two mesylate methyl signals at δ 3.10 and 3.11 in the ^{1}H NMR spectrum of **7**. Reaction of **7** with NaI and Zn in DMF at 80 °C afforded the olefin acetonide **8** in 75% yield. The ESMS exhibited a sodiated molecular ion $[M+Na]^+$ at *m/z* 509 and a pseudo-molecular ion $[M+H]^+$ at *m/z* 487, corresponding to a molecular formula of $C_{30}H_{46}O_5$. This was confirmed by positive-ion HRFABMS which exhibited a pseudo-molecular ion $[M+H]^+$at *m/z* 487.3428. The ^{1}H NMR spectrum of **8** indicated the presence of two olefinic (H-2 and H-3) signals at δ 5.52 and 5.69. The rest of the ^{1}H NMR spectroscopic data were consistent with structure (Scheme 1).

Dihydroxylation of the olefin acetonide **8** with OsO_4 in pyridine, followed by treatment with 5% aq. $NaHSO_3$ afforded two products in high yield. The more polar product (58% yield) was identified as 20-hydroxyecdysone 20,22-acetonide (**5**) by comparison of spectroscopic (IR, ^{1}H NMR and mass spectral) data with the reported value.[9] The less polar product (32% yield) was compound **9**, the C-2 and C-3 epimer of **5**. That the ecdysteroid **5** was the major product was expected, since dihydroxylation of **8** took place on the less-hindered β-face. The ^{1}H and ^{13}C NMR spectroscopic signals of **9** were assigned from 2D (COSY, HMQC, HMBC) and DEPT techniques and were found to be much different from those of **5**. A striking difference was the unusual downfield H-9 signal of **9** (in C_5D_5N) at δ 4.70, whereas that of **5** appeared at δ 3.54. A close proximity of H-9 and the 2α-hydroxyl group resulted in a large downfield shift of the former signal. A marked upfield shift of the H-5 signal of **9** at δ 2.37, as compared with that of **5** at δ 2.99, was also noted. The strong steric interaction between the 2α-hydroxyl group and H-9 might lead to facile C-5 epimerization of **9**. The structure of this minor dihydroxylation product could possibly, therefore, be **9** or its C-5 epimer of **9**. To prove whether the stereochemistry at C-5 was in the β-orientation, a NOE experiment was performed. The key experiment was to irradiate the 19-Me signal to see if enhancement of the H-5 signal would occur.[11] The result, however, was not conclusive since the H-5 signal was obscured by other signals. Compound **9** was therefore subjected to acetylation to the corresponding 2,3,25-triacetate acetonide **10**. Assignments of the NMR spectroscopic signals of **10** were achieved by 2D NMR techniques. Irradiation at the 19-Me frequency of **10** resulted in NOE enhancement of the H-5 signal at δ 2.20, whereas irradiation at the H-9 frequency caused enhancement of the 2α-acetoxyl signal at δ 1.98. To confirm that the position of the H-5 resonance was at δ 2.20, the H-3 resonance was irradiated and enhancement of this proton signal was also observed. The results indicated that H-5 of compound **10** was in the β-orientation. It was thus concluded that compound **9** was a 5β-ecdysteroid as shown. Acetonide deprotection of **9** with 70% AcOH in the presence of the phase transfer catalyst benzyltrimethylammonium chloride afforded 2,3-*diepi*-20-hydroxyecdysone (**3**) in 81% yield.

In order to increase the ratio of the product **9**:**5**, asymmetric dihydroxylation[12] was investigated. The chiral ligands used were those of the dihydroquinidine (DHQD) series, that is,



Scheme 1. Synthesis of ecdysteroid analogues **3** and **4**. Reagents and conditions: (a) CH_3COCH_3, *p*-TsOH; (b) MsCl, pyridine; (c) NaI, Zn, DMF, 80 °C; (d) OsO_4, ligand, solvent (see text); (e) Ac_2O, pyridine; (f) 70% AcOH, $PhCH_2NMe_3^+Cl^-$; (g) 2% Na_2CO_3, MeOH; (h) 70% AcOH, $PhCH_2NMe_3^+Cl^-$.

dihydroquinidine 4-methyl-2-quinolyl ether (DHQD-MQE), dihydroquinidine 9-phenanthryl ether (DHQD-PE) and dihydroquinidine 1,4-phthalazinediyl diether $(DHQD)_2$-PHAL), and the dihydroquinine (DHQ) series, that is, DHQ-MQE, DHQ-PE and $(DHQ)_2$-PHAL (Table 1). The best **9**:**5** product ratio was 4:1, the chiral ligand of which was $(DHQD)_2$-PHAL. In this case the yield of **9** was raised to 68%. The overall yield of **3** from the starting ecdysteroid **1** was 25%, based on the utilization of the chiral ligand $(DHQD)_2$-PHAL in the dihydroxylation step.

To effect C-5 epimerization, compound **9** was treated with 2% Na_2CO_3 in MeOH and, as expected, epimerization occurred more readily than the 2β,3β-dihydroxyl analogue[7] (e.g., compound **5**) to give the corresponding 5α-analogue **11** in 80% yield. The *trans*-A/B ring fusion of **11** was evident from a large upfield shift (1.47 ppm) of H-9 in going from **9** to **11**. A downfield shift (0.65 ppm) of H-5 signal of **11** indicated the proximity of this proton and the 3α-hydroxyl group. The H-5 proton of **11** was further confirmed to be in the α-orientation by NOE experiments. Thus irradiation at the H-5 frequency did not cause enhancement of the 19-Me signal at δ 0.96, whereas irradiation at the H-9 frequency resulted in enhancement of the H-5 signal at δ 3.02. Compound **11** was subjected to deacetonation to give 2,3-*diepi*-5α-20-hydroxyecdysone (**4**) in 72% yield, the spectroscopic data of which were consistent with the structure. The overall yields of **4** from the starting ecdysteroid **1** was 18%, or 58% from compound **9**.

Table 1. Asymmetric dihydroxylation of compound **8**

Entry	Ligand	Ratio of products **5**:**9**	Yield (%)
1	DHQD-MQE	5:6	77
2	DHQD-PE	7:3	83
3	$(DHQD)_2$-PHAL	1:4	85
4	DHQ-MQE	7:3	76
5	DHQ-PE	3:1	80
6	$(DHQ)_2$-PHAL	5:4	84

The ratio of the ligand:OsO_4: compound **8** was 3:3:1. *tert*-BuOH–THF–H_2O (7:4:1) was used as a solvent.

2.1. Biological activity

The *Musca* bioassay[13] has been used to evaluate moulting activity of ecdysteroid and their analogues in our study. As expected for a 3α-hydroxy ecdysteroid, compound **3** which is the 2α,3α-analogue of the parent ecdysteroid **1** was much less active; it was 30-fold less active than compound **1**. Surprisingly, compound **4**, the 5α-analogue of compound **3** and was expected to be inactive,[4] was active in the assay. It was 42-fold less active than compound **1**. The activity of **4**, though it was approximately 1.5-fold less active than that of **3**, deserved special attention. One possible explanation for the activity of **4** was that it could bind to the ecdysteroid receptor by analogy to that which occurred in castasterone (**2**). Unlike **2**, compound **4** possesses a 6-keto-7-ene system, the essential structural requirement for moulting activity. The α-nature of the 2- and 3-hydroxyl groups resulted in effective binding to the receptor and this could possibly compensate the *trans*-A/B ring junction of **4**. An alternative explanation was that compound **4** could undergo in vivo C-5 epimerization to compound **3**. The unfavorable steric interaction of the 2α-hydroxyl group and H-9 in **3** could, in part, be compensated for by the absence of 1,3-diaxial interaction between 19-Me and the 2β- and 4β-H (see Fig. 1). One supported example was the activity of compound **12**, a 2-deoxy-5α-ecdysteroid analogue, which exhibited low moulting activity in the *Musca* assay.[14] Whether the first or second hypothesis was more likely could not be judged from the existing data.

3. Experimental

3.1. General experimental procedures

Melting points were determined on an Electrothermal melting point apparatus and were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 400 spectrometer. FAB and ES mass spectra were measured on a Finnigan MAT 90 and a Bruker Esquire-LC instruments. Column chromatography and TLC were carried out using Merck silica gel 60 (<0.063 mm) and precoated silica gel 60 F_{254} plates, respectively. Spots on TLC were visualized under UV light and by spraying with anisaldehyde–H_2SO_4 reagent followed by heating.

3.1.1. 20-Hydroxyecdysone 20,22-acetonide 2,3-dimesylate (7). Compound **5**[9] (1.4 g, 2.69 mmol) was dissolved in pyridine (4 mL) and the mixture stirred at 0–5 °C for 10 min, then mesyl chloride (1.5 mL, 19.30 mmol) was added. The reaction mixture was left to stir at 0–5 °C for 1 h and at ambient temperature for another 1 h. Water was added and the mixture extracted with $CHCl_3$ (4×25 mL). The combined chloroform extract was washed with water, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was subjected to column chromatography (silica gel 50 g) using $CHCl_3$–MeOH, with gradually increasing concentration of MeOH, to give 20-hydroxyecdysone 20,22-acetonide 2,3-dimesylate (**7**) (1.2 g, 66%) eluted by $CHCl_3$–MeOH (98.5:1.5) and 20-hydroxyecdysone 20,22-acetonide 2-mesylate (**6**) (490 mg, 30%), eluted by $CHCl_3$–MeOH (96:4).

Compound **6**. Spectroscopic (^{1}H NMR and mass spectral) data were identical to those reported in literature.[10]

Compound **7**. Amorphous; ν_{max} 3436, 2971, 1660, 1449, 1354, 1176, 1106, 1024, 909 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77 (s, 3H, 18-Me), 1.03 (br s, 3H, 19-Me), 1.14 (s, 3H, 21-Me), 1.22 (s, 3H, 26-Me), 1.23 (s, 3H, 27-Me), 1.31, 1.39 (each s, 2×3H, acetonide Me), 2.22 (dd, J=9.1, 7.9 Hz, 1H, H-17), 2.98 (m, 1H, H-9), 3.10, 3.11 (each s, 2×3H, 2-OMs, 3-OMs), 3.63 (dd, J=9.4, 2.4 Hz, 1H, H-22), 4.94 (m, 1H, H-2), 5.12 (br s, 1H, H-3), 5.87 (d, J=2.1 Hz, 1H, H-7); ESMS m/z (% rel. intensity) 699 $[M+Na]^+$(100)]; HRFABMS (positive ion mode) m/z 677.3045 $[M+H]^+$ (calcd for $C_{32}H_{52}O_{11}S_2-H$, 677.3029).

3.1.2. 2,3-Didehydro-2,3-dideoxy-20-hydroxyecdysone 20,22-acetonide (8). Compound **7** (960 mg, 1.42 mmol) was dissolved in DMF (5 mL) and NaI (820 mg, 5.47 mmol) and zinc dust (196 mg, 3 mmol) was added. The reaction mixture was left to stir at 80 °C for 3 days. Water was added and the mixture was extracted with $CHCl_3$. The combined $CHCl_3$ layer was washed with water, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to dryness. The product was purified by column chromatography (silica gel 30 g) using $CHCl_3$–MeOH with gradually increasing concentration of MeOH to give compound **8** (520 mg, 75%), eluted by $CHCl_3$–MeOH (99:1).

Compound **8**. Colorless needles (from $CHCl_3$–MeOH), mp 117–119 °C; ν_{max} 3426, 2971, 1659, 1443, 1376, 1213, 1200 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75 (s, 3H, 18-Me), 1.02 (s, 3H, 19-Me), 1.12 (s, 3H, 21-Me), 1.20 (s, 3H, 26-Me), 1.21 (s, 3H, 27-Me), 1.29, 1.38 (each s, 2×3H, acetonide Me), 2.22 (t, J=ca 9 Hz, 1H, H-17), 2.85 (br m, 1H, H-9), 3.63 (br d, J=7.8 Hz, 1H, H-22), 5.50 and 5.67 (each br d, J=10 Hz, 2×1H, H-2 and H-3), 5.76 (d, J=1.3 Hz, 1H, H-7); ESMS (positive ion mode) m/z (% rel. intensity) 995 $[2M+Na]^+$ (25), 509 $[M+Na]^+$ (100), 487 $[M+H]^+$ (17); HRFABMS (positive ion mode) m/z 487.3428 $[M+H]^+$ (calcd for $C_{30}H_{46}O_5+H$, 487.3423).

3.1.3. Reaction of compound 8 with osmium tetroxide. Synthesis of 2,3-*diepi*-20-hydroxyecdysone 20,22-acetonide (9) and 20-hydroxyecdysone 20,22-acetonide (5). To a solution of compound **8** (134 mg, 0.275 mmol) in pyridine (0.8 mL) was added OsO_4 in pyridine (0.55 mL, prepared by dissolving 500 mg of OsO_4 in 3 mL of pyridine and the amount used was equivalent to 92 mg or 0.36 mmol of OsO_4). The mixture was stirred for 5 min and 5% $NaHSO_3$ (2 mL) was added. Stirring was continued for 15 min and the mixture was extracted with EtOAc (3×15 mL). The combined organic layer was washed with water, dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude mixture (150 mg) was subjected to column chromatography (silica gel 25 g), using $CHCl_3$–MeOH as eluting solvent, with increasing amount of MeOH. Fractions eluted by $CHCl_3$–MeOH (95:5) afforded 46 mg (32%) of 2,3-*diepi*-20-hydroxyecdysone 20,22-acetonide (**9**). The second fraction (83 mg, 58%) eluted by $CHCl_3$–MeOH (94:6), was identified as 20-hydroxyecdysone 20,22-acetonide (**5**).

Compound **5**. Colorless needles (from acetone–hexane), mp 221–223 °C (lit.[9] 222–224 °C); ν_{max} 3423, 2974, 1649, 1454, 1377, 1216, 1170, 1103, 1057, 1001, 877 cm^{-1}; ^{1}H NMR (400 MHz, C_5D_5N) δ 1.00, 1.03 (each s, 2×3H, 18-Me, 19-Me), 1.32 (s, 3H, acetonide Me),[a] 1.34 (s, 3H, 26-Me), 1.35 (s, 3H, 27-Me), 1.44 (s, 3H, acetonide Me), 1.53 (s, 3H, 21-Me),[a] 2.75 (t, J=8.6 Hz, 1H, H-17), 2.99 (dd, J=13.1, 3.5 Hz, 1H, H-5), 3.54 (m, 1H, H-9), 3.93 (dd, J=9.6, 2.4 Hz, 1H, H-22), 4.16 (m, 1H, H-2), 4.22 (br s, 1H, H-3), 6.24 (d, J=2.1 Hz, 1H, H-7), (‘a’ stands for the assignments may be reversed for signals with the same superscript); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (s, 3H, 18-Me), 0.93 (s, 3H, 19-Me), 1.12 (s, 3H, 21-Me), 1.18 (s, 3H, 26-Me),[b] 1.26 (s, 3H, 27-Me),[b] 1.29,[b] 1.38 (each s, 2×3H, acetonide Me), 2.38 (dd, J=12.9, 4.4 Hz, 1H, H-5), 2.95 (m, 1H, H-9), 3.59 (m, 1H, H-22), 3.81 (m, 1H, H-2), 4.01 (br s, 1H, H-3), 5.81 (d, J=1.8 Hz, 1H, H-7), (‘b’ stands for the assignments may be reversed for signals with the same superscript); ESMS (positive ion mode) m/z (% rel. intensity) 543 $[M+Na]^+$ (100); HRFABMS (negative ion mode) *m/z* 519.3322 [M−H]$^-$. (calcd for $C_{30}H_{48}O_7$−H, 519.3321).

Compound **9**. Amorphous; ν_{max} 3418, 2970, 1654, 1458, 1384, 1258, 1200, 1173, 1075, 1002, 927, 867 cm^{-1}; ^{1}H NMR (400 MHz, C_5D_5N) δ 0.99 (br s, 3H, 19-Me), 1.03 (s, 3H, 18-Me), 1.30 (s, 3H, 21-Me), 1.37 (s, 2×3H, 26-Me, 27-Me), 1.45, 1.53 (each s, 2×3H, acetonide Me), 2.37 (obscured signal, 1H, H-5), 2.77 (t, *J*=8.3 Hz, 1H, H-17), 3.92 (obscured signal, 1H, H-3), 3.94 (dd, *J*=9.3, 2.8 Hz, 1H, H-22), 4.33 (br s, $W_{1/2}$=12 Hz, 1H, H-2), 4.70 (br, 1H, H-9), 6.22 (d, *J*=2.3 Hz, 1H, H-7); ^{13}C NMR (100 MHz, C_5D_5N) δ 17.3 (C-18), 21.3 (C-16), 22.1 (C-11), 22.4 (C-21), 24.2 (C-19), 24.4 (C-23), 27.2 (acetonide Me), 29.4 (acetonide Me), 29.7 (C-4), 29.8 (C-26), 30.1 (C-27), 31.6 (C-12), 31.8 (C-15), 36.2 (C-9), 36.6 (C-10), 39.9 (C-1), 42.1 (C-24), 47.9 (C-13), 49.9 (C-17), 57.7 (C-5), 69.2 (C-25), 70.4 (C-2), 71.5 (C-3), 82.5 (C-22), 84.0 (C-14), 85.1 (C-20), 106.9 (acetonide C), 121.1 (C-7), 167.8 (C-8), 202.1 (C-6); HRFABMS (negative ion mode) *m/z* 519.3324 [M−H]$^-$. (calcd for $C_{30}H_{48}O_7$−H, 519.3321).

3.2. Asymmetric dihydroxylation of 8 with OsO_4 and chiral ligands

General procedure. To a solution of 0.03 mmol of a chiral ligand in *tert*-BuOH−THF−H_2O (7:4:1, 0.6 mL) was added a THF solution of OsO_4 (14 μL, 0.03 mmol. The solution was prepared by dissolving 500 mg of OsO_4 in 9 mL of THF.) and the mixture stirred for 3 min. A solution of the olefin acetonide **8** (5 mg, 0.01 mmol) in *tert*-BuOH−THF−H_2O (7:4:1, 0.5 mL) was then added and stirring continued for 5 min. The ratio of the ligand, OsO_4 and olefin acetonide was 3:3:1. A 5% solution of $NaHSO_3$ (10 mL) was added and stirring continued for another 10 min. The mixture was extracted with EtOAc (4×20 mL); the combined organic phase was evaporated and the residue was chromatographed to separate compounds **5** and **9** from the ligand. Since the two products could easily be separated from each other by column chromatography, the **5**:**9** ratio for each ligand was determined from the isolated products **5** and **9**. The results are shown in Table 1.

3.2.1. Acetylation of compound 9. A mixture of compound **9** (9 mg, 0.017 mmol), Ac_2O (0.1 mL, 1.05 mmol) and pyridine (0.7 mL) was stirred for 6 h. The reaction mixture was worked up in the usual manner and the product purified by column chromatography to give 2,3-*diepi*-20-hydroxyecdysone 2,3,25-triacetate (**10**) (8 mg, 72%).

Compound **10**. Amorphous; ν_{max} 3482, 2977, 1744, 1666, 1458, 1370, 1246, 1168, 1137, 1106, 928, 874 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (s, 3H, 18-Me), 0.94 (br s, 3H, 19-Me), 1.12 (s, 3H, 21-Me), 1.29, 1.38 (each s, 2×3H, acetonide Me), 1.43 (s, 3H, 26-Me), 1.45 (s, 3H, 27-Me), 1.97 (s, 2×3H, 3-OAc, 25-OAc), 1.98 (s, 3H, 2-OAc), 2.20 (partially obscured signal, 1H, H-5), 3.59 (dd, *J*=ca 9, 2.5 Hz, 1H, H-22), 3.75 (br, $W_{1/2}$=21 Hz, 1H, H-9), 4.88 (br, $W_{1/2}$=20 Hz, 1H, H-3), 5.26 (br s, $W_{1/2}$=13 Hz 1H, H-2), 5.86 (d, *J*=1.9 Hz, 1H, H-7); ^{13}C NMR (100 MHz, C_5D_5N) δ 17.1 (C-18), 20.9 (acetate Me), 21.1 (2×C, acetate Me), 21.9 (C-21), 23.2 (C-16), 23.6 (C-19), 25.7 (C-26), 26.1 (C-27), 26.8 (acetonide Me), 28.9 (acetonide Me), 30.9, 31.9 (C-12, C-15), 35.0 (C-9), 36.1 (C-10), 36.7 (C-1), 38.5 (C-24), 47.2 (C-13), 49.0 (C-17), 55.8 (C-5), 69.3, 71.0 (C-2, C-3), 81.4 (C-22), 82.0 (C-25), 84.0 (C-20), 84.9 (C-14), 106.8 (acetonide C), 120.9 (C-7), 165.8 (C-8), 170.0 (2×C, acetate CO), 170.5 (acetate CO), 200.6 (C-6); HRFABMS (positive ion mode) *m/z* 647.3787 [M+H]$^+$. (calcd for $C_{36}H_{54}O_{10}$+H, 647.3787).

3.2.2. Acetonide deprotection of compound 9. Compound **9** (36 mg, 0.069 mmol) was dissolved in 70% AcOH (0.7 mL, excess) and benzyltrimethylammonium chloride (25 mg, 0.135 mmol) was added. The reaction mixture was left to stir for 4 h; water was then added and the mixture extracted with *n*-BuOH (3×15 mL). The combined organic layer was washed with water; the solvent was removed by co-evaporation with water under reduced pressure. The crude product was purified by column chromatography using $CHCl_3$−MeOH as eluting solvent to afford 2,3-*diepi*-20-hydroxyecdysone (**3**) (27 mg, 81%).

Compound **3**. Colorless needles (from MeOH−EtOAc), mp 204–206 °C; ν_{max} 3420, 2965, 1654, 1383, 1065, 929 cm^{-1}; ^{1}H NMR (400 MHz, C_5D_5N) δ 1.00 (s, 3H, 19-Me), 1.22 (s, 3H, 18-Me), 1.38 (s, 2×3H, 26-Me, 27-Me), 1.54 (s, 3H, 21-Me), 2.40 (obscured signal, 1H, H-5), 3.00 (t, *J*=8.9 Hz, 1H, H-17), 3.87 (br d, *J*=8.7 Hz, 1H, H-22), 3.90 (obscured signal, 1H, H-3), 4.34 (br s, $W_{1/2}$=8.5 Hz, 1H, H-2), 4.76 (br m, 1H, H-9), 6.22 (d, *J*=2.6 Hz, 1H, H-7); ^{13}C NMR (100 MHz, C_5D_5N) δ 18.0 (C-18), 21.4 (C-16), 21.5 (C-11), 21.6 (C-21), 24.2 (C-19), 27.5 (C-23), 29.8 (C-4), 29.9 (C-26), 30.3 (C-27), 31.8 (C-12), 32.1 (C-15), 36.3 (C-9), 36.7 (C-10), 39.9 (C-1), 42.7 (C-24), 48.2 (C-13), 50.1 (C-17), 57.8 (C-5), 69.6 (C-25), 70.5 (C-2), 71.6 (C-3), 76.9 (C-20), 77.5 (C-22), 84.1 (C-14), 121.0 (C-7), 168.4 (C-8), 202.2 (C-6); HRFABMS (negative ion mode) *m/z* 479.3001 [M−H]$^-$. (calcd for $C_{27}H_{44}O_7$−H, 479.3008).

3.2.3. Epimerization of compound 9. A mixture of compound **9** (35 mg, 0.067 mmol) in MeOH (0.8 mL) and 2% Na_2CO_3 (0.2 mL, 0.038 mmol) was stirred at ambient temperature for 5 h and water was then added. The solution was extracted with *n*-BuOH (3×10 mL); the combined butanol layer was washed with water and the solvent removed by co-evaporation with water. The product was purified by column chromatography to afford 2,3-*diepi*-5α-20-hydroxyecdysone 20,22-acetonide (**11**) (28 mg, 80%).

Compound **11**. Amorphous; ν_{max} 3422, 2971, 2942, 1664, 1458, 1375, 1219, 1175, 1105, 1054, 1001, 905, 868 cm^{-1}; ^{1}H NMR (400 MHz, C_5D_5N) δ 0.95 (s, 3H, 19-Me), 0.99 (s, 3H, 18-Me), 1.30 (s, 3H, 21-Me), 1.35 (s, 2×3H, 26-Me, 27-Me), 1.43, 1.52 (each s, 2×3H, acetonide Me), 2.74 (t, *J*=ca 8 Hz, 1H, H-17), 3.02 (br d, *J*=11.1 Hz, 1H, H-5), 3.23 (m, 1H, H-9), 3.93 (br d, *J*=8.5 Hz, 1H, H-22), 4.02 (m, $W_{1/2}$=21 Hz, 1H, H-2), 4.42 (br s, $W_{1/2}$=8 Hz, 1H, H-3), 6.16 (br s, 1H, H-7); ^{13}C NMR (100 MHz, C_5D_5N) δ 13.6 (C-19), 17.3 (C-18), 20.8 (C-16), 22.0 (C-11), 22.4 (C-21), 24.4 (C-23), 27.2 (acetonide Me), 28.2 (C-4), 29.5 (acetonide Me), 29.9 (C-26), 30.1 (C-27), 31.5 (C-12), 31.6 (C-15), 40.3 (C-10), 41.2 (C-1), 42.2 (C-24), 46.7 (C-9), 47.6 (C-13), 48.7 (C-5), 49.9 (C-17), 68.3 (C-2), 69.1 (C-3), 69.3 (C-25), 82.5 (C-22), 83.9 (C-14), 85.1 (C-20), 106.9 (acetonide C), 123.3 (C-7), 164.4 (C-8), 201.7 (C-6);

HRFABMS (negative ion mode) *m/z* 519.3313 $[M-H]^-$. (calcd for $C_{30}H_{48}O_7-H$, 519.3322).

3.2.4. Acetonide deprotection of compound 11. Compound **11** (15 mg, 0.029 mmol) was subjected to acetonide deprotection in the same manner as described for the preparation of **3** from **9**. The product was purified by column chromatography to afford 2,3-*diepi*-5α-20-hydroxyecdysone (**4**) (10 mg, 72%).

Compound **4**. Amorphous; ν_{max} 3415, 2925, 1660, 1384, 1062 cm^{-1}; ^1H NMR (400 MHz, C_5D_5N) δ 0.84 (s, 3H, 19-Me), 1.21 (s, 3H, 18-Me), 1.38 (s, 2×3H, 26-Me, 27-Me), 1.58 (s, 3H, 21-Me), 2.99 (t, J=9.2 Hz, 1H, H-17), 3.03 (dd, J=12.4, 3.6 Hz, 1H, H-5), 3.28 (m, 1H, H-9), 3.89 (br d, J=8.9 Hz, 1H, H-22), 4.04 (m, $W_{1/2}$=20 Hz, 1H, H-2), 4.44 (br s, $W_{1/2}$=9 Hz, 1H, H-3), 6.18 (d, J=2.4 Hz, 1H, H-7); ^{13}C NMR (100 MHz, C_5D_5N) δ 13.6 (C-19), 17.9 (C-18), 20.9 (C-16),[a] 21.4 (C-11),[a] 21.7 (C-21), 27.4 (C-23),[b] 28.3 (C-4),[b] 29.9 (C-26), 30.2 (C-27), 31.8 (C-12, C-15), 40.3 (C-10), 41.3 (C-1), 42.7 (C-24), 46.7 (C-9), 47.9 (C-13), 48.7 (C-5), 50.1 (C-17), 68.4 (C-2), 69.1 (C-3), 69.6 (C-25), 76.9 (C-20), 79.8 (C-22), 84.0 (C-14), 123.3 (C-7), 164.9 (C-8), 201.8 (C-6), ('a and b' stand for assignments may be reversed for signals with the same superscript); HRFABMS (negative ion mode) *m/z* 479.3018 $[M-H]^-$. (calcd for $C_{27}H_{44}O_7-H$, 479.3008).

3.5. Moulting bioassay

Compounds **3** and **4** were subjected to the *Musca* bioassay, using *Musca domestica* larvae.[13] The purity of the ecdysteroid and their analogues was checked by reversed-phase HPLC. The bioassay results were scored[15] and EC_{50}, the molar concentration of each steroid required to effect puparium formation of 50% effectiveness, of each compound was determined by plotting concentrations against % effectiveness of puparium formation.[16] The EC_{50} values of compounds **3** and **4** were 5.0×10^{-4} and 7.0×10^{-4} M, respectively, whereas that of the reference compound **1** was 1.65×10^{-5} M.

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The direct conversion of carbamates to ureas using aluminum amides

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Abstract—The conversion of carbamates into ureas using aluminum amide complexes is reported. This reaction is a convenient method to prepare bi-, tri- and tetra-substituted ureas from carbamate-protected primary or secondary amines by reaction with primary or secondary amines in the presence of stoichometric quantities of trimethylaluminum. A reactivity trend of the various carbamates was observed and methyl and benzyl carbamates were reacted selectively in the presence of *t*-butyl carbamates.

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1. Introduction

The urea functional group plays an important role in organic and medicinal chemistry; many biologically active compounds either contain the urea functionality[1] or are synthesized from urea-containing starting materials.[2] In addition, ureas have been utilized for the synthesis of peptidomimetic compounds whereby the amide bond of the peptide is replaced by a urea bond so that the peptide mimic possesses many of the key structural features of the parent peptide, but has increased bioavailability since the urea bond is not susceptible to proteolytic cleavage.[3] Accordingly, simple and efficient methods for the synthesis of ureas are of interest. Since ureas are derived from amine constituents, a common method for their preparation involves conversion of the first amine component to an isocyanate or an activated carbamate[4] (e.g., *p*-nitrophenyl) followed by reaction with the second amine component. However, the shortcomings of this methodology become apparent when the first amine component bears more than one substituent. Specifically, secondary amines cannot be converted to the corresponding isocyanates and secondary *p*-nitrophenyl carbamates suffer from low reactivity toward a second amine nucleophile; in the latter case, more drastic conditions such as the preparation of the corresponding carbamoyl chloride[5] are required. Furthermore, quite often in any given synthetic sequence, the first amino component may have been previously protected by a common carbamate protecting group such as Boc, Cbz, Fmoc, Alloc or methyl carbamate, and thus, prior removal of such a protecting group adds yet another step to the aforementioned two step reaction sequence. Although the direct conversion of carbamate-protected primary amines into ureas has been reported,[6] in both cases, carbamate-protected secondary amines could not be used since these reactions proceed via the in situ conversion of the carbamate to the isocyanate by reaction with a halosilane. Accordingly, a simple and efficient method that enables the conversion of both carbamate-protected primary and secondary amines into the corresponding di-, tri- and tetra- substituted ureas is of great interest and importance to synthetic chemists.

Our own interest in the synthesis of ureas stems from our recent studies in the solid-phase synthesis of heterocycle libraries.[7] Here, we have utilized an ester moiety to link the target library scaffold to the polymer-support; a Lewis acid-mediated amidation reaction[8] was employed to afford an array of amide cleavage products.[9] Lewis acid-mediated amide bond forming reactions have been used extensively in synthetic chemistry and a plethora of reagents including $AlMe_3$ and $AlCl_3$ have been used. In addition, the use of aluminum amides has also been applied toward the synthesis of guanidines[10] and the ring opening of oxazolidinones to form hydroxyl ureas.[11] More recently, we have also expanded the scope of amide forming reactions using 1,2-phenylenediamines or 1,2-aminothiophenols as substrates to produce the corresponding benzimidazole or benzothiazole cleavage products from polymer-bound ester substrates.[12] Unexpectedly, during our investigations of Lewis acid mediated C–N bond forming reactions, we also discovered that under mild conditions, carbamates are converted into the corresponding ureas by reaction with aluminum amides. Reported herein are these findings.

Keywords: Ureas; Carbamate; Lewis acid.

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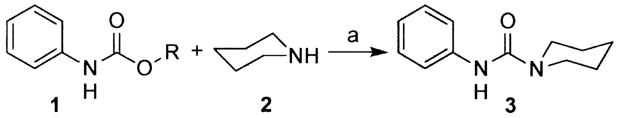
2. Results and discussion

To begin with, we investigated the conversion of a series of carbamate protected anilines **1**, into the corresponding ureas **3**, Scheme 1, Table 1. In this study, we tested the most widely used carbamate protecting groups, such as methyl carbamate, Boc, Cbz, Alloc, Troc, Fmoc and Teoc.[13] In most instances, when the carbamates **1a–g** were treated with an excess of piperidine **2** and $AlMe_3$ (amine/metal/carbamate ratio 3:2.5:1) the corresponding urea **3** was formed in good to excellent yields after only 2–5 h. at room temperature. When the *t*-butyl carbamate **1b** was used (Boc), the rate of conversion proved to be very slow as estimated by TLC; however, when heated to 50 °C this reaction was complete within 1.5 h. The only example that gave a poor yield in these experiments was the Fmoc-protected aniline **1f** where the desired product **3** was only isolated in 34% yield. This low yield was attributed to the high lability of the Fmoc group to piperidine **2**.



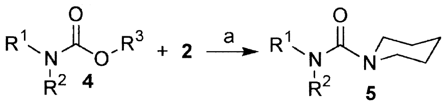
Scheme 1. Reagents and conditions: (a) **2** (3 equiv.), $AlMe_3$ (2.5 equiv.), toluene.

Table 1.

Entry	Substrate (R=)		Temperature (°C)	Time (h)	Yield (%)
1	**1a**	CH_3	Room temperature	2.5	78
2	**1b**	*t*-Butyl	50	1.5	92
3	**1c**	Bn	Room temperature	3.5	93
4	**1d**	Allyl	Room temperature	2	89
5	**1e**	Cl_3CCH_2	Room temperature	2	96
6	**1f**	Fluorenylmethyl	80	2	34[a]
7	**1g**	$Me_3Si(CH_2)_2$	Room temperature	5	90

[a] 5 equiv. of $AlMe_3$ used.

With these results in hand, the next variable to be investigated was the effect of the type, and number of substituents on the nitrogen atom of the carbamate. Thus, this study would enable us to assess the scope of the Lewis acid mediated reaction with regards to establishing the reactivity of mono- and di-substituted carbamates **4** and the ease of preparation of the corresponding tri- and tetra-substituted ureas **5**, Scheme 2, Table 2.



Scheme 2. Reagents and conditions: (a) **2** (3 equiv.), $AlMe_3$ (2.5 equiv.), toluene.

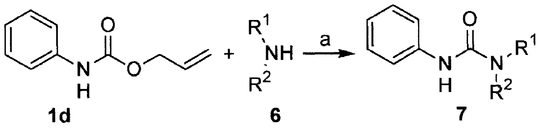
Table 2.

Entry	Sub.	R^1	R^2	R^3	Temperature (°C)	Time (h)	Prod.	Yield (%)
1	**4a**	Bn	H	Bn	50	4.5	**5a**	95
2	**4b**	Ph	Me	Et	110	3	**5b**	96
3	**4c**	$Ph(CH_2)_2$	H	Et	50	4	**5c**	98
4	**4d**	$-(CH_2)_4-$		Bn	110	3	**5d**	91[a]
5	**4e**	Ph	Ph	Et	110	5	**5e**	99

[a] Phenylethylamine used in place of piperidine.

Once again, the reaction showed broad scope and excellent reliability. There was a discernable difference between the rate of conversion of primary and secondary carbamates **4** into the respective ureas **5**. For example, when ethyl carbamate **4b** was reacted with the piperidine/$AlMe_3$ adduct (amine/metal/substrate ratio 3:2.5:1), the reaction had to be heated to 110 °C to give the desired product **5b** in 96% yield after 3 h. However, our previous experiments had shown that the primary amine **1a** (aniline methyl carbamate) was readily converted into the desired urea **3** at room temperature over a similar reaction time (Table 1, entry 1 vs Table 2, entry 2). A similar trend was observed when carbamates derived from secondary amines, *N*-Cbz piperidine and diphenylamine *N*-ethyl carbamate were converted into the corresponding urea products **5d** and **5e** (Table 2, entries 4 and 5); in both cases, the reactions had to be heated to 110 °C to enable good conversion to the desired product in an acceptable period of time.

We also investigated what effect the nature of the amine component **6** of the reaction would have on the rate of formation of the urea product **7**, Scheme 3, Table 3. It appears that both the nucleophilicity of the amine coupling partner and the steric bulk of the amine substituents have a dramatic effect on the rate of conversion into the desired ureas. For example, when butylamine **6** (R^1=Bu, R^2=H) was reacted with *N*-Alloc aniline **1d**, the corresponding urea **7a** was formed in 99% yield after heating at 50 °C for 30 min; however, when the bulky diisopropylamine **6** (R^1=R^2=*i*-Pr) was used, the corresponding urea **7c** was formed in 94% yield after heating to 50 °C for 1 h (Table 3, entries 1 and 3). In addition, when benzylamine **6** was used in the reaction, the desired urea **7b** was formed within 30 min. but when the similar sized but when less nucleophilic aniline **6** (R^1=Ph, R^2=H) was used, the reaction time had to be extended to 4 h to give the corresponding urea **7d** in 83% yield (Table 3, entries 2 vs 4). Finally, when diphenylamine **6** (R^1=R^2=Ph) was used, the reaction required heating to 110 °C to achieve and acceptable rate of conversion to product **7f**.



Scheme 3. Reagents and conditions: (a) **6** (3 equiv.), $AlMe_3$ (2.5 equiv.), toluene.

Table 3.

Entry	R^1	R^2	Temperature (°C)	Time	Product	Yield (%)
1	Bu	H	50	0.5	**7a**	99
2	Bn	H	50	0.5	**7b**	94
3	*i*-Pr	*i*-Pr	50	1	**7c**	94
4	Ph	H	50	4	**7d**	83
5	Me	Ph	50	5	**7e**	95
6	Ph	Ph	110	2	**7f**	97

We note that when inexpensive and readily available amine starting materials were used, a slight excess of the amine over the carbamate was employed to drive the reaction to completion in shorter period of time, although further experiments have shown that with more valuable amines or for chemoselective reactions, the stoichiometry can be reduced (amine/metal/substrate ratio 1.1:1:1). The use of a slight excess of amine is also not critical to the work up and purification of the desired urea products. After completion of the reaction, (estimated by TLC), the reaction was quenched using water and then passed through a strong-acid ion exchange resin to remove unreacted starting materials and aluminum salt byproducts to furnish an essentially pure product.

The final part of our study was to investigate if we could selectively react one carbamate over another and also, selectively react a carbamate over an ester or vice versa. The first of these experiments involved the preparation of the bis-carbamate **8** that was synthesized from 4-nitro aniline by protecting the aniline with a Boc group, followed by reduction of the nitro group to the amine, which was then converted to the benzyl carbamate (Cbz). When **8** was reacted with 1 equiv. of the piperidine trimethylaluminum adduct at room temperature for 24 h, the expected reaction occurred exclusively at the Cbz group, and the Boc protected product **9** was isolated in 95% yield. A Boc and Cbz-protected alkyl diamine **10** was also prepared and subjected to similar urea formation conditions. Once again, the Cbz group was selectively reacted in the presence of a Boc group to give the desired product **11** in 92% isolated yield.

We also discovered that esters are significantly more reactive than the corresponding carbamate under Lewis acid promoted C–N bond forming conditions. When Cbz protected glycine methyl ester **12a** was reacted with 1 equiv. of the piperidine trimethylaluminum adduct at room temperature for 24 h the corresponding amides **13** was formed exclusively in 92% yield. Moreover, we also investigated the reaction of Cbz glycine benzyl ester **12b** to unequivocally prove that the ester can be selectively reacted in the presence of a similarly functionalized carbamate, the corresponding amide **13** was similarly formed in 92% yield. Our observations consolidate previous findings by Martin and co-workers for the synthesis of carbamate protected peptide fragments via aluminum amide intermediates.[14]

Our final investigation of these competition experiments was to see if we could tune the reactivity of both the carbamate and ester groups to achieve selective reaction of the urea in the presence of an ester. Accordingly, methoxy carbamate glycine *t*-butyl ester **14** was prepared and reacted with 1 equiv. of the piperidine trimethylaluminum adduct. Unfortunately, this experiment failed since both groups reacted at similar rates; this reaction afforded a mixture of the piperidine amide urea **15** in 46% yield and the remainder was unreacted starting material **14** (Scheme 4).

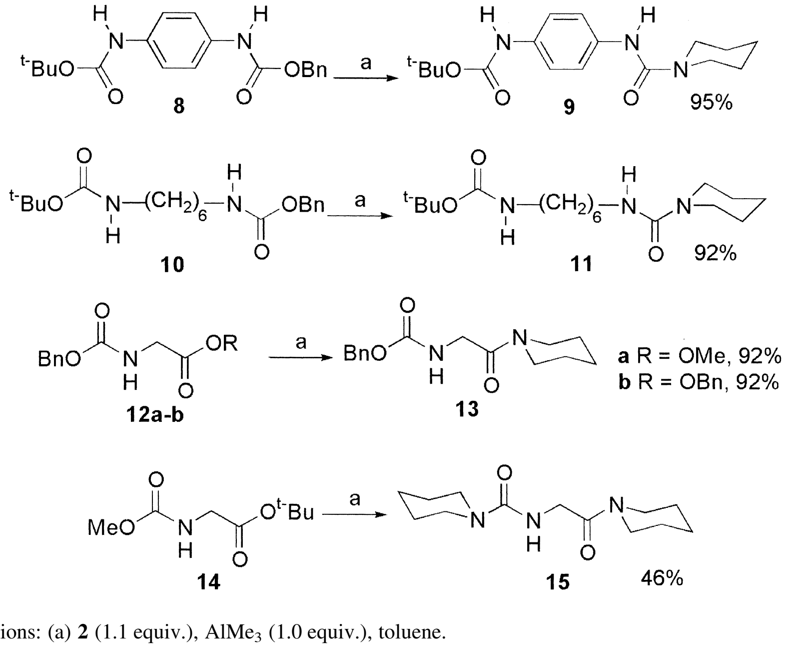
3. Conclusion

In summary, we have developed a highly efficient method for the direct conversion of carbamates into the corresponding ureas. Our method enabled the synthesis of di-, tri- and tetra- substituted ureas and we have also been able to show complete chemoselectivity in the reaction of one carbamate over another. Further investigations into the reaction of carbonyls with aluminum amides are ongoing in our laboratory and will be reported in due course.

4. Experimental

4.1. Representative procedure

Trimethylaluminum (2.0 M in toluene, 1.25 mL,



Scheme 4. Reagents and conditions: (a) **2** (1.1 equiv.), $AlMe_3$ (1.0 equiv.), toluene.

2.50 mmol) was slowly added to a solution of piperidine **2** (0.30 mL, 3.00 mmol) in toluene (5 mL) at 0 °C under argon. After being stirred for 10 min at 0 °C, the resulting solution was allowed to warm up to room temperature and then stirred for 1 h. The mixture was added dropwise to a stirred solution of the *N*-Boc-aniline **1b** (152.6 mg, 1.00 mmol) and toluene (3 mL) in a 40 mL vial at 0 °C under argon and the resulting solution was heated to 50 °C for 1.5 h. The reaction was quenched by the addition of a mixture of THF (10 mL) and H_2O (3 mL) and stirring was continued for a further 20 min before the solution was passed through a work-up cartridge that contained a strong acid ion exchange resin (DOWEX 500WX2-200) that was further eluted with THF. The combined filtrates were concentrated under reduced pressure to yield the crude product was then purified by column chromatography over silica (3% CH_3CN in $CHCl_3$) to give *N*-phenyl-*N*′,*N*′-pentamethylene urea as a colorless solid (159.5 mg, 0.78 mmol, 78%).

4.2. Spectroscopic data

4.2.1. Compound 3. Colorless solid; mp 169.5–171 °C; IR 3284, 2925, 2855, 1629, 1591, 1533, 1434 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.56–1.65 (6H, m), 3.42–3.44 (4H, m), 6.49 (1H, br s), 6.99–7.02 (1H, m), 7.24–7.27 (2H, m), 7.34–7.36 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.3 (t), 25.6 (t), 45.2 (t), 119.8 (d), 122.7 (d), 128.7 (d), 139.3 (s), 155.0 (s); HRMS *m*/*z*=205.1334 [M+H], calcd for $C_{12}H_{17}N_2O$=205.1335.

4.2.2. Compound 5a. Colorless solid; mp 102 °C; IR 3339, 2927, 2850, 1622, 1533 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.52–1.62 (6H, m), 3.32–3.34 (4H, m), 4.42 (2H, d, *J*=5.5 Hz), 4.75 (1H, br s), 7.24–7.34 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4 (t), 25.6 (t), 44.9 (t), 45.0 (t), 127.2 (d), 127.7 (d), 128.5 (d), 139.6 (s), 157.5 (s); HRMS *m*/*z*=219.1491 [M+H], calcd for $C_{13}H_{19}N_2O$=219.1492.

4.2.3. Compound 5b. Colorless oil; IR 2934, 1635, 1594, 1495, 1429, 1399 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.24–1.29 (4H, m), 1.36–1.41 (2H, m), 3.07–3.10 (4H, m), 3.13 (3H, s), 6.99–7.01 (3H, m), 7.22–7.25 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.2 (t), 25.1 (t), 39.1 (q), 46.4 (t), 123.2 (d), 123.8 (d), 129.0 (d), 146.9 (s), 160.9 (s); HRMS *m*/*z*=219.1490 [M+H], calcd for $C_{13}H_{19}N_2O$=219.1492.

4.2.4. Compound 5c. Colorless solid; mp 78–78.5 °C; IR 3320, 2916, 2851, 1615, 1541 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.48–1.59 (6H, m), 2.81 (2H, t, *J*=7.0 Hz), 3.24–3.26 (4H, m), 3.47 (2H, dd, *J*=7.0, 12.8 Hz), 7.18–7.31 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.4 (t), 25.5 (t), 36.4 (t), 42.0 (t), 44.8 (t), 126.3 (d), 128.5 (d), 128.8 (d), 139.5 (s), 157.5 (s); HRMS *m*/*z*=233.1648 [M+H], calcd for $C_{14}H_{21}N_2O$=233.1648.

4.2.5. Compound 5d. Colorless oil; IR 2928, 2849, 1639, 1413 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.52–1.60 (12H, m), 3.15–3.17 (8H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.8 (t), 25.8 (t), 47.9 (t), 164.8 (s); HRMS *m*/*z*=197.1651 [M+H], calcd for $C_{11}H_{21}N_2O$=197.1648.

4.2.6. Compound 5e. Colorless solid; mp 117.5–118 °C; IR 2940, 1641, 1588, 1490, 1421 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.38–1.55 (6H, m), 3.32–3.34 (4H, m), 7.03–7.12 (6H, m), 7.28–7.31 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.4 (t), 25.4 (t), 46.5 (t), 124.4 (d), 124.8 (d), 129.1 (d), 145.1 (s), 159.8 (s); HRMS *m*/*z*=281.1650 [M+H], calcd for $C_{18}H_{20}N_2O$=281.1648.

4.2.7. Compound 7a. Colorless solid; mp 129 °C; IR 3378, 2960, 2932, 2870, 1652, 1597, 1552, 1498 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 0.94 (3H, t, *J*=7 Hz), 1.34–1.43 (2H, m), 1.47–1.53 (2H, m), 3.18 (2H, t, *J*=7.0 Hz), 6.93–6.96 (1H, m), 7.20–7.24 (2H, m), 7.31–7.33 (2H, m); ^{13}C NMR (125 MHz, CD_3OD) δ 14.1 (q), 21.0 (t), 33.4 (t), 40.5 (t), 120.1 (d), 123.3 (d), 129.8 (d), 141.0 (s), 158.4 (s); HRMS *m*/*z*=193.1336 [M+H], calcd for $C_{11}H_{16}N_2O$=193.1335.

4.2.8. Compound 7b. Colorless solid; colorless solid; mp 169.5–170 °C; IR 3301, 1599, 1545, 1498, 1469, 1441, 1310, 1222 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 4.34 (2H, d, *J*=5.9 Hz), 6.65 (1H, t, *J*=5.9 Hz), 6.92–6.95 (1H, m), 7.24–7.30 (3H, m), 7.34–7.39 (4H, m), 7.44–7.46 (2H, m), 8.59 (1H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ 43.7 (t), 118.6 (d), 122.0 (d), 127.7 (d), 128.1 (d), 129.3 (d), 129.6 (d), 141.3 (s), 141.4 (s), 156.2 (s); HRMS *m*/*z*=227.1178 [M+H], calcd for $C_{14}H_{15}N_2O$=227.1179.

4.2.9. Compound 7c. Colorless solid; mp 113–115 °C; IR 3271, 2961, 2930, 1630, 1594, 1525, 1501, 1444 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.32 (12H, d, *J*=7.0 Hz), 3.98 (2H, quartet, *J*=7.0 Hz), 6.21 (1H, br s), 6.98–7.16 (1H, m), 7.25–7.28 (2H, m), 7.35–7.32 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5 (q), 45.4 (d), 119.6 (d), 122.6 (d), 128.8 (d), 139.3 (s), 154.6 (s); HRMS *m*/*z*=221.1650 [M+H], calcd for $C_{13}H_{21}N_2O$=221.1648.

4.2.10. Compound 7d. Colorless solid; mp 243 °C; IR 3271, 3034, 1645, 1592, 1545, 1496, 1439 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 6.99–7.02 (2H, m), 7.30–7.34 (4H, m), 7.49–7.51 (4H, m), 8.70 (2H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ 119.1 (d), 122.8 (d), 129.7 (d), 140.7 (s), 153.5 (s); HRMS *m*/*z*=213.1023 [M+H], calcd for $C_{13}H_{13}N_2O$=213.1022.

4.2.11. Compound 7e. Colorless solid; mp 97–99 °C; IR 3270, 3059, 2927, 1652, 1592, 1523, 1493, 1437 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.35 (3H, s), 6.23 (1H, br s), 6.97–7.01 (1H, m), 7.22–7.29 (4H, m), 7.33–7.39 (3H, m), 7.47–7.50 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.2 (q), 130.3 (d), 138.8 (s), 142.9 (s), 154.4 (s); HRMS *m*/*z*=227.1182 [M+H], calcd for $C_{14}H_{15}N_2O$=227.1179.

4.2.12. Compound 7f. Yellow solid; mp 106–107 °C; IR 3409, 1669, 1593, 1515, 1486, 1435 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.45 (1H, br s), 7.02–7.04 (1H, m), 7.25–7.42 (14H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 119.3 (d), 123.3 (d), 126.7 (d), 127.5 (d), 128.9 (d), 129.6 (d), 138.4 (s), 142.3 (s); HRMS *m*/*z*=289.1328 [M+H], calcd for $C_{19}H_{17}N_2O$=289.1335.

4.2.13. Compound 9. Colorless solid; mp >300 °C; IR 3305, 2934, 1693, 1641, 1543, 1514, 1416 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 1.46 (9H, s), 1.43–1.49 (4H, m), 1.54–1.58 (2H, m), 3.38 (4H, t, J=5.7 Hz), 7.27–7.30 (4H, m), 8.28 (1H, s), 9.13 (1H, br s); ^{13}C NMR (150 MHz, DMSO-d_6) δ 24.1 (t), 25.5 (t), 28.2 (q), 44.6 (t), 78.6 (s), 118.2 (d), 120.3 (d), 133.6 (s), 135.2 (s), 152.9 (s), 155.0 (s); HRMS m/z=320.1969 [M+H], calcd for $C_{17}H_{26}N_3O_3$=320.1969.

4.2.14. Compound 11. Colorless solid; mp 94–96 °C; IR cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19–1.23 (4H, m), 1.36 (9H, s), 1.32–1.40 (8H, m), 1.48–1.53 (2H, m), 2.88 (2H, q, J=6.6 Hz), 2.97 (2H, q, J=6.6 Hz), 3.22 (4H, t, J=5.3 Hz), 6.32 (1H, t, J=5.3 Hz), 6.76 (1H, t, J=5.3 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 24.2 (t), 25.4 (t), 26.1 (t), 26.1 (t), 28.3 (q), 29.5 (t), 29.9 (t), 44.3 (t), 77.3 (s), 155.6 (s), 157.3 (s); HRMS m/z=350.2412 [M+Na], calcd for $C_{17}H_{33}N_3O_3Na$=350.2414.

4.2.15. Compound 13. Colorless solid; mp 106–107 °C; IR 3309, 2940, 2923, 1713, 1631, 1442 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51–1.57 (4H, m), 1.61–1.66 (2H, m), 3.29 (2H, br dd, J=5.1, 5.1 Hz), 3.54 (2H, br dd, J=5.1, 5.1 Hz), 3.99 (2H, d, J=4.0 Hz), 5.11 (2H, s), 5.89 (1H, br s), 7.28–7.36 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.2 (t), 25.3 (t), 26.0 (t), 42.5 (t), 43.0 (t), 45.3 (t), 66.7 (t), 127.9 (d), 127.9 (d), 128.4 (d), 136.4 (s), 156.1 (s), 165.8 (s); HRMS m/z=277.1546 [M+H], calcd for $C_{15}H_{21}N_2O_3$=277.1547.

4.2.16. Compound 14. Colorless oil; IR 3348, 2980, 1707, 1523, 1367 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (3H, s), 1.41 (3H, s), 1.42 (3H, s), 3.63 (3H, s), 3.79–3.81 (2H, m), 5.31 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.9 (q), 43.2 (t), 52.2 (q), 81.9 (s), 156.9 (s), 169.2 (s); HRMS m/z=212.0894 [M+Na], calcd for $C_8H_{15}NO_4Na$=212.0863.

4.2.17. Compound 15. Colorless oil; IR 3385, 2929, 2853, 1618, 1509, 1440, 1251, 1222 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47–1.64 (12H, m), 3.29–3.34 (6H, m), 3.50–3.54 (2H, m), 3.99 (2H, d, J=3.3 Hz), 5.62 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.3 (t), 24.3 (t), 25.3 (t), 25.5 (t), 26.0 (t), 42.5 (t), 43.0 (t), 44.7 (t), 45.2 (t), 157.1 (s), 167.2 (s); HRMS m/z=254.1859 [M+H], calcd for $C_{13}H_{24}N_3O_2$=254.1863.

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A stereoselective synthesis of 9-(3-*O*-benzyl-5-*O*-tetrahydropyranyl-β-D-arabinofuranosyl)adenine, a potentially useful intermediate for ribonucleoside synthesis☆,☆☆

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Abstract—A novel synthesis for preparing 9-(3-*O*-benzyl-5-*O*-tetrahydropyranyl-β-D-arabinofuranosyl)adenine (**6**) has been developed which does not require sub zero temperatures or exotic reagents. A key step in this synthesis is the selective protection of the 3′-OH of ara-A with a benzyl group. The 5′-OH is then selectively protected with DHP to yield **6**, a potentially useful intermediate. A synthesis of 9-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)adenine (**1**, FddA), an anti-viral compound, is given to illustrate the utility of this new approach.

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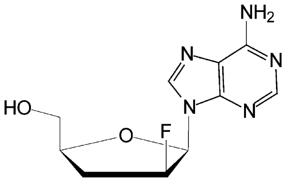
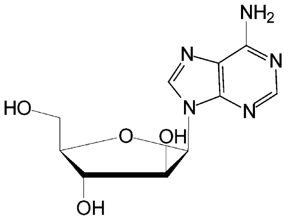
1. Introduction

Purine nucleosides bearing fluorine at C2′ have been studied intensely the past few years because of their biological activity. For example, 9-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)adenine (**1**, FddA) has been investigated for its anti-viral activity against HIV.[1] Several methods for synthesizing **1** have been reported,[1b,2] all of which take one of two general approaches: (1) coupling of a fluorinated sugar with a purine base,[1a,2a] and (2) fluorination and transformation of a pre-formed nucleoside derivative.[2b–g] A key step in the latter, more attractive synthetic approach is the selective protection of 3′-OH of the ribonucleosides prior to fluorination at the 2′ position. The similar reactivity of the 2′ and 3′-OH groups of ribonucleosides makes selective protection of either of these functionalities difficult. There are a limited number of selective methods for protecting 3′-OH of purine ribonucleosides.[3] Herein is reported a new way to conveniently protect 9-(β-D-arabinofuranosyl)adenine (**2**, ara-A) at 3′-OH. Once 3′-OH is selectively protected the 5′-OH can be easily protected with a different blocking group to afford a useful intermediate for nucleoside synthesis. This intermediate was used in a convenient method for preparing **1**.



1 (FddA)



2 (ara-A)

2. Results and discussion

Commercially available **2** is easily converted to 9-(2,3-anhydro-β-D-lyxofuranosyl)adenine (**3**) in high yield.[4a–c] Nucleophiles such as acetate[4c] and azide[4d] preferentially attack the α-face of **3** at C3′ yielding 3′-substituted adenine arabinosides (**4a**-**b**, Scheme 1). We have now demonstrated that when a salt of benzyl alcohol is employed for the nucleophilic ring-opening, 9-(3-*O*-benzyl-β-D-arabinofuranosyl)adenine (**4c**) is obtained in 74% yield. The preparation of **4c** is performed in benzyl alcohol solvent with the sodium salt of benzyl alcohol, as generated by NaH or *t*-BuONa. The sodium counter ion seems to give the best results but potassium and magnesium have also been used successfully. Desired isomer **4c** is formed preferentially over the 2′-*O*-benzyl isomer (**5c**) in a ratio of ~6:1. This manipulation effectively provides ara-A that is blocked by a benzyl group at 3′-OH. The benzyl fragment is an excellent

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Keywords: Fluororibonucleoside; Ara-A; 9-(3-*O*-Benzyl-5-*O*-tetrahydropyranyl-β-D-arabinofuranosyl)adenine; 9-(2,3-Dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)adenine; FddA.

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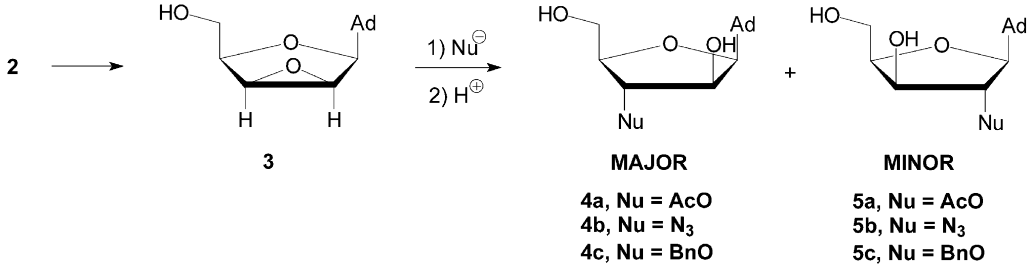


Scheme 1.

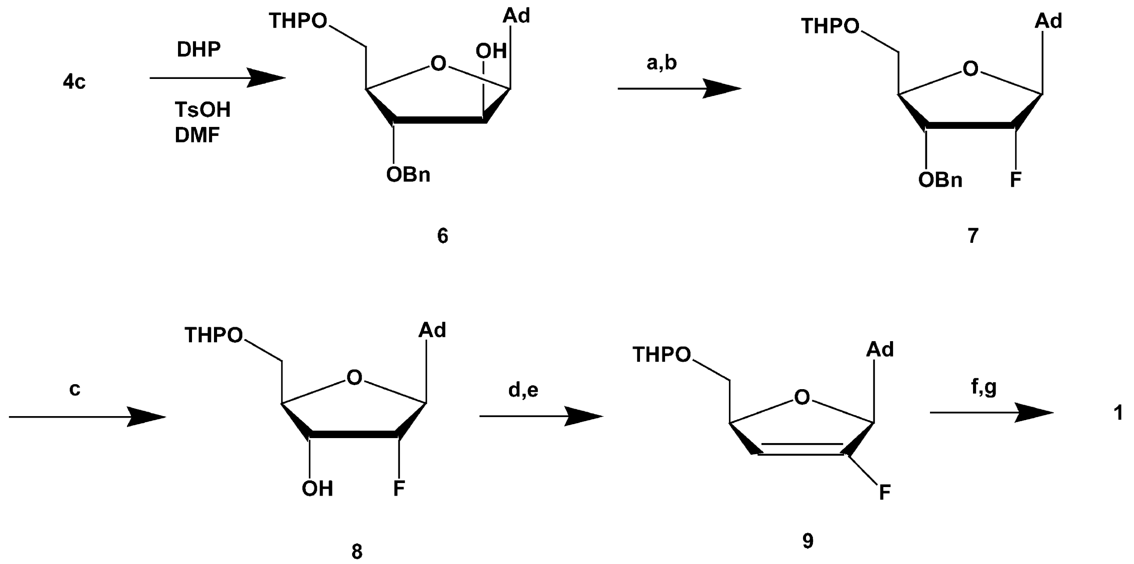
protecting group for preparing 2′-fluororibonucleosides because it will survive fluorination conditions, will not migrate, as is often seen for acetyl and benzoyl groups, and can be selectively removed.

With the 3′-OH blocked, the primary 5′-OH can be protected easily and selectively to leave only the 2′-OH free for fluorination. A variety of reagents can be used to block 5′-OH but dihydropyran (DHP) appears to be the most amenable to the downstream chemistry for preparing **1**. The resulting tetrahydropyranyl group will not be removed under the hydrogenation conditions used to remove the benzyl-protecting group and will not be affected by the fluorination conditions. Hence, when **4c** is reacted with DHP in DMF at 0 °C, the desired 9-(3-*O*-benzyl-5-*O*-tetrahydropyranyl-β-D-arabinofuranosyl)adenine (**6**) is obtained in 85% yield after column chromatography. Thus, ara-A derivatives bearing different protecting groups on 3′-OH and 5′-OH are easily obtainable. The presence of different protecting groups at 3′ and 5′ provides synthetic flexibility because it allows selective removal of either group.

Once the 3′- and 5′-OH groups have been blocked, the 2′-OH can be converted to a leaving group and displaced by fluoride. Fluorination of purine nucleosides by S_N2 displacement at the β-face of C2′ is notoriously difficult[1b,2f–g] while fluorination from the α-face is readily accomplished.[5] Marquez, et al.[2c] took advantage of this behavior in their synthesis of **1** by fluorinating a protected ara-A derivative from the α-face, eliminating to a vinyl fluoride intermediate and selectively hydrogenating. By this sequence, they were able to effectively invert the stereochemistry at C2′ while deoxygenating C3′ to produce **1**. The same general approach can be used to transform **6** into **1** (Scheme 2).

Fluorination of **6** was accomplished by converting the 2′-OH to the triflate and displacing with tetrabutylammonium fluoride in THF to yield **7** in 65% yield after column chromatography to remove the elimination co-product and ammonium salts. The benzyl protecting group of **7** can be removed, without affecting the THP group, by hydrogenolysis using Pearlman's catalyst and cyclohexene as a hydrogen donor.[6] Thus, **7** was refluxed in ethanol and cyclohexene in the presence of 20–40% (based on weight of **7**) dry Pearlman's catalyst to afford **8** in 81% isolated yield. Interestingly, Pd/C and hydrogen at 150 °C and 180 psi removed only the THP group. Under these conditions, the hydrogenation catalyst may behave like a Lewis acid causing transketalation of the THP group with the ethanol solvent.

Reaction of **8** with Tf_2O in the presence of DMAP and pyridine was rapid and clean. The reaction mixture was washed with 10% Na_2CO_3 (aq.) and concentrated to isolate



Scheme 2. Key: (a) Tf_2O, DMAP, pyridine, CH_2Cl_2, 0 °C; (b) TBAF, THF, 0 °C; (c) $Pd(OH)_2/C$ (20%), cyclohexene, EtOH, reflux; (d) Tf_2O, DMAP, pyridine, CH_2Cl_2, 0 °C; (e) *t*-BuOK, DMSO, rt; (f) H_2, Pd/C (10%), THF; (g) pyridinium DOWEX 50, EtOH, MeOH.

the triflate intermediate, which is quite stable. The crude triflate was dissolved in DMSO and treated with potassium *tert*-butoxide at ambient temperature. The vinyl fluoride, **9**, was isolated in 85% yield. Hydrogenation of **9** was performed in a non-protic solvent in order to avoid removal of the THP group at this point. The THP group lends solubility to the reduced product, **10**, which aids in its removal from the hydrogenation catalyst support. After filtering and washing the catalyst, the THP group was removed using the mild deprotection method of Uesugi, et al.[7] The solution is stirred with pyridinium DOWEX 50. After a few hours, the THP group is removed cleanly. FddA, **1**, is thus obtained in 80% yield from **9**.

3. Conclusion

We have developed a simple and efficient method to selectively protect and deprotect 3′- and 5′-OH of ara-A (**2**) which is potentially useful for the synthesis of a variety of adenosine derivatives. This ability of selective protection of ara-A with different blocking groups allows great synthetic flexibility. This methodology has been employed to prepare FddA (**1**) from commercially available ara-A (**2**) by a relatively short synthetic sequence in 28% overall yield without the use of expensive protecting groups or undesirable fluorinating reagents.

4. Experimental

4.1. General

All new compounds were determined to be >95% pure by HPLC and NMR.

4.1.1. 9-(3-*O*-Benzyl-β-D-arabinofuranosyl)adenine (4c). Fresh sodium *tert*-butoxide (81.0 g, 0.843 mol) was added to benzyl alcohol (700 mL). After stirring 10 min., the yellow solution was cooled to room temperature. Dry 9-(2,3-anhydro-β-D-lyxofuranosyl)adenine (**3**)[4d] (70.0 g, 0.281 mol) was added to the solution over a 5 min period. The tan slurry was heated to 65 °C for 7 h. The resulting brown solution was cooled to 25 °C and quenched with acetic acid (51.0 g) and water (200 mL). The upper, organic layer was separated and concentrated in vacuo. The residue was purified by silica gel column chromatography to give **4c** (74.34 g, 74% yield) and **5c** (12.25 g, 12% yield) as off-white solids.

Compound **4c**. ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 8.19 (1H, s, HC_8), 8.12 (1H, s, HC_2), 7.25–7.48 (5H, m, Ph), 7.24 (2H, br.s, H_2N), 6.24 (1H, d, HC'_1, J=4.9 Hz), 5.81 (1H, d, HOC'_2, J=4.9 Hz), 5.19 (1H, t, HOC'_5, J=5.3 Hz), 4.70 (1H, d, $H'C$–Ph, J=11.8 Hz), 4.62 (1H, d, $H''C$–Ph, J=11.8 Hz), 4.36 (1H, m, HC'_2), 4.13 (1H, dd, HC'_3, J_1=J_2=3.8 Hz), 3.98 (1H, ddd, HC'_4, J_1=3.8 Hz, J_2=J_3=5.1 Hz), 3.65 (2H, m, $H_2C'_5$). Signal assignment was made on the basis of the COSY experiment. ^{13}C NMR (75 MHz, Me_2SO-d_6): δ 155.9, 152.5, 149.3, 140.2, 138.1, 128.3 (2C), 127.6 (3C), 118.2, 83.8, 83.4, 82.4, 73.7, 70.9, 61.2. MS (high res.) actual 357.1425, calculated 357.1437.

Compound **5c**. ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 8.26 (1H, s, HC_8), 8.18 (1H, s, HC_2), 7.43 (2H, br.s, H_2N), 7.22–7.33 (5H, m, Ph), 6.08 (1H, br.s, HC'_1), 5.99 (1H, br.s, HOC'_3), 4.82 (1H, br.s, HOC'_5), 4.68 (2H, br. s, H_2C–Ph), 4.26 (2H, m, HC'_3+HC'_2), 4.13 (1H, m, HC'_4), 3.78 (1H, dd, $H''C'_5$, J_1=5.1 Hz, J_2=10.9 Hz), 3.68 (1H, dd, $H'C'_5$, J_1=6.26 Hz, J_2=10.9 Hz). Signal assignment was made on the basis of the COSY experiment. ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.9, 152.2, 148.5, 139.5, 137.6, 128.3 (2C), 127.7, 127.7 (2C), 118.9, 88.3, 87.6, 84.0, 72.8, 71.0, 59.3. Column chromatography can be avoided if crude **4c** is recrystallized from 3:1 methanol/water. The yield from two crops is 49%.

4.1.2. 9-(3-*O*-Benzyl-5-*O*-tetrahydropyranyl-β-D-arabinofuranosyl)adenine (6). To a 0 °C solution of **4c** (33.0 g, 0.092 mol) and dried *p*-toluenesulfonic acid (35.3 g, 0.205 mol) in anhydrous *N*,*N*-dimethylformamide (500 mL) was added 3,4-dihydro-2*H*-pyran (77.7 g, 0.923 mol). The reaction progress was monitored by HPLC. After <5% **4c** remained, the reaction mixture was treated with 10% $NaHCO_3$ (aq, 300 mL). The mixture was diluted with water (1.2 L) and extracted with chloroform (2×1 L). The organic layers were combined, dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed through a column of silica gel. Fractions containing the product were combined and concentrated to afford **6** as an off-white solid (34.5 g, 85% yield). There are two diastereomers with a ratio 1:1 due to a non-stereoselective attachment of the THP group. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23–8.18 (2H, 4 separate s, HC_8+HC_2), 7.36–7.26 (5H, m, Ph), 6.36 (1/2H, d, $H_1C'_1$, J=3.7 Hz), 6.34 (1/2H, d, $H_2C'_1$, J=3.7 Hz), 6.30 (2H, H_2N), 5.60 (1H, br.s, HO), 4.77 (1/2H, d, H'_1C–Ph, J=11.6 Hz), 4.76 (1/2H, d, H'_2C–Ph, J=11.6 Hz), 4.67 (1/2H, m, H_1CO_2–THP), 4.65 (1H, d, H''_1C–Ph, J=11.6 Hz), 4.65 (1H, d, H''_2C–Ph, J=11.6 Hz), 4.59 (1/2H, m, H_2CO_2–THP), 4.53 (1/2H, dd, $H_1C'_2$, J_1=2.87 Hz, J_2=3.7 Hz), 4.54 (1/2H, dd, $H_2C'_2$, J_1=2.9 Hz, J_2=3.7 Hz), 4.29 (1/2H, m, $H_1C'_4$), 4.28 (1/2H, m, $H_2C'_4$), 4.25 (1/2H, dd, $H_1C'_3$, J_1=2.9 Hz, J_2=3.3 Hz), 4.19 (1/2H, dd, $H_2C'_2$, J_1=2.9 Hz, J_2=3.7 Hz), 4.07 (1/2H, dd, $H'_2C'_5$, J_1=3.6 Hz, J_2=10.8 Hz), 3.97 (1/2H, dd, $H'_1C'_5$, J_1=3.6 Hz, J_2=10.8 Hz), 3.81 (1/2H, m, H'_2CO–THP), 3.71 (1/2H, dd, $H''_2C'_5$, J_1=3.6 Hz, J_2=10.8 Hz), 3.69 (1/2H, m, H'_1CO–THP), 3.58 (1/2H, dd, $H''_2C'_5$, J_1=3.59 Hz, J_2=10.8 Hz), 3.49 (1H, m, H_2CO–THP), 1.8–1.5 (6H, m, THP). Signal assignment was made on the basis of the COSY experiment of a recrystallized sample that has some enrichment of one stereoisomer. ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.7 (1C), 153.2 (1/2C), 153.1 (1/2C), 150.0 (1/2C), 149.9 (1/2C), 140.9 (1/2C), 140.7 (1/2), 137.6 (1/2C), 137.5 (1/2C), 128.9 (2C), 128.4 (1C), 128.1 (1C), 128.1 (1C), 119.6 (1/2C), 119.5 (1/2C), 99.38 (1/2C), 99.35 (1/2C), 86.1 (1C), 84.06 (1/2C), 83.95 (1/2C), 82.1 (1/2C), 82.0 (1/2C), 74.5 (1/2C), 74.4 (1/2C), 72.3 (1C), 67.24 (1/2C), 67.19 (1/2C), 62.53 (1/2C), 62.49 (1/2C), 30.26 (1/2C), 30.24 (1/2C), 25.4 (1/2C), 25.1 (1/2C), 19.4 (1/2C), 19.3 (1/2C). MS (high res.) actual 442.2072, calculated 442.2090.

4.1.3. 9-(3-*O*-Benzyl-2-deoxy-2-fluoro-5-*O*-tetrahydropyranyl-β-D-arabinofuranosyl)adenine (7). 4-Dimethylaminopyridine (21.6 g, 0.177 mol), pyridine (37 mL), and **6** (24.0 g, 0.054 mol) were dissolved in CH_2Cl_2 (1,440 mL) and cooled to 0 °C under nitrogen. Trifluoromethanesulfonic acid anhydride (25.1 g, 0.089 mol) was added dropwise over 20 min. After 1 h., the reaction mixture was poured into sat. $\mathrm{NaHCO_3}$ (aq., 1.8 L). The organic layer was removed and the aqueous washed with $\mathrm{CH_2Cl_2}$ (3×350 mL). The organic layers were combined, dried over $\mathrm{Na_2SO_4}$, and concentrated at below 25 °C. The residue was taken up in THF (100 mL) and evaporated to remove all traces of $\mathrm{CH_2Cl_2}$. The residue was dissolved in THF (550 mL) and cooled, under nitrogen, to 0 °C. A solution of 1 M tetrabutylammonium fluoride in THF (109 mL, 0.109 mol) was added over 30 min. The reaction progress was monitored by HPLC. After 18 h the reaction was finished. The solvent was stripped on a rotary evaporator and the residue was dissolved in $\mathrm{CH_2Cl_2}$ (500 mL) and washed with sat. NaCl (aq., 3×250 mL). The organic layer was dried over $\mathrm{Na_2SO_4}$ and concentrated. The residue was chromatographed through a column of silica gel. The desired product, **7**, was obtained as a pale yellow solid (15.7 g, 65% yield). ^{1}H NMR (300 MHz, $\mathrm{CDCl_3}$): δ 8.34 (1/2H, s, $\mathrm{H_1C_8}$), 8.32 (1/2H, s, $\mathrm{H_2C_8}$), 8.20 (1/2H, s, $\mathrm{H_1C_2}$), 8.18 (1/2H, s, $\mathrm{H_2C_2}$), 7.40–7.25 (5H, m, Ph), 6.34 (1/2H, dd, $\mathrm{H_1C'_1}$, $J_1=1.9$ Hz, $J_2=11.7$ Hz), 6.29 (1/2H, dd, $\mathrm{H_2C'_1}$, $J_1=1.9$ Hz, $J_2=11.7$ Hz), 5.90 (2H, br.s, $\mathrm{H_2N}$), 5.46 (1H, dm, HCF, $J=51.6$ Hz), 4.79 (1H, dd, $\mathrm{H'C{-}Ph}$, $J_1=5.0$ Hz, $J_2=11.7$ Hz), 4.62 (1H, m, $\mathrm{H''C{-}Ph}$), 4.67–4.38 (3H, m, $\mathrm{HC'3{+}HC'4{+}HCO_2{-}THP}$), 4.17 (1/2H, dd, $\mathrm{H'_1C'_5}$, $J_1=2.2$ Hz, $J_2=11.5$ Hz), 3.98 (1/2H, dd, $\mathrm{H'_2C'_5}$, $J_1=2.9$ Hz, $J_2=11.5$ Hz), 3.82 (1/2H, dd, $\mathrm{H''_2C'_5}$, $J_1=2.4$ Hz, $J_2=11.5$ Hz), 3.79 (1/2H, m, $\mathrm{H'_1CO{-}THP}$), 3.69 (1/2H, m, $\mathrm{H'_2CO{-}THP}$), 3.53 (1/2H, dd, $\mathrm{H''_1C'_5}$, $J_1=3.35$ Hz, $J_2=11.5$ Hz), 3.48 (1H, m, $\mathrm{H''_1CO{-}THP{+}H''_2CO{-}THP}$), 1.80–1.40 (6H, m, THP). Signal assignment was done on the basis of the COSY experiment. ^{13}C NMR (75 MHz, $\mathrm{CDCl_3}$): δ 155.64 (1/2C), 155.63 (1/2C), 153.36 (1/2C), 153.31 (1/2C), 149.44 (1/2C), 149.35 (1/2C), 139.4 (1/2C), 139.2 (1/2), 137.17 (1/2C), 137.16 (1/2C), 128.73 (1C), 128.71 (1C), 128.5 (1/2C), 128.4 (1/2C), 128.3 (1C), 128.2 (1C), 120.2 (1/2C), 120.1 (1/2C), 99.3 (1/2C), 99.2 (1/2C), 91.9 (1/2C, d, $\mathrm{C'_2{-}F}$, $J=190.4$ Hz), 91.7 (1/2C, d, $\mathrm{C''_2{-}F}$, $J=189.8$ Hz), 87.8 (1/2C, d, $\mathrm{C'_1{-}F}$, $J=33.2$ Hz), 87.5 (1/2C, d, $\mathrm{C''_1{-}F}$, $J=32.7$ Hz), 81.3 (1/2C), 81.0 (1/2C), 75.2 (1/2C, d, $\mathrm{C'_3{-}F}$, $J=33.0$ Hz), 75.0 (1/2C, d, $\mathrm{C''_3{-}F}$, $J=33.0$ Hz), 73.1 (1/2C), 73.0 (1C), 65.7 (1/2C), 65.4 (1/2C), 62.5 (1/2C), 62.3 (1/2C), 30.6 (1/2C), 30.4 (1/2C), 25.4 (1/2C), 25.3 (1/2C), 19.6 (1/2C), 19.4 (1/2C). ^{19}F NMR (282.3 MHz, $\mathrm{CDCl_3}$): δ −202.58 ($\mathrm{F_1}$, ddd, $J_1=16.9$ Hz, $J_2=18.8$ Hz, $J_3=52.6$ Hz), −203.30 ($\mathrm{F_2}$, ddd, $J_1=15.9$ Hz, $J_2=18.8$ Hz, $J_3=55.5$ Hz). MS (high res.) actual 444.2042, calculated 444.2047.

4.1.4. 9-(2-Deoxy-2-fluoro-5-*O*-tetrahydropyranyl-β-D-arabinofuranosyl)adenine (8). Pearlman's catalyst (0.20 g, 20% Pd by wt. on a dry basis, 57% water) was dried by slurrying in absolute EtOH (25 mL) and concentrating to dryness. The dried catalyst was added to a solution of **7** (0.20 g, 0.45 mmol) in absolute EtOH (14 mL) and cyclohexene (2 mL). The reaction mixture was refluxed for 18 h at which time **8** was essentially gone. The catalyst was filtered and washed well with hot EtOH (3×10 mL) and THF (15 mL). The filtrate was concentrated to dryness and the residue was passed through a short column of silica gel eluting with $\mathrm{CHCl_3/MeOH}$ (15:1). The appropriate fractions were combined and concentrated to afford **8** as a white, foamy solid (0.13 g, 81% yield). The first product fractions contained one stereoisomer: ^{1}H NMR (300 MHz, $\mathrm{Me_2SO}$-d_6): δ 8.29 (1H, s, $\mathrm{HC_8}$), 8.14 (1H, s, $\mathrm{HC_2}$), 7.35 (2H, br.s, $\mathrm{H_2N}$), 6.23 (1H, dd, $\mathrm{HC'_1}$, $J_1=1.7$ Hz, $J_2=18.0$ Hz), 5.79 (1H, d, HO, $J=6.5$ Hz), 5.43 (1H, ddd, $\mathrm{HC'_2{-}F}$, $J_1=1.9$ Hz, $J_2=4.1$ Hz, $J=52.9$ Hz), 4.60 (2H, m, $\mathrm{HC'_3{+}HCO_2{-}THP}$), 4.08 (1H, m, $\mathrm{HC'_4}$), 3.79 (1H, dd, $\mathrm{H'C'_5}$, $J_1=4.1$ Hz, $J_2=11.5$ Hz), 3.70 (1H, dd, $\mathrm{H''C'_5}$, $J_1=2.6$ Hz, $J_2=11.5$ Hz), 3.68 (1H, m, $\mathrm{H'CO{-}THP}$), 3.41 (1H, m, $\mathrm{H''CO{-}THP}$), 1.73–1.37 (6H, m, THP). Signal assignment was done on the basis of the COSY experiment. ^{13}C NMR (75 MHz, $\mathrm{Me_2SO}$-d_6): δ 156.0, 152.8, 148.8, 139.0, 118.9, 97.7, 93.5 (d, $\mathrm{C'_2{-}F}$, $J=185.8$ Hz), 85.9 (d, $\mathrm{C'_1{-}F}$, $J=33.8$ Hz), 79.2, 68.3 (d, $\mathrm{C'_3{-}F}$, $J=16.1$ Hz), 65.1, 61.0, 30.0, 24.9, 18.8. ^{19}F NMR (282.3 MHz, $\mathrm{Me_2SO}$-d_6): δ −202.19 (ddd, $J_1=17.8$ Hz, $J_2=21.7$ Hz, $J_3=52.5$ Hz). The last few main product fractions contained the second stereo-isomer: ^{1}H NMR (300 MHz, $\mathrm{Me_2SO}$-d_6): δ 8.32 (1H, s, $\mathrm{HC_8}$), 8.14 (1H, s, $\mathrm{HC_2}$), 7.35 (2H, br.s, $\mathrm{H_2N}$), 6.22 (1H, dd, $\mathrm{HC'_1}$, $J_1=1.9$ Hz, $J_2=18.7$ Hz), 5.80 (1H, d, HO, $J=6.2$ Hz), 5.42 (1H, ddd, $\mathrm{HC'_2{-}F}$, $J_1=1.9$ Hz, $J_2=4.5$ Hz, $J=55.1$ Hz), 4.62 (2H, m, $\mathrm{HC'_3{+}HCO_2{-}THP}$), 4.10 (1H, m, $\mathrm{HC'_4}$), 3.98 (1H, dd, $\mathrm{H'C'_5}$, $J_1=2.4$ Hz, $J_2=11.5$ Hz), 3.64 (1H, m, $\mathrm{H'CO{-}THP}$), 3.58 (1H, dd, $\mathrm{H''C'_5}$, $J_1=5.0$ Hz, $J_2=11.5$ Hz), 3.41 (1H, m, $\mathrm{H''CO{-}THP}$), 1.73–1.37 (6H, m, THP). Signal assignment was done on the basis of the COSY experiment. ^{13}C NMR (75 MHz, $\mathrm{Me_2SO}$-d_6): δ 156.1, 152.8, 148.8, 139.2, 119.0, 98.1, 93.6 (d, $\mathrm{C'_2{-}F}$, $J=185.6$ Hz), 86.0 (d, $\mathrm{C'_1{-}F}$, $J=33.5$ Hz), 81.5, 68.4 (d, $\mathrm{C'_3{-}F}$, $J=16.0$ Hz), 66.0, 61.0, 29.9, 24.9, 18.8. ^{19}F NMR (282.3 MHz, $\mathrm{Me_2SO}$-d_6): δ −201.94 (ddd, $J_1=18.9$ Hz, $J_2=22.0$ Hz, $J_3=52.5$ Hz). MS (high res.) actual 353.1483, calculated 353.1499.

4.1.5. 9-(2,3-Deoxy-2-fluoro-5-*O*-tetrahydropyranyl-β-D-*glycero*-pent-2-enofuranosyl)adenine (9). 4-Dimethylaminopyridine (0.79 g, 6.5 mmol), pyridine (1.4 mL), and **8** (0.70 g, 2.0 mmol) were dissolved in $\mathrm{CH_2Cl_2}$ (52 mL) and cooled to 0 °C under nitrogen. Trifluoromethanesulfonic acid anhydride (0.92 g, 3.3 mmol) was added dropwise over 5 min. After 2 h, the reaction mixture was poured into sat. $\mathrm{NaHCO_3}$ (aq., 50 mL) and extracted with EtOAc (3×15 mL). The extracts were combined and dried over $\mathrm{MgSO_4}$. The residual oil was dissolved in DMSO (63 mL) and treated with potassium *tert*-butoxide (0.44 g, 4.0 mmol). The solution immediately became dark red. After 30 min, $\mathrm{NH_4OAc}$ (0.38 g, 4.0 mmol) was added to quench the mixture. The DMSO solvent was stripped in vacuo to leave a yellow oil. The oil was purified by silica gel column chromatography to yield **9** as a white solid (0.56 g, 85% yield). ^{1}H NMR (300 MHz, $\mathrm{CDCl_3}$): δ 8.39 (1/2H, s, $\mathrm{H_1C_8}$), 8.38 (1/2H, s, $\mathrm{H_2C_8}$), 8.29 (1/2H, d, $\mathrm{H_1C_2}$, $J=1.0$ Hz), 8.24 (1/2H, d, $\mathrm{H_2C_2}$, $J=0.7$ Hz), 6.95 (1H, m, $\mathrm{HC'_3}$), 6.34 (1H, td, $\mathrm{H_1C'_1}$, $J_1=1.2$ Hz, $J_2=7.2$ Hz), 5.68 (2H, br.s, $\mathrm{H_2N}$), 5.09 (1H, m, $\mathrm{HC'_4}$), 4.62 (1/2H, dd, $\mathrm{H_1CO{-}THP}$, $J_1=2.9$ Hz, $J_2=3.9$ Hz), 4.56 (1/2H, dd, $\mathrm{H_2CO{-}THP}$, $J_1=2.9$ Hz, $J_2=4.8$ Hz), 3.99 (1H, m, $\mathrm{H'C'_5}$), 3.79 (1H, m, $\mathrm{HCO{-}THP}$), 3.61 (1H, m, $\mathrm{H''C'_5}$), 3.50 (1H, m, $\mathrm{HCO{-}THP}$), 1.92–1.45 (6H, m, THP). Signal assignment was done on the basis of the COSY experiment. ^{13}C NMR (75 MHz, $\mathrm{CDCl_3}$): δ 155.40 (1/2C), 155.37 (1/2C), 153.45 (1/2C, d, $\mathrm{C'_2{-}F}$, $J=283.4$ Hz), 153.44 (1C), 152.4 (1/2C, d, $\mathrm{C'_2{-}F}$, $J=283.4$ Hz), 150.7 (1C), 139.4 (1/2C), 139.0 (1/2C), 119.5 (1C), 106.0 (1/2C,d, $J=8.3$ Hz), 105.0 (1/2C, d,

$J=8.3$ Hz), 99.6 (1/2C), 99.5 (1/2C), 81.9 (1/2C, d, $J=28.9$ Hz), 81.8 (1/2C), 81.7 (1/2C, d, $J=28.9$ Hz), 81.6 (1/2C), 68.5 (1/2C), 68.1 (1/2C), 62.9 (1/2C), 62.4 (1/2C), 30.4 (1/2C), 30.3 (1/2C), 25.3 (1/2C), 25.1 (1/2C), 19.8 (1/2C), 19.4 (1/2C). ^{19}F NMR (282.3 MHz, CDCl$_3$): δ −136.06 (F$_1$, ddd, $J_1=1.4$ Hz, $J_2=J_3=5.3$ Hz), −136.29 (F$_2$, ddd, $J_1=2.7$ Hz, $J_2=J_3=5.1$ Hz). MS (high res.) actual 335.1405, calculated 335.1394.

4.1.6. 9-(2,3-Dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)-adenine (1, FddA). A solution of **9** (1.24 g, 3.7 mmol) in THF (150 mL) was charged into a shaker bottle with 10% Pd/C (0.62 g). The mixture was hydrogenated at room temperature and 70 psi H$_2$ pressure. The reaction was monitored by LC/MS. After 55 h the reaction was complete so the catalyst was filtered and washed with THF (25 mL). The solvent was removed with a rotary evaporator to leave 1.08 g of a pale yellow solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.33 (1H, s, HC$_8$), 8.20 (1/2H, d, H$_1$C$_2$, $J=2.6$ Hz), 8.17 (1/2H, d, H$_2$C$_2$, $J=2.9$ Hz), 6.38 (1/2H, dd, H_1C_1', $J_1=3.6$ Hz, $J_3=17.2$ Hz), 6.33 (1/2H, dd, H_2C_1', $J_1=3.4$ Hz, $J_2=18.4$ Hz), 6.00 (2H, br.s, H$_2$N), 5.29 (1H, dm, HCF, $J=53.4$ Hz), 4.71 (1H, m, HCO$_2$−THP), 4.45 (1H, m, HC_4'), 3.98 (1H, m, $H_1'C_5'$), 3.88 (1H, m, H'CO−THP), 3.69 (1H, m, $H_1''C_5'$), 3.56 (1H, m, H''CO−THP), 2.48 (2H, m, $C_3'H_2$), 1.90−1.50 (6H, m, THP). Signal assignment was done on the basis of the COSY experiment. ^{13}C NMR (75 MHz, CDCl$_3$): δ 156.0 (1C), 153.5 (1C), 150.2 (1C), 140.5 (1/2C), 140.4 (1/2C), 119.5 (1C), 99.6 (1/2C), 99.5 (1/2C), 91.2 (1/2C, d, C_2'−F, $J=190.9$ Hz), 91.1 (1/2C, d, C_2''−F, $J=190.2$ Hz), 85.1 (1/2C, d, C_1'−F, $J=16.6$ Hz), 84.9 (1/2C, d, C_1''−F, $J=16.6$ Hz), 76.49 (1/2C), 76.48 (1/2C), 69.7 (1/2C), 69.2 (1/2C), 62.8 (1/2C), 62.7 (1/2C), 34.2 (1/2C, d, C_3', $J=20.6$ Hz), 33.8 (1/2C, d, C_3'', $J=20.6$ Hz), 30.9 (1/2C), 30.8 (1/2C), 25.7 (1C), 19.8 (1/2C), 19.7 (1/2C). ^{19}F NMR (282.3 MHz, CDCl$_3$): δ −186.8 (F$_1$, m), −187.4 (F$_2$, m). MS (high res.) actual 337.1550, calculated 337.1550. The crude solid was dissolved in 5:1 MeOH/EtOH (42 mL) and stirred with pyridinium DOWEX 50 W×2−100[8] for 2 h. The resin was filtered and washed with MeOH (25 mL), 1:1:1 pyridine/triethylamine/water (100 mL) and MeOH (25 mL). The solution was distilled to dryness to leave 0.75 g of **1** (80% from **9**). An analytical sample, which is identical to a standard sample of **1**, can be prepared by recrystallizing from EtOH (50 mL).

5. Supplementary information

NMR spectral data and high resolution mass spectra are available for each new compound.

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8. Prepared by stirring DOWEX 50W×2−100 (2.2 g) with pyridine (10 mL) for 5 min and decanting the excess pyridine. The resin was then washed several times with MeOH.

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Tetrahedron

$5'$-Noraristeromycin possessing a C-$1'$ cyclopentyl double bond: a new carbanucleoside structural prototype

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Abstract—Prior to this work only two examples of carbanucleosides possessing a C-$1'$/C-$6'$ double bond had been reported and they were minor derivatized side products arising during other targeted syntheses. To develop this structural feature into a new class of potential antiviral agents, the $5'$-nor derivative of aristeromycin with such an olefinic structure (**6**) represents the first example. In this regard, treatment of ($1'S$,$2'S$,$3'S$,$4'R$,$5'S$)-6-chloro-9-($2'$,$3'$-*iso*propylidenedioxy-$6'$-oxabicyclo[3.1.0]hex-$4'$-yl)purine (**7**) with sodium methoxide yielded **6** via an E_2'-like elimination pathway. A convenient way to the C-$4'$ epimer of **6** (that is, **17**) also arose during these studies and is described. Antiviral analysis of **6** and **17** failed to produce any significant activity.

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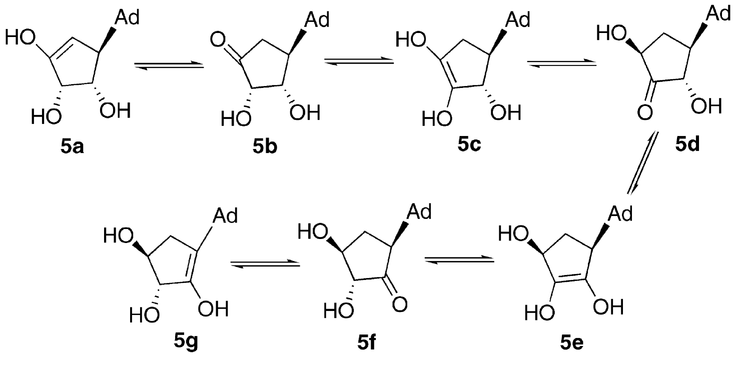
1. Introduction

Carbanucleosides have moved to a prominent position in biochemistry and medicinal chemistry.[1] Within this class of compounds are the unsaturated neplanocins (**1-3**)[1a] and the $5'$-nor carbanucleosides (for example, $5'$-noraristeromycin, **4**).[2,3] Imposing the neplanocin structure on $5'$-nor carbanucleosides (for example, **5a**) would be complicated by the participation of **5a** in the enol–keto tautomeric cascade[4] depicted in Scheme 1. However, the allylic alcoholic isomer of the **5**-series, **6** (Scheme 2), with the C-$1'$/C-$6'$ (herein designated C-$1'$/C-$2'$) double bond,[3] would be a neplanocin-related analogue that would not be vulnerable to the alkene relocations of **5**. This class of carbanucleosides has received very little attention.[5] It is with this and the biological properties of **4** in mind that compound **6** was sought. Its synthesis and that of its C-$3'$-epimer (**17**) and their antiviral properties are described here (Fig. 1).

A key step in our retrosynthetic analysis to **6** (Scheme 2) was the selective epoxide ring opening of **7** using alkoxide[6] in an E_2' process involving base abstraction of the C-$4'$ hydrogen. Compound **7** was foreseen to be available in several steps from 6-chloropurine (**8**) and (−)-($4R$,$5R$)-4,5-(*iso*propylidenedioxy)cyclopent-2-en-1-one (**9**).[7] Two alternative procedures were considered for modifying **9**



Ad=9-Adenyl

Scheme 1.

Keywords: Neplanocin analogs; Mitsunobu coupling; Epoxide ring opening; Antiviral.

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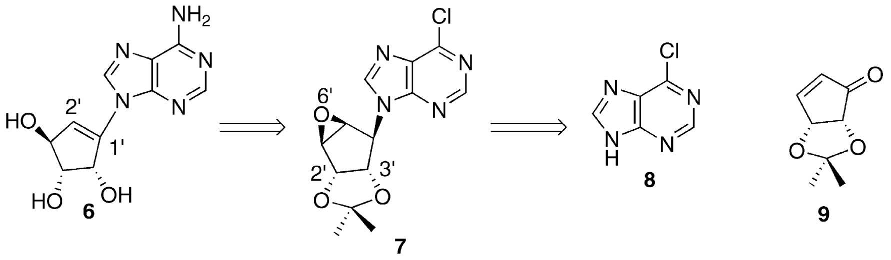


Scheme 2.

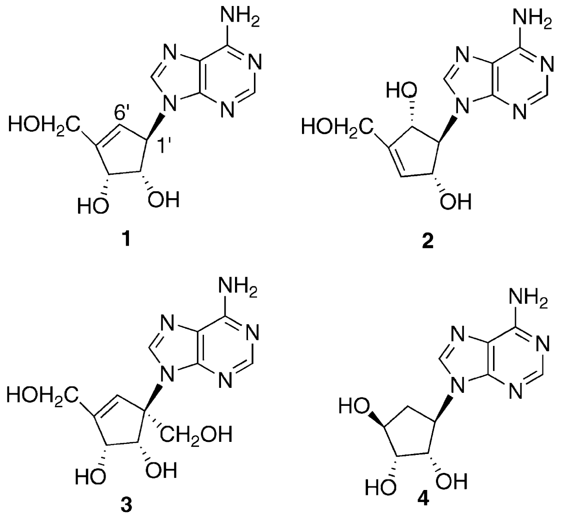
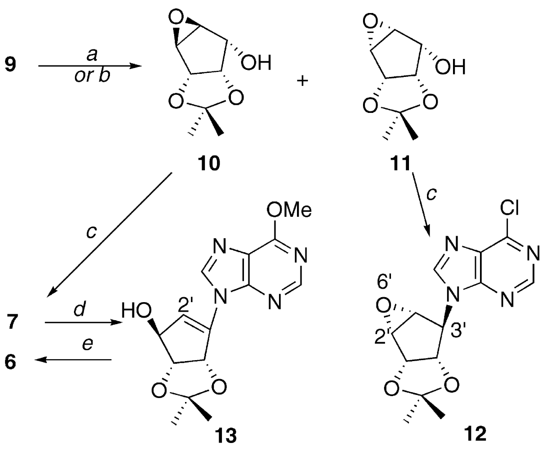


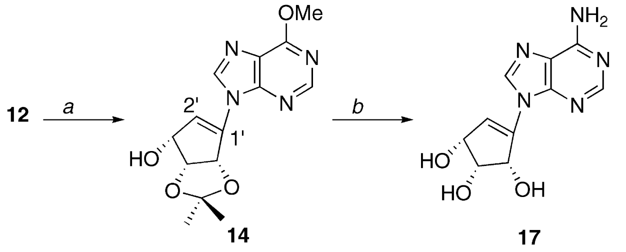
Figure 1. Ref. 3.

prior to a coupling with **8** (Scheme 3): (i) olefinic epoxidation[8] followed by carbonyl reduction (path a) and, conversely, (ii) reduction of the ketone followed by epoxidation (path b). In the former case, only the β-epoxide **10** was obtained whereas, via the latter method, both **10** and the α-epoxide **11** were realized.[9] Mitsunobu coupling of **10** (obtained from either method but pathway *a* was preferred because of higher yield in less reaction time) with **8** provided **7**. In a similar way, **11** yielded **12**.



Scheme 3. Reaction conditions: (a)(i) *t*-BuOOH, Triton B, THF, MeOH (92%); (ii) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH (**10** only, 75%); (b)(i) same as (a)(ii); (ii) *m*-CPBA, CH_2Cl_2 (**10**, 37%; **11**, 12%); (c) 6-chloropurine, Ph_3P, DIAD, THF (63% for **7**; 56% for **12**); (d) NaOMe, MeOH, 2 h, rt (89%); (e)(i) NH_3, MeOH; (ii) 0.5 N HCl, MeOH (73%).

Treatment of **7** with sodium methoxide at room temperature for 2 h gave **13** (Scheme 3). On the other hand, similar reaction conditions with epoxide **12** led to only methoxy substitution of the 6-chloro substituent; only by refluxing for 15 h could **12** be converted to **14** (Scheme 4).



Scheme 4. Reaction conditions: (a) NaOMe, MeOH, reflux, 15 h (93%); (b)(i) NH_3, MeOH; (ii) 0.5 N HCl, MeOH (56%).

The structure of **13** was assigned by NMR methods. In that regard, D_2O exchange of the hydroxyl hydrogen along with ^{1}H COSY permitted assignment of the hydrogens of the cyclopentenyl ring. HMBC then showed correlation between H-8 (8.3 ppm) and C-2′ (121 ppm) (Fig. 2). The C-2′ was assigned by correlation (HMQC) with the olefinic H-2′ (assigned by ^{1}H COSY). All other HMBC and HMQC correlations support **13** as the structure. Furthermore, NOE measurements demonstrated a correlation between H-4′ and H-5′ (cyclopentenyl numbering) but no correlation between H-3′ and H-4′ (Fig. 2). Thus, H-3′ and H-4′ are *anti* to each other.

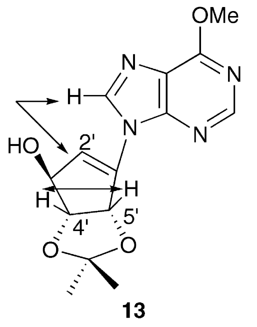
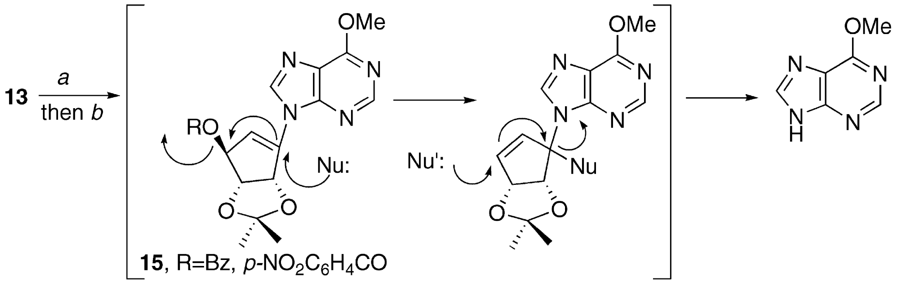


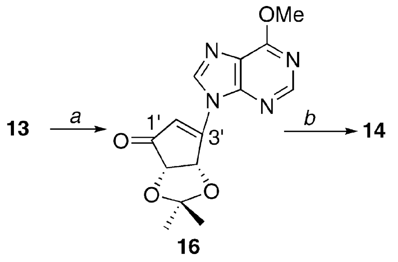
Figure 2.

In contrast to **13**, the structure of **14** was difficult to confirm by NMR. Thus, a chemical structure proof was sought. For that purpose, attempts to employ a Mitsunobu inversion of the 3′-hydroxyl of **13** to compare to **14** consistently led to loss of the cyclopentenyl ring and isolation of 6-methoxypurine (Scheme 5). This result is postulated to have occurred via dual attack of **15** by the nucleophiles present under the



Scheme 5. Reaction conditions: (a) $PhCO_2H$ or p-$NO_2C_6H_4CO_2H$, DIAD, PPh_3; (b) for R=Bz, Nu=NH_3/MeOH or NaOMe/MeOH; for R=p-$NO_2C_6H_4CO$, Nu=K_2CO_3/MeOH.

Mitsunobu inversion conditions. Alternatively, oxidation of **13** with pyridinium chlorochromate to **16** was followed by stereoselective reduction of this enone with Luche's reagent[10] to yield a product whose spectral data was identical to that previously assigned as **14** (Scheme 6).



Scheme 6. Reaction conditions: (a) PCC, Celite, CH_2Cl_2 (88%); (b) $NaBH_4$; $CeCl_3{\cdot}7H_2O$, MeOH (85%).

The desired **6** was obtained by ammonolysis of **13** with subsequent removal of the *iso*propylidene protecting group with 0.5 N hydrochloric acid (Scheme 3).

The epimer **17** was synthesized from **14** by a route similar to that for obtaining **6** from **13** (Scheme 4).

If desired, the L-like derivatives of **6** and **17** could be prepared by beginning with the enantiomer of **9**.[11] This procedure is also adaptable to other heterocyclic bases.[12]

Compounds **6** and **17** were subjected to antiviral analysis[13] and found to be inactive and to display no cytotoxicity except for **6** towards the Daudi host cells (IC_{50} 11.3 μg/mL; ganciclovir IC_{50} 40 μg/mL, acyclovir $IC_{50}>50$ μg/mL) used in the Epstein-Barr assay.

2. Experimental

2.1. Materials and methods

Melting points were recorded on a Meltemp II melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 250 spectrometer (operated at 250 or 62.5 MHz, respectively). All ^1H chemical shifts are reported in δ relative to internal standard tetramethylsilane (TMS, δ 0.00). ^{13}C chemical shifts are reported in δ relative to $CDCl_3$ (center of triplet, δ 77.23) or relative to DMSO-d_6 (center of septet, δ 39.51). The spin multiplicities are indicated by the symbols s (singlet), d (doublet), dd (doublet of doublets), t (triplet), m (multiplet), and br (broad). Coupling constants (J) are expressed in Hz. Atlantic Microlabs, Atlanta, Georgia, performed the elemental analyses. Reactions were monitored by thin layer chromatography (TLC) using 0.25 mm E. Merck silica gel 60-F_{254} precoated silica gel plates with visualization by irradiation with a Mineral light UVGL-25 lamp or exposure to iodine vapor. Column chromatography was performed on Whatman silica gel (average particle size 5–25 μm, 60 Å) and elution with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials. The reactions were generally carried out in a N_2 atmosphere under anhydrous conditions.

2.1.1. (1*S*,2*R*,3*S*,4*S*,5*S*)-4-Hydroxy-2,3-*iso*propylidenedioxy-6-oxabicyclo[3.1.0]-hexane (10) and (1*R*,2*R*,3*S*,4*S*,5*R*)-4-hydroxy-2,3-*iso*propylidenedioxy-6-oxa-bicyclo[3.1.0]hexane (11).

Method a. To a solution of enone **9** (0.72 g, 4.5 mmol) and *t*-butyl hydrogen peroxide (0.63 mL, 4.5 mmol, 70% wt in H_2O) in THF (20 mL) in a salt-ice bath was added Triton B (1.08 mL, 40% in MeOH) dropwise. The reaction was then stirred for 2 h at the same temperature. The reaction mixture was quenched by adding ice H_2O (5 mL) and the solvents removed. The residue was extracted with EtOAc (2×10 mL) and dried ($MgSO_4$). The organic solvent was evaporated to give a pale yellow oil (700 mg, 92%), which was used directly in the next step without further purification.

To the solution of the yellow oil (600 mg, 3.52 mmol) and $CeCl_3{\cdot}7H_2O$ (1.31 g) at 0 °C in MeOH (10 mL) was added $NaBH_4$ (170 mg, 4.59 mmol) portionwise. The reaction mixture was stirred at 0 °C for 10 min and evaporated. The residue was diluted with H_2O (10 mL), extracted with EtOAc (3×20 mL) and dried ($MgSO_4$). Evaporation of the organic solvent gave the β-epoxide **10** as a light yellow oil (450 mg, 75%), which was pure enough for the use in the preparation of **7**: ^1H NMR ($CDCl_3$) δ 4.70 (d, J=5.5 Hz, 1H), 4.49 (t, J=5.7 Hz, 1H), 4.09 (t, J=5.5 Hz, 1H), 3.64 (s, 1H), 3.62 (s, 1H), 2.86 (d, J=5.4 Hz, 1H), 1.59 (s, 3H), 1.39 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 113.8, 80.5, 77.7, 68.9, 60.8, 58.4, 26.4, 24.7.

Method b. To a solution of the allylic alcohol (from reduction of the enone **9**[14]) (6.0 g, 38.9 mmol) in CH_2Cl_2 (100 mL) was added *m*-CPBA (5.25 g, 75% max by weight) at room temperature. The mixture was refluxed for 5 days. The reaction mixture was then diluted with CH_2Cl_2 (100 mL), washed with saturated Na_2CO_3 solution

(3×100 mL), brine (100 mL) and dried ($MgSO_4$). The organic layer was filtered and evaporated. The resulting residue was purified by column chromatography (EtOAc/hexanes, 1:10 and 1:2) to give some remaining starting material, β-epoxide **10** (2.43 g, 37%) and α-epoxide **11** (0.74 g, 12%) as a light yellow oil; **11**: ^{1}H NMR ($CDCl_3$) δ 4.65 (d, *J*=6.7 Hz, 1H), 4.48 (t, *J*=6.8 Hz, 1H), 4.23 (d, *J*=6.7 Hz, 1H), 3.53 (d, *J*=2.0 Hz, 1H), 3.49 (d, *J*=2.0 Hz, 1H), 2.77 (brs, 1H), 1.59 (s, 3H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 114.8, 79.3, 76.3, 70.8, 62.3, 56.7, 26.5, 26.2. Both **10** and **11** were too unstable for microanalysis but were of sufficient purity to use in the synthesis of **7** and **12**, respectively.

2.1.2. (1′*S*,2′*S*,3′*S*,4′*R*,5′*S*)-6-Chloro-9-(2′,3′-*iso*propylidenedioxy-6′-oxabicyclo-[3.1.0]hex-4′-yl)purine (7). To a stirred suspension of 6-chloropurine (2.05 g, 13.62 mmol) and triphenylphosphine (3.58 g, 13.62 mmol) in THF (20 mL) at −10 °C was added, dropwise, di*iso*propyl azodicarboxylate (2.48 g, 13.62 mmol). This mixture was stirred at −10 °C for 10 min and then stirred at room temperature for 15 min. To this mixture was added a solution of **10** (2.3 g, 13.72 mmol) in dry THF (10 mL). The new mixture was stirred at room temperature for 48 h and concentrated under vacuum. Column chromatography with hexanes–EtOAc (4:1) provided a white solid of desired **7** (2.7 g, 63%), mp 142–143 °C; ^{1}H NMR ($CDCl_3$) δ 8.80 (s, 1H), 8.39 (s, 1H), 5.35 (t, *J*=1.2 Hz, 1H), 4.94 (d, *J*=3.5 Hz, 1H), 4.47 (d, *J*=2.8 Hz, 1H), 3.93 (s, 1H), 3.92 (s, 1H), 1.61 (s, 3H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 152.6, 152.2, 151.5, 143.9, 131.5, 114.1, 85.8, 79.5, 77.4, 62.3, 59.0, 27.2, 24.7. Anal. Calcd for $C_{13}H_{13}ClN_4O_3$: C, 50.58; H, 4.24; N, 18.15. Found: C, 50.76; H, 4.32; N, 18.07.

2.1.3. (1′*R*,2′*S*,3′*S*,4′*R*,5′*S*)-6-Chloro-9-(2′,3′-*iso*propylidenedioxy-6′-oxabicyclo-[3.1.0]hex-4′-yl)purine (12). To a stirring suspension of 6-chloropurine (0.635 g, 4.27 mmol) and triphenylphosphine (1.12 g, 4.27 mmol) in THF (10 mL) at −10 °C was added, dropwise, di*iso*propyl azodicarboxylate (0.8 g, 4.27 mmol). This mixture was stirred at −10 °C for 10 min and then stirred at room temperature for 15 min. To this mixture was then added a solution of **11** (0.74 g, 4.3 mmol) in dry THF (5 mL). The new mixture was stirred at room temperature for 48 h and concentrated under vacuum. Column chromatography with hexanes–EtOAc (4:1) provided a white solid of desired **12** (0.76 g, 56%), mp 175–176 °C; ^{1}H NMR ($CDCl_3$) δ 8.74 (s, 1H), 8.14 (s, 1H), 5.33 (d, *J*=7.0 Hz, 1H), 5.08 (s, 1H), 4.80 (d, *J*=6.99 Hz, 1H), 3.92 (s, 1H), 3.68 (s, 1H), 1.60 (s, 3H), 1.29 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 152.4, 152.0, 151.5, 144.7, 114.3, 86.7, 80.2, 77.4, 60.6, 60.6, 60.4, 26.3, 26.6. Anal. Calcd for $C_{13}H_{13}ClN_4O_3$: C, 50.58; H, 4.24; N, 18.15. Found: C, 50.36; H, 4.24; N, 18.39.

2.1.4. (3′*S*,4′*R*,5′*S*)-9-(3′-Hydroxy-4′,5′-isopropylidenedioxycyclopenten-1′-yl)6-methoxypurine (13). To a stirred solution of epoxide **7** (110 mg, 0.36 mmol) in dry THF (5 mL) at room temperature under N_2 was added sodium methoxide solution (0.217 mmol, 25% wt in MeOH). The mixture was stirred at room temperature for 2 h and evaporated. Water (5 mL) was added to the residue and extracted with EtOAc (3×10 mL). The combined extracts were dried (Mg_2SO_4), filtered, and evaporated to provide **13** as a white solid (97 mg, 89%), mp 154 °C; ^{1}H NMR ($CDCl_3$) δ 8.61 (s, 1H, H-2), 8.36 (s, 1H, H-8), 6.92 (d, *J*=2.4 Hz, 1H, H-2′), 5.69 (d, *J*=5.6 Hz, 1H, H-5′), 4.98 (m, 1H, H-3′), 4.71 (d, *J*=5.7 Hz, 1H, H-4′), 4.21 (s, 3H, OMe), 2.25 (d, *J*=5.7 Hz, 1H, OH), 1.43 (s, 3H, Me), 1.40 (s, 3H, Me); ^{13}C NMR ($CDCl_3$) δ 163.1, 154.7, 140.0, 140.0, 124.0, 121.1, 115.1, 86.7, 84.0, 80.3, 79.1, 56.2, 29.1, 27.8. Anal. Calcd for $C_{14}H_{16}N_4O_4$: C, 55.26; H, 5.26; 18.42. Found: C, 55.09; H, 5.31; N, 18.22.

2.1.5. (3′*R*,4′*R*,5′*S*)-9-(3′-Hydroxy-4′,5′-isopropylidenedioxycyclopenten-1′-yl)6-methoxypurine (14). To a stirring solution of epoxide **12** (480 mg, 1.57 mmol) in 10 mL of dry THF at room temperature under N_2 was added sodium methoxide solution (1 mL, 3.14 mmol, 25% wt in MeOH). The mixture was refluxed overnight at 70 °C and the solvents removed. To the residue was added H_2O (10 mL) and this mixture extracted with EtOAc (3×10 mL). The combined extracts were evaporated and further purified by column chromatography with hexanes–EtOAc (1:2) to give **14** as a white solid (450 mg, 93%), mp 147–148 °C; ^{1}H NMR ($CDCl_3$) δ 8.61 (s, 1H), 8.37 (s, 1H), 6.85 (s, 1H), 5.46 (d, *J*=5.5 Hz, 1H), 4.93 (t, *J*=5.5 Hz, 1H), 4.90 (m, 1H), 4.21 (d, *J*=0.7 Hz, 3H), 2.81 (brs, 1H, OH), 1.49 (s, 3H), 1.45 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.5, 153.1, 152.1, 140.5, 135.4, 122.3, 122.2, 114.0, 81.8, 77.7, 72.4, 54.6, 27.8, 26.7. Anal. Calcd for $C_{14}H_{16}N_4O_4$: C, 55.26; H, 5.26; 18.42. Found: C, 55.45; H, 5.36; N, 18.20.

Compound **14** was also prepared from **16** in the following way: To a stirring solution of **16** (100 mg, 0.33 mmol) (preparation below) and $CeCl_3{\cdot}7H_2O$ (130 mg) in MeOH (10 mL) was added, portionwise, $NaBH_4$ (35 mg) at 0 °C. The mixture was then stirred at the same temperature for 10 min. The mixture was evaporated. The residue was diluted by addition of saturated aq. NH_4Cl (10 mL) and this extracted with EtOAc (30 mL) and dried (Na_2SO_4). Evaporation of solvent gave **14** as a white solid (85 mg, 85%) whose spectral properties were identical to **14** obtained from **12**.

2.1.6. (4′*S*,5′*S*)-9-(4′5′-Isopropylidenedioxy-1′-oxocyclopent-2-enyl)-6-methoxypurine (16). To a solution of **13** (152 mg, 0.5 mmol) in dry CH_2Cl_2 under N_2 was added PCC (324 mg, 1.5 mmol). The mixture was stirred for 1 h, filtered with Celite and evaporated. The resulting residue was purified by column chromatography using hexanes–EtOAc (1:1) to give **16** as a white solid (130 mg, 88%), mp 195 °C; ^{1}H NMR ($CDCl_3$) δ 8.67 (s, 1H), 8.45 (s, 1H), 7.32 (s, 1H), 5.69 (d, *J*=5.7 Hz, 1H), 4.74 (d, *J*=5.6 Hz, 1H), 4.23 (s, 3H), 1.52 (s, 3H), 1.45 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 199.0, 161.7, 159.8, 154.0, 152.2, 139.9, 122.9, 117.8, 116.9, 77.5, 54.9, 27.5, 26.4.[15] Anal. Calcd for $C_{14}H_{14}N_4O_4$: C, 55.63; H, 4.67; N; 18.53. Found: C, 55.71; H, 4.68; N, 18.50.

2.1.7. (3′*S*,4′*R*,5′*S*)-9-(3′,4′,5′-Trihydroxycyclopent-1-enyl)purine (6). A solution of **13** (160 mg, 0.53 mmol) in MeOH (20 mL) saturated with NH_3 was heated at 120 °C for three days in a Parr stainless steel sealed reaction vessel. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (MeOH–CH_2Cl_2, 1:20) to give protected **6** as a white solid, mp

219–220 °C; ^{1}H NMR (DMSO) δ 8.30 (s, 1H), 8.25 (s, 1H), 7.47 (s, 2H), 6.63 (d, J=3.1 Hz, 1H), 5.88 (dd, J=1.0, 6.9 Hz, 1H), 5.47 (d, J=5.8 Hz, 1H), 4.66 (m, 1H), 4.53 (d, J=5.8 Hz, 1H), 1.35 (s, 3H), 1.28 (s, 3H).

The white solid from the last step was dissolved in 0.5 N HCl solution in MeOH (20 mL). This mixture was stirred at room temperature for 0.5 h. The mixture was evaporated to dryness to give a solid (100 mg, 76% after 2 steps) that was recrystallized from MeOH/H_2O to provide **6** as a white solid, mp 167 °C dec.; $[\alpha]_D^{22.9}$=+42.702 (c, 0.187 DMSO); ^{1}H NMR (DMSO) δ 8.32 (s, 1H), 8.23 (s, 1H), 7.43 (s, 2H), 6.56 (d, J=1.6 Hz, 1H), 5.24 (s, 3H), 5.01 (d, J=5.7 Hz, 1H), 4.60 (s, 1H), 3.80 (t, J=4.9 Hz, 1H); ^{13}C NMR (DMSO) δ 155.9, 152.9, 149.2, 138.3, 136.0, 120.8, 119.0, 78.3, 77.1, 71.4. Anal. Calcd for $C_{10}H_{11}N_5O_3\cdot1.1H_2O$: C, 44.62; H, 4.90; N, 26.02. Found: C, 44.47; H, 4.74; N, 25.89.

2.1.8. (3′*R*,4′*R*,5′*S*)-9-(3′,4′,5′-Trihydroxycyclopent-1-enyl)purine (17). Compound **17** was achieved as a white solid from **14** in 56% yield using the same method as for the synthesis of **6** from **13**, mp 208 °C dec.; $[\alpha]_D^{22.9}$=−2.81 (c, 0.121 DMSO); ^{1}H NMR (DMSO) δ 8.37(s, 1H), 8.23 (s, 1H), 7.42, (s, 2H), 6.68 (s, 1H), 5.17 (s, 1H), 4.87 (m, 2H), 4.47 (s, 2H), 4.11 (t, J=5.3 Hz, 1H); ^{13}C NMR (DMSO) δ 156.1 (2C), 153.2, 149.4, 138.7, 138.1, 119.3, 119.0, 71.4, 69.5.[15] Anal. Calcd for $C_{10}H_{11}O_3N_5\cdot0.2H_2O$: C, 47.50; H, 4.51, N, 27.71. Found: C, 47.47, H, 4.45, N, 27.44.

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This research was supported by funds from the Department of Health and Human Services (AI 48495 and AI 56540), which is appreciated. We are also indebted to the following individuals for providing the antiviral data[13] following their standard procedures: Dr. Erik De Clercq, the Rega Institute, Leuven Belgium; Dr. Earl Kern, University of Alabama at Birmingham, Birmingham, AL; Dr. Brent Korba, Georgetown University, Washington, DC; and, Dr. Robert Sidwell, Utah State University, Logan, UT. The assistance of Dr. Lyle Castle of the Idaho State University, Pocatello, Idaho, in using NMR to determine the structure of **13** is gratefully acknowledged.

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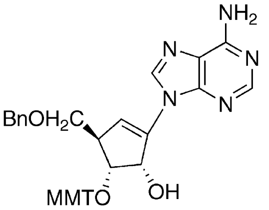
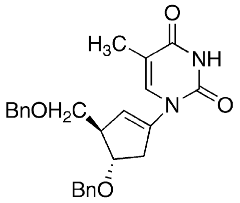


i



ii

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Tetrahedron

α-Oxoketene dithioacetals mediated heteroaromatic annulation protocol for benzoheterocycles: an efficient regiocontrolled synthesis of highly substituted and annulated indazoles

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Abstract—An efficient regiocontrolled synthesis of highly substituted and annulated indazoles involving base induced addition–elimination of 1,3-diphenyl-5-cyanomethylpyrazole to a variety of acyclic and cyclic α-oxoketene, followed by acid assisted cycloaromatization of the resulting conjugate adducts has been reported.

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1. Introduction

Indazole and its derivatives have gained considerable importance in medicinal chemistry in view of their promising pharmacological properties.[1,2] Several indazoles are found to exhibit significant levels of activity as HIV protease inhibitors,[3,4] serotonin 5-HT$_{1\alpha}$, 5-HT$_2$[5] and 5-HT$_3$ receptor antagonists,[6,7] acetylcholinesterase inhibitors[8] and aldol reductase inhibitors,[9] whereas 1-[3-(dimethylamino)-propyl]-5-methyl-3-phenyl-1*H*-indazole (FS-32) has been shown to be a potent antidepressant drug candidate.[2] Several methods for the synthesis of indazoles and their derivatives have been reported in the literature,[1–3,10–12] most of them involving construction of the pyrazole moiety on preconstructed benzenoid derivatives. On the other hand, the methods based on the more easily accessible pyrazole precursors are scantily described in the literature.[13] During the course of our heteroaromatic annulation[14] studies involving [3+3] cyclocondensation of α-oxoketene dithioacetals (1,3-bielectrophilic components) with various heteroallyl anions (1,3-binucleophilic components), we had demonstrated earlier that it is possible to tune up the reactivity of ambident heteroallyl anions derived from various methyl-substituted heterocycles towards α-oxoketene dithioacetals in either regiospecific 1,2-addition fashion or conjugate 1,4-addition–elimination pathway.[15] In general, the heteroallyl anions stabilized by electron withdrawing group such as nitrile are shown to add to α-oxoketene dithioacetals initially in conjugate addition–elimination fashion,[5h–i,15b] whereas the corresponding lithiomethyl species generated by deprotonation of methyl-substituted heterocycles were found to be less discriminate displaying either 1,2- or 1,4-addition pattern.[15d,e,15g,15j–m] Subsequent acid induced (or spontaneous) cycloaromatization of these adducts leads to the formation of either linearly substituted/annulated (1,2-addition) or angularly substituted/annulated (conjugate addition–elimination) benzoheterocycles (or bridged azaheterocycles) in highly regiospecific fashion.[14,15] We have shown in our earlier studies that the lithium 5-lithiomethyl-3-methylpyrazole-1-carboxylate generated by deprotonation-protection of 3,5-dimethylpyrazole undergoes 1,2-addition with various α-oxoketene dithioacetals to give carbinol acetals[15e] which on acid induced cycloaromatization afford the pyrazolo[1,5-*a*]pyridines instead of the expected indazoles via intramolecular cyclization at electron-rich nitrogen of the pyrazole ring rather than at C-4 position. We have also reported in our earlier work, the regiospecific deprotonation of 2,3-dimethyl-1-phenylpyrazolin-5-one (antipyrine) to give the corresponding 3-lithiomethyl species which was shown to undergo highly regioselective γ-1,4 addition to α-oxoketene dithioacetals followed by cycloaromatization in the presence of $BF_3{\cdot}Et_2O$ to afford a range of novel substituted and condensed indazolones in good yields.[13a] Also in a recent paper, we have developed another approach for substituted and fused indazolones by anionic [4+2] cycloaddition of dihydropyrazolin-5-one dienolate (generated by deprotonation of 2,3-dimethyl-4-formyl-1-phenylpyrazolin-5-one) with a variety of dienophiles.[13b] In continuation of these studies, we now report an efficient synthesis of angularly substituted

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Keywords: α-Oxoketene dithioacetals; Heteroaromatic annulation; Benzoheterocycles; Indazoles.

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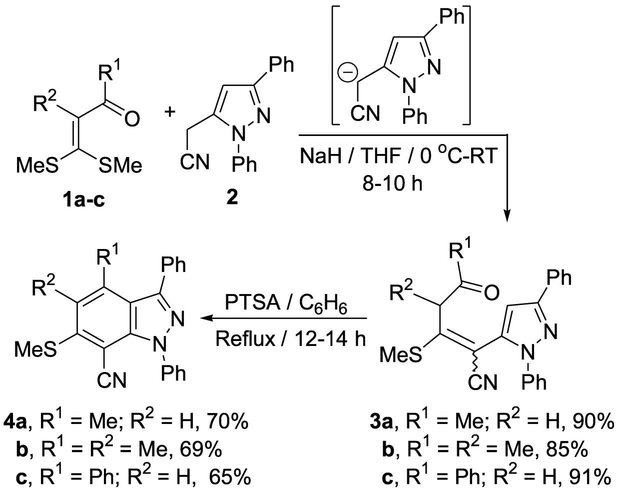
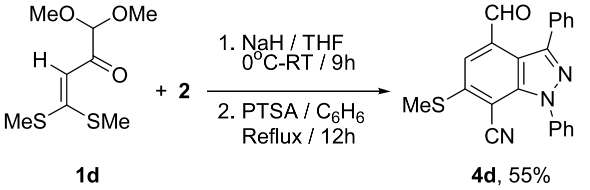
and fused indazoles involving base-induced conjugate addition of 1,3-diphenyl-5-cyanomethylpyrazole **2** with α-oxoketene dithioacetals followed by acid induced cycloaromatization of the resulting conjugate adducts.

2. Results and discussion

Our previous studies on the synthesis of carbazoles,[15i] indoles[15h] and benzothiophenes[15b] via [3+3] cycloaromatization of α-oxoketene dithioacetals with various heteroallyl anions have demonstrated that the cyano group is especially useful for stabilizing the negative charge on the heterocyclic side chain of 1,3-binucleophilic component. We therefore selected 1,3-diphenyl-5-cyanomethylpyrazole (**2**) as an anionic component in the present benzoannulation process. Thus in a typical experiment, the α-oxoketene dithioacetal **1a** was reacted with **2** in the presence of sodium hydride in THF at 0 °C to give the adduct **3a** (R^1=Me, R^2=H) in 90% yield. The adduct **3a** was purified by crystallization for spectral characterization which showed it to exist in the tautomeric β,γ-unsaturated keto form **3a** exclusively. The adduct **3a** was subjected to cycloaromatization in the presence of various protic (H_3PO_4, TFA, PTSA) and Lewis acids ($BF_3{\cdot}Et_2O$, $SnCl_4$), when the cyclization was found to be most efficient (in terms of yield and work-up) in the presence of *p*-toluenesulfonic acid (PTSA) in refluxing benzene yielding 7-cyano-1,3-diphenyl-4-methyl-6-(methylthio)indazole (**4a**) in 70% yield (Scheme 1). This reaction sequence could also be extended for the synthesis of other substituted indazole derivatives **4b-c** from the respective α-oxoketene dithioacetals **1b-c** in good yields with full regiocontrol of the substituent positions (Scheme 1). Cycloaromatization of α-oxoketene dithioacetal **1d** (from pyruvaldehyde dimethylacetal) with **2** under similar conditions furnished directly the corresponding 7-cyano-4-formylindazole **4d** in 55% yield via in situ hydrolysis of the acetal group (Scheme 2). The structures of all these newly synthesized indazoles **4a-d** were established with the help of spectral and analytical data. In one of the experiments, the 7-cyanoindazole **4c** was subjected to acid induced hydrolysis–decarboxylation to give the corresponding 1,3,4-tris(phenyl)-6-(methylthio)indazole **5c** (88%), which on Raney-Ni dethiomethylation afforded the corresponding sulfur free indazole **6c** in 92% yield (Scheme 3).



Scheme 1.



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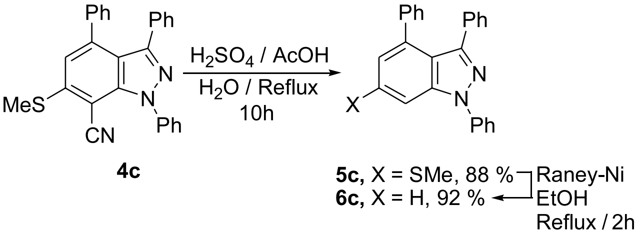
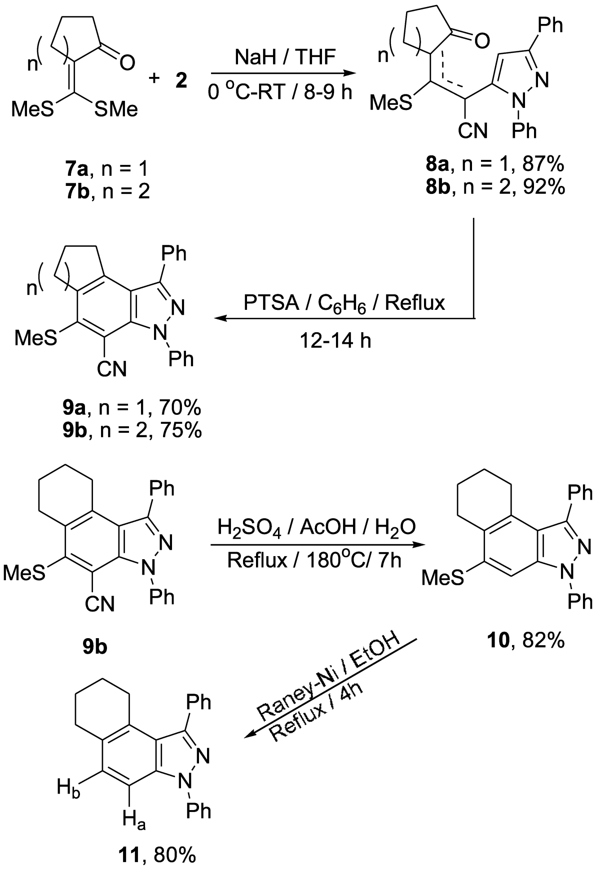
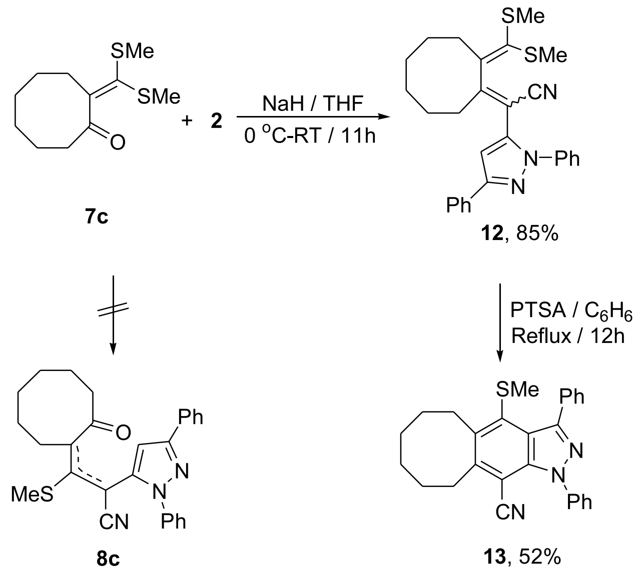


Scheme 3.

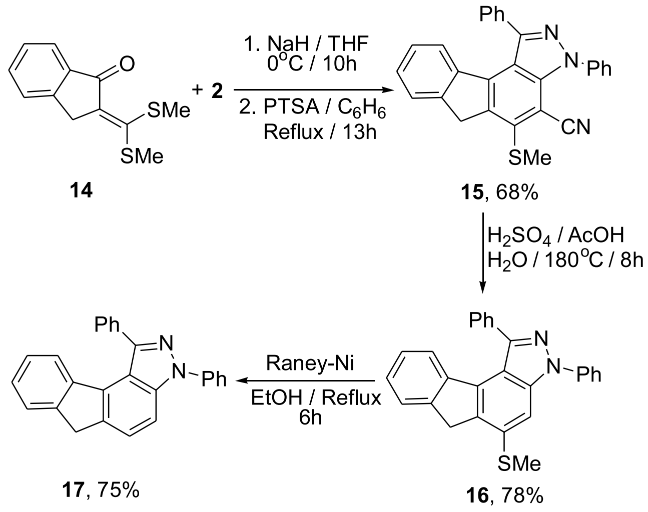
The conjugate addition–cycloaromatization protocol was next extended for the synthesis of annulated indazoles and the results are shown in Schemes 4–7. Thus, the base-induced conjugate addition of **2** with cyclic ketene dithioacetals **7a-b** from cyclopentanone and cyclohexanone, respectively, proceeded smoothly to give the respective adducts **8a-b** in high yields, these underwent facile



Scheme 4.



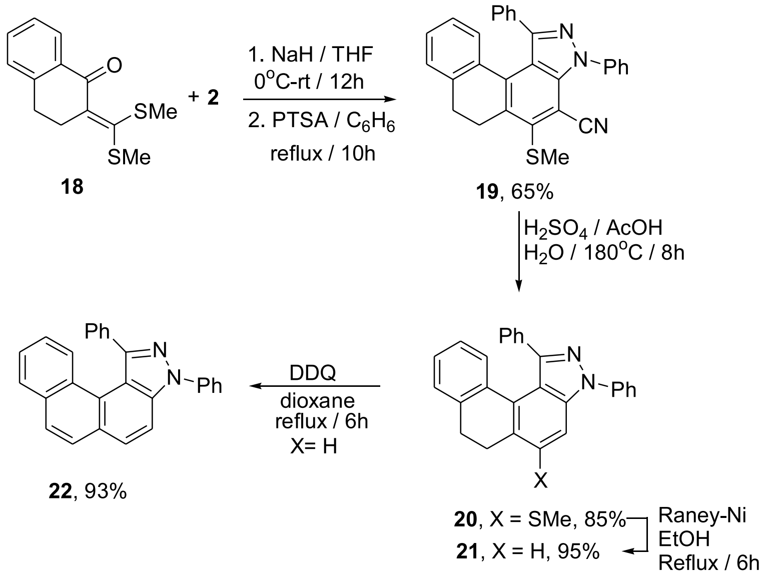
Scheme 5.



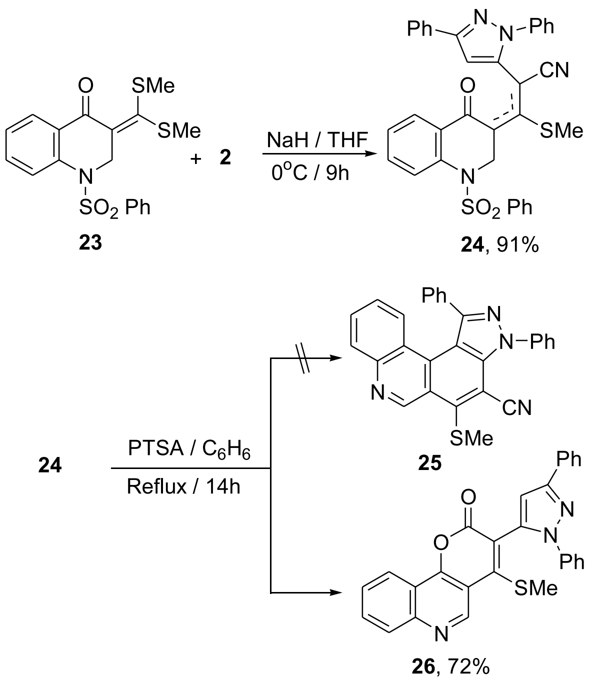
Scheme 6.

cyclization in the presence of PTSA/benzene yielding the corresponding tricyclic indazoles **9a-b** in 70 and 75% yields, respectively. The regiochemistry of one of the annulated indazole **9b** was established by its acid-induced hydrolysis–decarboxylation followed by reductive dethiomethylation of the resulting **10** to furnish 1,3-diphenyl-6,7,8,9-tetrahydrobenzo[*e*] indazole **11** in 80% yield (Scheme 4). The ^{1}H NMR spectrum of **11** displayed signals due to the two aromatic protons (H_a and H_b) as *ortho* coupled doublets (J=8.8 Hz) at δ 7.16 and 7.50, respectively, which unequivocally established the angular regiochemistry of the product **9b** formed through conjugate 1,4-addition–elimination of the carbanion from **2** with **7b**. Interestingly, the base-induced addition of the pyrazole **2** with ketene dithioacetal **7c** from cyclooctanone did not give the expected conjugate adduct **8c** and the product isolated (85%) was characterized as the adduct **12** formed by aldol condensation of pyrazoleacetonitrile **2** with **7c**. Apparently, the conformationally flexible cyclooctane ring of **7c** disturbs the planar structure of its enone functionality resulting in the nucleophilic attack of the carbanion derived from **2** on more electrophilic carbonyl group to give the aldol condensation product **12** exclusively. Subsequent cycloaromatization of **12** (via electrocyclization) on prolonged refluxing in benzene in the presence of PTSA afforded the corresponding linearly fused indazole **13** in 52% yield (Scheme 5). The structure of **13** was fully established with help of spectral and analytical data.

The versatility of our heteroaromatic annulation protocol was further demonstrated by the synthesis of tetracyclic angularly fused indazoles **15** and **19** by extrapolation of this reaction sequence under standard conditions to α-oxoketene dithioacetals **14** and **18** derived from indan-1-one and α-tetralone, respectively (Schemes 6 and 7). The annulated indazoles **15** and **19** on sequential hydrolysis–decarboxylation and Raney-Ni dethiomethylation of the resulting **16** and **20** under earlier reported conditions afforded the corresponding sulfur free tetracyclic angularly fused indazoles **17** and **21** in overall high yields (Schemes 6 and 7). The dihydroindazole **21** was transformed into the



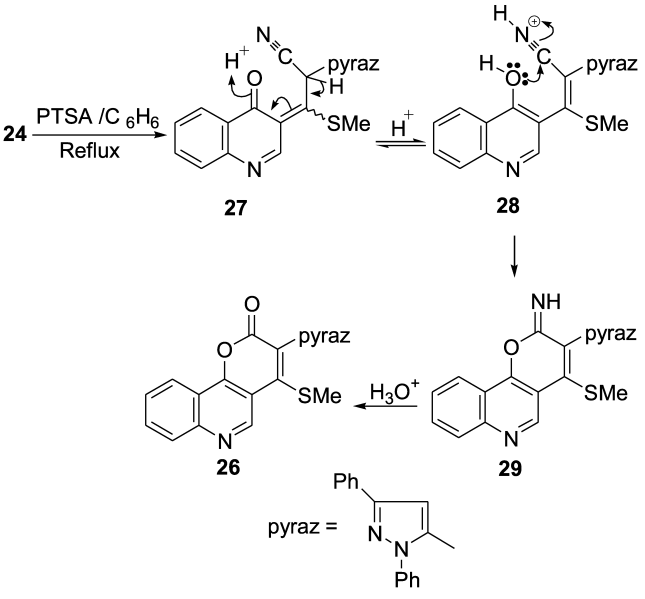
Scheme 7.



Scheme 8.

corresponding fully aromatic tetracyclic indazole **22** (93%) by dehydrogenation with DDQ (Scheme 7). The structures of all the newly synthesized indazoles **15-17** and **19-22** were established with the help of spectral and analytical data.

Finally, we have extended our studies to oxoketene dithioacetal **23** obtained from *N*-(benzenesulfonyl)-4-quinolone with a view to synthesize the tetracyclic azaindazole framework **25** (Scheme 8). Thus, the ketene dithioacetal **23** underwent facile base-induced conjugate-addition–elimination with **2** to afford the corresponding adduct **24** in nearly quantitative yield. However, the acid-induced cycloaromatization of **24** under earlier described conditions did not yield the expected tetracyclic azaindazole **25**, the product (72%) isolated after work-up was characterized as the pyrano[3,2-*c*]quinoline **26** on the basis of its spectral and analytical data. Our attempts to obtain indazole **25** from **24** in the presence of other protic and Lewis acids were not successful yielding only intractable reaction mixtures. The possible mechanism for the formation of the observed product **26** from **24** is shown in Scheme 9. The hydroxyquinoline intermediate **28** formed by debenzenesulfonylation[16] and tautomerization of the adduct **24** (via intermediate **27**) undergoes intramolecular nucleophilie attack of hydroxy group on nitrile functionality to give imine intermediate **29** which on subsequent hydrolysis affords the pyrano[3,2-*c*]quinoline **26** (Scheme 9).



Scheme 9.

3. Conclusion

In summary, the two steps [3+3] annulation of 1,3-diphenyl-5-cyanomethylindazole (**2**) with a range of α-oxoketene dithioacetals affords a variety of novel substituted and annulated indazoles in good yields with high regioselectivity. The above study has clearly demonstrated that the α-oxoketene dithioacetal mediated aromatic and heteroaromatic annulation protocol[14a] provides a general route for the construction of complex heteroaromatics from easily available precursors in highly regioselective manner. In view of the wide range of biological activities displayed by indazole derivatives, the above methodology can be extended for generating library of substituted indazoles. Our efforts in this direction are in progress.

4. Experimental

4.1. General

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ and TMS was used as an internal standard. Melting points were uncorrected. Chromatographic purification was conducted by column chromatography using 100–200 mesh silica gel obtained from standard firms. Raney-Nickel was prepared according to the reported method.[17] The 1,3-diphenyl-5-cyanomethylpyrazole (**2**) was prepared according to literature method.[18] The known α-oxoketene dithioacetals were prepared according to the earlier reported procedure.[14a,19]

4.2. General procedure for base induced addition of 1,3-diphenyl-5-cyanomethylpyrazole (2) to α-oxoketene dithioacetals

A solution of 1,3-diphenyl-5-cyanomethylpyrazole (**2**) (0.57 g, 2.2 mmol) in THF (15 mL) was added dropwise to a stirring suspension of NaH (0.1 g, 2.4 mmol, 60%) in THF (15 mL) at 0 °C under N_2 atmosphere. After 1 h, a solution of the appropriate α-oxoketene dithioacetal (2 mmol) in THF (15 mL) was slowly added at 0 °C and the reaction mixture was allowed to warm to room temperature with stirring during 8–10 h. It was then poured into cold saturated ammonium chloride solution (50 mL) and extracted with DCM (3×20 mL). The organic layer was washed with H_2O (3×50 mL), brine (50 mL), dried

(Na_2SO_4) and the solvent evaporated in vacuo. A few of the adducts **3a**, **3c** and **12** were purified by crystallization (ether–DCM) for characterization and their spectral and analytical data are given below. The other adducts were used as such for further cyclization.

4.2.1. 2-(1,3-Diphenyl-1*H*-5-pyrazolyl)-3-methylthio-5-oxo-hexen-2-carbonitrile (3a). Yield (0.56 g, 75%, isolated yield) as a pale yellow solid, mp 151–2 °C; [found: C, 70.78; H, 5.11; N, 11.29. $C_{22}H_{19}N_3SO$ requires C, 70.75; H, 5.13; N, 11.25%]; R_f (20% EtOAc/hexane) 0.38; ν_{max}(KBr) 3066, 2924, 2201, 1719, 1498 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.81–7.87 (2H, m, ArH), 7.57–7.60 (2H, m, ArH), 7.49–7.45 (2H, m, ArH), 7.39–7.43 (3H, m, ArH), 7.30–7.34 (1H, m, ArH), 6.87 (1H, s, ArH), 3.89 (2H, s, C*H*$_2$), 2.23 (3H, s, SC*H*$_3$), 2.22 (3H, s, C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 200.8 (C=O), 160.2 (*C*(SCH_3)=C(CN)), 152.1 (C), 139.1 (C), 134.0 (C), 132.4 (C), 129.2 (CH), 128.6 (CH), 128.3 (CH), 128.2 (CH), 125.7 (CH), 124.3 (CH), 115.9 (CN), 107.2 (CH), 98.9 (C(SCH_3)=*C*(CN)), 48.7 (CH_2), 29.5 (CH_3), 15.0 (SCH_3); *m*/*z* 374 (100 MH^+).

4.2.2. 2-(1,3-Diphenyl-1*H*-5-pyrazolyl)-3-methylthio-5-oxo-5-phenyl-penten-2-carbonitrile (3c). Yield (0.61 g, 70%) as a colourless solid, mp 169–170 °C; [found: C, 74.41; H, 4.90; N, 9.68. $C_{27}H_{21}N_3SO$ requires C, 74.46; H, 4.86; N, 9.65%]; R_f (20% EtOAc/hexane) 0.30; ν_{max} (KBr) 3059, 2923, 2199, 1680, 1593, 1535 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.00 (2H, d, *J*=8.0 Hz, ArH), 7.90 (2H, d, *J*=8.0 Hz, ArH),7.69 (2H, d, *J*=8.3 Hz, ArH), 7.64 (1H, t, *J*=7.8 Hz, ArH), 7.51 (4H, dt, *J*=1.7, 7.8 Hz, ArH), 7.40–7.45 (3H, m, ArH), 7.33–7.38 (1H, m, ArH), 6.96 (1H, s, ArH), 4.52 (2H, s, C*H*$_2$), 2.22 (3H, s, SC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 192.6 (C=O), 160.8 (*C*(SCH_3)=C(CN)), 152.0 (C), 139.2 (C), 135.5 (C), 134.17 (CH), 134.11 (C), 132.6 (C), 129.2 (CH), 128.9 (CH), 128.7 (CH), 128.20 (CH), 128.18 (CH), 128.08 (CH), 125.8 (CH), 124.2 (CH), 115.9 (CN), 107.5 (CH), 99.4 (C(SCH_3)=*C*(CN)), 44.1 (CH_2), 15.2 (SCH_3); *m*/*z* 436 (100 MH^+).

4.2.3. 2-[2-Bis(methylthio)methylenecyclooctylidene]-2-(1,3-diphenyl-1*H*-5-pyrazolyl) acetonitrile (12). Yield (0.80 g, 85%) as a yellow solid, mp 158–9 °C; [found: C, 71.33; H, 6.16; N, 8.95. $C_{28}H_{29}N_3S_2$ requires C, 71.30; H, 6.20; N, 8.91%]; R_f (40% EtOAc/hexane) 0.28; ν_{max}(KBr) 2919, 2210, 1666, 1595 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.92 (2H, d, *J*=7.8 Hz, ArH), 7.78 (2H, d, *J*=7.8 Hz, ArH), 7.39–7.50 (4H, m, ArH), 7.29–7.33 (2H, m, ArH), 6.85 (1H, s, ArH), 2.56–2.62 (1H, m, C*H*), 2.44–2.49 (1H, m, C*H*), 2.26–2.32 (1H, m, C*H*$_2$), 2.24 (3H, s, SC*H*$_3$), 2.09–2.14 (1H, m, C*H*$_2$), 1.96 (3H, s, SCH_3), 1.76–1.79 (2H, m, C*H*$_2$), 1.52–1.73 (6H, m, C*H*$_2$); δ_C (100 MHz, $CDCl_3$) 166.8 (C), 155.6 (C), 151.9 (C), 140.0 (C), 139.2 (C), 134.8 (C), 133.0 (C), 131.9 (C), 128.7 (CH), 128.5 (CH), 127.9 (CH), 127.5 (CH), 125.8 (CH), 124.4 (CH), 118.8 (CN), 106.4 (CH), 34.3 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 28.0 (CH_2), 27.1 (CH_2), 24.8 (CH_2), 14.8 (SCH_3), 14.3 (SCH_3).

4.3. General procedure for the synthesis of substituted indazoles 4a-d, 9a-b, 13, 15, 19 and pyranoquinoline 26

To a solution of adduct (ca. 1 mmol) in dry benzene (25 mL), *p*-toluenesulphonic acid (0.35 g, 2 mmol) was added and the reaction mixture was refluxed with stirring for 10–14 h (monitored by TLC). It was neutralized with $NaHCO_3$ solution and extracted with benzene (3×20 mL). The combined extracts were washed with H_2O (3×100 mL), brine (100 mL), dried (Na_2SO_4) and the solvent evaporated at reduced pressure. The crude product was purified by column chromatography using EtOAc/hexane (1:9) as eluent to give pure indazole.

4.3.1. 7-Cyano-1,3-diphenyl-4-methyl-6-methylthio-1*H*-indazole (4a). Yield (0.25 g, 70%) as a colourless solid, mp 167–8 °C; [found: C, 74.39; H, 4.84; N, 11.80. $C_{22}H_{17}N_3S$ requires C, 74.34; H, 4.82; N, 11.82%]; R_f (20% EtOAc/hexane) 0.58; ν_{max}(KBr) 2918, 2211, 1514, 1433 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.53–7.59 (6H, m, ArH), 7.50–7.52 (2H, m, ArH), 7.45–7.46 (2H, m, ArH), 6.91 (1H, s, ArH), 2.60 (3H, s, SC*H*$_3$), 2.39 (3H, s, C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 148.1 (C), 146.6 (C), 139.8 (C), 138.7 (C), 138.0 (C), 132.9 (C), 129.9 (CH), 129.4 (CH), 128.8 (CH), 128.7 (CH), 128.0 (CH), 127.3 (CH), 121.2 (C), 120.4 (CH), 113.7 (CN), 90.3 (C), 20.7 (CH_3), 16.2 (SCH_3); *m*/*z* 355 (80 M^+), 352 (100 $M-3^+$).

4.3.2. 7-Cyano-4,5-dimethyl-1,3-diphenyl-6-methylthio-1*H*-indazole (4b). Yield (0.26 g, 69%) as a colourless solid, mp 165–6 °C; [found: C, 74.73; H, 5.21; N, 11.40. $C_{23}H_{19}N_3S$ requires C, 74.77; H, 5.18; N, 11.37%]; R_f (20% EtOAc/hexane) 0.54; ν_{max}(KBr) 2922, 2219, 1653, 1573, 1497 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.57–7.59 (4H, m, ArH), 7.51–7.56 (4H, m, ArH), 7.46–7.49 (2H, m, ArH), 2.62 (3H, s, SC*H*$_3$), 2.48 (3H, s, C*H*$_3$), 2.36 (3H, s, C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 147.7 (C), 142.9 (C), 138.3 (C), 138.1 (C), 137.3 (C), 133.5 (C), 133.4 (C), 130.2 (CH), 129.4 (CH), 128.8 (CH), 128.6 (CH), 128.2 (CH), 127.5 (CH), 123.8 (C), 114.9 (CN), 98.2 (C), 19.8 (CH_3), 18.16 (CH_3), 17.4 (SCH_3); *m*/*z* 369 (100 M^+), 354 (21).

4.3.3. 7-Cyano-6-methylthio-1,3,4-tris(phenyl)-1*H*-indazole (4c). Yield (0.27 g, 65%) as a colourless solid, mp 201–2 °C; [found: C, 77.71; H, 4.61; N, 10.02. $C_{27}H_{19}N_3S$ requires C, 77.67; H, 4.59; N, 10.06%]; R_f (20% EtOAc/hexane) 0.59; ν_{max}(KBr) 3060, 2920, 2214, 1496, 1425 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.62–7.64 (2H, m, ArH), 7.57–7.59 (2H, m, ArH), 7.56 (1H, s, ArH), 7.22 (1H, t, *J*=7.1 Hz, ArH), 7.12–7.18 (4H, m, ArH), 7.08–7.10 (4H, m, ArH), 7.01–7.05 (2H, m, ArH), 2.63 (3H, s, SC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 148.0 (C), 146.6 (C), 142.1 (C), 140.6 (C), 138.1 (C), 137.5 (C), 132.1 (C), 129.6 (CH), 129.3 (CH), 129.1 (CH), 128.9 (CH,), 128.2 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 127.4 (CH), 120.2 (CH), 119.1 (C), 113.6 (CN), 91.2 (C), 16.3 (SCH_3); *m*/*z* 417 (100, M^+), 370 (20).

4.3.4. 7-Cyano-1,3-diphenyl-4-formyl-6-methylthio-1*H*-indazole (4d). Yield (0.20 g, 55%) as a yellow solid, mp 200–1 °C; [found: C, 71.49; H, 4.11; N, 11.42. $C_{22}H_{15}N_3SO$ requires C, 71.52; H, 4.09; N, 11.37%]; R_f (20% EtOAc/hexane) 0.45; ν_{max}(KBr) 2922, 2854, 2212, 1695, 1570, 1496 cm^{-1}; δ_H (400 MHz, $CDCl_3$), 10.34 (1H, s, C*H*O), 7.74 (1H, s, ArH), 7.66–7.69 (2H, m, ArH), 7.58–7.61 (5H, m, ArH), 7.52–7.55 (3H, m, ArH), 2.70 (3H, s, SC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 188.8 (*C*HO), 147.8 (C), 146.6 (C), 141.1 (C), 137.5 (C), 133.1 (C), 131.9 (C), 130.1 (CH), 129.5 (CH), 129.4 (CH), 129.1 (CH), 129.0 (CH), 127.63 (CH), 127.59 (C), 120.5 (C), 117.5 (CH), 112.6 (CN), 16.1 (SCH_3); *m*/*z* 370 (100 MH^+), 342 (20).

4.3.5. 4-Cyano-1,3-diphenyl-5-methylthio-3,6,7,8-tetrahydrocyclopenta[*e*]indazole (9a). Yield (0.29 g, 70%) as a colourless solid, mp 197–8 °C; [found: C, 75.59; H, 5.04; N, 11.08. $C_{24}H_{19}N_3S$ requires C, 75.56; H, 5.02; N, 11.01%]; R_f (20% EtOAc/hexane) 0.59; ν_{max}(KBr) 2980, 2949, 2831, 2217, 1586, 1553, 1498 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.68 (2H, dd, *J*=2.0, 8.0 Hz, ArH), 7.56–7.60 (3H, m, ArH), 7.52–7.55 (2H, m, ArH), 7.43–7.51 (3H, m, ArH), 3.13 (4H, quint, *J*=7.8, C*H*$_2$–CH$_2$–C*H*$_2$), 2.56 (3H, s, SC*H*$_3$), 2.14 (2H, q, *J*=7.6 Hz, CH$_2$–C*H*$_2$–CH$_2$); δ_C (100 MHz, $CDCl_3$) 147.2 (C), 142.9 (C), 141.3 (C), 140.4 (C), 139.9 (C), 138.3 (C), 132.2 (C), 129.5 (CH), 129.4 (CH), 128.8 (CH), 128.7 (CH), 128.3 (CH), 127.5 (CH), 120.7 (C), 114.7 (CN), 96.5 (C), 34.3 (CH_2), 32.8 (CH_2), 24.8 (CH_2), 18.9 (SCH_3); *m*/*z* 381 (100 M^+), 366 (40), 333 (26), 289 (20).

4.3.6. 4-Cyano-1,3-diphenyl-5-methylthio-6,7,8,9-tetrahydro-3*H*-benzo[*e*]indazole (9b). Yield (0.30 g, 70%) as a colourless solid, mp 198–9 °C; [found: C, 75.95; H, 5.39; N, 10.64. $C_{25}H_{21}N_3S$ requires C, 75.92; H, 5.35; N, 10.62%]; R_f (20% EtOAc/hexane) 0.42; ν_{max}(KBr) 2941, 2856, 2217, 1595, 1569, 1496 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.54–7.60 (5H, m, ArH), 7.50–7.52 (3H, m, ArH), 7.45–7.47 (2H, m, ArH), 3.06 (2H, t, *J*=6.4 Hz, C*H*$_2$), 2.75 (2H, t, *J*=6.4 Hz, C*H*$_2$), 2.51 (3H, s, SC*H*$_3$), 1.82–1.88 (2H, m, C*H*$_2$), 1.63–1.69 (2H, m, C*H*$_2$); δ_C (100 MHz, $CDCl_3$) 147.7 (C), 143.9 (C), 138.19 (C), 138.16 (C), 138.0 (C), 133.8 (C), 133.3 (C), 130.1 (CH), 129.4 (CH), 128.8 (CH), 128.6 (CH), 128.1 (CH), 127.5 (CH), 122.9 (C), 114.7 (CN), 98.4 (C), 28.9 (CH_2), 28.6 (CH_2), 22.9 (CH_2), 21.8 (CH_2), 19.6 (SCH_3); *m*/*z* 396 (100 MH^+), 380 (43), 348 (20).

4.3.7. 11-Cyano-1,3-diphenyl-4-methylthio-5,6,7,8,9,10-hexahydro-1*H*-cycloocta[*f*]indazole (13). Yield (0.22 g, 52%) as a colourless solid, mp 197–8 °C; [found: C, 76.51; H, 5.99; N, 9.97. $C_{27}H_{25}N_3S$ requires C, 76.56; H, 5.95; N, 9.92%]; R_f (20% EtOAc/hexane) 0.52; ν_{max}(KBr): 2924, 2218, 1594, 1499 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.60–7.62 (2H, m, ArH), 7.52–7.58 (5H, m, ArH), 7.43–7.49 (3H, m, ArH), 3.24 (2H, t, *J*=6.1 Hz, C*H*$_2$), 2.94 (2H, t, *J*=6.1 Hz, C*H*$_2$), 2.55 (3H, s, SC*H*$_3$), 1.76–1.78 (2H, m, C*H*$_2$), 1.40–1.43 (2H, m, C*H*$_2$), 1.26–1.32 (4H, m, C*H*$_2$); δ_C (100 MHz, $CDCl_3$) 147.6 (C), 143.2 (C), 142.5 (C), 138.6 (C), 138.2 (C), 137.5 (C), 133.9 (C), 130.1 (CH), 129.4 (CH), 128.83 (CH), 128.78 (CH), 128.1 (CH), 127.5 (CH), 123.1 (C), 114.9 (CN), 98.8 (C), 31.3 (CH_2), 31.1 (CH_2), 28.8 (CH_2), 28.5 (CH_2), 26.5 (CH_2), 25.9 (CH_2), 20.8 (SCH_3); *m*/*z* 424 (100, MH^+).

4.3.8. 4-Cyano-1,3-diphenyl-5-methylthio-3,6-dihydro-indeno[1,2-*e*]indazole (15). Yield (0.29 g, 68%) as a colourless solid, mp 267–8 °C; [found: C, 79.25; H, 4.49; N, 9.80. $C_{28}H_{19}N_3S$ requires C, 79.29; H, 4.46; N, 9.78%]; R_f (20% EtOAc/hexane) 0.60; ν_{max}(KBr) 3054, 2919, 2214, 1555, 1497 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.64–7.67 (4H, m, ArH), 7.56–7.61 (5H, m, ArH), 7.51–754 (2H, m, ArH), 7.31 (1H, t, *J*=7.8 Hz, ArH), 6.99 (1H, t, *J*=7.8 Hz, ArH), 6.57 (1H, d, *J*=7.8 Hz, ArH), 4.15 (2H, s, C*H*$_2$), 2.66 (3H, s, SCH_3); δ_C (100 MHz, $CDCl_3$) 147.0 (C), 145.2 (C), 141.3 (C), 140.6 (C), 139.8 (C), 139.5 (C), 139.4 (C), 138.3 (C), 134.1 (C), 130.5 (CH), 129.8 (CH), 129.2 (CH), 128.9 (CH), 128.5 (CH), 128.2 (CH), 127.8 (CH), 126.6 (CH), 126.4 (CH), 124.6 (CH), 118.7 (C), 113.8 (CN), 96.6 (C), 38.3 (CH_2), 19.2 (SCH_3); *m*/*z* 430 (100 MH^+), 414 (20), 279 (20).

4.3.9. 4-Cyano-1,3-diphenyl-5-methylthio-6,7-dihydro-3*H*-naphtho[1,2-*e*]indazole (19). Yield (0,29 g, 65%) as a colourless solid, mp 220–1 °C; [found: C, 78.49; H, 4.81; N, 9.50. $C_{29}H_{21}N_3S$ requires C, 78.53; H, 4.77; N, 9.47%]; R_f (20% EtOAc/hexane) 0.50; ν_{max}(KBr) 3210, 3062, 2924, 2214, 1594, 1539 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.62–7.66 (2H, m, ArH), 7.54–7.62 (3H, m, ArH), 7.24–7.29 (4H, m, ArH), 7.16–7.19 (2H, m, ArH), 7.12 (1H, t, *J*=7.6 Hz, ArH), 6.83 (1H, d, *J*=7.6 Hz, ArH), 6.59 (1H, t, *J*=7.6Hz, ArH), 3,23 (2H, t, *J*=6.8 Hz, C*H*$_2$), 2.92 (2H, t, *J*=6.8 Hz, C*H*$_2$), 2.51 (3H, s, SCH_3); δ_C (100 MHz, $CDCl_3$) 147.3 (C), 141.4 (C), 140.5 (C), 138.9 (C), 138.3 (C), 136.6 (C), 135.7 (C), 133.2 (C), 131.2 (CH), 130.9 (C), 129.7 (CH), 129.5 (CH), 128.9 (CH), 128.7 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 126.7 (CH), 125.0 (CH), 119.2 (C), 114.7 (CN), 98.7 (C), 29.2 (CH_2), 27.4 (CH_2), 19.6 (SCH_3); *m*/*z* 444 (MH^+).

4.3.10. 3-(1,3-Diphenyl-1*H*-5-pyrazolyl)-4-methylthio-2*H*-pyrano[3,2-*c*]quinolin-2-one (26). Yield (0.33 g, 72%) as a yellow solid, mp 224–225 °C; [found: C, 72.91; H, 4.19; N, 9.12. $C_{28}H_{19}N_3O_2S$ requires C, 72.87; H, 4.15; N, 9.10%]; R_f (20% EtOAc/hexane) 0.35; ν_{max}(KBr) 3048, 2928, 1723, 1594, 1567 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.37 (1H, s, ArH), 8.47 (1H, d, *J*=8.3 Hz, ArH), 8.17 (1H, d, *J*=8.3 Hz, ArH), 7.94 (2H, d, *J*=7.6 Hz, ArH), 7.89 (1H, t, *J*=7.7 Hz, ArH), 7.71 (1H, t, *J*=7.7 Hz, ArH), 7.56 (2H, d, *J*=7.6 Hz, ArH), 7.40–7.46 (2H, m, ArH), 7.36–7.39 (2H, m, ArH), 7.29–7.34 (2H, m, ArH), 6.99 (1H, s, ArH), 2.18 (3H, s, SC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 157.2 (C=O), 155.1 (C), 154.9 (C), 152.3 (C), 148.8 (C), 147.0 (CH), 140.1 (C), 135.6 (C), 132.58 (CH), 132.53 (CH), 129.3 (CH), 129.0 (C), 128.7 (CH), 128.3 (CH), 128.2 (CH), 127.9 (CH), 125.9 (CH), 123.4 (CH), 122.5 (CH), 117.4 (C), 117.1 (C), 110.7 (C), 108.6 (CH), 17.1 (SCH_3); *m*/*z* 462 (100 MH^+), 414 (20) 386 (20).

4.4. General procedure for acid induced hydrolysis–decarboxylation indazoles 4c, 9b, 15 and 19

A solution of the respective indazole (1 mmol) in glacial AcOH/H_2O/conc. H_2SO_4 (1:1:1, 10 mL) was refluxed at 180 °C for 7–10 h (monitored by TLC). It was cooled and neutralized with sat. $NaHCO_3$ solution and extracted with DCM (3×25 mL), and the extract washed with H_2O (50 mL), brine (50 mL), dried (Na_2SO_4) and the solvent evaporated in vacuo to give crude product which was purified by column chromatography over silica gel using EtOAc/hexane (1:20) as eluent.

4.4.1. 6-Methylthio-1,3,4-tris(phenyl)-1*H*-7-indazole (5c). Yield (0.35 g, 88%) as a colourless solid, mp 189–190 °C; [found: C, 79.58; H, 5.17; N, 7.19. $C_{26}H_{20}N_2S$ requires C, 79.56; H, 5.14; N, 7.14%]; R_f (20% EtOAc/

hexane) 0.65; ν_{max}(KBr) 3048, 2919, 1962, 1592, 1493 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.79 (2H, d, *J*=7.3 Hz, ArH), 7.55–7.59 (3H, m, ArH), 7.40 (1H, t, *J*=7.6 Hz, ArH), 7.13–7.19 (6H, m, ArH), 7.12 (1H, d, *J*=1.4 Hz, ArH), 7.09 (2H, d, *J*=7.3 Hz, Ar H), 7.05 (2H, d, *J*=7.6 Hz, ArH), 2.57 (3H, s, SCH_3); δ_C (100 MHz, $CDCl_3$) 147.6 (C), 141.3 (C), 139.8 (C), 138.7 (C), 138.5 (C), 137.4 (C), 133.1 (C), 129.5 (CH), 129.32 (CH), 129.30 (CH), 127.6 (CH), 127.33 (CH), 127.28 (CH), 127.23 (CH), 127.0 (CH), 123.5 (CH), 122.43 (CH), 118.9 (C), 105.8 (CH), 16.1 (SCH_3); *m/z* 393 (100 MH^+), 392 (80, M^+).

4.4.2. 1,3-Diphenyl-5-methylthio-6,7,8,9-tetrahydro-3*H*-benzo[*e*]indazole (10). Yield (0.30 g, 82%) as a colourless solid, mp 151–152 °C; [found: C, 77.71; H, 5.94; N, 7.60. $C_{24}H_{22}N_2S$ requires C, 77.80; H, 5.98; N, 7.56%]; R_f (20% EtOAc/hexane) 0.58; ν_{max}(KBr) 3053, 2937, 1956, 1588, 1497 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.75 (2H, d, *J*=7.6 Hz, ArH), 7.59–7.62 (2H, m, ArH), 7.53 (2H, t, *J*=7.8 Hz, ArH), 7.43–7.48 (3H, m ArH), 7.35 (1H, t, *J*=7.8 Hz ArH), 7.32 (1H, s, ArH), 2.75 (2H, t, *J*=6.3 Hz CH_2), 2.69 (2H, t, *J*=6.3 Hz, CH_2) 2.49 (3H, s, SCH_3), 1.83–1.87 (2H, m, CH_2), 1.64–1.68 (2H, m, CH_2); δ_C [100 MHz, $CDCl_3$] 147.6 (C), 140.4 (C), 139.9 (C), 138.7 (C), 134.8 (C), 131.2 (C), 130.2 (CH), 129.5 (CH), 128.2 (CH), 127.9 (CH), 127.6 (C), 126.6 (CH), 123.2 (CH), 120.2 (C), 102.3 (CH), 28.4 (CH_2), 26.6 (CH_2), 22.9 (CH_2), 22.3 (CH_2), 15.3 (SCH_3); *m/z* 372 (100, MH^+) 323 (25).

4.4.3. 1,3-Diphenyl-5-methylthio-3,6-dihydroindeno[1,2-*e*]indazole (16). Yield (0.32 g, 78%) as a colourless solid, mp 172–3 °C; [found: C, 80.13; H, 5.01; N, 6.94. $C_{27}H_{20}N_2S$ requires C, 80.16; H, 4.98; N, 6.92%]; R_f (20% EtOAc/hexane) 0.60; ν_{max}(KBr) 3042, 2914, 1592, 1497 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.80 (2H, d, *J*=8.0 Hz, ArH), 7.69 (2H, d, *J*=6.4 Hz, ArH), 7.50–7.59 (6H, m, ArH), 7.48 (1H, s, ArH), 7.41 (1H, t, *J*=7.3 Hz, ArH), 7.21 (1H, t, *J*=7.8 Hz, ArH), 6.96 (1H, t, *J*=7.8 Hz, ArH), 6.56 (1H, d, *J*=7.8 Hz, ArH), 3.89 (2H, s, CH_2), 2.60 (3H, s, SCH_3); δ_C (100 MHz, $CDCl_3$) 146.9 (C), 144.1 (C), 141.5 (C), 140.9 (C), 140.0 (C), 135.9 (C), 135.6 (C), 135.2 (C), 134.4 (C), 130.6 (CH), 129.6 (CH), 128.8 (CH), 128.2 (CH), 127.0 (CH), 126.3 (CH), 126.2 (CH), 125.1 (CH), 124.3 (CH), 123.7 (CH), 116.8 (C), 103.5 (CH), 36.6 (CH_2), 15.0 (SCH_3); *m/z* 406 (100, $M2H^+$), 405 (90, MH^+), 357 (20).

4.4.4. 1,3-Diphenyl-5-methylthio-6,7-dihydro-3*H*-naphtho[1,2-*e*]indazole (20). Yield (0.36 g, 85%) as colourless solid, mp 192–3 °C; [found: C, 80.39; H, 5.27; N, 6.72. $C_{28}H_{22}N_2S$ requires C, 80.35; H, 5.30; N, 6.69%]; R_f (20% EtOAc/hexane) 0.65; ν_{max}(KBr) 3046, 2950, 2833, 1595, 1544, 1494 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.8 (2H, d, *J*=8.0 Hz, ArH), 7.57 (2H, t, *J*=8.0 Hz, ArH), 7.52 (1H, s, ArH), 7.37–7.43 (2H, m, ArH), 7.19–7.28 (5H, m, ArH), 7.05 (1H, t, *J*=7.6 Hz, ArH), 6.82 (1H, d, *J*=7.6 Hz, ArH), 6.59 (1H, t, *J*=7.6 Hz, ArH), 2.89–2.96 (4H, m, CH_2–CH_2), 2.52 (3H, s, SCH_3); δ_C (100 MHz, $CDCl_3$) 147.1 (C), 141.0 (C), 139.9 (C), 137.9 (C), 137.8 (C), 134.3 (C), 131.8 (C), 131.6 (C), 130.7 (CH), 130.0 (C), 129.6 (CH), 129.5 (CH), 127.7 (CH), 127.6 (CH), 127.0 (CH), 126.9 (CH), 126.5 (CH), 124.8 (CH), 123.6 (CH), 116.6 (C), 105.0 (CH), 29.1 (CH_2), 25.7 (CH_2), 16.0 (SCH_3); *m/z* 419 (100 MH^+), 418 (90, M^+), 370 (25).

4.5. General procedure for dethiomethylation of indazoles 5c, 10, 16 and 20 with Raney Nickel

To a solution of corresponding indazole (1 mmol) in ethanol (30 mL), was added Raney Nickel (W4, four times by weight) and the suspension was stirred at 70–80 °C for 2–6 h (monitored by TLC). The reaction mixture was filtered through sintered funnel and the residue was washed with ethanol. The filtrate was concentrated in vacuo and passed through small silica gel column using 2% EtOAc/hexane as eluent.

4.5.1. 1,3,4-Tris(phenyl)-1*H*-7-indazole (6c). Yield (0.32 g, 92%) as a colourless solid, mp 159–60 °C; [found: C, 86.71; H, 5.21; N, 8.11. $C_{25}H_{18}N_2$ requires C, 86.68; H, 5.24; N, 8.09%]; R_f (20% EtOAc/hexane) 0.68; ν_{max}(KBr) 3071, 1591, 1563, 1495, 1444 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.76–7.82 (3H, m, ArH), 7.53–7.57 (2H, m, ArH), 7.48–7.52 (1H, m, ArH), 7.37 (1H, dt, *J*=1.2, 7.6 Hz, ArH), 7.13–7.22 (7H, m, ArH), 7.03–7.09 (4H, m, ArH); δ_C (100 MHz, $CDCl_3$) 147.6 (C), 140.6 (C), 139.9 (C), 139.2 (C), 137.3 (C), 133.3 (C), 129.42 (CH), 129.40 (CH), 129.37 (CH), 127.5 (CH), 127.3 (CH), 127.2 (CH), 127.1 (CH), 126.9 (CH), 126.8 (CH), 123.4 (CH), 123.0 (CH) 120.7 (C), 109.3 (CH); *m/z* 347 (100, MH^+), 346 (60, M^+).

4.5.2. 1,3-Diphenyl-6,7,8,9-tetrahydro-3*H*-benzo[*e*]indazole (11). Yield (0.26 g, 80%) as a colourless solid, mp 116–7 °C; [found: C, 85.18; H, 6.19; N, 8.59. $C_{23}H_{20}N_2$ requires C, 85.15; H, 6.21; N, 8.63%]; R_f (20% EtOAc/hexane) 0.61; ν_{max}(KBr) 3046, 2935, 1592, 1495, 1442 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.75 (2H, d, *J*=7.8 Hz, ArH), 7.60–7.63 (2H, m, ArH), 7.51–7.54 (2H, m, ArH), 7.50 (1H, d, *J*=8.8 Hz), 7.41–7.47 (3H, m, ArH), 7.33 (1H, t, *J*=7.3 Hz, ArH), 7.16 (1H, d *J*=8.8 Hz, ArH), 2.87 (2H, t, *J*=6.4 Hz, CH_2), 2.68 (2H, t, *J*=6.4 Hz, CH_2), 1.78–1.84 (2H, m, CH_2), 1.66–1.72 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 147.5 (C), 140.1 (C), 138.5 (C), 134.9 (C), 130.9 (C), 130.3 (CH), 129.8 (CH), 129.7 (C), 129.3 (CH), 128.1 (CH), 127.8 (CH), 126.5 (CH), 123.1 (CH), 122.8 (C), 107.9 (CH), 29.4 (CH_2), 27.8 (CH_2), 23.0 (CH_2), 22.9 (CH_2); *m/z* 325 (100 MH^+), 324 (70, M^+).

4.5.3. 1,3-Diphenyl-3,6-dihydroindeno[1,2-*e*]indazole (17). Yield (0.27 g, 75%) as a colourless solid, mp 135–6 °C; [found: C, 87.16; H, 5.09; N, 7.79. $C_{26}H_{18}N_2$ requires C, 87.12; H, 5.06; N, 7.82%]; R_f (20% EtOAc/hexane) 0.65; ν_{max}(KBr) 3051, 2920, 1952, 1592, 1495 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.81 (2H, d, *J*=7.8 Hz, ArH), 7.73 (1H, d, *J*=8.8 Hz, ArH), 7.71 (2H, d, *J*=7.8 Hz, ArH), 7.63 (1H, d, *J*=8.8 Hz, ArH), 7.51–7.58 (6H, m, ArH), 7.39 (1H, t, *J*=7.6 Hz, ArH), 7.19 (1H, t, *J*=7.6 Hz, ArH), 6.96 (1H, t, *J*=7.6 Hz, ArH), 6.55 (1H, d, *J*=7.6 Hz, ArH), 3.99 (2H, s, CH_2); δ_C (400 MHz, $CDCl_3$) 146.8 (C), 144.5 (C), 141.2 (C), 140.5 (C), 140.0 (C), 137.9 (C), 135.4 (C), 134.8 (C), 130.6 (CH), 129.4 (CH), 128.7 (CH), 128.2 (CH), 126.9 (CH), 126.2 (CH), 125.9 (CH), 124.9 (CH), 124.3 (CH), 124.1 (CH), 123.7 (CH), 118.9 (C), 108.9 (CH), 37.5 (CH_2); *m/z* 359 (100, MH+), 358 (60, M^+), 281 (20) 254 (30).

4.5.4. 1,3-Diphenyl-6,7-dihydro-3*H*-naphtho[1,2-*e*]indazole (21). Yield (0.35 g, 95%) as a colourless solid, mp

63–65 °C; [found: C, 87.10; H, 5.39; N, 7.48. $C_{27}H_{20}N_2$ requires C, 87.07; H, 5.41; N, 7.52%]; R_f (20% EtOAc/hexane) 0.69; ν_{max}(KBr) 3045, 2954, 2935, 2886, 1591, 1493, 1450 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.80 (2H, d, J=7.8 Hz, ArH), 7.66 (1H, d, J=8.5 Hz, ArH), 7.55 (2H, t, J=7.8 Hz, ArH), 7.40 (2H, d, J=7.8 Hz, ArH), 7.38 (1H, d, J=8.5 Hz, ArH), 7.21–7.28 (5H, m, ArH), 7.05 (1H, t, J=7.6 Hz, ArH), 6.82 (1H, d, J=7.6 Hz, ArH), 6.60 (1H, t, J=7.6 Hz, ArH), 2.90 (4H, s, CH_2–CH_2); δ_C (100 MHz, $CDCl_3$) 146.9 (C), 141.1 (C), 139.9 (C), 138.2 (C), 134.7 (C), 133.2 (C), 131.9 (C), 130.6 (CH), 129.6 (CH), 129.4 (CH), 127.75 (CH), 127.7 (CH), 127.6 (CH), 126.89 (C), 126.86 (CH), 126.83 (CH), 126.6 (CH), 124.8 (CH), 123.61 (CH), 118.7 (C), 109.2 (CH), 29.5 (CH_2), 29.4 (CH_2); *m/z* 373 (100 MH^+), 372 (80 M^+).

4.5.5. Dehydrogenation of indazole 21 with DDQ. A solution of **21** (0.37 g, 1 mmol) and DDQ (0.45 g, 2 mmol) was refluxed in dioxane for 6 h. The reaction mixture was cooled and poured into ice-cold water and extracted with DCM (3×20 mL). The organic layer was washed with brine (30 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was passed through small silica gel column using 2% EtOAc/hexane as eluent to give **22** (0.34 g, 93%) as a colourless solid, mp 153–154 °C; [found: C, 87.56; H, 4.93; N, 7.59. $C_{27}H_{18}N_2$ requires C, 87.54; H, 4.90; N, 7.56%]; R_f (20% EtOAc/hexane) 0.69; ν_{max}(KBr) 3047, 1950, 1886, 1589, 1499, 1450 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.86–7.93 (5H, m, ArH), 7.82–7.85 (3H, m, ArH), 7.59 (2H, t, J=7.7 Hz, ArH), 7.52–7.55 (2H, m, ArH), 7.39–7.46 (2H, m, ArH), 7.32–7.38 (3H, m, ArH), 6.95 (1H, dt, J=1.2, 7.7 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 148.6 (C), 140.5 (C), 139.6 (C), 136.1 (C), 133.1 (C), 130.6 (CH), 129.5 (CH), 129.3 (CH), 129.2 (CH), 128.8 (C), 128.2 (CH), 127.9 (CH), 127.8 (C), 127.5 (CH), 127.3 (CH), 126.9 (CH), 126.2 (CH), 125.8 (CH), 125.7 (C), 124.2 (CH), 124.1 (CH), 117.1 (C), 110.7 (CH); *m/z* 371 (100 MH^+), 370 (90, M^+), 267 (20).

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Development of predictive models of π-facial selectivity; a critical study of nucleophilic addition to sterically unbiased ketones

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Abstract—Quantum chemical calculations at B3LYP/6-31G* and semiempirical levels have been performed on a series of sterically unbiased ketones, where facial differentiation during nucleophilic additions is electronically induced through distal functional groups. The face selectivity data for fifty-four substrates representing nine different skeleta were computed and compared with the available experimental data on thirty-eight of them. The predictive abilities of various computational methods such as, charge model, hydride model, LiH transition state model, Cieplak hyperconjugation effect estimated by NBO analysis and the cation complexation model have been evaluated. A comparison of the computed and experimental face-selectivity data indicates that the hydride model and the LiH transition state model at the semiempirical levels are the best choices to predict diastereoselectivity. Unexpectedly, the performance of charge, hydride and LiH transition state models are inferior at the B3LYP level compared to the semiempirical methods in predicting the facial selectivities. On the other hand, the Cieplak type hyperconjugation evaluated using the NBO analysis, and cation complexation model are less reliable despite the fact that these two involve higher (B3LYP/6-31G*) level calculations. The inadequate performance of the charge model, NBO and the cation complexation models were traced to their emphasis on only one or two factors which are responsible for stereodifferentiation and undermining of the other subtle aspects involving a combination of orbital and electrostatic effects. On the other hand, the hydride and LiH transition state models, at semiempirical levels, provide reliable results to model the face-selectivities.
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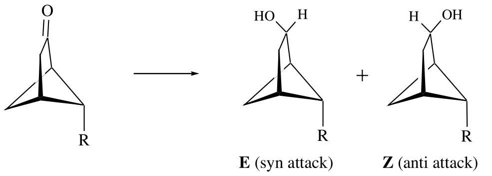
1. Introduction

Induction of face-selectivity in nucleophilic addition to the carbonyl group through remote electronic perturbations is an elegant approach towards stereoselective bond formation. Systems have been designed where the carbonyl group is positioned in an isosteric environment but remote electronic modification through distal substituents can be used to achieve significant levels of diastereoselectivity during nucleophilic additions through face-selection (Scheme 1).[1–3] It is now well recognized that long range electronic effects can play decisive roles in determining π-facial selectivity. However, precise nature of these effects and how exactly they engender stereo-differentiation during nucleophilic addition is not quite clear, despite many incisive experimental probes and a variety of theoretical models.[4–18] Geometric and orbital distortions, electrostatic effects, different types of specific orbital interactions (Felkin-Anh and Cieplak type) have been analyzed to understand the observed results.[4,5] The Cieplak model highlights the importance of *anti*-periplanar C–C σ bond donations to the σ* of the incipient bond C–H at the transition state.[5] The direction of the pyramidalization of the carbonyl carbon upon metal ion/proton complexation was shown to be a simple predictive model to explain the observed face selectivities.[9] The role of electrostatic interactions, Felkin-Anh model, Houk's LiH transition state model, desymmetrization of the π-orbital, etc. were some of the other attempts put forward to rationalize the face selectivities.[4–7] The computationally attractive hydride and charge models at semi-empirical levels proposed earlier were remarkably successful in explaining the observed face selectivities in a large number of sterically unbiased ketones.[6,10–17] Although, the role of solvent effects on the dynamics of stereoselective processes is well recognized, the theoretical approaches involving solvent effects are scarce.[19]



Scheme 1. An example of the nucleophilic addition (all reductions were carried out using $NaBH_4$ at 0 °C with methanol as the solvent) reaction with a sterically unbiased ketone.

Modeling face-selectivity has been a challenging task for

Keywords: Sterically unbiased ketones; π-Facial selectivity; Nucleophilic addition; NBO analysis; Cation complexation model.

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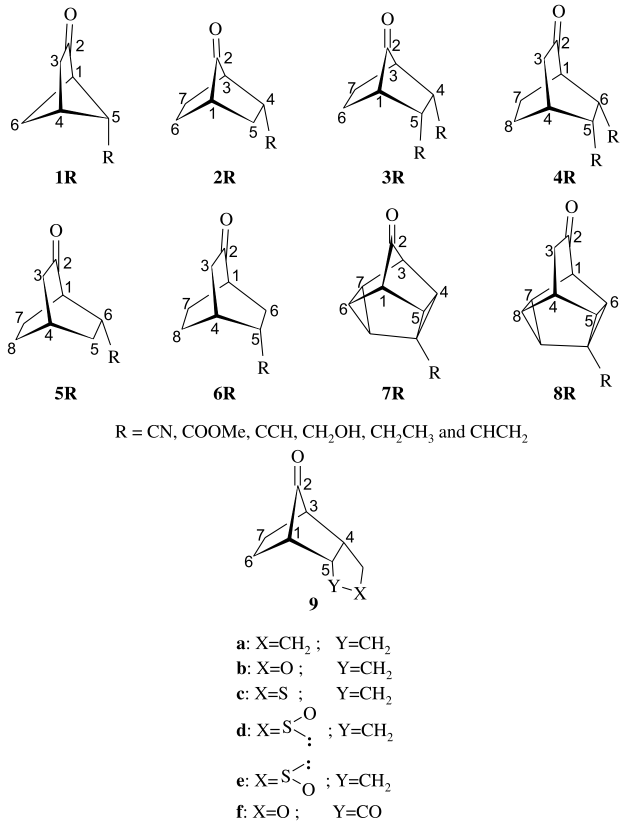
theoretical and computational methodologies.[1–9] The quest for providing simple and chemically intuitive models to predict π-facial selectivities continues to engage attention, though it is increasingly becoming evident that in most cases face-selectivities arise through an interplay of various factors acting either concordantly or discordantly. We make an attempt here to consolidate the experimental results reported from nine different probe systems **1R–8R** and **9a–f** and re-evaluate the observed selectivities in terms of the various existing computational models (Scheme 2).[10–17] All reductions were uniformly carried out using NaBH$_4$ at 0 °C with methanol as the solvent. Considering the importance of the topic, coupled with the lack of a unique reliable predictive model, we undertook a study to critically evaluate the applicability and limitations of various theoretical models. Towards this end, MNDO, AM1 and B3LYP/6-31G* level calculations have been employed to model the π-facial selectivity in these compounds with the charge, hydride and LiH transition state models. Hybrid density functional B3LYP calculations were also performed for the NBO analysis and cation complexation model. In this paper, we attempt to analyze the efficacy of these computational models in predicting the π-facial selectivity in nucleophilic addition reactions to sterically unbiased ketones.



Scheme 2. The nine different probes considered in the study.

2. Methodology

All 54 compounds, **1R–8R** and **9a–f**, selected in the present study, were fully optimized at the B3LYP/6-31G* level and at the semiempirical MNDO[20] and AM1[21] levels. The stationary points thus obtained were characterized by frequency calculations at the semiempirical levels and were confirmed as minima on their respective potential energy surfaces. Various conformers were considered for the compounds with conformationally flexible substituents to locate the global minima at the AM1 level. The transition states corresponding to the LiH addition to the two faces of the carbonyl group were located and characterized as saddle points using the frequency calculations at the semiempirical MNDO and AM1 levels of theory. The location of LiH transition state, charge model and hydride model calculations at B3LYP level were also carried out, but only in those cases (37) where the experimental facial selectivity results are available. NBO analyses were performed using the B3LYP/6-31G* optimized geometries to evaluate the Cieplak type hyperconjugation interactions using the NBO subroutine[22] implemented in the Gaussian 98 program package.[23] Geometry optimizations were also performed on the reactants with a proton complexed to the carbonyl oxygen at the B3LYP/6-31G* level. In the cation complexation model, the face selectivities depend on the direction of the C=O group pyramidalization in the protonated complexes. The semiempirical, AM1 and MNDO, calculations were performed using the MOPAC 2000 program package[24] and the B3LYP calculations were done using the Gaussian 98 suite of programs. The geometric parameters and the nature of the imaginary frequencies were examined using the graphical interface program, MOPLOT.[25]

3. Results and discussion

The results obtained using the charge and hydride models are presented first and are followed by a discussion on the performance of the LiH addition transition state model. In the following sections, the prediction of π-facial selectivity by Cieplak hyperconjugative stabilization, the NBO results, as measured by the interaction energy between the σ-bonds and $\pi^*_{C=O}$ are discussed. The principal dihedral angles of the protonated complexes are given next to examine the performance of the cation complexation model. Finally, a comparison of the predictive abilities of all these computational models is provided.

3.1. Charge and hydride models

The charge and hydride model calculations were carried out by placing a point charge (using sparkles option in MOPAC program package and point charges coupled with the massage keyword in G98) and hydride ion, respectively, 1.4 Å away from the carbonyl carbon on both sides along the trajectory perpendicular to the carbonyl face of the optimized reactant geometries.[6] The preferential facial attack is estimated from the relative energy differences of the two species which are expected to mimic the corresponding putative transition state structures. While the charge model considers exclusively the electrostatic effects, the hydride model takes into account both electrostatic and orbital effects. The predicted face selectivities of the systems under study using the charge and hydride models at the MNDO and AM1 levels are depicted in Table 1. Among the 54 structures considered in the present study, the experimental face selectivity values are available

Table 1. The relative energies (kcal/mol) for *syn* and *anti* face additions calculated using the charge and hydride models at the MNDO and AM1 levels[a] and the experimental diastereoselection

Structure	Charge model				Hydride model				Expt.
	MNDO		AM1		MNDO		AM1		
	syn	*anti*	*syn*	*anti*	*syn*	*anti*	*syn*	*anti*	
1CN	0.26	0.00	0.00	1.85	0.00	0.67	0.00	1.19	75/25
1COOMe	1.65	0.00	0.00	0.56	0.00	0.47	0.00	1.02	66/34
1CCH	2.00	0.00	0.37	0.00	0.04	0.00	0.00	0.38	60/40
1CH$_2$OH	3.95	0.00	3.27	0.00	0.63	0.00	0.23	0.00	48/52
1CH$_2$CH$_3$	4.29	0.00	3.02	0.00	0.78	0.00	0.41	0.00	47/53
1CHCH$_2$	3.06	0.00	3.50	0.00	0.38	0.00	0.68	0.00	44/56
2CN	0.00	1.88	0.00	4.09	0.00	1.40	0.00	1.96	88/12
2COOMe	0.00	0.60	0.00	3.84	0.00	1.26	0.00	2.20	68/32
2CCH	0.88	0.00	0.00	1.05	0.00	0.13	0.00	0.79	69/31
2CH$_2$OH	2.62	0.00	1.25	0.00	0.37	0.00	0.00	0.26	—
2CH$_2$CH$_3$	4.47	0.00	3.28	0.00	1.08	0.00	0.59	0.00	35/65
2CHCH$_2$	3.24	0.00	1.22	0.00	0.84	0.00	0.05	0.00	43/57
3CN	0.00	3.34	0.00	7.73	0.00	2.61	0.00	3.77	—
3COOMe	0.00	1.01	0.00	6.70	0.00	2.22	0.00	4.08	84/16
3CCH	2.04	0.00	0.00	1.57	0.00	0.17	0.00	1.44	—
3CH$_2$OH	6.77	0.00	5.03	0.00	1.39	0.00	0.48	0.00	40/60
3CH$_2$CH$_3$	8.47	0.00	6.77	0.00	2.13	0.00	1.28	0.00	20/80
3CHCH$_2$	6.82	0.00	5.84	0.00	1.71	0.00	1.29	0.00	36/64
4CN	0.00	1.13	0.00	3.73	0.00	1.61	0.00	2.18	—
4COOMe	1.77	0.00	0.00	1.00	0.00	1.72	0.00	2.82	70/30
4CCH	1.89	0.00	0.00	0.51	0.00	0.21	0.00	1.01	—
4CH$_2$OH	4.42	0.00	8.08	0.00	0.95	0.00	0.00	0.81	52/48
4CH$_2$CH$_3$	4.89	0.00	1.75	0.00	1.11	0.00	1.15	0.00	39/61
4CHCH$_2$	5.16	0.00	4.09	0.00	0.90	0.00	0.51	0.00	50/50
5CN	0.00	0.66	0.00	4.59	0.00	0.88	0.00	0.98	—
5COOMe	0.45	0.00	0.00	7.24	0.00	0.60	0.00	0.75	65/35
5CCH	1.30	0.00	0.00	2.90	0.03	0.00	0.00	0.07	—
5CH$_2$OH	3.86	0.00	0.80	0.00	1.00	0.00	0.33	0.00	—
5CH$_2$CH$_3$	3.77	0.00	0.87	0.00	0.89	0.00	0.87	0.00	—
5CHCH$_2$	3.56	0.00	0.46	0.00	0.88	0.00	1.01	0.00	—
6CN	0.00	0.90	0.13	0.00	0.00	0.89	0.00	1.41	—
6COOMe	0.00	0.16	1.94	0.00	0.00	0.77	0.00	1.53	62/38
6CCH	0.41	0.00	1.99	0.00	0.00	0.32	0.00	1.06	—
6CH$_2$OH	1.31	0.00	3.89	0.00	0.00	0.16	0.00	0.88	—
6CH$_2$CH$_3$	3.04	0.00	3.13	0.00	0.27	0.00	0.00	0.45	—
6CHCH$_2$	1.60	0.00	3.41	0.00	0.03	0.00	0.00	0.54	—
7CN	0.00	3.99	0.00	4.53	0.00	1.65	0.00	1.67	84/16
7COOMe	0.00	4.89	0.00	5.02	0.00	1.70	0.00	1.89	79/21
7CCH	0.00	2.17	0.00	3.13	0.00	0.93	0.00	1.18	76/24
7CH$_2$OH	0.00	1.53	0.00	2.45	0.00	0.81	0.00	0.96	56/44
7CH$_2$CH$_3$	0.00	0.95	0.00	0.55	0.00	0.55	0.00	0.32	48/52
7CHCH$_2$	0.00	1.37	0.00	1.62	0.00	0.72	0.00	0.68	60/40
8CN	0.00	1.82	0.00	1.17	0.00	0.81	0.00	0.71	59/41
8COOMe	0.00	1.43	0.00	1.55	0.00	0.69	0.00	0.52	59/41
8CCH	0.00	1.08	0.00	1.29	0.00	0.48	0.00	0.44	57/43
8CH$_2$OH	0.35	0.00	0.00	0.01	0.05	0.00	0.00	0.13	53/47
8CH$_2$CH$_3$	0.00	0.58	0.00	0.01	0.00	0.31	0.00	0.08	—
8CHCH$_2$	0.00	0.46	0.00	0.58	0.00	0.28	0.00	0.26	57/43
9a	6.41	0.00	3.93	0.00	1.20	0.00	0.34	0.00	25/75
9b	4.58	0.00	0.70	0.00	0.25	0.00	0.00	0.72	47/53
9c	4.05	0.00	1.54	0.00	0.26	0.00	0.00	0.36	44/56
9d	3.65	0.00	2.67	0.00	0.18	0.00	0.00	0.14	42/58
9e	1.30	0.00	0.00	3.12	0.00	1.02	0.00	2.01	53/47
9f	0.76	0.00	0.00	4.82	0.00	1.35	0.00	2.46	84/16

[a] A value of 0.00 denotes a preference of the corresponding side attack.

for 38 substrates and enable an assessment of the predictive ability of a given computational model and are collected in the same Table. The B3LYP relative energies of the charge and hydride model transition states of the compounds for which experimental data are available are depicted in Table 2.[26]

Charge model at AM1 level reproduces the observed diastereoselection for all **1R** compounds except when R=CCH, whereas MNDO uniformly predicts *anti* addition for all **1R** compounds, which results in incorrect prediction in a few cases. On the other hand, hydride model at both MNDO and AM1 levels reproduces the experimental results in a fairly satisfactory manner. Importantly, the trends in the computed energy difference between the *syn* and *anti* attack correlate well with the observed selectivity. Charge model with AM1 method reproduces the π-facial selectivity of **2R** for all the substituents, but the MNDO level fails to account

Table 2. The relative energies (kcal/mol) for *syn* and *anti* face additions calculated using the charge, hydride and LiH TS models at the B3LYP/6-31G* level[a]

Structure	Charge		Hydride		LiH	
	syn	*anti*	*syn*	*anti*	*syn*	*anti*
1CN	0.00	3.70	0.00	1.28	0.00	1.16
1COOMe	0.00	2.81	1.95	0.00	0.00	0.46
1CCH	0.00	3.17	0.15	0.00	0.00	0.41
1CH$_2$OH	0.00	0.76	1.03	0.00	0.14	0.00
1CH$_2$CH$_3$	0.00	2.00	1.89	0.00	0.09	0.00
1CHCH$_2$	0.00	3.40	1.46	0.00	0.00	0.34
2CN	0.00	5.51	0.00	2.66	0.00	2.24
2COOMe	0.00	4.75	0.00	3.69	0.00	1.57
2CCH	0.00	4.82	0.07	0.00	0.00	1.05
2CH$_2$CH$_3$	0.00	2.77	4.51	0.00	0.38	0.00
2CHCH$_2$	0.00	3.99	0.00	0.63	1.08	0.00
3COOMe	0.00	7.87	0.00	3.16	0.00	1.65
3CH$_2$OH	0.00	3.07	4.52	0.00	0.14	0.00
3CH$_2$CH$_3$	0.00	5.43	7.82	0.00	0.51	0.00
3CHCH$_2$	0.00	5.99	9.56	0.00	0.17	0.00
4COOMe	0.00	0.00	0.00	0.00	0.00	1.42
4CH$_2$OH	0.00	0.91	0.00	1.84	0.29	0.00
4CH$_2$CH$_3$	0.00	1.58	6.52	0.00	0.27	0.00
5COOMe	0.00	2.19	0.10	0.00	0.00	2.08
6COOMe	0.00	1.73	0.00	1.56	0.00	0.39
7CN	0.00	0.00	0.00	8.57	0.00	0.78
7COOMe	1.14	0.00	0.00	7.03	0.00	0.15
7CCH	0.06	0.00	0.00	6.21	0.00	0.46
7CH$_2$OH	1.26	0.00	0.21	0.00	0.00	0.31
7CH$_2$CH$_3$	0.00	0.37	0.25	0.00	0.06	0.00
7CHCH$_2$	0.32	0.00	0.00	3.79	0.00	0.09
8CN	0.00	0.79	0.00	2.62	0.00	0.35
8COOMe	1.17	0.00	0.00	0.30	0.49	0.00
8CCH	0.00	0.55	0.00	1.64	0.00	0.08
8CH$_2$OH	0.00	0.08	0.20	0.00	0.02	0.00
8CHCH$_2$	0.00	0.41	0.00	1.58	0.11	0.00
9a	0.00	3.76	7.45	0.00	0.87	0.00
9b	0.00	5.02	4.49	0.00	0.00	0.15
9c	0.00	6.43	2.65	0.00	0.00	0.78
9d	0.00	5.48	0.63	0.00	0.00	0.93
9e	0.00	9.09	0.00	1.22	0.00	2.44
9f	0.00	5.48	2.19	0.00	0.00	1.15

[a] A value of 0.00 denotes a preference of the corresponding side attack.

for the *syn* selectivity of **2CCH**. The results obtained with hydride model at both MNDO and AM1 methods are in good agreement with experimental results.

In substrates **3R**, charge and hydride models at both AM1 and MNDO levels reproduce correctly the experimentally observed facial preferences. All methods predict uniform *syn* preference for **3CN** and **4CN**, for which the experimental data is not available. Similarly, for **3CCH**, where the experimental selectivity is not known, hydride and AM1 charge models predict *syn* selectivity whereas MNDO charge model predicts *anti* addition. In the case of **4R**, hydride model at AM1 level is relatively more satisfactory but the loss of selectivity for **4CHCH$_2$** could not be reproduced. The experimental selectivities for **5COOMe** and **6COOMe** are reproduced by both hydride and charge models at the AM1 level. It is also predicted that for **5CN** and **6CN**, the nucleophile would prefer *syn* attack compared to *anti* attack. Similarly, computation reveals that **5CCH** and **6CCH** favor *syn* addition, whereas **5CH$_2$OH**, **5CH$_2$CH$_3$** and **5CHCH$_2$** prefer *anti* addition. For **6R**, charge and hydride models predict opposite selectivities in most of the cases.

Table 3. The relative energies of the LiH addition transition[a] states from the *syn* and *anti* side obtained at MNDO and AM1 levels. All values are given in kcal/mol

Structure	Transition state			
	MNDO		AM1	
	syn	*anti*	*syn*	*anti*
1CN	0.00	0.26	0.00	0.58
1COOMe	0.05	0.00	0.00	0.34
1CCH	0.14	0.00	0.00	0.17
1CH$_2$OH	0.48	0.00	0.27	0.00
1CH$_2$CH$_3$	0.32	0.00	0.24	0.00
1CHCH$_2$	0.30	0.00	0.24	0.00
2CN	0.00	0.55	0.00	0.93
2COOMe	0.00	0.37	0.00	0.80
2CCH	0.00	0.00	0.00	0.42
2CH$_2$OH	0.20	0.00	0.03	0.00
2CH$_2$CH$_3$	0.31	0.00	0.20	0.00
2CHCH$_2$	0.25	0.00	0.55	0.00
3CN	0.00	1.07	0.00	1.87
3COOMe	0.00	0.55	0.00	1.57
3CCH	0.01	0.00	0.00	0.83
3CH$_2$OH	0.57	0.00	0.29	0.00
3CH$_2$CH$_3$	0.65	0.00	0.47	0.00
3CHCH$_2$	0.53	0.00	0.22	0.00
4CN	0.00	0.76	0.00	1.18
4COOMe	0.00	0.22	0.00	0.69
4CCH	0.01	0.00	0.00	0.50
4CH$_2$OH	0.59	0.00	0.61	0.00
4CH$_2$CH$_3$	0.49	0.00	0.35	0.00
4CHCH$_2$	0.39	0.00	0.21	0.00
5CN	0.00	0.46	0.00	0.90
5COOMe	0.00	0.11	0.00	0.74
5CCH	0.01	0.00	0.00	0.49
5CH$_2$OH	0.48	0.00	0.27	0.00
5CH$_2$CH$_3$	0.30	0.00	0.12	0.00
5CHCH$_2$	0.28	0.00	0.03	0.00
6CN	0.00	0.33	0.00	0.32
6COOMe	0.00	0.21	0.00	0.13
6CCH	0.00	0.01	0.00	0.04
6CH$_2$OH	0.08	0.00	0.16	0.00
6CH$_2$CH$_3$	0.14	0.00	0.25	0.00
6CHCH$_2$	0.12	0.00	0.15	0.00
7CN	0.00	0.43	0.00	0.45
7COOMe	0.00	0.33	0.00	0.32
7CCH	0.00	0.15	0.00	0.19
7CH$_2$OH	0.00	0.22	0.00	0.30
7CH$_2$CH$_3$	0.00	0.07	0.00	0.02
7CHCH$_2$	0.00	0.07	0.00	0.08
8CN	0.00	0.29	0.00	0.28
8COOMe	0.00	0.20	0.00	0.14
8CCH	0.00	0.10	0.00	0.11
8CH$_2$OH	0.00	0.01	0.00	0.02
8CH$_2$CH$_3$	0.00	0.04	0.08	0.00
8CHCH$_2$	0.00	0.03	0.00	0.04
9a	0.47	0.00	0.17	0.00
9b	0.10	0.00	0.00	0.36
9c	0.07	0.00	0.00	0.29
9d	0.18	0.00	0.00	0.21
9e	0.00	0.49	0.00	1.28
9f	0.00	0.47	0.00	1.02

[a] A value of 0.00 denotes a preference of the corresponding side attack.

All the methods applied here correctly reproduce the experimentally observed *syn* preference, except for **7CH$_2$CH$_3$**, and encouragingly the computed magnitudes of the relative energies match with the ratios highlighting the superiority of hydride model. However, the marginal *anti* preference of **7CH$_2$CH$_3$** could not be reproduced at any level of theory albeit the magnitude of the computed energy differences is negligibly small. The consistently observed *syn* selectivity of system **8R** with any type of substituent is supported by the computed results.

3.2. LiH addition transition state model

LiH addition transition states have been widely used to model the real transition state in nucleophilic addition to ketones.[7] The transition states were obtained by approaching the Li–H, parallel to the C=O along the plane, where H and Li are oriented towards C and O of carbonyl respectively on either side of the π-plane. Tables 2 and 3 depict the energy differences between the *syn* and *anti* transition states obtained at the DFT, and the semiempirical levels of theory respectively; comparison with the available experimental results points to an excellent predictive ability of this approach especially at the semiempirical levels. The relative energies of the *syn* and *anti* side attacks of LiH to **1R** computed at the AM1 level explain the diastereoselection, whereas performance at the MNDO level is slightly less satisfactory. However, the qualitative trends of the relative energy differences correlate well with the experimental values. Similar to **1R**, while AM1 could reproduce the experimental selectivity for **2R**, the MNDO level could not differentiate the two faces as the energies of *syn* and *anti* transition states are the same for **2CCH**. *anti*-Selectivity is predicted for **2CH$_2$OH** by both AM1 and MNDO levels, for which the experimental data is not available. However, both AM1 and MNDO levels reproduce the observed diastereoselection in **2R**. Experimental results on **3CN**, **4CN**, **5CN** and **6CN** are not known; LiH transition states predict preferential *syn* attack at both levels, similar to the charge and hydride models. The relative energies of the *syn* and *anti* LiH transition states of **3R** very well account for the observed selectivities in **3R**. Encouragingly, both economically attractive MNDO and AM1 levels perform equally well for all probe systems except **1R** and **9a–f**. Similar to the situation in the charge and hydride models, the performance of the hybrid density functional theory level is inferior compared to that of the semiempirical methods.

3.3. NBO analysis

The second order perturbative analysis in the NBO procedure is used to estimate the Cieplak type hyperconjugative effect, namely the interaction energies between the σ of the C–C bond *anti*-periplanar to the incipient C–H bond being formed and the π^* of the carbonyl.[8] Table 4 gives the interaction energies between all the Cieplak type interactions (involving the primary anti-periplanar σ_{C-C} and other involved σ bonds) with $\pi^*_{C=O}$ from the *syn* and *anti* sides obtained at the B3LYP/6-31G* level. The NBO analysis could reproduce the experimental selectivities only in about 40% of the cases. The highly electron withdrawing CN substituted compounds are expected to show smaller interaction energies between the σ of *syn* C–C bond and the $\pi^*_{C=O}$ compared to those between the σ of *anti* C–C bond and the $\pi^*_{C=O}$. But, in **1CN** and **2CN**, the interaction energies in the *syn* side C–C bond are greater than those from the *anti* side C–C bond indicating an *anti* preference. Also, the trend followed by the interaction energies does not correlate well with the experimental data.[27]

Table 4. The interaction energies (in kcal/mol) between all the Cieplak type interactions with $\pi^*_{C=O}$ using NBO along with the principle dihedral angles (in degrees) in the proton complexed reactants obtained at the B3LYP/6-31G* level.[a] All values are given in degrees

Structure	NBO ($\sigma-\pi^*$)		Cation complexation model			
	syn	*anti*	*syn*		*anti*	
			D1	D2	D3	D4
1CN	9.19	8.75	138.0	—	136.7	—
1COOMe	9.47	8.82	133.4	—	141.5	—
1CCH	9.48	8.85	132.1	—	143.3	—
1CH$_2$OH	9.32	9.19	135.0	—	139.4	—
1CH$_2$CH$_3$	9.37	9.14	130.4	—	144.4	—
1CHCH$_2$	9.67	8.94	130.7	—	144.8	—
2CN	7.33	6.92	128.9	128.5	120.2	121.2
2COOMe	7.33	7.40	124.9	127.5	123.3	122.6
2CCH	7.47	7.00	123.0	123.1	126.4	126.7
2CH$_2$CH$_3$	7.40	7.25	116.6	120.5	131.3	129.6
2CHCH$_2$	7.29	7.43	120.1	125.4	128.2	125.0
3COOMe	7.63	7.23	127.4[b]	124.0[b]	120.0[b]	124.0[b]
3CH$_2$OH	7.35	7.27	115.6[b]	114.7[b]	132.6[b]	132.6[b]
3CH$_2$CH$_3$	7.59	7.08	114.2[b]	112.3[b]	133.7[b]	135.9[b]
3CHCH$_2$	7.81	6.70	112.1[b]	112.9[b]	135.9[b]	135.2[b]
4COOMe	6.74	8.08	121.2	—	122.0	—
4CH$_2$OH	7.16	8.10	118.1	—	124.7	—
4CH$_2$CH$_3$	8.63	6.67	114.7	—	128.8	—
5COOMe	7.68	7.63	131.1	—	112.9	—
6COOMe	7.27	7.83	125.4	—	119.6	—
7CN	7.11	8.09	147.1	146.3	105.9	106.9
7COOMe	7.09	8.26	146.6	145.8	106.6	107.4
7CCH	7.30	8.10	147.0	146.2	106.2	107.1
7CH$_2$OH	7.92	7.78	105.8	106.7	147.7	146.9
7CH$_2$CH$_3$	7.87	7.78	107.1	107.9	146.4	145.6
7CHCH$_2$	7.37	8.09	144.9	144.1	108.4	109.2
8CN	7.39	7.48	142.1	—	122.9	—
8COOMe	7.38	7.52	122.9	—	126.4	—
8CCH	7.46	7.53	120.4	—	128.7	—
8CH$_2$OH	7.54	7.53	118.9	—	130.4	—
8CHCH$_2$	7.52	7.52	116.9	—	132.5	—
9a	7.53	6.92	111.1	110.5	135.9	136.7
9b	7.52	6.95	113.7	113.4	133.5	133.7
9c	7.23	7.06	116.4	116.1	130.3	130.5
9d	7.08	7.03	110.4	110.0	136.6	136.9
9e	7.13	7.08	126.1	126.1	120.7	120.7
9f	7.59	6.84	121.3	116.3	127.0	131.1

[a] If D1>D3 and D2>D4, syn attack is preferred and if D3>D1 and D4>D2, *anti* attack is preferred. For **1R**, D1=∠O-2-1-5 and D3=∠O-2-1-6; for systems **2R**, **3R**, **7R** and **9a–f**, D1=∠O-2-1-5, D2=∠O-2-3-4, D3=∠O-2-1-6 and D4=∠O-2-3-7; and for systems **4R**, **5R**, **6R** and **8R**, D1=∠O-2-1-6 and D3=∠O-2-1-7. Here, O denotes the carbonyl carbon, where the nucleophilic addition occurs.

[b] Taken from Ref. 28.

3.4. Cation complexation model

This approach critically analyzes the pyramidalization of the carbonyl carbon or the tilting of the carbonyl group towards one of the sides upon complexation with proton or cations like Li$^+$ and Na$^+$.[9] According to this model, if the carbonyl group is tilted towards one of the sides upon complexation, the nucleophilic addition will be preferred from the other side. The principal dihedral angles in the proton complexed reactants, which estimate the pyramidalization of the carbonyl carbon upon proton complexation, obtained at the B3LYP/6-31G* level are given in Table 4. Calculations were done only on those systems where the experimental data are available. The atom numbering used in the Table is illustrated in Scheme 2. This model reproduces the selectivity in about 70% of the

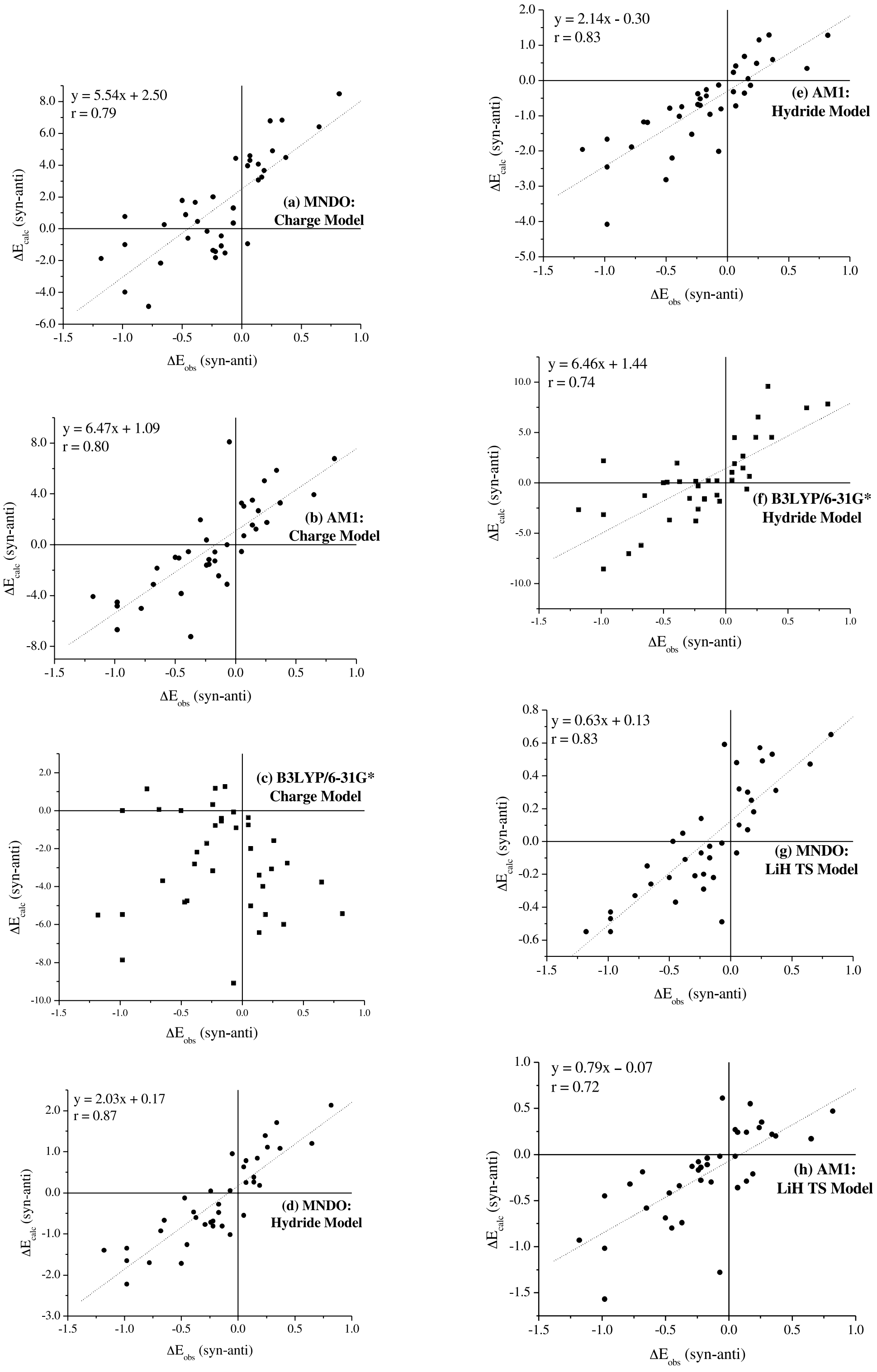


Figure 1 (*legend opposite*)

experimental cases, however, a closer look reveals that the degree of tilting of the carbonyl group does not seem to have any correlation with the extent of selectivity. For example, the experimental results indicate that **9e** has marginal preference for *syn* (*syn*:*anti* ratio is 53:47), this model correctly predicts *syn* selectivity. However, **9f** is observed to undergo preferential *syn* addition (*syn*:*anti* ratio is 84:16); the cation complexation model predicts a preferential *anti* attack. Thus the cation complexation model, which considers primarily one aspect of all the possible factors, does not seem to have a reliable predictive ability, especially in the presence of overriding electrostatic and orbital effects around the transition state region along the trajectory of the nucleophilic attack.

3.5. Assessing the predictive ability

The foregoing discussion highlights the intricacies of the

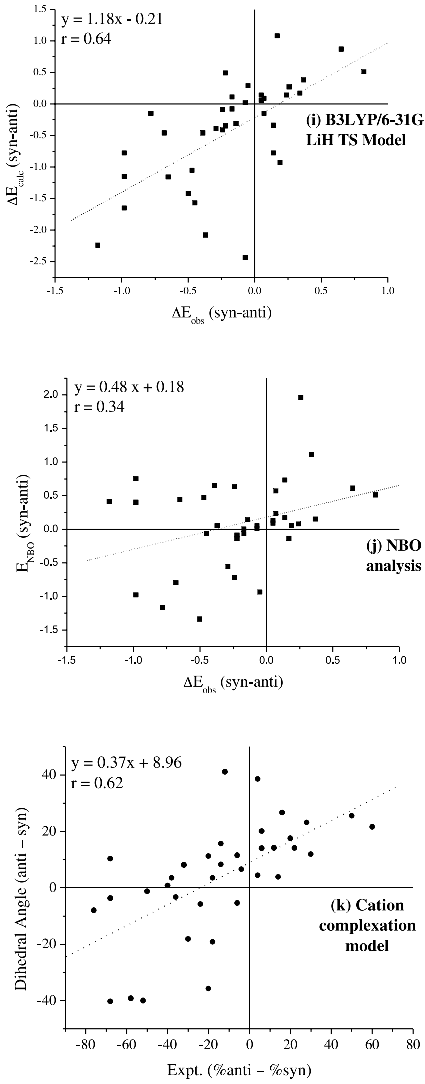


Figure 1. The correlation of the experimental face selectivities with the predicted selectivity values by charge model (a, b, c), hydride model (d, e, f), LiH transition state model (g, h, i), NBO analysis (j) and cation complexation model (k). The ‘*r*’ values corresponding to each of the linear fit are given in the corresponding figures.

problem and it is necessary to ascertain the predictive ability of a given model in quantitative terms. The relative performance of the eight theoretical models is assessed through a comparison of the predicted values with the available experimental results, Figure 1.

Figure 1a–k gives the correlation of the observed and the computed facial selectivities obtained using various computational models discussed above. In all the figures, the points, which lie within the diagonal boxes (lower left side to upper right side), provide the correct qualitative picture. The linear equations employed to fit the data of the computed selectivities with the experimental ones along with the correlation coefficients are given in Figure 1. A quick look at the figures indicate that while most points lie within the correct region, the number of points present outside the boxes is significant for the NBO and cation complexation models. The correlation constant (*r*) values for the linear fits given in the corresponding figures indicate the quality of the linear fit of each of the method and the intercept value in the linear equation gives the deviation from the perfect prediction. The comparison of the ‘*r*’ values indicates that the hydride model and the LiH TS model, especially at the MNDO level, are better compared to the other models. A quick look at Figure 1 indicates that the performance of hydride and LiH transition state models is consistently better than that of charge model. Such results can be understood due to the complete neglect of orbital interactions in the charge model, while the hydride and LiH transition state models incorporate both charge and overlap effects. However, it is quite surprising to see that the performance of generally more reliable B3LYP method is clearly inferior to both the semiempirical methods. NBO analysis fails in predicting both the direction of the selectivity and the extent of selectivity. Even though the cation complexation model is successful in predicting the facial preferences in about 70% of the cases, the trends in the predicted selectivity do not match with the experimental data.

While predicting the direction of selectivity is a crucial first step for any model, estimation of the extent of selectivity is also an equally important aspect. The predictive abilities of molecular modeling approaches need not have a correct basis to provide data that agrees with experiments and chance correlations could not be avoided.[29] Thus, both factors namely the prediction of the direction and the extent have to be taken to ascertain the credibility of a given model. Thus, the quality of linear correlation between the *syn*/*anti* preferences and the parameters chosen to distinguish the preferences is drawn to assess the reliability of the models. Here, the correlation coefficient value *r* gives an idea about the ability of the methods to yield reasonable trends. Thus, the statistical analysis indicates that the hydride model were the best choices. However, the correlation coefficient values of 0.62 and 0.34 for the cation complexation and NBO analyses indicate the absolute limitations of these models in predicting the extent of selectivity. The intercept value close to zero and the correlation coefficient closer to unity gauges the performance of a given model. Therefore, the analysis quantifies the better performance of hydride and LiH transition state models compared to the rest.

4. Conclusions

The present study reports semiempirical (MNDO and AM1) and hybrid density functional theory (B3LYP) calculations on several probe systems wherein the two faces of the carbonyl group are in isosteric environment, but are electronically differentiated. The predictive ability of several methods such as the hydride model, the charge model, the LiH transition state model, Cieplak hyperconjugation effect estimated by NBO analysis and cation complexation model are critically analyzed in both qualitative and quantitative terms. Our studies reveal that the hydride model, at both MNDO and AM1 levels, is a sensible way to obtain quick insights into the π-facial selectivity in the nucleophilic additions to sterically unbiased ketones. Clearly, hydride, LiH transition state and charge models perform better at the semiempirical levels compared to the computationally expensive B3LYP level of theory, a result which is difficult to comprehend. The performance of the

LiH addition transition state model is comparable to that of the hydride model. The computationally expensive calculations of NBO and cation complexation models are aimed at singling out one or two key factors, which are responsible for the stereodifferentiation. Nonetheless, even at the B3LYP level, the predictive ability of the hydride and LiH transition state models are better compared to the charge model, Cieplak type hyperconjugation interactions from NBO analysis and cation complexation model. However, considering the fact that the preference for facial selectivity depends on an intricate mix of mutually independent and subtle electronic and electrostatic factors, any model that relies heavily on a single aspect is not expected to yield reliable results. The superior performance of the hydride model to predict the π-facial selectivities over the other models in this class of compounds indicates its ability to judiciously accommodate the cumulative effects due to orbital and electrostatic origins. Thus, the present study proposes that hydride model is a reliable and economic model to estimate the π-facial selectivity of nucleophilic addition to sterically unbiased ketones.

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Tetrahedron

1,3-Dipolar cycloaddition of stabilised and non-stabilised azomethine ylides derived from uracil polyoxin C (UPoC): access to nikkomycin analogues

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Abstract—Cascade thermal and decarboxylative cycloaddition reactions of uracil polyoxin C (UPoC) with mono- and di-carbonyl compounds in the presence of a dipolarophile leads, via stabilised and non-stabilised azomethine ylides respectively, to a series of polyoxin cycloadducts related to Nikkomycin B in good to excellent yields and high diastereoselectivity.

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1. Introduction

The nikkomycins[1] and neopolyoxins[2] are a group of nucleoside di- and tri-peptide antibiotics produced by *Streptomyces tandea* and *S. cocaoi ssp. asoensis*. Representative examples of these intriguing natural products include nikkomycin B (**1**), nikkomycin J (**2**) and nikkomycin Bx (**3**). These compounds are potent chitin synthetase inhibitors and they exhibit fungicidal, insecticidal and acaricidal activities.[1,2] The inhibition of *botrytis cinerea*, *pyricularia oryzae*, and *candida albicans* by the neopolyoxins is particularly noteworthy.[2]

Uracil polyoxin C (UPoC)[3] (**4**) is the carboxy terminal nucleoside amino acid common to many members of the polyoxin and nikkomycin family and is a versatile relay intermediate for the synthesis of analogues.[2,4] The polyoxins (**5**)[5] exhibit marked and selective activity against phytopathogenic fungi whilst being non-toxic to bacteria, plants, or animals.[6] Their effectiveness against *candida albicans* is particularly important since this organism causes major disease problems for AIDS patients.[7] As a consequence of these biological effects derivatives of these compounds are attractive targets for synthesis.

The decarboxylative route to azomethine ylides via imines of α-amino acids when coupled to a subsequent cycloaddition[8–11] has provided access to bicyclic pyrrolidines,[8] biomimetic examples of the mode of action of pyridoxal and pyruvate based enzyme decarboxylases,[9] a new route to spirocyclic and bridged-ring compounds,[10,11] and medium rings via ring expansion of cyclic secondary α-amino acids.[12] This versatile methodology has now been applied to the synthesis of new analogues of UPoC.

2. Decarboxylative cycloaddition reactions

Cascade thermal reactions of uracil polyoxin C (UPoC) with mono- and di-carbonyl compounds in the presence of *N*-methylmaleimide (NMM) and *N*-phenyl maleimide (NPM) leads, via an intermediate azomethine ylide, to a series of polyoxin cycloadducts in excellent yield.

The reactions were performed in DMF using 2 mol equiv. of carbonyl compound and 1 mol equiv. of *N*-methyl maleimide or *N*-phenyl maleimide. Thus UPoC (**4**) reacted with methyl pyruvate and NMM or NPM (DMF, 70 °C, 26 h) to afford 9:1 and 12:1 mixtures of cycloadducts (**6a**, **7a**) and (**6b**, **7b**) respectively in 94 and 96% yield. The relative stereochemistry of the pyrrolidinyl substituents of the major chiral *endo*-isomers (**6a**) and (**6b**) were determined from NOE data and 2D-COSY studies. In the case of (**6a**) irradiation of 3-H effected enhancement of the signals for 1-Me (6%) and 3a-H (7.95%) whilst irradiation of 3a-H effected enhancement of the signals for 3-H (5.65%) and 6a-H (4.4%). Irradiation of 1-Me effected enhancement of

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Keywords: Uracil polyoxin C; Nikkomycin; Azomethine ylide; 1,3-Dipolar cycloaddition; Chitin synthetase inhibitors; Decarboxylative cycloaddition; Semi-empirical; Calculations.

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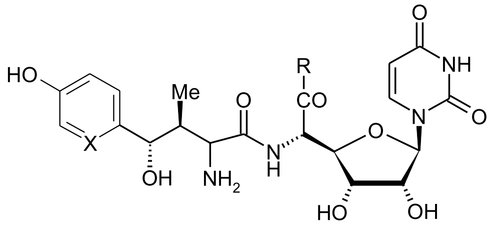
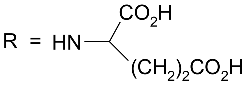
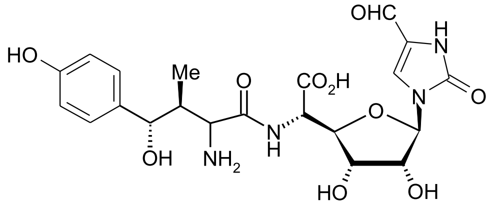


(1) R = OH, X = CH

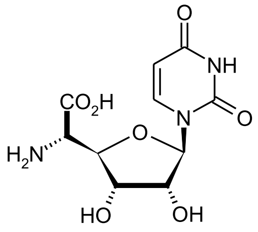
(2) R =



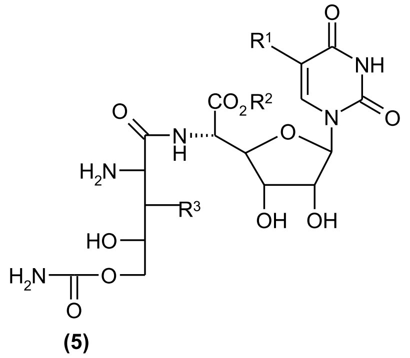
$R = HN{-}CH(CO_2H)(CH_2)_2CO_2H$, X = N



(3)



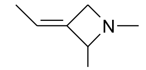
(4)



(5)

$R^1 = CH_2OH, CO_2H, CH_3, H$

R^2 =



$R^3 = OH, H$

the signals for 6a-H (4.6%) and 3-H (2.25%). Irradiation of 3-H effected enhancement of coincident signals for 2′-H, 3′-H and 4′-H (11.3%) and irradiation of 3a-H effected enhancement of the signals for 2′-H, 3′-H and 4′-H (4.3%). There are two possible diastereoisomeric cycloadducts (**6a**) and (**7a**), arising from *endo*-cycloaddition to either diastereotopic face of the azomethine ylide *syn* 1 (**8**),[8,11] and these are indistinguishable from these data. However, the absolute stereochemistry of (**6b**) was determined by an X-ray crystal structure (Fig. 1).

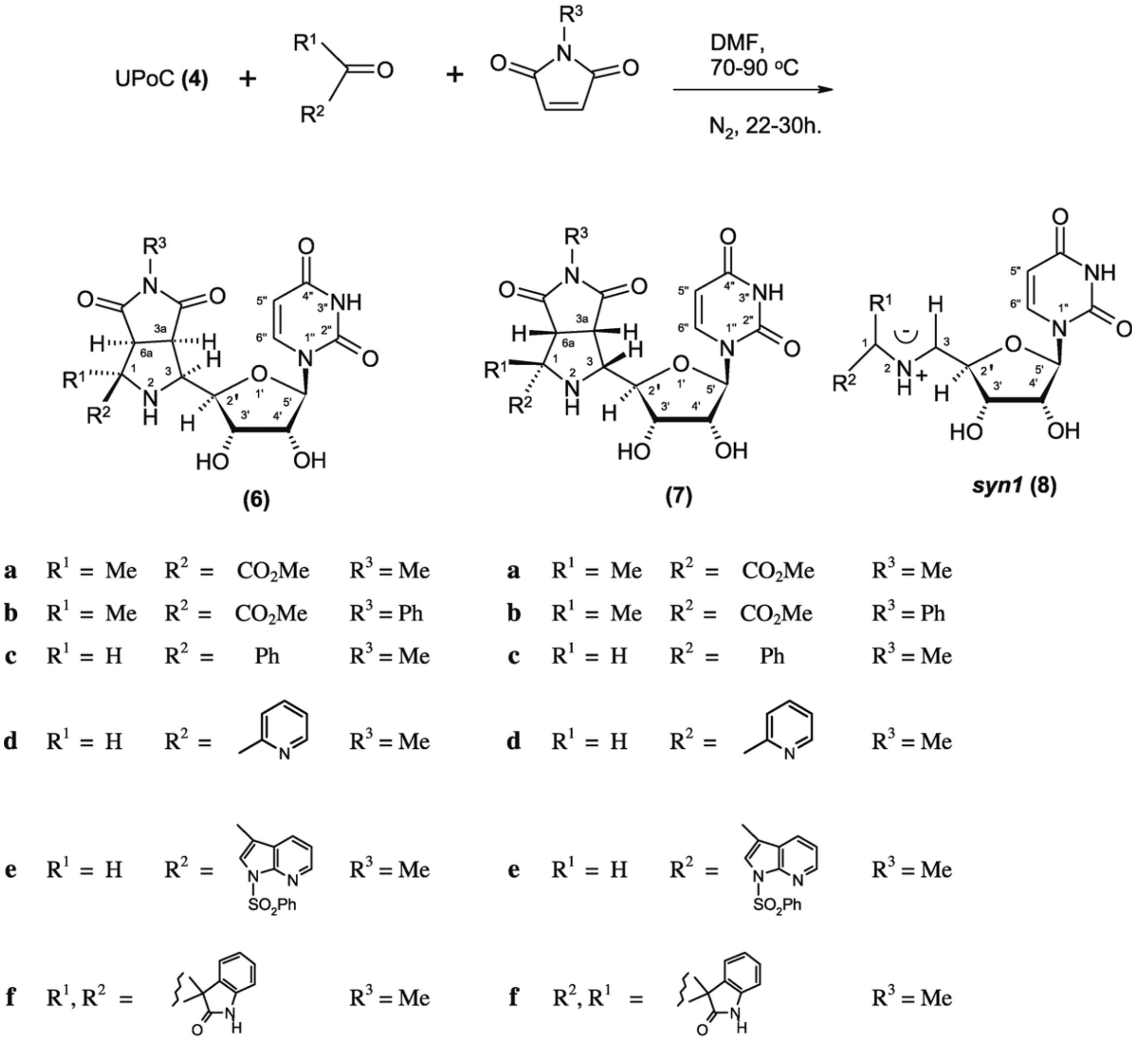
Figure 1 unequivocally establishes the absolute stereochemistry of the new stereocentres created in the cycloaddition as 1*S*,3*S*,3a*S* and 6a*R*. Hence the cycloaddition proceeds via *endo* addition to the 1 (si), 3 (re)- face of *syn* 1 (**8**). The minor isomers could not be isolated in a pure form. The stereochemical preference for the formation of dipole *syn* 1 (**8**) is discussed in detail later.

UPoC (**4**) reacted with benzaldehyde and NMM under the same conditions over 24 h to yield a 3:1 mixture of cycloadducts (**6c**) and (**7c**) in 78% combined yield. The minor isomer could not be isolated in a pure form. The stereochemistry of the major *endo*-product (**6c**) was established from NOE data and 2D-COSY studies. Thus irradiation of 3-H effected enhancement of coincident signals for 3a-H+6a-H (4.2%) and irradiation of 1-H effected enhancement of the signals for 3a-H+6a-H (11.8%) and 3-H (4.9%). Irradiation of 3-H effected enhancement of the signals for 3′-H (8.2%) and irradiation of 1-H effected enhancement of the signals for 2′-H (9.7%). Irradiation of 2′-H effected enhancement of the signals for 1-H (9.7%) and 3a-H+6a-H (4.35%).

Reaction of (**4**) with 2-pyridine carboxaldehyde and NMM occurred over 22 h in DMF at 65 °C to afford a 4:3 mixture of cycloadducts (**6d**) and (**7d**) (52%). The isomeric mixture could not be separated and analysis of the ^1H NMR spectrum of the mixture was difficult due to overlapping signals. Hence the relative stereochemistry of the major isomer was not firmly established but the protons were assigned based on 2D-COSY studies and by analogy with related systems.

The product from the reaction (DMF, 80 °C, 22 h) of UPoC (**4**), *N*-phenylsulphonyl indolyl-3-aldehyde and NMM consisted of a 1:1 mixture of cycloadducts (**6e**) and (**7e**) in 74% yield. The relative stereochemistry of the pyrrolidinyl substituents of (**6e**) was established from NOE data and 2D-COSY studies. Thus irradiation of 3a-H effected enhancement of the signals for 6a-H (5.5%) and 3-H (3.5%) whilst irradiation of 1-H effected enhancement of the signals for 6a-H (6%).

Isatin, UPoC (**4**) and NMM react under similar conditions (DMF, 90 °C, 30 h) affording a 2:1 mixture of cycloadducts (**6f**) and (**7f**) in 82% combined yield. The second most abundant isomer could not be isolated in a pure form. The *cis*-3,3a-stereochemistry of the pyrrolidine ring of the major isomer (**6f**) was determined from NOE data [irradiation of 3a-H effected enhancement of the signals for 3-H (15%)]



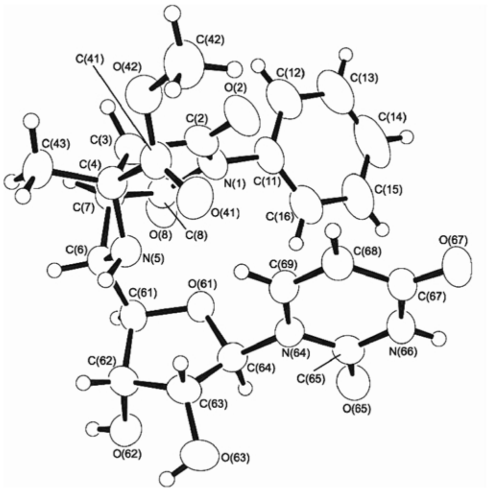
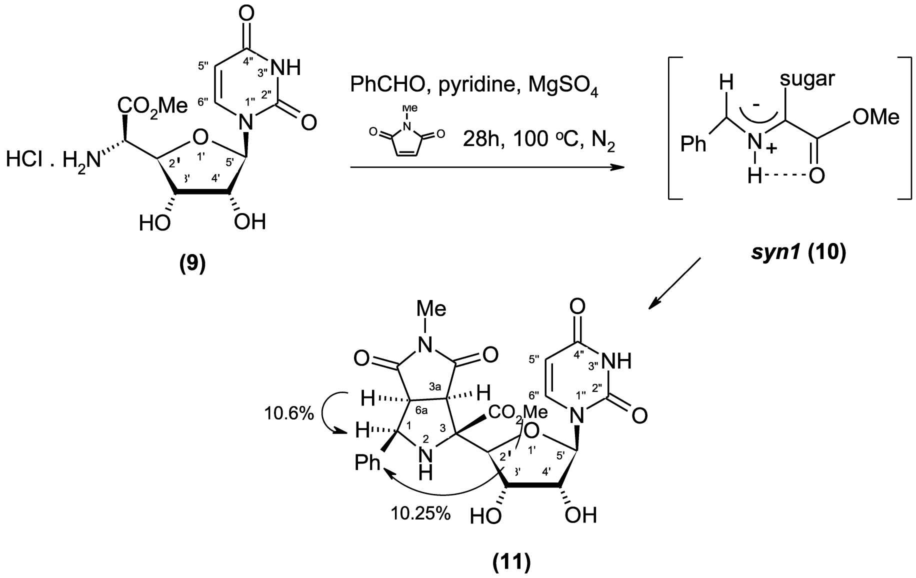


Figure 1. X-ray crystal structure of (**6b**).

whilst the stereochemistry at C-1 is assigned on the basis of previous studies.[13]

3. Cascade imine formation-prototropy-cycloaddition

UPoC methyl ester hydrochloride (**9**),[14] benzaldehyde and NMM were reacted (pyridine, $MgSO_4$, 100 °C, 28 h) to give a single cycloadduct (**11**) in 32% yield via azomethine ylide *syn* 1 (**10**) (Scheme 1). The relative stereochemistry of the pyrrolidinyl substituents of (**11**) was established from NOE data and 2D-COSY studies. Thus irradiation of 1-H effected enhancement of the signals for 6a-H (10.6%) whilst irradiation of 6a-H effected enhancement of the signals for

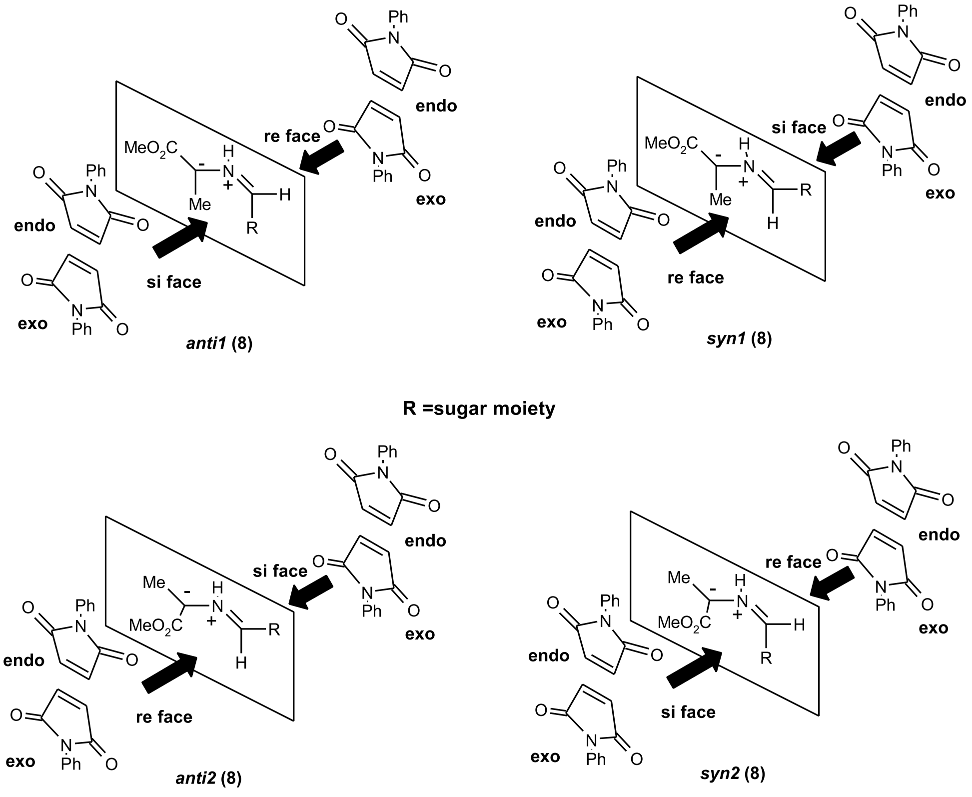


Scheme 1. Stereoselective in situ formation and cycloaddition of dipole (**10**).

1-H (10.15%) and 3a-H (8.45%). Irradiation of 3a-H effected enhancement of the signals for 6a-H (12.3%) and irradiation of CO_2Me effected enhancement of the signals for ArH (10.25%). Again there are two possible *endo*-diastereoisomeric cycloadducts corresponding to *endo*-cycloaddition to the two diastereotopic faces of dipole *syn* 1 (**10**). We have rationalised the stereocontrol in these cycloadditions using semi-empirical calculations as described below (Scheme 2).

4. Rationalisation of stereocontrol using semi-empirical calculations

The stereoselectivity observed in the cycloadditions of both dipoles (**8**) and (**10**) is remarkable, especially in light of the fact that each dipole can adopt four possible geometries (denoted *syn* 1, *anti* 1, *syn* 2, and *anti* 2 respectively, Scheme 2). Additionally, each of these four geometrical isomers can undergo cycloaddition from the



Scheme 2. Possible cycloaddition modes for *syn* 1, *syn* 2, *anti* 1, and *anti* 2 geometries of dipole (**8**).

Table 1. Calculated heats of formation, for 1,3-dipoles (**8**) and their cycloaddition transition states to NPM

Dipoles (**8**)/H_f^a	H_f^a and imaginary vibrational frequencies[b] ν_i of transition states from dipoles (**8**)							
	endo				*exo*			
	re		*si*		*re*		*si*	
syn 1, −253.47	−234.33	(−467.40)	−239.04	(−467.40)	−236.83	(−426.66)	−236.56	(−448.91)
anti 1, −231.73	−230.80	(−447.20)	−223.67	(−425.25)	−224.54	(−513.90)	−223.67	(−498.38)
syn 2, −247.65	−219.67	(−332.81)	−230.72	(−348.11)	−224.52	(−455.11)	−228.04	(−405.29)
anti 2, −253.52	−234.47	(−405.29)	−237.31	(−408.59)	−239.84	(−426.35)	−239.09	(−445.19)

[a] Heats of formation in kcal mol^{-1}, obtained using AM1 Hamiltonian after full geometry optimisation and corrected for solvation.[15]

[b] All transition structures were characterized by observing them to have a single negative vibrational frequency corresponding to the reaction coordinate following a normal mode analysis (figures in brackets in cm^{-1}).

Table 2. Calculated activation energies, E_a, for cycloaddition of dipoles (**8**) to NPM

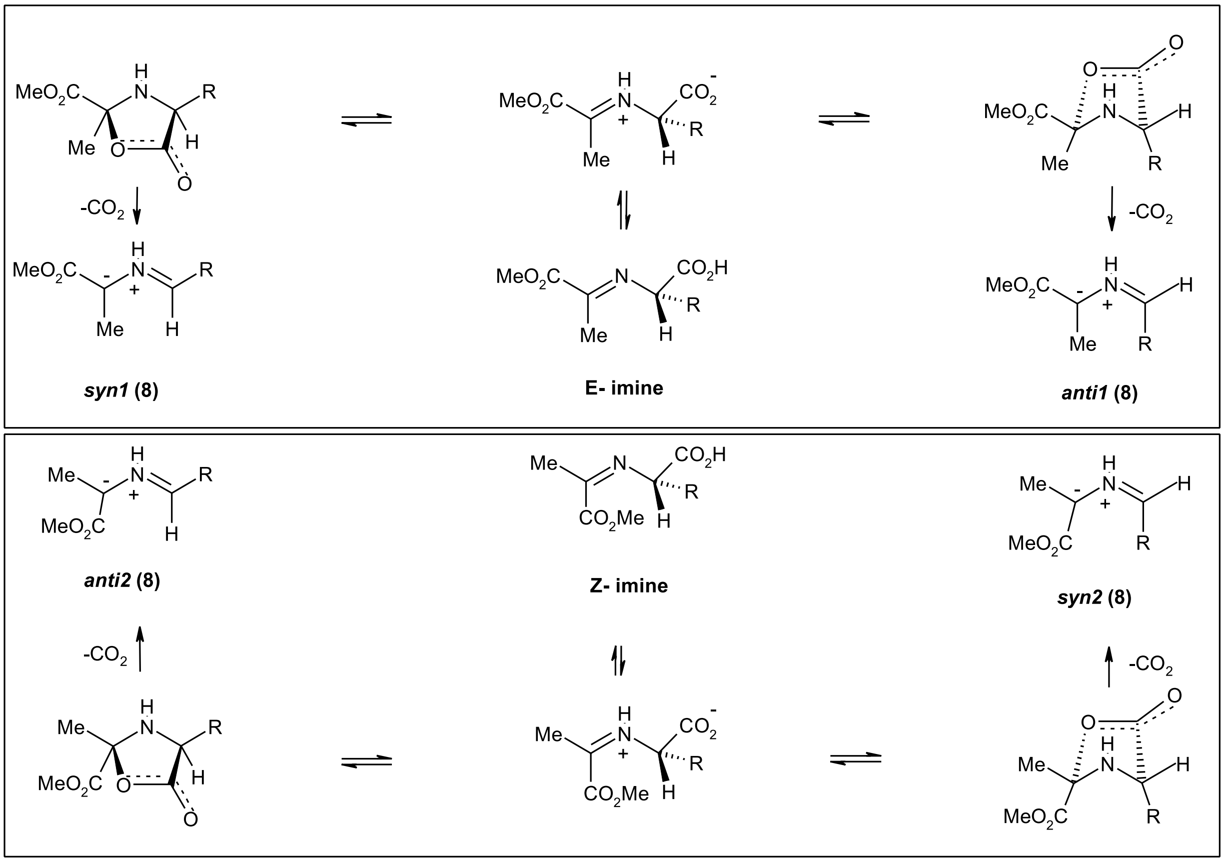
Entry	Dipole (**8**)	Cycloaddition activation energies, E_a^a			
		endo		*exo*	
		re	*si*	*re*	*si*
1	*syn* 1	19.56	14.85	17.06	17.33
2	*anti* 1	20.56	16.59	26.82	27.69
3	*syn* 2	28.40	17.34	23.55	20.03
4	*anti* 2	19.47	16.63	14.10	14.85

[a] Energies in kcal mol^{-1}. This energy is the difference between the sum of the heats of formation of dipole+NPM (H_f=−0.42 kcal mol^{-1}) and the heat of formation of the corresponding transition state.

two non-equivalent dipole faces (termed *re* and *si* respectively, where this refers to the prochirality at the carbon of the dipole attached to the sugar moiety, Scheme 2) and in both *endo* and *exo* modes (Scheme 2). We have used semi-empirical calculations to probe the factors that may give rise to the high diastereocontrol within these cycloadditions.

4.1. (a) Decarboxylative generation and subsequent cycloadditions of dipole (8)

We chose to investigate the cycloadditions of dipole **8**, (R^1=Me, R^2=CO_2Me) with *N*-phenyl maleimide (NPM), which had been observed to yield mainly one diastereoisomeric cycloadduct (**6b**) for which the stereochemistry had been unambiguously assigned using X-ray crystallography. The heats of formation of all the four geometric



Scheme 3. Formation of 1,3-dipoles (**8**) from decarboxylation of imines.

Table 3. Calculated heats of formation for 1,3-dipoles (**8**) and their cycloaddition transition states to NPM

Entry	Reaction	H_f(TS)[a]	ν_i[b]	E_a[c]
1	*E*→*anti* 1 (**8**)	−324.72	−497.59	31.52
2	*E*→*syn* 1 (**8**)	−340.02	−497.59	16.22
3	*Z*→*syn* 2 (**8**)	−340.96	−497.59	26.71
4	*Z*→*anti* 2 (**8**)	−313.35	−497.59	53.32

[a] Heats of formation in kcal mol^{-1}, obtained using AM1 Hamiltonian after full geometry optimisation and corrected for solvation.[15]

[b] All transition structures were characterized by observing them to have a single negative vibrational frequency corresponding to the reaction coordinate following a normal mode analysis (figures in brackets and expressed in cm^{-1}).

[c] Energies in kcal mol^{-1}. This energy is the difference between the heat of formation of the transition state and that calculated for the corresponding imine (*E*-imine, H_f=−356.24 kcal mol^{-1}, *Z*-imine, H_f=−367.67 kcal mol^{-1}).

forms of dipole (**8**) together with the 16 possible transition states (Scheme 2) for cycloaddition of (**8**) to *N*-phenyl maleimide, and the corresponding activation energies are shown in Tables 1 and 2.

Additionally, in order to establish a broad picture of the energetics involved in the whole reaction sequence, the generation of dipoles (**8**) via decarboxylative condensation of (**4**) with methyl pyruvate was investigated using semi-empirical calculations (Scheme 3). Each of the two possible imines resulting from the initial condensation can give rise to two particular dipoles respectively via decarboxylation (Scheme 3). The calculated heats of formation of each of the four decarboxylative transition states (H_f(TS)), together with the corresponding activation energies (E_a) are given in Table 3. Clearly these data indicate a strong preference for the reaction to proceed via decarboxylation of the E-imine to yield the *syn* 1 geometrical isomer of dipole (**8**), (Table 3, entry 2). Inspection of this transition structure reveals the existence of an intramolecular H-bond (length=2.14 Å) between the dipole NH and the C-2 carbonyl present on the uracil ring. (Fig. 2).

This transition structure also contains an H-bond (length=2.12 Å) between the C═O within the departing CO_2 molecule and the 3′-OH of the sugar (Fig. 2).

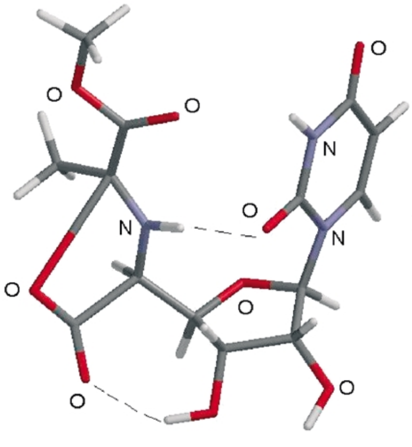


Figure 2. Calculated transition structure leading to dipole: syn 1 (8) showing H-bonding (dashed lines).

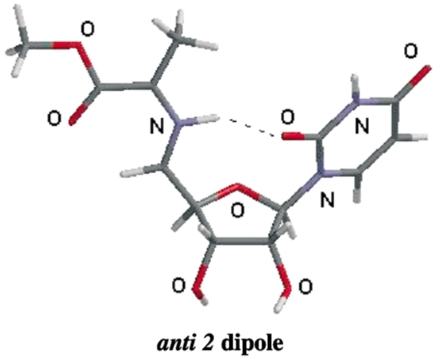


Figure 3. Calculated structure of *anti* 2 (**8**).

It would appear that this hydrogen bonding is important in stabilising this particular arrangement and promoting the formation of the *syn* 1 dipole. This intramolecular H-bonding feature involving the dipole N–H and uracil C═O is also apparent in the calculated structures of the *syn* 1- and *anti* 2-dipoles and here also appears to make important contributions in stabilising these dipole geometries (Figs. 3 and 4). The ubiquitous role of hydrogen bonding in structure and mechanism is well known[16] and these theoretical insights suggest novel ways of controlling dipole stereochemistry by distal functionality.

Another interesting feature of the transition structures from the decarboxylations is the very long C–O bond linking the departing CO_2 fragment to the dipole (see for example, Fig. 2). This implies that these decarboxylations are highly asynchronous and may be tend towards being more accurately described as involving CO_2 loss from an intermediate zwitterionic imminium carboxylate rather than from concerted decarboxylation from an intermediate oxazolidinone. As these calculations were performed in a simulated DMF solvent,[16] this asynchronicity would be expected to be maximised, and it would be interesting to investigate the effect of solvent polarity on the predicted mechanism of decarboxylation. In our previous studies on the stereochemistry[8] and mechanism[11] of related processes we had favoured the concerted route via the oxazolidinone.

The energetically favoured *E*→*syn* 1 (**8**) transition state restricts the reaction outcome to formation of an adduct derived from the *syn* 1-dipole (Table 2, entry 1). Here, the energetics clearly favour formation of the *endo* adduct

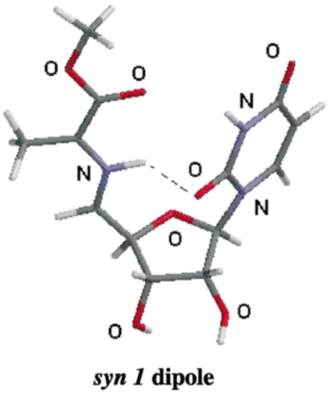
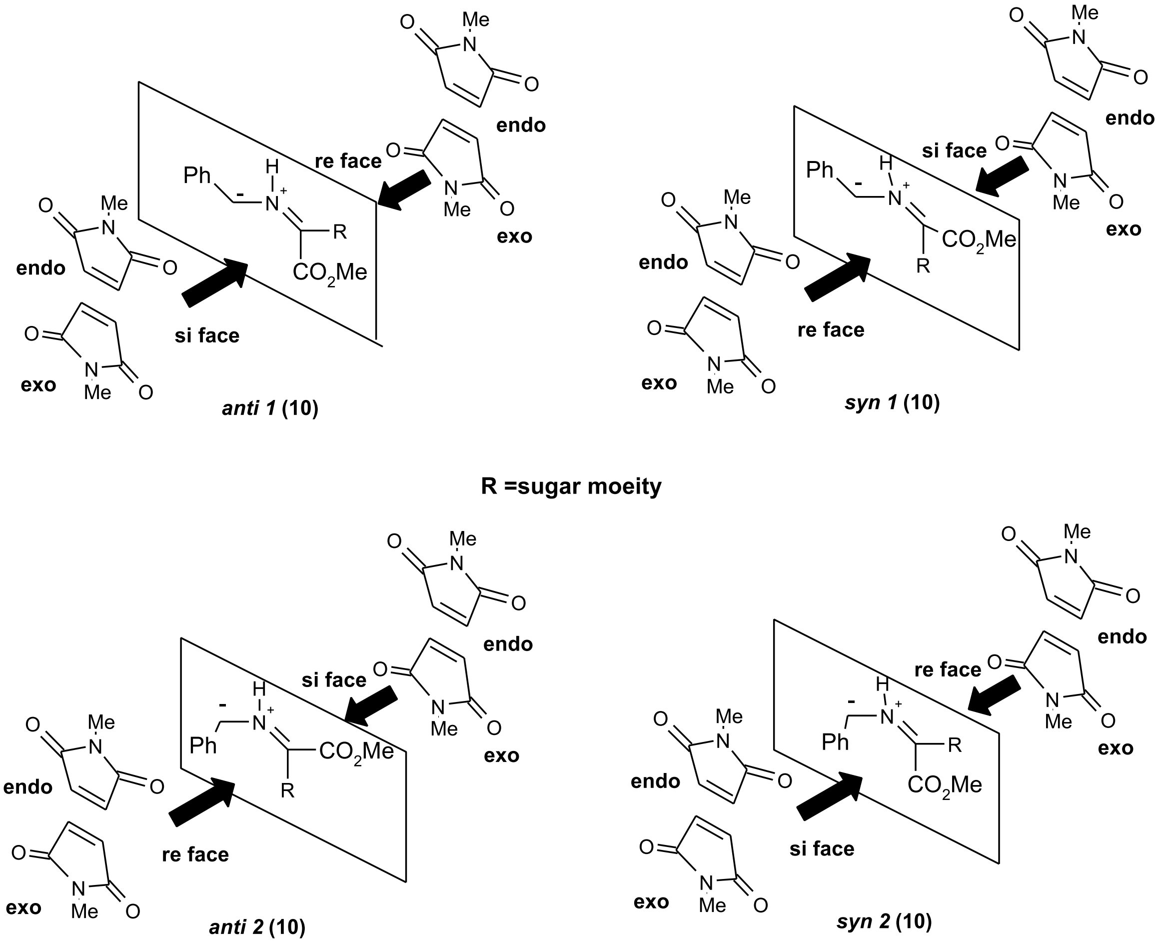


Figure 4. Calculated structure of dipole *syn* 1 (**8**).



anti 1 (10)

syn 1 (10)

R =sugar moeity

anti 2 (10)

syn 2 (10)

Scheme 4. Possible cycloaddition modes for *syn* 1, *syn* 2, *anti* 1, and *anti* 2 geometries of dipole (**10**).

resulting from addition to the *si* face of the dipole to yield adduct (**6b**) in complete agreement with our experimental observations. This diastereoselectivity appears to be a direct consequence of the uracil-derived intramolecular H-bonding which acts to lock the conformation of the dipole and directs the attack of the dipolarophile from the least-hindered face of the dipole.

4.2. (b) 1,2-Prototropic generation and subsequent cycloadditions of dipole (10)

Similar geometrical outcomes to those for the cycloadditions of dipole (**8**) can be applied to the reaction of dipole (**10**) with NMM (Scheme 4).

The calculated heats of formation of the transition states and the corresponding activation energies for these various cycloaddition modes are given in Tables 4 and 5.

Unlike the case for the generation of dipoles (**8**) via irreversible decarboxylation, the generation of dipoles (**10**) presumably involves a reversible formal 1,2-prototropic shift in the initially formed imines following the condensation reaction. In terms of thermodynamic stability, this means that *syn* 1 dipole (**10**) will dominate this equilibrium as it is between 4.5 and 12 kcal mol^{-1} lower in energy than the alternative dipole geometries (Table 4, column 1). It is interesting that in the case of dipole (**10**), although the intramolecular H-bonding involving the uracil ring and the

Table 4. Calculated heats of formation for 1,3-dipoles (**10**) and their cycloaddition transition states to NMM

Dipoles (**10**)/H_f[a]	H_f[a] and imaginary vibrational frequencies[b] ν_i of transition states from dipoles (**10**)							
	endo				*exo*			
	re		*si*		*re*		*si*	
syn 1, −242.02	−232.49	(−467.30)	−233.46	(−467.30)	−214.13	(−465.35)	−227.23	(−414.98)
anti 1 −237.62	−234.32	(−468.48)	−232.51	(−460.66)	−235.90	(−513.90)	−239.69	(−475.91)
syn 2, −229.95	−225.78	(−426.92)	−220.20	(−462.49)	−222.23	(−523.90)	−217.78	(−465.52)
anti 2, −230.63	−224.68	(−460.71)	−140.75	(−528.85)	−216.74	(−516.78)	−215.63	(−465.52)

[a] Heats of formation in kcal mol^{-1}, obtained using AM1 Hamiltonian after full geometry optimisation and corrected for solvation.[15]

[b] All transition structures were characterized by observing them to have a single negative vibrational frequency corresponding to the reaction coordinate following a normal mode analysis (figures in brackets and expressed in cm^{-1}).

Table 5. Calculated activation energies, E_a, for cycloaddition of dipoles (**10**) to NMM

Entry	Dipole (**10**)	Cycloaddition activation energies, E_a[a]			
		endo		*exo*	
		re	*si*	*re*	*si*
1	*syn* 1	20.59	19.62	38.95	25.85
2	*anti* 1	21.53	23.34	19.95	16.16
3	*syn* 2	22.54	28.12	26.23	30.54
4	*anti* 2	22.45	106.38	30.39	26.06

[a] Energies in kcal mol^{-1}. This energy is the difference between the sum of the heats of formation of dipole+NMM (H_f=−11.06 kcal mol^{-1}) and the heat of formation of the corresponding transition state.

dipole N–H is present in the *anti* 1 and *syn* 2 geometries, these are not the most stable forms and both are higher in energy than the *syn* 1 form in which this H-bonding is absent. It is noted however that the *syn* 1 dipole has a considerably greater calculated electronic dipole moment (5.95 D in a simulated solvent environment) compared to that of either the *anti* 1 (2.44 D) or the *syn* 2 (2.02 D) dipoles and so presumably derives considerable stabilisation from the fact that the calculations were performed where solvation from a polar solvent is simulated.[15]

Within the possible transition structures resulting from cycloaddition of the *syn* 1 dipole, those due to an *endo* approach of the dipolarophile are clearly favoured over the *exo*-derived systems (entry 1, Table 5). The predicted balance between either *si* or *re* addition is essentially even however, with *si* addition only very slightly favoured over *re*. In fact, as described above, this reaction gives a moderate yield of adduct (**11**) whose stereochemistry corresponds to the predicted *syn* 1-*endo*-*si* cycloaddition mode. Based on our calculations, we would expect some of the alternative *syn* 1-*endo*-*re* adduct to have also been obtained, and although no other cycloadducts could be isolated from the reaction mixture, we cannot rule out the possible presence of this isomer.

In summary, condensation of either UPoC itself or the corresponding ester with aldehydes and ketones gives ready access to 1,3-dipoles either via formal 1,2-prototropic- or decarboxylative processes respectively.

The geometry within these 1,3-dipoles is predicted to be highly stereodefined and, due to their inherent asymmetry, they can undergo diastereoselective cycloadditions.

This stereocontrol is predicted to be particularly relevant in the case of the dipoles (**8**) derived from decarboxylation, where an intramolecular H-bond involving the N–H of the dipole and a carbonyl group of the uracil moiety restricts the conformational flexibility of the dipole relative to the sugar moiety and results in highly diastereoselective reactions via cycloaddition occurring from the most accessible face of the dipole. It should be possible to design a range of systems which take advantage of this ability to define the diastereofacial selectivity of such dipoles via remote H-bonding using appropriately-positioned substituents.

4.3. Bioactivity of compounds

The nikkomycin analogues (**6a-f**) were inactive at 125 μg/ml when tested against strains of *Aspergillus fumigatus*, and *Candida albians*.

5. Experimental

5.1. General

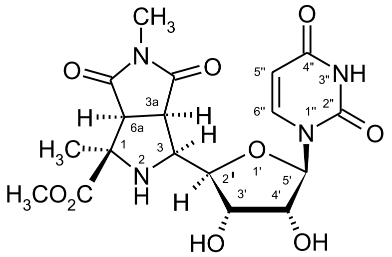
Nuclear magnetic resonance spectra were determined at 300, 400, 500 MHz Bruker spectrometers as specified. Chemical shifts are given in parts per million (δ) downfield from tetramethylsilane as internal standard. Spectra were determined in the solvent specified. The following abbreviations are used; s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad, brs=broad singlet and app=apparent.

Flash column chromatography was performed using silica gel 60 (230–400 mesh). Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Microanalyses were obtained using a Carlo–Erba Model 1106 instrument. Mass spectra were recorded at 70 eV on a VG Autospec mass spectrometer. Specific rotations were measured at ambient temperature with an Optical Activity Ltd, AA-1000 polarimeter. All solvents were purified according to procedures given in Purification of Laboratory Chemicals, D. D. Perrin, W. L. F. Armarego, D. R. Perrin, Permagon Press, 1980.

5.1.1. Cycloadducts (6a) and (7a). A mixture of uracil polyoxin C (UpoC) (4) (0.1 g, 0.35 mmol), methyl pyruvate (0.071 g, 0.7 mmol) and NMM (0.04 g, 0.35 mmol) in degassed DMF (10 ml) was stirred and heated from room temperature to 70 °C over 30 min and heating at this temperature was maintained for 26 h under a N_2 atmosphere. Flash chromatography, eluting with 9:1 v/v EtOAc–ethanol afforded the product (0.144 g, 94%) as a 9:1 mixture of (**6a**) and (**7a**). Attempts to separate the isomers by crystallisation from CH_2Cl_2–petroleum ether (60–80 °C) resulted in the same 9:1 isomeric mixture as pale yellow prisms. The minor isomer could not be isolated in a pure form and was not studied further. Mp (mixed isomers) 147–152 °C, $[\alpha]_D^{20}$=+50.8 (C, 1 g/100 ml, EtOH). Found: C, 48.15; H, 4.6; N, 10.10. $C_{18}H_{22}N_4O_9.0.5H_2O$ requires: C, 48.3; H, 4.9; N, 12.5%. HRMS: 438.1465, $C_{18}H_{22}N_4O_9$ requires: 438.1474. *m*/*z* (%) (FAB): 439 (M+1, 49), 379 (5), 227 (29), 149 (9), 97 (31), 83 (43), 69 (61) and 55 (100).

5.1.2. Major isomer (6a): (1*R*,3*S*,3a*R*,6a*S*)-3-[(2′*R*,3′*S*,4′*R*,5′*R*)-5′-(2″,4″-dioxo-3″,5″-dihydro-2*H*-pyrimidin-1″-yl)-3″,4″-dihydroxy-tetrahydro-furan-2-yl]-1,5-dimethyl-4,6-dioxo-octahydro-pyrrolo[3,4-*c*]pyrrole-1-carboxylic acid methyl ester). δ (300 MHz) (acetone-d_6) assigned from the spectrum of the mixture: 9.96 (br, 1H, NHC=O), 8.32 (d, 1H, *J*=8.1 Hz, 6″-H), 5.84 (d, 1H, *J*=5.2 Hz, 5′-H), 5.5 (d, 1H, *J*=8.1 Hz, 5″-H), 4.2 (m, 3H, 2′-H, 3′-H, 4′-H), 4.0 (app. d, 1H, *J*=9.8 Hz, 3-H), 3.73 (s, 3H, CO_2Me), 3.51 (dd, 1H, *J*=8.1, 9.8 Hz, 3a-H), 3.32 (d, 1H, *J*=8.1 Hz, 6a-H), 2.6 (s, 3H, NMe) and 1.46 (s, 3H, Me). NOE data:

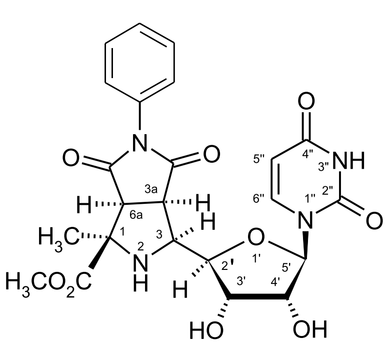
	Enhancement (%)								
Signal irradiated	6″-H	5′-*H*	5″-H	2′-H, 3′-H, 4′-H	3-H	3a-H	Me	6a-H	CO_2Me
6″-H		2.5	8.2	4.25					
5′-H				4.3					
5″-H	3.1								
2′-H, 3′-H, 4′-H	2.0	3.65			3.05				
3-H		1.3		11.3		7.95	6.0		
3a-H				4.3	5.65			4.4	
6a-H						1.75	2.75		2.0
CO_2Me							3.0		
Me					2.25			4.6	



5.1.3. Cycloadducts (6b) and (7b). A stirred mixture of (UpoC) (4) (0.1 g, 0.35 mmol), methyl pyruvate (0.071 g, 0.7 mmol) and NPM (0.060 g, 0.35 mmol) in degassed DMF (10 ml) was heated from room temperature to 70 °C over 30 min and heating at this temperature was maintained for 26 h under a N_2 atmosphere. Flash chromatography, eluting with 10:1 v/v EtOAc–ethanol afforded the product (0.168 g, 96%) as a 12:1 mixture of (**6b**) and (**7b**) as a pale yellow amorphous solid. HPLC separation employed a Luna, C18 (2) 10 μm 250×4.6 mm, column eluting with 15:85 v/v $MeCN/H_2O$, flow rate: 0.7 ml/min with UV detection at 254 nm. The major isomer was obtained as pale yellow needles. Mp 161–164 °C, $[\alpha]_D^{20}$=+60.2 (C, 1 g/100 ml, EtOH). Found (mixed isomers): C, 53.6; H, 4.95; N, 10.2 $C_{23}H_{24}N_4O_9.H_2O$ requires: C, 53.3; H, 5.0; N, 10.8%. HRMS(ES): 523.1436, $C_{18}H_{23}N_4O_9Na$ requires: 523.1441. *m/z* (%) (FAB): 501 (M+1, 100), 441 (10), 329 (9), 287 (25) and 149 (10).

5.1.4. Major isomer (6b): (1*R*,3*S*,3a*R*,6a*S*)-3-[(2′*R*,3′*S*,4′*R*,5′*R*)-5′-(2″,4″-dioxo-3″,5″-dihydro-2*H*-pyrimidin-1″-yl)-3″,4″-dihydroxy-tetrahydro-furan-2-yl]-1-methyl-4,6-dioxo-5-phenyl-octahydro-pyrrolo[3,4-*c*]pyrrole-1-carboxylic acid methyl ester). δ (500 MHz) (acetone-d_6): 9.85 (br, 1H, NHC=O), 8.34 (d, 1H, *J*=8.1 Hz, 6″-H), 7.30 (m, 3H, Ar-H), 7.15 (m, 2H, Ar-H), 5.98 (d, 1H, *J*=5.8 Hz, 5′-H), 5.45 (d, 1H, *J*=8.1 Hz, 5″-H), 4.62 (br, 1H, NH), 4.45 (m, 1H, 2′-H), 4.41 (m, 1H, 4′-H), 4.38 (m, 1H, 3′-H), 4.10 (app. d, 1H, *J*=8.6 Hz, 3-H), 3.74 (s, 3H, CO_2Me), 3.68 (dd, 1H, *J*=8.6, 9.0 Hz, 3a-H), 3.59 (d, 1H, *J*=9.0 Hz, 6a-H), 2.76 (br, 2H, OH) and 1.54 (s, 3H, Me). ^{13}C(125 MHz) (acetone-d_6): 23.37 (CH), 46.34 (CH), 51.6 (CH), 55.89 (CH), 59.88 (CH), 67.28 (q), 72.33 (CH), 73.07 (CH), 81.83 (CH), 88.82 (CH), 102.49 (CH), 126.23 (2C, CH), 127.75 (CH), 128.34 (2C, CH), 132.95 (q), 141.86 (CH), 150.84 (q), 162.37 (q), 172.9 (q), 174.45 (q), 175.01 (q). *m/z* (%) (ES): 523 (M+Na, 100). NOE data:

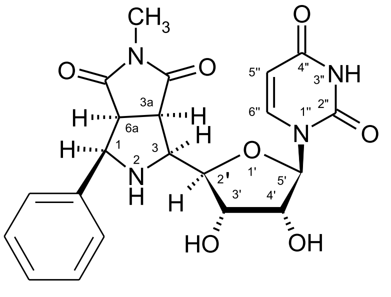
	Enhancement (%)								
Signal irradiated	6″-H	5′-*H*	5″-H	4′-H	3-H	3a-H	3′-H	6a-H	CO_2Me
6″-H		4.65	13.8						
5″-H	7.67								
2′-H	1.0	3.0			6.2				
3-H				8.8		10.0	3.2		
6a-H						16.7			3.3
CO_2Me			1.0						
Me					2.65	1.0		3.9	1.0
4′-H	9.0				2.0				
3′-H	5.5				3.2				



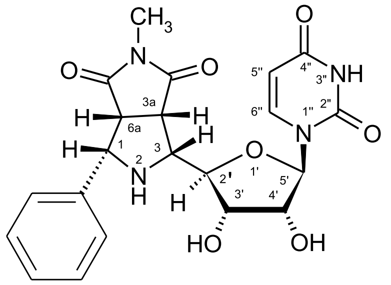
5.1.5. Cycloadducts (6c) and (7c). A stirred mixture of uracil polyoxin C(4) (0.1 g, 0.35 mmol), benzaldehyde (0.09 g, 0.76 mmol) and NMM (0.04 g, 0.35 mmol) in degassed DMF (10 ml) was heated from room temperature to 80 °C over 30 min and heating at this temperature was maintained for 22 h under a N_2 atmosphere. Flash chromatography, eluting with 9:1 v/v EtOAc–ethanol afforded the product (0.121 g, 78%) as a 3:1 mixture of (**6c**) and (**7c**). The isomeric mixture crystallised from CH_2Cl_2–petroleum ether (60–80 °C) as pale yellow prisms. Mp 173–177 °C. Found: C, 55.25; H, 4.95; N, 12.5, $C_{21}H_{22}N_4O_7.0.5H_2O$ requires: C, 55.85; H, 5.15; N, 12.4%. HRMS: 442.1488. $C_{21}H_{22}N_4O_7$ requires: 442.1495 *m*/*z* (%) (FAB): 443 (M+1, 100), 331 (19), 229 (55), 144 (18) and 69 (22).

5.1.6. Major isomer (6c): (1*R*,3*S*,3a*R*,6a*S*)-3-[(2′*R*,3′*S*,4′*R*,5′*R*)-5′-(2′,4′-dioxo-3′,5′-dihydro-2*H*-pyrimidin-1″-yl)-3″,4″-dihydroxy-tetrahydro-furan-2-yl]-5-methyl-1-phenyl-tetrahydro-pyrrolo[3,4-*c*]pyrrole-4,6-dione). δ (400 MHz) (acetone-d_6) assigned from the spectrum of the isomeric mixture: 10.2 (br, 1H, NHC=O), 7.8 (d, 1H, J=8.1 Hz, 6″-H), 7.3–7.2 (m, 5H, Ar-H), 5.90 (d, 1H, J=4.5 Hz, 5′-H), 5.61 (d, 1H, J=8.1 Hz, 5″-H), 4.8 (d, 1H, J=8.4 Hz, 1-H), 4.0 (m, 1H, 4′-H), 4.33 (m, 1H, 3′-H), 4.41 (m, 1H, 2′-H), 3.90 (app. d, 1H, J=7.5 Hz, 3-H), 3.56–3.49 (m, 2H, 3a-H and 6a-H) and 2.74 (s, 3H, NMe). NOE data:

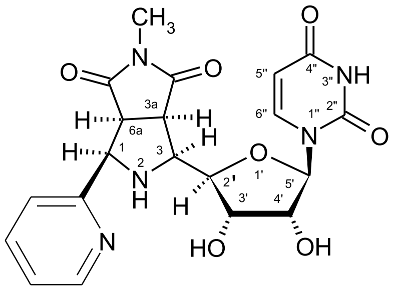
	Enhancement (%)									
Signal irradiated	6″-H	5′-*H*	5″-H	1-H	4′-H	3′-H	2′-H	3-H	3a-H, 6a-H	Ar-H
6″-H		5.5	7.5							
5′-*H*	3.5				2.5		2.7			
5″-					7.2					
1-H							9.7	4.9	11.8	12.6
4′-H	5.2									
3′-H	3.45	5.7				4.1		7.7	4.35	
2′-H		4.5		5.65					4.7	
3-H						8.2			4.2	
3a-H, 6a-H				6.2	4.2		5.5	4.2		



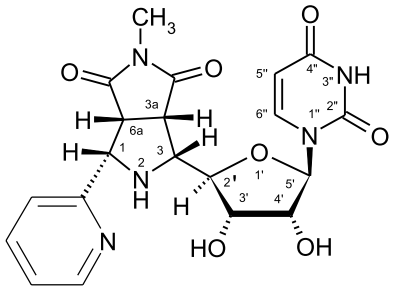
5.1.7. Minor isomer(7c): (1*S*,3*R*,3a*S*,6a*R*)-3-[(2′*R*,3′*S*,4′*R*,5′*R*)-5′-(2′,4′-dioxo-3′,5′-dihydro-2*H*-pyrimidin-1″-yl)-3″,4″-dihydroxy-tetrahydro-furan-2-yl]-5-methyl-1-phenyl-tetrahydro-pyrrolo[3,4-*c*]pyrrole-4,6-dione. δ (400 MHz) (acetone-d_6) assigned from the spectrum of the isomeric mixture: 10.2 (br, 1H, NHC=O), 7.8 (d, 1H, J=8.1 Hz, 6″-H), 7.3–7.2 (m, 5H, Ar-H), 5.90 (d, 1H, J=4.5 Hz, 5′-H), 5.72 (d, 1H, J=8.1 Hz, 5″-H), 4.9 (d, 1H, J=8.4 Hz, 1-H), 4.65 (m, 1H, 4′-H), 4.40 (m, 1H, 3′-H), 4.41 (m, 1H, 2′-H), 3.90 (app. d, 1H, J=7.5 Hz, 3-H), 3.56–3.49 (m, 2H, 3a-H and 6a-H) and 2.73 (s, 3H, NMe).



5.1.8. Cycloadducts (6d) and (7d): (1*R*,3*S*,3a*R*,6a*S*)-3-[(2′*R*,3′*S*,4′*R*,5′*R*)-5′-(2″,4″-dioxo-3′,5′-dihydro-2*H*-pyrimidin-1″-yl)-3″,4″-dihydroxy-tetrahydro-furan-2-yl]-5-methyl-1-pyridin-2yl-tetrahydro-pyrrolo[3,4-*c*]pyrrole-4,6-dione) and (1*S*,3*R*,3a*S*,6a*R*)-3-[(2′*R*,3′*S*,4′*R*,5′*R*)-5′-(2″,4″-dioxo-3′,5′-dihydro-2*H*-pyrimidin-1″-yl)-3″,4″-dihydroxy-tetrahydro-furan-2-yl]-5-methyl-1-pyridin-2yl-tetrahydro-pyrrolo[3,4-*c*]pyrrole-4,6-dione). A stirred mixture of uracil polyoxin C(4) (0.1 g, 0.35 mmol), pyridine-2-carboxaldehyde (0.15 g, 1.4 mmol) and NMM (0.04 g, 0.35 mmol) in degassed DMF (10 ml) was heated from room temperature to 65 °C over 30 min and heating at this temperature was maintained for 24 h under a N_2 atmosphere. Flash chromatography, eluting with 9:1 v/v EtOAc–ethanol afforded the product (0.08 g, 55%) as a 4:3 mixture of isomers together with trace amounts of a third isomer. The mixed isomers crystallised from CH_2Cl_2–petroleum ether (60–80 °C) as pale yellow prisms. Mp 169–174 °C. HRMS: 443.1446, $C_{20}H_{21}N_5O_7$ requires: 443.1441, δ (400 MHz) (MeOH-d_4) (mixed isomers): 8.44 (d, 1H, J=4.8 Hz, pyridine-H, isomers), 7.83 (d, 1H, J=8.1 Hz, 6″-H, isomers), 7.72 (m, 1H, pyridine-H, isomers), 7.82 and 7.25 (2×m, 2H, pyridine H), 5.85 and 5.82 (2×d, 1H, J=4.7 Hz, 6a-H and 5′-H isomers), 5.77 and 5.65 (2×d, 1H, J=8.1 Hz, 5″-H, isomers), 4.28 (m, 2H, 1-H, and 4′-H, isomers), 4.01 (m, 2H, 6a-H and 3′-H, isomers), 3.61 and 3.46 (2×m, 3H, 3a-H, 2′-H and 3′-H isomers) and 2.75 (25, 3H, *N*Me, isomers). *m*/*z* (%) (FAB): 444 (M+1, 94), 332 (12), 230 (32), 113 (45), 97 (23), 83 (46), 69 (77) and 57 (100).



(6d)

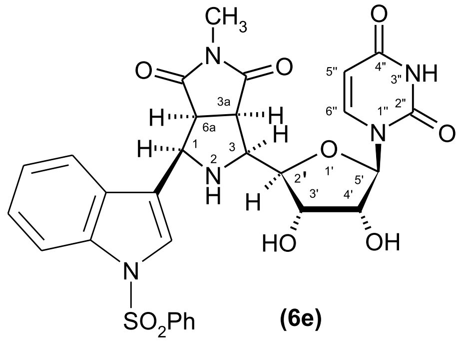


(7d)

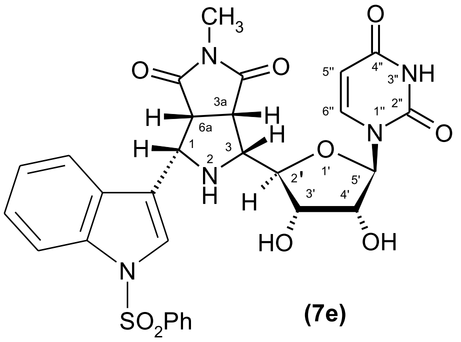
5.1.9. Cycloadducts (6e) and (7e): (1*R*,3*S*,3a*R*,6a*S*)-1-(1-benzenesulphonyl-1-*H*-indol-3-yl)-3-[(2′*R*,3′*S*,4′*R*,5′*R*)-5′-(2″,4″-dioxo-3″,4″-dihydro-2*H*-pyrimidin-1-yl)-3″,4″-dihydroxy-tetrahidro-furan-2-yl]-5-methyl-tetrahydro-pyrrolo[3,4-*c*]pyrrole-4,6-dione) (6e) and (1*S*,3*R*,3a*S*,6a*R*)-1-(1-benzenesulphonyl-1-*H*-indol-3-yl)-3-[(2′*R*,3′*S*,4′*R*,5′*R*)-5′-(2″,4″-dioxo-3″,4″-dihydro-2*H*-pyrimidin-1-yl)-3″,4″-dihydroxy-tetrahydro-furan-2-yl]-5-methyl-tetrahydro-pyrrolo[3,4-*c*]pyrrole-4,6-dione) (7e). A stirred mixture of uracil polyoxin C (0.1 g, 0.35 mmol), *N*-sulphonyl indole-3-carboxaldehyde (0.19 g, 0.7 mmol) and NMM (0.04 g, 0.35 mmol) in degassed DMF (10 ml) was heated from room temparature to 80 °C over 30 min and heating at this temperature was maintained for 24 h under N_2. Flash chromatography, eluting with 9:1 v/v EtOAc–ethanol afforded the product (0.16 g, 72%) as a 1:1 mixture of isomers. Crystallisation from CH_2Cl_2–petroleum ether (60–80 °C) gave one isomer, slightly contaminated with the other isomer, as pale yellow amorphous solid. Mp 167–171 °C. $[\alpha]_D^{20}=+12$ (0.5 g/100 ml EtOH. Found (mixed isomers): C, 54.75; H, 4.7; N, 10.7; S, 4.95; $C_{29}H_{27}N_5O_9$ S.H_2O: C, 54.45; H, 4.5; N, 10.90, S, 5.0%. *m*/*z* (%) (FAB): 622 (M+1, 100), 510 (19), 480 (22), 408 (28) and 365 (14), 113 (19), 97 (31), 83 (45) and 69 (74).

Compound (**6e**). Found: C, 55.35; H, 4.55; N, 10.75: S, 5.1, $C_{29}H_{27}N_5O_9$ S.0.5H_2O requires: C, 55.25; H, 4.45; N, 11.1, S, 5.1%. HRMS: 621.1517 $C_{29}H_{27}N_5O_9$ S.H_2O requires: 621.1529. δ (400 MHz) (Methanol-d_6): 10.2 (br, 1H, NHC═O), 8.4–7.6 (m, 11H, Ar-H, 6″-H and CH═C), 5.80 (d, 1H, 4.5 Hz, 5′-H), 5.32 (d, 1H, *J*=8.1 Hz, 5″-H), 4.9 (br, 1H, 2′-H), 4.40–4.35 (m, 2H, 4′-H+2-H), 4.30 (app. t, 1H, *J*=4.6 Hz, 1-H), 3.94 (dd, 1H, *J*=8.9, 4.6 Hz, 6a-H), 3.90 (app. d, 1H, *J*=7.0 Hz, 3-H), 3.75 (d, 1H, *J*=7.8 Hz, 3′-H), 3.66 (dd, 1H, *J*=8.9, 7.0 Hz, 3a-H) and 2.85 (s, 3H, *N*Me). *m*/*z* (%) (FAB): 622 (M+H, 100), 510 (21), 408 (42), 127 (44), 113 (35) and 69 (23).

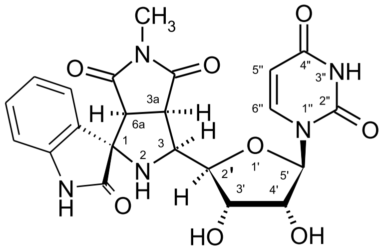
5.1.10. Cycloadducts (6f) and (7f). A mixture of uracil polyoxin C(4) (0.1 g, 0.35 mmol), isatin (0.12 g, 0.70 mmol) and NMM (0.04 g, 0.35 mmol) in degassed DMF (10 ml) was heated from room temperature to 90 °C over 30 min and heating at this temperature was maintained for 30 h under a N_2 atmosphere. Flash chromatography, eluting with 9:1 v/v EtOAc–ethanol afforded the product (0.138 g, 82%) as a 2:1 isomer mixture. Crystallisation from CH_2Cl_2–petroleum ether (60–80 °C) resulted in the same 2:1 isomeric mixture as a pale yellow amorphous solid. Mp 254–259 °C. Found (mixed isomers): C, 50.6; H, 4.5; N, 13.8. $C_{22}H_{22}N_5O_8$ 2.H_2O requires: C, 50.85; H, 4.8; N, 13.5%. *m*/*z* (%) (FAB): 484 (M+1, 100), 312 (20), 270 (51), 185 (20), 113 (20) and 77 (10).



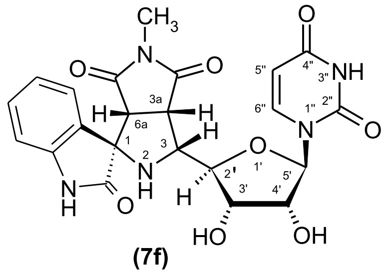
(6e)



(7e)



(6f)



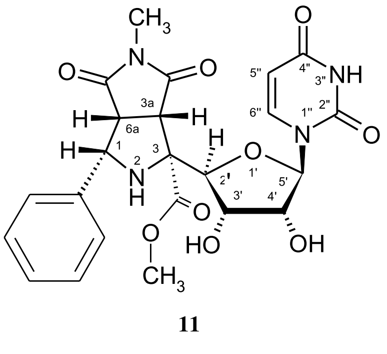
(7f)

5.1.11. Major isomer (6f). δ (400 MHz) (MeOH-d_4) assigned from the spectrum of the isomeric mixture: 8.0 (d, 1H, *J*=8.1 Hz, 6”-H), 7.3–6.8 (m, 4H, Ar-H), 5.80 (d, 1H, J=4.8 Hz, 5′-H), 5.64 (d, 1H, J=8.1 Hz, 5″-H), 4.61 (d, 1H, J=8.2 Hz, 6a-H), 4.42 (m, 1H, 2′-H), 4.15 (m, 2H, 3′-H+4′-H), 3.72 (app. t, 1H, J=8.2 Hz, 3a-H), 3.43 (app. d, 1H, J=8.2 Hz, 3-H) and 2.91 (s, 3H, *N*Me).

5.1.12. Minor isomer (7f). δ (400 MHz) (MeOH-d_4) assigned from the spectrum of the isomeric mixture: 7.68 (d, 1H, J=8.1 Hz, 6″-H), 7.3–6.8 (m, 4H, Ar-H), 5.82 (d, 1H, J=4.8 Hz, 5′-H), 5.73 (d, 1H, J=8.1 Hz, 5″-H), 4.63 (d, 1H, J=8.6 Hz, 6a-H), 4.24 (m, 1H, 2′-H), 4.15 (m, 2H, 3′-H+4′-H), 4.52 (dd, 1H, J=8.6, 7.8 Hz, 3a-H), 3.50 (app. d, 1H, J=7.8 Hz, 3-H) and 3.0 (s, 3H, *N*Me).

5.1.13. (1*S*,3*S*,3a*S*,6a*R*)-3-[(2′*R*,3′*S*,4′*R*,5′*R*)-5′-(2″,4″-Dioxo-3″,4″-dihydro-2*H*-pyrimidin-1-yl)-3″,4″-dihydroxy-tetrahydro-furan-2-yl]-5-methyl-4,6-dioxo-1-phenyl-octahydro-pyrrolo[3,4-*c*]pyrrole-1-carboxylic acid methyl ester) (11). UPoC methyl ester hydrochloride (**9**)[13] (0.15 g, 0.45 mmol), NMM (0.055 g, 0.5 mmol), benzaldehyde (0.1 g, 0.9 mmol) and anhydrous magnesium sulphate (0.5 g) were stirred in pyridine (15 ml) at 100 °C for 28 h. Dichloromethane was added to the cooled solution which was then washed with water (2×20 ml), dried ($MgSO_4$), filtered and the filtrate evaporated under reduced pressure. Flash chromatography of the residue, eluting with 9:1 v/v EtOAc–EtOH afforded (11) (0.07 g, 32%) as a brown solid. Attempted crystallisation from CH_2Cl_2–petroleum ether (60–80 °C) afforded a pale brown amorphous solid. Mp 154–159 °C. HRMS: 500.1569, $C_{23}H_{24}N_4O_9$ requires: 500.1569, δ (400 MHz), (acetone-d_6): 10.1 (br, 1H, NHC=O), 7.66 (d, 1H, J=8.1 Hz, 6″-H), 7.4–7.1 (m, 5H, Ar-H), 5.65 (m, 2H, 5′-H, 5″-H), 5.16 (t, 1H, J=6.1 Hz, 2′-H), 5.0 (1H, d, J=6.8 Hz, *N*H), 4.94 (dd, 1H, J=8.2, 6.8 Hz, 1-H), 3.78 (dd, 1H, J=8.2, 5.1 Hz, 6a-H), 3.45 (d, 1H, J=5.1 Hz, 3a-H), 3.43 (s, 3H, OMe) and 2.80 (s, 3H, *N*Me). *m/z* (%) (FAB): 501 (M+1, 10), 149 (20), 109 (18), 95 (34), 81 (48), 69 (72) and 55 (100). NOE data:

	Enhancement (%)										
Signal irradiated	6″-H	5′-*H*, 5″-H	2′-H	1-H	3′-H	4′-H	6a-H	3a-H	Ar-H	OMe	NH
6″-H		11.4									
5′-*H*, 5″-H	7.6				1.6	2.5				4.5	
2′-H					2.0	5.2		2.9			
1-H							10.6		11.2		
3′-H		5.0	4.9								
4′-H	4.3	10.1			7.9					1.4	9.2
6a-H				10.2				8.45			
3a-H			5.1				12.3				
CO_2Me	3.9	8.1			4.9				10.25		



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5.2. Single-crystal X-ray analysis

Crystallographic data for **6b** was measured on a Nonius Kappa CCD area-detector diffractometer using a mixture of area detector ω- and ϕ-scans and graphite monochromated Mo K_α radiation (λ=0.71073 Å). The structure was solved by direct methods using SHELXS-86[17] and were refined by full-matrix least-squares (based on F^2) using SHELXL-97.[18] The weighting scheme used was $w=[\sigma^2(F_o^2)+(0.1148P)^2+3.8871P]^{-1}$ where $P=(F_o^2+2F_c^2)/3$. All non-hydrogen atoms were refined with anisotropic displacement parameters whilst hydrogen atoms were constrained to predicted positions using a riding model. The final absolute configuration was based on the known chirality of the uracil polyoxin starting material. The residuals wR_2 and R_1, given below, are defined as $wR_2=(\sum[w(F_o^2-F_c^2)^2]/\sum[wF_o^2]^2)^{1/2}$ and $R_1=\sum||F_o|-|F_c||/\sum|F_o|$.

Full supplementary crystallographic data, which include hydrogen co-ordinates, thermal parameters and complete bond lengths and angles, have been deposited at the Cambridge Crystallographic Data Centre and are available on request.(**6b**, CCDC 214092).

Crystal data for **6b**. $C_{23}H_{24}N_4O_9.H_2O$, 0.31×0.31×0.13 mm, M=518.48, trigonal, space group $R\bar{3}$, a=25.5247(9), c=9.9448(3) Å, U=5611.1(3) Å^3, Z=4, D_c=1.38 Mg m^{-3}, μ=0.11 mm^{-1}, F(000)=2448, T=150 K.

Data collection. 1.0<2θ<52.0°; 4863 unique data were collected [R_{int}=0.052]; 4248 reflections with F_o >4.0 $\sigma(F_o)$.

Structure refinement. Number of parameters=339, goodness of fit, s=1.043; wR_2=0.1698, R_1=0.0607.

Acknowledgements

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Narcissistic aggregation of steroid compounds in diluted solution elucidated by CSI-MS, PFG NMR and X-ray analysis

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Abstract—Large-scale aggregated chain structures of progesterone, estrone, cortisone, hydrocortisone and cholic acid were observed in diluted solution by means of cold-spray ionization mass spectrometry (CSI-MS) and pulsed field gradient (PFG) NMR. The crystal structures were determined by X-ray crystallography, and the relationship between the crystal and solution structures is discussed. It is suggested that the intermolecular hydrogen bondings observed in the crystal might be partly retained in diluted solution.
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1. Introduction

We recently developed a direct solution analysis method, cold-spray ionization (CSI)-MS,[1,2] a variant of electrospray ionization (ESI)-MS[3] operating at low temperature. The optimum spray temperature is estimated to be around −20 °C. Generally, solvents show a higher dielectric constant at low temperature. This fact, as well as the solvation of the molecule, promotes electrolytic dissociation to form the molecular ion in solution, because desolvation should not occur readily at such a low temperature. Therefore, it should be possible to detect extremely labile complexes without decomposition. The CSI apparatus has been refined and applied to investigations of the solution structures of primary biomolecules, labile organic species including Grignard reagents, asymmetric catalysts and supramolecules.[4,5] This method allows simple and precise characterization of labile non-covalent complexes, which are difficult or impossible to observe by conventional MS techniques.

In the course of our studies of biomolecular solution structures by using CSI-MS, we have found large-scale hydrogen bonding aggregates, or chain clusters, of nucleosides, amino acids and monosaccharides in diluted solution.[6,7] Interestingly, the crystal structures of these compounds exhibit strong intermolecular hydrogen bonding to form chain structures, apparently identical with the large-scale aggregates observed in solution by CSI-MS. Similar chain structures were also observed in lipids and micelles including steroid compounds. In this report, we present a detailed behavior of the large-scale aggregated chain structures (chain clusters) of steroid compounds observed in solution by means of CSI-MS and PFG NMR. The solution structures are compared with those observed in the crystalline state by single-crystal X-ray analyses.

2. Results

2.1. Cold-spray ionization mass spectrometry

The CSI mass spectra of progesterone **1**, estrone **2**, cortisone **3**, hydrocortisone **4** and cholic acid **5** are shown in Figure 1.

Characteristic chain structures based on strong intermolecular hydrogen bonding in the cases of **3**, **4** and **5** were clearly present in solution, yielding a series of clusters. Ion peaks assigned as $[n\mathrm{M}+\mathrm{Na}]^+$ (n=1 to 12 or 13), were seen in the range of m/z 0–5000 for these compounds. In the case of **2**, intermolecular interaction appeared to be weaker, based the CSI mass spectrum (Fig. 1(b)). The strength of the intermolecular interaction for each compound might depend on the number of hydroxyl or carboxyl groups attached. As expected, no chain cluster was observed in the CSI mass spectrum of **1**, which has neither hydroxyl nor

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Keywords: Hydrogen bonding; Steroid compounds; Cold-spray ionization mass spectrometry; PFG NMR; Diffusion; X-ray; Chain structure.

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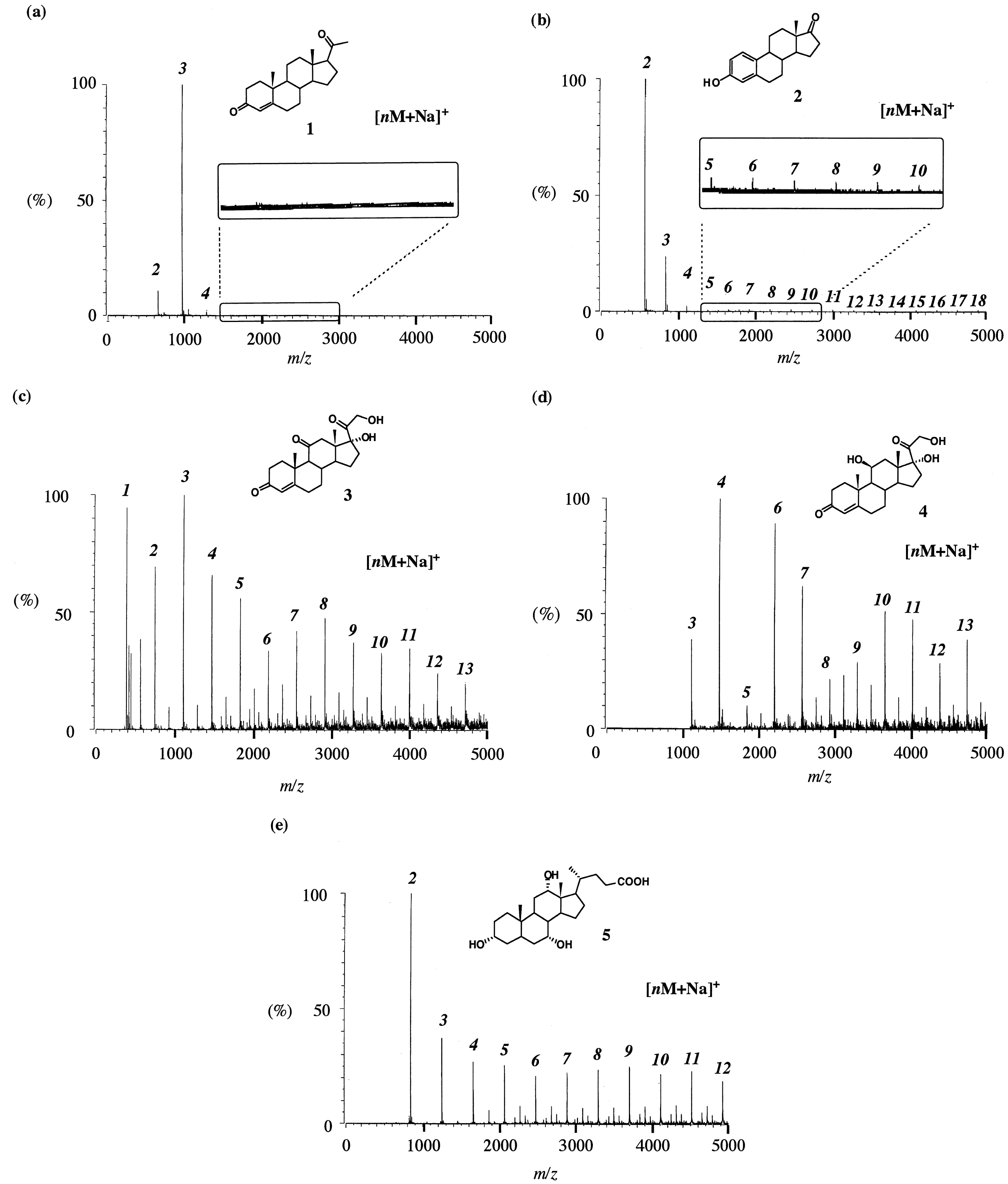

Figure 1. Cold-spray ionization mass spectra of steroid compounds: (a) **1**; (b) **2**; (c) **3**; (d) **4**; (e) **5**.

carboxyl groups. This result is consistent with the X-ray analysis findings, which will be discussed later.

2.2. PFG NMR diffusion studies

Recently, it was demonstrated that PFG NMR is a useful method for the characterization of a variety of interacting systems in solution.[8–10] First, we examined the diffusion coefficients of molecules practically having no hydrogen bonding for comparison with those of the steroid compounds. As shown in Figure 2(a), the compounds adopted for this calibration study were ethyl acetate **6**, methylcyclohexane **7**, xylenes **8**, methyl benzoate **9**, pyrene **10**, isopropyl palmitate **11** and tri-*n*-caprylin **12**. No hydrogen bonding of these compounds is expected, because they have neither hydroxyl nor carboxyl groups.

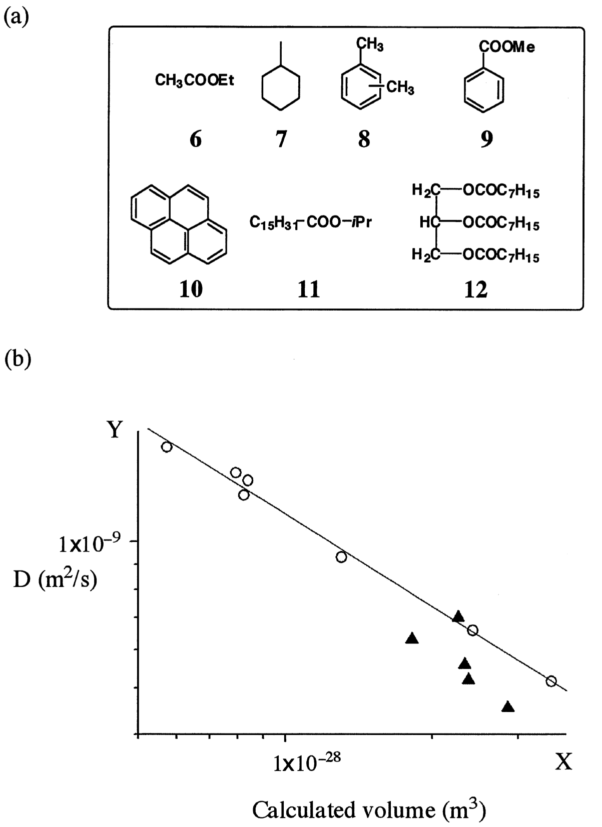

Figure 2. (a) The molecular structures adopted for calibration, and (b) relation of observed diffusion coefficients versus calculated molecular volume for compounds **6**-**12** (○) and the steroid compounds **1**-**5** (▲). The *X*- and *Y*-axes are logarithmic.

A calibration profile was obtained from the observed diffusion coefficients and molecular volumes calculated by using MOPAC[11] [Fig. 2(b), Table 1]. Diffusion coefficients were obtained as a function of molecular volume instead of molecular weight.[12,13]

The attenuation of signal intensities is given by Eq. 1.[14]

$$I = I_0 \exp(-kD) \qquad (1)$$

Here $k=[(\gamma G\delta)^2(\Delta-\delta/3-\tau/2)]$, where γ is the gyromagnetic ratio of ^{1}H, G is the gradient strength, D is the diffusion coefficient, δ is the field gradient pulse duration, Δ is the diffusion time and τ is the gradient delay. Diffusion coefficients were calculated as a function of the value of k by using Eq. 1. The calculated diffusion coefficients obtained from the calibration curve in Figure 2(b) and the observed diffusion coefficients in PFG NMR experiments are shown in Table 2.

Table 1. The calculated molecular volumes of compounds **1**-**12**. These values were calculated by using MOPAC

	Compound	Volume ($\times 10^{-29}$ m^3)
Steroid	1	22.5
	2	18.1
	3	23.2
	4	23.6
	5	28.4
Reference	6	5.73
	7	8.37
	8	7.91
	9	8.22
	10	13.0
	11	24.1
	12	34.9

Table 2. The observed and calculated diffusion coefficients of steroid compounds

Steroid	$D_{\text{obs.}}$ ($\times 10^{-10}$ m^2/s)[a]	$D_{\text{cal.}}$ ($\times 10^{-10}$ m^2/s)[b]
1	6.98	6.78
2	6.29	7.77
3	5.58	6.65
4	5.18	6.58
5	4.54	5.85

[a] Value obtained by NMR observation.

[b] Value obtained by calculation using the equation from the calibration plot ($y=2.53\times 10^{-27}x^{-0.63}$) in Figure 2(b).

In the case of **1**, the observed diffusion coefficient is almost identical with the calculated value. This result indicates that **1** has no intermolecular interactions. On the other hand, the diffusion coefficients of **2**-**5** were slightly different from the calculated values, presumably because hydrogen bonding occurs to afford molecular clusters. These findings are consistent with the results of CSI-MS, which also indicated the existence of clusters based on hydrogen bonding in solution. It is suggested that PFG NMR data reflect the size of the molecular aggregates formed by non-covalent interactions such as hydrogen bonding.

2.3. X-ray analysis

The crystal structures of these compounds were then elucidated by means of X-ray diffraction. The crystal structures obtained are shown in Figure 3.

Although no intermolecular interaction based on hydrogen bonding was observed because of the absence of hydroxyl and/or carboxyl groups in **1**,[15] other species having these functional groups exhibited liner or two-dimensional chain structures in the crystal. The head-to-tail interaction of hydroxyl and ketone groups was seen in the case of **2**.[16] In the cases of **3**,[17] **4**[17] and **5**,[18] plural intermolecular hydrogen bonds were observed in the crystal. Solvent molecule(s), methanol, were included in **4** and **5**. Compounds **2**-**5**, exhibited two, four, seven and eight hydrogen bondings, respectively. Very strong hydrogen bonding, with a distance of 2.594(3) Å, was observed between the hydroxyl group at the 5-position and OH of the carboxyl group in **5**. Almost all the hydrogen-bonding distances ranged from 2.7 to 3.0 Å.

3. Discussion

We have elucidated the structures of five steroid compounds having different numbers of polar functional groups (OH and/or COOH) in solution by using CSI-MS. Clear differences of the aggregated structures, according to the number of polar groups, were found in methanol solution. Though the formation of large-scale aggregated clusters was not observed in the case of **1**, which has no polar functional groups, large clusters were observed for compounds with such functional group(s). The degree of the clustering

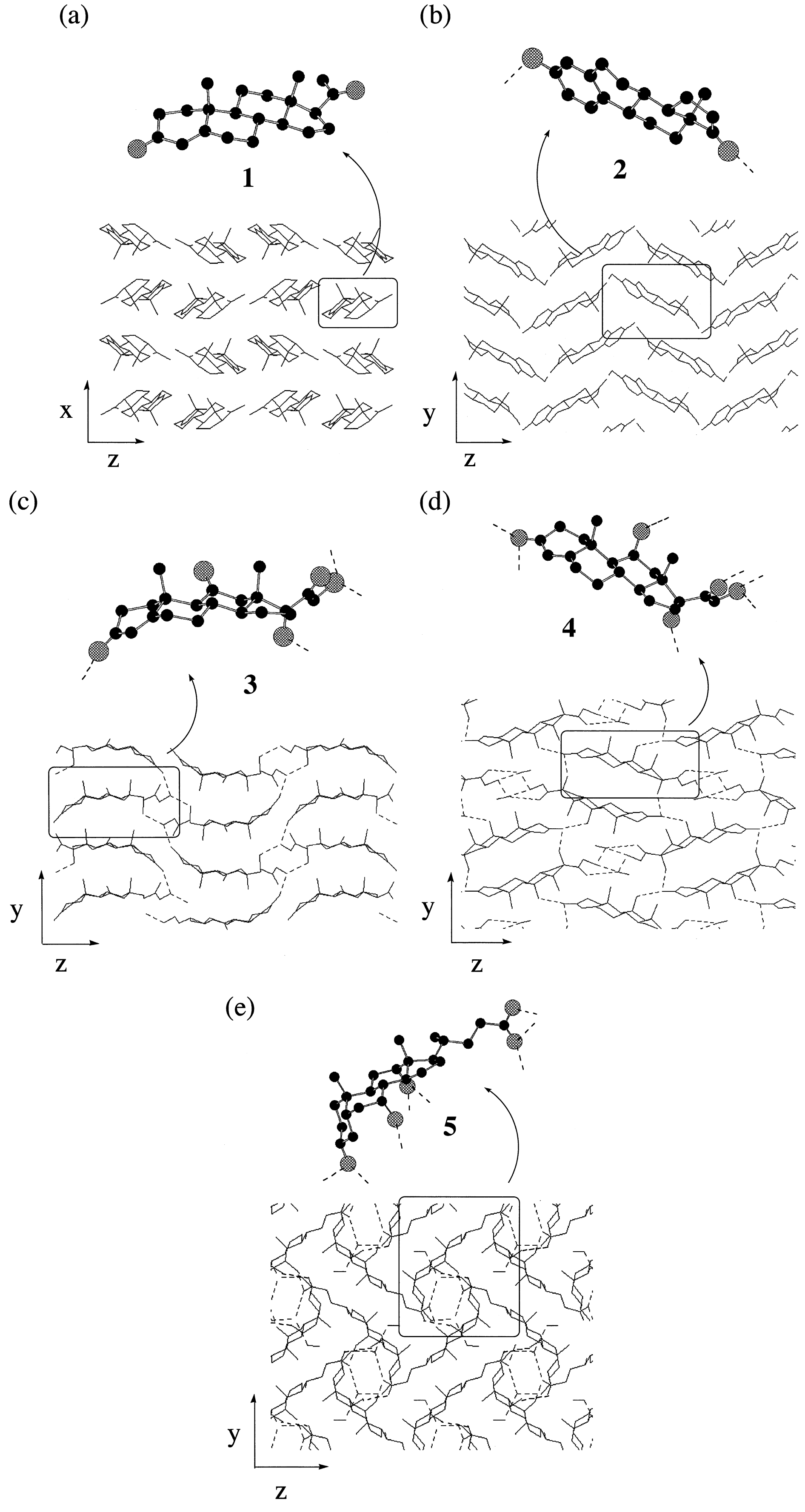

Figure 3. (a)–(e) present the crystal structure of **1**-**5**, respectively. Dotted lines indicate hydrogen bonding.

tended to increase with increased in the number of functional groups.

Moreover, PFG NMR measurements were also applied to the same solutions (CD_3OD:D_2O=98:2, 10 mM) as used for CSI-MS. A calibration profile was obtained based on molecular volume, instead of molecular weight, and intermolecular interactions based on hydrogen bonding in solution were confirmed by comparing the two series of compounds using the calibration profile. However, the measured diffusion coefficients could not be used to distinguish cluster-forming propensity.

In the case of CSI-MS measurement, large-scale aggregated clusters of the steroid compounds were easily detected in solution, because these clusters were stably ionized at low temperature. The CSI-MS findings were supported by the results of X-ray crystallography, which revealed strong hydrogen bonding in the crystal lattice. It is suggested that the structures of the large clusters observed by CSI-MS might be similar to those observed in the crystal. Further, no large cluster was detected in the case of **1**, which showed no hydrogen bonding in the crystal.

4. Conclusion

We identified large-scale-aggregated structures of steroid compounds in solution by using CSI-MS and PFG NMR and in the solid state by X-ray crystallography. The structures in solution and in the solid state were broadly similar, being based on hydrogen bonding. The average size of the clusters of each steroid compound was estimated in PFG NMR diffusion experiments. These compounds appear to maintain ordered clusters based on hydrogen bonding in diluted solution, at least in part, instead diffusing randomly as individual molecules, as has been generally accepted. We have observed this unprecedented phenomenon by CSI-MS, which can clearly confirm the existence of such clusters. This narcissistic aggregation might be strongly related to the biological activity of these compounds, and this will be examined in near future.

5. Experimental

Steroid compounds **1**, **2**, **3**, **4** and **5** were purchased from Tokyo Kasei Kogyo Co., Ltd. Compounds **6-12** were also commercial products. All reagents were used without purification. Deuterated solvents, 99.8% d_4-methanol and 99.9% deuterium oxide, were purchased from Merck Ltd and Cambridge Isotope Laboratories, Inc., respectively.

CSI-MS measurements were performed with a sector (BE) mass spectrometer (JMS-700, JEOL) equipped with a CSI source. Typical measurement conditions are as follows: ionization mode, positive CSI; acceleration voltage, 5.0 kV; needle voltage, 0 kV; orifice voltage, 40 kV; sample flow rate, 8 μl/min; solvent, CH_3OH:H_2O=98:2; sample concentration, 10 mM; spray temperature, −20 °C; resolution (10% valley definition), 1000.

NMR diffusion experiments were carried out in a JEOL JNM LA-600 spectrometer. The measurement conditions were as follows: pulse sequence, Bipolar-Pulse-Pair Stimulated-Echo (BPP-STE);[19] gradient length, 0.8–1.5 ms; diffusion time, 100–110 ms; solvent, CD_3OD:D_2O=98:2; temperature, 10 °C; sample concentration, 10 mM. The gradient strength was varied in 15 steps to 30 G/cm. Diffusion coefficients were measured after 1 h at 10 °C for stabilization, with 3 mm I.D. sample tubes to decrease the influence of thermal convection.

All NMR diffusion experiments employed the BPP-STE pulse sequence. We used the proton signal of the C-18 methyl group in the steroid backbone for determination of diffusion coefficients, because it is a singlet peak and this group is not involved in hydrogen bonding. The NMR signals showed single exponential decay. The diffusion coefficients were calculated by curve fitting of the peak intensities of the C-18 methyl proton and k in Eq. 1.

Single crystals were obtained by recrystallization from methanol at room temperature. A Bruker SMART 1000 CCD diffractometer with graphite-monochromated Mo K_α radiation was used. The structures were solved by the direct method and refined by the full-matrix least-squares method. All non-hydrogen atoms were refined anisotropically.

All calculations were performed using the teXsan crystal structure solution software package.

5.1. X-ray crystallography

5.1.1. Progesterone 1. $C_{21}H_{30}O_2$, M=314.47, orthorhombic, space group $P2_12_12_1$(#19), a=10.287(3), b=12.524(4), c=13.701(4), V=1765.318(8) Å^3, Z=4, D_{calc}=1.18 g cm^{-3}, T=173.2 K, μ=0.74 cm^{-1}, (Mo K_α=0.71069 Å), R=0.044 (R_w=0.055) for 10476 observed reflections [I>2.0$\sigma(I)$], GOF=1.344. (CCDC 228768).

5.1.2. Estrone 2. $C_{18}H_{22}O_2$, M=270.37, orthorhombic, space group $P2_12_12_1$(#19), a=7.773(10), b=9.983(13), c=18.412(2), V=1428.816(3) Å^3, Z=4, D_{calc}=1.26 g cm^{-3}, T=173.2 K, μ=0.80 cm^{-1}, (Mo K_α=0.71069 Å), R=0.034 (R_w=0.040) for 8517 observed reflections [I>2.0$\sigma(I)$], GOF=1.364. (CCDC 228769).

5.1.3. Cortisone 3. $C_{21}H_{28}O_5$, M=360.45, orthorhombic, space group $P2_12_12_1$(#19), a=7.785(2), b=10.001(3), c=23.610(6), V=1838.264(7) Å^3, Z=4, D_{calc}=1.30 g cm^{-3}, T=173.2 K, μ=0.92 cm^{-1}, (Mo K_α=0.71069 Å), R=0.032 (R_w=0.036) for 10936 observed reflections [I>2.0$\sigma(I)$], GOF=0.881. (CCDC 228770).

5.1.4. Hydrocortisone 4. $C_{21}H_{30}O_5(CH_3OH)$, M=394.51, orthorhombic, space group $P2_12_12_1$(#19), a=7.680(2), b=14.230(4), c=18.439(5), V=2015.050(8) Å^3, Z=4, D_{calc}=1.30 g cm^{-3}, T=173.2 K, μ=0.93 cm^{-1}, (Mo K_α=0.71069 Å), R=0.043 (R_w=0.056) for 12276 observed reflections [I>2.0$\sigma(I)$], GOF=1.071. (CCDC 228771).

5.1.5. Cholic acid 5. $C_{24}H_{40}O_5(CH_3OH)(H_2O)$, M=458.63, orthorhombic, space group $P2_12_12_1$(#19), a=11.283(3), b=14.434(4), c=15.383(4), V=2505.291(9) Å^3, Z=4, D_{calc}=1.22 g cm^{-3}, T=173.2 K, μ=0.87 cm^{-1}, (Mo K_α=

0.71069 Å), $R=0.046$ ($R_w=0.054$) for 14967 observed reflections [$I>2.0\sigma(I)$], GOF=1.287. (CCDC 228772).

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Synthesis of 3-hydroxyindolin-2-one alkaloids, (±)-donaxaridine and (±)-convolutamydines A and E, through enolization–Claisen rearrangement of 2-allyloxyindolin-3-ones

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Abstract—Claisen rearrangement triggered by enolization of 2-allyloxyindolin-3-ones with DBU was performed in order to prepare 3-allyl-3-hydroxyindolin-2-ones. Total synthesis of 3-hydroxyindolin-2-one alkaloids, (±)-donaxaridine, as well as (±)-convolutamydines A and E, was achieved by transformation of the allyl moiety of 3-allyl-3-hydroxyindolin-2-ones.

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1. Introduction

3-Substituted 3-hydroxyindolin-2-ones are useful synthetic intermediates for alkaloids and biologically active compounds such as donaxaridine (**1**),[1] convolutamydines (**2**),[2] dioxibrassinine,[3] welwitindolinone C,[4] 3′-hydroxyglucoisatisin,[5] and TMC-95s,[6] in addition to several others (Fig. 1) .[7] In particular, 3-allyl-3-hydroxyindolin-2-ones are attractive intermediates for synthesis of biologically active compounds. Although a number of routes to 3-substituted 3-hydroxyindolin-2-ones are known,[8–17] there are relatively few synthetic methods for 3-allyl-3-hydroxyindolin-2-ones. The known examples are addition of allylmetallic (indium,[18] gallium[19] and boran[20]) reagents to isatin, but there are difficulties in obtaining the desired 3-allyl-3-hydroxyindolin-2-one owing to the low regioselectivity of the allylic reaction site.[18,19] Reaction of allylmagnesium chloride with isatin resulted in diallylation to give only 2,2-diallylindolin-3-one.[21] Recently, Mérour et al.[21] reported alkaline hydrolysis of 2-ethoxycarbonyl-2-allyloxyindolin-3-ones followed by decarboxylation and Claisen rearrangement to give 3-allyl-3-hydroxyindolin-2-one. We have previously shown a synthetic methodology for regioselective introduction of an allyl moiety to an indole nucleus using Claisen rearrangement, converting 3-allyloxyindole to 2-allylindolin-3-one,[22] 3-alkyl-2-allyloxyindole to 3-alkyl-3-allylindolin-2-one[23] and 3-vinyloxyindoline to 4-carbamoylmethylindoles.[24] We herein report a method for synthesis of the 3-hydroxyindolin-2-one alkaloids, (±)-donaxaridine (**1**) as well as (±)-convolutamydines A (**2a**) and E (**2b**), using Claisen rearrangement triggered by enolization of 2-allyloxyindolin-3-ones **3** to 3-allyl-3-hydroxyindolin-2-ones **4** (Scheme 1).

2. Results and discussion

2.1. Preparation of 3-allyl-3-hydroxyindolin-2-ones

The starting 2-allyloxyindolin-3-ones **3** were readily available using our synthetic method.[23] Initially, we examined the enolization of 2-allyloxyindolin-3-one **3a** with DBU and DBN as a base under several reaction conditions and the results are summarized in Table 1. When **3a** was treated with DBU at 40 °C in acetonitrile, the desired enolization readily took place through Claisen rearrangement of an intermediary indole to afford 3-allyl-3-hydroxyindolin-2-one **4a**, its deacetyl derivative **5a**, and carboxylic acid **6** in 9, 12, and 36% yields, respectively (Scheme 2 and Table 1, entry 1). It is known that Claisen rearrangement of the enolate of α-allyloxy carbonyl compounds competes with [2,3]-Wittig rearrangement.[25] However, comparison of the ^{13}C NMR spectrum of **5a** with those of 3-hydroxyindolin-2-one **7** and 2-hydroxyindolin-3-one **8**[26] shows that the product in the reaction of **4a** is not the [2,3]-Wittig rearrangement product **5a′** but the Claisen rearrangement product **5a** (Fig. 2). Formation of **5a** and **6** is effected by hydrolysis of **4a** under basic reaction conditions, and thus **4a** was smoothly hydrolyzed with lithium hydroxide at room temperature to give **5a** in 85% yield. When the reaction was performed in methylene chloride

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Keywords: DBU; Allylalcohol; Osmium tetraoxide; Wacker oxidation; Molybdenum peroxide.

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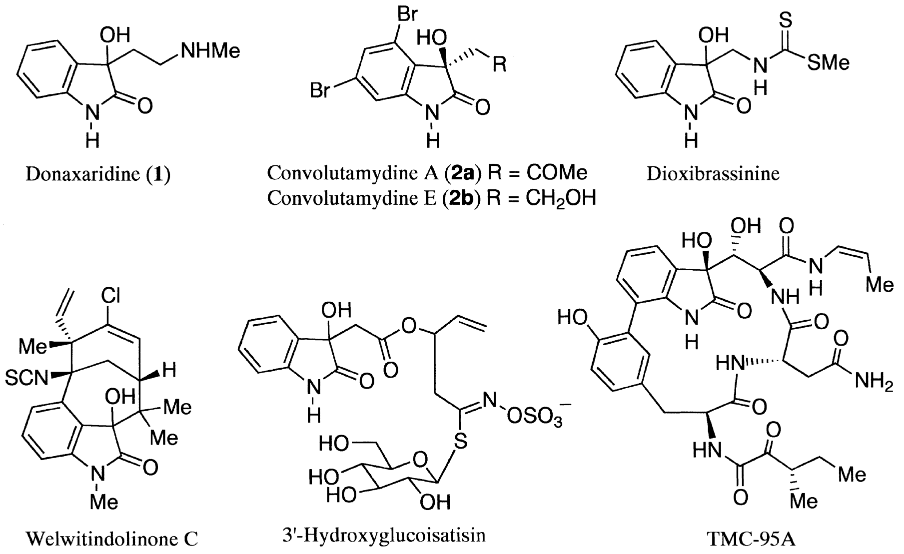


Donaxaridine (**1**)

Convolutamydine A (**2a**) R = COMe
Convolutamydine E (**2b**) R = CH$_2$OH

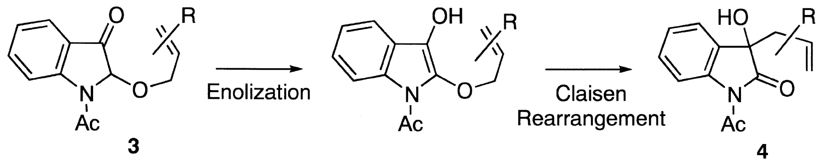
Dioxibrassinine

Welwitindolinone C

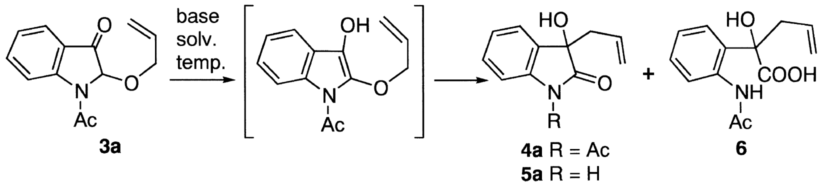
3'-Hydroxyglucoisatisin

TMC-95A

Figure 1. 3-Hydroxy-indolin-2-one alkaloids.



Scheme 1. Enolization–Claisen rearrangement.



Scheme 2. Enolization–Claisen rearrangement of 2-allyloxyindolin-3-one **3a**.

Table 1. Reaction conditions in enolization–Claisen rearrangement of 2-allyloxyin, rdolin-3-one **3a**

Entry	Base	Solvent	Reaction temperature (°C)	Reaction time (min)	Yield (%)		
					4a	**5a**	**6**
1	DBU	MeCN	40	30	9	12	36
2	DBU	CH$_2$Cl$_2$	40	10	12	16	30
3	DBU	Toluene	40	20	70	16	—
4	DBU	Toluene	rt	80	56	13	—
5	DBU	Toluene	110	5	—	55	3
6	DBN	Toluene	40	10	2	70	2
7	DBN	Toluene	rt	60	—	63	6

instead of acetonitrile, the reaction was completed in a shorter time, though by-product **6** was still formed (entry 2). Using toluene as the reaction solvent resulted in reduced formation of **6**, thus improving the total yields of **4a** and **5a** (entry 3). Further attempts to carry out the reaction at various temperatures (entries 4 and 5) confirmed that the reaction conditions shown in entry 3 were the most suitable. When DBN was used instead of DBU, the reaction proceeded more smoothly to give the desired **5a** as the chief product in good yield; however, small amounts of by-product **6** were formed (entries 6 and 7).

Next, we investigated the DBU-promoted reaction of various 2-allyloxyindolin-3-ones **3b-f**. The results are summarized in Scheme 3 and Table 2. When **3b** was treated with DBU in toluene at 40 °C for 10 min, 3-(2-methyl-2-buten-2-yl)-3-hydroxyindolin-2-one **4b** and the deacetylated **5b** were obtained in 70 and 9% yields (entry 1). The

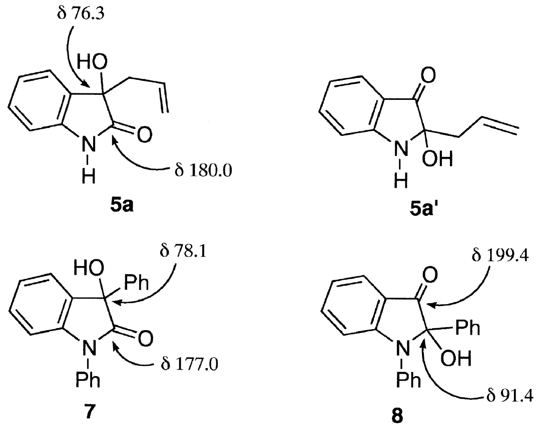
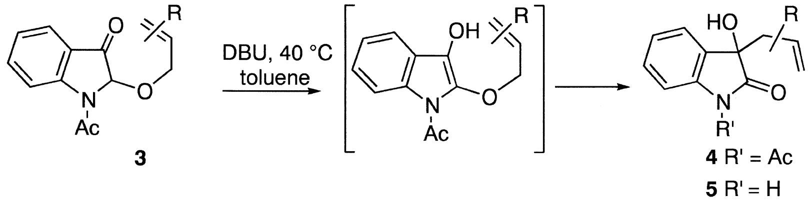


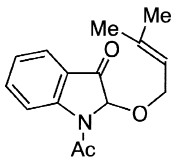
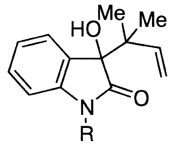
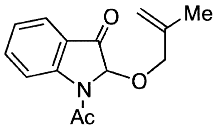
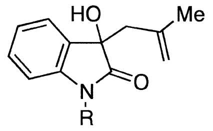
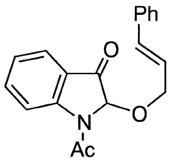
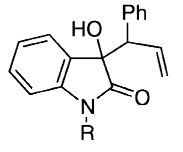
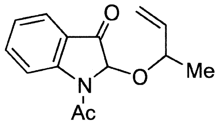
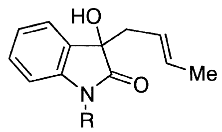
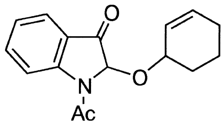
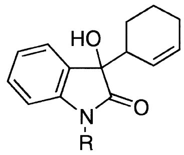
Figure 2. ^{13}C NMR spectra of hydroxyindolin-2-ones and 2-hydroxyindolin-3-one.

reaction of **3c** under the same conditions required prolonged heating (120 min) to give the Claisen products **4c** and **5c** in moderate yields (entry 2). A similar reaction of (*E*)-cinnamyl derivative **3d** for 20 min afforded a mixture of the diastereoisomers of **4d** (50%, 1.5:1) together with **5d** (20%) (entry 3). As examples of secondary rather than primary ethers, reactions of 2-buten-2-yl and cyclo-2-hexenyl derivatives **3e** and **3f** were performed. The reaction of **3e** proceeded through stereoselective Claisen rearrangement to give (*E*)-buten-2-ylindolin-3-ones **4e** (54%) and **5e** (8%) (entry 4). The (*E*)-product **4e** is predominantly produced via chair-like transition state **A** which is more favorable than boat-like transition state **B** (Fig. 3).[25] For the reaction of **3f**, **4f** and **5f** were obtained as respective mixtures of their diastereoisomers (4:1) in 59% and 18% yields (entry 5).



Scheme 3. Enolization–Claisen rearrangement of 2 allyloxyindolin 3-one **3b**-**f**.

Table 2. Preparation of 3-allyl-3-hydroxyindolin-2-ones **4** and **5**

Entry	Indolin-3-one **3**		Reaction time (min)	Product (yield)	
1		**3b**	10		**4b** (70%) **5b** (9%)
2		**3c**	120		**4c** (45%) **5c** (10%)
3		**3d**	20		**4d** (50%)[a] **5d** (20%)[a]
4		**3e**	10		**4e** (54%) **5e** (8%)
5		**3f**	80		**4f** (59%)[a] **5f** (18%)[a]

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[a] The ratio of diastereomers measured by HPLC; **4d** (1:1.4), **5d** (1.1:1), **4f** (2:1), **5f** (4:1).

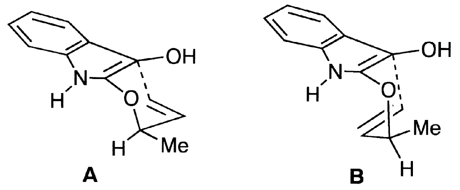


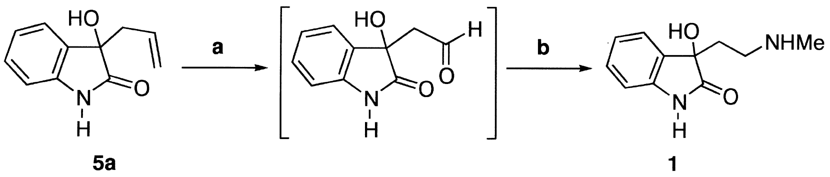
Figure 3. Transition states **A** and **B** in Claisen rearrangement of **3e**.

2.2. Synthesis of (±)-donaxaridine and (±)-convolutamydines A and E

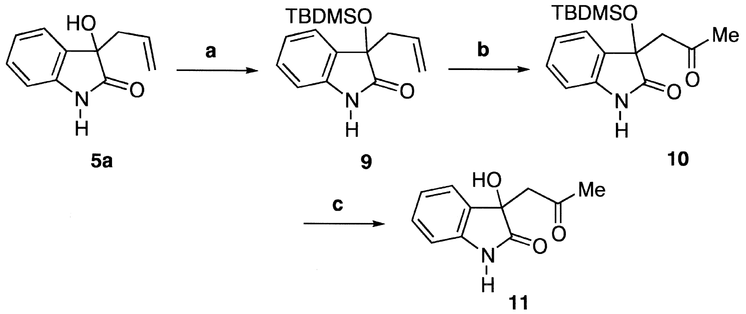
For the synthesis of 3-hydroxyindolin-2-one alkaloids, donaxaridine (**1**) and convolutamydines A (**2a**) and E (**2b**), we attempted transformation of the allyl group of 3-allyl-3-hydroxyindolin-2-one **5a** to aldehyde and acetonyl groups. When **5a** was treated with OsO_4 and *N*-methylmorpholine *N*-oxide (NMO) followed by $NaIO_4$, the unstable aldehyde was obtained and used in the following reaction without purification. Reductive amination of the aldehyde with $NaBH_3CN$ in the presence of methylammonium chloride gave the 3-methylaminoethyl-3-hydroxyindolin-2-one (±)-donaxaridine (**1**) in 41% overall yield from **5a** (Scheme 4). All spectral data are identical to those of the natural and synthetic samples.[1]

For transformation of the allyl group to the acetonyl group, we utilized Wacker oxidation because Wacker oxidation of olefins containing β-oxygenated functional groups with O_2–$PdCl_2$–$CuCl_2$ or –CuCl in DMF–H_2O regioselectively afforded the corresponding ketones.[27] However, Wacker oxidation of **5a** and its *O*-TBDMS derivative **9** under these conditions was very slow (Scheme 5 and Table 3, entries 1–5). When **9** was allowed to react with O_2–$PdCl_2$–CuCl in 1,4-dioxane-H_2O, the desired Wacker oxidation readily took place to afford **10** in high yield (entry 6). In addition, the reaction using other Pd catalysts was attempted to give moderate results (entries 7 and 8). Deprotection of **10** with tetrabutylammonium fluoride (TBAF) and acetic acid gave the 3-acetonyl-3-hydroxyindolin-2-one **11** in moderate yield.[28]

Finally, we applied these preparative methods to the total synthesis of (±)-convolutamydines A (**2a**) and E (**2b**). 4,6-Dibromoindolin-3-one **14** was readily obtained from 4,6-dibromoindole **12**[29] by molybdenum peroxide oxidation followed by demethoxylation[30] in 50% overall



Scheme 4. Reagents: (a) OsO_4, NMO, MeCN, rt, 2 h and then $NaIO_4$, dioxane–H_2O (2:1), rt, 10 min. (b) $MeNH_2$·HCl, MeOH, rt, 3 h and then $NaBH_3CN$, rt, 36 h, 41% (overall yield from **5a**).



Scheme 5. Reagents: (a) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 3 days, 73%. (b) See Table 3. (c) TBAF, AcOH, 0 °C to rt, 50%.

Table 3. Wacker oxidation of 3-allylindolin-2-ones **5a** and **9** with O_2

Entry	Olefin	Reagents (equiv.)	Solvents	Temperature (°C)	Time	Yield (%)
1	**5a**	$PdCl_2$–$CuCl_2$ (0.1:1)	DMF–H_2O[a]	rt	1 week	—
2	**9**	$PdCl_2$–$CuCl_2$ (0.1:1)	DMF–H_2O[a]	rt	1 week	8
3	**9**	$PdCl_2$–$CuCl_2$ (1:10)	DMF–H_2O[a]	rt	1 week	10
4	**9**	$PdCl_2$–$CuCl_2$ (1:10)	DMF–H_2O[a]	50	1 week	11
5	**9**	$PdCl_2$–CuCl (0.1:1)	DMF–H_2O[a]	50	4 days	5
6	**9**	$PdCl_2$–CuCl (0.1:1)	dioxane–H_2O[a]	50	5 h	88
7	**9**	$PdCl_2(PhCN)_2$–$CuCl_2$ (0.1:1)	DMF–H_2O[a]	50	1 day	25
8	**9**	Na_2PdCl_2–*t*-BuO_2H (0.2:1.5)	AcOH–H_2O[b]	50	5 h	71

[a] The ratio of solvents (7:1).
[b] The ratio of solvents (1:1).

yield. Successive bromination of **14**, substitution with allyl alcohol, DBU-promoted enolization–Claisen rearrangement of **15** and hydrolysis with LiOH gave the desired 4,6-dibromo-3-hydroxyindolin-2-one **16** in 84% yield (Scheme 6). The OsO_4–$NaIO_4$ oxidation of **16** followed by $NaBH_4$ reduction yielded (±)-convolutamydine E (**2b**) in 65% yield (Scheme 7).

Synthesis of (±)-convolutamydine A (**2a**) was achieved by TBDMS protection of **16** followed by Wacker oxidation of **17**[31] and deprotection of **18** with tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TAS-F) (Scheme 7).[32] All spectral data of **2a** and **2b** are identical to those of the natural and synthetic samples.[2]

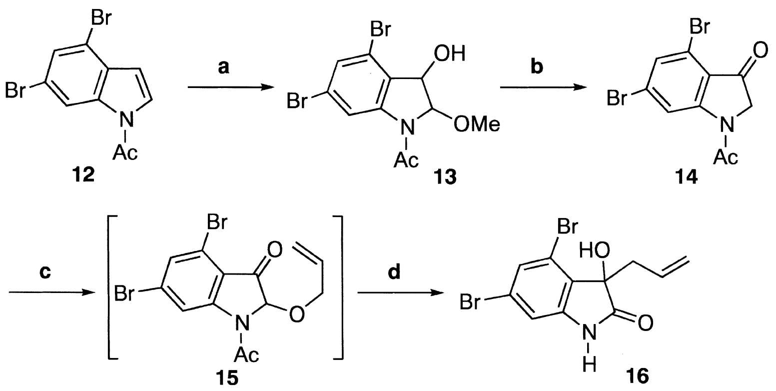
3. Conclusion

In conclusion, we have presented a general and useful method for synthesis of 3-allyl-3-hydroxyindolin-2-ones **5** using Claisen rearrangement triggered by DBU-promoted enolization of 2-allyloxyindolin-3-ones **3**. As examples of the synthetic utility of **5**, we performed transformation of the allyl group in **5a** to aldehyde and acetonyl groups, and respectively applied these methodologies to achieve total synthesis of (±)-donaxaridine (**1**) as well as (±)-convolutamydines A (**2a**) and E (**2b**).

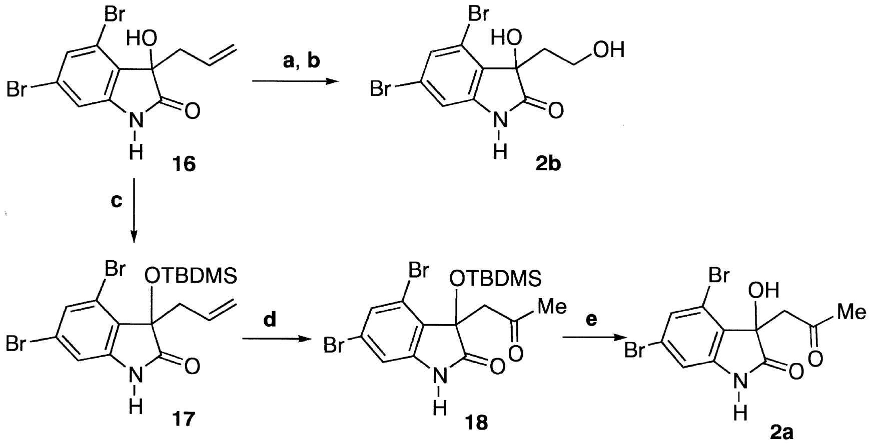
4. Experimental

4.1. General

^1H NMR spectra were obtained using a JEOL JNM-EX-300, JNM-EX-400, or JNM-LA-500 spectrometer with tetramethylsilane as an internal standard. *J*-Values are given in Hz. Mass spectra were obtained using a JEOL JMS-DX302 or JMS-700 instrument with a direct inlet system operating at 70 eV. IR spectra were recorded with a Shimadzu FTIR-8100 spectrophotometer. All mp values are uncorrected, and were measured on a Yanagimoto micromelting point apparatus. HPLC was performed on a JASCO PU-1580 with a JASCO Finepak SIL-5 column. Elemental analyses were obtained using a Yanaco CHN Corder MT-6 elemental analyzer. Column chromatography was carried out on silica gel (Kanto Chemical Co. Inc., Silica Gel 60N, 100–200 mesh and Merck, Silica Gel 60, 230–400 mesh). Preparative TLC was undertaken using Merck Silica Gel 60 F_{254}.



Scheme 6. Reagents: (a) MoO_5·HMPA, MeOH, rt, 1 week, 90%. (b) CSA, MeCN, reflux, 56%. (c) Br_2, CH_2Cl_2, 0 °C, for 2h, and then allyl alcohol, MS 4A, DMF, rt, for 2 days. (d) DBU, toluene, 40 °C, 3 h, and then LiOH, MeOH, rt, 3 days, 84% (overall yield from **14**).



Scheme 7. Reagents: (a) OsO_4, NMO, MeCN, rt 1 h, and then $NaIO_4$, dioxane–H_2O, rt, 1 h. (b) $NaBH_4$ MeOH, 0 °C, 30 min., 65% (c) TBDMSOTf, 2,6-lutidine, 0 °C to rt, 3 days, and then AcOH, H_2O, THF, 80 °C, 2 h, 69%. (d) $PdCl_2$, CuCl, dioxane–H_2O (7:1), 50 °C, 24 h, 12%, (e) TAS–F, 0–15 °C, 2.5 h, 75%.

4.2. General procedure for the preparation of 3-allyl-3-hydroxyindolin-2-ones 4-5

A solution of 2-allyloxyindolin-3-ones **3** (1.0 mmol) and DBU or DBN (1.0 mmol) in dry solvent (13 ml) as shown in Table 1 was stirred at a designated temperature (rt ~110 °C) under nitrogen atmosphere for a designated period (10–120 min), as shown in Tables 1 and 2. The reaction mixture was neutralized with AcOH at 0 °C and extracted with EtOAc. The extract was washed with H_2O, dried over $MgSO_4$, and concentrated under reduced pressure to give a residue. The residue was subjected to chromatography on a silica gel column with EtOAc–hexane (1:1–2) as an eluent to give 3-allyl-3-hydroxyindolin-2-ones **4**, deacetyl derivatives **5**, and carboxylic acid **6**.

4.2.1. 1-Acetyl-3-allyl-3-hydroxyindolin-2-one (4a). Mp 98–101 °C (EtOAc–hexane). IR ($CHCl_3$) cm^{-1}: 3559, 1763, 1717. ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.59 (3H, s, –Ac), 2.60 (1H, dd, *J*=13.1, 8.8 Hz, $-CH_2-$), 2.68 (1H, dd, *J*=13.1, 6.2 Hz, $-CH_2-$), 2.80 (1H, br, –OH), 5.07 (1H, d, *J*=11.2 Hz, $-\mathrm{CH{=}C}\mathit{H}_2$), 5.08 (1H, d, *J*=16.0 Hz, $-\mathrm{CH{=}C}\mathit{H}_2$), 5.49 (1H, m, $-\mathrm{C}\mathit{H}{=}\mathrm{CH}_2$), 7.19 (1H, td, *J*=7.5, 1.0 Hz, Ar-H), 7.32 (1H, td, *J*=7.5, 1.5 Hz, Ar-H), 7.37 (1H, ddd, *J*=7.5, 1.5, 0.6 Hz, Ar-H), 8.15 (1H, d, *J*=7.5 Hz, Ar-H). MS *m/z* (%): 231 (M^+, 11), 190 (47), 162 (22), 148 (100), 43 (11). HRMS *m/z* calcd for $C_{13}H_{13}NO_3$: 231.0895. Found: 231.0896. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.39; H, 5.72; N, 5.82.

4.2.2. 3-Allyl-3-hydroxyindolin-2-one (5a). Mp 112–115 °C (EtOAc–hexane); [lit.[20] 123–124 °C]. IR ($CHCl_3$) cm^{-1}: 1728, 1624. ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.61 (1H, dd, *J*=13.2, 8.5 Hz, $-CH_2-$), 2.75 (1H, dd, *J*=13.2, 6.3 Hz, $-CH_2-$), 3.65 (1H, brs, –OH), 5.10 (1H, d, *J*=18.1 Hz, $-\mathrm{CH{=}C}\mathit{H}_2$), 5.11 (1H, d, *J*=8.8 Hz, $-\mathrm{CH{=}C}\mathit{H}_2$), 5.65 (1H, m, $-\mathrm{C}\mathit{H}{=}\mathrm{CH}_2$), 6.88 (1H, d, *J*=7.6 Hz, Ar-H), 7.07 (1H, t, *J*=7.6 Hz, Ar-H), 7.25 (1H, t, *J*=7.3 Hz, Ar-H), 7.36 (1H, d, *J*=7.3 Hz, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 42.9, 76.3, 110.3, 120.4, 122.9, 124.3, 129.5, 130.06, 130.14, 140.1, 180.0. MS *m/z* (%): 189 (M^+, 9), 148 (100), 120 (3), 92 (3), 65 (3), 39 (2). HRMS *m/z* calcd for $C_{11}H_{11}NO_2$: 189.0790. Found: 189.0788.

4.2.3. 1-Acetyl-3-(2-methyl-3-buten-2-yl)-3-hydroxyindolin-2-one (4b). Mp 73–75 °C (EtOAc–hexane). IR ($CHCl_3$) cm^{-1}: 3565, 1765, 1713. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.06 (3H, s, C–Me), 1.17 (3H, s, C–Me), 2.61 (3H, s, –Ac), 2.84 (1H, brs, –OH), 5.14 (1H, dd, *J*=17.6, 1.1 Hz, $-\mathrm{CH{=}C}\mathit{H}_2$), 5.22 (1H, dd, *J*=10.8, 1.1 Hz, $-\mathrm{CH{=}C}\mathit{H}_2$), 5.94 (1H, dd, *J*=17.6, 10.8 Hz, $-\mathrm{C}\mathit{H}{=}\mathrm{CH}_2$), 7.21 (1H, td, *J*=7.5, 1.1 Hz, Ar-H), 7.36 (1H, td, *J*=7.7, 1.5 Hz, Ar-H), 7.42 (1H, dd, *J*=7.5, 1.5 Hz, Ar-H), 8.21 (1H, dt, *J*=8.4, 0.6 Hz, Ar-H). MS *m/z* (%): 259 (M^+, 0.2), 217 (0.2), 191 (100), 162 (9), 149 (80), 69 (55), 41 (14). HRMS *m/z* calcd for $C_{15}H_{17}NO_3$: 259.1208. Found: 259.1208.

4.2.4. 3-(2-Methyl-3-buten-2-yl)-3-hydroxyindolin-2-one (5b). Mp 188–190 °C (EtOAc–hexane). IR ($CHCl_3$) cm^{-1}: 3431, 1732. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.12 (3H, s, C–Me), 1.18 (3H, s, C–Me), 2.84 (1H, brs, –OH), 5.15 (1H, dd, *J*=17.4, 1.2 Hz, $-\mathrm{CH{=}C}\mathit{H}_2$), 5.24 (1H, dd, *J*=10.8, 1.2 Hz, $-\mathrm{CH{=}C}\mathit{H}_2$), 6.19 (1H, dd, *J*=17.4, 10.8 Hz, $-\mathrm{C}\mathit{H}{=}\mathrm{CH}_2$), 6.81 (1H, d, *J*=7.6 Hz, Ar-H), 7.02 (1H, td, *J*=7.6, 0.9 Hz, Ar-H), 7.25 (1H, td, *J*=7.6 1.3 Hz, Ar-H), 7.37 (1H, dd, *J*=7.6, 0.7 Hz, Ar-H). MS *m/z* (%): 217 (M^+, 2), 149 (100), 119 (3), 69 (15), 41 (7). HRMS *m/z* calcd for $C_{13}H_{15}NO_2$: 217.1103. Found: 217.1098. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 72.05; H, 6.99; N, 6.17.

4.2.5. 1-Acetyl-3-(2-methyl-2-propenyl)-3-hydroxyindolin-2-one (4c). Viscous oil. IR ($CHCl_3$) cm^{-1}: 3559, 1765, 1713. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.40 (3H, s, $-\mathrm{C}\mathit{Me}{=}\mathrm{CH}_2$), 2.60 (3H, s, –Ac), 2.66 (1H, d, *J*=12.9 Hz, $-CH_2-$), 2.75 (1H, dd, *J*=12.9, 0.7 Hz, $-CH_2-$), 2.98 (1H, br, –OH), 4.63 (1H, d, *J*=0.9 Hz, $-\mathrm{CMe{=}C}\mathit{H}_2$), 4.80 (1H, t, *J*=1.7 Hz, $-\mathrm{CMe{=}C}\mathit{H}_2$), 7.24 (1H, td, *J*=7.4, 1.1 Hz, Ar-H), 7.37 (1H, td, *J*=7.4, 1.5 Hz, Ar-H), 7.42 (1H, ddd, *J*=7.4, 1.5, 0.6 Hz, Ar-H), 8.18 (1H, d, *J*=7.7 Hz, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 23.8, 26.5, 47.2, 76.4, 116.5, 116.6, 123.9, 125.4, 128.8, 130.1, 138.3, 139.6, 170.3, 178.5. MS *m/z* (%): 245 (M^+, 22), 190 (42), 162 (31), 148 (100), 130 (3), 102 (3), 90 (4), 43 (10). HRMS *m/z* calcd for $C_{14}H_{15}NO_3$: 245.1052. Found: 245.1052.

4.2.6. 3-(2-Methyl-2-propenyl)-3-hydroxyindolin-2-one (5c). Mp 163 °C (EtOAc–hexane). IR ($CHCl_3$) cm^{-1}: 3435, 1736. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.54 (3H, s, $-\mathrm{C}\mathit{Me}{=}\mathrm{CH}_2$), 1.60 (1H, br, –OH), 2.68 (2H, s, $-\mathrm{C}\mathit{H}_2-$), 4.65 (1H, d, *J*=1.1 Hz, $-\mathrm{CMe{=}C}\mathit{H}_2$), 4.78 (1H, t, *J*=1.7 Hz, $-\mathrm{CMe{=}C}\mathit{H}_2$), 6.83 (1H, d, *J*=7.5 Hz, Ar-H), 7.05 (1H, td, *J*=7.5, 0.9 Hz, Ar-H), 7.24 (1H, td, *J*=7.5, 1.3 Hz, Ar-H), 7.35 (1H, d, *J*=7.5 Hz, Ar-H), 7.76 (1H, br, –NH). MS *m/z* (%): 203 (M^+, 11), 185 (4), 148 (100), 119 (5), 92 (3), 65 (3). HRMS *m/z* calcd for $C_{12}H_{13}NO_2$: 203.0946. Found: 203.0945. Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.74; H, 6.54; N, 6.55.

4.2.7. 1-Acetyl-3-(1-phenyl-2-propenyl)-3-hydroxyindolin-2-one (4d). Viscous oil. IR ($CHCl_3$) cm^{-1}: 3550, 1765, 1715. ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.31 (3H×0.6, s, –Ac), 2.55 (3H×0.4, s, –Ac), 2.97 (1H×0.6, br, –OH), 3.18 (1H×0.4, br, –OH), 3.82 (1H×0.4, d, *J*=10.5 Hz, $-\mathrm{C}\mathit{H}$-Ph), 3.86 (1H×0.6, d, *J*=8.3 Hz, $-\mathrm{C}\mathit{H}$-Ph), 5.26 (1H×0.6, dt, *J*=16.9, 1.3 Hz, $-\mathrm{CH{=}C}\mathit{H}_2$), 5.39 (1H, ddd, *J*=10.5, 2.4, 1.3 Hz, $-\mathrm{CH{=}C}\mathit{H}_2$), 5.43 (1H×0.4, dd, *J*=16.9, 1.3 Hz, $-\mathrm{CH{=}C}\mathit{H}_2$), 6.30 (1H×0.4, m, $-\mathrm{C}\mathit{H}{=}\mathrm{CH}_2$), 6.37 (1H×0.6, m, $-\mathrm{C}\mathit{H}{=}\mathrm{CH}_2$), 6.70 (1H, m, Ar-H), 6.9–7.5 (7H, m, Ph, Ar-H), 7.97 (1H×0.4, d, *J*=8.1 Hz, Ar-H), 7.99 (1H×0.6, d, *J*=7.9 Hz, Ar-H). MS *m/z* (%): 307 (M^+, 0.3), 289 (0.5), 247 (0.6), 148 (12), 117 (100), 91 (4). HRMS *m/z* calcd for $C_{19}H_{17}NO_3$: 307.1208. Found: 307.1205.

The ratio (1:1.4) of two diastereoisomers was determined by HPLC.

4.2.8. 3-(1-Phenyl-2-propenyl)-3-hydroxyindolin-2-one (5d). Mp 179–181 °C (EtOAc–hexane) [lit.[18] mp 160–162 °C; 1:1 diastereomer mixture]. IR ($CHCl_3$) cm^{-1}: 3420, 1736. ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.79 (1H, brs, –OH), 3.85 (1H×0.4, d, *J*=9.7 Hz, $-\mathrm{C}\mathit{H}$-Ph), 3.88 (1H×0.6, d, *J*=8.1 Hz, $-\mathrm{C}\mathit{H}$-Ph), 5.25 (1H×0.4, dt, *J*=17.0, 1.4 Hz,

$-\mathrm{CH{=}C}H_2$), 5.3–5.4 (1H, m, $-\mathrm{CH{=}C}H_2$), 5.44 (1H×0.6, dd, J=17.0, 1.4 Hz, $-\mathrm{CH{=}C}H_2$), 6.3–6.55 (1H, m, $-\mathrm{C}H{=}\mathrm{CH_2}$), 6.63 (1H, m, Ar-H), 6.8–7.55 (7H, m, Ar-H). MS *m/z* (%): 265 (M^+, 2), 247 (2), 148 (38), 117 (100), 91 (7). HRMS *m/z* calcd for $C_{17}H_{15}NO_2$: 265.1103. Found: 265.1095.

The ratio (1.1:1) of two diastereoisomers was determined by HPLC.

4.2.9. (*E*)-1-Acetyl-3-(2-butenyl)-3-hydroxyindolin-2-one (4e). Mp 50–55 °C (EtOAc–hexane). IR ($CHCl_3$) cm^{-1}: 3561, 1765, 1713. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.60 (3H, d, J=6.3 Hz, $-\mathrm{CH{=}CH}Me$), 2.61 (3H, s, –Ac), 2.5–2.69 (2H, m, $-\mathrm{C}H_2-\mathrm{CH{=}CH}$), 2.97 (1H, br, –OH), 5.19 (1H, dddd, J=15.2, 8.7, 6.3, 1.7 Hz, $-\mathrm{C}H{=}\mathrm{CHMe}$), 5.56 (1H, dq, J=15.2, 6.3 Hz, $-\mathrm{CH{=}C}H\mathrm{Me}$), 7.23 (1H, td, J=7.5, 1.1 Hz, Ar-H), 7.36 (1H, td, J=7.5, 1.8 Hz, Ar-H), 7.42 (1H, ddd, J=7.5, 1.5, 0.6 Hz, Ar-H), 8.18 (1H, d, J=8.2 Hz, Ar-H). MS *m/z* (%): 245 (M^+, 12), 203 (3), 191 (43), 162 (32), 148 (100), 130 (3), 102 (3), 90 (4), 43(11). HRMS *m/z* calcd for $C_{14}H_{15}NO_3$: 245.1051. Found: 245.1053.

4.2.10. (*E*)-3-(2-Butenyl)-3-hydroxyindolin-2-one (5e). Mp 115–120 °C (EtOAc–hexane). IR ($CHCl_3$) cm^{-1}: 3435, 1726. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.61 (3H, d, J=6.4 Hz, $-\mathrm{CH{=}CH}Me$), 2.52 (1H, dd, J=13.5, 8.5 Hz, $-\mathrm{C}H_2-\mathrm{CH{=}CH}$), 2.63 (1H, dd, J=13.5, 6.4 Hz, $-\mathrm{C}H_2-\mathrm{CH{=}CH}$), 5.31 (1H, ddd, J=15.0, 8.4, 6.4 Hz, $-\mathrm{C}H{=}\mathrm{CHMe}$), 5.63 (1H, dq, J=15.0, 6.4 Hz, $-\mathrm{CH{=}C}H\mathrm{Me}$), 6.84 (1H, d, J=7.6 Hz, Ar-H), 7.06 (1H, td, J=7.6, 0.9 Hz, Ar-H), 7.25 (1H, td, J=7.6, 1.3 Hz, Ar-H), 7.34 (1H, d, J=7.6 Hz, Ar-H), 7.67 (1H, br, –NH). MS *m/z* (%): 203 (M^+, 12), 185 (7), 170 (8), 148 (100), 119 (3), 92 (4), 65 (3). HRMS *m/z* calcd for $C_{12}H_{13}NO_2$: 203.0946. Found: 203.0943.

4.2.11. 1-Acetyl-3-(2-cyclohexenyl)-3-hydroxyindolin-2-one (4f). Mp 158–160 °C (EtOAc–hexane). IR ($CHCl_3$) cm^{-1}: 3550, 1738. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.7–2.0 (6H, m, $-(\mathrm{CH_2})_3-$), 2.58 and 2.59 (3H, s, –COMe), 2.77 (1H, m, $-\mathrm{C}H-\mathrm{CH_2}-$), 5.6–5.9 (2H, m, $-\mathrm{CH{=}CH}-$), 7.1–7.2 (1H, m, Ar-H), 7.25–7.4 (2H, m, Ar-H), 8.17 (1H, d, J=8.3 Hz, Ar-H). MS *m/z* (%): 271 (M^+, 1), 253 (9), 211 (12), 191 (100), 149 (69), 81 (73), 43 (8). HRMS *m/z* calcd for $C_{16}H_{17}NO_3$: 271.1208. Found: 271.1210.

The ratio (2:1) of two diastereoisomers was determined by HPLC.

4.2.12. 3-(2-Cyclohexenyl)-3-hydroxyindolin-2-one (5f). Mp 158–163 °C (EtOAc–hexane). IR ($CHCl_3$) cm^{-1}: 3440, 1728. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.87 (1H, m, –CH), 1.4–2.0 (5H, m, $-(\mathrm{CH_2})_3-$), 2.80 (1H, m, $-\mathrm{C}H-\mathrm{CH_2}-$), 5.6–5.8 (2H×0.2, m, $-\mathrm{CH{=}CH}-$), 5.95 (1H×0.8, m, $-\mathrm{C}H{=}\mathrm{CH}-$), 6.07 (1H×0.8, m, $-\mathrm{CH{=}C}H-$), 6.85 (1H, d, J=7.5 Hz, Ar-H), 7.04 (1H×0.8, td, J=7.5, 0.9 Hz, Ar-H), 7.07 (1H×0.2, td, J=7.5, 0.9 Hz, Ar-H), 7.3–7.45 (2H, m, Ar-H). MS *m/z* (%): 229 (M^+, 3), 149 (100), 119 (3), 92 (3), 81 (23), 65 (3). HRMS *m/z* calcd for $C_{14}H_{15}NO_2$: 229.1103. Found: 229.1094. Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.04; H, 6.34; N, 5.88. The ratio (4:1) of two diastereoisomers was determined by HPLC.

4.2.13. 2-[2-(Acetylamino)phenyl]-2-hydroxypent-4-enoic acid (6). Viscous oil. IR ($CHCl_3$) cm^{-1}: 3437, 3368, 1740, 1624. ^{1}H NMR ($CDCl_3$, 300MHz) δ: 2.07 (3H, s, –COMe), 2.61 (1H, dd, J=13.6, 7.9 Hz, $-\mathrm{C}H_2-\mathrm{CH}{=}$), 2.81 (1H, ddt, J=13.6, 6.4, 1.2 Hz, $-\mathrm{C}H_2-\mathrm{CH}{=}$), 5.09 (1H, dq, J=17.2, 1.0 Hz, $-\mathrm{CH{=}C}H_2$), 5.10 (1H, dq, J=9.5, 1.0 Hz, $-\mathrm{CH{=}C}H_2$), 5.62 (1H, dddd, J=16.3, 11.0, 8.3, 6.6 Hz, $-\mathrm{C}H{=}\mathrm{CH_2}$), 6.85 (1H, d, J=7.7 Hz, Ar-H), 7.03 (1H, td, J=7.5, 0.9 Hz, Ar-H), 7.21 (1H, d, J=7.7 Hz, Ar-H), 7.26 (1H, td, J=7.7, 1.3 Hz, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 22.6, 40.9, 79.4, 110. 0, 120.7, 122.6, 123.3, 127.6, 129.2, 129.7, 140.6, 169.0, 171.2, 175.6. MS *m/z* (%): 213 (M^+-H_2O, 23), 190 (13), 148 (100). HRMS (M^+-H_2O) *m/z* calcd for $C_{13}H_{13}NO_3$: 231.0896. Found: 231.0900.

4.3. Synthesis of (±)-donaxaridine (1)

4.3.1. Hydrolysis of 1-acetyl-3-allyl-3-hydroxyindolin-2-one (4a) to 3-allyl-3-hydroxyindolin-2-one (5a). A solution of **4a** (51 mg, 0.2 mmol) and LiOH (10%, 0.1 ml) in MeOH (2 ml) was stirred at room temperature for 75 min. The resulting mixture was evaporated under reduced pressure to give a residue, which was extracted with EtOAc. The extract was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel with EtOAc–hexane (2:1) as an eluent to give **5a** (45 mg, 85%).

4.3.2. 3-(2-Methylaminoethyl)-3-hydroxyindolin-2-one [(±)-donaxaridine, 1]. A solution of **5a** (89 mg, 0.47 mmol), OsO_4 (4% in water, 182 μl, d=4.9, 0.14 mmol), and NMO (50% in water, 194 μl, d=1.13, 0.94 mmol) in MeCN (3.5 ml) was stirred at room temperature for 2 h. The reaction mixture was filtered through Celite® 545. The filtrate was concentrated under reduced pressure to give a residue containing 1,2-diol. A solution of the residue and $NaIO_4$ (100 mg, 0.78 mmol) in 1,4-dioxane–H_2O (1.5 ml, 2:1) was stirred at room temperature for 10 min. After diluting the resulting mixture with diethyl ether, the organic layer was washed with H_2O, and the aqueous layer was extracted with EtOAc. The combined organic solution was dried over $MgSO_4$, and concentrated under reduced pressure to give the crude aldehyde **7** [IR ($CHCl_3$) cm^{-1}; 3435, 1738, 1728. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.95 (1H, dd, J=16.6, 1.7 Hz, $-\mathrm{C}H_2\mathrm{CHO}$), 3.02 (1H, dd, J=16.6, 1.7 Hz, $-\mathrm{C}H_2\mathrm{CHO}$), 4.24 (1H, br, OH), 6.89 (1H, d, J=7.7 Hz, Ar-H), 7.05 (1H, t, J=7.7 Hz, Ar-H), 7.25 (1H, t, J=7.7 Hz, Ar-H), 7.32 (1H, d, J=7.7 Hz, Ar-H), 8.54 (1H, br, NH), 9.80 (1H, t, J=1.7 Hz, $-\mathrm{CH_2C}H\mathrm{O}$)], which was used without further purification because of its instability.

A solution of **7** and $MeNH_2\cdot HCl$ (56 mg, 0.85 mmol) in MeOH (2.7 ml) was stirred at room temperature. After disappearance of **7** was confirmed by TLC (3 h), $NaBH_3CN$ (82 mg, 1.3 mmol) was added to the reaction mixture at room temperature. The mixture was stirred for 36 h and extracted with CH_2Cl_2. The extract was washed with H_2O, dried over $MgSO_4$, and concentrated under reduced pressure to give a residue. The residue was subjected to chromatography on a silica gel column with EtOAc–hexane (2: 1) as an eluent to give (±)-donaxaridine (**1**, 40 mg, 41%). Mp 175 °C; [lit.[1a] 175–176 °C]. IR (KBr) cm^{-1}; 3404, 3236, 1673, 1613, 1470, 1308. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.42 (1H, td, *J*=12.8, 9.0 Hz, –C–C*H*$_2$–CH_2–), 2.77 (1H, ddd, *J*=12.8, 6.2, 1.7 Hz, –C–C*H*$_2$–CH_2–), 2.97 (3H, s, –NMe), 3.26 (1H, td, *J*=9.5, 6.2 Hz, –C*H*$_2$–N–), 3.34 (1H, ddd, *J*=9.5, 9.5, 1.7 Hz, –C*H*$_2$–N–), 4.31 (1H, brs, –OH), 4.71 (1H, br, –NH), 6.69 (1H, td, *J*=7.6, 1.3 Hz, Ar-H), 6.72 (1H, dd, *J*=7.9, 0.7 Hz, Ar-H), 6.88 (1H, dd, *J*=7.6, 1.5 Hz, Ar-H), 7.11 (1H, td, *J*=7.6, 1.5 Hz, Ar-H). MS *m/z* (%): 206 (M^+, 100), 188 (9), 177 (8), 173 (7), 159 (6), 149 (42), 148 (11), 147 (29), 146 (37), 135 (24), 130 (19), 120 (58), 93 (13), 92 (18), 77 (6), 65 (15), 58 (43). HRMS *m/z* calcd for $C_{11}H_{14}N_2O_2$:206.1055. Found: 206.1050.

4.4. Synthesis of 3-acetonyl-3-hydroxyindolin-2-one (11)

4.4.1. 3-Allyl-3-*tert*-butyldimethylsilyloxyindolin-2-one (9). A solution of 3-hydroxyindolin-2-one **5a** (57 mg, 0.3 mmol), 2,6-lutidine (128 mg, 1.2 mmol), and *tert*-butyldimethylsilyl triflate (317 mg, 1.2 mmol) in dry CH_2Cl_2 (4 ml) was stirred at 0 °C to room temperature for 1 h. The reaction mixture was diluted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a residue, of which a solution in THF–AcOH–H_2O (1:1:1, l ml) was stirred at 80 °C for 5 h. The resulting mixture was diluted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography with EtOAc–hexane (1:3) as an eluent to give TBDMS ether **9** (67 mg, 73%). viscous oil. IR ($CHCl_3$) cm^{-1}: 1720. ^{1}H NMR (300 MHz, $CDCl_3$) δ: −0.26 (3H, s, –SiMe), 0.06 (3H, s, –SiMe), 0.87 (9H, s, –Si^{t}Bu), 2.53 (1H, dd, *J*=13.4, 8.2 Hz, –C*H*$_2$CH=), 2.74 (1H, dd, *J*=13.4, 6.4 Hz, –C*H*$_2$CH=), 5.02 (2H, m, –CH=C*H*$_2$), 5.66 (1H, m, –C*H*=CH_2), 6.86 (1H, d, *J*=7.7 Hz, Ar-H), 7.03 (1H, dd, *J*=7.7, 8.3 Hz, Ar-H), 7.25 (2H, m, Ar-H), 8.74 (1H, brs, –NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: −3.9, −3.5, 18.2, 25.8, 44.3, 78.0, 110.2, 119.1, 122.2, 124.6, 129.2, 130.9, 131.0, 140.0, 180.0. MS (FAB) *m/z* (%): 304 (MH^+, 11), 246 (18), 205 (19), 172 (100). HRMS (FAB, MH^+) *m/z* calcd for $C_{17}H_{26}NO_2Si$: 304.1733. Found: 304.1739.

4.4.2. Typical procedure for Wacker oxidation of 3-allylindolin-2-one 9 to 3-(2-oxopropyl)-3-TBDMS-oxy-indolin-2-one (10). A suspension of palladium (II) chloride (8 mg, 0.0043 mmol) and copper (I) chloride (4.3 mg, 0.043 mmol) in dioxane–H_2O (7:1, 1 ml) was vigorously stirred with bubbling oxygen gas at room temperature for 1 h. The indolin-2-one **9** (13 mg, 0.043 mmol) was added to the mixture. After heating at 50 °C for 5 h, the reaction mixture was cooled to room temperature and diluted with CH_2Cl_2. The precipitate was filtered off, and the filtrate was dried over $MgSO_4$, and evaporated off. The obtained residue was purified by flash silica gel column chromatography with EtOAc–hexane (2:3) as an eluent to give 3-(2-oxopropyl)-indolin-2-one **10** (12 mg, 88%). viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: −0.19 (3H, s, –SiMe), 0.08 (3H, s, –SiMe), 0.95 (9H, s, –Si^{t}Bu), 2.14 (3H, s, –COMe), 3.07 (1H, d, *J*=15.9 Hz, –CH_2CO–), 3.25 (1H, d, *J*=15.9 Hz, –CH_2CO–), 6.83 (1H, d, *J*=7.8 Hz, Ar-H), 7.02 (1H, t, *J*=7.8 Hz, Ar-H), 7.21–7.29 (2H, m, Ar-H), 7.46 (1H, brs, –NH). MS (FAB) *m/z* (%): 320 (MH^+, 54), 262 (37), 188 (38), 146 (100), 73 (44). HRMS (FAB, MH^+) *m/z* calcd for $C_{17}H_{25}NO_3Si$: 320.1682. Found: 320.1671.

4.4.3. 3-(2-Oxopropyl)-3-hydroxyindolin-2-one (11). A solution of TBDMS derivative **10** (8.4 mg, 0.026 mmol), TBAF (1.0 M, 22 μl, 22 μmol), and AcOH (15 μl) in THF (1 ml) was stirred at room temperature for 3 days. After addition of EtOAc, the organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by preparative TLC with EtOAc as a developing solvent to give 3-hydroxy-indolin-2-one **11** (2.5 mg, 50%). Mp 165–168 °C [lit.[9a] mp 166–168 °C]. IR ($CHCl_3$) cm^{-1}: 3445, 1740, 1624. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.20 (3H, s, –COMe), 2.97 (1H, d, *J*=17.0 Hz, –C*H*$_2$CO–), 3.19 (1H, d, *J*=17.0 Hz, –C*H*$_2$CO–), 4.37 (1H, br, –OH), 6.87 (1H, d, *J*=7.5 Hz, Ar-H), 7.05 (1H, td, *J*=7.5, 0.9 Hz, Ar-H), 7.27 (1H, td, *J*=7.5, 1.2 Hz, Ar-H), 7.35 (1H, d, *J*=7.5 Hz, Ar-H), 7.65 (1H, br, –NH). MS *m/z* (%): 205 (M^+, 88), 187 (24), 172 (27), 162 (98), 148 (100), 120 (72), 92 (41), 43 (36). HRMS *m/z* calcd for $C_{11}H_{11}NO_3$: 205.0739. Found: 205.0742.

4.5. Syntheses of (±)-convolutamydines A (2a) and E (2b)

4.5.1. 1-Acetyl-4,6-dibromo-3-hydroxy-2-methoxy-indoline (13). A solution of 1-acetyl-4,6-dibromoindole[29] (**12**, 7.0 g, 22.0 mmol) and hexamethylphosphoramide-oxodiperoxomolybdenum (VI) (MoO_5·HMPA) (17.2 g 46.3 mmol) in MeOH (450 ml) was stirred at room temperature for a week. The resulting mixture was concentrated under reduced pressure, treated with sat. Na_2SO_3, and extracted with CH_2Cl_2. The extract was washed with H_2O, dried over $MgSO_4$, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography with EtOAc–hexane (1:1) as an eluent to give 3-hydroxy-2-methoxyindoline **13** (7.2 g, 90%). Mp 165–168 °C (CH_2Cl_2). IR ($CHCl_3$) cm^{-1}: 3600, 1686. ^{1}H NMR ?300 MHz, $CDCl_3$) δ: 2.32 (3H, s, N–COMe), 2.37 (1H, brs, OH), 3.43 (3H, s, –OMe), 4.89 (1H, brs, –C*H*–OH), 5.28 (1H, brs, –C*H*–OMe), 7.46 (1H, d, *J*=1.7 Hz, Ar-H), 8.27 (1H, br, Ar-H). MS *m/z* (%): 367 (M+4, 25), 365 (M+2, 53), 363 (M^+, 26), 324 (47), 322 (89), 320 (43), 292 (62), 290 (100), 288 (46), 280 (26), 278 (21), 263 (16), 213 (10), 211 (16), 149 (13), 43 (59). HRMS *m/z* calcd for $C_{11}H_{11}Br_2NO_3$: 362.9106. Found: 362.9106.

4.5.2. 1-Acetyl-4,6-dibromoindolin-3-one (14). A solution of **13** (364 mg, 1.0 mmol) and 10-camphorsulfonic acid (715 mg, 3.08 mmol) in MeCN was heated under reflux for 30 min. The reaction mixture was evaporated under reduced pressure and extracted with EtOAc. The extract was washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduce pressure. The residue was purified by silica gel column chromatography with EtOAc–hexane (1:1) as an eluent to give indolin-3-one **14** (186 mg, 56%). Mp 160–164 °C (EtOAc–hexane). IR ($CHCl_3$) cm^{-1}: 1727, 1693. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.33 (3H, s, N–COMe), 4.32 (2H, s, $COCH_2N$–), 7.49

(1H, d, *J*=1.5 Hz, Ar-H), 8.76 (1H, brs, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 24.5, 56.7, 119.5, 120.4, 121.5, 131.5, 132.1, 155.0, 167.8, 190.7. MS *m/z* (%): 335 (M+4, 23), 333 (M+2, 47), 331 (M^+, 24), 293 (48), 291 (100), 289 (51), 263 (23), 43 (25). HRMS *m/z* calcd for $C_{10}H_7Br_2NO_2$: 330.8844. Found: 330.8836.

4.5.3. 3-Allyl-4,6-dibromo-3-hydroxyindolin-2-one (16). A solution of bromine (1.0 M in CH_2Cl_2, 78 μl) was added to a solution of **14** (7.8 mg, 23.5 μmol) in CH_2Cl_2 at 0 °C for 2 h. The reaction mixture was extracted with EtOAc, and the extract was then washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduce pressure to give a residue. A mixture of the residue (9.7 mg), allyl alcohol (*d*=0.85, 6.2 μl, 91 μmol) and MS 4A (22 mg) in DMF (1 ml) was stirred at room temperature for 2 days. The reaction mixture was diluted with diethyl ether and filtrated through Celite® 545. The filtrate was evaporated under reduced pressure to give a residue, which was extracted with EtOAc and 5% NH_4OH. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The obtained residue (9.1 mg) and DBU (3.6 mg, 23.5 μmol) in toluene (1 ml) was stirred at 40 °C for 3 h. The mixture was neutralized with AcOH, diluted in H_2O, and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. A mixture of the residue and 10% LiOH (25 μl) in MeOH was stirred at room temperature for 3 days. After evaporation, an EtOAc solution of the residue was washed with H_2O and brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography with EtOAc–hexane (1:1) as an eluent to give indolin-2-one **16** (6.9 mg, 84%). Mp 220–222 °C (EtOAc–hexane). IR (KBr) cm^{-1}: 3378, 1733, 1641. ^{1}H NMR (300 MHz, acetone-d_6) δ: 2.59 (1H, dd, *J*=12.8, 7.4 Hz, $-CH_2-$), 3.08 (1H, dd, *J*=12.8, 7.4 Hz, $-CH_2-$), 4.77 (1H, ddt, *J*=10.1, 2.2, 1.3 Hz, $=CH_2$), 4.91 (1H, ddt, *J*=17.3, 2.2, 1.3 Hz, $=CH_2$), 5.09 (1H, s, –OH), 5.22 (1H, ddt, *J*=17.3, 10.1, 7.4 Hz, $-CH{=}CH_2$), 6.94 (1H, d, *J*=1.7 Hz, Ar-H), 7.22 (1H, d, *J*=1.7 Hz, Ar-H). MS *m/z* (%): 349 (M+4, 2), 347 (M+2, 4), 345 (M^+, 2), 308 (49), 306 (100), 304 (51). HRMS *m/z* calcd for $C_{11}H_9Br_2NO_2$: 344.9000. Found: 344.9003.

4.5.4. (±)-Convolutamydine E (2b). A solution of 3-allylindolin-2-one **16** (10 mg, 29 μmol), OsO_4 (4% aqueous solution, *d*=1.04, 53 μl, 8.7 μmol), and NMO (50% aqueous solution, *d*=1.13, 13 μl, 63 μmol) in MeCN (3 ml) was stirred at room temperature for 1 h. The reaction mixture was evaporated under reduced pressure. A solution of the residue and $NaIO_4$ (7.5 mg, 30 μmol) in aqueous 1,4-dioxan (3 ml) was stirred at room temperature for 1 h. The reaction mixture was extracted with EtOAc, and the extract was then washed with H_2O and brine, dried over $MgSO_4$, and concentrated under reduced pressure. To a solution of the residue in MeOH (2 ml), $NaBH_4$ (11 mg, 0.3 mmol) was gradually added at 0 °C, and the mixture was then stirred at 0 °C for 30 min. After adding aqueous NH_4Cl followed by evaporating the MeOH under reduced pressure, the residue was extracted with EtOAc. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc–hexane (3:1) as an eluent to give (±)-convolutamydine E (**2b**, 6.6 mg, 65%). Mp 204–206 °C ($CHCl_3$) [lit.[2c] oil]. IR (KBr) cm^{-1}: 3350, 1736, 1605, 1261, 1088, 801. ^{1}H NMR (300 MHz, C_5D_5N) δ: 3.10 (2H, t, *J*=7.3 Hz, $-C-CH_2CH_2O-$), 3.96 (2H, m, $-C-CH_2CH_2O-$), 7.02 (1H, d, *J*=1.6 Hz, Ar-H), 7.41 (1H, d, *J*=1.6 Hz, Ar-H), 8.31 (1H, s, –NH). ^{13}C NMR (C_5D_5N, 125 MHz) δ: 39.3, 58.1, 77.4, 112.6, 112.6, 120.9, 128.2, 130.2, 146.7, 180.6. MS (FAB) *m/z* (%): 354 (MH^++4, 50), 352 (MH^++2, 99), 350 (MH^+, 53), 336 (20), 334 (32), 332 (16), 306 (57), 304 (100), 302 (50). HRMS (FAB, MH^+) *m/z* calcd for $C_{10}H_9Br_2NO_3$: 349.9027. Found: 349.9031.

4.5.5. 3-Allyl-4,6-dibromo-3-(*tert*-butyldimethylsilyloxy)indolin-2-one (17). A solution of 3-hydroxyindolin-2-one **16** (59 mg, 0.17 mmol), TBDMSOTf (235 mg, 0.89 mmol), and 2,6-lutidin (95 mg, 0.89 mmol) in CH_2Cl_2 was stirred at 0 °C to room temperature. After 3 days, the reaction mixture was quenched with brine and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and concentrated under reduced pressure. A solution of the residue in AcOH–THF–H_2O (1:1:1, 1 ml) was stirred at 80 °C for 2 h. After cooling, the reaction mixture was extracted with EtOAc. The extract was washed with H_2O and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column with EtOAc–hexane (1:4) as an eluent to give 3-silyloxy-indolin-2-one **17** (56 mg, 69%). Viscous oil. IR ($CHCl_3$) cm^{-1}: 3427, 1732, 1641. ^{1}H NMR (300 MHz, $CDCl_3$) δ: −0.13 (3H, s, –SiMe), 0.06 (3H, s, –SiMe), 0.90 (9H, s, –Si^{t}Bu), 2.78 (1H, dd, *J*=12.8, 7.5 Hz, $=CH-CH-$), 3.24 (1H, dd, *J*=12.8, 7.0 Hz, $=CH-CH-$), 4.92 (1H, d, *J*=9.9 Hz, $C{=}CH_2$), 5.17 (1H, d, *J*=16.5 Hz, $C{=}CH_2$), 5.29 (1H, m, $-CH{=}CH_2$), 6.97 (1H, d, *J*=1.4 Hz, Ar-H), 7.34 (1H, d, *J*=1.4 Hz, Ar-H), 8.25 (1H, br, NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: −3.5, −3.4, 18.4, 25.8, 40.7, 79.3, 112.3, 120.0, 120.5, 123.2, 127.8, 129.4, 129.7, 142.6, 177.3. MS (FAB) *m/z* (%): 464 (MH^++4, 4), 462 (MH^++2, 7), 460 (MH^+, 5), 4221 (7), 420 (10), 4187 (6), 4065 (15), 404 (24), 402 (12), 365 (12), 363 23), 361 12), 332 (51), 330 (100), 328 (52). HRMS (FAB, MH^+) *m/z* calcd for $C_{17}H_{23}Br_2NO_2Si$: 459.9943. Found: 459.9920.

4.5.6. 4,6-Dibromo-3-(*tert*-butyldimethylsilyloxy)-3-(2-oxopropyl)indolin-2-one (18). A suspension of palladium (II) chloride (3.2 mg, 0. 019 mmol) and copper (I) chloride (18.8 mg, 0.19 mmol) in dioxane–H_2O (7:1, 3 ml) was vigorously stirred with bubbling oxygen gas at room temperature for 1 h under oxygen atmosphere. The indolin-2-one **17** (87 mg, 0.19 mmol) was added to the mixture. After heating at 50 °C for 24 h, the reaction mixture was cooled to room temperature and diluted with CH_2Cl_2. The precipitate was filtered off, and the filtrate was dried over $MgSO_4$, and evaporated off. The obtained residue was purified by flash silica gel column chromatography with EtOAc–hexane (1:1) as an eluent to give 3-(*tert*-butyldimethylsilyloxy)-3-(2-oxopropyl)indolin-2-one (**18**, 11 mg, 12%). Viscous oil. IR ($CHCl_3$) cm^{-1}: 3431, 1747, 1718. ^{1}H NMR (300 MHz, $CDCl_3$) δ: −0.21 (3H, s, –SiMe), 0.04 (3H, s, –SiMe), 0.87 (9H, s, –Si^{t}Bu), 2.08 (3H, s, –COMe), 3.31 (1H, d, *J*=18.2 Hz, –CHCO–), 3.99 (1H, d, *J*=18.2 Hz, –CHCO–), 6.97 (1H, d, *J*=1.4 Hz, Ar-H), 7.27 (1H, d, *J*=1.4 Hz, Ar-H), 7.56 (1H, br, –NH). MS (FAB) *m/z* (%): 480

(MH$^+$+4, 14), 478 (MH$^+$+2, 26), 476 (MH$^+$, 13), 422 (12), 420 (23), 418 12), 348 (16), 346 (30), 344 (16), 306 (50), 34 (100), 302 (34). HRMS (FAB, MH$^+$) *m/z* calcd for $C_{17}H_{23}Br_2NO_3Si$: 475.9892. Found: 475.9879.

4.5.7. (±)-Convolutamydine A (2a). Tris(dimethylamino)-sulfur (trimethylsilyl)difluoride (TAS-F) (6.4 mg, 23 μmol) was gradually added to a stirred solution of indolin-2-one **17** (11 mg, 23 μmol) in dry DMF (1 ml) at 0 °C. The mixture was stirred at 15 °C for 2.5 h, diluted with EtOAc, washed with sat. $KHSO_4$, and extracted with EtOAc. The extract was dried over $MgSO_4$ and evaporated. The obtained residue was purified by silica gel column chromatography with EtOAc–hexane (3:2) as an eluent to give (±)-convolutamydine A (**2a**, 6.3 mg, 75%). Mp 192–195 °C (EtOAc–hexane) [lit.[2b] mp 190–195 °C]. IR ($CHCl_3$) cm^{-1}: 3430, 1747, 1610. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.16 (3H, s, –COMe), 3.34 (1H, d, J=17.3 Hz, –CHCO–), 3.73 (1H, d, J=17.3 Hz, –CHCO–), 5.12 (1H, br, –OH), 7.00 (1H, d, J=1.6 Hz, Ar-H), 7.32 (1H, d, J=1.7 Hz, Ar-H), 7.74 (1H, s, –NH). MS *m/z* (%): 365 (M+4, 20), 363 (M+2, 42), 361 (M$^+$, 21), 322 (8), 320 (16), 318 (10), 308 (47), 306 (100), 304 (59), 279 (44), 277 (91), 275 (48), 252 (14), 250 (31), 248 (18), 170 (18), 168 (18), 88 (12). HRMS *m/z* calcd for $C_{11}H_9Br_2NO_3$: 360.8949. Found: 360.8947.

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Synthesis of extended spacer-linked neooligodeoxysaccharides by metathesis olefination and evaluation of their RNA-binding properties

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Abstract—The preparation of linear 1,4-butanediol-linked oligodeoxysugars **50**–**53**, **58** and **60** is described which are potential binders to polynucleotides. Various aminodeoxymonosaccharides **9**, **13**–**18**, **30**, **31** and **40**–**42** which are either allylated at the anomeric center or at C4 were subjected to the metathesis olefination protocol. Depending on the position of allylation *E*/*Z*-mixtures of C_2-symmetric head-to-head or tail-to-tail homodimers were formed. Among them, saccharides **13**, **30**, **31** and **40** were transformed into the corresponding 1,4-butanediol linked disaccharides **50**–**53** by catalytic hydrogenation of the central olefinic double bond and exhaustive deprotection. In order to target extended spacer-linked neooligosaccharides homodimeric aminoglycoside **37** was bisallylated and subjected to cross metathesis conditions using methyl 4-*O*-allyl daunosamide **40** as reaction partner which yielded two desired trimeric and tetrameric linearly spacer-linked daunosamine derivatives. After hydrogenation and deprotection two additional probes **58** and **60** for nucleic acid binding studies were at hand.
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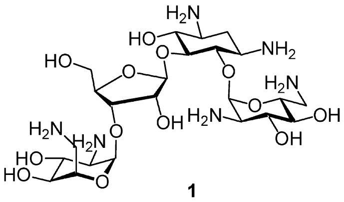
1. Introduction

Oligocationic compounds, like protonable polyamines and guanidines often play key roles in various biological processes. The pharmacological activity of these molecules is due to their ability to specifically bind to polynucleotides thus giving rise to the possibility of inhibiting DNA duplication[1] or RNA catalysis, or the forcing of RNA into an alternate conformation.[2] Aminodeoxy sugars present in glycoconjugates like the anthracycline antibiotic daunomycin as well as amino glycoside antibiotics like neomycin B (**1**) typically target polynucleotides. The major drawback of aminoglycosides in medicinal applications, however, is their significant oto- and nephrotoxicity.[2,3] Still, despite the emergence of aminoglycoside-modifying enzymes[4] some aminoglycosides such as gentamicin C_{1a} and tobramycin are used in clinical practice. Nevertheless, their basic scaffold together with a variety of different techniques for joining monomeric subunits make them ideal for the synthesis of new selective and potentially less toxic structures that can be used for studying ligand binding to oligonucleotides and thus lead to modified aminoglycosides with better resistance towards bacteria.[5]



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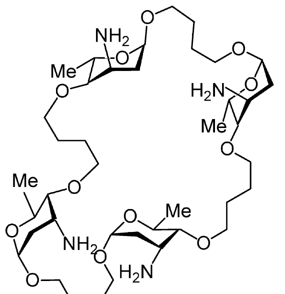

2

Recently, we initiated a project on the preparation of new 1,4-butanediol-linked oligomeric deoxysugars, most of them containing amino groups.[6] The synthetic strategy allows to rapidly assemble extended linear and cyclic oligosaccharides like **2**[7–9] which can serve as probes for studying interactions with oligonucleotides. Their oligomeric character in association with the larger number of amino groups which are essential for efficient binding should lead to cooperative effects[10] and hence tighter binding to oligonucleotides. The major advantage of our synthetic approach is the fact that once the monomeric

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Keywords: Aminoglycosides; Carbohydrates; Metathesis; Olefination; Rearrangement; RNA-binding.

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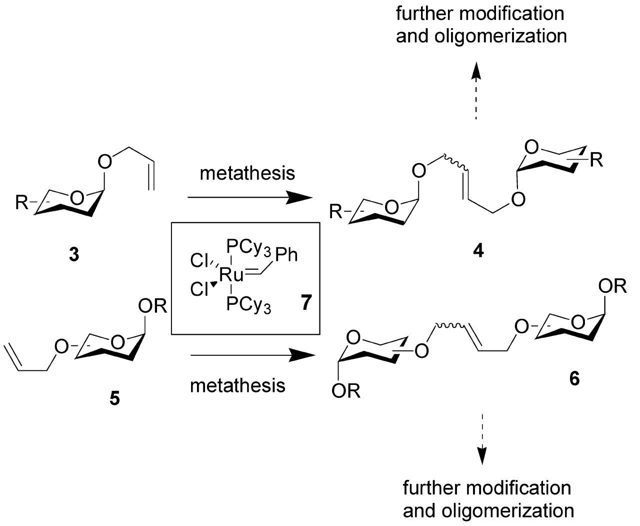
building blocks are at hand the problem of stereocontrol of the anomeric center does not need to be considered in the following coupling steps.

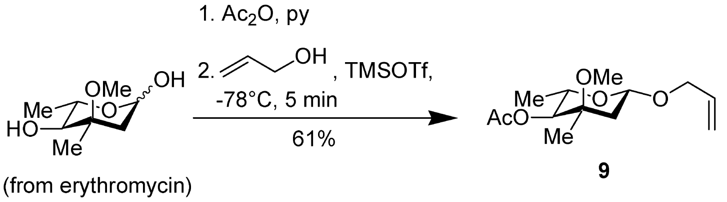
In this report we give a comprehensive summary of our synthetic studies towards novel linear 1,4-butanediol-linked neooligodeoxysaccharides. The 1,4-butane diol linkage between two adjacent deoxysugar moieties is efficiently constructed by metathesis-based alkene dimerization[11] of appropriately allylated glycosides using the Grubbs precatalyst **7** (Scheme 1). Depending on the attachment of the allyl group in hexoses **3** or **5** either head-to-head **4** or tail-to-tail **6** dimers are formed which can be further modified or oligomerized.



Scheme 1. Concepts for the homodimerization of pyranoses by metathesis olefination.

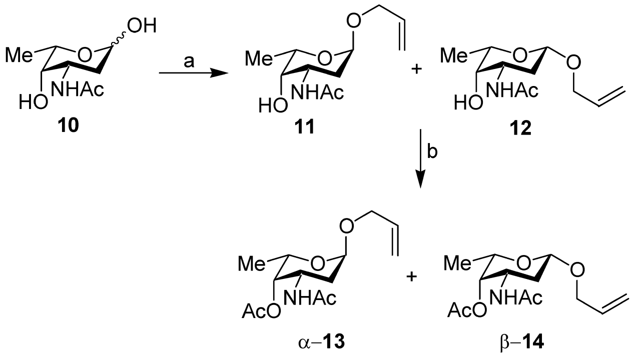
2. Results and discussions

A diverse number of allylated hexoses had to be prepared prior to dimerization and oligomerization. The monomeric *O*-allylated building blocks **9**, **13–18**, **30**, **31** and **40–42** (Tables 1–3) were prepared as pure isomers according to literature procedures.[12,13] Most syntheses of these allylated products started from D-glucose, D-galactose, L-rhamnose and L-fucose. In contrast to these purely synthetic approaches, the methyl-branched allyl glycoside **9** (see also Table 1, entry 5) was obtained from erythromycin which had been degraded under strongly acidic conditions (0.75 N HCl, 20 h, rt, 90%) to furnish L-cladinose **8** (Scheme 2). L-Cladinose was transformed into allyl glycoside **9** by two standard reactions. Only the β-anomer is formed upon glycosidation which can be ascribed to the quaternary center at C-3 and the axial methyl group which limits access of the allyl alcohol from the α-face.



Scheme 2. Preparation of allyl cladinoside **9**.

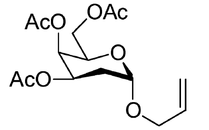
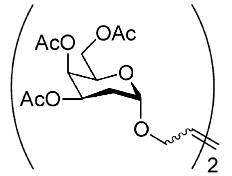
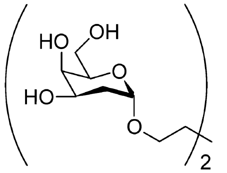
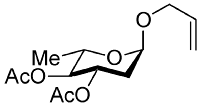
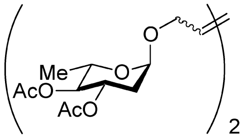
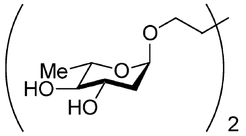
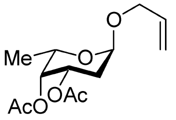
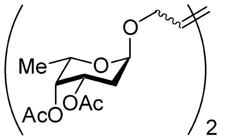
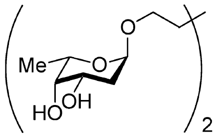
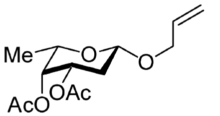
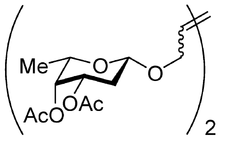
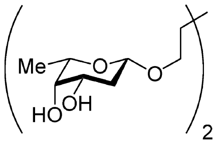
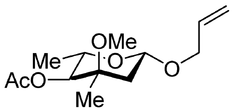
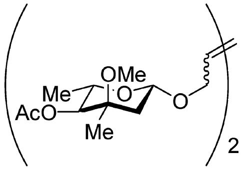
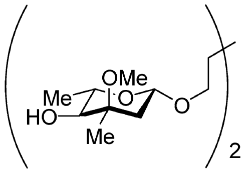
N-Protected L-daunosamine **10** was prepared in 20 g scale from D-mannose according to Horton and Weckerle.[14] *O*-Allylation afforded anomeric allyl glycosides **11** and **12** in 82% which could be separated by column chromatography. 4-*O*-Acylation yielded the two monomeric building blocks α-**13** and β-**14** (Scheme 3).



Scheme 3. Preparation of *N*-acetyl-daunosamides **13** and **14**. Reagents and conditions: (a) allyl alcohol, Dowex 50 ($H^{\oplus}$-form), 70 °C (82% for two steps), separation; (b) Ac_2O, py, 4-DMAP$_{cat.}$, rt (for **13**: quant.; for **14**: 94%).

In the following, a set of homodimeric 1,4-butanediol linked deoxyhexoses were prepared by utilizing Grubbs metathesis catalyst **7**. In Table 1 dimerization of allyl glycosides **9** and **15–18** is shown. Apart from β-allyl glycoside **18** the metathesis products **19–23** are commonly formed as *E*/*Z*-mixtures with similar ratios (commonly around 5–6:1; for **22**: *E*/*Z*=3.8:1 and for **23**: *E*/*Z*=3.5:1). The *E*-selectivity of this process is in full accordance with most intermolecular metathesis olefinations described in the literature. The preferential formation of *trans*-α,β-disubstituted metallocyclobutane intermediates is responsible for this preferred *E*-selectivity.[15] The ratios of the inseparable *E*/*Z*-mixtures described in this report were assigned by ^1H and ^{13}C NMR spectroscopy and the correlation spectra derived therefrom. Determination of the ratio has typically been achieved by indirect methods such as analysis of the chemical shifts of olefinic carbon atoms in the ^{13}C NMR spectrum.[16] It is based on the observation, that the carbon atom in the α-position of *Z*-configured olefines is magnetically more shielded than the allylic carbon atom in the corresponding *E*-configured isomer. This phenomenon is called γ-effect and leads to a ca. 5 ppm upfield shift for the *Z*-isomer. In conjunction with our synthetic efforts in this field, the group of Glaser recently developed a new NMR-technique which

Table 1. Preparation of head-to-head 1,4-butanediol linked 2-deoxy hexoses

Entry	Allyl glycoside		Head-to-head homodimers by metathesis[a,b]	Yield *E*/*Z*-ratio	Deprotected 1,4-butanediol linked homodimer[a,b]	Yield
1		**15**		**19** (41%) *E*/*Z*=5:1[c]		**24** (99%)
2		**16**		**20** (50%) *E*/*Z*=5:1[d]		**25** (99%)
3		**17**		**21** (60%) *E*/*Z*=6:1		**26** (98%)
4		**18**		**22** (84%) *E*/*Z*=3.8:1		**27** (99%)
5		**9**		**23** (87%) *E*/*Z*=3.5:1		**28** (95%)

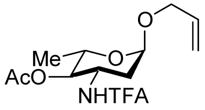
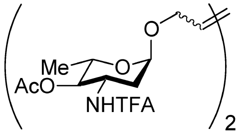
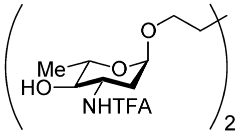
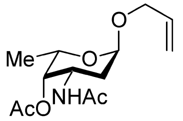
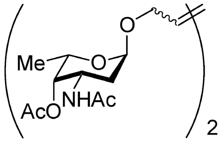
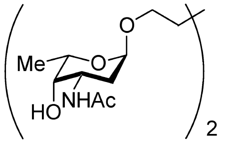
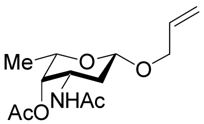
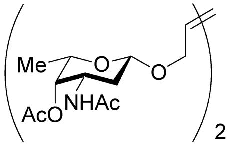
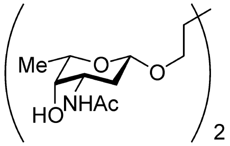
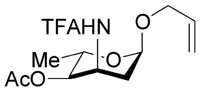
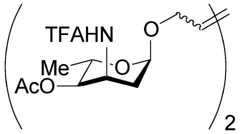
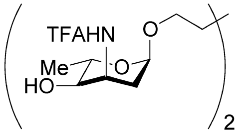
[a] For experimental details refer to Section 4.

[b] Product ratios were determined from the ^{1}H NMR spectra of the crude products; yields refer to isolated yields of pure products.

[c] Only 51% of starting material were transformed.

[d] Only 66% of starting material were transformed.

Table 2. Preparation of head-to-head 1,4-butanediol linked 3-amino-2,3-dideoxy hexoses

Entry	Allyl glycoside		Head-to-head homodimers by metathesis[a,b]	Yield *E*/*Z*-ratio	Deprotected 1,4-butanediol linked homodimer[b]	Yield
1		**30**		**32** (87%) *E*/*Z*=2.5:1		**36** (98%)
2		**13**		**33** (82%) *E*/*Z*=3.3:1		**37** (83%)
3		**14**		**34** (73%) *E*/*Z*=1:2		**38** (78%)
4		**31**		**35** (54%) *E*/*Z*=2.5:1		**39** (85%)

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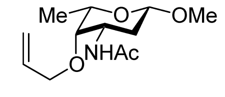
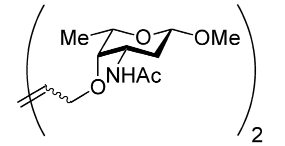
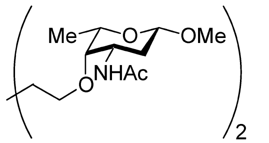
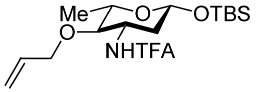
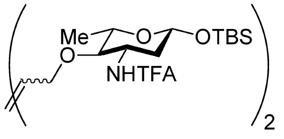
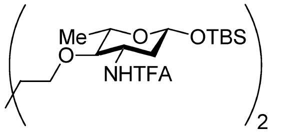
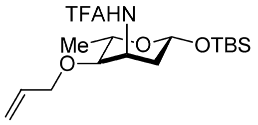
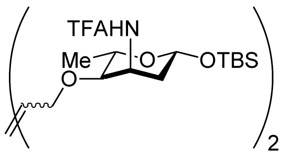
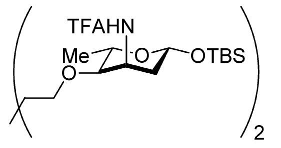
[a] For experimental details refer to Section 4.

[b] Product ratios were determined from the ^{1}H NMR spectra of the crude products; yields refer to isolated yields of pure products.

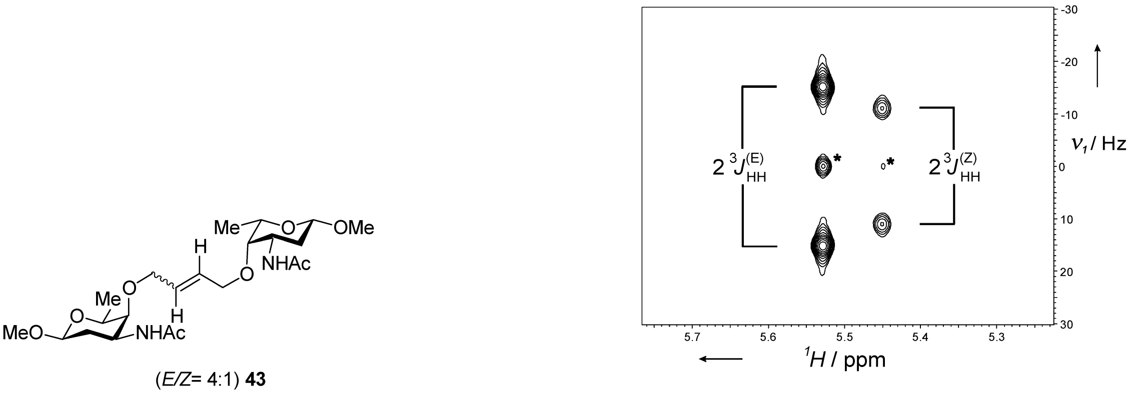
Table 3. Preparation of tail-to-tail 1,4-butanediol linked 3-amino-2,3-dideoxy hexoses

Entry	4-*O*-Allylated glycoside	Tail-to-tail homodimers by metathesis[a,b]	Yield *E*/*Z*-ratio	Deprotected 1,4-butanediol linked homodimer[b]	Yield
1	 **40**		**43** (90%) *E*/*Z*=5:1		**46** (99%)
2	 **41**		**44** (89%) *E*/*Z*=6:1		**47** (95%)
3	 **42**		**45** (62%) *E*/*Z*=only *E*-isomer detected[c]		**48** (82%)

[a] For experimental details refer to Section 4.

[b] Product ratios were determined from the ^{1}H NMR spectra of the crude products; yields refer to isolated yields of pure products.

[c] Enolethers **49** were formed in 30% yield.

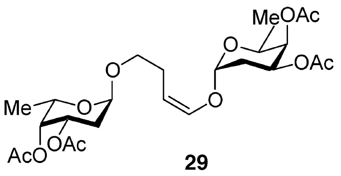


(*E*/*Z*= 4:1) **43**

Figure 1. Determination of the double bond configuration of the homodimeric metathesis product **43** by NMR-spectroscopy.

allows to distinguish vicinal protons as found in C_2-symmetrical *E*- and *Z*- alkenes, respectively. In this two dimensional experiment the ^3J(H,H)-coupling of interest is evolved under selective isotopic mixing conditions and the proton signal is acquired. Besides a significant sensitivity gain the experiment permits a straightforward interpretation, since only the desired ^3J(H,H)-coupling gives rise to an observable splitting.[17] The advantages of this method are (i) short recording time and (ii) direct determination of coupling constants *J* of the central vicinal alkenic hydrogens in C_2-symmetric compounds. We routinely used this new NMR-tool for determining the *E*/*Z*-ratio of the metathesis products as exemplified for tail-to-tail homodimer **43** (vide supra) in Figure 1.

In some cases (entries 1 and 2), the reduced yields for the dimers is associated with incomplete transformation. The amount of catalyst **7** employed was substrate dependent. Often, the catalyst was added in up to three portions which in some cases accumulated to 10 mol%. In the case of allyl 2-deoxy-α-L-fucoside **17**, the metathesis step yielded an unsymmetrical byproduct which was characterized as the *Z*-configured enol ether **29** (17%). It is obvious that the catalyst is not only able to catalyze dimerization but also promotes prototopic rearrangements of double bonds in allyl ethers. This property of catalyst **7** has been observed before by various research groups.[5,18]



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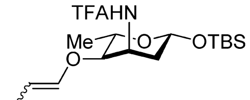
The primary olefination products were further modified by reduction of the olefinic double bond [10% Pd/C, H_2, trace Et_3N, $MeOH/CH_2Cl_2$ (2:1) or PtO_2, H_2, ethyl acetate, rt] and complete removal of the *O*-protection [NaOMe, MeOH, 0 °C to rt or Amberlyst A-21 (hydroxide form), MeOH, rt] to furnish C_2-symmetric dimers **24–28** in excellent yield.

In analogy to the deoxygenated allyl glycosides listed in Table 1, we utilized this synthetic sequence for the preparation of 1,4-butanediol-linked aminodeoxy saccharides **36–39** starting from **13**, **14**, **30** and **31** (Table 2). Under similar reaction conditions as described above, homodimers **32–35** were formed with less pronounced *E*/*Z*-selectivity which in the case of β-allyl glycoside **14** leads to reversed selectivity (Table 2, entry 3). Acetyl as well as trifluoracetyl protection of the amino groups were tolerable under the olefination conditions,[4] while the azido functionality is not compatible. The more polar 4-hydroxy analogue of allyl glycoside **13** is less suitable as a substrate for the metathesis olefination. The dimerization proceeded in only 47% (*E*/*Z*=4.5:1) isolated yield. Finally, catalytic hydrogenation of the intermediate alkene gave homodimer **37** in 95% yield.

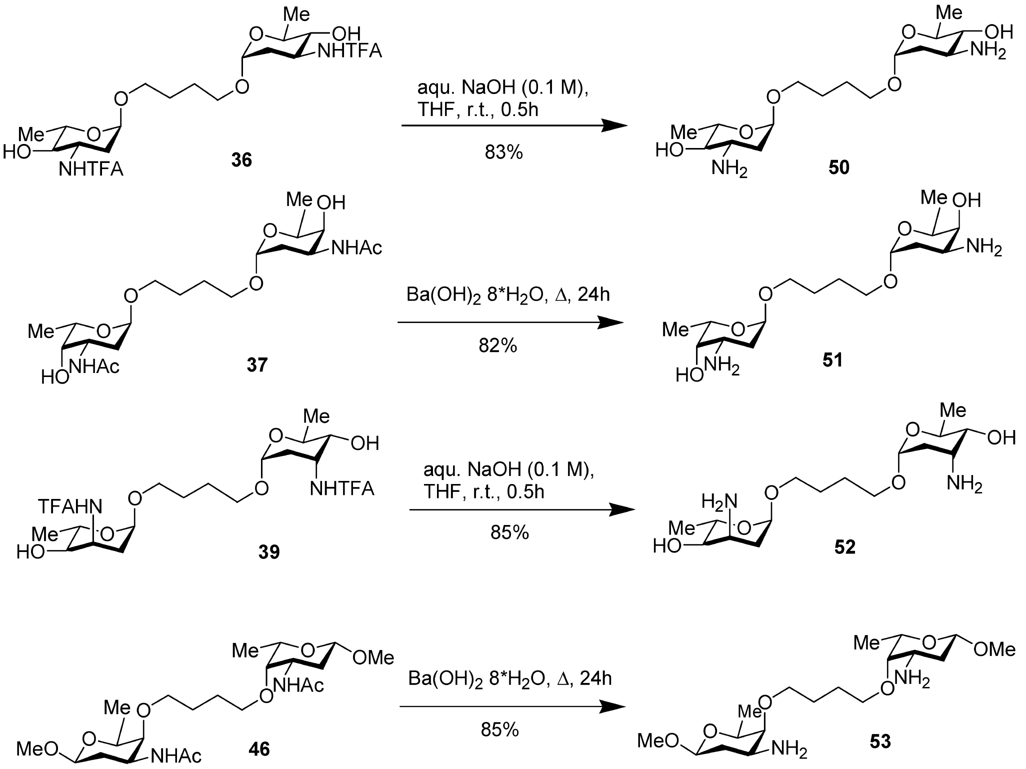
In addition, we conducted metathesis olefination reactions on 4-*O*-allylated aminoglycosides **40–42** which yield tail-to-tail homodimers **43–45** in very good yield and for substrates **40** and **41** with the expected *E*/*Z*-selectivity (Table 3). *Ribo*-configured aminoglycoside **42** which contains an axially orientated trifluoacetamido group yielded homodimer **45** with exclusive *E*-selectivity. The yield was reduced due to formation of enolether **49** which resulted from rearrangement of the olefinic double bond in the starting allyl ether.[7,16] As continuation of the work reduction of the alkenic double bond yielded 1,4-butanediols **46–48**. It should be noted that silyl glycosides **47** and **48** are very versatile dimers as two glycosyl donor functionalities are present which can conveniently be utilized for further derivatization or extension by glycosidation.[17,18]



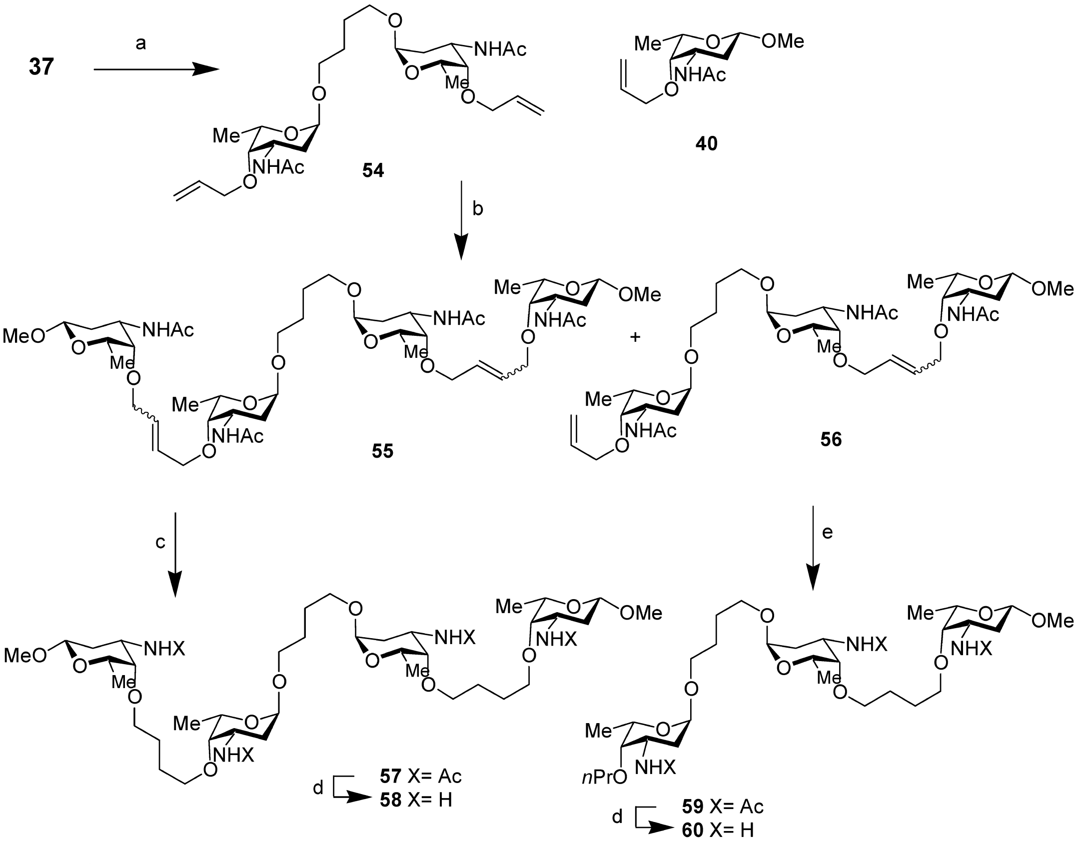
49

Removal of the amino protection is achieved under standard hydrolytic conditions as exemplified for homodimers **36**, **37**, **39** and **46** (Scheme 4). The resulting diamines **50–53** were isolated in good yields after chromatographic purification on a RP-18 phase.

In the next phase of the project extention of the linear homodimeric aminoglycosides was envisaged (Scheme 5). Starting from diol **37** bisallylation was achieved under neutral conditions using excess of allyl iodide in the presence of freshly prepared silver oxide. The bisallylated neodisaccharide **54** underwent metathesis olefination in the presence of 4-*O*-allylated methyl daunosamide **40** to give two olefination products **55** (16%) and **56** (27%) as complex



Scheme 4. Deprotection of acylated homodimers.



Scheme 5. Preparation of linear spacer-linked tri- and tetrasaccharides. Reagents and conditions: (a) 6 equiv. allyl iodide, Ag_2O, CH_3CN, Δ, 48 h (96%); (b) 4.6 equiv. **40** and **7** (3.6 mol%), benzene$_{abs.}$, rt, 1 h, then **7** (2.4 mol%), Δ, 14 h (**55**: 16%; **56**: 27%; **43**: 50%); (c) 10% Pd–C, H_2, trace Et_3N, MeOH, CH_2Cl_2 (2:1), rt, 24 h; (d) $Ba(OH)_2 \cdot 8H_2O$, H_2O, Δ, 30 h (**58**: 64% for two steps; **60**: 84% for two steps); (e) PtO_2, H_2, ethyl acetate, CH_2Cl_2, MeOH (16:8:1), rt, 20 h (92%).

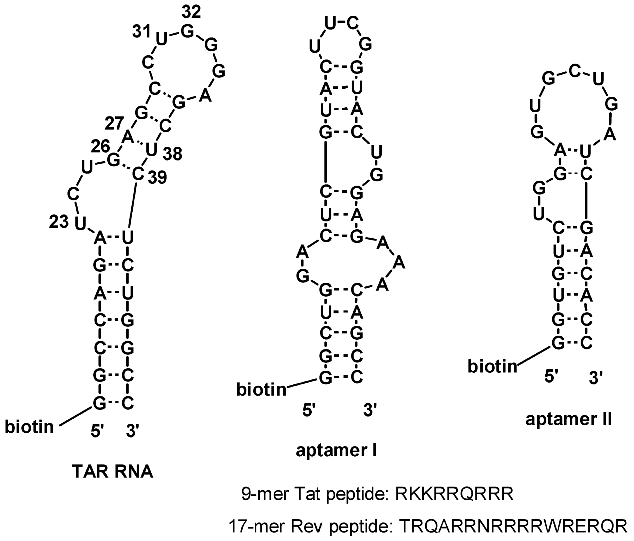


Figure 2. TAR-RNA, aptamers, 9-mer peptide and 17-mer peptide.

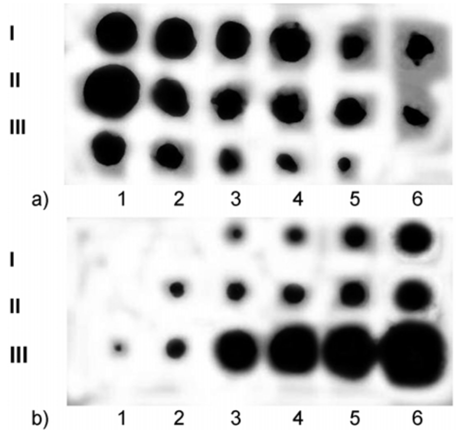


Figure 3. Dot blot analysis of Tat-TAR binding in the presence of the aminoglycosides **2**, **58** and **60**. Dot blot analysis of Tat-TAR binding in the presence of the aminoglycosides 2, 58 and 60 at concentrations varying from 1.2 to 22 mM. TAR 0.16 μM, 9-mer peptide 222 μM. Lane I, linear neotrisaccharide 58; lane II, linear neotetrasaccharide 60; lane III, cyclic neotetrasaccharide 2: (a) above: nitrocellulose membrane (retains peptide-bound RNA); (b) below: positively-charged nylon membrane (retains unbound RNA). The aminoglycoside concentration was increased from left to right.

mixtures of *E*/*Z*-isomers along with homodimer **43** (see Table 3, entry 1) (50% based on **40**) which resulted from dimerization of the starting monosaccharide. In order to suppress facile macrocyclization[5] the monomeric 4-*O*-allyl daunosamide **40** had to be employed in 6-fold excess.

In order to evaluate the RNA-affinity of these extended linear aminoglycosides we screened for aminoglycosides that interfere with the binding of proteins with RNA. Screening was conducted for about twenty aminoglycosides including 1,4-butanediol linked derivatives. For the three aminoglycosides **2**, **58** as well as **60** we observed non specific binding to RNA in a simplified HPLC system.[19] Then, three RNAs were chosen as the targets for further binding studies. First the HIV-1 TAR-RNA was selected for which binding of the Tat protein (Fig. 2) is well characterized and the known interaction between the RNA and the peptide could therefore be used in competitive binding studies.[20] In order compare the interaction with other RNAs, two aptamers selected for binding to the REV protein were investigated in competitive dot blot experiments with the 17-mer binding protein.[21] The interaction of the Tat protein with the TAR-RNA is a pivotal event in the life cycle of the HIV virus and inhibiting this particular interaction could be of great medicinal use.

For screening of the aminoglycoside library, the different behavior of peptide-bound and peptide-free RNA was utilized. In an typical binding-experiment the TAR-RNA (0.16 μM) and the 9-mer Tat peptide (222 μM) were incubated for 15 min. Then, the different aminoglycosides were added in concentrations varying from 1.2 to 22 mM for the individual aminoglycoside subunits.

After additional 15 min the mixture was filtered with the aid of a dot-blot apparatus in which first a nitrocellulose membrane (retains RNA-peptide complexes) and secondly a positively charged nylon membrane (retains all RNA) had been inserted. Filtration of the above mentioned individual binding-assays then results in separation of both, the peptide-bound and the aminoglycoside-bound RNA on separate membranes. In Figure 3 the dot blot results for the aminoglycosides **2**, **58** and **60** are shown. Figure 3 (top) shows the peptide bound fraction of the TAR-RNA at the nitrocellulose membrane.

The amount of aminoglycoside subunits increased from left to right (1.2–22 mM) with an concomitant decrease of the peptide bound RNA. Lane I depicts the dot blots for linear trimer **58**, lane II for linear tetramer **60** and lane III the cyclic tetramer **2**. Figure 3 (bottom) shows the results of the same experiments on the positively charged nylon membrane. It can be seen that in the case of the cyclic tetramer **2** most of the RNA at a aminoglycoside concentration higher than 5.6 mM is peptide free and has passed the nitrocellulose membrane. Surprisingly, an extraordinary increase in binding affinity was observed when cyclic tetramer **2** was employed implying that not only the increase of positive charges and the potential of forming hydrogen bonds but also the conformation of the ligand adds significantly to these interactions.[22] These findings suggest that particularly cyclic tetrameric structures interfere significantly with the TAR–Tat interaction. For comparison the two aptamers were also used in dot blot experiments. Here we used a 17-mer peptide with a binding constant of ca. 100 μM with respect to the two aptamer RNAs. These binding constants are approximately 10-fold stronger than the one for the Tat–TAR interaction (1 mM). As a consequence we had to use the aminoglycoside **2** at a 10-fold higher concentration compared to the Tat-TAR experiment. The dot blot experiments shown in Figure 4. In these dot blot experiments the aptamers (0.16 μM) and the 17-mer Rev peptide (100 μM) were incubated for 25 min. Then, aminoglycoside **2** was added in concentration ranging from 1 to 200 mM. In Figure 4 (top) the peptide-bound aptamers are shown. Figure 4 (bottom) represents the aptamer content that has passed the first membrane and was collected on the nylon membrane. It can be seen that aminoglycoside **2** substitutes the peptide from aptamer II at lower concentrations compared to aptamer I. Since this

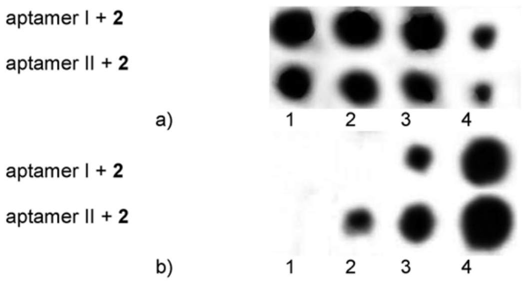


Figure 4. Dot blot analysis of aptamers in the presence of the aminoglycosides **2**. Dot blot analysis of aptamers in the presence of the aminoglycoside 2 at 80, 120, 160 and 200 mM. Aptamer 0.16 μM, 17-mer peptide 100 μM. Lane I: aptamerI+2; lane II: aptamerII+2: a) above: nitrocellulose membrane (retains peptide-bound RNA); b) below: positively-charged nylon membrane (retains unbound RNA). The aminoglycoside concentration was increased from left to right.

binding assay utilizes the different behavior of peptide-bound vs peptide-free RNA, no exact measurement of the aminoglycoside-RNA binding constant can be obtained since binding of the aminoglycoside can occur while the RNA is still bound to the peptide.

3. Conclusion

In summary, we described a rapid synthetic route towards 1,4-butanediol linked neoaminodeoxyoligosaccharides by employing the metathesis olefination. The synthetic strategy is based on a modular approach by using stereochemically defined hexose building blocks. The assembling of the chains is rapidly achieved without considering stereochemical aspects, which commonly arises when glycosidation protocols are exploited. Preliminary binding studies with selected RNAs revealed that in comparison to their linear counterparts macrocyclic spacer-linked aminoglycosides can efficiently bind to the TAR-RNA.

4. Experimental

4.1. General remarks and starting materials

All temperatures quoted are uncorrected. Optical rotations were recorded on a Perkin–Elmer 141 polarimeter (wavelength 589 nm) and are given in 10^{-1} deg cm^2 g^{-1}. ^{1}H NMR, ^{13}C NMR, ^{1}H, ^{1}H and ^{1}H, ^{13}C COSY as well as NOESY spectra were recorded on a Bruker DPX 200-NMR and a ARX 400-NMR spectrometer for solutions in $CDCl_3$ using residual $CHCl_3$ as internal standard (7.26 ppm) unless otherwise stated. Multiplicities are described using the following abbreviations: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. Chemical shift values of ^{13}C NMR spectra are reported as values in ppm relative to residual $CHCl_3$ (77 ppm) as internal standards. The multiplicities refer to the resonances in the off-resonance spectra and were elucidated using the distortionless enhancement by polarization transfer (DEPT) spectral editing technique, with secondary pulses at 90 and 135°. Multiplicities are reported using the following abbreviations: s=singlet (due to quaternary carbon), d=doublet (methine), q=quartet (methyl), t=triplet (methylene). Mass spectra were recorded on a type LCT-spectrometer (Micromass). In addition, fast atom bombardment (FAB) mass spectra were obtained on a BG Analytical ZAB-2F (Ion Tech FAB gun, 8 kV, Xe carrier gas). Ion mass (*m/z*) signals are reported as values in atomic mass units followed, in parentheses, by the peak intensities relative to the base peak (100%). Combustion analyses were performed by the Institut für Pharmazeutische Chemie, Technische Universität Braunschweig and the Institut für Organische Chemie, Universität Hannover. All solvents used were of reagent grade and were further dried. Reactions were monitored by thin layer chromatography (TLC) on silica gel 60 F^{254} (E. Merck, Darmstadt) and spots were detected either by UV-absorption or by charring with H_2SO_4/4-methoxybenzaldehyde in methanol. Preparative column chromatography was performed on silica gel 60 (E. Merck, Darmstadt).

Compounds **11**, **13**, **14**, **21**, **26**, **33**, **34**, **37** and **38** were prepared according to reference.[6b] Hexoses **31**, **35**, **39**, **41**, **42**, **44**, **45**, **47** and **48** were obtained following the procedure described by us before.[7] Aminoglycoside **10** was prepared by a classical procedure accurately described in reference.[14] Hexose **15** was obtained according to the reported procedure in Ref. 23. The allyl aminoglycosides **17** and **18** were prepared as described in Ref. 24.

For the sake of convenience linear spacer-linked tri- and tetramers **55**, **56**, **57**, **58**, **59** and **60** are given the indices I, II, III for the individual pyranoses starting with the methyl glycoside moiety which is designated the label I.

4.1.1. Allyl 4-*O*-acetyl-2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-β-L-ribo-hexopyranoside (9). L-Cladinose **8** (1.0 g, 5.7 mmol) was dissolved in pyridine (20 ml) and acetic anhydride (6.4 mol, 9 ml) with stirring at 0 °C for 2 h. To this solution was added a mixture of water and dichloromethane (1:1, 14 ml). The aqueous phase was extracted with dichloromethane (3×10 ml). The combined organic extracts were washed with brine (40 ml), dried ($MgSO_4$) and evaporated in vacuum. The residue was dissolved in absolute allyl alcohol (0.6 ml) and absolute ether (10 ml) and stirred at −78 °C. After 15 min trimethyltrifluoromethane sulfonate (0.5 equiv., 556 mg) in ether was added and stirring was continued for 5 min. The mixture was hydrolyzed with aqueous saturated ammonium chloride and was allowed to warm up to rt. After washing with dichloromethane (3×10 ml) the combined organic extracts were dried ($MgSO_4$) and evaporated in vacuum. The crude product was purified by column chromatography over silica gel (petroleum ether/ethyl acetate=5:1) to yield momomer **9** (0.90 g, 3.5 mmol; 61%).

Compound **9**. Colorless oil; $[\alpha]_D^{20}=-33.5$ ($CHCl_3$, $c=1$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.91 (ddd, 1H, J=17.2, 10.4, 5.1 Hz, CH=), 5.27 (dq, 1H, J=17.3, 1.9 Hz, CHH'=CH–), 5.17 (ddd, 1H, J=10.4, 3.5, 1.9 Hz, CHH'=CH–), 4.72 (dd, 1H, J=9.7, 2.0 Hz, 1-H), 4.65 (d, 1H, J=9.7 Hz, 4-H), 4.35 (ddt 1H, J=12.7, 5.2, 1.5 Hz, OCHH'), 4.02 (ddt, 1H, J=12.8, 6.2, 1.4 Hz, OCHH'), 3.95 (dq, 1H, J=9.7, 6.3 Hz, 5-H), 3.26 (s, 3H, CH_3O), 2.22 (dd, 1H, J=14.2, 2.0 Hz, 2_{eq}-H), 2.12 (s, 3H, CH_3CO), 1.52 (dd, 1H, J=14.2, 9.7 Hz, 2_{ax}-H), 1.14 (d, 3H, J=6.3 Hz, 6-H), 1.12 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.5, 134.3, 117.1, 97.2, 78.6, 74.6, 69.6, 67.9, 49.6, 39.3, 20.9, 20.6, 17.6; HRMS for $C_{13}H_{22}O_5$ (M^++MeCN+Na): calcd 322.1630, found 322.1637.

4.1.2. Allyl 3-acetamido-2,3,6-trideoxy-α-L-lyxo-hexopyranoside (11) and allyl 3-acetamido-2,3,6-trideoxy-β-L-lyxo-hexopyranoside (12). Methyl 3-acetamido-2,3,6-trideoxy-β-L-lyxo-hexopyranoside (500 mg, 2.46 mmol) was hydrolyzed to yield **10**. The crude product was not further purified but was directly employed for the next allylation step. In the following the suspension of Dowex-50 (H^+-form) in allyl alcohol was heated under reflux for 30 min, filtered and finally washed with absolute allyl alcohol. The resin (1.19 g) was added to a solution of the crude material **10** which was dissolved in absolute allyl alcohol (25 ml). The suspension was stirred at 70 °C for 1 h, at which time TLC dichloromethane/methanol=10:1) indicated that the allylation was complete. The mixture was filtered with suction while hot and washed with acetone. After addition of triethyl amine (2 ml) the combined filtrates were concentrated in vacuum to give an oily residue. This crude material was purified by column chromatography (dichloromethane/methanol=10:1) to afford two fractions of the α- and β-isomers (α/β=5.8:1) of the title compounds **11** and **12** (461 mg, 2.01 mmol; 82% for two steps). The physical and spectroscopic data for α-isomer were reported in Refs. 6b,7.

Compound **12**. Colorless oil; ^1H NMR (200 MHz, $CDCl_3$): δ=6.38 (d, 1H, J=8.4 Hz, NH), 5.89 (dddd, 1H, J=17.2, 10.4, 6.0, 5.2 Hz, CH=), 5.25 (dq, 1H, J=17.2, 1.8 Hz, CHH′=CH–), 5.21 (d, 1H, J=4.2 Hz, 1-H), 5.18 (dq, 1H, J=10.4, 1.5 Hz, CHH'=CH–), 4.36 (ddt, 1H, J=8.6, 2.8, 1.8 Hz, 3-H), 4.20 (ddt, 1H, J=12.8, 5.2, 1.5 Hz, OCHH′), 3.97 (ddt, 1H, J=12.8, 6.0, 1.4 Hz, OCHH'), 3.75 (q, 1H, J=6.0 Hz, 5-H), 3.73 (d, 1H, J=3.0 Hz, 4-H), 2.88 (d, 1H, J=3.6 Hz, OH), 2.19 (ddd, 1H, J=13.8, 8.6, 4.8 Hz, 2-H_{ax}), 1.94 (s, 3H, CH_3CO), 1.82 (dd, 1H, J=13.8, 1.8 Hz, 2-H_{eq}), 1.20 (d, 3H, J=6.0 Hz, 6-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=169.6, 134.2, 117.1, 102.9, 89.6, 67.9, 67.8, 49.5, 38.9, 23.2, 18.7); calcd (%) for $C_{11}H_{19}NO_4$ (229.13): C 57.62, H 8.35, N 6.10, found C 57.81, H 8.31, N 5.98.

4.1.3. Allyl 3-acetamido-4-*O*-acetyl-2,3,6-trideoxy-β-L-lyxo-hexopyranoside (14). Allyl 3-acetamido-2,3,6-trideoxy-β-L-lyxo-hexopyranoside **12** (208 mg, 0.91 mmol) was dissolved under nitrogen in dry dichloromethane (10 ml). To this solution were added triethyl amine (1 ml) and acetic anhydride (1.2 equiv., 0.10 ml). After addition of a small amount of 4-dimethylamino pyridine (0.2 equiv., 22 mg) the mixture was stirred at rt for 1 h, whereupon TLC (petroleum ether/ethyl acetate 5:1) revealed that the acetylation was completed. The mixture was concentrated in vacuum and the crude product was purified by passing it through a silica gel column (dichloromethane, methanol, trace of triethyl amine) to give the pure title compound **14** (232 mg, 0.86 mmol; 94%). The hexopyranoside **14** was directly used for the next step without further characterization.

4.1.4. Allyl 3,4-di-*O*-acetyl-2,6-didesoxy-α-L-arabino-hexopyranoside (16). To a stirred solution of 3,4-di-*O*-acetyl-L-rhamnal (5 g, 23 mmol) and allyl alcohol (2 g, 34.5 mmol, 1.5 equiv.) in dry dichloromethane (50 ml) was added polymer-bound $PPh_3\cdot HBr$ (20 mg). The reaction mixture was stirred at rt for 24 h, filtered through a pad of Celite and concentrated under reduced pressure. The crude product was finally purified by column chromatography (ethyl acetate/petroleum ether=1:6) to furnish the pure title compound **16** (2.6 g, 9.6 mmol; 41%).

Compound **16**. Colorless oil; $[\alpha]_D^{20}=-156.3$ (c=1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ=5.89 (dddd, J=16.7, 11.0, 5.8, 5.3 Hz, 1H, CH=), 5.30 (ddd, 1H, J=9.3, 5.4, 2.1 Hz, 3-H), 5.29 (dq, J=17.1, 1.6 Hz, 1H, CHH′=CH), 5.18 (dq, 1H, J=10.4, 1.4 Hz, CHH'=CH), 4.90 (d, 1H, J=3.1 Hz, 1-H), 4.73 (t, 1H, J=9.6 Hz, 4-H), 4.13 (ddt, 1H, J=12.9, 5.1, 1.5 Hz, OCHH′), 3.94 (ddt, 1H, J=13.0, 6.1, 1.3 Hz, OCHH'), 3.86 (dq, 1H, J=9.8, 6.2 Hz, 5-H), 2.24 (ddd, 1H, J=12.9, 5.4, 1.2 Hz, 2-H_{ax}), 2.04, 1.99 (2s, 6H, 2×CH_3CO), 1.79 (ddd, 1H, J=12.8, 11.7, 3.7 Hz, 2-H_{eq}), 1.17 (d, 3H, J=6.3 Hz, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.51, 134.27, 117.46, 96.21, 75.20, 69.40, 66.00, 68.21, 35.58, 21.30, 21.12, 17.82; LRMS (ESI) for $C_{13}H_{20}O_6$: 336.15 (100) $[M+CH_3CN+Na]^+$.

4.1.5. 1,4-Di-(3′,4′,6′-tri-*O*-acetyl-2′-deoxy-α-D-lyxo-hexopyranosidyl)-2-butene (19). Allyl 2-deoxy-3,4,6-tri-*O*-acetyl-α-D-lyxo-hexopyranoside **15** (50 mg, 0.15 mmol) was dried under reduced pressure (10^{-2} Torr) for about 5 h and dissolved under nitrogen in absolute benzene (6 ml). To this solution was added the Grubbs catalyst **7** (15 μmol, 10 mol %). The purple solution was stirred at 50 °C for 4 h, at which time the reaction mixture was concentrated under reduced pressure. After addition of 15 ml diethyl ether and 0.5 ml triethyl amine stirring was continued under air for 2 h. Then, the solvent was removed in vacuum to yield a crude product, which was subsequently purified by column chromatography (R_f=0.24, petroleum ether/ethyl acetate=1:1) to furnish the pure title compound **19** (39 mg, 61.6 μmol; 41%, E/Z=5:1) as an inseparable mixture of stereoisomers. The material was directly used for the next step. Selected spectroscopic date: ^{13}C NMR (50 MHz, $CDCl_3$): δ=170.5, 170.3, 170.0, 128.6, 77.0, 66.7, 66.6, 66.1, 62.4, 30.0, 20.8, 20.7, 20.6.

4.1.6. 1,4-Di-(3′,4′-di-*O*-acetyl-2′,6′-dideoxy-α-D-arabino-hexopyranosidyl)-2-butene (20). Allyl 3,4-di-*O*-acetyl-2,6-dideoxy-α-L-arabino-hexopyranoside **16** (21 mg, 77 μmol) was dried in vacuum (10^{-2} Torr) for about 5 h and was dissolved under nitrogen in absolute benzene (3 ml). To this solution the Grubbs catalyst **7** (8 μmol, 10 mol %) was added. The purple solution was stirred at 50 °C for 4 h, at which time the reaction mixture was concentrated under reduced pressure. After addition of 10 ml diethyl ether and 0.3 ml triethyl amine stirring was continued under air for 2 h. Then, the solvent was removed in vacuum to afford a crude product, which was subsequently purified by column chromatography (R_f=0.55, petroleum ether/ethyl acetate=1:1) to furnish the title compound **20** (10 mg, 19.4 μmol; 50%, E/Z=5:1) as an inseparable mixture of stereoisomers. The material was directly used for the next step. Selected spectroscopic data: ^{13}C NMR (50 MHz, $CDCl_3$) δ=170.3, 128.6, 96.0, 74.8, 69.0, 65.7, 66.9, 35.2, 21.0, 20,8, 17.5; LRMS (ESI) for $C_{24}H_{36}O_{12}$: 539.4 (M^++Na^+).

4.1.7. 1,4-Di-(3′,4′-di-*O*-acetyl-2′,6′-dideoxy-β-L-lyxo-hexopyranosyl)-2-butene-1,4-diol (22). Allyl 3,4-di-*O*-acetyl-2,6-dideoxy-β-L-lyxo-hexopyranoside **18** (25 mg, 0.092 mmol) was dried in vacuum (10^{-2} Torr) for about 5 h and dissolved under nitrogen in absolute benzene (10 ml). To this solution the Grubbs catalyst **7** (5 mg, 6.6 mol%, after 14 h a second portion of 4 mg, 5.3 mol%) was added. The purple solution was stirred for 14 h at rt and then at 50 °C for 5 h, at which time the reaction mixture was concentrated under reduced pressure. After addition of diethyl ether (30 ml) and triethyl amine (1 ml) stirring was continued for 2 h under air. Then, the solvent was removed in vacuum to afford a crude product, which was subsequently purified by column chromatography (R_f=0.20; petroleum ether/ethyl acetate 4:1) to give the title compound **22** (20 mg, 39 μmol; 84.4%, *E*/*Z*=3.8:1) as an inseparable mixture of stereoisomers. The material was directly used for the next step. Selected spectroscopic data: ^{1}H NMR (200 MHz, $\mathrm{CDCl_3}$ with a trace amount of $\mathrm{CD_3OD}$): δ=5.83 (t, 2H, J=2.9 Hz, 2×=CH), 5.09 (dd, 2H, J=2.8, 0.8 Hz, 2×4-H), 4.97 (ddd, 2H, J=11.6, 6.0, 3.2 Hz, 2×3-H), 4.55 (dd, 2H, J=8.0, 3.8 Hz, 2×1-H), 4.41 (dm, 2H, J=12.6 Hz, 2×OC*H*H′), 4.08 (dm, 2H, J=12.8 Hz, 2×OCH*H*′), 3.66 (dq, 2H, J=6.4, 1.0 Hz, 2×5-H), 2.15 (s, 6H, 2×$\mathrm{CH_3CO}$), 2.06–1.86 (m, 4H, 2×2-$\mathrm{H_{eq}}$ and 2×2-$\mathrm{H_{ax}}$), 2.00 (s, 6H, 2×$\mathrm{CH_3CO}$), 1.22 (d, 6H, J=6.4 Hz, 2×6-H); ^{13}C NMR (50 MHz, $\mathrm{CDCl_3}$ with a trace amount of $\mathrm{CD_3OD}$): δ=170.8, 170.2, 129.0, 98.8, 69.2, 69.0, 68.6, 68.7, 31.7, 20.9, 20.8, 16.5; Selected ^{1}H NMR data for *Z*-isomer: ^{1}H NMR (200 MHz, $\mathrm{CDCl_3}$ with a trace amount of $\mathrm{CD_3OD}$): δ=5.75 (t, 2H, J=4.1 Hz, 2×CH=).

4.1.8. 1,4-Di-(4′-*O*-acetyl-2′,6′-dideoxy-3′-*C*-methyl-3′-*O*-methyl-β-L-ribo-hexopyranosyl)-2-butene-1,4-diol (23). Allyl 4-*O*-acetyl-2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-β-L-ribo-hexopyranoside **9** (100 mg, 0.39 mmol) was dried in vacuum (10^{-2} Torr) for about 5 h and dissolved under nitrogen in dry benzene (25 ml). To this solution was added the Grubbs catalyst **7** (19 mg, 6 mol%; after 14 h a second portion 13 mg, 4 mol%). The purple solution was stirred for 14 h at rt and then at 50 °C for 5 h, at which time the reaction mixture was concentrated under reduced pressure. After addition of diethyl ether (30 ml) and triethyl amine (1 ml) stirring under air was continued for 2 h. Then, the solvent was removed in vacuum to afford a crude product, which was subsequently purified by column chromatography (petroleum ether/ethyl acetate=5:1) to give the title compound **23** (70 mg, 0.17 mmol; 87%, *E*/*Z*=3.5:1) as an inseparable mixture of stereoisomers. The material was directly used for the next step. Selected spectroscopic data: ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$): δ=5.82 [t, 2H, J=3.0 Hz, 2×CH=(*trans*)], 5.71 [t, 2H, J=4.1 Hz, 2×CH=(*cis*)], 4.70 (dd, 2H, J=9.7, 2.0 Hz, 2×1-H), 4.64 (d, 2H, J=9.8 Hz, 2×4-H), 4.35 (ddd, 2H, J=11.5, 2.7, 1.2 Hz, 2×OC*H*H′), 4.02 (ddd, 2H, J=11.4, 3.3, 1.4 Hz, 2×OCH*H*′), 3.94 (dq, 2H, J=9.7, 6.3 Hz, 2×5-H), 3.26 (s, 6H, 2×$\mathrm{CH_3O}$), 2.20 (dd, 2H, J=14.2, 2.0 Hz, 2×2_{eq}-H), 2.12 (s, 6H, 2×CH_3CO), 1.49 (dd, 2H, J=14.2, 9.7 Hz, 2×2_{ax}-H), 1.13 (d, 6H, J=6.3 Hz, 2×6-H), 1.11 (s, 6H, 2×$\mathrm{CH_3}$); ^{13}C NMR (100 MHz, $\mathrm{CDCl_3}$): δ=170.5, 129.0, 97.3, 78.6, 74.6, 68.6, 67.9, 49.6, 39.3, 20.9, 20.6, 17.6.

4.1.9. 1,4-Di-(2′-deoxy-α-D-lyxo-hexopyranosidyl)-butane (24). To a stirred solution of 1, 4-di-(3′,4′,6′-tri-*O*-acetyl-2′-deoxy-α-D-lyxo-hexopyranosidyl)-butane **19** (40 mg, 0.063 mmol) in methanol (10 ml) Amberlite A-26 ($\mathrm{OH^-}$ form; 0.2 g) was added. The mixture was shaken at rt for 24 h, then filtered and the solvent was evaporated under reduced pressure. Finally, the product was dried under reduced pressure for 4 h to afford the title compound **24** (24 mg, 62.8 μmol, 99%).

Compound **24**. Colorless oil; $[\alpha]_D^{24}=+4.2$ (c=0.96, $\mathrm{CH_3OH}$); ^{1}H NMR (400 MHz, $\mathrm{CD_3OD}$, $\mathrm{CH_3OD}$=3.31 ppm): δ=4.87 (d, J=3.0 Hz, 1H, H-1), 3.93–3.83 (m, 1H), 3.76–3.57 (m, 5H), 3.40–3.24 (m, 1H), 1.90 (ddd, J=12.8, 12.0, 4.0 Hz, 1H, H-2_{eq}), 1.71 (dd, J=12.8, 4.4 Hz, 1H, H-2_{ax}), 1.67–1.55 (m, 2H, $\mathrm{OCH_2C}H_2$); ^{13}C NMR (50 MHz, $\mathrm{CD_3OD}$, $\mathrm{CD_3OD}$=49.0 ppm): δ=98.9, 72.4, 69.6, 66.7, 68.1, 63.2, 33.7, 27.5; LRMS (ESI) for $\mathrm{C_{16}H_{30}O_{10}}$: 405.2 ($\mathrm{M^+ + Na^+}$).

4.1.10. 1,4-Di-(2′,6′-dideoxy-α-D-arabino-hexopyranosidyl)-butane (25). To a stirred solution of 1,4-di-(3′,4′-di-*O*-acetyl-2′,6′-dideoxy-α-D-arabino-hexopyranosidyl)-butane **20** (10 mg, 19.3 μmol) in methanol (5 ml) Amberlite A-26 ($\mathrm{OH^-}$ form; 0.05 g) was added. The mixture was shaken at rt for 12 h, then filtered and the solvent was evaporated under reduced pressure. Finally, the product was dried under reduced pressure for 4 h to afford the title compound **25** (6.8 mg, 19.3 μmol, 99%).

Compound **25**. Colorless oil; ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$): δ=4.83 (d, J=3.0 Hz, 1H, H-1), 3.95–3.82 (m, 1H), 3.71–3.55 (m, 1H), 3.13–3.00 (m, 1H), 2.73, 2.58 (2s, 2×1H, 2OH), 2.49–2.41 (m, 1H), 2.17–2.05 (m, 1H), 1.75–1.56 (m, 2H), 1.29 (d, J=6.2 Hz, 3H, H-6), 1.36–1.20 (m, 1H, H-2_{eq}), 0.96–0.83 (m, 1H, H-2_{ax}); ^{13}C NMR (100 MHz, $\mathrm{CDCl_3}$): δ=97.3, 78.1, 69.2, 67.5, 67.0, 37.8, 26.5, 17.7; LRMS (ESI) for $\mathrm{C_{16}H_{30}O_6}$: 373.1 ($\mathrm{M^+ + Na^+}$).

4.1.11. 1,4-Di-(2′,6′-dideoxy-β-L-lyxo-hexopyranosyl)-1,4-butanediol (27). A suspension of 10% Pd/C (15 mg) in methanol (6 ml) was stirred under an hydrogen atmosphere for 30 min. 1,4-Di-(2′,6′-dideoxy-β-L-lyxo-hexopyranosyl)-2-butene-1,4-diol **22** (10 mg, 0.02 mmol) dissolved in a solvent mixture consisting of methanol (6 ml) and dichloromethane (6 ml) was added to the suspension. After successive addition of triethyl amine (0.1 ml) the mixture was stirred at rt for another 20 h, whereupon TLC analysis (R_f=0.28, dichloromethane/methanol=7:1) indicated that the hydrogenation was completed. The catalyst was filtered and washed with a mixture of dichloromethane and methanol (1:1). The combined filtrates were evaporated in vacuum to give a crude product, which was purified by flash column chromatography. However, the product was still contaminated with some ammonium salts. The material was taken up in aqueous sodium bicarbonate and the solution was evaporated again in vacuum to afford a residue which was extracted with chloroform. Filtration and concentration of the combined filtrates under reduced pressure afforded the title compound **27** (10 mg, 29 μmol, 99%).

Compound **27**. Colorless oil; ^{1}H NMR (200 MHz, $\mathrm{CDCl_3}$ with a trace amount of $\mathrm{CD_3OD}$): δ=4.32 (t, 2H, J=9.6, 2.2 Hz, 2×1-H), 3.87–3.76 (m, 2H, 2×OC*H*H′), 3.60 (ddd, 2H, J=12.0, 5.0, 3.2 Hz, 2×3-H), 3.42 (d, 2H, J=2.0 Hz, 2×4-H), 3.38–3.27 (m, 2H, 2×OCH*H*′ and 2×5-H), 1.87 (ddd, 2H, *J*=12.6, 5.0, 2.0 Hz, 2×2-H$_{eq}$), 1.57 (m, 4H, CH$_2$CH$_2$), 1.62–1.51 (m, 2H, 2×2-H$_{ax}$), 1.23 (d, 6H, *J*=6.5 Hz, 2×6-H); ^{13}C NMR (50 MHz, CDCl$_3$ with a trace amount of CD$_3$OD): *δ*=99.9, 70.4, 70.0, 68.6, 68.7, 34.3, 26.0, 16.4; HRMS ($C_{16}H_{30}NaO_8$): calcd. 373.1839 [M+Na]$^+$, found 373.1836.

4.1.12. 1,4-Di-(2′,6′-dideoxy-3′-*C*-methyl-3′-*O*-methyl-β-L-ribo-hexopyranosyl)-1,4-butanediol (28). To a solution of 1,4-di-(4′-*O*-acetyl-2′,6′-dideoxy-3′-*C*-methyl-3′-*O*-methyl-β-L-ribo-hexopyranosyl)-2-butene-1,4-diol **23** (70 mg, 0.17 mmol) in a mixed solvent system consisting of ethyl acetate, dichloromethane and methanol (16:8:1; 12.5 ml) was added PtO$_2$ (6.0 mg). The suspension was stirred under hydrogen atmosphere at rt for 24 h, after which time the hydrogenation was completed according to TLC analysis (petroleum ether/ethyl acetate 2:1). The reaction was terminated by addition of triethyl amine (1 ml), followed by filtration with suction and concentration under reduced pressure. To a solution of this crude material in methanol (10 ml) Amberlite A-26 (hydroxide form, 0.4 g) was added. The mixture was shaken at rt for 24 h and filtered. The filtrate was concentrated under reduced pressure. The crude material obtained was purified by flash column chromatography (petroleum ether/ethyl acetate=1:1) to furnish the hydrogenated product **28** (65 mg, 0.16 mmol, 95%).

Compound **28**. Colorless oil; $[\alpha]_D^{20}$=+18.7 (*c*=1; CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$): *δ*=4.54 (dd, 2H, *J*=9.7, 1.9 Hz, 2×1-H), 3.90–3.84 (m, 2H, 2×OC*H*H′), 3.56 (dq, 2H, *J*=9.4, 6.2 Hz, 2×5-H), 3.45–3.39 (m, 2H, 2×OC*H*H′), 3.24 (s, 6H, 2×CH$_3$O), 2.96 (dd, 2H, *J*=10.4, 9.7 Hz, 2×4-H), 2.21 (dd, 2H, *J*=14.4, 1.9 Hz, 2×2$_{eq}$-H), 2.09 (d, 2H, *J*=11.0 Hz, 2×OH), 1.67–1.63 (m, 4H, CH$_2$CH$_2$)1.38 (dd, 2H, *J*=14.4, 9.7 Hz, 2×2$_{ax}$-H), 1.29 (d, 6H, *J*=6.3 Hz, 2×6-H), 1.23 (s, 6H, 2×CH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$): *δ*=97.8, 78.1, 75.0, 70.9, 68.7, 49.0, 38.0, 26.3, 21.1, 18.2; HRMS for $C_{20}H_{38}O_8$ (M$^+$+Na$^+$): calcd 429.2464, found 429.2457.

4.1.13. Allyl 4-*O*-acetyl-3-trifluoroacetamido-2,3,6-trideoxy-α-L-arabino-hexopyranoside (30). Allyl 3-trifluoroacetamido-2,3,6-trideoxy-α-L-arabino-hexopyranoside (crude product; about 3.92 mmol) was dissolved under nitrogen in dry dichloromethane (20 ml). To this solution were added triethyl amine (1.5 equiv., 0.79 ml) and acetic anhydride (1.5 equiv., 0.56 ml). After addition of a small amount of 4-dimethylamino pyridine (DMAP; about 5 mg) the mixture was stirred at rt for 1 h, whereupon TLC (petroleum ether/ethyl acetate=5:1) showed that acetylation was completed. The mixture was concentrated in vacuum to afford a crude material which was purified by passing it through a silica gel column (*R*$_f$=0.24; petroleum ether/ethyl acetate=5:1) containing 2% of triethyl amine to give the title compound **30** (1.09 g, 3.35 mmol; 86% for four steps).

Compound **30**. Colorless oil; ^{1}H NMR (200 MHz, CDCl$_3$): *δ*=7.02 (d, 1H, *J*=8.0 Hz, NH), 5.88 (ddt, 1H, *J*=17.4, 10.2, 5.4 Hz, CH=), 5.28 (dq, 2H, *J*=17.4, 1.8 Hz, C*H*H′=CH–), 5.18 (dq, 1H, *J*=10.2, 1.6 Hz, CH*H*′=CH–), 4.92 (t, 1H, *J*=3.0 Hz, 1-H), 4.63 (t, 1H, *J*=10.2 Hz, 4-H), 4.59–4.47 (m, 1H, 3-H), 4.14 (ddt, 1H, *J*=13.2, 5.0, 1.4 Hz, OC*H*H′), 3.95 (ddt, 1H, *J*=13.2, 5.0, 1.4 Hz, OCH*H*′), 3.94 (dq, 1H, *J*=9.2, 6.0 Hz, 5-H), 2.23 (ddd, 1H, *J*=12.8, 4.4, 1.0 Hz, 2-H$_{eq}$), 2.05 (s, 3H, CH$_3$CO), 1.75 (td, 1H, *J*=12.6, 3.6 Hz, 2-H$_{ax}$), 1.17 (d, 3H, *J*=6.4 Hz, 6-H); ^{13}C NMR (50 MHz, CDCl$_3$): *δ*=172.0, 157.0, 133.8, 117.3, 115.6, 95.2, 75.4, 67.9, 65.6, 47.6, 35.5, 20.6, 17.6; calcd (%) for $C_{13}H_{18}F_3NO_5$ (325.28): C 48.00, H 5.58, N 4.31, found C 48.11, H 5.52, N 4.20.

4.1.14. 1,4-Di-(3′-trifluoroacetamido-4′-*O*-acetyl-2′,3′,6′-trideoxy-α-L-arabino-hexopyranosyl)-2-butene-1,4-diol (32). Allyl 4-*O*-acetyl-3-trifluoroacetamido-2,3,6-trideoxy-α-L-arabino-hexopyranoside **30** (224 mg, 0.69 mmol) was dried in vacuum (10^{-2} Torr) for about 5 h and was dissolved under nitrogen in absolute benzene (40 ml). To this solution the Grubbs catalyst **7** was added in two portions (22 mg, 3.9 mol%; 9 mg, 1.6 mol %). The purple solution was stirred for 2 h at rt and then at 50 °C for 24 h, at which time the reaction mixture was concentrated under reduced pressure. After addition of diethyl ether (30 ml) and triethyl amine (1 ml) stirring was continued under air for 2 h. Then the solvent was removed in vacuum to afford a crude product, which was subsequently purified by column chromatography (petroleum ether/ethyl acetate=3:1 then 1:1, *R*$_f$=0.20, petroleum ether/ethyl acetate=2:1) to give the title compounds **32** (186 mg, 0.30 mmol, 87%, *E*/*Z*=2.5:1) as an inseparable mixture of stereoisomers. The material was directly used for the next step. Selected spectroscopic data: ^{1}H NMR (200 MHz, CDCl$_3$): *δ*=6.67 (d, 2H, *J*=6.6 Hz, 2×NH), 5.83 (t, 2H, *J*=2.9 Hz, 2×CH=), 4.90 (d, 2H, *J*=3.2 Hz, 2×1-H), 4.57 (t, 2H, *J*=9.6 Hz, 2×4-H), 4.55–4.39 (m, 2H, 2×3-H), 4.22–4.09 (m, 2H, 2×OC*H*H′), 4.05–3.92 (m, 4H, 2×OCH*H*′ and 2×5-H), 2.31 (ddd, 2H, *J*=13.0, 4.4, 1.2 Hz, 2×2-H$_{eq}$), 2.08 (s, 6H, 2×CH$_3$CO), 1.74 (dt, 2H, *J*=12.8, 3.6 Hz, 2×2-H$_{ax}$), 1.20 (d, 6H, *J*=6.4 Hz, 2×6-H); ^{13}C NMR (50 MHz, CDCl$_3$): *δ*=170.0, 156.9, 128.6, 116.0, 95.4, 75.1, 66.9, 65.7, 48.1, 35.6, 20.6, 17.6; selected ^{1}H NMR data for the *Z*-isomer: ^{1}H NMR (200 MHz, CDCl$_3$): *δ*=5.75 (t, 2H, *J*=4.0 Hz, 2×CH=), 1.19 (d, 6H, *J*=6.2 Hz, 2×6-H).

4.1.15. 1,4-Di-(4′-*O*-acetyl-3′-trifluoroacetamido-2′,3′,6′-trideoxy-α-L-arabino-hexopyranosyl)-1,4-butanediol (36). To a solution of 1,4-di-(3′-trifluoroacetamido-4′-*O*-acetyl-2′,3′,6′-trideoxy-α-L-arabino-hexopyranosyl)-2-butene-1,4-diol **32** (192 mg, 0.31 mmol) in ethyl acetate (20 ml) was added PtO$_2$ (6.0 mg). The suspension was stirred under an hydrogen atmosphere at rt for 24 h, after which time the reduction was completed according to TLC analysis (*R*$_f$=0.38, petroleum ether/ethyl acetate 2:1). The reaction was terminated by addition of triethyl amine (1 ml), which was followed by filtration with suction and evaporation under reduced pressure to afford a crude product. This material was purified by flash column chromatography (petroleum ether/ethyl acetate=1:1) to furnish the hydrogenated product **36** (188 mg, 0.30 mmol; 98%).

Compound **36**. Colorless oil; ^{1}H NMR (200 MHz, CDCl$_3$): *δ*=7.70 (d, 2H, *J*=8.2 Hz, 2×NH), 4.81 (d, 2H, *J*=2.8 Hz, 2×1-H), 4.54 (t, 2H, *J*=10.2 Hz, 2×4-H), 4.50–4.38 (m, 2H, 2×3-H), 3.87 (dq, 2H, *J*=10.0, 6.4 Hz, 2×5-H), 3.70–3.57

(m, 2H, 2×OC*H*H′), 3.42–3.31 (m, 2H, 2×OCH*H′*), 2.11 (ddd, 2H, *J*=13.0, 4.8, 1.0 Hz, 2×2-H_{eq}), 2.02 (s, 6H, 2×CH_3CO), 1.76 (dt, 2H, *J*=12.4, 3.2 Hz, 2×2-H_{ax}), 1.64 (m, 4H, CH_2CH_2), 1.14 (d, 6H, *J*=6.4 Hz, 2×6-H); ^{13}C NMR (50 MHz, $CDCl_3$): *δ*=171.7, 156.8, 115.7, 96.0, 75.2, 67.2, 65.6, 47.3, 35.3, 26.2, 20.5, 17.5; calcd (%) for $C_{20}H_{30}F_6N_2O_8$ (540.45): C 44.45, H 5.59, N 5.18, found C 44.49, H 5.52, N 5.23.

4.1.16. Methyl 3-acetamido-4-allyl-2,3,6-trideoxy-β-L-lyxo-hexopyranoside (40). A nitrogen flask was equipped with a condenser and flushed with nitrogen. Methyl 3-acetamido-2,3,6-trideoxy-β-L-lyxo-hexopyranoside (118 mg, 0.58 mmol) dissolved in dry acetonitrile (10 ml) was added at rt under nitrogen. After addition of freshly precipitated and dry silver oxide (140 mg, 0.6 mmol) allyl iodide (0.2 ml, 2.18 mmol) was added dropwise to the suspension. The mixture was refluxed for 20 h, whereupon the suspension was filtered with suction through a pad of Celite and washed with the mixed solvent system of methanol and dichloromethane. The combined filtrates were evaporated under reduced pressure to afford a crude product. Purification by column chromatography (R_f=0.48; CH_2Cl_2/MeOH=10:1) afforded the pure title compound **40** (27 mg, 0.52 mmol, 90%).

Compound **40**. Colorless crystals; mp: 163–165 °C; $[\alpha]_D^{24}$=−48.4 (*c*=0.99, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): *δ*=5.92 (dddd, 1H, *J*=17.2, 10.0, 6.4, 5.4 Hz, CH=), 5.76 (d, 1H, *J*=8.3 Hz, NH), 5.26 (dq, 1H, *J*=17.2, 1.8 Hz, C*H*H′=CH–), 5.18 (dq, 1H, *J*=10.2, 1.4 Hz, CH*H′*=CH–), 4.35 (dd, 1H, *J*=9.6, 2.3 Hz, 1-H), 4.26 (ddt, 1H, *J*=12.7, 5.5, 1.4 Hz, OC*H*H′), 4.09 (m, 1H, 3-H), 3.96 (ddt, 1H, *J*=12.7, 5.5, 1.4 Hz, OCH*H′*), 3.54 (dq, 1H, *J*=6.4, 1.1 Hz, 5-H), 3.46 (s, 3H, OCH_3), 3.28 (d, 1H, *J*=3.0 Hz, 4-H), 1.97 (s, 3H, CH_3CO), 1.79 (ddd, 1H, *J*=12.2, 4.6, 2.3 Hz, 2-H_{eq}), 1.60 (dt, 1H, *J*=12.6, 9.4 Hz, 2-H_{ax}), 1.31 (d, 3H, *J*=6.6 Hz, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=169.3, 134.7, 117.5, 101.1, 76.7, 75.0, 71.6, 56.3, 47.9, 32.5, 23.4, 17.2; calcd (%) for $C_{12}H_{21}NO_4$ (243.30): C 59.24, H 8.70, N 5.76, found C 59.06, H 8.61, N 5.54.

4.1.17. 1,4-Bis (methyl-3′-acetamido-2′,3′,6′-trideoxy-β-L-lyxo-hexopyranos-4′-yl)-2-butene-1,4-diol (43). Methyl 3-acetamido-4-allyl-2,3,6-trideoxy-β-L-lyxo-hexopyranoside **40** (219 mg, 0.9 mmol) was dried in vacuum (10^{-2} Torr) for more than 5 h and was dissolved under nitrogen in absolute benzene (10 ml). To this solution was added the Grubbs catalyst **7** (56 mg, 0.068 mmol, 7.6 mol%). The purple solution was refluxed at 90–100 °C for 10 h, at which time the reaction mixture was cooled to rt and concentrated under reduced pressure. After addition of diethyl ether (30 ml) and triethyl amine (1 ml) stirring was continued under air for 2 h. Then, the solvent was removed in vacuum to afford a crude material, which was subsequently purified by column chromatography (ethyl acetate, then dichloromethane/methanol 10:1; R_f=0.30) to give the title compounds **43** (170 mg, 0.37 mmol, 90%; *E*/*Z*=4:1).

Compound **43**. Colorless oil; $[\alpha]_D^{24}$=−94.6 (*c*=1.86, $CHCl_3$/MeOH 1:1); ^1H NMR (400 MHz, $CDCl_3$ with a trace amount of CD_3OD): *δ*=7.12 (br d, 2H, 2×NH), 5.81 (t, 2H, *J*=3.0 Hz, 2×–)C*H*=CH_2), 4.39 (dd, 2H, *J*=8.4, 3.2 Hz, 2×1-H), 4.07 (br d, 2H, *J*=6.6 Hz, 2×OC*H*H′), 3.98–3.94 (m, 4H, 2×OCH*H′* and 2×3-H), 3.58 (q, 2H, *J*=6.4 Hz, 2×5-H), 3.49 (s, 6H, 2×OCH_3), 3.35 (m, 2H, 2×4-H), 1.99 (s, 6H, 2×C*H*$_3$CO), 1.80–1.55 (m, 4H, 2×2-H_{eq} and 2×2-H_{ax}), 1.29 (d, 6H, *J*=6.4 Hz, 2×6-H); ^{13}C NMR (50 MHz, $CDCl_3$ with a trace amount of CD_3OD): *δ*=170.5, 129.0, 101.2, 76.1, 73.7, 71.4, 56.2, 48.1, 31.6, 22.5, 16.8; selected ^1H NMR data for the alkenic double bond of the *Z*-isomer: ^1H NMR (400 MHz, $CDCl_3$ with a trace amount of CD_3OD): *δ*=5.74 (t, 2H, *J*=4.0 Hz, 2×–C*H*=CH_2), 4.19 (m, 4H, 2×OCH_2), 2.01 (s, 6H, 2×C*H*$_3$CO), 1.32 (d, 6H, *J*=6.4 Hz, 2×6-H); calcd (%) for $C_{22}H_{38}N_2O_8$ (458.55): C 57.62, H 8.35, N 6.11, found C 57.79, H 8.18, N 6.00.

4.1.18. 1,4-Bis (methyl-3′-acetamido-2′,3′,6′-trideoxy-β-L-lyxo-hexopyranos-4′-yl)-1,4-butanediol (46). A solution of 10% Pd/C (17 mg) in methanol (6 ml) was stirred under an hydrogen atmosphere for 30 min. The metathesis product **43** (44 mg, 0.096 mmol) dissolved in a solvent system consisting of dichloromethane and methanol (3:1; 16 ml) was added to this suspension. After successive addition of triethyl amine (0.11 ml) the mixture was stirred at rt for additional 5 h, after which time the hydrogenation was terminated by addition of a second portion of triethyl amine (1 ml). The catalyst was filtered and washed with the solvent mixture consisting of dichloromethane and methanol (R_f=0.35, dichloromethane/methanol=10:1). The combined filtrates were evaporated in vacuum to give a crude material which was purified by passing it through a silica gel column to furnish the title compound **46** (44 mg, 0.096 mmol, 99%).

Compound **46**. Colorless oil; ^1H NMR (200 MHz, $CDCl_3$ with a trace amount of CD_3OD): *δ*=4.20 (dd, 2H, *J*=6.6, 3.2 Hz, 2×1-H), 4.05 (s, 2H, 2×NH), 3.80 (ddd, 2H, *J*=11.2, 6.6, 3.2 Hz, 2×3-H), 3.39 (q, 2H, *J*=6.2 Hz, 2×5-H), 3.42–3.33 (m, 4H, 2×OCH_2), 3.30 (s, 6H, 2×OCH_3), 3.11 (d, 2H, *J*=2.7 Hz, 2×4-H), 1.81 (s, 6H, 2×CH_3CO), 1.57–1.46 (m, 6H, 2×2-H_{eq} and CH_2CH_2), 1.49 (dt, 2H, *J*=12.4, 8.8 Hz, 2×2-H_{ax}), 1.29 (d, 6H, *J*=6.4 Hz, 2×6-H); ^{13}C NMR (50 MHz, $CDCl_3$ with a trace amount of CD_3OD): *δ*=170.7, 101.1, 76.2, 74.0, 71.3, 55.9, 48.3, 31.2, 26.5, 22.0, 16.5; HRMS ($C_{22}H_{40}N_2NaO_2$): calcd. 483.2683 $[M+Na]^+$, found 483.2686.

4.1.19. 1,4-Di-(3′-amino-2′,3′,6′-trideoxy-α-L-arabino-hexopyranosyl)-1,4-butanediol (50). The hydrogenated product **36** was dissolved in a mixture of THF and 0.1M aqueous NaOH (1:3; 24 ml). This mixture was stirred at rt for 14 h, at which time TLC indicated that the deprotection was completed. After neutralization with dry ice (pH 7–8), the solution was concentrated to 2 ml under reduced pressure and the residue was subsequently subjected to a small column (800 mg of a reversed phase C-18; gradient water to methanol) to yield the target product **50** (21.4 mg, 61.4 μmol; 83.4%, for two steps).

Compound **50**. Colorless crystals; m.p.: 148–150 °C; $[\alpha]_D^{24}$=−121.4 (*c*=1.07; MeOH/$CHCl_3$ 2:1); ^1H NMR (200 MHz, $CDCl_3$ with CD_3OD): *δ*=4.68 (d, 2H, *J*=3.2 Hz, 2×1-H), 3.65 (br s, 4H, 2×NH_2), 3.60–3.50 (m, 2H, 2×OC*H*H′), 3.50 (dq, 2H, J=9.4, 6.0 Hz, 2×5-H), 3.80–3.69 (m, 2H, 2×3-H), 3.02–2.85 (m, 2H, 2×OCH*H*′), 2.73 (t, 2H, J=9.2 Hz, 2×4-H), 1.88 (dd, 2H, J=13.0, 4.0 Hz, 2×2-$H_{eq)}$, 1.53 (m, 4H, CH_2CH_2), 1.42 (ddd, 2H, J=13.0, 12.0, 3.8 Hz, 2×2-H_{ax}), 1.27 (d, 6H, J=6.0 Hz, 2×6-H); ^{13}C NMR (50 MHz, $CDCl_3$ with CD_3OD): δ=96.5, 77.7, 68.0, 66.7, 49.6, 37.7, 26.2, 17.4; LRMS (DCI) for $C_{16}H_{32}N_2O_6$: 349.3 (100) (M+H$^+$(, 697.7 (2) (2M+H$^+$).

4.1.20. 1,4-Di-(2′,3′,6′-trideoxy-α-L-lyxo-hexopyranosyl)-1,4-butanediol (51). Homodimer **37** (50.2 mg, 0.116 mmol) was dissolved at rt in water (20 ml) and barium hydroxide octahydrate (4.0 g, about 2 g/10 ml water) was added. The solution was stirred magnetically while it vigorously boiled under reflux (130–140 °C). After 24 h TLC (dichloromethane/methanol=5:1) indicated the completion of the saponification. To this mixture solid carbon dioxide was added and the precipitate was filtered. The filtrate was treated with Amberlite IRA-900 (OH$^-$ form, 20 ml) by stirring for 30 min. After filtration the filtrate was evaporated to give a residue, which, still containing some barium carbonate, was taken up in chloroform. The organic layer afforded the deprotected homodimer **51** (33 mg, 0.095 mmol, 82%) after evaporation in vacuum.

Compound **51**. Colorless oil; ^1H NMR (200 MHz, $CDCl_3$): δ=4.83 (d, 2H, J=2.0 Hz, 2×1-H), 3.87 (q, 2H, J=6.6 Hz, 2×5-H), 3.67–3.60 (m, 2H, 2×OC*H*H′), 3.41 (d, 2H, J=2.0 Hz, 2×4-H), 3.41–3.32 (m, 2H, 2×OCH*H*′), 3.23 (m, 2H, 2×3-H), 1.94 (br s, 8H, 2×2-H_{eq}, 2×NH_2 and 2×OH), 1.69–1.60 (m, 6H, 2×2-H_{ax} and CH_2CH_2), 1.26 (d, 6H, J=6.4 Hz, 2×6-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=97.1, 71.0, 67.0, 65.8, 46.4, 32.9, 26.5, 17.0; DCI-MS: m/z (%)=349.2 (100) (M+H$^+$), 697.4 (2) (2M+H$^+$).

4.1.21. 1,4-Di-(3′-amino-2′,3′,6′-trideoxy-α-L-ribo-hexopyranosyl)-1,4-butanediol (52). 1,4-Di-(3′-trifluoroacetamino-2′,3′,6′-trideoxy-α-L-ribo-hexopyranosyl)-1,4-butanediol **39** (36.9 mg, 0.069 mmol) was dissolved in a mixture of tetrahydrofuran and 0.1M aqueous NaOH (1:3, 12 ml). The solution was stirred at rt for 30 min, at which time TLC indicated that the deprotection was completed. After neutralization with dry ice (pH 7–8), the solution was concentrated under reduced pressure to 2 ml. This residue was subjected to column chromatography (reversed phase C-18; gradient water to methanol) to afford the target product **52** (20.5 mg, 59 μmol, 85%).

Compound **52**. Colorless oil; $[\alpha]_D^{24}=-159.6$ (c=1.03; MeOH/$CHCl_3$=2:1); ^1H NMR (200 MHz, $CDCl_3$): δ=4.80 (s, 2H, 2×1-H), 3.73–3.62 (m, 2H, 2×OCHH′), 3.58 (dq, 2H, J=9.2, 6.2 Hz, 2×5-H), 3.38–3.25 (m, 2H, 2×OC*H*H′), 3.17–3.00 (m, 4H, 2×3-H and 2×4-H), 2.60–2.10 (b, 4H, 2×NH_2), 1.96 (bs, 4H, 2×2-H_{eq} and 2×2-H_{ax}), 1.63 (m, 4H, CH_2CH_2), 1.27 (d, 6H, J=6.4 Hz, 2×6-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=97.4, 71.0, 67.3, 64.2, 47.4, 36.5, 26.6, 17.9; LRMS (DCI) for $C_{16}H_{32}N_2O_6$: 349.3 (100) (M+H$^+$), 697.7 (2) (2M+H$^+$).

4.1.22. 1,4-Bis (methyl-3′-amino-2′,3′,6′-trideoxy-β-L-lyxo-hexopyranos-4′-yl)-1,4-butanediol (53). Homodimer **46** (56 mg, 0.12 mmol) was dissolved in water (20 ml) at rt and barium hydroxide octahydrate (4.0 g, about 2 g/10 ml water) was added. The solution was stirred magnetically while it vigorously boiled under reflux (130–140 °C). After 48 h TLC (dichloromethane/methanol=5:1) indicated the completion of the saponification. Solid carbon dioxide was added to this suspension and the precipitate was filtered off. The filtrate was treated with Amberlite IRA-900 (OH$^-$ form, 20 ml) and the suspension was stirred for additional 30 min. After filtration, the solution was evaporated under reduced pressure to give a residue, which, still containing some barium carbonate, was taken up in chloroform. The organic layer afforded the deprotected homodimer **53** (16 mg, 42 μmol; 85%) after concentration in vacuum.

^{13}C NMR (50 MHz, $CDCl_3$ with a trace amount of CD_3OD): δ=101.5, 75.6, 74.4, 71.7, 56.3, 49.5, 29.6, 27.1, 17.5; LRMS (ES): $C_{18}H_{36}N_2O_6$: 377.4 (100) (M+H$^+$), 399.5 (31) (M+Na$^+$).

4.1.23. 1,4-Bis (3′-acetamido-4′-*O*-allyl-2′,3′,6′-trideoxy-*α*-L-lyxo-hexopyranosyl)-1,4-butanediol (54). A nitrogen flask was equipped with a condenser and was flushed with nitrogen. Diol **37** (80 mg, 0.185 mmol) in dry acetonitrile (20 ml) was added at rt under nitrogen. After addition of freshly precipitated and dry silver oxide (155 mg, 0.68 mmol) and allyl iodide (0.2 ml, 2.17 mmol, 6 equiv.) the suspension was refluxed at 100 °C for 1.5 h, whereupon the suspension was filtered with suction through a pad of Celite. After washing of the Celite with a mixture of methanol and dichloromethane the combined filtrates were concentrated under reduced pressure to afford a crude material. Purification by column chromatography on silica gel (CH_2Cl_2/MeOH=10:1) yielded homodimer **54** (91 mg, 0.178 mmol; 96%).

Compound **54**. Colorless oil; ^1H NMR (200 MHz, $CDCl_3$): δ=5.92 (dddd, 2H, J=17.2, 10.4, 6.2, 5.4 Hz, 2×CH_2=C*H*CH_2O), 5.61 (d, 2H, J=8.8 Hz, 2×NH), 5.25 (dq, 2H, J=17.2, 1.5 Hz, 2×C*H*H′=CHCH_2O), 5.18 (dq, 2H, J=10.2, 1.3 Hz, 2×CH*H*′=CHCH_2O), 4.84 (d, 2H, J=2.4 Hz, 2×1-H), 4.45–4.31 (m, 2H, 2×3-H), 4.22 (ddt, 2H, J=12.8, 5.4, 1.4 Hz, 2×OC*H*H’CH=CH_2), 3.98 (ddt, 2H, J=12.8, 5.4, 1.4 Hz, 2×OCH*H*′CH=CH_2), 3.91 (q, 2H, J=6.4 Hz, 2×5-H), 3.58 (m, 2H, 2×OC*H*H′), 3.39 (d, 2H, J=2.2 Hz, 2×4-H), 3.38–3.21 (m, 2H, 2×OCH*H*′), 1.95 (s, 6H, 2×C*H*$_3$CONH), 1.79 (dt, 2H, J=12.6, 3.6 Hz, 2×2-H_{ax}), 1.71–1.61 (m, 2H, 2×2-H_{eq}), 1.59 (m, 4H, CH_2CH_2), 1.21 (d, 6H, J=6.6 Hz, 2×6-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=169.3, 134.7, 117.4, 96.8, 77.7, 75.0, 67.0, 65.9, 44.9, 30.8, 26.4, 23.4, 17.3; calcd (%) for $C_{28}H_{44}N_2O_8$ (512.64): C 60.92, H 8.65, N 5.46, found C 60.81, H 8.57, N 5.41.

4.1.24. Cross metathesis between 1,4-bis(3′-acetamido-2′,3′,6′-trideoxy-4′-O-allyl-α-L-lyxo-hexopyranosyl)-1,4-butanediol (54) and allyl ether 40 and preparation of trimer 56 and tetramer 55. Methyl 3-acetamido-4-allyl-2,3,6-trideoxy-β-L-lyxo-hexopyranoside **40** (127 mg, 0.522 mmol) and 1,4-bis (3′-acetamido-4′-*O*-allyl-2′,3′,6′-trideoxy-*α*-L-lyxo-hexopyranosyl)-1, 4-butanediol **54** (62 mg, 0.121 mmol) with a molar ratio of 4.3:1 were dried in high vacuum (10^{-2} Torr) for more than 5 h and dissolved under nitrogen in absolute benzene (20 ml). To this solution was added Grubbs’s catalyst **7** in two portions (20 mg, 0.024 mmol then 14 mg, 0.017 mmol). The purple solution was allowed to stir at rt for 14 h followed by additional stirring for 6 h at 95 °C. The reaction was terminated by concentration under reduced pressure. After addition of diethyl ether (30 ml) and triethyl amine (1 ml) stirring was continued under air for 2 h. The solvent was removed under reduced pressure to afford a mixture of crude products, which was subsequently purified by column chromatography (dichloromethane/methanol=10:1). Pure compounds of cross metathesis products **55** (18 mg, 19 μmol, 16%) and **56** (24 mg, 33 μmol, 27%), along with homodimer from methyl 3-acetamido-4-allyl-2,3,6-trideoxy-β-L-lyxo-hexopyranoside **40** (60 mg, 50.2%) were collected.

Compound **56**. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.07–5.82 (m, 1H, CH_2=C*H*CH_2O), 5.83 (t, 2H, *J*=3.0 Hz, O–CH_2–C*H*=C*H*–CH_2–O), 5.63, 5.56 (2d, 3H, *J*=8.8 Hz, NH^I, NH^{II}, NH^{III}), 5.28 (dq, 1H, *J*=17.2, 1.2 Hz, CH*H′*=$CHCH_2O$), 5.20 (dq, 1H, *J*=10.2, 1.0 Hz, CH*H′*=$CHCH_2O$), 4.85 (t, 2H, *J*=2.0 Hz, 1-H^{II}, 1-H^{III}), 4.46–4.34 (m, 2H, 3-H^{II}, 3-H^{III}), 4.36 (dd, 1H, *J*=9.2, 2.3 Hz, 1-H^I), 4.25–3.90 (m, 7H, 3-H^I, OC*H*$_2$CH=CH_2, O–C*H*$_2$–CH=CH–C*H*$_2$–O), 3.94 (q, 2H, *J*=6.4 Hz, 5-H^{II}, 5-H^{III}), 3.64–3.55 (m, 2H, 2×OCH*H′*-CH_2–), 3.56 (q, 1H, *J*=6.2 Hz, 5-H^I), 3.48 (s, 3H, OCH_3), 3.42–3.31 (m, 2H, 2×OCH*H′*-CH_2–), 3.40 (d, 2H, *J*=2.8 Hz, 4-H^{II}, 4-H^{III}), 3.31 (d, 1H, *J*=3.0 Hz, 4-H^I), 2.01, 2.00, 1.97 (3s, 9H, 3×C*H*$_3$CO–), 1.88–1.56 (m, 10H, 3×2-H, 2×OCH_2C*H*$_2$), 1.31 (d, 3H, *J*=6.4 Hz, 6-H^I), 1.23, 1.22 (2d, 6H, *J*=6.4 Hz, 6-H^{II} and 6-H^{III}); ^{13}C NMR (100 MHz, $CDCl_3$ with a trace amount of CD_3OD): δ=170.6, 170.4, 134.3, 129.1, 129.0, 117.2, 101.1, 96.6, 76.8, 76.7, 74.7, 73.5, 73.5, 71.3, 66.8, 65.7, 65.7, 56.0, 48.1, 45.0, 44.9, 31.4, 29.8, 26.0, 22.3, 22.2, 22.1, 16.7, 16.7, 16.6; HRMS ($C_{36}H_{61}N_3NaO_{12}$): calcd. 750.4153 $[M+Na]^+$, found 750.4147.

Compound **55**. Colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ=5.86 (d, 2H, *J*=8.4 Hz, 2×NH^I), 5.83 (m, 4H, 2×–OCH_2–C*H*=C*H*–CH_2O–), 5.66 (d, 2H, *J*=8.6 Hz, 2×NH^{II}), 4.85 (d, 2H, *J*=2.6 Hz, 2×1-H^{II}), 4.43–4.30 (m, 2H, 2×3-H^{II}), 4.35 (dd, 2H, *J*=9.2, 2.0 Hz, 2×1-H^I), 4.25–4.07 (m, 2H, 2×3-H^I), 4.19 (d and m, 4H, *J*=12.8 Hz, 2×–OC*H′H*–CH=CH–C*H′H*O–), 4.04 (d and m, 4H, *J*=12.8 Hz, 2×–OC*H′H*–CH=CH–C*H′H*O–), 3.93 (q, 2H, *J*=6.4 Hz, 2×5-H^{II}), 3.63–3.41 (m, 4H, 2×OC*H*$_2$-CH_2–), 3.55 (q, 2H, *J*=6.4 Hz, 2×5-H^I), 3.45 (s, 6H, 2×OCH_3), 3.38 (d, 2H, *J*=2.4 Hz, 2×4-H^{II}), 3.31 (d, 2H, *J*=3.0 Hz, 2×4-H^I), 2.00, 1.99 (2s, 12H, 2×CH_3CO^I and 2×CH_3CO^{II}), 1.83–1.58 (m, 12H, 4×2-H, 2×OCH_2C*H*$_2$–), 1.30 (d, 6H, *J*=6.4 Hz, 2×6-H^I), 1.22 (d, 6H, *J*=6.5 Hz, 2×6-H^{II}); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.6, 170.5, 129.7, 129.0, 101.1, 96.7, 77.0, 75.9, 73.6, 73.6, 71.4, 66.9, 65.7, 56.1, 48.1, 45.0, 31.6, 29.8, 26.2, 26.1, 25.9, 22.4, 22.3, 16.8, 16.7; HRMS ($C_{46}H_{78}N_4NaO_{16}$): calcd. 965.5311 $[M+Na]^+$, found 965.5302.

4.1.25. Hydrogenation of tetramer 55 to tetramer 57 with saturated spacer linkers. A solution of 10% Pd–C (12 mg) in 6 ml methanol was stirred under hydrogen for 30 min and to this suspension was added the metathesis product **55** (17 mg, 18 μmol) in a solvent system consisting of methanol (12 ml) and dichlormethane (4 ml). After a successive addition of triethyl amine (0.1 ml) the mixture was allowed to stir at rt for additional 24 h, after which time the hydrogenation was terminated by adding triethyl amine (1 ml). The catalyst was filtered off and washed with the mixed solvent (dichloromethane/methanol=10:1). The combined filtrates were evaporated in vacuum to give a crude product **57**. The material was directly employed in the next step.

Selected spectroscopic data: ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.94 (d, 2H, *J*=8.6 Hz, 2×NH^I), 5.77 (d, 2H, *J*=8.2 Hz, 2×NH^{II}), 4.82 (d, 2H, *J*=3.0 Hz, 2×1-H^{II}), 4.44–4.38 (m, 2H, 2×3-H^{II}), 4.32 (dd, 2H, *J*=9.4, 2.0 Hz, 2×1-H^I), 4.09–4.03 (m, 2H, 2×3-H^I), 3.89 (q, 2H, *J*=6.4 Hz, 2×5-H^{II}), 3.64–3.30 (m, 12H, 6×OC*H*$_2$-CH_2–), 3.51 (q, 2H, *J*=6.4 Hz, 2×5-H^I), 3.45 (s, 6H, 2×OCH_3), 3.36 (d, 2H, *J*=3.0 Hz, 2×4-H^{II}), 3.23 (d, 2H, *J*=2.4 Hz, 2×4-H^I), 1.99, 1.98 (2s, 12H, 2×CH_3CO^I and 2×CH_3CO^{II}), 1.80–1.55 (m, 20H, 4×2-H, 6×OCH_2C*H*$_2$–), 1.27 (d, 6H, *J*=6.2 Hz, 2×6-H^I), 1.19 (d, 6H, *J*=6.2 Hz, 2×6-H^{II}); ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.5, 169.4, 101.2, 96.8, 77.8, 76.8, 74.2, 74.0, 71.6, 66.9, 65.9, 56.3, 48.2, 45.2, 32.3, 30.5, 27.3, 27.0, 26.3, 23.4, 23.3, 17.2, 17.1; LRMS (DCI) for $C_{46}H_{82}N_4O_{16}$: 947.9 (100) $(M+H^+)$, 964.9 (14) $(M+NH_4^+)$.

4.1.26. Hydrolysis of tetramer 57 to the target 1,4-butanediol-linked tetradaunosamides 58. Tetramer **57** (17 mg, 0.018 mmol) was dissolved at rt in water (10 ml) and barium hydroxide octahydrate (2.0 g in 10 ml water) was added. The solution was stirred under refluxing conditions (130–140 °C) for 30 h. To this mixture solid carbon dioxide was added and the precipitate was filtered off. The filtrate was treated with Amberlite IRA-904 (OH^- form, 10 ml) and stirred for 30 min. After filtration the solution was evaporated to give a residue, which still contained traces of barium carbonate. It was taken up in chloroform and the crude product **58** (9 mg, 12 μmol, 64.3% for two steps) was purified by column chromatography over a RP-18 (800 mg).

Compound **58**. Colorless oil; $[\alpha]_D^{24}=-73.3$ (*c*=0.32, $CHCl_3$/MeOH 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.81 (d, 2H, *J*=2.4 Hz, 2×1-H^{II}), 4.26 (dd, 2H, *J*=9.6, 2.0 Hz, 2×1-H^I), 3.82 (q, 2H, *J*=6.4 Hz, 2×5-H^{II}), 3.69–3.65 (m, 4H, 4×OCH*H′*-CH_2–), 3.63–3.57 (m, 6H, 6×OCH*H′*-CH_2–), 3.46 (s, 6H, 2×OCH_3), 3.45 (q, 2H, *J*=6.4 Hz, 2×5-H^I), 3.38–3.31 (m, 2H, 2×OCH*H′*-CH_2–), 3.15 (d, 2H, *J*=2.5 Hz, 2×4-H^{II}), 3.11 (m, 2H, 2×3-H^{II}), 3.06 (d, 2H, *J*=3.0 Hz, 2×4-H^I), 2.80 (ddd, 2H, *J*=12.0, 4.2, 3.4 Hz, 2×3-H^I), 1.77–1.52 (m, 28H, 4×NH_2, 4×2-H, 6×OCH_2C*H*$_2$–), 1.31 (d, 6H, *J*=6.4 Hz, 2×6-H^I), 1.22 (d, 6H, *J*=6.4 Hz, 2×6-H^{II}); ^{13}C NMR (100 MHz, $CDCl_3$): δ=101.6, 97.3, 80.8, 79.8, 74.5, 74.4, 72.1, 66.9, 66.9, 56.2, 51.1, 47.0, 36.9, 35.5, 27.2, 27.1, 26.4, 17.5, 17.2; LRMS (DCI) for $C_{38}H_{74}N_4O_{12}$: 779.0 (100) $(M+H^+)$.

4.1.27. Hydrogenation of trimer 56 for preparation of trimer 59 with saturated aliphatic linkages. To a solution of **56** (25 mg, 0.034 mmol) in 12.5 ml of a mixed solvent (ethyl acetate/dichloromethane/methanol=16:8:1) was added PtO_2 (7.7 mg). The suspension was stirred under hydrogen at rt for 16 h, after which time the reduction was complete (TLC: petroleum ether/ethyl acetate=4:1). The reaction was terminated by addition of triethyl amine (1 ml), followed by filtration with suction and evaporation under reduced pressure. The crude product obtained was purified by flash column chromatography (petroleum ether/ethyl acetate=6:1) to furnish the hydrogenated product **59** (23 mg, 31 μmol, 92%).

Compound **59**. Colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ=5.84 (d, 1H, J=8.5 Hz, NH^{I}), 5.68 (d, 1H, J=8.6 Hz, NH^{II}), 5.58 (d, 1H, J=8.5 Hz, NH^{III}), 4.84 (t, 2H, J=3.2 Hz, 1-H-b, 1-H^{III}), 4.42–4.33 (m, 2H, 3-H^{II}, 3-H^{III}), 4.34 (dd, 1H, J=9.4, 2.0 Hz, 1-H^{I}), 4.12–4.04 (m, 1H, 3-H^{I}), 3.91 (dq, 2H, J=6.4, 2.2 Hz, 5-H^{II}, 5-H^{III}), 3.67–3.50 (m, 7H, OCHH'CH$_2$CH$_3$, 2×OCH_2-CH$_2$-, 2×OCHH'-CH$_2$–), 3.53 (q, 1H, J=6.4 Hz, 5-H^{I}), 3.47 (s, 3H, OCH$_3$), 3.41 (dt, 1H, J=9.6, 7.2 Hz, OCHH'CH$_2$CH$_3$), 3.38–3.32 (m, 2H, 2×OCHH'-CH$_2$–), 3.31 (d, 2H, J=2.8 Hz, 4-H-b, 4-H^{III}), 3.24 (d, 1H, J=2.6 Hz, 4-H^{I}), 2.00, 1.99, 1.97 (3s, 9H, 3×CH$_3$CO), 1.80–1.56 (m, 16H, 3×2-H, 4×OCH$_2$CH_2, OCH$_2$CH_2CH$_3$), 1.29 (d, 3H, J=6.4 Hz, 6-H^{I}), 1.22, 1.21 (2d, 6H, J=6.4 Hz, 6-H^{II} and 6-H^{III}), 0.94 (t, 3H, J=7.3 Hz, OCH$_2$CH$_2$CH_3); ^{13}C NMR (50 MHz, CDCl$_3$): δ=169.4, 169.2, 101.2, 96.8, 77.8, 76.9, 76.0, 74.2, 74.1, 71.6, 67.0, 66.1, 56.4, 48.2, 45.0, 32.4, 30.8, 27.4, 27.1, 26.4, 23.5, 23.4, 23.3, 17.3, 17.1, 10.7; LRMS (DCI) for $C_{36}H_{65}N_3O_{12}$: 732.8 (100) (M+H$^+$), 747.8 (11) (M+NH$_4^+$).

4.1.28. Hydrolysis of trimer 59 and synthesis of 1,4-butanediol-linked tridaunosamides 60. Trimer **59** (23 mg, 31 μmol) was dissolved at rt in water (20 ml) and barium hydroxide octahydrate (4.5 g) was added. The solution was stirred under refluxing conditions (130–140 °C) for 24 h. To this mixture solid carbon dioxide was added and the precipitate was filtered off. The filtrate was treated with Amberlite IRA-904 (OH$^-$ form, 20 ml) and stirred for 30 min. After filtration the solution was evaporated to give a residue, which, still containing some barium carbonate, was taken up in chloroform. The organic layer afforded the deprotected trimer **60** (16 mg, 26 μmol, 84%) after evaporation in vacuum.

Compound **60**. Colorless oil; $[\alpha]_D^{24}=-70.9$ (c=0.46, CHCl$_3$/MeOH=3:1); ^{1}H 1NMR (400 MHz, CDCl$_3$): δ=4.80 (t, 2H, J=3.4 Hz, 1-H^{II}, 1-H^{III}), 4.24 (dd, 1H, J=9.5, 2.0 Hz, 1-H^{I}), 3.81 (qd, 2H, J=6.4, 2.2 Hz, 5-H^{II}, 5-H^{III}), 3.69–3.61 (m, 3H, OCHH'CH$_2$CH$_3$, 2×OCHH'-CH$_2$–), 3.63–3.54 (m, 4H, 4×OCHH'-CH$_{2-}$–), 3.51 (dt, 1H, J=8.8, 7.2 Hz, OCHH'CH$_2$CH$_3$), 3.44 (s, 3H, OCH$_3$), 3.42 (q, 1H, J=6.4 Hz, 5-H^{I}), 3.37–3.29 (m, 2H, 2×OCHH'-CH$_2$–), 3.13 (br s, 2H, 4-H^{II}, 4-H^{III}), 3.11–3.05 (m, 2H, 3-H^{II}, 3-H^{III}), 3.04 (d, 1H, J=2.8 Hz, 4-H^{I}), 2.78 (ddd, 1H, J=12.3, 4.1, 3.2 Hz, 3-H^{I}), 1.74–1.53 (m, 22H, 3×NH$_2$, 3×2-H, 6×OCH$_2$CH_2-, OCH$_2$CH_2CH$_3$), 1.28 (d, 3H, J=6.4 Hz, 6-H^{I}), 1.21, 1.20 (2d, 6H, J=6.4 Hz, 6-H^{II}, 6-H^{III}), 0.91 (t, 3H, J=7.3 Hz, OCH$_2$CH$_2$CH_3); ^{13}C NMR (100 MHz, CDCl$_3$): δ=101.5, 97.2, 80.7, 79.7, 76.2, 74.4, 74.3, 72.1, 66.9, 66.8, 56.2, 51.0, 46.9, 36.9, 35.4, 27.1, 27.1, 26.4, 23.5, 17.3, 17.2, 10.5; LRMS (DCI) for $C_{30}H_{59}N_3O_9$: 606.6 (100) (M+H+).

4.2. Additional information on RNA dot blot experiments

For the sake of better comparison in the dot blot experiments the aminoglycoside concentrations are give in concentrations of the individual carbohydrate subunits (22, 11.2, 7.6, 5.6, 2.4 and 1.2 mM). The actual concentration for the trimer: 0.4, 0.8, 1.8, 2.5, 3.7 and 7.3 mM; for the tetramers: 0.3, 0.6, 1.4, 1.9, 2.8 and 5.5 mM. Dot blot experiments with the two aptamers were performed with an aptamer concentration of 0.16 μM, 100 μM 17-mer Rev peptide and aminoglycoside **2** ranging from 1 to 200 mM in an overalls volume of 20 μl. Binding experiments were performed in an overall volume of 40 μl, containing 10 mM Tris·HCl (pH=7.5), 70 mM NaCl, 0.2 mM EDTA, 5% glycerol. The TAR-RNA (0.16 μM) and the 9-mer Tat peptide (222 μM) were first incubated for 30 min. Then the aminoglycosides had been added and the mixture was incubated for additional 30 min. After that time the mixture was filtered through a dot blot apparatus in which two membranes, on top a nitrocellulose membrane and below a positively charged nylon membrane had been inserted. After filtration the two membranes were separated and the nylon membrane was 'backed' at 80 °C for 30 min. The RNA on the nitrocellulose membrane was blotted onto a positively nylon membrane and was then further treated as mentioned above. After immobilization at 80 °C followed by the wash protocol from Ambion, the RNA was visualized with streptavidin/alkaline phosphatase and CDP-star on kodak film.

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Synthesis of 1,4,5,16-tetrahydroxytetraphenylene

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Dedicated to Professor Cheng-Ye Yuan on the occasion of his 80th birthday

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Abstract—This paper concerns the synthesis of 1,4,5,16-tetrahydroxytetraphenylene, which may function as a building block for the construction of molecular scaffolds. The synthesis of 1,4,5,16-tetrahydroxytetraphenylene was realized by stepwise Diels–Alder reactions to form two benzene rings using 1,10-dimethoxydibenzo[*a*,*e*]cyclooctene as a precursor. This key intermediate, in turn, could be obtained by photo-rearrangement of its corresponding barrelene.

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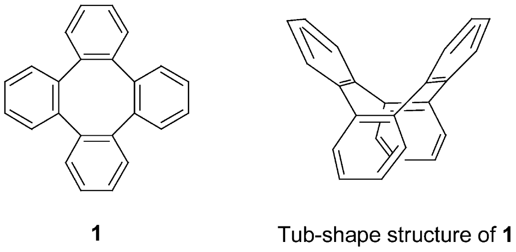
1. Introduction

Tetraphenylene (tetrabenzo[*a*,*c*,*e*,*g*]cyclooctatetraene) (**1**) is a structurally highly interesting molecule; it contains four benzene rings, which are disposed alternately above and below the main plane of the molecule, this molecule belongs to a D_{2d} symmetry point group (Scheme 1).[1]



Scheme 1.

Triggered by the aforementioned reasons, we have begun a research program with the aim to construct three-dimensional molecular scaffolds using tetraphenylenols as building blocks. In our program, we would like to synthesize five tetraphenylenols **2**,[2] **3**, **4**, **5** and **6**[3] (Scheme 2), as different modules which would subsequently serve to build various molecular scaffolds.

As can be seen, the hydroxyl groups of these tetraphenylenols are placing in different positions which could be interconnected with guest molecules via non-covalent interaction,[4] or with central metal linkages via covalent interaction[5] in diversified combination to form ordered linear, two- and three-dimensional scaffolds.

In this paper, we would like to report the synthesis of 1,4,5,16-tetrahydroxytetraphenylene (**4**), by employing 1,10-dimethoxydibenzo[*a*,*e*]cyclooctene (**9**) as the key intermediate.

2. Results and discussion

After the first synthesis of tetraphenylene (**1**) was reported in 1943,[6] considerable efforts has been devoted to the improved synthesis of **1** and its derivatives.[7] Because of the structural characteristics of our target molecule, we would like to utilize an eight-membered ring compound **9** as a precursor. Two benzene rings will then be introduced into the skeleton of **9** via stepwise Dieds–Alder reactions.[8] The retro-synthetic pathway is shown in Scheme 3. It is noteworthy that in our synthetic route, four hydroxyl groups could be introduced in a regiospecific manner.

As can be seen in Scheme 4, the hydroxyl groups in 1,10-dihydroxyanthraquinone (**11**) were converted to methoxy groups.[9] The protected anthraquinone **12** was then reduced smoothly to its corresponding anthracene **13** in the presence of zinc under an alkaline environment.[10] With 1,8-dimethoxyanthracene (**13**) in hand, a Diels–Alder reaction[11] between the anthracene **13** and dimethyl acetylenedicarboxylate (DMAD) provided dimethyl

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Keywords: Diels–Alder reaction; Tetraphenylene; Strained acetylene; Photo-rearrangement.

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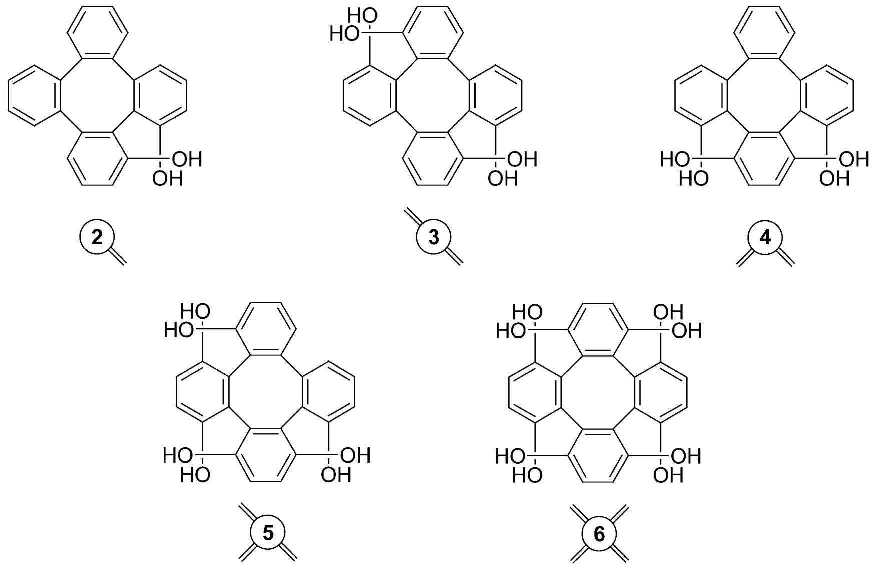
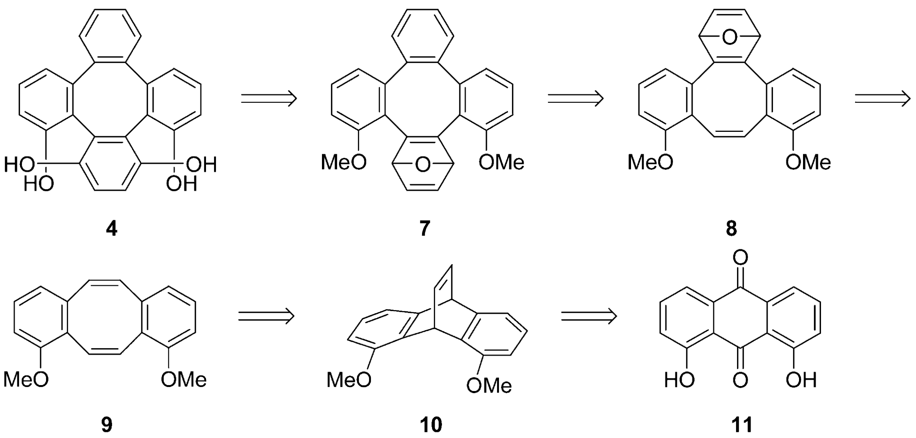
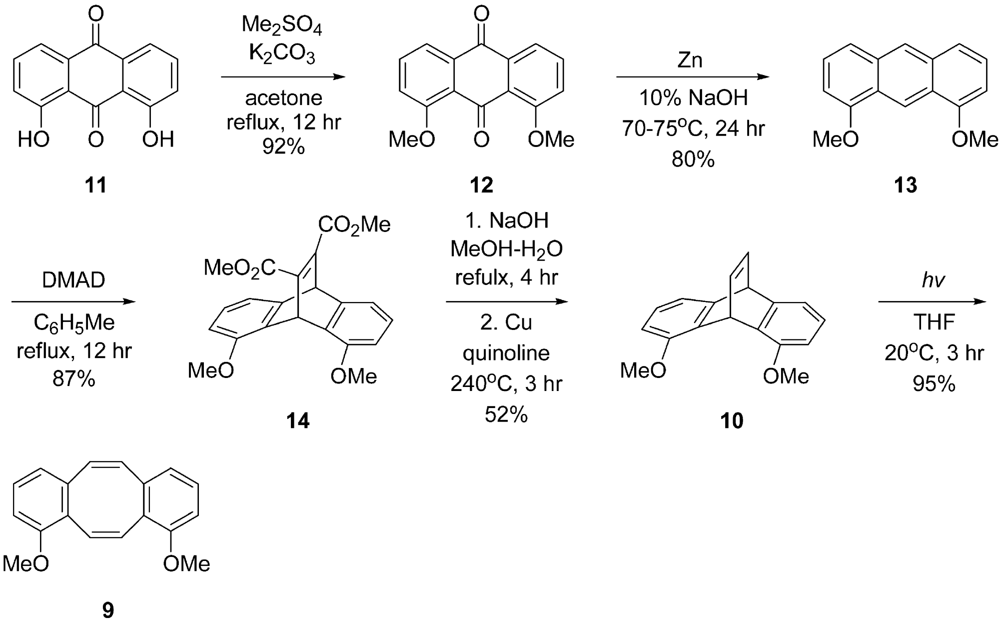


Scheme 2.



Scheme 3.



Scheme 4.

9,10-dihydro-9,10-etheno-1,8-dimethoxyanthracene-11,12-dicarboxylate (**14**) in high yield.[12] This adduct was allowed to undergo a saponification step to provide the corresponding diacid, whose reductive bisdecarboxylation yielded 1,8-dimethoxybarrelene (**10**).[12] In the proton NMR spectrum of barrelene **10**, two bridge-head protons show two sets of doublet of doublets at δ 5.17–5.19 and δ 6.10–6.13, respectively. Photoinduced isomerization of barrelene **10** furnished dibenzo[*a*,*e*]cyclooctene **9** in an excellent yield.[13] A significant difference was found in the proton NMR spectra between barrelene **10** and dibenzo[*a*,*e*]cyclooctene **9**, which is a direct evidence for the success of photo rearrangement. As mentioned above, for barrelene **10**, two bridge-head protons give two sets of doublet of doublets, while the rearrangement product show two sets of singlets at δ 6.73 and 6.74 which could be attributed to the olefinic protons in the central cyclooctene ring.

After a sufficient amount of the key intermediate, namely 1,10-dimethoxydibenzo[*a*,*e*]cyclooctene (**9**) was secured, the next step was to construct the pivotal tribenzo[*a*,*c*,*e*]-cyclooctene skeleton. The synthesis of tribenzo[*a*,*c*,*e*]cyclooctene framework was not expected to be trivial, as can be revealed by a literature survey.[14]

First, bromination[15] of dibenzo[*a*,*e*]cyclooctene **9** with one molar equivalent of bromine at 0 °C in CCl_4 gave a mixture of 5,6-dibromo-5,6-dihydro-1,10-dimethoxydibenzo[*a*,*e*]-cyclooctene (**15**) and 11,12-dibromo-11,12-dihydro-1,10-dimethoxydibenzo[*a*,*e*]cyclooctene (**16**). The two isomers were used directly without separation and purification in the next dehydrobromination step by using potassium *tert*-butoxide as the base.[16] The reactive strained alkynes, after their generation, underwent Diels–Alder reaction with furan to yield endoxide **8** and endoxide **17**, respectively. Moreover, another product was found to be 5-*tert*-butoxy-1,10-dimethoxydibenzo[*a*,*c*]cyclooctene (**18**) which was generated in only 10% yield.[17] A notable singlet at δ 1.20 was found in the proton NMR spectrum of compound **18** which was due to the absorption of the *tert*-butyl group. The structure of the major endoxide **8** was confirmed by an X-ray crystallographic study (Fig. 1). To obtain the tribenzo[*a*,*c*,*e*]cyclooctene framework, **8** was deoxygenated by the low-valent-titanium reagent,[18] yielding 1,12-dimethoxytribenzo[*a*,*c*,*e*]cyclooctene (**19**) (Scheme 5). The resonances of the proton NMR spectrum are assigned as the following. Thus, the singlet at δ 3.80 corresponds to the methoxy protons. The olefinic protons (H-13, H-14) absorb as a singlet at δ 6.73. Also, two sets of doublet of doublets belonging to the benzenoid protons (H-2, H-4, H-9, H-11) appear at δ 6.74–6.81. The multiplet due to the absorption of the two protons (H-6, H-7) overlaps with those of H-3 and H-10 in the region of δ 7.14–7.7.19. Finally, the doublet of doublets at δ 6.36–6.39 (J=5.7 Hz, 3.6 Hz) can be attributed to two protons (H-5, H-8) of the newly constructed benzene ring. The HRMS (EI) of **19** shows a molecular peak at *m*/*z* 314.1305 (Calcd for $C_{22}H_{18}O_2$: 314.1307). Furthermore, the elemental analysis result is

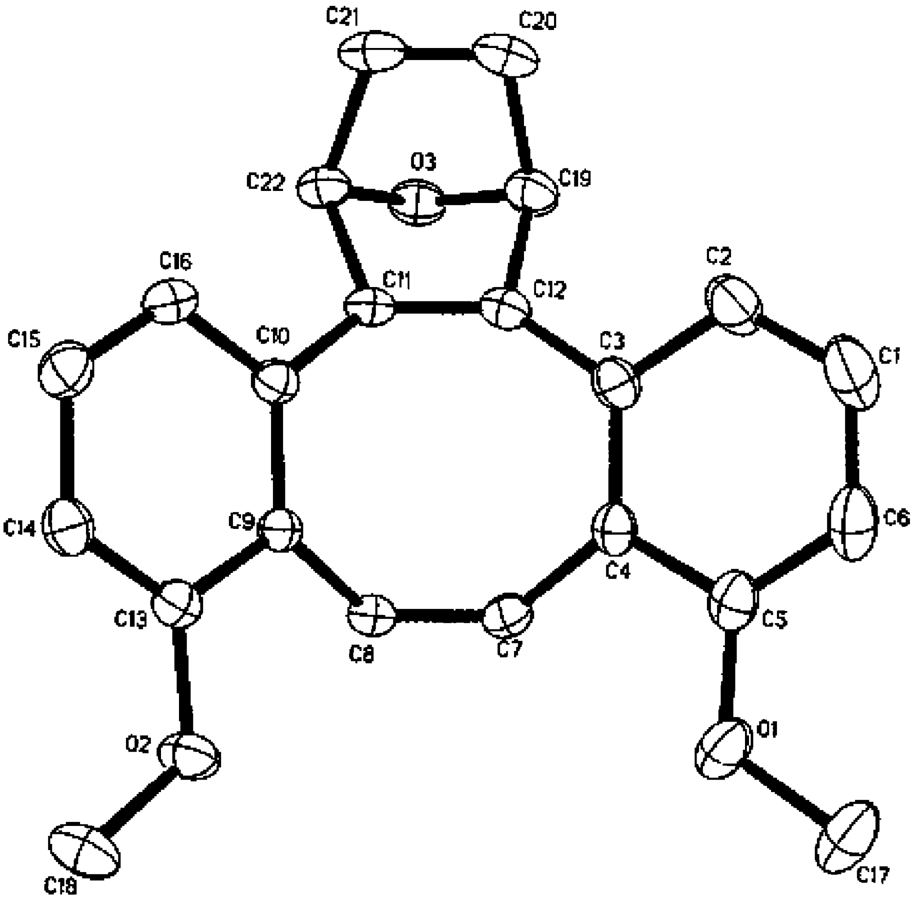
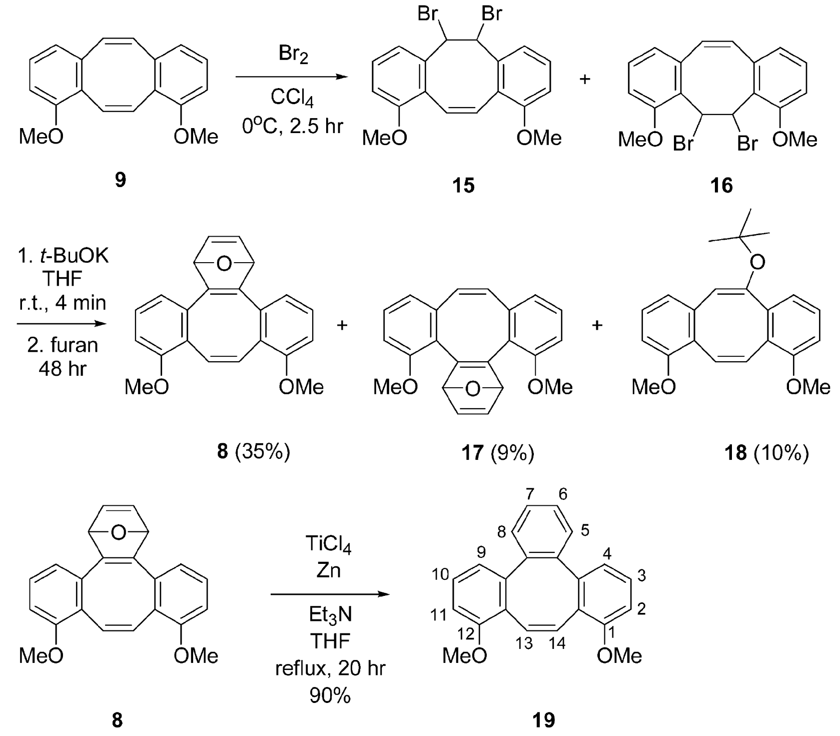
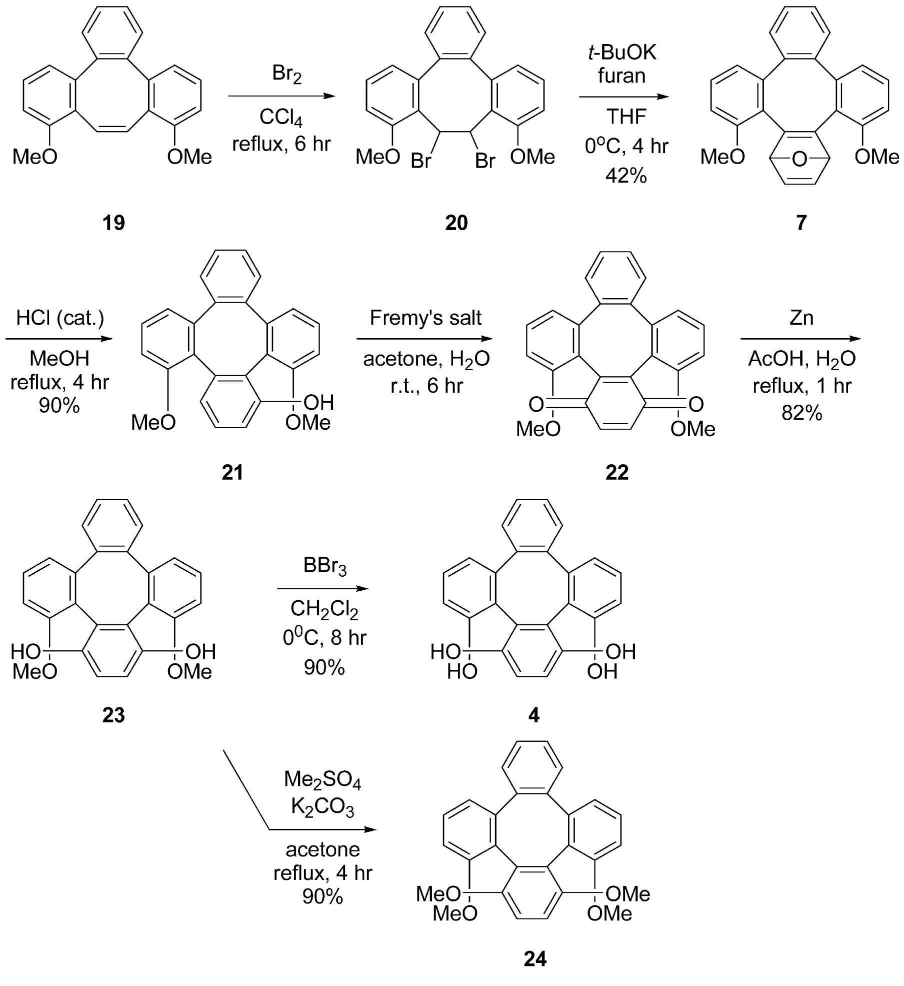


Figure 1. Molecular structure and atom labeling of **8**. H atoms have been omitted for clarity. Ellipsoids are drawn at the 30% probability level.



Scheme 5.



Scheme 6.

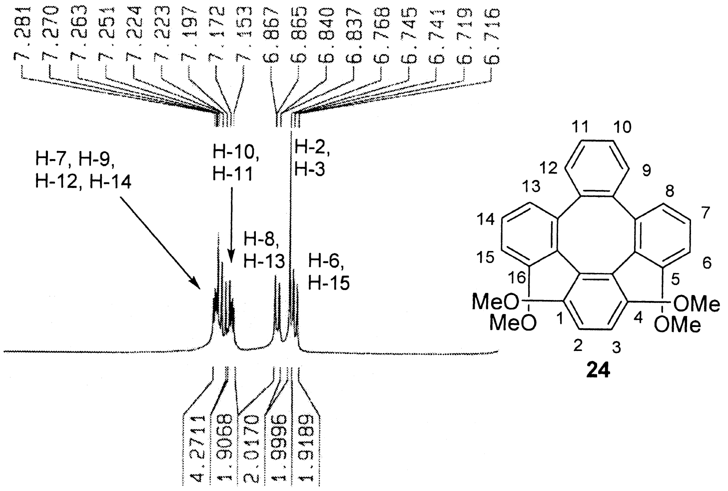


Figure 2. The proton NMR spectrum of **24** with characterization in aromatic region.

consistent with the structure of **19** (Anal. Calcd for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77. Found: C, 84.28; H, 5.82).

With **19** in hand, the introduction of the remaining dihydroxybenzene ring towards the realization of our target was then preformed.

As can be seen in Scheme 6, bromine was used again to brominate the double bond of **19**. However, the solubility of dibromide **20** is generally low in common solvents and it was difficult to purify **20** by column chromatography. As a result, the crude product was directly used in the dehydrobromination step and the freshly generated strained alkyne was trapped by furan concomitantly to give endoxide **7** in 42% yield in two steps.[16,17] With endoxide **7** in hand, acid catalyzed ring opening reaction was performed to lead to phenol **21** smoothly.[19] Since the structure of phenol **21** is unsymmetrical, its proton NMR signals are quite complicated. The chemical shifts of two methoxy groups are found at δ 3.68 and 3.74, respectively. The phenolic proton resonates at δ 4.88. The benzenoid protons absorb at δ 6.74–6.86 (multiplet, 6H), and 7.12–7.26 (multiplet, 7H). The molecular peak found in its HRMS (FAB) spectrum is 380.1418 (Calcd for $C_{26}H_{20}O_3$: 380.1412).

To oxidize phenol to quinone, the typical reagent, Fremy's salt[20] was employed. Through a radical mechanism, phenol **21** was successfully oxidized to quinone **22** by Fremy's salt. Due to the low solubility and the almost identical polarities of phenol **21** and quinone **22**, it was difficult to separate **21** and **22** by column chromatography. Since phenol **21** would not affect the reduction reaction from quinone **22** to hydroquinone **23**, we directly reduced the crude products with zinc powder to form hydroquinone **23** under an acidic condition.[21] The reacted yield was found to be 82% in two steps. Finally, the remaining two methoxy groups were deprotected by BBr_3 to give our target molecule, 1,4,5,16-tetrahydroxytetraphenylene (**4**) in high yield.[22] Furthermore, the free hydroxyl groups on **23** could also be protected by dimethyl sulfate to give tetramethoxytetraphenylene **24** (Scheme 6).

As expected, tetramethoxytetraphenylene **24** is a highly stable compound with a sharp melting point (mp 204 °C). However, tetrahydroxytetraphenylene **4** is relatively unstable when it was exposed to air and light without protection.

The splitting patterns shown in the proton NMR spectra of these three tetraphenylene derivatives, namely **4**, **23** and **24** are quite similar at the downfield region (δ 6.7–7.4). However, we can still easily identify them by the number of methoxy signals at about δ 3.7 in their spectra. In Figure 2, the downfield region in the proton NMR spectrum of tetramethoxytetraphenylene **24** with full characterization is shown.

In summary, the synthesis of 1,4,5,16-tetrahydroxytetraphenylene (**4**), through 1,4-endoxo-1,4-dihydro-8,11-dimethoxytribenzo[*a*,*c*,*e*]cyclooctene (**8**) as the intermediate, was accomplished in 15 steps and the total yield was found to be 3%.

3. Experimental

3.1. General

All reagents and solvents were reagent grade. Further purification and drying by standard method[23] were employed when necessary. All evaporations of organic solvents were carried out with a rotary evaporator in conjunction with a water aspirator. The plates used for thin-layer chromatography (TLC) were E. Merck silica gel $60F_{254}$ (0.25 mm thickness) precoated on aluminum plates, and they were visualized under both long (365 nm) and short (254 nm) UV light. Compounds on TLC plates were visualized with a spray of 5% dodecamolybdophosphoric acid in ethanol and with subsequent heating. Column chromatography was performed using E. Merck silica gel (230–400 mesh).

Melting points were measured on a Reichert Microscope apparatus and were uncorrected. NMR spectra were recorded on a Bruker DPX-300 spectrometer (300.13 MHz for ^1H and 75.47 MHz for ^{13}C). All NMR measurements were carried out at room temperature in deuterated chloroform solution unless otherwise stated. Chemical shifts are reported as parts per million (ppm) in δ units on the scale downfield from tetramethylsilane (TMS) or relative to the resonance of chloroform solvent (7.26 ppm in the ^{1}H, 77.0 ppm for the central line of the triplet in the ^{13}C modes, respectively). Coupling constants (J) are reported in hertz (Hz). Splitting pattern are described as 's' (singlet); 'd' (doublet); 't' (triplet); 'q' (quartet); 'm' (multiplet). ^{1}H NMR data are reported in this order: chemical shifts; multiplicity; coupling constant(s), number(s) of proton. Mass spectra (MS and HRMS) were obtained with a Thermofinnigan MAT95XL spectrometer, and recorded at an ionization energy of 70 eV unless otherwise stated. In all case, signals are reported as m/z. Elemental analyses were performed at Shanghai Institute of Organic Chemistry, The Chinese Academy of Sciences and MEDAC LTD at Brunel Science Centre, UK.

3.1.1. 1,8-Dimethoxyanthraquinone (12).[24] To a vigorously stirred solution of 1,8-dihydroxyanthraquinone (**11**) (20.0 g, 83 mmol) in acetone (500 mL) was added K_2CO_3 (15 g). Then the mixture was heated to reflux and dimethyl sulfate (23 mL, 250 mmol) was added through a dropping funnel in 1 h. The mixture was refluxed for a further 12 h. After cooling to room temperature, the residue was filtered off and washed with acetone (2×20 mL). The combined organic solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel (500 g, hexanes/EtOAc 3:1) to afford 1,8-dimethoxyanthraquinone (**12**) (21.1 g, 92%) as a yellow solid: mp 223–224 °C (lit.[25] 223–235 °C); ^{1}H NMR ($CDCl_3$) δ 4.00 (s, 6H), 7.30 (dd, J=8.4 Hz, 0.6 Hz, 2H), 7.63 (dd, J=8.0, 8.0 Hz, 2H), 7.82 (dd, J=7.8, 1.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 56.5, 118.0, 118.9, 124.0, 133.9, 134.7, 159.4, 182.9, 184.0.

3.1.2. 1,8-Dimethoxyanthracene (13).[26] To a 10% NaOH solution (300 mL) of 1,8-dimethoxyanthraquinone (**12**) (20.0 g, 74.6 mmol) was added zinc powder (25.0 g, 382 mmol). The mixture was stirred and heated for 24 h, and then the reaction mixture was filtered and the filtered cake was washed with CH_2Cl_2 (5×300 mL). The organic extracts were combined and evaporated. The residue was chromatographed on silica gel (1000 g, hexanes/EtOAc 9:1) to give 1,8-dimethoxyanthracene (**13**) (14.2 g, 80%) as yellow needles: mp 198–199 °C (lit.[26] 199–200 °C); ^{1}H NMR ($CDCl_3$) δ 4.09 (s, 6H), 6.74 (d, J=7.5 Hz, 2H), 7.40 (dd, J=8.1, 8.1 Hz, 2H), 7.59 (d, J=8.7 Hz, 2H), 8.34 (s, 1H), 9.28 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.4, 101.5, 115.7, 120.2, 124.4, 125.1, 125.6, 132.9, 155.9.

3.1.3. Dimethyl 9,10-dihydro-9,10-etheno-1,8-dimethoxyanthracene-11,12-dicarboxylate (14). A mixture of 1,8-dimethoxyanthracene (**13**) (10.0 g, 42.0 mmol) and dimethyl acetylenedicarboxylate (8.9 g, 63.0 mmol) in toluene (25 mL) was refluxed with stirring for 12 h. The reaction mixture was cooled with an ice water bath and filtered by suction. The filtered cake was washed with ice cooled absolute ethanol (3×5 mL), and dried at room temperature to give the crude product (13.9 g, 87%). Recrystallization from absolute ethanol afforded dimethyl 9,10-dihydro-9,10-etheno-1,8-dimethoxyanthracene-11,12-dicarboxylate (**14**) (12.8 g, 80%) as a white solid: mp 263–265 °C; ^{1}H NMR ($CDCl_3$) δ 3.77 (s, 3H), 3.80 (s, 3H), 3.85 (s, 6H), 5.49 (s, 1H), 6.36 (s, 1H), 6.61 (dd, J=8.1, 0.6 Hz, 2H), 6.96 (dd, J=7.8, 7.8 Hz, 2H), 7.03 (d, J=6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 39.6, 52.3, 52.3, 52.5, 55.9, 109.0, 116.6, 126.2, 131.4, 146.7, 147.0, 148.5, 154.7, 165.8, 166.3. Anal. Calcd for $C_{22}H_{20}O_6$: C, 69.46; H, 5.30. Found: C, 69.18; H, 5.42.

3.1.4. 1,8-Dimethoxybarrelene (10).[27] To a stirred solution of NaOH (15.0 g, 380 mmol) in 40% aqueous methanol (300 mL) was added dimethyl 9,10-dihydro-9,10-etheno-1,8-dimethoxyanthracene-11,12-dicarboxylate (**14**) (10.0 g, 26.3 mmol). The mixture was allowed to reflux for 4 h, and was then cooled to room temperature. The reaction mixture was acidified with 36% HCl to pH 2, filtered with suction filtration and dried under vacuum without further purification to give 9,10-dihydro-9,10-etheno-1,8-dimethoxyanthracene-11,12-dicarboxylic acid.

To a vigorously stirred solution of 9,10-dihydro-9,10-etheno-1,8-dimethoxyanthracene-11,12-dicarboxylic acid (vide supra) (10.0 g, 29.8 mmol) in quinoline (250 mL) was added copper powder (9.4 g, 142.0 mmol). The reaction mixture was refluxed for 3 h under N_2. After cooling to room temperature, CH_2Cl_2 (250 mL) was added to the mixture and the residue was then filtered. The filtrate was washed with 1 N HCl (4×200 mL) and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on a silica gel column (600 g, hexanes/EtOAc 10:1) to afford 1,8-dimethoxybarrelene (**10**) (4.1 g, 52%) as colorless crystals: mp 210–211 °C (lit.[27] 211–212 °C); ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 6H), 5.18 (dd, J=5.4, 1.5 Hz, 1H), 6.12 (dd, J=5.4, 1.8 Hz, 1H), 6.60 (dd, J=7.8, 0.9 Hz, 2H), 6.91–7.06 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 37.4, 51.6, 55.8, 108.2, 116.1, 125.1, 133.8, 139.7, 140.3, 149.1, 154.0. Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.84; H, 6.17.

3.1.5. 1,10-Dimethoxydibenzo[*a*,*e*]cyclooctene (9). A solution of 1,8-dimethoxybarrelene (**10**) (1.0 g, 3.79 mmol) in degassed anhydrous THF (500 mL) was irradiated with a mercury lamp (125 W medium pressure) at room temperature for 3 h under a nitrogen atmosphere. After evaporation of the solvent, chromatography on silica gel (100 g, hexanes/EtOAc 7:1) afforded 1,10-dimethoxydibenzo[*a*,*e*]-cyclooctene (**9**) (0.95 g, 95%) as colorless crystals: mp 207–208 °C; ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 6H), 6.65–6.70 (m, 4H), 6.73 (s, 2H), 6.74 (s, 2H) 7.14 (dd, J=8.0, 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 55.5, 108.5, 121.1, 126.5, 127.8, 129.2, 133.0, 138.5, 157.3. Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.93; H, 6.16.

3.1.6. 5,6-Dibromo-5,6-dihydro-1,10-dimethoxydibenzo[*a*,*e*]cyclooctene (15); 11,12-dibromo-11,12-dihydro-1,10-dimethoxydibenzo[*a*,*e*]cyclooctene (16). To a suspension of 1,10-dimethoxydibenzo[*a*,*e*]cyclooctene (**9**) (0.60 g, 2.3 mmol) in anhydrous CCl_4 (50 mL) was added slowly a solution of bromine (0.36 g, 2.3 mmol) in anhydrous CCl_4 (10 mL) through a dropping funnel within 2 h at 0 °C under N_2. After addition, the temperature was slowly allow to rise to room temperature and the mixture was stirred for an additional 30 min. The reaction was quenched by addition of 10% $Na_2S_2O_5$ (3 mL). The mixture was extracted with CH_2Cl_2 (2×10 mL), and the combined organic extract was dried over $MgSO_4$ and evaporated under reduced pressure to give a mixture of 5,6-dibromo-5,6-dihydro-1,10-dimethoxydibenzo[*a*,*e*]cyclooctene (**15**) and 11,12-dibromo-11,12-dihydro-1,10-dimethoxydibenzo[*a*,*e*]-cyclooctene (**16**) as a white solid. These compounds were not purified further and were used immediately in the next step.

3.1.7. 1,4-Endoxo-1,4-dihydro-8,11-dimethoxytribenzo[*a*,*c*,*e*]cyclooctene (8); 1,4-endoxo-1,4-dihydro-5,14-dimethoxytribenzo[*a*,*c*,*e*]cyclooctene (17); 5-*tert*-butoxy-1,10-dimethoxydibenzo[*a*,*c*]cyclooctene (18). To a solution of freshly sublimed KO-*t*-Bu (0.76 g 6.8 mmol) in anhydrous THF (40 mL) and furan (20 mL) under N_2 was added slowly a solution of previously prepared dibromides **15** and **16** (1.0 g, 2.3 mmol) (vide supra) in anhydrous THF (40 mL) and furan (20 mL) within 3 min. After the solution was stirred for 1 min, brine (15 mL) was added. The organic layer was separated and dried over $MgSO_4$, and the filtrate was then stirred for further 48 h under N_2. The solvent was evaporated under reduced pressure and the residue was separated by flash column chromatography on silica gel (30 g, hexanes/EtOAc 3:1) to give 1,4-endoxo-1,4-dihydro-8,11-dimethoxytribenzo[*a*,*c*,*e*]cyclooctene (**8**) (260 mg, 35%), 1,4-endoxo-1,4-dihydro-5,14-dimethoxytribenzo[*a*,*c*,*e*]cyclooctene (**17**) (70 mg, 9%) and 5-*tert*-butoxy-1,10-dimethoxydibenzoc[*a*,*c*]cyclooctene (**18**) (80 mg, 10%).

Data of **8**: mp 150–151 °C; ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 6H), 5.44–5.45 (m, 2H), 6.36 (dd, *J*=7.8, 0.9 Hz, 2H), 6.62 (s, 2H), 6.71 (dd, *J*=7.8, 8.1 Hz, 2H), 7.17 (dd, *J*=8.0, 8.0 Hz, 2H), 7.40 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 55.6, 87.9, 109.2, 114.8, 126.4, 128.3, 129.9, 136.4, 142.5, 151.5, 157.8. MS *m*/*z* 330 (M^+). HRMS (EI) Calcd for $C_{22}H_{18}O_3$: 330.1256. Found: 330.1250. Crystallization from 20% EtOAc in CH_2Cl_2 at room temperature gave colorless crystals, which were sufficiently good for an X-ray crystallographic analysis.

Data of **17**: mp 145–146 °C; ^{1}H NMR ($CDCl_3$) δ 3.75 (s, 6H), 5.40–5.41 (m, 2H), 6.41 (s, 2H), 6.65 (dd, *J*=8.1, 0.6 Hz, 2H), 6.70 (dd, *J*=7.8, 0.9 Hz, 2H), 7.14 (dd, *J*=7.4, 7.4 Hz, 2H), 7.16 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 55.2, 87.4, 108.9, 122.0, 124.2, 128.2, 133.4, 138.6, 142.5, 152.4, 158.0. MS *m*/*z* 330 (M^+). HRMS (EI) Calcd for $C_{22}H_{18}O_3$: 330.1256. Found: 330.1247.

Data of **18**: mp 198–199 °C; ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 9H), 3.77 (s, 6H), 6.37 (s, 1H), 6.61–6.86 (m, 5H), 6.99 (d, *J*=7.8 Hz, 1H), 7.07–7.16 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 29.2, 55.5, 78.4, 108.1, 109.3, 120.2, 121.8, 126.1, 126.6, 127.6, 127.8, 128.9, 130.3, 137.6, 140.0, 151.8, 156.7, 157.3. MS *m*/*z* 279 ($M^+-C_4H_9$). HRMS (EI) Calcd for $C_{22}H_{24}O_3$: 279.1021. Found: 279.1019.

3.1.8. 1,12-Dimethoxytribenzo[*a*,*c*,*e*]cyclooctene (19). Anhydrous THF (6 mL) was added to titanium(IV) chloride (1.0 mL, 9.1 mmol) dropwise under N_2 with stirring at 0 °C. Zinc powder (0.80 g, 12 mmol) was added, and was followed by triethylamine (0.30 mL, 2.2 mmol). After refluxing for 30 min, a suspension of 1,4-endoxo-1,4-dihydro-8,11-dimethoxytribenzo[*a*,*c*,*e*]cyclooctene (**8**) (0.50 g, 1.5 mmol) in anhydrous THF (30 mL) was added dropwise to the low-valent-titanium solution. The reaction mixture was then stirred at refluxing temperature for 20 h. Sat. K_2CO_3 (5 mL) was added, and was followed by extraction with CH_2Cl_2 (3×20 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and evaporated. Chromatography on a column of silica gel (25 g, hexanes/EtOAc 10:1) gave 1,12-dimethoxytribenzo[*a*,*c*,*e*]cyclooctene (**19**) (0.43 g 90%) as colorless crystals: mp 212–213 °C; ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 6H), 6.73 (s, 2H), 6.76 (dd, *J*=8.4, 0.9 Hz, 2H), 6.79 (dd, *J*=7.5, 0.9 Hz, 2H), 7.14–7.19 (m, 4H), 7.38 (dd, *J*=5.7, 3.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 55.7, 109.0, 122.1, 126.6, 127.1, 127.9, 128.9, 129.7, 141.9, 143.0, 156.3; MS *m*/*z* 314 (M^+). HRMS (EI) Calcd for $C_{22}H_{18}O_2$: 314.1307. Found: 314.1305. Anal. Calcd for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77. Found: C, 84.28; H, 5.82.

3.1.9. 13,14-Dibromo-13,14-dihydro-1,12-dimethoxytribenzo[*a*,*c*,*e*]cyclooctene (20). To a suspension of 1,12-dimethoxytribenzo[*a*,*c*,*e*]cyclooctene (**19**) (0.25 g, 0.81 mmol) in anhydrous CCl_4 (47 mL) was added bromine (0.26 g 3.2 mmol). The mixture was stirred and refluxed for 6 h, and then cooled to room temperature. The reaction was quenched by addition of 10% $Na_2S_2O_5$ (3 mL), and extracted with CH_2Cl_2 (2×10 mL). The combined organic extract was dried over $MgSO_4$ and evaporated under reduced pressure to give 13,14-dibromo-13,14-dihydro-1,12-dimethoxytribenzo[*a*,*c*,*e*]cyclooctene (**20**) as a white solid. This compound was not purified further and was used immediately in the next step.

3.1.10. 1,4-Endoxo-1,4-dihydro-5,16-dimethoxytetrabenzo[*a*,*c*,*e*,*g*]cyclooctene (7). To a solution of freshly sublimed KO-*t*-Bu (0.48 g 4.3 mmol) in anhydrous THF (15 mL) and furan (15 mL) under N_2 was added dropwise a solution of the previously prepared dibromides **20** (vide supra) in anhydrous THF (25 mL) and furan (12 mL) within 60 min. After the solution was stirred for 3 h, 0.5 N HCl (10 mL) was added. The mixture was extracted with CH_2Cl_2 (3×20 mL). The combined organic extract was washed with brine (10 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel (30 g, hexanes/EtOAc 3:1) to give 1,4-endoxo-1,4-dihydro-5,16-dimethoxytetrabenzo[*a*,*c*,*e*,*g*]cyclooctene (**7**) (0.13 g, 42%) as colorless crystals: mp 251–253 °C; ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 6H), 5.65 (d, *J*=0.9 Hz, 2H), 6.59 (d, *J*=0.9 Hz, 2H), 6.79–6.84 (m, 4H), 6.97 (dd, *J*=5.7, 3.3 Hz, 2H), 7.20–2.26 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 55.7, 85.5, 109.3, 122.1, 123.1, 126.6, 128.8, 130.7, 140.8, 143.3, 144.0, 151.6, 157.2; MS *m*/*z* 381 (M^++1), 380 (M^+). HRMS (FAB) Calcd for $C_{26}H_{21}O_3$: 381.1491. Found: 381.1483.

3.1.11. 1-Hydroxy-5,16-dimethoxytetrabenzo[*a*,*c*,*e*,*g*]-cyclooctene (21). A mixture of 1,4-endoxo-1,4-dihydro-5,16-dimethoxytetrabenzo[*a*,*c*,*e*,*g*]cyclooctene (**7**) (0.10 g, 0.26 mmol) and 36% HCl (0.5 mL) in MeOH (30 mL) was refluxed with stirring for 4 h. After cooling to room temperature, the reaction was quenched by addition of brine (15 mL), and extracted with CH_2Cl_2 (3×20 mL). The combined organic extract was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was separated by flash column chromatography on silica gel

(10 g, hexanes/EtOAc 3:1) to give 1-hydroxy-5,16-dimethoxytetrabenzo[*a*,*c*,*e*,*g*]cyclooctene (**21**) (90 mg 90%) as a white solid: mp 284–285 °C; ^{1}H NMR ($CDCl_3$) δ 3.68 (s, 3H), 3.74 (s, 3H), 4.88 (s, 1H), 6.74 (dd, J=2.7, 1.2 Hz, 1H), 6.77 (dd, J=2.7, 0.9 Hz, 1H), 6.80 (dd, J=8.1, 1.2 Hz, 1H), 6.84 (s, 1H), 6.86 (d, J=0.9 Hz, 1H), 6.90 (dd, J=8.4, 0.9 Hz, 1H), 7.10–7.17 (m, 3H), 7.19–7.29 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 56.2, 56.5, 110.9, 114.2, 121.5, 122.6, 122.8, 123.8, 124.0, 127.1, 127.3, 127.8, 127.9, 128.0, 128.0, 128.3, 129.1, 130.2, 138.5, 140.8, 141.2, 143.1, 145.0, 152.5, 155.9, 156.1. MS *m/e* 381 (M^++1), 380 (M^+). HRMS (FAB) Calcd for $C_{26}H_{20}O_3$: 380.1412. Found: 380.1418.

3.1.12. 1,4-Dioxo-1,4-dihydro-5,16-dimethoxytetrabenzo[*a*,*c*,*e*,*g*]cyclooctene (22). To a vigorously stirred solution of 1-hydroxy-5,16-dimethoxytetrabenzo[*a*,*c*,*e*,*g*]-cyclooctene (**21**) (50 mg 0.13 mmol) in acetone (6 mL) was added a buffer solution (Na_2HPO_4, NaH_2PO_4, *p*H=5.8, 6 mL) of Fremy's salt (174 mg, 0.65 mmol). The resulting mixture was vigorously stirred for 6 h. The mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic extract was dried over $MgSO_4$ and evaporated under reduced pressure to give 1,4-dioxo-5,16-dimethoxytetrabenzo[*a*,*c*,*e*,*g*]cyclooctene (**22**), which was used in the next step without further purification and characterization.

3.1.13.1,4-Dihydroxy-5,16-dimethoxytetrabenzo[*a*,*c*,*e*,*g*]-cyclooctene (23). A mixture of 1,4-dioxo-1,4-dihydro-5,16-dimethoxytetrabenzo[*a*,*c*,*e*,*g*]cyclooctene (**22**) (vide supra) and zinc powder (60 mg, 0.92 mmol) in acetic acid: water (2:1) solution (8 mL) was refluxed with stirring for 1 h. The mixture was extracted with CH_2Cl_2 (3×15 mL). The combined organic extract was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (8 g, hexanes/EtOAc 1:1) to give 1,4-dihydroxy-5,16-dimethoxytetrabenzo[*a*,*c*,*e*,*g*]cyclooctene (**23**) [17 mg, 82% (reacted yield)] as a white solid: mp 241–242 °C; ^{1}H NMR (CD_2Cl_2) δ 3.77 (s, 6H), 4.56 (s, 2H), 6.70 (s, 2H), 6.83 (dd, J=7.5, 0.9 Hz, 2H) 6.79 (dd, J=7.5, 0.9 Hz, 2H), 7.17 (dd, J=5.7, 2.4 Hz, 2H) 7.28–7.33 (m, 4H); ^{13}C NMR (CD_2Cl_2) δ 56.9, 111.3, 116.2, 123.1, 125.5, 128.0, 128.6, 129.4, 129.8, 141.3, 145.0, 147.1, 156.5. MS *m/e* 396 (M^+). HRMS (EI) Calcd for $C_{26}H_{20}O_4$: 396.1362. Found 396.1353.

3.1.14. 1,4,5,16-Tetrahydroxytetraphenylene (4). To a vigorously stirred solution of 1,4-dihydroxy-5,16-dimethoxytetrabenzo[*a*,*c*,*e*,*g*]cyclooctene (**23**) (10 mg 0.025 mmol) in CH_2Cl_2 (4 mL) at 0 °C was added BBr_3 (0.1 mM, 0.5 mL) in CH_2Cl_2 slowly. The mixture was stirred for 8 h at 0 °C. After that the temperature was allowed to slowly rise to room temperature. The reaction was quenched by addition of brine (2 mL), and extracted with CH_2Cl_2 (2×5 mL). The combined organic extract was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was separated by flash column chromatography on silica gel (4 g, hexanes/EtOAc 1:2) to give 1,4,5,16-tetrahydroxytetraphenylene (**4**) (8.3 mg, 90%) as a white solid: mp 135 °C (dec); ^{1}H NMR (d^6-Acetone) δ 6.58 (dd, J=7.5, 0.9 Hz, 2H), 6.62 (s, 2H), 6.74 (dd, J=8.1, 1.2 Hz, 2H), 7.06 (dd, J=7.8, 7.8 Hz, 2H), 7.14–7.17 (m, 2H), 7.22–7.25 (m, 2H); ^{13}C NMR (d^6-Acetone) δ 144.5, 121.6, 126.7, 127.2, 128.5, 128.6, 128.6, 130.5, 136.8, 141.0, 143.1, 151.6; MS *m/z* 368 (M^+). HRMS (FAB) Calcd for $C_{24}H_{16}O_4$: 368.1049. Found 368.1038.

3.1.15. 1,4,5,16-Tetramethoxytetraphenylene (24). To a vigorously stirred solution of 1,4-dihydroxy-5,16-dimethoxytetrabenzo[*a*,*c*,*e*,*g*]cyclooctene (**23**) (10 mg 0.025 mmol) in acetone (4 mL) was added K_2CO_3 (14 mg). Then the mixture was heated to reflux and dimethyl sulfate (0.01 mL, 0.1 mmol) was added. The mixture was refluxed for a further 4 h and NaOH (0.05 g) was added. After cooling to room temperature, the residue was filtered off and washed with acetone (2 mL). The combined organic solvent was washed with brine (3 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (6 g, hexanes/EtOAc, 3:1) to give 1,4,5,16-tetramethoxytetraphenylene (**24**) (9.6 mg, 90%) as a white solid: mp 204 °C; ^{1}H NMR (CD_2Cl_2) δ 3.63 (s, 6H), 3.72 (s, 6H), 6.73 (dd, J=7.5, 0.9 Hz, 2H), 6.77 (s, 2H), 6.86 (dd, J=8.1, 0.9 Hz, 2H), 7.16 (dd, J=5.7, 3.3 Hz, 2H), 7.20–7.28 (m, 4H); ^{13}C NMR (CD_2Cl_2) δ 56.7, 56.8, 110.7, 111.0, 122.0, 126.9, 127.7, 128.6, 128.7, 128.9, 141.9, 143.6, 151.6, 157.4; MS *m/e* 424 (M^+). HRMS (EI) Calcd for $C_{28}H_{24}O_4$: 424.1675. Found: 424.1661.

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