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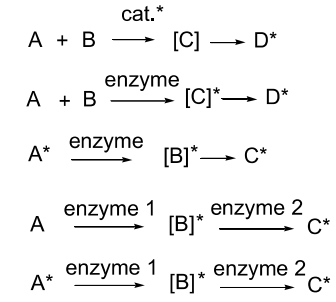
Contents

REPORT

Asymmetric domino reactions are reviewed for the first time. The second part of the review includes asymmetric domino reactions catalysed by chiral catalysts and asymmetric biocatalysed domino reactions and covers the classification and characteristics of these asymmetric domino reactions, together with their most recent applications. This compilation clearly demonstrates the power and economical interest of asymmetric catalysed domino reactions in the field of synthetic organic chemistry including the asymmetric biocatalysed domino reactions.



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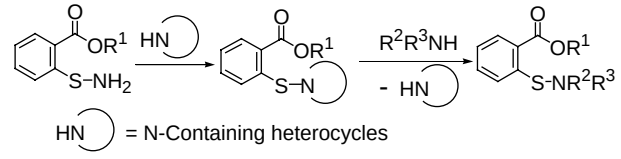
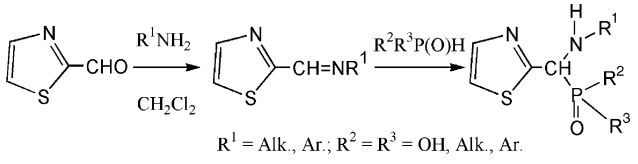
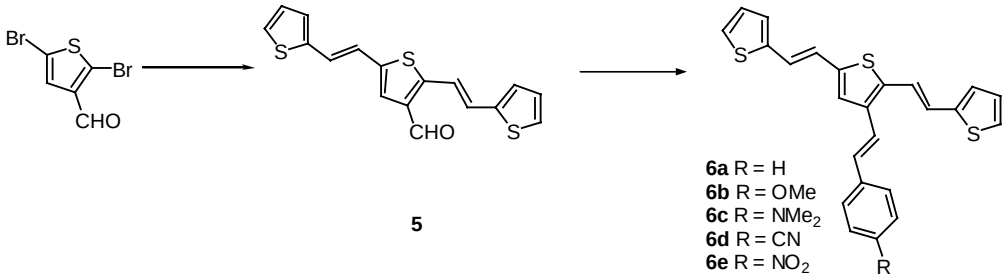
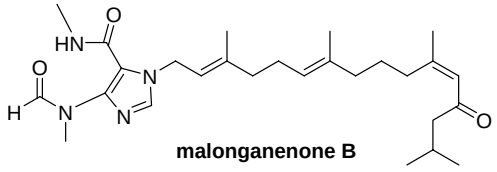
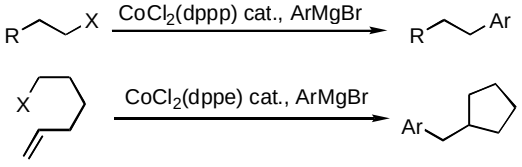
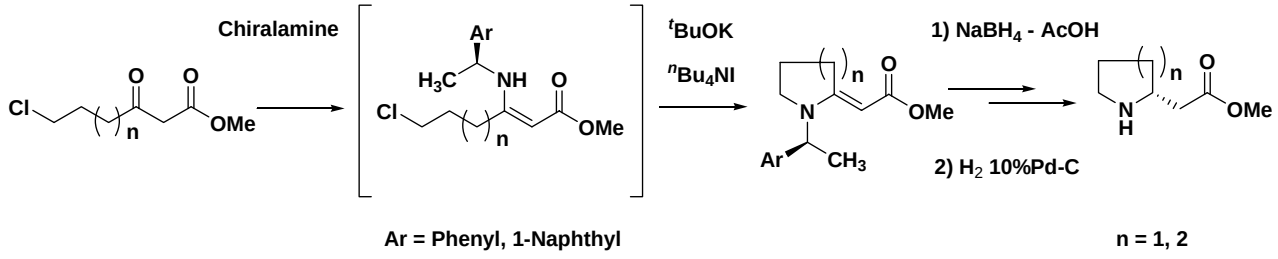


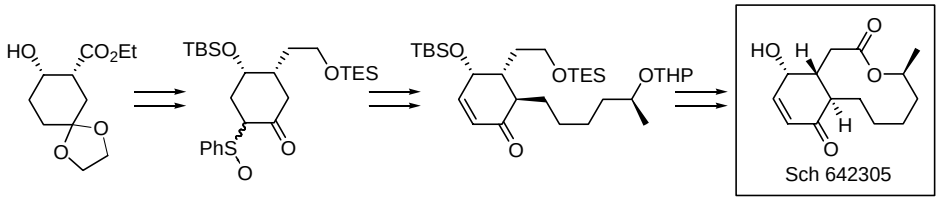


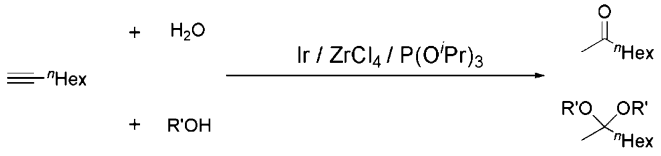


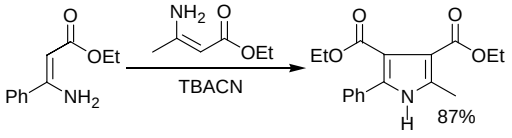


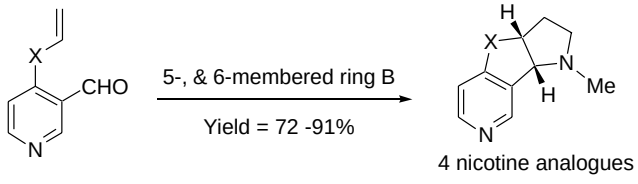


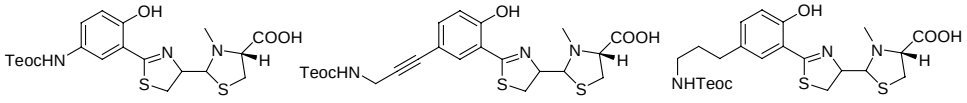


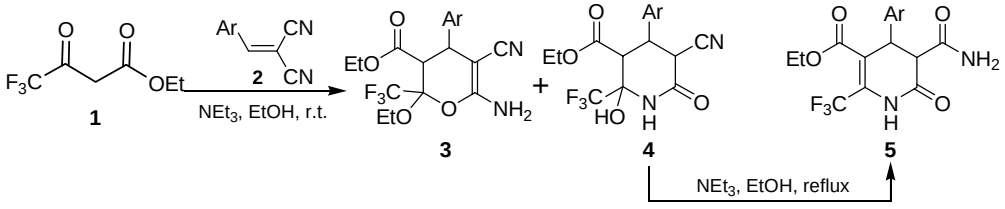


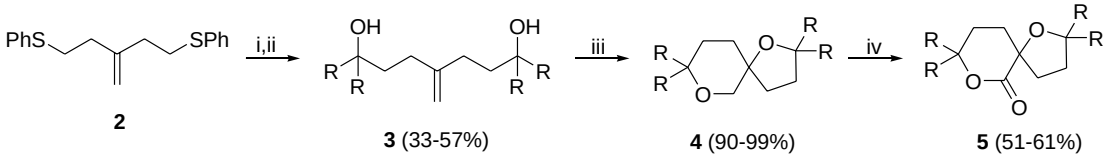




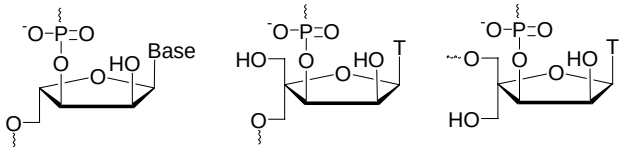


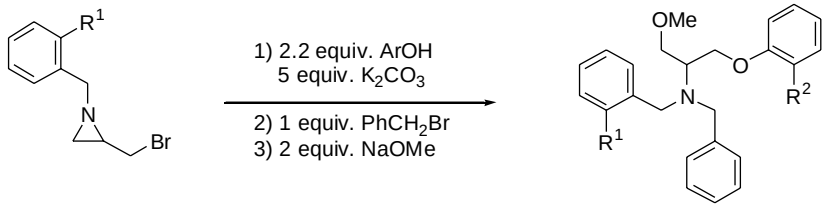


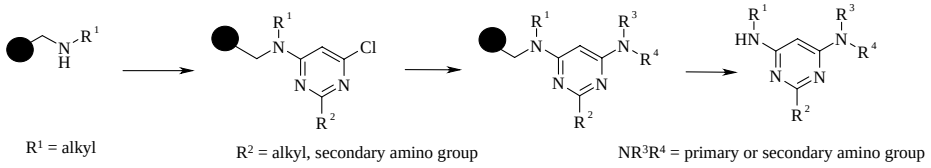


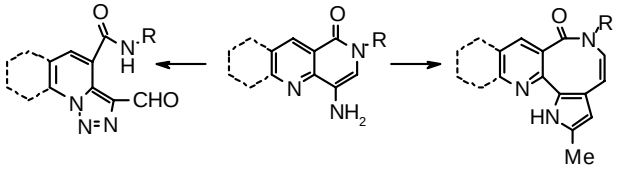


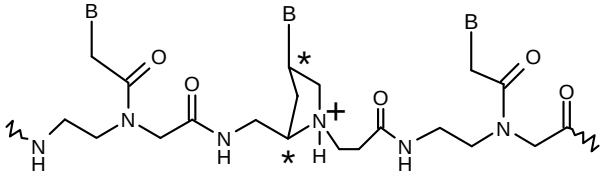
i, Li, DTBB (cat.), R_2CO, THF, 0 °C; ii, H_2O; iii, I_2, AgOTf, Na_2CO_3, THF, rt; iv, $RuCl_3 \cdot xH_2O$ (cat.), $NaIO_4$, CCl_4, H_2O, CTAB, reflux.

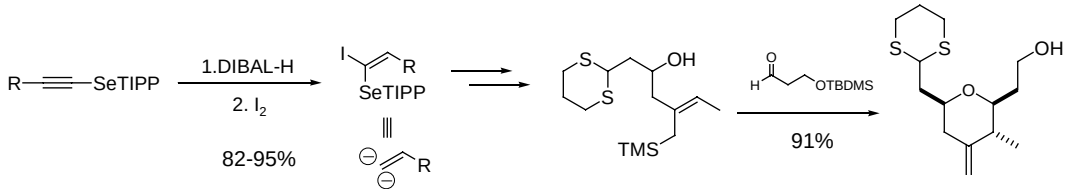


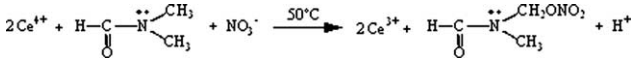


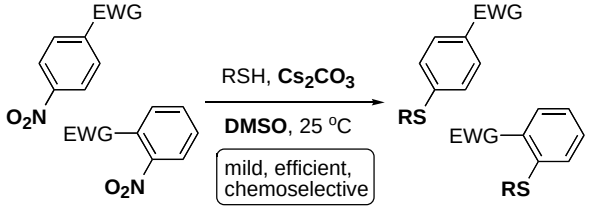


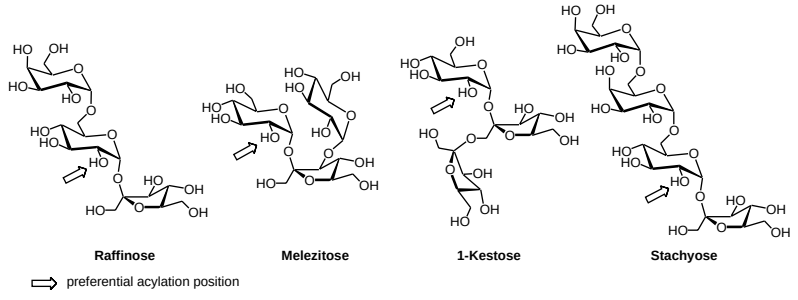


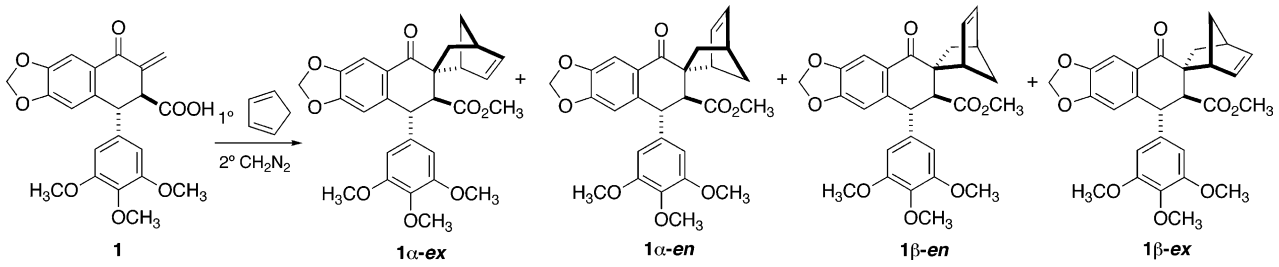




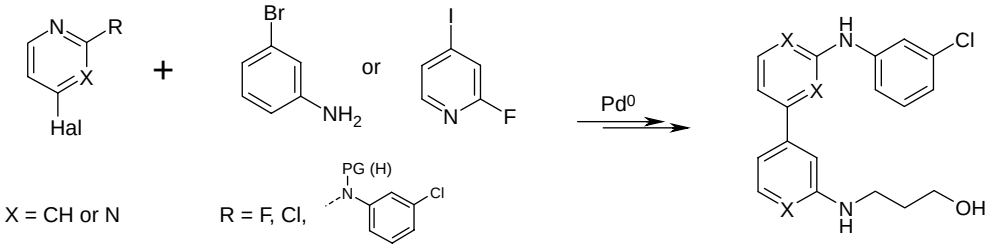


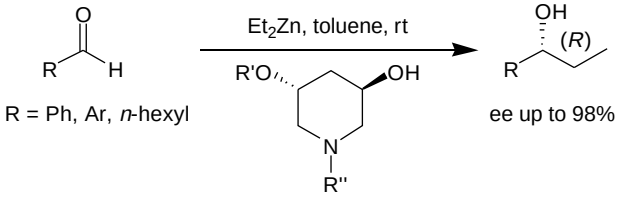


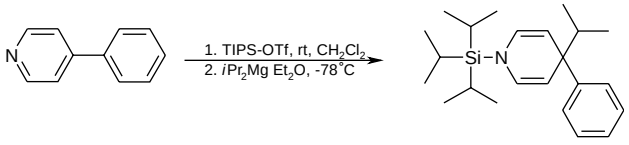


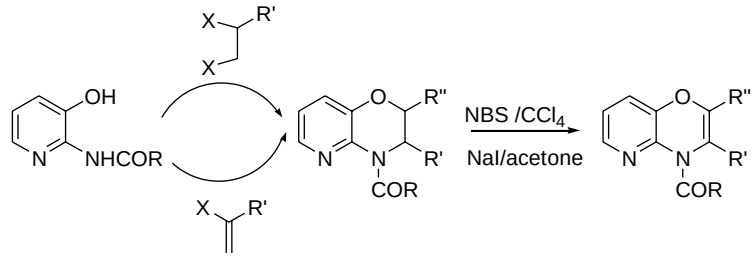


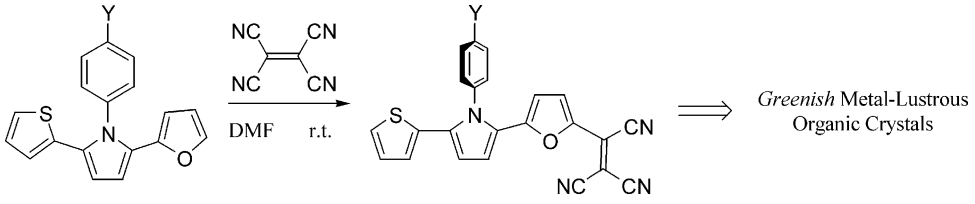
The synthesis of novel structural analogs of known phenylamino-pyrimidine-type protein kinase C inhibitors is reported. Key step of the reaction sequence was a Pd-catalyzed Negishi type cross-coupling reaction.

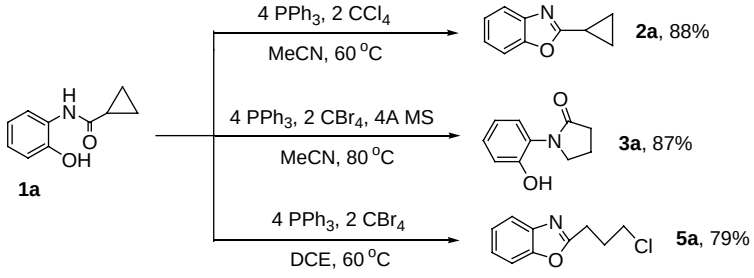












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Asymmetric domino reactions. Part B: Reactions based on the use of chiral catalysts and biocatalysts

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Contents

Keywords: Asymmetric Domino reactions; Chiral catalysts; Biocatalysts.

Abbreviations used: Ac, acetyl; Acac, acetylacetone; Ala, alanine; Ar, aryl; BINAP, 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl; BINOL, 1,1′-bi-2-naphthol; $BF_3{\cdot}Et_2O$, boron trifluoride etherate; Bn, benzyl; Boc, *tert*-butoxycarbonyl; BQ, benzoylquinine; Bu, butyl; Bz, benoyl; c, cyclo; Cbz, benzyloxycarbonyl; CMP, cytosine monophosphate; Cob, cobyrinic acid; COD, cyclooctadiene; Cp, cyclopentadienyl; dba, (*E*,*E*)-dibenzylideneacetone; de, diastereomeric excess; dr, diastereomeric ratio; DAIB, dimethylamino isoborneol; DEAD, diethyl azodicarboxylate; DIB, *o*-diiodobenzene; DIOP, 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane; DMF, dimethylformamide; DMSO, dimethylsulphoxide; DMTC, 5,5-dimethyl thiazolidinium-4-carboxylate; DUPHOS, 1,2-bis(phospholano)benzene; ee, enantiomeric excess; Et, ethyl; EWG, electron-withdrawing; FMOC, 9-fluorenylmethoxycarbonyl; Fu, furan; Hex, hexyl; Me, methyl; Ms, mesyl; MOM, methoxymethyl; Nbd, norbornadiene; NMDPP, (neomenthyl)-diphenylphosphane; Np, naphthyl; Nu, nucleophile; ONf, nonaflate; PBG, phorphobilinogen; PCC, pyridinium chlorochromate; Pent, pentyl; Ph, phenyl; Pr, propyl; py, pyridine; quinap, 1-(2-diphenylphosphino-1-naphthyl)-isoquinoline; salen, 1,2-bis(salicylidenamino)ethane; SAM, *S*-adenosylmethionine; TADDOL, $\alpha,\alpha\alpha'\alpha'$-tetraphenyl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol; TBAF, tetra-*n*-butylammonium fluoride; TBDMS, *tert*-butyldimethylsilyl; TBDPS, *tert*-butyldiphenylsilyl; Tf, trifluoromethanesulphonyl; TFA, trifluoroacetic acid; THF, tetrahydrofuran; THP, tetrahydropyranyl; TMS, trimethylsilyl; TMSOTf, trimethylsilyl trifluoromethanesulphonate; Tol, toluene; Tr, triphenylmethyl(trityl); Ts, 4-toluenesulphonyl(tosyl); UDP, uridine-5′-diphosphate.

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1. Introduction

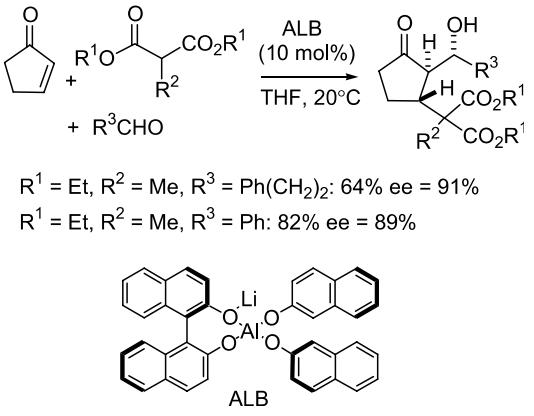
Tietze has defined a domino reaction as involving two or more bond-forming transformations, which take place under the same reaction conditions, without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed by bond formation or fragmentation in the previous step.[1] Domino reactions can be classified according to the mechanism of the single steps, which may be of the same or different types (cationic, anionic, radical, pericyclic, or transition-metal-catalysed transformations). The quality and importance of a domino reaction can be correlated to the number of bonds generated in such a process and the increase in complexity. The reactions can be performed as single-, two- and multicomponent transformations. Thus, most, but not all, of the known multicomponent processes can be defined as a subgroup of domino reactions. The use of domino and domino multicomponent reactions in asymmetric synthesis is increasing constantly. Such single-step reactions allow the synthesis of a wide range of complex molecules in an economically favourable way by using processes that are reasonably simple. Domino reactions have gained wide acceptance, because they increase synthetic efficiency by decreasing the number of laboratory operations required and the quantities of chemicals and solvents used. The proliferation of domino reactions is evidenced by the number of recent reviews covering the literature through 1992.[2] The asymmetric aspect of the domino methodology has not, however, been reviewed (excepted for multicomponent reactions[3]) and, with this report, the author would like to fill this gap. The synthesis of optically active chiral compounds, which play an important role in medicine and materials, is one of the most fascinating aspects of modern organic synthesis. Of the methods available for preparing such compounds, catalytic asymmetric synthesis has attracted most attention. The economical interest in combinations of chiral catalytic processes with domino reactions is obvious. As in Part A of this review, the domino reactions are catalogued on the basis of the reaction intermediates or, in some cases, the reaction types involved in the first two synthetic steps. It is, of course, impossible to locate all the published examples of asymmetric domino reactions, since many of these are incorporated in total syntheses described under different keywords. The examples cited in this review have been selected to highlight the most promising applications of asymmetric domino reactions to organic synthesis. In order to facilitate presentation, the review has been divided into two parts. Part A[4] deals with domino reactions using chiral auxiliaries, whereas Part B includes domino reactions catalysed by chiral catalysts and biocatalysts.

2. Chiral catalysts

The catalytic asymmetric formation of chiral building blocks represents an increasingly important field in organic chemistry, owing to the usefulness of these products in further synthetic transformations. The catalytic enantioselective formation of C–C bonds is a widely developed method for achieving this goal and a number of reactions and methodologies have been developed.[5] Among the various asymmetric C–C bond-forming reactions, the direct catalytic domino reactions are of particular interest, as multiple stereogenic centres can be formed in a single reaction. To the best of the author's knowledge, no examples are known for cationic sequences catalysed by chiral catalysts.

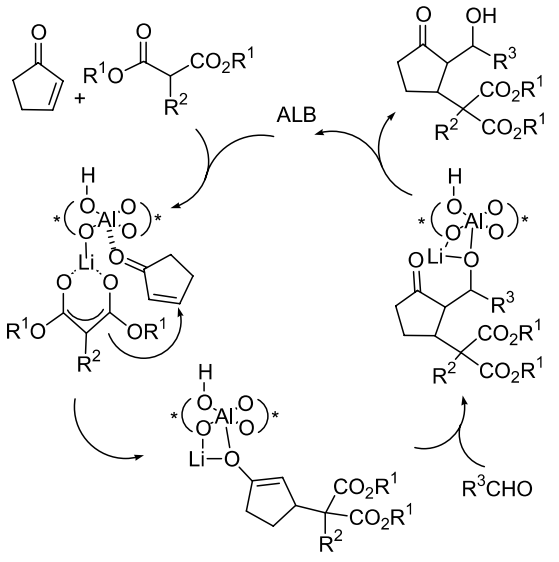
2.1. Anionic primary step

2.1.1. Anionic–anionic reactions. The first catalytic asymmetric domino Michael aldol reaction was reported by Shibasaki et al. in 1996.[6] This domino reaction was promoted by the catalytic use of a heterobimetallic multifunctional asymmetric complex, for example, AlLibis[(*R*)-binaphthoxide] complex (ALB) (Scheme 1). The usefulness of this methodology was demonstrated by its further application to the catalytic asymmetric synthesis of 11-deoxy-$PGF_{1\alpha}$.[7]



Scheme 1. Catalytic asymmetric Michael aldol reaction promoted by AlLi-(*R*)-binaphthoxide complex.

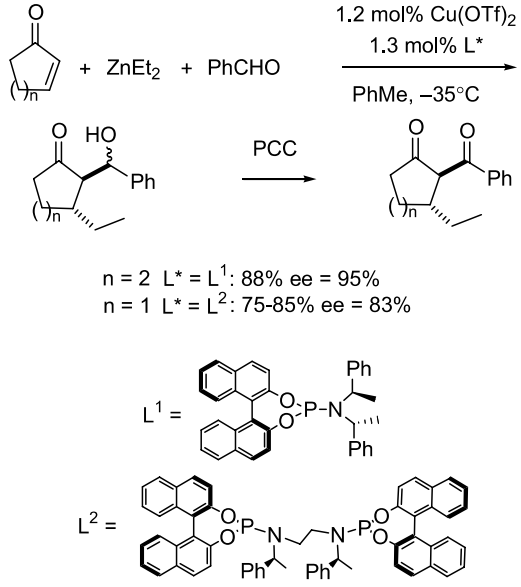
In addition, these authors have described the reaction pathway in this three-component coupling reaction as follows (Scheme 2). The reaction of diethyl malonate with AlLi-(*R*)-binaphthoxide complex gives the corresponding lithium enolate. This latter enolate then reacts with cyclopentenone, which is pre-coordinated to the aluminium, to give an aluminium enolate enantioselectively. Further



Scheme 2. Possible mechanism for asymmetric domino Michael aldol reaction catalysed by ALB.

reaction of this latter enolate with aldehyde would lead to an alkoxide. Although it is unclear whether the aluminium or lithium alkoxide is generated, the resulting alkoxide then abstracts a hydrogen atom from an acidic OH group to give the three-component coupling product and regenerates the ALB complex, which completes the catalytic cycle.

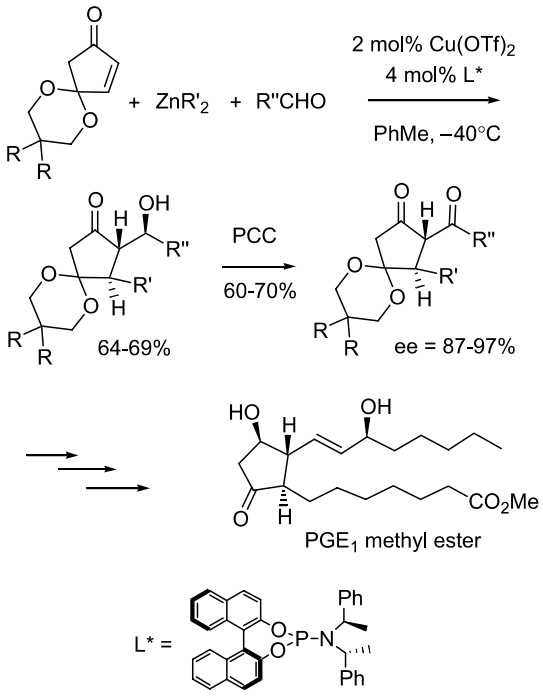
First reported in 1996 by Noyori et al.,[8] the catalytic enantioselective domino 1,4-addition-enolate trapping reaction of dialkylzinc reagents to enones was re-investigated by Feringa et al. in the presence of new copper complexes of bidentate chiral phosphoramidites prepared from TADDOL and BINOL.[9] Thus, these ligands were successfully involved in the copper-catalysed enantioselective conjugate addition aldol reaction of diethylzinc to 2-cyclopentenone in the presence of benzaldehyde (Scheme 3). Other enantioselective Michael aldol reactions have been reported such as those involving the Michael addition of silyl phenyl selenide or sulphide derivatives to vinyl ketone derivatives mediated by a chiral acyloxyborane.[10] Hayashi et al. have shown that it was also possible to use various 9-aryl-9-borabicyclo[3.3.1]-nonanes as a source of nucleophile activated by a chiral rhodium complex.[11] In 2004, a new domino Michael aldol reaction was introduced, in which the addition of diethylaluminium iodide to propiolate derivatives in the presence of aldehydes was catalysed by chiral salen-type ligands.[12]



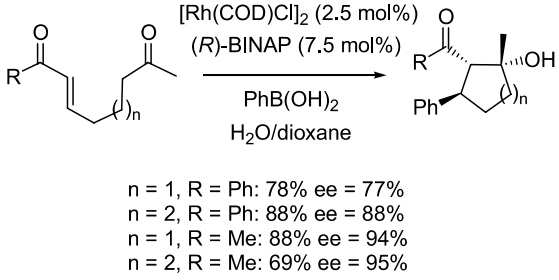
Scheme 3. Asymmetric domino conjugate addition aldol reaction with cyclic enones.

The usefulness of this methodology was illustrated by its application to cyclopenten-3,5-dione monoacetals, suppling the key step in the total synthesis of (−)-prostaglandin E_1 methyl ester (Scheme 4).[13] The reactions depicted in Schemes 1, 3 and 4 involve three-components and, consequently, could also be included in Section 2.6.

In 2003, Krische et al. reported a domino conjugate addition-aldol cyclisation reaction based on an enantioselective catalytic carbometallative aldol cycloreduction of aromatic and aliphatic mono-enone mono-ketone derivatives, providing five- and six-membered ring products (Scheme 5).[14]



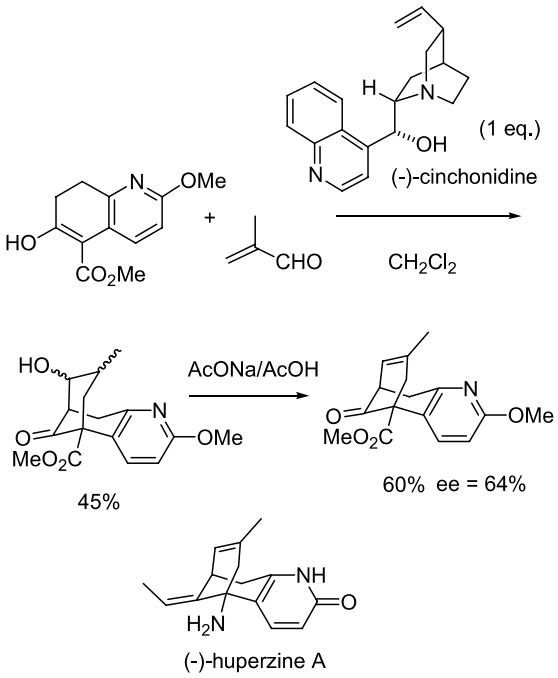
Scheme 4. Synthesis of PGE_1 methyl ester by enantioselective domino 1,4-addition aldol reaction.



Scheme 5. Catalytic enantioselective domino carbometallative aldol cycloreduction reaction.

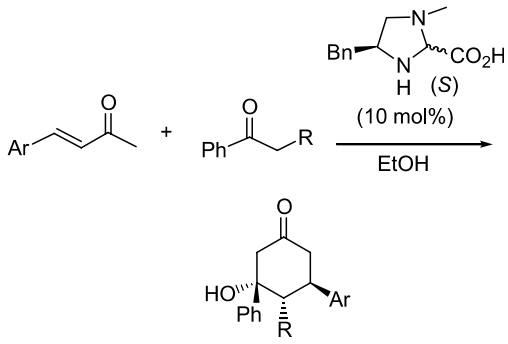
Chiral amine catalysts such as *Cinchona* alkaloids have been shown to catalyse an enantioselective domino Michael aldol reaction of a β-ketoester with methacrolein. This reaction was the key step to construct the 5,9-methanocycloocta[*b*]pyridine system characterising the tricyclic structure of (−)-huperzine A (Scheme 6).[15] Thus, it was demonstrated that simple chiral organic molecules could be alternatives to metal-based catalysts.

In 2005, Gryko reported the asymmetric domino Michael aldol reaction of 1,3-diketones with methyl vinyl ketone in the presence of L-proline, providing highly substituted chiral cyclohexanones.[16] This family of chiral catalysts was also used by Hatakeyama et al. for the development of an asymmetric version of the Baylis–Hillman reaction.[17] More recently, Jorgensen et al. achieved the first highly enantio- and diastereoselective organocatalytic domino Michael aldol reaction of β-diketones, β-ketosulphones, and β-ketoesters with α,β-unsaturated ketones.[18] This reaction was catalysed by an imidazolidine catalyst, easily prepared from phenylalanine. The very mild conditions, inexpensive catalyst, and chromatography-free procedure made this



Scheme 6. Asymmetric domino Michael aldol reaction promoted by *Cinchona* alkaloids.

domino reaction an attractive approach to optically active cyclohexanone building blocks (Scheme 7 and Table 1).

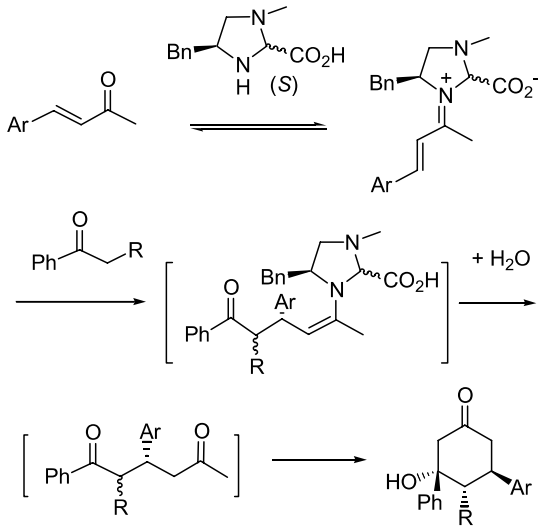


Scheme 7. Enantioselective organocatalytic domino Michael aldol reaction.

Table 1.

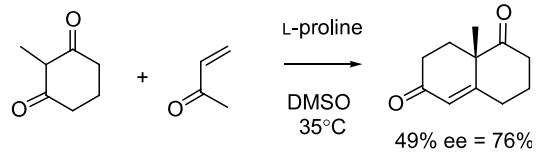
Ar	R	Yield (%)	de (%)	ee (%)
Ph	CO_2Et	60	>94	88
Ph	CO_2Bn	80	>94	95
p-ClC_6H_4	CO_2Bn	60	>94	93
2-Pyrimidyl	CO_2Bn	84	>94	89
Ph	COPh	56	>95	91
p-$NO_2C_6H_4$	COPh	47	>95	87
2-Furyl	SO_2Ph	59	>95	85
Ph	SO_2Ph	93	>95	96
p-ClC_6H_4	SO_2Ph	95	>95	94
p-HOC_6H_4	SO_2Ph	87	>95	98
2-Furyl	SO_2Ph	77	>95	94

As shown in Scheme 8, the catalyst was believed to have three roles during the reaction: (1) activation of the Michael acceptor by iminium ion formation, (2) deprotonation of the Michael donor, and (3) acting as a base catalyst for the intramolecular aldol step.



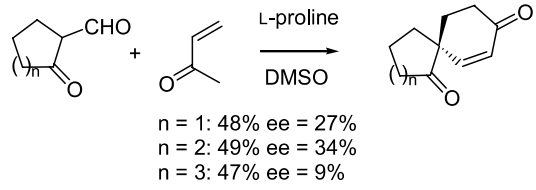
Scheme 8. Mechanism of chiral imidazoline-catalysed domino Michael aldol reaction.

In 2000, Barbas et al. showed that L-proline could act as an efficient catalyst of the one pot Robinson annulation reaction, providing the enantiopure Wieland–Miescher ketone, which has proved to be a particularly useful synthon for the construction of a variety of biologically active compounds (Scheme 9).[19]



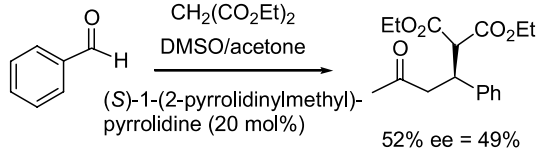
Scheme 9. Proline-catalysed asymmetric domino Robinson annulation reaction.

In addition, Swaminathan et al. have extended this methodology to annulation of a number of 2-formylcyclononones and have obtained the corresponding optically active spiroenediones (Scheme 10).[20]



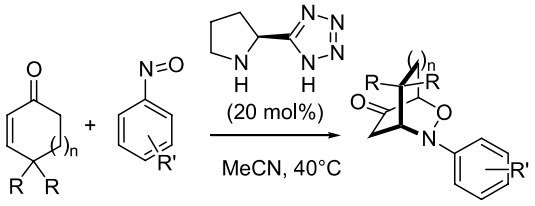
Scheme 10. Asymmetric domino Robinson annulation of formylcyclononones.

On the other hand, asymmetric domino Michael-terminated processes are also present in the literature such as the one pot Knoevenagel Michael reaction reported by Barbas that directly converted an aldehyde into the final Michael adduct via chiral amine catalysis of both steps (Scheme 11).[21]



Scheme 11. (*S*)-1-(2-Pyrrolidinylmethyl)-pyrrolidine-induced domino Knoevenagel Michael reaction.

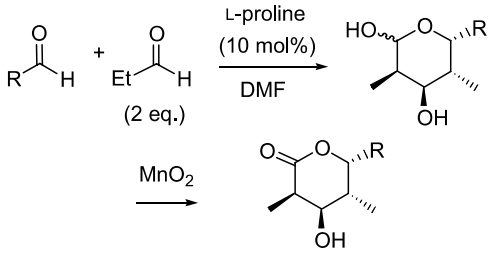
Another example of an enantioselective Michael-terminated process was reported by Yamamoto et al. in 2004.[22] This domino *O*-nitroso aldol Michael reaction catalysed by a pyrrolidine-based tetrazole gave rise to nitroso Diels–Alder adducts (Scheme 12).



n = 1, R = Me, R' = H: 64% ee = 99%
n = 1, R = R' = H: 34% ee = 99%
n = 1, R = Ph, R' = H: 56% ee = 99%
n = 1, R,R = (OCH_2CH_2O), R' = H: 61% ee = 98%
n = 1, R = Me, R' = 3,5-Me_2: 52% ee = 98%
n = 1, R = Me, R' = 4-Br: 50% ee = 99%
n = 2, R = Me, R' = H: 14% ee = 99%

Scheme 12. Enantioselective domino *O*-nitroso aldol Michael reaction.

L-Proline-catalysed direct asymmetric assembly reactions involving three aldehyde components were developed in 2002, providing the remarkably simple preparation of polyketides in an enzyme-like assembly process.[23] This asymmetric double aldol reaction led to the formation of pyranoses, which were further converted into the corresponding δ-lactones by oxidation (Scheme 13). At the same time, Barbas et al. reported the proline-catalysed one-step asymmetric synthesis of 5-hydroxy-(2*E*)-hexenal from the self-aldol reaction of acetaldehyde.[24]

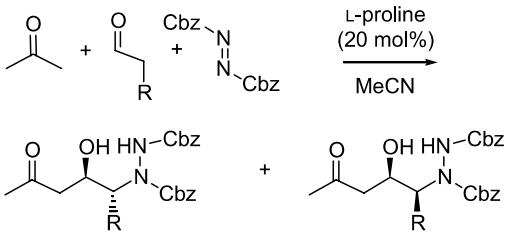


R = Et: 53% ee = 47%
R = *i*-Pr: 32% ee = 12%
R = *i*-Bu: 24% ee = 11%

Scheme 13. L-Proline-catalysed asymmetric double aldol reaction.

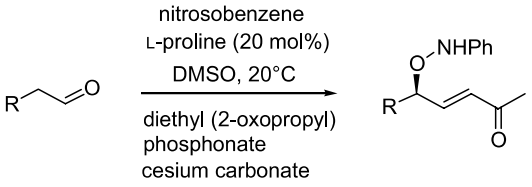
In order to extend the above methodology, Chowdari et al. developed this assembly reaction in the presence of aldehydes, ketones, and azodicarboxylic acid esters to provide optically active β-aminoalcohols.[25] This result was the first example of assembly reactions that used directly both aldehydes and ketones as donors in one pot (Scheme 14).

In addition, L-proline was involved in an enantioselective synthesis of *O*-amino-substituted allylic alcohols by an asymmetric domino aminoxylation olefination reaction of aldehydes under ambient conditions (room temperature, air and moisture were tolerated).[26] Indeed, the process enabled reactive α-aminoaldehydes to be trapped in situ by Wadsworth–Emmons–Horner olefination (Scheme 15).



R = Me: 82% *anti:syn* = 28/72 ee (*anti:syn*) = 98:78
R = Bn: 83% *anti:syn* = 45/55 ee (*anti:syn*) = 99:91
R = *n*-Pent: 82% *anti:syn* = 44/56 ee (*anti:syn*) = 99:61
R = Me: 85% *anti:syn* = 54/46 ee (*anti:syn*) = 99:34

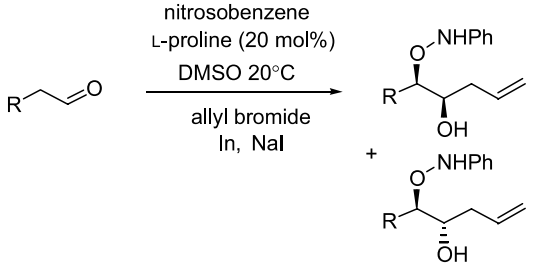
Scheme 14. Proline-catalysed asymmetric assembly reactions of acetone, dibenzyl azodicarboxylate and aldehydes.



R = *i*-Pr: 74% ee = 98%
R = Me: 56% ee = 98%
R = Bn: 81% ee = 97%
R = *n*-Bu: 69% ee = 99%
R = *n*-Pr: 70% ee = 97%
R = allyl: 71% ee = 98%

Scheme 15. L-Proline-promoted asymmetric domino aminoxylation olefination reaction of aldehydes.

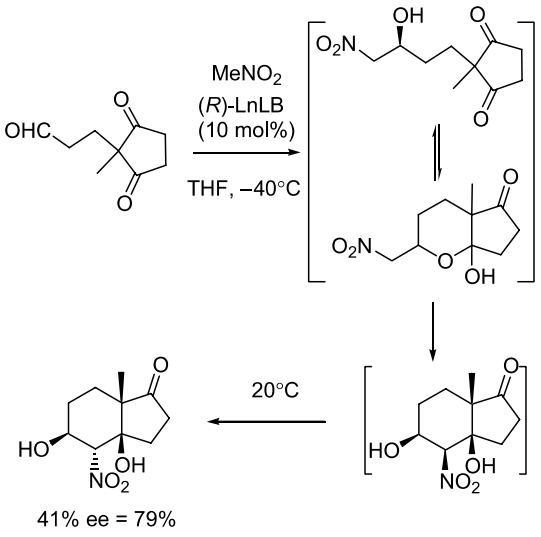
The same conditions were applied to the domino aminoxylation allylation reaction of aldehydes in order to prepare enantiopure mono-substituted 1,2-diols (Scheme 16).[27] The proline-catalysed α-aminoxylation of aldehydes was followed by in situ indium-promoted allylation.



R = *i*-Pr: 71% dr(*syn:anti*) = 5:3 ee(*syn:anti*) = 99%:97%
R = Me: 80% dr(*syn:anti*) = 3:2 ee(*syn:anti*) = 98%:98%
R = *n*-Pr: 65% dr(*syn:anti*) = 3:2 ee(*syn:anti*) = 98%:98%
R = Bu: 82% dr(*syn:anti*) = 3:2 ee(*syn:anti*) = 98%:98%
R = Bn: 74% dr(*syn:anti*) = 3:2 ee(*syn:anti*) = 99%:99%

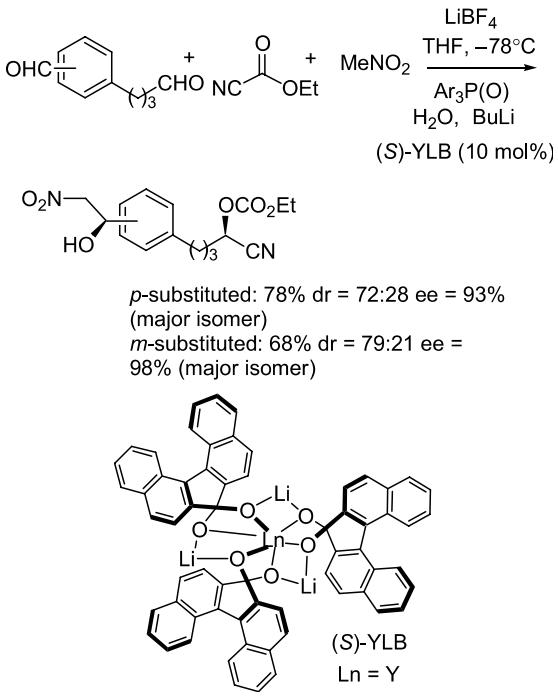
Scheme 16. L-proline-promoted asymmetric domino aminoxylation allylation reaction of aldehydes.

The first domino inter-intramolecular catalytic asymmetric nitroaldol reaction using a $LnLi_3${*tris*[(*R*)-binaphthoxide]} complex (LnLB; Ln: lanthanoid) was developed by Shibasaki et al., providing easy access to optically active 3α,5-dihydroxy-7α-methyl-4-nitro-3α,4,5,6,7,7α-hexahydro-1-indanones (Scheme 17).[28]



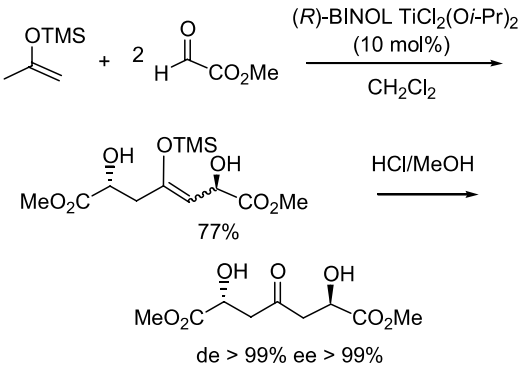
Scheme 17. Chiral lanthanoid complex-promoted domino inter-intramolecular nitroaldol reaction.

In the same context, the first asymmetric domino cyanation nitroaldol reaction using a YLi_3{*tris*[(−)-binaphthoxide]} single catalyst component was performed by these authors. Tuning the chiral environment in YLB with achiral additives such as $Ar_3P(O)$ and $LiBF_4$ had a key role in this reaction (Scheme 18).[29] This reaction, which involves three-components, could also be included in Section 2.6.



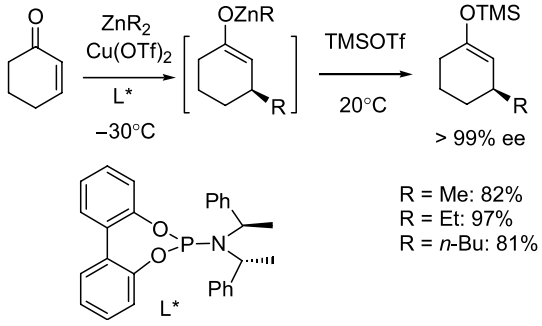
Scheme 18. Domino catalytic cyanation nitroaldol reaction.

A binaphthol-derived chiral titanium complex has been used as the catalyst of the first domino and two-directional asymmetric catalysis of the Mukaiyama aldol reaction.[30] Indeed, upon addition of an excess amount of an aldehyde, the Mukaiyama aldol reaction of a silyl ether proceeded in a tandem and two-directional fashion to give the corresponding silyl enol ether in >99% ee (Scheme 19).



Scheme 19. Asymmetric catalytic domino two-directional Mukaiyama aldol reaction.

Domino conjugate addition-silylation and addition-cyclopropanation reactions were developed by Alexakis et al. in 2002.[31] Both of these reactions were copper catalysed in the presence of chiral phosphoramidate ligands. In the former reaction, zinc enolates, resulting from the copper-catalysed conjugate addition of dialkylzinc reagents to enones, could be trapped as silyl enol ethers with TMSOTf (Scheme 20). Similarly, these zinc enolates could be trapped by various electrophiles such as acetals, ketals or orthoesters.[32]

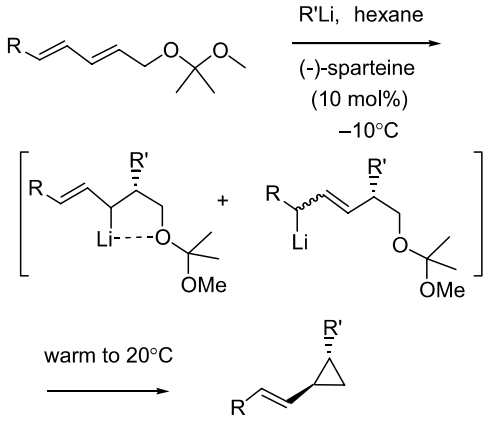


Scheme 20. Domino asymmetric conjugate addition silylation reaction of zinc enolates.

In order to prepare chiral vinylcyclopropanes, Marek et al. developed the first domino catalytic asymmetric carbolithiation reaction of dienyl systems, followed by 1,3-intramolecular elimination.[33] This reaction, catalysed by (−)-sparteine, involved (1) the enantiofacial choice of a dienyl system by the chiral organolithium, and (2) the stereoselective 1,3-elimination into the corresponding cyclopropane. This method represented one of the first syntheses of vinylcyclopropanes with substoichiometric amounts of chiral ligands (Scheme 21).

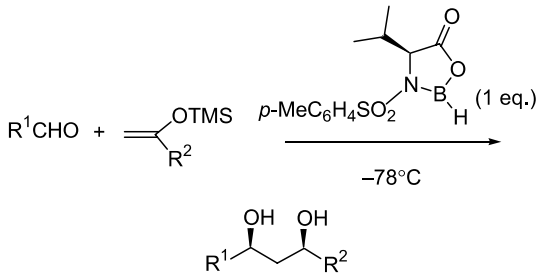
In 1994, Kiyooka et al. reported a domino aldol reaction reduction in which the double asymmetric inductions were effectively accomplished by only one promoter.[34] Indeed, a chiral borane turned out to successively promote the asymmetric aldol reaction of aldehydes with silyl enol ethers and the following asymmetric reduction in one pot, to afford chiral *syn*-1,3-diols (Scheme 22).

Finally, an enantioselective synthesis of aziridines was based on the asymmetric one pot aziridination of imines with alkyl bromides via the imino Corey–Chaykovsky



R = *c*-Hex, R' = *n*-Bu: 70% ee = 72%
R = *n*-Hex, R' = *c*-Hex: 61% ee = 50%
R = *n*-Bu, R' = Ph: 53% ee = 83%
R = *n*-Hex, R' = Ph: 45% ee = 73%
R = TMS, R' = *n*-Bu: 60% ee = 55%
R = TMS, R' = *n*-Hex: 52% ee = 52%
R = *i*-Pr, R' = *n*-Bu: 60% ee = 54%

Scheme 21. Asymmetric domino carbolithiation elimination reaction.



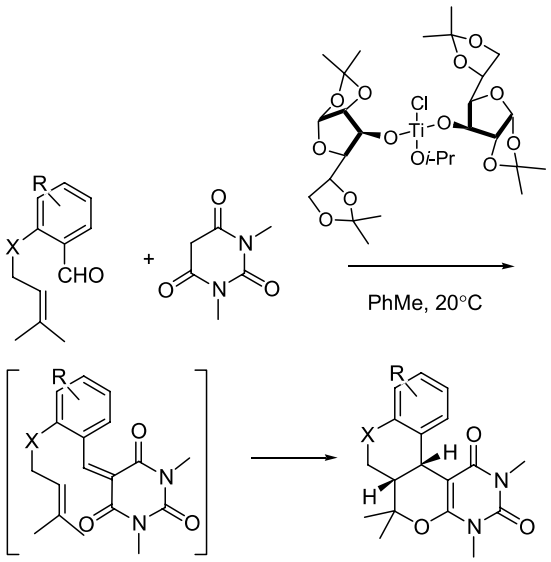
R^1 = *i*-Pr, R^2 = Ph: 60% ee = 94%
R^1 = *i*-Pr, R^2 = $BnO(CH_2)_2$: 55% ee = 86%
R^1 = *i*-Pr, R^2 = *n*-Hex: 70% ee = 99%
R^1 = *n*-Pr, R^2 = Ph: 63% ee = 96%
R^1 = *n*-Pr, R^2 = *n*-Hex: 66% ee = 98%
R^1 = C_6H_5, R^2 = *n*-Hex: 53% ee = 85%

Scheme 22. Asymmetric domino aldol reduction reaction.

reaction mediated by chiral sulphide. The use of a camphor-derived chiral sulphide mediator allowed high enantioselectivities (≤98% ee).[35]

2.1.2. Anionic–pericyclic reactions. In 1992, Tietze et al. reported an enantioselective domino Knoevenagel hetero Diels–Alder reaction, which was actually the first enantioselective domino reaction.[36] A chiral titanium Lewis acid was a potent mediator for the intramolecular hetero Diels–Alder reaction of 1-oxa-1,3-butadienes prepared in situ by a Knoevenagel condensation of aromatic aldehydes and *N*,*N*′-dimethylbarbituric acid (Scheme 23).

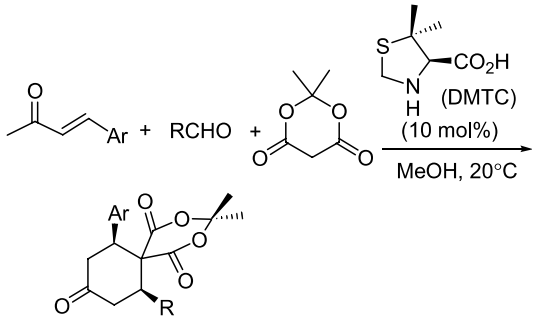
In the same context, Barbas et al. reported in 2003 the first organocatalytic asymmetric domino Knoevenagel Diels–Alder reaction that produced highly substituted spiro[5,5]-undecane-1,5,9-triones from commercially available 4-substituted-3-buten-2-ones, aldehydes, and 2,2-dimethyl-



R = H, X = O: 81% ee = 68%
R = 3-OMe, X = O: 68% ee = 75%
R = 4-OMe, X = O: 72% ee = 80%
R = 5-OMe, X = O: 86% ee = 88%
R = 3-Me, X = O: 58% ee = 71%
R = H, X = CH_2: 55% ee = 68%

Scheme 23. Enantioselective domino Knoevenagel hetero Diels–Alder reaction.

1,3-dioxane-4,6-dione in the presence of a catalytic amount of a chiral amino acid such as 5,5-dimethyl-thiazolidinium-4-carboxylate (DMTC) (Scheme 24).[37] This three-component reaction could also be included in Section 2.6.

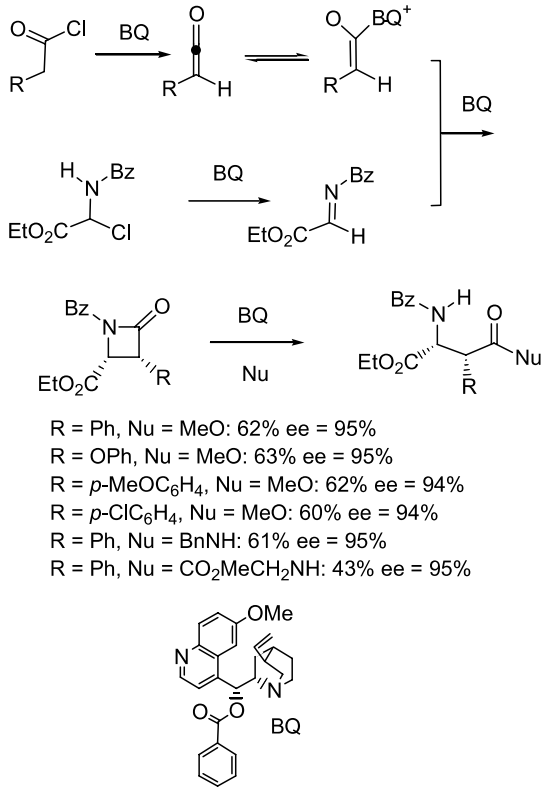


Ar = Ph, R = *p*-$NO_2C_6H_4$: 88% ee = 86%
Ar = Ph, R = *p*-CNC_6H_4: 80% ee = 84%
Ar = 1-naphthalenyl, R = *p*-$NO_2C_6H_4$: 93% ee = 99%
Ar = 2-furanyl, R = *p*-$NO_2C_6H_4$: 85% ee = 88%
Ar = 2-thiophenyl, R = *p*-$NO_2C_6H_4$: 75% ee = 99%

Scheme 24. DMTC-catalysed domino Knoevenagel Diels–Alder reaction.

On the other hand, the same authors have developed amine-catalysed domino Diels–Alder reactions between α,β-unsaturated ketones with nitro-olefins.[38] Either (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine or L-proline catalysed the in situ-generation and reaction of 2-amino-1,3-dienes, to provide cyclohexanone derivatives in good yield (≤87%) in one-step with modest enantioselectivity (≤38% ee). Another chiral amine, for example, benzoylquinine (BQ), was involved as catalyst in the asymmetric synthesis of β-substituted aspartic acid derivatives through a four-stage,

one pot procedure.[39] It was demonstrated that this nucleophilic catalyst served up to four discrete roles in the procedure: catalytic dehydrogenation of acid chlorides to form ketenes; catalytic dehydrohalogenation of α-chloroamines to form the corresponding imines; catalytic [2+2]-cycloaddition to produce intermediate acyl β-lactams; and, finally, nucleophilic ring opening to afford the optically active aspartic acid derivatives (Scheme 25). It must be noted that the first example of an enantioselective one pot synthesis of β-lactams was reported by Cinquini et al., in 1995, using an *N*-methylephedrine derivative as a chiral ligand of BCl_3. This latter chiral catalyst induced the reaction of enolates of 2-pyridylthioesters with achiral imines.[40]

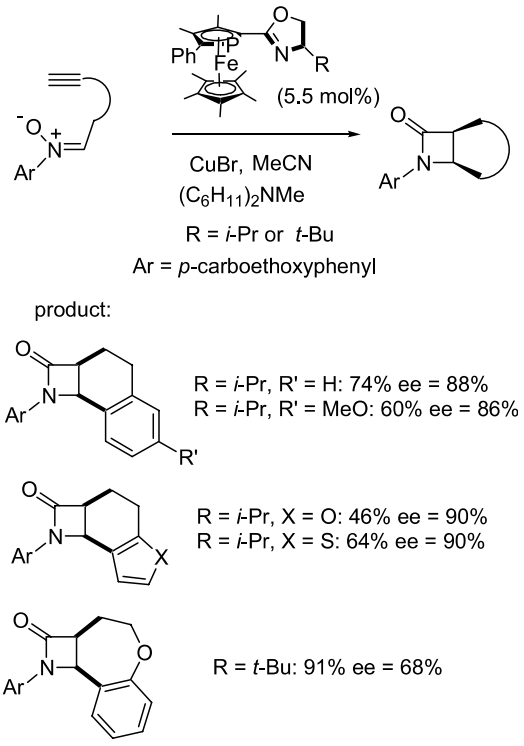


Scheme 25. One pot asymmetric domino synthesis of aspartic acid derivatives.

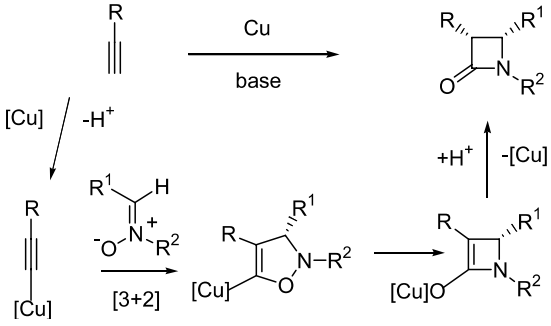
In addition, these authors developed a bifunctional catalyst system in which a chiral nucleophile was paired with an achiral Lewis acidic metal salt to effect a similar asymmetric synthesis of β-lactams.[41] Other chiral β-lactams were prepared by copper-catalysed intramolecular Kinugasa reactions and interception of an intermediate (enolate) in the reaction cascade.[42] The reaction was carried out in the presence of catalytic amounts of planar-chiral phosphaferrocene-oxazolines (Scheme 26).

An outline of a possible mechanism for the Kinugasa reaction is depicted in Scheme 27.

Asymmetric cascade 1,3-dipolar cycloaddition reactions of imines were studied by Grigg in 1995, allowing successful approaches to various chiral pyrrolidines by using metals



Scheme 26. Asymmetric intramolecular Kinugasa reactions.

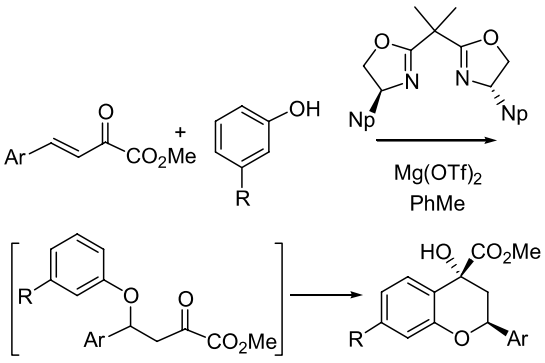


Scheme 27. Possible mechanism for Kinugasa reaction.

such as Mn(II) or Co(II) in combination with chiral ligands.[43]

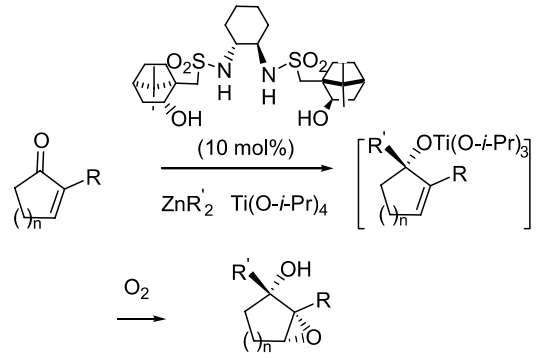
2.1.3. Anionic–miscellaneous reactions. In 2003, Jorgensen et al. reported the synthesis of optically active functionalised chromanes by a catalytic asymmetric domino oxa-Michael addition Friedel-Crafts alkylation reaction.[44] Bisoxazolines were involved as the chiral ligands in combination with $Mg(OTf)_2$ (Scheme 28).

In 2003, Walsh et al. performed a one pot enantioselective ketone alkylation diastereoselective epoxidation reaction.[45] The protocol consisted simply of capping the reaction with a balloon of dioxygen when the asymmetric addition of ZnR_2 to the enone was complete (Scheme 29). Very recently, this methodology was applied to the one pot asymmetric synthesis of acyclic chiral epoxyalcohols via a domino vinylation epoxidation reaction.[46]



R = OMe, Ar = Ph: 77% ee = 80%
R = OMe, Ar = *p*-BrC_6H_4: 45% ee = 66%
R = OMe, Ar = *p*-ClC_6H_4: 39% ee = 74%
R = NMe_2, Ar = *p*-ClC_6H_4: 95% ee = 18%

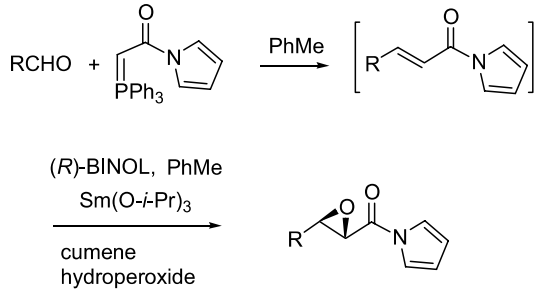
Scheme 28. Asymmetric domino oxa-Michael addition Friedel-Crafts alkylation reaction.



R = Me, R' = Me, n = 2: 82% ee = 99%
R = Me, R' = Et, n = 2: 80% ee = 99%
R = Me, R' = Me, n = 1: 50% ee = 98%
R = Me, R' = Et, n = 1: 60% ee = 97%
R = Pent, R' = Me, n = 1: 67% ee = 99%
R = Pent, R' = Et, n = 1: 60% ee = 99%

Scheme 29. Asymmetric domino alkylation epoxidation reaction.

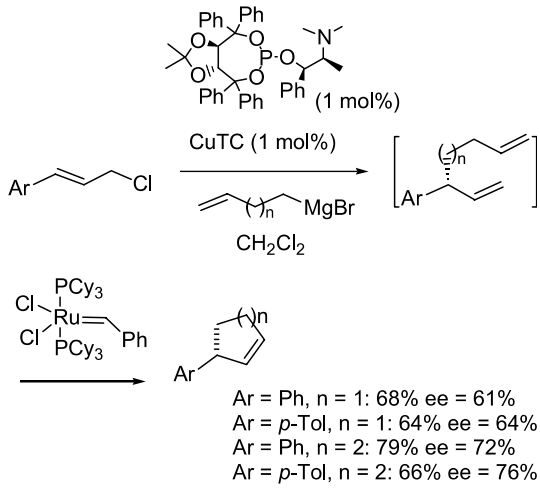
In 2004, Shibasaki et al. developed a domino Wittig olefination catalytic asymmetric epoxidation reaction, providing efficient one pot access to optically active epoxides from various aldehydes (Scheme 30).[47]



R = Ph: 96% ee = 99.5%
R = naphthalene: 100% ee = 99%
R = *p*-MeC_6H_4: 92% ee = 99%
R = *p*-$MeOC_6H_4$: 87% ee = 98%
R = *p*-ClC_6H_4: 100% ee = 99%

Scheme 30. Domino Wittig olefination asymmetric epoxidation reaction.

In 2002, Alexakis et al. showed that Grubbs' catalyst was compatible with excess Grignard reagent and copper salts by developing the first enantioselective domino substitution metathesis.[48] Thus, Grignard reagents underwent enantioselective copper-catalysed S_N2' substitution on achiral allylic chlorides, and the resulting terminal alkene could be submitted to metathesis, providing new chiral synthons (Scheme 31).

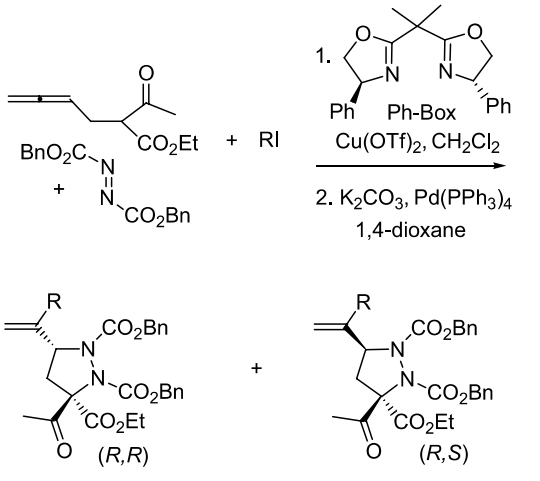


Ar = Ph, n = 1: 68% ee = 61%
Ar = *p*-Tol, n = 1: 64% ee = 64%
Ar = Ph, n = 2: 79% ee = 72%
Ar = *p*-Tol, n = 2: 66% ee = 76%

CuTC: copper thiophene-2-carboxylate

Scheme 31. Asymmetric domino substitution metathesis reaction.

Optically active pyrazolidine derivatives have been constructed by the Cu- and Pd-catalysed asymmetric domino addition cyclisation reaction of 2-(2′,3′-dienyl)-β-ketoesters, organic halides, and dibenzyl azodicarboxylate (DBAD) (Scheme 32).[49] This three-component reaction could also be included in Section 2.6.

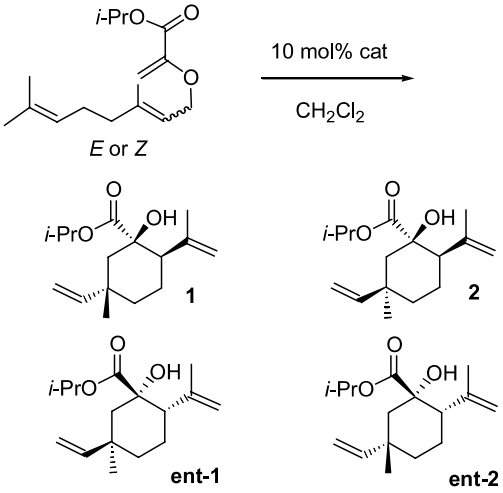


R	Yield (%)	dr (*R*,*R*:*R*,*S*)	ee (*R*,*R*) (%)	ee (*R*,*S*) (%)
p-Tol	85	33:67	98	98
p-$MeOC_6H_4$	95	34:66	98	98
p-BrC_6H_4	94	36:64	97	98
p-$NO_2C_6H_4$	97	40:60	98	99
thiophen-2-yl	71	36:64	91	99

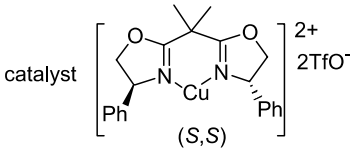
Scheme 32. Asymmetric domino addition cyclisation reaction.

2.2. Pericyclic primary step

The first catalytic processes including Claisen rearrangements had been planned as domino reactions. An initial enantioselectively catalysed step generated the allyl vinyl backbone for the consecutive sigmatropic rearrangement. The first successful enantioselective catalytic Claisen rearrangement for the construction of newly defined C–C bonds was published by Hiersemann et al.[50] This domino Claisen rearrangement intramolecular carbonyl-ene reaction was catalysed by chiral copper(II) bis(oxazolines) (Scheme 33).

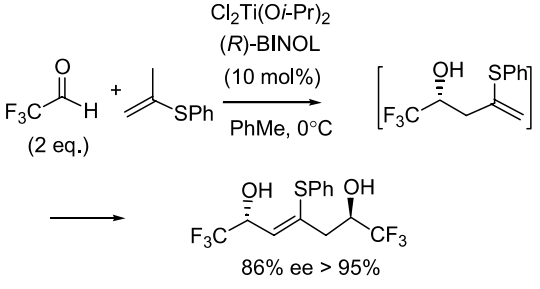


Substrate	Catalyst	Yield (%)	dr	ee (%)
E	(*S*,*S*)	98	**1**:**2** = 89:11	98
E	(*R*,*R*)	92	**ent-1**:**ent-2** = 89:11	99
Z	(*S*,*S*)	93	**1**:**2** = 19:81	99
Z	(*R*,*R*)	93	**ent-1**:**ent-2** = 20:80	99



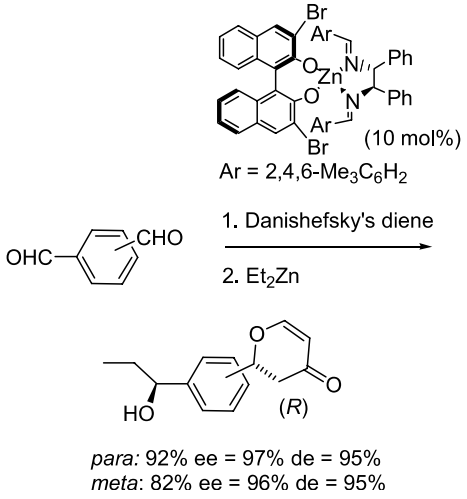
Scheme 33. Catalytic asymmetric domino Claisen rearrangement carbonyl-ene reaction.

Mikami et al. have demonstrated that a binaphthol-derived chiral titanium complex could promote a domino and two-directional asymmetric fluoral-ene reaction, providing a new type of antiferroelectric liquid crystalline molecules (Scheme 34).[51]



Scheme 34. Asymmetric domino two-directional carbonyl-ene reaction with fluoral.

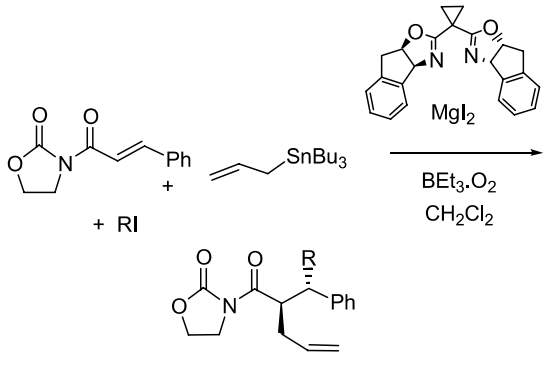
In addition, Ding et al. have achieved the integration of two asymmetric reactions in one pot with the promotion of a single catalyst for the hetero Diels–Alder reaction of Danishefsky's diene and diethylzinc addition to aldehydes (Scheme 35).[52] Indeed, this strategy demonstrated the ability of a single catalyst to promote two distinct enantioselective reactions in one pot. This three-component reaction could also be included in Section 2.6.



Scheme 35. Asymmetric domino hetero Diels–Alder diethylzinc addition reaction.

2.3. Radical sequences

The first examples where two C–C bonds were formed with high stereocontrol by nucleophilic radical addition to an enolate followed by trapping with an allylstannane were reported by Sibi et al. in 2001.[53] In these unusual domino three-component intermolecular addition intermolecular trapping reactions involving acyclic systems, chirality was established at both β- and α-centres with control over both absolute and relative stereochemistry (Scheme 36).

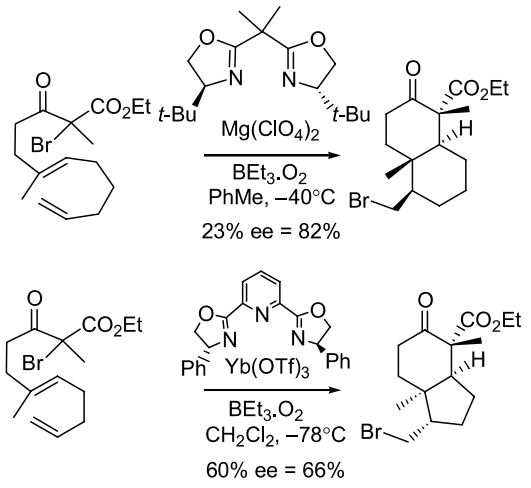


R = *c*-Hex: 80% de = 96% ee = 92%
R = *i*-Pr: 93% de = 94% ee = 93%
R = *t*-Bu: 84% de = 98% ee = 97%
R = Et: 79% de = 94% ee = 77%

Scheme 36. Enantioselective domino radical reaction.

Other chiral Lewis acid-promoted enantioselective atom-transfer radical tandem cyclisation reactions were developed by Yang et al., providing excellent methods for

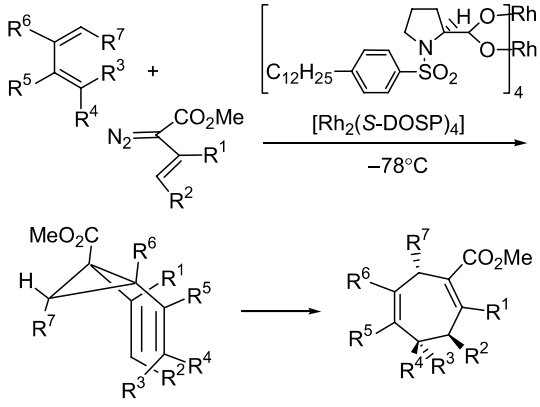
the construction of polycyclic ring skeletons under mild and neutral conditions (Scheme 37).[54]



Scheme 37. Enantioselective atom-transfer radical tandem cyclisation reactions.

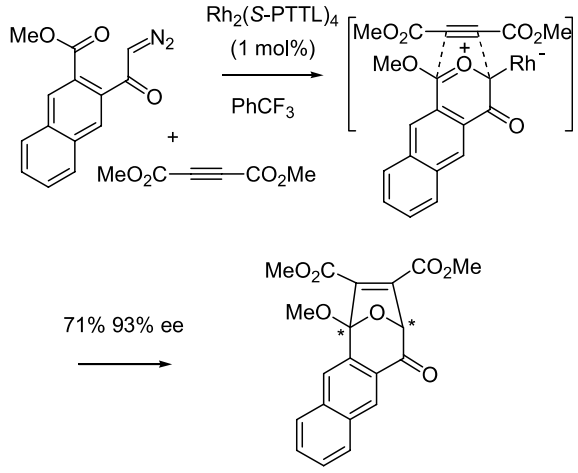
2.4. Carbene sequences

In 1998, Davies et al. reported a domino asymmetric cyclopropanation Cope rearrangement reaction using rhodium(II) (*N*-dodecylbenzenesulphonyl)prolinate [Rh_2-(*S*-DOSP)$_4$].[55] In this process, decomposition of vinyl diazoacetates by the chiral catalyst in the presence of dienes resulted in a direct and highly enantioselective method for the formation of *cis*-divinylcyclopropanes. A combination of this process with a subsequent Cope rearrangement resulted in a highly enantioselective synthesis of a variety of cycloheptadienes containing multiple stereogenic centres (Scheme 38). The same methodology was extended to the enantioselective synthesis of various fused cycloheptadienes,[56] allowing the total synthesis of 5-*epi*-tremulenolide.[57]



Scheme 38. Asymmetric domino cyclopropanation Cope rearrangement reaction.

The domino carbonyl ylide formation and 1,3-dipolar cycloaddition methodology extensively advanced by the Padwa group with dirhodium(II) carboxylate catalysts is rapidly becoming recognised as a potentially powerful means for the construction of highly substituted oxygen-containing heterocycles.[58] Hashimoto et al. have shown that enantioselective 1,3-dipolar cycloaddition of the ester-carbonyl ylides derived from methyl 2-(diazoacetyl)-benzoate and 3-(diazoacetyl)-2-naphthoate with dipolarophiles could be effected with the aid of dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate] [Rh_2(*S*-PTTL)$_4$], affording the cycloadducts in up to 93% yield (Scheme 39).[59]

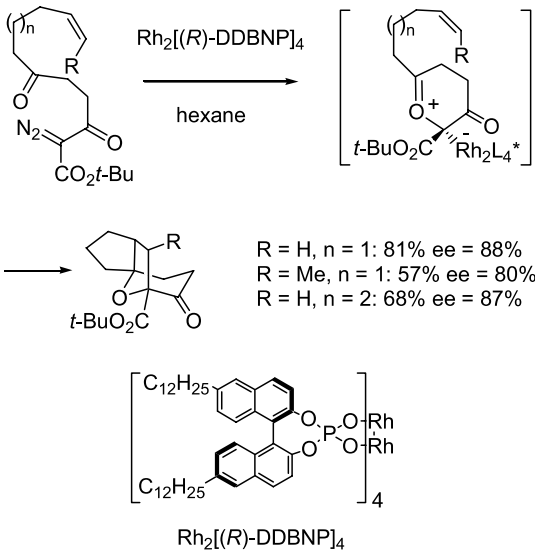


Scheme 39. Enantioselective domino intermolecular 1,3-dipolar cycloaddition reaction of ester-carbonyl ylides.

Hodgson et al. have extended the scope of this reaction to dipolarophiles, which did not contain electron-withdrawing substituents on the reacting π-bond such as phenylacetylene, or strained alkene dipolarophiles, in the presence of 2-diazo-3,6-diketoester-derived carbonyl ylides.[60] Various chiral rhodium catalysts were involved to promote the reaction, giving values for ee ≤92%. In 2003, an intramolecular version of this reaction was developed by these authors.[61] They demonstrated that enantioselective intramolecular 1,3-dipolar cycloadditions of unsaturated 2-diazo-3,6-diketoester-derived carbonyl ylides showed a promising scope in terms of asymmetric induction as the tethered alkene/alkyne dipolarophile component was varied (Scheme 40). In order to develop a better understanding of the factors affecting asymmetric induction in this emerging asymmetric process, the same methodology was successfully applied to α-aryl-α-diazodiones.[62] The results showed that electronic effects clearly played a role in determining the level of asymmetric induction, since the more electron-deficient cycloaddition precursor delivered the higher enantioselectivity.

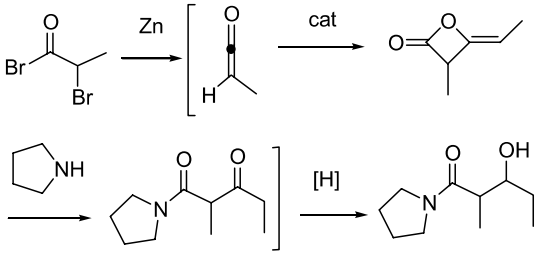
2.5. Miscellaneous sequences

In 1998, Calter et al. reported one pot, catalytic, asymmetric syntheses of all four stereoisomers of a dipropionate synthon, based on a chiral amine-catalysed dimerisation of methylketene, generated in situ from α-bromopropionyl bromide (Scheme 41).[63] Trapping of the ketene dimer with a



Scheme 40. Asymmetric domino carbonyl ylide formation intramolecular [3+2] cycloaddition reaction.

secondary amine, followed by reduction under the appropriate conditions, affords either diastereomer of the dipropionate synthon.

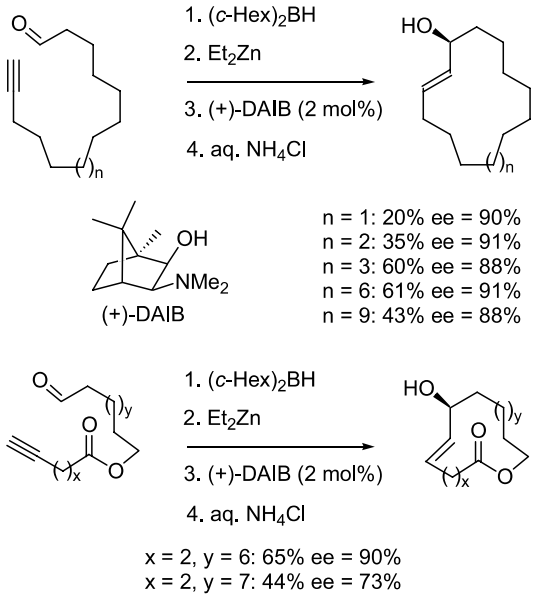


Catalyst	Reduction conditions	Yield (%)	ee (%) (confign)
quinidine	$KB(H)Et_3$	48	98 (2*S*,3*S*)
quinidine	$Zn(OTf)_2$ $NaBH_4$	42	99 (2*S*,3*R*)
trimethylsilyl quinine	$KB(H)Et_3$	48	96 (2*R*,3*R*)
trimethylsilyl quinine	$Zn(OTf)_2$ $NaBH_4$	42	96 (2*R*,3*S*)

Scheme 41. In situ generation and asymmetric dimerisation of ketene.

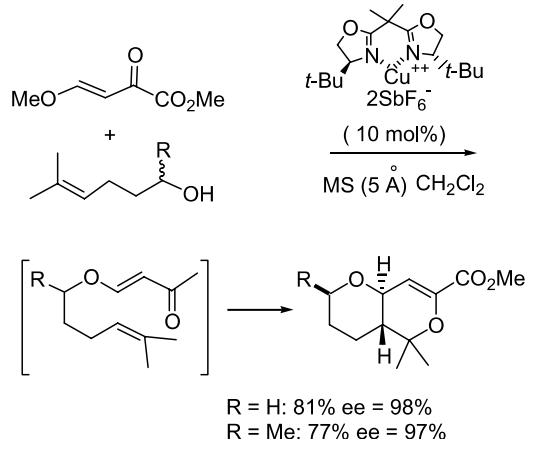
An asymmetric synthesis of macrocyclic (*E*)-allylic alcohols was elaborated by Oppolzer et al., starting from ω-alkynals via intramolecular 1-alkenylzinc/aldehyde additions.[64] This one pot procedure involved, successively, akyne monohydroboration, boron- to -zinc transmetallation, and [(+)-DAIB]-catalysed enantioselective intramolecular ring closure to the aldehyde function (Scheme 42). This methodology offered an efficient approach to various naturally occurring chiral carbocycles and macrolides.

An efficient catalytic double asymmetric induction during a new type of catalytic domino transetherification intramolecular hetero Diels–Alder reaction has been developed, leading to enantiomerically enriched *trans*-fused hydropyranopyran derivatives by using methyl (*E*)-4-methoxy-2-oxo-3-butenoate and δ,ε-unsaturated alcohols in the



Scheme 42. Asymmetric domino hydroboration transmetallation intramolecular ring closure.

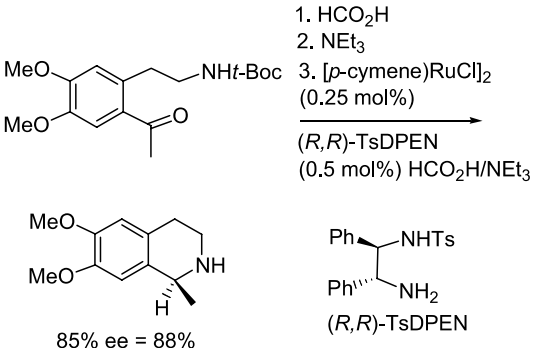
presence of (*S*,*S*)-*t*-Bu-bis(oxazoline)-$Cu(SbF_6)_2$ and molecular sieves (5 Å) (Scheme 43).[65]



Scheme 43. Asymmetric domino transetherification intramolecular hetero Diels–Alder reaction.

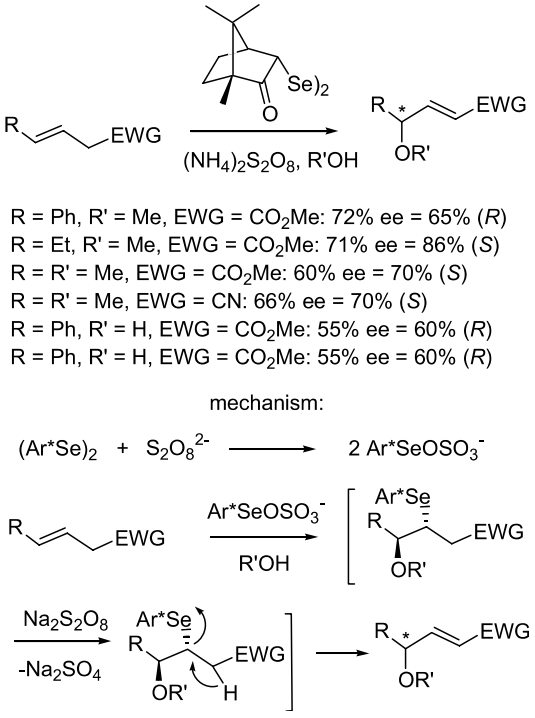
In 2003, Wills et al. reported a one pot process for the enantioselective synthesis of amines via reductive amination under transfer hydrogenation conditions.[66] Indeed, a chiral bicyclic amine could be prepared directly from a *t*-Boc-protected amino ketone by a one pot deprotection/formation of imine/cyclisation/reduction sequence (Scheme 44). A chiral monotosylated diamine (TsDPEN) was adopted as the optimal ligand for this process when used in formic acid/triethylamine, which acted both as the solvent and the hydrogen source.

In 1998, Wirth et al. showed that only catalytic amounts of chiral selenium reagents were necessary to achieve a one pot sequence of methoxyselenenylation and oxidative β-hydride elimination of alkenes.[67] Tiecco et al. applied this domino reaction to various β,γ-unsaturated esters and nitriles, which afforded, by treatment with chiral



Scheme 44. Asymmetric domino deprotection/formation of imine/cyclisation/reduction process.

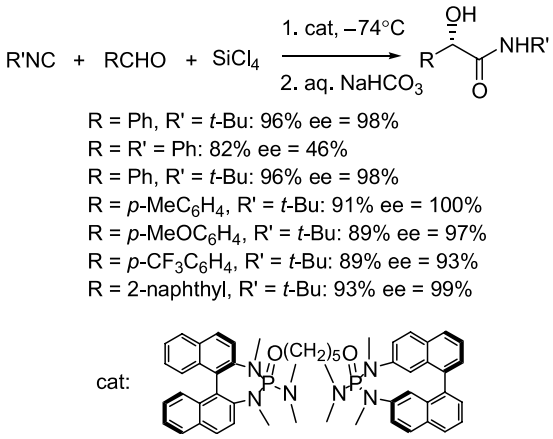
diselenides, the corresponding enantiomerically enriched γ-alkoxy- or γ-hydroxy-α,β-unsaturated derivatives (Scheme 45).[68]



Scheme 45. Asymmetric domino oxyselenenylation deselenenylation reaction.

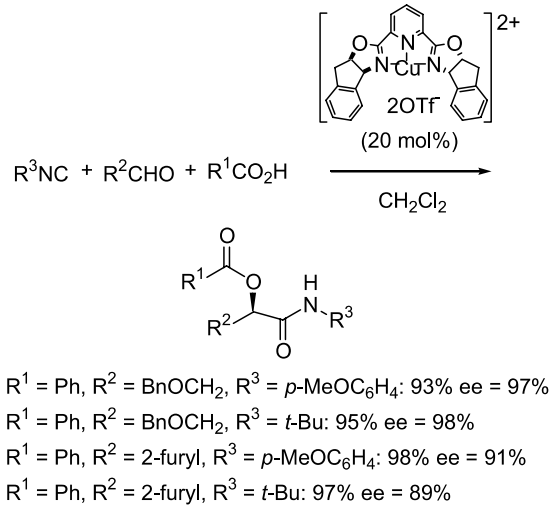
2.6. Domino multicomponent reactions

Despite intense interest, there are still few reports of enantioselective multicomponent reactions (MCRs) for the synthesis of stereochemically complex polycyclic compounds.[69] The most prominent of the isocyanide-based MCRs[70] are the Passerini reaction of isocyanides, oxo components and carboxylic acids, and the Ugi reaction involving isocyanides, oxo components, primary amines, and carboxylic acids, respectively. The first example of an enantioselective Passerini MCR using a chiral Lewis acid catalyst was reported by Dömling et al. in 2003.[71] Better enantioselectivities were obtained in the case of Passerini-type reactions by using a chiral biphosphoramide-$SiCl_4$ system as catalyst (Scheme 46).[72]



Scheme 46. Lewis-base-catalysed enantioselective Passerini-type reaction.

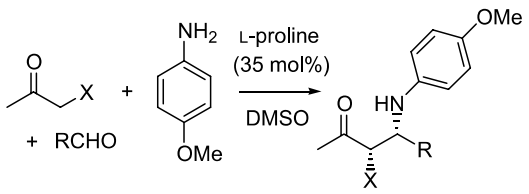
A very efficient catalytic asymmetric version of the Passerini reaction was reported by Schreiber et al. in 2004 using a tridentate bis(oxazolinyl)pyridine (pybox)-Cu(II) Lewis acid with substrates capable of bidentate coordination (Scheme 47).[73]



Scheme 47. (Pybox)-Cu(II)-catalysed Passerini reaction.

The Mannich reaction is enormously useful for the construction of nitrogenous molecules. In this transformation, three-components, a ketone, an aldehyde, and an amine, react to form a β-aminoketone.[74] The first direct catalytic asymmetric Mannich reaction reported in 1999 by Shibasaki et al. was based on the use of a heterobimetallic complex, for example, AlLibis(binaphthoxide) and $La(OTf)_3 \cdot nH_2O$.[75] Although the yields (≤16%) and the ees (≤64%) were modest, these authors have succeeded in extending the reaction to aminomethyl ethers. Jorgensen et al. have developed direct asymmetric Mannich reactions involving activated ketones as donors, which were catalysed by chiral copper(II) bisoxazoline (box) complexes.[76] Kobayashi et al. have employed zirconium alkoxides in the presence of 6,6-dibromobinaphthol to catalyse the Mannich reaction of a protected hydroxyaldehyde, a silyl enol ether derived from ethyl thioacetate, and an aniline derivative, providing the corresponding chiral β-aminothioester.[77] Highly enantioselective three-component

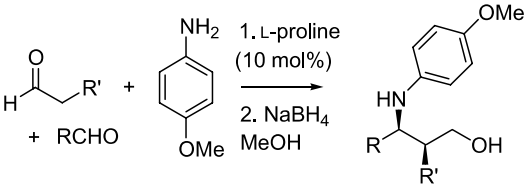
Mannich reactions were reported for the first time by List et al., involving proline as catalyst (Scheme 48).[78]



X = H, R = *p*-$NO_2C_6H_4$: 50% ee = 94%
X = H, R = 2-naphthyl: 35% ee = 96%
X = H, R = *i*-Bu: 90% ee = 93%
X = H, R = CH_2OBn: 82% ee = 75%
X = OH, R = *i*-Pr: 57% ee = 65%
X = OH, R = *p*-$NO_2C_6H_4$: 92% ee = 99%
X = OH, R = *p*-$NO_2C_6H_4$: 92% ee = 99%
X = OMe, R = *p*-BrC_6H_4: 90% ee = 98%

Scheme 48. Proline-catalysed direct Mannich reaction.

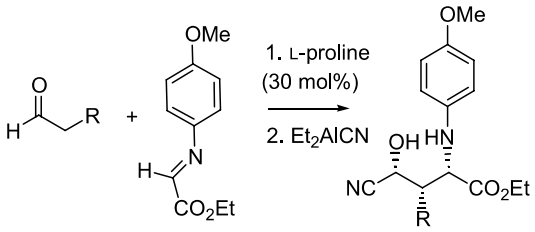
In 2001, Barbas et al. reported equivalent results for the same organocatalytic reactions performed in the presence of the penicillamine derivative, L-5,5-dimethylthiazolidine-4-carboxylic acid, instead of L-proline.[79] Similarly, Cordova et al. disclosed direct organocatalytic Mannich reactions between aqueous formaldehyde and ketones that furnished under the same conditions the corresponding optically active α-aminomethylated ketones with yields of up to 94% and >99% ee.[80] These authors, together with Hayashi's group, developed at the same time the first direct asymmetric Mannich reactions of aldehydes.[81] Such a system would comprise a Mannich reaction in which one aldehyde was employed as the Mannich donor and the other was used as a component of the Mannich acceptor to afford a synthetically versatile intermediate, a β-aminoaldehyde. Since this latter compound decomposed during purification by chromatography on silica gel, it was isolated after reduction with $NaBH_4$ to the corresponding β-aminoalcohol (Scheme 49).



R = Ph, R' = Me: 90% ee = 98%
R = Ph, R' = Et: 85% ee = 97%
R = *p*-BrC_6H_4, R' = Me: 85% ee = 95%
R = *p*-$NO_2C_6H_4$, R' = Me: 93% ee = 99%
R = *p*-ClC_6H_4, R' = Me: 91% ee = 98%
R = *p*-MeC_6H_4, R' = Me: 95% ee = 86%

Scheme 49. Direct asymmetric Mannich reaction with aldehydes.

On the other hand, one pot asymmetric Mannich hydrocyanation reactions were described by Barbas et al.[82] Indeed, L-proline-catalysed reaction of aldehydes with protected α-imino ethyl glyoxylate followed by the addition of $AlEt_2CN$ provided highly enantiomerically pure β-cyano-hydroxymethyl α-amino acid derivatives (Scheme 50).

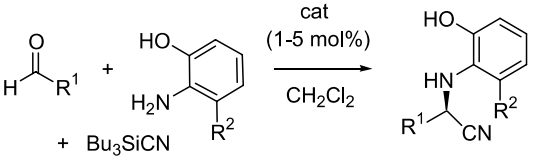


R = *n*-Bu: 60% ee = 93%
R = *n*-Pent: 68% ee = 98%
R = *n*-Hex: 65% ee = 98%
R = Bn: 62% ee = 99%

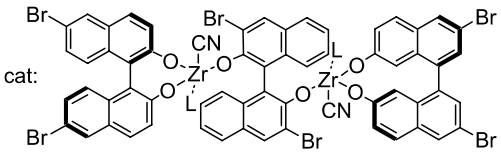
Scheme 50. One pot asymmetric domino Mannich hydrocyanation reaction.

In addition, these authors have developed one pot Mannich indium-promoted allylation reactions by treating the intermediate Mannich product with allyl bromide in the presence of indium.[83] The corresponding optically active γ-allyl-substituted α-amino acid derivatives were obtained in ≤99% ee.

The Strecker amino acids synthesis consists of the treatment of aldehydes with ammonia and hydrogen cyanide (or their equivalents), and subsequent hydrolysis of the intermediate α-amino nitriles, providing the α-amino acids. In 2000, Kobayashi et al. reported a highly efficient catalytic asymmetric Strecker reaction of aldimines with tributyltin cyanide, proceeding smoothly in the presence of a chiral zirconium catalyst (Scheme 51).[84]



R^1 = Ph, R^2 = H: 80% ee = 86%
R^1 = $Ph(CH_2)_2$, R^2 = Me: 85% ee = 94%
R^1 = C_8H_{17}, R^2 = Me: 93% ee = 91%
R^1 = *i*-Bu, R^2 = Me: 99% ee = 94%
R^1 = *c*-C_6H_{11}, R^2 = Me: 95% ee = 94%
R^1 = *t*-Bu, R^2 = Me: 100% ee = 88%



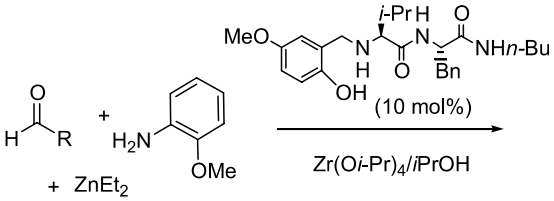
L = *N*-methylimidazole

Scheme 51. Chiral zirconium-catalysed Strecker reaction.

The cyanation of pyridines, the Reissert–Henze reaction, may be considered as a variant of the Strecker reaction. An asymmetric multicomponent version of this reaction has been performed with different functionalised quinoline derivatives and a chiral binaphthol in the presence of diethylaluminium chloride, TMSCN and a carbonyl chloride.[85] The same methodology was applied to the cyanation of different 1-substituted isoquinolines, yielding the corresponding α,α-disubstituted aminonitriles.[86]

The synthetic utility of this methodology was demonstrated by its application to the formal synthesis of the dopamine D_4 receptor-selective antagonist, CP-293019.[87]

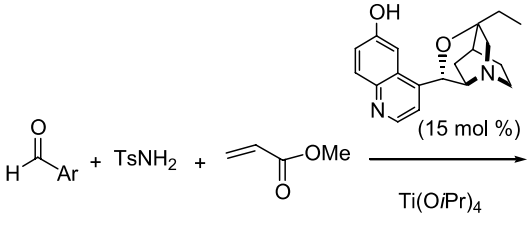
Zirconium-catalysed asymmetric multicomponent reactions were developed in 2001 by Hoveyda et al., involving the addition of alkylzincs to aliphatic imines in a single vessel and avoiding the isolation of the unstable imine (Scheme 52).[88]



R = Bu: 69% ee = 97%
R = Hex: 62% ee = 97%
R = $Ph(CH_2)_2$: 98% ee = 94%
R = $Br(CH_2)_5$: 57% ee = 95%
R = $(CH_2)_3OH$: 64% ee = 97%
R = *c*-Pr: 83% ee = 98%

Scheme 52. Asymmetric three-component catalytic synthesis of aliphatic amines.

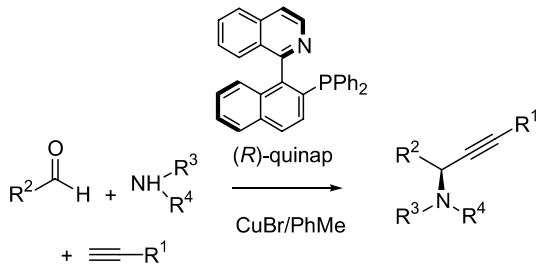
Various chiral allylamines have been obtained by the reaction of 1-phenylpropyne, triethylborane, and *N*-methyl aryl imines catalysed by a nickel complex and a chiral phosphane.[89] The enantioselectivity of this reaction could be improved by the use of a chiral ferrocenyl monophosphane instead of a chiral phosphane.[90] An in situ formation of imine was also involved in an asymmetric one pot version of a three-component aza-Baylis–Hillman reaction reported by Adolfsson et al.[91] Chiral quinuclidine derivatives were employed to catalyse the reaction between arylaldehydes, tosylamide and alkyl acrylates or acrylonitrile (Scheme 53).



Ar = Ph: 78% ee = 68%
Ar = *m*-$NO_2C_6H_4$: 94% ee = 63%
Ar = *p*-$NO_2C_6H_4$: 95% ee = 61%
Ar = *m*-ClC_6H_4: 95% ee = 67%
Ar = furyl: 95% ee = 74%

Scheme 53. Asymmetric three-component aza-Baylis–Hillman reaction.

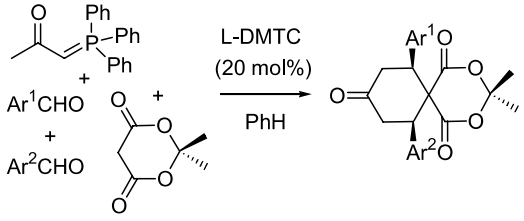
In order to prepare chiral propargylamines, Knochel et al. have examined a new three-component reaction between an alkyne, an aldehyde, and a secondary amine in the presence of CuBr and (*R*)-quinap (Scheme 54).[92] Carreira et al. have proposed an alternative ligand, a new chiral biaryl ligand derived from phthalazine, for this reaction, which gave similar results.[93]



R^1 = Ph, R^2 = *i*-Bu, R^3 = Bn: 98% ee = 86%
R^1 = *p*-BrC_6H_4, R^2 = *i*-Pr, R^3 = Bn: 99% ee = 83%
R^1 = TMS, R^2 = *i*-Pr, R^3 = Bn: 87% ee = 92%
R^1 = TMS, R^2 = *c*-Hex, R^3 = Bn: 99% ee = 92%
R^1 = TMS, R^2 = 1-Et-Pr, R^3 = Bn: 72% ee = 96%

Scheme 54. Enantioselective three-component synthesis of propargylamines.

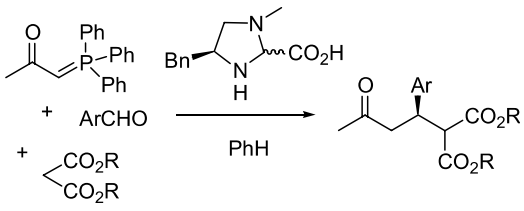
In 2004, Barbas et al. reported an organocatalytic asymmetric four-component Wittig Knoevenagel Diels–Alder reaction sequence, in order to generate an enantioselective synthesis of spirolactones in one pot.[94] Thus, the L-DMTC (L-5,5-dimethyl thiazolidinium-4-carboxylate)-catalysed reaction of *trans*-enone, aldehydes, and Meldrum's acid led to the formation of optically active substituted spiro[5.5]undecanes (Scheme 55).



Ar^1 = Ph, Ar^2 = *p*-$NO_2C_6H_4$: 83% ee = 69%
Ar^1 = *p*-$NO_2C_6H_4$, Ar^2 = Ph: 80% ee = 42%
Ar^1 = Ph, Ar^2 = *p*-CNC_6H_4: 85% ee = 70%

Scheme 55. Asymmetric four-component Wittig Knoevenagel Diels–Alder reaction.

Additionally, these authors studied the asymmetric three-component Michael reaction of phosphorane, benzaldehyde, and malonate under chiral imidazolidine catalysis (Scheme 56).[94]



Ar = Ph, R = Et: 65% ee = 90%
Ar = *o*-$NO_2C_6H_4$, R = Bn: 84% ee = 91%

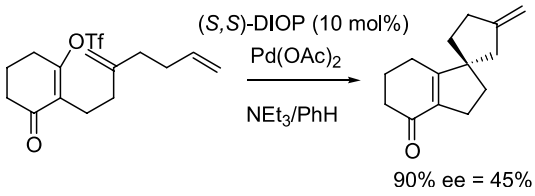
Scheme 56. Asymmetric three-component Michael reaction.

In 2004, Hopkins et al. reported a new multicomponent reaction involving the coupling of arylboronic acids with

allenes and aldehydes, giving rise to various homoallylic alcohols.[95] This reaction was catalysed by a chiral π-allylpalladium complex, but gave only a low enantioselectivity. Finally, D,L-proline was found to catalyse efficiently the one pot trimolecular condensation of indoles, a sugar hydroxyaldehyde, and Meldrum's acid, followed by intramolecular cyclisation with the evolution of carbon dioxide and elimination of acetone, to afford perhydrofuro[3,2-*b*]pyran-5-ones in high diastereoselectivity.[96]

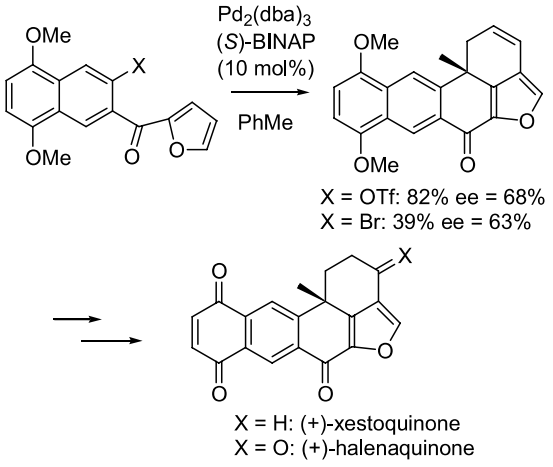
2.7. Transition-metal-catalysed sequences

2.7.1. Domino reactions including a Heck reaction. A powerful extension of palladium-catalysed transformations, also of economic interest, is the development and use of multiple Pd-catalysed transformations, which may be performed in a domino fashion.[97,98] The possibility of extending the scope of intramolecular enantioselective Heck reactions to inclusion in Pd-mediated domino polyene cyclisation was demonstrated in 1989 by Overman in his first report on the generation of a quaternary chiral centre from a triene, to give the corresponding spirocycle (Scheme 57).[99]



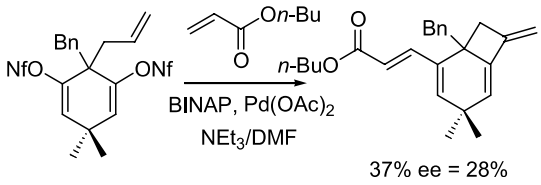
Scheme 57. Asymmetric domino intramolecular Heck reaction.

Keay et al. have recently reported the asymmetric synthesis of (+)-xestoquinone from a pentacyclic intermediate, which was obtained via a one pot cyclisation of a triflate under enantioselective Heck reaction conditions, thus demonstrating the feasibility of a domino asymmetric Heck reaction (Scheme 58).[100] A similar methodology was applied to the synthesis of (+)-halenaquinone.[101,102,103,104] A remote substituent effect on the enantioselectivity was demonstrated by Keay et al., since a surprisingly higher ee (≤96%) was obtained when the aryl group became phenyl instead of naphthyl.



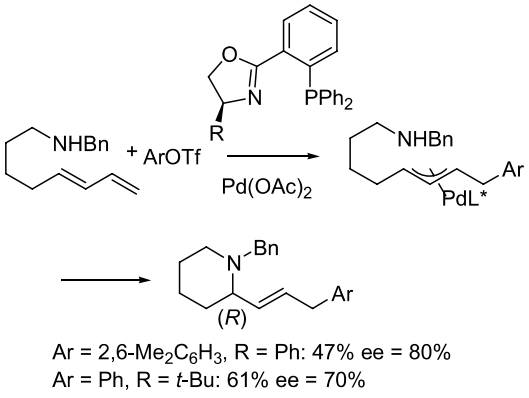
Scheme 58. Synthesis of (+)-xestoquinone via domino intramolecular Heck reaction.

Bräse has reported the palladium-catalysed enantioselective desymmetrisation of a bisnonaflate on reaction with butyl acrylate in the presence of BINAP to give the corresponding bicyclic tetraene with a quaternary carbon centre (Scheme 59).[105]



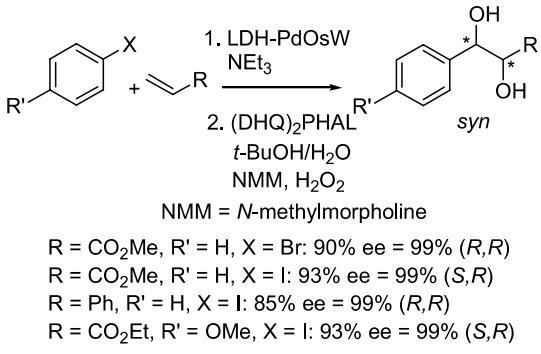
Scheme 59. Asymmetric domino intramolecular Heck reaction of bisnonaflate.

A novel enantioselective two-component domino Heck-allylic amination reaction of an α,ω-amino-1,3-diene to give the corresponding chiral piperidine derivative has recently been described by Helmchen et al. in the presence of chiral phosphino–oxazoline ligands (Scheme 60).[106]



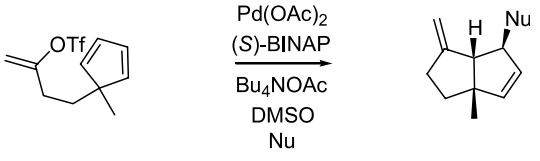
Scheme 60. Asymmetric domino Heck-allylic amination reaction of α,ω-amino-1,3-diene.

In 2003, Choudary et al. reported a one pot biomimic synthesis of chiral diols via Heck coupling N-oxidation asymmetric dihydroxylation mediated by a recyclable trifunctional heterogeneous catalyst (layered double hydroxides (LDH)-PdOsW) consisting of active palladium, tungsten, and osmium species embedded in a single matrix (Scheme 61).[107] This protocol involving a Sharpless chiral ligand, for example, [(DHQD)$_2$PHAL] [1,4-bis(9-*O*-dihydroquinidinyl)phthalazine], was applied to the synthesis of diltiazem and the taxol side chain.



Scheme 61. Heck coupling N-oxidation asymmetric dihydroxylation reaction.

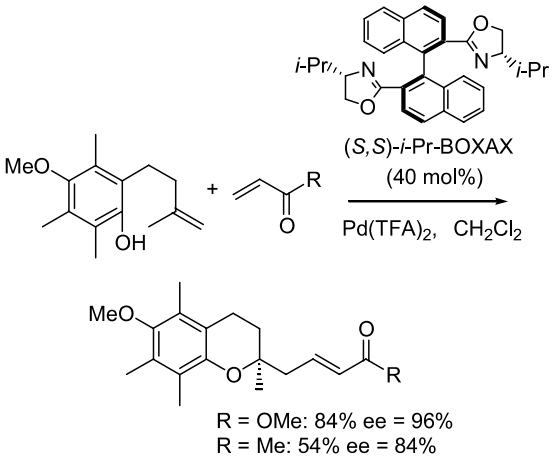
An asymmetric Heck reaction carbanion capture process was achieved for the first time by Shibasaki et al., making possible the catalytic asymmetric synthesis of various functionalised bicyclo[3.3.0]octane derivatives (Scheme 62).[108]



Nu = $NaCH_2(CO_2Me)_2$: 92% ee = 83%
Nu = $Na(CO_2Et)_2CH(CH_2)_2OTBDPS$: 77% ee = 87%
Nu = $NaCH_2(SO_2Ph)_2$: 83% ee = 94%
Nu = $NaCH_2(COMe)(CO_2Me)$: 74% ee = 83%
Nu = $NaCH_2(CO_2Me)(COCH_2Cl)$: 67% ee = 80%
Nu = $NaCH_2(COPh)_2$: 90% ee = 80%
Nu = NaOAc: 89% ee = 80%
Nu = NaNHBn: 76% ee = 81%

Scheme 62. Asymmetric Heck reaction carbanion capture process.

Very recently, Tietze et al. developed a palladium-catalysed enantioselective domino reaction for the efficient synthesis of vitamin E.[109] This sequence comprised an enantioselective Wacker oxidation and a subsequent Heck reaction catalysed by $Pd(TFA)_2$ in the presence of the chiral ligand, (*S*,*S*)-*i*-Pr-BOXAX, depicted in Scheme 63.



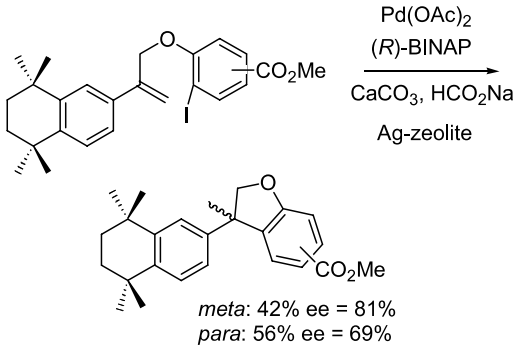
R = OMe: 84% ee = 96%
R = Me: 54% ee = 84%

Scheme 63. Asymmetric domino Wacker oxidation Heck reaction.

In 1998, Diaz et al. developed an enantioselective domino reaction consisting of an intramolecular Heck cyclisation hydride-capture process in order to prepare novel conformationally restricted retinoids in the presence of Pd-(*R*)-BINAP (Scheme 64).[110]

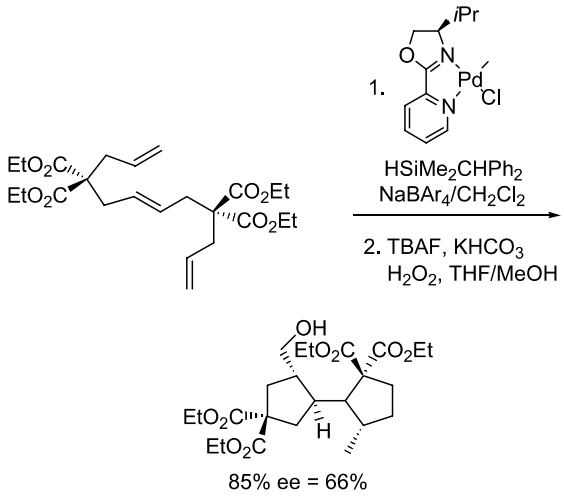
2.7.2. Other transition-metal-catalysed reactions. In 2001, Pei et al. reported an asymmetric domino cyclisation hydrosilylation reaction of a triene, forming the corresponding tethered bicyclopentane, using a chiral pyridine–oxazoline–Pd complex (Scheme 65).[111]

In 2001, Arai et al. reported a highly efficient enantioselective Pd-catalysed asymmetric domino cyclisation employing a dialkyl carbinol substrate, leading to the corresponding bicyclic compound (Scheme 66).[112] These authors suggested a domino oxy- and carbopalladation process as a plausible mechanism for this unprecedented reaction.



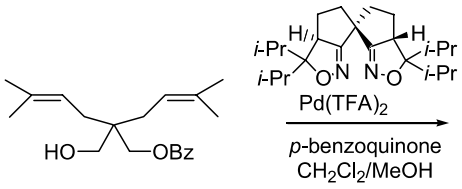
meta: 42% ee = 81%
para: 56% ee = 69%

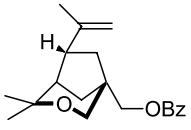
Scheme 64. Asymmetric domino Heck reductive cyclisation reaction.



85% ee = 66%

Scheme 65. Asymmetric domino cyclisation hydrosilylation reaction.



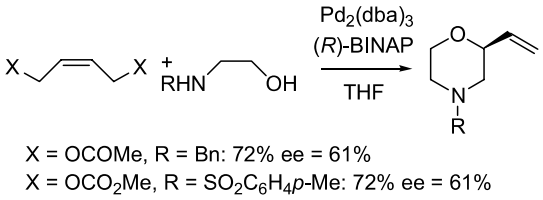


89% ee = 82%

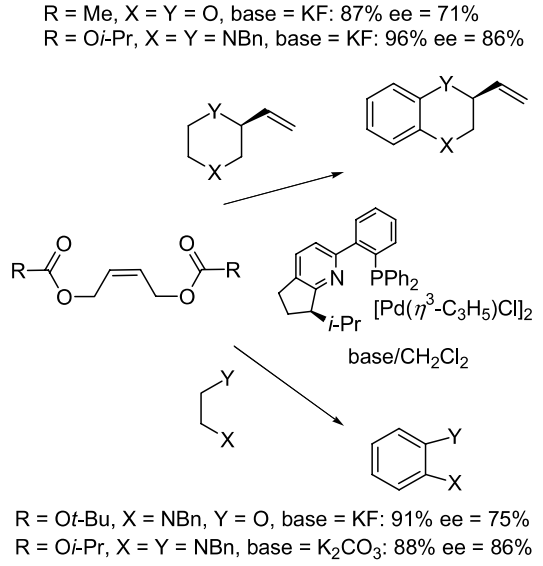
Scheme 66. Asymmetric domino Wacker-type cyclisation reaction.

Palladium-catalysed asymmetric tandem allylic substitutions using chiral ligands [(*R*)-BINAP] were developed in 1993 by Hayashi et al., in order to prepare optically active morpholines (Scheme 67).[113]

Better results were recently obtained by Ito et al. using a chiral 2-(phosphinophenyl)pyridine ligand for the palladium-catalysed domino allylic substitution[114] of 1,4-diacyloxy- or 1,4-bis(alkoxycarbonyloxy)-2-butenes using a 1,2-heterofunctionalised compound as nucleophile (Scheme 68).[115]

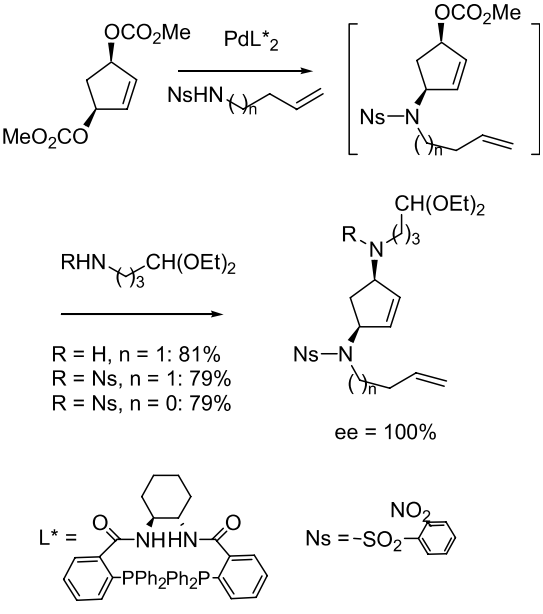


Scheme 67. Asymmetric Pd-catalysed domino allylic substitution reaction.



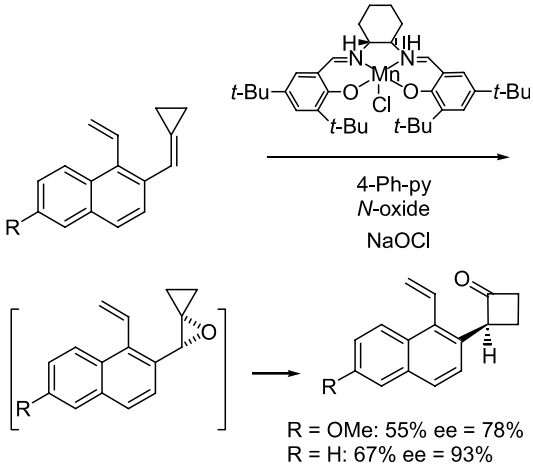
Scheme 68. Asymmetric Pd-catalysed domino allylic substitution reactions.

An asymmetric palladium-catalysed domino three-component allylic alkylation reaction of a chiral dicarbonate has given access to chiral tetraponerines with an all-cis stereochemistry and to all of the desired ring sizes.[116] The catalyst (PdL^*_2) was prepared from a chiral diphosphine (L*) and a tris(dibenzylideneacetone)dipalladium(0) chloroform complex in THF (Scheme 69).



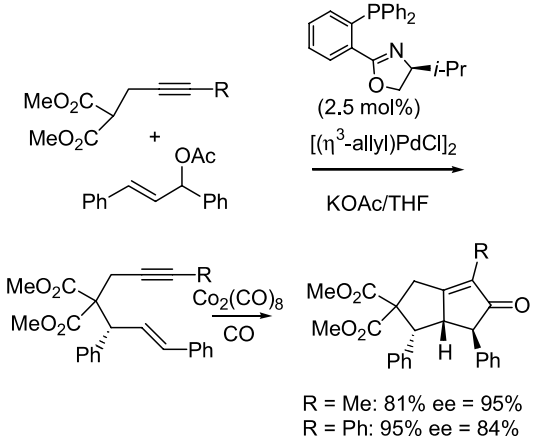
Scheme 69. Asymmetric Pd-catalysed domino allylic alkylation reaction.

On the other hand, a cascade asymmetric epoxidation ring-expansion reaction of cyclopropylidene was examined by Ihara et al (Scheme 70).[117] This procedure was catalysed by a chiral (salen)Mn^{III} complex and applied to the total synthesis of (+)-equilenin.



Scheme 70. Asymmetric domino epoxidation ring-expansion reaction.

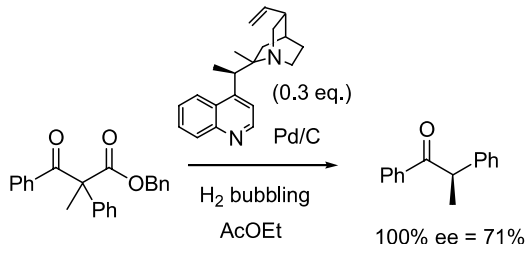
A tandem action of a homogeneous chiral Pd(II) catalyst and a heterogeneous Co/C catalyst led to a two-step, one pot highly enantioselective Pauson–Khand-type reaction, depicted in Scheme 71.[118]



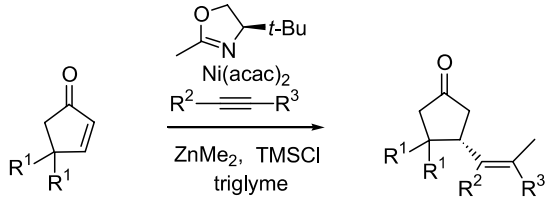
Scheme 71. Asymmetric domino Pd-catalysed allylic alkylation Pauson–Khand-type reaction.

An unusual one pot catalytic deprotection decarboxylation asymmetric tautomerisation of β-ketoesters was studied by Muzart et al., providing an easy access to various chiral ketones.[119] This palladium-induced procedure was performed in the presence of chiral β-aminoalcohols and allowed the synthesis of either cyclic ketones such as indanones, tetralones, and chromanones, or linear ketones (Scheme 72).

Simple chiral monodentate oxazolines have been employed as chiral ligands in a nickel-catalysed asymmetric multiple-component reaction involving cyclic enones, alkynes, $ZnMe_2$, and Me_3SiCl (Scheme 73).[120]

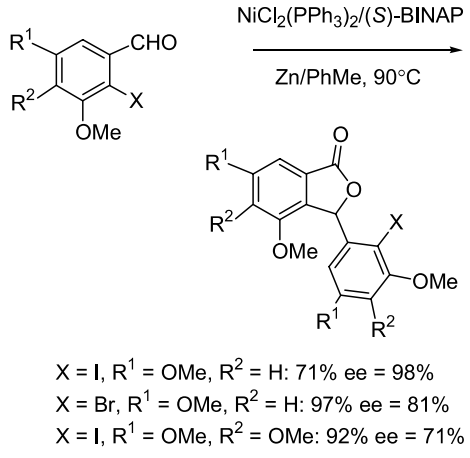


Scheme 72. One pot deprotection decarboxylation asymmetric tautomerisation of β-ketoesters.



Scheme 73. Nickel-catalysed asymmetric multiple-component coupling.

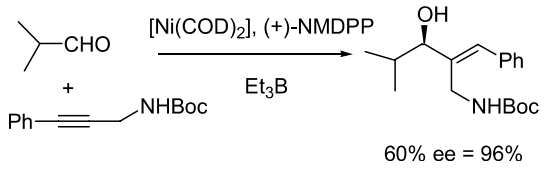
Nickel was also used for the catalysis of an asymmetric domino addition cyclisation reaction performed in the presence of chiral bidentate ligands such as BINAP, providing a useful method to synthesise optically active halogen-substituted phthalides (Scheme 74).[121]



Scheme 74. Nickel-catalysed asymmetric domino addition cyclisation reaction.

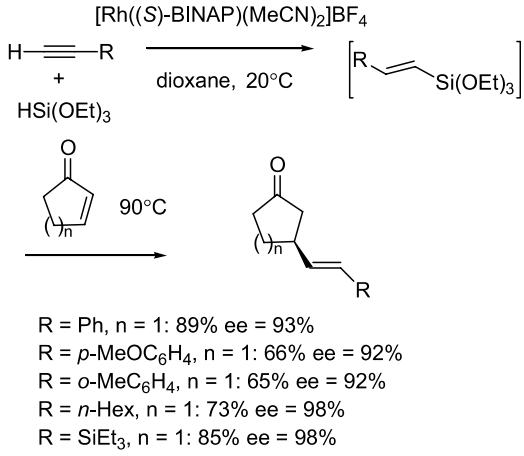
More recently, Ikeda et al. reported the enantioselective reductive coupling of aldehydes and alkynes using Et_3B.[122] When (+)-(neomenthyl)diphenylphosphane (NMDPP) was treated as a chiral ligand in this catalytic reaction, a trisubstituted allylic alcohol was obtained in 96% ee with high regio- and stereoselectivities (Scheme 75).

Hayashi et al. have shown that chiral rhodium complexes catalysed the 1,4-addition of alkenylsilanes, in situ generated by the hydrosilylation of alkynes, via a one pot procedure in which a rhodium/(*S*)-BINAP complex induced the two successive reactions (Scheme 76).[123] The same



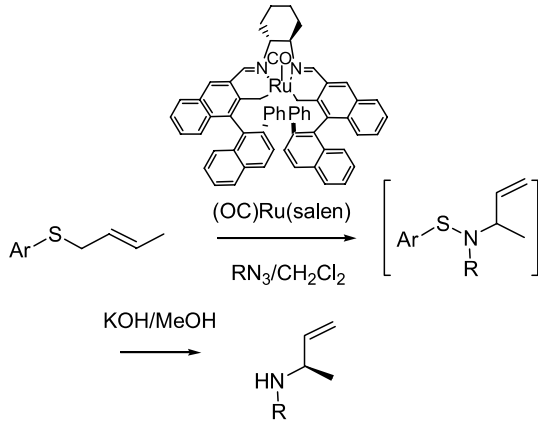
Scheme 75. Nickel-catalysed enantioselective reductive coupling of aldehyde and alkyne.

methodology was applied to the 1,4-addition of alkenylboranes in situ generated by the hydroboration of alkynes.[124]



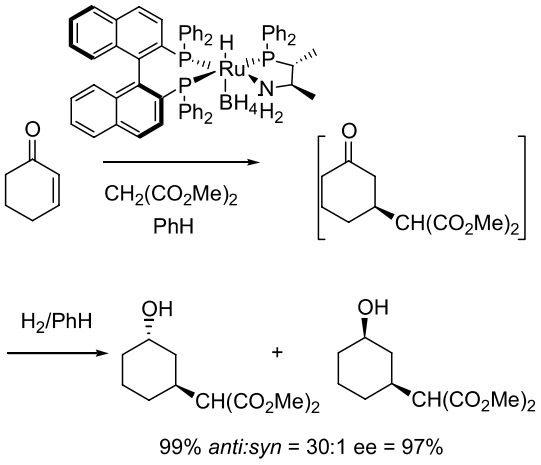
Scheme 76. Asymmetric domino rhodium-catalysed hydrosilylation 1,4-addition reaction of alkynes.

Asymmetric C–N bond formation could be achieved in a highly enantioselective manner by using (OC)Ru(salen)-catalysed domino sulphimidation [2,3]sigmatropic rearrangement reactions of allyl aryl sulphides with *p*-toluenesulphonyl azide, followed by hydrolysis, leading to *N*-allyl arylsulphonamides (Scheme 77).[125]



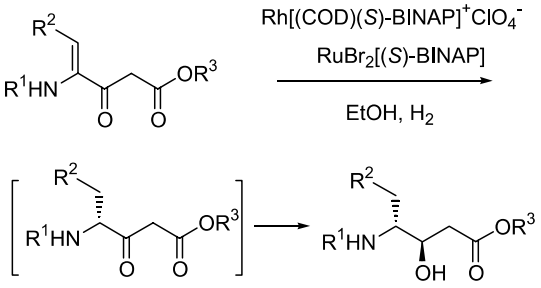
Scheme 77. Asymmetric domino sulphimidation [2,3]sigmatropic rearrangement reaction of allyl aryl sulphides.

Very recently, Morris et al. demonstrated that ruthenium hydride borohydride complexes containing β-aminophosphine ligands could promote, in the same flask, an enantioselective Michael addition and a hydrogenation reaction (Scheme 78).[126]



Scheme 78. Asymmetric domino Michael addition hydrogenation reaction.

A double asymmetric hydrogenation was performed in the presence of both rhodium(I) and ruthenium(II) chiral phosphine complexes.[127] Thus, the domino asymmetric hydrogenation reaction of γ-(acylamino)-γ,δ-unsaturated-β-ketoesters provided the two possible corresponding statin analogues in the presence of both Rh(I) and Ru(II) chiral catalysts (Scheme 79).

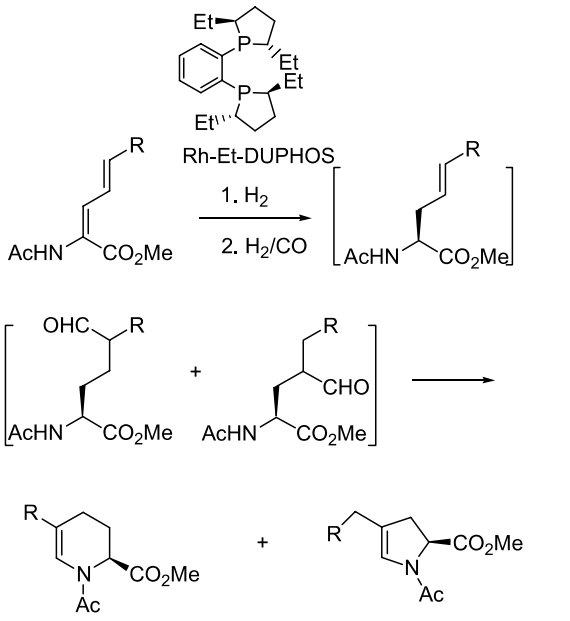


R1 = Ac, R2 = Ph, R3 = Et: 99% ee = 95%
R1 = Ac, R2 = Ph, R3 = Me: 99% ee = 95%
R1 = Boc, R2 = Ph, R3 = Et: 99% ee = 95%
R1 = Ac, R2 = *p*-ClC6H4, R3 = Et: 90% ee = 95%

Scheme 79. Rh(I)- and Ru(II)-catalysed asymmetric domino hydrogenation reaction.

Another asymmetric hydrogenation involving the synthesis of cyclic amino acids was incorporated in a domino hydrogenation hydroformylation reaction.[128] In this case, only one catalyst system promoted successively the reaction of prochiral dienamide esters with H_2, followed by H_2/CO, using Rh(I)-Et-DUPHOS (Scheme 80).

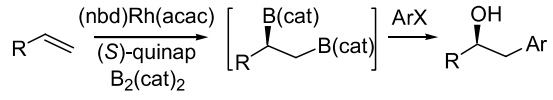
In 2004, Morken et al. developed a catalytic asymmetric carbohydroxylation of alkenes by a domino diboration Suzuki cross-coupling oxidation reaction.[129] Chiral



R = H: 91% piperidine:pyrrolidine dr = 54:46 % ee = 95:99
R = Me: 81% piperidine:pyrrolidine dr = 56:44 % ee = 95:99

Scheme 80. Asymmetric domino hydrogenation hydroformylation reaction.

nonsymmetric 1,2-diboron adducts, generated by catalytic enantioselective diboration, reacted in situ with aryl halides in which the less hindered C–B bond participated in cross-coupling. The remaining C–B bond was then oxidised (Scheme 81).



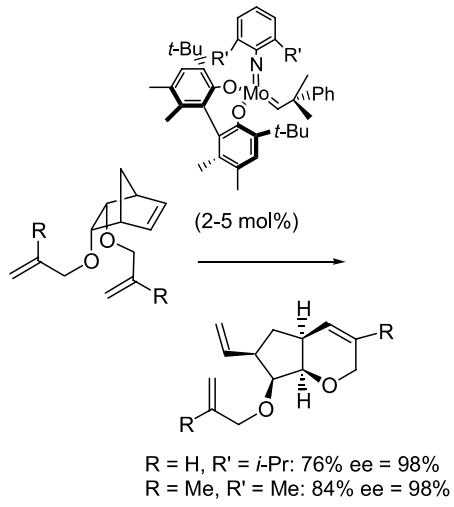
nbd = norbornadiene

R = *t*-Bu, ArX = PhOTf: 76% ee = 94%
R = *t*-Bu, ArX = *p*-BrC6H4NO2: 62% ee = 94%
R = *t*-Bu, ArX = *m*-BrC6H4OMe: 77% ee = 95%
R = BnOCH2(Me)2C, ArX = *m*-Br-py: 58% ee = 93%
R = *p*-TolCH2(Me)2C, ArX = *p*-BrC6H4CHO: 48% ee = 76%

Scheme 81. Asymmetric domino diboration Suzuki coupling oxidation reaction.

Domino metatheses are combinations of ring-opening metatheses (ROMs), ring-closing metatheses (RCMs), and cross metatheses (CMs). Catalytic asymmetric versions of these reactions have been recently developed such as those involving strained disubstituted cyclic alkenes promoted by chiral Mo complexes (Scheme 82).[130]

The application of domino metathesis reactions to *N*-alkylated derivatives of 2-azanorbornenones allowed the enantioselective synthesis of pyrrolizidine, quinolizidine, pyrrolidinoazepine, and pyrrolidinoazocine derivatives in a straightforward process.[131] In addition, Fürstner et al. reported a catalytic approach to (*R*)-(+)-muscopyridine, based on an iron-catalysed alkyl–aryl cross-coupling method.[132]



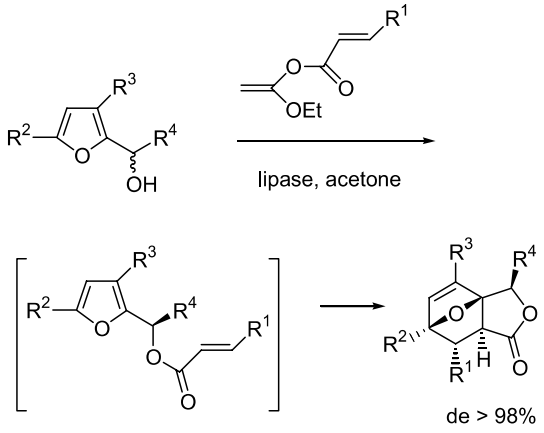
Scheme 82. Asymmetric domino Mo-catalysed asymmetric ring-opening metathesis ring-closing metathesis reaction.

3. Asymmetric biocatalysed domino reactions

Since the prototypes of domino processes are the sequential transformations catalysed in nature by biocatalysts, the incorporation of enzymatic transformations in a series of sequential nonenzymatic reactions could open up new and promising opportunities for organic synthesis. The first successful combination of enzymatic with nonenzymatic transformations in a nonasymmetric domino reaction sequence was reported by Waldmann et al. in 1996.[133] Asymmetric biocatalysed domino reactions can be divided into two categories of reactions, that is, the asymmetric enzyme-triggered domino reactions,[134] and the asymmetric multienzymatic one pot reactions.

3.1. Asymmetric enzyme-triggered domino reactions

In contrast with the traditional asymmetric chemo-catalysed domino reactions, only a few examples of asymmetric domino reactions have been reported in which the initiation of the reaction cascade consisted of a biotransformation. The synthetic potential to conduct the domino processes in an asymmetric fashion may conveniently be achieved by making use of the unparalleled chemo-, stereo-, and enantioselectivity of enzymes.[135] Thus, in the case of the sequence of events being triggered by a biocatalyst, the cascade may proceed in a highly asymmetric fashion to furnish products in a nonracemic form. In the first step, the enzyme modifies an enzyme-labile trigger group within the starting material, for example, via oxidation, hydrolysis of an ester or epoxide, transesterification of an alcohol, etc., giving access to a reactive intermediate. This latter intermediate may bear a liberated negative charge, which can deliver electrons to a π-system, or may act as a nucleophile. Consequently, the intermediate immediately undergoes a subsequent domino reaction, which may consist of a fragmentation, a rearrangement, or a cyclisation such as a Diels–Alder reaction. An elegant asymmetric domino Diels–Alder reaction following an enzymatic kinetic resolution using a 1-ethoxyvinyl ester was reported by Kita et al. in 1998.[136] Kinetic resolution of racemic furfuryl alcohol derivatives was accomplished via acyl transfer catalysed by a *Pseudomonas* sp. lipase preparation, employing an enol ester as acyl donor in the first step. In this way, the diene and dienophile were linked on to each other and, at the same time, asymmetry was introduced into the system by means of kinetic resolution. The second step constituted of intramolecular Diels–Alder reaction, providing the corresponding optically active 7-oxabicyclo[2.2.1]heptene derivative (Scheme 83).

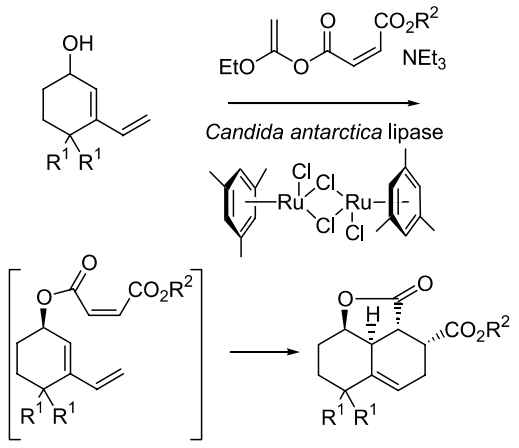


$R^1 = CO_2Me$, $R^2 = H$, $R^3 = R^4 = Me$: 43% ee = 84%
$R^1 = CO_2Me$, $R^2 = H$, $R^3 = Me$, $R^4 = Et$: 45% ee = 99%
$R^1 = CO_2Me$, $R^2 = Me$, $R^3 = Br$, $R^4 = Et$: 35% ee = 95%
$R^1 = CO_2Me$, $R^2 = CH_2OMe$, $R^3 = Br$, $R^4 = Et$: 43% ee = 94%
$R^1 = CO_2Et$, $R^2 = H$, $R^3 = Me$, $R^4 = Et$: 46% ee = 99%
$R^1 = CO_2Et$, $R^2 = H$, $R^3 = Br$, $R^4 = Et$: 43% ee = 96%
$R^1 = CO_2Et$, $R^2 = Me$, $R^3 = Br$, $R^4 = Et$: 30% ee = 95%
$R^1 = CO_2Et$, $R^2 = CH_2OMe$, $R^3 = Br$, $R^4 = Et$: 45% ee = 96%
$R^1 = COMe$, $R^2 = H$, $R^3 = Br$, $R^4 = Et$: 40% ee = 99%
$R^1 = COMe$, $R^2 = Me$, $R^3 = Br$, $R^4 = Et$: 34% ee = 99%
$R^1 = COMe$, $R^2 = CH_2OMe$, $R^3 = Br$, $R^4 = Et$: 36% ee = 93%

Scheme 83. Asymmetric enzyme-triggered Diels–Alder reaction.

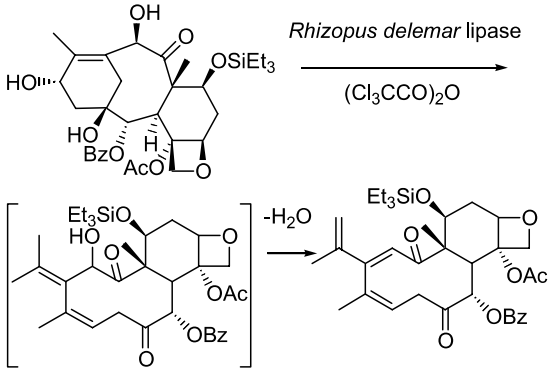
More recently, these authors have reported a combination of the domino reaction concept and the dynamic kinetic resolution (DKR) protocol[137] comprising the first lipase-catalysed domino process that combined the DKR of racemic alcohols by using 1-ethoxyvinyl esters and the Diels–Alder reaction of the intermediates. Their finding that ruthenium catalysts produced a rapid racemisation of the slow-reacting (*S*)-enantiomers was the key to the success of this process, which provided useful chiral intermediates for natural products such as compactin and forskolin (Scheme 84).

Other enzyme-triggered rearrangements such as an enzymatic dehydration-initiated rearrangement have been observed during the development of a new strategy for the synthesis of paclitaxel.[138] The 7-triethylsilyl derivative of 10-deacetylbaccatine III served as the starting material for this cascade reaction. The 13-hydroxy group of this latter substrate was regioselectively acylated by *Rhizopus delemar* lipase in the presence of trichloroacetic anhydride as the acyl donor. It was assumed that, after the first dehydration rearrangement had formed the intermediate α-hydroxyketone, the latter underwent a second dehydration (Scheme 85).



R^1 = H, R^2 = Et: 86% ee = 95%
R^1 = H, R^2 = Me: 83% ee = 93%
R^1 = R^2 = Me: 81% ee = 91%
R^1,R^1 = $S(CH_2)_3S$, R^2 = Et: 69% ee = 93%

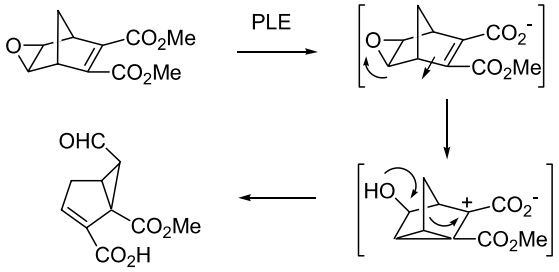
Scheme 84. Asymmetric enzyme-triggered Diels–Alder reaction combined with DKR.



Scheme 85. Enzymatic selective dehydration and skeletal rearrangement of paclitaxel precursors.

Domino reactions initiated by an enzymatically liberated (negative) charge have an enzyme-catalysed hydrolytic starting step in common, during which a carboxy ester moiety is cleaved. The latter leads to the liberation of an anion, which does not participate in the subsequent reaction, but donates electrons into the molecule, initiating a domino reaction involving fragmentation or rearrangement. As an example, an enzyme-triggered asymmetric rearrangement was reported by Ohno et al.[139] This unusual enzyme-triggered asymmetric rearrangement was observed when attempting to hydrolyse a symmetric tricyclic diester in an asymmetric fashion using porcine liver esterase (PLE), the expected chiral monoester not being obtained, but, rather, the product turned out to be a bicyclo[3.1.0]hexane framework (Scheme 86). Actually, a hemiester was, indeed, first formed by hydrolysis, but this immediately underwent a Meinwald rearrangement to furnish the final enantiomerically enriched product.

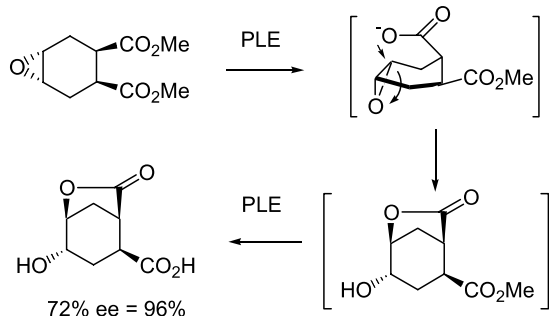
Other types of enzyme-triggered domino reactions are those initiated by an enzymatically liberated nucleophile. Instead



100% ee = 48%

Scheme 86. Asymmetric enzyme-triggered Meinwald rearrangement.

of undergoing a fragmentation or rearrangement reaction, the carboxylate or hydroxy group, formed during (enzymatic) ester hydrolysis or epoxide ring opening, can also act as a nucleophile by attacking an electrophile during the cascade reaction. The electrophile usually consisted of an epoxide or a related species such as a halide. Domino reactions of this type can start with the enzymatic hydrolysis of an ester or epoxide to liberate a nucleophile ($-CO_2^-$ or –OH), which opens an epoxide in an intramolecular S_N2 reaction in the second step. Thus, the final product formed is a lactone ($-CO_2^-$ acting as nucleophile) or a (hydroxy)-tetrahydrofuran (–OH acting as nucleophile). Such a cascade reaction was observed upon asymmetric hydrolysis of a *meso*-epoxy diester using PLE (Scheme 87).[140] It was found that the more accessible (equatorial) carboxy ester moiety was selectively hydrolysed, liberating an intermediate carboxylate anion, which, in turn, acted as a nucleophile for opening the epoxide moiety to furnish the corresponding hydroxy-γ-lactone. In order to undergo lactone formation, the intermediate epoxycarboxylate has to undergo a conformational change, which converted the second (remaining) axial ester moiety into the more accessible equatorial position. As a consequence, it could now be additionally hydrolysed by PLE and this led to the final chiral product.

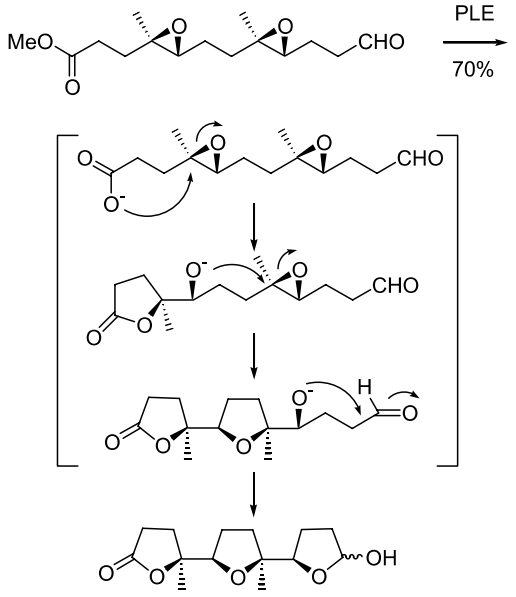


72% ee = 96%

Scheme 87. γ-Lactone formation initiated by enzymatically liberated nucleophile ($-CO_2^-$).

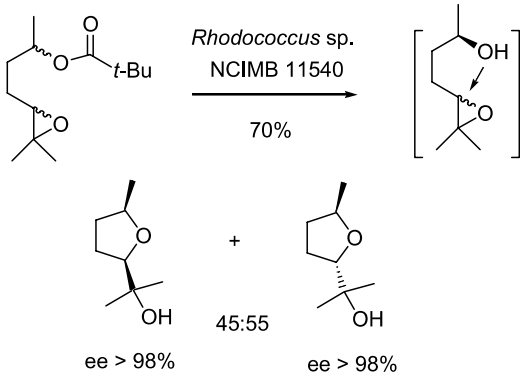
A related, but even more complex, domino reaction is depicted in Scheme 88. Again, the cascade was started by the enzymatic hydrolysis of an ester liberating a nucleophile ($-CO_2^-$), which opened an epoxide to furnish the corresponding lactone, together with a free alkoxy moiety in the δ-position. The latter alkoxide underwent another (intramolecular) nucleophilic attack on the second epoxide

to furnish a tetrahydrofuran derivative. At the end of this cascade, the resulting alkoxide was trapped by forming a hemiacetal with an aldehyde, bringing the cascade to a halt.[141]



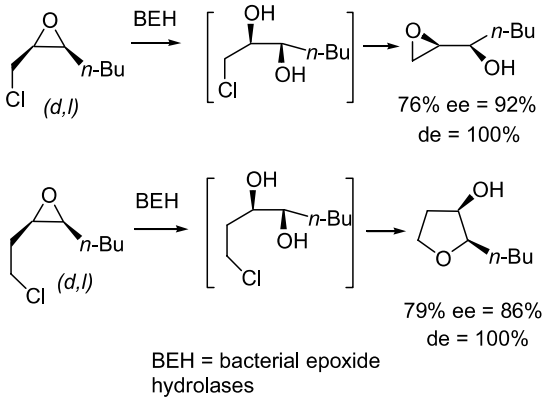
Scheme 88. Enzymatic liberation of nucleophile ($-CO_2^-$) followed by three-step S_N2 cascade involving two epoxy groups.

Instead of an enzymatically generated carboxylate anion, an alcohol group (derived from a biocatalysed ester or epoxide hydrolysis) may also serve as the nucleophile to open an epoxy moiety in a cascade reaction (Scheme 89), for example, treatment of a diastereomeric mixture of an epoxyester with a crude immobilised enzyme preparation (Novo SP 409), or whole lyophilised cells of *Rhodococcus erythropolis* NCIMB 11540, gave the corresponding intermediate alcohol via kinetic resolution of the secondary alcohol moiety. The latter spontaneously opened the epoxide in an S_N2 fashion to furnish the corresponding diastereomeric tetrahydrofuran derivatives, which could be separated by column chromatography.[142] Both compounds were bioactive constituents of bark beetle pheromones.



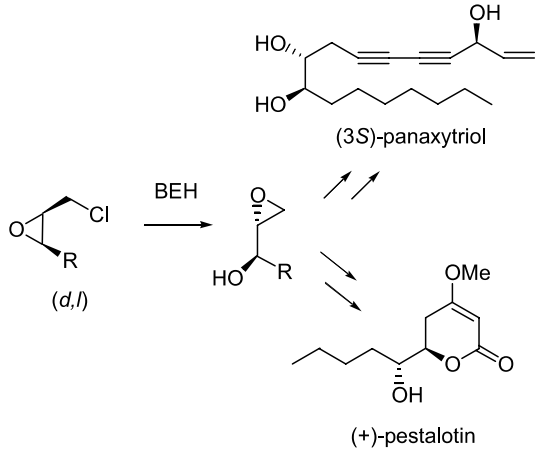
Scheme 89. Cyclisation initiated by enzymatically generated nucleophile (–OH) attacking an epoxide.

In all of the cases described above, the nucleophile acting during the cascade was liberated by hydrolysis of an ester. In the following example, the nucleophile was generated by enzymatic hydrolysis of an epoxide to form the corresponding diol. This involved the biohydrolysis of racemic 2,3-disubstituted *cis*-chloroalkyl-epoxides, which turned out to initiate a cascade reaction (Scheme 90). First, both enantiomers of the racemic epoxide were hydrolysed by bacterial epoxide hydrolases (BEH) (*Mycobacterium paraffinicum* NCIMB 10420) in an enantioconvergent fashion to furnish the expected corresponding diols, which, however, underwent spontaneous ring closure to yield the corresponding cyclic products. The cyclisation reaction showed some resemblance to a Payne-type rearrangement.[143]



Scheme 90. Enzyme-triggered cyclisation of haloalkyl-oxiranes catalysed by epoxide hydrolases.

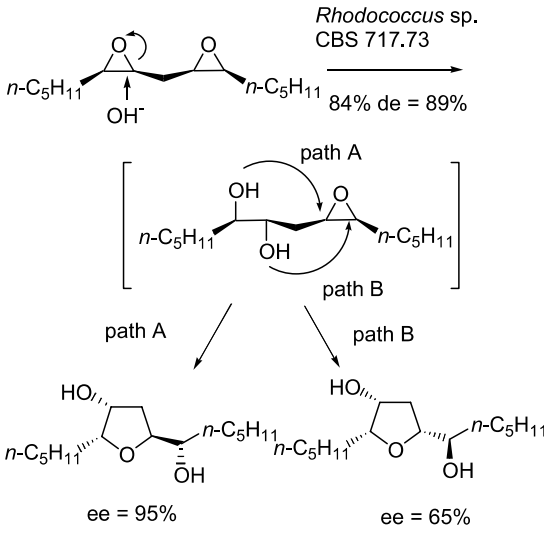
The synthetic potential of these building blocks was demonstrated by the asymmetric synthesis of four bioactive compounds, such as (3*S*)-panaxytriol (Scheme 91),[144] an antileukemic constituent of ginseng roots, (+)-pestalotin (Scheme 91),[145] a phytohormone, pityol,[146] a pheromone, and a natural bicyclic acetal.[146]



Scheme 91. Synthetic applications of enzyme-triggered cascade reactions.

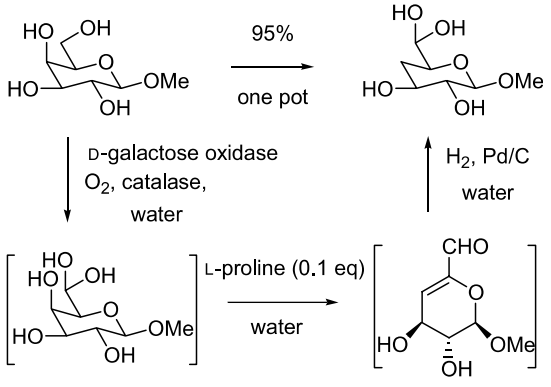
In order to test the limits of the stereocontrol, the enzyme-triggered cyclisation of bis-epoxides was investigated (Scheme 92).[147] In this study, four enzymatic trigger

pathways were leading to four possible stereoisomeric tetrahydrofuran products through two secondary pathways. Careful elucidation of the products obtained showed that the *meso-cis-cis*-oxirane was converted through an enzyme-triggered cascade via a single dominant pathway into a chiral dihydroxy-tetrahydrofuran derivative containing four stereogenic centres as the sole product. Compounds of this type constitute the central core of *Annonaceous* acetogenins, which exhibit a range of biological effects, such as antitumour, antimalarial, pesticidal, and immunosuppressive activities.



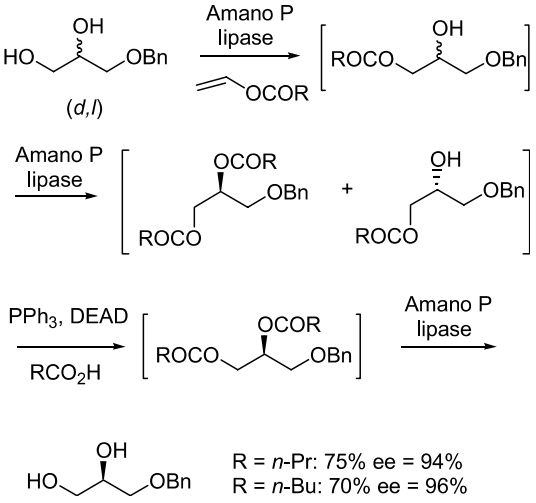
Scheme 92. Enzyme-triggered rearrangement of *meso*-bis-epoxides.

In addition, in certain cases, asymmetric hydrolysis of thioesters, liberating thiols, has been accomplished using esterases/lipases.[148] In 2002, Kieboom et al. developed consecutive catalytic oxidation (oxygen, D-galactose oxidase), dehydration (L-proline) and reduction (hydrogen, palladium) of methyl β-D-galactoside in water at neutral pH, yielding methyl 4-deoxy-6-aldehydo-β-D-glucoside without any intermediate recovery steps, demonstrating the potential power of a multicatalytic approach, using both bio- and chemo-catalysts, for carbohydrate conversions without the use of protective groups or stoichiometric amounts of reagents (Scheme 93).[149]



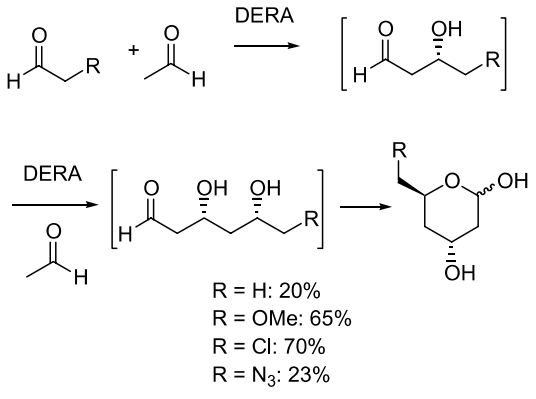
Scheme 93. One pot bio- and chemo-catalysed reactions of D-galactose derivative.

On the other hand, a new efficient chemoenzymatic enantioselective methology for the production of 3-*O*-benzyl-glycerol has been developed.[150] This one pot procedure was based on the sequential enzymatic acylation-Mitsunobu inversion-enzymatic hydrolysis (Amano P lipase) of racemic 1-*O*-benzylglycerol, which has been performed without isolation of the intermediates (Scheme 94).



Scheme 94. One pot chemoenzymatic enantioselective synthesis of 3-*O*-benzyl-glycerol.

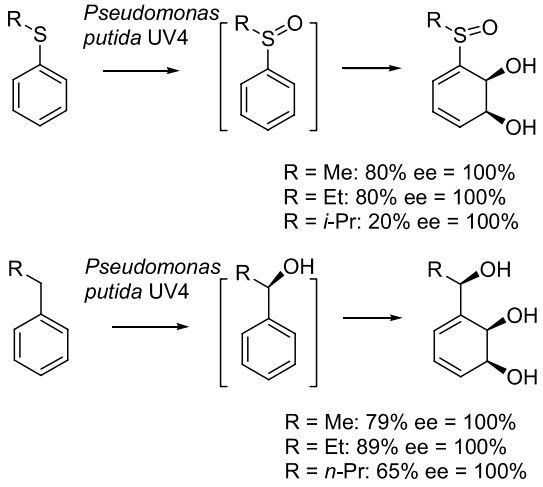
In 1994, Wong et al. reported an asymmetric domino aldol reaction involving three aldehyde substrates catalysed by 2-deoxyribose-5-phosphate aldolase (DERA).[151] The reaction started with a stereospecific addition of acetaldehyde to a substituted acetaldehyde to form a 3-hydroxy-4-substituted-butyraldehyde, which subsequently reacted with another acetaldehyde to form a 2,4-dideoxyhexose derivative, also in a stereospecific manner (Scheme 95). The enzymatic products constituted useful chiral synthons of HMG-CoA reductase inhibitors and 1,3-polyol systems (the enantiomeric purity was not detailed).



Scheme 95. Asymmetric domino aldol reaction catalysed by DERA.

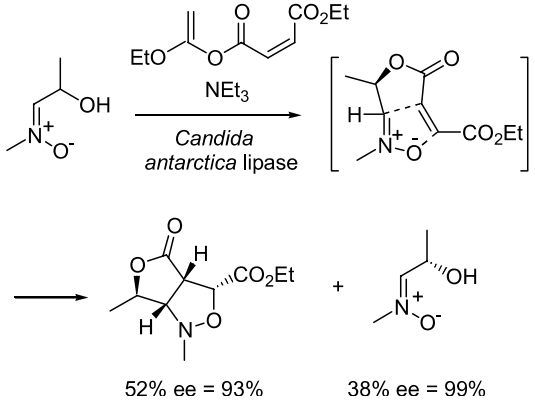
In 2002, Boyd et al. reported the domino dioxygenase-catalysed trioxygenation of alkyl phenyl sulphides, yielding the corresponding enantiopure *cis*-dihydrodiol sulphoxides via a domino monosulphoxidation *cis*-dihydroxylation reaction.[152] The same conditions employing whole cells of

Pseudomonas putida UV4 as source of toluene dioxygenase (TDO) were applied to alkylbenzenes, providing the corresponding chiral triols (Scheme 96).



Scheme 96. Domino dioxygenase-catalysed trioxygenation reaction of alkyl phenyl sulphides and alkylbenzenes.

In the course of developing a concise asymmetric total synthesis of (−)-rosmarinecine, Kita et al. developed, in 2005, a lipase-catalysed domino kinetic resolution of α-hydroxynitrone intramolecular 1,3-dipolar cycloaddition reactions (Scheme 97).[153]

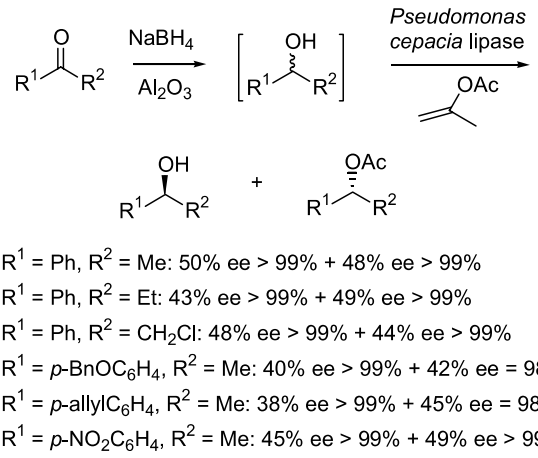


Scheme 97. Lipase-catalysed domino kinetic resolution of α-hydroxynitrone intramolecular 1,3-dipolar cycloaddition reaction.

In contrast, a few examples of domino chemoenzymatic reactions have involved the chemical reaction as the first step of the sequence. As an example, Kamal et al. have developed domino reactions involving the reduction of acetophenones with sodium borohydride in the presence of neutral alumina followed by enantioselective acylation catalysed by *Pseudomonas cepacia* lipase in one pot (Scheme 98).[154] This new protocol for lipase-mediated resolution involved for the first time the use of lipases in the presence of borohydride.

3.2. Asymmetric multienzymatic one pot reactions

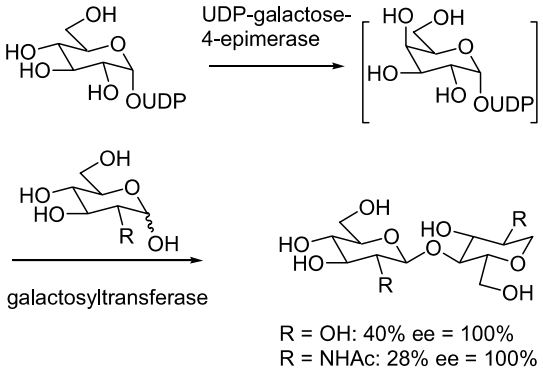
A highly interesting approach in the application of domino reactions is the use of a multienzyme cocktail to catalyse



Scheme 98. Domino lipase-catalysed synthesis of chiral alcohols from carbonyl compounds.

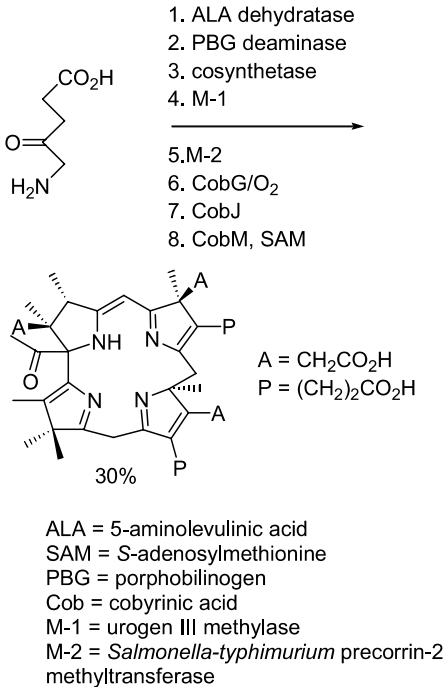
different reactions. It is now evident that the multienzyme synthesis of natural products has passed from feasibility to practical reality and that there is no limit to the number of enzymes that can be combined in a single reactor to produce a complex structure in good yield and in a domino fashion. What is truly remarkable is the lack of product/substrate inhibition, which is probably due to the irreversible nature of many of the later steps in a given sequence. As an early example, Längström et al. reported, in 1990, the multienzymatic synthesis of carboxy-^{11}C-labelled L-tyrosine, L-DOPA, L-tryptophan and 5-hydroxy-L-tryptophan starting from racemic [1-^{11}C]alanine with enantiomeric purities higher than 99%.[155] The enzymatic reactions were performed using, simultaneously, D-amino acid oxidase, catalase, glutamic-pyruvic transaminase, and β-tyrosinase (for L-tyrosine and L-DOPA), or tryptophanase (for L-tryptophan and 5-hydroxy-L-tryptophan), in a one pot reaction. In 1991, Gygax et al. described the synthesis of β-D-glucuronides by a one pot multienzyme system with in situ regeneration of uridine 5′-diphosphoglucuronic acid.[156] This stereoselective simple reaction involved the use of glucose-1-phosphate as a donor of the glucuronic acid moiety and phosphoenolpyruvate and NAD (nicotinamide adenine dinucleotide) as co-substrates. On the other hand, Thiem et al. have shown that galactosyltransferase catalysed the galactosylation of oligosaccharides terminated by glucose and by 2-acetamido-2-deoxy-glucopyranose, respectively.[157] The glycosyl donor, uridine-5′-diphospho-galactose, was generated in situ by the treatment of UDP-glucose with UDP-galactose-4-epimerase. In the presence of a glycosyl acceptor and galactosyltransferase, the corresponding galactosylated oligosaccharide was obtained (Scheme 99).

In 1993, Wong et al. reported a multienzyme system for a one pot synthesis of sialyl oligosaccharides through a combined use of β-galactosidase and α(2,6)-sialyltransferase coupled with regeneration in situ of CMP-sialic acid.[158] Thus, the synthesis of sialyl oligosaccharides has been achieved with a β-galactosidase-catalysed galactosylation of an acceptor followed by a sialyltransferase-catalysed sialylation with regeneration in situ of CMP-sialic acid. In 1994, another multienzyme cocktail was used for the domino synthesis of precorrin-5, starting from



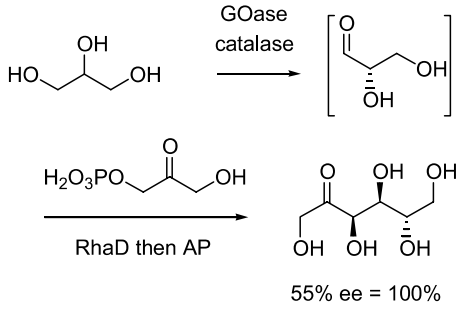
Scheme 99. Synthesis of galactose-terminated oligosaccharides by multienzyme system.

δ-aminolevulinic acid. In this transformation, eight different enzymes have been used including ALA-dehydratase to form porphobilinogen (PBG) as well as PBG deaminase and cosynthetase to give the tetracyclic uroporphyrinogen III (Scheme 100).[159]



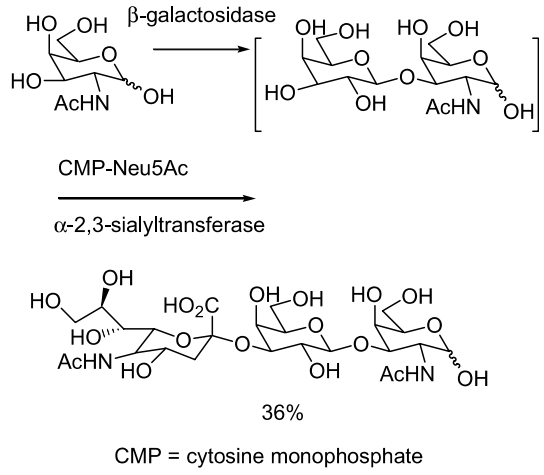
Scheme 100. Multienzyme cocktail for domino synthesis of precorrin-5.

In 1995, Wong et al. reported a domino aldol reaction catalysed by the aldolases, 2-deoxyribose 5-phosphate aldolase (DERA) and fructose 1,6-diphosphate aldolase (RAMA). This multienzyme system was used to catalyse a ternary crossed aldol between an α-substituted acetaldehyde derivative, acetaldehyde, and dihydroxyacetone phosphate.[160] At the same time, these authors have developed an enzymatic synthesis of enantiomerically pure L-fructose from dihydroxyacetone phosphate (DHAP) and L-glyceraldehyde, carried out by a multienzyme system comprising rhamnulose-1-phosphate aldolase (RhaD) and acid phosphatase (AP) using a stereospecific aldol addition reaction by this aldolase.[161] This latter methodology suffered, however, from two limitations. Firstly, L-glyceraldehyde is not commercially available and, secondly, this starting material is known to be thermodynamically metastable and decomposes easily. In this way, L-glyceraldehyde could be produced in situ from glycerol in the presence of galactose oxidase (GOase), catalase, rhamnulose-1-phosphate aldolase (RhaD), and acid phosphatase (AP) (Scheme 101).[162]



Scheme 101. Multienzyme system for domino synthesis of L-fructose.

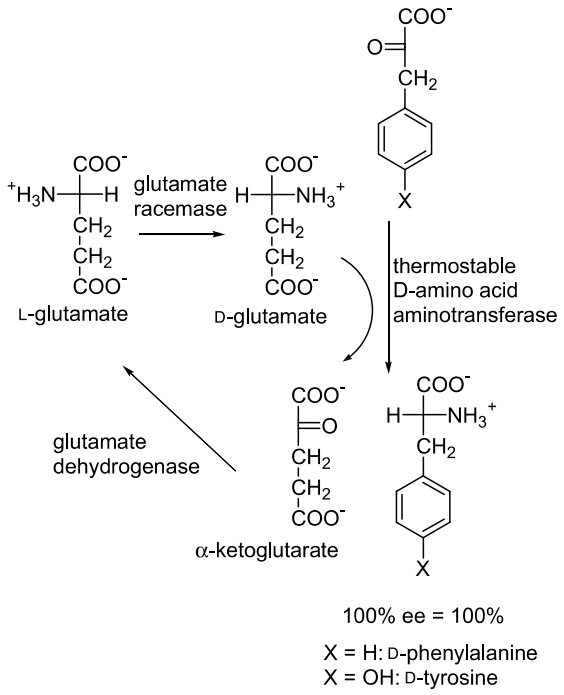
Kren et al. have developed a sequential multienzyme one pot system with cofactor regeneration in order to prepare rather complicated hetero-oligoglycosides such as the sialylated antigen T-epitope (Scheme 102).[163]



Scheme 102. One pot synthesis of sialyl T-antigen via multienzyme system.

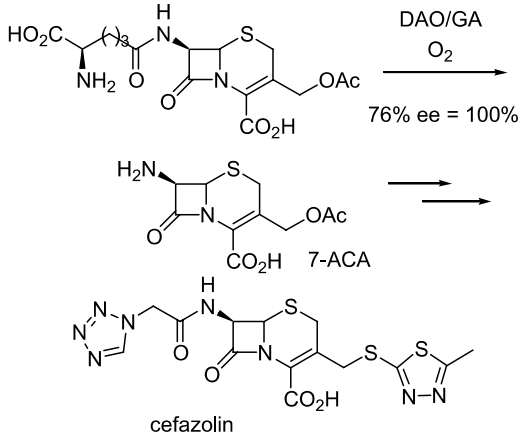
In another example, Duggan et al. supplied erythrose-4-phosphate and the unnatural substrate, 3-fluorophosphoenolpyruvate, to enzymes of the shikimate biosynthetic pathway to produce unnatural (*R*)- and (*S*)-6-fluoro analogues of shikimic acid, potentially useful as antibiotics.[164] In 1999, Sung et al. reported the production of aromatic D-amino acids from α-ketoacids and ammonia by the coupling of four enzyme reactions.[165] The multienzyme system composed of glutamate racemase, thermostable D-amino acid aminotransferase, glutamate dehydrogenase and formate dehydrogenase was employed for the synthesis of the enantiomerically pure D-amino acids, D-phenylalanine and D-tyrosine, from the corresponding α-ketoacids, phenylpyruvate and hydroxyphenylpyruvate, respectively (Scheme 103).

In 1997, Guisàn et al. reported the enzymatic deacylation of cephalosporin C in one batch by the simultaneous use of D-amino acid oxidase (DAO) from *Trigonopsis variabilis*,



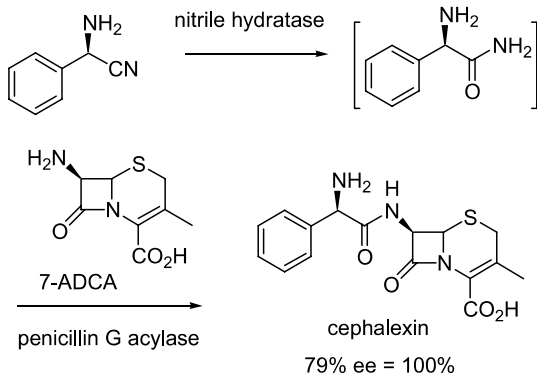
Scheme 103. Multienzyme synthesis of D-amino acids.

glutaryl acylase (GA) from *Acetobacter* sp., and a continuous flow of O_2.[166] This domino enzymatic reaction was included in a one pot, three-step chemoenzymatic synthesis of 3′-functionalised cephalosporins (e.g., cefazolin) involving three consecutive biotransformations catalysed by DAO and GA at the same time, and then by penicillin G acylase in a fully aqueous medium. DAO is known to catalyse the oxidative deamination of the α-aminoadipic side chain of cephalosporin C to give the α-ketoadipic derivative. A further decarboxylation in the presence of O_2 gives the glutaryl analogue, which is then deacylated by GA to obtain 7-aminocephalosporanic acid (7-ACA) (Scheme 104).



Scheme 104. Multienzyme cocktail for domino synthesis of cefazolin.

In 2002, Sheldon et al. reported a two-step, one pot enzymatic synthesis of cephalexin from D-phenylglycine nitrile.[167] The nitrile hydratase-catalysed hydration of D-phenylglycine nitrile to the corresponding amide was combined with the penicillin G acylase-catalysed acylation of 7-ADCA with the in situ-formed amide to afford a two-step, one pot synthesis of cephalexin (Scheme 105).



Scheme 105. Synthesis of cephalexin via one pot cascade of two enzymatic reactions.

4. Conclusions

This review clearly demonstrates the power and economic interest of asymmetric catalysed domino reactions in the field of synthetic organic chemistry. The development of new asymmetric processes such as asymmetric catalysed domino reactions for producing chiral elaborate structures in a rapid, atom-economic, and efficient manner has become an important area of research in organic synthesis. In addition, this review demonstrates that, by making use of the asymmetric catalytic potential of biocatalysts, enzyme-triggered cascade reactions may be turned into highly efficient protocols for the asymmetric synthesis of bioactive materials.

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Biographical sketch

Hélène Pellissier was born in Gap, France. She carried out her PhD under the supervision of Dr. G. Gil in Marseille and then entered the Centre National de la Recherche Scientifique in 1988. After a postdoctoral period in Professor K.P.C. Vollhardt's group, she joined the group of Professor M. Santelli in Marseille in 1992, where she focused on the chemistry of BISTRO and its large application in organic synthesis. Thus, she developed several new very short total syntheses of steroids starting from 1,3-butadiene and benzocyclobutenes.

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The synthesis and reaction of *N*-sulfenyl heterocycles: development of effective sulfenylating reagents

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Abstract—Various *N*-sulfenyl heterocycles were synthesized by transamination of sulfenamides using a chlorine gas-free method. The *N*-sulfenyl heterocycles behaved as sulfenylating reagents of anilines; *N*-sulfenylbenzimidazoles were the most effective.

1. Introduction

Compounds containing divalent sulfur–nitrogen bonds, especially sulfenamides, are attractive for their diverse industrial and medicinal applications.[1] Recently, another utility of sulfenamides was reported: some sulfenamides catalyzed oxidation of alcohols (with halogenating reagents as oxidant) to the corresponding carbonyl compounds.[2]

The sulfenamides have generally been synthesized by sulfenylation of amines or amination of thiols.[1,3] To synthesize sulfenylating reagents such as sulfenyl chlorides, chlorine gas was used as the chlorinating reagent. Because the use of chlorine gas sometimes caused undesired complications during laboratory procedures, chlorine gas-free synthetic methods for the sulfenamides have been evaluated.

In previous papers, we reported that both *N*-sulfenyl-1,2-benzisothiazolin-3-ones[4] and *N*-acylsulfenamides[5] were effective sulfenylating reagents for the synthesis of *N*-substituted sulfenamides. These sulfenylating reagents were synthesized by a chlorine gas-free procedure: the transamination of *N*-unsubstituted sulfenamides with 1,2-benzisothiazolin-3-ones[6] or the acylation of *N*-unsubstituted sulfenamides.[7] In the former derivatives, the heterocycles worked as effective leaving groups similar to azoles as leaving groups in *N*-acylazoles in nucleophilic reactions.[8] Although the syntheses of some 2-nitro- and 2,4-dinitrobenzenesulfenyl azoles were reported, sulfenyl chlorides were used in those syntheses.

We also reported that various *N*,*N*-disubstituted sulfenamides were synthesized by the treatment of *N*-unsubstituted sulfenamides with the corresponding amines.[9] In the current study, *N*-containing heterocycles were used as amines, and *N*-sulfenyl heterocycles were synthesized by the transamination of *N*-unsubstituted sulfenamides.

2. Results and discussion

Our first synthesis was an *N*-sulfenylimidazole. Ethyl 2-sulfenamoylbenzoate (**1a**) was treated with imidazole in toluene at 100 °C for 5 h according to the reported transamination procedure.[9] Formation of the desired *N*-[(2-ethoxycarbonylbenzene)sulfenyl]imidazole (**2a**) was confirmed by NMR spectrum after isolation by column chromatography. This product was a viscous liquid that was difficult to isolate in pure form. Furthermore, **2a** decomposed to diethyl 2,2′-dithiodibenzoate during storage. It was reported that sulfenylation of imidazoles with aromatic sulfenyl chlorides produced exclusively diaryl disulfides, and *N*-sulfenylimidazoles were not synthesized by sulfenylation.[10] However, *N*-sulfenylbenzimidazoles were prepared by the reaction of benzimidazole with sulfenyl chlorides in the usual manner.[11] For these reasons, *N*-[(2-ethoxycarbonylbenzene)sulfenyl]benzimidazoles (rather than the obtained *N*-sulfenylimidazole (**2a**)) were the next targets for synthesis.

After the mixture of benzimidazole and ethyl 2-sulfenamoylbenzoate (**1a**) was heated at 100 °C for 5 h, a stable solid

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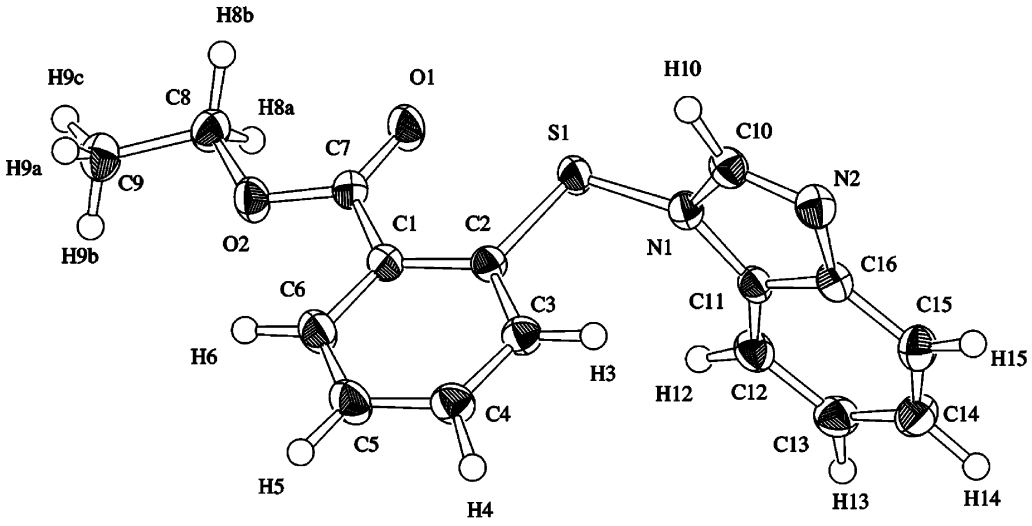


Figure 1. Crystal structure of **2b**.

compound was isolated from the reaction mixture by column chromatography. Spectral data and elemental analysis showed the structure of the product to be consistent with that of *N*-[(2-ethoxycarbonylbenzene)sulfenyl]benzimidazole (**2b**). A single crystal of this compound was obtained, and the structure of the product was confirmed by X-ray crystal analysis (Fig. 1). In the ^{1}H NMR spectrum, the absorption of one aromatic proton was observed in high field, δ 6.10 ppm. X-ray crystal analytical data showed that the 3-H on the benzene ring was located over the benzimidazole ring, causing the high field shift observed in the ^{1}H NMR spectrum.

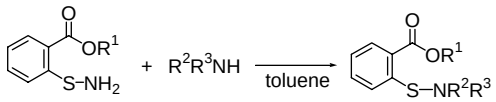
Various *N*-containing heterocycles were treated with the sulfenamides to synthesize *N*-sulfenyl heterocycles; the results are summarized in Table 1. Benzazoles produced high yields of *N*-sulfenyl substituted benzazoles. However, the yield of *N*-sulfenylphthalimide (**2h**) was only 37% (entry 9). The ^{1}H NMR spectra of all the products showed characteristic aromatic proton shift to the high field. In the reaction of methyl 2-sulfenamoylbenzoate (**1b**) at 100 °C, intramolecular cyclization occurred and 1,2-benzisothiazolin-3-one was formed.[12] Therefore, the yields of *N*-sulfenyl heterocycles decreased and *N*-[(2-methoxycarbonylbenzene)-sulfenyl]-1,2-benzisothiazolin-3-one (**2l**) was formed as a by-product with a 17% yield (footnote to entry 3). The yield of **2c** was increased by lowering the reaction temperature to 80 °C (entry 4). 3,5-Dimethylpyrazole produced a stable *N*-sulfenylated product (**2i**) with a high yield (entries 10 and 11), but imidazole produced an unstable product.

To evaluate the utility of sulfenylating reagents in the preparation of *N*-sulfenyl heterocycles, substitution reactions with anilines as nucleophiles were carried out. When *N*-sulfenylbenzimidazole (**2b**) was refluxed with *p*-methylaniline in methanol for 3 h, substitution occurred on the sulfur atom, and *N*-substituted sulfenamide (**4a**) (95% yield) and benzimidazole (96% yield) were isolated. Reactions of the *N*-sulfenyl heterocycles with anilines were carried out under the same conditions; the results are summarized in Table 2. Because *N*-sulfenylimidazole (**2a**) was difficult to handle (see above), the reactions of **2a** were carried out without isolation of **2a** (entry 1). The yields were calculated based on the sulfenamide (**1a**). As reported previously, transamination of sulfenamides (**1**) occurred when they were heated in the presence of anilines.[9] *N*-Substituted sulfenamides could be synthesized in the reaction of **1a** with anilines under methanol refluxing conditions, but the yields were higher when *N*-sulfenyl heterocycles (**2**) were used.

p-Methylaniline produced high yields of **3a** except for the reactions of **2f** and **2h** (entries 6 and 9). It was reported that the reaction of *N*-sulfenylphthalimides with amines gave open-ring products[13] or sulfenamide derivatives.[14] However, the reaction of **2h** with *p*-methylaniline did not proceed and unreacted **2h** was recovered (entry 6). Although *N*-sulfenylphthalimides had been used as sulfenyl reagents, the yield of **2h** and its reactivity with anilines were low. These results indicate that **2h** is not a suitable sulfenylating reagent. The yields of sulfenamide (**3**) decreased when anilines with electron-withdrawing groups were used. It was shown that the rate of these substitution reactions correlated to the nucleophilicity of anilines. *p*-Cyanophenyl substituted sulfenamide (**3d**) was obtained only when using benzimidazole (**2b**), benzotriazole (**2d**), or 3,5-dimethylpyrazole (**2i**) as the starting material. When substituted anilines with electron-withdrawing groups were employed, the solvent reacted with **2** to form a methyl sulfenate derivative (**4**). From these results, it appears that *N*-sulfenylbenzimidazole (**2b**), with its high yield in preparation, stable crystalline structure, and high reactivity with anilines, was the most effective compound for sulfenylation among the compounds prepared.

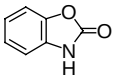
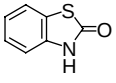
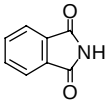
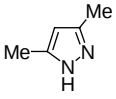
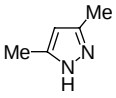
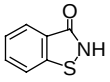
Various *N*-sulfenylbenzimidazoles were synthesized; the results are listed in Table 3. The reaction of (*o*-substituted benzene)sulfenamides with benzimidazole gave *N*-sulfenylbenzimidazoles in good yields. However, (*o*-unsubstituted benzene)sulfenylbenzimidazoles were not synthesized by transamination of sulfenamides. Unsubstituted sulfenamides are usually less stable, and a few could be isolated as stable substances, which are heterocyclic, electron-withdrawing group substituted aromatic, triphenylmethyl,

Table 1. Synthesis of *N*-sulfenyl heterocycles[a]

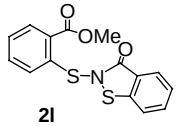


1a: R^1=Et
1b: R^1=Me

2

Entry	**1**	R^2R^3NH	Temperature (°C)	Time (h)	Product	Yield (%)[b]
1	**1a**		100	5	**2a**	51
2	**1a**		100	5	**2b**	92
3[c]	**1b**		100	5	**2c**	54
4	**1b**		80	10	**2c**	78
5	**1a**		100	5	**2d**	95
6	**1a**		100	8	**2e**	78
7	**1a**		100	5	**2f**	73
8	**1a**		100	10	**2g**	77
9	**1a**		100	5	**2h**	37
10	**1a**		100	5	**2i**	90
11	**1b**		80	6	**2j**	50
12[6]	**1a**		100	5	**2k**	66

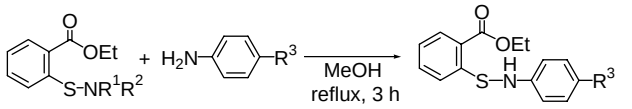
[a] Compound **1**, 2.0 mmol; heterocycles, 2.2 mmol; toluene, 20 mL.
[b] Isolated product.
[c] Compound **2l** was isolated in 17% yield.



2l

and polyhalogenized alkyl sulfenamides as shown in a review.[15] Therefore, it was necessary for transamination reactions under heating conditions to possess such substituents; otherwise unsubstituted sulfenamides, such as benzenesulfenamide or *p*-methylbenzenesulfenamide, decomposed to the corresponding disulfides. Furthermore, *N*-(*p*-ethoxycarbonylbenzene)sulfenyl- and *N*-(*p*-nitrobenzene)sulfenylbenzimidazoles were not prepared. It was reported that nucleophilic attack by the benzimidazole nitrogen of *N*-sulfenylbenzimidazoles occurred on the sulfenyl sulfur atom of another sulfenamide molecule.[11b] It seems that *o*-substituents on the benzenesulfenamide

Table 2. Reaction of *N*-sulfenyl heterocycles with substituted anilines[a]

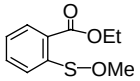


1, **2**

3a: R^3 = Me; **3b**: R^3 = H
3c: R^3 = Cl; **3d**: R^3 = CN

Entry	**1** or **2**	Yield of **3** (%)[b]			
		3a	**3b**	**3c**	**3d**
1[c]	**2a**	86	71	69	5
2	**2b**	95	89	81	43
3	**2d**	98	92	64 (21)	39 (5)
4	**2f**	39			
5	**2g**	80 (11)	48 (17)	7 (38)	0 (32)
6	**2h**	0			
7	**2i**	89	76	35	25
8	**2k**	93	89	12	0 (5)
9	**1a**	69 (12)	26 (12)	8 (11)	0

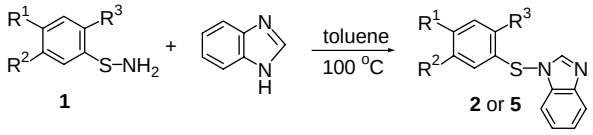
[a] Compound **1** or **2**, 0.35 mmol; aniline 0.5 mmol; MeOH, 7 mL; reflux; 3 h.
[b] Isolated product. The yields in the parentheses show those of methyl (2-ethoxycarbonylbenzene)sulfenate (**4**).



4

[c] Compound **2a** was not isolated. The yields were calculated based on **1a**.

Table 3. Synthesis of *N*-sulfenylbenzimidazoles[a]



1 **2** or **5**

Entry	Sulfenamide	R^1	R^2	R^3	Time (h)	*N*-Sulfenyl-benzimidazole	Yield (%)[b]
1	**1a**	H	H	CO_2Et	5	**2b**	92
2	**1b**	H	H	CO_2Me	5	**2c**	54
3	**1c**	H	H	CO_2Pr^i	5	**5a**	91
4	**1d**	H	Cl	CO_2Et	10	**5b**	34
5	**1e**	Cl	H	CO_2Et	14	**5c**	63
6	**1f**	MeO	MeO	CO_2Et	11	**5d**	79
7	**1g**	H	H	NO_2	6	**5e**	50

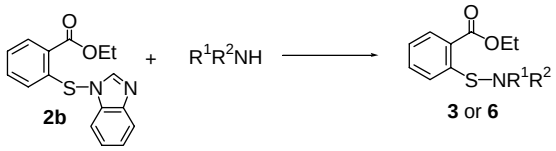
[a] Compound **1**, 2.0 mmol; benzimidazole, 2.0 mmol; toluene, 20 mL.
[b] Isolated product.

hindered the attack by the benzimidazole nitrogen and *N*-sulfenylbenzimidazoles were isolated in good yield. As a result, *o*-substituents on the benzene ring stabilized the unsubstituted sulfenamides during transamination as well as the formed *N*-sulfenylbenzimidazoles. Moreover, *o*-substituents were suitable for the following heterocyclic compound synthesis.[4,12]

Sulfenylation of amines were carried out using *N*-sulfenylbenzimidazole (**2b**); the results are shown in Table 4. First, the reactions of **2b** with primary amines were carried out. The yield of *p*-cyanophenyl substituted sulfenamide (**3d**) increased to 70% by longer reaction time (entry 1) although the yield of **2d** was 43% for 3 h (Table 2, entry 2). Benzylamine reacted with **2b** in good yields under the conditions of methanol reflux for 1.5 h or room temperature for 24 h (entries 2 and 3). Although cyclohexylamine and *t*-butylamine afforded sulfenamides **6b** and **6c** in good yields, respectively, cumylamine gave sulfenamide **6d** in 46% yield but methyl sulfenate **4** was obtained in 28% yield as a by-product under the conditions of methanol reflux for 3 h (entry 6). Therefore, the reaction was carried out in toluene at 100 °C to prevent formation of **4**, and **6d** was obtained in 83% yield (entry 7). The reactions of **2b** with secondary amines afforded *N*,*N*-disubstituted sulfenamides in good yields (entries 7–9). However, it took long reaction time for the reaction with *N*-methylaniline to obtain *N*-methyl-*N*-phenylsulfenamide (**6h**) (entry 11), and diphenylamine did not react with **2b** due to weak nuceophilicity.

Although the sulfenylation of *p*-chloroaniline with *N*-unsubstituted sulfenamide **1a** was very slow, that of benzimidazole produced a high yield of **2b**. Therefore, the synthesis of *N*-chlorophenyl substituted sulfenamide (**3c**) by the sulfenylation with *N*-sulfenyl heterocycles that formed

Table 4. Reaction of *N*-sulfenylbenzimidazole (**2b**) with amines[a]

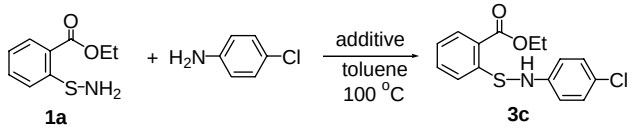


Entry	R^1	R^2	Solvent	Temperature (°C)	Time (h)	Product	Yield (%)[b]
1	*p*-NCC_6H_4	H	MeOH	Reflux	7	**3d**	70
2	$PhCH_2$	H	MeOH	rt	24	**6a**	88
3	$PhCH_2$	H	MeOH	Reflux	1.5	**6a**	86
4	Cyclohexyl	H	MeOH	Reflux	2	**6b**	94
5	*t*-Bu	H	MeOH	70[c]	3	**6c**	79
6	$PhMe_2C$	H	MeOH	Reflux	3	**6d**	46
7	$PhMe_2C$	H	Toluene	100	4.5	**6d**	83
8	Et	Et	MeOH	70[c]	3	**6e**	79
9	$–(CH_2)_4–$		Toluene	100	3	**6f**	86
10	$–(CH_2)_2–O–(CH_2)_2–$		Toluene	100[c]	5	**6g**	95
11	Ph	Me	Toluene	100	20	**6h**	81

[a] *N*-Sulfenylbenzimidazole (**2b**), 0.5 mmol; amine 0.6 mmol; solvent 10 mL.
[b] Isolated product.
[c] In a sealed tube.

in situ was attempted. The results are listed in Table 5. The reaction of **1a** with *p*-chloroaniline produced **3c** with only 6% yield after heating in toluene for 10 h (entry 1). When an equivalent amount of benzimidazole was added to this reaction system, the yield of **3c** increased to 68% (entry 2). *N*-Sulfenylbenzimidazole (**2b**) was formed in situ, and *p*-chloroaniline reacted with **2b** to give the product. Since intermediary *N*-sulfenyl heterocycles were not isolated, imidazole could be used as an additive, and **3c** was obtained with a yield of 75% (entry 5). Addition of 1-methylimidazole also accelerated the formation of **3c** (entry 7). After the reaction of *N*-sulfenyl heterocycles with anilines, the heterocycles were regenerated as leaving groups. Therefore, a catalytic amount of heterocycle was enough to accelerate the reactions (entries 3 and 6).

Table 5. Reaction of sulfenamide (**1a**) with *p*-chloroaniline in the presence of an additive[a]



Entry	Additive	Equiv	Time (h)	Yield (%)[b]
1	—	—	10	6
2	Benzimidazole	1.0	10	68
3	Benzimidazole	0.1	10	19
4	Imidazole	1.0	5	22
5	Imidazole	1.0	12	75
6	Imidazole	0.1	10	52
7	1-Methylimidazole	1.0	10	39

[a] Sulfenamide (**1a**), 0.5 mmol; *p*-chloroaniline 0.6 mmol; toluene 10 mL.
[b] Isolated product.

3. Conclusion

N-Containing heterocycles reacted with 2-sulfenamoylbenzoates when heated to produce high yields of *N*-(2-alkoxycarbonylbenzene)sulfenyl heterocycles. The reactivity of the *N*-sulfenyl heterocycles with substituted anilines was compared; *N*-sulfenylbenzimidazoles produced better yields of *N*-sulfenylanilines than did other heterocycles. Various kinds of *N*-substituted sulfenamides were synthesized by the reaction of *N*-sulfenylbenzimidazoles with amines. In the sulfenylation of anilines with 2-sulfenylbenzoates, the yields of sulfenamides improved by adding heterocycles to the reaction system.

4. Experimental

4.1. General

Melting points were determined on a Mettler FP90 microscopic plate and are uncorrected. ^1H and ^{13}C NMR spectra were obtained with a JEOL LA-500 spectrometer, and chemical shifts (δ) are reported in parts per million relative to internal tetramethylsilane and $CDCl_3$, respectively. IR spectra were recorded on a JASCO FT IR-5300 spectrophotometer. Silica gel column chromatography was carried out on Merck silica gel 60 (0.063–0.200 mm). Elemental analysis was performed by the Analytical Center at the National Institute of Advanced Industrial Science and Technology. Sulfenamides (**1**) were prepared by the method described in our previous paper.[12]

4.2. General procedure for the synthesis of *N*-sulfenyl heterocycles

To a solution of **1** (2.0 mmol) in toluene (20 mL) was added a heterocycle (2.2 mmol), and the reaction was carried out under the conditions described in Table 1. The solvent was then evaporated, and a crude reaction mixture was chromatographed on silica gel with appropriate eluent.

4.2.1. *N*-[(2-Ethoxycarbonylbenzene)sulfenyl]imidazole (2a). Oil; $R_f=0.5$ (CH_2Cl_2/ethyl acetate=1:1); ^1H NMR (500 MHz, $CDCl_3$): δ 1.45 (3H, t, $J=7.0$ Hz), 4.46 (2H, q, $J=7.0$ Hz), 6.11 (1H, d, $J=7.6$ Hz), 7.08 (1H, t, $J=1.2$ Hz), 7.22–7.28 (2H, m), 7.39 (1H, td, $J=7.6$, 1.2 Hz),

7.67 (1H, s), 8.07 (1H, dd, J=7.6, 1.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.2, 62.0, 121.6, 123.6, 125.0, 125.4, 130.6, 131.1, 133.9, 143.2, 145.5, 167.1; IR (KBr): ν_{max} 2983, 1688, 1463, 1280, 1156, 1057, 743 cm^{-1}; HRMS: Calcd for $C_{12}H_{12}N_2O_2S$: 248.0619. Found: 248.0597.

4.2.2. *N*-[(2-Ethoxycarbonylbenzene)sulfenyl]benzimidazole (2b). Mp 136.8–138.0 °C (from ethyl acetate–hexane); R_f=0.3 (CH_2Cl_2/ethyl acetate=20:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 (3H, t, J=7.3 Hz), 4.50 (2H, q, J=7.3 Hz), 6.10 (1H, d, J=7.9 Hz), 7.20–7.27 (2H, m), 7.34 (1H, t, J=7.6 Hz), 7.37 (1H, t, J=7.6 Hz), 7.51 (1H, d, J=7.9 Hz), 7.90 (1H, d, J=7.6 Hz), 8.03 (1H, s), 8.11 (1H, d, J=7.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3, 62.1, 111.0, 120.8, 121.8, 123.5, 124.2, 124.5, 125.5, 131.0, 133.8, 136.2, 143.9, 144.3, 148.3, 167.2; IR (KBr): ν_{max} 1692, 1146, 748 cm^{-1}. Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39. Found: C, 64.55; H, 4.67; N, 9.15.

4.2.3. *N*-[(2-Methoxycarbonylbenzene)sulfenyl]benzimidazole (2c). Mp 167.2–169.2 °C (from ethyl acetate–hexane); R_f=0.5 (CH_2Cl_2/ethyl acetate=10:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.04 (3H, s), 6.11 (1H, dd, J=8.2, 1.2 Hz), 7.21–7.29 (2H, m), 7.33–7.40 (2H, m), 7.51 (1H, dd, J=7.2, 0.9 Hz), 7.90 (1H, dt, J=7.9, 0.9 Hz), 8.04 (1H, s), 8.09 (1H, dd, J=7.9, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 52.9, 111.0, 120.8, 121.9, 123.5, 123.8, 124.5, 125.5, 131.0, 133.9, 136.2, 143.9, 144.3, 148.3, 167.6; IR (KBr): ν_{max} 1698, 1433, 1300, 1142, 748 cm^{-1}. Anal. Calcd for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85. Found: C, 63.26; H, 4.15; N, 9.66.

4.2.4. *N*-[(2-Ethoxycarbonylbenzene)sulfenyl]benzotriazole (2d). Mp 152.0–154.0 °C (from ethyl acetate–hexane); R_f=0.5 (CH_2Cl_2/ethyl acetate=100:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.49 (3H, t, J=7.3 Hz), 4.50 (2H, q, J=7.3 Hz), 5.85–5.87 (1H, m), 7.21–7.26 (2H, m), 7.47 (1H, ddd, J=8.2, 7.0, 0.9 Hz), 7.55 (1H, ddd, J=7.9, 7.0, 0.9 Hz), 7.63 (1H, dt, J=8.2, 0.9 Hz), 8.09–8.11 (1H, m), 8.19 (1H, dt, J=8.2, 0.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.4, 62.3, 110.5, 120.5, 122.1, 124.2, 124.8, 125.7, 128.9, 130.8, 133.8, 137.2, 143.6, 145.9, 167.4; IR (KBr): ν_{max} 1687, 1300, 1007, 748 cm^{-1}. Anal. Calcd for $C_{15}H_{13}N_3O_2S$: C, 60.18; H, 4.38; N, 14.04. Found: C, 60.18; H, 4.28; N, 13.82.

4.2.5. *N*-[(2-Ethoxycarbonylbenzene)sulfenyl]benzoxazol-2-one (2e). Mp 166.5–168.3 °C (from ethyl acetate–hexane); R_f=0.5 (CH_2Cl_2/ethyl acetate=100:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45 (3H, t, J=7.2 Hz), 4.47 (2H, q, J=7.2 Hz), 6.82 (1H, dd, J=8.2, 0.6 Hz), 7.17–7.25 (5H, m), 7.40–7.43 (1H, m), 8.10 (1H, dd, J=7.8, 1.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.2, 62.1, 110.4, 110.5, 121.4, 123.9, 124.4, 124.8, 125.5, 131.2, 132.3, 133.6, 141.8, 143.2, 155.2, 167.1; IR (KBr): ν_{max} 1793, 1684, 1474, 1274, 750 cm^{-1}. Anal. Calcd for $C_{16}H_{13}NO_4S$: C, 60.94, H, 4.16, N, 4.44. Found: C, 60.89; H, 4.13; N, 4.32.

4.2.6. *N*-[(2-Ethoxycarbonylbenzene)sulfenyl]benzothiazol-2-one (2f). Mp 138.8–139.5 °C (from ethyl acetate–hexane); R_f=0.7 (CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45 (3H, t, J=7.0 Hz), 4.47 (2H, q, J=7.0 Hz), 6.70 (1H, dd, J=8.2, 0.6 Hz), 7.21–7.29 (3H, m), 7.35–7.40 (2H, m), 7.48 (1H, dd, J=7.6, 1.5 Hz), 8.10 (1H, dd, J=7.9, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3, 62.1, 113.3, 121.7, 122.8, 123.0, 124.7, 125.0, 125.4, 126.9, 131.3, 133.7, 137.9, 141.9, 167.2, 171.4; IR (KBr): ν_{max} 1701, 1458, 1281, 1138, 747 cm^{-1}. Anal. Calcd for $C_{16}H_{13}NO_3S_2$: C, 57.99; H, 3.95; N, 4.23. Found: C, 57.99; H, 3.85; N, 4.15.

4.2.7. *N*-[(2-Ethoxycarbonylbenzene)sulfenyl]-2,1-benzisothiazoline-3-one (2g). Mp 160.8–161.8 °C (from ethyl acetate–hexane); R_f=0.6 (CH_2Cl_2/ethyl acetate=100:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45 (3H, t, J=7.3 Hz), 4.46 (2H, q, J=7.3 Hz), 6.84 (1H, dd, J=8.2, 0.6 Hz), 7.16 (1H, ddd, J=7.9, 6.7, 1.2 Hz), 7.26 (1H, ddd, J=7.9, 7.3, 0.6 Hz), 7.42 (1H, ddd, J=8.2, 7.3, 1.2 Hz), 7.54 (1H, dd, J=6.7, 1.5 Hz), 7.57 (1H, ddd, J=7.9, 7.3, 1.5 Hz), 7.89 (1H, dd, J=7.3, 1.2 Hz), 8.10 (1H, dd, J=7.9, 1.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3, 62.0, 113.6, 121.5, 121.9, 122.9, 123.8, 124.6, 125.5, 131.2, 133.6, 134.6, 144.6, 155.3, 167.0, 190.0; IR (KBr): ν_{max} 1682, 1601, 1468, 1312, 1154, 941, 897, 743 cm^{-1}. Anal. Calcd for $C_{16}H_{13}NO_3S_2$: C, 57.99; H, 3.95; N, 4.23. Found: C, 58.32; H, 3.78; N, 4.11.

4.2.8. *N*-[(2-Ethoxycarbonylbenzene)sulfenyl]phthalimide (2h). Mp 228.0–229.0 °C (from ethyl acetate); R_f=0.6 (CH_2Cl_2/ethyl acetate=10:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.44 (3H, t, J=7.3 Hz), 4.46 (2H, q, J=7.3 Hz), 6.87 (1H, dd, J=8.2, 0.9 Hz), 7.22 (1H, td, J=7.9, 1.2 Hz), 7.39 (1H, ddd, J=8.2, 7.3, 1.5 Hz), 7.85–7.86 (2H, m), 8.02–8.02 (2H, m), 8.08 (1H, dd, J=7.9, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3, 61.9, 121.5, 124.2, 125.1, 125.2, 131.2, 132.2, 133.3, 134.9, 142.6, 166.9, 168.1; IR (KBr): ν_{max} 1740, 1688, 1273, 1046, 748, 711 cm^{-1}. Anal. Calcd for $C_{17}H_{13}NO_4S$: C, 62.37; H, 4.00; N, 4.28. Found: C, 62.41; H, 3.84; N, 4.28.

4.2.9. *N*-[(2-Ethoxycarbonylbenzene)sulfenyl]-3,5-dimethylpyrazole (2i). Mp 95.2–96.2 °C (from hexane); R_f=0.6 (CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.43 (3H, t, J=7.2 Hz), 2.26 (3H, s), 2.30 (3H, s), 4.44 (2H, q, J=7.2 Hz), 6.04 (1H, dd, J=8.2, 0.9 Hz), 6.06 (1H, s), 7.19 (1H, td, J=7.9, 0.9 Hz), 7.36 (1H, ddd, J=8.2, 7.3, 1.4 Hz), 8.04 (1H, dd, J=7.9, 1.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.7, 14.0, 14.3, 61.8, 107.5, 122.4, 123.9, 125.0, 130.7, 133.6, 146.4, 147.6, 152.4, 166.8; IR (KBr): ν_{max} 1686, 1562, 1462, 1294, 743 cm^{-1}. Anal. Calcd for $C_{14}H_{16}N_2O_2S$: C, 60.85; H, 5.84; N, 10.14. Found: C, 60.95; H, 5.79; 10.10.

4.2.10. *N*-[(2-Methoxycarbonylbenzene)sulfenyl]-3,5-dimethylpyrazole (2j). Mp 91.8–93.2 °C (from hexane); R_f=0.5 (CH_2Cl_2/ethyl acetate=10:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.26 (3H, s), 2.30 (3H, s), 3.98 (3H, s), 6.04 (1H, dd, J=8.2, 0.9 Hz), 6.07 (1H, s), 7.19 (1H, ddd, J=7.8, 7.3, 0.9 Hz), 7.37 (1H, ddd, J=8.2, 7.3, 1.5 Hz), 8.02 (1H, dd, J=7.8, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.7, 14.0, 52.6, 103.2, 107.6, 122.4, 123.5, 125.0, 130.7, 133.7, 146.5, 147.5, 152.4, 161.1, 167.2; IR (KBr): ν_{max} 1695, 1564, 1462, 1437, 1278, 790, 752 cm^{-1}. Anal. Calcd for $C_{13}H_{14}N_2O_2S$: C, 59.52; H, 5.38; N, 10.68. Found: C, 59.61; H, 5.30; N, 10.34.

4.2.11. *N*-[(2-Methoxycarbonylbenzene)sulfenyl]-1,2-benzisothiazolin-3-one (2l).[12] Mp 187.5–189 °C (from benzene–hexane); R_f=0.5 (CH_2Cl_2/ethyl acetate=20:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.98 (3H, s), 6.83 (1H, dd, J=8.2, 0.6 Hz), 7.24 (1H, td, J=7.5, 0.9 Hz), 7.40–7.47 (2H, m), 7.57 (1H, d, J=7.9 Hz), 7.71 (1H, ddd, J=8.2, 7.0, 0.9 Hz), 8.06 (1H, dd, J=7.9, 1.4 Hz), 8.13 (1H, d, J=7.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 52.7, 120.6, 122.0, 122.8, 124.4, 125.3, 125.7, 127.8, 131.0, 133.1, 133.6, 142.9, 143.4, 167.1, 167.4; IR (KBr): ν_{max} 1680, 1317, 1281, 1107, 733 cm^{-1}.

4.3. X-ray crystallographic analysis of 2b

X-ray crystallographic analysis was carried out on a Rigaku AFC7R diffractometer using a rotating anode with graphite monochromated Mo Kα radiation (λ=0.7107 Å). Crystal data for **2b**: $C_{16}H_{14}N_2O_2S$, M=298.36, monoclinic, space group $P2_1/c$ (No. 14), a=7.6501(18), b=8.0237(13), c=23.6292(10) Å, β=92.058(9)°, V=1449.5(4) Å^3, T=173(2) K, Z=4, D_{calcd}=1.367 g cm^{-3}, μ=0.229 mm^{-1}; goodness of fit=1.034; $R1$ [$I>2\sigma(I)$]=0.0335, $wR2$=0.0777 (all data).

Selected bond distances (Å) and angles (°) are shown as follows: S(1)–N(1) 1.7015(12), S(1)–C(2) 1.7863(14); O(1)–C(7) 1.2119(18), C(1)–C(7) 1.475(2); N(1)–S(1)–C(2) 100.35(6), S(1)–N(1)–C(11) 127.62(10), C(2)–C(1)–C(7) 119.38(12), S(1)–C(2)–C(3) 122.04(11), O(1)–C(7)–C(1) 123.18(13). 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 285609. 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].

4.4. General procedure for reaction of 2 with anilines

To a solution of **2** (0.35 mmol) in methanol (7 mL) was added an aniline (0.5 mmol). After 3 h of refluxing, the solvent was evaporated and a crude reaction mixture was chromatographed on silica gel with dichloromethane or dichloromethane–hexane (2/1). The structures of products **3a** and **3b** were identical to those of the compounds that we previously reported.[4,9]

4.4.1. Ethyl *N*-(*p*-chlorophenyl)-2-sulfenamoylbenzoate (3c). Mp 110.0–110.7 °C (from ethyl acetate–hexane); R_f=0.5 (CH_2Cl_2/hexane=2:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.43 (3H, t, J=7.3 Hz), 4.42 (2H, q, J=7.0 Hz), 5.09 (1H, s), 6.90–6.93 (2H, m), 7.14–7.20 (3H, m), 7.42–7.43 (2H, m), 8.07 (1H, dt, J=7.6, 0.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3, 61.5, 115.7, 122.3, 124.4, 124.6, 125.1, 129.2, 131.3, 132.9, 145.0, 147.4, 166.7; IR (KBr): ν_{max} 3355, 1684, 1493, 1271, 1144, 1101, 820, 745 cm^{-1}. Anal. Calcd for $C_{15}H_{14}ClNO_2S$: C, 58.53; H, 4.58; N, 4.55. Found: C, 58.51; H, 4.52; N, 4.46.

4.4.2. Ethyl *N*-(*p*-cyanophenyl)-2-sulfenamoylbenzoate (3d). Mp 148.0–149.5 °C (from ethyl acetate–hexane); R_f=0.5 (CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.44 (3H, t, J=7.3 Hz), 4.43 (2H, q, J=7.3 Hz), 5.49 (1H, s), 7.03 (2H, dd, J=7.0, 2.1 Hz), 7.22 (1H, td, J=7.5, 1.2 Hz), 7.34 (1H, d, J=7.5 Hz), 7.44 (1H, td, J=7.5, 1.5 Hz), 7.49 (2H, dd, J=7.0, 2.1 Hz), 8.09 (1H, td, J=7.9, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3, 61.6, 103.0, 114.9, 119.6, 122.0, 124.7, 124.8, 131.4, 133.1, 133.8, 146.1, 150.6, 166.8; IR (KBr): ν_{max} 3322, 2220, 1688, 1603, 1507, 1462, 1277, 1146, 895, 831, 745 cm^{-1}. Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39. Found: C, 64.23; H, 4.65; N, 9.39.

4.4.3. Methyl (2-ethoxycarbonylbenzene)sulfenate (4). Bp 150 °C (13.3 Pa); R_f=0.4 (CH_2Cl_2/hexane=1:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.39 (3H, t, J=7.2 Hz), 3.79 (3H, s), 4.39 (2H, q, J=7.2 Hz), 7.17–7.20 (1H, m), 7.59–7.61 (2H, m), 8.02 (1H, d, J=7.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3, 61.6, 64.2, 119.9, 121.8, 123.6, 130.5, 133.1, 149.2, 167.0; IR (neat): ν_{max} 2981, 1685, 1460, 1280, 989, 743, 692 cm^{-1}. Anal. Calcd for $C_{10}H_{12}O_3S$: C, 56.58; H, 5.70. Found: C, 56.57; H, 5.71.

4.5. General procedure for the synthesis of *N*-sulfenylbenzimidazoles

To a solution of a sulfenamide (2.0 mmol) in toluene (20 mL) was added benzimidazole (2.2 mmol), and the reaction was carried out under the conditions described in Table 3. The solvent was then evaporated, and a crude reaction mixture was chromatographed on silica gel with appropriate eluent.

4.5.1. *N*-[(2-Isopropoxycarbonylbenzene)sulfenyl]benzimidazole (5a). Mp 113.5–115.0 °C (from hexane); R_f=0.5 (ethyl acetate/hexane=1:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45 (6H, d, J=6.1 Hz), 5.36 (1H, hept, J=6.1 Hz), 6.09 (1H, dd, J=8.2, 0.9 Hz), 7.20–7.27 (2H, m), 7.33–7.39 (2H, m), 7.52 (1H, dd, J=7.8, 1.5 Hz), 7.90 (1H, dd, J=7.1, 1.5 Hz), 8.03 (1H, s), 8.09 (1H, dd, J=7.6, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.0, 70.0, 111.0, 120.8, 121.8, 123.5, 124.4, 124.6, 125.4, 131.0, 133.7, 136.2, 144.0, 144.1, 148.3, 166.8; IR (KBr): ν_{max} 1696, 1296, 1177, 1101, 741 cm^{-1}. Anal. Calcd for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.16; N, 8.97. Found: C, 65.22; H, 5.07; N, 8.99.

4.5.2. *N*-[(4-Chloro-2-ethoxycarbonylbenzene)sulfenyl]-benzimidazole (5b). Mp 145.7–146.7 °C (from ethyl acetate–hexane); R_f=0.4 (CH_2Cl_2/acetone=20:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.47 (3H, t, J=7.0 Hz), 4.49 (2H, q, J=7.0 Hz), 6.12 (1H, d, J=1.8 Hz), 7.17 (1H, dd, J=8.5, 1.8 Hz), 7.38 (2H, m), 7.51 (1H, dd, J=8.8, 1.5 Hz), 7.91 (1H, dd, J=8.5, 1.5 Hz), 8.02 (1H, d, J=8.2 Hz), 8.03 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3, 62.4, 110.8, 121.0, 121.8, 122.6, 123.7, 124.7, 126.0, 132.1, 135.9, 140.9, 143.9, 146.3, 147.9, 166.5; IR (KBr): ν_{max} 1696, 1580, 1443, 1273, 1098, 747 cm^{-1}. Anal. Calcd for $C_{16}H_{13}ClN_2O_2S$: C, 57.74; H, 3.94; N, 8.42. Found: C, 57.82; H, 3.71; N, 8.31.

4.5.3. *N*-[(5-Chloro-2-ethoxycarbonylbenzene)sulfenyl]-benzimidazole (5c). Mp 128.4–129.4 °C (from ethyl acetate–hexane); R_f=0.4 (CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 (3H, t, J=7.0 Hz), 4.50 (2H, q, J=7.0 Hz), 6.02 (1H, d, J=8.8 Hz), 7.21 (1H, dd, J=8.8, 2.4 Hz), 7.33–7.40 (2H, m), 7.48 (1H, dd, J=7.6, 1.5 Hz), 7.90 (1H, dd, J=7.9, 1.5 Hz), 8.02 (1H, s), 8.07 (1H, d, J=2.4 Hz);

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3, 62.6, 110.9, 120.9, 123.3, 123.7, 124.6, 125.3, 130.7, 131.7, 133.7, 136.0, 142.7, 143.9, 148.1, 166.2; IR (KBr): ν_{max} 1694, 1443, 1310, 1250, 1169, 1128, 1040, 737 cm^{-1}. Anal. Calcd for $C_{16}H_{13}ClN_2O_2S$: C, 57.74; H, 3.94; N, 8.42. Found: C, 57.90; H, 3.85; N, 8.25.

4.5.4. *N*-[(4,5-Dimethoxy-2-ethoxycarbonylbenzene)-sulfenyl]benzimidazole (5d). Mp 161.7–163.7 °C (from ethyl acetate–hexane); R_f=0.4 (CH_2Cl_2/acetone/methanol=100:10:2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 (3H, t, J=7.0 Hz), 3.20 (3H, s), 3.89 (3H, s), 4.48 (2H, q, J=7.0 Hz), 5.31 (1H, s), 7.33–7.37 (2H, m), 7.50 (1H, s), 7.53 (1H, d, J=5.2 Hz), 7.88 (1H, d, J=5.2 Hz), 8.07 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.5, 55.5, 56.2, 61.9, 104.1, 111.2, 112.6, 115.9, 120.7, 123.5, 124.5, 136.2, 137.8, 143.8, 148.6, 153.9, 166.9; IR (KBr): ν_{max} 1672, 1508, 1476, 1443, 1292, 1211, 1179, 1020, 737 cm^{-1}. Anal. Calcd for $C_{18}H_{18}N_2O_4S$: C, 60.32; H, 5.06; N, 7.82. Found: C, 60.36; H, 4.95; N, 7.66.

4.5.5. *N*-[(2-Nitrobenzene)sulfenyl]benzimidazole (5e). Mp 167.0–168.8 °C (from ethyl acetate) (lit.,[16] 164.5–165 °C); R_f=0.2 (CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.23 (1H, dd, J=8.2, 1.2 Hz), 7.35–7.44 (4H, m), 7.50 (1H, dd, J=7.2, 1.2 Hz), 7.92 (1H, dd, J=7.2, 1.2 Hz), 8.06 (1H, s), 8.39 (1H, dd, J=8.1, 1.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 110.5, 120.8, 123.1, 123.7, 124.6, 125.6, 126.4, 135.0, 135.4, 139.7, 142.1, 143.6, 147.4; IR (KBr): ν_{max} 3064, 1590, 1566, 1514, 1447, 1332, 1310, 1260, 1173, 1146, 738 cm^{-1}.

4.6. General procedure for reaction of 2a with amines

To a solution of **2a** (0.5 mmol) in methanol (10 mL) was added an aniline (0.6 mmol). The reaction was carried out under the conditions described in Table 4. The solvent was then evaporated, and a crude reaction mixture was chromatographed on silica gel with appropriate eluent. The structures of products **6a**, **6c**, **6d**, **6e**, **6f**, and **6g** were identical to those of the compounds that we previously reported.[9]

4.6.1. Ethyl *N*-cyclohexyl-2-sulfenamoylbenzoate (6b). Mp 69.0–70.7 °C (from hexane); R_f=0.4 (CH_2Cl_2/hexane=2:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.14–1.26 (6H, m), 1.39 (3H, t, J=7.2 Hz), 1.71–1.74 (2H, m), 2.04–2.07 (2H, m), 2.53 (1H, br s), 2.71 (1H, br s), 4.37 (2H, q, J=7.2 Hz), 7.12 (1H, ddd, J=7.8, 7.0, 1.2 Hz), 7.50 (1H, ddd, J=8.2, 7.0, 1.4 Hz), 7.94 (1H, dd, J=8.2, 0.6 Hz), 8.00 (1H, dd, J=7.8, 1.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.4, 24.9, 25.9, 34.0, 59.1, 61.0, 122.9, 123.3, 124.0, 131.1, 132.2, 150.0, 166.5; IR (KBr): ν_{max} 3301, 2927, 1685, 1264, 1145, 1051, 738 cm^{-1}. Anal. Calcd for $C_{15}H_{21}NO_2S$: C, 64.48; H, 7.58; N, 5.01. Found: C, 64.48; H, 7.55; N, 4.90.

4.6.2. Ethyl *N*-methyl-*N*-phenyl-2-sulfenamoylbenzoate (6h). Mp 78.2–79.7 °C (from hexane); R_f=0.5 (CH_2Cl_2/hexane=2:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.44 (3H, t, J=7.3 Hz), 3.47 (3H, s), 4.43 (2H, q, J=7.3 Hz), 5.49 (1H, s), 7.03 (2H, dd, J=7.0, 2.1 Hz), 7.22 (1H, td, J=7.5, 1.2 Hz), 7.34 (1H, d, J=7.5 Hz), 7.44 (1H, td, J=7.5, 1.5 Hz), 7.49 (2H, dd, J=7.0, 2.1 Hz), 8.09 (1H, td, J=7.9, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.4, 43.3, 61.4, 114.6, 119.3, 122.3, 124.2, 124.4, 129.1, 131.5, 132.9, 147.3, 149.1, 166.7; IR (KBr): ν_{max} 1696, 1599, 1295, 1460, 1368, 1271, 1148, 1086, 862, 748, 691 cm^{-1}. Anal. Calcd for $C_{16}H_{17}NO_2S$: C, 66.87; H, 5.96; N, 4.87. Found: C, 66.88; H, 5.97; N, 4.87.

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Synthesis of thiazole aminophosphine oxides, aminophosphonic and aminophosphinic acids and Cu(II) binding abilities of thiazole aminophosphonic acids

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Abstract—A series of new aminophosphine oxides, aminophosphonic and aminophosphinic acids derived from thiazole was synthesized by addition of phosphine oxides or silylated phosphorus esters to the corresponding thiazole aldimines. The thiazole aldimines were obtained from 2-thiazole aldehyde and primary amines by a standard procedure. The corresponding phosphine oxides were obtained by alkylation of diethyl phosphite or ethyl phenylphosphinate with the appropriate Grignard reagents. The silylated phosphorus esters were prepared from trimethyl phosphite and from methyl- or phenylphosphinic ethyl ester by treatment with bromotrimethylsilane. The coordination ability towards Cu(II) ions are described for two obtained aminophosphonate ligands.

1. Introduction

Aminophosphonic acids, as phosphorus analogues of α-aminocarboxylic acids, are of great interest due to a significant biological activity.[1] Some of them are powerful herbicides and have found a wide commercial application, as for example, the phosphonomethylglycine (the glyphosate).[2] Some representatives of aminophosphonates have demonstrated promising enzyme inhibitory activity, as for example, HIV protease antagonists[3] and collagenase inhibitors[4] and biological activities are often related to their metal ion binding abilities.[1,5] In the last decades, an intensive synthetic work was performed in the preparation of aminophosphonates,[6] some of them being analogues of natural amino acids and others being analogues of important unnatural amino acids.[7]

To the best to our knowledge, aminophosphonates possessing a thiazole moiety are unknown. A basic difficulty in the synthesis of parent heterocyclic aminophosphonates[8] is an inapplicability of known, regular procedures for synthesis of the typical aminophosphonates. Therefore, there is a need to search for new methods, which could be more useful in preparation of heterocyclic aminophosphonates.

Recently, some heterocyclic derivatives of aminomethylphosphonic acid were prepared; for example, the furan derivatives,[8–10] imidazole and pyrazole derivatives,[11] thiophene derivatives,[12] and pyridine derivatives.[13,14] The prevailing synthetic route used in the preparation of these heterocyclic aminophosphonate derivatives was Fields' method,[15] and depended generally on addition of dialkyl phosphites to heterocyclic aldimines. This method was not suitable as a general synthetic procedure for most heterocyclic aminophosphonates, because, in some cases, decomposition of the heterocyclic moieties was observed, or, due to a cleavage of a C–P bond in the formed aminophosphonates.[13,14,16]

During the last few years, a new kind of silicon–phosphorus based reagent for synthesis of organophosphorus compounds has been developed.[17–20] Application of these reagents enabled the synthesis of heterocyclic α-aminophosphonate compounds.[18] It was found that silylated phosphorus acid esters were effective reagents for preparation of heterocyclic, fragile aminophosphonates from aldimines.[21–23]

In this paper, we wish to report the first synthesis of aminophosphonic and aminophosphinic acids derived from

Keywords: Aminophosphonic acids; Heterocyclic derivatives; Grignard reagent.
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thiazole, by exploitation of the recently described methods. We report, additionally, the synthesis of thiazole aminophosphine oxides, which are parent compounds of the thiazole aminophosphonic and aminophosphinic acids. Earlier studies have shown that aminophosphonates bearing imidazole, pyrazole or pyridine moiety were effective ligands for metal ions, especially Cu(II).[24–27] The coordination properties of thiazole phosphonate ligands using potentiometric and spectroscopic methods are also reported here.

2. Results and discussion

2.1. Synthesis of aminophosphonic and aminophosphinic acids

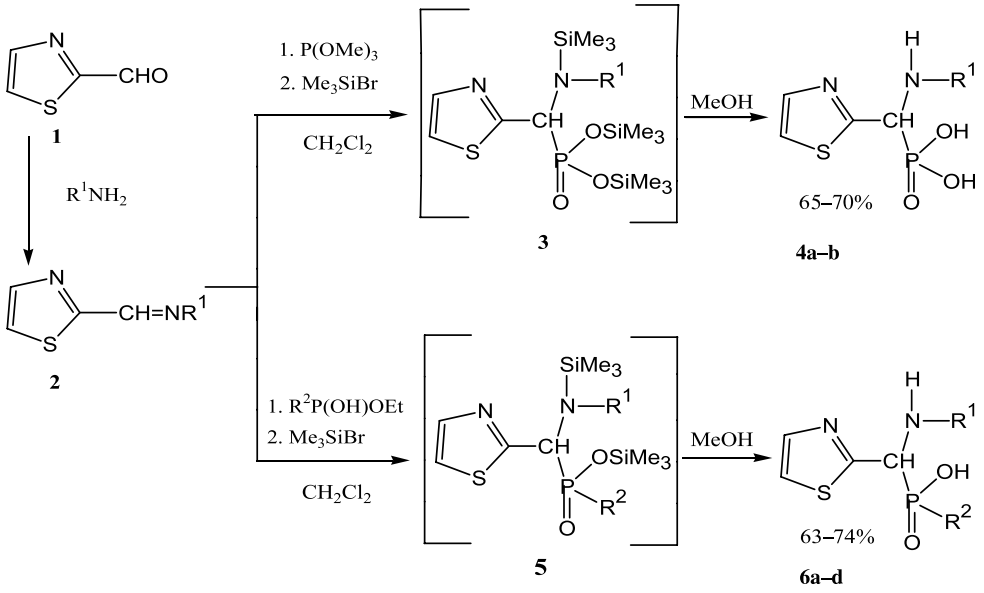
The syntheses of thiazole aminophosphonic and aminophosphinic acids are illustrated in Scheme 1. 2-Thiazole aldehyde[28] **1** reacted easily with aliphatic or aromatic primary amines in dichloromethane to give the corresponding aldimines **2**. The aldimines were reacted directly with silylated phosphorus esters to form the thiazole aminophosphonic, or aminophosphinic silylated esters **3** and **5**, as intermediates, which were then deprotected giving the thiazole aminophosphonic and aminophosphinic acids **4a**,**b** and **6a**–**d** (Scheme 1).

Silylated in situ phosphoesters used for addition to the imines were prepared from trimethyl phosphite (in the case of preparation of thiazole aminophosphonic acids) or from methyl-, or phenylphosphinate ethyl ester (in the case of preparation of thiazole aminophosphinic acids), by treatment of the corresponding phosphoesters with bromotrimethylsilane. Nucleophilic addition of the silylated phosphorus esters to imines proceeded easily at room temperature for 24 h. Formed silylated phosphonic and phosphinic intermediates, **3** and **5** (Scheme 1) were then treated with methanol, as a dealkylating agent, to give the final aminophosphonic **4a**–**b** and aminophosphinic acids **6a**–**d**.

The silylated phosphoesters were found to be good nucleophiles toward the imines. The presence of a bulky trimethylsilyl group in the formed phosphonate or phosphonite-like ester increases the power of such a nucleophile due to formation of a stable, three-coordinated phosphorus moiety with a free electron pair at phosphorus. Also, lack of the possibility of tautomerization in the formed three-coordinated, silylated phosphorus ester into less nucleophilic four-coordinated phosphonate-like ester, additionally secure a nucleophilic character of the applied reagent.

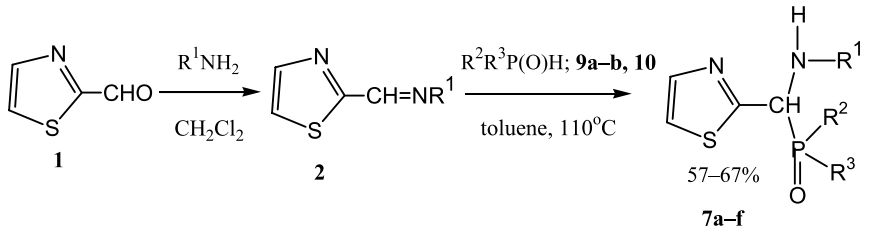
The use of bromotrimethylsilane (BrTMS) resulted in an easier silylation process of the alkyl phosphoesters, due to a higher reactivity of the BrTMS, in comparison with chlorotrimethylosilane, which is frequently used for silylation reactions.[17,18] Application of BrTMS for deprotection of phosphonate esters gave excellent results and allowed, in our case, to obtain the desired thiazole aminophosphonic and aminophosphinic acids by a direct way, in high yield and purity.

The described method presents a substantial improvement in the synthesis of heterocyclic aminophosphonic and aminophosphinic acids. After slight modifications, the present method can also be applied for synthesis of the monoalkyl esters of aminophosphonic acids, which are not easily available compounds.[22] Such a method is useful for synthesis of aminophosphonates possessing heterocyclic, fragile moieties.



4a: R^1 = *n*-Bu; **4b:** R^1 = CH_2Ph; **6a:** R^1 = *n*-Bu, R^2= Ph; **6b:** R^1 = CH_2Ph, R^2 = Ph; **6c:** R^1 = *n*-Bu, R^2 = CH_3; **6d:** R^1 = CH_2Ph, R^2 = CH_3.

Scheme 1. Synthesis of thiazole aminophosphonic and aminophosphinic acids.

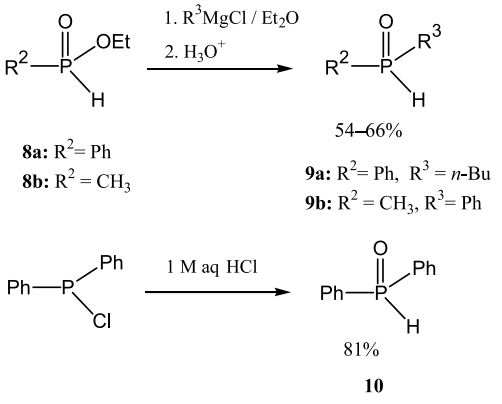


7a: R^1 = *n*-Bu, R^2= Ph, R^3 = *n*-Bu; **7b:** R^1 = CH_2Ph, R^2= Ph, R^3 = *n*-Bu
7c: R^1 = *n*-Bu, R^2 = CH_3, R^3= Ph; **7d:** R^1 = CH_2Ph, R^2 = CH_3, R^3 = Ph
7e: R^1 = *n*-Bu, R^2 = R^3 = Ph; **7f:** R^1 = CH_2Ph, R^2 = R^3 = Ph

Scheme 2. Synthesis of thiazole aminophosphine oxides.

2.2. Synthesis of thiazole aminophosphine oxides

In this paper, we describe a facile approach to new thiazole aminophosphine oxides, which are parent compounds to the thiazole aminophosphonic and aminophosphinic acids **4** and **6**. The method is based on addition of phosphinous acids (also called phosphine oxides, due to existence of such tautomeric a form) to thiazole aldimines **2**. Such addition of phosphine oxides to thiazole aldimines occurred readily in boiling toluene, to give the expected products, that is, the thiazole aminophosphine oxides **7a–f** (Scheme 2). As a result, a series of new thiazole aminophosphine oxides **7**, with varied substituents on phosphorus and nitrogen atoms, was obtained. Some of the thiazole aminophosphine oxides **7** were isolated and purified as oxalate salts. Oxalates were formed as crystalline solids when the aminophosphines **7** were treated with oxalic acid in acetone solution.



Scheme 3. Synthesis of phosphine oxides.

Phosphine oxides **9a–b** used in the presented synthetic procedure, were prepared from H-phosphinates (methyl- or phenylphosphinate ethyl esters) and Grignard reagents, according to a literature method [29] (Scheme 3). In turn, the diphenyl phosphine oxide (diphenylphosphinous acid, **10**) was simply obtained from chlorodiphenylphosphine and aqueous HCl, following the literature method.[30]

The synthesized thiazole aminophosphine oxides **7a–d** were mixtures of diastereoisomers (as shown by their NMR spectra). ^{31}P NMR shifts of the thiazole aminophosphine oxides depend largely on electronegativity of the substituent attached to the phosphorus atom. For example, the ^{31}P signals of diphenyl derivatives **7e**,**f** are placed between 30 and 32 ppm, compared to the corresponding signals of methyl-phenylphosphine derivatives **7c**,**d**, which are observed in the range of 41–44 ppm, and the *n*-butylphenyl-phosphine oxides **7a**,**b**, which are in the 42–46 ppm, respectively.

2.3. Complexation of Cu(II) ions by 4a and 4b

Coordination properties of the obtained products were measured for thiazole aminophosphonic acids **4a** and **4b**,

Table 1. Stability constants of proton (log *K*) and copper(II) complexes (log *β*)

	4a	**4b**	Imid-Bu[27]	Imid-Ph[27]	Pyrid-Bu[26]	Pyrid-Ph[26]
log *K*(HL)	8.67	7.56	10.22	9.06	10.14	9.04
log *K*(H_2L)	4.83	4.72	6.05	5.89	5.20	5.21
log *K*(H_3L)	—	—	4.30	4.07	1.72	3.82
log *β*(CuHL)	12.75	—	18.27	16.59	16.50	—
log *β*(CuL)	9.10	8.09	14.74	13.23	—	—
log *β*(CuH_2L_2)	—	—	35.04	32.11	31.35	29.11
log *β*($CuHL_2$)	—	—	28.93	25.77	26.81	25.01
log *β*(CuL_2)	14.45	13.17	20.67	18.10	20.90	19.38
log *β*($CuH_{-1}L_2$)	—	—	11.16	—	—	—
p*K*(CuHL)	3.65	—	3.53	3.36	—	—
p*K*(CuH_2L_2)	—	—	6.11	6.34	4.54	4.10
p*K*($CuHL_2$)	—	—	8.26	7.67	5.91	5.63
p*K*(CuL_2)	—	—	9.51	—	—	—

which were soluble in aqueous solutions. The thiazole aminophosphinic acids **6** and aminophosphine oxides **7** were not appropriate for potentiometric studies, due to precipitation of the ligands in a higher pH range. Both ligands (**4a**, **4b**) behave as H_2L acids. Two protonation constants of **4a** log $K=8.67$ and 4.83 may be assigned to amino and phosphonate functions, respectively. Similar log K values are observed for **4b**, 7.56 and 4.71. The protonation constant of benzylamino substituted nitrogen (**4b**) is distinctly lower than that of *N*-butylamino derivative (Table 1), while the basicities of the phosphonate function are rather similar to each other. The analogous derivatives with the imidazole[27] or pyridine[26] moiety behave in a similar way, although the basicities of amino groups of thiazole derivatives are much lower than those of imidazole, or pyridine aminophosphonates (Table 1). This indicates a much higher degree of electron withdrawing abilities of thiazole when compared to imidazole, or pyridine rings.

According to the calculations based on potentiometric data, **4a** and **4b** form two major complexes CuL and CuL_2 (Table 1, Fig. 1). The stability constants of the **4a** complexes are distinctly higher than those of **4b** due to the higher basicity of the amino function of the ligand. The d–d transitions observed around 640–660 and 610–630 nm indicate the involvement of two or four nitrogen donors in the binding of Cu(II) ion in CuL and CuL_2, respectively, (Table 2).[24–27] Also, EPR parameters, especially the values

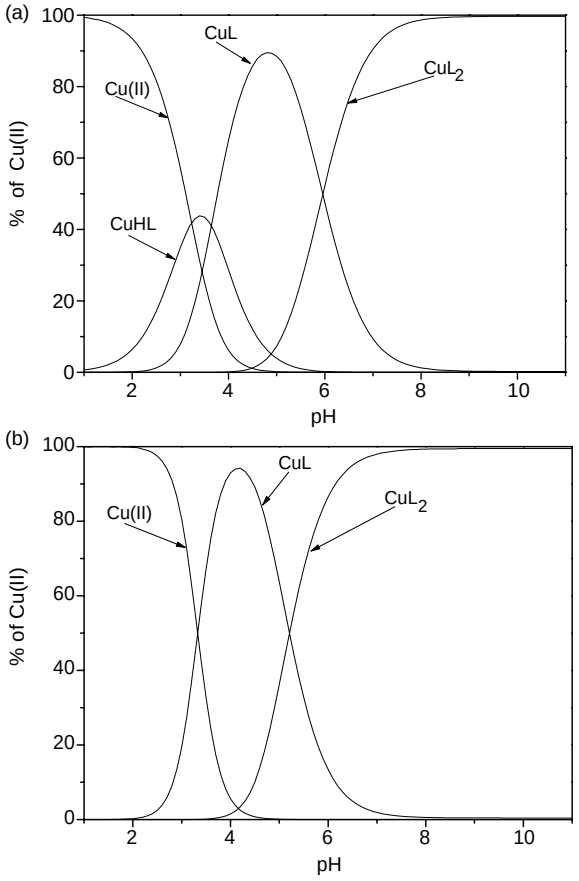


Figure 1. Species distribution curves for the complexes formed in the (a) Cu(II)-**4a**; (b) Cu(II)-**4b** system as a function of pH. $C_{Cu(II)}=1.0\times10^{-3}$ mol dm^{-3}, $C_L=4.0\times10^{-3}$ mol dm^{-3}.

Table 2. Spectroscopic parameters for Cu(II) complexes formed by studied ligands

Ligands		UV–vis		EPR	
		λ (nm)	ε (dm^3 mol^{-1} cm^{-1})	A_{II}	g_{II}
L1-**4a**	CuHL	693	48	140	2.347
	CuL	643	76	155	2.290
	CuL_2	612	86	187	2.222
L2-**4b**	CuL	667	86	155	2.281
	CuL_2	634	84	190	2.231

of $A_{II}=155$ and 190 G support such a coordination mode.[24–27] In the CuHL, species observed for **4a** the coordination mode $\{N_{thiazole}, PO_3^{2-}\}$ seems to be the most likely. The d–d trasition at 693 nm support the one nitrogen coordination (Table 2).[26] Thus, thiazole and amino nitrogen are basic for the metal ion coordination although the presence of the phosphonate function modulates the binding ability of the aminophosphonic acid distinctly. The thiazole moiety with its least basic nitrogen donor is a very effective chelating agent for Cu(II) ions although both pyridine and imidazole derivatives are more powerful ligands.

3. Conclusions

New thiazole aminophosphine oxides, thiazole aminophosphonic and aminophosphinic acids were synthesized in a simple way, from the corresponding aldimines and secondary phosphine oxides, or silylated phosphorus esters. It was demonstrated that thiazole aminophosphonic acids are effective ligands for complexation of Cu(II) ions.

4. Experimental

NMR spectra were recorded on a Bruker Avance TM DRX spectrometer, in D_2O, 10% D_2O/D_2SO_4, or $CDCl_3$ solutions, respectively. IR spectra were recorded on a Perkin Elmer 1600 FTIR spectrophotometer. MS analyses were determined on a Finnigan TSQ 700 instrument (electrospray ionization on mode: ESI +Q1MS) in Department of Chemistry, University of Wrocław. Melting points were determined using an Electrothermal 9200 apparatus and a Boetius hot-stage apparatus and were uncorrected. Elemental analyses were done in Department of Chemistry, University of Wrocław. All commercially available materials were used as received from the supplier (Aldrich Company).

4.1. Synthesis of reagents

Ethyl methylphosphinate (**8b**) was prepared from methyldichlorophosphine, as described in the literature.[31]

4.1.1. *n*-Butylphenylphosphine oxide[32] (9a). To a 2.0 M solution of *n*-BuMgCl (10.0 mL, 20.0 mmol) in dry diethyl ether (20 mL) ethyl phenylphosphinate (1.70 g, 10.0 mmol) was added dropwise at 0 °C with stirring. Then, the reaction mixture was refluxed for 2 h, cooled (ice bath) and aqueous

25% H_2SO_4 (30 mL) was slowly added. The organic layer was separated and discarded. The remaining aqueous layer was extracted with CH_2Cl_2 (5×30 mL). The combined organic extracts were shaken with the solid K_2CO_3 and dried over anhydrous Na_2SO_4. After evaporation of the filtrate, the crude *n*-butylphenylphosphine oxide **9a** was obtained as colorless oil. Yield: 66% (1.2 g). ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 8.13–6.59 (dt, 1H, P–*H*, J_{H-P}=463 Hz, J=3.7 Hz), 7.61–7.36 (m, 5H, Ph*H*), 1.93–1.83 (m, 2H, PCH_2(CH_2)$_2$$CH_3$), 1.54–1.13 (m, 4H, CH_2(CH_2)$_2$$CH_3$), 0.92–0.87 (m, 3H, C$H_3$). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 29.66 (s).

4.1.2. Methylphenylphosphine oxide[33] (9b). The title compound was prepared using PhMgCl (2.0 M solution in diethyl ether, 16.0 mL, 32.0 mmol) and ethyl methylphosphinate **8b** (1.7 g, 16.0 mmol). The procedure for preparation of **9a** was exactly followed and **9b** obtained as colorless oil. Yield: 54% (1.2 g). ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 8.24–6.65 (dq, 1H, P–*H*, J_{H-P}=476.3 Hz, J=3.8 Hz), 7.64–7.29 (m, 5H, Ph*H*), 1.77 (dd, 3H, P–CH_3, J=13.9, 3.8 Hz). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 22.30 (s).

Aldimines **2** were prepared from 2-formylthiazole (**1**) and primary amines, according to the following procedure: aldehyde **1** (0.47 g, 2.5 mmol) was dissolved in dry CH_2Cl_2 (25 mL) and an appropriate amine was added (2.5 mmol). The mixture was stirred for 24 h at room temperature and dried over anhydrous Na_2SO_4, filtered and the filtrate evaporated to give the crude imines **2**, which were used directly in a next step.

4.2. General procedure for preparation of 2-thiazole aminophosphonic acids 4a–b and aminophosphinic acids 6a–d

To a solution of crude imine **2** (2.5 mmol) in dichloromethane (25 mL) trimethyl phosphite was added (0.32 g, 2.5 mmol), followed by bromotrimethylsilane (1.6 g, 10 mmol). The mixture was stirred for 24 h at room temperature and evaporated under reduced pressure. The resulted oil was treated with methanol (5 mL) and refrigerated for several hours. The products (thiazole aminophosphonic acids **4a**–**b**) separated as white solids and were collected by filtration, washed with diethyl ether and dried.

Phosphinic acids **6a**–**d** were obtained in the following way: the ethyl phenylphosphinate (**8a**) (0.45 g, 2.5 mmol), or ethyl methylphosphinate (**8b**) (0.28 g, 2.5 mmol), was added to solution of crude imine **2** in dry CH_2Cl_2 (25 mL). Bromotrimethylsilane (1.2 g, 7.5 mmol) was then added and the whole mixture was stirred for 24 h, at room temperature. After this, the mixture was evaporated, the resulted oil treated with 5 mL MeOH and refrigerated for several hours. The separated products were filtered and dried to give the aminophosphinic acids **6a**–**d** as white solids.

4.2.1. Thiazole-2-yl-methyl(*N*-butylamino)phosphonic acid (4a). A white solid. Yield: 0.40 g (65%), mp 220–224 °C. ^{1}H NMR; δ_H (D_2O/10% D_2SO_4; 300 MHz): 7.67 (d, 1H, thiazole-4, J=3.4 Hz), 7.55 (d, 1H, thiazole-5, J=3.4 Hz), 4.82 (d, 1H, C*H*–P, J=16.6 Hz), 2.89–2.68 (m, 2H, NHCH_2), 1.38–1.26 (m, 2H, C$H_2$$CH_2$), 1.08–1.01 (m, 2H, CH_2CH_2), 0.57–0.48 (m, 3H, CH_3). ^{31}P NMR; δ_P (D_2O/D_2SO_4; 121.5 MHz): 6.91 (s). IR, ν_{max} (KBr): 3439 (NH); 3109; 2964; 2837; 2811; 2681; 2328; 1616; 1558; 1492; 1466; 1385; 1225; 1185 (P=O); 1076; 984; 926; 850; 748; 642; 567 cm^{-1}. MS; (ESI+Q1MS): 273.2 (100, M^++Na). Anal. Calcd for $C_8H_{15}N_2O_3PS$, requires C, 38.39; H, 6.04; N, 11.19; found: C, 38.34; H, 6.18; N, 11.10%.

4.2.2. Thiazole-2-yl-methyl-(*N*-benzylamino)phosphonic acid (4b). A white solid. Yield: 0.50 g (70%), mp 185–187 °C. ^{1}H NMR; δ_H (D_2O/10% D_2SO_4; 300 MHz): 7.56 (d, 1H, thiazole-4, J=3.3 Hz), 7.40 (d, 1H, thiazole-5, J=3.3 Hz), 6.99–6.89 (m, 5H, Ph*H*), 4.86 (d, 1H, C*H*–P, J=18.7 Hz), 3.94 (s, 2H, NHCH_2Ph). ^{31}P NMR; δ_P (D_2O/D_2SO_4; 121.5 MHz): 6.06 (s). IR, ν_{max} (KBr): 3492, 3407 (NH); 3040; 2886; 2614; 2486, 2398; 1662; 1576; 1456; 1466; 1382; 1277; 1187 (P=O); 1118; 937; 864; 743; 636; 555; 490, 460 cm^{-1}. MS; (ESI+Q1MS): 307.2 (100, M^++Na). Anal. Calcd for $C_{11}H_{13}N_2O_3PS$, requires C, 46.48; H, 4.61; N, 9.85; found: C, 46.40; H, 4.75; N, 9.81%.

4.2.3. Thiazole-2-yl-methyl-(*N*-butylamino)-phenylphosphinic acid (6a). A white solid. Yield: 0.57 g (74%), mp 157–160 °C. ^{1}H NMR; δ_H (D_2O/10% D_2SO_4; 300 MHz): 8.61 (d, 1H, thiazole-4, J=3.3 Hz), 8.57 (d, 1H, thiazole-5, J=3.3 Hz), 8.00–7.82 (m, 5H, Ph*H*), 5.23 (d, 1H, C*H*–P, J=19.6 Hz), 3.59–3.51 (m, 2H, NHCH_2), 2.07–1.97 (m, 2H, C$H_2$$CH_2$), 1.75–1.62 (m, 2H, CH_2CH_2), 1.19 (t, 3H, CH_3, J=7.3 Hz). ^{31}P NMR; δ_P (D_2O/D_2SO_4; 121.5 MHz): 19.62 (s). MS; IR, ν_{max} (KBr): 3394 (NH); 3060; 2961; 2777; 1591; 1487; 1441; 1316; 1216 (P=O); 1131; 990; 938; 750; 718; 695; 547; 505 cm^{-1}. (ESI+Q1MS): 333.3 (100, M^++Na). Anal. Calcd for $C_{14}H_{19}N_2O_2PS$, requires C, 54.18; H, 6.17; N, 9.03; found: C, 54.15; H, 6.21; N, 8.97%.

4.2.4. Thiazole-2-yl-methyl-(*N*-benzylamino)-phenylphosphinic acid (6b). A white solid. Yield: 0.53 g (63%), mp 217–220 °C. ^{1}H NMR; δ_H (D_2O/10% D_2SO_4; 300 MHz): 8.50 (d, 1H, thiazole-4, J=3.3 Hz), 7.30 (d, 1H, thiazole-5, J=3.3 Hz), 8.20–8.03 (m, 10H, Ph*H*), 5.22 (d, 1H, C*H*–P, J=18.7 Hz), 4.71 (s, 2H, NHCH_2Ph). ^{31}P NMR; δ_P (D_2O/D_2SO_4; 121.5 MHz): 19.64 (s). IR, ν_{max} (KBr): 3620; 3446 (NH); 3047; 2963; 2930; 2848; 2730; 2603; 1617; 1476; 1437; 1366; 1169 (P=O); 1131; 1026; 997; 918; 891; 743; 732; 695; 645; 602; 566; 510 cm^{-1}. MS; (ESI+Q1MS): 345.3 (100, M^++1). Anal. Calcd for $C_{17}H_{17}N_2O_2PS$, requires C, 59.29; H, 4.98; N, 8.13; found: C, 59.18; H, 5.02; N, 8.09%.

4.2.5. Thiazole-2-yl-methyl-(*N*-butylamino)-methylphosphinic acid (6c). A white solid. Yield: 0.41 g (67%), mp 168–172 °C. ^{1}H NMR; δ_H (D_2O/10% D_2SO_4; 300 MHz): 8.59 (d, 1H, thiazole-4, J=3.3 Hz), 8.57 (d, 1H, thiazole-5, J=3.3 Hz), 5.26 (d, 1H, C*H*–P, J=17.6 Hz), 3.56–3.50 (m, 2H, NHCH_2), 1.79–1.70 (m, 2H, C$H_2$$CH_2$), 1.40–1.32 (m, 2H, CH_2CH_2), 1.17 (t, 3H, CH_3, J=7.3 Hz), 1.02 (d, 3H, PCH_3, J=14.3 Hz). ^{31}P NMR; δ_P (D_2O/D_2SO_4; 121.5 MHz): 29.80 (s) ppm. IR, ν_{max} (KBr): 3313 (NH); 3243; 2951; 2908; 2878; 1587; 1487; 1421; 1198 (P=O); 1123; 995; 928; 755; 708; 695; 504 cm^{-1}

MS; (ESI+Q1MS): 271.3 (100, M^++Na). Anal. Calcd for $C_9H_{17}N_2O_2PS$, requires C, 43.54; H, 6.90; N, 11.28; found: C, 43.45; H, 7.01; N, 11.21%.

4.2.6. Thiazole-2-yl-methyl-(*N*-benzylamino)methylphosphinic acid (6d). A white solid. Yield: 0.50 g (72%), mp 210–214 °C. ^{1}H NMR; δ_H (D_2O/10% D_2SO_4; 300 MHz): 8.50 (d, 1H, thiazole-4, J=3.3 Hz), 8.25 (d, 1H, thiazole-5, J=3.3 Hz), 8.20–8.03 (m, 5H, Ph*H*), 4.90 (d, 1H, C*H*–P, J=17.7 Hz), 4.64 (s, 2H, NHCH_2Ph), 1.10 (d, 3H, PCH_3, J=14.3 Hz). ^{31}P NMR; δ_P (D_2O/D_2SO_4; 121.5 MHz): 30.45 (s) ppm. IR, ν_{max} (KBr): 3386 (NH); 3045; 2960; 2928; 2863; 1604; 1485; 1326; 1181 (P=O); 1154; 938; 887; 733; 649; 596; 561; 504 cm^{-1}. MS; (ESI+Q1MS): 305.3 (100, M^++Na). Anal. Calcd for $C_{12}H_{15}N_2O_2PS$, requires C, 51.06; H, 5.36; N, 9.92; found: C, 50.99; H, 5.43; N, 9.87%.

4.3. General procedure for preparation of 2-thiazole aminophosphine oxides (7a–f)

To a solution of crude imine **2** (2.5 mmol) in dry toluene (25 mL), the appropriate phosphine oxide (**9** or **10**) was added (2.5 mmol). The mixture was stirred overnight at room temperature and then refluxed for 2 h to complete the reaction. After evaporation of the solvent, crude thiazole aminophosphine oxides were obtained as solids, or thick oils. Compounds **7e** and **7f** (solids) were purified by crystallization from toluene–hexane solution. Compounds **7a–d** (oils) were purified as oxalate salts, obtained by the following procedure: the crude product (~2.5 mmol) was dissolved in acetone (10 mL) and treated with acetone solution of oxalic acid (10 mL, containing 0.61 g $(COOH)_2\cdot 2H_2O$). After cooling, the separated crystals were collected by filtration and dried on air to give oxalates **7a–d**, as white, crystalline solids.

Oxalates **7a–d**, treated with an excess of aqueous sodium bicarbonate and extracted with methylene chloride give the pure thiazole aminophosphine oxides, as thick oils.

4.3.1. Thiazole-2-yl-methyl(*N*-butylamino)-butylphenylphosphine oxide, oxalate (7a). A crystalline solid. Yield: 0.79 g (67%), mp: 104–106 °C. ^{1}H NMR; δ_H (D_2O; 300 MHz): 7.70–7.37 (m, 7H, thiazole-4, thiazole-5, Ph*H*), 5.63 (d, 0.5H, C*H*–P, J=11.6 Hz), 5.58 (d, 0.5H, C*H*–P, J=11.6 Hz), 3.98–3.76 (m, 4H, NHCH_2, PCH_2), 1.59–1.20 [(m, 8H, NHCH$_2$(CH_2)$_2$ and PCH$_2$(CH_2)$_2$)], 0.97–0.80 (m, 6H, 2×CH_3). ^{31}P NMR; δ_P (D_2O; 121.5 MHz): 46.61 (s) and 45.83 (s), in a ratio 1:0.80 (two diastereomers). IR, ν_{max} (KBr): 3489; 3410 (NH); 3110; 2956; 2806; 1742; 1662; 1479; 1445; 1403; 1174 (P=O); 786; 741; 696; 551; 482 cm^{-1}. MS; (ESI+Q1MS): 373.4 (100, M^++Na). Anal. Calcd for $C_{18}H_{27}N_2OPS\cdot 2\times(COOH)_2$, requires C, 49.81; H, 5.89; N, 5.28; found: C, 49.80; H, 5.94; N, 5.25%.

4.3.2. Thiazole-2-yl-methyl(*N*-benzylamino)-butylphenylphosphine oxide, oxalate (7b). A crystalline solid. Yield: 0.73 g (58%), mp 120–122 °C. ^{1}H NMR; δ_H (D_2O; 300 MHz): 7.48–7.19 (m, 12H, thiazole-4, thiazole-5, 2×Ph*H*), 4.73 (d, 0.5H, C*H*–P, J=14.6 Hz), 4.69 (d, 0.5H, C*H*–P, J=14.6 Hz) 4.05–3.99 (m, 2H, NHCH_2Ph), 2.41–2.36 (m, 2H, PCH_2), 1.50–1.45 [(m, 4H, PCH$_2$(CH_2)$_2$)], 0.97–0.92 (m, 3H, CH_3). ^{31}P NMR; δ_P (D_2O; 121.5 MHz): 43.02 (s) and 42.31 (s), in a ratio 1:0.83 (two diastereomers). IR, ν_{max} (KBr): 3491; 3415 (NH); 2965; 2810; 1668; 1481; 1449; 1408; 1183 (P=O); 792; 744; 690; 541; 531; 491 cm^{-1}. MS; (ESI+Q1MS): 407.5 (100, M^++Na). Anal. Calcd for $C_{21}H_{25}N_2OPS\cdot 2\times(COOH)_2$, requires C, 53.19; H, 5.18; N, 4.96; found: C, 53.08; H, 5.34; N, 4.75%.

4.3.3. Thiazole-2-yl-methyl(*N*-butylamino)-methylphenylphosphine oxide, oxalate (7c). A crystalline solid. Yield: 0.67 g (62%), mp 132–135 °C. ^{1}H NMR; δ_H (D_2O; 300 MHz): 7.67–7.47 (m, 7H, thiazole-4, thiazole-5, Ph*H*), 5.63 (d, 0.5H, C*H*–P, J=12.6 Hz), 5.59 (d, 0.5H, C*H*–P, J=12.6 Hz), 3.95–3.90 (m, 2H, NHCH_2), 1.54–1.49 (m, 4H, CH_2CH_2), 1.57 (d, 1.5H, PCH_3, J=13.0 Hz), 1.47 (d, 1.5H, PCH_3, J=13.0 Hz), 0.87–0.84 (m, 3H, CH_3). ^{31}P NMR; δ_P (D_2O; 121.5 MHz): 44.21 and 43.83 (s), in a ratio 1:0.90 (two diastereomers). IR, ν_{max} (KBr): 3465; 3389 (NH); 3090; 2951; 2803; 1656; 1471; 1408; 1204; 1186 (P=O); 780; 739; 678; 541; 491 cm^{-1}. MS; (ESI+Q1MS): 331.4 (100, M^++Na). Anal. Calcd for $C_{15}H_{21}N_2OPS\cdot 2\times(COOH)_2$, requires C, 46.72; H, 5.16; N, 5.74; found: C, 46.58; H, 5.24; N, 5.70%.

4.3.4. Thiazole-2-yl-methyl(*N*-benzylamino)-methylphenylphosphine oxide, oxalate (7d). A crystalline solid. Yield: 0.65 g (57%), mp 142–145 °C. ^{1}H NMR; δ_H (D_2O; 300 MHz): 7.50–7.21 (m, 12H, thiazole-4, thiazole-5, 2×Ph*H*), 4.64 (d, 0.5H, C*H*–P, J=12.6 Hz), 4.60 (d, 0.5H, C*H*–P, J=12.6 Hz), 4.04–4.00 (m, 2H, NHCH_2Ph), 1.60 (d, 1.5H, PCH_3, J=12.9 Hz), 1.45 (d, 1.5H, PCH_3, J=12.9 Hz). ^{31}P NMR; δ_P (D_2O; 121.5 MHz): 41.22 and 40.31 (s), in a ratio 1:0.88 (two diastereomers). IR, ν_{max} (KBr): 3466; 3398 (NH); 2954; 2812; 1675; 1443; 1440; 1194 (P=O); 801; 756; 692; 547 cm^{-1}. (ESI+Q1MS): 365.4 (100, M^++Na). Anal. Calcd for $C_{18}H_{19}N_2OPS\cdot 2\times(COOH)_2$, requires C, 50.58; H, 4.44; N, 5.36; found: C, 50.55; H, 4.48; N, 5.23%.

4.3.5. Thiazole-2-yl-methyl(*N*-butylamino)-diphenylphosphine oxide (7e). A white solid. Yield: 0.59 g (65%), mp 110–112 °C. ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 7.88–7.18 (m, 12H, thiazole-4, thiazole-5, 2×Ph*H*), 5.03 (d, 1H, C*H*–P, J=12.6 Hz), 2.67–2.51 (m, 2H, NHCH_2), 1.42–1.20 (m, 4H, CH_2CH_2), 0.85 (t, 3H, CH_3, J=7.5 Hz). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 Hz): 30.93 (s). IR, ν_{max} (KBr): 3445; 3275 (NH); 3054; 2923; 2868; 1627; 1592; 1484; 1435; 1379; 1182 (P=O); 1116; 999; 829; 722; 690; 644; 554; 507 cm^{-1}. (ESI+Q1MS): 393.4 (100, M^++Na). Anal. Calcd for $C_{20}H_{23}N_2OPS$, requires C, 64.85; H, 6.26; N, 7.56; found: C, 64.80; H, 6.34; N, 7.49%.

4.3.6. Thiazole-2-yl-methyl(*N*-benzylamino)-diphenylphosphine oxide (7f). A white solid. Yield: 0.58 g (58%), mp 138–141 °C. ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 7.84–7.15 (m, 17H, thiazole-4, thiazole-5, 3×Ph*H*), 4.98 (d, 1H, C*H*–P, J=12.3 Hz), 3.95–3.90 (m, 2H, NHCH_2Ph). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 Hz): 31.45 (s). IR, ν_{max} (KBr): 3434 (NH); 3054; 2923; 2855; 2606; 2206; 1634; 1497; 1436; 1380; 1315; 1187 (P=O); 1166; 1124; 1073; 1038; 1021; 917; 857; 799; 699; 555; 507; 489 cm^{-1}. (ESI+Q1MS): 427.5 (100, M^++Na). Anal. Calcd for

$C_{23}H_{21}N_2OPS$, requires C, 68.30; H, 5.23; N, 6.93; found: C, 68.23; H, 5.36; N, 6.87%.

4.4. Potentiometric and spectroscopic studies of Cu(II) complexes with 4a and 4b

4.4.1. Potentiometric measurements. The purities and exact concentrations of the stock solutions of the ligands were confirmed pH-metrically by the Gran method.[34] The concentration of the Cu(II) stock solution was measured gravimetrically via precipitation of the quinolin-8-olate.

The stability constants both for protons and Cu(II) complexes of the studied ligands were determined by pH-metric titration of 1.5–2.0 cm^3 samples at the pH range 2.5–11.0. The ligand concentration 2.5–3.0 mmol dm^{-3}; metal to ligand molar ratios 1:2, 1:4, 1:6; ionic strength adjusted to 0.1 mol dm^{-3} with KNO_3; duplicate pH titration calibrated in concentration;[35] temperature 25 °C.

The pH was measured with MOLSPIN automatic titration system with a microcombined glass-calomel electrode calibrated daily. Titration data were used to calculate the stability constants ($\beta_{pqr}=[M_pH_rL_q]/[M]^p[H]^r[L]^q$) with a SUPERQUAD computer program.[36] Standard deviations quoted refer to random errors only.

4.4.2. Spectroscopic measurements. The absorption spectra were recorded on a Beckman DU 650 spectrophotometer. The EPR spectra were recorded, in 1:2 ethane-1,2-diol/water (v/v), on a Bruker ESP 300E spectrometer at the X-band (9.3 GHz) at 120 K. The concentrations used in the spectroscopic measurements were similar to those given for potentiometric titrations. The results of potentiometric and spectroscopic studies are collected in Tables 1 and 2.

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Synthesis and characterization of novel styryl-substituted oligothienylenevinylenes

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Abstract—A number of 3-monosubstituted bis(thienylvinyl)thiophenes, suitable for the preparation of electronically-variable poly(thienylenevinylene)s have been synthesized for the first time. These materials have been characterized by both NMR spectroscopy and mass spectrometry, and a single crystal X-ray structure analysis of (*E*,*E*)-3-(5,5-dimethyl[1,3]dioxin-2-yl)-2,5-bis(2-thien-2-ylvinyl)thiophene has shown that the planarity of the terthienylenevinylene chain is maintained on substitution at the 3 position of the central thiophene ring. UV/visible spectroscopy measurements are reported and cyclic voltammetric measurements show that, with the exception of (*E*,*E*,*E*)-2,5-bis(2-thien-2-ylvinyl)-3-(2-(4-dimethylaminophenyl)vinyl)-thiophene, electroactive films are produced on electrochemical oxidation of the monomers.

1. Introduction

Since their discovery in 1977,[1,2] conjugated polymers and oligomers have been extensively investigated for use in applications such as solar cells, actuators, light emitting diodes and non-linear optical materials.[3] Prominent among the conjugated materials studied to date are the oligo- and polythiophenes. These materials have good chemical stability in both their oxidized and reduced states, and a wide variety of functionality can be readily built onto the monomers whether thiophene, bithiophene, or terthiophene.[4–10]

The introduction of vinylene bridges between thiophene moieties improves the electronic properties of the resulting thienylenevinylene polymers[11–16] by decreasing the aromaticity and enhancing both the planarity[17] and the effective conjugation length.[15,18,19] However, the introduction of more that one vinylene bridge leads to a decrease in chemical stability with no significant improvement in the electronic properties,[20] as does the introducion of an acetylene bridge.[14] The HOMO–LUMO gap in thienylenevinylene polymers decrease with increasing number of carbons in the conjugated chain and large red shifts in λ_{max} are observed.[18] This gives rise to the possible fabrication of conjugated polymers that are transparent in the visible region of the electromagnetic spectrum and which might be used in the fabrication of LEDs operating in the infrared. Furthermore, the increased electron affinity associated with a low-lying LUMO level allows for the fabrication of LEDs with stable metal electrodes.[9]

Another way in which the electronic properties of thiophene oligomers and polymers may be tuned is to introduce functionality to the polymer chain, typically in the form of aromatic substituents. Thus, poly(3-arylthiophenes) have improved doping capacity and cyclability compared with polythiophene,[21,22] and fusing benzene to thiophene leads to poly(isothianaphthene), the prototypical small band gap polymer.[23] In contrast to the planar-fused benzene ring of the isothianaphtene, the 3-aryl substituents are twisted out of the plane of the polymer backbone, reducing their electronic impact as well as disrupting the polymer interchain interactions. The styryl group is an alternative and readily accessible aromatic functionality, which should not have these disadvantages and may enhance a planar morphology. Attempts to polymerise styrylthiophenes, however, have not been so successful. Electrochemical homopolymerization of 3-styrylthiophene resulted in a nonconductive material, presumably through side-chain polymerization, and other styryl derivatives showed similar behaviour.[24] However, electrically conductive polymers have been obtained by copolymerisation of styryl-substituted thiophenes with 3-methylthiophene,[25] and an improvement in the photoconductivity of polythiophene was accomplished on copolymerisation of thiophene and 3-(4-nitrostyryl)thiophene.[26] Copolymers of bithiophene and *para*-substituted (*E*)-3-styrylthiophenes have also been

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shown to produce photovoltaic responses in photoelectrochemical cells.[27] Whilst these copolymerizations undoubtedly lead to improvement in desirable polymer properties, their irregular and random structure makes it difficult to deconvolute the role of the substituent in these improvements.

An alternative approach to the formation of regioregular styryl-functionalised oligo- and polythiophenes is to polymerize styryl substituted terthiophene monomers and towards this end we have reported the syntheses of a range of terthiophenes functionalized at the 3′-position with styryl moieties.[4,5,28–31] We have demonstrated that the styryl functionality can control oligomer regioregularity and provides advantages in some applications. However, styrylterthiophenes largely form dimers on oxidative polymerization as a result of 'polaron trapping'.[6] Given the decreased aromaticity in thienylenevinylene polymers,[17] this effect may not be so pronounced in styrylthienylenevinylenes and consequently polymers rather than dimers may be produced.

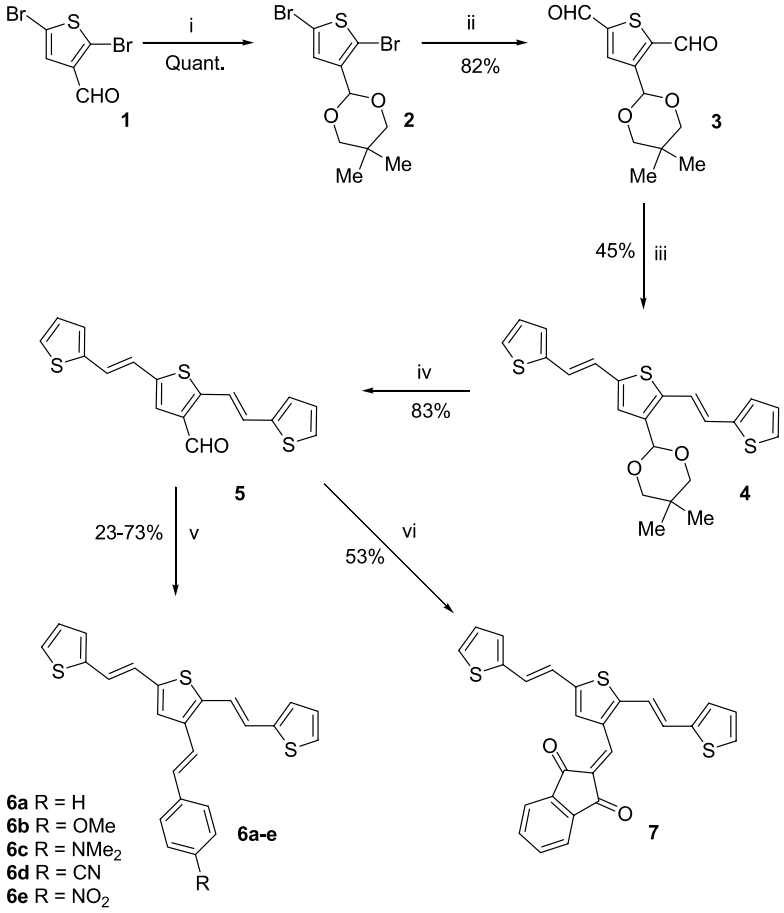
With the eventual aim of producing conjugated styryl-substituted oligo(thienylenevinylene)s we describe in this paper the synthesis of six novel (*E*,*E*,*E*)-3′-styrylbis(thienylvinyl)thiophenes and report on their spectral and electrochemical properties. It should be noted that to the best of our knowledge, no examples of 3-vinyl substituted bis(thienylvinyl)thiophenes have been reported to date. The facile synthesis of thienylenevinylene-3-carboxyaldehyde **5** reported here potentially provides access to a wide variety of other bis(thienylvinyl)thiophene substituents.

2. Results and discussion

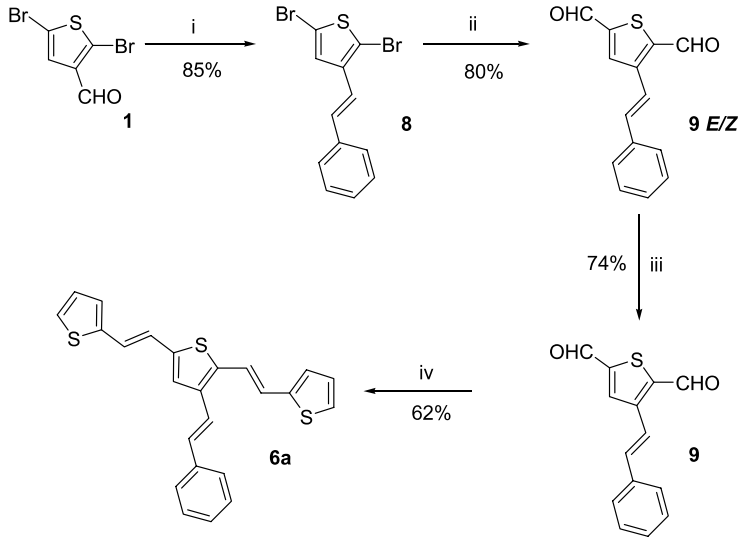
2.1. Synthesis

Several methods have been used to syntheses oligothienylenevinylenes including the McMurry reaction,[18,32–34] Wittig condensation,[33,35,36] Wittig–Horner condensation,[18,19,37–39] and others[11,12,16,40–42] Of these, the Wittig condensation is economic and straightforward and allows the ready introduction of a wide variety of donor/acceptor-functionalized aromatic substituents.

The precursor to the bis(thienylvinyl)thiophene backbone, protected trialdehyde **3** (Scheme 1), was synthesised in 80% yield, by lithiation of the dibromo derivative **2** using a slight excess of *n*-butyl lithium, followed by DMF formylation. No monosubstituted product was observed and increasing the lithiation time above 30 min did not improve the reaction yield. The styryl functionality was introduced in an analogous manner to that used for terthiophenes,[5] with



Scheme 1. (i) 2,2-Dimethyl-1,3-propanediol, PTSA, toluene, reflux, quantitative; (ii) *n*-BuLi, DMF, THF, −78 °C, 82%; (iii) thiophen-2-ylmethyltriphenylphosphonium bromide, DBU, THF, reflux, 45%; (iv) TFAA, dichloromethane, rt, 83%; (v) phosphonium salt, DBU, THF, reflux, 23–73%; (vi) 1,3-indandione, piperidine, dichloromethane, rt, 53%.



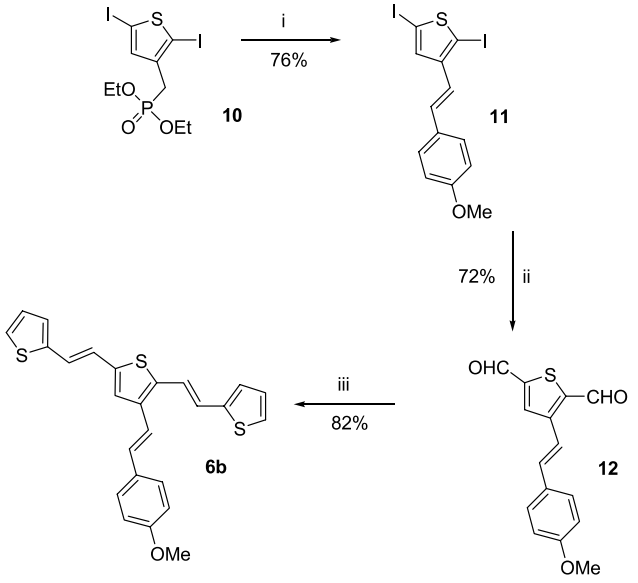
Scheme 2. (i) Benzyltriphenylphosphonium chloride, THF, DBU, reflux, 85%; (ii) −78 °C, *n*-BuLi, THF, DMF, 80%; (iii) I_2 3 equiv, dichloromethane, rt, 7 days, 74%; (iv) thiophen-2-ylmethyltriphenylphosphonium bromide, DBU, THF, reflux, 62%.

the key intermediate being aldehyde **5**. A Wittig condensation of **3** with thiophen-2-ylmethyltriphenylphosphonium bromide gave **4** as a pure *E*,*E* isomer. Increasing the reaction time decreased the product yield significantly. The products of monodecarbonylation of the thiophene dicarbaldehyde derivatives, observed previously in the presence of a strong base,[20] were not detected here. Deprotection of **4** by trifluoroacetic acid in dichloromethane gave **5** in high yield together with some traces of polymeric side products.

The Wittig condensations between aldehyde **5** and the appropriate phosphonium salts were carried out in boiling THF with DBU as base to give the corresponding 3-styryl derivatives **6a–e**. While **6b–e** were obtained as pure *E* isomers, the phenyl derivative **6a** was obtained as an inseparable mixture of 1:1 *E*/*Z* isomers, which suggests that the *Z*-isomer of an unsubstituted styryl derivative is more stable than one with an electron withdrawing or donating group. Compound **7** was synthesized, in high yield, by a Knoevenagel condensation of aldehyde **5** with an equimolar amount of 1,3-indandione in THF with piperidine as the base.

Since it proved impossible to separate the *E* and *Z* isomers of **6a** an alternative, but less general, synthetic path was devised (Scheme 2). The styryl functionality was first introduced through a condensation of aldehyde **1** with benzyltriphenylphosphonium chloride to give **8** (85%) as an inseparable *E*/*Z* 1:1 mixture. The conversion of **8** to an isomeric mixture of the dialdehyde *E*/*Z* **9** was readily achieved as described for **3** above. Isomerization of *E*/*Z* **9** was succesfully carried out in dichloromethane at room temperature using iodine. After a reaction time of 7 days less than 10% of the *Z* isomer was present, and this was readily removed by chromatography to give pure *E*-**9**. This material, in a Wittig reaction with thiophen-2-ylmethyltriphenylphosphonium bromide, gave **6a** as the pure *E*,*E*,*E* isomer.

The yields of compounds **6b**,**c**, that is, those containing electron releasing groups, is only average to low, so the approach utilised for **6a** was investigated as an alternative pathway for the synthesis of **6b** (Scheme 3). For these electron donating materials, the styryl functionality was introduced using diiodothiophene phosphonate **10**, previously prepared for the first time in our laboratory.[43] This compound was condensed with the appropriate aldehyde, under Horner–Emmons conditions, to give styryl derivative **11** as the *E* isomer with only minor traces of the *Z* isomer. Treatment of **11** with *n*-butyl lithium and DMF gave the dialdehyde **12** in high yield. Double Wittig condensation of **12** with thiophen-2-ylmethyltriphenylphosphonium bromide gave **6b** in high yield as the pure *E*,*E*,*E* isomer. The yield by this route, after four steps, is 40%, which is significantly better than that used in Scheme 1 (21%). However, this approach is not suitable for compounds that contain groups sensitive to *n*-butyl lithium.



Scheme 3. (i) 4-Methoxybenzaldehyde, *t*-BuOK, THF, rt, 76%; (ii) *n*-BuLi, DMF, THF, −78 °C, 72%; (iii) thiophen-2-ylmethyltriphenylphosphonium bromide, DBU, THF, reflux, 82%.

2.2. NMR spectroscopy

Analysis of the target compounds by NMR spectroscopy reveals signals that are common to all compounds. Molecules **6b–e** all contain *para*-substituted aromatic rings, that give rise to characteristic AA′BB′ or AA′XX′ spectra, according to the magnitude of the chemical shift separation between the two types of protons. In cyano derivative **6d**, for example, this is only 0.07 ppm, whereas in nitro derivative **6e** it is 0.58 ppm as a result of the strong deshielding effect of the nitro group on the adjacent protons. The vinylic proton resonances appear as two doublets with a coupling of approximately 16 Hz, typical of an *E* configuration. The nature of the styryl substituent has little, if any, effect on the chemical shifts of the 2- and 5-vinyl protons (see Fig. 1) but there are larger variations in the chemical shifts of the 3-vinyl protons of the styryl groups as a result of shielding or deshielding effects induced by the substituent on the benzene ring. The nature of the vinyl substituent also has little effect on the H4 resonance of the inner thiophene ring, which appears as a singlet over the very narrow range of 7.17–7.19. The proton resonances of the outer thiophene rings exhibit AMX spectra and the assignments of the H3, H4, and H5 protons of each ring was achieved with the aid of COSY experiments. This established a coupling between the H4 proton and the 3-vinyl proton, and a further long range five-bond coupling between the 3-vinyl proton and the 2-vinyl proton was identified in compounds **6a**, **6d** and **6e**. These correlations allow for an unambiguous assignment of the outer thiophene resonances to specific thiophene rings. It is interesting to note that the chemical shifts of the thiophene H5′ and H5″ protons are identical in compounds **6a–c**, and differ by only 0.02 ppm in compounds **6d** and **6e**. In the corresponding terthiophene monomers the chemical shifts in these positions differ by between 0.11 ppm (R=NMe_2) and 0.15 ppm (R=CN).[5]

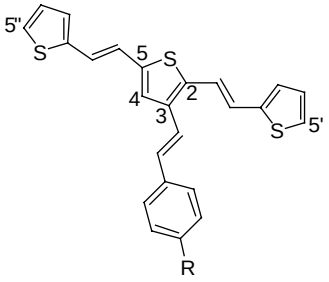


Figure 1. Generalized styryl-substituted bis(thienylvinyl)thiophene structure showing the numbering.

The spectrum of **7** is similar to those of compounds **6a–e**. The main differences are shifts to low fields of the resonances of both the 3-vinyl proton and the thiophene-4H proton by 1 and 1.4 ppm, respectively, both as a result of intramolecular hydrogen bonding between the respective protons and the closest oxygen of the neighbouring indandione ring. The 2-vinyl protons undergo a smaller downfield shift of about 0.2 ppm whilst the chemical shifts of the 5-vinyl protons are little affected, as are the chemical shifts of the outer thiophene protons.

2.3. Electronic absorption spectra

The electronic absorption spectra of compounds **6a**, **6c**, and **6e** are shown in Figure 2. The spectra of compounds **6b** and **6d** are similar in appearance to that of **6a**. All spectra are characterised by an absorption band with a λ_{max} in the range 422 nm (**6d**) to 436 nm (**6c**) indicating that, despite the planarity and therefore increased conjugation of the styryl group, the nature of the *para* substituent on the benzene ring has little effect on the HOMO–LUMO gap in these compounds. Previous work has shown that the position of the absorption maximum of alkyl substituted thienylene-vinylene oligomers is largely determined by the number of carbon atoms in the conjugated chain,[18] with λ_{max} for (*E*,*E*)-2,5-bis(2′-thienylvinyl)-3,4-dibutylthiophene (16 carbon atoms in the conjugated chain) in CH_2Cl_2 being 423 nm. It is clear from the above that the molecular orbitals contributing to this band must be primarily situated along the thienylenevinylene backbone, as has been observed for the corresponding terthiophenes.[44]

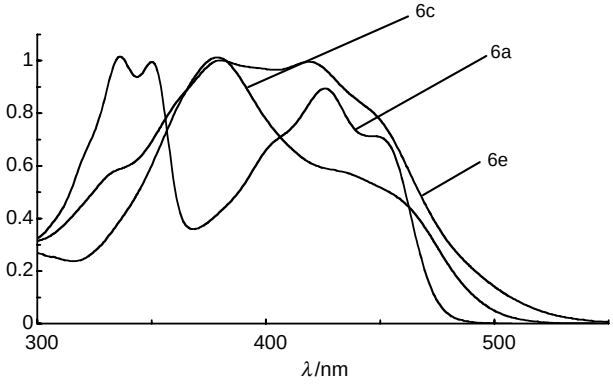


Figure 2. The normalized absorption spectra of **6a**, **6c** and **6e** in CH_2Cl_2 solvent.

Vibronic structure is present in all compounds **6a–e**, as previously reported for thienylenevinylene oligomers,[18,19,45] although it is much less resolved in **6c**. In **6a**, for example, the 0–0 transition is at 452 nm with vibronic side bands at 428 and 405 nm. The energy difference between successive maxima is thus 0.15 eV, a value consistent with a C=C stretching mode ($\sim$1200 cm^{-1}) strongly coupled to the electronic structure.[46] The $\sim$0.15 eV separation between excited state vibrational levels is common to all the styryl-substituted thienylenevinylenes.

The band to lower wavelengths is due to transitions between molecular orbitals associated with the styryl substituent as it is absent in thienylenevinylene oligomers with no styryl substituent. The variation in λ_{max} for this band is much greater than that for the high-wavelength band, ranging from 337 nm for **6a** to 379 nm for **6e**, consistent with the expected influence of the electron donating and withdrawing groups. Vibronic structure is clearly observed in this band in compounds **6a**, **6b**, and **6d**, and less clearly in **6e**. As in the high-wavelength band, the separation between successive maxima corresponds to 0.15 eV and can be associated with a C=C stretching mode.

The spectrum of **7** exhibits two broad bands with λ_{max} values of 378 and 520 nm. The low wavelength band has shoulders at 409 and 431 nm with a ~0.15 eV separation between excited state vibrational levels. The band at 520 nm is most likely the result of intramolecular charge transfer.[47–49]

2.4. X-ray structure analysis of 3-(5,5-dimethyl[1,3]-dioxin-2-yl)-2,5-bis(2-thien-2-ylvinyl) thiophene (4)

Attempts to grow single crystals of the target compounds were unsuccessful. However, crystals of sufficient quality for X-ray determination were obtained for compound **4**. The crystal structure of this compound (Fig. 3) illustrates that the planarity of the conjugated terthienylenevinylene chain is maintained on introduction of the β-substituent as observed by Roncali et al.[19] in the only comparable crystal structure of tetra(thienylenevinylene). The dihedral angles between the S(1) and S(2) rings, the S(2) and S(3) rings, and the S(1) and S(3) rings are, respectively, 8.1(2), 7.2(2), and 8.5(2)°, and the thiophene rings are perfectly planar.

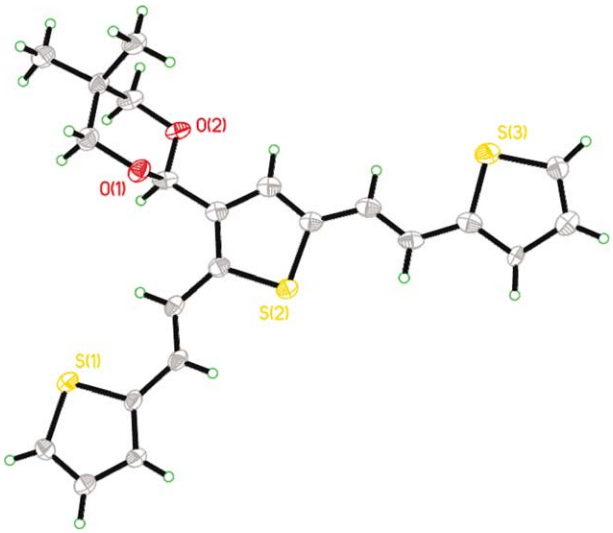


Figure 3. The crystal structure of **4**. Displacement ellipsoids were set at 50% of probability.

For terthiophene ring systems with substituents in the β-position of the central ring, the rings are far from coplanar. For example, in the case of 3′-phenyl-2,2′:5′,2″-terthiophene,[50] the two outer rings are twisted by −156 and 138.4° with respect to the central thiophene ring. With a styryl group in the 3-position, the torsion angle between the outer ring closest to the alkene linker on the central thiophene ring is −148.6° and the corresponding angle on the other side of the central thiophene ring is −151.2°.[5] This steric interaction that leads to a distortion of the thiophene rings has also been observed in other 3-substituted terthiophenes.[49] Thus, compared with terthiophene oligomers, the addition of the alkene spacers between the rings leads to an increase in the π-orbital overlap along the oligomer backbone.

2.5. Cyclic voltammetry

Cyclic voltammograms (CVs) for compounds **6a–e** are similar in appearance and those for **6e** are shown in Figure 4. The oxidation onset potential of **6a** (0.56 V) is lower than that measured for styrylterthiophene (0.74 V on a microelectrode), due to the greater stability of the bis(thienylvinyl)thiophene radical cation as a result of the extra conjugation introduced by the vinyl linkers. Oxidation onset potentials of 0.56 V are also measured for the compounds **6d**, and **6e** indicating that the reactivity of the 5′ and 5″ positions are not significantly affected by electron-withdrawing substituents at the *para*-position on the benzene ring. In contrast, the oxidation onset potential for **6b** is lower at 0.44 V, due to a stabilization of the resulting radical cation by the electron-donating substituent. Subsequent cycles show two oxidation peaks, the peak at potentials less than 0.5 V is the result of oxidation of the deposited electroactive film, and the cathodic peaks are most likely due to reduction of the oxidised film back to neutral material.

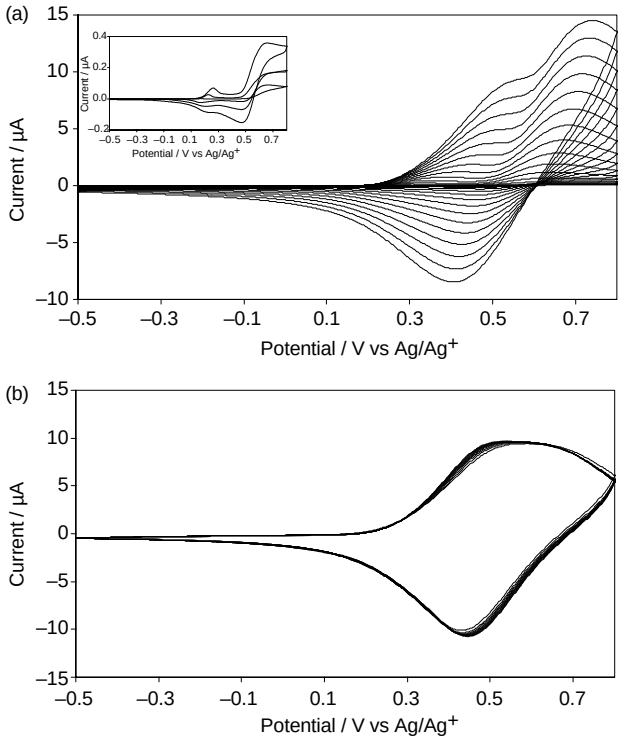


Figure 4. (a) Potentiodynamic growth of **6e** on a Pt microelectrode. Monomer concentration: 5 mM. Supporting electrolyte: 1:1 DCM–acetonitrile/0.1 M TBAP. Scan rate: 100 mV s^{-1}. The insert represents the first three cycles. (b) Post growth cycling of **6e** deposited on a Pt micro electrode. Supporting electrolyte: acetonitrile/0.1 TBAP. Scan rate: 100 mV s^{-1}.

The growth cyclic voltammogram of **6c** is different to that of the other samples. A much lower oxidation onset potential of 0.22 V is observed, and four oxidation and four reduction peaks are produced on the first scan. Subsequent scans show an increase in oxidation onset potential, and a decreasing growth in current with each cycle, indicating the deposition of poorly conducting material. These observations suggest that processes other than polymerisation through the 5′ and

5″ positions are occurring, possibly involving the dimethylamino substituent.[51,52]

Post-growth CVs of the electrochemically deposited films (see Fig. 4b for that of **6e**) reveal a considerable variation in the stability of the depositions. Those produced from **6b** and **6e** are quite stable, **6d** gives rise to a film that exhibits a gradual decrease in current with increasing cycle number, and the fall in current is rapid on post cycling of the films produced from **6a** and **6c**.

3. Conclusions

Wittig chemistry provides a convenient and straightforward method for the synthesis of β-styryl-functionalized bis(thienylvinyl)thiophenes. The electronic absorption spectra of all the molecules exhibit red shifts compared to those of the corresponding oligothiophenes as a result of an enhanced planarity, as confirmed by single crystal X-ray structural analysis of (*E*,*E*)-3-(5,5-dimethyl[1,3]dioxin-2-yl)-2,5-bis(2-thien-2-ylvinyl)thiophen, and the consequent increase in the effective conjugation lengths. The λ_{max} values fall in a narrow range and are similar to those observed in unsubstituted oligothienylenevinylenes showing that the nature of the styryl substituent has little effect on the HOMO–LUMO gap in these compounds. With the exception of the dimethylamino derivative **6c**, electroactive films are produced on electrochemical oxidation of the bis(thienylvinyl)thiophene monomers. A full investigation into the polymerization of these materials is currently underway.

4. Experimental

4.1. General

NMR spectra were recorded on a Bruker Avance 400 spectrometer using TMS as the internal standard. In some cases not all of the carbon resonances were resolved due to the overlap of peaks. The UV spectra were recorded on a Shimadzu UV3101PC spectrometer using dichloromethane as the solvent. The melting points are uncorrected. All new compounds were determined to be greater than 95% pure by ^{1}H NMR spectroscopy.

Cyclic voltammograms were recorded in air using an Autolab Potentiostat Galvanostat running Autolab GPES software. A one compartment, three-electrode glass cell was used for all measurements. The cell incorporated a platinum mesh counter electrode, a silver/silver chloride reference electrode, and the working electrode was a platinum microelectrode with a 10 μm^2 surface area. The scan rate used was 100 mV s^{-1} and the scans were started from the most negative potential. Films were grown using cyclic voltammetry between the limits of −0.5 and 0.8 V in 5 mM monomer solutions in 1:1 DCM–acetonitrile/0.1 M TBAP. Post growth electrochemistry was performed in acetonitrile/0.1 M TBAP monomer-free solutions. All solutions were freshly prepared and solutions were degassed by ultrasonification immediately prior to measurement.

Crystals for X-ray analysis were obtained by slow evaporation of ethanol. Data were collected on a Siemens SMART CCD diffractometer at 273 K with graphite-monochromated Mo Kα radiation (λ 0.71073 Å) using $\omega/2\theta$ scans. The structures were determined by means of direct methods[53] and refined by the full-matrix least squares technique.[54] All hydrogen atoms were obtained from the electron differential Fourier map and refined using a riding-model (C–H bonds set to 0.93 Å). Crystallographic data (excluding structure factors) for the structure in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 271152. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB 2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

2,5-Dibromo-3-thiophenylcarbaldehyde (**1**),[5] 5,5-dimethyl-2-(2,5-dibromothiophen-3-yl)[1,3]dioxane (**2**)[5] and thiophen-2-ylmethyltriphenylphosphonium bromide,[55] were synthesized according to literature procedures. Other reagents used in the syntheses were obtained from commercial sources.

4.1.1. 3-(5,5-Dimethyl-[1,3]dioxan-2-yl)thiophene-2,5-dicarbaldehyde (3). Dibromide **2** (5.10 g, 0.015 mol) was dissolved in dry THF (75 mL), cooled to −78 °C, and a solution of 2.5 mol L^{-1} *n*-butyl lithium in hexane (14 mL, 0.035 mol) was added dropwise by a syringe. The resulting mixture was stirred at −78 °C for 30 min before a solution of dry DMF (6.60 g, 0.09 mol) in THF (10 mL) was added. The reaction mixture was left to reach room temperature, stirred for 30 min, and poured into 1 mol L^{-1} hydrochloric acid (150 mL) before being extracted twice with diethyl ether. The organic layer was separated, dried over magnesium sulphate and evaporated to dryness at 50 °C under reduced pressure to give a brownish oil. After purification on silica, using 30% ethyl acetate in hexane as eluent, a colourless oil was obtained (3.11 g, 82%). Recrystallization from hexane at −20 °C gave colourless crystals: mp 69–70 °C; δ_H (400 MHz, $CDCl_3$) 10.35 (1H, s, 2-C*H*O), 9.97 (1H, s, 5-C*H*O), 7.91 (1H, s, Th*H*4), 5.81 (1H, s, diox-*H*2), 3.81 (2H, d, J=11 Hz, CH_2), 3.70 (2H, d, J=11 Hz, CH_2), 1.29 (3H, s, *Me*), 0.84 (3H, s, *Me*); δ_C (100.6 MHz, $CDCl_3$) 184.3, 183.3, 147.1, 145.9, 135.4, 97.2, 77.7, 30.2, 23.1, 21.8; *m*/*z* (EI) 254 (39, M$^+$), 185 (10), 168 (72), 139 (28), 70 (35), 56 (100), 41 (57), 39 (34%); HRMS (EI): M$^+$, found 254.06010. $C_{12}H_{14}O_2S$ requires 254.0613; ν_{max} (KBr) 3320, 3110, 2960, 2865, 1675, 1665, 1545, 1465, 1380, 1365, 1335, 1310, 1225, 1205, 1150, 1110, 1020, 1010 cm^{-1}.

4.1.2. (*E*,*E*)-3-(5,5-Dimethyl[1,3]dioxin-2-yl)-2,5-bis(2-thien-2-ylvinyl)thiophene (4). Dialdehyde **3** (2.54 g, 0.010 mol) and triphenylthiophen-2-ylmethylphosphonium bromide (9.67 g, 0.022 mol) were dispersed in dry THF (75 mL). DBU (7.5 g, 0.05 mol) was added and the resulting mixture was refluxed under argon for 5 h. The reaction mixture was poured into 1 mol L^{-1} hydrochloric acid (300 mL) before being extracted twice with dichloromethane. The organic extracts were dried over magnesium sulphate and evaporated to dryness at 50 °C under vacuum to yield a dark-brown oil. Purification on silica, using 30% ethyl acetate in hexane as eluent, and recrystallization from

a dichloromethane/methanol mixture gave fine yellow prisms (1.86 g, 45%): mp 172–174 °C; δ_H (400 MHz, $CDCl_3$) 7.27 (d, 1H, $J=15.7$ Hz, 5-vinyl-H), 7.19 (1H, dd, $J=5.2$, 1.0 Hz, Th-*H*5′), 7.17 (1H, dd, $J=5.2$, 1.0 Hz, Th-*H*5″), 7.08 (1H, s, Th-*H*4), 7.04 (1H, dd, $J=3.6$, 1.0 Hz, Th-*H*3′), 7.03 (1H, dd, $J=3.6$, 1.0 Hz, Th-*H*3′), 7.02 (1H, d, $J=15.7$ Hz, 2-vinyl-*H*), 7.00 (1H, d, $J=15.8$ Hz, 5-vinyl-*H*), 6.99 (1H, dd, $J=5.2$, 3.6 Hz, Th-*H*4′), 6.98 (1H, dd. $J=5.2$, 3.6 Hz, Th-*H*4″), 6.93 (1H, d, $J=15.8$ Hz, 5-vinyl-*H*), 5.52 (1H, s, diox-*H*2), 7.79–3.77 (2H, m, CH_2), 3.67–3.64 (2H, m, CH_2), 1.35 (3H, s, CH_3), 0.81 (3H, s, CH_3); δ_C (100.6 MHz, $CDCl_3$) 142.5, 142.3, 139.8, 138.3, 137.0, 127.7, 126.8, 126.5, 126.2, 124.7, 124.5, 122.6, 121.8, 121.2, 119.5, 97.8, 77.7, 30.2, 23.2, 21.9; *m/z* (EI) 414 (100, M^+), 344 (15), 328 (24), 317 (14), 266 (12), 97 (10%); HRMS (EI): M^+ found 414.0780. $C_{22}H_{22}O_2S_3$ requires 414.0782; ν_{max} (KBr) 3105, 3015, 2950, 2860, 1461, 1430, 1400, 1375, 1354, 1330, 1310, 1280, 1235, 1210, 1155, 1105, 1040, 1015, 1000 cm^{-1}.

4.1.3. (*E*,*E*)-2,5-Bis(2-thien-2-ylvinyl)thiophene-3-carbaldehyde (5). Compound **4** (1.45 g, 3.5 mmol) was dissolved in dichloromethane (15 mL), then trifluoroacetic acid (15 mL) and water (5 mL) were added. The resulting mixture was stirred at room temperature for 1.5 h, placed into the separating funnel and the organic layer collected, washed with water, then with a saturated solution of sodium bicarbonate and dried over magnesium sulphate. The solvent was removed under vacuum at 50 °C and the residue was purified on silica using pure dichloromethane as eluent. The red-orange solid on recrystallization from a dichloromethane–methanol mixture gave fine red needles (0.95 g, 83%): mp 115–116 °C; δ_H (400 MHz, $CDCl_3$) 10.08 (1H, s, C*H*O), 7.70 (1H, d, $J=16.0$ Hz, 2-vinyl-*H*), 7.31 (1H, dd, $J=5.0$, 1.2 Hz, Th-*H*5′), 7.26 (1H, s, Th-*H*4), 7.25 (1H, d, $J=16.0$ Hz, 2-vinyl-*H*), 7.23 (1H, dd, $J=5.0$, 1.2 Hz, Th-*H*5″), 7.17 (1H, dd, $J=3.6$, 1.2 Hz, Th-*H*3′), 7.07 (1H, dd, $J=3.6$, 1.2 Hz, Th-*H*3″), 7.04 (1H, dd, $J=5.0$, 3.6 Hz, Th-*H*4′), 7.01 (1H, dd, $J=5.0$, 3.6 Hz, Th-*H*4″) 7.00 (1H, d, $J=16.0$ Hz, 5-vinyl-*H*), 6.93 (1H, d, $J=16$ Hz, 5-vinyl-*H*); δ_C (100.6 MHz, $CDCl_3$) 184.0, 149.8, 141.6, 141.5, 140.0, 136.9, 128.3, 128.0, 127.8, 127.0, 126.9, 126.6, 126.5, 125.3, 123.6, 120.2, 117.8; *m/z* (EI) 328 (100, M^+), 295 (20), 266 (22), 134 (10), 156 (10%); HRMS (EI): M^+ found 328.0047. $C_{17}H_{12}OS_3$ requires 328.0050; ν_{max} (KBr) 3080, 1660, 1600, 1530, 1505, 1460, 1425, 1385, 1350, 1280, 1195, 1145, 1045 cm^{-1}.

4.2. General procedure for preparation of styryl derivatives 6b–e

Aldehyde **5** (104 mg, 0.32 mmol) and 1.2 equiv of phosphonium salt were dispersed in THF (10 mL). To the suspension DBU (1.0 g, 6.7 mmol) was added and the mixture refluxed overnight under argon. The reaction mixture was then diluted with dichloromethane and washed with 1 mol L^{-1} hydrochloric acid. The organic layer was separated, dried over magnesium sulphate and the solvents were removed under vacuum at 50 °C. The residue was purified on silica using pure dichloromethane as an eluent and recrystallized.

4.2.1. (*E*,*E*,*E*)-2,5-Bis(2-thien-2-ylvinyl)-3-(2-(4-methoxyphenyl)vinyl)thiophene (6b). Recrystallization from dichloromethane/methanol yielded yellow needles (69%): mp 171–172 °C; δ_H (400 MHz, $CDCl_3$) 7.46 (2H, d, $J=8.6$ Hz, Ar-*H*), 7.24 (1H, d, $J=16.1$ Hz, 2-vinyl-*H*), 7.21 (2H, dd, $J=5.5$, 1.2 Hz, Th-*H*5′, *H*5″), 7.19 (1H, s, Th-*H*4), 7.09 (1H, d, $J=16.0$ Hz, 3-vinyl-*H*), 7.06 (2H, dd, $J=5.5$, 3.6 Hz, Th-*H*3′, *H*3″), 7.05 (1H, d, $J=16.0$ Hz, 5-vinyl-*H*),7.03 (1H, d, $J=16.1$ Hz, 2-vinyl-*H*), 7.02 (1H, d, $J=16.0$ Hz, 5-vinyl-*H*), 7.01 (2H, dd, $J=3.6$, 1.2 Hz, Th-*H*4′, *H*4″), 6.92 (2H, d, $J=8.6$ Hz, Ar-*H*), 6.84 (1H, d, $J=16.0$ Hz, 3-vinyl-*H*), 3.84 (3H, s, CH_3); δ_C (100.6 MHz, $CDCl_3$) 142.7, 142.2, 139.9, 137.8, 136.3, 130.0, 129.5, 127.8, 127.7, 127.6, 126.4, 126.3, 125.0, 124.7, 124.6, 122.4, 121.9, 121.2, 119.1, 118.2, 55.3; *m/z* (EI) 432 (100, M^+), 335 (18), 311 (11), 121 (10%); HRMS (EI): M^+ found 432.0673. $C_{25}H_{20}OS_3$ requires 432.0676; λ_{max} nm (ε) 343 (48,500), 357 (49,500), 406 sh (28,500), 429 (33,000), 453 (24,000).

4.2.2. (*E*,*E*,*E*)-2,5-Bis(2-thien-2-ylvinyl)-3-(2-(4-dimethylaminophenyl)vinyl)thiophene (6c). Recrystallization from dichloromethane/methanol yielded fragile orange plates (23%): mp 205–206 °C; δ_H (400 MHz, $CDCl_3$) 7.42 (2H, d, $J=8.8$ Hz, Ar-*H*); 7.25 (1H, d, $J=15.6$ Hz, 2-vinyl-*H*), 7.19 (2H, dd, $J=5.5$, 1.2 Hz, Th-*H*5′, *H*5″), 7.18 (1H, s, Th-*H*4), 7.05 (2H, dd, $J=5.5$, 3.6 Hz, Th-*H*3′, *H*3″), 7.04 (1H, d, $J=16.0$ Hz, 3-vinyl-*H*), 7.02–6.98 (5H, m, Th-*H*4′, *H*4″, 2×5-vinyl-*H*, 2-vinyl-*H*), 6.88 (1H, d, $J=15.6$ Hz, 3-vinyl-*H*), 6.73 (2H, d, $J=8.8$ Hz, Ar-*H*), 2.99 (6H, s, NCH_3); δ_C (100.6 MHz, $CDCl_3$) 150.3, 142.7, 142.4, 139.8, 138.5, 135.4, 130.6, 127.8, 127.7, 127.6, 126.3, 126.0, 125.1, 124.6, 124.4, 122.2, 121.4, 121.3, 119.4, 116.1, 112.5, 40.4; *m/z* (EI) 445 (100, M^+), 348 (19), 222 (10), 134 (52), 105 (24), 91 (33), 69 (22), 57 (31), 49 (44%); HRMS (EI): M^+ found 445.0994. $C_{26}H_{23}NS_3$ requires 445.0993; λ_{max} nm (ε) 378 (60,000), 436 sh (33,500).

4.2.3. (*E*,*E*,*E*)-2,5-Bis(2-thien-2-ylvinyl)-3-(2-(4-cyanophenyl)vinyl)thiophene (6d). Recrystallization from dichloromethane/methanol yielded yellow prisms (73%): mp 172–173 °C; δ_H (400 MHz, $CDCl_3$) 7.63 (2H, d, $J=8.4$ Hz, Ar-*H*), 7.56 (2H, d, $J=8.4$ Hz, Ar-*H*), 7.29 (1H, d, $J=16.1$ Hz, 3-vinyl-*H*), 7.24 (1H, d, $J=5.2$ Hz, Th-*H*5′), 7.22 (1H, d, $J=5.2$ Hz, Th-*H*5″), 7.19 (1H, d, $J=15.3$ Hz, 2-vinyl-*H*), 7.17 (1H, s, Th-*H*4), 7.09 (1H, d, $J=3.6$ Hz, Th-*H*3′), 7.08 (1H, d, $J=15.3$ Hz, 2-vinyl-*H*), 7.06 (1H, d, $J=3.6$ Hz, Th-*H*3″), 7.03 (1H, dd, $J=5.2$, 3.6 Hz, Th-*H*4′), 7.02 (1H, d, $J=16.0$ Hz, 5-vinyl-*H*), 7.01 (1H, dd, $J=5.2$, 3.6 Hz, Th-*H*4″), 6.96 (1H, d, $J=16.0$ Hz, 5-vinyl-*H*), 6.89 (1H, d, $J=16.1$ Hz, 3-vinyl-*H*); δ_C (100.6 MHz, $CDCl_3$) 142.2, 142.0, 141.8, 140.4, 138.9, 136.3, 132.5, 127.9, 127.8, 127.7, 126.9, 126.8, 126.7, 125.1, 125.0, 124.5, 123.5, 123.1, 122.9, 120.8, 118.4, 110.6; *m/z* (EI) 247 (100, M^+), 330 (18), 97 (15), 91 (12%); HRMS (EI): M^+ found 427.0526. $C_{25}H_{17}NS_3$ requires 427.0523; λ_{max} nm (ε) 346 (49,500), 361 (49,500), 427 (39,000), 451 sh (32,000).

4.2.4. (*E*,*E*,*E*)-2,5-Bis(2-thien-2-ylvinyl)-3-(2-(4-nitrophenyl)vinyl)thiophene (6e). Recrystallization from dichloromethane/methanol yielded red plates and blocks (70%): mp 185–186 °C; δ_H (400 MHz, $CDCl_3$) 8.22 (2H, m, Ar-*H*), 7.61 (2H, m, Ar-*H*), 7.64 (1H, d, $J=16.1$ Hz,

3-vinyl-*H*), 7.25 (1H, d, $J=4.8$ Hz, Th-*H*5′), 7.23 (1H, d, $J=4.8$ Hz, Th-*H*5″), 7.20 (1H, d, $J=16.0$ Hz, 2-vinyl-*H*), 7.18 (1H, s, Th-*H*4), 7.10 (1H, d, $J=3.6$ Hz, Th-*H*4′), 7.07 (1H, d, $J=16.0$ Hz, 2-vinyl-*H*), 7.06 (1H, d, $J=3.6$ Hz, Th-*H*3″), 7.02 (1H, d, $J=15.6$ Hz, 5-vinyl-*H*), 7.02 (1H, dd, $J=4.8$, 3.6 Hz, Th-4′), 7.01 (1H, dd, $J=4.8$, 3.6 Hz, Th-4″), 6.96 (1H, d, $J=15.6$ Hz, 5-vinyl-*H*), 6.94 (1H, d, $J=16.1$ Hz, 3-vinyl-*H*); δ_C (100.6 MHz, $CDCl_3$) 146.7, 143.8, 142.2, 142.0, 140.4, 139.4, 136.2, 127.9, 127.8, 127.1, 127.0, 126.7, 125.2, 125.0, 124.4, 124.3, 124.2, 123.3, 123.0, 120.8, 118.3; *m/z* (EI) 447 (100, M^+), 445 (22), 417 (48), 350 (13), 106 (27), 105 (14), 97 (12), 91 (18), 55 (17), 43 (19%); HRMS (EI): M^+ found 447.0414. $C_{24}H_{17}NO_2S_3$ requires 447.0421; λ_{max} nm (ε) 335 (23,500), 379 (39,500), 422 (39,500), 446 sh (32,000).

4.2.5. (*E*,*E*)-2,5-Bis(2-thien-2-ylvinyl)-3-(1,3-indandion-2-ylmethylen)thiophene (7). Aldehyde **5** (77 mg, 0.23 mmol) and 1,3-indandione (0.034 g, 0.23 mmol) were dissolved in dry THF (10 mL) and piperidine (1 mL, 10 mmol) was added. The colour of the reaction mixture immediately turned to deep red. After stirring overnight at room temperature the reaction mixture was diluted with dichloromethane and washed with 1 mol L^{-1} hydrochloric acid. The organic layer dried over magnesium sulphate and the solvents were removed under vacuum at 50 °C. The residue was purified on silica using pure dichloromethane as an eluent and recrystallization from dichloromethane/methanol yielded red irregular crystals (57 mg, 53%): mp 186 °C dec; δ_H (400 MHz, $CDCl_3$) 8.60 (1H, s, Th-*H*4), 7.98–7.95 (2H, m, Ar-*H*), 7.96 (1H, s, 3-vinyl-*H*), 7.80–7.78 (2H, m, Ar-*H*), 7.42 (1H, d, $J=15.5$ Hz, 2-vinyl-*H*), 7.32 (1H, d, $J=5.0$ Hz, Th-*H*5′), 7.26 (1H, d, $J=15.5$ Hz, 2-vinyl-*H*), 7.22 (1H, d, Th-*H*5″), 7.19 (1H, d, $J=3.6$ Hz, Th-*H*3′), 7.09–7.03 (4H, m, Th-*H*3″, 5-vinyl-*H*, Th-*H*4′), 7.00 (1H, dd, $J=5.0$, 3.6 Hz, Th-*H*4″); δ_C (100.6 MHz, $CDCl_3$) 190.7, 189.3, 153.2, 142.6, 142.0, 141.6, 140.0, 139.4, 135.1, 135.0, 133.58, 133.55, 130.5, 128.5, 128.1, 127.7, 126.9, 126.8, 126.7, 126.6, 125.2, 123.3, 123.1, 123.0, 120.9, 117.6; *m/z* (EI) 456 (11, M^+), 307 (24), 289 (12), 155 (26), 154 (100), 137 (57), 136 (67), 120 (12), 107 (24), 89 (22), 77 (23%); HRMS (EI): M^+ found 456.0313. $C_{26}H_{16}O_2S_3$ requires 456.0313; λ_{max} nm (ε) 377 (48,500), 400 sh (40,000), 517 (18,000).

4.2.6. 3-(2-Phenylvinyl)-2,5-dibromothiophene (8). Dibromide **1** (9.67 g, 0.036 mol) and benzyltriphenylphosphonium chloride (13.93 g, 0.036 mol) were dispersed in THF (100 mL). To the resulting suspension DBU (10 g, 6.6 mmol) was added and the resulting mixture refluxed overnight under argon. The resulting reaction mixture was diluted with dichloromethane and washed with 1 mol L^{-1} hydrochloric acid. The organic layer was separated, dried over magnesium sulphate and the solvents removed under vacuum at 50 °C. The residue was purified on silica using 10% ethyl acetate in hexane as eluent to give a yellow oil (10.5 g, 85%): δ_H (400 MHz, $CDCl_3$) 7.51 (2H, m, *E*-Ph-*H*), 7.37–7.35 (3H, m, *E*-Ph-*H*), 7.29–7.23 (5H, m, *Z*-Ph-*H*), 7.23 (1H, s, Th-*H*4-*E*), 7.01 (1H, d, $J=12.8$ Hz, vinyl-*H*-*Z*), 6.91 (1H, d, $J=12.8$ Hz, vinyl-*H*-*Z*), 6.69 (1H, d, $J=16.0$ Hz, vinyl-*H*-*E*), 6.60 (1H, s, Th-*H*4-*Z*), 6.33 (1H, d, $J=16.0$ Hz, vinyl-*H*-*E*); δ_C (100.6 MHz, $CDCl_3$) 139.1, 138.3, 136.6, 136.4, 132.2, 131.3, 130.2, 128.8, 128.7, 128.4, 128.2, 127.8, 127.4, 126.6, 121.6, 120.0, 111.9, 111.6, 110.5, 110.1; *m/z* (EI) 346 (6, M^+), 344 (12), 342 (7), 184 (100), 139 (11), 92 (12%); HRMS (EI): M^+ found 341.8710. $C_{12}H_8Br_2S$ requires 341.8713.

4.2.7. (*E*)-3-(2-Phenylvinyl)thiophene-2,5-dicarbaldehyde (9). Compound **8** (1.65 g, 4.8 mmol) was dissolved in dry THF (30 mL), cooled to −78 °C and a 2.5 mol L^{-1} solution of *n*-butyl lithium in hexane (3.8 mL, 9.5 mmol) was added dropwise with a syringe. The resulting mixture was stirred at −78 °C for 15 min then dry DMF (6.6 g, 20 mmol) dissolved in THF (5 mL) was added. The reaction mixture was allowed to reach room temperature for 30 min before being poured into 150 mL of 1 mol L^{-1} hydrochloric acid and extracted twice with dichloromethane. The organic layers were dried over magnesium sulphate and evaporated to dryness under reduced pressure at 50 °C to yield a dark oil. After purification on silica using dichloromethane as eluent yellow crystals of *E*/*Z* **9** were obtained (0.92 g, 80%). *Isomerization procedure*. Compound *E*/*Z* **9** (1.69 g, 7 mmol) was dissolved in dichloromethane (50 mL) and iodine (5.33 g, 21 mmol) was added. The resulting mixture was stirred at room temperature for 7 days then washed with saturated solution of sodium thiosulphate and water. The organic layer was dried over magnesium sulphate, evaporated to dryness and the residue was purified on silica using dichloromethane as eluent. Recrystallization from an ethanol–water mixture yielded thin yellow needles of **9** (1.25 g, 74%): mp 133–134 °C; δ_H (400 MHz, $CDCl_3$) 10.29 (1H, s, 2-C*H*O), 10.03 (1H, s, 5-C*H*O), 8.09 (1H, s, Th-*H*4), 7.69 (1H, d, $J=16.2$ Hz, vinyl-*H*), 7.57–7.55 (2H, m, Ph-*H*), 7.44–7.40 (3H, m, Ph-*H*), 7.24 (1H, d, $J=16.2$ Hz, vinyl-*H*); δ_C (100.6 MHz, $CDCl_3$) 183.4, 182.8, 147.9, 146.1, 141.8, 135.9, 135.7, 133.5, 129.3, 129.0, 127.1, 118.4; *m/z* (EI) 242 (100, M^+), 213 (22), 185 (62), 184 (37), 165 (11), 152 (20), 141 (16), 92 (10%); HRMS (EI): M^+ found 242.0399. $C_{14}H_{10}O_2S$ requires 242.0402.

4.2.8. (*E*,*E*,*E*)-2,5-Bis(2-thien-2-ylvinyl)-3-(2-phenylvinyl)thiophene (6a). Compound **9** (1.21 g, 5 mmol) and thiophen-2-ylmethyltriphenylphosphonium bromide (4.83 g, 11 mmol) were dispersed in dry THF (30 mL). DBU (3.00 g, 19.7 mmol) was added and the mixture was refluxed under argon overnight. The resulting reaction mixture was poured into of 1 mol L^{-1} hydrochloric acid (100 mL) and extracted twice with dichloromethane. The organic layers were dried over magnesium sulphate and evaporated to dryness under reduced pressure at 50 °C. The residue was purified on silica using 20% ethyl acetate in hexane as eluent and recrystallized from dichloromethane–methanol mixture to give irregular yellow-orange blocks (1.24 g, 62%): mp 156–157 °C; δ_H (400 MHz, $CDCl_3$) 7.52 (3H, m, Ph-*H*), 7.37 (1H, d, $J=15.9$ Hz, 3-vinyl-*H*), 7.36 (2H, s, Ph-*H*), 7.27 (1H, d, $J=15.9$ Hz, 3-vinyl-*H*), 7.29–20 (4H, m, Th-*H*5′, *H*5″, *H*3′, *H*3″), 7.22 (1H, d, $J=16.0$ Hz, 2-vinyl-*H*), 7.20 (1H, d, $J=15.9$ Hz, 5-vinyl-*H*), 7.19 (1H, s, Th-*H*4), 7.06 (1H, dd, $J=5.2$, 3.6 Hz, Th-*H*4′), 7.02 (1H, d, $J=16.0$ Hz, 2-vinyl-*H*), 7.00 (11H, dd, $J=5.2$, 3.6 Hz, Th-*H*4″), 6.93 (d, 1H, $J=15.9$ Hz, 5-vinyl-H); δ_C (100.6 MHz, $CDCl_3$) 142.6, 142.2, 137.4, 127.3, 137.1, 129.9, 128.9, 128.7, 128.3, 127.8, 127.7, 126.5, 125.0, 124.7, 124.6, 122.5, 122.2, 121.1, 120.2, 118.9; *m/z* (EI) 402 (100, M^+), 311 (12), 305 (21), 292 (10%); HRMS (EI): M^+

found 402.0568. $C_{24}H_{18}S_3$ requires 402.0571; λ_{max} nm (ε): 336 (39,500), 351 (38,500), 406 sh (25,000), 428 (31,000), 451 (24,500).

4.2.9. (*E*)-3-(2-(4-Methoxyphenyl)vinyl)-2,5-diiodothiophene (11). Compound **10** (4.86 g, 10 mmol) and 4-methoxybenzaldehyde (1.43 g, 11 mmol) were dissolved in THF (50 mL) and cooled to 0 °C. To the resulting solution potassium *tert*-butoxide (2.24 g, 20 mmol) was added, the cooling bath was removed and the resulting mixture stirred at room temperature overnight under argon. The resulting reaction mixture was diluted with dichloromethane and washed with 1 mol L^{-1} hydrochloric acid. The organic layer was dried over magnesium sulphate and the solvents were removed under vacuum at 50 °C. The residue was purified on silica using 30% dichloromethane in hexane as eluent and recrystallized from ethanol to give fine white needles (3.55 g, 76%): mp 99–100 °C; δ_H (400 MHz, $CDCl_3$) 7.45–7.43 (2H, m, Ar-*H*), 7.29 (1H, s, Th-*H*4), 6.91–6.89 (2H, m, Ar-*H*), 6.86 (1H, d, $J=16.2$ Hz, vinyl-*H*), 6.75 (1H, d, $J=16.2$ Hz, vinyl-*H*), 3.83 (3H, s, OCH_3); δ_C (100.6 MHz, $CDCl_3$) 159.7, 145.3, 134.4, 131.1, 129.3, 127.9, 114.2, 78.6, 77.2, 55.3; *m/z* (EI) 468 (73, M^+), 342 (13), 214 (100), 199 (21), 171 (48), 107 (10%); HRMS (EI): M^+ found 467.8543. $C_{13}H_{10}I_2OS$ requires 467.8542.

4.2.10. (*E*)-3-(2-(4-Methoxyphenyl)vinyl)thiophene-2,5-dicarbaldehyde (12). Compound **11** (2.43 g, 5 mmol) was dissolved in dry THF (20 mL), cooled to −78 °C, and a 2.5 mol L^{-1} solution of *n*-butyl lithium in hexane (4 mL, 0.010 mol) was added dropwise with a syringe. The resulting mixture was stirred at −78 °C for 15 min, after which, a solution of dry DMF (2.19 g, 0.03 mol) in THF (1 mL) was added. The reaction mixture was allowed to reach room temperature before being poured into 1 mol L^{-1} hydrochloric acid (150 mL) and extracted twice with dichloromethane. The organic layer was separated, dried over magnesium sulphate and evaporated to dryness under reduced pressure at 50 °C to give a brownish oil. Purification on silica, using dichloromethane as eluent followed by recrystallization from ethanol yielded yellow crystals (0.98 g, 72%): mp 142–144 °C; δ_H (400 MHz, $CDCl_3$) 10.26 (1H, s, 2-C*H*O), 10.01 (1H, s, 5-C*H*O); 8.05 (1H, s, Th-*H*4), 7.54 (1H, d, $J=16$ Hz, vinyl-*H*), 7.50–7.48 (2H, m, Ar-*H*), 7.18 (1H, d, $J=16$ Hz, vinyl-*H*), 6.95–6.92 (2H, m, Ar-*H*), 3.85 (3H, s, OCH_3); δ_C (100.6 MHz, $CDCl_3$) 183.5, 182.8, 160.5, 147.8, 146.6, 141.0, 135.5, 133.4, 128.5, 128.3, 116.2, 114.4, 55.4; *m/z* (EI) 272 (100, M^+), 215 (16), 200 (18), 184 (12), 108 (10%); HRMS (EI): M^+ found 272.0508. $C_{15}H_{12}O_3S$ requires 272.0507.

4.2.11. (*E*,*E*,*E*)-2,5-Bis(2-thien-2-ylvinyl)-3-(2-(4-methoxyphenyl)vinyl)thiophene (6b). Compound **13** (0.27 g, 1 mmol) and thiophen-2-ylmethyltriphenylphosphonium bromide (0.97 g, 2.2 mmol) were dispersed in dry THF (50 mL). DBU (1.0 g, 6.6 mmol) was added and the mixture was refluxed overnight under argon. The resulting reaction mixture was poured into 1 mol L^{-1} hydrochloric acid (100 mL) and extracted twice with dichloromethane. The organic layers were dried over magnesium sulphate and evaporated to dryness under vacuum at 50 °C. The residue was purified on silica using 20% ethyl acetate in hexane as eluent and recrystallized from dichloromethane–methanol mixture to give fine yellow needles of **6b**. (0.35 g, 82%).

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Malonganenones A–C, novel tetraprenylated alkaloids from the Mozambique gorgonian *Leptogorgia gilchristi*

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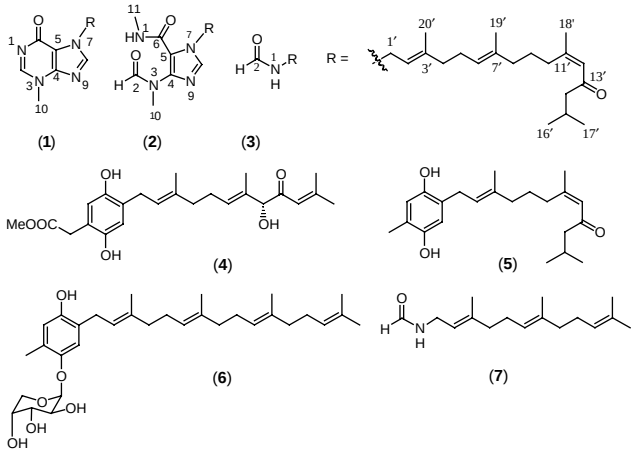
Abstract—Three novel tetraprenylated alkaloids, malonganenones A–C (**1**–**3**), were isolated from the gorgonian *Leptogorgia gilchristi* collected near Ponto Malongane, Mozambique. Compound **1** is the first 3,7-disubstituted hypoxanthine to be discovered from a marine source, while **2** and **3** represent the first formamides to be isolated from gorgonians. The unexpected facile exchange of the formamide proton of **2** with a deuteron originating from the NMR solvent used for spectroscopic analysis hampered initial attempts at the structural elucidation of this compound. The anti-oesophageal cancer activities of **1**–**3** are compared with that of rietone (**4**), a related triprenylated compound previously isolated from a South African soft coral.

1. Introduction

Gorgonians produce a plethora of novel natural products with diverse carbon skeletons and biological activities. There have, however, been very few examples of nitrogenous compounds reported from gorgonian species. Examples include nucleosides,[1] diterpene alkaloids,[2–4] sphingosines,[5] and a β-carboline carboxylic acid.[6] In continuation of our search for novel anti-oesophageal cancer agents from southern African marine invertebrates,[7] we have examined a moderately cytotoxic methanol extract of the gorgonian *Leptogorgia gilchristi* collected off a reef near Ponto Malongane, Mozambique. Exhaustive chromatography of an EtOAc partition fraction of the *L. gilchristi* extract yielded three novel cytotoxic tetraprenylated alkaloids, malonganenones A–C (**1**–**3**). Interestingly, polyprenylated metabolites are relatively common in southern African octocorals. We have previously reported the isolation of rietone (**4**) from the soft coral *Alcyonium fauri*[8] and a cohort of nine closely related triprenylated quinones and hydroquinones, for example, **5** from the arminacean nudibranch *Leminda millecra*, a conspicuous predator of various southern African octocorals including the gorgonian *Leptogorgia palma*.[9] A tetraprenylhydroquinone, nephthoside (**6**), has also been isolated from a southern African soft coral *Nephthea* sp.[10]



2. Results and discussion

Initial attempts to isolate **1**–**3** were unsuccessful. Although several fractions generated from silica flash-chromatography and normal-phase HPLC appeared to contain single compounds from ^{1}H NMR ($CDCl_3$), the corresponding

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Table 1. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR data of **1**, **2**, and **3**

Position	**1**[a]				**2**[b]				**3**[b]			
	δ_C	δ_H	mult. J (Hz), Int.	$^{1}J_{C,H}$[c]	δ_C	δ_H	mult. J (Hz), Int.	$^{1}J_{C,H}$[c]	δ_C	δ_H	mult. J (Hz), Int.	$^{1}J_{C,H}$[c]
1	—	—	—	—	—	8.00	br q (4.9), 1H	—	—	8.00	br s, 1H	—
2	149.9	8.25	d (2.3), 1H	—	162.2	8.18	s, 1H	199	160.6	7.97	s, 1H	189
4	149.1	—	—	—	140.1	—	—	—	—	—	—	—
5	115.9	—	—	—	117.0	—	—	—	—	—	—	—
6	164.5	—	—	—	159.9	—	—	—	—	—	—	—
8	143.3	8.08	br s, 1H	213	136.3	7.66	d (2.5), 1H	210	—	—	—	—
10	35.5	3.87	d (2.6), 3H	143	31.2	3.07	s, 3H	140	—	—	—	—
11	—	—	—	—	25.7	2.70	d (4.5), 3H	138	—	—	—	—
1′	45.5	5.07	t (7.2), 2H	142	43.8	4.72	dd (6.5, 3.4), 2H	141	35.0	3.67	dd (10.5, 6.3), 2H	137
2′	119.9	5.50	dddd (7.1, 6.0, 2.3, 1.1), 1H	158	119.3	5.25	t (6.8), 1H	158	120.8	5.12	t (6.3), 1H	155
3′	143.5	—	—	—	140.3	—	—	—	137.5	—	—	—
4′	40.4	2.16	mult., 2H	—	38.9	2.00	mult., 2H	—	38.9	2.02	mult., 2H	—
5′	27.0	2.13	mult., 2H	—	25.7	2.05	mult., 2H	—	25.9	2.04	mult., 2H	—
6′	125.1	5.08	t (7.1), 1H	150	127.6	5.05	t (5.9), 1H	—	120.8	5.08	t (6.2), 1H	151
7′	136.3	—	—	—	134.6	—	—	—	134.5	—	—	—
8′	40.8	1.95	t (7.3), 2H	—	39.1	1.95	mult., 2H	—	39.3	1.95	mult., 2H	—
9′	27.6	1.46	mult., 2H	—	25.8	1.47	mult., 2H	—	25.8	1.45	mult., 2H	—
10′	34.4	2.46	td (8.0, 6.2), 2H	—	32.6	2.42	dd (8.1, 7.6), 2H	—	32.6	2.43	t (7.8), 2H	—
11′	161.2	—	—	—	157.7	—	—	—	157.8	—	—	—
12′	125.0	6.12	br d (1.5), 1H	155	124.1	6.10	s, 1H	152	124.1	6.10	s, 1H	154
13′	202.8	—	—	—	199.6	—	—	—	199.7	—	—	—
14′	54.3	2.26	d (7.1), 2H	124	54.3	2.24	t (7.9), 2H	125	52.6	2.24	d (7.0), 2H	125
15′	26.7	2.06	mult., 1H	—	24.4	2.02	mult., 1H	—	24.5	2.04	mult., 1H	—
16′	22.9	0.90	dt (6.7, 2.1), 3H	125	22.3	0.85	dt (6.0, 2.1), 3H	125	22.3	0.84	d (6.6), 6H	125
17′	22.9	0.90	dt (6.7, 2.1), 3H	125	22.3	0.85	dt (6.0, 2.1)3H	125	22.3	0.84	d (6.6), 6H	125
18′	25.6	1.87	d (1.3), 3H	127	24.8	1.83	d (0.9), 3H	126	24.9	1.83	d (1.0), 3H	126
19′	16.0	1.57	s, 3H	125	15.6	1.55	s, 3H	125	15.6	1.56	s, 3H	125
20′	16.6	1.83	s, 3H	126	15.7	1.70	s, 3H	126	15.9	1.62	s, 3H	126

[a] CD_3OD.
[b] d_6-DMSO.
[c] Detected as one-bond correlations in HMBC experiment.

^{13}C spectra revealed a doubling of resonances, which we initially attributed to possible acid catalysed *E*/*Z* isomerization of an enone functionality (evident from the preliminary NMR data) either during silica chromatography or from NMR analysis performed in $CDCl_3$ solution. Acetylation of this mixture of perceived isomers, in an attempt to improve their chromatographic properties, did not resolve the apparent isomeric mixture. Compounds **1**–**3** were eventually successfully isolated using non silica-based chromatography (polymeric reversed-phase separation followed by normal-phase flash-chromatography and HPLC using diol solid supports) and by avoiding $CDCl_3$ as an NMR solvent.

Malonganenone A (**1**; 29 mg) was isolated as a colorless glass. The molecular formula of **1**, established as $C_{26}H_{38}N_4O_2$ from HRFABMS data ($[M+H]^+$, 439.3730, calcd 439.3730), implied ten degrees of unsaturation. Two carbonyl stretching bands (1681, 1643 cm^{-1}) were the only significant absorbances observed in the IR spectrum. All 38 proton resonances were observed in the ^1H NMR spectrum (CD_3OD) indicating that no exchangeable protons were present. Conversely, only 25 carbon resonances were observed in the ^{13}C NMR spectrum, with a pair of overlapping signals assigned to the terminal methyl groups of the side-chain. Of the 25 carbon resonances observed (Table 1), three could be attributed to a trisubstituted enone functionality (δ_C C=O, 202.8, C=C 161.2, 125.0), four to two trisubstituted olefins (δ_C 143.5, 119.9 and 136.3, 125.1), two to a tetrasubstituted olefin (δ_C 149.1, 115.9), and one each to an imine (δ_C 149.9), a purine carbonyl (δ_C 164.5) and a *N*-methyl (δ_C 35.5), and finally three to vinylic methyls (δ_C 25.6, 16.6, 16.0). These carbon resonances accounted for eight degrees of unsaturation, which therefore required **1** to contain a bicyclic moiety.

The structure of the tetraprenyl side-chain of **1** was readily deduced from standard analysis of COSY and HMBC data. The proton resonances of the terminal isopropyl moiety of the tetraprenyl side-chain were assigned from a COSY cross-peak between the overlapping methyl resonances (H_3-16′ and H_3-17′) and the methine proton (H-15′). A further COSY correlation was observed between H-15′ and the methylene protons H_2-14′ while HMBC correlations from the olefinic proton H-12′, H_2-14′ and H-15′ to the α,β unsaturated carbonyl C-13′ (δ_C 202.8) linked the terminal isopropyl to the trisubstitutued enone moiety. Contiguous methylene groups in the tetraprenyl side-chain were assigned from COSY correlations, which were then connected on the basis of two- and three-bond HMBC correlations from the three vinylic methyls (Fig. 1). The geometries of the three olefins in the tetraprenyl side-chain were established from analysis of both chemical shift and NOE data. The ^{13}C chemical shift of vinyl methyl C-18′ (δ_C 25.6) in **1** was in accordance with the chemical shift of the analogous olefinic methyl in **5** (δ_C 25.2)[9] and suggested that the $\Delta^{11'}$ olefin in **1** also possessed a *Z* geometry. The $\Delta^{11'}$ *Z* assignment was further supported by an NOE correlation between H_3-18′ and H-12′. The ^{13}C chemical shifts of the two other olefinic methyls C-19′ and C-20′ (δ_C 16.6 and 16.0) in the tetraprenyl side-chain were consistent with *E* geometries for the $\Delta^{2'}$ and $\Delta^{6'}$ olefins, respectively.[9]

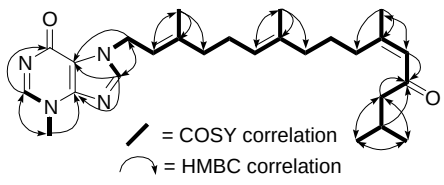


Figure 1. Key COSY and HMBC correlations used to establish the structure of **1**.

The evidence needed to position a bicyclic moiety at C-1′ in the side-chain of **1** was conclusively provided by a long range ^4J COSY correlation observed between the methylene protons H_2-1′ and the deshielded aromatic proton H-8 in addition to reciprocal HMBC correlations between these protons and their corresponding carbon resonances. HMBC data also unequivocally established the structure of the bicyclic ring system ($C_4H_2N_4O$) as a 3,7-disubstituted hypoxanthine (Fig. 1). Interestingly, there has only been one previous report of a dialkylated hypoxanthine marine natural product viz. 1,9-dimethylhypoxanthine isolated from the sponge *Spongosorites* collected off South Australia.[11] Conversely, hypoxanthine containing nucleosides (inosines) are more common, for example, trachycladine B from the Australian sponge *Trachycladus laevisiruifer*,[12] shimofuridins A–G from the tunicate *Aplidium multiplicatum*[13,14] and 3′-*O*-(α-D-glucosyl)inosine from the crustacean *Ligia exotica*.[15] Malonganenone A (**1**) is the first example of a 3,7-disubstituted hypoxanthine natural product from a marine source.

The molecular formula of malonganenone B (**2**; 14 mg), also isolated as a colorless glass, was established with some difficulty as $C_{27}H_{43}N_4O_3$ ($[M+H]^+$ 471.3335, calcd 471.3341) from HRESIMS data where a much larger peak at *m*/*z* 472.3398 dominated the HRESI mass spectrum. We eventually confirmed that this latter peak matched a formula of $C_{27}H_{42}DN_4O_3$, which suggested that one proton in **2** had been exchanged for a deuteron during the acquisition of the NMR data (CD_3OD) prior to mass spectral analysis. Comparison of the 1D and 2D NMR data of **2** (d_6-DMSO) with those of **1** (Table 1) confirmed that both compounds shared the same tetraprenyl side-chain structure, which accounted for four of the nine double bond equivalents required by the molecular formula, and limited the differences between these compounds to a cyclic moiety at C-1′.

HMBC data (Fig. 2) proved crucial in positioning a trisubstituted imidazole ring at C-1′ and provided evidence in support of the *N*-methylamide and *N*-methylformamide

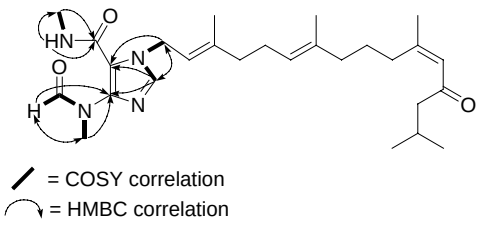


Figure 2. Key COSY and HMBC correlations used to establish the structure of the trisubstituted imidazole ring of **2**.

substituents on this ring. The sequence of HMBC correlations from H_2-1′ to C-8 and C-5 and from H-8 to both C-4 and C-5 together with the ^1H and ^{13}C chemical shifts of H-8 and C-4, C-5 and C-8 were reminiscent of those observed for the imidazole portion of the hypoxanthine ring system in **1** and suggested that both compounds shared an imidazole ring at C-1′.

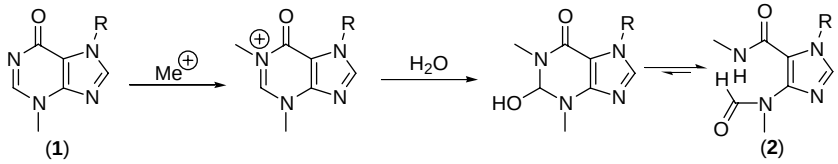
Establishing the structure of the *N*-methylformamide substituent on the imidazole ring proved to be challenging. HMBC correlations from the *N*-methyl protons (H_3-10) to C-4 quickly confirmed the attachment of an *N*-Me substituent at C-4 analogous to **1**. The *N*-methyl proton resonance (H_3-10), however, showed further HMBC correlations to two weak carbonyl resonances (δ_C 161.5 and 162.2) not observed in the ^{13}C NMR spectrum of **2** recorded at 100 MHz. A weak one-bond ^{13}C–^1H correlation was noted from the less shielded of the two resonances (δ_C 162.2) to proton H-2 in the HSQC spectrum. The integration of H-2 initially yielded a very small value when compared to integral values for other resonances observed in the ^1H spectrum of **2** (ca. 10% of H-8). Paradoxically, the H-2 resonance was sufficiently strong to detect a weak HMBC correlation from this proton to C-4 and C-10. A weak but significant $^1J_{C,H}$ coupling constant (199 Hz) for H-2/C-2 was measured in the HMBC spectrum which, although slightly larger, did compare favorably with that of DMF (191 Hz).[16] These NMR data were therefore deemed sufficient for the tentative incorporation of H-2 into a *N*,*N*-disubstituted formamide moiety and the presence of this functionality thus precluded the *N*-Me substituent at C-4 from being included in a second ring as in **1**.

The remaining substituent on the imidazole ring was established as an *N*-methylamide from a COSY correlation between the methyl doublet (H_3-11) and the broad exchangeable proton quartet (H-1) in addition to HMBC correlations from these protons to the amide carbonyl C-6 (δ_C 159.9). Although HMBC data could not place the *N*-methylamide substituent unequivocally at C-5, this was the only possible position for attachment of this substituent given the quaternary character of C-5 and the evidence supporting the positioning of the other two substituents at C-4 and N-7 on the imidazole ring.

The reduced proton integral for H-2, the HMBC evidence for two carbonyl ^{13}C resonances with similar chemical shifts and the presence of a deuterated analogue of **2** inferred from the HRESIMS data suggested that the formamide proton, H-2, had been exchanged for a deuteron while **2** was dissolved in the CD_3OD NMR solvent. This solvent had been used for all the NMR analyses during the isolation protocol and also for the initial structural elucidation studies. To confirm the suspected deuteron exchange with the formamide proton, the deuterated sample of **2** was lyophilized, re-dissolved in MeOH and allowed to stand for several days at room temperature, the MeOH removed under reduced pressure and the sample dried and dissolved in d_6-DMSO for further NMR analysis. As anticipated, the integral value of the H-2 resonance when the ^1H NMR spectrum of **2** was acquired in d_6-DMSO was found to be in accordance with other one proton signals in the ^1H NMR spectrum of this compound. The apparent splitting of the carbonyl resonance was attributed to the deuterium isotope effect in which the deuterated carbon is more shielded than the equivalent protonated carbon.[16,17] In addition, the absence of resonances in the ^{13}C NMR spectrum of **2** for these two forms of the carbonyl could have resulted from the small amount of the protonated formamide carbonyl carbon (δ_C 162.2) present in solution, and the reduction in signal intensity of the deuterated formamide carbonyl carbon (δ_C 161.5) through the combined effect of quadrupolar splitting of the ^{13}C resonance by the deuterium and also the generally longer T_1-relaxation time of ^{13}C–D.[16,17] Deuterium isotopic effects have been used previously in the structural elucidation of marine natural products although generally these have involved long range couplings over two or three-bonds.[18,19]

Although we were unable to establish the mechanistic details of the deuterium exchange of the acidic formamide proton in **2**, such exchange is not unprecedented in *N*,*N*-disubstitutued formamides and Simchen et al.[20,21] have reported this exchange to be particularly prevalent in CD_3OD solutions of the acetal derivatives of these compounds. The structural similarities between **1** and **2** suggest a possible biosynthetic link between these two compounds (Scheme 1).

Malonganenone C (**3**; 4 mg) was isolated as a yellow solid and the molecular formula readily deduced from HRESIMS as $C_{21}H_{36}NO_2$ ($[M+H]^+$ 334.2752, calcd 334.2746). The molecular formula of **3** differed from **1** by the loss of five carbons, three protons and three nitrogens, and thus precluded the presence of either the purine or imidazole rings characteristic of **1** and **2**, respectively. In particular, the molecular formula required only five double-bond equivalents as opposed to the ten required for **1** or nine for **2**. Careful analysis of the COSY and HMBC spectra of **3** again confirmed the presence of the same side-chain as that found in **1** and **2**, which left only one carbon, one oxygen, one nitrogen and two protons to be assigned. A one-bond coupling noted between the remaining carbonyl resonance (δ_C 160.6) and the deshielded proton resonance (δ_H 7.97, H-2) in the HSQC spectrum suggested that the only way to accommodate this aldehyde moiety was as part of a formamide functionality. The presence of the terminal formamide was supported by reciprocal HMBC correlations



Scheme 1. Putative biosynthesis of **2** from **1**.

Table 2. Anti-oesophageal cancer activity of **1**–**4**

Compound	IC_{50} (μM)						
	WHCO1	WHCO5	WHCO6	KYSE70	KYSE180	KYSE520	MCF12
1	17.0	31.6	29.1	35.9	21.7	17.8	20.7
2	25.1	>100.0	50.7	26.9	24.6	18.9	18.7
3	57.7	55.7	58.6	55.0	35.5	>100.0	>100.0
4	49.1	32.2	40.9	>100.0	50.6	84.9	7.3

from the formamide proton (H-2) to C-1′ of the side-chain and from H_2-1′ to the formamide carbonyl carbon (C-2). The chemical shifts of the formamide moiety were in complete agreement with those observed for other previously reported formamides, both natural products,[22–24] and also the synthetic product **7**, which possesses a triprenylated functionality analogous to that found in **1**–**3**.[25] Finally, a one-bond correlation was observed in the HMBC spectrum of **3**, which allowed the $^1J_{C,H}$ value of the formamide to be measured as 189 Hz (Table 1), comparing favorably with the literature value of 190 Hz.[17]

Oesophageal cancer is a prevalent form of cancer amongst the poor rural populations in southern Africa, and its prevalence is attributed to a combination of extraneous factors including alcohol use, the inadvertent ingestion of carcinogenic fungal toxins from contaminated grain, and the continuous exposure of many individuals to excessive wood and cigarette smoke.[26] With the age-standardized incidence rate of oesophageal cancer (16.22 per 100,000) in South Africa greater than those observed in many other parts of the world, we have initiated a program in South Africa to search for potential anti-oesophageal cancer agents from marine organisms.[7,27] Cisplatin and 5-fluoruracil are the common chemotherapeutic agents presently used to treat oesophageal cancer. However, even if either of these agents are administered following an early diagnosis of the disease, they can only effect remission in 20–30% of patients.[27] Given the moderate cytotoxicity of the original *L. gilchristi* extract, malonganenones A–C (**1**–**3**) were evaluated against several oesophageal cancer cells lines (WHCO1, WHCO5, WHCO6, KYSE70, KYSE180, KYSE520). MCF12 cells, derived from a benign breast tumour, were used as a control cell line, and activity was compared to the triprenyl hydroquinone rietone (**4**) (Table 2). All three malonganenones showed moderate cytotoxicity against almost all seven-cell lines with **1** the most and **3** the least active. Interestingly, while **1** exhibited activity against WHCO1 cells comparable with that of cisplatin (IC_{50}=15 μM), **3** appeared to be more selectively active than **1** or **2** against the oesophageal cancer cell lines compared to the control line (MCF12), which may indicate its potential as a chemotherapeutic agent with fewer side effects. Compound **4** showed varying activity against the oesophageal cancer cell lines, but high cytotoxicity against the control cell line. The anti-microbial activity of **1** was also evaluated against the human pathogenic bacteria *Staphylococcus aureus* (gram positive) and *Escherichia coli* (gram negative), and the fungus *Aspergillus niger* at concentrations of 20 and 100 μg/disk in zone inhibition assays (disk diameter=10 mm). No inhibition by **1** was noted against *E. coli* or *A. niger* and only mild activity (17 mm mean inhibition zone) against *S. aureus* was observed at 100 μg/disk.

3. Conclusion

The paucity of purine, rearranged purine and formamide secondary metabolites from marine gorgonians contributes to the significance of our discovery of malonganenones A–C (**1**–**3**) in extracts of *L. gilchristi*. The prenylated side-chains of **1**–**3** form a common link between these compounds and known prenylated hydroquinones and quinones isolated from other southern African octocoral species and a nudibranch *L. millecra* known to prey exclusively on both soft corals and gorgonians.[9] Interestingly, three of the nine prenylated metabolites previously obtained from *L. millecra* share the uncommon *Z* configuration of the α,β unsaturated ketone functionality also found in **1**–**3**.[9] The incorporation of deuterium into **2** from the CD_3OD used as an NMR solvent confounded initial attempts at the structural elucidation of this compound and serves as a caution to those involved in natural product structural elucidation that the unusual functional groups often found in natural products can have unexpected interactions with solvents commonly used for NMR analysis. The moderate cytotoxicity of **1**–**3** towards oesophageal cancer cell lines was established.

4. Experimental

4.1. General

IR spectra were collected using a Perkin-Elmer Spectrum 2000 FT spectrometer with compounds as films (neat) on NaCl plates. UV spectra were recorded using a Varian Cary 500 UV–vis–NIR spectrophotometer. NMR spectra were measured on a Brüker AVANCE 400 MHz spectrometer using standard pulse sequences. Chemical shifts are reported in ppm and are referenced to residual solvent resonances (CD_2HOD δ_H 3.31, δ_C 49.00 or d_5-DMSO δ_H 2.50, δ_C 39.52).[28] HRFABMS data were obtained on a JEOL SX102 FABMS at the Potchefstroom campus of the North West University or using a Waters API Q-TOF Ultima ESI mass spectrometer at Stellenbosch University. Diaion HP-20 polystyrene divinylbenzene beads (supplied by Supelco) and Macherey-Nagel Chroma-Bond OH Diol (0.45 μm) were used for initial chromatographic separations. High-performance liquid chromatography was performed using a Macherey-Nagel Nuecleosil 100-7-OH Diol semi-preparative column (10 mm i.d., 250 mm) on an HP Agilent 1100 series gradient HPLC system equipped with diode array detection.

4.2. Collection and extraction of *L. gilchristi* and isolation of 1–3

Specimens of *L. gilchristi* (Hickson 1904) [Phylum: Cnidaria, Class: Anthozoa, Order: Alcyonacea, Family: Gorgoniidae] were collected by SCUBA at a depth of 20 m from a reef near Ponto Malongane, Mozambique in the autumn of 1995 and frozen immediately after collection. Freeze dried specimens of *L. gilchristi* (148 g) were exhaustively extracted with MeOH, and the MeOH extract concentrated in vacuo and partitioned between H_2O and EtOAc. The two partition fractions were evaporated to dryness under reduced pressure to yield an aqueous fraction (4.29 g) and an organic fraction (3.08 g), respectively. A portion (915 mg) of the organic fraction was re-dissolved in MeOH (50 mL), diluted with H_2O (5 mL) and partitioned with hexane (2×25 mL) to remove fats. Both partition fractions were evaporated to give a MeOH (655 mg) and a hexane (271 mg) fraction. The MeOH fraction was loaded onto an HP-20 column (1.25×10 cm, 50 mL) and eluted with aliquots (150 mL) of increasing concentration of Me_2CO in H_2O (0, 25, 50, 70, 90 and 100% Me_2CO). The 70% $Me_2CO_{(aq)}$ eluent was concentrated in vaccuo (415 mg), re-dissolved in MeOH (ca. 5 mL) and evaporated onto a small portion of diol stationary phase (1 mL). The diol onto which the organic material had been absorbed was transferred as a hexane slurry onto a flash column of diol (1×11 cm, 9 mL), which was eluted with aliquots (100 mL) of (i) hexane, (ii) EtOAc/50% hexane, (iii) EtOAc, (iv) 50% MeOH/50% EtOAc, (v) MeOH and (vi) 50% H_2O/50% MeOH. Elution (iii) (145 mg) from the diol flash column was further chromatographed using diol HPLC under isocratic conditions (2.5% MeOH/97.5% EtOAc) to yield malonganenone A (**1**) (29 mg). Elution (ii) (80 mg) was further chromatographed using diol HPLC with gradient elution from 30% EtOAc/70% hexane to EtOAc to yield malonganenone C (**3**) (4 mg). Finally, one of the HPLC fractions collected from the gradient elution was re-chromatographed on diol HPLC under isocratic conditions (75% EtOAc/25% hexane) to give malonganenone B (**2**) (14 mg).

4.3. Malonganenone A (1)

Colorless glass; UV (MeOH) λ_{max} (ε) 221 (30,900), 252 (28,800); ν_{max} (liquid film) 2956, 2870, 1681, 1643, 1383, 1203, 1012 cm^{-1}; δ_H and δ_C, see Table 1; HRMS (FAB): MH^+, found 439.3073. $C_{26}H_{38}N_4O_2$ requires 439.3073.

4.3.1. Malonganenone B (2). Colorless glass; UV (MeOH) λ_{max} (ε) 238 (14,400); ν_{max} (liquid film) 2956, 2858, 1653, 1642, 1556, 1377, 1212, 1138 cm^{-1}; δ_H and δ_C (d_6-DMSO), see Table 1; δ_H (400 MHz, CD_3OD) δ 8.23 (1H, s, H-2), 7.68 (1H, d, J=2.1 Hz, H-8), 6.14 (1H, dd, J=2.6, 1.4 Hz, H-12′), 5.32 (1H, m, H-2′), 5.12 (1H, dddd, J=6.8, 6.4, 2.5, 1.3 Hz, H-6′), 4.82 (2H, dd, J=7.2, 3.4 Hz, H-1′), 3.20 (3H, s, H-10), 2.85 (3H, s, H-11), 2.50 (2H, dd, J=8.0, 6.2 Hz, H-10′), 2.28 (2H, td, J=9.5, 2.5 Hz, H-14′), 2.15 (2H, m, H-5′), 2.11 (2H, m, H-4′), 2.08 (1H, m, H-15′), 2.04 (2H, m, H-8′), 1.89 (3H, d, J=1.3 Hz, H-18′), 1.77 (3H, s, H-20′), 1.61 (3H, s, H-19′), 1.54 (2H, dd, J=15.4, 8.1 Hz, H-9′), 0.91 (6H, dt, J=6.7, 2.0 Hz, H-16′, H-17′); δ_C (100 MHz, CD_3OD) δ 203.0 (C, C-13′), 163.8 (CH, C-2), 162.4 (C, C-6), 161.3 (s, C-11′), 143.3 (s, C-3′), 141.6 (s, C-4), 138.2 (d, C-8), 136.4 (s, C-7′), 125.1 (d, C-6′), 125.0 (d, C-12′), 119.8 (d, C-2′), 119.5 (s, C-5), 54.3 (t, C-14′), 45.8 (t, C-1′), 40.9 (t, C-8′), 40.5 (t, C-4′), 34.5 (t, C-10′), 32.4 (q, C-10), 27.6 (t, C-9′), 27.3 (t, C-5′), 26.5 (q, C-11), 26.4 (d, C-15′), 25.6 (q, C-18′), 22.9 (q, C-16′), 22.9 (q, C-17′), 16.5 (q, C-20′), 16.0 (q, C-19′); HRMS (ESI): MH^+, found 471.3341. $C_{27}H_{43}N_4O_3$ requires 471.3335, MH^+, found 472.3397. $C_{27}H_{42}DN_4O_3$ requires 472.3398.

4.3.2. Malonganenone C (3). Yellow solid; UV (MeOH) λ_{max} (ε) 230 (8800), 276 (1400); ν_{max} (liquid film) 3321, 2958, 2023, 2863, 1727, 1682, 1616, 1384, 1275, 1126, 1074 cm^{-1}; δ_H and δ_C (d_6-DMSO) see Table 1; δ_H (400 MHz, CD_3OD) δ 8.01 (1H, d, J=2.8 Hz, H-2), 6.15 (1H, s, H-12′), 5.21 (1H, tdt, J=6.9, 2.5, 1.2 Hz, H-2′), 5.13 (1H, tt, J=6.8, 1.2 Hz, H-6′), 3.81 (2H, d, J=6.6 Hz, H-1′), 2.28 (2H, d, J=7.1 Hz, H-14′), 2.51 (2H, td, J=7.8, 6.3 Hz, H-10′), 2.13 (2H, m, H-5′), 2.12 (2H, m, H-4′), 2.07 (1H, m, H-15′), 2.04 (2H, m, H-8′), 1.89 (3H, d, J=1.3 Hz, H-18′), 1.70 (3H, s, H-20′), 1.62 (3H, s, H-19′), 1.54 (2H, m, H-9′), 0.92 (6H, d, J=6.7 Hz, H-16′, H-17′); δ_C (100 MHz, CD_3OD) δ 203.1 (s, C-13′), 163.4 (s, C-2), 161.5 (s, C-11′), 140.7 (s, C-3′), 136.1 (s, C-7′), 125.4 (d, C-6′), 125.0, (d, C-12′), 121.0 (d, C-2′), 54.4 (t, C-14′), 40.9 (t, C-8′), 40.5 (t, C-4′), 36.8 (t, C-1′), 34.5 (t, C-10′), 27.7 (t, C-9′), 27.3 (t, C-5′), 26.5 (d, C-15′), 25.8 (q, C-18′), 22.9 (q, C-16′), 22.9 (q, C-17′), 16.2 (q, C-20′), 15.9, (q, C-19′); HRMS (ESI): MH^+, found 334.2752. $C_{21}H_{36}NO_2$ requires 334.2746.

4.4. Bioassays

Anti-oesophageal cancer bioassays were carried out as described previously.[7]

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Cobalt-catalyzed cross-coupling reactions of alkyl halides with aryl Grignard reagents and their application to sequential radical cyclization/cross-coupling reactions

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Abstract—Reactions of alkyl halides with arylmagnesium bromides in the presence of cobalt(II)(diphosphine) complexes are discussed. Treatment of 1-bromooctane with phenylmagnesium bromide with the aid of a catalytic amount of $CoCl_2$(dppp) [DPPP = 1,3-bis(diphenylphosphino)propane] yielded octylbenzene in good yield. The reaction mechanism would include single electron transfer from an electron-rich cobalt complex to alkyl halide to generate the corresponding alkyl radical. The mechanism was justified by $CoCl_2$(dppe)-catalyzed [DPPE = 1,2-bis(diphenylphosphino)ethane] sequential radical cyclization/cross-coupling reactions of 6-halo-1-hexene derivatives that yielded benzyl-substituted cyclopentane skeletons.

1. Introduction

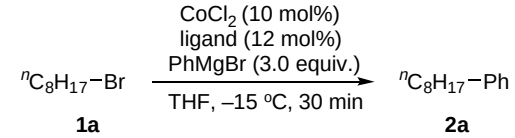
Transition metal-catalyzed cross-coupling reactions provide powerful tools for carbon–carbon bond formation. The cross-coupling reactions of β-hydrogen-containing unactivated alkyl halides with organometallic reagents had been difficult because of slow oxidative addition of alkyl halides to low valent transition metal and β-hydride elimination from alkyl-transition metal intermediates. For the past decade, considerable efforts have been made to overcome the difficulty in the use of alkyl halides in the cross-coupling reactions.[1,2] We have been interested in the potential of cobalt catalysts in the cross-coupling reaction.[3,4] Here we report the full details of the cobalt-catalyzed reaction of alkyl halides with arylmagnesium bromides.[5]

2. Results and discussions

2.1. Cobalt-catalyzed cross-coupling reactions of alkyl halides with aryl Grignard reagents

The coupling reaction of 1-bromooctane (**1a**) with phenyl Grignard reagent was first investigated (Table 1). A number of ligands were screened, and 1,3-bis(diphenylphosphino)propane (DPPP) proved to be outstandingly effective for the phenylation reaction at −15 °C. Other ligands such as DPPE and DPPF were much less effective. The choice of the solvent was essential to obtain **2a** in satisfactory yield. A similar reaction in ether resulted in very low yield of **2a**. The excess, 3 equiv in this case, of the Grignard reagent is essential to attain satisfactory yield. The reaction with a stoichiometric amount of PhMgBr was sluggish.

Table 1. Cobalt-catalyzed phenylation reaction of 1-bromooctane (**1a**)



1a **2a**

Entry	Ligand	Yield (%)
1	DPPM	3
2	DPPE	15
3	DPPP	65
4	DPPH	1
5	DPPF	1
6	PPh_3 (24 mol%)	3
7	TMEDA	5

Ligands DPPM–DPPH represent $Ph_2P(CH_2)_nPPh_2$, $n=1$: DPPM; $n=2$: DPPE; $n=3$: DPPP; $n=6$: DPPH. DPPF and TMEDA denote 1,1′-bis(diphenylphosphino)ferrocene and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, respectively.

Keywords: Cross-coupling reaction; Cobalt; Aryl Grignard reagent; Radical reaction.
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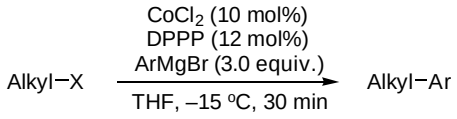
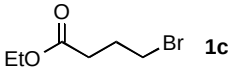
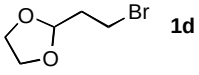
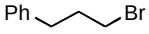
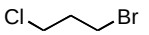
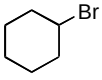
Various combinations of organic halides and aryl Grignard reagents were examined (Table 2). Not only phenyl Grignard reagent but also 4-methoxyphenyl and 2-thienyl Grignard reagents participated in the cross-coupling reaction. Unfortunately, the reaction with 2-methylphenyl Grignard reagent resulted in failure, yielding octane and 1-octene with half of **1a** untouched. Alkyl iodide **1b** was inferior to the corresponding bromide as the coupling partner. Ester and chloro moieties survived under the reaction conditions. Bromocyclohexane was subjected to the cobalt-catalyzed phenylation at 0 °C to yield cyclohexylbenzene in only 24% yield.

Table 2. Cobalt-catalyzed cross-coupling reactions of alkyl halides with aryl Grignard reagents



Entry	1	ArMgBr	2	Yield (%)
1	$^{n}C_8H_{17}$–Br **1a**	4-CH_3O–C_6H_4MgBr	**2b**	67
2	$^{n}C_8H_{17}$–Br **1a**	(2-Thienyl)MgBr	**2c**	54
3	$^{n}C_8H_{17}$–Br **1a**	2-CH_3–C_6H_4MgBr	**2d**	<1
4	$^{n}C_8H_{17}$–I **1b**	PhMgBr	**2a**	33
5	 **1c**	PhMgBr	**2e**	49
6	 **1d**	PhMgBr	**2f**	60
7	 **1e**	PhMgBr	**2g**	63
8	 **1f**	PhMgBr	**2h**	47
9	 **1g**	PhMgBr	**2i**	24

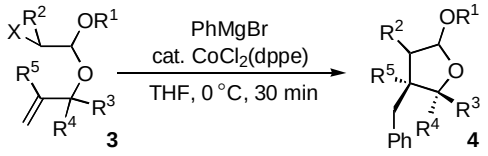
2.2. Cobalt-catalyzed sequential radical cyclization/cross-coupling reaction

We are tempted to assume that the oxidative addition process in this coupling reaction would proceed via a single electron transfer from an electron-rich cobalt complex to alkyl halide. Although oxidative addition of alkyl halides is much slower than that of aryl and vinyl halides via a three-centered addition mechanism, single electron transfer to alkyl halides allows facile activation of alkyl halides.

The single electron transfer that would operate in the present system was verified by the reactions of Ueno–Stork halo acetals **3**, which serves as a radical probe.[6] Treatment of bromo acetal **3a** with phenylmagnesium bromide in THF at 0 °C in the presence of $CoCl_2$(dppe) for 30 min afforded phenylated cyclic acetal **4a** in 80% yield (Table 3, entry 1). Several ligands such as TMEDA, DPPM, DPPE, DPPP, DPPB, PPh_3, and $P(OPh)_3$ were screened. Among them, DPPE proved to be extremely efficient. The use of other ligands resulted in lower yields of the phenylated product **4a** and formation of a non-phenylated byproduct (30–50%). $CoCl_2$ by itself and $CoCl(PPh_3)_3$ did not give satisfactory results. Use of a cobaloxime, $Co(dmgH)_2PyCl$,[7] resulted in recovery of **3a**.

A variety of halo acetals were examined, and the results are illustrated in Table 3, Scheme 1, and Scheme 2. Halo acetals bearing a terminal alkene moiety underwent phenylative cyclization to furnish the corresponding benzyl-substituted tetrahydrofuran derivatives in good to excellent yields (Table 3). It is noteworthy that the stereochemistry of the products was quite similar to that in the previous reports of radical reductive cyclization reactions.[8] This observation is highly suggestive of the same transition state of the cyclization step in the present reaction as in the free radical reaction. The allylic alcohols that constitute the substrates **3** were not detected in the reaction mixture. This means that β-alkoxy elimination, which could be facilitated by halogen–metal exchange did

Table 3. Cobalt-catalyzed phenylative cyclization[a]



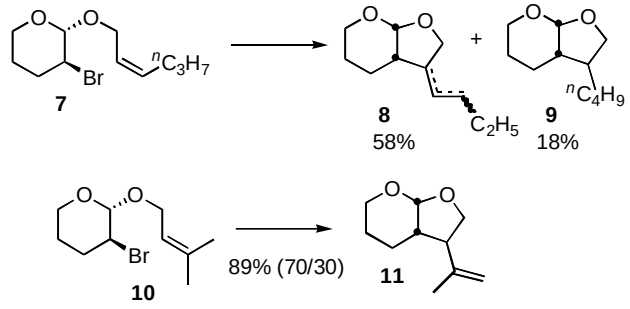
Entry	3	X	R^1	R^2	R^3	R^4	R^5	4	Yield (%)[b]
1	**3a**	Br	$^{n}C_4H_9$	H	H	$^{n}C_5H_{11}$	H	**4a**	80 (55:45)
2	**3b**	I	$^{n}C_4H_9$	H	H	$^{n}C_5H_{11}$	H	**4a**	78 (55:45)
3	**3c**	Cl	$^{n}C_4H_9$	H	H	$^{n}C_5H_{11}$	H	**4a**	No reaction
4	**3d**	Br	$(CH_2)_3$	—	H	$^{n}C_5H_{11}$	H	**4b**	71 (51:49)
5	**3e**	Br	$(CH_2)_3$	—	CH_3	CH_3	H	**4c**	84 (62:38)
6	**3f**	I	$(CH_2)_3$	—	CH_3	CH_3	H	**4c**	84 (60:40)
7	**3g**	Br	$(CH_2)_3$	—	H	H	CH_3	**4d**	51 (>99:1)
8	**3h**	I	$(CH_2)_3$	—	H	H	H	**4e**	21 (91:9)

[a] Substrate **3** (0.50 mmol), $CoCl_2$(dppe) (0.05 mmol), PhMgBr (1.1 mmol in 1 mL of THF), and THF (1 mL) were employed.

[b] Diastereomeric ratios are in parentheses. For **4a**, the $^{n}C_5H_{11}$ and benzyl groups are always on the opposite positions and the diastereoisomerism originates from the position of the R^1O group relative to the $^{n}C_5H_{11}$/benzyl groups. For **4b**, the $^{n}C_5H_{11}$ and benzyl groups are again trans and the positions of the R^1O and R^2 groups are always cis. Thus, the diastereoisomerism of **4b** emerges from the relative stereochemistry of the fused position and the $^{n}C_5H_{11}$/benzyl groups. For **4c**–**4e**, the relationship between the fused position and the benzyl group is responsible for the diastereoisomerism.

5a: R = H, X = I, Y = 4-CH_3–$C_6H_4SO_2N$ **6a**: 81% (Ar = Ph)
5b: R = $^nC_5H_{11}$, X = Br, Y = O **6b**: 59% (Ar = Ph)
5c: R = H, X = I, Y = CH_2 **6c**: 59% (Ar = 4-CH_3O–C_6H_4)

Scheme 1.



Scheme 2.

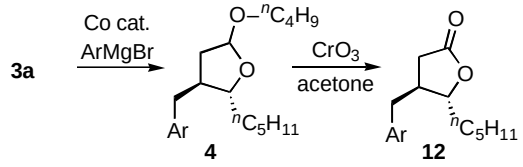
not take place. The β,β-di(alkoxy)alkylcobalt, if formed, probably undergoes fast β-alkoxy elimination. Hence, a mechanism involving halogen–cobalt exchange followed by intramolecular carbocobaltation might be improbable. Radical reaction is a preferable methodology to construct a quaternary carbon. This is indeed the case of **3g**, and bicyclic acetal **4d** was obtained as a single isomer. However, the reaction of **3h**, which has no substituents on the allyloxy group was sluggish. The expected product **4e** was obtained in only 21% yield in addition to allylbenzene. Chloro acetal **3c** resisted the reaction.

Nitrogen-containing substrate **5a** was also subjected to the cyclization reaction in the presence of the cobalt catalyst to yield 3-benzylpyrrolidine derivative **6a** (Scheme 1). Synthesis of carbocycle **6c** was also successful. Cyclic product **6c**, in addition to a small amount of biphenyl, was the only product in the ^1H NMR spectrum of the crude reaction mixture. Volatile methylcyclopentane and 1,5-hexadiene were the major byproducts (detectable by GC).

Cyclization onto an internal alkene moiety did not allow incorporation of a phenyl group (Scheme 2). Treatment of **7** with PhMgBr in the presence of $CoCl_2$(dppe) furnished a mixture of regio- and stereoisomers in regard to the double bond formed, accompanied with the non-phenylated cyclic acetal **9**. When **10** was employed, **11** was obtained exclusively via regioselective β-hydride elimination.

Not only PhMgBr but also a wide range of aryl Grignard reagents, including a 2-thienylmagnesium reagent, were available for use (Table 4). Jones oxidation of the products yielded β-arylmethyl-γ-lactones, which can be useful building blocks of some ligands.[9] Unfortunately, introduction of 2-substituted aryl groups was problematic. Steric effect of the substituents on a metal center is likely to interfere with the catalytic cycle.

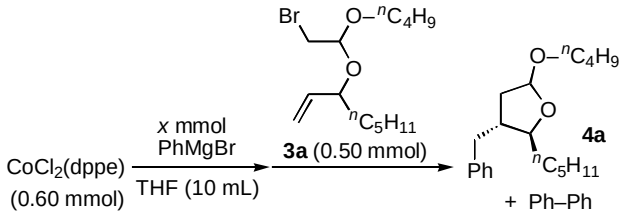
Table 4. Radical cyclization with various arylmagnesium bromides



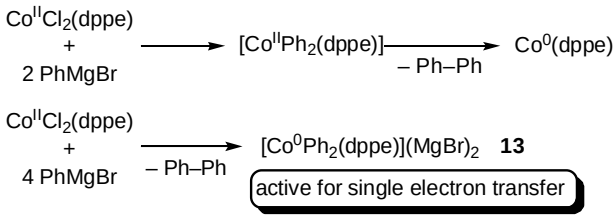
Entry	Ar	Yield of **4** (%)	Yield of **12** (%)
1	C_6H_5	**4a**, 80	**12a**, 97
2	3-CF_3–C_6H_4	**4f**, 65	**12b**, 83
3	4-CH_3O–C_6H_4	**4g**, 81	**12c**, 95
4	2-CH_3O–C_6H_4	**4h**, <5	—
5	2-CH_3–C_6H_4	**4i**, <15	—
6	2-Thienyl	**4j**, 63	**12d**, 75

2.3. Mechanism of cobalt-catalyzed phenylation reaction

To gain information about the reaction mechanism, the reaction of **3a** with a stoichiometric cobalt complex was examined with varying amounts of PhMgBr (Scheme 3). Treatment of **3a** (0.50 mmol) with a cobalt complex, prepared from 0.60 mmol of $CoCl_2$(dppe) and 1.2 mmol of PhMgBr, provided a trace of **4a**. Most of **3a** was recovered and 0.6 mmol of biphenyl was obtained. Accordingly, Co(II)Ph_2(dppe) was unstable under the



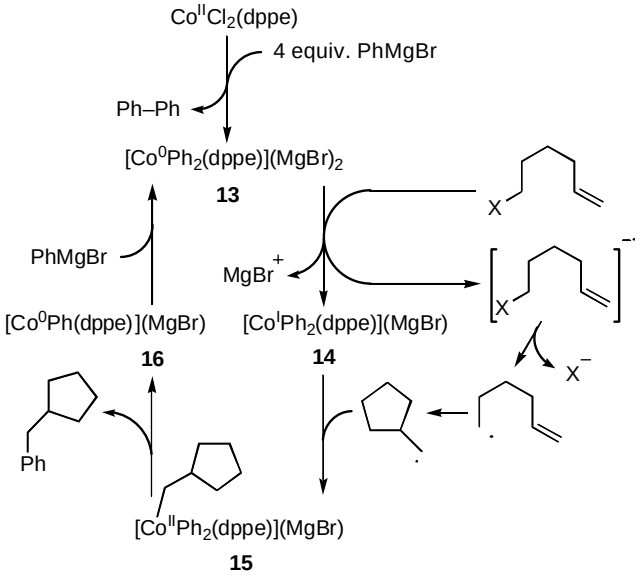
x	**3a**	**4a**	Ph–Ph
1.2	> 90%	Trace	0.6 mmol
1.8	> 80%	ca. 10%	0.6 mmol
2.4	< 5%	31%	0.8 mmol
3.0	< 1%	38%	0.7 mmol



Scheme 3.

reaction conditions and underwent reductive elimination. In fact, in the absence of **3a**, treatment of $CoCl_2$(dppe) with 2 equiv of PhMgBr in THF at 0 °C for 1 min and for 5 min gave biphenyl in 57 and 99% yields, respectively. A cobalt reagent, prepared from 0.60 mmol of $CoCl_2$(dppe) and 1.8 mmol of PhMgBr, also yield biphenyl (0.6 mmol), and most of **3a** remained unchanged. A complex generated by 0.60 mmol of $CoCl_2$(dppe) and 2.4 mmol of PhMgBr dramatically changed the outcome. The phenylated product **4a** was obtained in reasonable yield (31%), along with biphenyl (0.8 mmol) and other byproducts. Five equivalents of PhMgBr (3.0 mmol) exhibited outcome similar to 4 equiv of PhMgBr. Hence, the cobalt complex that is active for this reaction can be a 17-electron ate complex $[Co^0Ph_2(dppe)](MgBr)_2$ (**13**).

According to these results, we are tempted to propose a draft mechanism for the catalytic reaction as shown in Scheme 4. The reaction of $CoCl_2$(dppe) with 4 equiv of PhMgBr gives $[Co^0Ph_2(dppe)](MgBr)_2$ (**13**) with concomitant production of 1 equiv of biphenyl. The low valent ate complex effects a single electron transfer to a substrate to yield the anion radical of the substrate and cobalt(I) complex **14**. The immediate loss of bromide from the anion radical affords 5-hexenyl radical intermediate, which is transformed into a cyclopentylmethyl radical. The cobalt species **14** would then recombine with the carbon-centered radical to form divalent cobalt species **15**. Following reductive elimination provides the product and the cobalt(0) complex **16**, which is reconverted into **13** by the action of the remaining PhMgBr.



Scheme 4. A possible mechanism.

3. Conclusion

$CoCl_2$(dppp) effected cross-coupling reactions of primary alkyl halides and aryl Grignard reagents efficiently. The reaction can contribute to the establishment of universal cross-coupling reaction that allows arbitrary carbon–carbon bond formation. $CoCl_2$(dppe) catalyzed the sequential cyclization/cross-coupling reactions of 6-halo-1-hexene derivatives and aryl Grignard reagents to afford benzylcyclopentane skeletons. The sequential reaction not only provides a new method for multibond formation in a single operation but also justifies the existence of alkyl radical intermediates in the cross-coupling reaction.

4. Experimental

4.1. General

^{1}H NMR (300 MHz) and ^{13}C NMR (75.3 MHz) spectra were taken on a Varian GEMINI 300 spectrometer in $CDCl_3$ as a solvent, and chemical shifts were given in δ value with tetramethylsilane as an internal standard. IR spectra were determined on a JASCO IR-810 spectrometer. TLC analyses were performed on commercial glass plates bearing a 0.25 mm layer of Merck silica gel $60F_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography. The elemental analyses were carried out at the Elemental Analysis Center of Kyoto University.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Phosphine ligands were purchased from Tokyo Kasei Kogyo. Anhydrous $CoCl_2$ was purchased from Wako Pure Chemicals. The reaction was quite sensitive to water. Commercially available anhydrous $CoCl_2$ may contain some water. Completely anhydrous salt is clear blue, whereas purchased $CoCl_2$ is somewhat reddish-blue. Handling $CoCl_2$ under air as usual also caused low yield. Therefore, in each experiment, $CoCl_2$ was dried in a reaction flask carefully under reduced pressure (0.5 Torr) by heating with a hair dryer for 30 min immediately before use. Reaction flasks and syringes used were oven-dried and were cooled over silica gel in a desiccator. The preparation of halo acetals was carried out according to a literature method[8c] with corresponding vinyl ethers, allylic alcohols, and *N*-halosuccinimide.

4.2. General procedure for the cross-coupling reactions of alkyl halides with aryl Grignard reagents

The reaction of **1a** with phenyl Grignard reagent is representative. Anhydrous cobalt(II) chloride (13 mg, 0.10 mmol) was placed in a 30 mL reaction flask and heated in vacuo with a hair dryer. DPPP (50 mg, 0.12 mmol) and anhydrous THF (3.0 mL) were then added under argon. After the mixture was stirred at 25 °C for 5 min, 1-bromooctane (**1a**, 193 mg, 1.0 mmol) and phenylmagnesium bromide (1.0 M THF solution, 3.0 mL, 3.0 mmol) were sequentially added dropwise at −15 °C. While the Grignard reagent was being added, the mixture turned brown. After being stirred at −15 °C for 30 min, the reaction mixture was quenched with saturated ammonium chloride. The products were extracted with ethyl acetate (20 mL×3) and the combined organic layer was dried over sodium sulfate and concentrated. Silica gel column purification of the crude product with hexane as an eluent provided octylbenzene (**2a**, 123 mg, 0.65 mmol) in 65% yield.

4.3. A typical procedure for sequential radical cyclization/cross-coupling reaction

Anhydrous cobalt(II) chloride (6.5 mg, 0.05 mmol) was placed in a 25 mL flask and was heated with a hair dryer in vacuo for 30 min. After the color of cobalt salt became blue, anhydrous THF (1 mL) was added under argon. The mixture was stirred for about 15 min until it became homogeneous. A solution of 1,2-bis(diphenylphosphino)ethane in THF (0.33 M, 0.15 mL, 0.05 mmol) was then added to provide a green solution. Substrate **3a** (0.15 g, 0.50 mmol) and phenylmagnesium bromide (1.0 M THF solution, 1.1 mL, 1.1 mmol) were successively added dropwise to the reaction mixture at 0 °C. While the Grignard reagent was being added, the mixture turned black. After being stirred for 30 min at 0 °C, the reaction mixture was poured into saturated ammonium chloride solution. The products were extracted with ethyl acetate (20 mL×3). The combined organic layer was dried over Na_2SO_4 and was concentrated. Silica gel column purification (hexane/ethyl acetate =20:1) of the crude product provided **4a** (0.12 g, 0.40 mmol) in 80% yield.

To obtain the corresponding lactone, **4a** was subjected to Jones oxidation. The crude oil can be directly oxidized in a similar manner. The oil was dissolved in acetone (5 mL), and Jones oxidant was added until the color of the mixture remained greenish-orange. Usual workup followed by silica gel column purification afforded **12a** in 97% yield.

4.4. Stereochemical assignment of the products

The trans stereochemistry of **12** was determined by comparison with known compounds that have an analogous structure. The chemical shifts of the γ-proton seem diagnostic of the stereochemistry. In the literature of Reissig,[10] the γ-protons of *trans*-β,γ-dialkyl-γ-lactones appeared at δ 4.01–4.45, whereas those of the cis isomers appeared at δ 4.43–4.71. In the present case, γ-proton of β-(arylmethyl)-γ-nonanolactone appeared at δ 4.2, which is strongly suggestive of trans relative configuration, given that the aryl group would have little influence on the chemical shift. NOE experiments, which showed small yet clear NOE, also revealed the selective formation of trans lactone (Fig. 1).

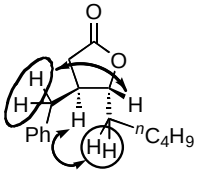
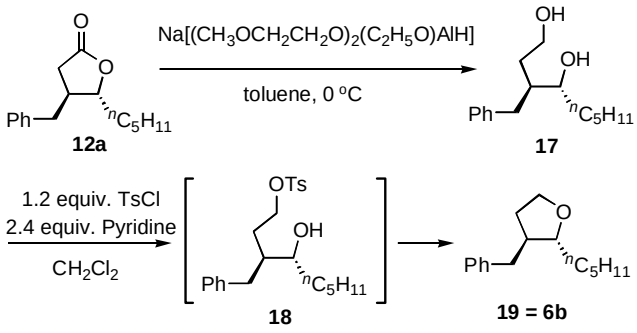


Figure 1. NOE correlation in lactone **12a**.

The relative configurations of bicyclic acetals **4** were not determined. The diastereomeric ratios in these phenylative cyclizations are similar to those in the previous free radical reductive cyclizations. It is worth noting that free radical cyclization of 4-substituted-5-hexenyl radical always afforded *trans*-1,2-substituted cyclopentane.[11]

The configuration of **6b** was determined as follows (Scheme 5). Reduction of trans lactone **12a** with 3 equimolar amount of $Na[(CH_3OCH_2CH_2O)_2(C_2H_5O)AlH]$ in toluene yielded diol **17** quantitatively.[12] Tosylation of secondary alcohol is much slower than that of primary one. Accordingly, crude diol **17** was subjected to monotosylation conditions (1.2 equiv TsCl/2.4 equiv pyridine/CH_2Cl_2, 0−25 °C). Expected mono-tosylated **18** underwent cyclization in the same pot to form tetrahydrofuran derivative **19** directly. The ^1H NMR spectrum of **19** was identical with **6b**, which clearly suggests **6b** was a trans isomer.



Scheme 5.

4.5. Characterization data

Spectral data for (**2b**,[13] **2c**,[14] **2d**,[15] **2e**,[16] **2f**,[17] **3**,[8c–f] **7–9**,[8d,f] **11**[8d]) were found in the literature. Spectral data of **4a**, **4f**, **4g**, and **4j** are not described here. The corresponding lactones were analyzed.

4.5.1. 7-Benzyl-8-pentyl-2,9-dioxabicyclo[4.3.0]nonane (4b). IR (neat) 2920, 2856, 1605, 1496, 1454, 1148, 1098, 966, 899, 748, 699 cm^{-1}; ^1H NMR ($CDCl_3$) For major isomer: δ 0.84 (t, *J*=6.9 Hz, 3H), 1.15–1.74 (m, 12H), 1.85–1.93 (m, 1H), 2.15–2.26 (m, 1H), 2.65 (dd, *J*=7.2, 13.8 Hz, 1H), 2.77 (dd, *J*=6.3, 13.8 Hz, 1H), 3.36 (dt, *J*=2.1, 11.1 Hz, 1H), 3.76 (dt, *J*=3.0, 8.7 Hz, 1H), 3.82–3.90 (m, 1H), 4.92 (d, *J*=3.9 Hz, 1H), 7.14–7.31 (m, 5H), for minor isomer: δ 0.87 (t, *J*=6.9 Hz, 3H), 1.17–1.83 (m, 12H), 1.85–1.96 (m, 1H), 2.20–2.31 (m, 1H), 2.66 (d, *J*=7.8 Hz, 2H), 3.60–3.64 (m, 1H), 3.76–3.84 (m, 1H), 3.90–3.96 (m, 1H), 5.26 (d, *J*=3.6 Hz, 1H), 7.17–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) For major isomer: δ 13.88, 20.65, 22.39 (2C), 26.08, 31.56, 36.65, 38.26, 44.60 (2C), 64.37, 85.94, 101.53, 126.29, 128.46 (2C), 129.01 (2C), 139.88, for minor isomer: δ 13.87, 20.19, 22.44, 23.18, 25.73, 31.82, 33.06, 35.23, 37.14, 47.89, 60.94, 80.87, 100.68, 126.17, 128.53 (2C), 128.56 (2C), 140.44. Found: C, 78.90; H, 9.96%. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78%.

4.5.2. 7-Benzyl-8,8-dimethyl-2,9-dioxabicyclo[4.3.0]-nonane (4c). IR (neat) 2946, 2880, 1738, 1496, 1454, 1384, 1242, 1144, 985, 906, 868, 747, 731, 698 cm^{-1}; ^1H NMR ($CDCl_3$) For major isomer: δ 1.15 (s, 3H), 1.18 (s, 3H), 1.50–1.83 (m, 4H), 1.96–2.06 (m, 1H), 2.50–2.75 (m, 3H), 3.36 (dt, *J*=2.4, 11.4 Hz, 1H), 3.82–3.90 (m, 1H), 4.88 (d, *J*=3.6 Hz, 1H), 7.19–7.33 (m, 5H), for minor isomer: δ 1.25 (s, 3H), 1.36 (s, 3H), 1.42–1.74 (m, 4H), 1.83–1.95

(m, 1H), 2.46 (dt, J=10.2, 6.0 Hz, 1H), 2.65 (dd, J=14.1, 6.0 Hz, 1H), 2.72 (dd, J=10.2, 14.1 Hz, 1H), 3.64 (dt, J=10.2, 2.7 Hz, 1H), 3.83 (dt, J=2.7, 11.1 Hz, 1H), 5.22 (d, J=3.6 Hz, 1H), 7.18–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) For major isomer: δ 20.22, 21.89, 24.33, 20.35, 35.00, 44.10, 46.35, 64.34, 84.84, 100.55, 126.12, 128.38 (2C), 128.79 (2C), 140.38, for minor isomer: δ 20.24, 23.38, 25.57, 30.94, 31.62, 38.04, 51.03, 60.67, 79.35, 98.66, 126.13, 128.50 (2C), 128.56 (2C), 140.61. Found: C, 77.91; H, 9.24%. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00%.

4.5.3. 7-Benzyl-7-methyl-2,9-dioxabicyclo[4.3.0]nonane (4d). IR (neat) 2920, 2862, 1604, 1496, 1453, 1411, 1381, 1278, 1245, 1137, 1084, 1049, 1022, 964, 942, 895, 754, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.98 (s, 3H), 1.52–1.79 (m, 4H), 1.90–2.00 (m, 1H), 2.62 (d, J=13.5 Hz, 1H), 2.85 (d, J=13.5 Hz, 1H), 3.40 (d, J=8.1 Hz, 1H), 3.60–3.82 (m, 2H), 4.13 (d, J=8.1 Hz, 1H), 5.45 (d, J=3.9 Hz, 1H), 7.11–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.26, 23.03, 23.84, 40.16, 44.18, 44.55, 61.15, 76.13, 101.76, 126.24, 128.21 (2C), 129.92 (2C), 138.58. Found: C, 77.36; H, 8.80%. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.58%.

4.5.4. 7-Benzyl-2,9-dioxabicyclo[4.3.0]nonane (4e). IR (neat) 2916, 1604, 1492, 1453, 1404, 1251, 1136, 1021, 947, 903, 750, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$) For major isomer: δ 1.50–1.67 (m, 3H), 1.72–1.81 (m, 1H), 1.92–2.01 (m, 1H), 2.58–2.78 (m, 3H), 3.61–3.68 (m, 1H), 3.77 (t, J=9.0 Hz, 2H), 3.88 (t, J=7.5 Hz, 1H), 5.28 (d, J=3.9 Hz, 1H), 7.15–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) For major isomer: δ 19.42, 23.02, 33.26, 36.46, 42.41, 60.91, 69.82, 101.97, 126.23, 128.41 (2C), 128.58 (2C), 140.20. Found: C, 76.75; H, 8.31%. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.51%.

4.5.5. *N*-(2-Iodoethyl)-*N*-[(4-methylphenyl)sulfonyl]-2-propenamine (5a). IR (Nujol) 2856, 1688, 1597, 1454, 1377, 1356, 1335, 1277, 1157, 1109, 1036, 997, 926, 901, 808, 775, 702, 663, 604 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3H), 3.21–3.26 (m, 2H), 3.40–3.45 (m, 2H), 3.80 (d, J=6.6 Hz, 2H), 5.16–5.23 (m, 2H), 5.62–5.75 (m, 1H), 7.33 (d, J=7.8 Hz, 2H), 7.70 (d, J=7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 1.84, 21.40, 50.05, 51.60, 119.69, 127.16 (2C), 129.91 (2C), 132.94, 136.35, 143.76. Found: C, 39.49; H, 4.34; N, 3.70%. Calcd for $C_{12}H_{16}O_2NSI$: C, 39.46; H, 4.42; N, 3.84%.

4.5.6. 3-(2-Bromoethoxy)-1-octene (5b). IR (neat) 2952, 2926, 2856, 1460, 1422, 1321, 1275, 1112, 1083, 994, 927, 726 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J=6.6 Hz, 3H), 1.22–1.68 (m, 8H), 3.45 (t, J=6.6 Hz, 2H), 3.60 (ddd, J=5.7, 6.9, 10.8 Hz, 1H), 3.64–3.71 (m, 1H), 3.81 (dt, J=10.8, 6.3 Hz, 1H), 5.16–5.23 (m, 2H), 5.62–5.74 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.92, 22.48, 24.89, 30.68, 31.63, 35.27, 68.31, 82.01, 117.06, 139.00. Found: C, 50.81; H, 7.96%. Calcd for $C_{10}H_{19}OBr$: C, 51.08; H, 8.14%.

4.5.7. 1-[4-(Methylphenyl)sulfonyl]-3-benzylpyrrolidine (6a). IR (neat) 3022, 2920, 2856, 1599, 1495, 1455, 1345, 1162, 1094, 1032, 816, 743, 701, 662 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.42–1.54 (m, 1H), 1.81–1.91 (m, 1H), 2.26–2.36 (m, 1H), 2.43 (s, 3H), 2.33 (d, J=7.5 Hz, 2H), 2.91 (dd, J=7.5, 9.9 Hz, 1H), 3.18 (dt, J=9.9, 7.5 Hz, 1H), 3.31–3.42 (d, J=8.1 Hz, 2H), 7.05 (d, J=8.1 Hz, 2H), 7.16–7.33 (m, 5H), 7.69 (d, J=8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.32, 30.89, 38.87, 40.22, 47.25, 52.66, 126.28, 127.49 (2C), 128.47 (2C), 128.58 (2C), 129.64 (2C), 133.89, 139.74, 143.37. Found: C, 68.28; H, 6.69; N, 4.36%. Calcd for $C_{18}H_{21}O_2NS$: C, 68.54; H, 6.71; N, 4.44%.

4.5.8. *trans*-3-Benzyl-1-oxa-2-pentylcyclopentane (6b). IR (neat) 3022, 2922, 2854, 1604, 1496, 1455, 1380, 1110, 1078, 1032, 1007, 905, 743, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J=6.75 Hz, 3H), 1.19–1.48 (m, 8H), 1.57–1.68 (m, 1H), 1.89–2.11 (m, 2H), 2.54 (dd, J=9.3, 13.5 Hz, 1H), 2.78 (dd, J=5.7, 13.5 Hz, 1H), 3.49–3.55 (m, 1H), 3.80 (dd, J=6.2, 7.4 Hz, 2H), 7.15–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.90, 22.47, 25.93, 31.81, 32.41, 34.62, 39.25, 46.10, 66.62, 84.15, 126.07, 128.42 (2C), 128.85 (2C), 140.80. Found: C, 82.72; H, 10.61%. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41%.

4.5.9. 1-Cyclopentylmethyl-4-methoxybenzene (6c). IR (neat) 2946, 2862, 1613, 1584, 1513, 1464, 1299, 1246, 1177, 1039, 829, 806, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.12–1.24 (m, 2H), 1.42–1.75 (m, 6H), 1.99–2.09 (m, 1H), 2.54 (d, J=7.5 Hz, 2H), 3.78 (s, 3H), 6.82 (d, J=8.7 Hz, 2H), 7.08 (d, J=8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 24.83 (2C), 32.30 (2C), 41.07, 42.10, 55.15, 113.57 (2C), 129.70 (2C), 134.61, 157.71. Found: C, 82.12; H, 9.72%. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53%.

4.5.10. *trans*-3-Bromo-2-(3-methyl-2-butenoxy)-1-oxacyclohexane (10). IR (neat) 2924, 2872, 2852, 1776, 1676, 1442, 1377, 1204, 1130, 1086, 1072, 1021, 946, 869, 727 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.47–1.59 (m, 1H), 1.69 (s, 3H), 1.76 (s, 3H), 1.86–2.00 (m, 2H), 2.34–2.45 (m, 1H), 3.58 (ddd, J=8.4, 6.3, 5.1 Hz, 1H), 3.88–4.02 (m, 2H), 4.08 (dd, J=11.7, 6.9 Hz, 1H), 4.22 (dd, J=11.7, 6.6 Hz, 1H), 4.63 (d, J=5.1 Hz, 1H), 5.36 (dd, J=6.9, 6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 17.83, 23.16, 25.67, 29.99, 49.48, 62.36, 64.26, 99.94, 120.11, 138.09. Found: C, 48.28; H, 6.62%. Calcd for $C_{10}H_{17}BrO_2$: C, 48.21; H, 6.88%.

4.5.11. *trans*-β-Benzyl-γ-nonanolactone (12a). IR (neat) 2928, 2856, 1768, 1604, 1455, 1205, 1173, 999, 944, 751, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J=3.9 Hz, 3H), 1.16–1.58 (m, 8H), 2.29 (dd, J=7.5, 16.8 Hz, 1H), 2.39–2.51 (m, 1H), 2.59 (dd, J=8.1, 16.8 Hz, 1H), 2.68 (dd, J=8.1, 14.1 Hz, 1H), 2.83 (dd, J=6.6, 13.5 Hz, 1H), 4.20 (q, J=6.0 Hz, 1H), 7.13–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.80, 22.30, 25.05, 31.30, 34.35, 34.73, 39.06, 42.33, 85.29, 126.86, 128.81 (2C), 128.84 (2C), 138.43, 176.46. Found: C, 77.91; H, 9.19%. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00%.

4.5.12. *trans*-β-[(3-Trifluoromethylphenyl)methyl]-γ-nonanolactone (12b). IR (neat) 2930, 2858, 1779, 1452, 1330, 1160, 1118, 1074, 1062, 947, 800, 704, 657 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J=6.8 Hz, 3H), 1.19–1.60 (m, 8H), 2.29 (dd, J=7.5, 16.8 Hz, 1H), 2.42–2.54 (m, 1H), 2.61 (dd, J=8.3, 16.8 Hz, 1H), 2.76 (dd, J=8.4, 13.8 Hz, 1H), 2.91 (dd, J=6.6, 13.8 Hz, 1H), 4.20 (q, J=6.0 Hz, 1H), 7.35–7.54 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 13.72, 22.25, 25.01, 31.23, 34.32, 34.56, 38.77, 42.09, 85.02, 123.77 (q, J=3.7 Hz), 124.01 (q, J=271.3 Hz), 125.37 (q, J=3.7 Hz),

129.33, 131.22 (q, J=31.9 Hz), 132.21, 139.46, 175.90. Found: C, 64.95; H, 6.77%. Calcd for $C_{17}H_{21}O_2F_3$: C, 64.96; H, 6.73%.

4.5.13. *trans*-β-[(4-Methoxyphenyl)methyl]-γ-nonanolactone (12c). IR (neat) 2924, 2856, 1771, 1613, 1513, 1466, 1249, 1179, 1035, 945, 818, 752 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, J=6.75 Hz, 3H), 1.20–1.59 (m, 8H), 2.28 (dd, J=7.5, 16.8 Hz, 1H), 2.35–2.47 (m, 1H), 2.59 (dd, J=8.1, 16.8 Hz, 1H), 2.63 (dd, J=8.1, 13.8 Hz, 1H), 2.77 (dd, J=6.6, 13.8 Hz, 1H), 3.80 (s, 3H), 4.19 (q, J=6.0 Hz, 1H), 6.85 (d, J=8.7 Hz, 2H), 7.06 (d, J=8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.80, 22.31, 25.05, 31.29, 34.36, 34.65, 38.14, 42.46, 55.20, 85.23, 114.16 (2C), 129.77 (2C), 130.40, 158.53, 176.50. Found: C, 73.66; H, 8.87%. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75%.

4.5.14. *trans*-β-(2-Thienylmethyl)-γ-nonanolactone (12d). IR (neat) 2928, 2856, 1771, 1467, 1439, 1421, 1260, 1204, 1182, 1000, 945, 850, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, J=6.8 Hz, 3H), 1.00–1.63 (m, 8H), 2.34 (dd, J=7.5, 17.1 Hz, 1H), 2.42–2.53 (m, 1H), 2.70 (dd, J=8.4, 20.1 Hz, 1H), 2.92 (dd, J=7.8, 14.7 Hz, 1H), 3.04 (dd, J=6.6, 14.7 Hz, 1H), 4.23 (q, J=6.3 Hz, 1H), 6.82 (d, J=3.3 Hz, 1H), 6.95 (dd, J=3.3, 5.1 Hz, 1H), 7.19 (d, J=5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.81, 22.30, 25.02, 31.28, 33.10, 34.49, 34.58, 42.48, 84.98, 124.33, 125.82, 127.14, 140.62, 176.18. Found: C, 66.64; H, 8.17%. Calcd for $C_{14}H_{20}O_2S$: C, 66.63; H, 7.99%.

Acknowledgements

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Practical method for the synthesis of (*R*)-homopipecolinic acid and (*R*)-homoproline esters from ω-chloroalkanoic acids and available chiral amines

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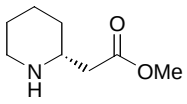
Abstract—A practical synthesis of (*R*)-homopipecolinic acid methyl ester **1** and (*R*)-homoproline methyl ester **2** was performed utilizing (i) a direct intramolecular cyclization of ω-chloro-β-enamino esters **11** and **12**, which were prepared from available (*S*)-1-phenylethylamine or (*S*)-1-(1-naphthyl)ethylamine and ω-chloro-β-keto esters **5** and **10**, respectively and (ii) a highly diastereoselective $NaBH_4$ reduction followed by hydrogenolysis. The present method is a short-step process using inexpensive and readily available substrates and reagents with fewer wasted materials.

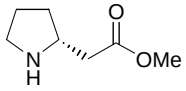
1. Introduction

Considerable attention has been focused on chiral piperidine and pyrrolidine derivatives, especially as key synthetic precursors of a variety of biologically active alkaloids. Among them, methyl (*R*)-(2-piperidino)acetate [(*R*)-homopipecolinic acid methyl ester] (**1**) and methyl (*R*)-(2-pyrrolidino)acetate [(*R*)-homoproline methyl ester] (**2**) are two attractive chiral building blocks for the synthesis of natural alkaloids[1] and useful pharmaceuticals.[2] There are several methods to synthesize these compounds;[3] the Lhommet's protocol[4] and the Michael type addition of chiral amines to α,β-unsaturated esters, followed by cyclizations utilizing either alkylation[5] or ring-closing metathesis.[6]

Lhommet and co-workers extensively investigated the synthesis of various chiral cyclic β-amino acid esters, which serve as key intermediates for the synthesis of alkaloids.[4] Their study began with the utilization of the Eschenmoser sulfide contraction,[7] which requires the tedious removal of undesirable sulfur-containing by-products, for the next Pd-catalyzed hydrogenation step.[4a–d,8] To resolve these problems, they developed three efficient alternative synthetic methods that utilize ω-chloro-2-alkynoates,[4e] ω-chloro-β-keto esters, and ω-oxo-2-alkynoates.[4f] Due to the multi-steps and/or expensive starting materials and reagents, there remains a need for an easier, more practical, and less expensive method.



1



2

As outlined in Scheme 1, we disclose a new practical synthetic method of **1** and **2**, which involves (i) the preparation of β-keto esters; (ii) β-enamino ester formation using available chiral benzylamines; (iii) regioselective cyclization; (iv) highly diastereoselective $NaBH_4$ reduction and (v) hydrogenolysis.

2. Results and discussion

The preparation of ω-chloro-β-keto ester precursors **5** and **10** is illustrated in Scheme 2. C-Acylation of Meldram's acid with 5-chloropentanoic acid (**3**) was performed using a condensation reagent, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl), to give product **4** in 95% yield. Methanolysis of **4** gave methyl 7-chloro-3-oxoheptanoate (**5**) quantitatively, which was used for the next step without any purification procedure such as distillation or column chromatography. On the other hand, a similar reaction using 4-chlorobutanoic acid (**6**) did

Keywords: Chiral amines; Intramolecular cyclization; Keto esters; Diastereoselective reduction.
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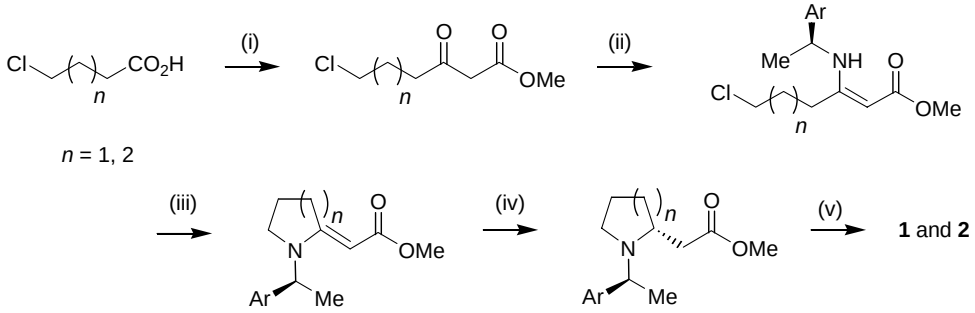
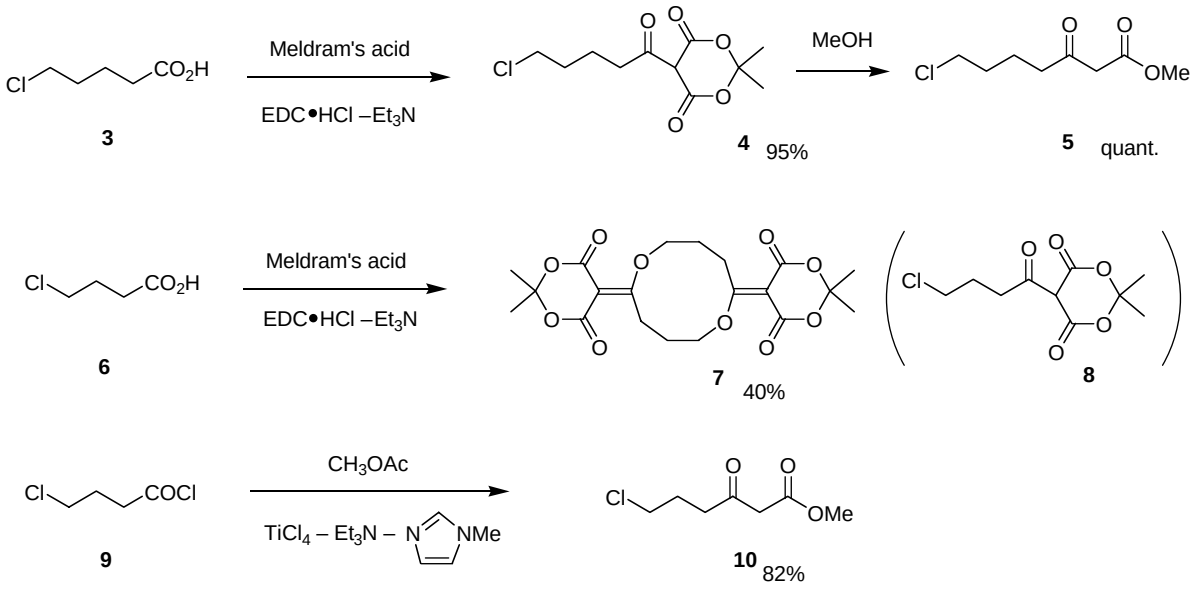


Scheme 1.

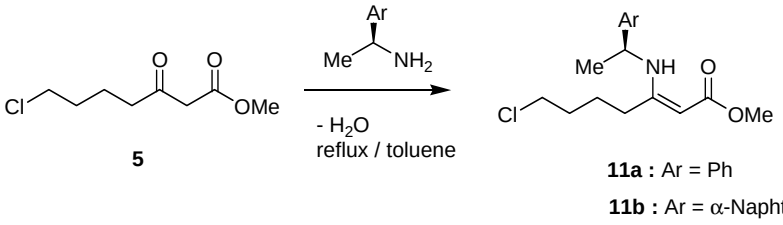


Scheme 2.

not result in the formation of the desired product **8**, but rather in the side formation of dimerized product **7** mainly under the identical conditions. We attribute this unexpected result to the fact that intermediate **8** is very labile due to the high reactivity of the 4-(γ-)chloro atom (neighboring group participation).[9] To solve the problem, we utilized Ti-Crossed Claisen condensation of acid chloride **9** with methyl acetate, which successfully afforded the desired β-keto ester **10** in good yield.[10]

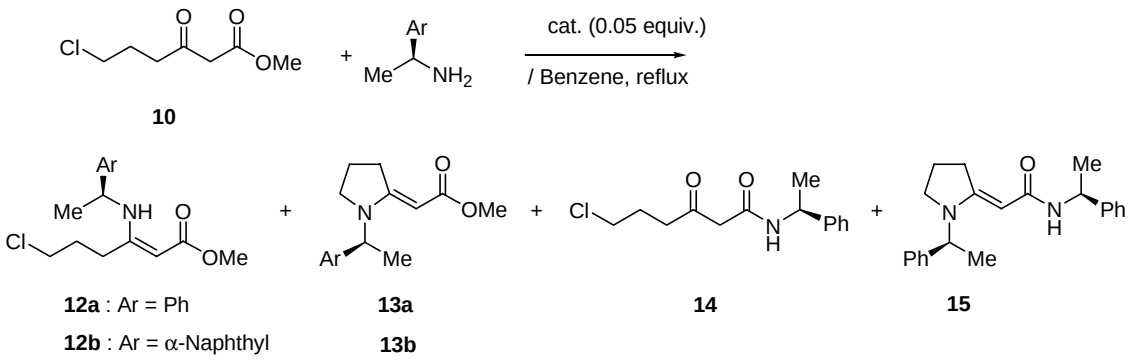
According to the reported method,[11] the condensation of **5** with readily available chiral amines, (*S*)-1-phenylethylamine and (*S*)-1-(1-naphthyl)ethylamine, smoothly proceeded to give the corresponding β-enamino esters **11a** (64%) and **11b** (69%), respectively, using the *p*-TsOH·H_2O catalyst (0.05 equiv) in toluene under convenient azeotropic conditions (Scheme 3). Note that, due to the instability of **11a** and **11b** against SiO_2 column chromatographic purification, one-pot procedure for the subsequent cyclization leading to **16a** and **16b**, respectively, should be desired (see Section 3).

A similar reaction between **10** and (*S*)-1-phenylethylamine gave the desired β-enamino ester **12a** and cyclized-homoproline ester **13a**; however, both resulted in poor yields, with considerable amounts of undesirable β-keto amides **14** and **15** (Table 1, entry 1). A longer reaction period did not improve the total yield of **12a** and **13a**, and increased the formation of **15** (entry 2), probably because the reactivity of the ketone function of **10** paralleled that of the ester. To solve this problem, we applied the $TiCl_4$-catalyzed method for β-enamino ester formation:[12] the side



Scheme 3.

Table 1.



10

12a : Ar = Ph
12b : Ar = α-Naphthyl

13a
13b

14

15

Entry	Cat.	Ar / Me / NH$_2$ (equiv)	Time (h)	Yield (%)[a]				
				12a	**13a**	**14**	**15**	Recovery of **10**
1[b]	TsOH·H$_2$O	1.5	1	28	6	18	6	42
2[b]			4	20	16	11	44	8
3	TiCl$_4$	1.2	4	50	8	Trace	Trace	35
4		1.4	4	61	15	Trace	Trace	24
5		1.5	4	73	15	Trace	Trace	12
6	SnCl$_4$	1.5	4	68	14	Trace	Trace	18
7	TiCl$_4$		6	78	19	Trace	Trace	Trace
8[c]			6	94	4	Trace	Trace	Trace
9[c,d]			6	96 (**12b**)	3 (**13b**)	—	—	Trace

[a] Determined by ^{1}H NMR.
[b] Toluene was used as a solvent and refluxed with removal of H$_2$O using Dean–Starks apparatus.
[c] Cyclohexane was used as a solvent.
[d] (*S*)-1-(1-Naphthyl)ethylamine was used instead of (*S*)-1-phenylethylamine.

formation of **14** and **15** was completely suppressed (entries 3–5). The use of $SnCl_4$ was somewhat inferior to that of $TiCl_4$ (entry 6). Under optimized conditions, the desired enamine **12a** (or its analog, **12b**) together with homoproline **13a** (or **13b**) resulted in a total 97% (or 99%) yield (entries 8 and 9).

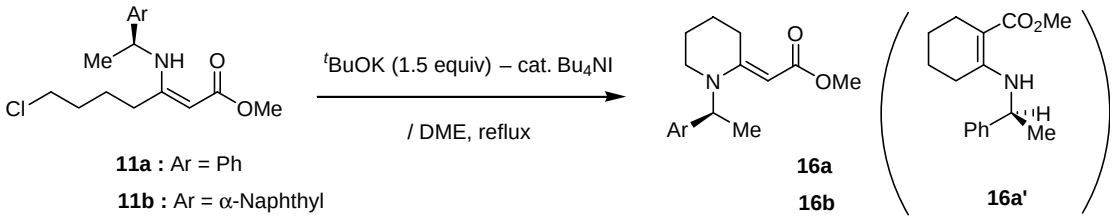
Next, we investigated the cyclization reaction of β-enamino ester **11a** and **11b** into homopipecolinic acid esters **16a** and **16b**, respectively, using ^{t}BuOK as a base (Table 2). The use of ^{t}BuOK alone resulted in slow conversion of the reaction with poor yield of **16a** (entry 1). To facilitate the reaction, 0.1 equiv of Bu_4NI was used as a co-catalyst and remarkable effects were observed; a shorter reaction time (1 h) and higher yield (55%) (entry 2). An increase in the number of Bu_4NI equivalents (0.2 and 0.4 equiv) did not affect the reaction yield, but rather the reaction became sluggish; that is, the purity of **16a** decreased (entries 3 and 4). The naphthyl analog **16b** also underwent the reaction smoothly (entry 5). Note that homoproline esters **13a** and **13b** were synthesized in better yield than **16a** and **16b** (entries 6 and 7), probably because of the advantageous five-membered ring formation.

The reaction between **5** and (*S*)-1-phenylethylamine using two different reagents (Na_2SO_4–Na_2HPO_4–cat. I_2[13] and Na_2CO_3–cat. Bu_4NI) resulted in competitive C-cyclization to give mainly compound **16a′**,[4f] a regioisomer of **16a**. The mechanism underlying the successful result of the desired regioselectivity using ^{t}BuOK–cat. Bu_4NI is not clear at present. We assume that the reported reaction proceeds via the enamine C-alkylation pathway, whereas ^{t}BuOK is sufficiently strong enough to eventually deprotonate amine hydrogen via the N-alkylation pathway. Wang and co-workers described another notable N-cyclization, which seems to be a back-to front mode of the present reaction; that is, N-alkylation occurs first, followed by enamine formation.[3f]

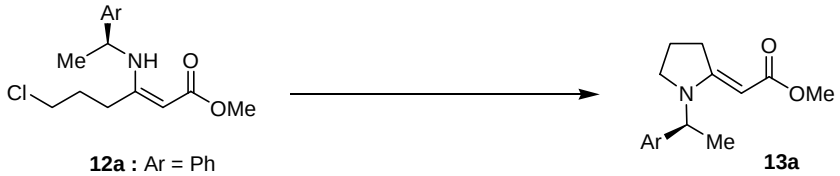
Next, we discuss diastereoselective reduction of *N*-protected homopipecolinic acid esters **16a**, **16b**, and homoproline esters **13a**, and **13b**, followed by deprotection, leading to (*R*)-homoproline methyl esters **2** and (*R*)-homopipecolinic acid methyl esters **1**. Catalytic hydrogenation of *N*-protected homoproline esters using the PtO_2 catalyst was previously reported.[4a,f] The MeCH(Cl)OCOCl mediated deprotection method is also documented.[5] We examined the reduction using readily available $NaBH_4$ of **16a**, **16b**, **13a**, and **13b**, which proceeded smoothly to give the desired products **17a**, **17b**, **18a**, and **18b**, respectively, with high stereoselectivity (Table 3). Compared with reported methods (entries 1–3),[14] $NaBH_4$ reduction in DME–AcOH mixed solvent gave almost similar results (entry 4). Compound **17b** (84% de) was isolated by its HCl salt, which was purified by recrystallization in 2-propanol to give pure product **17b** (98% de) in 56% total isolated yield. Note that naphthyl analogs **17b** and **18b** were obtained in good yield with excellent de (entries 6 and 8). This result would be a promising method to avoid column chromatographic purification from starting substrates **3** and **6**.

A proposed mechanism for the present stereoselective reduction, exemplified by naphthyl β-enamino ester **16b**,

Table 2. Intramolecular cyclization of β-enamino esters **11a**, **11b**, **12a**, and **12b**



11a : Ar = Ph
11b : Ar = α-Naphthyl
16a
16b
16a'

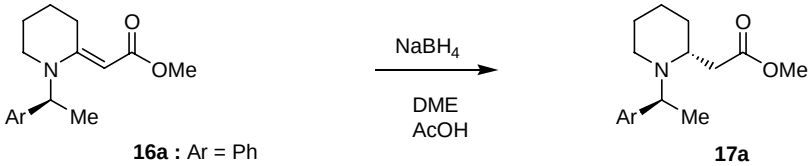


12a : Ar = Ph
12b : Ar = α-Naphthyl
13a
13b

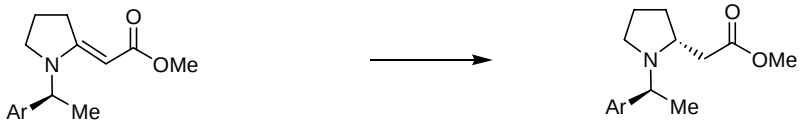
Entry	β-Enamino ester	Bu_4NI (equiv)	Time (h)	Product	Purity (%)[a]	Yield (%)[b]
1	**11a**	None	4	**16a**	—	27
2	**11a**	0.1	1	**16a**	97	55[c]
3	**11a**	0.2	1	**16a**	89	56[c]
4	**11a**	0.4	1	**16a**	86	55[c]
5	**11b**	0.1	1	**16b**	—	68
6	**12a**	0.1	1	**13a**	—	84
7	**12b**	0.1	1	**13b**	—	89

[a] Quantitative HPLC analysis: Column (YMC ODS-AM302; 5 μm, 4.6 mm×150 mm), mobil phase (H_2O/CH_3CN=30:70).
[b] Isolated yield.
[c] Calculated yield based on the purity of both starting material and product.

Table 3. Diastereoselective reduction of cyclized enamines **13** and **16** using $NaBH_4$[a]



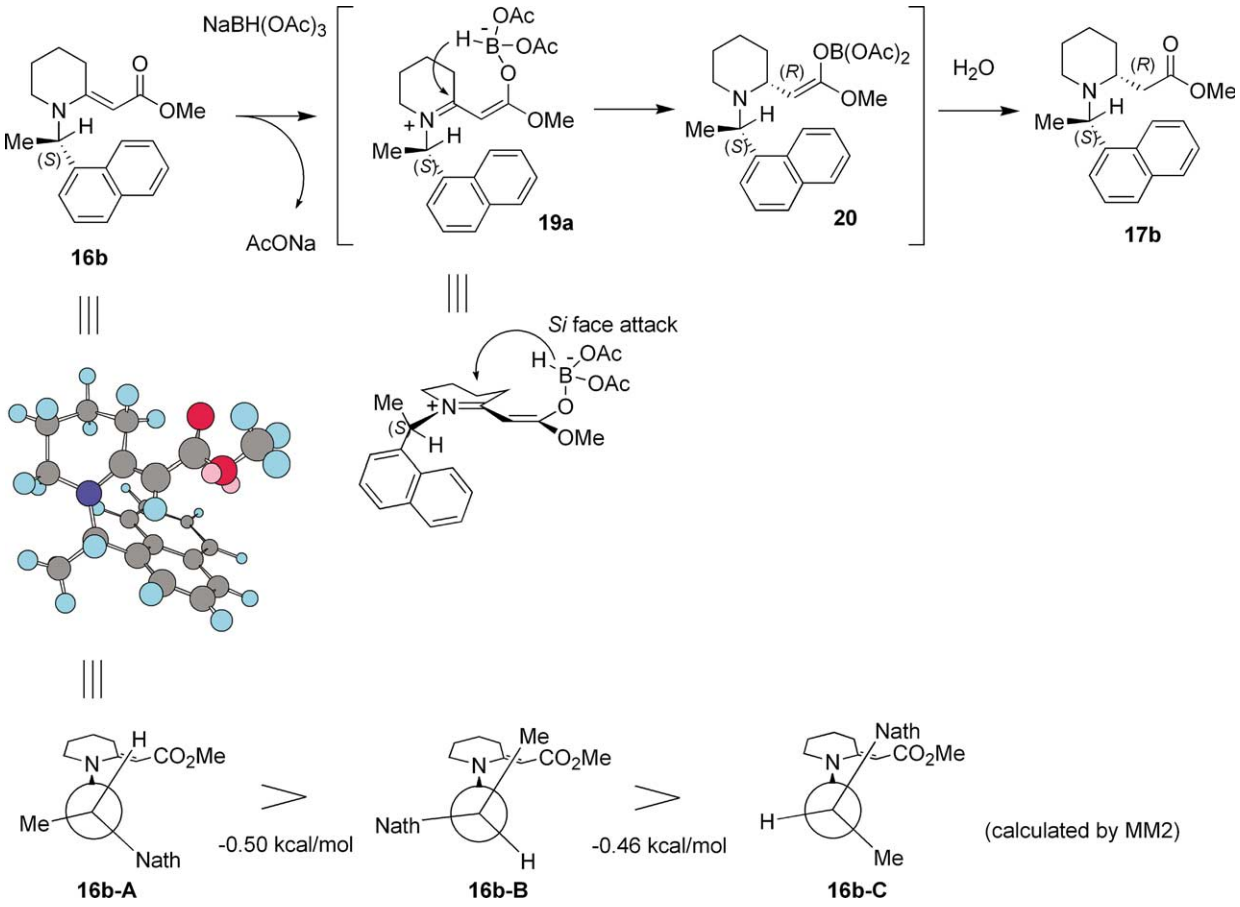
16a : Ar = Ph
16b : Ar = α-Naphthyl
17a
17b



13a : Ar = Ph
13b : Ar = α-Naphthyl
18a
18b

Entry	Enamine	Reaction condition	Solvent	Product de (%)[b]	Yield (%)[c]
1	**16a**	H_2 (balloon), PtO_2 (0.2W) rt, 18 h	DME	**17a** 86	77[d]
2	**16a**	$NaBH(OAc)_3$ (100 mol%) rt, 18 h	DME	**17a** 84	72
3	**16a**	$NaBH(OAc)_3$ (100 mol%) rt, 7 h	DME	**17a** 80	80[e]
4	**16a**	$NaBH_4$ (100 mol%) rt, 2 h	DME–AcOH (4/1)	**17a** 84	68
5	**16a**	$NaBH_4$ (400 mol%) rt, 3 h	MeOH	**17a** 62	69
6	**16b**	$NaBH_4$ (100 mol%) rt, 2 h	DME–AcOH (4/1)	**17b** 94	88
7	**13a**	$NaBH_4$ (100 mol%) rt, 2 h	DME–AcOH (4/1)	**18a** 62	79
8	**13b**	$NaBH_4$ (100 mol%) rt, 2 h	DME–AcOH (4/1)	**18b** 92	89

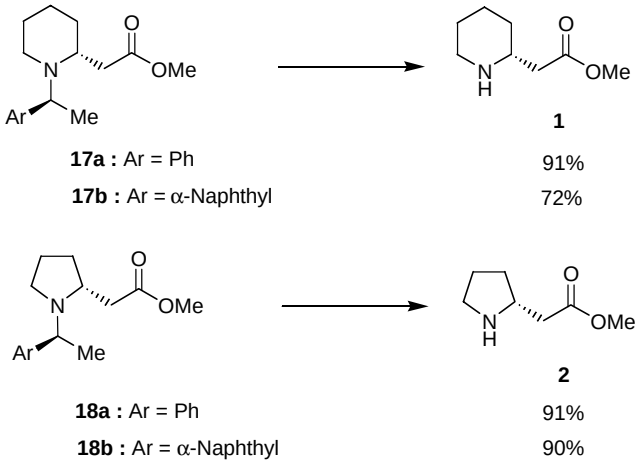
[a] The reaction conversion and diastereomeric excess were checked by either HPLC analysis: Column (YMC ODS-AM302; 5 μm, 4.6 mm×150 mm), mobil phase (H_2O/CH_3CN=70:30) or ^1H NMR integration for **18a**.
[b] de was checked before a chromatographic purification.
[c] Calculated yield based on the product purity.
[d] The reaction did not complete after 18 h.
[e] Conversion of HPLC analysis.



Scheme 4.

is as follows (Scheme 4). Ester **16b** has a preferential conformation of **16b-A** rather than **16b-B** or **16b-C**; Computer-assisted conformation analysis supports this assumption [MM2 force field, Chem3D 5.0 Windows, CambridgeSoft Corporation (Cambridge Scientific Computing, Inc.), Cambridge, Massachusetts, USA]. Initially, the reaction of **16b-A** with $NaBH(OAc)_3$, generated by $NaBH_4$ and AcOH, produces (*Z*)-β-iminium borate **19a**, which was in turn transformed into β-amino boron-enolate **20** by the intramolecular reduction; bulky naphthyl group hangs over the *Re* face of **19a** and hydride transfer occurs from less hindered *Si* face. Final hydrolysis of **20** affords the desired β-amino ester **17b**.

Final stage of the present syntheses, that is, deprotection of **17a** and **17b** was performed by catalytic hydrogenation using H_2–10% Pd–C to give (*R*)-homopipecolinic acid methyl ester **1** in good yield in contrast to the reported description (Scheme 5).[5] The analytical data of **1** was identical with that of the authentic sample[12] with high optical purity (98% ee). (*R*)-homoproline methyl ester (**2**) was obtained in a similar manner (91% ee).



Scheme 5.

In conclusion, we performed an efficient practical method for the synthesis of two useful chiral building brocks, (*R*)-homopipecolinic acid methyl ester **1** and (*R*)-homoproline methyl ester **2**.

3. Experimental

3.1. General

All reagents and solvents were commercially available. Flash column chromatography was performed with silica gel Merck 60 (230–400 mesh ASTM). ^{1}H NMR spectra were recorded on a Bruker AC200P (200 MHz), or a on a JEOL DELTA 300 spectrometer, operating at 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR. Melting points were determined on a hot stage microscope apparatus (Yanagimoto) and were uncorrected. NMR spectra were recorded Chemical shifts (δ ppm) in $CDCl_3$ were reported downfield from TMS (=0) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to $CDCl_3$ (77.00 ppm) as an internal reference. IR Spectra were recorded on a JASCO FT/IR-5300 spectrophotometer. Optical rotations were measured on a JASCO DIP-370 (Δ 589 nm). Mass spectra were measured on a JEOL JMS-T100LC spectrometer. HPLC analyses were performed using a Shimadzu 10A apparatus.

3.1.1. 2,2-Dimethyl-5-(5-chloropentanoyl)-1,3-dioxane-4,6-dione (4). Meldram's acid (10.0 g, 69 mmol) was added to a stirred solution of 5-chlorohexanoic acid (**1b**, 9.5 g, 69 mmol), 4-dimethylaminopyridine (2.1 g, 17 mmol), Et_3N (14.0 g, 139 mmol), and EDC hydrochloride (14.6 g, 76 mmol) in CH_2Cl_2 (200 mL) at 0–5 °C. After stirring at 20–25 °C for 24 h, the mixture was concentrated, and extracted with AcOEt (200 mL). The organic phase was washed with 1 M HCl (200 mL), water, brine, dried ($MgSO_4$), and concentrated to give the desired product **4** (17.4 g, 95%).

Viscid yellowish oil. Leaving the oil at room temperature it solidified; mp 40–41 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.74 (s, 6H), 1.85–1.95 (m, 4H), 3.08–3.16 (m, 2H), 3.52–3.64 (m, 2H), 15.35 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 23.16, 26.77, 31.90, 34.77, 44.23, 91.40, 104.90, 197.08; HRMS (ESI) calcd for $C_{11}H_{15}ClO_5$ ($M-H^+$) 261.0530, found 261.0529. Anal. Calcd for $C_{11}H_{15}ClO_5$: C, 50.29; H, 5.76. Found: C, 49.9; H, 5.5.

3.1.2. 2,7-Bis(4,4-dimethyl-3,5-dioxo-2,6-dionecyclohexylidene)[1,6]dioxetane (7). Following the procedure for the preparation of **4**, the reaction of **6** (5.0 g, 40 mmol) gave not the desired product but dimeric compound **3b** (3.45 g, 40%) as a main product.

Colorless solid; mp 145–148 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.71 (s, 12H), 2.18–2.34 (m, 4H), 3.53 (t, 4H, J=7.9 Hz), 4.78 (t, 4H, J=7.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 21.80, 26.88, 36.16, 77.42, 91.57, 103.22, 159.83, 162.95, 190.35; IR (KBr) 3430, 2986, 1741, 1707, 1537, 1304, 1209 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{24}O_{10}$ ($M+Na^+$) 447.1267, found 447.1270. Anal. Calcd for $C_{20}H_{24}O_{10}$: C, 56.60; H, 5.70. Found: C, 56.8; H, 5.9.

3.1.3. Methyl 6-chloro-3-oxohexanoate (10).[3a,4f] 4-Chlorobutanoyl chloride (**9**; 5.07 g, 30 mmol) was added to a stirred solution of AcOMe (3.56 g, 48 mmol) and *N*-methylimidazole (2.96 g, 36 mmol) in toluene (90 mL) at 0–5 °C under an Ar atmosphere, followed by being stirred at the same temperature for 10 min. $TiCl_4$ (18.78 g, 99 mmol) and *N*,*N*-diisopropylethylamine (13.96 g, 108 mmol) were successively added to the mixture at 0–5 °C, which was stirred at same temperature for 30 min. Water was added to the mixture, which was extracted three times with ether. The combined organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated to give crude oil (6.00 g). Purification by silica gel column chromatography (hexane/AcOEt=20:1) gave the desired product **10** (4.39 g, 82%).

Yellowish oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.08 (quin, 2H, J=6.5 Hz), 2.76 (t, 2H, J=6.9 Hz), 3.48 (s, 2H), 3.59 (t, 2H, J=6.5 Hz), 3.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 25.85, 39.43, 43.90, 48.82, 52.16, 167.27, 201.46; IR (neat) 2957, 1748, 1719, 1439, 1408, 1325, 1265 cm^{-1}; HRMS (ESI) calcd for $C_7H_{11}ClO_3$ ($M+Na^+$) 201.0294, found 201.0300.

3.1.4. Methyl 3-[1(*S*)-phenylethylamino]-7-chlorohept-2-enoate (11a). Methyl 7-chloro-3-oxoheptanoate (**5**; 96 mg, 0.50 mmol) was added to a stirred solution of (*S*)-phenylethylamine (91 mg, 0.75 mmol) and *p*-TsOH·H_2O (5 mg, 0.03 mmol) in toluene (1.5 mL). After reflux for 1 h using Dean–Stark apparatus with continual removal of water, water was added to the mixture, which was extracted three times with ether. The combined organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated to give crude oil (~100% ^{1}H NMR conversion yield), which was purified by silica gel column chromatography (hexane/AcOEt=10:1) gave the desired product **11a** (95 mg, 64%). Because **11a** was somewhat labile to silica gel column chromatography, the isolated yield decreased. One-pot reaction improved the yield (See the preparation of **16a**).

Yellowish oil; $[\alpha]_D^{27}$ +403.9 (*c* 1.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.41–1.51 (1H, m), 1.53 (3H, d, J=7.2 Hz), 1.56–1.86 (3H, m), 1.87–2.05 (1H, m), 2.10–2.22 (1H, m), 3.42 (2H, t, J=6.2 Hz), 3.67 (3H, s), 4.50 (1H, s), 4.64 (1H, quin, J=7.2 Hz), 7.20–7.38 (4H, m), 8.95–9.07 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 25.10, 31.43, 31.78, 44.34, 50.04, 52.47, 82.20, 125.34, 127.14, 128.80, 145.03, 164.58, 171.10; IR (neat) 3279, 2948, 1655, 1607, 1258 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{22}ClNO_2$ ($M+Na^+$) 318.1237, found 318.1232.

3.1.5. Methyl 3-[1(*S*)-naphthylethylamino]-7-chlorohept-2-enoate (11b). Following the procedure for the preparation of **11a**, the reaction using **5** (96 mg, 0.50 mmol) and (*S*)-naphthylethylamine (128 mg, 0.75 mmol), gave the desired product **11b** (120 mg, 69%). (~100% ^{1}H NMR conversion yield). **11b** was somewhat labile to silica gel column chromatography.

Yellowish oil; $[\alpha]_D^{24}$ +443.0 (*c* 1.74, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.40–1.62 (4H, m), 1.66 (3H, d, J=7.2 Hz), 1.82–1.95 (1H, m), 2.00–2.13 (1H, m), 3.30 (2H, t, J=6.2 Hz), 3.72 (3H, s), 4.55 (1H, s), 5.45 (1H, quin, J=

7.2 Hz), 7.42–7.62 (4H, m), 7.72–7.80 (1H, m), 7.87–7.93 (1H, m), 8.00–8.06 (1H, m), 9.17–9.25 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 24.12, 25.06, 31.41, 31.71, 44.26, 48.54, 50.09, 82.61, 121.81, 122.41, 125.64, 125.85, 126.38, 127.61, 129.15, 129.73, 133.78, 140.80, 164.60, 171.20; IR (neat) 3283, 2948, 1653, 1605, 1262 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{24}ClNO_2$ ($M+Na^+$) 368.1393, found 368.1397.

3.1.6. Methyl 3-[1(*S*)-phenylethylamino]-6-chlorohex-2-enoate (12a) (Table 1, entry 8). $TiCl_4$ (3 μL, 0.03 mmol) was added to a stirred solution of **10** (89 mg, 0.5 mmol) and (*S*)-phenylethylamine (81 mg, 0.75 mmol) in cyclohexane (2.0 mL) at 20–25 °C. The reaction mixture was refluxed for 6 h. Water was added to the mixture, which was extracted three times with ether. The combined organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated to give crude oil (94% ^{1}H NMR conversion yield), which was purified by silica gel column chromatography (hexane/AcOEt=10:1) to give the desired product **12a** (104 mg, 74%). Compound **12a** was somewhat labile to silica gel column chromatography.

Yellowish oil; $[\alpha]_D^{26}$ +299.9 (*c* 1.57, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.53 (3H, d, *J*=7.2 Hz), 1.73–1.98 (2H, m), 2.03–2.20 (1H, m), 2.26–2.41 (1H, m), 3.37–3.57 (2H, m), 3.67 (3H, s), 4.51 (1H, s), 4.67 (1H, quin, *J*=7.2 Hz), 7.19–7.39 (5H, m), 8.96–9.08 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 25.07, 29.37, 30.80, 44.00, 50.06, 52.47, 82.51, 125.36, 127.16, 128.80, 144.88, 163.66, 171.02.

3.1.7. Methyl 3-[1(*S*)-naphthylethylamino]-6-chlorohex-2-enoate (12b) (Table 1, entry 9). Following the procedure for the preparation of **12a**, the reaction using **10a** (89 mg, 0.5 mmol) and (*S*)-naphthylethylamine (128 mg, 0.75 mmol), gave the desired product **12b** (96% ^{1}H NMR conversion yield) (130 mg, 78%). Compound **12b** was somewhat labile to silica gel column chromatography.

Yellowish oil; $[\alpha]_D^{24}$ +325.4 (*c* 1.74, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.65 (3H, d, *J*=6.9 Hz), 1.68–1.94 (2H, m), 1.96–2.08 (1H, m), 2.19–2.32 (1H, m), 3.23–3.34 (1H, m), 3.36–3.48 (1H, m), 3.71 (3H, s), 4.58 (1H, s), 5.48 (1H, quin, *J*=6.9 Hz), 7.40–7.59 (4H, m), 7.71–7.79 (1H, m), 7.85–7.91 (1H, m), 7.94–8.07 (1H, m), 9.09–9.31 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 24.07, 29.19, 30.74, 43.73, 48.55, 50.07, 82.89, 121.89, 122.26, 125.60, 125.74, 126.29, 127.59, 129.05, 129.64, 133.73, 140.63, 163.66, 171.07; IR (neat) 3281, 2948, 1653, 1607, 1262 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{22}ClNO_2$ ($M+Na^+$) 354.1237, found 354.1233.

3.1.8. *p*-TsOH·H_2O catalyzed reaction of methyl 6-chloro-3-oxohexanoate (10) with (*S*)-phenylethylamine (Table 1, entry 2). Methyl 6-chloro-3-oxohexanoate **10** (179 mg, 1.0 mmol,) was added to a stirred solution of (*S*)-phenylethylamine (182 mg, 1.5 mmol) and *p*-TsOH·H_2O (10 mg, 0.05 mmol) in toluene (3 mL) at room temperature. After reflux for 4 h using Dean–Stark apparatus with continual removal of water, water was added to the mixture, which was extracted three times with ether. The combined organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated to give crude oil [^{1}H NMR conversion yields; **12a** (20%), **13a** (16%), **14** (11%), **15** (44%)]. The mixture was purified by silica gel column chromatography (hexane/AcOEt=1:1) to give the products **12a** (28 mg, 10%), **13a** (29 mg, 12%), **14** (27 mg, 10%), **15** (117 mg, 35%).

3.1.9. 6-Chloro-3-oxo-*N*-[1(*S*)-phenylethyl]hexanamide (14). Yellowish oil; $[\alpha]_D^{26}$ −64.7 (*c* 0.42, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.50 (3H, d, *J*=7.2 Hz), 4.67 (2H, quin, *J*=6.2 Hz), 2.71–7.77 (2H, m), 3.42–3.44 (1H, m), 3.56 (2H, t, *J*=6.2 Hz), 5.12 (1H, quin, *J*=6.2 Hz), 7.20–7.39 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 15.26, 22.04, 25.87, 40.48, 43.94, 49.04, 49.18, 65.83, 126.05, 127.38, 128.70, 142.93, 164.31, 205.67; IR (KBr) 3283, 3061, 2973, 2928, 1721, 1495, 1547 cm^{-1}.

3.1.10. 1-(1(*S*)-Phenylethyl)-2-[(1(*S*)-phenylethylaminocarbonyl)methylidene]pyrrolidine (15). Yellowish oil; $[\alpha]_D^{26}$ −176.4 (*c* 1.29, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.46 (d, 3H, *J*=6.2 Hz), 1.52 (d, 3H, *J*=7.0 Hz), 1.76–1.99 (m, 2H), 3.00–3.44 (m, 4H), 4.49 (s, 1H), 4.77 (br s, 1H), 5.13 (br s, 2H), 7.16–7.38 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 15.16, 16.84, 21.22, 22.39, 32.29, 46.58, 47.99, 52.64, 65.72, 81.01, 126.12, 126.41, 126.66, 127.15, 128.32, 128.47, 140.81, 144.76, 161.84; IR (neat) 3293, 2975, 1638, 1580, 1213, 1177 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{26}N_2O$ ($M+Na^+$) 357.1943, found 357.1939.

3.1.11. 1-[(1*S*)-Phenylethyl]-2-[(methoxycarbonyl)-methylidene]piperidine (16a).[4a,15] (one-pot reaction from 1,3-dioxane-4,6-dione 4) 1,3-Dioxane-4,6-dione **4** (3.00 g, 11 mmol) was added to a stirred solution of MeOH (30 mL) and the mixture was refluxed for 2 h. After cool down to room temperature the mixture was concentrated to give methyl 7-chloro-3-oxoheptanoate (**5**). To the residual oil of was added toluene (45 mL), (*S*)-phenylethylamine (1.66 g, 14 mmol), and *p*-TsOH·H_2O (0.13 g, 0.68 mmol). After reflux for 1 h using Dean–Stark trap with continual removal of water, the mixture was concentrated to give product **11a**, to which was added DME (45 mL), ^{t}BuOK (1.92 g, 17 mmol), and Bu_4NI (0.42 g, 1.1 mmol). After reflux for 1 h, the mixture was concentrated and dissolved with AcOEt (100 mL), which was extracted with 0.2 M HCl (15 mL×3). Separated combined aqueous phase was adjusted to pH 8–9 using Na_2CO_3, and then re-extracted with AcOEt (25 mL×2). Combined separated organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated to give the desired product **16a** (1.68 g, 57%).

Yellowish orange solid; mp 50–52 °C; $[\alpha]_D^{25}$ −126.0 (*c* 0.88, CH_2Cl_2); {lit.,[4e] $[\alpha]_D^{20}$ −121 (*c* 1.10, CH_2Cl_2)}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.53 (d, 3H, *J*=6.9 Hz), 1.54–1.74 (m, 4H), 2.75–2.90 (m, 1H), 2.90–3.06 (m, 1H), 3.10–3.30 (m, 2H), 3.61 (s, 3H), 4.87 (s, 1H), 5.13 (q, 1H, *J*=6.9 Hz), 7.20–7.40 (m, 5H); Mass (TIC, *m*/*z*): 282 (M+Na); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 15.2, 19.3, 23.0, 26.3, 41.9, 49.9, 55.2, 81.4, 126.9, 127.4, 128.6, 140.4, 164.0, 169.8; IR (KBr) 2949, 2868, 1684, 1589, 1142 cm^{-1}.

3.1.12. 1-[(1*S*)-Naphthylethyl]-2-[(methoxycarbonyl)-methylidene]piperidine (16b). Following the procedure

for the preparation of **16a**, use of (*S*)-naphthylethylamine (445 mg, 2.6 mmol) and **4** (545 mg, 2.0 mmol) gave the desired product **16b** (418 mg, 68%).

Pale yellow solid; mp 146–148 °C; $[\alpha]_D^{25}$ −153.3 (*c* 1.58, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) *δ*: 1.20–1.60 (m, 4H), 1.65 (d, 3H, *J*=6.8 Hz), 2.35–2.50 (m, 1H), 2.80–2.98 (m, 1H), 3.22 (t, 2H, *J*=6.4 Hz), 3.69 (s, 3H), 5.12 (s, 1H), 5.61 (q, 1H, *J*=6.8 Hz), 7.42–7.60 (m, 4H), 7.62–7.74 (m, 1H), 7.78–7.94 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) *δ*: 13.7, 18.9, 22.9, 26.3, 41.5, 50.0, 52.6, 80.9, 123.6, 124.7, 124.8, 126.0, 126.9, 128.7, 128.9, 131.9, 133.7, 135.5, 162.9, 169.9. Mass (TIC, *m*/*z*): 332 (M+Na). Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.3; H, 7.2; N, 4.3.

3.1.13. 1-[(1*S*)-Phenylethyl]-2-[(methoxycarbonyl)-methylidene]pyrrolidine (13a).[4a,15] $TiCl_4$ (65 mg, 0.25 mmol) was added to a stirred solution of β-keto ester **10** (894 mg, 5.00 mmol) and (*S*)-phenylethylamine (916 mg, 7.50 mmol) in cyclohexane (20 mL) at 20–25 °C. The reaction mixture was refluxed for 6 h. After cool down to room temperature, water was added to the mixture, which was extracted three times with ether. The combined organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated to give product sufficiently pure β-enamine **12a**, to which was added DME (20 mL), ^{t}BuOK (841 mg, 7.50 mmol), and Bu_4NI (185 mg, 0.50 mmol). After reflux for 1 h, the reaction mixture was concentrated and dissolved with AcOEt (20 mL) and then extracted with 0.2 M HCl (15 mL×3). Combined separated aqueous phase was adjusted to pH 8–9 using Na_2CO_3, and then re-extracted with AcOEt (25 mL×2). Combined separated organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated to give the desired product **13a** (1.06 g, 86%).

Yellowish orange solid; mp 68–70 °C; $[\alpha]_D^{25}$ −251.1 (*c* 0.94, EtOH); {lit.,[4e] $[\alpha]_D^{20}$ −256 (*c* 1.10, EtOH)}; ^1H NMR ($CDCl_3$, 300 MHz) *δ*: 1.55 (d, 3H, *J*=6.9 Hz), 1.75–2.02 (m, 2H), 3.05–3.23 (m, 2H), 3.23–3.40 (m, 2H), 3.61 (s, 3H), 4.68 (s, 1H), 4.87 (q, 1H, *J*=6.9 Hz), 7.19–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 16.73, 20.84, 32.77, 47.13, 49.91, 52.87, 77.82, 126.51, 127.40, 128.57, 140.31, 164.90, 169.91; IR (KBr) 2949, 2868, 1684, 1589, 1142 cm^{-1}.

3.1.14. 1-[(1*S*)-Naphthylethyl]-2-[(methoxycarbonyl)-methylidene]pyrrolidine (13b). Following the procedure for the preparation of **13a**, the reaction using **10** (0.72 g, 4.0 mmol) and (*S*)-naphthylethylamine (1.30 g, 6.0 mmol) gave the desired product **13b** (1.32 g, 89%).

Yellowish orange solid; mp 123–125 °C; $[\alpha]_D^{25}$ −197.3 (*c* 1.82, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) *δ*: 1.66 (d, 3H, *J*=6.9 Hz), 1.72–1.90 (m, 2H), 2.48–2.59 (m, 1H), 3.06–3.33 (m, 3H), 3.69 (s, 3H), 4.94 (s, 1H), 5.44 (q, 1H, *J*=6.9 Hz), 7.42–7.55 (m, 4H), 7.66–7.74 (m, 1H), 7.79–7.91 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 14.26, 20.76, 32.87, 47.13, 49.58, 50.06, 77.36, 123.01, 123.68, 124.99, 125.99, 126.96, 128.76, 131.67, 133.64, 135.28, 164.17, 170.12; IR (KBr) 2973, 2940, 1678, 1582, 1140 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{21}NO_2$ ($M+Na^+$) 318.1470, found 318.1472. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.1; H, 6.9; N, 4.6.

3.1.15. Methyl[(1*S*)-phenylethyl]-2(*R*)-piperidylacetate (17a).[4g] $NaBH_4$ (29 mg, 0.77 mmol) was added to a stirred solution of **16a** (200 mg, 0.77 mmol) in DME (8 mL) and CH_3CO_2H (2 mL) at 10–15 °C. After stirring at 20–25 °C for 2 h, the mixture was concentrated and then 10% NaOH aqueous solution (20 mL) was added to the mixture, which was extracted with AcOEt (15 mL×2). Combined separated organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated to give crude oil (248 mg). Purification by silica gel column chromatography (hexane/AcOEt=5:1) gave the desired product **17a** (137 mg, 68, 84% de).

The de was checked by HPLC analysis [UV (wave length, 230 nm), Mobil phase (H_2O/CH_3CN=70:30), Column (YMC ODS-AM302; 5 μm, 4.6 mm×150 mm), Column temperature (40 °C), Flow rate (1 mL/min)]. The retention times of (1*S*,2*S*)-isomer and (1*S*,2*R*)-isomer were 7.2 and 9.8 min, respectively. Further purification using column chromatography gave pure (1*S*,2*R*)- and (1*S*,2*S*)-isomers. (1*S*,2*R*)-Isomer: $[\alpha]_D^{24}$ −35.3 (*c* 1.84, $CHCl_3$); colorless oil; ^1H NMR ($CDCl_3$, 200 MHz) *δ*: 1.29 (d, 3H, *J*=6.7 Hz), 1.35–1.68 (m, 5H), 1.68–1.88 (m, 1H), 2.14–2.40 (m, 2H), 2.50–2.60 (m, 2H), 3.42–3.55 (m, 1H), 3.68 (s, 3H), 3.70 (q, 1H, *J*=6.7 Hz), 7.18–7.40 (m, 5H); IR (neat) 3050, 2971, 2876, 1736 cm^{-1}; ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 17.86, 20.77, 25.57, 29.96, 31.93, 44.92, 51.53, 52.34, 59.26, 126.49, 127.25, 128.11, 146.11, 173.60; IR (neat) 3407, 2934, 1736, 1443, 1161 cm^{-1}; Mass (TIC, *m*/*z*): 262 (M+1). (1*S*,2*S*)-Isomer: ^1H NMR ($CDCl_3$, 200 MHz) *δ*: 1.33 (d, 3H, *J*=6.7 Hz), 1.38–1.74 (m, 6H), 2.39–2.75 (m, 4H), 3.10–3.26 (m, 1H), 3.60 (s, 3H), 3.82 (q, 1H, *J*=6.7 Hz), 7.18–7.37 (m, 5H). Mass (TIC, *m*/*z*): 262 (M+1).

3.1.16. Methyl[(1*S*)-naphthylethyl]-2(*R*)-piperidylacetate (17b). Following the procedure for the preparation of **17a**, the reaction using **16b** (160 mg, 0.517 mmol) gave the desired product **17b** (142 mg, 88, 94% de). The retention times of (1*S*,2*S*)- and (1*S*,2*R*)-isomers, using HPLC analysis described above, were 11.7 and 13.3 min, respectively. Further purification using column chromatography gave a pure (1*S*,2*R*)-isomer.

Colorless oil; $[\alpha]_D^{27}$ −83.2 (*c* 1.54, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) *δ*: 1.26–1.40 (m, 1H); 1.46 (d, 3H, *J*=6.6 Hz); 1.61–1.70 (m, 6H); 2.18–2.33 (m, 1H); 2.33–2.48 (m, 1H); 2.60–2.86 (m, 2H); 3.60–3.77 (m, 1H); 3.70 (s, 3H); 4.42 (q, 1H, *J*=6.6 Hz); 7.38–7.55 (m, 3H); 7.60–7.90 (m, 3H); 8.40–8.54 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 18.18, 20.21, 25.62, 29.63, 30.51, 45.07, 51.53, 52.12, 56.90, 123.94, 124.53, 125.14, 125.24, 125.41, 127.10, 128.64, 131.57, 134.00, 141.36, 173.69; IR (KBr) 2934, 1736, 1437, 1161 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{25}NO_2$ ($M+H^+$) 312.1964, found 312.1696.

3.1.17. Methyl 1-[(1*S*)-phenylethyl]-(2*R*)-pyrrolidyl-acetate (18a). Following the procedure for the preparation of **17a**, the reaction using **13a** (245 mg, 1.0 mmol) gave the desired product **18a** (195 mg, 79% yield, 62% de).

Yellowish oil (diastreomixtures); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.38 (d, 2.43H, J=6.5 Hz), 1.43 (d, 0.57H, J=6.9 Hz), 1.50–2.03 (m, 5H), 2.06–2.86 (m, 4H), 3.08–3.02 (m, 0.19H), 3.23–3.38 (m, 0.81H), 3.60 (s, 2.43H), 3.65 (m, 0.19H), 3.67–3.80 (m, 1H), 7.18–7.40 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.03, 18.03, 20.82, 22.08, 22.70, 30.71, 39.08, 40.00, 49.50, 50.00, 51.11, 56.64, 57.84, 60.17, 60.38, 60.63, 126.70, 127.39, 127.58, 127.96, 128.04, 142.97, 144.92, 170.87, 172.76; IR (neat) 3028, 2971, 2876, 1738 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{21}NO_2$ ($M+H^+$) 248.1651, found 248.1648. The retention times of (1*S*,2*S*)- and (1*S*,2*R*)-isomers, using HPLC analysis described above, were same 4.83 min. Further purification using column chromatography gave a pure (1*S*,2*R*)-isomer; $[\alpha]_D^{25}$ −10.2 (*c* 0.97, $CHCl_3$).

3.1.18. Methyl 1-[(1*S*)-Naphthylethyl]-2(*R*)-pyrrolidyl-acetate (18b). Following the procedure for the preparation of **18a**, the reaction using **13b** (295 mg, 1.0 mmol) gave the desired product **18b** (260 mg, 89% yield, 92% de). The retention times of (1*S*,2*S*)- and (1*S*,2*R*)-isomers, using HPLC analysis described above, were 13.3 and 11.7 min, respectively. Further purification using column chromatography gave a pure (1*S*,2*R*)-isomer.

Colorless oil; $[\alpha]_D^{24}$ −7.6 (*c* 1.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.51 (d, 3H, J=6.9 Hz), 1.53–1.62 (m, 1H), 1.63–1.75 (m, 2H), 1.90–2.08 (m, 1H), 2.20 (dd, 1H, J=9.6 Hz, J_{gem}=14.5 Hz), 2.52 (dd, 1H, J=4.1 Hz, J_{gem}=14.5 Hz), 2.56–2.68 (m, 1H), 3.33–3.45 (m, 1H), 3.58 (s, 3H), 4.53 (q, 1H, J=6.9 Hz), 7.37–7.52 (m, 3H), 7.53–7.60 (m, 1H), 7.69–7.76 (m, 1H), 7.79–7.88 (m, 1H), 8.37–8.45 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 17.15, 22.35, 30.90, 38.32, 49.03, 51.26, 56.27, 58.15, 124.10, 124.54, 125.15, 125.21, 125.36, 127.39, 128.59, 131.48, 133.91, 140.64, 172.95; IR (neat) 3050, 2971, 2876, 1736 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{23}NO_2$ ($M+H^+$) 298.1807, found 298.1805.

3.1.19. Methyl(*R*)-(2-piperidino)acetate[(*R*)-homopipecolinic acid methyl ester] (1).[3d,g] Compound **17a** (233 mg, 0.892 mmol, >99% de) was added to a stirred suspension of 10% Pd–C (50% wet, 47 mg) in DME (15 mL) at 20–25 °C with a H_2 balloon. After stirring for 17 h, the reaction mixture was filtered through a plug Celite®, and concentrated to give the desired product **1** (127 mg, 91% yield, 98% ee).

In the case of this method using **17b** (307 mg, 0.98 mmol, 99% de), an additional work-up process was necessary for the isolation of **1**. After concentration, 0.2 M aqueous HCl was added to a residual oil, which was washed with AcOEt to eliminate 1-ethylnaphthalene. Successive neutralization of the aqueous phase with Na_2CO_3, which was reextracted with AcOEt, followed by the concentration of the organic phase to give the desired product **1** (111 mg, 72% yield, 98% ee). The enantioselectivity was checked by the chiral derivatization to *N*-*R*-(+)-1-phenylethylcarbamate of **1** using *N*-succinimidyl *R*-(+)-1-phenylethyl carbamate[16] and HPLC analysis [UV (wave length; 220 nm), Mobile phase (pH 6.5 phosphoric acid buffer/CH_3CN=70:30), Column (ULTRON VX-ODS; 5 μm, 4.6 mm×150 mm), Column temperature (25 °C)]. Colorless oil; $[\alpha]_D^{24}$ −16.5 (*c* 1.00, MeOH); {lit.,[3g] $[\alpha]_D^{26}$ +3.9 (*c* 0.64, $CHCl_3$), the antipodal (*S*) isomer}, ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.05–1.85 (m, 6H), 1.95–2.08 (br s, 1H), 2.30–2.42 (m, 2H), 2.58–2.76 (m, 1H), 2.80–3.10 (m, 2H), 3.68 (s, 3H); Mass (TIC, *m*/*z*): 158 (M+1).

3.1.20. Methyl (*R*)-(2-pyrrolidino)acetate [(*R*)-homoproline methyl ester] (2).[17] Compound **18a** (247 mg, 1 mmol, 62% de) was added to a stirred suspension of 10% Pd–C (50% wet, 108 mg) in MeOH (3 mL) at 20–25 °C with a H_2 balloon. After stirring for 14 h, the reaction mixture was filtered through a plug Celite®, and concentrated to give crude oil (154 mg). Purification by Florisil® column chromatography (hexane to MeOH/Et_3N=10:1) to give the desired product **2** (130 mg, 91, 62% ee). The enantioselectivity was checked by the chiral derivatization and HPLC analysis described above. Yellowish oil; $[\alpha]_D^{25}$ −4.3 (*c* 1.01, $CHCl_3$); {lit.,[18] $[\alpha]_D$ +7.0 (*c* 2.6, $CHCl_3$), the antipodal (*S*) isomer}.

Following the procedure for the preparation of **2**, the reaction using **18b** (297 mg, 1 mmol, 92% de) gave **2** (128 mg, 90, 91% ee), $[\alpha]_D^{25}$ −6.3 (*c* 1.85, $CHCl_3$).

Yellowish oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.27–1.42 (m, 1H), 1.64–1.85 (m, 2H), 1.87–2.01 (m, 1H), 2.43 (dd, 1H, J=7.9 Hz, J_{gem}=15.5 Hz), 2.50 (dd, 1H, J=5.50 Hz, J_{gem}=15.5 Hz), 2.83–2.94 (m, 1H), 2.95–3.05 (m, 1H), 3.36–3.48 (m, 1H), 3.68 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 24.88, 31.11, 40.52, 46.18, 51.42, 54.84, 172.80; IR (neat) 3401, 2957, 1736, 1620, 1418 cm^{-1}.

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Stereoselective synthesis of Sch 642305, an inhibitor of bacterial DNA primase

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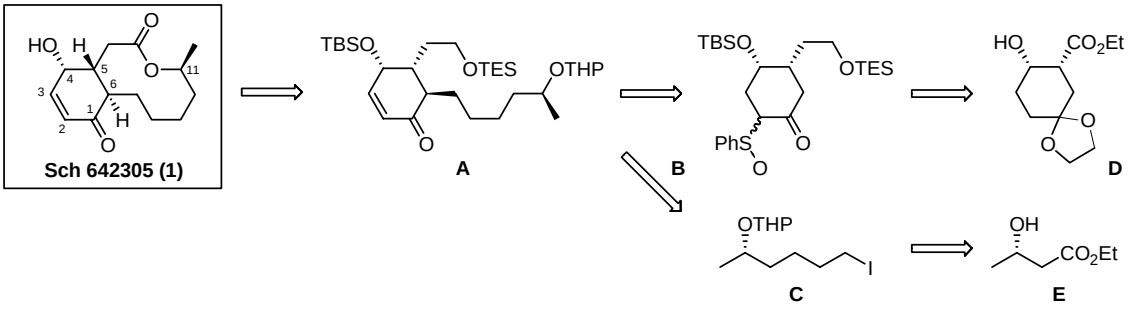
Abstract—Sch 642305 is a fungal nonanolide, which inhibits bacterial DNA primase and HIV-1 Tat transactivation. The enantioselective synthesis of Sch 642305 was succeeded starting from useful chiral building block via stereoselective dianion alkylation of β-ketosulfoxide and lactonization.

1. Introduction

Recently, mechanism-based drugs have been remarkably noticed, since they will potentially provide selective treatments for various diseases such as infections and cancers. In 2003, Chu et al. isolated Sch 642305 from *Penicillium verrucosum* as a potent inhibitor of bacterial DNA primase.[1] Because DNA primase is necessary for the replication of chromosomal DNA,[2,3] this compound is thought to provide an alternative treatment for infectious diseases. In addition, Jayasuriya and co-workers recently reported that Sch 642305 potently inhibits HIV-1 Tat transactivation.[4] A number of bioactive nonanolides have been isolated from a variety of fungal species.[5,6] Sch 642305 has a structure including 10-membered lactone fused with 4-hydroxycyclohexenone. Its unique structure as well as the significant biological activities prompted us to undertake the synthesis of this compound. During our work in progress, Mehta and Shinde also reported the total synthesis of Sch 642305, using ring closing metathesis as a key step.[7]

2. Results and discussion

Our retrosynthesis is shown in Scheme 1. We selected lactonization as a ring closing step. The precursor for the lactonization **A** would be prepared from dianion of β-ketosulfoxide **B** and iodide **C**. The ketosulfoxide **B** would be synthesized from a chiral building block **D**, which has been developed in our laboratory.[8,9] The iodide **C** would be obtained from chiral 3-hydroxybutylate **E**.[10,11]



Scheme 1. Synthetic plan.

Keywords: DNA primase; Sch 642305; Lactonization.
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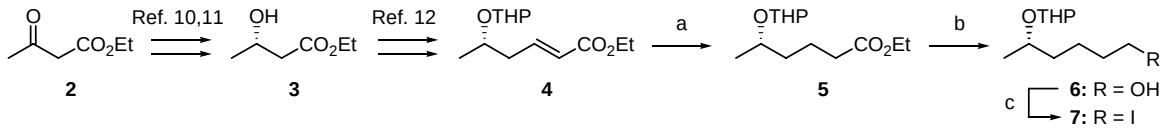
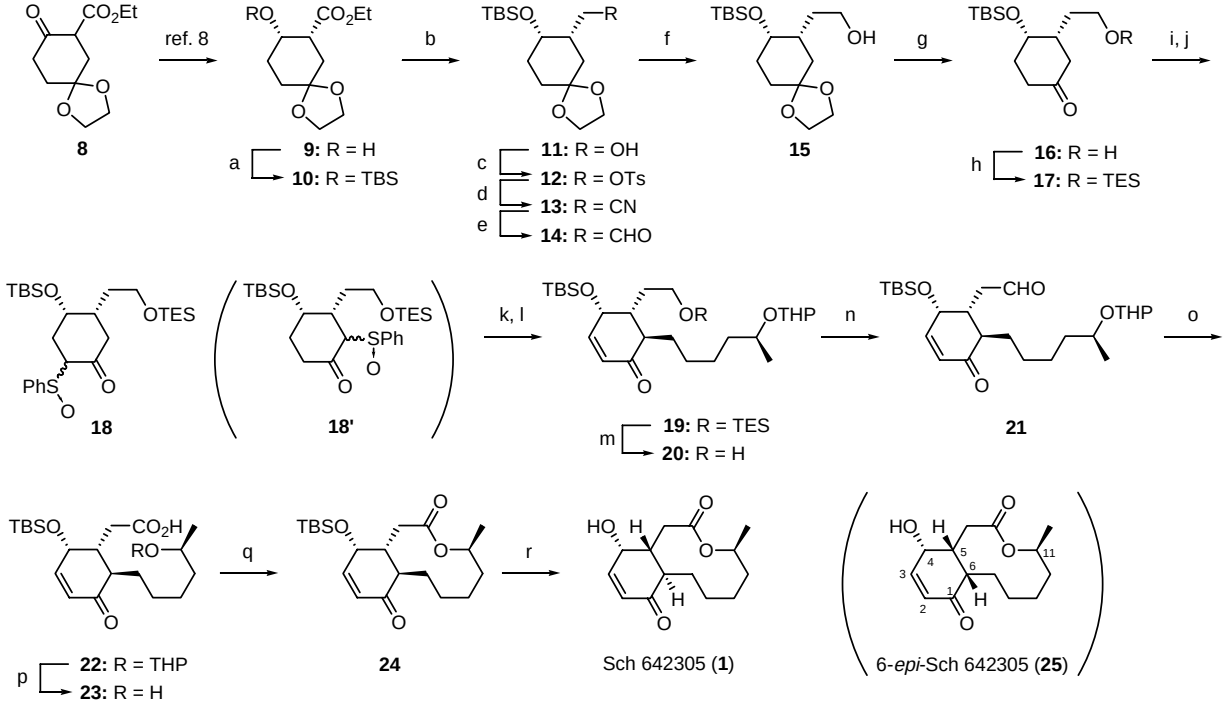


Scheme 2. Reagents and conditions: (a) H_2, Pd–C, EtOAc, 95%; (b) $LiAlH_4$, ether, 98%; (c) I_2, PPh_3, imidazole, CH_2Cl_2 87%.

Preparation of iodide **7** (=**C**) is shown in Scheme 2. Optically active (*S*)-3-hydroxybutylate **3** (98% ee) could be easily prepared in a large amount from ethyl acetoacetate (**2**) via stereoselective reduction by baker's yeast and enzymatic improvement of the optical purity.[10,11] This compound was subjected to C2 elongation by the reported procedure[12] to afford α,β-unsaturated ester **4**. Hydrogenation of **4** was followed by LAH reduction to give alcohol **6**,[13–15] which was converted to the corresponding iodide **7** in a usual manner.

Hydroxyl group of another chiral building block **9** (99% ee),[8] which could be prepared in a large quantity via stereoselective reduction of **8** by baker's yeast, was protected as TBS ether (Scheme 3) to give **10**. After the reduction of ester group in **10**, resulting alcohol was converted to the corresponding tosylate **12**. Transformation to nitrile **13** and subsequent two-step reduction gave alcohol **15** in good yield. Ketone was liberated by transacetalization and hydroxyl group was then protected as TES ether to afford **17**. This ketone was treated with LDA and phenyl benzenethiosulfonate to give a sulfide, which was oxidized to corresponding sulfoxide **18** (60% as a diastereomeric mixture) together with its regioisomer **18′** (17%). After the easy removal of **18′** by silica gel chromatography, β-ketosulfoxide **18** was subjected to regio- and stereoselective alkylation with the iodide **7** by dianion procedure[16–18] and subsequent thermal elimination afforded tri-substituted cyclohexenone **19** as a single isomer in a moderate yield. As we expected, the alkylation occurred selectively from the less hindered β-face of the dianion. Selective removal of TES group of **19** and two-step oxidation were followed by removal of THP group to give hydroxy acid **23**, the lactonization precursor. It was subjected to Yamaguchi's method[19,20] to afford 10-membered lactone **24** (73%) successfully with a small amount of a dimeric lactone (13%). The final step, removal of TBS group, was found to be slightly difficult. Deprotection of **24** with TBAF or $HF\cdot NEt_3$ gave a decomposed product mainly and the desired compound was obtained only in low yield. Other conditions (*p*-TsOH in MeOH, Dowex®-50 in MeOH, KF-18-crown-6 in MeCN, or neutralized TBAF with HF in THF) resulted in a partial epimerization at C-6 position (β:α=3:1–1:1, see Section 3). During our efforts as above, Mehta and Shinde reported the successful removal of TBDPS group using TBAF–AcOH in their synthesis of Sch 642305.[7] According to their procedure, we also succeeded in the synthesis of Sch 642305 without epimerization. The NMR data of synthesized **1** were identical to those reported.[1,7] Its specific



Scheme 3. Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, quant.; (b) DIBAL, CH_2Cl_2, 94%; (c) TsCl, TEA, DMAP, CH_2Cl_2, 89%; (d) NaCN, DMSO, 93%; (e) DIBAL, CH_2Cl_2, 93%; (f) $NaBH_4$, EtOH, 99%; (g) *p*-TsOH, Me_2CO, quant.; (h) TESCl, TEA, CH_2Cl_2, quant.; (i) LDA, $PhSO_2SPh$, THF; (j) MCPBA, CH_2Cl_2, 60% in two steps; (k) LDA, **7**, THF; (l) $CaCO_3$, tol. 47% in two steps; (m) HF, CH_3CN, 98%; (n) Dess–Martin periodinane, CH_2Cl_2, 84%; (o) $NaClO_2$, 2-methyl-2-butene, $NaH_2PO_4\cdot 2H_2O$, *tert*-BuOH, water, 90%; (p) $MgBr_2\cdot Et_2O$, ether, quant.; (q) 2,4,6-trichlorobenzoylchloride, TEA, THF then DMAP, tol., 73%; (r) TBAF, AcOH, THF, 87%.

rotation {$[\alpha]_D^{29}$ +74 (*c* 0.50, MeOH)} and mp (151–153 °C) were slightly larger than those reported for natural Sch 642305 {$[\alpha]_D$ +67.44 (*c* 0.50, MeOH), mp 143–145 °C}.[1]

In conclusion, we have accomplished a stereoselective synthesis of Sch 642305 starting from two chiral sources, which were prepared by stereoselective reductions with baker's yeast. Alkylation of β-ketosulfoxide by dianion procedure selectively afforded the desired stereochemistry and Yamaguchi's lactonization was also successful in good yield. The overall yield was 10% in 18 steps started from chiral building block **9**. As fungal nonanolides have interesting biological activities, we wish our syntheses[21,22] of these compounds would offer any useful information for further investigation on the related fields.

3. Experimental

3.1. General

Optical rotations were recorded with a JASCO DIP-1000 polarimeter. IR spectra were measured with a JASCO FT/IR-230 spectrophotometer. ^1H and ^{13}C NMR were recorded on JEOL JNM AL300 or JEOL JNM GSX500. Chemical shifts (δ) were referenced to the residual solvent peak as the internal standard ($CDCl_3$: $\delta_H=7.26$, $\delta_C=77.0$; CD_3OD: $\delta_H=3.30$, $\delta_C=49.0$). Mass spectra were recorded on JEOL JMS-700T. Column chromatography was performed using Merck silica gel 60 (0.060–0.200 mm). TLC was carried out on Merck glass plates precoated with silica gel 60 F_{254} (0.25 mm). Melting points are uncorrected values.

3.2. Synthetic studies

3.2.1. Ethyl (*S*)-5-tetrahydropyranyloxyhexanoate (5). To a solution of unsaturated ester **4** (4.97 g, 21.8 mmol) in ethyl acetate (40 ml) was added 5% Pd/C (1.3 g) and the mixture was stirred at room temperature for 5 h under H_2. The mixture was filtered through Celite® and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (1/1) gave **5** (4.75 g, 95%) as a colorless oil.

Spectroscopic data were identical to those reported.[14]

3.2.2. (*S*)-5-Tetrahydropyranyloxyhexan-1-ol (6). To a solution of ester **5** (4.89 g, 21.2 mmol) in ether (60 ml) was added $LiAlH_4$ (0.53 g, 14 mmol) at 0 °C and the mixture was stirred at 0 °C for 1 h under argon. The reaction mixture was quenched with MeOH, poured into saturated NH_4Cl solution and extracted with ether. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (1/1) gave **6** (4.19 g, 98%) as a colorless oil.

Spectroscopic data were identical to those reported.[14]

3.2.3. (*S*)-1-Iodo-5-tetrahydropyranyloxyhexane (7). To a solution of alcohol **6** (2.19 g, 10.8 mmol), imidazole (2.94 g, 43.2 mmol) and PPh_3 (2.94 g, 11.2 mmol) in CH_2Cl_2 (30 ml) was added iodine (3.3 g, 13 mmol) at 0 °C and the mixture was stirred at room temperature for 3 h. This mixture was poured into saturated NH_4Cl solution and extracted with ether. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with toluene–ethyl acetate (20/1) gave **7** (2.94 g, 87%) as a slightly yellow oil.

$n_D^{27}=1.5019$. $[\alpha]_D^{26}$ +1.6 (*c* 1.0, $CHCl_3$). IR (film): $\nu=1454$, 1372, 1282, 1258, 1131, 1022, 870, 813 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): $\delta=1.12$ (1.5H, d, $J=6.3$ Hz), 1.23 (1.5H, d, $J=6.3$ Hz), 1.35–1.9 (12H, m), 3.19 (1H, t, $J=6.9$ Hz), 3.21 (1H, t, $J=6.9$ Hz), 3.45–3.55 (1H, m), 3.65–3.95 (2H, m), 4.6–4.75 (1H, m). FAB-HRMS *m/z* calcd for $C_{11}H_{22}IO_2$ $[M+H]^+$ 313.0664, found 313.0658.

3.2.4. Ethyl (1*R*,2*S*)-5,5-ethylenedioxy-2-(*tert*-butyldimethylsilyloxy)cyclohexanecarboxylate (10). A solution of alcohol **9** (6.00 g, 26.1 mmol), TBSOTf (6.2 ml, 27 mmol) and 2,6-lutidine (6.1 ml, 52 mmol) in CH_2Cl_2 (100 ml) was stirred at room temperature for 2 h. The reaction mixture was poured into saturated NH_4Cl solution and extracted with ether. The organic layer was washed with 1 N HCl, saturated $NaHCO_3$ solution and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (4/1) gave **10** (9.03 g, quant.) as a slightly yellow oil.

$n_D^{27}=1.4600$. $[\alpha]_D^{26}$ +24 (*c* 1.0, $CHCl_3$). IR (film): $\nu=1739$, 1254, 1182, 1086, 1065, 1041, 833 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): $\delta=-0.01$ (3H, s), 0.04 (3H, s), 0.85 (9H, s), 1.25 (3H, t, $J=7.2$ Hz), 1.51 (1H, m), 1.7–1.85 (3H, m), 1.95 (1H, dt, $J=6.0$, 12.6 Hz), 2.16 (1H, t, $J=13.2$ Hz), 2.66 (1H, ddd, $J=13.2$, 3.6, 2.4 Hz), 3.85–4.25 (6H, m), 4.42 (1H, m). FAB-HRMS *m/z* calcd for $C_{17}H_{33}O_5Si$ $[M+H]^+$ 345.2097, found 345.2059.

3.2.5. [(1*S*,2*S*)-5,5-Ethylenedioxy-2-(*tert*-butyldimethylsilyloxy)cyclohexyl]methanol (11). To a solution of ester **10** (10.6 g, 30.9 mmol) in dry CH_2Cl_2 (150 ml) was added 1.01 M solution of DIBAL in toluene (67.3 ml, 68.0 mmol) dropwise at −78 °C and the mixture was stirred at −78 °C for 2 h under argon. The reaction mixture was quenched with MeOH, poured into saturated Rochelle's salt solution and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (2/1–1/1) gave **11** (9.08 g, 97%) as an amorphous solid.

$[\alpha]_D^{26}$ +34 (*c* 1.0, $CHCl_3$). IR (Nujol): $\nu=3479$, 1253, 1108, 1076, 1032, 832 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): $\delta=$ 0.08 (6H, s), 0.90 (9H, s), 1.45–2.0 (7H, m), 3.55–3.7 (2H, m), 3.9–4.0 (4H, m), 4.08 (1H, m). FAB-HRMS *m/z* calcd for $C_{15}H_{31}O_4Si$ $[M+H]^+$ 303.1992, found 303.1969.

3.2.6. [(1*S*,2*S*)-5,5-Ethylenedioxy-2-(*tert*-butyldimethylsilyloxy)cyclohexyl]methyl *p*-toluenesulfonate (12). To a solution of alcohol **11** (9.08 g, 30.0 mmol), triethylamine (12.5 ml, 90.0 mmol) and DMAP (367 mg, 3.00 mmol) in CH_2Cl_2 (150 ml) was added TsCl (6.86 g, 36.0 mmol) at

0 °C and the mixture was stirred at room temperature for 16 h. The reaction mixture was poured into saturated NH_4Cl solution and extracted with ether. The organic layer was washed with 1 N HCl, saturated $NaHCO_3$ solution and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (3/1) gave **12** (12.2 g, 89%) as colorless crystals.

Mp 65–67 °C. $[\alpha]_D^{24}$ +32 (*c* 1.0, $CHCl_3$). IR (Nujol): ν= 1595, 1254, 1188, 1176, 1102, 1072, 957, 835, 665 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): δ= −0.03 (3H, s), 0.02 (3H, s), 0.81 (9H, s), 1.35–1.8 (5H, m), 1.87 (1H, dt, *J*=4.2, 12.9 Hz), 2.0–2.15 (1H, m), 2.45 (3H, s), 3.76 (1H, dd, *J*= 9.0, 6.6 Hz), 3.85–4.05 (6H, m), 7.34 (2H, d, *J*=8.1 Hz), 7.77 (2H, d, *J*=8.1 Hz). FAB-HRMS *m/z* calcd for $C_{22}H_{37}O_6SSi$ $[M+H]^+$ 457.2080, found 457.2079.

3.2.7. [(1*R*,2*S*)-5,5-Ethylenedioxy-2-(*tert*-butyldimethylsilyloxy)cyclohexyl]acetonitrile (13). A mixture of tosylate **12** (19.2 g, 42.0 mmol), NaCN (3.1 g, 63 mmol) and DMSO (150 ml) was heated to 100 °C and stirred for 4 h. After cooling, the reaction mixture was diluted with 150 ml of ether and washed with water and brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was recrystallized from hexane to give **13** (12.2 g, 93%) as colorless needles.

Mp 49–51 °C. $[\alpha]_D^{24}$ +31 (*c* 1.0, $CHCl_3$). IR (Nujol): ν= 2246, 1253, 1144, 1103, 1065, 994, 838 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): δ=0.09 (3H, s), 0.10 (3H, s), 0.90 (9H, s), 1.45–1.95 (6H, m), 2.12 (1H, br m), 2.25 (1H, dd, *J*=16.5, 6.9 Hz), 2.38 (1H, dd, *J*=16.5, 8.4 Hz), 3.9–4.05 (5H, m). FAB-HRMS *m/z* calcd for $C_{16}H_{30}NO_3Si$ $[M+H]^+$ 312.1995, found 312.1969.

3.2.8. 2-[(1*R*,2*S*)-5,5-Ethylenedioxy-2-(*tert*-butyldimethylsilyloxy)cyclohexyl]acetaldehyde (14). To a solution of nitrile **13** (1.00 g, 3.21 mmol) in dry CH_2Cl_2 (20 ml) was added 1.01 M solution of DIBAL in toluene (3.4 ml, 3.4 mmol) dropwise at −78 °C and the mixture was stirred at −78 °C for 2.5 h under argon. The reaction mixture was quenched with MeOH, poured into saturated Rochelle's salt solution and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (4/1–2/1) gave **14** (0.93 g, 94%) as an amorphous solid.

$[\alpha]_D^{24}$ +29 (*c* 1.0, $CHCl_3$). IR (film): ν=1726, 1103, 1067, 999, 832, 773 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): δ= 0.02 (3H, s), 0.05 (3H, s), 0.88 (9H, s), 1.45–1.6 (2H, m), 1.7–1.8 (3H, m), 1.89 (1H, dt, *J*=5.7, 12.0 Hz), 2.2–2.5 (2H, m), 2.56 (1H, m), 3.85 (1H, m), 3.9–3.95 (4H, m), 9.77 (1H, t, *J*=1.8 Hz). FAB-HRMS *m/z* calcd for $C_{16}H_{31}O_4Si$ $[M+H]^+$ 315.1992, found 315.1965.

3.2.9. 2-[(1*R*,2*S*)-5,5-Ethylenedioxy-2-(*tert*-butyldimethylsilyloxy)cyclohexyl]ethanol (15). To a solution of sodium borohydride (1.9 g, 50 mmol) in EtOH (120 ml) was slowly added a solution of aldehyde **14** (8.00 g, 25.4 mmol) in EtOH (30 ml) at −20 °C. The reaction mixture was stirred at 0 °C for 3 h, poured into saturated NH_4Cl solution and extracted with ether. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (5/1–1/1) gave **15** (7.96 g, 99%) as colorless needles.

Mp 51–52 °C. $[\alpha]_D^{26}$ +19 (*c* 1.0, $CHCl_3$). IR (Nujol): ν= 3340, 1251, 1142, 1076, 1037, 996, 834 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): δ=0.05 (3H, s), 0.06 (3H, s), 0.90 (9H, s), 1.4–1.95 (9H, m), 3.67 (2H, t, *J*=6.3 Hz), 3.8–3.85 (1H, m), 3.85–4.0 (4H, m). FAB-HRMS *m/z* calcd for $C_{16}H_{33}O_4Si$ $[M+H]^+$ 317.2148, found 317.2153.

3.2.10. (3*R*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-3-(2-hydroxyethyl)cyclohexanone (16). A solution of acetal **15** (1.00 g, 3.16 mmol) and *p*-toluenesulfonic acid monohydrate (59 mg, 0.31 mmol) in acetone (100 ml) was stirred at room temperature for 2 days. The reaction mixture was poured into saturated ammonium sulfate solution. The organic layer was concentrated in vacuo and the residue was dissolved in EtOAc. The aqueous layer was extracted with EtOAc. Combined organic layers were washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (1/1) gave **16** (0.86 g, quant.) as a colorless oil.

n_D^{27}=1.4701. $[\alpha]_D^{26}$ +18 (*c* 1.0, $CHCl_3$). IR (film): ν=3417, 1713, 1254, 1059, 837, 775 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): δ=0.11 (6H, s), 0.93 (9H, s), 1.54 (1H, m), 1.7–1.9 (2H, m), 2.0–2.15 (2H, m), 2.15–2.3 (2H, m), 2.48 (1H, t, *J*=13.2 Hz), 2.66 (1H, dt, *J*=6.3, 13.5 Hz), 3.6–3.75 (2H, m), 4.03 (1H, br m). FAB-HRMS *m/z* calcd for $C_{14}H_{29}O_3Si$ $[M+H]^+$ 273.1886, found 273.1852.

3.2.11. (3*R*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-3-(2-triethylsilyloxyethyl)cyclohexanone (17). Triethylamine (2.20 ml, 15.8 mmol) and TESCl (690 μl, 4.11 mmol) were added to a solution of alcohol **16** (860 mg, 3.16 mmol) in CH_2Cl_2 (30 ml). The reaction mixture was stirred at room temperature for 45 min, poured into saturated NH_4Cl solution and extracted with ether. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (20/1) gave **17** (1.23 g, quant.) as a colorless oil.

n_D^{27}=1.4614. $[\alpha]_D^{27}$ +1.9 (*c* 1.0, $CHCl_3$). IR (film): ν=1721, 1254, 1080, 835, 742 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): δ=0.11 (6H, s), 0.58 (6H, q, *J*=7.8 Hz), 0.92 (9H, s), 0.94 (9H, t, *J*=7.8 Hz), 1.48 (1H, m), 1.71 (1H, m), 1.81 (1H, m), 2.0–2.15 (2H, m), 2.15–2.25 (2H, m), 2.47 (1H, t, *J*= 13.5 Hz), 2.67 (1H, dt, *J*=6.0, 13.5 Hz), 3.61 (1H, dt, *J*= 10.5, 6.3 Hz), 3.66 (1H, dt, *J*=10.5, 6.3 Hz), 4.01 (1H, br m). FAB-HRMS *m/z* calcd for $C_{20}H_{43}O_3Si_2$ $[M+H]^+$ 387.2751, found 387.2753.

3.2.12. (2*RS*,4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-2-phenylsulfinyl-5-(2-triethylsilyloxyethyl)cyclohexanone (18). To a solution of diisopropylamine (701 μl, 5.00 mmol) in THF (20 ml) was added 1.56 M solution of *n*-BuLi

(3.3 ml, 5.0 mmol) dropwise at −20 °C and stirred for 45 min under argon. This solution was cooled down to −78 °C and a solution of ketone **17** (1.93 g, 5.00 mmol) in THF (5 ml) was slowly added to it. Stirring for 3 min was followed by dropwise addition of a solution of phenyl benzenethiosulfonate (1.25 g, 5.0 mmol) in THF (5 ml). The reaction mixture was stirred at −78 °C for 1 h, poured into saturated NH_4Cl solution and extracted with ether. The organic layer was washed with 1 N HCl, saturated $NaHCO_3$ solution and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (20/1) gave a diastereomeric mixture of sulfides (2.68 g) as slightly yellow solids. This mixture was used for next reaction without further purification.

A solution of MCPBA (ca. 80%, 1.1 g, 5.1 mmol) in CH_2Cl_2 (10 ml) was added to a mixture of crude sulfides (2.68 g) in CH_2Cl_2 (20 ml) at −78 °C and stirred for 1 h. The reaction mixture was poured into 10% $Na_2S_2O_3$ solution and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (6/1) gave **18** (1.53 g, 60% in two steps) and its regioisomer **18′** (0.43 g, 17% in two steps).

$n_D^{27}=1.5069$. $[\alpha]_D^{27}$ −2.6 (*c* 1.0, $CHCl_3$). IR (film): $\nu=1714$, 1087, 1047, 1006, 836, 776, 747 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): $\delta=-0.36$, −0.11, −0.02, 0.02, 0.11, 0.22 (total 6H, 6 singlets), 0.53 (3H, q, $J=4.1$ Hz), 0.58 (3H, q, $J=4.1$ Hz), 0.75–1.0 (18H, m), 1.35–1.7 (2H, m), 1.8–2.8 (5H, m), 3.5–3.7 (2H, m), 4.0–4.15 (2H, m), 7.45–7.55 (4H, m), 7.65–7.7 (1H, m). FAB-HRMS *m/z* calcd for $C_{26}H_{47}O_4SSi_2$ $[M+H]^+$ 511.2734, found 511.2758.

3.2.13. (4*S*,5*R*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-6-[(*S*)-5-tetrahydropyranyloxyhexyl]-5-(2-triethylsilyloxyethyl)cyclohex-2-en-1-one (19). To a solution of diisopropylamine (463 μl, 3.30 mmol) in THF (25 ml) was added 1.56 M solution of *n*-BuLi (2.1 ml, 3.3 mmol) in hexane dropwise at −20 °C and stirred for 45 min under argon. This mixture was cooled down to −60 °C, a solution of ketosulfoxide **18** (675 mg, 1.32 mmol) in THF (4 ml) was slowly added to this mixture (the color of reaction mixture was immediately changed to orange). After stirring for 5 min, iodide **7** (478 mg, 1.53 mmol) was added to the mixture at −60 °C and stirring was kept for 30 min until the orange color was changed to pale yellow. The reaction mixture was poured into saturated NH_4Cl solution and extracted with ether. The organic layer was washed with 1 N HCl, saturated $NaHCO_3$ solution and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (6/1–4/1) gave a crude oil (590 mg). This crude product was used for the next reaction without further purification.

A mixture of crude product (590 mg), $CaCO_3$ (0.5 g, 5 mmol) and toluene (20 ml) was stirred at 100 °C for 2 h. The reaction mixture was filtered through Celite® and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (15/1) gave **19** (354 mg, 47% in two steps) as a slightly yellow oil. $n_D^{27}=1.4773$. $[\alpha]_D^{24}$ +147 (*c* 1.0, $CHCl_3$). IR (film): $\nu=$ 1680, 1254, 1108, 1022, 837, 773 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): $\delta=0.11$ (6H, s), 0.57 (6H, q, $J=$ 7.8 Hz), 0.90 (9H, s), 0.94 (9H, t, $J=7.8$ Hz), 1.10 (1.5H, d, $J=6.0$ Hz), 1.21 (1.5H, d, $J=6.0$ Hz), 1.2–1.7 (15H, m), 1.75–1.8 (1H, m), 1.95–2.1 (1H, m), 2.25–2.4 (1H, m), 2,45–2.6 (1H, m), 3.45–3.55 (1H, m), 3.64 (2H, t, $J=$ 9.9 Hz), 3.65–3.95 (1H, m), 4.65–4.8 (2H, m), 5.82 (1H, d, $J=9.9$ Hz), 6.63 (1H, d, $J=9.9$ Hz). FAB-HRMS *m/z* calcd for $C_{31}H_{61}O_5Si_2$ $[M+H]^+$ 569.4058, found 569.4055.

3.2.14. (4*S*,5*R*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-(2-hydroxyethyl)-6-[(*S*)-5-tetrahydropyranyloxyhexyl]-cyclohex-2-en-1-one (20). To a solution of TES ether **19** (685 mg, 1.20 mmol) in acetonitrile (40 ml) was added 0.23 N HF (1 ml) at room temperature and stirred for 15 min. The reaction mixture was diluted with ether, washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (2/1) gave **20** (538 mg, 98%) as a colorless oil.

$n_D^{27}=1.4842$. $[\alpha]_D^{24}$ +99 (*c* 1.0, $CHCl_3$). IR (film): $\nu=3486$, 1680, 1112, 1022, 837, 774, 668 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): $\delta=0.15$ (6H, s), 0.93 (9H, s), 1.10 (1.5H, d, $J=$ 6.0 Hz), 1.21 (1.5H, d, $J=6.0$ Hz), 1.3–1.95 (15H, m), 2.02 (1H, m), 2.25–2.35 (1H, m), 2.45–2.5 (1H, m), 3.45–3.55 (1H, m), 3.6–3.8 (3H, m), 3.8–3.95 (1H, m), 4.6–4.7 (1H, m), 4.75–4.8 (1H, m), 5.85 (1H, d, $J=9.0$ Hz), 6.64 (1H, d, $J=9.0$ Hz). FAB-HRMS *m/z* calcd for $C_{25}H_{47}O_5Si$ $[M+H]^+$ 455.3193, found 455.3193.

3.2.15. {(1*R*,2*S*,6*R*)-2-(*tert*-Butyldimethylsilyloxy)-6-[(*S*)-5-tetrahydropyranyloxyhexyl]-5-oxocyclohex-3-en-1-yl}acetaldehyde (21). To a solution of alcohol **20** (770 mg, 1.69 mmol) in CH_2Cl_2 (20 ml) was added Dess–Martin periodinane (1.08 g, 2.54 mmol) at 0 °C and stirred for 1 h under argon. The reaction mixture was poured into 10% $Na_2S_2O_3$ solution and extracted with ether. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (10/1–2/1) gave **21** (641 mg, 84%) as a colorless oil.

$n_D^{27}=1.4837$. $[\alpha]_D^{28}$ +118 (*c* 1.0, $CHCl_3$). IR (film): $\nu=$ 1726, 1680, 1109, 1023, 773 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): $\delta=0.10$ (3H, s), 0.13 (3H, s), 0.90 (9H, s), 1.11 (1.5H, d, $J=6.0$ Hz), 1.22 (1.5H, d, $J=6.0$ Hz), 1.25–1.85 (14H, m), 2.2–2.45 (2H, m), 2.8–2.95 (2H, m), 3.45–3.55 (1H, m), 3.65–3.8 (1H, m), 3.8–4.95 (1H, m), 4.6–4.65 (0.5H, m), 4.65–4.7 (0.5H, m), 4.75–4.8 (1H, m), 5.87 (1H, d, $J=7.8$ Hz), 6.61 (1H, d, $J=7.8$ Hz), 9.77 (1H, t, $J=$ 1.2 Hz). FAB-HRMS *m/z* calcd for $C_{25}H_{45}O_5Si$ $[M+H]^+$ 453.3036, found 453.3065.

3.2.16. {(1*R*,2*S*,6*R*)-2-(*tert*-Butyldimethylsilyloxy)-6-[(*S*)-5-tetrahydropyranyloxyhexyl]-5-oxocyclohex-3-en-1-yl}acetic acid (22). To a solution of aldehyde **21** (600 mg, 1.33 mmol) and 2-methyl-2-butene (2 ml) in *tert*-BuOH (15 ml) was added a solution of $NaH_2PO_4\cdot 2H_2O$ (1.04 g, 6.65 mmol) and $NaClO_2$ (0.24 g, 2.66 mmol) in water

(15 ml) at 0 °C and stirred for 1 h. The reaction mixture was poured into 10% $Na_2S_2O_3$ solution and extracted with ethyl acetate. The organic layer was washed with 0.1 N HCl and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (2/1) gave **22** (557 mg, 90%) as a colorless oil.

$n_D^{27}=1.4856$. $[\alpha]_D^{28}$ +131 (*c* 1.0, $CHCl_3$). IR (film): $\nu=$ 1711, 1679, 1466, 1385, 1255, 1109, 1024 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): $\delta=0.12$ (3H, s), 0.13 (3H, s), 0.91 (9H, s), 1.10 (1.5H, d, $J=6.0$ Hz), 1.21 (1.5H, d, $J=$ 6.0 Hz), 1.25–1.85 (14H, m), 2.15–2.3 (1H, m), 2.49 (1H, m), 2.7–2.85 (2H, m), 3.45–3.55 (1H, m), 3.65–3.8 (1H, m), 3.85–4.0 (1H, m), 4.6–4.7 (1H, m), 4.74 (1H, m), 5.88 (1H, d, $J=9.0$ Hz), 6.63 (1H, d, $J=9.0$ Hz). FAB-HRMS *m/z* calcd for $C_{25}H_{45}O_6Si$ $[M+H]^+$ 469.2985, found 469.2990.

3.2.17. {(1*R*,2*S*,6*R*)-2-(*tert*-Butyldimethylsilyloxy)-6-[(*S*)-5-hydroxyhexyl]-5-oxocyclohex-3-en-1-yl}acetic acid (23). To a solution of THP ether **22** (150 mg, 0.32 mmol) in ether (6 ml) was added $MgBr_2\cdot Et_2O$ (248 mg, 0.96 mmol) at 0 °C under argon. The reaction mixture was stirred at room temperature for 2 h and poured into saturated NH_4Cl solution. Water was added to the mixture until dark red precipitate was completely dissolved and the resulting solution was extracted with EtOAc. The organic layer was washed with 0.1 N HCl and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with chloroform–methanol (50/1) gave **23** (128 mg, quant.) as a slightly yellow oil.

$n_D^{27}=1.4883$. $[\alpha]_D^{26}$ +88 (*c* 1.0, $CHCl_3$). IR (film): $\nu=3454$, 1713, 1681, 1253, 1101, 837, 779 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): $\delta=0.12$ (3H, s), 0.13 (3H, s), 0.91 (9H, s), 1.18 (3H, d, $J=6.0$ Hz), 1.25–1.75 (8H, m), 2.22 (1H, dd, $J=16.5$, 7.8 Hz), 2.51 (1H, m), 2.7–2.85 (2H, m), 3.81 (1H, m), 4.75 (1H, m), 5.88 (1H, d, $J=9.9$ Hz), 6.63 (1H, d, $J=9.9$ Hz). FAB-HRMS *m/z* calcd for $C_{20}H_{37}O_5Si$ $[M+H]^+$ 385.2410, found 385.2421.

3.2.18. *O*-(*tert*-Butyldimethylsilyl)Sch 642305 (24). Triethylamine (15 mg, 0.15 mmol) and 2,4,6-trichlorobenzoyl chloride (19 µl, 0.13 mmol) were added to a solution of the hydroxy acid **23** (40 mg, 0.10 mmol) in THF (1 ml). The reaction mixture was stirred at room temperature for 3 h and then filtered through Celite® under argon. The resultant solution was added slowly using syringe pump to a refluxing solution of DMAP (244 mg, 2.00 mmol) in dry toluene (100 ml) over 14 h. After the addition was complete, the reaction mixture was stirred for additional 1 h and concentrated in vacuo. The residue was dissolved in ether and washed with 1 N HCl, saturated $NaHCO_3$ solution and brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–ethyl acetate (20/1) gave **24** (28 mg, 73%) as colorless crystals and a small amount of dimeric lactone (5 mg).

Mp 104–106 °C. $[\alpha]_D^{27}$ +56 (*c* 1.0, $CHCl_3$). IR (Nujol): $\nu=1722$, 1671, 1255, 1163, 1088, 1036 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): $\delta=0.08$ (3H, s), 0.11 (3H, s), 0.88 (9H, s), 1.09 (1H, m), 1.26 (3H, d, $J=6.6$ Hz), 1.34 (1H, m), 1.5–1.7 (4H, m), 2.0–2.3 (2H, m), 2.4–2.9 (4H, m), 4.23 (1H, m), 5.09 (1H, m), 5.97 (1H, d, $J=9.9$ Hz), 6.85 (1H, dd, $J=9.9$, 5.7 Hz). FAB-HRMS *m/z* calcd for $C_{20}H_{35}O_4Si$ $[M+H]^+$ 367.2305, found 367.2297.

3.2.19. Sch 642305 (1). A mixture of 1.01 M solution of TBAF in THF (600 µl, 0.6 mmol) and acetic acid (36 mg, 0.6 mmol) was added to a solution of TBS ether **24** (20 mg, 0.05 mmol) in THF (1.5 ml) and stirred at room temperature for 3 h under argon. The reaction mixture was poured into saturated NH_4Cl solution and extracted with ether. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by preparative TLC [hexane–ether (3/1)] and recrystallization from acetone–hexane to give **1** (12 mg, 87%) as colorless needles.

Mp 151–153 °C. $[\alpha]_D^{29}$ +74 (*c* 0.50, CH_3OH). IR (KBr): $\nu=$ 3472, 2933, 1703, 1659, 1255, 1201, 1083, 874 cm^{-1}. ^1H NMR (500 MHz in CD_3OD): $\delta=1.08$ (1H, ddd, $J=14.0$, 10.5, 3.8 Hz), 1.2–1.4 (3H, m), 1.27 (3H, d, $J=6.7$ Hz), 1.54 (1H, m), 1.83 (1H, m), 2.05–2.2 (2H, m), 2.53 (1H, dd, $J=16.8$, 11.5 Hz), 2.64 (1H, dt, $J=11.5$, 3.8 Hz), 2.67 (1H, dd, $J=16.8$, 2.4 Hz), 2.81 (1H, ddt, $J=3.5$, 2.4, 11.5 Hz), 4.21 (1H, dd, $J=5.6$, 3.5 Hz), 5.05 (1H, m), 5.96 (1H, d, $J=$ 9.9 Hz), 7.02 (1H, dd, $J=9.9$, 5.6 Hz). ^{13}C NMR (125 MHz in CD_3OD): $\delta=18.6$, 22.6, 24.2, 30.8, 37.9, 39.9, 47.8, 67.2, 74.7, 130.7, 149.5, 173.8, 202.4. FAB-HRMS *m/z* calcd for $C_{14}H_{21}O_4$ $[M+H]^+$ 253.1440, found 253.1444.

3.2.20. 6-*epi*-Sch 642305 (25). Partial epimerization at C-6 position was observed under the several conditions for the deprotection of TBS ether **24**. Treatment of **24** with *p*-toluenesulfonic acid in MeOH or KF and 18-crown-6 in acetonitrile gave about 1:1 mixture of **1** and **25**. Treatment of **24** with Dowex®-50 in MeOH gave approximately 3:1 mixture of **1** and **25**. These isomers were easily separated by preparative TLC [hexane–ether (3/1)]. The structure of **25** was confirmed by NOE experiments. NOEs were observed between 4-H, 5-H and 6-H.

^1H NMR (500 MHz in CD_3OD): $\delta=0.8$–1.15 (2H, m), 1.25–1.65 (3H, m), 1.28 (3H, d, $J=6.6$ Hz), 1.87 (1H, m), 2.0–2.25 (2H, m), 2.09 (1H, dd, $J=17.1$, 12.3 Hz), 2.36 (1H, dt, $J=12.3$, 3.3 Hz), 2.84 (1H, dd, $J=17.1$, 2.4 Hz), 3.32 (1H, m), 4.90 (1H, m), 5.04 (1H, m), 5.99 (1H, dd, $J=$ 10.2, 2.7 Hz), 6.67 (1H, dt, $J=10.2$, 1.8 Hz). FAB-HRMS *m/z* calcd for $C_{14}H_{21}O_4$ $[M+H]^+$ 253.1440, found 253.1444.

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Iridium complex-catalyzed addition of water and alcohols to non-activated terminal alkynes

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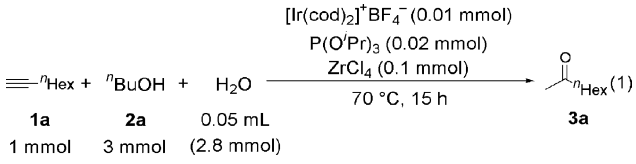
Abstract—The addition of water and alcohols to non-activated terminal alkynes was found to be promoted by an iridium complex combined with Lewis acid and phosphite. Thus, terminal alkynes reacted with water or alcohols to give ketones or ketals, respectively, in good to excellent yields. α,ω-Diyne like 1,7-octadiyne was converted into 1-(2-methyl-cyclopent-1-enyl)ethanone through the intramoleculer aldol condensation of the resulting 2,7-octanedione induced by Lewis acid.

1. Introduction

Addition of oxygen nucleophile to non-activated alkynes is an important tool to construct a carbon–oxygen bond.[1] In particular, metal-catalyzed hydration of alkynes is the most straightforward and environmentally-benign method to prepare ketones and aldehydes. There has been considerable works done on the addition of water to non-activated alkynes using transition metals. Conventionally, the hydration was carried out using toxic Hg(II) salts[2] to enhance the reaction. Several works on the addition of alcohols to alkynes have been reported by the use of various transition metals such as silver(I),[3] osmium(II),[4] palladium(II),[5] platinum(II),[6] rhodium(III)[7] and so on.[8] Recently, Wakatsuki et al. developed the addition of water to alkynes catalyzed by Ru(II) complexes to form predominantly anti-Markovnikov hydration products such as aldehydes.[9] Hayashi et al. showed that the hydration of alkynes was achieved by Au(I) with high turnover frequency (TOF) ($\sim$15,600 h^{-1}).[10] However, there has been only limited study so far on the addition of water and alcohols to alkynes by iridium catalysts.[11] Previously, we reported that the addition of carboxylic acids to non-activated alkynes leading to vinyl esters was efficiently catalyzed by iridium complexes.[12] In continuation of our studies to develop a new catalytic reaction using iridium complexes, we now found that the addition of water and alcohols to non-activated alkynes was enhanced by $[IrCl(cod)]_2$ or $[Ir(cod)_2]^+BF_4^-$ combined with a Lewis acid such as $ZrCl_4$, $GdCl_3$ and $AlCl_3$. In this paper, we wish to report the iridium-catalyzed reaction of alkynes with oxygen nucleophiles like water or alcohols.

2. Results and discussion

In the first place, we examined the reaction of 1-octyne (**1a**) with 1-butanol (**2a**) in the presence of water catalyzed by several Ir-complexes under various conditions (Eq. 1 and Table 1).



The reaction of **1a** (1 mmol) with **2a** (3 mmol) and water (0.05 mL, ca. 2.8 mmol) under the influence of $[Ir(cod)_2]^+BF_4^-$ (0.01 mmol), $P(O^iPr)_3$ (0.02 mmol) and $ZrCl_4$ (0.1 mmol) at 70 °C for 15 h (standard reaction conditions) led to 2-octanone (**3a**) in high yield (96%), but not 2-octanone dibutylketal (**4aa**) (entry 1). The reaction in the absence of alcohol **2a** resulted in low yield of **3a** (45%) at 60% conversion (entry 2). When water was removed from the reaction system, the reaction proceeded somewhat slowly to form **4aa** in 56% yield (entry 3). This may suggest that the reaction proceeds successively through the formation of ketal **4aa** followed by hydrolysis of the resulting ketal with water. It was found that the yield of **3a** was markedly decreased in the absence of

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Table 1. Addition of water to **1a** catalyzed by iridium complex under various reaction conditions

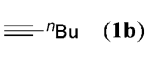
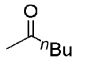
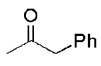
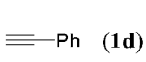
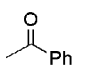
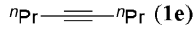
Entry	Ir-complex	Conditions	Conv. (%)	Yield (%)
1	$[Ir(cod)_2]^+BF_4^-$	Standard[a]	99	96
2[b]	$[Ir(cod)_2]^+BF_4^-$	Without **2a**	60	45
3[c]	$[Ir(cod)_2]^+BF_4^-$	Without H_2O	59	56 (**4aa**)
4	$[Ir(cod)_2]^+BF_4^-$	Without $ZrCl_4$	22	2
5	$[Ir(cod)_2]^+BF_4^-$	Without $P(O^iPr)_3$	27	15
6	None	Standard	No reaction	
7	$[IrCl(cod)]_2$	Standard	99	93
8[d]	$[Ir(cod)_2]^+BF_4^-$	Standard	99	71
9[e]	$[Ir(cod)_2]^+BF_4^-$	Without $ZrCl_4$	No reaction	

[a] Compound **1a** (1 mmol) was allowed to react with **2a** (3 mmol) and H_2O (0.05 mL, ca. 2.8 mmol) in the presence of Ir-complex (0.01 mmol), $P(O^iPr)_3$ (0.02 mmol) and $ZrCl_4$ (0.1 mmol) at 70 °C for 15 h.
[b] Toluene (1 mL) was used as a solvent.
[c] 2-Octanone dibutylketal (**4aa**) was formed.
[d] MeOH (**2b**) (3 mmol) was used instead of **2a**.
[e] $Gd(OTf)_3$ was used instead of $ZrCl_4$.

either $P(O^iPr)_3$ or $ZrCl_4$ (entries 4 and 5). Needless to say, the reaction did not take place at all without the Ir-complex (entry 6). The reaction using $[IrCl(cod)]_2$ in place of $[Ir(cod)_2]^+BF_4^-$ under standard conditions afforded **3a** in good yield (93%) (entry 7). When methanol (**2b**) was employed instead of **2a** under these conditions, **3a** was obtained in slightly lower yield (71%) (entry 8). In addition, the present Ir-catalyzed reaction with $Gd(OTf)_3$ in place of $ZrCl_4$ did not occur at all.

Table 2 shows the representative results of the reaction of several alkynes with **2a** and water catalyzed by $[Ir(cod)_2]^+BF_4^-$ under standard conditions. The reaction of 1-hexyne (**1b**) and 3-phenyl-1-propyne (**1c**) led to almost the same results as that of **1a** (entries 1 and 2), while phenyl acetylene (**1d**) was less reactive than **1a** to give acetophenone (**3d**) in 70% yield (entry 3). Unfortunately, internal alkyne like 4-octyne (**1e**) did not react at all under these conditions (entry 4).

Table 2. Addition of water to various alkynes catalyzed by $[Ir(cod)_2]^+BF_4^-$ [a]

Entry	Alkyne	Product	Conv, (%)	Yield (%)
1	 (**1b**)	 (**3b**)	99	77
2	 (**1c**)	 (**3c**)	99	82
3	 (**1d**)	 (**3d**)	73	70
4	 (**1e**)	No reaction		

[a] Compound **1** (1 mmol) was allowed to react with **2a** (3 mmol) and H_2O (0.05 mL, ca. 2.8 mmol) in the presence of $[Ir(cod)_2]^+BF_4^-$ (0.01 mmol), $P(O^iPr)_3$ (0.02 mmol) and $ZrCl_4$ (0.1 mmol) at 70 °C for 15 h (standard conditions).

Thus, the addition of water to terminal alkynes was successfully achieved by the $[Ir(cod)_2]^+BF_4^-/P(O^iPr)_3/ZrCl_4$ system in alcohols and water to afford the corresponding ketones in good yields, whereas the addition of alcohols of alkynes without water gave ketals in low yields (Table 1, entries 1 and 3).

In order to improve the yield of the ketal, the addition of **2b** to **1a** by $[Ir(cod)_2]^+BF_4^-$ was examined in the presence of phosphine or phosphite ligands and Lewis acids under several conditions (Eq. 2 and Table 3).

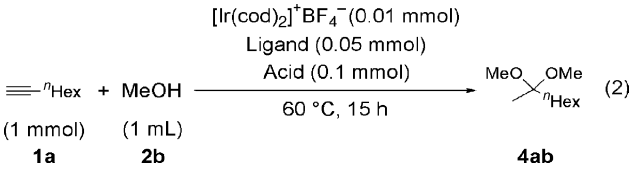


Table 3. Addition of methanol (**2b**) to **1a** catalyzed by $[Ir(cod)_2]^+BF_4^-$ combinated with ligand and acid[a]

Entry	Ligand	Acid	Conv. (%)	Yield (%)
1	$P(OEt)_3$	$AlCl_3$	98	93
2	None	$AlCl_3$	26	9
3	PPh_3	$AlCl_3$	34	<1
4	Dppe	$AlCl_3$	12	nd
5	$P(OMe)_3$	$AlCl_3$	99	90
6	$P(OEt)_3$	None	9	1
7	$P(OEt)_3$	$ZrCl_4$	89	86
8	$P(OEt)_3$	concd HCl	99	76
9	$P(OEt)_3$	TsOH	2	1

[a] Compound **1a** (1 mmol) was allowed to react in the presence of $[Ir(cod)_2]^+BF_4^-$ (0.01 mmol), ligand (0.05 mmol) and acid (0.1 mmol) in methanol (**2b**) (1 mL) at 60 °C for 15 h.

It was found that the reaction took place smoothly when $[Ir(cod)_2]^+BF_4^-$ together with $P(OEt)_3$ and Lewis acid like $AlCl_3$ or $ZrCl_4$ was used. For instance, **1a** reacted with **2b** in the presence of $[Ir(cod)_2]^+BF_4^-$, $P(OEt)_3$ and $AlCl_3$ at 60 °C for 15 h to afford **4ab** in good yield (93%) (entry 1). Removing either the ligand or Lewis acid from the catalytic system resulted in low yield of **4ab** (entries 2 and 6). PPh_3 and bidentate ligand like dppe were inert for the present reaction (entries 3 and 4). It was found that concd HCl served as a good additive, but *p*-toluenesulfuric acid did not induce the reaction (entries 8 and 9). From these results and the result as shown in Table 1 entry 9, Cl^- seems to be essential in the present reaction.

On the basis of these results, the reaction of terminal alkynes with various alcohols was examined (Eq. 3 and Table 4).

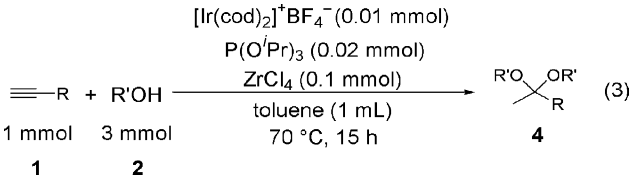


Table 4. Addition of various alcohols to alkynes catalyzed by $[Ir(cod)_2]^+BF_4^-$ [a]

Entry	Alkyne	Alcohol	Conv. (%)	Yield (%)
1	**1a**	**2a**	92	80 (**4aa**)
2	**1a**	**2c**	90	56 (**4ac**)
3	**1a**	**2d**	88	52 (**4ad**)
4[b]	**1a**	**2e**	99	70 (**4ae**)
5[b]	**1a**	**2f**	99	86 (**4af**)
6[b]	**1a**	**2g**	95	46 (**4ag**)
7	**1d**	**2b**	48	35 (**4bb**)

[a] Compound **1** (1 mmol) was allowed to react with **2** (3 mmol) in the presence of $[Ir(cod)_2]^+BF_4^-$ (0.01 mmol), $P(O^iPr)_3$ (0.02 mmol) and $ZrCl_4$ (0.1 mmol) in toluene (1 mL) at 70 °C for 15 h.
[b] In 1,4-dioxane (1 mL) at 100 °C.

It was found that the use of toluene as a solvent brought about good results. For example, buthanol (**2a**) added to **1a** to give **4aa** in 80% yield (entry 1). The reaction with hexanol (**2c**) and benzyl alcohol (**2d**) gave the corresponding ketals in moderate yields (entries 2 and 3). Various glycols such as ethylene glycol (**2e**), 1,2-butanediol (**2f**) and 1,2-heptanediol (**2g**) easily added to **1a** (entries 4 to 6).[13] Phenyl acetylene (**1d**) was resistant the addition of **2b**, and acetophenone dibuthyl acetal was formed in low yield (entry 7).

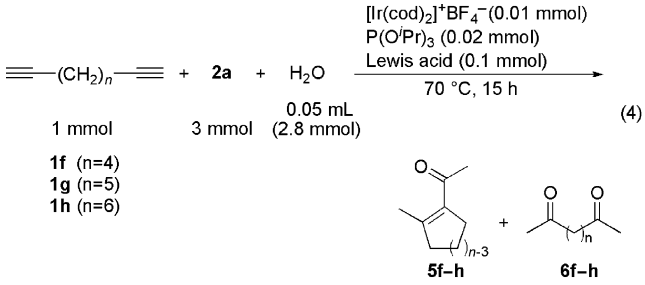
Finally, we tried the addition of water to α,ω-diyne (Eq. 4 and Table 5). There are few reports on the addition of water to α,ω-diynes.[14]

Table 5. Addition of various alcohols to α,ω-diynes catalyzed by $[Ir(cod)_2]^+BF_4^-$ [a]

Entry	Alkyne	Lewis acid	Conv. (%)	Yield (%)	
				5	**6**
1	**1f**	$ZrCl_4$	92	84	5
2	**1f**	$HfCl_4$	94	87	5
3	**1f**	$GdCl_3$	99	34	47
4	**1g**	$ZrCl_4$	78	60	8
5	**1g**	$GdCl_3$	92	2	80
6	**1h**	$ZrCl_3$	99	nd	96
7	**1h**	$GdCl_3$	94	nd	89

[a] α,ω-Diyne (1 mmol) was allowed to react with **2a** (3 mmol) and H_2O (0.05 mL, ca. 2.8 mmol) in the presence of $[Ir(cod)_2]^+BF_4^-$ (0.01 mmol), $P(O^iPr)_3$ (0.02 mmol) and Lewis acid (0.1 mmol) at 70 °C for 15 h.

1,7-Octadiyne (**1f**) was found to be converted to 1-(2-methylcyclopent-1-enyl)ethanone (**5f**) in 84% yield by allowing **1f** to react with water catalyzed by an iridium complex combined with Lewis acid in the presence of **2a** (entry 1). The formation of **5f** was rationally explained by assuming the intramolecular aldol condensation of the resulting 2,7-octadione (**6f**) by Lewis acid, $ZrCl_4$, during the reaction. $HfCl_4$ was also an efficient co-catalyst for the condensation to form **5f** in 87% yield (entry 2). However, $GdCl_3$ resulted in **5f** in low yield probably due to its weak basicity (entry 3). 1,8-Nonadiyne (**1g**) produced a mixture of aldol condensation product **5g** and diketone **6g** by the use of $ZrCl_4$ (entry 4), while **6g** was obtained in 80% yield when $GdCl_3$ was used as a Lewis acid (entry 5). 1,9-Decadiyne (**1h**) afforded exclusively diketone **6h** under these reaction conditions because of the difficulty of the formation of the seven-membered ring product corresponding to **5h** (entries 6 and 7).



In summary, we have succeeded in the addition of water and alcohols to non-activated alkynes by an iridium complex combined phosphite ligand and Lewis acid. The reaction of α,ω-diyne with water afforded aldol-condensation products in good yields.

3. Experimental

3.1. General procedure

^1H and ^{13}C NMR were measured at 270 and 67.5 MHz, respectively, in $CDCl_3$ with TMS as the internal standard. Infrared (IR) spectra were measured as thin films on NaCl plate or KBr press disk. A GLC analysis was performed with a flame ionization detector using a 0.2 mm×25 m capillary column (OV-17). Mass spectra were determined at an ionizing voltage of 70 eV. All starting materials, catalysts, and initiators were purchased from commercial sources and used without further treatment. The yields of products were estimated from the peak areas based on the internal standard technique.

3.2. General procedure for the addition of water to alkyne

An apparatus, consisting of a shulenk, inlet tube sealed with a rubber septum, and magnetic stirring bar, is evacuated, then flushed with argon. A buthanol (3 mmol) solution of triisopropyl phosphite (0.02 mmol), $[Ir(cod)_2]^+BF_4^-$ (0.01 mmol), and $ZrCl_4$ (0.1 mmol) was placed in the flask. To this solution are added alkyne (1 mmol) and water (0.05 mL, ca. 2.8 mmol) at room temperature. The reaction was carried out at 70 °C for 15 h. Removal of the solvent under reduced pressure afforded a cloudy solution, which was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate=9:1) to give the corresponding product. The products were characterized by ^1H and ^{13}C NMR, IR, and GC–MS, respectively.

3.3. General procedure for the addition of alcohol to alkyne

An apparatus, consisting of a shulenk, inlet tube sealed with a rubber septum, and magnetic stirring bar, is evacuated, then flushed with argon. A toluene (1 mL) solution of triisopropyl phosphite (0.02 mmol), $[Ir(cod)_2]^+BF_4^-$ (0.01 mmol), and $ZrCl_4$ (0.1 mmol) was placed in the

flask. To this solution are added alkyne (1 mmol) and alcohol (3 mmol) at room temperature. The reaction was carried out at 70 °C for 15 h. Removal of the solvent under reduced pressure afforded a cloudy solution, which was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 15:1) to give the corresponding product. The products were characterized by ^{1}H and ^{13}C NMR, IR, and GC–MS, respectively.

3.3.1. 2-Hexyl-2-methyl-1,3-dioxolane (4ae). ^{1}H NMR δ 3.97–3.90 (m, 4H), 1.65–1.61 (t, $J=6.7$ Hz, 2H), 1.38–1.29 (m, 11H), 0.90–0.87 (t, $J=7.2$ Hz, 3H); ^{13}C NMR δ 110.2, 64.5, 39.2, 31.7, 29.4, 24.0, 23.8, 22.5, 14.0; IR (NaCl) 2932, 2873, 1208, 1080 cm^{-1}; HRMS (EI): calcd for $C_{10}H_{20}O_2$ $[M-H]^+$: 172.1463; found: 172.1466.

3.3.2. 4-Ethyl-2-hexyl-2-methyl-1,3-dioxolane (4af). ^{1}H NMR δ 3.96–3.87 (m, 3H), 1.63–1.58 (t, $J=6.7$ Hz, 2H), 1.44–1.28 (m, 13 H), 0.92–0.86 (m, 6H); ^{13}C NMR δ 110.9, 68.8, 62.8, 40.6, 32.1, 29.9, 25.2, 24.6, 23.2, 22.8, 14.8; IR (NaCl) 2944, 2877, 1221, 1099 cm^{-1}; HRMS (EI): calcd for $C_{12}H_{24}O_2$ $[M-H]^+$: 200.1776; found: 200.1772.

3.3.3. 2-Hexyl-2-methyl-4-pentyl-1,3-dioxolane (4ag). ^{1}H NMR δ 3.99–3.89 (m, 3H), 1.68–1.64 (t, $J=6.7$ Hz, 2H), 1.49–1.26 (m, 19 H), 0.92–0.86 (m, 6H); ^{13}C NMR δ 112.6, 69.2, 62.2, 39.6, 33.2, 31.1, 29.4, 24.8, 24.2, 23.2, 22.9, 18.2, 14.1; IR (NaCl) 2932, 2873, 1208, 1080 cm^{-1}; HRMS (EI): calcd for $C_{15}H_{30}O_2$ $[M-H]^+$: 242.2246; found: 242.2250.

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Synthesis of highly substituted pyrroles via oxidative free radical reactions of β-aminocinnamates

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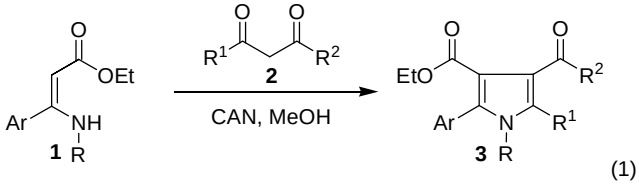
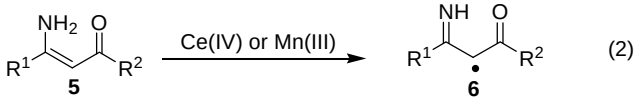
Abstract—Oxidative free radical reactions of β-aminocinnamates are described. Imine radicals produced by tetra-*n*-butylammonium cerium(IV) nitrate (TBACN) oxidation of enamines undergo efficient addition to the C–C double bond of β-aminocinnamates. This TBACN mediated free radical reaction between β-aminocinnamates and enamines provides a novel method for the synthesis of highly substituted pyrroles. The direct TBACN oxidation of β-aminocinnamates gave the dimerization products effectively.

1. Introduction

Free radical reactions have become increasingly important in organic synthesis in the last two decades.[1] The oxidative addition of an electrophilic carbon-centered radical to alkenes mediated by metal salts has received considerable attention in the organic synthesis for the construction of carbon–carbon bonds. Among these, manganese(III) acetate and cerium(IV) ammonium nitrate (CAN) have been used most efficiently.[1d–f,2,3] Pyrrole derivatives represent a class of compounds of great important in heterocyclic chemistry primarily due to the fact that pyrroles are important substructures of pharmaceutical agents and also of numerous natural products.[4] Accordingly, substantial attention has been paid to develop efficient methods for the synthesis of pyrroles.[5] Earlier, we have reported that oxidative free radical reactions between β-anilinocinnamate **1** and 1,3-dicarbonyl compound **2** produced the desired pyrrole products **3** (29–54%) and dimerization product **4** (0–18%) (Eq. 1).[6] Imine radical **6** can be generated from the oxidation of enamine **5** by metal salts (Eq. 2) and it undergoes efficient addition to the C–C double bond.[7] We describe here a much more effective method for the synthesis of highly substituted pyrroles via the oxidative free radical reaction between β-aminocinnamates and enamines.





2. Results and discussion

The oxidative free radical reaction between β-anilinocinnamate **1** and enamine **5** was first examined (Eq. 3). When β-anilinocinnamate **1a** was treated with enamine **5a** and CAN in MeOH at room temperature, pyrrole **3a** was obtained in 54% yield and no dimerization product **4a** could be found (Table 1, entry 1). A plausible mechanism for this reaction is shown in Scheme 1. Initiation occurs with CAN oxidation of enamine **5a** to produce imine radical **6a**.

Keywords: Tetra-*n*-butylammonium cerium(IV) nitrate; Oxidative; Free radical; β-Aminocinnamates.
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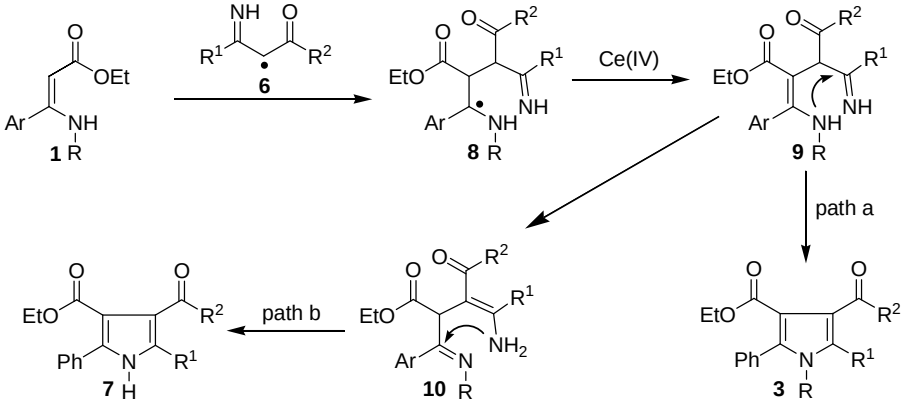
Table 1. Free radical reactions of β-aminocinnamates

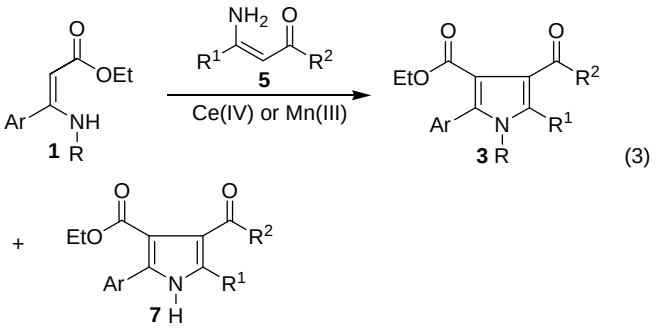
Entry	β-Aminocinnamate	Enamine	Oxidant	Solvent	Product (yield (%))
1	**1a**: R=*p*-ClPh, Ar=Ph	**5a**: R^1=Me, R^2=OEt	CAN	MeOH	**3a** (54)
2	**1a**: R=*p*-ClPh, Ar=Ph	**5a**: R^1=Me, R^2=OEt	$Me(OAc)_3$	HOAc	**3a** (62)
3	**1a**: R=*p*-ClPh, Ar=Ph	**5a**: R^1=Me, R^2=OEt	TBACN	MeOH	**3a** (92)
4	**1a**: R=*p*-ClPh, Ar=Ph	**5a**: R^1=Me, R^2=OEt	TBACN	MeCN	**3a** (88)
5	**1a**: R=*p*-ClPh, Ar=Ph	**5a**: R^1=Me, R^2=OEt	TBACN	$CHCl_3$	**3a** (92)
6	**1a**: R=*p*-ClPh, Ar=Ph	**5b**: R^1=Et, R^2=OMe	TBACN	MeOH	**3b** (61) **7b** (30)
7	**1a**: R=*p*-ClPh, Ar=Ph	**5b**: R^1=Et, R^2=OMe	TBACN	$CHCl_3$	**3b** (81)
8	**1a**: R=*p*-ClPh, Ar=Ph	**5c**: R^1=^{i}Pr, R^2=OEt	TBACN	MeOH	**3c** (17) **7c** (55)
9	**1a**: R=*p*-ClPh, Ar=Ph	**5c**: R^1=^{i}Pr, R^2=OEt	TBACN	$CHCl_3$	**3c** (45) **7c** (30)
10	**1a**: R=*p*-ClPh, Ar=Ph	**5d**: R^1=Pr, R^2=OEt	TBACN	$CHCl_3$	**3d** (75)
11	**1a**: R=*p*-ClPh, Ar=Ph	**5e**: R^1=Me, R^2=Me	TBACN	$CHCl_3$	**3e** (79)
12	**1a**: R=*p*-ClPh, Ar=Ph	**5f**: R^1=Et, R^2=Et	TBACN	$CHCl_3$	**3f** (61)
13	**1b**: R=*p*-BrPh, Ar=Ph	**5a**: R^1=Me, R^2=OEt	TBACN	$CHCl_3$	**3g** (94)
14	**1c**: R=*p*-EtO_2CPh, Ar=Ph	**5a**: R^1=Me, R^2=OEt	TBACN	$CHCl_3$	**3h** (91)
15	**1d**: R=Ph, Ar=Ph	**5a**: R^1=Me, R^2=OEt	TBACN	$CHCl_3$	**3i** (96)
16	**1e**: R=CH_2CN, Ar=Ph	**5a**: R^1=Me, R^2=OEt	TBACN	$CHCl_3$	**3j** (76)
17	**11a**: Ar=Ph	**5a**: R^1=Me, R^2=OEt	CAN	MeOH	**7a** (59)
18	**11a**: Ar=Ph	**5a**: R^1=Me, R^2=OEt	TBACN	MeOH	**7a** (87)
19	**11a**: Ar=Ph	**5a**: R^1=Me, R^2=OEt	TBACN	MeCN	**7a** (92)
20	**11a**: Ar=Ph	**5a**: R^1=Me, R^2=OEt	TBACN	$CHCl_3$	**7a** (89)
21	**11a**: Ar=Ph	**5b**: R^1=Et, R^2=OMe	TBACN	MeOH	**7b** (89)
22	**11a**: Ar=Ph	**5c**: R^1=^{i}Pr, R^2=OEt	TBACN	MeOH	**7c** (84)
23	**11a**: Ar=Ph	**5e**: R^1=Me, R^2=Me	TBACN	MeOH	**7d** (69) **12a** (14)
24	**11a**: Ar=Ph	**5f**: R^1=Et, R^2=Et	TBACN	MeOH	**7e** (72)

This radical intermediate **6a** undergoes intermolecular addition followed by oxidation to give **9a**, which undergoes nucleophilic addition of anilino group followed by elimination of ammonia to produce pyrrole **3a** (path a). There is no trace of another expected pyrrole product **7a** can be detected, which is presumably derived from the nucleophilic addition of amino group of **10a** (path b). With $Mn(OAc)_3$ in HOAc, pyrrole **3a** was obtained in 62% yield (entry 2). It has been reported that tetra-*n*-butylammonium cerium(IV) nitrate (TBACN) oxidized 1,3-dicarbonyl compounds more slowly than CAN.[8] We expected that pyrrole **3a** could be generated in a better result by using TBACN. Indeed, with TBACN, the reaction between β-anilinocinnamate **1a** and enamine **5a** in MeOH afforded pyrrole **3a** in an impressive 92% yield (entry 3).[9] With other enamines **5b** and **5c**, in addition to the formation of products **3b** and **3c**, pyrroles **7b** and **7c** were also obtained (entries 6 and 8). The ratios of **3/7** decrease as the size of substituents (R^1) on enamine **5** increases. This is presumably due to the steric effect exerted by R^1 group—the addition rate of anilino group (path a) was retarded by the larger R^1 and competitive nucleophilic addition of amino group (path b) occurred. In attempt to investigate the range of solvents compatible with this reaction, this reaction was performed in various solvents. With enamine **5a**, the change of solvent to CH_3CN or $CHCl_3$ gave only pyrrole **3a** in a similar yield (entries 4 and 5). With enamine **5b**, we are surprised to found that pyrrole **3b** was obtained in a much better yield (81%) from **1a** and no pyrrole **7b** could be isolated by using $CHCl_3$ as solvent (entry 7). Since TBACN/$CHCl_3$ is the most effective reaction condition for the formation of pyrrole **3**, so the scope of this reaction was explored with a variety of β-anilinocinnamate **1** and enamine **5** using the TBACN/$CHCl_3$ conditions. As shown in Table 1, this method proved to be of general applicability on β-anilinocinnamate **1** and enamine **5**. In most cases, β-anilinocinnamate **1** was smoothly converted to the corresponding pyrrole **3** selectively in excellent to good



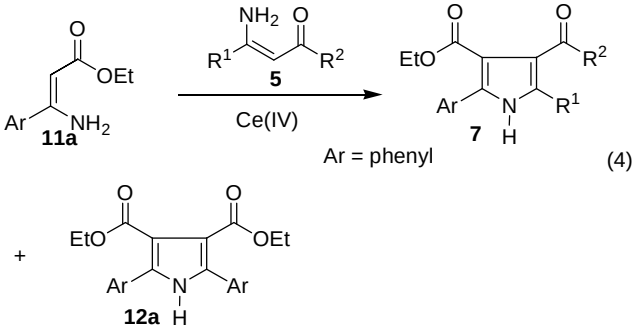
Scheme 1.

yield (entries 9–15). In addition, when β-alkylaminocinnamate **1e** was reacted with enamine **5a** under similar conditions, pyrrole **3j** was obtained in 76% yield (entry 16).



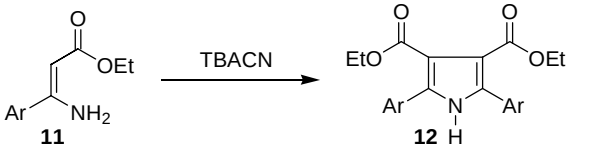
(3)

The oxidative free radical reaction of β-aminocinnamate **11a** was next studied (Eq. 4). Reaction of β-aminocinnamate **11a** with enamine **5a** and CAN in MeOH afforded pyrrole **7a** in 59% yield (entry 17) and the reaction yield was increased to 87% by replacing CAN with TBACN (entry 18). We also examined the effect of various solvents on the yield of pyrrole **7a**. Use MeCN or $CHCl_3$ as solvent, pyrrole **7a** was formed in a similar result (entries 19 and 20). Based on these results, we also examined this TBACN mediated reaction of β-aminocinnamate **11a** with various enamines **5** in MeOH and the results were also summarized in Table 1 (entries 21–24). Again, the reaction worked well and pyrrole **7** was formed in good yield. For an unknown reason, with enamine **5e**, in addition to the desired pyrrole **7e**, the dimerization product **12a** was also isolated (entry 23).



(4)

The preparation of highly substituted C_2-symmetric pyrroles by the oxidative dimerization of enamino esters has been reported.[6,10] On the basis of the generation of dimerization product **12a** in the reaction between β-aminocinnamate **11a** and enamine **5e**, we expected that the direct TBACN oxidation of β-aminocinnamate **11** would produce dimerization product **12** effectively (Eq. 5). Indeed, the formation of dimerization product **12a** (82%) was achieved by the oxidation of β-aminocinnamate **11a** with TBACN in methanol. Analogous results were obtained with other β-aminocinnamates **11** and were summarized in Table 2 (entries 1–5). The *N*-alkyl substituted β-aminocinnamate **1e** also underwent the direct TBACN oxidation reaction, producing pyrrole **4c** in a much better yield than that performed with CAN (entry 6).[6] The TBACN mediated oxidative dimerization of β-anilinocinnamates **1** was also studied. As shown in Table 2, while β-aminocinnamate **11a**–**11e** was converted to the corresponding dimerization product **12** in good yields (entries 1–5), the dimerization of β-anilinocinnamate **1** was less productive (entries 7 and 8).



(5)

Table 2. Oxidative dimerization of β-aminocinnamates

Entry	β-Aminocinnamate	Product (yield (%))
1	**11a**: Ar=Ph	**12a** (82)
2	**11b**: Ar=*p*-Tolyl	**12b** (80)
3	**11c**: Ar=*p*-BrPh	**12c** (88)
4	**11d**: Ar=*p*-ClPh	**12d** (87)
5	**11e**: R=*p*-NO_2Ph	**12e** (96)
6	**1e**: R=CH_2CN, Ar=Ph	**4c** (75)
7	**1a**: R=*p*-ClPh, Ar=Ph	**4a** (41)
8	**1c**: R=*p*-EtO_2CPh, Ar=Ph	**4b** (46)

In conclusion, imine radical **6** generated from the TBACN oxidation of enamine **5** undergoes efficient addition to the C–C double bond of β-aminocinnamates. This free radical reaction provides a novel method for the synthesis of highly substituted pyrroles from readily available β-aminocinnamates and enamines. The dimerization product **12** can also be synthesized effectively by the direct TBACN oxidation of β-aminocinnamate **11**.

3. Experimental

3.1. General considerations

Melting points are uncorrected. Infrared spectra were taken with a Hitachi 260-30 spectrometer. The NMR spectra were recorded on a Brucker AVANCE 300, AMX-400 or AVANCE 500 spectrometer. Chemical shifts are reported in ppm relative to TMS as internal reference. Elemental analyses were performed with Heraeus CHN-Rapid Analyzer. Analytical thin-layer chromatography was performed with precoated silica gel 60 F-254 plates (0.25 mm thick) from EM Laboratories and visualized by UV light. The reaction mixture was purified by column chromatography over EM Laboratories silica gel (70–230 mesh). The starting β-aminocinnamates **1**[10b,11a] and **11**[11b] were synthesized according to literature procedures. TBACN was prepared with CAN and tetra-*n*-butylammonium hydrogen sulfate.[12] Spectra data of pyrroles **3a**–**j** and dimerization products **4a**–**c** have been reported.[6]

3.2. Typical experimental procedure for the free radical reaction between β-aminocinnamates and enamines

A solution of 132 mg (0.69 mmol) of ethyl 3-aminocinnamate (**11a**), 446 mg (3.46 mmol) of ethyl 3-aminocrotonate (**5a**) and 1.39 g (1.39 mmol) of TBACN in 10 mL of MeOH was stirred at room temperature for 30 min and another 1.39 g (1.39 mmol) of TBACN was added. After

stirred for another 30 min, the reaction mixture was diluted with EtOAc (100 mL), washed with aq satd $NaHSO_3$ (50 mL) and H_2O (3×50 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over 15 g of silica gel (EtOAc/hexane, 1:4) followed by recrystallization (EtOAc–hexane) to give 182 mg (87%) of pyrrole **7a**.

3.2.1. 3,4-Diethoxycarbonyl-2-methyl-5-phenylpyrrole (7a). White crystals; mp 100–101 °C; IR ($CHCl_3$) 3455, 3305, 2990, 1700, 1445, 1285, 1095 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, J=7.1 Hz, 3H, CH_3), 1.33 (t, J=7.2 Hz, 3H, CH_3), 2.51 (s, 3H, CH_3), 4.27 (q, J=7.1 Hz, 2H, OCH_2), 4.28 (q, J=7.2 Hz, 2H, OCH_2), 7.27–7.42 (m, 3H, ArH), 7.42–7.50 (m, 2H, ArH), 8.37 (br s, 1H, NH); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 12.7 (q), 14.0 (q), 14.2 (q), 59.9 (t), 61.0 (t), 112.1 (s), 114.5 (s), 126.9 (2d), 127.8 (d), 128.5 (2d), 130.6 (s), 130.9 (s), 135.4 (s), 164.7 (s), 167.1 (s). Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.76; H, 6.35; N, 4.64.

3.2.2. 4-Ethoxycarbonyl-2-ethyl-3-methoxycarbonyl-5-phenylpyrrole (7b). White crystals; mp 88–89 °C; IR ($CHCl_3$) 3455, 3310, 2985, 1690, 1450, 1285, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J=7.1 Hz, 6H, $2CH_3$), 2.93 (q, J=7.6 Hz, 2H, CH_2), 3.80 (s, 3H, OCH_3), 4.26 (q, J=7.1 Hz, 2H, OCH_2), 7.28–7.39 (m, 3H, ArH), 7.43–7.49 (m, 2H, ArH), 8.50 (br s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.6 (q), 14.0 (q), 20.2 (t), 51.1 (q), 61.0 (t), 111.3 (s), 114.6 (s), 127.1 (2d), 127.9 (d), 128.6 (2d), 130.8 (s), 130.9 (s), 140.9 (s), 165.0 (s), 166.8 (s). Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.72; H, 6.38; N, 4.63.

3.2.3. 3,4-Diethoxycarbonyl-2-isopropyl-5-phenylpyrrole (7c). White crystals; mp 118–119 °C; IR ($CHCl_3$) 3460, 3315, 2980, 1700, 1445, 1280, 1230 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J=7.2 Hz, 3H, CH_3), 1.29 (d, J=7.0 Hz, 6H, $2CH_3$), 1.31 (t, J=7.1 Hz, 3H, CH_3), 3.70 (septet, J=7.0 Hz, 1H, CH), 4.24 (q, J=7.2 Hz, 2H, OCH_2), 4.25 (q, J=7.1 Hz, 2H, OCH_2), 7.28–7.39 (m, 3H, ArH), 7.43–7.49 (m, 2H, ArH), 8.52 (br s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.0 (q), 14.2 (q), 21.9 (2q), 25.8 (d), 60.0 (t), 60.9 (t), 111.1 (s), 114.5 (s), 127.3 (2d), 128.0 (d), 128.6 (2d), 130.7 (s), 131.1 (s), 144.3 (s), 164.5 (s), 166.6 (s). Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.23; H, 7.10; N, 4.25.

3.2.4. 3-Acetyl-4-ethoxycarbonyl-2-methyl-5-phenylpyrrole (7d). White crystals; mp 92–93 °C; IR ($CHCl_3$) 3450, 3280, 3000, 1705, 1655, 1420, 1120 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.21 (t, J=7.1 Hz, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 4.22 (q, J=7.1 Hz, 2H, OCH_2), 7.31–7.40 (m, 3H, ArH), 7.46 (d, J=7.4 Hz, 2H, ArH), 8.60 (br s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.2 (q), 13.9 (q), 30.3 (q), 60.9 (t), 113.3 (s), 122.8 (s), 127.9 (2d), 128.2 (d), 128.4 (2d), 131.0 (s), 132.8 (s), 133.7 (s), 166.4 (s), 196.5 (s). Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.71; H, 6.36; N, 5.17.

3.2.5. 3-Ethoxycarbonyl-5-ethyl-2-phenyl-4-propionylpyrrole (7e). White crystals; mp 113–114 °C; IR ($CHCl_3$) 3450, 3300, 2985, 1700, 1450, 1270 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (t, J=7.3 Hz, 3H, CH_3), 1.18 (t, J=7.1 Hz, 3H, CH_3), 1.26 (t, J=7.6 Hz, 3H, CH_3), 2.77 (q, J=7.3 Hz, 2H, CH_2), 2.82 (q, J=7.6 Hz, 2H, CH_2), 4.21 (q, J=7.1 Hz, 2H, OCH_2), 7.33–7.43 (m, 3H, ArH), 7.46–7.52 (m, 2H, ArH), 8.32 (br s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 8.6 (q), 13.9 (2q), 20.2 (t), 35.9 (t), 60.7 (t), 112.4 (s), 122.2 (s), 128.26 (3d), 128.30 (2d), 131.3 (s), 133.6 (s), 138.1 (s), 166.0 (s), 201.0 (s). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.32; H, 7.13; N, 4.64.

3.3. Typical procedure for the oxidative dimerization reaction of β-aminocinnamates

A solution of 138 mg (0.72 mmol) of ethyl 3-aminocinnamate (**11a**), and 722 mg (0.72 mmol) of TBACN in 10 mL of MeOH was stirred at room temperature for 30 min. After the work-up as described for the preparation of pyrrole **7a**, the residue was chromatographed over 15 g of silica gel (EtOAc/hexane, 1:6) followed by recrystallization (EtOAc–hexane) to give dimerization product **12a** (107 mg, 82%).

3.3.1. 3,4-Diethoxycarbonyl-2,5-diphenylpyrrole (12a). White crystals; mp 149–150 °C; IR ($CHCl_3$) 3450, 2990, 1715, 1490, 1225, 1125 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J=7.1 Hz, 6H, $2CH_3$), 4.24 (q, J=7.1 Hz, 4H, $2OCH_2$), 7.39–7.44 (m, 6H, ArH), 7.51–7.59 (m, 4H, ArH), 8.59 (br s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.0 (2q), 60.7 (2t), 114.5 (2s), 128.1 (4d), 128.5 (6d), 130.9 (2s), 134.2 (2s), 165.2 (2s). Anal. Calcd for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85. Found: C, 72.63; H, 5.83; N, 3.83.

3.3.2. 3,4-Diethoxycarbonyl-2,5-di-(*p*-tolyl)pyrrole (12b). White crystals; mp 137–138 °C; IR (KBr) 3265, 2980, 1725, 1680, 1220 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J=7.1 Hz, 6H, $2CH_3$), 2.37 (s, 6H, $2CH_3$), 4.23 (q, J=7.1 Hz, 4H, $2OCH_2$), 7.20 (d, J=8.1 Hz, 4H, ArH), 7.44 (d, J=8.1 Hz, 4H, ArH), 8.54 (br s, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.0 (2q), 21.3 (2q), 60.6 (2t), 114.0 (2s), 128.0 (4d), 129.1 (4d), 134.2 (2s), 138.4 (2s), 165.3 (2s). Anal. Calcd for $C_{24}H_{25}NO_4$: C, 73.64; H, 6.44; N, 3.57. Found: C, 73.61; H, 6.41; N, 3.55.

3.3.3. 2,5-Di-(*p*-bromophenyl)-3,4-diethoxycarbonylpyrrole (12c). White crystals; mp 211–212 °C; IR (KBr) 3290, 2980, 1700, 1485, 1285 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J=7.1 Hz, 6H, $2CH_3$), 4.25 (q, J=7.1 Hz, 4H, $2OCH_2$), 7.40–7.46 (m, 4H, ArH), 7.52–7.57 (m, 4H, ArH), 8.55 (br s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.0 (2q), 60.9 (2t), 115.0 (2s), 123.0 (2s), 129.5 (2s), 129.7 (4d), 131.8 (4d), 133.3 (2s), 164.9 (2s). Anal. Calcd for $C_{22}H_{19}Br_2NO_4$: C, 50.70; H, 3.68; N, 2.69. Found: C, 50.83; H, 3.66; N, 2.68.

3.3.4. 2,5-Di-(*p*-chlorophenyl)-3,4-diethoxycarbonylpyrrole (12d). White crystals; mp 222–223 °C; IR (KBr) 3295, 2980, 1700, 1485, 1450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, J=7.1 Hz, 6H, $2CH_3$), 4.26 (q, J=7.1 Hz, 4H, $2OCH_2$), 7.40 (d, J=8.5 Hz, 4H, ArH), 7.51 (d, J=8.5 Hz, 4H, ArH), 8.48 (br s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.1 (2q), 60.9 (2t), 115.0 (2s), 128.9 (4d), 129.1 (2s), 129.5 (4d), 133.3 (2s), 134.8 (2s),

164.8 (2s). Anal. Calcd for $C_{22}H_{19}Cl_2NO_4$: C, 61.12; H, 4.43; N, 3.24. Found: C, 61.13; H, 4.42; N, 3.23.

3.3.5. 3,4-Diethoxycarbonyl-2,5-di-(*p*-nitrophenyl)-pyrrole (12e). Yellow crystals; mp 217–218 °C; IR (KBr) 3230, 1740, 1680, 1345, 1225 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, $J=7.1$ Hz, 6H, $2CH_3$), 4.30 (q, $J=7.1$ Hz, 4H, $2OCH_2$), 7.76 (d, $J=8.8$ Hz, 4H, ArH), 8.29 (d, $J=8.8$ Hz, 4H, ArH), 9.01 (br s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.0 (2q), 61.4 (2t), 117.1 (2s), 123.9 (4d), 128.8 (4d), 132.7 (2s), 136.5 (2s), 147.6 (2s), 164.3 (2s). Anal. Calcd for $C_{22}H_{19}N_3O_8$: C, 58.28; H, 4.22; N, 9.27. Found: C, 58.37; H, 4.23; N, 9.30.

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Synthesis of conformationally restricted nicotine analogues by intramolecular [3+2] cycloaddition

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Abstract—We describe the synthesis of a series of conformationally constrained nicotine analogues **2**–**5** from appropriate pyridine-containing enals, featuring an intramolecular azomethine ylide–alkene [3+2] cycloaddition. The objective of the current project is to develop new selective nAChRs-targeting ligands. Of the nicotine analogues that we have studied, the conformation-restricting ring B unit can be either a five-membered carbocycle, or a six-membered carbocycle or heterocycle. The present work constitutes a general method for rapid assembly of other related tricyclic nicotine analogues.

1. Introduction

(−)-Nicotine (**1**, Fig. 1) is a well-known alkaloid present in tobacco at 0.2–5% levels and can target and activate nicotinic acetylcholine receptors (nAChRs), a family of ligand-gated ion channels widely distributed in the human brain.[1] These receptors participate in various biological processes related to numerous nervous system disorders.[2] Over the past decades, nicotine analogues have aroused tremendous attention in the areas of both organic synthesis and medicinal chemistry, because of the therapeutic potential of (−)-nicotine for the central nervous system (CNS) disorders such as Alzheimer's, Parkinson's, and Tourette's diseases.[2] Among the nicotine analogues, those with constrained conformation have emerged as the most attractive candidates for new selective nAChRs-targeting ligands.[2a,3,4] This phenomenon might partially be accounted for by the discovery of epibatidine, an alkaloid with a rigid structure, which displays strong activity despite of its toxicity.[5] Furthermore, molecular modeling approaches have illustrated that the two rings of nicotine structure are skewed and approximately perpendicular to one another in order to secure low energy conformations.[3,6]

Aiming at the cures for nervous system disorders, we have been engaged in designing, synthesizing, and evaluating new selective nAChRs-targeting ligands for years. In this paper, we wish to disclose our findings in constructing conformationally restricted, tricyclic, nicotine analogues **2**,[4a,b] **3**,[4j] **4**,[4g,7] and **5** (Fig. 1). The conformational rigidity was achieved as a result of a one- (in **2**) or two-atom (in **3**–**5**) bridge erected between C-4 and C-5′ of nicotine (**1**). Our synthesis features an intramolecular azomethine ylide–alkene [3+2] cycloaddition[4a,b,8] in effectively assembling the tricyclic framework of these ligands.

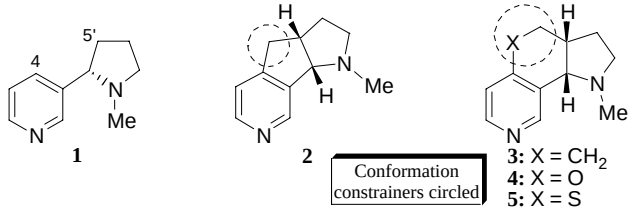

Figure 1.

Keywords: Conformationally restricted; Intramolecular [3+2] cycloaddition; Nicotine analogues; Synthesis.
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2. Results and discussion

The general strategy to synthesize the nicotine analogues in question is outlined in Figure 2. The ligands represented by structure **6** were envisioned to be obtainable from appropriate pyridine-containing enal **8** via azomethine ylide **7**. Intramolecular [3+2] cycloaddition constitutes a perfect choice in achieving the desired transformation.

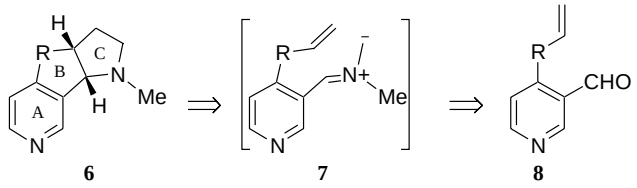
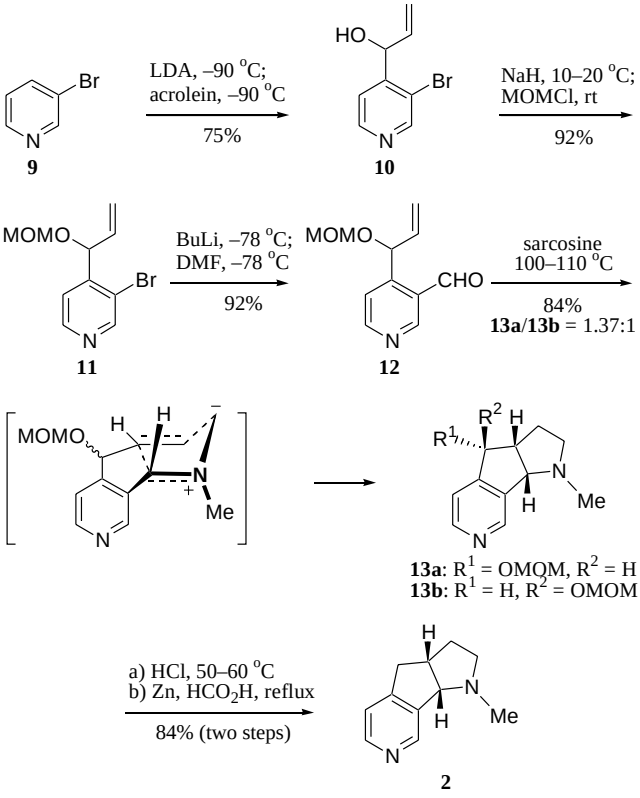


Figure 2.

2.1. Synthesis of nicotine analogue with five-membered carbocyclic ring B

As outlined in Scheme 1, the synthesis of nicotine analogue **2** commenced from 3-bromopyridine (**9**). *Ortho* lithiation with LDA at −90 °C followed by treatment with acrolein at the same temperature furnished alcohol **10** in good yield (75%). Deprotonation at lower temperature than −78 °C resulted in higher yield of the product by diminishing pyridyne formation. Alcohol **10** was protected as ether **11** by exposure to MOMCl in the presence of NaH. Use of a slight excess of base, compared to MOMCl, was found to be effective in preventing the formation of the rearranged enol ether byproducts. Formylation of **11** (BuLi, −78 °C; DMF, −78 °C) led conveniently to aldehyde **12** in 92% yield, setting the stage for intramolecular azomethine ylide–alkene [3+2] cycloaddition. After extensive experimentation, we found that treatment of **12** with sarcosine in DMF at 100–110 °C for 6 h effected the desired cycloaddition to give two isomers **13a/13b** in a combined yield of 84% and in a diastereomeric ratio of 1.37:1 (deduced from ^{1}H NMR integrals). The structures of **13a** and **13b** were assigned based on the coupling constants for the hydrogen atoms at C-4 (J=8.1, 4.5 Hz, respectively). Deprotection of **13a/13b** mixture (4 M HCl, 50–60 °C) followed by zinc-mediated reductive dehydroxylation (Zn powder, formic acid, reflux) afforded **2** in 84% overall yield for the two steps.[4b]

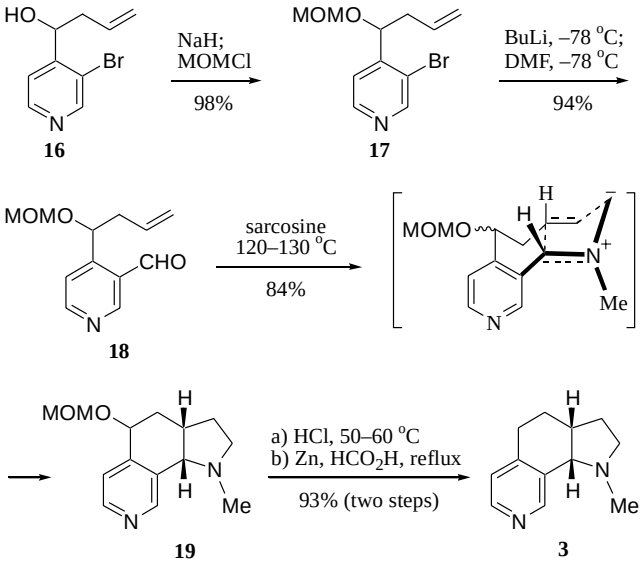


Scheme 1.

A second-generation synthesis of **2** was accomplished in only two steps. In this case, the precursor for the intramolecular azomethine ylide–alkene [3+2] cycloaddition, that is, 4-allyl-3-pyridinecarboxaldehyde (**15**), was formed efficaciously in a single step from 3-pyridinecarboxaldehyde (**14**) via sequential in situ protection, *ortho* lithiation, cuprate formation, allylation, and deprotection. The cuprate formation plays a vital role in minimizing/eliminating the extent of multiple alkylation.[4a]

2.2. Synthesis of nicotine analogue with six-membered carbocyclic ring B

As shown in Scheme 2, the synthesis of **3** started with a known alcohol, **16**, which was prepared by a Barbier reaction of 3-bromo-4-pyridinecarboxaldehyde with allyl bromide and zinc powder.[9] Protection of **16** as MOM ether (NaH, rt; MOMCl, rt, 98%) followed by formylation at C-3 (BuLi, −78 °C; DMF, −78 °C, 94%) afforded enal **18** in high yield. Exposure of **18** to sarcosine in DMF at 120–130 °C for 8 h effected the desired intramolecular azomethine ylide–alkene [3+2] cycloaddition to produce a pair of diastereomers **19** (dr=2.57:1) in a combined yield of 84%. By following the protocol developed for **13a/13b** (Scheme 1), the cycloaddition products **19** underwent deprotection (6 M HCl, 50–60 °C) and the subsequent zinc-mediated reductive dehydroxylation (Zn powder,

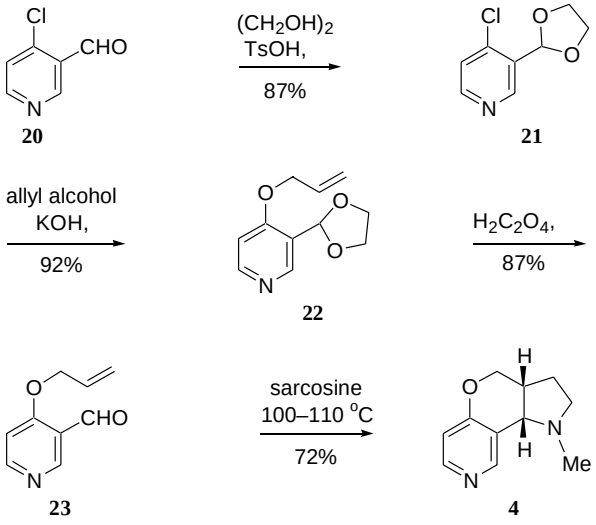


Scheme 2.

formic acid, reflux) to lead to **3**[4j] in 93% overall yield for the two steps.

2.3. Synthesis of nicotine analogue with six-membered oxygen-containing heterocyclic ring B

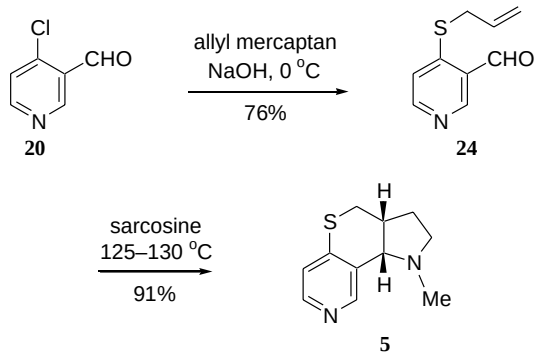
The preparation of the cycloaddition precursor, enal **23**, was not as trivial as expected. Direct treatment of 4-chloro-3-pyridinecarboxaldehyde[10] (**20**) with allyl alcohol and KOH in refluxing THF gave rise to 4-chloro-3-(hydroxymethyl)-pyridine. However, after being protected as the acetal **21** (ethylene glycol, $TsOH\cdot H_2O$, benzene, reflux, 87%), the etherification at the C-4 of the pyridine ring (allyl alcohol, KOH, THF, reflux) proceeded cleanly to furnish allyl ether **22** in 92% (Scheme 3). Heating **22** with oxalic acid dihydrate in refluxing acetone–water (1/1) effected acetal deprotection to provide in 87% yield enal **23**, which underwent intramolecular azomethine ylide–alkene [3+2] cycloaddition to form the oxygen-containing tricycle **4** in moderate yield (72%) when heated with sarcosine in DMF at 100–110 °C.



Scheme 3.

2.4. Synthesis of nicotine analogue with six-membered sulfur-containing heterocyclic ring B

Reaction 4-chloro-3-pyridinecarboxaldehyde[10] (**20**) with allyl mercaptan (generated in situ from thiourea and allyl bromide in basic medium) and NaOH in ethanol at rt resulted in the formation of thioether **24** (76%) (Scheme 4), which was contrary to what we observed with the etherification of **20** with allyl alcohol. Obviously the reaction condition for thioetherification was much milder because of the stronger nucleophilicity of allyl mercaptan compared to that of allyl alcohol. Finally, upon treatment with sarcosine in hot DMF (125–130 °C), enal **24** was converted to the sulfur-containing tricycle **5** in 91% yield through intramolecular azomethine ylide–alkene [3+2] cycloaddition. According to our literature search, compound **5** represents a new nicotine analogue with restricted conformation.



Scheme 4.

3. Conclusion

In summary, we have accomplished the synthesis of a series of conformationally constrained nicotine analogues **2–5** from appropriate pyridine-containing enals, featuring an intramolecular azomethine ylide–alkene [3+2] cycloaddition. The objective of the current project is to develop new selective nAChRs-targeting ligands. Of the nicotine analogues that we have studied, the conformation-restricting ring B unit can be either a five-membered carbocycle, or a six-membered carbocycle or heterocycle. The pharmacological investigations of these compounds are under way. The present work constitutes a general method for rapid assembly of other related tricyclic nicotine analogues.

4. Experimental

4.1. General

Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ (^1H at 300 MHz and ^{13}C at 75.47 MHz) using TMS as the internal standard. Column chromatography was performed on silica gel. CH_2Cl_2, DMF and diisopropylamine were stored over calcium hydride and freshly distilled prior to use. THF and benzene were distilled over sodium benzophenone ketyl prior to use. Ethanol was distilled over magnesium prior to use.

4.1.1. 3-Bromo-4-(1-hydroxy-2-propenyl)pyridine (10). BuLi (1.6 M, 8.00 mL, 12.8 mmol) was added to a solution of diisopropylamine (2.00 mL, 14.3 mmol) in THF (26 mL) at −78 °C over 10 min. After 30 min, the resultant LDA solution was cooled to −90 °C, and a solution of 3-bromopyridine (0.90 mL, 9.3 mmol) in THF (3 mL) was added dropwise at this temperature over 3 min. The mixture was stirred for 25 min, and then a solution of acrolein (1.10 mL, 16.5 mmol) in THF (5 mL) was added dropwise over 40 min. The mixture was warmed up to −78 °C and stirred for 2 h, quenched with saturated aqueous $NaHCO_3$ solution (2 mL) at −78 °C, warmed up to rt, and evaporated. The residue was partitioned between CH_2Cl_2 and aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (EtOAc/hexanes, 1:10–1:5) to give **10** (1.50 g, 75%) as colorless

crystals: mp 61–62 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.07–4.21 (br s, 1H), 5.22 (d, J=0.9 Hz, 1H), 5.25–5.50 (m, 2H), 5.88–5.99 (m, 1H), 7.52 (d, J=4.8 Hz, 1H), 8.40 (d, J=4.8 Hz, 1H), 8.54 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 72.3, 116.9, 120.4, 122.5, 137.0, 148.3, 151.1, 151.4. MS (EI): 215, 213 (M^+). Anal. Calcd for C_8H_8BrNO: C, 44.89; H, 3.77; N, 6.54. Found: C, 45.02; H, 3.57; N, 6.40.

4.1.2. 3-Bromo-4-(1-(methoxymethoxy)-2-propenyl)-pyridine (11). To a 100-mL three-necked flask equipped with two dropping funnels and a nitrogen gas inlet tube, were added 60% mineral oil dispersion of NaH (620 mg, 15.5 mmol) and anhydrous THF (50 mL). While the temperature of the suspension was maintained between 10–20 °C, a solution of **10** (2.20 g, 10.3 mmol) in THF (10 mL) was added dropwise over 10 min. Then a solution of MOMCl (1.02 mL, 13.4 mmol) in THF (15 mL) was added immediately over 10 min at 10–20 °C. The resultant mixture was stirred at rt for 3 h. Saturated aqueous $NaHCO_3$ (20 mL) was added carefully to the solution, and the mixture was concentrated to remove THF. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (Et_2O/petroleum ether, 10:1) to give **11** (2.44 g, 92%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.28 (s, 3H), 4.55 (d, J=6.7 Hz, 1H), 4.70 (d, J=6.7 Hz, 1H), 5.20–5.37 (m, 3H), 5.70–5.78 (m, 1H), 7.40 (d, J=5.0 Hz, 1H), 8.45 (d, J=5.0 Hz, 1H), 8.61 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.6, 75.8, 94.2, 118.1, 120.7, 122.6, 134.8, 148.4, 148.7, 151.8. MS (EI): 259, 257 (M^+). Anal. Calcd for $C_{10}H_{12}BrNO_2$: C, 46.53; H, 4.69; N, 5.43. Found: C, 46.72; H, 4.80; N, 5.60.

4.1.3. 4-(1-(Methoxymethoxy)-2-propenyl)-3-pyridinecarboxaldehyde (12). BuLi (1.6 M, 2.00 mL, 3.20 mmol) was added dropwise to a solution of **11** (686 mg, 2.66 mmol) in THF (25 mL) at −78 °C over 10 min. After 1 h, a solution of DMF (0.30 mL, 3.9 mmol) in THF (3 mL) was added at −78 °C over 10 min. The mixture was stirred at this temperature for 1 h, quenched with saturated aqueous $NaHCO_3$ solution at −78 °C, warmed up to rt, and evaporated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (EtOAc/petroleum ether, 1:10–1:5) to afford **12** as a pale yellow oil (506 mg, 92%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.34 (s, 3H), 4.63 (d, J=6.6 Hz, 1H), 4.79 (d, J=6.6 Hz, 1H), 5.22–5.42 (m, 2H), 5.86–5.98 (m, 2H), 7.64 (d, J=5.2 Hz, 1H), 8.80 (d, J=5.2 Hz, 1H), 9.01 (s, 1H), 10.31 (s, 1H). MS (EI): 207 (M^+).

4.1.4. (3a*R*,4*R,8b*S*)-4-(Methoxymethoxy)-1-methyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,2-*f*]pyridine (13a) and (3a*S*,4*R**,8b*R*)-4-(methoxymethoxy)-1-methyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,2-*f*]pyridine (13b).** A mixture of aldehyde **12** (1.21 g, 5.84 mmol) and sarcosine (546 mg, 6.13 mmol) in DMF (30 mL) was heated under N_2 at 100–110 °C for 6 h, cooled to rt, and evaporated. The residue was diluted with brine (10 mL) and extracted with $CHCl_3$–IPA (3/1). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (EtOH/CH_2Cl_2, 1:10) to give **13a/13b** mixture (1.15 g, 84%, **13a/13b**=1.37:1, as judged by ^{1}H NMR integrals of **13a/13b** mixture) as a pale yellow oil, which was suitable for use in the next step. Compound **13a**: R_f=0.23; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.86–1.89 (m, 1H), 1.98–2.00 (m, 1H), 2.58–2.62 (m, 1H), 2.63 (s, 3H), 2.86–2.92 (m, 1H), 3.28–3.33 (m, 1H), 3.50 (s, 3H), 3.98 (d, J=7.8 Hz, 1H), 4.82–4.83 (m, 2H), 5.04 (d, J=8.1 Hz, 1H), 7.29–7.33 (m, 1H), 8.52–8.55 (m, 1H), 8.67 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.2, 41.8, 46.0, 55.8, 57.2, 71.6, 77.9, 96.4, 120.3, 138.1, 147.0, 148.8, 151.4. MS (EI): 235 (M^++H). Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.39; H, 7.87; N, 11.89. Compound **13b**: R_f=0.20; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.88–1.96 (m, 1H), 2.23–2.27 (m, 1H), 2.50 (s, 3H), 2.52–2.58 (m, 1H), 3.03–3.11 (m, 2H), 3.46 (s, 3H), 3.87 (d, J=7.8 Hz, 1H), 4.81–4.87 (m, 2H), 5.07 (d, J=4.5 Hz, 1H), 7.33 (d, J=4.8 Hz, 1H), 8.57 (d, J=4.8 Hz, 1H), 8.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.1, 41.7, 45.8, 55.7, 57.1, 71.4, 77.8, 96.3, 120.2, 138.0, 146.8, 148.6, 151.3. MS (EI): 234 (M^+). Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.41; H, 7.80; N, 12.01.

4.1.5. *cis*-1-Methyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,2-*f*]-pyridine (2). MOM ethers **13a/13b** (270 mg, 1.15 mmol) was heated in 4 M HCl (4 mL) at 50–60 °C for 6 h, cooled to rt, neutralized with 50% NaOH, and extracted with $CHCl_3$–IPA (3/1). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated. The residue was mixed with zinc powder (560 mg, 8.57 mmol) and formic acid (12.5 mL), refluxed for 25 h, and cooled to rt. The solid was filtered off and washed thoroughly with $CHCl_3$–IPA (3/1). The filtrate was concentrated under reduced pressure, the residue was diluted with saturated aqueous $NaHCO_3$ solution and extracted with $CHCl_3$–IPA (3/1). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was chromatographed (petroleum ether/CH_2Cl_2/MeOH, 10:10:1) to give 169 mg (84%) of **2** as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.62–1.74 (m, 1H), 2.15–2.25 (m, 1H), 2.44–2.55 (m, 1H), 2.55 (s, 3H), 2.77–2.86 (m, 1H), 2.99–3.21 (m, 3H), 3.80 (d, J=7.6 Hz, 1H), 7.13 (d, J=5.2 Hz, 1H), 8.42 (d, J=5.2 Hz, 1H), 8.60 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 32.2, 39.2, 40.5, 41.9, 57.6, 73.4, 120.3, 139.2, 145.8, 148.3, 153.0. MS (EI): 174 (M^+). Anal. Calcd for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.69; H, 7.84; N, 16.38.

4.1.6. 3-Bromo-4-(1-(methoxymethoxy)-3-butenyl)pyridine (17). To a suspension of NaH (60% in mineral oil, 620 mg, 15.5 mmol) in dry THF (100 mL) under a nitrogen atmosphere, was added a solution of **16** (2.30 g, 10.1 mmol) in dry THF (20 mL). After the mixture was stirred at rt for 20 min, a solution of MOMCl (1.0 mL, 13 mmol) in dry THF (15 mL) was slowly added. The mixture was stirred at rt for 2 h, diluted with saturated aqueous $NaHCO_3$ solution, evaporated, and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (EtOAc/petroleum ether, 1:10) to give **17** (2.69 g, 98%) as a colorless solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.43–2.54 (m, 2H), 3.35 (s, 3H), 4.52 (d, J=6.6 Hz, 1H), 4.63 (d, J=6.9 Hz, 1H), 5.01 (dd, J=7.8, 4.4 Hz, 1H), 5.07 (t, J=1.1 Hz, 1H), 5.11 (d, J=4.8 Hz, 1H), 5.75–5.90 (m, 1H), 7.42 (d, J=4.8 Hz, 1H), 8.51 (d, J=5.1 Hz, 1H), 8.66

(s, 1H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 39.9, 55.6, 75.5, 94.9, 117.9, 120.5, 122.3, 133.1, 148.2, 149.8, 151.6. MS (EI) 272 (M^+, 25), 230 (36). Anal. Calcd for $C_{11}H_{14}BrNO_2$: C, 48.55; H, 5.19; N, 5.15. Found: C, 48.41; H, 5.17; N, 5.19.

4.1.7. 4-(1-(Methoxymethoxy)-3-butenyl)-3-pyridinecarboxaldehyde (18). A solution of *n*-BuLi (2.2 M, 4.4 mL, 9.7 mmol) in hexane was added dropwise to a solution of **17** (2.22 g, 8.16 mmol) in dry THF (80 mL) at −78 °C under a nitrogen atmosphere. After the mixture was stirred at −78 °C for 20 min, a solution of DMF (0.95 mL, 12 mmol) in dry THF (10 mL) was introduced. The mixture was stirred at −78 °C for 30 min, allowed to warm to rt, stirred at rt for 30 min, diluted with saturated aqueous $NaHCO_3$ solution, evaporated, and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (EtOAc/petroleum ether, 1:10) to give **18** (1.70 g, 94%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.22–2.34 (m, 2H), 3.13 (s, 3H), 4.35 (dd, J=6.9, 1.5 Hz, 1H), 4.47 (dd, J=6.6, 1.2 Hz, 1H), 4.84–4.86 (m, 1H), 4.90 (t, J=1.2 Hz, 1H), 5.41 (dd, J=7.5, 4.8 Hz, 1H), 5.64–5.70 (m, 1H), 7.46 (d, J=5.1 Hz, 1H), 8.60 (dd, J=5.0, 1.4 Hz, 1H), 8.81 (s, 1H), 10.08 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 41.2, 55.4, 72.9, 95.0, 117.7, 121.2, 127.8, 133.3, 153.0, 153.6, 154.3, 191.4. MS (EI) 180 (M−41, 22), 45 (100).

4.1.8. 2,3,3a,4,5,9b-Hexahydro-5-(methoxymethoxy)-1-methyl-1*H*-pyrrolo[3,2,-*h*]isoquinoline (19). A solution of **18** (534 mg, 2.41 mmol) and sarcosine (236 mg, 2.65 mmol) in DMF (15 mL) was heated at 125–130 °C under N_2 for 8 h, cooled to rt, and evaporated. The residue was diluted with brine and extracted with $CHCl_3$–IPA (3/1). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (CH_3OH/EtOAc, 1:20) to give a pair of diastereomers **19** (505 mg, 84%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) diastereomers, 2.57:1, δ 1.53–1.66 (m, 1H), 1.70–1.82 (m, 0.28H), 1.88 (td, J=11.9, 11.7 Hz, 0.72H), 2.05–2.22 (m, 2H), 2.26 (s, 0.84H), 2.41 (dt, J=9.0, 9.0 Hz, 1H), 2.45 (s, 2.16), 2.49–2.56 (m, 0.72H), 2.67–2.70 (m, 0.28H), 3.04 (t, J=7.8 Hz, 0.28H), 3.06 (d, J=6.6 Hz, 1H), 3.24 (td, J=8.1, 3.0 Hz, 0.72H), 3.47 (s, 0.84H), 3.49 (s, 2.16H), 4.60 (dd, J=11.0, 5.3 Hz, 0.72H), 4.79 (d, J=6.0 Hz, 0.28H), 4.82 (t, J=6.5 Hz, 0.28H), 4.83 (d, J=6.3 Hz, 0.72H), 4.91 (d, J=6.0 Hz, 0.28H), 4.94 (d, J=6.0 Hz, 0.72H), 7.46 (d, J=4.8 Hz, 0.72H), 7.49 (d, J=5.1 Hz, 0.28H), 8.37 (s, 0.28H), 8.49 (s, 0.72H), 8.50 (d, J=5.1 Hz, 0.72H), 8.54 (d, J=5.1 Hz, 0.28H). MS (EI) 249 (M+1, 7), 248 (M^+, 0.6), 203 (91), 43 (100). Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.77; H, 7.81; N, 11.21.

The major product. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.56–1.67 (m, 1H), 1.82–1.94 (m, 1H), 2.08–2.20 (m, 2H), 2.40–2.59 (m, 2H), 2.46 (s, 3H), 3.11 (d, J=5.4 Hz, 1H), 3.25 (td, J=9.0, 3.0 Hz, 1H), 3.48 (s, 3H), 4.61 (dd, J=11.0, 5.3 Hz, 1H), 4.81 (dd, J=6.9, 1.2 Hz, 1H), 4.94 (dd, J=6.8, 1.4 Hz, 1H), 7.47 (d, J=5.1 Hz, 1H), 8.47–8.53 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 29.4, 33.3, 36.4, 40.7, 55.3, 55.5, 62.9, 73.4, 95.3, 120.2, 130.4, 147.4, 148.1, 150.5.

The minor product. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.55–1.65 (m, 1H), 1.73–1.86 (m, 1H), 2.10 (ddd, J=12.8, 4.1, 2.7 Hz, 1H), 2.17–2.29 (m, 2H), 2.29 (s, 3H), 2.72 (t, J=7.4 Hz, 1H), 3.11 (td, J=8.1, 8.0 Hz, 2H), 3.47 (s, 3H), 4.81 (t, J=3.9 Hz, 1H), 4.83 (dd, J=6.8, 1.7 Hz, 1H), 4.91 (dd, J=6.9, 1.8 Hz, 1H), 7.51 (d, J=4.8 Hz, 1H), 8.38 (s, 1H), 8.55 (d, J=5.1 Hz, 1H).

4.1.9. 2,3,3a,4,5,9b-Hexahydro-1-methyl-1*H*-pyrrolo[3,2,-*h*]-soquinoline (3). A mixture of the two isomers of **19** (399 mg, 1.61 mmol) and 6 M HCl (20 mL) was heated at 50–60 °C under N_2 for 8 h, cooled to rt, neutralized with saturated aqueous $NaHCO_3$ solution, and extracted with $CHCl_3$–IPA (3/1). The combined organic layers were dried over $MgSO_4$, and filtered. Evaporation of the volatiles gave the crude products of diastereomeric 2,3,3a,4,5,9b-hexahydro-5-hydroxy-1-methyl-1*H*-pyrrolo[3,2,-*h*]isoquinoline, which could be used directly for the next reaction.

A mixture of the above-mentioned crude alcohols and zinc power (816 mg, 12.5 mmol) in anhydrous formic acid (40 mL) was heated at reflux for 15 h under N_2, cooled to rt, and evaporated. The residue was diluted with saturated aqueous $NaHCO_3$ solution and extracted with $CHCl_3$–IPA (3/1). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (CH_3OH/EtOAc, 1:20) to give **3** (281 mg, 93% for two steps from **19**) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.56–1.62 (m, 1H), 1.69–1.84 (m, 2H), 2.09–2.16 (m, 1H), 2.24–2.39 (m, 1H), 2.34 (s, 3H), 2.51–2.62 (m, 2H), 2.78–2.88 (m, 1H), 3.08–3.11 (m, 2H), 7.09 (dd, J=4.7, 2.0 Hz, 1H), 8.34 (d, J=2.7 Hz, 1H), 8.40 (dd, J=5.0, 2.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 26.1, 28.9, 29.7, 36.0, 40.3, 55.6, 64.4, 123.4, 132.1, 148.0, 149.4, 150.2. MS (EI) 188 (M^+, 68), 187 (100). Anal. Calcd for $C_{12}H_{16}N_2\cdot 2HCl\cdot 1/3H_2O$ (the HCl salt of **3**): C, 53.94; H, 7.04; N, 10.48. Found: C, 54.04; H, 7.22; N, 10.44.

4.1.10. 4-Chloro-3-(1,3-dioxolan-2-yl)pyridine (21). A mixture of **20** (270 mg, 1.91 mmol), ethylene glycol (0.55 mL, 9.9 mmol) and the *p*-toluenesulfonic acid monohydrate (328 mg, 1.72 mmol) in benzene (30 mL) was boiled for 3 h, cooled to rt, made basic with aqueous sodium hydroxide solution, and extracted with ether. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (EtOAc/petroleum ether, 1:5) to give **21** (307 mg, 87%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.00–4.13 (m, 2H), 4.14–4.25 (m, 2H), 6.17 (s, 1H), 7.33 (d, J=5.4 Hz, 1H), 8.50 (d, J=5.1 Hz, 1H), 8.77 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 65.6, 99.9, 124.6, 131.1, 143.5, 149.3, 151.0. MS (EI) 184 (M−1). Anal. Calcd for $C_8H_8ClNO_2$: C, 51.77; H, 4.34; N, 7.55. Found: C, 51.81; H, 4.24; N, 7.43.

4.1.11. 4-(Allyloxy)-3-(1,3-dioxolan-2-yl)pyridine (22). A mixture of **21** (88 mg, 0.47 mmol), allyl alcohol (0.50 mL, 7.4 mmol) and KOH (819 mg, 14.6 mmol) in THF (20 mL) was heated at reflux for 6 h, cooled to rt, made basic with aqueous sodium hydroxide solution, and extracted with ether. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (EtOAc/petroleum ether, 2:5) to give **22** (90 mg,

92%) as a colorless solid: mp 65–67 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.99–4.10 (m, 2H), 4.10–4.21 (m, 2H), 4.66 (d, J=5.4 Hz, 2H), 5.33 (dd, J=10.5, 1.2 Hz, 1H), 5.43 (dd, J=17.7, 1.2 Hz, 1H), 5.99–6.03 (m, 1H), 6.20 (s, 1H), 6.79 (d, J=5.7 Hz, 1H), 8.47 (d, J=6.0 Hz, 1H), 8.62 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 65.4, 68.8, 98.8, 107.2, 118.4, 122.1, 131.8, 148.8, 152.0, 162.8. MS (EI) 206 (M−1). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.76; H, 6.31; N, 6.69.

4.1.12. 4-(Allyloxy)nicotinaldehyde (23). A mixture of **22** (180 mg, 0.869 mmol) and oxalic acid dihydrate (547 mg, 4.34 mmol) in acetone and water (1:1, 40 mL) was heated at reflux overnight, cooled to rt, made basic with aqueous sodium hydroxide solution, and extracted with ether. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (EtOAc/petroleum ether, 2:5) to give **23** (123 mg, 87%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.70 (d, J=5.0 Hz, 2H), 5.36 (dd, J=10.5, 1.2 Hz, 1H), 5.44 (dd, J=17.1, 1.2 Hz, 1H), 5.96–6.09 (m, 1H), 6.88 (d, J=6.0 Hz, 1H), 8.57 (dd, J=6.0, 1.5 Hz, 1H), 8.85 (s, 1H), 10.46 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 69.2, 108.1, 119.1, 120.5, 130.9, 150.7, 155.8, 165.7, 188.6; MS (EI) 162 (M−1). Anal. Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 65.86; H, 5.56; N, 8.40.

4.1.13. 2,3,3a,4,5,9b-Hexahydro-1-methyl-5-oxa-1*H*-pyrrolo[3,2,-*h*]isoquinoline (4). A solution of **23** (156 mg, 0.956 mmol) and sarcosine (94.0 mg, 1.06 mmol) in DMF (15 mL) was heated at 100–110 °C under N_2 for 8 h, cooled to rt, and evaporated. The residue was diluted with brine and extracted with $CHCl_3$–IPA (3/1). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (EtOAc/petroleum ether, 2:5) to give **4** (131 mg, 72%) as a pale oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.41–1.46 (m, 1H), 2.08–2.13 (m, 1H), 2.30–2.46 (m, 2H), 2.44 (s, 3H), 2.94 (d, J=5.1 Hz, 1H), 3.13 (td, J=9.0, 2.1 Hz, 1H), 3.92 (dd, J=11.4, 10.8 Hz, 1H), 4.12 (dd, J=10.8, 5.4 Hz, 1H), 6.80 (d, J=5.4 Hz, 1H), 8.30 (d, J=5.4 Hz, 1H), 8.34 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 24.5, 34.0, 39.4, 54.5, 60.1, 67.6, 112.3, 117.6, 149.8, 152.7, 161.6. MS (EI) 189 (M−1). Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.73. Found: C, 69.30; H, 7.42; N, 14.82.

4.1.14. 4-(Allylthio)nicotinaldehyde (24). A solution of allyl bromide (0.24 mL, 2.8 mmol) and thiourea (210 mg, 2.76 mmol) in absolute ethanol (20 mL) was refluxed for 1 h. After NaOH (220 mg, 5.50 mmol) was added, the reaction mixture was refluxed for another 1 h and cooled to 0 °C. After compound **20** (260 mg, 1.84 mmol) was introduced to the system, the mixture was stirred at 0 °C for 1 h, diluted with cold water, and extracted with ether. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (EtOAc/petroleum ether, 1:5) to give **24** (251 mg, 76%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.68 (dd, J=5.4, 1.2 Hz, 2H), 5.29 (dd, J=9.9, 1.2 Hz, 1H), 5.42 (dd, J=17.1, 1.2 Hz, 1H), 5.88–5.95 (m, 1H), 7.29 (d, J=5.4 Hz, 1H), 8.53 (dd, J=5.7, 1.2 Hz, 1H), 8.85 (s, 1H), 10.2 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 33.9, 119.5, 119.8, 128.0, 131.0, 152.2, 153.0, 155.0, 190.3. MS (EI) 179 (M^+). Anal. Calcd for C_9H_9NOS: C, 60.31; H, 5.06; N, 7.81. Found: C, 60.41; H, 5.28; N, 7.88.

4.1.15. 2,3,3a,4,5,9b-Hexahydro-1-methyl-5-thia-1*H*-pyrrolo[3,2,-*h*]isoquinoline (5). A solution of **24** (136 mg, 0.759 mmol) and sarcosine (74 mg, 0.83 mmol) in DMF (15 mL) was heated at 125–130 °C under N_2 for 8 h, cooled to rt, evaporated, diluted with brine, and extracted with $CHCl_3$–IPA (3/1). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (EtOAc/petroleum ether, 2:5) to give **5** (143 mg, 91%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.90–1.94 (m, 1H), 2.14–2.17 (m, 1H), 2.31 (s, 3H), 2.31–2.36 (m, 1H), 2.74 (d, J=9.9 Hz, 2H), 2.92–2.99 (m, 1H), 3.12–3.19 (m, 2H), 7.18 (d, J=5.1 Hz, 1H), 8.25 (s, 1H), 8.26 (d, J=5.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 28.8, 32.0, 37.7, 40.1, 54.5, 63.9, 122.9, 129.0, 147.3, 147.5, 151.7. MS (EI) 206 (M^+). Anal. Calcd for $C_{11}H_{14}N_2S$: C, 64.04; H, 6.84; N, 13.58. Found: C, 63.74; H, 7.17; N, 13.97.

Acknowledgements

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Synthesis of functionalized analogs of pyochelin, a siderophore of *Pseudomonas aeruginosa* and *Burkholderia cepacia*

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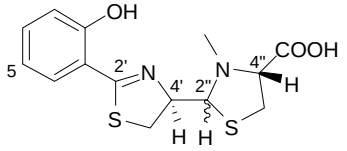
Abstract—Using an improved synthesis of pyochelin, a siderophore common to several pathogenic *Pseudomonas* species, three functionalized pyochelin analogs were efficiently synthesized starting from appropriate 2-hydroxybenzonitriles.

1. Introduction

Iron is a crucial element for aerobic life, unfortunately its bioavailability is limited by the low solubility of iron(III) at physiological pHs. To overcome this problem, microorganisms have developed very efficient iron uptake systems mediated by low molecular weight molecules called siderophores.[1] Under iron limited conditions, microorganisms synthesize and excrete these molecules into the extracellular medium in order to chelate iron(III). In Gram-negative bacteria, the siderophore–iron(III) complex is recognized and transported by a specific outer membrane receptor. The uptake process is driven by the proton motive force of the inner membrane via an inner membrane complex composed of TonB, ExbB and ExbD proteins.[2,3] *Pseudomonas aeruginosa* and *Burkholderia cepacia*, are two opportunistic Gram-negative bacteria, causes of severe and often lethal lung infections especially for cystic fibrosis and aids affected patients.[4] The low permeability of the outer membrane of these bacteria and the increasing antibiotic mediated selective pressure raised emerging multiresistant strains. During infection, these bacteria are in the host in an iron limited environment: higher eucaryotes contain substantial amount of this metal but tightly associated with transport and storage proteins and not freely available for pathogens. Consequently, the level of free iron in biological fluids is usually estimated to be only 10^{-18} M and *P. aeruginosa* and *B. cepacia* use siderophores to compete for iron with the host.

One way to increase the efficiency of antibiotics targeting these bacteria is the Trojan horse strategy where antibiotics are coupled to siderophores and transported across the bacterial membranes via the iron uptake pathways.[5] Such an approach has been already developed giving promising results with the pyoverdine mediated iron uptake system.[6] A disavantage of the pyoverdine iron uptake pathway is that each *P. aeruginosa* strain produces its own pyoverdine along with a corresponding specific transporter.[7] Very few crossfeeding have been observed between these different pyoverdines and their corresponding transporters. For the pyochelin **1** pathway, this siderophore is produced by all *P. aeruginosa* and *B. cepacia* strains.[8] Therefore, pyochelin is a more interesting candidate for such a prodrug strategy and the bactericidial activity of pyochelin–antibiotic conjugate should be more extended compared with pyoverdine based prodrugs (Fig. 1).



Pyochelin **1**

Figure 1. Structure of pyochelin **1**.

In view of its use as a versatile antibiotic vector, pyochelin **1** was functionalized in order to be further connected to the selected antibiotics. Taking into account the distance

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between the heteroatoms involved in iron chelation and the easiness of synthetic access, the fact that bulky C5-substituted analogs of pyochelin were shown to transport iron at reasonable rates,[9] position 5 on the aromatic ring was selected in a first approach to host an amine function. The synthesis of such pyochelin analogs was thus planned using the improved protocol adapted from a total synthesis of pyochelin **1** previously published.[10] According to this procedure, pyochelin analogs **2**, **3** and **4** were thus synthesized starting, respectively, from amino substituted 2-hydroxybenzonitriles **5**, **6** and **7** (Fig. 2).

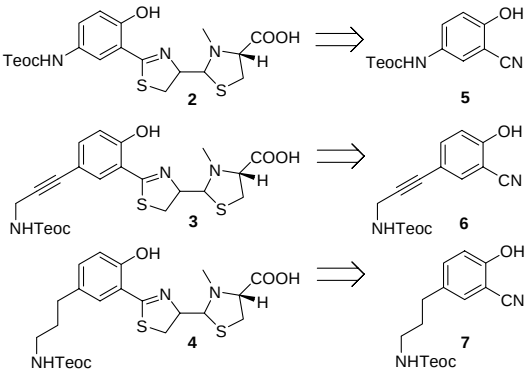
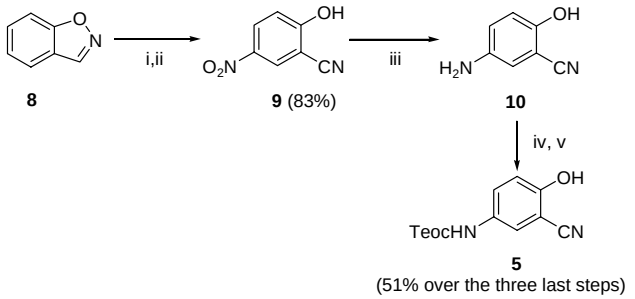


Figure 2. Retrosynthetic routes to functionalized pyochelins **2**, **3** and **4**.

In analog **2** the functionality is directly grafted on pyochelin whereas analogs **3** and **4** offer some alternative in terms of distance and flexibility towards the siderophore. All along the synthesis, the amine was protected with a trimethylsilylethoxycarbonyl (Teoc) group,[11] in order to facilitate purifications and to avoid side reactions. This protecting group was chosen for its good stability during the synthetic process and for the easiness and mildness of the deprotection conditions. In this paper, we describe the synthesis of functionalized 2-hydroxybenzonitriles **5**, **6** and **7** and their efficient conversions into the three unprecedented pyochelin analogs **2**, **3** and **4**.

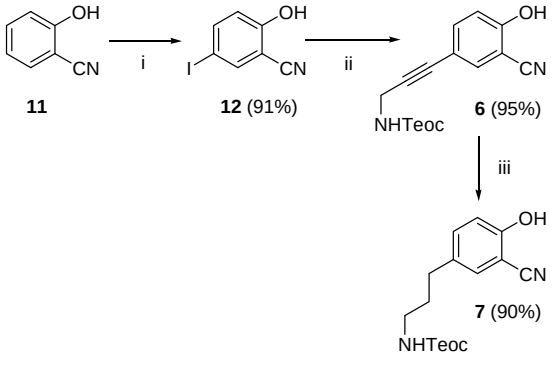
2. Results and discussion

The 2-hydroxybenzonitrile derivative **5** was prepared starting from 1,2-benzisoxazole **8**. The regioselective nitration of **8** with a sulfonitric mixture,[12] and the subsequent hydrolysis in basic conditions of the oxazole moiety led to the expected 5-nitro-2-benzonitrile **9** isolated in 83% overall yield.[13] The nitro function was then reduced into an amine. Using $TiCl_3$ in MeOH the expected amine **10** was isolated in an average yield after a tedious purification protocol.[14] A quite quantitative yield was obtained by catalytic hydrogenation using palladium on charcoal: the resulting amine **10** was quite unstable and had either to be stored at $-20\,^{\circ}C$ in the dark and under argon or immediately used as such for the next step. Since, the phenol function of compound **10** appeared to be more reactive than the amine function, amine **10** was treated with more than a two fold excess of *p*-nitrophenyl-trimethylsilylethyl-carbonate[15] and yielded a Teoc bisprotected compound. Further treatment of the crude mixture with sodium carbonate in refluxing wet acetone induced the selective deprotection of phenol and gave carbamate **5** isolated in an overall 51% yield over the three last steps (Scheme 1).



Scheme 1. Synthesis of functionalized 2-hydroxybenzonitrile **5**. (i) HNO_3, H_2SO_4, 0 °C. (ii) NaOH, H_2O/EtOH, 20 °C. (iii) H_2, Pd/C 10%, EtOH, 20 °C. (iv) *p*-$NO_2(C_6H_4)OCOCH_2CH_2Si(CH_3)_3$, pyridine, DMAP, CH_2Cl_2 reflux. (v) Na_2CO_3, H_2O/acetone reflux.

Cyanophenols **6** and **7** were both prepared starting from commercially available 2-hydroxybenzonitrile **11**. In a first step, compound **11** was converted in excellent yield into the iodinated derivative **12** using *N*-iodosuccinimide in presence of HBF_4 at low temperature.[16] Iodo compound **12** was then coupled to Teoc protected propargylamine **13**[17] via a Sonogashira coupling reaction, using a catalytic amount of $Pd(PPh_3)_4$, copper(I)iodide and DIPEA in DMF.[18] Thus, the expected substituted 2-hydroxybenzonitrile **6** was isolated in excellent yield and catalytically reduced in compound **7** with hydrogen over palladium adsorbed on charcoal. In this step, an extended hydrogenation cause the reduction of both the alkyne triple bond and the nitrile group. However, when the course of the reaction was carefully checked, the expected carbamate **7** was isolated usually in 90% yield (Scheme 2).



Scheme 2. Synthesis of functionalized 2-hydroxybenzonitriles **6** and **7**. (i) NIS, $HBF_4 \cdot Et_2O$, CH_3CN, $-10\,^{\circ}C$. (ii) **13**, $Pd(PPh_3)_4$, CuI, DIPEA, DMF, 20 °C. (iii) H_2, Pd/C 10%, EtOH, 20 °C.

Having in hand the different 2-hydroxybenzonitriles, the synthesis of the pyochelin analogs was then investigated. In natural pyochelin, the absolute configurations are $4'R$ and $4''R$ while configuration at C2″ is wobble and C2″:can readily be epimerized. During the synthesis of pyochelin, partial racemization occurs at C4′ while the absolute configuration at C4″ remains unaffected thus affording a mixture of pyochelin **a** ($4'R$,$2''R$,$4''R$), **b** ($4'R$,$2''S$,$4''R$), and

neopyochelin **c** (4′*S*,2″*R*,4″*R*) and **d** (4′*S*,2″*S*,4″*R*) (Fig. 3).[19,10a,d]

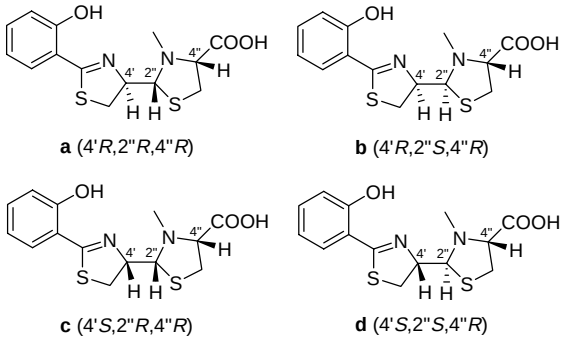
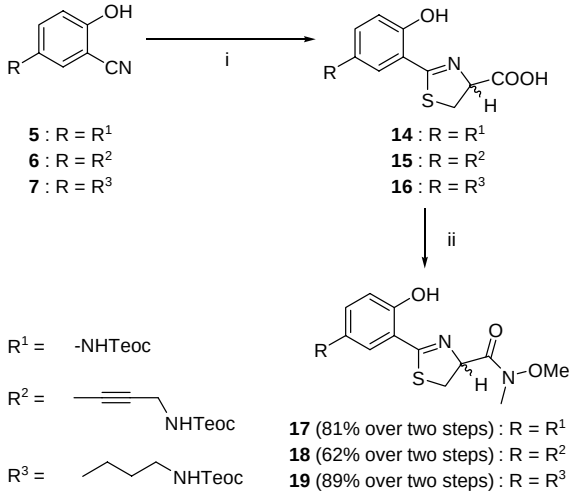


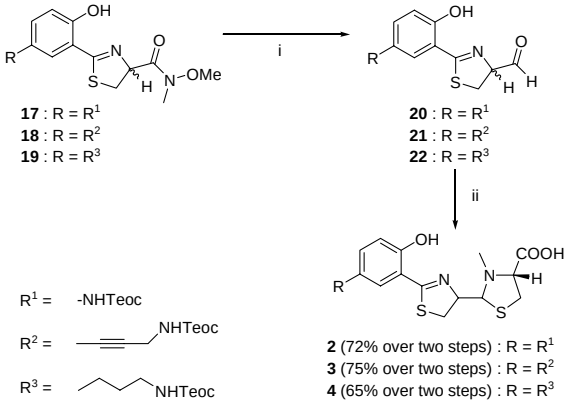
Figure 3. The four diastereoisomers of synthetic pyochelin.

On the other hand, pyochelin and neopyochelin were tested in iron uptake experiments and proved to transport iron with almost the same rate.[9] Our data indicate clearly that the configuration at C4′ is not determining in the recognition by the receptor FptA and in the iron transport process. We thus chose to use the inexpensive (*R*)-cysteine, as starting material for the condensation with the functionalized 2-hydroxybenzonitriles. The three hydroxybenzonitriles **5**, **6** and **7** were converted into the thiazolines **14**, **15** and **16** when treated with (*R*)-cysteine in a refluxing mixture of MeOH and phosphate buffer (0.1 M, pH 6.4). Thiazolines **14**, **15** and **16** were used without further purification to synthesize the corresponding Weinreb amides **17**, **18** and **19**. For this purpose, we modified the procedure we described previously by reacting **14**, **15** and **16** with *N*,*O*-dimethylhydroxylamine and *N*,*N*-dimethylaminopropyl-ethylcarbodiimide hydrochloride (EDCI). Under these conditions, hydroxamic esters **17**, **18** and **19** were easily isolated in good to excellent yield after two steps using a very simple work-up. (Scheme 3).



Scheme 3. Conversion of 2-hydroxybenzonitriles **5**, **6** and **7** into the hydroxamic esters **17**, **18** and **19**. (i) (*R*)-cysteine, phosphate buffer 0.1 M, pH 6.4, MeOH, 60 °C. (ii) $CH_3NHOCH_3 \cdot HCl$, DIPEA, EDCI, CH_2Cl_2, 0–20 °C.

The Weinreb amides **17**, **18** and **19** were then reduced to the corresponding aldehydes **20**, **21** and **22** using $LiAlH_4$.[20] The resulting aldehydes were very sensitive and thus were used straightforward without further purification. Condensation with *N*-methylcysteine,[21] in presence of potassium acetate in hydroethanolic medium furnished the expected functionalized pyochelins **2**, **3** and **4** in 65–75% yield over two steps (Scheme 4).



Scheme 4. Conversion of the hydroxamic esters **17**, **18** and **19** into the pyochelin analogs **2**, **3** and **4**. (i) $LiAlH_4$, THF, −40 to −10 °C. (ii) (*R*)-*N*-Methylcysteine·HCl, AcOK, $EtOH/H_2O$, 20 °C.

The ratios between the four stereoisomers **a**, **b**, **c** and **d** of each analog were the following: **2** (5/10/60/25), **3** (15/15/45/25) and **4** (20/10/50/20). These diastereoisomeric ratios were determined using ^1H NMR and comparing integration of the characteristic *N*-methyl signals. In addition, using COSY and ^1H–^{13}C correlation it was then possible to assign the chemical shifts of each the four diastereoisomers. The relative configurations of the stereocenters were unambiguously assigned by NOESY experiments. When proton H2″ was saturated, a marked Overhauser effect with H4″ proton was observed for **a** (4′*R*,2″*R*,4″*R*) and **c** (4′*S*,2″*R*,4″*R*) isomers whereas no nuclear Overhauser effect was observed for **b** (4′*R*,2″*S*,4″*R*) and **d** (4′*S*,2″*S*,4″*R*).

3. Conclusion

In summary, we report in this article very efficient synthetic ways to three unprecedented functionalized pyochelins: analog **2** was obtained in nine steps (30% overall yield) starting from the commercially available 1,2-benzisoxazole whereas analogs **3** and **4** were prepared starting from 2-hydroxybenzonitrile in six steps (40% overall yield) and seven steps (45% overall yield), respectively. These analogs will be used to build Trojan horse type antibiotic conjugates, which will be tested on different pathogenic clinical strains of *Pseudomonas aeruginosa* and *Burkholderia cepacia*.

4. Experimental

4.1. General procedures

All the reactions were carried out in glassware under inert argon atmosphere. Solvents used were of analytical grade

purity. DMF was distilled prior to use and was stored over activated 4 Å molecular sieves. Pyridine and *N*,*N*-diisopropylethylamine (DIPEA) were distilled and stored over KOH. Reactions were monitored by thin-layer chromatography (TLC) using Merck precoated silica gel $60F^{254}$ (0.25 mm). Column chromatographies were performed using Merck kieselgel 60 (63–200 μm). Melting points were determined with a Stuart Scientific Bibby SMP3 apparatus and were uncorrected. IR spectra were scanned neat using a Perkin Elmer Spectrum One spectrophotometer. NMR spectra were recorded either on a Bruker Avance 300 (300 MHz for ^{1}H and 75 MHz for ^{13}C), a Bruker Avance 400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) or a Bruker Avance 500 (500 MHz for ^{1}H and 125 MHz for ^{13}C). Elemental analyses were performed in the Service d'Analyses de l'Institut de Chimie at the Université Louis Pasteur of Strasbourg. Mass spectra were recorded in the Service de Spectrométrie de Masse de l'Institut de Chimie at the Université Louis Pasteur of Strasbourg and were measured after calibration in ES-TOF experiments performed on a Bruker Daltonic MicroTOF mass spectrometer.

4.2. Protocols, analytical and spectral data

4.2.1. (3-Cyano-4-hydroxy-phenyl)-carbamic acid 2-trimethylsilyl-ethyl ester (5). To a solution of nitro compound **9**[11,12] (500 mg, 3.05 mmol) in EtOH (100 mL) was added Pd/C 10% (158 mg, 0.15 mmol). The suspension was degassed under reduced pressure and then stirred under a hydrogen atmosphere. When all the starting material had been consumed, the mixture was degassed with argon before being filtered over Celite 545. The filtrate was evaporated under reduced pressure and the dark solid residue consisting predominantly of amine **10** was used without further purification for the next synthetic step. The crude amine **10** was dissolved in pyridine (7 mL) then *p*-nitrophenyl-trimethylsilylethylcarbonate (2.39 g, 8.44 mmol) and DMAP (233 mg, 1.91 mmol) were added. This solution was kept at 50 °C during 48 h before being evaporated under reduced pressure. The crude oil was dissolved in a mixture of acetone (20 mL) and water (20 mL) and Na_2CO_3 (2.00 g, 18.87 mmol) was added. This suspension was refluxed (60 °C) during 24 h before being cooled down to room temperature. The mixture was diluted with water (30 mL) and extracted with Et_2O (3×20 mL). The collected organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The yellow deliquescent crude mixture was chromatographed on a silica gel column (30 g of SiO_2, CH_2Cl_2/MeOH: 95:5) leading to the expected substituted carbamate **5** (432 mg, 1.56 mmol, overall yield starting from nitro compound **9**: 51%) isolated as a pale yellow solid. Mp 133–136 °C; IR (neat) 3351, 3216, 2958, 2901, 2245, 1765, 1703, 1605, 1548, 1506, 1427, 1365, 1251, 1227, 1205, 1169, 1115, 1060, 1041, 975, 931, 885, 825, 766, 730, 697. ^{1}H NMR $CDCl_3$, 300 MHz) δ 0.09 (s, 9H), 1.05 (m, 2H), 4.27 (m, 2H), 6.53 (br s, 1H), 6.91 (d, J=8.8 Hz, 1H), 7.41 (dd, J=2.5, 8.8 Hz, 1H), 7.56 (d, J=2.5 Hz, 1H); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ 0.0 (3C), 19.7, 64.9, 101.9, 118.5, 118.9, 124.0, 127.5, 134.6, 156.2, 157.5. ESI-TOF *m*/*z* 579 ($2M+Na^+$), 857 ($3M+Na^+$). Anal. Calcd for $C_{13}H_{18}N_2O_3Si$: C, 56.09; H, 6.52; N, 10.06. Found C, 55.83; H, 6.55; N, 9.79.

4.2.2. 2-Hydroxy-5-iodobenzonitrile (12). To a solution of 2-hydroxybenzonitrile **11** (1.00 g, 8.30 mmol) in dry acetonitrile (7.5 mL), HBF_4 (1.8 mL of 54% solution in Et_2O) was added dropwise at −20 °C. *N*-Iodosuccinimide (2.00 g, 9.13 mmol) was then added portionwise as such a rate that the reaction temperature does not exceed −10 °C. The mixture was then warmed up to room temperature, vigorously stirred during 4 h, treated with an aqueous solution of $NaHSO_3$ 38% (20 mL) and extracted with *t*-butylmethylether (2×30 mL). The collected organic layers were then washed with brine (30 mL) and dried over Na_2SO_4. After filtration, the orange-brown solid was adsorbed on silica before being filtered on a silica gel column (30 g of SiO_2, CH_2Cl_2) leading to compound **12** (1.85 g, 7.55 mmol, yield: 91%) isolated as a white powder. Mp 169–172 °C; IR (neat) 3165, 2245, 1589, 1489, 1400, 1354, 1294, 1263, 1231, 1170, 1118, 1072, 950, 892, 873, 852, 815, 755, 730, 682. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ 6.92 (d, J=9.0 Hz, 1H), 7.79 (dd, J=2.0, 9.0 Hz, 1H), 7.90 (d, J=2.0 Hz, 1H), 10.08 (br s, 1H); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ 80.4, 103.2, 115.5, 119.3, 141.8, 143.8, 160.4. SM-EI *m*/*z* 245. Anal. Calcd for C_7H_4INO: C, 34.31; H, 1.65; N, 5.72. Found C, 34.35; H, 1.70; N, 5.68.

4.2.3. Prop-2-ynyl-carbamic acid 2-trimethylsilylethyl-ester (13). Solid *p*-nitrophenyl-trimethylsilylethylcarbonate[15] (1150 mg, 4.07 mmol) was added to a solution of propargylamine (515 μL, 7.51 mmol), DIPEA (800 μL, 4.59 mmol), DMAP (10 mg) in CH_2Cl_2 (14 mL), and the solution was refluxed for 48 h. The reaction mixture was then cooled to room temperature, diluted with CH_2Cl_2 and washed twice with saturated aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4, solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (hexane/Et_2O: 9:1 then hexane/Et_2O: 8:2), to give carbamic ester **13** as a colorless oil (740 mg, 3.71 mmol, yield: 81%);[17] IR (neat) 3312, 2954, 1697, 1517, 1424, 1349, 1324, 1248, 1178, 1139, 1043, 973, 946, 857, 834, 767, 694. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.00 (s, 9H), 0.96 (t, J=8.6 Hz, 2H), 2.21 (t, J=2.3 Hz, 1H), 3.94 (dd, J=2.3, 5.6 Hz, 2H), 4.16 (t, J=8.6 Hz, 2H), 4.86 (br s, 1H); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ −1.5 (3C), 17.7, 30.6, 53.4, 71.3, 79.9, 156.3.

4.2.4. [3-(3-Cyano-4-hydroxy-phenyl)-prop-2-ynyl]-carbamic acid 2-trimethylsilylethyl ester (6). A solution of iodinated compound **12** (707 mg, 2.88 mmol), carbamic ester **13** (748 mg, 3.75 mmol) and DIPEA (2.40 mL, 1780 mg, 13.80 mmol) in freshly distilled DMF (13 mL) was cooled down to 0 °C and degassed under reduced pressure. $Pd(PPh_3)_4$ (172 mg, 0.15 mmol) and CuI (116 mg, 0.61 mmol) were then successively added under argon. The mixture was degassed again at 0 °C and then warmed up at room temperature and stirred 2 h. DMF was then removed by distillation under reduced pressure and the crude mixture was adsorbed on silica before being chromatographed on a silica gel column (40 g of SiO_2, hexane/Et_2O: 2:1 then hexane/Et_2O: 1:1). The acetylenic compound **6** (869 mg, 2.74 mmol, yield: 95%) was isolated as a yellow foamy solid. Mp 80–82 °C; IR (neat) 3400, 3130, 2954, 2230, 1668, 1605, 1537, 1508, 1412, 1376, 1355, 1305, 1261, 1250, 1217, 1176, 1142, 1111, 1069, 1043, 1006, 942, 890, 855, 836, 769, 726, 693, 662. ^{1}H NMR ($CDCl_3$, 300 MHz) δ

0.06 (s, 9H), 1.02 (t, $J=8.4$ Hz, 2H), 4.16 (d, $J=5.9$ Hz, 2H), 4.24 (t, $J=8.4$ Hz, 2H), 5.01 (br s, 1H), 6.93 (d, $J=8.7$ Hz, 1H), 7.27 (d, $J=8.7$ Hz, 1H), 7.50 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −1.5 (3C), 17.7, 31.4, 64.3, 84.9, 91.1, 100.0, 114.6, 115.9, 116.8, 136.2, 137.6, 157.2, 159.6; ESI-TOF *m/z* 655 ($2M+Na^+$), 971 ($3M+Na^+$). Anal. Calcd for $C_{16}H_{20}N_2O_3Si$: C, 60.73; H, 6.37; N, 8.85. Found C, 60.87; H, 6.25; N, 8.34.

4.2.5. [3-(3-Cyano-4-hydroxy-phenyl)-propyl]-carbamic acid 2-trimethylsilylethyl ester (7). To a solution of acetylenic carbamate **6** (700 mg, 2.22 mmol) in EtOH (40 mL) was added Pd/C 10% (260 mg, 0.22 mmol). The suspension was degassed under reduced pressure and then stirred under hydrogen atmosphere. When all the starting material had been consumed, the mixture was degassed with argon before being filtered on Celite. The filtrate was evaporated under reduced pressure and the oily residue was chromatographed on a silica gel column (30 g of SiO_2, hexane/Et_2O: 1:1) leading to the expected substituted 2-hydroxybenzonitrile **7** (640 mg, 2.00 mmol, yield: 90%) isolated as a thick colorless oil, which slowly crystallized upon storage in the refrigerator. Mp 89–91 °C; IR (neat) 3389, 3135, 2956, 2928, 2910, 2861, 2236, 1668, 1611, 1598, 1532, 1515, 1461, 1428, 1374, 1307, 1275, 1260, 1251, 1210, 1174, 1143, 1115, 1064, 1020, 980, 951, 934, 887, 837, 825, 782, 762, 694, 677. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.06 (s, 9H), 0.98 (t, $J=8.6$ Hz, 2H), 1.78 (p, $J=7.5$ Hz, 2H), 2.56 (t, $J=7.5$ Hz, 2H), 3.17 (q, $J=6.6$ Hz, 2H), 4.16 (t, $J=8.6$ Hz, 2H), 4.80 (br s, 1H), 6.90 (d, $J=8.3$ Hz, 1H), 7.21 (d, $J=8.3$ Hz, 1H), 7.26 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −1.5 (3C), 17.7, 31.3, 31.5, 40.3, 63.6, 99.3, 116.5, 117.0, 132.2, 133.0, 134.1, 157.6, 158.0. ESI-TOF *m/z* 321 ($M+H^+$), 343 ($M+Na^+$), 359 ($M+K^+$), 663 ($2M+Na^+$). Anal. Calcd for $C_{16}H_{24}N_2O_3Si$: C, 59.97; H, 7.55; N, 8.74. Found C, 59.68; H, 7.70; N, 8.24.

4.3. General procedure for Weinreb amides (17), (18) and (19)

Substituted 2-hydroxybenzonitriles **5**, **6** or **7** (1.00 equiv) and (*R*)-cysteine (2.00 equiv) were dissolved in methanol (8 mL/mmol of substituted 2-hydroxybenzonitrile). The suspension was warmed up to 50 °C then 0.1 M phosphate buffer pH 6.4 (8 mL/mmol of substituted 2-hydroxybenzonitrile) was added. The mixture was vigorously stirred at 60 °C during 36 h. The resulting yellow solution was cooled down to room temperature before being diluted with water and acidified to pH 2.0 by addition of solid citric acid. After extraction with CH_2Cl_2, the collected organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude thiazolines **14**, **15** and **16** isolated as yellow powders were used without further purification for the next step. Thiazoline was dissolved in CH_2Cl_2 (25 mL/mmol of thiazoline), the solution was cooled down to 0 °C. EDCI (1.10 equiv) was then added, immediately followed by a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (1.20 equiv) and DIPEA (1.20 equiv) in CH_2Cl_2 (25 mL/mmol of *N*,*O*-dimethylhydroxylamine hydrochloride). The mixture was allowed to warm up to room temperature and was stirred during 2 h. The mixture was directly adsorbed on silica before being chromatographed on a silica gel column eluted with hexane/Et_2O: 1:1, leading to the expected Weinreb amides **17**, **18** or **19**.

4.3.1. {4-Hydroxy-3-[4-(methoxy-methyl-carbamoyl)-4,5-dihydro-thiazol-2-yl]-phenyl}-carbamic acid 2-trimethylsilyl-ethylester (17). Isolated as a white powder (overall yield over two steps from **5**: 81%). Mp 119–122 °C; IR (neat) 3300, 2953, 1716, 1645, 1561, 1486, 1459, 1433, 1394, 1344, 1293, 1230, 1193, 1179, 1062, 994, 964, 947, 860, 834, 810, 767, 693, 664. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.00 (s, 9H), 0.98 (m, 2H), 3.24 (s, 3H), 3.42 (dd, $J=9.3$, 10.9 Hz, 1H), 3.70 (br t, $J=10.9$ Hz, 1H), 3.77 (s, 3H), 4.18 (m, 2H), 5.62 (br t, $J=9.3$ Hz, 1H), 6.65 (br s, 1H), 6.85 (d, $J=8.9$ Hz, 1H), 7.26 (br d, $J=8.9$ Hz, 1H), 7.44 (br s, 1H), 12.5 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.0 (3C), 19.2, 34.1, 34.5, 63.3, 65.0, 76.2, 117.2, 118.9, 122.6, 126.7, 131.0, 155.6, 156.7, 171.3, 175.4. ESI-TOF *m/z* 426 ($M+H^+$), 448 ($M+Na^+$), 851 ($2M+H^+$), 873 ($2M+Na^+$). Anal. Calcd for $C_{18}H_{27}N_3O_5SSi$: C, 50.80; H, 6.39; N, 9.87. Found C, 50.86; H, 6.13; N, 9.83.

4.3.2. (3-{4-Hydroxy-3-[4-(methoxy-methyl-carbamoyl)-4,5-dihydro-thiazol-2-yl]-phenyl}-prop-2-ynyl)-carbamic acid 2-trimethylsilylethylester (18). Isolated as a yellow solid (overall yield over two steps from **6**: 62%). Mp 160–162 °C; IR (neat) 3316, 2952, 1711, 1668, 1619, 1561, 1520, 1486, 1425, 1391, 1355, 1323, 1292, 1248, 1201, 1178, 1130, 1044, 1002, 970, 943, 891, 858, 832, 768, 735, 695, 662. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.05 (s, 9H), 1.01 (t, $J=8.3$ Hz, 2H), 3.30 (s, 3H), 3.50 (dd, $J=9.4$, 10.5 Hz, 2H), 3.79 (t, $J=10.5$ Hz, 2H), 4.09 (d, $J=5.9$ Hz, 2H), 4.12 (t, $J=8.3$ Hz, 2H), 4.78 (br s, 1H), 5.69 (t, $J=9.4$ Hz, 1H), 6.92 (d, $J=8.5$ Hz, 1H), 7.39 (dd, $J=2.0$, 8.5 Hz, 1H), 7.50 (d, $J=2.0$ Hz, 1H), 12.5 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −1.5 (3C), 17.7, 31.5, 32.6, 33.0, 61.8, 63.5, 74.6, 82.2, 84.0, 113.2, 116.0, 117.4, 134.2, 136.5, 156.3, 159.2, 169.5, 173.6; ESI-TOF *m/z* 464 ($M+H^+$), 927 ($2M+H^+$). Anal. Calcd for $C_{21}H_{29}N_3O_5SSi$: C, 54.40; H, 6.30; N, 9.06. Found C, 54.76; H, 6.46; N, 8.82.

4.3.3. (3-{4-Hydroxy-3-[4-(methoxy-methyl-carbamoyl)-4,5-dihydro-thiazol-2-yl]-phenyl}-propyl)-carbamic acid 2-trimethylsilanylethylester (19). Isolated as a white solid (overall yield over two steps from **7**: 89%). Mp 160–162 °C; IR (neat) 3347, 2926, 2854, 1715, 1672, 1628, 1597, 1567, 1521, 1491, 1388, 1248, 1176, 1138, 1043, 1007, 988, 966, 858, 834, 767, 735, 694. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.00 (s, 9H), 0.94 (t, $J=8.6$ Hz, 2H), 1.74 (p, $J=7.5$ Hz, 2H), 2.54 (t, $J=7.5$ Hz, 2H), 3.15 (m, 2H), 3.25 (s, 3H), 3.43 (dd, $J=9.5$, 11.0 Hz, 2H), 3.73 (t, $J=9.5$ Hz, 1H), 3.79 (s, 3H), 4.41 (t, $J=8.6$ Hz, 2H), 4.71 (br s, 1H), 5.64 (t, $J=8.9$ Hz, 1H), 6.86 (d, $J=8.2$ Hz, 1H), 7.15 (m, 2H); 12.11 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −1.5 (3C), 17.7, 29.7, 31.9, 32.6, 32.9, 40.4, 61.8, 62.9, 76.6, 115.9, 117.7, 130.1, 131.9, 133.5, 156.8, 157.2, 169.7, 173.9. ESI-TOF *m/z* 468 ($M+H^+$); HRMS calcd for $C_{21}H_{34}N_3O_5SSi$ 468.1983, found 468.1981. Anal. Calcd for $C_{21}H_{34}N_3O_5SSi$: C, 53.93; H, 7.11; N, 8.99. Found C, 53.71; H, 7.25; N, 8.27.

4.4. General procedure for functionalized pyochelin derivatives (2), (3) and (4)

To a solution of Weinreb amide **17**, **18** or **19** in dry THF (16 mL/mmol of Weinreb amide), cooled down to −40 °C, $LiAlH_4$ (1.30 equiv of a 1 M solution in THF) was injected dropwise. The reaction temperature was allowed to rise

to −20 °C in 30 min. The reaction mixture was then hydrolyzed by successive additions of a saturated aqueous solution of NH_4Cl (12 mL/mmol of $LiAlH_4$) then a 1 M aqueous solution of $KHSO_4$ (5 mL/mmol of $LiAlH_4$). The mixture was warmed up to room temperature and vigourously stirring was applied until two phases were formed. After partition and extraction with Et_2O, the organic layers were collected, dried over Na_2SO_4, filtered before being evaporated. The crude aldehyde, very sensitive to oxidation, was used directly for subsequent reaction. It was dissolved into a mixture of ethanol (20 mL/mmol of Weinreb amide) and water (6 mL/mmol of Weinreb amide) and to this solution were successively added, potassium acetate (6.65 equiv) and (*R*)-*N*-methylcysteine hydrochloride (2.12 equiv). The mixture was then gently stirred in the dark during 14 h (overnight) before being diluted with water (30 mL) then washed with hexane (30 ml). The aqueous layer was then acidified to pH 4.0 by addition of solid citric acid before being extracted with CH_2Cl_2. The organic layers were collected, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The expected functionalized pyochelins **2**, **3** and **4** are isolated first as yellow foams then were dissolved in cyclohexane containing a minimun of CH_2Cl_2. After evaporation of the solvent under reduced pressure, the expected pyochelins were isolated as yellow powders.

4.4.1. 2′-[2-Hydroxy-5-(2-trimethylsilyl-ethoxycarbonyl-amino)-phenyl]-3-methyl-2,3,4,5,4′,5′-hexahydro-[2,4′]-bisthiazolyl-4-carboxylic acid (2). Isolated as a pale yellow powder (overall yield over two steps from **17**: 72%), proportions: **2a/2b/2c/2d**: 5/10/60/25. IR (neat) 3301, 2952, 2891, 1698, 1628, 1568, 1544, 1494, 1431, 1394, 1299, 1224, 1191, 1061, 996, 954, 928, 857, 834, 766, 693; HRMS calcd for $C_{20}H_{28}N_3O_5S_2Si$ 482.1245, found 482.1240.

4.4.2. (2c) (4′*S*,2″*R*,4″*R*). ^{1}H NMR (300 MHz, CD_3COCD_3) δ 0.00 (s, 9H, $(CH_3)_3Si$), 1.03 (t, J=8.5 Hz, 2H, CH_2–Si), 2.63 (s, 3H, N–CH_3), 3.31 (dd, J=7.0–11.2 Hz, 1H, H5″), 3.45 (dd, J=7.0–11.2 Hz, 1H, H5″), 3.53 (dd, J=8.4–11.3 Hz, 1H, H5′), 3.63 (dd, J=8.4–11.3 Hz, 1H, H5′), 4.01 (dd, J=5.4–7.0 Hz, 1H, H4″), 4.21 (t, J=8.5 Hz, 2H, CH_2–O), 4.34 (d, J=8.4 Hz, 1H, H2″), 4.83 (q, J=8.4 Hz, 1H, H4′), 6.87 (dd, J=1.4–6.4 Hz, 1H, H3), 7.50 (d, J=1.4 Hz, 1H, H4), 7.77 (s, 1H, H6), 8.49 (br s, 1H, N*H*). ^{13}C NMR (125 MHz, CD_3COCD_3) δ −1.5 ($(CH_3)_3Si$), 18.2 (CH_2–Si), 33.5 (C5″), 34.9 (C5′), 44.8 (N–CH_3), 63.2 (CH_2–O), 73.9 (C4″), 79.4 (C2″), 83.4 (C4′), 116.5 (C1), 117.8 (C3), 120.6 (C6), 125.1 (C4), 131.9 (C5), 154.8 (O*C*ONH), 155.6 (C2), 172.3 (C2′), 172.9 (*C*OOH).

4.4.3. (2d) (4′*S*, 2″*S*, 4″*R*). ^{1}H NMR (300 MHz, CD_3COCD_3) δ 0.00 (s, 9H, $(CH_3)_3Si$), 1.03 (t, J=8.5 Hz, 2H, CH_2–Si), 2.70 (s, 3H, N–CH_3), 3.06 (dd, J=2.0–10.4 Hz, 1H, H5″), 3.18–3.27 (m, 1H, H5″), 3.38–3.50 (m, 2H, H5′), 4.21 (t, J=8.5 Hz, 2H, CH_2–O), 4.24 (dd, J=2.0–6.6 Hz, 1H, H4″), 5.05 (d, J=4.7 Hz, 1H, H2″), 5.28 (td, J=4.7–9.0 Hz, 1H, H4′), 6.87 (dd, J=1.4–6.4 Hz, 1H, H3), 7.50 (d, J=1.4 Hz, 1H, H4), 7.77 (s, 1H, H6), 8.49 (br s, 1H, N*H*). ^{13}C NMR (125 MHz, CD_3COCD_3) δ −1.5 ($(CH_3)_3Si$), 18.2 (CH_2–Si), 32.2 (C5′), 32.3 (C5″), 36.2 (N–CH_3), 63.2 (CH_2–O), 70.5 (C4″), 73.6 (C2″), 79.3 (C4′), 116.5 (C1), 117.8 (C3), 120.6 (C6), 125.1 (C4), 131.9 (C5), 154.8 (O*C*ONH), 155.6 (C2), 172.3 (C2′), 172.9 (*C*OOH).

4.4.4. (2a) (4′*R*,2″*R*,4″*R*). ^{1}H NMR (300 MHz, CD_3COCD_3) δ 0.00 (s, 9H, $(CH_3)_3Si$), 1.03 (t, J=8.5 Hz, 2H, CH_2–Si), 2.64 (s, 3H, N–CH_3), 3.18–3.27 (m, 2H, H5″), 3.49 (d, J=9.0 Hz, 2H, H5′), 3.73 (dd, J=7.0–7.9 Hz, 1H, H4″), 4.21 (t, J=8.5 Hz, 2H, CH_2–O), 4.61 (d, J=5.4 Hz, 1H, H2″), 5.21 (td, J=5.4–9.0 Hz, 1H, H4′), 6.87 (dd, J=1.4–6.4 Hz, 1H, H3), 7.50 (d, J=1.4 Hz, 1H, H4), 7.77 (s, 1H, H6), 8.49 (br s, 1H, N*H*). ^{13}C NMR (125 MHz, CD_3COCD_3) δ −1.5 ($(CH_3)_3Si$), 18.2 (CH_2–Si), 32.8 (C5′), 33.1 (C5″), 41.3 (N–CH_3), 63.2 (CH_2–O), 73.3 (C4″), 77.1 (C2″), 80.3 (C4′), 116.5 (C1), 117.8 (C3), 120.6 (C6), 125.1 (C4), 131.9 (C5), 154.8 (O*C*ONH), 155.6 (C2), 172.3 (C2′), 172.9 (*C*OOH).

4.4.5. (2b) (4′*R*,2″*S*,4″*R*). ^{1}H NMR (300 MHz, CD_3COCD_3) δ 0.00 (s, 9H, $(CH_3)_3Si$), 1.03 (t, J=8.5 Hz, 2H, CH_2–Si), 2.49 (s, 3H, N–CH_3), 3.18–3.27 (m, 2H, H5″), 3.43–3.49 (m, 1H, H5′), 3.63–3.68 (m, 1H, H5′), 4.18–4.28 (m, 1H, H4″), 4.21 (t, J=8.5 Hz, 2H, CH_2–O), 4.55 (d, J=8.2 Hz, 1H, H2″), 5.01 (q, J=8.2 Hz, 1H, H4′), 6.87 (dd, J=1.4–6.4 Hz, 1H, H3), 7.50 (d, J=1.4 Hz, 1H, H4), 7.77 (s, 1H, H6), 8.49 (br s, 1H, N*H*). ^{13}C NMR (125 MHz, CD_3COCD_3) δ −1.5 ($(CH_3)_3Si$), 18.2 (CH_2–Si), 32.1 (C5″), 35.1 (C5′), 37.8 (N–CH_3), 63.2 (CH_2–O), 71.0 (C4″), 77.9 (C2″), 81.2 (C4′), 116.5 (C1), 117.8 (C3), 120.6 (C6), 125.1 (C4), 131.9 (C5), 154.8 (O*C*ONH), 155.6 (C2), 172.3 (C2′), 172.9 (*C*OOH).

4.4.6. 2′-{2-Hydroxy-5-[3-(2-trimethylsilyl-ethoxy-carbonylamino)-prop-1-ynyl]-phenyl}-3-methyl-2,3,4,5,4′,5′-hexahydro-[2,4′]bisthiazolyl-4-carboxylic acid (3). Isolated as a pale yellow powder (overall yield over two steps from **18**: 75%), proportions: **3a/3b/3c/3d**: 15/15/45/25. IR (neat) 3320, 2953, 1709, 1619, 1569, 1525, 1487, 1395, 1324, 1247, 1196, 1128, 1041, 939, 857, 833, 775, 694; HRMS calcd for $C_{23}H_{30}N_3O_5S_2Si$ 520.1402, found 520.1408.

4.4.7. (3c) (4′*S*,2″*R*,4″*R*). ^{1}H NMR (300 MHz, CD_3COCD_3) δ 0.00 (s, 9H, $(CH_3)_3Si$), 0.86 (t, J=8.1 Hz, 2H, CH_2–Si), 2.63 (s, 3H, N–CH_3), 3.35 (dd, J=6.9–11.0 Hz, 1H, H5″), 3.44 (dd, J=5.2–11.0 Hz, 1H, H5″), 3.55 (dd, J=8.4–11.5 Hz, 1H, H5′), 3.66 (dd, J=8.4–11.5 Hz, 1H, H5′), 4.01 (dd, J=5.2–6.9 Hz, 1H, H4″), 4.12 (d, J=5.4 Hz, 2H, CH_2–N), 4.14 (t, J=8.1 Hz, 2H, CH_2–O), 4.34 (d, J=8.4 Hz, 1H, H2″), 4.84 (q, J=8.4 Hz, 1H, H4′), 6.59 (br s, 1H, N*H*), 6.91–6.95 (m, 1H, H3), 7.40–7.44 (m, 2H, H6+H4). ^{13}C NMR (125 MHz, CD_3COCD_3) δ −1.5 ($(CH_3)_3Si$), 18.2 (CH_2–Si), 31.5 (CH_2–N), 33.5 (C5″), 35.0 (C5′), 44.7 (N–CH_3), 63.0 (CH_2–O), 73.7 (C4″), 79.2 (C2″), 81.5 (C≡*C*–Ar), 83.1 (C4′), 86.2 (*C*≡C–Ar), 114.3 (C5), 116.9 (C1), 118.2 (C3), 134.1 (C6), 136.9 (C4), 157.1 (O*C*ONH), 159.9 (C2), 171.6 (C2′), 174.9 (COOH).

4.4.8. (3d) (4′*S*,2″*S*,4″*R*). ^{1}H NMR (300 MHz, CD_3COCD_3) δ 0.00 (s, 9H, $(CH_3)_3Si$), 0.86 (t, J=8.1 Hz, 2H, CH_2–Si), 2.70 (s, 3H, N–CH_3), 3.05 (dd, J=2.4–10.4 Hz, 1H, H5″), 3.20–3.26 (m, 1H, H5″), 3.42–3.56 (m, 2H, H5′), 4.12 (d, J=5.4 Hz, 2H, CH_2–N), 4.14 (t, J=8.1 Hz, 2H, CH_2–O), 4.24 (dd, J=2.4–6.6 Hz, 1H, H4″), 5.05 (d, J=

4.7 Hz, 1H, H2″), 5.30 (td, J=4.7–9.3 Hz, 1H, H4′), 6.59 (br s, 1H, N*H*), 6.91–6.95 (m, 1H, H3), 7.40–7.44 (m, 2H, H6+H4). ^{13}C NMR (125 MHz, CD_3COCD_3) δ −1.5 ((CH_3)$_3$Si), 18.2 (CH_2–Si), 31.5 (CH_2–N), 32.2 (C5′), 32.3 (C5″), 36.0 (N–CH_3), 63.0 (CH_2–O), 70.3 (C4″), 73.3 (C2″), 79.0 (C4′), 81.5 (C≡*C*–Ar), 86.2 (*C*≡C–Ar), 114.3 (C5), 116.9 (C1), 118.2 (C3), 134.1 (C6), 136.9 (C4), 157.1 (O*C*ONH), 159.9 (C2), 171.6 (C2′), 174.9 (*C*OOH).

4.4.9. (3a) (4′*R*,2″*R*,4″*R*). ^{1}H NMR (300 MHz, CD_3COCD_3) δ 0.00 (s, 9H, (CH_3)$_3$Si), 0.86 (t, J=8.1 Hz, 2H, CH_2–Si), 2.63 (s, 3H, N–CH_3), 3.20–3.24 (m, 2H, H5″), 3.52 (d, J=9.3 Hz, 2H, H5′), 3.71 (dd, J=6.8–8.0 Hz, 1H, H4″), 4.12 (d, J=5.4 Hz, 2H, CH_2–N), 4.14 (t, J=8.1 Hz, 2H, CH_2–O), 4.61 (d, J=5.5 Hz, 1H, H2″), 5.21 (td, J=5.5–9.3 Hz, 1H, H4′), 6.59 (br s, 1H, N*H*), 6.91–6.95 (m, 1H, H3), 7.40–7.44 (m, 2H, H6+H4). ^{13}C NMR (125 MHz, CD_3COCD_3) δ −1.5 ((CH_3)$_3$Si), 18.2 (CH_2–Si), 31.5 (CH_2–N), 32.8 (C5′), 33.1 (C5″), 41.3 (N–CH_3), 63.0 (CH_2–O), 73.2 (C4″), 76.9 (C2″), 80.1 (C4′), 81.5 (C≡*C*–Ar), 86.2 (*C*≡C–Ar), 114.3 (C5), 116.9 (C1), 118.2 (C3), 134.1 (C6), 136.9 (C4), 157.1 (O*C*ONH), 159.9 (C2), 171.6 (C2′), 174.9 (*C*OOH).

4.4.10. (3b) (4′*R*,2″*S*,4″*R*). ^{1}H NMR (300 MHz, CD_3COCD_3) δ 0.00 (s, 9H, (CH_3)$_3$Si), 0.86 (t, J=8.1 Hz, 2H, CH_2–Si), 2.50 (s, 3H, N–CH_3), 3.20–3.26 (m, 2H, H5″), 3.47–3.52 (m, 1H, H5′), 3.68–3.72 (m, 1H, H5′), 4.12 (d, J=5.4 Hz, 2H, CH_2–N), 4.14 (t, J=8.1 Hz, 2H, CH_2–O), 4.23 (t, J=6.8 Hz, 1H, H4″), 4.55 (d, J=8.1 Hz, 1H, H2″), 5.02 (q, J=8.1 Hz, 1H, H4′), 6.59 (br s, 1H, N*H*), 6.91–6.95 (m, 1H, H3), 7.40–7.44 (m, 2H, H6+H4). ^{13}C NMR (125 MHz, CD_3COCD_3) δ −1.5 ((CH_3)$_3$Si), 18.2 (CH_2–Si), 31.5 (CH_2–N), 32.0 (C5″), 35.0 (C5′), 37.7 (N–CH_3), 63.0 (CH_2–O), 70.8 (C4″), 77.7 (C2″), 80.9 (C4′), 81.5 (C≡*C*–Ar), 86.2 (*C*≡C–Ar), 114.3 (C5), 116.9 (C1), 118.2 (C3), 134.1 (C6), 136.9 (C4), 157.1 (O*C*ONH), 159.9 (C2), 171.6 (C2′), 174.9 (*C*OOH).

4.4.11. 2′-{2-Hydroxy-5-[3-(2-trimethylsilyl-ethoxy-carbonylamino)-propyl]-phenyl}-3-methyl-2,3,4,5,4′,5′-hexahydro-[2,4′]bisthiazolyl-4-carboxylic acid (4). Isolated as a yellow powder (overall yield over two steps from **19**: 65%), proportions: **4a/4b/4c/4d**: 20/10/50/20. IR (neat) 3326, 2950, 1695, 1626, 1569, 1528, 1492, 1248, 1100, 857, 834, 775, 693; HRMS calcd for $C_{23}H_{36}N_3O_5S_2Si$ 526.1860, found 526.1851.

4.4.12. (4c) (4′*S*,2″*R*,4″*R*). ^{1}H NMR (300 MHz, CD_3COCD_3) δ 0.00 (s, 9H, (CH_3)$_3$Si), 0.96 (t, J=8.2 Hz, 2H, CH_2–Si), 1.79 (p, J=7.2 Hz, 2H, C–CH_2–C), 2.62 (t, J=7.9 Hz, 2H, CH_2–Ar), 2.63 (s, 3H, N–CH_3), 3.11–3.17 (m, 2H, CH_2–N), 3.30 (dd, J=6.8–11.0 Hz, 1H, H5″), 3.44 (dd, J=5.2–11.0 Hz, 1H, H5″), 3.55 (dd, J=8.4–11.4 Hz, 1H, H5′), 3.62 (dd, J=8.4–11.4 Hz, 1H, H5′), 4.01 (dd, J=5.2–6.8 Hz, 1H, H4″), 4.10 (t, J=8.2 Hz, 2H, CH_2–O), 4.33 (d, J=8.4 Hz, 1H, H2″), 4.83 (q, J=8.4 Hz, 1H, H4′), 6.18 (br s, 1H, N*H*), 6.87 (d, J=8.2 Hz, 1H, H3), 7.26 (s, 1H, H6), 7.28 (d, J=2.0 Hz, 1H, H4). ^{13}C NMR (125 MHz, CD_3COCD_3) δ −1.5 ((CH_3)$_3$Si), 18.3 (CH_2–Si), 32.5 (CH_2–Ar), 32.7 (C–CH_2–C), 34.4 (C5″), 34.7 (C5′), 40.7 (CH_2–N), 44.7 (N–CH_3), 62.4 (CH_2–O), 73.8 (C4″), 79.3 (C2″), 83.4 (C4′), 116.6 (C1), 117.6 (C3), 130.6 (C6), 133.3 (C5), 134.2 (C4), 157.0 (O*C*ONH), 158.1 (C2), 172.0 (C2′), 173.1 (*C*OOH).

4.4.13. (4d) (4′*S*,2″*S*,4″*R*). ^{1}H NMR (300 MHz, CD_3COCD_3) δ 0.00 (s, 9H, (CH_3)$_3$Si), 0.96 (t, J=8.2 Hz, 2H, CH_2–Si), 1.79 (p, J=7.2 Hz, 2H, C–CH_2–C), 2.62 (t, J=7.9 Hz, 2H, CH_2–Ar), 2.71 (s, 3H, N–CH_3), 3.06 (dd, J=2.4–9.7 Hz, 1H, H5″), 3.11–3.17 (m, 2H, CH_2–N), 3.18–3.24 (m, 1H, H5″), 3.40 (dd, J=9.1–11.0 Hz, 1H, H5′), 3.46 (dd, J=9.1–11.0 Hz, 1H, H5′), 4.10 (t, J=8.2 Hz, 2H, CH_2–O), 4.25 (dd, J=2.4–6.2 Hz, 1H, H4″), 5.05 (d, J=4.6 Hz, 1H, H2″), 5.27 (td, J=4.6–9.1 Hz, 1H, H4′), 6.18 (br s, 1H, N*H*), 6.87 (d, J=8.2 Hz, 1H, H3), 7.26 (s, 1H, H6), 7.28 (d, J=2.0 Hz, 1H, H4). ^{13}C NMR (125 MHz, CD_3COCD_3) δ −1.5 ((CH_3)$_3$Si), 18.3 (CH_2–Si), 32.1 (C5′), 32.2 (C5″), 32.5 (CH_2–Ar), 32.7 (C–CH_2–C), 36.1 (N–CH_3), 40.7 (CH_2–N), 62.4 (CH_2–O), 70.4 (C4″), 73.6 (C2″), 79.2 (C4′), 116.6 (C1), 117.6 (C3), 130.6 (C6), 133.3 (C5), 134.2 (C4), 157.0 (O*C*ONH), 158.1 (C2), 172.0 (C2′), 173.1 (*C*OOH).

4.4.14. (4a) (4′*R*,2″*R*,4″*R*). ^{1}H NMR (300 MHz, CD_3COCD_3) δ 0.00 (s, 9H, (CH_3)$_3$Si), 0.96 (t, J=8.2 Hz, 2H, CH_2–Si), 1.79 (p, J=7.2 Hz, 2H, C–CH_2–C), 2.62 (t, J=7.9 Hz, 2H, CH_2–Ar), 2.64 (s, 3H, N–CH_3), 3.11–3.17 (m, 2H, CH_2–N), 3.18–3.20 (m, 2H, H5″), 3.48 (d, J=9.1 Hz, 2H, H5′), 3.71 (dd, J=6.7–8.2 Hz, 1H, H4″), 4.10 (t, J=8.2 Hz, 2H, CH_2–O), 4.62 (d, J=5.4 Hz, 1H, H2″), 5.19 (td, J=5.4–9.1 Hz, 1H, H4′), 6.18 (br s, 1H, N*H*), 6.87 (d, J=8.2 Hz, 1H, H3), 7.26 (s, 1H, H6), 7.28 (d, J=2.0 Hz, 1H, H4). ^{13}C NMR (125 MHz, CD_3COCD_3) δ −1.5 ((CH_3)$_3$Si), 18.3 (CH_2–Si), 32.5 (CH_2–Ar), 32.7 (C–CH_2–C), 32.7 (C5′), 33.0 (C5″), 40.7 (CH_2–N), 41.4 (N–CH_3), 62.4 (CH_2–O), 73.2 (C4″), 77.1 (C2″), 80.2 (C4′), 116.6 (C1), 117.6 (C3), 130.6 (C6), 133.3 (C5), 134.2 (C4), 157.0 (O*C*ONH), 158.1 (C2), 172.0 (C2′), 173.1 (*C*OOH).

4.4.15. (4b) (4′*R*,2″*S*,4″*R*). ^{1}H NMR (300 MHz, CD_3COCD_3) δ 0.00 (s, 9H, (CH_3)$_3$Si), 0.96 (t, J=8.2 Hz, 2H, CH_2–Si), 1.79 (p, J=7.2 Hz, 2H, C–CH_2–C), 2.50 (s, 3H, N–CH_3), 2.62 (t, J=7.9 Hz, 2H, CH_2–Ar), 3.11–3.17 (m, 2H, CH_2–N), 3.21–3.24 (m, 2H, H5″), 3.45 (dd, J=9.0–11.5 Hz, 1H, H5′), 3.65 (dd, J=9.0–11.5 Hz, 1H, H5′), 4.10 (t, J=8.2 Hz, 2H, CH_2–O), 4.23 (t, J=6.8 Hz, 1H, H4″), 4.55 (d, J=8.2 Hz, 1H, H2″), 5.00 (q, J=8.2 Hz, 1H, H4′), 6.18 (br s, 1H, N*H*), 6.87 (d, J=8.2 Hz, 1H, H3), 7.26 (s, 1H, H6), 7.28 (d, J=2.0 Hz, 1H, H4). ^{13}C NMR (125 MHz, CD_3COCD_3) δ −1.5 ((CH_3)$_3$Si), 18.3 (CH_2–Si), 32.0 (C5″), 32.5 (CH_2–Ar), 32.7 (C–CH_2–C), 34.8 (C5′), 37.7 (N–CH_3), 40.7 (CH_2–N), 62.4 (CH_2–O), 70.9 (C4″), 77.8 (C2″), 81.1 (C4′), 116.6 (C1), 117.6 (C3), 130.6 (C6), 133.3 (C5), 134.2 (C4), 157.0 (O*C*ONH), 158.1 (C2), 172.0 (C2), 173.1 (*C*OOH).

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Study on the reactions of ethyl 4,4,4-trifluoro-3-oxobutanoate with arylidenemalononitriles

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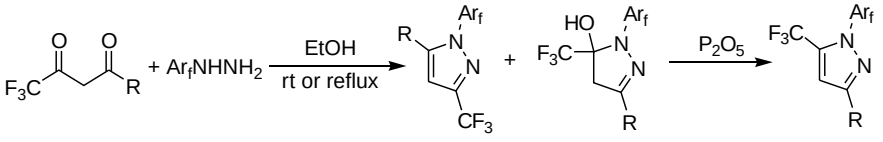
Abstract—In the presence of a catalytic amount of NEt_3, ethyl 4,4,4-trifluoro-3-oxobutanoate **1** reacted readily with arylidenemalononitriles **2** in ethanol at room temperature. It gave two products 2-trifluoromethyl-3,4-dihydro-2*H*-pyran derivatives **3** and 2-(trifluoromethyl)piperidine derivatives **4**, the ratio of **3** and **4** was depended on the substrates **2** and reaction solvents. Reflux of the ethanol solution of **4** with a catalytic amount of NEt_3 afforded 2-trifluoromethyl-1,4,5,6-tetrahydropyridine derivatives **5** in moderate to good yields. The structures of new compounds **3**, **4** and **5** were determined by spectral methods, microanalysis and X-ray diffraction analysis. A possible reaction mechanism for the formation of **3**, **4** and **5** was presented.

1. Introduction

It is well known that 1,3-dicarbonyl compounds reacted with the α,β-unsaturated carbonyl compounds or acrylonitrile derivatives through Michael addition reaction,[1] some adducts could further proceed intramolecular condensation to give cyclic compounds.[2] Furthermore, the selective incorporation of a fluorine atom or fluoroalkyl group into aromatic or heterocyclic system frequently confers biological or physical properties to such molecules.[3] The reactions of fluorinated-1,3-dicarbonyl compounds as fluorine-containing building blocks have been studied extensively.[4,5] For example, our group have reported the reaction of trifluoromethyl-1,3-diketone with per(poly)-fluorophenylhydrazines.[5]



However, to the best of our knowledge, the reactions of trifluoromethyl-containing 1,3-dicarbonyl compounds with arylidenemalononitriles have not been reported. In this paper, we wish to describe our recent study on the reactions of ethyl 4,4,4-trifluoro-3-oxobutanoate **1** with arylidenemalononitriles **2**.

2. Results and discussion

2.1. Reaction of 4,4,4-trifluoro-3-oxobutanoate 1 with arylidenemalononitriles 2

Firstly, the reaction of ethyl 4,4,4-trifluoro-3-oxobutanoate **1** with benzylidenemalononitrile **2a** was investigated as a model reaction. To a solution of **2a** (3 mmol) in ethanol (10 ml, AR, 99.7%) was added an equimolecular amount of ethyl 4,4,4-trifluoro-3-oxobutanoate **1** and a catalytic amount of NEt_3 (0.5 mmol). After stirring of the mixture for 6 h at room temperature, the TLC analysis showed that the starting materials disappeared and two new compounds formed. After removal of the solvent under reduced pressure, the residue was separated and purified by column chromatography on silica gel using petroleum ether–ethyl acetate (4/1, v/v) as the eluent, compound **3a** was first isolated as a white solid in 59% yield and the more polar product **4a** was obtained later in 32% yield (scheme 1).

Keywords: Ethyl 4,4,4-trifluoro-3-oxobutanoate; Arylidenemalononitriles; Heterocycles; X-ray diffraction analysis.
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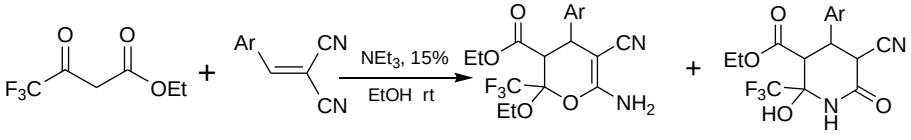


1 2 3 4

Ar=

2a	Ph	2f	*p*-FC_6H_4
2b	*p*-$MeOC_6H_4$	2g	*p*-$O_2NC_6H_4$
2c	*p*-HOC_6H_4	2h	Furan-2-yl
2d	*p*-MeC_6H_4	2i	α-Naphthyl
2e	*p*-ClC_6H_4		

Scheme 1.

The structures of **3a** and **4a** were determined by spectral methods and elemental analysis. The ^{1}H NMR spectrum of **3a** in $CDCl_3$ consisted of eight peaks; they were at δ 0.99 (t, J=7.2 Hz, 3H), 3.88 (q, J=7.2 Hz, 2H), 1.32 (t, J=7.2 Hz, 3H), 3.95 (q, J=7.2 Hz, 2H), 2.94 (d, J=11.7 Hz, 1H), 4.13 (d, J=11.7 Hz, 1H), 4.66 (br, s, 2H), and 7.25–7.34 (m, 5H), corresponding to two ethoxyl groups(CH_3CH_2O), two six-membered ring protons, $CONH_2$ and five aromatic protons. The coupling constant of the vicinal six-membered ring protons in **3a** was 11.7 Hz, which indicated a trans confirmation of the vicinal hydrogen atoms.[6] In its ^{19}F NMR spectrum, the chemical shift of CF_3 group of **3a** was a singlet peak at δ −77.33, which indicated it was bonded to the sp^3 saturated carbon atom. The MS spectrum of **3a** had a strong molecular ion peak at m/z 384 (M^+, 39.7%), and the base peak was at m/z 171 (M^+−EtO–CO_2Et–CF_3–CN, 100%). Meanwhile, the typical and strong absorptions at 3422 and 2203 cm^{-1} in IR spectrum confirmed the existence of NH_2 and CN groups in **3a**. The compound **4a** had eight peaks in its ^{1}H NMR spectrum, they were at δ 0.78 (t, J=7.2 Hz, 3H), 3.28 (dd, J=9, 3 Hz, 1H), 3.86 (q, J=7.2 Hz, 2H), 3.86 (d, J=9 Hz, 1H), 3.87 (d, J=3 Hz, 1H), 6.0 (br, s, 1H), 6.59 (br, s, 1H) and 7.26–7.44 (m, 5H). The ^{19}F NMR spectrum of **4a** was a singlet peak at δ −84.39. Compound **4a** had a weak molecular ion peak at m/z 356 (M^+, 3.68%) and the base peak was at m/z 239 (M^+−H_2O–CO_2Et–CN, 100%). The strong absorptions at 3257, 2273, 1735 and 1690 cm^{-1} in IR were corresponding to OH, NH, CN, CO_2Et and $CONH_2$ groups, respectively. Under the same reaction condition, other arylidenemalononitriles such as **2b–i** reacted with ethyl 4,4,4-trifluoro-3-oxobutanoate **1** to afford the similar reaction products. All the reaction results were summarized in Table 1.

Table 1. Reaction of $CF_3COCH_2CO_2Et$ **1** and arylidenemalononitriles **2**[a]

Entry	Ar in **2**	Time (h)	Yields (%)[b]			
			Product **3** and **4**			
1	**2a** C_6H_5	6	**3a**	59	**4a**	32
2	**2b** *p*-$MeOC_6H_4$	48	**3b**	16	**4b**	62
3	**2c** *p*-HOC_6H_4	72	**3c**	27	**4c**	35
4	**2d** *p*-MeC_6H_4	24	**3d**	20	**4d**	71
5	**2e** *p*-ClC_6H_4	6	**3e**	51	**4e**	32
6	**2f** *p*-FC_6H_4	6	**3f**	80	**4f**	Trace[c]
7	**2g** *p*-$NO_2C_6H_4$	6	**3g**	20	**4g**	60
8	**2h** Furan-2-yl-	50	**3h**	70	**4h**	Trace[c]
9	**2i** α-Naphthyl-	50	**3i**	80	**4i**	Trace[c]

[a] Reaction conditions: **1** (3 mmol), **2** (3 mmol), NEt_3 (0.5 mmol), ethanol (10 ml, AR 99.7%), room temperature.
[b] Isolated yields.
[c] Not isolated.

The steric structures of **3d** and **4d** were further determined by the single crystal X-ray crystallographic study. It was

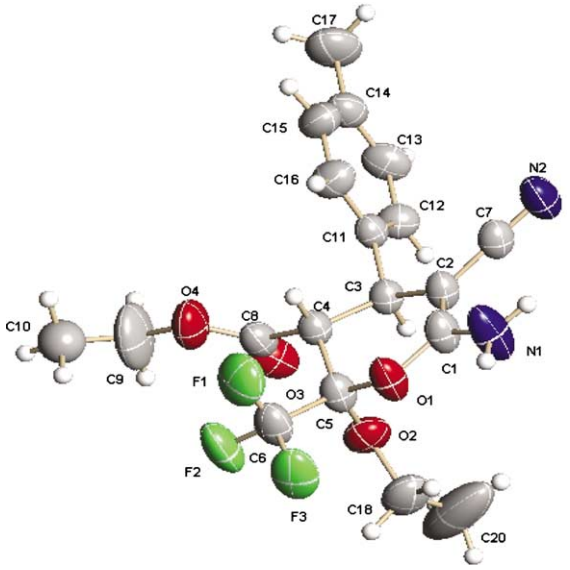


Figure 1. The ORTEP view of **3d**.

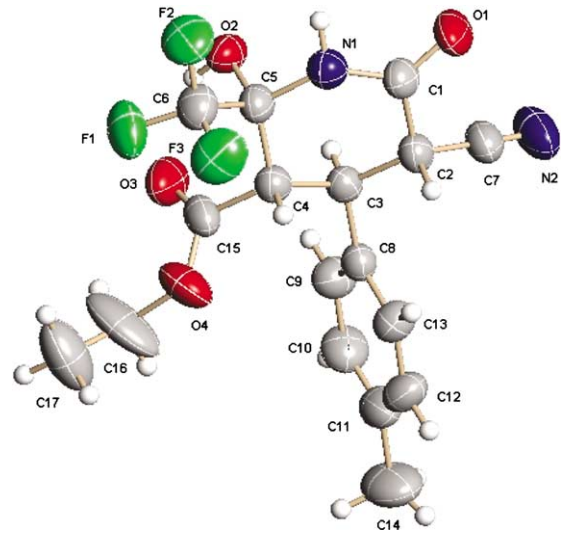
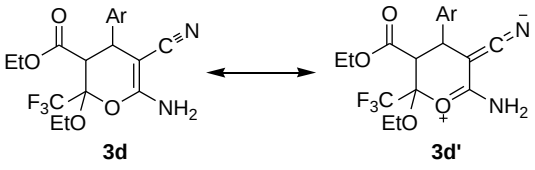


Figure 2. The ORTEP view of **4d**.

Table 2. Selected bond lengths (Å), bond angles (°) of **3d**, **4d** and **5d**

3d		4d		5d	
		Bond lengths			
O(1)–C(1)	1.361(4)	O(1)–C(1)	1.202.(2)	O(1)–C(1)	1.220(2)
O(1)–C(5)	1.422(3)	O(2)–C(5)	1.405(2)	O(2)–C(7)	1.207(3)
O(2)–C(5)	1.361(4)	N(1)–C(1)	1.350(2)	O(3)–C(8)	1.193(3)
N(1)–C(1)	1.324(4)	N(1)–C(5)	1.428(2)	N(1)–C(1)	1.356(3)
N(2)–C(7)	1.146(4)	N(2)–C(7)	1.131(2)	N(1)–C(5)	1.403(3)
C(1)–C(2)	1.347(4)	C(1)–C(2)	1.522(3)	C(1)–C(2)	1.513(3)
C(2)–C(3)	1.509(4)	C(2)–C(3)	1.528(3)	C(2)–C(3)	1.533(3)
C(2)–C(7)	1.404(4)	C(2)–C(7)	1.459(3)	C(2)–C(7)	1.541(3)
C(3)–C(4)	1.541(4)	C(3)–C(4)	1.538(3)	C(3)–C(4)	1.508(3)
C(4)–C(5)	1.535(4)	C(4)–C(5)	1.529(3)	C(4)–C(5)	1.335(3)
		Bond angles			
N(1)–C(1)–C(2)	127.2(3)	O(1)–C(1)–N(1)	122.45(18)	O(1)–C(1)–N(1)	122.0(2)
N(1)–C(1)–O(1)	110.2(3)	O(1)–C(1)–C(2)	121.44(17)	O(1)–C(1)–C(2)	122.5(2)
C(2)–C(1)–O(1)	122.6(3)	N(1)–C(1)–C(2)	116.00(17)	N(1)–C(1)–C(2)	115.4(2)
C(1)–C(2)–C(7)	117.9(3)	C(7)–C(2)–C(1)	108.40(16)	C(5)–C(4)–C(8)	125.9(2)
C(1)–C(2)–C(3)	122.0(3)	C(7)–C(2)–C(3)	111.64(16)	C(5)–C(4)–C(3)	120.1(2)
C(7)– C(2)–C(3)	120.2(3)	C(1)–C(2)–C(3)	114.88(15)	C(8)–C(4)–C(3)	113.93(19)
O(1)–C(5)–C(4)	110.8(3)	C(2)–C(3)–C(4)	107.78(15)	C(4)–C(5)–N(1)	121.3(2)
C(1)–O(1)–C(5)	118.7(2)	C(1)–N(1)–C(5)	125.40(16)	C(4)–C(5)–C(6)	126.3(2)
N(2)–C(7)–C(2)	178.9(3)	N(2)–C(7)–C(2)	179.0(3)	N(1)–C(5)–C(6)	112.42(19)

unambiguous to observe the trans relationship between the vicinal six-membered ring protons in compound **3d** and **4d** (Figs. 1 and 2). The selected bond lengths and bond angles of **3d** and **4d** were listed in Table 2. The bond lengths of O(1)–C(1), C(1)–C(2), C(2)–C(7), and N(2)–C(7) in **3d** was 1.361(4), 1.347(4), 1.404(4), and 1.146(4) Å, respectively, indicating that compounds **3** consisted of a conjugated system in O(1)–C(1)–C(2)–C(7)–N(2) as shown in Scheme 2.



Scheme 2.

2.2. Solvent effect on the reaction of 1 with 2

According to the structures of **3** and **4**, it was clear that the solvent EtOH and H_2O participated in the reaction. To investigate the solvent effects, this reaction was carried out in several different solvent systems; all the results were summarized in Table 3.

In absolute ethanol (entry 2, Table 3), the reaction of **1** with **2a** completed within 7 h and gave **3a** exclusively in 85% yield. Using methanol (AR, 99.5%) as the solvent, the similar product **3a′** was obtained in a yield of 80% accompanying with a small amount of **4a** (10%) (entry 9, Table 3). In aqueous ethanol ($C_2H_5OH/H_2O=2:1$), the reaction of **1** with **2a** completed within 3 h and gave **4a** as a major product (80%) accompanying with a 10% yield of **3a** (entry 3, Table 3). Meanwhile, when the reaction of **1** with **2a** was carried out in water, it required 48 h to finish the reaction, because of the poor solubility of the starting materials in water, and it afforded **4a** (90%) as the exclusive product. In unpurified solvent of CH_3CN (AR) or CH_2Cl_2 (AR), the product **4a** was isolated in 60 and 55%, respectively, without formation of **3a**. However, in absolute

Table 3. Reaction of $CF_3COCH_2CO_2Et$ **1** and **2a** in different solvents[a]

Entry	Solvent	Time (h)	Product yields (%)[b]	
			3a	**4a**
1	EtOH[c]	6	59	32
2	EtOH[d]	7	85	0
3	EtOH–H_2O(2/1)	3	10	80
4	H_2O	48	0	90
5	CH_3CN[d]	6	No reaction	No reaction
6	CH_3CN[c]	4	0	60
7	CH_2Cl_2[d]	6	No reaction	No reaction
8	CH_2Cl_2[c]	4	0	55
9	CH_3OH[c]	7	80(**3a′**)[e]	10
10	CH_3OH[d]	8	85	0

[a] Reaction conditions: **1** (3 mmol), **2** (3 mmol), NEt_3 (0.5 mmol), room temperature.
[b] Isolated yields.
[c] AR and without purification.
[d] Absolute solvent.
[e] Structure of **3a′**.

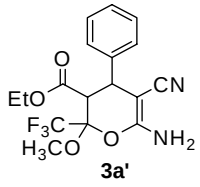
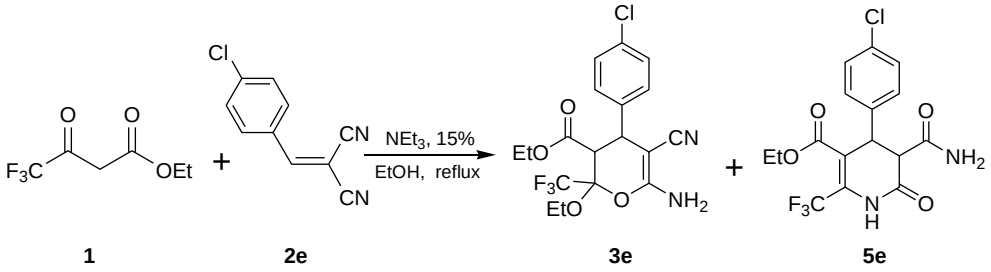


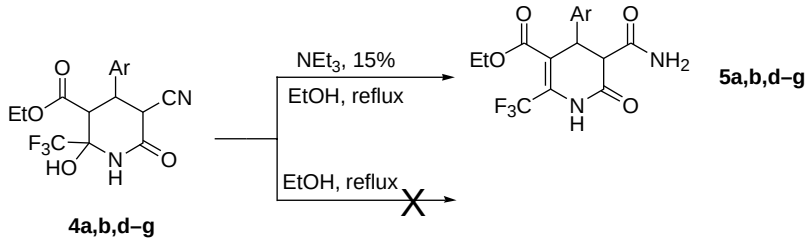
Table 4. Reaction of $CF_3COCH_2CO_2Et$ **1** with **2** in EtOH–H_2O (2/1, v/v)[a]

Entry	Ar in **2**	Time (h)	Yields (%)[b]	
			3	**4**
1	**2a** C_6H_5–	3	**3a** 10	**4a** 80
2	**2b** *p*-$MeOC_4H_5$–	5	**3b** 5	**4b** 78
3	**2d** *p*-MeC_4H_5–	4.5	**3d** 5	**4d** 63
4	**2e** *p*-ClC_4H_5–	3	**3e** 7	**4e** 69
5	**2f** *p*-FC_4H_5–	4	**3f** 8	**4f** 75
6	**2g** *p*-$NO_2C_4H_5$–	3	**3g** 5	**4g** 75
7	**2h** 2-Furanyl–	5	Trace	—[c]
8	**2i** α-Naphthyl–	6	Trace	—[c]

[a] Reaction conditions: **1** (3 mmol), **2** (3 mmol), NEt_3 (0.5 mmol), room temperature.
[b] Isolated yields.
[c] Decomposed on the workup.



Scheme 3.



Scheme 4.

CH_3CN or CH_2Cl_2, no reaction occurred (entries 5 and 7, Table 3).

When the reaction was carried out in aqueous ethanol ($C_2H_5OH/H_2O=2:1$), the reaction time was dramatically reduced comparing to that required in ethanol (Table 1). Under this condition, compounds **4a**–**b**,**d**–**g** were isolated as the major products. Unfortunately, the **4h** and **4i** were not isolated because the products decomposed and gave a complex mixture during the work-up. All the results were listed in Table 4.

It should be noted that the primary Michael addition products could not be obtained under the investigated reaction conditions, because they readily undergo the consecutive and irreversible reaction. This phenomenon should be attributed to the strong electronic withdrawing nature of CF_3, leading to the carbonyl group was much more easily to be attacked by the nucleophiles such as ethanol or water.

As shown in Table 1, it was found that reactions of arylidenemalononitriles **2b**–**d** (entries 2–4, Table 1), which have an electronic donating group on the para position of the phenyl group with ethyl 4,4,4-trifluoro-3-oxobutanoate **1** required longer reaction time comparing to other arylidenemalononitriles such as **2a** and **2e**,**f**,**g** (entries 5–7, Table 1), which bear an electronic withdrawing group on the para position of phenyl group. This result was similar to the kinetic studies on the Michael reaction of arylidenemalononitriles.[7] The reaction of **1** with **2f**, **2h** and **2i** (entries 6, 8, and 9, Table 1) afforded **3f**, **3h**, and **3i** in 80, 70, and 80% yields, respectively, but the corresponding **4f**, **4h**, and **4i** were not isolated. The electronic effect of substituted group (in Table 1) affecting the ratio of products **3** and **4** could not be explained at this stage.

2.3. Transformation of 4 to 5

The above results prompted us to further study the temperature effect on this reaction. A mixture of the reaction of **1** (3 mmol) and an equimolecular amount of 2-(4-chlorobenzylidene)malononitrile **2e** with a catalytic amount of Et_3N (0.5 mmol) was refluxed in ethanol (10 ml, AR 99.7%). After stirring for 6 h, TLC analysis showed the reaction was completed and a new compound formed in addition to the expected product **3e**, but no **4e** was detected by TLC. A new compound ethyl 5-carbamoyl-4-(4-chlorophenyl)-6-oxo-2-(trifluoromethyl)-1,4,5,6-tetrahydropyridine-3-carboxylate **5e** was isolated in 20% yield along with **3e** in 50% isolated yield (Scheme 3). It could be speculated that under the reflux condition, compound **4e** could be transformed into compound **5e**.

Thus, a series of transformation of **4** to **5** was investigated. As expected, reflux of the solution of **4a** (2 mmol) in 8 ml ethanol (AR 99.7%) with NEt_3 (0.3 mmol) afforded **5a** in 69% yield. In the absence of a catalytic amount of NEt_3, no reaction occurred. Under the same reaction conditions, a series of new compounds **5b**,**d**–**g** was also obtained (Scheme 4). The reaction results were listed in Table 5.

Table 5. Transformation of **4** to **5** in EtOH in the presence of NEt_3[a]

Entry	4	Time (h)	Product 5	Yield (%)[b]
1	**4a**	4	**5a**	69
2	**4b**	4	**5b**	53
3	**4d**	4	**5d**	66
4	**4e**	4	**5e**	80
5	**4f**	4	**5f**	65
6	**4g**	4	**5g**	50

[a] Reaction condition: **4** (2 mmol), NEt_3 (0.3 mmol), refluxed in ethanol (8 ml AR, 99.7%).
[b] Isolated yields.

All the new compounds **5** were fully characterized. For example, the ^1H NMR spectrum of **5a** in $CDCl_3$ showed eight peaks: they were at δ 1.19 (t, $J=7.2$ Hz, 3H), 3.61 (d, $J=3$ Hz, 1H), 4.17 (q, $J=7.2$ Hz, 2H), 4.91 (s, 1H), 5.49 (br, s, 1H), 6.19 (br, s, 1H), 7.2–7.37 (m, 5H,), 7.52 (br, s, 1H). It was noteworthy that the signals of two protons attached to nitrogen atom of amide group showed two

different chemical shifts at δ 5.49 and 6.19, respectively. In its ^{19}F NMR spectrum, the chemical shift of CF_3 group in **5a** was a singlet peak at δ −64.27, indicating that it was bonded to the unsaturated sp^2 carbon atom. The MS spectrum of **5a** showed its weak molecular ion peak at *m/z* 356 (M^+, 1.98%) and the base peak at 312 (M^+-CONH_2, 100%). Meanwhile, in the IR spectrum of **5a**, no absorption peaks in the range of 2000–2400 cm^{-1}, indicating that there was no cyano group in **5a**. Furthermore, the steric structure of **5d** was further confirmed by single crystal X-ray diffraction analysis (Fig. 3). The selected bond lengths and bond angles of **5d** were also listed in Table 2. The crystal data and structure refinement parameters of **3d**, **4d** and **5d** were listed in Table 6.

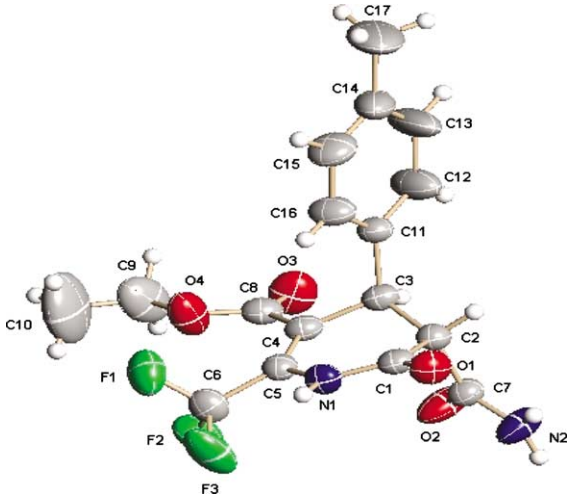
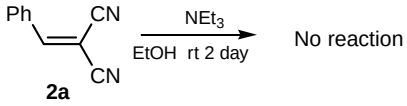


Figure 3. The ORTEP view of **5d**.

2.4. Mechanism

According to the structure of **3**, which has the ethoxyl group at the 2-position of the ring, while **4** had a lactam unit, it was clear that the ethanol and water participated in the reaction processes, respectively. To determine how the cyano group hydrolyzed during the reaction, a solution of **2a** in ethanol with a catalytic amount of NEt_3 was carried out. After stirring for 2 days at room temperature, TLC analysis showed that no reaction occurred and the starting material **2a** remained (Scheme 5), which indicated that the cyano group hydrolyzed after the formation of intermediate **A**. Moreover, to this reaction, a catalytic amount of Et_3N was necessary, otherwise the reaction did not occur even with prolonged reaction time.



Scheme 5.

Based on these results above, a possible mechanism for the formation of **3**, **4** and **5** was illustrated in Scheme 6. Firstly, the Michael adduct intermediate **A** was formed by Michael addition reaction, and then the solvent ethanol attacked trifluoroacetyl group of the intermediate **A**, followed by the intramolecular attack to the enimine to form the six-membered ring product **3**. Alternatively, the intermediate **A** could be hydrolyzed by water to form **B**, then through intramolecular condensation yielding the cyclic product **4**. At refluxed temperature, **4** could be transformed into **5** by losing a water molecule, and followed by the hydrolysis of the cyano group. However, it should be noted that in the absence of a catalytic amount of NEt_3, **5** could not be

Table 6. The crystal data of **3d**, **4d** and **5d**

	3d	**4d**	**5d**
CCDC	28,4791	28,4792	28,4793
Empirial formula	$C_{19}H_{21}F_3N_2O_4$	$C_{17}H_{17}F_3N_2O_4$	$C_{17}H_{17}F_3N_2O_4$
*F*w	398.38	370.33	370.33
Temp (K)	293(2)	293(2)	293(2)
Wavelength (Å)	0.71073	0.71073	0.71073
Cryst syst	Triclinic	Monoclinic	Monoclinic
Space group	*P*−1	*P*2(1)/*c*	*C*2/*c*
Unit cell dimens			
a (Å)	8.3233(10)	8.3300(9)	20.197(2)
b (Å)	9.5566(12)	10.4557(11)	11.6217(14)
c (Å)	13.1239(16)	20.118(2)	15.4193(18)
α (°)	76.801(2)	90	90
β (°)	80.048(2)	91.672(2)	94.328(2)
γ (°)	88.410(2)	90	90
Volume ($Å^3$)	1001.0(2)	1751.4(3)	3609.0(7)
Z	2	4	8
Calcd density (Mg/m^3)	1.322	1.404	1.363
Absorp coeff (mm^{-1})	0.111	0.121	0.117
F(000)	416	768	1536
Cryst size (mm)	0.516×0.427×0.368	0.506×0.427×0.218	0.505×0.332×0.070
θ Range for data collection (°)	1.62–26.00	2.03–27.00	2.02–27.00
Goodness-of-fit on F^2	1.055	1.002	0.839
Final *R* indices	*R*1=0.0793	*R*1=0.0519	*R*1=0.0523
[$I>2\sigma$ (*I*)]	*wR*2=0.2410	*wR*2=0.1396	*wR*2=0.1151
R indices (all data)	*R*1=0.0982	*R*1=0.0796	*R*1=0.1083
	*wR*2=0.2601	*wR*2=0.1532	*wR*2=0.1321
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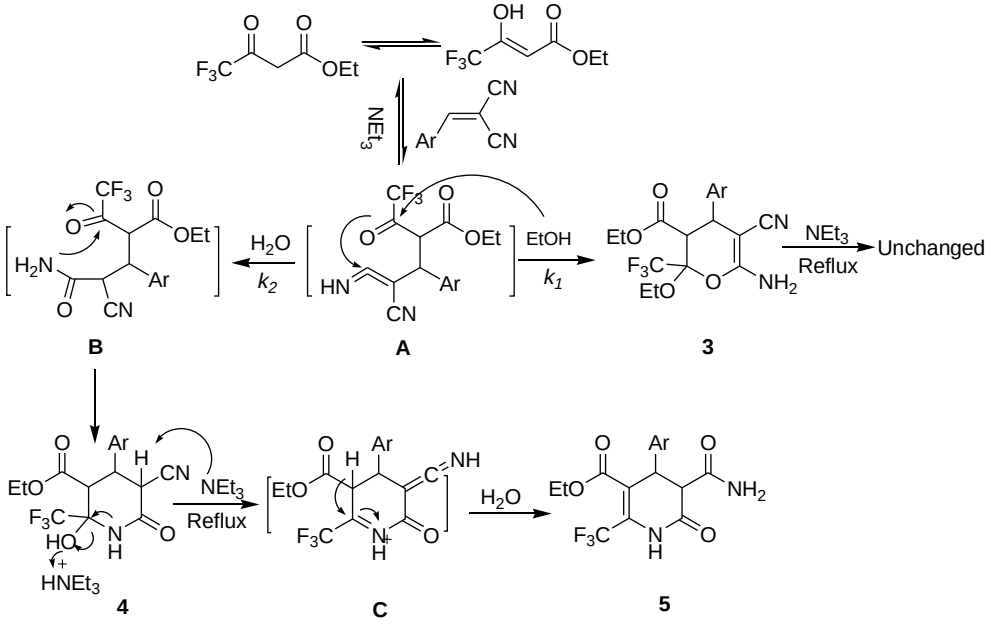

Scheme 6.

obtained under the refluxed condition. This should be partly attributed to the active proton of the vicinal cyano group in compound **4**, which could assist the hydrolysis by the intermediate **C** as depicted in scheme 6. In contrast, the cyano group in compound **3** was much more stable than that in compound **4**, it resisted to hydrolysis and remained unchanged under the refluxed condition, this was partly because there existed a conjugated system in compound **3** as mentioned above, partly because there was no active proton at the vicinal position of cyano group in compound **3**. Furthermore, in the aqueous EtOH, the reaction could complete within a shorter time (Table 4), which manifested that the rate constant k_2 for the formation of **4** from intermediate **A** should be larger than the rate constant k_1 for the formation of **3**.

3. Conclusions

In summary, the reaction of $CF_3COCH_2CO_2Et$ **1** with arylidenemalononitriles **2** under NEt_3 catalysis was studied in detail. Different reaction conditions gave different results. In ethanol (AR, 99.7%) the reaction gave two products 2-trifluoromethyl-3,4-dihydro-2*H*-pyrans derivatives **3** and 2-(trifluoromethyl)piperidine derivatives **4**. When it was carried out in aqueous ethanol ($C_2H_5OH/H_2O=2:1$), **4** became the major product. In absolute ethanol, **3** was the exclusive product. In CH_3CN or CH_2Cl_2 (AR) the reaction only afforded **4**, whereas in absolute CH_3CN or CH_2Cl_2, no reaction occurred. Reflux of **4** with the catalysis of NEt_3 in ethanol afforded 2-trifluoromethyl-1,4,5,6-tetrahydropyridines derivatives **5**. Further chemical transformation of above compounds now is under investigation.

4. Experimental

Melting points were measured in Melt-Temp apparatus and were uncorrected. ^1H and ^{19}F NMR spectra were recorded in $CDCl_3$ (unless mentioned in text) Bruker AM-300 instruments with Me_4Si and $CFCl_3$ (with upfield negative) as the internal and external standards, respectively. IR spectra were obtained with a Nicolet AV-360 spectrophotometer. Lower resolution mass spectrum were obtained on Finnigan GC–MS 4021 using the electron impact ionization technique (70 ev). High-resolution mass spectra (HRMS) were obtained on Ionspec 4.7 T FTMS using MALDI/DHB. Elemental analyses were performed by this Institute. X-ray diffraction crystal structure analysis was obtained on Bruker P4 instrument.

4.1. General procedure for the reaction of ethyl 4,4,4-trifluoro-3-oxobutanoate 1 with arylidenemalononitriles 2a in ethanol

To a 50 ml round bottle flask containing **2a** (462 mg, 3 mmol) was added 10 ml ethanol, and then ethyl 4,4,4-trifluoro-3-oxobutanoate **1** (552 mg, 3 mmol) and NEt_3 (0.5 mmol) were added under stirring at room temperature. The mixture was continuously stirred at room temperature. After 6 h, the TLC analysis showed the reaction was finished. The solvent was evaporated and the residue was chromatographed on a silica column using petroleum ether–ethyl acetate (4/1, v/v) as eluent to afford the **3a** (512 mg, 59%) and **4a** (299 mg, 32%), respectively. The two solid products were recrystallized from petroleum ether/ethyl acetate to give the pure compounds.

4.1.1. Ethyl 6-amino-5-cyano-2-ethoxy-4-phenyl-2-trifluoromethyl-3,4-dihydro-2*H*-pyran-3-carboxylate 3a. White solid; mp 154–156 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.99 (t, $J=7.2$ Hz, 3H), 1.32 (t, $J=7.2$ Hz, 3H), 2.94 (d, $J=11.7$ Hz, 1H), 3.88 (q, $J=7.2$ Hz, 2H), 3.95 (q, $J=7.2$ Hz, 2H), 4.13 (d, $J=11.7$ Hz, 1H), 4.66 (br, s, 2H), 7.25–7.36 (m, 5H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −77.33 (s, 3F); IR (KBr) υ_{max} 3422, 3330, 3285, 2992, 2203, 1735, 1670, 1615 cm^{-1}; MS (70 eV, EI) *m*/*z* (%) 385 (MH^+, 8.02), 384 (M^+, 39.70), 355 (M^+-Et, 5.74), 338

(M^+ −EtOH, 8.24), 309 (M^+ −Et–EtOH, 6.88), 265 (M^+ −CO_2Et–EtOH, 65.83), 292 (M^+ −2EtOH, 10.33), 223 (M^+ −2EtOH–CF_3, 4.95), 171 (M^+ −EtO–CO_2Et–CF_3–CN, 100), 69 (CF_3^+, 14.65). Anal. Calcd for $C_{18}H_{19}F_3N_2O_4$: C, 56.25%; H, 4.95%; N, 7.29%. Found: C, 56.14%; H, 5.16%; N, 7.23%.

4.1.2. Ethyl 5-cyano-2-hydroxy-6-oxo-4-phenyl-2-(trifluoromethyl)piperidine-3-carboxylate 4a. White solid; mp 163–166 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.78 (t, J=7.2 Hz, 3H), 3.28 (dd, J=9, 3 Hz, 1H), 3.86 (q, J=7.2 Hz, 2H), 3.86 (d, J=9 Hz, 1H), 3.87 (d, J=3 Hz, 1H), 6.0 (br, s, 1H), 6.59 (br, s, 1H), 7.26–7.44 (m, 5H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −84.39 (s, 3F); IR (KBr) υ_{max} 3257, 3138, 2989, 2273, 1735, 1690 cm^{-1}; MS (70 eV, EI) *m/z* (%): 356 (M^+, 3.68), 265 (M^+ −H_2O–CO_2Et, 67.70), 239 (M^+ −H_2O–CO_2Et–CN, 100), 69 (CF_3^+, 11.70). Anal. Calcd for $C_{16}H_{15}F_3N_2O_4$: C, 53.93%; H, 4.21%; N, 7.87%. Found: C, 53.98%; H, 4.22%; N, 7.84%.

4.1.3. Ethyl 6-amino-5-cyano-2-methoxy-4-phenyl-2-trifluoromethyl-3,4-dihydro-2*H*-pyran-3-carboxylate 3a′ (reaction in methanol). White solid; mp 153–155 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.98 (t, J=7.2 Hz, 3H), 2.95 (d, J=11.4 Hz, 1H), 3.60 (s, 3H), 3.95 (q, J=7.2 Hz, 2H), 4.10 (d, J=11.4 Hz, 1H), 4.72 (br, s, 2H), 7.23–7.35 (m, 5H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −76.99 (s, 3F); IR (KBr) υ_{max} 3439, 3336, 2963, 2199, 1732, 1673, 1605, 1465 cm^{-1}; MS (70 eV, EI) *m/z* (%) 370 (M^+, 28.40), 338 (M^+ −CH_3OH, 2.85), 265 (M^+ −CO_2Et–CH_3OH, 78.11), 171 (M^+ −CH_3O–CO_2Et–CF_3–CN, 100), 69 (CF_3^+, 6.52). Anal. Calcd for $C_{17}H_{17}F_3N_2O_4$: C, 55.14%; H, 4.59%; N, 7.57%. Found: C, 54.90%; H, 4.64%; N, 7.52%.

4.1.4. Ethyl 6-amino-5-cyano-2-ethoxy-4-(4-methoxyphenyl)-2-trifluoromethyl-3,4-dihydro-2*H*-pyran-3-carboxylate 3b. White solid; mp 168–169 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.01 (t, J=7.2 Hz, 3H), 1.29 (t, J=7.2 Hz, 3H), 2.89 (d, J=11.7 Hz, 1H), 3.77 (s, 3H), 3.86 (q, J=7.2 Hz, 2H), 3.95 (q, J=7.2 Hz, 2H), 4.07 (d, J=11.7 Hz, 1H), 4.68 (br, s, 2H), 6.84 (d, J_{AB}=8.7 Hz, 2H), 7.16 (d, J_{AB}=8.7 Hz, 2H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −77.37 (s, 3F); IR (KBr) υ_{max} 3438, 3348, 3186, 2992, 2193, 1736, 1647, 1601, 1517 cm^{-1}; MS (70 eV, EI) *m/z* (%) 415 (MH^+, 3.03), 414 (M^+, 13.24); 385 (M^+ −Et, 1.42), 368 (M^+ −EtOH, 2.82), 295 (M^+ −CO_2Et–EtOH, 31.00), 202 (M^+ +1–EtO–CO_2Et–CF_3–CN, 100), 69 (CF_3^+, 2.81). Anal. Calcd for $C_{19}H_{21}F_3N_2O_5$: C, 55.07%; H, 5.07%; N, 6.76%. Found: C, 55.07%; H, 5.20%; N, 6.72%.

4.1.5. Ethyl 5-cyano-2-hydroxy-4-(4-methoxyphenyl)-6-oxo-2-(trifluoromethyl)-piperidine-3-carboxylate 4b. White solid; mp 162–164 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85 (t, J=7.2 Hz, 3H), 3.24 (dd, J=7.2, 4.8 Hz, 1H), 3.82 (s, 3H), 3.80 (J=4.8 Hz, 1H), 3.81 (J=7.2 Hz, 1H), 3.90 (q, J=7.2 Hz, 2H) 5.98 (br, s, 1H), 6.71 (br, s, 1H), 6.92 (d, J_{AB}=8.4 Hz, 2H), 7.20 (d, J_{AB}=8.4 Hz, 2H); ^{19}F NMR δ ($CDCl_3$, 282 MHz) −84.36 (s, 3F); IR (KBr) υ_{max} 3554, 3459, 3325, 3071, 2261, 1733, 1689, 1613, 1518 cm^{-1}; MS (70 eV, EI) *m/z* (%): 386 (M^+, 17.58), 359 (M^+ −HCN, 8.93), 295 (M^+ −H_2O–CO_2Et, 100), 269 (M^+ −H_2O–CO_2Et–CN, 48.92), 69 (CF_3^+, 5.75); HRMS for $C_{17}H_{17}F_3N_2O_5Na^{+1}$ Calcd: 409.0982. Found: 409.0999.

4.1.6. Ethyl 6-amino-5-cyano-2-ethoxy-4-(4-hydroxyphenyl)-2-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-3-carboxylate 3c. White solid; mp 188–191 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.03 (t, J=7.2 Hz, 3H), 1.30 (t, J=7.2 Hz, 3H), 2.92 (d, J=11.7 Hz, 1H), 3.88 (q, J=6.9 Hz, 2H), 3.97 (q, J=7.2 Hz, 2H), 4.07 (d, J=11.7 Hz, 1H), 4.66 (br, s, 2H), 5.88 (s, 1H), 6.72 (d, J_{AB}=8.4 Hz, 2H), 7.09 (d, J_{AB}=8.7 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −77.36 (s, 3F); IR (KBr) υ_{max} 3421, 3333, 3290, 2203, 1730, 1665, 1600 cm^{-1}; MS (*m/z*, %): 401 (MH^+, 3.64), 400 (M^+, 16.08), 371 (M^+ −Et, 2.14), 354 (M^+ −EtOH, 4.50), 281 (M^+ − CO_2Et–EtOH, 46.23), 188 (M^+ +1−EtO–CO_2Et–CF_3–CN, 100), 69 (CF_3^+, 5.91). Anal. Calcd for $C_{18}H_{19}F_3N_2O_5$: C, 54.00%; H, 4.75%; N, 7.00%. Found: C, 53.96%; H, 4.85%; N, 7.06%.

4.1.7. Ethyl 5-cyano-2-hydroxy-4-(4-hydroxyphenyl)-6-oxo-2-(trifluoromethyl)-piperidine-3-carboxylate 4c. White solid; mp 215–217 °C; ^{1}H NMR (CD_3COCD_3, 300 MHz) δ 0.87 (t, J=7.2 Hz, 3H), 3.64 (d, J=12.3 Hz, 1H), 3.83–3.95 (m, 3H), 4.48 (d, J=12.3 Hz, 1H), 6.56 (br, s, 1H), 6.83–6.88 (m, 2H), 7.32–7.36 (m, 2H), 8.42 (br, s, 1H), 8.56 (br, s, 1H); ^{19}F NMR (CD_3COCD_3, 282 MHz) δ −83.63 (s, 3F); IR (KBr) υ_{max} 3563, 3531, 3481, 3298, 2976, 2258, 1732, 1703, 1615, 1599, 1520 cm^{-1}; MS (70 eV, EI) *m/z* (%): 372 (M^+, 9.54), 327 (M^+ −EtO, 7.53), 281 (M^+ −H_2O–CO_2Et, 100), 255 (M^+ −H_2O–CO_2Et–CN, 45.43), 69 (CF_3^+, 20.31). Anal. Calcd for $C_{16}H_{15}F_3N_2O_5$: C, 51.61%; H, 4.03%; N, 7.53%, Found: C, 51.67%; H, 4.02%; N, 7.52%.

4.1.8. Ethyl 6-amino-5-cyano-2-ethoxy-4-*p*-tolyl-2-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-3-carboxylate 3d. White solid; mp 179–181 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.02 (t, J=7.2 Hz, 3H), 1.30 (t, J=7.2 Hz, 3H), 2.32 (s, 3H), 2.92 (d, J=11.7 Hz, 1H), 3.87 (q, J=7.2 Hz, 2H), 3.96 (q, J=7.2 Hz, 2H), 4.09 (d, J=11.7 Hz, 1H), 4.64 (br, s, 2H), 7.13 (m, 4H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −77.34 (s, 3F); IR (KBr) υ_{max} 3449, 3273, 3222, 3182, 2987, 2197, 1740, 1647, 1599, 1518 cm^{-1}; MS (70 eV, EI) *m/z* (%) 399 (MH^+, 4.86), 398 (M^+, 21.07), 369 (M^+ −Et, 2.55), 352 (M^+ −EtOH, 4.15), 323 (M^+ −Et–EtOH, 3.77), 306 (M^+ −2EtOH, 8.88), 279 (M^+ −CO_2Et–EtOH, 60.60), 185 (M^+ −EtO–CO_2Et–CF_3–CN, 100), 69 (CF_3^+, 6.63). Anal. Calcd for $C_{19}H_{21}F_3N_2O_4$: C, 57.29%; H, 5.28%; N, 7.04%. Found: C, 57.46%; H, 5.53%, N, 7.01%.

4.1.9. Ethyl 5-cyano-2-hydroxy-6-oxo-4-*p*-tolyl-2-(trifluoromethyl)-piperidine-3-carboxylate 4d. White solid; mp 147–149 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.8 (t, J=7.2 Hz, 3H), 2.35 (s, 3H), 3.27 (d, J=10.8 Hz, 1H), 3.85 (q, J=7.2 Hz, 2H), 3.78–3.91 (m, 2H), 6.03 (br, s, 1H), 6.87 (br, s, 1H), 7.15–7.26 (m, 4H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −84.30 (s, 3F); IR (KBr) υ_{max} 3273, 3187, 2900, 2257, 1728, 1516, 1477 cm^{-1}; MS (70 eV, EI) *m/z* (%): 370 (M^+, 2.30), 279 (M^+ −H_2O–CO_2Et, 41.34), 253 (M^+ −H_2O–CO_2Et–CN, 50.00), 69 (CF_3^+, 34.60). Anal. Calcd for $C_{17}H_{17}F_3N_2O_4$: C, 55.14%; H, 4.59%; N, 7.57%. Found: C, 55.24%; H, 4.81%; N, 7.60%.

4.1.10. Ethyl 6-amino-4-(4-chlorophenyl)-5-cyano-2-ethoxy-2-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-3-carboxylate 3e. White solid; mp 138–140 °C; ^{1}H

NMR ($CDCl_3$, 300 MHz) δ 1.03 (t, J=7.2 Hz, 3H), 1.30 (t, J=7.2 Hz, 3H), 2.88 (d, J=11.7 Hz, 1H), 4.12 (d, J=11.7 Hz, 1H), 3.87 (q, J=7.2 Hz, 2H), 3.96 (q, J=7.2 Hz, 2H), 4.66 (br, s, 2H), 7.18–7.32 (m, 4H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −77.20 ppm; IR (KBr) υ_{max} 3421, 3329, 2988, 2189, 1749, 1655, 1598, 1492 cm^{-1}; MS (70 eV, EI) *m/z* (%) 420/418 (M^+, 8.97/25.14), 374/372 (M^+ −EtOH, 5.20/10.31), 345/343 (M^+ −Et–EtOH, 3.44/5.93), 328/326 (M^+ −2EtOH, 6.53/7.30), 301/299 (M^+ −CO_2Et–EtOH, 34.92/76.23), 207/205 (M^+ −EtO–CO_2Et–CF_3–CN, 100/84.31), 69 (CF_3^+, 14.84); HRMS for $C_{18}H_{18}ClF_3N_2O_4Na^{+1}$ Calcd: 441.0799. Found: 441.0819.

4.1.11. Ethyl 4-(4-chlorophenyl)-5-cyano-2-hydroxy-6-oxo-2-(trifluoromethyl)-piperidine-3-carboxylate 4e. White solid; mp 146–148 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, J=7.2 Hz, 3H), 3.25 (d, J=10.8 Hz, 1H), 3.82–3.86 (m, 2H), 3.90 (q, J=7.2 Hz, 2H), 5.91 (br, s, 1H), 6.52 (br, s, 1H), 7.23–7.43 (m, 4H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −84.36 (s, 3F); IR (KBr) υ_{max} 3268 (br), 3182, 2900, 2258, 1708, 1590, 1492 cm^{-1}; MS (70 eV, EI) *m/z* (%): 392/390 (M^+, 2.15/6.20), 301/299 (M^+ −H_2O–CO_2Et, 30.72/80.20), 275/273 (M^+ −H_2O–CO_2Et–CN, 40.17/100), 69 (CF_3^+, 11.13). Anal. Calcd for $C_{16}H_{14}ClF_3N_2O_4$: C, 49.17%; H, 3.59%; N, 7.17%. Found: C, 49.15%; H, 3.59%; N, 7.27%.

4.1.12. Ethyl 6-amino-5-cyano-2-ethoxy-4-(4-fluorophenyl)-2-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-3-carboxylate 3f. White solid; mp 123–128 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.01 (t, J=7.2 Hz, 3H), 1.29 (t, J=6.9 Hz, 3H), 2.87 (d, J=12.0 Hz, 1H), 3.89 (q, J=6.9 Hz, 2H), 3.96 (q, J=7.2 Hz, 2H), 4.12 (d, J=12.0 Hz, 1H), 4.78 (br, s, 2H), 6.98–7.04 (m, 2H, Ar–H), 7.21–7.26 (m, 2H, Ar–H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −77.29 (s, 3F), −114.4 (m, 1F); IR (KBr) υ_{max} 3489, 3332, 2195, 1748, 1738, 4660, 1608, 1596, 1346 cm^{-1}; MS (70 eV, EI) *m/z* (%) 403 (MH^+, 6.92), 402 (M^+, 24.19), 373 (M^+ −Et, 4.59), 356 (M^+ −EtOH, 10.15), 283 (M^+ − CO_2Et–EtOH, 76.42), 189 (M^+ −EtO–CO_2Et–CF_3–CN, 100), 69 (CF_3^+, 8.78). Anal. Calcd for $C_{18}H_{18}F_4N_2O_4$: C, 53.73%; H, 4.48%; N, 6.97%. Found: C, 53.75%; H, 4.56%; N, 6.93%.

4.1.13. Ethyl 5-cyano-4-(4-fluorophenyl)-2-hydroxy-6-oxo-2-(trifluoromethyl)-piperidine-3-carboxylate 4f. White solid; mp 147–150 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, J=7.2 Hz, 3H), 3.25 (d, J=10.8 Hz, 1H), 3.78–3.95 (m, 4H), 5.92 (br, s, 1H), 6.50 (br, s, 1H), 7.11–7.32 (m, 4H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −84.56 (s, 3F), −111.4 (m, 1F); IR (KBr) υ_{max} 3309, 3292, 3243, 1734, 1689, 1516, 1379 cm^{-1}; MS (70 eV, EI) *m/z* (%): 374 (M^+, 3.15), 283 (M^+ −H_2O–CO_2Et, 77.32), 257 (M^+ −H_2O–CO_2Et–CN, 100), 69 (CF_3^+, 18.23). Anal. Calcd for $C_{16}H_{14}F_4N_2O_4$: C, 51.34%; H, 3.74%; N, 7.49%. Found: C, 50.95%; H, 3.93%; N, 7.47%.

4.1.14. Ethyl 6-amino-5-cyano-2-ethoxy-4-(4-nitrophenyl)-2-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-3-carboxylate 3g. White solid; mp 72–74 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.04 (t, J=7.2 Hz, 3H), 1.32 (t, J=7.2 Hz, 3H), 2.92 (d, J=11.7 Hz), 3.89 (q, J=7.2 Hz, 2H), 3.96 (q, J=7.2 Hz, 2H), 4.40 (d, J=11.7 Hz, 1H), 4.74 (br, s, 2H), 7.46–7.51 (m, 2H), 8.20–8.23 (m, 2H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −77.17 (s, 3F), IR (KBr) υ_{max} 3453, 3329, 2987, 2199, 1741, 1654, 1524, 1350 cm^{-1}; MS (70 eV, EI) *m/z* (%) 431 (M^++2, 4.50), 400 (M^+ −Et, 3.11), 383 (M^+ −EtOH, 6.59), 310 (M^+ −CO_2Et–EtOH, 29.34), 69 (CF_3^+, 16.49). Anal. Calcd for $C_{18}H_{18}F_3N_3O_6$: C, 50.35%; H, 4.20%; N, 9.79%. Found: C, 50.46%; H, 4.14%; N, 9.85%.

4.1.15. Ethyl 5-cyano-2-hydroxy-4-(4-nitrophenyl)-6-oxo-2-(trifluoromethyl)-piperidine-3-carboxylate 4g. White solid; mp 174–175 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, J=7.2 Hz, 3H), 3.36 (d, J=12 Hz, 1H), 3.84–4.07 (m, 4H), 5.78 (br, s, 1H), 6.62 (br, s, 1H), 7.53 (d, J_{AB}=8.4 Hz, 2H), 8.31 (d, J_{AB}=8.4 Hz, 2H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −84.41 (s, 3F); IR (KBr) υ_{max} 3545, 3484, 3291, 2270, 1729, 1702, 1640, 1609, 1523 cm^{-1}; MS (70 eV, EI) *m/z* (%): 310 (M^+ −H_2O–CO_2Et, 25.47), 284 (M^+ −H_2O–CO_2Et–CN, 100), 69 (CF_3^+, 6.89); HRMS for $C_{16}H_{14}F_3N_3O_6Na^{+1}$ Calcd: 424.0727. Found: 424.0743.

4.1.16. Ethyl 6-amino-5-cyano-2-ethoxy-4-(furan-2-yl)-2-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-3-carboxylate 3h. White solid; mp 178–179 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.11 (t, J=7.2 Hz, 3H), 1.28 (t, J=7.2 Hz, 3H), 3.18 (d, J=11.7 Hz, 1H), 3.85 (q, J=7.2 Hz, 2H), 4.06 (q, J=7.2 Hz, 2H), 4.30 (d, J=11.7 Hz, 1H), 4.59 (br, s, 2H), 6.28–6.31 (m, 1H), 7.24–7.27 (m, 1H), 7.35–7.37 (m, 1H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −77.32 (s, 3F); IR (KBr) υ_{max} 3415, 3333, 2198, 1736, 1663, 1616, 1376 cm^{-1}; MS (70 eV, EI) *m/z* (%) 374 (M^+, 100), 345 (M^+ −Et, 12.28), 328 (M^+ −EtOH, 67.46), 255 (M^+ −CO_2Et–EtOH, 95.93), 69 (CF_3^+, 22.10). Anal. Calcd for $C_{16}H_{17}F_3N_2O_5$: C, 51.34%; H, 4.55%; N, 7.49%. Found: C, 51.53%; H, 4.86%; N, 7.48%.

4.1.17. Ethyl 6-amino-5-cyano-2-ethoxy-4-(naphthalen-1-yl)-2-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-3-carboxylate 3i. White solid; mp 198–199 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.73 (t, J=7.2 Hz, 3H), 1.39 (t, J=7.1 Hz, 3H), 3.20 (d, J=11.7 Hz, 1H), 3.69 (q, J=7.2 Hz, 2H), 3.95 (q, J=7.2 Hz, 2H), 4.64 (br, s, 2H), 5.16 (d, J=11.7 Hz), 7.33–7.58 (m, 4H), 7.77–8.00 (m, 2H), 8.26 (d, J=8.4 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −76.9 (s, 3F); IR (KBr) υ_{max} 3419, 3321, 3194, 2203, 1741, 1655, 1606, 1375 cm^{-1}; MS (70 eV, EI) *m/z* (%): 435 (M^++1, 74.52), 434 (M^+, 3.16), 405 (M^+ −Et, 4.56), 315 (M^+ − CO_2Et–EtOH, 76.83), 233 (M^+ −EtO–CO_2Et–CF_3–CN, 29.41), 69 (CF_3^+, 21.88). Anal. Calcd for $C_{22}H_{21}F_3N_2O_4$: C, 60.83%; H, 4.84%; N, 6.45%. Found: C, 61.05%; H, 4.85%; N, 6.27%.

4.2. General procedures for the transformation of 4 to 5

To the solution of **4a** (2 mmol in 8 ml ethanol) was added NEt_3 (0.3 mmol) under stirring, and then the mixture was heated to reflux. After 6 h, the TLC analysis showed the reaction was completed. After removal of the solvent under reduced pressure the residue was purified by column chromatography on silica gel using petroleum and ethyl acetate (6/4, v/v) as eluent. Recrystallization from petroleum and ethyl acetate gave the pure **5a**.

4.2.1. Ethyl 5-carbamoyl-6-oxo-4-phenyl-2-(trifluoromethyl)-1,4,5,6-tetrahydropyridine-3-carboxylate 5a. White solid; mp 160–163 °C; ^{1}H NMR ($CDCl_3$) δ 1.19 (t, J=7.2 Hz, 3H), 3.61 (d, J=3 Hz, 1H), 4.17 (q, J=7.2 Hz,

2H), 4.91 (s, 1H), 5.49 (br, s, 1H), 6.19 (br, s, 1H), 7.2–7.37 (m, 5H), 7.52 (br, s, 1H); ^{19}F NMR δ −64.27 (s, 3F); IR (KBr) ν_{max} 3444, 3232, 3169, 1701, 1680, 1305, 1159 cm^{-1}; MS (70 eV, EI) *m/z* (%): 356 (M^+, 1.98), 312 (M^+-CONH_2, 100), 69 (CF_3, 7.23), 44 ($CONH_2^+$, 53.82). Anal. Calcd for $C_{16}H_{15}F_3N_2O_4$: C, 53.93%; H, 4.21%; N, 7.87%. Found: C, 53.87%; H, 4.38%; N, 7.85%.

4.2.2. Ethyl 5-carbamoyl-4-(4-methoxyphenyl)-6-oxo-2-(trifluoromethyl)-1,4,5,6-tetrahydropyridine-3-carboxylate 5b. White solid; mp 151–153 °C; ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J=7.2 Hz, 3H), 3.58 (d, J=3.6 Hz, 1H), 3.78 (s, 3H) 4.16 (q, J=7.2 Hz, 3H), 4.83 (s, 1H), 5.51 (br, s, 1H), 6.18 (br, s, 1H), 6.85 (d, J_{AB}=8.4 Hz, 2H), 7.27 (d, J_{AB}=8.4 Hz, 2H), 7.54 (br, s, 1H); ^{19}F NMR δ −62.95 (s, 3F); IR (KBr) ν_{max} 3403, 3170, 2943, 1682, 1611, 1512, 1307, 1180 cm^{-1}; MS (70 eV, EI) *m/z* (%): 386 (M^+, 2.21), 342 (M^+-CONH_2, 100), 69 (CF_3, 7.46), 44 ($CONH_2^+$, 44.48). Anal. Calcd for $C_{17}H_{17}F_3N_2O_5$: C, 52.85%; H, 4.40%; N, 7.25%. Found: C, 52.95%; H, 4.49%; N, 7.34%.

4.2.3. Ethyl 5-carbamoyl-6-oxo-4-*p*-tolyl-2-(trifluoromethyl)-1,4,5,6-tetrahydropyridine-3-carboxylate 5d. White solid; mp 155–158 °C; ^{1}H NMR ($CDCl_3$) δ 1.19 (t, J=7.2 Hz, 3H), 2.31 (s, 3H), 3.58 (d, J=2.7 Hz, 1H), 4.15 (q, J=7.2 Hz, 2H), 4.83 (s, H), 5.76 (br, s, 1H), 6.22 (br, s, 1H), 7.07–7.14 (m, 4H), 7.98 (br, s, 1H); ^{19}F NMR δ −64.32 (s, 3F); IR (KBr) ν_{max} 3446, 3048, 3232, 3146, 1701, 1637, 1607, 1307, 1165 cm^{-1}; MS (70 eV, EI) *m/z* (%): 370 (M^+, 0.52), 326 (M^+-CONH_2, 100), 69 (CF_3, 1.55), 44 ($CONH_2^+$, 4.32). Anal. Calcd for $C_{17}H_{17}F_3N_2O_4$: C, 55.14%; H, 4.59%; N, 7.57%. Found: 55.08%; H, 4.56%; N, 7.70%.

4.2.4. Ethyl 5-carbamoyl-4-(4-chlorophenyl)-6-oxo-2-(trifluoromethyl)-1,4,5,6-tetrahydropyridine-3-carboxylate 5e. White solid; mp 176–178 °C; ^{1}H NMR ($CDCl_3$) δ 1.21 (t, J=7.2 Hz, 3H), 3.56 (d, J=3 Hz, 1H), 4.17 (q, J=7.2 Hz, 2H), 4.89 (s, 1H), 5.52 (br, 1H), 6.19 (br, s, 1H), 7.14–7.17 (m, 2H), 7.27–7.51 (m, 2H), 7.75 (br, s, 1H); ^{19}F NMR δ −64.30 (s, 3F); IR (KBr) ν_{max} 3446, 3228, 3139, 2952, 1701, 1603, 1493, 1372, 1303, 1165 cm^{-1}; MS (70 eV, EI) *m/z* (%): 390 (M^+, 0.71), 348/346 (M^+-CONH_2, 37.11/100), 69 (CF_3, 4.88), 44 ($CONH_2^+$, 10.35). Anal. Calcd for $C_{16}H_{14}ClF_3N_2O_4$: C, 49.17%; H, 3.59%; N, 7.17%. Found: 49.10%; H, 3.74%; N, 7.17%.

4.2.5. Ethyl 5-carbamoyl-4-(4-fluorophenyl)-6-oxo-2-(trifluoromethyl)-1,4,5,6-tetrahydropyridine-3-carboxylate. 5f. White solid; mp 137–139 °C; ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J=7.2 Hz, 3H), 3.57 (d, J=3.3 Hz, 1H), 4.16 (q, J=7.2 Hz, 2H), 4.90 (s, 1H), 5.55 (br, s, 1H), 6.20 (br, s, 1H), 6.96–7.07 (m, 2H), 7.18–7.28 (m, 2H), 7.51 (br, s, 1H); ^{19}F NMR δ −64.36 (s, 3F), −114.23 (m, 1F); IR (KBr) ν_{max} 3444, 1697 (br), 1606, 1373, 1305, 1163 cm^{-1}; MS (70 eV, EI) *m/z* (%): 374 (M^+, 0.50), 330 (M^+-CONH_2, 100), 69 (CF_3, 2.85), 44 ($CONH_2^+$, 5.85); HRMS for $C_{16}H_{14}F_4N_2O_4Na^{+1}$ Calcd: 397.0781. Found: 397.0794.

4.2.6. Ethyl 5-carbamoyl-4-(4-nitrophenyl)-6-oxo-2-(trifluoromethyl)-1,4,5,6-tetrahydropyridine-3-carboxylate 5g. White solid; mp 190–195 °C; ^{1}H NMR ($CDCl_3$) δ 1.21 (t, J=7.2 Hz, 3H), 3.59 (d, J=3 Hz, 1H), 4.18 (q, J=7.2 Hz, 2H), 5.05 (s, 1H), 5.50 (br, 1H), 6.24 (br, s, 1H), 7.41–7.43 (m, 2H), 7.48 (br, s, 1H), 8.21–8.24 (m, 2H); ^{19}F NMR δ −64.22 (s, 3F), IR (KBr) ν_{max} 3408, 3217, 3119, 1716, 1678, 1624, 1599, 1519, 1353, 1305 cm^{-1}; MS (70 eV, EI) *m/z* (%): 401 (M^+, 0.59), 357 (M^+-44, 100), 69 (CF_3, 4.28), 44 ($CONH_2^+$, 13.25). Anal. Calcd for $C_{16}H_{14}F_3N_3O_6$: C, 47.88%; H, 3.49%; N, 10.47%. Found: 47.92%; H, 3.43%; N, 10.58%.

4.3. X-ray crystal structure data of compounds 3d, 4d and 5d

Intensity data were collected at 293(2) K on Bruker P4 diffractometer with graphite monochromator and Mo Kα radiation (λ=0.71073 Å). The structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically, hydrogen atoms were included but not refined. The final cycle of full matrix least-squares refinement was based on $F2$, respectively. All calculations were performed using SHELXS-97 and SHELXL-97 programs. X-ray data for compounds **3d**, **4d** and **5d** are listed in Table 6.

Crystallographic data have been deposited to the Cambridge Crystallographic Data Center, CCDC 284791 for **3d**, 284792 for **4d** and 284793 for **5d**. Copies of the information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.ac.uk), upon request.

Acknowledgements

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A direct synthesis of 1,7-dioxaspiro[4.5]decanes from the new 3-methylidenepentane-1,5-dianion synthon

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Dedicated to Professor Víctor Riera on occasion of his 70th birthday

Abstract—4-Phenylsulfanyl-2-(2-phenylsulfanylethyl)but-1-ene (**2**) has proved to be an appropriate and new 3-methylidenepentane-1,5-dianion synthon. The reaction of **2** with an excess of lithium powder and a catalytic amount of DTBB (2.5%) in the presence of a carbonyl compound in THF at 0 °C, leads, after hydrolysis, to the expected methylidenic diols **3**. These diols undergo double intramolecular iodoetherification promoted by a silver salt, to furnish the corresponding 1,7-dioxaspiro[4.5]decanes (**4**) in very high yields. The oxidation of compounds **4** to the corresponding lactones is also studied.

1. Introduction

A variety of different methylidene dianion synthons have been developed during the last decade in order to study their reactivity and possible applications. Most of the attention has been devoted to the trimethylenemethane dianion synthons (**I**) since they are readily accessible and can react with one or two electrophiles, allowing the incorporation of two equal or different moieties, respectively.[1] The versatility of the resulting structures resides on the presence of a methylidenic unit, which can be subjected to further transformations. Less attention has been paid, however, to trimethylenemethane dianion homologue synthons such as 2-methylidenebutane-1,4- (**II**)[2] or 3-methylidenepentane-1,5-dianion (**III**) synthons (Chart 1).

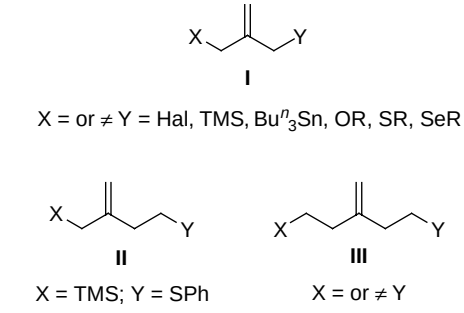

Chart 1.

On the other hand, spirocyclic ethers are widespread in Nature and have attracted much attention from the synthetic point of view. Especially abundant are the 1,5-dioxaspiro[2.4]heptane[3] and 1,7-dioxaspiro[4.4]nonane[4] skeletons, which can be found in many natural products with interesting biological activities. Within the 1,*n*-dioxaspiro[4.5]decane series, those in the ketal form like 1,4-dioxa- (Chart 2, $n=4$) and 1,6-dioxaspiro[4.5]decanes (Chart 2, $n=6$) are well known and easy to prepare, whereas compounds containing the 1,8-dioxaspiro[4.5]decane unit[5] (Chart 2, $n=8$) are less frequent but have also been deeply studied in the last decade.

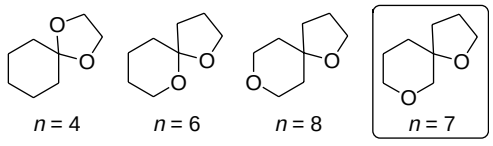

Chart 2. 1,*n*-Dioxaspiro[4.5]decanes.

Keywords: Dianion synthon; Spirocyclic ethers; Intermolecular hydrogen bonding; DTBB-catalysed lithiation.
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In contrast, the 1,7-dioxaspiro[4.5]decane moiety (Chart 2, $n=7$) is very uncommon in Nature and has been little studied at a methodological and synthetic level. Thus, it can be found, in its lactone form, in the structure of camelliatannin G (**IV**, isolated from the leaves of *Camellia japonica* and belonging to a family of complex tannins that show *anti*-HIV activity)[6] or in stemotinine (**V**) and isostemotinine (isolated from the roots of *Stemona tuberose* Lour., which are used in Chinese medicine as insecticides and anticough agents).[7] The mentioned unit is also present in the widely studied reduction products of both artemisinin and its derivatives (i.e., **VI**)[8] as well as in a variety of compounds with use as plant growth regulators and herbicides (i.e., **VII**).[9]

Most of the synthetic chemistry directed to the preparation of the title compounds involves specific carbohydrate scaffolds in which different type of substituents on a preformed tetrahydropyran[10] or tetrahydrofuran[11] ring are subjected to intramolecular cyclisation. For instance, the spirocyclic compound **VIII** was prepared by intramolecular six-membered lactol formation,[11] whereas **IX** was obtained by ring-closing metathesis of a 3-allyloxy-3-vinyl tetrahydropyran moiety.[12] To the best of our knowledge there is only one methodology that starts from a completely acyclic precursor and gives the desired spirocyclic unit (but unsaturated) in one step. This strategy gives rise to spirocyclic dihydropyrans like **X** by double ring-closing metathesis of a proper dioxatetraene precursor.[13] A more indirect route, also from an acyclic precursor, utilised the ring-closing metathesis and hydroformylation reactions as the key steps.[14] 1,7-Dioxaspiro[4.5]decane lactones have received even less attention and have been always synthesized as 1,7-dioxaspiro[4.5]decan-2-ones [see the spirocyclic unit highlighted in stemotinine (**V**), Chart 3].[15] However, no report refers to the synthesis of 1,7-dioxaspiro[4.5]decan-6-ones [see the spirocyclic unit highlighted in camelliatannin G (**IV**), Chart 3].

In recent years, we have shown an increasing interest in developing new and versatile methylidenic dianion synthons. As a result of different studies, we found out that 2-chloromethyl-3-chloroprop-1-ene (**XI**) and 2-chloromethyl-3-(2-methoxyethoxy)prop-1-ene (**XII**) allowed the incorporation of two equal or different electrophilic fragments, respectively, through a one-pot arene-catalysed lithiation (Chart 4).[16] These two dianion synthons were successfully applied to the synthesis of fused bicyclic[17] and spirocyclic[18] polyether structures. In a more recent study, we have preliminary introduced 4-phenylsulfanyl-2-(2-phenylsulfanylethyl)but-1-ene (**2**), as a new 3-methylidenepentane-1,5-dianion synthon that has found application in the straight synthesis of 1,7-dioxaspiro[4.5]decanes and perhydropyrano[2,3-*b*]pyrans.[19]

We want to report herein about the scope and limitations of 4-phenylsulfanyl-2-(2-phenylsulfanylethyl)but-1-ene (**2**) as a dianion synthon by studying its reactivity against a large variety of carbonyl compounds, including chiral ketones and aldehydes. The resulting diols can be cyclised to the corresponding 1,7-dioxaspiro[4.5]decanes under the promotion of a silver salt. An improved method to oxidise 1,7-dioxaspiro[4.5]decanes to the corresponding lactones is also described.

2. Results and discussion

We tried first to prepare 4-phenylsulfanyl-2-(2-phenylsulfanylethyl)but-1-ene (**2**) by nucleophilic

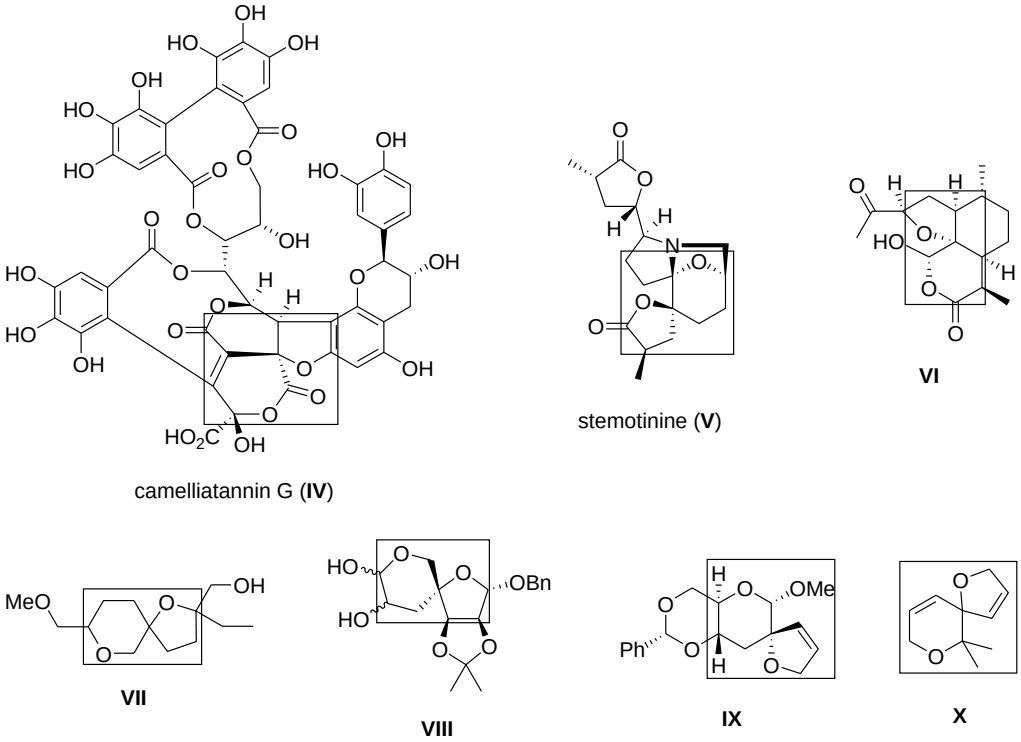


Chart 3.

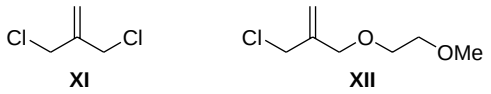


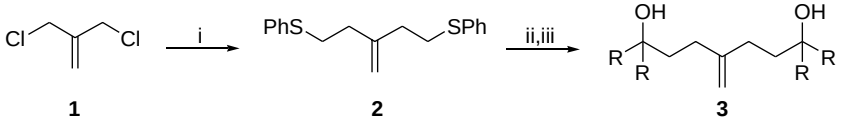
Chart 4.

substitution from commercially available 2-chloromethyl-3-chloroprop-1-ene (**1**) and phenylthiomethyllithium, following Corey's method.[20] This reaction, however, failed and instead, a variant had to be introduced involving the organocuprate reagent derived from $PhSCH_2Li$ and CuCN, affording **2** in 82% yield (Scheme 1). Treatment of compound **2** with an excess of lithium powder (1:7 molar ratio) and a catalytic amount of DTBB (4,4′-di-*tert*-butylbiphenyl, 1:0.1 molar ratio, 2.5 mol%), in the presence of different carbonyl compounds (Barbier conditions)[21] in THF, at 0 °C for 2 h, led, after hydrolysis with water, to the corresponding methylidenic diols **3** (Scheme 1 and Table 1). A wide variety of ketones were studied as electrophiles including linear (Table 1, entries 1 and 2), branched (Table 1, entries 3 and 4), cycloalkyl substituted (Table 1, entry 5), cyclic (Table 1, entries 6 and 7), heterocyclic (Table 1, entries 8 and 9) and polycyclic (Table 1, entry 10) ketones, the corresponding methylidenic diols **3** being obtained in modest yields after column chromatography. More interesting was the use of the chiral ketones (−)-menthone (Table 1, entry 11), (±)-norcamphor (Table 1, entry 12), and (−)-fenchone (Table 1, entry 13) as electrophiles. The reaction of the intermediate organolithium species with these electrophiles led to the corresponding C_2-symmetric diols as single diastereoisomers. The nucleophilic attack to the carbonyl group was equatorial for (−)-menthone and *exo* for (±)-norcamphor and (−)-fenchone, diols **3k** and **3m** being obtained as single enantiomers. A crystallographic study of compounds **3l** and **3m** is included in Section 3. In contrast to the reactivity exhibited by ketones, aldehydes were somewhat more reluctant to react under the above described conditions. Nonetheless, an example using pivalaldehyde is included, which gave a ca. 1:1 mixture of diastereoisomers.

With the methylidenic diols **3** in hand, we tried to cyclise them under our previously published iodoetherification conditions.[18] However, the reaction with the system I_2, Ag_2O, dioxane/H_2O 7:1, rt, gave mainly the intermediate iodohydrin, whereas the starting diol remained practically unaltered with the system NaH, THF, I_2, 0 °C to rt. New reaction conditions were developed and optimised by varying the base (Na_2CO_3, Et_3N) and the silver source (AgOTf, AgOAc), the best results being achieved using I_2, AgOTf, and Na_2CO_3 in THF at rt. Under those reaction conditions, some of the diols **3** readily underwent double intramolecular cyclisation to the corresponding 1,7-dioxaspiro[4.5]decanes **4** in excellent isolated yields without any further purification (Scheme 2 and Table 2). It is worthy of note that those diols containing electrophilic fragments derived from cyclic ketones rendered structurally interesting trispiro compounds in a very straight manner (Table 2, entries 5–9). Among them, compound **4h** (Table 2, entry 7) is of a particular interest due to its trispirocyclic polyether skeleton. Compound **4m** (Table 2, entry 9) was obtained as a 1.73:1 mixture of diastereoisomers, the chiral nature of the precursor diol exhibiting, therefore, a low asymmetric induction toward the generation of the new stereocentre in the spirocyclic core. The presence of the 1,7-dioxaspiro[4.5]decane moiety in compounds **4** was determined by spectroscopic means, and unequivocally established by X-ray crystallography of compound **4j** (Table 2, entry 8) (see Section 3).

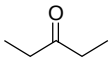
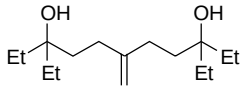
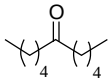
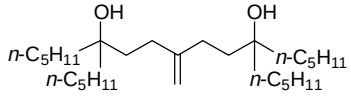
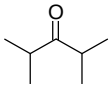
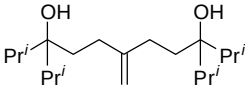
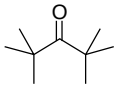
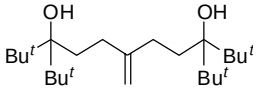
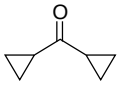
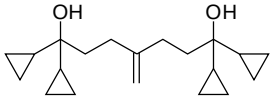
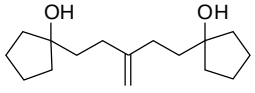
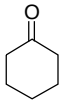
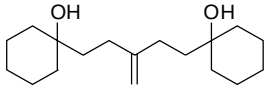
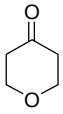
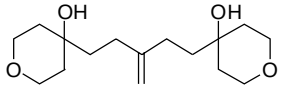
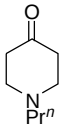
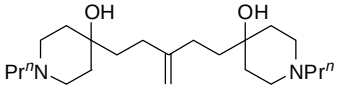
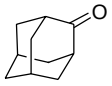
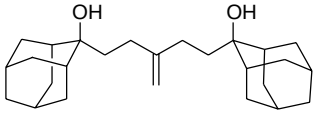
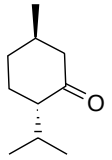
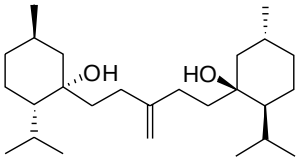
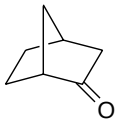
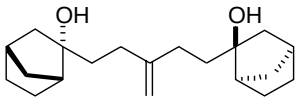
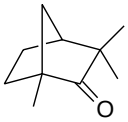
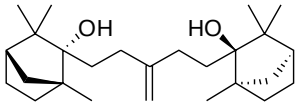
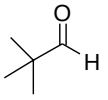
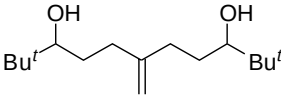
It is noteworthy that, in contrast to the homologous 1,5-dioxaspiro[2.4]heptanes,[18b] 1,6-dioxaspiro[3.4]octanes,[18a] or 1,7-dioxaspiro[4.4]nonanes,[18c,d] which exhibited in ^1H NMR a standard AB system for the CH_2O group in the tetrahydrofuran ring, in the present case the situation is quite different. In fact, all the 1,7-dioxaspiro[4.5]decanes prepared showed one of the CH_2O protons split (as a dd), inside an AB system (see Section 5.4). This particular behaviour was attributed to a long-range 4σ-bond coupling involving the equatorial protons attached to the carbon atoms 6 and 10 (Figs. 1 and 2). The different $^4J_{eq-eq}$ values observed lie in the 0–2 Hz range expected for that spin–spin coupling in cyclohexanes,[22] what additionally confirms the presence of a tetrahydro-2*H*-pyran ring.

We devised the possibility to transform diols **3** into the corresponding 1,7-dioxaspiro[4.5]decan-6-ones by oxidation adjacent to the tetrahydropyran oxygen atom. Compound **4b** was used as a model substrate and subjected to the ruthenium-catalysed oxidation under the conditions described in the literature[23] and applied by us to other homologue spirocyclic ethers.[18b–d] This compound, however, showed to be reluctant to oxidation when treated with a catalytic amount of RuO_2 (0.15 equiv) and an excess of $NaIO_4$ (4.88 equiv), in CCl_4–H_2O (1/1) at rt (Scheme 3). Thus, only 29% conversion was obtained after the standard reaction time of 24 h (Table 3, entry 1). A moderate conversion of 61% was reached after 1 week, whereas the more desired 95% conversion was only achieved after a prohibitive reaction time of 36 days (Fig. 3). We made an effort in order to improve the above mentioned results by varying the different parameters involved in this transformation, namely: the ruthenium catalyst, the stoichiometric oxidising agent, the solvent, presence or absence of a phase-transfer agent, as well as the reaction conditions. As it is shown in Table 3, very poor results were obtained in most cases, independently of the parameters and reaction conditions used. Even the methodology developed by Balavoine et al. for the oxidation of cyclic ethers, involving the use of hydrated $RuCl_3$, failed (Table 3, entry 10).[24] We observed, however, that, in general, these low conversions were reached irrespective of the reaction time. From this

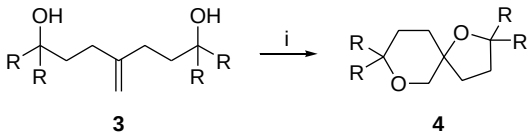


Scheme 1. Reagents and conditions: (i) $PhSCH_2Li$, CuCN, LiCl, 0 °C, 2 h; (ii) Li, DTBB (2.5 mol%), R_2CO, THF, 0 °C, 2 h; (iii) H_2O.

Table 1. Preparation of the methylidenic diols **3**

Entry	Electrophile	Product **3**[a]		
		No.	Structure	Yield (%)[b]
1		**3a**		55
2		**3b**		50
3		**3c**		52
4		**3d**		54
5		**3e**		41
6		**3f**		57
7		**3g**		58
8		**3h**		37[c]
9		**3i**		35[c]
10		**3j**		33[d]
11		**3k**		48[e]
12		**3l**		47[f]
13		**3m**		49[e]
14		**3n**		42[g]

[a] All products were ≥95% pure (GLC and/or 300 MHz ^{1}H NMR) and were fully characterised by spectroscopic means (IR, ^{1}H and ^{13}C NMR, and MS).
[b] Isolated yield after column chromatography, unless otherwise stated (silica gel, hexane/EtOAc), based on the starting compound **2**.
[c] Purification by column chromatography was carried out with EtOAc/MeOH as eluant.
[d] Isolated yield after recrystallisation with hexane.
[e] As a single enantiomer.
[f] As a single diastereoisomer.
[g] As a ca. 1:1 mixture of diastereoisomers.



Scheme 2. I_2, AgOTf, Na_2CO_3, THF, rt, 5–12 h.

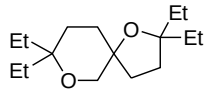
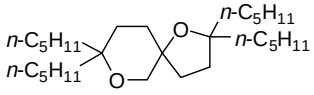
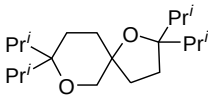
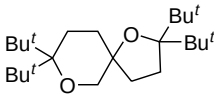
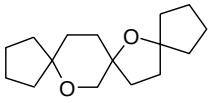
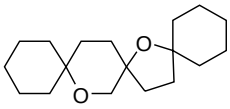
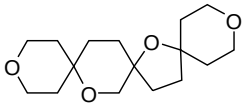
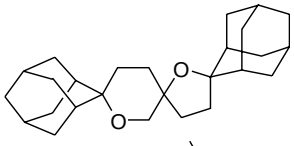
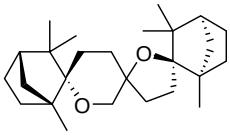
3. X-ray crystallographic study

The structure of compounds **3l**, **3m**, and **4j** was unequivocally established by X-ray crystallography.

3.1. Compound 3l [(±)-norcamphor derivative]

Figure 4 shows a single molecule of the diol **3l** in which it can be seen how the dianion attack to the carbonyl group of

Table 2. Preparation of the 1,7-dioxaspiro[4,5]decanes **4**

Entry	Reaction time (h)	Product 4[a]		
		No.	Structure	Yield (%)[b]
1	12	**4a**		95
2	12	**4b**		96
3	12	**4c**		94
4	5	**4d**		94
5	12	**4f**		95
6	12	**4g**		99
7	12	**4h**		94
8	6	**4j**		98
9	6	**4m**		90[c]

[a] All products were ≥95% pure (GLC and/or 300 MHz ^{1}H NMR) and were fully characterised by spectroscopic means (IR, ^{1}H and ^{13}C NMR, and MS).
[b] Isolated yield of pure **4** from the reaction crude, unless otherwise stated, based on the starting diol **3**.
[c] Isolated yield after column chromatography (silica gel, hexane/EtOAc), based on the starting compound **3**. Compound obtained as a 1.73:1 mixture of diastereoisomers.

observation it might be inferred that the reaction proceeds fast at the beginning but at some stage the catalyst gets completely deactivated and interrupts the catalytic cycle. This fact led us to try the addition of the catalyst and the stoichiometric oxidising agent in several portions, this method providing the best conversion within a reasonable reaction time (Table 3, entry 13). By using this procedure, several representative 1,7-dioxaspiro[4.5]decanes were transformed into the corresponding lactones, 1,7-dioxaspiro[4.5]decan-6-ones, in fair yields (Chart 5).

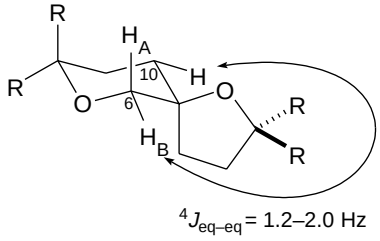


Figure 1. Long-range 4σ-bond diequatorial coupling in the tetrahydro-2*H*-pyran ring of the 1,7-dioxaspiro[4.5]decanes **4**.

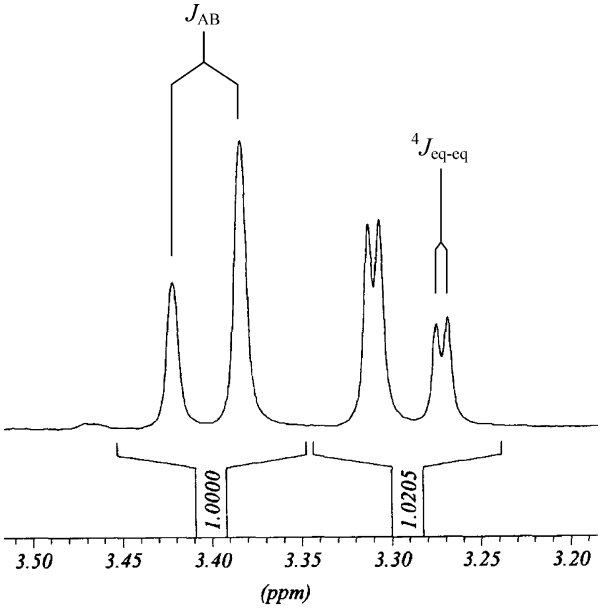
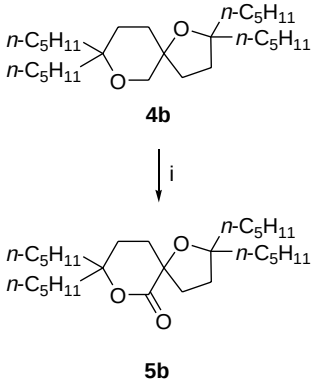


Figure 2. Typical ^{1}H NMR region for the CH_2O group of the 1,7-dioxaspiro[4.5]decanes **4**.



Scheme 3. (i) RuO_2 (cat.), $NaIO_4$, CCl_4, H_2O, rt.

(±)-norcamphor took place following an *exo* direction, giving rise to the corresponding *endo* diol. Interestingly, intermolecular hydrogen bonding was observed involving the four hydroxyl groups of two diol molecules (Fig. 5). A cross-shape orientation of the two diol molecules minimised steric hindrance facilitating the intermolecular hydrogen bonding through a near-square arrangement of the four hydroxyl groups. In addition, one of the diol molecules in the asymmetric part of the unit cell exhibits a static disorder for one of the norbornyl moieties, in such a way that 50% of the molecules at that position have a symmetry binary axis, whereas for the other 50% of the molecules this kind of axis is absent (Fig. 5).

3.2. Compound 3m [(−)-fenchone derivative]

The structure of enantiomerically pure **3m** could be also confirmed by X-ray crystallographic analysis. In this case, as in the case of compound **3l**, an *exo* dianion attack to the carbonyl group of (−)-fenchone was also preferred (Fig. 6). A 50% disorder is observed affecting the hydroxyl group hydrogen (Fig. 6). At one of the positions, a hydrogen bond is formed involving the hydroxyl group of a neighbour molecule. At the other position, however, has no acceptor within the bonding distance (Fig. 6). In the crystal, the hydroxyl group hydrogen atoms are 50% located at the positions showed in bold bond, whereas the other 50% are located as shown in hashed bond (Figs. 7 and 8). In contrast with the hydrogen bonding observed for diol **3l**, in this case each hydroxyl group is hydrogen-bonded to a different diol molecule, thus leading to a wavy three-dimensional scaffold (Fig. 8).

3.3. Compound 4j

X-ray crystallographic analysis of compound **4j** unequivocally confirmed the presence of the 1,7-dioxaspiro[4.5]-decane moiety in compounds **4** (Fig. 9). The crystal is a non-merohedric twin, which can be solved after calculating the twin law matrix using the ROTAX programme.[25]

Table 3. Oxidation of compound **4b**

Entry	Catalyst	Re-oxidant	Solvent	Additive	Physical activation	Time (h)	Conversion (%)[a]
1	RuO_2	$NaIO_4$	CCl_4–H_2O	—	—	24	29
2	RuO_2	$NaIO_4$	CCl_4–H_2O	—	Thermal (50 °C)	24	25
3	RuO_2	$NaIO_4$	CCl_4–H_2O	—	Thermal (reflux)	48	39
4	RuO_2	$NaIO_4$	CCl_4–H_2O–MeCN	—	—	24	7
5	RuO_2	$NaIO_4$	CCl_4–H_2O–MeCN	—	MW (3–10 bar, 65–80 °C)	0.17	15
6	RuO_2	$NaIO_4$	CCl_4–H_2O–MeCN	—	MW (3–10 bar, 65–80 °C) followed by ultrasounds	0.17+1	15
7	RuO_2	aq NaClO	CCl_4–H_2O	—	—	24	13
8	RuO_2	aq NaClO	CCl_4–H_2O	TBAB[b]	—	24	14
9	RuO_2	aq NaClO	CCl_4–H_2O	TBAB	MW (10 bar, 80 °C)	0.17	12
10	$RuCl_3 \cdot xH_2O$	aq NaClO	CH_2Cl_2	CTAB[c]		24	31
11	$RuCl_3 \cdot xH_2O$	$NaIO_4$	CH_2Cl_2	CTAB	Thermal or MW	24	30
12	$RuCl_3 \cdot xH_2O$	$NaIO_4$	CCl_4–H_2O	CTAB	—	24	48
13	$RuCl_3 \cdot xH_2O$[d]	$NaIO_4$	CCl_4–H_2O	CTAB	Thermal (reflux)	5	61

[a] Determined by GLC.
[b] TBAB, tetra-*n*-butylammonium bromide.
[c] CTAB, cetyltriethylammonium bromide.
[d] Added together with $NaIO_4$ as a water solution in five portions at intervals of 1 h.

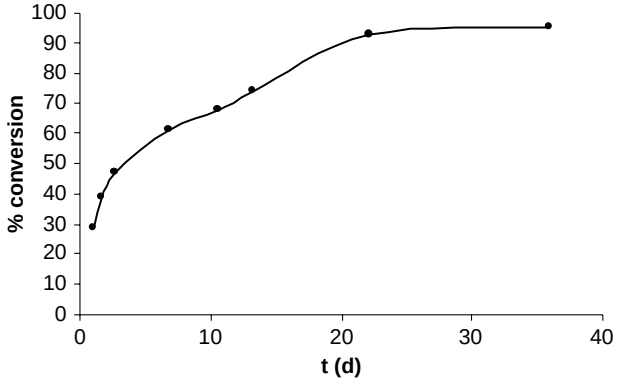
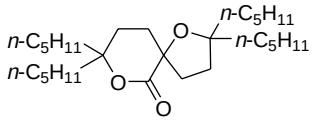
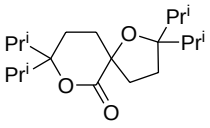


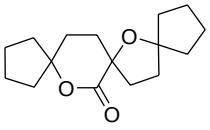
Figure 3. Graphic showing the oxidation of compound **4b** to **5b** versus time, under the conditions depicted in Scheme 3.



5b (61%)



5c (51%)



5f (52%)

Chart 5. Oxidation of compounds **4b**,**c**,**f** under the conditions shown in Table 3, entry 13.

4. Conclusion

In conclusion, we have developed a new 3-methylidene-pentane-1,5-dianion synthon, which has demonstrated to be very useful for the preparation of symmetrically substituted methylidenic 1,7-diols. These diols can be transformed into the corresponding 1,7-dioxaspiro[4.5]decanes in excellent yields and in a straightforward manner under the promotion of a silver salt. In addition, an improved method allows the oxidation of the mentioned spirocyclic ethers to the corresponding lactones.

5. Experimental

5.1. General

Melting points were obtained with a Reichert Thermovar apparatus. Optical rotations were measured with a Perkin-Elmer 341 polarimeter with a thermally jacketted 10 cm cell at approximately 20 °C. Concentrations (*c*) are given in g/100 mL and [α] values are given in units of 10^{-1} deg cm^2 g^{-1}. NMR spectra were recorded on a Bruker Avance 300 and Bruker Avance 400 (300 and 400 MHz for ^{1}H NMR, and 75 and 100 MHz for ^{13}C NMR, respectively) using $CDCl_3$ as solvent and TMS as internal standard; chemical shifts are given in δ (ppm) and coupling constants (*J*) in Hz. Mass spectra (EI) were obtained at 70 eV on a Shimadzu QP-5000 and Agilent 5973 spectrometers, fragment ions in *m*/*z* with relative intensities (%) in parenthesis. HRMS analyses were carried out on a Finnigan MAT95S spectrometer. Elemental analyses were performed on a Carlo Erba CHNS-O EA1108 elemental analyser. The purity of volatile and the chromatographic analyses (GLC) were determined with a Hewlett Packard HP-5890 instrument equipped with a flame ionisation detector and a 30 m capillary column (0.32 mm diametre, 0.25 μm film thickness), using nitrogen (2 mL/min) as carrier gas, $T_{injector}=275$ °C, $T_{column}=60$ °C (3 min) and 60–270 °C (15 °C/min); retention times (t_r) are given under these conditions. Column chromatography was performed using silica gel 60 of 40–60 microns. Thin-layer chromatography was carried out on TLC plastic sheets with silica gel 60 F_{254} (Merck). THF was directly used without any purification (Acros, 99.9%). Lithium powder was commercially available (MEDALCHEMY S.L.).

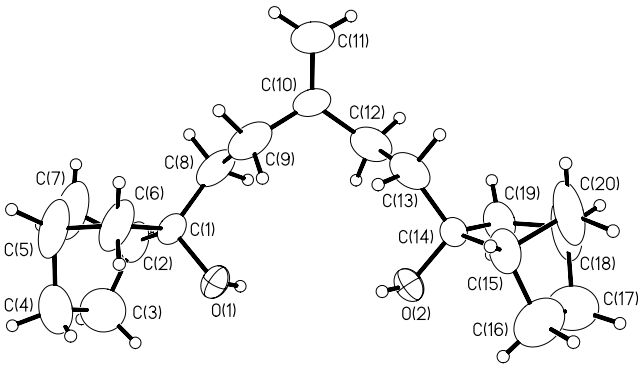


Figure 4. Plot showing the X-ray structure and atomic numbering for one non-disordered molecule of the diol **3l**.

5.2. Procedure for the preparation of 4-phenylsulfanyl-2-(2-phenylsulfanylethyl)but-1-ene (2)

n-BuLi (14.00 mL, 22 mmol) was added to a solution of thioanisole (2.34 mL, 20 mmol) in dry THF (50 mL), the resulting solution being stirred for 15 min at rt. Then, a light-blue solution of LiCl (1.86 g, 44 mmol) and CuCN (2.00 g, 22 mmol) in dry THF (50 mL) was added at 0 °C. Once the deep-brown organocopper reagent was generated (ca. 15 min), 2-chloromethyl-3-chloroprop-1-ene (**1**) (1.17 mL, 10 mmol) was added at 0 °C. The mixture was stirred for 2 h and hydrolised with water (10 mL), followed by the addition of aq 25% ammonia (10 mL) and extraction with hexane (3×30 mL). It is recommended to wash the organic phase with more aq ammonia solution in the case of some remaining emulsion. The organic phases were dried over anhydrous $MgSO_4$, the solvents were evaporated under reduced pressure (15 Torr), and the residue was purified by column chromatography (silica gel, hexane/EtOAc), furnishing 2.42 g (82% yield) of compound **2**.

5.2.1. 4-Phenylsulfanyl-2-(2-phenylsulfanylethyl)but-1-ene (2). Orange oil; t_r 19.00; R_f 0.35 (hexane); ν (film) 3073, 3057, 1644, 896, 737, 690 (C=CH), 1941, 1868, 1791 cm^{-1} (comb.); δ_H 2.36 (4H, t, $J=6.9$ Hz, 2×CH_2CH_2S), 3.00 (4H, t, $J=6.9$ Hz, 2×CH_2S), 4.88 (2H,

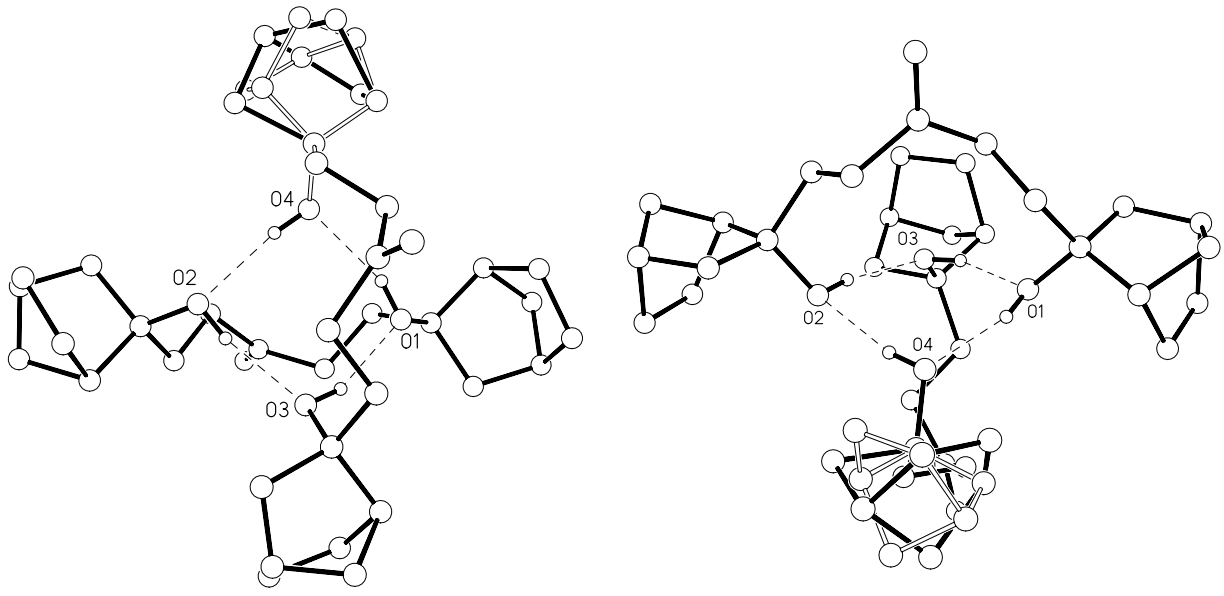


Figure 5. Two views of the hydrogen-bonding pattern between the hydroxyl groups of two molecules of the diol **3l** in the asymmetric part of the unit cell. The atoms are shown as spheres and the hydrogen atoms (except those involved in the hydrogen bonds) are omitted for clarity. Disorder components of the norbornyl moiety are shown with a different type of bond.

s, H_2C═C), 7.20–7.40 (10H, m, 10×ArH); δ_C 31.9 (2×CH_2S), 35.4 (2×CH_2CH_2S), 112.0 (H_2C═C), 126.0, 128.9, 129.2 (10×ArCH), 136.3 (2×ArC), 145.7 (C═CH_2); *m*/*z* 300 (M^+, 8%), 191 (34), 190 (46), 177 (10), 123 (100), 109 (10), 77 (10). HRMS calcd for $C_{18}H_{20}S_2$ 300.1006, found 300.0995.

5.3. General procedure for the preparation of diols 3

A solution of 4-phenylsulfanyl-2-(2-phenylsulfanylethyl)-but-1-ene (**2**) (300 mg, 1 mmol) and the corresponding carbonyl compound (2 mmol) in THF (4 mL) was added to a green suspension of lithium powder (50 mg, 7 mmol) and DTBB (27 mg, 0.1 mmol) in THF (3 mL) at 0 °C. After stirring for 2 h at 0 °C, the resulting mixture was hydrolysed with water (5 mL), extracted with EtOAc (3×10 mL), and the organic phases dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure (15 Torr) and the reaction crude purified by column chromatography [silica gel, hexane/EtOAc (compounds **3a**–**g**,**k**–**n**), EtOAc/MeOH (compounds **3h**,**i**)] or recrystallisation with hexane (compound **3j**).

5.3.1. 3,9-Diethyl-6-methyleneundecane-3,9-diol (3a). Colourless oil; t_r 14.08; R_f 0.38 (hexane/EtOAc 8:2); ν (film) 3384 (OH), 1644 cm^{-1} (C═CH); δ_H 0.87 (12H, t, J=7.5 Hz, 4×CH_3), 1.48 (8H, q, J=7.5 Hz, 4×CH_2CH_3), 1.52–1.65 (6H, m, 2×OH, 2×CH_2CH_2C═CH_2), 2.00–2.10 (4H, m, 2×CH_2C═CH_2), 4.75 (2H, s, H_2C═C); δ_C 7.8 (4×CH_3), 30.0, 30.9, 36.4 (4×CH_2CH_3, 2×CH_2CH_2), 74.6 (2×CO), 108.6 (H_2C═C), 150.7 (C═CH_2); *m*/*z* 238 (M^+-18, <1%), 209 (41), 191 (55), 149 (16), 141 (21), 138 (10), 137 (100), 136 (32), 135 (16), 125 (13), 124 (10), 123 (84), 121 (25), 109 (21), 107 (32), 96 (10), 95 (40), 93 (11), 87 (78), 85 (13), 83 (23), 81 (36), 69 (25), 67 (14), 57 (76), 55 (33). HRMS calcd for $C_{16}H_{32}O_2$ 256.2402, ($M^+-C_2H_5$) 227.2006, found 227.2007.

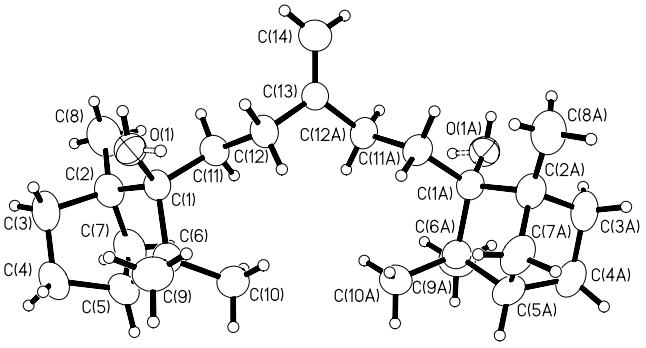


Figure 6. Plot showing the X-ray structure and atomic numbering for diol **3m**.

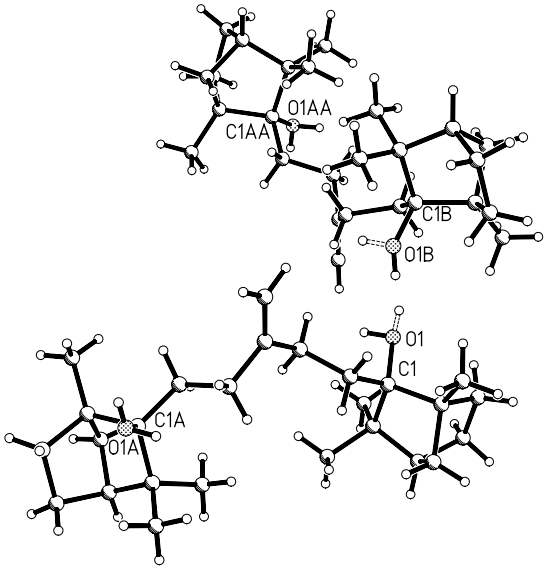


Figure 7. Plot showing the 50% disorder (hashed bonds) observed for the hydroxyl group hydrogen atoms in diol **3m**.

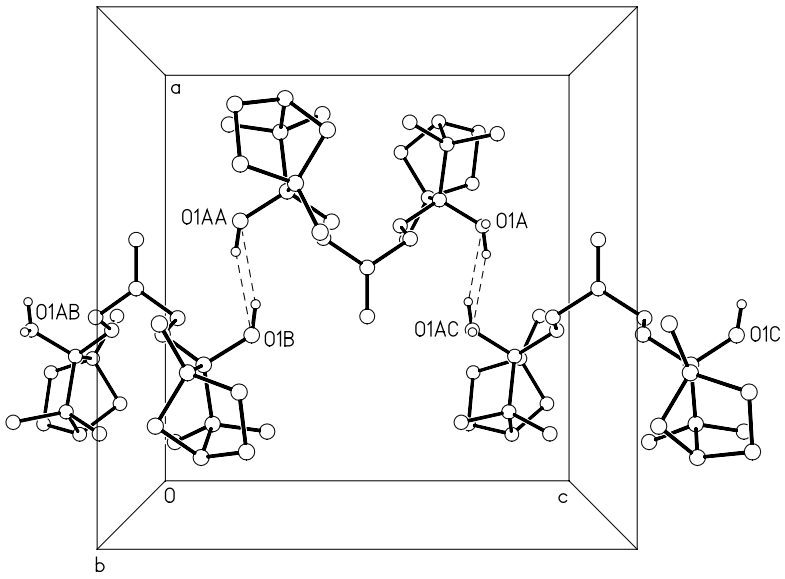


Figure 8. Unit cell plot showing the intermolecular hydrogen bonding between molecules of diol **3m** in the crystal. The hydrogen atoms, except the hydroxyl group hydrogen atoms, have been omitted for clarity.

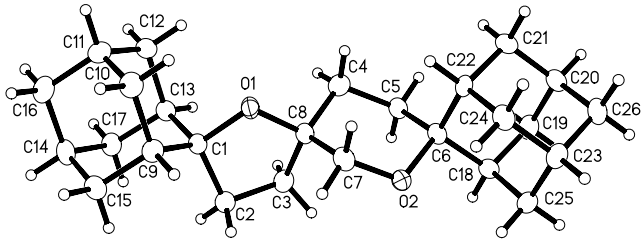


Figure 9. Plot showing the X-ray structure and atomic numbering for compound **4j**.

5.3.2. 9-Methylene-6,12-dipentylheptadecane-6,12-diol (3b). Colourless solid; t_r 23.75; R_f 0.45 (hexane/EtOAc 8:2); mp 65 °C; ν (KBr) 3426 (OH), 1022 cm^{-1} (CO); δ_H 0.89 (12H, t, $J=7.0$ Hz, 4×CH_3), 1.25–1.60 [38H, m, 4×$(CH_2)_4$, 2×C$H_2$$CH_2$C=$CH_2$, 2×OH], 2.00–2.10 (4H, m, 2×CH_2C=CH_2), 4.74 (2H, s, H_2C=C); δ_C 14.1 (4×CH_3), 22.6, 23.2, 30.0, 32.4, 37.4, 39.1 [4×$(CH_2)_4$, 2×CH_2CH_2], 74.4 (2×CO), 108.6 (H_2C=C), 150.7 (C=CH_2); *m/z* 388 (M^+-36, 10%), 336 (26), 335 (100), 331 (11), 318 (18), 317 (69), 236 (11), 225 (27), 222 (11), 221 (59), 220 (29), 207 (19), 179 (20), 172 (11), 171 (90), 167 (15), 165 (33), 163 (19), 151 (16), 149 (16), 137 (13), 127 (11), 123 (14), 111 (18), 110 (19), 109 (22), 99 (49), 97 (29), 95 (34), 93 (14), 83 (33), 81 (30), 71 (43), 69 (41), 67 (15), 57 (23), 55 (51). Anal. Calcd for $C_{28}H_{56}O_2$: C, 79.18; H, 13.29, found C, 79.29; H, 13.81.

5.3.3. 3,9-Diisopropyl-2,10-dimethyl-6-methyleneundecane-3,9-diol (3c). Colourless oil; t_r 16.09; R_f 0.52 (hexane/EtOAc 8:2); ν (film) 3463 (OH), 1645 (C=CH), 1380, 1365, 1020 cm^{-1}(CO); δ_H 0.90–1.00 (24H, m, 8×CH_3), 1.60–1.70, 1.85–1.95 (10H, 2m, 4×CH, 2×CH_2COH, 2×OH), 2.00–2.10 (4H, m, 2×CH_2C=CH_2), 4.74 (2H, s, H_2C=C); δ_C 17.3, 17.6 (8×CH_3), 30.7, 32.3 (2×CH_2CH_2), 34.0 (4×CH), 77.2 (2×CO), 108.4 (H_2C=C), 151.1 (C=CH_2); *m/z* 312 (M^+, <1%), 251 (46), 233 (33), 191 (10), 177 (22), 165 (20), 163 (20), 153 (37), 151 (11), 149 (12), 141 (10), 137 (26), 135 (19), 123 (25), 121 (21), 115 (26), 111 (57), 109 (48), 107 (14), 99 (14), 97 (17), 95 (45), 93 (11), 83 (21), 81 (23), 71 (100), 69 (51), 67 (13), 57 (13), 55 (28). HRMS calcd for $C_{20}H_{40}O_2$ 312.3028, found 312.3028.

5.3.4. 3,9-Di(*tert*-butyl)-2,2,10,10-tetramethyl-6-methyleneundecane-3,9-diol (3d). Colourless solid; t_r 18.43; R_f 0.80 (hexane/EtOAc 8:2); mp 40–42 °C; ν (KBr) 3367 (OH), 1647 cm^{-1} (C=CH); δ_H 1.06 (36H, s, 12×CH_3), 1.70–1.85 (4H, m, 2×CH_2CO), 2.00–2.15, 2.35–2.45 (6H, 2m, 2×OH, 2×CH_2C=CH_2), 4.76 (2H, s, H_2C=C); δ_C 28.6 (12×CH_3), 31.8, 33.0 (2×CH_2CH_2), 42.6 (4×$C$$CH_3$), 79.6 (2×CO), 108.6 ($H_2C$=C), 152.0 ($C$=$CH_2$); *m/z* 350 ($M^+-18$, <1%), 238 (10), 237 (59), 209 (12), 167 (34), 155 (10), 143 (10), 137 (31), 109 (17), 87 (21), 85 (14), 83 (40), 69 (10), 57 (100). Anal. Calcd for $C_{24}H_{48}O_2$: C, 78.20; H, 13.12, found C, 78.25; H, 12.99.

5.3.5. 1,1,7,7-Tetracyclopropyl-4-methyleneheptane-1,7-diol (3e). Colourless oil; t_r 17.26; R_f 0.42 (hexane/EtOAc 8:2); ν (film) 3483 (OH), 3084 (cyclopropyl CH), 1643 (C=CH), 1020 cm^{-1} (CO); δ_H 0.30–0.50 (16H, m, 8×CH_2CH), 0.75–0.95 (4H, m, 4×CH), 1.70–1.80 (4H, m, 2×C$H_2$$CH_2$C=$CH_2$), 2.20–2.35 (6H, m, 2×C$H_2$C=$CH_2$, 2×OH), 4.77 (2H, s, H_2C=C); δ_C −0.6, 0.8 (8×$C$$H_2$CH), 18.4 (4×CH), 30.4, 40.6 (2×CH_2CH_2CO), 70.8 (2×CO), 108.2 (H_2C=C), 151.0 (C=CH_2); *m/z* 286 (M^+-18, <1%), 245 (11), 147 (11), 145 (13), 133 (16), 131 (21), 120 (16), 119 (35), 117 (23), 111 (100), 108 (21), 107 (24), 106 (12), 105 (34), 95 (12), 93 (29), 92 (12), 91 (55), 81 (14), 79 (47), 77 (24), 69 (84), 67 (24), 55 (27). HRMS calcd for $C_{20}H_{32}O_2$ 304.2402, (M^+-H_2O) 286.2297, found 286.2301.

5.3.6. 1-{3-[2-(1-Hydroxycyclopentyl)ethyl]but-3-enyl}-cyclopentan-1-ol (3f). Colourless oil; t_r 15.50; R_f 0.50 (hexane/EtOAc 8:2); ν (film) 3384 (OH), 1643 cm^{-1} (C=CH); δ_H 1.40–2.00 [22H, m, 2×$(CH_2)_4$, 2×C$H_2$$CH_2$-C=$CH_2$, 2×OH], 2.10–2.25 (4H, m, 2×CH_2C=CH_2),

4.76 (2H, s, H_2C=C); δ_C 23.7, 31.3, 39.5, 39.7 (12×CH_2), 82.4 (2×CO), 108.6 (H_2C=C), 150.9 (C=CH_2); *m/z* 234 (M^+-18, <1%), 150 (11), 147 (32), 139 (45), 135 (69), 134 (100), 133 (13), 122 (11), 121 (58), 120 (13), 119 (43), 109 (10), 108 (21), 107 (21), 106 (20), 105 (32), 95 (20), 94 (17), 93 (41), 92 (13), 91 (22), 85 (48), 83 (10), 82 (10), 81 (48), 80 (22), 79 (41), 77 (11), 69 (15), 68 (12), 67 (51), 57 (19), 55 (40), 53 (12). HRMS calcd for $C_{16}H_{28}O_2$ 252.2089, found 252.2097.

5.3.7. 1-{3-[2-(1-Hydroxycyclohexyl)ethyl]but-3-enyl}-cyclohexan-1-ol (3g). Colourless oil; t_r 16.88; R_f 0.40 (hexane/EtOAc 8:2); ν (film) 3354 (OH), 1645 cm^{-1} (C=CH); δ_H 1.30–1.65 [24H, m, 2×$(CH_2)_5$, 2×C$H_2$$CH_2$-C=$CH_2$], 1.65 (2H, br s, 2×OH), 2.05–2.20 (4H, m, 2×CH_2C=CH_2), 4.73 (2H, s, H_2C=C); δ_C 22.2, 25.8, 29.3, 37.3, 40.5 (14×CH_2), 71.4 (2×CO), 108.6 (H_2C=C), 151.1 (C=CH_2); *m/z* 280 (M^+, <1%), 244 (18), 201 (14), 165 (11), 164 (24), 161 (26), 153 (44), 150 (10), 149 (74), 148 (100), 147 (11), 136 (15), 135 (87), 134 (16), 133 (26), 122 (11), 121 (14), 119 (13), 109 (13), 108 (15), 107 (22), 106 (22), 105 (20), 99 (80), 96 (10), 95 (42), 93 (27), 91 (15), 83 (10), 82 (10), 81 (82), 79 (30), 69 (20), 67 (32), 55 (44). HRMS calcd for $C_{18}H_{32}O_2$ 280.2402, found 280.2412.

5.3.8. 4-{3-[2-(4-Hydroxytetrahydro-2*H*-4-pyranyl)-ethyl]but-3-enyl}tetrahydro-2*H*-pyran-4-ol (3h). Colourless solid; t_r 17.59; R_f 0.51 (MeOH/EtOAc 1:9); mp 110 °C; ν (KBr) 3416 (OH), 1644 (C=CH), 1096 cm^{-1} (CO); δ_H 1.45–1.60 (12H, m, 2×CH_2CH_2C=CH_2, 2×C$H_2$$CH_2$-$OCH_2CH_2$), 2.10–2.30 (4H, m, 2×C$H_2$C=$CH_2$), 3.70–3.80 (10H, m, 2×OH, 4×CH_2O), 4.79 (2H, 2s, H_2C=C); δ_C 28.9, 37.6, 41.2 (2×CH_2CH_2C=CH_2, 2×C$H_2$$CH_2$-$OCH_2CH_2$), 63.8 (4×$CH_2O$), 69.0 (2×CO), 109.5 ($H_2C$=C), 149.9 (C=$CH_2$); *m/z* 266 ($M^+-18$, 2%), 167 (11), 166 (10), 155 (22), 151 (14), 150 (26), 138 (24), 137 (16), 122 (12), 121 (17), 120 (11), 119 (17), 110 (11), 109 (42), 107 (24), 106 (10), 105 (17), 101 (51), 99 (38), 97 (22), 96 (100), 95 (14), 94 (10), 93 (23), 91 (17), 83 (50), 81 (19), 79 (24), 73 (15), 71 (42), 69 (12), 68 (15), 67 (21), 55 (55), 53 (21). Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92, found C, 67.69; H, 10.01.

5.3.9. 4-{3-[2-(4-Hydroxy-1-propyl-4-piperidyl)ethyl]-but-3-enyl}-1-propylpiperidin-4-ol (3i). Colourless oil; t_r 21.71; R_f 0.20 (MeOH); ν (film) 3372 (OH), 1649 (C=CH), 1032 cm^{-1} (CO); δ_H 0.94 (6H, t, J=7.49 Hz, 2×C$H_3$$CH_2$), 1.55–2.20 (20H, m, 2×CH_2CH_2C=CH_2, 6×C$H_2$$CH_2$N), 2.50–2.70, 2.85–3.05 (14H, 2m, 2×OH, 6×CH_2N), 4.76 (2H, s, H_2C=C); δ_C 11.6 (2×CH_3), 18.9 (2×C$H_2$$CH_3$), 29.1, 35.3, 40.4 (2×C$H_2CH_2$C=$CH_2$, 4×COC$H_2$$CH_2$N), 49.1, 59.8 (6×$CH_2$N), 68.5 (2×CO), 109.7 ($H_2C$=C), 149.5 (C=$CH_2$); *m/z* 366 ($M^+$, 3%), 224 (25), 198 (32), 180 (16), 170 (12), 154 (25), 150 (10), 145 (11), 142 (11), 141 (10), 140 (100), 137 (10), 124 (11), 98 (34), 86 (13), 72 (16), 70 (16), 56 (14). HRMS calcd for $C_{22}H_{42}N_2O_2$ 366.3246, found 366.3257.

5.3.10. 2-{3-[2-(2-Hydroxy-2-adamantyl)ethyl]but-3-enyl}adamantan-2-ol (3j). Colourless solid; R_f 0.61 (hexane/EtOAc 8:2); mp 167 °C (sub.); ν (KBr) 3324 (OH), 1650 cm^{-1} (C=CH); δ_H 1.50–2.25 (36H, m, 8×CH, 14×CH_2), 2.50 (2H, br s, 2×OH), 4.75 (2H, s, H_2C=C); δ_C 27.2, 27.5, 34.8, 36.8 (8×CH), 28.5, 33.0, 34.5, 35.2, 35.5, 36.9, 38.3 (14×CH_2), 75.1 (2×CO), 108.8 (H_2C=C), 151.7 (C=CH_2); *m/z* 384 (M^+, <1%), 349 (15), 348 (51), 337 (17), 218 (14), 217 (62), 216 (21), 214 (10), 213 (26), 206 (10), 205 (62), 201 (11), 200 (21), 187 (30), 161 (12), 152 (12), 151 (100), 149 (14), 148 (22), 135 (17), 121 (12), 107 (14), 105 (15), 95 (11), 93 (18), 91 (24), 81 (20), 79 (27), 67 (18), 55 (15). Anal. Calcd for $C_{26}H_{40}O_2$: C, 81.20; H, 10.48, found C, 81.23; H, 10.48.

5.3.11. (1*S*,2*S*,5*R*)-1-(3-{2-[(1*S*,2*S*,5*R*)-1-Hydroxy-2-isopropyl-5-methylcyclohexyl]ethyl}but-3-enyl)-2-isopropyl-5-methylcyclohexan-1-ol (3k). Colourless oil; t_r 20.04; R_f 0.43 (hexane/EtOAc 8:2); $[\alpha]_D^{20}$ +4.7 (*c* 1.0, $CHCl_3$); ν (film) 3457 cm^{-1} (OH); δ_H 0.75–1.00 (18H, m, 6×CH_3), 1.05–1.85 (22H, m, 6×CH, 6×CH_2CH, 2×C$H_2$$CH_2$-C=$CH_2$), 1.95–2.10 (6H, m, 2×OH, 2×CH_2C=CH_2), 4.76 (2H, s, H_2C=C); δ_C 18.2, 22.5, 23.6, 25.6, 28.1, 47.9 (6×CH_3, 6×CH), 20.5, 30.5, 35.1, 39.4, 46.7 (10×CH_2), 75.1 (2×CO), 108.7 (H_2C=C), 150.3 (C=CH_2); *m/z* 392 (M^+, <1%), 209 (15), 204 (17), 191 (56), 189 (11), 177 (19), 175 (15), 163 (12), 162 (11), 161 (63), 155 (37), 151 (21), 150 (37), 149 (23), 147 (13), 138 (15), 137 (37), 135 (21), 123 (16), 121 (15), 119 (10), 111 (15), 109 (40), 108 (19), 107 (27), 105 (20), 97 (15), 95 (100), 93 (30), 91 (20), 83 (24), 82 (12), 81 (96), 79 (24), 71 (13), 69 (91), 67 (35), 57 (21), 55 (66). HRMS calcd for $C_{26}H_{48}O_2$ 392.3654, found 392.3649.

5.3.12. (1*R,2*S**,4*S**)-2-(3-{2-[(1*R**,2*S**,4*S**)-2-Hydroxybicyclo[2.2.1]hept-2-yl]ethyl}but-3-enyl)bicyclo[2.2.1]-heptan-2-ol (3l).** Colourless solid; t_r 18.17; R_f 0.41 (hexane/EtOAc 8:2); mp 100–102 °C; ν (KBr) 3383 (OH), 1644 cm^{-1} (C=CH); δ_H 1.05–1.15, 1.25–1.70, 1.85–2.00, 2.05–2.25 (30H, 4m, 4×$CH_2$$CH_2$, 4×$CH_2$CH, 2×OH), 4.76 (2H, s, H_2C=C); δ_C 22.1, 28.5, 30.0, 38.7, 40.3, 45.8 (4×$CH_2$$CH_2$, 4×C$H_2$CH), 37.1, 46.7 (4×CH), 79.6 (2×CO), 108.7 (H_2C=C), 151.2 (C=CH_2); *m/z* 304 (M^+, <1%), 268 (24), 176 (45), 175 (21), 166 (12), 165 (100), 161 (29), 160 (66), 148 (17), 147 (43), 133 (12), 132 (17), 131 (15), 121 (11), 119 (20), 111 (47), 109 (12), 108 (19), 107 (25), 106 (12), 105 (20), 95 (27), 94 (10), 93 (34), 92 (11), 91 (29), 83 (34), 81 (33), 80 (16), 79 (36), 77 (13), 69 (11), 68 (12), 67 (58), 66 (19), 55 (33). Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59, found C, 78.99; H, 10.5.

5.3.13. (1*R*,2*S*,4*S*)-2-(3-{2-[(1*R*,2*S*,4*S*)-2-Hydroxy-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl]ethyl}but-3-enyl)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-ol (3m). Colourless solid; t_r 21.41; R_f 0.43 (hexane/EtOAc 8:2); mp 121–122 °C; $[\alpha]_D^{20}$ −20.1 (*c* 1.1, $CHCl_3$); ν (KBr) 3507 (OH), 1642 (C=CH), 1072 cm^{-1} (CO); δ_H 0.95–1.10 (18H, m, 6×CH_3), 1.30–1.50, 1.60–1.75, 1.85–2.30 (24H, 3m, 2×CH, 4×$CH_2$$CH_2$, 2×CC$H_2$CH, 2×OH), 4.76 (2H, s, H_2C=C); δ_C 18.1, 22.6, 27.7 (6×CH_3), 24.9, 30.7, 31.6, 34.0, 41.1 (4×$CH_2$$CH_2$, 2×C$CH_2$CH), 44.4, 52.8 (4×C$CH_3$), 50.2 (2×CH), 81.1 (2×CO), 108.3 (H_2C=C), 152.2 (C=CH_2); *m/z* 388 (M^+, <1%), 370 (26), 290 (10), 208 (10), 207 (60), 203 (12), 202 (16), 191 (10), 189 (20), 151 (12), 149 (21), 147 (20), 137 (11), 135 (14), 133 (18), 125 (41), 124 (12), 123 (74), 122 (13), 121 (18), 119 (10), 109 (22), 107 (37), 105 (15), 95 (19), 93 (17), 91 (10), 83 (14), 81 (100), 79 (16), 69 (48), 67

(22), 55 (19). Anal. Calcd for $C_{26}H_{44}O_2$: C, 80.35; H, 11.41, found C, 80.22; H, 11.29.

5.3.14. DL and *meso*-2,2,10,10-Tetramethyl-6-methyleneundecane-3,9-diol (3n). Colourless solid; t_r 13.52; R_f 0.50 (hexane/EtOAc 8:2); mp 65–67 °C; ν (KBr) 3395 (OH), 1639 (C=CH), 1018 cm^{-1} (CO); δ_H 0.90 (36H, s, 12×CH_3), 1.35–1.45, 1.60–1.80 (12H, 2m, 4×CH_2CH, 4×OH), 2.00–2.15, 2.25–2.35 (8H, 2m, 4×CH_2C=CH_2), 3.15–3.25 (4H, m, 4×CH), 4.79 (4H, s, H_2C=C); δ_C 25.7 (12×CH_3), 29.4, 29.5, 33.4, 33.6 (4×CH_2CH_2), 34.9 (4×$C$$CH_3$), 79.5, 79.6 (4×CH), 109.2, 109.3 (2×H_2C=C), 150.1, 150.2 (2×C=CH_2); *m/z* 238 (M^+-18, 1%), 181 (18), 163 (45), 137 (30), 135 (13), 123 (22), 121 (18), 111 (14), 109 (26), 107 (30), 100 (25), 97 (17), 96 (17), 95 (37), 93 (32), 87 (14), 85 (44), 84 (10), 83 (100), 82 (21), 81 (32), 79 (14), 71 (16), 70 (20), 69 (46), 67 (16), 57 (73), 55 (29). HRMS calcd for $C_{16}H_{32}O_2$ 256.2402, found 256.2402.

5.4. General procedure for the preparation of 1,7-dioxaspiro[4.5]decanes 4

Iodine (382 mg, 1.5 mmol) was added to a solution of the diol **3** (1 mmol) in THF (10 mL) and the mixture was stirred at rt for 5 min. After the addition of Na_2CO_3 (159 mg, 1.5 mmol) and AgOTf (771 mg, 3 mmol), a white-yellow precipitate was rapidly formed. Additional stirring for 24 h was followed by filtration through a short column containing a layer of Celite over silica gel, using hexane as eluant. Washing with a saturated solution of Na_2SO_3 is recommended if the filtrate is coloured. The resulting solution was dried over Na_2SO_4 and the solvents evaporated under reduced pressure (15 Torr), giving a reaction crude that contained the pure compound **4**, which did not require any further purification.

5.4.1. 2,2,8,8-Tetraethyl-1,7-dioxaspiro[4.5]decane (4a). Colourless oil; t_r 13.04; R_f 0.67 (hexane/EtOAc 8:2); ν (film) 1052 cm^{-1} (CO); δ_H 0.75–0.95 (12H, m, 4×CH_3), 1.25–2.05 (16H, m, 4×C$H_2$$CH_3$, 2×$CH_2CH_2$), 3.27, 3.38 [2H, AB system, J_{AB}=11.3, 3.27 Hz (C$H_{eq}H_{ax}$O, $^4J_{eq-eq}$=2.0 Hz), 3.38 (C$H_{ax}H_{eq}$O)]; δ_C 7.2, 7.7, 8.6, 8.7 (4×CH_3), 29.3, 30.1, 30.9, 31.3, 31.6, 32.8, 33.3, 33.4 (4×$C$$H_2CH_3$, 2×$CH_2CH_2$), 67.9 ($CH_2O$), 74.8, 79.8, 85.9 (3×C); *m/z* 254 (M^+, 1%), 225 (13), 189 (10), 154 (26), 153 (13), 140 (13), 135 (21), 133 (11), 111 (19), 101 (100), 98 (12), 97 (15), 57 (20), 55 (18). HRMS calcd for $C_{16}H_{30}O_2$ 254.2246, found 254.2229.

5.4.2. 2,2,8,8-Tetra(*n*-pentyl)-1,7-dioxaspiro[4.5]decane (4b). Colourless oil; t_r 19.50; R_f 0.68 (hexane/EtOAc 8:2); ν (film) 1067 cm^{-1} (CO); δ_H 0.85–0.90 (12H, m, 4×CH_3), 1.20–2.15 (40H, m, 10×CH_2CH_2), 3.24, 3.38 [2H, AB system, J_{AB}=11.2, 3.24 Hz (C$H_{eq}H_{ax}$O, $^4J_{eq-eq}$=1.2 Hz), 3.38 (C$H_{ax}H_{eq}$O)]; δ_C 14.1 (4×CH_3), 22.6, 22.7, 23.1, 23.9, 24.1, 31.8, 32.4, 32.5, 33.0, 33.5, 34.3, 38.7, 39.4, 39.7, 40.2, (10×CH_2CH_2), 67.9 (CH_2O), 74.6, 79.8, 85.4 (3×C); *m/z* 422 (M^+, <1%), 351 (19), 186 (13), 185 (100). HRMS calcd for $C_{28}H_{54}O_2$ 422.4124, found 422.4103.

5.4.3. 2,2,8,8-Tetraisopropyl-1,7-dioxaspiro[4.5]decane (4c). Colourless oil; t_r 15.33; R_f 0.66 (hexane/EtOAc 8:2); ν (film) 1382, 1365, 1065 cm^{-1} (CO); δ_H 0.80–0.95 (24H, m, 8×CH_3), 1.45–2.05 (10H, m, 2×CH_2CH_2, 2×C$H$$CH_3$), 2.45–2.55 (2H, m, 2×C$H$$CH_3$), 3.33, 3.44 (2H, AB system, J_{AB}=11.2 Hz); δ_C 18.3, 18.5, 18.6, 18.7, 18.8, 18.9 (6×CH_3), 23.6, 28.0, 31.9, 34.0 (2×CH_2CH_2), 27.6, 32.0, 33.4, 34.1 (4×CH), 67.9 (CH_2O), 77.2, 80.1, 90.4 (3×C); *m/z* 295 (M^+-15, <1%), 268 (19), 267 (100), 249 (24), 231 (12), 179 (10), 163 (44), 137 (13), 129 (36), 125 (32), 121 (12), 112 (14), 109 (12), 107 (19), 97 (10), 95 (14), 93 (11), 83 (13), 81 (12), 71 (34), 69 (30), 59 (12), 55 (16). HRMS calcd for $C_{20}H_{38}O_2$ 310.2872, ($M^+-C_3H_7$) 267.2319, found 267.2319.

5.4.4. 2,2,8,8-Tetra(*tert*-butyl)-1,7-dioxaspiro[4.5]decane (4d). Colourless oil; t_r 19.12; R_f 0.80 (hexane/EtOAc 9:1); ν (film) 1112 cm^{-1} (CO); δ_H 1.00–1.15 (36H, m, 12×CH_3), 1.20–2.00 (8H, m, 2×CH_2CH_2), 3.35, 3.41 [2H, AB system, J_{AB}=11.7, 3.35 Hz (C$H_{eq}H_{ax}$O, $^4J_{eq-eq}$=2.1 Hz), 3.41 (C$H_{ax}H_{eq}$O)]; δ_C 26.5, 27.7, 28.4, 28.6, 28.9, 29.2, 29.3, 29.5, 29.7, (12×CH_3), 29.3, 30.8, 31.6, 32.9, (2×CH_2CH_2), 42.9 (4×$C$$CH_3$) 67.4 ($CH_2O$), 76.6, 79.5, 85.3 (3×CO); *m/z* 309 (M^+-57, 27%), 253 (11), 235 (23), 135 (24), 109 (14), 57 (100). HRMS calcd for $C_{24}H_{46}O_2$ 366.3498, found 366.3486.

5.4.5. Trispiro[cyclopentane-1,2′-tetrahydrofuran-5′,3″-tetrahydro-2*H*-pyran-6″,1‴-cyclopentane] (4f). Colourless oil; t_r 14.17; R_f 0.61 (hexane/EtOAc 8:2); ν (film) 1073 cm^{-1} (CO); δ_H 1.30–2.15 (24H, m, 6×CH_2CH_2), 3.33, 3.39 [2H, AB system, J_{AB}=11.5, 3.33 Hz (C$H_{eq}H_{ax}$O, $^4J_{eq-eq}$=1.9 Hz), 3.39 (C$H_{ax}H_{eq}$O)]; δ_C 23.6, 23.9, 24.1, 33.5, 33.8, 33.9, 34.5, 36.4, 38.9, 39.3, 39.7 (6×CH_2CH_2), 69.5 (CH_2O), 79.4, 83.2, 91.2 (3×C); *m/z* 250 (M^+, 3%), 152 (55), 151 (13), 138 (27), 99 (100), 96 (11), 95 (29), 81 (10), 80 (16), 67 (12), 55 (10). HRMS calcd for $C_{16}H_{26}O_2$ 250.1933, found 250.1940.

5.4.6. Trispiro[cyclohexane-1,2′-tetrahydrofuran-5′,3″-tetrahydro-2*H*-pyran-6″,1‴-cyclohexane] (4g). Colourless oil; t_r 15.94; R_f 0.60 (hexane/EtOAc 8:2); ν (film) 1070 cm^{-1} (CO); δ_H 1.20–2.10 (28H, m, 14×CH_2CH_2), 3.29, 3.40 [2H, AB system, J_{AB}=11.4, 3.29 Hz (C$H_{eq}H_{ax}$O, $^4J_{eq-eq}$=1.9 Hz), 3.40 (C$H_{ax}H_{eq}$O)]; δ_C 21.6, 22.0, 24.1, 24.2, 25.6, 26.2, 30.7, 32.8, 33.3, 37.7, 38.7, 39.5 (14×$C$$H_2CH_2$), 67.8 ($CH_2O$), 71.5, 79.5, 83.0 (3×C); *m/z* 278 (M^+, 7%), 166 (42), 165 (13), 152 (15), 113 (100), 109 (14), 95 (12), 94 (26), 81 (12), 67 (13), 55 (12). HRMS calcd for $C_{18}H_{30}O_2$ 278.2246, found 278.2222.

5.4.7. Trispiro[oxacyclohexane-4,2′-tetrahydrofuran-5′,3″-tetrahydro-2*H*-pyran-6″,4‴-oxacyclohexane] (4h). Colourless oil; t_r 16.99; R_f 0.50 (hexane/EtOAc 1:1); ν (film) 1102 cm^{-1} (CO); δ_H 1.40–2.15 (16H, m, 4×CH_2CH_2O, 2×CCH_2CH_2C), 3.34, 3.41 [2H, AB system, J_{AB}=11.6, 3.34 Hz (C$H_{eq}H_{ax}$O, $^4J_{eq-eq}$=1.6 Hz), 3.41 (C$H_{ax}H_{eq}$O)], 3.55–3.90 (8H, m, 4×CH_2CH_2O); δ_C 32.0, 32.3, 33.0, 34.1, 35.4, 36.8, 38.9, 39.3 (4×$C$$H_2CH_2O$, 2×C$CH_2CH_2$C), 63.6, 63.7, 65.5, 65.6, 67.9 (5×CH_2O), 69.1, 77.2, 79.9 (3×CO); *m/z* 282 (M^+, 1%), 169 (13), 168 (43), 167 (10), 154 (11), 115 (100), 109 (10), 96 (30). HRMS calcd for $C_{16}H_{26}O_4$ 282.1831, found 282.1826.

5.4.8. Trispiro[adamantane-2,2′-tetrahydrofuran-5′,3″-tetrahydro-2*H*-pyran-6″,2‴-adamantane] (4j). Colourless solid; t_r 18.33; R_f 0.65 (hexane/EtOAc 8:2); mp 157–158 °C; ν (KBr) 1011 cm^{-1} (CO); δ_H 1.50–2.25 (36H, m, 8×CH, 2×CH_2CH_2, 10×CH_2CH), 3.27, 3.38 [2H, AB system, J_{AB}=11.6, 3.27 Hz ($CH_{eq}H_{ax}O$, $^4J_{eq-eq}$=1.7 Hz), 3.38 ($CH_{ax}H_{eq}O$)]; δ_C 27.1, 27.2, 27.5, 27.8, 29.3, 29.6, 38.3, 39.7 (8×CH), 30.4, 31.9, 32.8, 32.9, 33.4, 33.8, 33.9, 34.1, 34.2, 34.3, 35.8, 36.1, 37.9, 38.2 (10×CH_2CH, 2×CH_2CH_2), 67.4 (CH_2O), 75.4, 79.2, 86.1 (3×C); *m/z* 306 (M^+-76, 2%), 284 (10), 151 (19), 135 (38), 134 (100), 119 (16), 105 (15), 93 (29), 92 (44), 91 (27), 80 (10), 79 (24), 77 (14). Anal. Calcd for $C_{26}H_{38}O_2$: C, 81.62; H, 10.01, found C, 81.63; H, 9.89.

5.4.9. Trispiro[{(1*R*,2*S*,4*S*)-1,3,3-trimethylbicyclo[2.2.1]-heptane}-2,2′-tetrahydrofuran-5′,3″-tetrahydro-2*H*-pyran-6″,2‴-{(1*R*,2*S*,4*S*)-1,3,3-trimethylbicyclo[2.2.1]-heptane}] (4m). Mixture of diastereoisomers (63:37). Colourless oil; t_r 19.65 (major) and 19.72 (minor); R_f 0.65 and 0.68 (hexane/EtOAc 8:2); ν (film) 1069 cm^{-1} (CO); δ_H 0.80–2.10 (80H, m, 8×CH_2CH_2, 4×CH_2CH, 12×CH_3), 3.25–3.45 (4H, m, 2×CH_2O); δ_C (major) 17.8, 19.4, 23.1, 23.6, 28.0, 28.4 (6×CH_3), 25.7, 25.8, 26.5, 29.4, 29.6, 29.9, 33.3, 34.9, 41.2, 41.3 (2×CH_2CH, 4×CH_2CH_2), 44.6, 51.5, 53.1, 53.2 (4×CCH_3), 49.3, 51.0 (2×CH), 70.4 (CH_2O), 78.9, 81.5, 92.1 (3×C); δ_C (minor) 18.1, 21.9, 22.2, 24.2, 27.7, 27.9 (6×CH_3), 25.6, 25.9, 26.3, 28.6, 29.8, 30.3, 34.2, 34.9, 41.4, 43.2 (2×CH_2CH, 4×CH_2CH_2), 43.4, 46.2, 52.1, 53.3 (4×CCH_3), 49.3, 49.4 (2×CH), 70.9 (CH_2O), 78.2, 80.9, 92.1 (3×C); *m/z* (major) 386 (M^+, 7%), 305 (22), 304 (100), 222 (15), 219 (13), 218 (25), 206 (48), 125 (11), 124 (10), 123 (18), 107 (13), 81 (43), 79 (10), 69 (18), 67 (10), 55 (10). *m/z* (minor) 386 (M^+, 9%), 305 (22), 304 (100), 222 (14), 219 (15), 218 (28), 207 (10), 206 (55), 125 (12), 124 (12), 123 (20), 109 (11), 107 (14), 81 (49), 79 (11), 69 (20), 67 (11), 55 (12). HRMS calcd for $C_{26}H_{42}O_2$ 386.3185, found [386.3174 (major), 386.3186 (minor)].

5.5. General procedure for the oxidation of 1,7-dioxaspiro[4.5]decanes 4 to lactones 5

A solution of $NaIO_4$ (1.04 g, 4.88 mmol) and $RuCl_3 \cdot xH_2O$ (33 mg) in water (5 mL) was added in five portions at intervals of 1 h over a solution of compound **4** (1 mmol) and cetyltrimethylammonium bromide (CTAB) (10 mg, 0.027 mmol) in CCl_4 (5 mL) at reflux. The reaction mixture was stirred for an additional hour, extracted with CCl_4 (3×5 mL), and dried over anhydrous $MgSO_4$. After evaporation of the solvent at reduced pressure (15 Torr), the residue was purified by column chromatography (silica gel, hexane/EtOAc).

5.5.1. 2,2,8,8-Tetrapentyl-1,7-dioxaspiro[4.5]decan-6-one (5b). Colourless oil; t_r 20.99; R_f 0.39 (hexane/EtOAc 8:2); ν (film) 1735 (C=O), 1095 cm^{-1} (CO); δ_H 0.85–0.95 (12H, m, 4×CH_3), 1.20–2.15 (40H, m, 10×CH_2CH_2); δ_C 14.0, 14.1 (4×CH_3), 22.5, 22.6, 23.1, 24.0, 24.3, 28.4, 32.1, 32.2, 32.4, 35.4, 36.6, 38.2, 38.8, 38.9, 39.1 (20×CH_2), 80.8, 86.9, 88.5 (3×C), 173.8 (C=O); *m/z* 407 (M^+-29, <1%), 390 (23), 365 (18), 338 (24), 337 (100), 321 (10), 237 (14), 225 (12), 224 (27), 168 (17), 167 (11), 166 (13), 155 (10), 153 (47), 123 (15), 110 (50), 99 (10), 95 (12), 83 (10), 69 (16), 55 (20). HRMS calcd for $C_{28}H_{52}O_3$ 436.3916, found 436.3911.

5.5.2. 2,2,8,8-Tetraisopropyl-1,7-dioxaspiro[4.5]decan-6-one (5c). Colourless oil; t_r 16.35; R_f 0.38 (hexane/EtOAc 8:2); ν (film) 1736 (C=O), 1112 cm^{-1} (CO); δ_H 0.80–1.00 (24H, m, 8×CH_3), 1.50–2.15 (12H, m, 4×CH, 2×CH_2CH_2); δ_C 17.3, 17.4, 17.9, 18.1, 18.5, 18.8, 19.0 (8×CH_3), 27.6, 29.5, 32.6, 35.5 (4×CH_2), 33.6, 33.9, 35.0, 36.1 (4×CH), 91.2, 92.2, 93.6 (3×C), 172.6 (CO); *m/z* 282 (M^+-42, 11%), 281 (64), 278 (11), 263 (11), 253 (46), 235 (21), 217 (10), 168 (16), 155 (15), 153 (17), 149 (21), 125 (100), 111 (24), 107 (10), 69 (29), 55 (13). HRMS calcd for $C_{20}H_{36}O_3$ 324.2664, ($M^+-C_3H_7$) 281.2111, found 281.2122.

5.5.3. Trispiro[cyclopentane-1,2′-tetrahydrofuran-5′,3″-(tetrahydropyran-2-one)-6″,1‴-cyclopentane] (5f). Colourless oil; t_r 15.27; R_f 0.41 (hexane/EtOAc 8:2); ν (film) 1735 (C=O), 1090 cm^{-1} (CO); δ_H 1.30–2.10 (24H, m, 12×CH_2); δ_C 22.1, 22.6, 23.8, 24.1, 25.9, 28.1, 30.0, 32.2, 35.2, 35.7 (12×CH_2), 79.9, 83.7, 86.4 (3×C), 172.9 (C=O); *m/z* 236 (M^+-28, 19%), 218 (16), 151 (26), 141 (11), 139 (15), 138 (100), 109 (15), 96 (15), 95 (69), 94 (19), 81 (27), 80 (49), 79 (17), 67 (18), 55 (19). HRMS calcd for $C_{16}H_{24}O_3$ 264.1725, found 264.1721.

5.6. X-ray crystallography

All compounds studied were recrystallised from hexane. Data collection was performed on a Bruker Smart CCD diffractometer, based on three ω-scan runs (starting $\omega=-34°$) at the values of $\phi=0$, 120, 240° with the detector at $2\theta=-32°$. For each of these runs, 606 frames were collected at 0.3° intervals. An additional run at $\phi=0°$ of 100 frames was collected to improve redundancy. The diffraction frames were integrated using the SAINT[26] programme and the integrated intensities were corrected for Lorentz-polarisation effects with SADABS.[27]

X-ray data for **3l**. $C_{20}H_{32}O_2$, M=304.46; monoclinic, a=16.018(4) Å, b=11.695(3) Å, c=19.445(4) Å, β=94.389(6)°; V=3632.1(1) $Å^3$; space group P 2(1)/c; Z=8; D_c=1.114 Mg m^{-3}; λ=0.71073 Å; μ=0.069 mm^{-1}; $F(000)$=1344; T=21±1 °C. The structure was solved by direct methods[28] and refined to all 5707 unique F_o^2 by full matrix least squares (SHELX97).[29] All the hydrogen atoms were placed at idealised positions and refined as rigid atoms. Final $wR2$=0.3760 for all data and 409 parameters; R_1=0.1218 for 2826 $F_o>4\sigma(F_o)$.

X-ray data for **3m**. $C_{26}H_{44}O_2$, M=388.61; orthorhombic, a=12.4239(19) Å, b=15.247(2) Å, c=12.357(2) Å; V=2340.8(6) $Å^3$; space group $C222(1)$; Z=4; D_c=1.103 Mg m^{-3}; λ=0.71073 Å; μ=0.067 mm^{-1}; $F(000)$=864; T=23±1 °C. The structure was solved by direct methods[28] and refined to all 1188 unique F_o^2 by full matrix least squares (SHELX97).[29] All the hydrogen atoms were placed at idealised positions and refined as rigid atoms. Final $wR2$=0.1200 for all data and 140 parameters; R_1=0.0421 for 1000 $F_o>4\sigma(F_o)$.

X-ray data for **4j**. $C_{26}H_{38}O_2$, M=382.56; triclinic, a=6.4617(10) Å, b=11.1766(18) Å, c=14.176(2) Å, α=

99.041(3)°, $\beta = 96.642(3)°$, $\gamma = 90.790(3)°$; $V = 1003.7(3)$ Å^3; space group $P\bar{1}$; $Z = 2$; $D_c = 1.266$ Mg m^{-3}; $\lambda = 0.71073$ Å; $\mu = 0.077$ mm^{-1}; $F(000) = 420$; $T = -100 \pm 1$ °C. The structure was solved by direct methods[28] and refined to all 8481 unique F_o^2 by full matrix least squares (SHELX97).[29] All the hydrogen atoms were placed at idealised positions and refined as rigid atoms. Final $wR2 = 0.1489$ for all data and 254 parameters; $R_1 = 0.0606$ for 4486 $F_o > 4\sigma(F_o)$.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 288641-288643. 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; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk/data_request/cif).

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Synthesis and RNA-selective hybridization of α-L-*ribo*- and β-D-*lyxo*-configured oligonucleotides

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Abstract—Three α-L-ribofuranosyl analogues of RNA nucleotides (α-L-RNA analogues) have been synthesized and incorporated into oligonucleotides using the phosphoramide approach on an automated DNA synthesizer. The 4′-*C*-hydroxymethyl-α-L-ribofuranosyl thymine monomer was furthermore synthesized. Relative to the unmodified duplexes, incorporation of a single α-L-RNA monomer into a DNA strand leads to reduced thermal stability of duplexes with DNA complements but unchanged thermal stability of duplexes with RNA complements, whereas incorporation of more than one α-L-RNA monomer lead to moderately decreased thermal stability also of duplexes with RNA complements. Efficient hybridization with an RNA complement and no melting transition with a DNA complement were observed with stereoregular chimeric oligonucleotides composed of a mixture of α-L-RNA and affinity enhancing α-L-LNA monomers (α-L-*ribo*-configured locked nucleic acid). Furthermore, duplexes formed between oligodeoxynucleotides containing an α-L-RNA monomer and complementary RNA were good substrates for *Escherichia coli* RNase H. RNA-selective hybridization was also achieved by the incorporation of 1-(4-*C*-hydroxymethyl-β-D-lyxofuranosyl)thymine monomers into a DNA strand, whereas stable duplexes were formed with both complementary DNA and RNA when these monomers were incorporated into an RNA strand.

1. Introduction

The utilization of modified oligonucleotides (ONs) in the antisense approach requires the formation of duplexes with mRNA in order to specifically inhibit their translation into proteins involved in various pathologic disorders. Essential properties of successful antisense oligonucleotides (AON) are good aqueous solubility, resistance against enzymatic degradation, high binding affinity and specificity for the target RNA strand.[1] It is furthermore desirable if they have the ability to recruit the endogenous enzyme RNase H. An AON basically has two possible modes of action, which both involve hybridization to the RNA target. One is steric blocking of the mRNA, and the other is recognition of the RNA·AON duplex as a substrate for the enzyme RNase H, which subsequently cleaves the RNA strand of the duplex. In the latter scenario, one AON is able to pacify multiple mRNA strands. A high binding affinity towards RNA is crucial, especially for the steric blocking approach. Conformational restriction of the single-stranded AON has the potential to favour duplex formation entropically by diminishing the loss of conformational freedom upon duplex formation. α-L-LNA (α-L-*ribo*-configured locked nucleic acid),[2,3] containing a 2′-*O*,4′-*C*-methylene linked furanose ring,[†] with three out of four chirality centers inverted relative to RNA, forms duplexes with complementary RNA and DNA with highly increased thermal stability and generally improved selectivity. α-L-LNA can be most adequately described as a DNA mimic as NMR spectroscopic studies of α-L-LNA·RNA duplexes and molecular dynamics simulation of fully modified α-L-LNA·RNA duplexes have shown the overall duplex geometry to be very similar to the corresponding unmodified DNA·RNA hybrid.[3] Fully modified and mix-meric α-L-LNA (consisting

Keywords: α-L-*ribo*-Configured nucleic acid (α-L-RNA); β-D-Lyxofuranosyl nucleotide; α-L-LNA; Preferential RNA hybridization; S-type furanose conformation; Thermal denaturation studies.
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[†] α-L-LNA (α-L-*ribo* configured diastereoisomer of LNA; defined as an oligonucleotide containing one or more 2′-*O*,4′-*C*-methylene-α-L-ribofuranosyl nucleotide monomers) has shown appealing hybridization properties despite its unnatural configuration. The furanose conformation of an α-L-LNA monomer is of N-type (C3′-*endo*, ^3E). For further information about the conformations of the nucleotides, see *Eur. J. Biochem.* **1983**, *131*, 9 (abbreviations and symbols for the description of conformations of polynucleotide chains, IUPAC-IUB Joint Commission on Biochemical Nomenclature). A similar, but more flexible, furanose conformation is likely for an α-L-RNA monomer.[5]

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of a mixture of α-L-LNA and unmodified DNA nucleotides) supported in vitro *Escherichia coli* RNase H-mediated cleavage of the RNA target, albeit at a very reduced rate and at high enzyme concentration.[3c] RNase H has been reported to bind to the minor groove of substrate RNA·DNA heteroduplexes adopting a duplex form intermediate between the A- and B-form, with a minor groove width also intermediate between that of the A- and B-forms.[4] The furanose conformations of the nucleotides in the RNA strand are of the N-type, whereas hybridization of a DNA strand to the RNA strand causes the furanose conformation of the DNA strand to change from the typical *S*-type (C2′-*endo*) into *E*-type conformations (O4′-*endo* range).[4] Thus, the activation of RNase H proposedly requires AONs with furanose rings able to adopt *E*-type (O4′-*endo*), or perhaps *S*-type (C2′-*endo*), conformations. The locked furanose conformations of α-L-LNA might therefore explain the limited ability of α-L-LNA·RNA duplexes to act as substrates for RNase H (high enzyme concentration and extended reaction time) despite the global DNA-mimicking nature of α-L-LNA in α-L-LNA:RNA duplexes.[3c]

α-L-RNA (α-L-*ribo*-configured RNA) has structural resemblance to α-L-LNA. The furanose conformation of an α-L-LNA monomer is of the *N*-type (C3′-*endo*, ^{3}E),[†] and a similar furanose conformation, although more flexible, is likely to be preferred for an α-L-RNA monomer as indicated by calculations.[5] We had previously in a preliminary form reported the synthesis and binding properties of the α-L-RNA monomer bearing a thymine unit as nucleobase ($^{\alpha L}$**T**, Fig. 1).[6] The α-L-RNA thymine monomer when incorporated into an ON impairs a higher tendency towards hybridization with an RNA complement than with a DNA complement. A single incorporation of an α-L-RNA nucleotide in a 9-mer mixed-base sequence (**ON3**) leads to unchanged thermal stability towards RNA and reduced thermal stability towards DNA ($\Delta T_m = -4$ °C) when compared to the DNA reference **ON1** (Table 1).[6] When three α-L-RNA monomers were incorporated (**ON4**), the destabilization against the RNA target was limited to −16 °C, whereas no co-operative transition above 5 °C could be detected against DNA.[6] 10-mer ONs composed of a mixture of α-L-RNA monomers and affinity enhancing α-L-LNA[2,3] monomers (**ON13** and **ON14**) displayed efficient hybridization to the corresponding RNA complement ($\Delta T_m = +10$ and +8 °C, respectively), whereas no hybridization towards the corresponding DNA complement could be detected under the applied conditions (Table 2).[6] Moreover, the stability of α-L-RNA/α-L-LNA chimera (**ON13** and **ON14**) towards 3′-exonucleolytic degradation in vitro (snake venom phosphodiesterase) is significantly improved relative to the unmodified DNA reference.[6] If the pronounced RNA selectivity obtained for **ON14** turns out to be a general feature of α-L-RNA/α-L-LNA chimeras, one may envision improved specificity compared to the current antisense molecules, which are known also to hybridize towards DNA targets. A similar pronounced RNA selectivity has been reported for a few other ON analogues, for example, β-L-DNA,[7] arabinonucleic acids,[8] 2′-*O*,3′-*C* linked bicyclic oligonucleotides,[9] and α-D-LNA.[10] However, their usefulness as antisense molecules is hampered either by comparatively low binding affinity toward RNA[7,8] or the necessity of using fully modified oligomers in order to obtain efficient RNA binding.[9,10] The results obtained with thymine α-L-RNA/α-L-LNA chimeras,[6] that is, high binding affinity, RNA-selective hybridization and serum stability motivated us to further investigate this class of RNA stereoisomers.

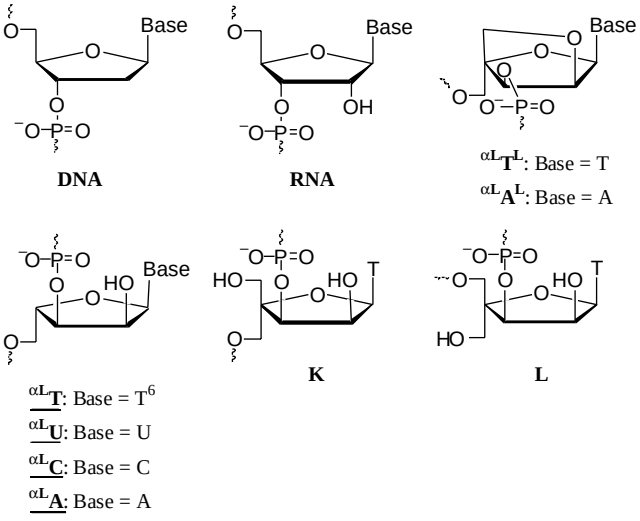


Figure 1. Structures of DNA, RNA, α-L-RNA ($^{\alpha L}$**T**, $^{\alpha L}$**U**, $^{\alpha L}$**C** and $^{\alpha L}$**A**), α-L-LNA ($^{\alpha L}$**T**^{L} and $^{\alpha L}$**A**^{L}),[2,3] 4′-*C*-hydroxymethyl-α-L-RNA (**K**) and 4′-*C*-hydroxymethyl-β-D-lyxofuranosyl (**L**) monomers. The short notations shown are used in Tables 1 and 2. T=thymin-1-yl, U=uracil-1-yl, C=cytosin-1-yl, A=adenin-9-yl.

Table 1. Thermal denaturation experiments[a]

		DNA	RNA
		T_m (ΔT_m) (°C)	T_m (ΔT_m) (°C)
ON1	5′-d(GTGATATGC)	30[b]/28[c] (Ref)	28[b]/26[c]/31[d] (Ref)
ON2	5′-r(GUGAUAUGC)	26 (Ref)	36 (Ref)
ON3	5′-d(GTGA($^{\alpha L}$**T**)ATGC)	26 (−4)[b]	28 (±0)[b]
ON4	5′-d(G($^{\alpha L}$**T**)GA($^{\alpha L}$**T**)A($^{\alpha L}$**T**)GC)	nt[b]	12 (−16)[b]
ON5	5′-d(GTGA**K**ATGC)	23 (−5)[c]	26 (±0)[c]
ON6	5′-d(G**K**GA**K**A**K**GC)	nt[d]	13 (−18)[d]
ON7	5′-d(GTGA**L**ATGC)	24 (−4)[c]	26 (±0)[c]
ON8	5′-d(G**L**GA**L**A**L**GC)	nt[c]	21 (−5)[c]
ON9	5′-r(GUGA**L**AUGC)	25 (−1)[c]	36 (±0)[c]
ON10	5′-r(G**L**GA**L**A**L**GC)	20 (−6)[c]	34 (−2)[c]

[a] Melting temperatures (T_m values) were obtained from the maxima of the first derivatives of the melting curves (A_{260} vs temperature) recorded in either medium salt buffer (10 mM sodium phosphate, 100 mM sodium chloride, 0.1 mM EDTA, pH 7.0)[b,c] or in high salt buffer (10 mM sodium phosphate, 700 mM sodium chloride, 0.1 mM EDTA, pH 7.0)[d] using 1.5[b]/1.0[c] μM concentrations of the two complementary strands (assuming identical extinction coefficients for all modified and unmodified nucleotides); ΔT_m values are changes in the T_m value relative to the unmodified reference duplex (Ref); A=adenin-9-yl monomer, C=cytosin-1-yl monomer, G=guanin-9-yl monomer, T=thymin-1-yl monomer, U=uracil-1-yl monomer; see Figure 1 for the structures of α-L-RNA nucleotide monomer ($^{\alpha L}$**T**), 4′-*C*-hydroxymethyl-α-L-RNA thymine monomer **K** and 4′-*C*-hydroxymethyl-β-D-lyxofuranosyl thymine monomer **L**; 'nt'-No co-operative melting transition; DNA sequences are shown as d(sequence) and RNA sequences are shown as r(sequence).

[b] Ref. 6.

This report is focused on the synthesis of the α-L-RNA monomers of three of the naturally occurring RNA monomers ($^{\alpha L}$**U**, $^{\alpha L}$**C** and $^{\alpha L}$**A**) (Fig. 1), their incorporation into

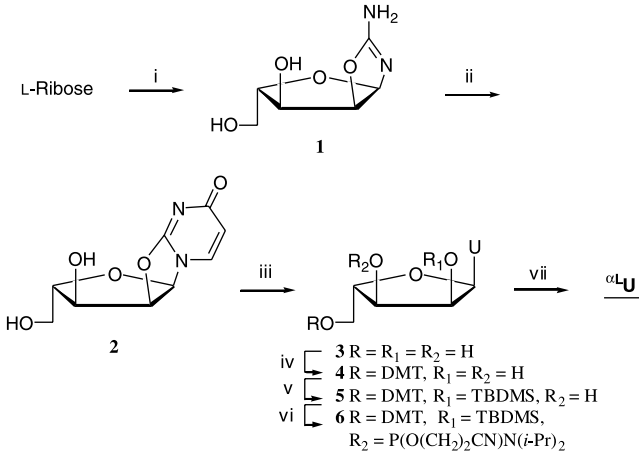
Table 2. Thermal denaturation experiments[a]

		DNA	RNA
		T_m (ΔT_m) (°C)	T_m (ΔT_m) (°C)
ON11	5′-T_{10}	20 (Ref)[b]	19 (Ref)[b]
ON12	5′-T_{14}	30 (Ref)[c]	28 (Ref)[c]
ON13	5′-($^{\alpha L}$**T**)$_4$($^{\alpha L}$**T**^{L})$_4$($^{\alpha L}$**T**)T	nt	29 (+10)[b]
ON14	5′-[($^{\alpha L}$**T**)($^{\alpha L}$**T**)(^{L})]$_4$($^{\alpha L}$**T**)T	nt	27 (+8)[b]
ON15	5′-T_5($^{\alpha L}$**T**)$_4T_5$	nt	11 (−17)[c]
ON16	5′-GTCTCTATGGACCT	45 (Ref)[c]	49 (Ref)[c]
ON17	5′-GTCTCTA($^{\alpha L}$**U**)GGACCT	41 (−4)[c]	47 (−2)[c]
ON18	5′-GTC($^{\alpha L}$**U**)CTATGGACCT	36 (−9)[c]	47 (−2)[c]
ON19	5′-G($^{\alpha L}$**U**)CTCTATGGACCT	40 (−5)[c]	47 (−2)[c]
ON20	5′-ATTATTATAAATTA	32 (Ref)[c]	24 (Ref)[c]
ON21	5′-$^{\alpha L}$(**A**^{L}**T**^{L}**U**^{L}**U**^{L}**T**^{L}**A**^{L}**U**^{L}**A**^{L}**A**^{L}**T**^{L}**T**^{L})A	nt	29 (+5)[c]
ON22	5′-TATTTACTTTC	23 (Ref)[c,d]	26 (Ref)[c,d]
ON23	5′-$^{\alpha L}$(**UA**^{L}**UT**^{L}**UA**^{L}**CT**^{L}**UT**^{L})C	nt	16 (−10)[c,d]
ON24	5′-T_7**L**T_6	21 (−9)[c]	23 (−5)[c]

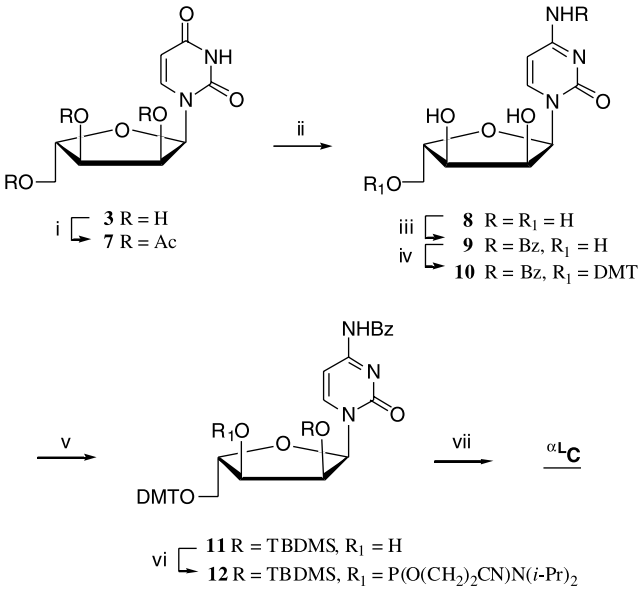
[a] Melting temperatures (T_m values) were obtained from the maxima of the first derivatives of the melting curves (A_{260} vs temperature) recorded in either medium salt buffer[b,c] or in high salt buffer (10 mM sodium phosphate, 1 M sodium chloride, 0.1 mM EDTA, pH 7.0)[d] using 1.5[b]/1.0[c] μM concentrations of the two complementary strands; see below Table 1 for other details; see Figure 1 for the structures of α-L-RNA nucleotide monomers ($^{\alpha L}$**T**, $^{\alpha L}$**U**, $^{\alpha L}$**C** and $^{\alpha L}$**A**), α-L-LNA monomers ($^{\alpha L}$**T**^{L} and $^{\alpha L}$**A**^{L}) and 4′-*C*-hydroxymethyl-β-D-lyxofuranosyl thymine monomer **L**; [d]DNA target [5′-d(AAAGTAAATA)] and RNA target [5′-r(AAAGUAAAUA)] containing a sequence complementary to the first ten monomers of **ON22** and **ON23** were used.

[b] Ref. 6.

oligonucleotides and the study of the stability of duplexes formed between these oligonucleotides and their complementary RNA and DNA strands. The enantiomeric α-D-ribonucleosides derived from uracil, cytosine and adenine have been described previously[11,12] but the low yields reported and the difficult separation of the anomeric mixture in the case of the adenine derivative make these strategies generally unsuitable for the preparation of the enantiomeric α-L-ribonucleosides. Moreover, the utilization of D-ribose as a starting material in these published strategies stimulated us, because of the high cost of L-ribose, to reconsider the strategies for the preparation of the phosphoramidite derivatives (Schemes 1–3).



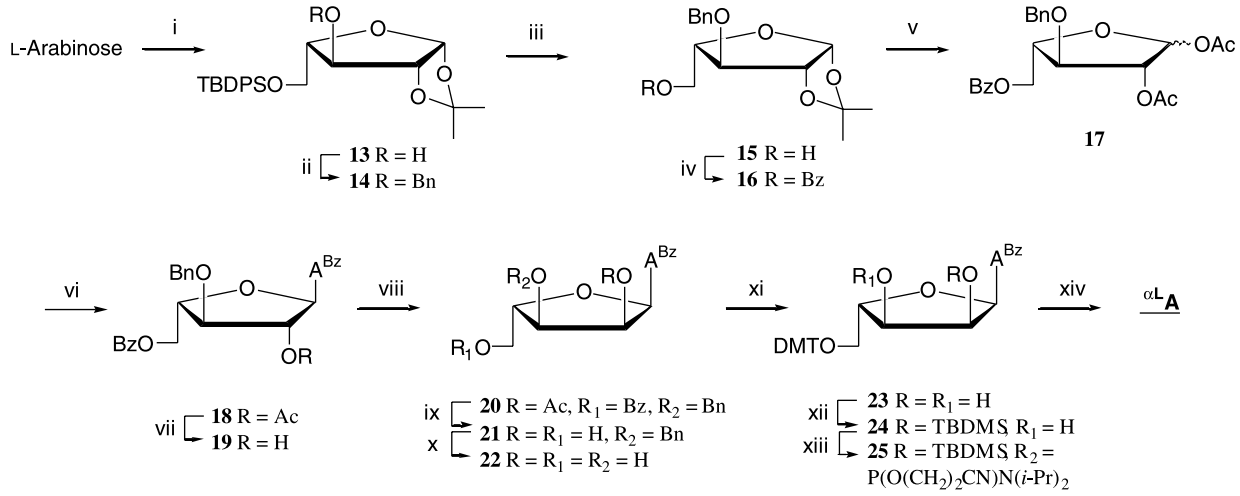
Scheme 1. Reagents and conditions (and yields): (i) NH_2CN, K_2CO_3, DMF, 90 °C (82%); (ii) methyl propiolate, EtOH, reflux (81%); (iii) aq HCl (0.2 N), reflux (77%); (iv) DMTCl, pyridine, rt; (v) TBDMSCl, imidazole, pyridine, rt (42% from **3**); (vi) $NC(CH_2)_2OP(Cl)N(i\text{-}Pr)_2$, $EtN(i\text{-}Pr)_2$, CH_2Cl_2, rt (70%); (vii) DNA synthesizer.



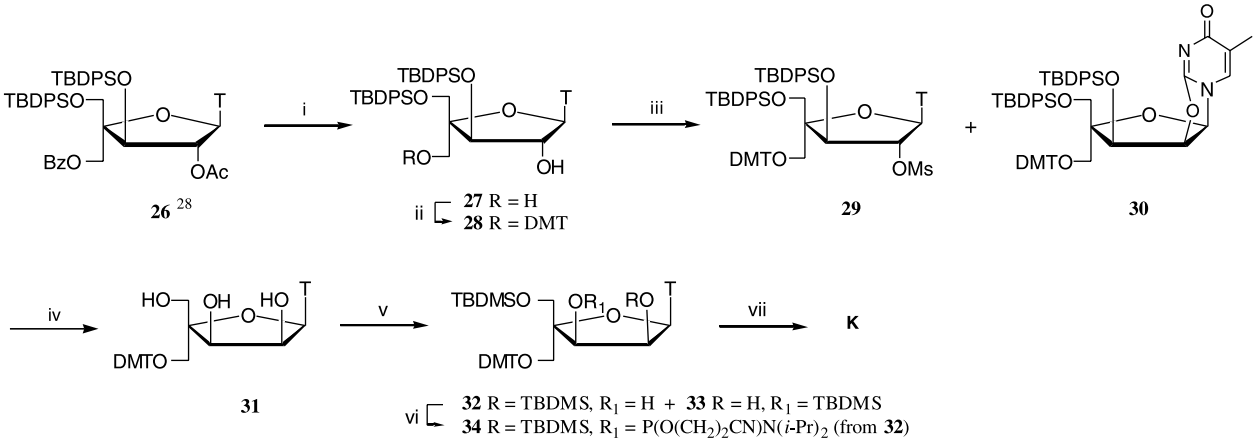
Scheme 2. Reagents and conditions (and yields): (i) Ac_2O, pyridine, rt (83%); (ii) (a) Lawesson's reagent, 1,2-dichloroethane, reflux, (b) saturated methanolic NH_3, 100 °C (74%); (iii) (a) TMSCl, pyridine, rt, (b) BzCl, rt, (c) aq NH_3, rt (77%); (iv) DMTCl, pyridine, rt (95%); (v) TBDMSCl, imidazole, pyridine, rt (49%); (vi) $NC(CH_2)_2OP(Cl)N(i\text{-}Pr)_2$, $EtN(i\text{-}Pr)_2$, CH_2Cl_2, rt (52%); (vii) DNA synthesizer.

ONs containing 4′-*C*-hydroxymethyl nucleotide monomers hybridize with both complementary DNA and RNA with virtually identical or slightly improved binding affinity compared to the unmodified duplexes.[13,14] The additional *C*-alkyl branch faces the minor groove for β-D-*ribo*-configured derivatives allowing attachment of molecular entities,[14,15] for example, intercalators, lipophilic groups, positive charged amines or a third strand to an ON. Furthermore, ONs containing C4′-substituted nucleotides have shown increased resistance towards enzymatic degradation.[13,16,17] In order to investigate the influence of the 4′-*C*-hydroxymethyl moiety of α-L-*ribo*-configured monomer **K** on the hybridization towards DNA and RNA complements, we synthesized phosphoramidite **34** and incorporated it into ONs (Scheme 4). The structural resemblance of the flexible monocyclic monomer **K** to the bicyclic α-L-LNA thymine monomer $^{\alpha L}$**T**^{L} added to its interest (Fig. 1).

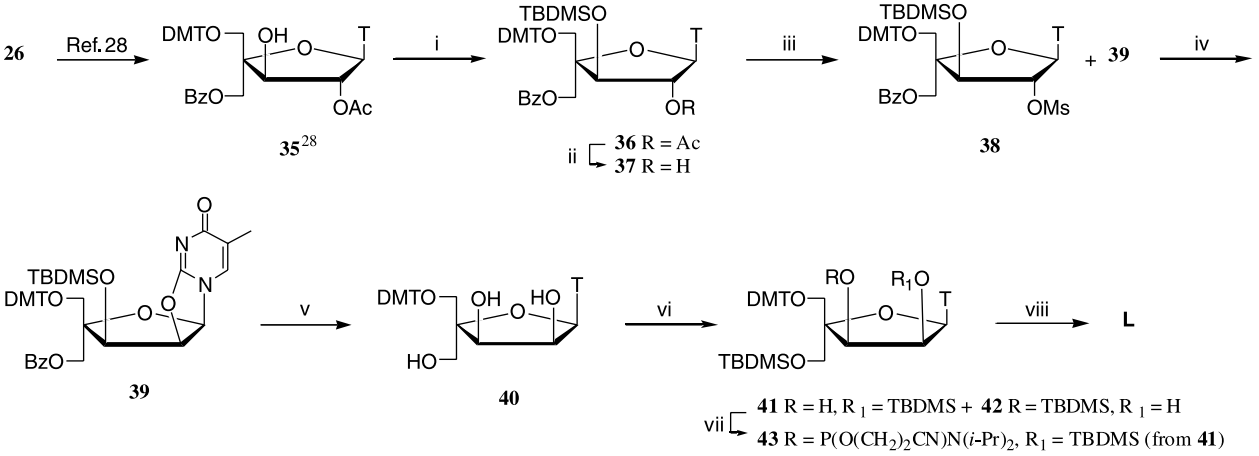
During the recent years a plethora of sugar-modified nucleoside analogues has been chemically synthesized with the aim of improving nucleic acid recognition. However, lyxofuranosyl nucleosides, containing all the three hydroxyls in the 'up' position, have received rather limited attention. Thus, there are only a few reports in the literature regarding their synthesis,[12,18] biological evaluation[19] and conformational investigation.[20] And, to the best of our knowledge, no attempts have been made to incorporate a lyxofuranosyl nucleotide monomer into an ON with the aim of evaluating its hybridization properties. To promote such investigation we describe here the synthesis of phosphoramidite **43** (Scheme 5), starting from the common intermediate **26**, required for the incorporation of 4′-*C*-hydroxymethyl-β-D-lyxofuranosyl thymine monomer **L** into ONs (Fig. 1).



Scheme 3. Reagents and conditions (and yields): (i) two steps (Ref. 24); (ii) BnBr, NaH (60% in mineral oil), DMF, 0 °C to rt (86%); (iii) TBAF, THF, rt (80%); (iv) BzCl, pyridine, rt (74%); (v) (a) aq AcOH (80%), cat. H_2SO_4, rt, (b) Ac_2O, pyridine, rt (73%); (vi) 6-*N*-benzoyladenine, $SnCl_4$, CH_3CN, rt (88%); (vii) half-saturated methanolic NH_3, 0 °C (92%); (viii) (a) Tf_2O, pyridine, CH_2Cl_2, −30 °C, (b) KOAc, 18-crown-6 ether, toluene, CH_2Cl_2, reflux (79%); (ix) aq NaOH (1 M), EtOH, pyridine, 0 °C; (x) Pd/C, HCO_2NH_4, abs EtOH, reflux (54% from **20**); (xi) DMTCl, pyridine, rt (92%); (xii) TBDMSCl, imidazole, pyridine, rt (48%); (xiii) $NC(CH_2)_2OP(Cl)N(i\text{-}Pr)_2$, $EtN(i\text{-}Pr)_2$, CH_2Cl_2, rt (73%); (xiv) DNA synthesizer.



Scheme 4. Reagents and conditions (and yields): (i) saturated methanolic NH_3, rt (96%); (ii) DMTCl, pyridine, rt, (97%); (iii) MsCl, DMAP, Et_3N, CH_2Cl_2, rt; (iv) aq NaOH (2 M), EtOH, H_2O, reflux (65% from **28**); (v) TBDMSCl, imidazole, pyridine, rt (**32**: 58% and **33**: 23%); (vi) $NC(CH_2)_2OP(Cl)N(i\text{-}Pr)_2$, $EtN(i\text{-}Pr)_2$, CH_2Cl_2, rt (71%); (vii) DNA synthesizer.



Scheme 5. Reagents and conditions (and yields): (i) TBDMSCl, imidazole, DMAP, DMF, 36 °C; (ii) saturated methanolic NH_3, MeOH, rt (80% from **35**); (iii) MsCl, Et_3N, DMAP, CH_2Cl_2, rt; (iv) DBU, CH_3CN, rt (83% from **37**); (v) aq NaOH (2 M), EtOH–H_2O (1/1), reflux (74%); (vi) TBDMSCl, imidazole, pyridine, rt (**41**: 36% and **42**: 53%); (vii) $NC(CH_2)_2OP(Cl)N(i\text{-}Pr)_2$, $EtN(i\text{-}Pr)_2$, CH_2Cl_2, rt (66%); (viii) DNA synthesizer.

2. Results and discussion

2.1. Synthesis of α-L-ribonucleosides 3, 9 and 22

α-L-Uridine was synthesized following a slightly modified procedure reported for the synthesis of the corresponding D-enantiomer.[11] In our hands, the synthesis of the oxazoline **1** was more efficient with potassium bicarbonate in DMF than with aqueous ammonia as previously described.[11] Oxazoline **1** was obtained in 82% yield from L-ribose. Reaction of **1** with methyl propiolate afforded the anhydro derivative **2** in 81% yield. Subsequent opening of this ring with acid under aqueous conditions afforded the desired α-L-uridine **3** in 77% yield. The ^{1}H NMR data of **3** were found to be consistent with the literature data for the corresponding D-enantiomer (Scheme 1).[12]

Compound **3** was per-acetylated with acetic anhydride in pyridine to give **7** in 83% yield. Synthesis of α-D-cytidine has been reported[12b] in a moderate 48% yield applying the Sung methodology[21] to furnish the D-enantiomer of **8**. Nevertheless, reaction of **7** with the Lawesson's reagent[22] followed by treatment with saturated methanolic ammonia afforded α-L-cytidine **8** in 74% yield. Using the transient protection method,[23] α-L-cytidine was *N*-benzoylated to afford nucleoside **9** in 77% yield. The ^{1}H NMR spectroscopic data for compounds **8** and **9** were found to be consistent with the literature data for their D-enantiomers (Scheme 2).[12b]

Using inexpensive L-arabinose as starting material, furanose **13** was prepared in a two step procedure developed by Dahlman et al.[24] The 3-hydroxy group of **13** was benzylated using benzyl bromide and sodium hydride in DMF to give furanose **14** in 86% yield. Cleavage of the silyl protecting group of **14** using TBAF gave derivative **15** (80% yield) that was benzoylated to give furanose **16** in 74% yield. The ^{1}H NMR spectroscopic data of furanoses **14** and **15** were consistent with the literature data for their D-enantiomer.[25] Finally, the glycosyl donor **17** was obtained by a standard two step procedure of isopropylidene group cleavage and acetylation of the 1- and 2-hydroxy functions in 73% overall yield. Furanose **17** was condensed with *N*-6-benzoyladenine under the conditions initially reported by Saneyoshi and Satoh[26] where the base is directly reacted with the *O*-acetylated sugar in the presence of stannic chloride. Coupling proceeded in 88% yield to afford nucleoside **18**. It can be noticed that the participation of the 2′-*O*-acetyl group provided only the desired α-anomer. Compound **18** was selectively deprotected at the 2′-position by the action of half-saturated methanolic ammonia to give nucleoside **19** in good yield (92%). Inversion of the configuration at C2′ proceeded in two steps. Firstly, the 2′-hydroxy group was activated by reaction with triflic anhydride followed by the reaction of the intermediate with potassium acetate to give the expected inverted nucleoside **20** in 79% yield. Nucleoside **20** was selectively deacylated at the 2′- and 5′-positions with aqueous sodium hydroxide in an ethanol–pyridine mixture following a previously described procedure[27] to give nucleoside **21** in 77% yield. Finally, debenzylation of compound **21** by treatment with ammonium formate and palladium on carbon produced *N*-6-benzoyl-α-L-adenosine **22** in a yield of 70% (Scheme 3). The ^{1}H NMR spectroscopic data of nucleoside **22** were consistent with the literature data for its D-enantiomer.[12b]

2.2. Synthesis of the α-L-RNA phosphoramidites 6, 12 and 25

Compounds **3**, **9** or **22** were O5′-dimethoxytritylated using standard conditions in satisfactory yields (95, 95 and 92%, respectively). Silylation of nucleosides **4**, **10** or **23** with *tert*-butyldimethylsilyl chloride (TBDMSCl) in the presence of imidazole and pyridine produced a mixture of a byproduct (fast eluting; assigned as the 2′-*O*-TBDMS isomers) and 3′-*O*-TBDMS (slow eluting) derivatives, which were separated by silica gel column chromatography. The ^{1}H NMR spectral data obtained for compounds **5**, **11** or **24** were found to be consistent with the literature data for their D-enantiomers.[12] Nucleosides **5**, **11** or **24** were dissolved in anhydrous dichloromethane and phosphitylated using 2-cyanoethyl *N*,*N*-diisopropylphosphoramidochloridite in the presence of *N*,*N*-diisopropylethylamine to give the corresponding phosphoramidites **6**, **12** and **25** in yields of 70, 52 and 73%, respectively.

2.3. Synthesis of the 1-(4-*C*-hydroxymethyl-α-L-ribofuranosyl)thymine phosphoramidite 34

Complete deacylation of 1-[2-*O*-acetyl-3,5-(di-*O*-*tert*-butyldiphenylsilyl)-4-*C*-benzoyloxymethyl-β-D-xylofuranosyl]thymine (**26**)[28] with saturated methanolic ammonia, followed by regioselective dimethoxytritilation afforded nucleoside **28**. Activation of the 2′-OH in nucleoside **28** by reaction with MsCl afforded the desired nucleoside **29** along with the 2,2′-anhydro nucleoside **30**. This crude mixture was refluxed under alkaline conditions, which also resulted in complete desilylation, affording triol **31**. Silylation of the triol **31** with 4 equiv of TBDMSCl afforded the desired 2′-*O*-TBDMS isomer **32** in 58% yield along with the 3′-*O*-isomer **33** (23% yield). Phosphitylation of **32** by the standard protocol afforded phosphoroamidite **34** (71% yield) that was used to incorporate monomer **K** into ONs (Scheme 4). To ascertain that no silyl migration occurred under the basic conditions applied during phosphitylation, the isomers of **34** were separated and characterized. The signals of H3′ appeared as a double doublet with a large $^2J_{H,P}$ coupling constant (major isomer: 13.7 Hz; minor isomer: 13.0 Hz) confirming that no silyl migration occurred during the course of the reaction.[29]

2.4. Synthesis of the 1-(4-*C*-hydroxymethyl-β-D-lyxofuranosyl)thymine phosphoramidite 43

Selective removal of the primary silyl protection in the common intermediate **26** proved difficult, probably due to silyl migration from the 3′-position. Therefore, complete desilylation of nucleoside **26** and subsequent O5′-tritylation followed by O3′-silylation furnished nucleoside **36** in 66% overall yield (from **26** via **35**). Deacetylation afforded nucleoside **37**, which upon mesylation yielded a mixture of nucleosides **38** and **39** (~3:1, as judged from analytical TLC). Concomitant treatment with aq NaOH furnished a complex mixture, presumably via desilylalation of **38**, followed by epoxide formation and then opening of the epoxide under alkaline conditions. The desired *lyxo*-configured nucleoside **40** was obtained by complete conversion of the crude mixture (**38**+

39) into O2′,C2-anhydronucleoside **39**, followed by treatment with aq NaOH in ethanol, affording nucleoside **40** in 61% overall yield (from **37**). Silylation of the triol **40** by reaction with 4 equiv of TBDMSCl afforded the desired 2′-*O*-TBDMS isomer **41** in 36% yield along with the O3′-isomer **42** (52%). O3′-phosphitylation of nucleoside **41** afforded phosphoroamidite **43** (66% yield) that was used to incorporate monomer **L** into ONs (Scheme 5). The signal of H3′ in **43** appeared as a double doublet with a large $^{2}J_{H,P}$ coupling constant (major isomer: 13.6 Hz) indicating that no silyl migration occurred during phosphitylation.

3. Synthesis of ONs and thermal denaturation studies

All oligomers **ON5**–**ON10**, **ON15**, **ON17**–**ON19**, **ON21**, **ON23** and **ON24** (Tables 1 and 2) were prepared in 0.2 μmol scale using the phosphoramidite approach (see the Section 7 for details). The composition of the oligomers was verified by MALDI-MS analysis (see the Section 7) and their purity (>80%) by capillary gel electrophoresis.

Results from hybridization experiments (T_m values) towards single-stranded DNA and RNA complements are shown in Tables 1 and 2. A single replacement of a DNA thymine monomer in a 9-mer mixed-base sequence by its α-L-RNA counterpart $^{\alpha L}$**T** resulted in destabilization of the duplex by 4 °C when hybridized to complementary DNA (Table 1, **ON3** relative to **ON1**), while no change in the duplex stability was seen when hybridized to the RNA complement.[6] Incorporation of a few isolated $^{\alpha L}$**T** monomers into a DNA strand reduced the affinity towards the RNA target ($\Delta T_m = -16$ °C, **ON4** relative to **ON1**), but the effect was more pronounced towards the DNA target (no co-operative transition above 5 °C could be detected).[6] A single incorporation of an α-L-RNA U monomer in a 14-mer mixed-base sequence **ON18** leads to a decrease in duplex stability against the DNA target ($\Delta T_m = -9$ °C) when compared to the DNA reference **ON16**; the effect is less detrimental when the substitution is either in the centre (**ON17**, $\Delta T_m = -4$ °C) or towards the 5′-end (**ON19**, $\Delta T_m = -5$ °C). However, against the RNA complement the stability ($T_m = 47$ °C, $\Delta T_m = -2$ °C) was comparable with that of the DNA·RNA reference duplex. The fact that incorporation of a single α-L-RNA monomer is tolerated in a duplex with complementary RNA is likely explained by conformational adaptation that is impossible for the relatively short duplexes following incorporation of more than one α-L-RNA monomer. The stereoregular (almost) fully modified α-L-RNA/α-L-LNA chimera **ON13**,[6] **ON14**[6] and **ON21** consisting of a mixture of α-L-RNA and α-L-LNA monomers displayed very efficient hybridization towards the RNA target ($\Delta T_m = +10$, $+8$ and $+5$ °C, respectively), whereas no hybridization towards the DNA target was detected. It should be noted that **ON15**, having four consecutive α-L-RNA T monomers and no α-L-LNA monomer, displayed significantly decreased affinity towards the RNA complement. Similar RNA-selective hybridization was seen with the α-L-RNA/α-L-LNA chimera **ON23** consisting of alternate α-L-RNA and α-L-LNA monomers. Thus, although no co-operative transition could be detected at medium salt conditions, a melting temperature was observed against the RNA target under high salt conditions.

A single incorporation of 1-(4-*C*-hydroxymethyl-α-L-ribofuranosyl)thymine monomer **K** in the middle of a 9-mer mixed-base sequence induced similar hybridization properties as incorporation of the α-L-RNA thymine monomer $^{\alpha L}$**T** (**ON5** compared to **ON3**), that is, a decrease in T_m value (−5 °C) against the DNA complement and no change against the RNA complement. The partly modified 9-mer containing three incorporations of monomer **K** induced a similar destabilizing effect ($\Delta T_m = -6$ °C/modification, **ON6** relative to **ON1**) on the duplex formed with complementary RNA as seen above with **ON4** containing three $^{\alpha L}$**T** monomers ($\Delta T_m = -5.3$ °C/modification, **ON4** relative to **ON1**), indicating no unfavorable steric hindrance due to the additional 4′-*C*-alkyl chain.

The 4′-*C*-hydroxymethyl-β-D-lyxofuranosyl thymine monomer **L**, containing all three hydroxyls in 'up' position, displayed some interesting hybridization properties. A single incorporation of monomer **L** in a 9-mer mixed-base sequence **ON7** showed preference for binding to its RNA complement (T_m unchanged) relative to its DNA complement ($\Delta T_m = -4$ °C). However, the duplex stability decreased when the modification was placed in the centre of a 14-mer homopyrimidine sequence (**ON24**, $\Delta T_m = -9$ °C against the DNA target and $\Delta T_m = -5$ °C against the RNA target). A T_m value of 21 °C was observed with the RNA complement hybridized to the partly modified stereoirregular 9-mer mixed-base sequence **ON8**, but no co-operative transition above 5 °C was observed with the DNA complement. In contrast, efficient recognition of both DNA and RNA targets was achieved when monomer **L** was incorporated into an RNA strand, and satisfactory binding affinity towards DNA and RNA complements was observed with one (**ON9**) and three (**ON10**) incorporations.

4. Molecular modeling

Molecular modeling (see the Section 7 for details) was used to rationalize the thermal stability results for monomers

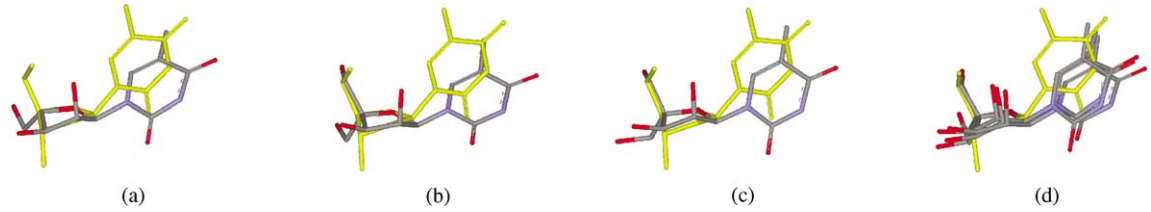


Figure 2. ON:DNA duplexes: (a) the tilted base is indicated for the overlaid structures of standard DNA thymine monomer (yellow) and $^{\alpha L}$**T** monomer; (b) overlaid structures of DNA (T) and **K** monomers; (c) overlaid structures of DNA (T) and **L** monomers; (d) the *S*-type furanose conformation is shown for standard DNA (yellow) and $^{\alpha L}$**T**, **K**, and **L** monomers (all monomer structures have been cut out of the corresponding duplex helix structure and overlaid with the sugar ring system kept fixed).

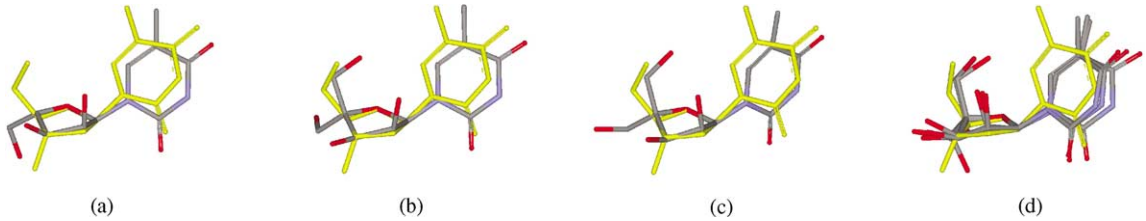


Figure 3. ON:RNA duplexes. See legend to Figure 2 for further details.

$^{\alpha L}$**T**, **K** and **L**. All monomers showed S-type furanose conformations[†] in both ON·DNA (Fig. 2) and ON·RNA (Fig. 3) hybrids. The most pronounced change was the tilting of the nucleobase in all the three modified monomers when compared to the reference DNA (T) monomer (Table 3).

Table 3. Torsion angle χ (O4′–C1′–N1–C2)

Modification	Torsion angle χ (°)	
	[ON:DNA]	[ON:RNA]
DNA-T (Ref)	−96	−135
$^{\alpha L}$**T**	−168	−156
K	−169	−152
L	−151	−97

The calculated structures for monomers $^{\alpha L}$**T**, **K**, and **L** are in agreement with the observed thermal stabilities. Single incorporations of the monomers $^{\alpha L}$**T**, **K**, or **L** in a 9-mer ON leads to reduced affinity towards the complementary DNA target, which can be attributed to significant change in the torsion angle χ in the modified monomers (Table 3). The base displacement causes reduced stacking within the strand and a loss of hydrogen bonding towards the complementary base. However, in duplexes with the RNA complement the change in the torsion angle χ in monomers $^{\alpha L}$**T**, **K**, and **L** (compared to DNA-T monomer) is more limited, which offers an explanation for the RNA-selective hybridization induced by the incorporation of these monomers.

5. RNase H cleavage

Stimulated by the satisfactory RNA binding characteristics of the α-L-RNA modified ONs, we studied RNase H degradation of [^{32}P] labelled RNA that was complementary to **ON16–ON19**. Hybridized samples were digested for different time intervals and the RNA was electrophoresed on an acryamide gel and visualized by autoradiography. Basic hydrolysis of RNA (Fig. 4) was used to identify the cleaved positions. As can be seen in Figure 4, the unmodified reference **ON16** mainly supports RNase H cleavage at phosphodiester bonds opposite positions 4–5, 6–7 and 7–8. **ON17** that is modified at position 8 is less efficiently cleaved than **ON16** showing no 4–5 cleavage band, a weak 5–6 band and a strong 7–8 band. This indicates that the modification interferes moderately with initial binding of RNase H but also shows that the enzyme can cleave opposite 5′ to the modification. **ON18** modified at position 4 provides an even better cleavage than the reference **ON16** with cleavage mainly opposite positions 6–7 and 7–8. The cleavage pattern for **ON19** modified at position 2 is very similar to the pattern seen with the reference **ON16**. The RNA complement can thus be cleaved both to the 3′ and 5′ site of α-L-RNA residues in the corresponding oligonucleotide, showing that RNase H cleavage can take place in close proximity to an α-L-RNA monomer. These results show that properly designed α-L-RNA/DNA mixmers can be attractive molecules for antisense applications.

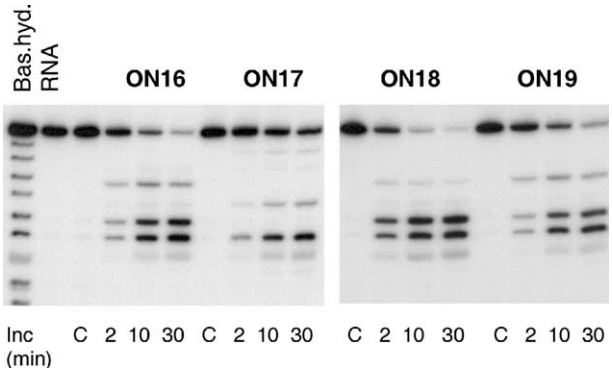


Figure 4. Autoradiogram showing gel electrophoresis of RNase H cleavage of labelled RNA hybridized to complementary **ON16–ON19**. **C** are hybridized samples incubated in the absence of RNase H.

6. Conclusion

Oligonucleotides containing α-L-RNA monomers display in general decreased duplex stability relative to the unmodified reference duplexes, but at the same time preferential binding towards the RNA complement. Despite the unnatural configuration of the α-L-RNA monomer, DNA ONs containing a single incorporation of an α-L-RNA monomer retain the ability to elicit RNase H activity. Moreover, increased binding affinity and RNA-selective hybridization was induced by combining the α-L-RNA monomers with affinity enhancing α-L-LNA monomers. As furthermore the α-L-RNA/α-L-LNA chimeras displayed significant stabilization towards 3′-exonucleolytic degradation,[6] these classes of molecules are excellent candidates for use within the antisense technology. The presence of a 4′-*C*-alkyl group in 4′-hydroxymethyl-α-L-RNA monomer **K** had no influence on the duplex stability when compared to the α-L-RNA monomer, and could therefore function as a handle for the attachment of amino functionalities to improve the binding affinity or the pharmacokinetic properties of ONs containing α-L-RNA monomers. RNA-selective hybridization was also achieved by the incorporation of 1-(4-*C*-hydroxymethyl-β-D-lyxofuranosyl)thymine monomer **L** into a DNA strand,

whereas stable duplexes towards both complementary DNA and RNA were formed upon incorporation of monomer **L** into an RNA strand.

7. Experimental

7.1. General

Reactions were conducted under an atmosphere of nitrogen when anhydrous solvents were used. All reactions were monitored by thin-layer chromatography (TLC) using silica plates with fluorescence indicator (SiO_2-60, F-254) visualizing under UV light and by revelation with 5% concd sulfuric acid in ethanol (v/v) followed by heating. Silica gel 60 (particle size 0.040–0.063 mm, Merck) was used for flash column chromatography. Light petroleum of the distillation range 60–80 °C was used. After column chromatography fractions containing product were pooled, evaporated to dryness under reduced pressure and dried for 12 h under vacuum to give the product unless otherwise specified. ^{1}H NMR spectra were recorded at 300 MHz, ^{13}C NMR spectra at 75.5 MHz, and ^{31}P NMR spectra at 121.5 MHz. Chemical shifts are reported in ppm relative to either tetramethylsilane or the deuterated solvent as internal standard for ^{1}H and ^{13}C NMR, and relative to 85% H_3PO_4 as external standard for ^{31}P NMR. Assignments of NMR spectra, when given, are based on 2D spectra and follow the standard carbohydrate/nucleoside nomenclature (the carbon atom of the C-4′-subsituent is numbered C5″). The assignments of methylene protons, when given, may be interchanged. Coupling constants (*J* values) are given in Hertz. MALDI-HRMS were recorded in positive ion mode on an IonSpec Fourier Transform mass spectrometer.

7.1.1. 2-Amino-α-L-ribofurano[1′,2′:4,5]-2-oxazoline (1). A mixture of L-ribose (2.00 g, 13.3 mmol), cyanamide (0.67 g, 16.0 mmol) and powdered potassium bicarbonate (0.07 g, 0.05 mmol) was stirred at 90 °C for 1 h in anhydrous DMF (15 mL). After cooling to room temperature, the mixture was evaporated under reduced pressure to half volume and the resulting solution was stored for 20 h at 5 °C. The precipitate obtained was filtered off and recrystallized from 96% aq EtOH to give 1.90 g of oxazoline **1** (82%) as a white solid material. δ_H (DMSO-d_6) 6.26 (2H, br s, NH_2), 5.58 (1H, d, J=4.8 Hz, H1′), 5.17 (1H, br s, OH), 4.59–4.56 (2H, m, H2′ and OH), 3.74–3.63 (2H, m, H3′ and H4′), 3.42–3.25 (2H, m, H5′); δ_C (DMSO-d_6) 163.8, 98.3, 80.8, 77.8, 71.2, 60.4; MALDI-MS: *m/z* 197 ($[M+Na]^+$, $C_6H_{10}N_2O_4Na^+$ calcd 197).

7.1.2. 2,2′-Anhydro-1-(α-L-ribofuranosyl)uracil (2). A mixture of oxazoline **1** (1.00 g, 5.75 mmol) in 96% aq EtOH (10 mL) and methyl propiolate (1.69 g, 20.1 mmol) was heated under reflux for 2 h. After cooling to room temperature, the reaction mixture was evaporated to dryness under reduced pressure and then coevaporated several times with 96% aq EtOH to give 1.05 g of nucleoside **2** as a white solid material (81%) after recrystallization from EtOH. δ_H (DMSO-d_6) δ 7.85 (1H, d, J=7.4 Hz, H6), 6.20 (1H, d, J=5.2 Hz, H1′), 5.88 (1H, d, J=7.4 Hz, H5), 5.74 (1H, d, J=6.9 Hz, 3′-OH), 5.23 (1H, t, J=5.2 Hz, H2′), 4.86 (1H, t, J=5.0 Hz, 5′-OH), 4.05 (1H, m, H3′), 3.70 (1H, dd, J=5.0, 12.0 Hz, H5′a), 3.57 (1H, m, H4′), 3.46 (1H, m, H5′b); δ_C (DMSO-d_6) 171.0, 160.7, 136.8, 108.8, 88.6, 81.4, 80.7, 69.8, 59.5; MALDI-MS: *m/z* 249 ($[M+Na]^+$, $C_9H_{10}N_2O_5Na^+$ calcd 249).

7.1.3. 1-(α-L-Ribofuranosyl)uracil (3). A solution of nucleoside **2** (2.17 g, 9.6 mmol) in aqueous hydrochloric acid (0.2 N, 10 mL) was refluxed for 1 h. After cooling to room temperature, the solution was neutralized using Amberlyst IRA 410 [OH^-]. The resin was filtered off and washed with lukewarm H_2O. The combined filtrate was evaporated to dryness under reduced pressure. The residue was purified on a silica gel column, [15% (v/v) MeOH in EtOAc] affording 1.80 g (77%) of nucleoside **3** as a white solid material. δ_C (DMSO-d_6) 163.5, 150.7, 142.8, 99.8, 85.1, 84.0, 70.4, 70.3, 61.2; MALDI-MS: *m/z* 267 ($[M+Na]^+$, $C_9H_{12}N_2O_6Na^+$ calcd 267). The ^{1}H NMR data of were found to be consistent with the literature data for the corresponding D-enantiomer.[12b]

7.1.4. 1-(5-*O*-(4,4′-Dimethoxytrityl)-α-L-ribofuranosyl)-uracil (4). 4,4′-Dimethoxytrityl chloride (0.43 g, 1.3 mmol) was added to a solution of nucleoside **3** (0.26 g, 1.07 mmol) in anhydrous pyridine (5 mL). The reaction mixture was stirred at room temperature for 12 h whereupon methanol (2 mL) was added. After stirring for additional 10 min, the mixture was poured into saturated aq $NaHCO_3$ (25 mL). Extraction was performed with $CHCl_3$ (3×20 mL), and the combined organic phase was dried (Na_2SO_4), filtered and evaporated to dryness under reduced pressure. The residue was purified by column chromatography [5–8% MeOH in $CHCl_3$ containing 0.5% Et_3N (v/v/v)] to give nucleoside **4** (550 mg) as a white foam. NMR spectroscopic data revealed the compound to be contaminated with traces of Et_3N. δ_C ($CDCl_3$) 164.3, 158.4, 150.9, 144.6, 142.7, 135.8, 135.7, 130.0, 129.9, 128.1, 127.8, 126.8, 113.2, 100.4, 86.6, 86.3, 84.3, 72.0, 71.2, 63.3, 55.2; MALDI-MS: *m/z* 569 ($[M+Na]^+$, $C_{30}H_{30}N_2O_8Na^+$ calcd 569). The ^{1}H NMR data were found to be consistent with the literature data for the corresponding D-enantiomer.[12b]

7.1.5. 1-(2-*O*-*tert*-Butyldimethylsilyl-5-*O*-(4,4′-dimethoxytrityl)-α-L-ribofuranosyl)uracil (5). Nucleoside **4** (3.20 g) and imidazole (1.04 g, 15.2 mmol) were dissolved in anhydrous pyridine (60 mL). TBDMSCl (1.15 g, 7.6 mmol) was added and the solution was stirred at room temperature for 24 h. The reaction mixture was then poured into saturated aq $NaHCO_3$ (120 mL) and extraction was performed with $CHCl_3$ (3×80 mL). The combined organic phase was dried (Na_2SO_4), filtered and evaporated to dryness under reduced pressure. The residue was purified by column chromatography [5–7% (v/v) acetone in CH_2Cl_2] yielding the 2′-*O*-*tert*-butyldimethylsilyl isomer **5** (2.90 g, 42% from **3**) as a clear oil and [9–10% (v/v) acetone in CH_2Cl_2] a byproduct tentatively assigned as the 3′-*O*-*tert*-butyldimethylsilyl isomer (yield not determined). δ_C ($CDCl_3$) 163.3, 158.7, 150.6, 149.9, 144.5, 142.0, 135.7, 135.4, 130.0, 128.1, 128.0, 127.1, 123.8, 113.4, 113.3, 101.0, 87.0, 85.9, 84.5, 72.8, 72.7, 64.2, 55.3, 25.7, 18.1, −5.2, −5.3; ESI-HRMS: *m/z* 683.2723 ($[M+Na]^+$, $C_{36}H_{44}N_2O_8SiNa^+$ calcd 683.2759). The ^{1}H NMR data were found to be consistent with the literature data for the corresponding D-enantiomer.[12a]

7.1.6. 1-(2-*O*-*tert*-Butyldimethylsilyl-3-*O*-[2-cyanoethoxy(diisopropylamino)phosphino]-5-*O*-(4,4′-dimethoxytrityl)-α-L-ribofuranosyl)uracil (6). To a stirred solution of nucleoside **5** (0.26 g, 0.40 mmol) in CH_2Cl_2 (10 mL) at room temperature was added *N*,*N*-diisopropylethylamine (0.69 mL, 3.95 mmol). After dropwise addition of 2-cyanoethyl *N*,*N*′-diisopropylphosphoramidochloridite (0.38 mL, 1.98 mmol), the reaction mixture was stirred for another 15 h. CH_2Cl_2 (20 mL) was added and the mixture was washed with saturated aq $NaHCO_3$ (25 mL). The organic phase was dried (Na_2SO_4), filtered and evaporated to dryness under reduced pressure. The residue was purified by column chromatography [45–50% EtOAc in *n*-hexane, containing 0.5% Et_3N (v/v/v)] to yield phosphoramidite **6** as a white foam (240 mg, 70%). δ_P (DMSO-d_6) 151.0, 149.9; ESI-HRMS: *m*/*z* 883.3838 ($[M+Na]^+$, $C_{45}H_{61}N_4O_9PSiNa^+$ calcd 883.3843).

7.1.7. 1-(2,3,5-Tri-*O*-acetyl-α-L-ribofuranosyl)uracil (7). Acetic anhydride (2.32 mL, 24.5 mmol) was added to a solution of nucleoside **3** (1.71 g, 7.0 mmol) in anhydrous pyridine (10 mL). The reaction mixture was stirred at room temperature for 12 h. MeOH (5 mL) was added and the reaction mixture was stirred for another 10 min and then concentrated to dryness under reduced pressure. The residue was dissolved in EtOAc (50 mL) and washing was performed first with saturated aq $NaHCO_3$ (25 mL) and then brine (25 mL). The separated organic phase was dried (Na_2SO_4), filtered and evaporated to dryness under reduced pressure. The residue was purified by column chromatography [3–5% (v/v) MeOH in $CHCl_3$] to afford nucleoside **7** (2.16 g, 83%) as a white foam. δ_H ($CDCl_3$) 9.47 (1H, br s, NH), 7.47 (1H, d, J=8.2 Hz, H6), 6.39 (1H, d, J=4.7 Hz, H1′), 5.77 (1H, d, J=8.1 Hz, H5), 5.71 (1H, t, J=4.9 Hz, H2′), 5.42 (1H, t, J=5.4 Hz, H3′), 4.55 (1H, m, H4′), 4.36 (1H, dd, J=3.2, 12.3 Hz, H5′a), 4.18 (1H, dd, J=4.2, 12.2 Hz, H5′b), 2.15, 2.07 and 2.03 (3H each, 3s, 3×$COCH_3$); δ_C ($CDCl_3$) 170.5, 169.3, 168.7, 163.3, 150.2, 140.2, 101.6, 84.3, 79.9, 70.9, 70.3, 63.1, 20.9, 20.5, 20.4; MALDI-HRMS: *m*/*z* 393.0885 ($[M+Na]^+$, $C_{15}H_{18}N_2O_9Na^+$ calcd 393.0905).

7.1.8. 1-(α-L-Ribofuranosyl)cytosine (8). The Lawesson's reagent (1.80 g, 4.45 mmol) was added to a stirred solution of nucleoside **7** (2.06 g, 5.57 mmol) in anhydrous 1,2-dichloroethane (50 mL). The reaction mixture was heated under reflux for 4 h and then cooled to room temperature. Methanol (20 mL) was added and the reaction mixture concentrated to dryness under reduced pressure. The residue was immediately dissolved in a saturated solution of ammonia in methanol (100 mL) and heated at 100 °C for 3 h in an autoclave. After cooling to room temperature, the reaction mixture was evaporated to dryness under reduced pressure. The residue was purified by column chromatography [5–10% (v/v) MeOH in EtOAc] to give nucleoside **8** (1.0 g, 74%) as a white powder. δ_C (DMSO-d_6) 165.5, 155.2, 143.1, 92.2, 85.6, 83.1, 70.6, 70.1, 61.1; MALDI-MS: *m*/*z* 266 ($[M+Na]^+$, $C_9H_{13}N_3O_5Na^+$ calcd 266). The ^1H NMR data were found to be consistent with the literature data for the corresponding D-enantiomer.[12b]

7.1.9. 4-*N*-Benzoyl-1-(α-L-ribofuranosyl)cytosine (9). To a stirred solution of nucleoside **8** (1.0 g, 4.11 mmol) in anhydrous pyridine (20 mL) at 0 °C was added trimethylchlorosilane (3.13 mL, 24.7 mmol). The reaction mixture was stirred at room temperature for 1 h whereupon benzoyl chloride (2.38 mL, 20.6 mmol) was added. After stirring for another 5 h the resulting mixture was cooled in an ice bath, H_2O (10 mL) was added and stirring was continued for additional 5 min. Aqueous ammonia (10 mL, 29%, w/w) was added, and the resulting mixture was stirred at room temperature for 15 min and evaporated to dryness under reduced pressure. The residue was coevaporated with toluene (2×5 mL) and then purified by column chromatography [5–8% (v/v) MeOH in EtOAc] affording nucleoside **9**, which was crystallized from absolute ethanol as colourless crystals (1.1 g, 77%). δ_C (DMSO-d_6) 167.2, 162.9, 154.6, 147.0, 133.2, 132.7, 128.4, 128.2, 95.0, 86.7, 83.7, 70.6, 70.0, 60.9; MALDI-HRMS: *m*/*z* 370.1009 ($[M+Na]^+$, $C_{16}H_{17}N_3O_6Na^+$ calcd 370.1015). The ^1H NMR data were found to be consistent with the literature data for the corresponding D-enantiomer.[12b]

7.1.10. 4-*N*-Benzoyl-1-[5-*O*-(4,4′-dimethoxytrityl)-α-L-ribofuranosyl]cytosine (10). 4,4′-Dimethoxytrityl chloride (0.33 g, 1.0 mmol) was added to a solution of nucleoside **9** (0.12 g, 0.49 mmol) in anhydrous pyridine (5 mL) and the resulting mixture was stirred at room temperature for 12 h. MeOH (2 mL) was added, stirring was continued for another 10 min whereupon the reaction mixture was poured into saturated aq $NaHCO_3$ (25 mL). Extraction was performed with $CHCl_3$ (3×20 mL), and the combined organic phase was dried (Na_2SO_4), filtered and evaporated to dryness under reduced pressure. The residue obtained was purified by column chromatography [6–8% (v/v) MeOH in $CHCl_3$] to furnish nucleoside **10** (180 mg, 95%) as a white foam. δ_C ($CDCl_3$) 166.7, 162.5, 158.6, 156.2, 146.5, 144.7, 136.0, 135.8, 133.2, 133.0, 130.2, 129.1, 128.2, 128.0, 127.8, 127.0, 113.3, 96.3, 88.9, 86.5, 84.5, 72.1, 71.3, 63.8, 55.3; MALDI-MS: *m*/*z* 649 ($[M+Na]^+$, $C_{37}H_{35}N_3O_8Na^+$ calcd 649). The ^1H NMR data were found to be consistent with the literature data for the corresponding D-enantiomer.[12b]

7.1.11. 4-*N*-Benzoyl-1-(2-*O*-*tert*-butyldimethylsilyl-5-*O*-(4,4′-dimethoxytrityl)-α-L-ribofuranosyl)cytosine (11). *tert*-Butyldimethylsilyl chloride (0.19 g, 1.05 mmol) was added to a solution of nucleoside **10** (0.44 g, 0.81 mmol) and imidazole (0.14 g, 2.10 mmol) in anhydrous pyridine (10 mL) and stirring was continued at room temperature for 24 h. The reaction mixture was poured into a saturated aq $NaHCO_3$ (25 mL) and extraction was performed with $CHCl_3$ (3×20 mL). The combined organic phase was dried (Na_2SO_4), filtered and evaporated to dryness under reduced pressure. The residue obtained was purified by column chromatography [5–8% (v/v) acetone in CH_2Cl_2] to give the 2′-*O*-*tert*-butyldimethylsilyl isomer **11** as a white foam (0.30 g, 49%). Further elution [8–10% (v/v) acetone in CH_2Cl_2] yielded a byproduct tentatively assigned as the 3′-*O*-*tert*-butyldimethylsilyl isomer (yield not determined). δ_C ($CDCl_3$) 162.1, 158.7, 146.5, 144.6, 135.8, 135.6, 133.3, 130.1, 129.2, 128.2, 128.1, 127.7, 127.1, 113.4, 95.5, 87.3, 86.9, 84.4, 73.0, 72.7, 64.0, 55.4, 25.9, 18.2, −5.1, −5.3; ESI-MS: *m*/*z* 786 ($[M+Na]^+$, $C_{43}H_{49}N_3O_8SiNa^+$ calcd 786). The ^1H NMR data were found to be consistent with the literature data for the corresponding D-enantiomer.[12b]

7.1.12. 4-*N*-Benzoyl-1-(2-*O*-*tert*-butyldimethylsilyl-3-*O*-[2-cyanoethoxy(diisopropylamino)phosphino]-5-*O*-(4,4′-dimethoxytrityl)-α-L-ribofuranosyl)cytosine (12). To a stirred solution of nucleoside **11** (70 mg, 0.09 mmol) and *N*,*N*-diisopropylethylamine (0.16 mL, 0.92 mmol) in CH_2Cl_2 (4 mL) at room temperature was added 2-cyanoethyl *N*,*N*′-diisopropylphosphoramidochloridite (0.09 mL, 0.46 mmol) and stirring was continued for 15 h. CH_2Cl_2 (10 mL) was added and the resulting mixture was washed with saturated aq $NaHCO_3$ (10 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated to dryness under reduced pressure. The residue obtained was purified by column chromatography [45–50% EtOAc in *n*-hexane, containing 0.5% Et_3N (v/v/v)] affording phosphoramidite **12** (50 mg, 52%) as a white foam. δ_P (DMSO-d_6) 151.4, 150.9.

7.1.13. 3-*O*-Benzyl-5-*O*-*tert*-butyldiphenylsilyl-1,2-*O*-isopropylidene-β-L-arabinofuranose (14). To a solution of 5-*O*-*tert*-butyldiphenylsilyl-1,2-*O*-isopropylidene-β-L-arabinofuranose **13**[24] (7.00 g, 16.4 mmol) in anhydrous DMF (50 mL) at 0 °C was added NaH (1.31 g, 60% suspension in mineral oil, 32.7 mmol) and benzyl bromide (3.9 mL, 32.7 mmol). The reaction mixture was stirred at room temperature for 5 h and then concentrated to dryness under reduced pressure. The residue obtained was dissolved in diethyl ether (100 mL) and washing was performed successively with saturated aq $NaHCO_3$ (100 mL) and brine (100 mL). The separated organic phase was dried (Na_2SO_4), filtered and evaporated to dryness under reduced pressure. The residue obtained was purified by column chromatography [5–10% (v/v) EtOAc in light petroleum] to afford nucleoside **14** as a clear oil (7.20 g, 86%). δ_C ($CDCl_3$) 137.5, 135.6, 135.5, 133.1, 129.7, 128.5, 127.8, 127.7, 127.68, 127.64, 112.4, 105.7, 85.2, 85.1, 82.8, 71.6, 63.4, 26.9, 26.8, 26.1, 19.2; MALDI-HRMS: *m*/*z* 541.2382 ($[M+Na]^+$, $C_{31}H_{38}O_5SiNa^+$ calcd 541.2386). The ^1H NMR data were found to be consistent with the literature data for the corresponding D-enantiomer.[25b]

7.1.14. 3-*O*-Benzyl-1,2-*O*-isopropylidene-β-L-arabinofuranose (15). To a solution of furanose **14** (9.84 g, 19.0 mmol) in THF (150 mL) was added TBAF (38.0 mL, 1 M in THF, 38.0 mmol) and stirring was continued at room temperature for 12 h. The reaction mixture was concentrated to dryness under reduced pressure and the residue dissolved in ethyl acetate (200 mL) whereupon washing was performed with brine (2×100 mL). The separated organic phase was dried (Na_2SO_4), filtered and evaporated to dryness under reduced pressure. The residue obtained was purified by column chromatography [3–5% (v/v) MeOH in CH_2Cl_2] to give furanose **15** (4.20 g, 80%) as a clear oil. δ_C ($CDCl_3$) 137.1, 128.5, 128.4, 128.0, 127.9, 127.7, 112.9, 105.5, 85.5, 85.2, 82.7, 71.8, 62.7, 27.1, 26.3; MALDI-MS: *m*/*z* 303.1207 ($[M+Na]^+$, $C_{15}H_{20}O_5Na^+$ calcd 303.1208). The ^1H NMR data were found to be consistent with the literature data for the corresponding D-enantiomer.[25]

7.1.15. 5-*O*-Benzoyl-3-*O*-benzyl-1,2-*O*-isopropylidene-β-L-arabinofuranose (16). Benzoyl chloride (1.6 mL, 13.9 mmol) was added dropwise to a solution of furanose **15** (2.60 g, 9.29 mmol) in anhydrous pyridine (10 mL) and the resulting mixture was stirred at room temperature for 2 h. The mixture was then concentrated to dryness under reduced pressure, the residue obtained was dissolved in ethyl acetate (100 mL), and washing was performed first with saturated aq $NaHCO_3$ (100 mL) and then with brine (100 mL). The separated organic phase was dried (Na_2SO_4), filtered, evaporated to dryness under reduced pressure and then coevaporated with toluene (2×5 mL). The residue obtained was purified by column chromatography [15–20% (v/v) EtOAc in light petroleum] to give furanose **16** (2.60 g, 74%) as a clear oil. δ_H ($CDCl_3$) 8.00 (2H, d, J=8.0 Hz), 7.59–7.25 (8H, m), 5.95 (1H, d, J=3.6 Hz, H1), 4.70 (1H, d, J=3.6 Hz, H2), 4.66 (1H, d, J=11.8 Hz, CH_2Ph), 4.58 (1H, d, J=11.9 Hz, CH_2Ph), 4.50–4.40 (3H, m, H4 and H5), 4.08 (1H, d, J=2.8 Hz, H3), 1.55 and 1.35 [3H each, 2s, CH_3(isopropylidene)]; δ_C ($CDCl_3$) 166.1, 136.9, 133.1, 129.7, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 113.1, 105.8, 84.8, 82.7, 82.2, 71.8, 64.3, 27.1, 26.3; MALDI-HRMS: *m*/*z* 407.1475 ($[M+Na]^+$, $C_{22}H_{24}O_6Na^+$ calcd 407.1471).

7.1.16. 1,2-Di-*O*-acetyl-5-*O*-benzoyl-3-*O*-benzyl-α,β-L-arabinofuranose (17). Concentrated sulfuric acid (0.02 mL) was added to a solution of furanose **16** (2.21 g, 5.76 mmol) in 80% aq acetic acid (20 mL) and stirring was continued for 1 h at 50 °C. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure to approximately half of the original volume. Pyridine (30 mL) and acetic anhydride (1.63 mL, 17.3 mmol) were added and the resulting mixture was stirred at 50 °C for 6 h and then concentrated to dryness under reduced pressure. The residue obtained was dissolved in ethyl acetate (50 mL) and then washed first with saturated aq $NaHCO_3$ (50 mL) followed by brine (50 mL). The separated organic phase was dried (Na_2SO_4), filtered, evaporated to dryness under reduced pressure and then coevaporated with toluene (2×5 mL). The residue obtained was purified by column chromatography [15–20% (v/v) EtOAc in light petroleum] yielding a 1:1 mixture of anomers **17** as a clear oil (1.80 g, 73%). δ_H ($CDCl_3$) 8.06–8.01 (4H, m), 7.60–7.55 (2H, m), 7.46–7.40 (4H, m), 7.30–7.26 (10H, m), 6.39 (1H, d, J=4.6 Hz), 6.23 (1H, s), 5.31 (1H, m), 5.27 (1H, s), 4.77 (1H, d, J=12.0 Hz), 4.70–4.34 (9H, m), 4.01–3.99 (2H, m), 2.12 (3H, s), 2.06 (3H, s), 2.05 (3H, s), 1.95 (3H, s), δ_C ($CDCl_3$) 169.6, 169.5, 169.2, 166.1, 166.0, 137.2, 137.1, 133.2, 133.1, 129.8, 129.7, 129.6, 129.5, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 99.9, 93.9, 83.1, 82.9, 80.6, 79.6, 79.5, 77.0, 72.7, 72.4, 64.3, 63.4, 21.1, 20.9, 20.7, 20.4; MALDI-HRMS: *m*/*z* 451.1375 ($[M+Na]^+$, $C_{23}H_{24}O_8Na^+$ calcd 451.1369).

7.1.17. 9-(2-*O*-Acetyl-5-*O*-benzoyl-3-*O*-benzyl-α-L-arabinofuranosyl)-6-*N*-benzoyladenine (18). To a suspension of anomers **17** (0.70 g, 1.64 mmol) and 6-*N*-benzoyladenine (0.59 g, 2.45 mmol) in anhydrous acetonitrile (6 mL) was added $SnCl_4$ (0.4 mL, 3.3 mmol) and the resulting mixture was stirred at room temperature for 4 h. Saturated aq $NaHCO_3$ was added until the evolution of carbon dioxide ceased whereupon the mixture was filtered through a layer of Celite 545, that was subsequently flushed with $CHCl_3$ (2×50 mL). The combined filtrate was washed successively with saturated aq $NaHCO_3$ (3×100 mL) and brine (2×100 mL), dried (Na_2SO_4), filtered and evaporated to dryness under reduced pressure. The residue obtained was purified by column chromatography [4–5% (v/v) MeOH in

$CHCl_3$] affording nucleoside **18** (870 mg, 88%) as a white solid material. δ_H ($CDCl_3$) 9.16 (1H, br s, NH), 8.81 (1H, s, H8), 8.39 (1H, s, H2), 8.04–8.00 (4H, m), 7.62–7.42 (6H, m), 7.28–7.23 (5H, m), 6.48 (1H, s, H1′), 5.81 (1H, t, J=1.4 Hz, H2′), 4.83 (1H, m, H4′), 4.73 (1H, d, J=11.9 Hz, CH_2Ph), 4.65 (1H, d, J=12.0 Hz, CH_2Ph), 4.51 (1H, d, J=5.4 Hz, H5′a), 4.50 (1H, d, J=5.6 Hz, H5′b), 4.24 (1H, dd, J=1.3, 3.3 Hz, H3′), 2.11 (3H, s, $COCH_3$); δ_C ($CDCl_3$) 169.7, 166.2, 164.7, 153.0, 151.8, 149.7, 141.6, 136.4, 133.7, 133.5, 132.9, 129.9, 129.5, 129.0, 128.7, 128.6, 128.4, 128.04, 128.01, 123.1, 88.5, 84.3, 82.7, 80.5, 72.7, 63.5, 20.9; MALDI-HRMS: m/z 630.1966 ([M+Na]$^+$, $C_{33}H_{29}N_5O_7Na^+$ calcd 630.1965).

7.1.18. 6-*N*-Benzoyl-9-(5-*O*-benzoyl-3-*O*-benzyl-α-L-arabinofuranosyl)adenine (19). To a solution of nucleoside **18** (0.64 g, 1.06 mmol) in MeOH (16 mL) was added saturated methanolic ammonia (16 mL) and the mixture was stirred at 0 °C for 1.5 h. The reaction mixture was concentrated to dryness under reduced pressure and the residue was coevaporated with toluene (5×10 mL). The residue obtained was purified by column chromatography [5–6% (v/v) MeOH in $CHCl_3$] affording nucleoside **19** (550 mg, 92%) as a white solid material. δ_H ($CDCl_3$) 9.07 (1H, br s, NH), 8.71 (1H, s, H8), 8.21 (1H, s, H2), 8.05–8.01 (4H, m), 7.62–7.43 (6H, m), 7.30–7.25 (5H, m), 6.12 (1H, d, J=4.0 Hz, H1′), 4.97 (1H, t, J=4.7 Hz, H2′), 4.80 (1H, d, J=11.9 Hz, CH_2Ph), 4.75 (1H, m, H4′), 4.71 (1H, d, J=12.0 Hz, CH_2Ph), 4.63 (1H, dd, J=3.7, 12.4 Hz, H5′a), 4.51 (1H, dd, J=5.0, 12.3 Hz, H5′b), 4.33 (1H, t, J=5.3 Hz, H3′); δ_C ($CDCl_3$) 166.4, 164.7, 152.5, 151.1, 149.6, 141.4, 137.2, 133.6, 133.5, 133.1, 129.9, 129.8, 129.7, 129.1, 128.7, 128.6, 128.5, 128.3, 128.1, 128.0, 123.2, 91.4, 82.3, 80.6, 72.7, 63.9; MALDI-HRMS: m/z 588.1863 ([M+Na]$^+$, $C_{31}H_{27}N_5O_6Na^+$ calcd 588.1859).

7.1.19. 9-(2-*O*-Acetyl-5-*O*-benzoyl-3-*O*-benzyl-α-L-ribofuranosyl)-6-*N*-benzoyladenine (20). Nucleoside **19** (0.45 g, 0.80 mmol) was dissolved in a mixture of anhydrous CH_2Cl_2 (20 mL) and anhydrous pyridine (4 mL). The stirred solution was cooled to −30 °C and trifluoromethanesulfonic anhydride (0.35 mL, 2.15 mmol) was added. After 1.5 h, the reaction mixture was allowed to warm to 0 °C and saturated aq $NaHCO_3$ (10 mL) and CH_2Cl_2 (60 mL) were added. The organic phase was separated, washed with saturated aq $NaHCO_3$ (3×70 mL), dried (Na_2SO_4), filtered and concentrated to dryness under reduced pressure. The residue was dissolved in a mixture of anhydrous toluene (24 mL) and anhydrous CH_2Cl_2 (24 mL) whereupon KOAc (0.39 g, 3.98 mmol) and 18-crown-6 (0.74 g, 2.79 mmol) were added at room temperature under stirring. The temperature was raised to 50 °C and stirring was continued for another 16 h. After cooling to room temperature, CH_2Cl_2 (100 mL) was added, and the reaction mixture was washed with saturated aq $NaHCO_3$ (3×50 mL), dried (Na_2SO_4), filtered and evaporated to dryness under reduced pressure. The residue obtained was purified by column chromatography [3–5% (v/v) MeOH in $CHCl_3$] to yield nucleoside **20** (380 mg, 79%) as a white solid material. δ_H ($CDCl_3$) 9.17 (1H, br s, NH), 8.80 (1H, s, H8), 8.35 (1H, s, H2), 8.04–7.43 (15H, m), 6.47 (1H, d, J=5.2 Hz, H1′), 5.87 (1H, m, H2′), 4.72–4.25 (6H, m, H3′, H4′, H5′ and CH_2Ph), 2.08 (3H, s, $COCH_3$); δ_C ($CDCl_3$) 169.3, 166.2, 164.9, 152.8, 149.8, 149.6, 142.8, 136.5, 133.6, 132.9, 129.8, 129.4, 129.1, 128.9, 128.8, 128.7, 128.6, 128.3, 128.2, 128.1, 125.4, 123.9, 82.7, 81.0, 76.8, 73.8, 70.9, 63.5, 20.6; MALDI-HRMS: m/z 630.1960 ([M+Na]$^+$, $C_{33}H_{29}N_5O_7Na^+$ calcd 630.1965).

7.1.20. 6-*N*-Benzoyl-9-(α-L-ribofuranosyl)adenine (22). Aqueous sodium hydroxide (1, 2.7 mL) was added to an ice-cold solution of nucleoside **20** (0.36 g, 0.59 mmol) in a mixture of ethanol (1.8 mL) and pyridine (3.5 mL). The reaction mixture stirred at 0 °C for 30 min and then neutralized with Dowex 50WX2(H^+). Dowex was filtered off and the filtrate was concentrated to dryness under reduced pressure. The oily residue was dissolved in EtOAc (100 mL) whereupon washing was performed using brine (2×75 mL). The separated organic phase was dried (Na_2SO_4), filtrated and concentrated to dryness under reduced pressure. The residue obtained was coevaporated with toluene and purified by column chromatography [3–5% MeOH in EtOAc] to give nucleoside **21** (tentatively assigned) as a white solid material (0.21 g). Ammonium formate (200 mg) and Pd/C (100 mg) were added to a solution of nucleoside **21** (0.21 g) in EtOH (5 mL). The resulting mixture was heated under reflux for 2 h, cooled to room temperature, filtered across a pad of Celite and then concentrated to dryness. The crude product was recrystallized from EtOH to give nucleoside **22** as white needles (0.12 g, 54% from **20**). δ_C (DMSO-d_6) 165.5, 152.6, 151.4, 149.9, 144.9, 133.4, 132.4, 128.5, 125.0, 85.3, 83.6, 70.7, 70.6, 61.4; MALDI-HRMS: m/z 394.1120 ([M+Na]$^+$, $C_{17}H_{17}N_5O_5Na^+$ calcd 394.1127). The ^{1}H NMR data were found to be consistent with the literature data for the corresponding D-enantiomer.[12b]

7.1.21. 6-*N*-Benzoyl-9-[5-*O*-(4,4′-dimethoxytrityl)-α-L-ribofuranosyl]adenine (23). 4,4′-Dimethoxytrityl chloride (0.33 g, 1.0 mmol) was added to a solution of nucleoside **22** (0.13 g, 0.35 mmol) in anhydrous pyridine (7 mL) and stirring was continued at room temperature for 12 h. MeOH (5 mL) was added and after stirring for another 10 min the reaction mixture was poured into saturated aq $NaHCO_3$ (25 mL). Extraction was performed with $CHCl_3$ (3×20 mL) and the combined organic phase was dried (Na_2SO_4), filtered and evaporated to dryness under reduced pressure. The residue obtained was purified by column chromatography [6–8% (v/v) MeOH in $CHCl_3$] affording nucleoside **23** (220 mg, 92%) as a white foam. δ_C ($CDCl_3$) 158.7, 152.0, 151.1, 149.4, 144.7, 143.9, 143.8, 135.9, 135.7, 133.7, 133.0, 130.2, 130.0, 129.0, 128.2, 128.1, 128.0, 127.9, 127.8, 127.1, 122.9, 113.4, 113.2, 87.2, 86.9, 86.0, 72.8, 72.2, 64.4, 55.4.; ESI-HRMS: m/z 696.2429 ([M+Na]$^+$, $C_{38}H_{35}N_5O_7Na^+$ calcd 696.2434). The ^{1}H NMR data were found to be consistent with the literature data for the corresponding D-enantiomer.[12b]

7.1.22. 6-*N*-Benzoyl-9-[2-*O*-*tert*-butyldimethylsilyl-5-*O*-(4,4′-dimethoxytrityl)-α-L-ribofuranosyl]adenine (24). *tert*-Butyldimethylsilyl chloride (0.06 g, 0.43 mmol) was added to a solution of nucleoside **23** (0.22 g, 0.33 mmol) and imidazole (0.06 g, 0.85 mmol) in anhydrous pyridine (5 mL) and stirring was continued at room temperature for 15 h. The reaction mixture was poured into saturated aq $NaHCO_3$ (25 mL) and extraction was performed with

$CHCl_3$ (3×20 mL). The combined organic phase was dried (Na_2SO_4), filtered and evaporated to dryness under reduced pressure. The residue obtained was purified by column chromatography [4–5% (v/v) acetone in CH_2Cl_2] to give the required 2′-*O*-*tert*-butyldimethylsilyl isomer **24** as a white foam (0.12 g, 48%). Further elution [5–7% (v/v) acetone in CH_2Cl_2] yielded a byproduct tentatively assigned as the 3′-*O*-*tert*-butyldimethylsilyl isomer (yield not determined). δ_C ($CDCl_3$) 164.6, 158.73, 158.71, 152.5, 151.8, 149.5, 144.6, 143.6, 135.7, 135.4, 133.9, 132.8, 130.1, 130.0, 128.9, 128.1, 127.9, 127.1, 122.6, 113.4, 113.37, 86.9, 85.8, 85.4, 73.2, 72.9, 64.4, 55.3, 25.4, 17.8, −5.2, −5.3; ESI-HRMS: *m/z* 810.3286 ($[M+Na]^+$, $C_{44}H_{49}N_5O_7SiNa^+$ calcd 810.3299). The ^1H NMR data were found to be consistent with the literature data for the corresponding D-enantiomer.[12b]

7.1.23. 6-*N*-Benzoyl-9-[2-*O*-*tert*-butyldimethylsilyl-3-*O*-(2-cyanoethoxy(diisopropylamino)phosphino)-5-*O*-(4,4′-dimethoxytrityl)-α-L-ribofuranosyl]adenine (25). To a stirred solution of nucleoside **24** (70 mg, 0.09 mmol) and *N*,*N*-diisopropylethylamine (0.16 mL, 0.92 mmol) in CH_2Cl_2 (2 mL) at room temperature was added 2-cyanoethyl *N*,*N*′-diisopropylphosphoramidochloridite (0.09 mL, 0.46 mmol) and stirring was continued for 15 h. CH_2Cl_2 (10 mL) was added and the resulting mixture was washed with saturated aq $NaHCO_3$ (10 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated to dryness under reduced pressure. The residue obtained was purified by column chromatography [50–55% EtOAc in *n*-hexane, containing 0.5% Et_3N (v/v/v)] furnishing phosphoramidite **25** (65 mg, 73%) as a white foam. δ_P (DMSO-d_6) 151.8, 150.4; ESI-MS *m/z* 988.4 $[M+H]^+$, 1010.5 ($[M+Na]^+$, $C_{53}H_{66}N_7O_8PSiNa^+$ calcd 1010.5).

7.1.24. 1-[3,5-Di-*O*-(*tert*-butyldiphenylsilyl)-4-*C*-hydroxymethyl-β-D-xylofuranosyl]thymine (27). A solution of nucleoside **26**[28] (5.50 g, 6.04 mmol) in saturated methanolic ammonia (100 mL) was stirred for 48 h at room temperature. After evaporation to dryness under reduced pressure, the resulting residue was coevaporated with toluene (2× 5 mL) and purified by column chromatography [60–66% (v/v) EtOAc in light petroleum] to afford nucleoside **27** (4.45 g, 96%) as a white solid material. R_f 0.24 (MeOH/CH_2Cl_2 15:85, v/v); δ_H ($CDCl_3$) 9.50 (1H, s), 7.66 (2H, dd, J=1.3, 7.9 Hz), 7.59 (2H, dd, J=1.3, 7.9 Hz), 7.50–7.31 (13H, m), 7.27–7.23 (4H, m), 5.86 (1H, d, J=2.9 Hz, H1′), 4.43 (1H, br s, 2′-OH), 4.41 (1H, d, J=2.7 Hz, H2′), 4.22 (1H, br s, H3′), 4.02 (1H, d, J=11.6 Hz, H5′a), 3.86 (1H, dd, J=4.5, 11.9 Hz, H5″a), 3.71 (1H, d, J=11.9 Hz, H5′b), 3.48 (1H, dd, J=6.0, 11.7 Hz, H5″b), 2.76 (1H, m, 5′-OH), 1.66 (3H, d, J=1.0 Hz, 5-CH_3), 1.06 and 0.91 (2× Si*C*(CH_3)$_3$); δ_C ($CDCl_3$) 164.1, 151.0, 136.0, 135.9, 135.8, 135.7, 132.9, 132.8, 132.6, 132.2, 130.3, 130.2, 130.0, 128.0, 127.9, 127.8, 110.8, 92.0, 90.7, 83.2, 79.6, 65.2, 63.6, 27.0, 26.9, 19.4, 19.2, 12.4; MALDI-MS: *m/z* 787 ($[M+Na]^+$, $C_{43}H_{52}N_2O_7Si_2Na^+$ calcd 787).

7.1.25. 1-[3,5-Di-*O*-(*tert*-butyldiphenylsilyl)-4-*C*-(4,4′-dimethoxytrityloxymethyl)-β-D-xylofuranosyl]thymine (28). 4,4′-Dimethoxytrityl chloride (2.05 g, 6.05 mmol) was added in one portion to a stirred solution of nucleoside **27** (4.2 g, 5.49 mmol) in anhydrous pyridine (20 mL). After stirring the mixture 12 h at room temperature, toluene (20 mL) was added and the solution was concentrated to approximately one-fourth the original volume under reduced pressure. CH_2Cl_2 (100 mL) was added whereupon washing was performed with saturated aq $NaHCO_3$ (2× 50 mL). The separated organic phase was dried (Na_2SO_4), filtered and concentrated to dryness under reduced pressure. The residue was coevaporated with toluene (2×10 mL) and then purified by column hromatography [40–50% EtOAc in light petroleum, containing 0.5% Et_3N (v/v/v)] to afford nucleoside **28** as a white solid (5.68 g, 97%). R_f 0.33 (MeOH/CH_2Cl_2 5:95, v/v); δ_H ($CDCl_3$) 8.89 (1H, s, NH), 7.64–7.61 (2H, m), 7.58–7.55 (2H, m), 7.48 (1H, d, J= 1.2 Hz, H6), 7.44–7.40 (7H, m), 7.36–7.30 (9H, m), 7.28–7.12 (9H, m), 6.73 (4H, d, J=8.7 Hz), 5.82 (1H, d, J= 3.7 Hz, H1′), 4.35 (1H, d, J=3.2 Hz, H3′), 4.07 (1H, m, H2′), 4.03 (1H, d, J=11.7 Hz, H5′a), 3.92 (1H, d, J= 11.8 Hz, H5′b), 3.77 and 3.76 (3H each, 2s, 2×OCH_3), 3.57 (1H, d, J=9.6 Hz, H5″a), 3.18 (1H, d, J=9.5 Hz, H5″b), 2.89 (1H, d, J=5.4 Hz, 2′-OH), 1.65 (3H, s, 5-CH_3), 1.00 and 0.83 (9H each, 2s, 2×C(CH_3)$_3$); δ_C ($CDCl_3$) 163.9 (C4), 158.5, 158.4, 150.8 (C2), 144.4, 136.0, 135.8, 135.7, 135.6, 135.5, 133.2, 133.0, 132.9, 132.0, 130.4, 130.2, 130.1, 129.9, 129.8, 128.4, 127.9, 127.8, 126.8, 113.2, 110.5 (C5), 91.4 (C1′), 89.9 (C4′), 87.0 (CAr_3), 83.2 (C2′), 80.0 (C3′), 65.0 and 63.6 (C5′ and C5″), 55.3 (2×OCH_3), 27.0 and 26.9 (2×C(*C*H_3)$_3$), 19.5 and 19.2 (2×Si*C*(CH_3)$_3$), 12.4 (5-CH_3); MALDI-HRMS: *m/z* 1089.4576 ($[M+Na]^+$, $C_{64}H_{70}N_2O_9Si_2Na^+$ calcd 1089.4512).

7.1.26. 1-[3,5-Di-*O*-(*tert*-butyldiphenylsilyl)-4-*C*-(4,4′-dimethoxytrityloxymethyl)-2-*O*-methanesulfonyl-β-D-xylofuranosyl]thymine (29) and 2,2′-anhydro-1-[3,5-di-*O*-(*tert*-butyldiphenylsilyl)-4-*C*-(4,4′-dimethoxytrityloxymethyl)-β-D-lyxofuranosyl]thymine (30). Nucleoside **28** (3.2 g, 3.0 mmol) was dissolved in a 1:1 mixture of anhydrous CH_2Cl_2–Et_3N (10 mL). DMAP (440 mg, 3.6 mmol) was added followed by methanesulfonyl chloride (413 mg, 3.6 mmol) and the resulting mixture was stirred at room temperature for 12 h. Analytical TLC showed the formation of two products. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washing was performed with saturated aq $NaHCO_3$ (2×50 mL). The separated organic phase was dried (Na_2SO_4), filtered and concentrated to dryness under reduced pressure. An analytical sample was purified by column chromatography [40–45% (v/v) EtOAc in light petroleum, containing 0.5% Et_3N (v/v/v)] to give as the major product nucleoside **29**, R_f 0.38 (MeOH/CH_2Cl_2 5:95, v/v), and [70–75% (v/v) EtOAc in light petroleum, containing 0.5% Et_3N (v/v/v)] as the minor product the anhydro nucleoside **30**, R_f 0.28 (MeOH/CH_2Cl_2 5:95, v/v), (both as white solid materials). Data for compound **29**: δ_H ($CDCl_3$) 8.70 (1H, s, NH), 7.70–7.68 (4H, m), 7.54–7.52 (2H, m), 7.47–7.25 (16H, m), 7.23–7.14 (8H, m), 6.76–6.73 (4H, m), 6.03 (1H, d, J=4.7 Hz, H1′), 5.17 (1H, dd, J=4.3, 4.7 Hz, H2′), 4.67 (1H, d, J=4.1 Hz, H3′), 4.17 (1H, d, J= 11.2 Hz, H5′a), 4.12 (1H, d, J=11.2 Hz, H5′b), 3.77 and 3.76 (3H each, 2s, 2×OCH_3), 3.39 (1H, d, J=9.4 Hz, H5″a), 3.09 (1H, d, J=9.1 Hz, H5″b), 2.50 (3H, s, SO_2CH_3), 1.44 (3H, s, 5-CH_3), 1.03 and 0.87 (9H each, 2s, 2×C(CH_3)$_3$); δ_C ($CDCl_3$) 163.5 (C4), 158.5, 150.4 (C2), 144.7, 136.0, 135.9, 135.8, 135.6, 135.4, 133.5, 132.9, 132.3, 131.1, 130.5, 130.3, 130.2, 129.9, 128.3, 128.1,

128.0, 127.9, 126.8, 113.2, 111.8 (C5), 88.3 (C4′), 86.7 (CAr_3), 85.6 (C1′), 85.2 (C2′), 77.0 (C3′), 64.4 (C5′), 62.5 (C5″), 55.3 (2×OCH_3), 38.3 (SO_2CH_3), 27.2 and 27.0 (2×$C(CH_3)_3$), 19.6 and 19.3 (2×$SiC(CH_3)_3$), 11.9 (5-CH_3); data for compound **30**: δ_H ($CDCl_3$) 7.57–7.54 (2H, m), 7.41–7.19 (22H, m), 7.16–7.07 (6H, m), 6.77–6.73 (4H, m), 6.07 (1H, d, J=6.2 Hz, H1′), 4.82 (1H, dd, J=6.0, 6.3 Hz, H2′), 4.65 (1H, d, J=5.9 Hz, H3′), 3.87 (1H, d, J=10.5 Hz, H5′a), 3.79 (6H, s, 2×OCH_3), 3.58 (1H, d, J=12.2 Hz, H5″a), 3.15 (1H, d, J=12.2 Hz, H5″b), 2.75 (1H, d, J=10.3 Hz, H5′b), 1.99 (3H, s, 5-CH_3), 0.88 and 0.81 (9H each, 2s, 2×$C(CH_3)_3$); δ_C ($CDCl_3$) 172.4 (C4), 159.9 (C2), 158.6, 144.5, 136.1, 135.8, 135.6, 135.5, 135.4, 133.1, 132.7, 132.5, 132.3, 130.3, 130.2, 130.1, 129.9, 129.8, 129.7, 128.1, 127.9, 127.8, 127.7, 127.6, 127.0, 119.0 (C5), 113.2, 90.8 (C4′), 89.3 (C1′), 86.9 (CAr_3), 81.2 (C2′), 73.3 (C3′), 64.9 and 64.4 (C5′ and C5″), 55.3 (2×OCH_3), 26.8 and 26.7 (2×$C(CH_3)_3$), 19.4 and 19.2 (2×$SiC(CH_3)_3$), 14.2 (5-CH_3); MALDI-HRMS: m/z 1071.4466 ($[M+Na]^+$, $C_{64}H_{68}N_2O_8Si_2Na^+$ calcd 1071.4406).

7.1.27. 1-[5-*O*-(4,4′-Dimethoxytrityloxymethyl)-4-*C*-hydroxymethyl-α-L-ribofuranosyl]thymine (31). The crude mixture (3.35 g) obtained from the mesylation of **28** was dissolved in ethanol (50 mL), H_2O (45 mL) and aq NaOH (2 M solution, 5.0 mL) were added and the resulting solution was heated under reflux for 16 h. Toluene (100 mL) was added and the resulting mixture was concentrated to approximately one-third of the original volume. After partitioning between EtOAc (200 mL) and saturated aq $NaHCO_3$ (200 mL), the aqueous phase was separated and extracted with EtOAc (100 mL). The combined organic phase was washed with brine (200 mL), dried (Na_2SO_4), filtered and concentrated to dryness under reduced pressure. The residue obtained was purified by column chromatography [4–6% MeOH in CH_2Cl_2, containing 0.5% Et_3N (v/v/v)] to afford nucleoside **31** as a white solid material (1.15 g, 65% from **28**). R_f 0.12 (MeOH/CH_2Cl_2 5:95, v/v); δ_H ($CDCl_3$) 10.30 (1H, s, NH), 7.81 (1H, s, H6), 7.40 (2H, d, J=7.3 Hz), 7.31–7.15 (7H, m), 6.81 (4H, d, J=8.5 Hz), 6.09 (1H, d, J=3.8 Hz, H1′), 4.66 (1H, dd, J=4.3, 4.6 Hz, H2′), 4.38 (1H, d, J=5.1 Hz, H3′), 3.90 (2H, br s, H5″), 3.74 (6H, s, 2×OCH_3), 3.25 (1H, d, J=9.9 Hz, H5′a), 3.17 (1H, d, J=10.1 Hz, H5′b), 1.81 (3H, s, 5-CH_3); δ_C ($CDCl_3$) 165.4, 158.6, 151.0, 144.5, 138.5, 135.6, 135.5, 130.2, 130.1, 128.1, 128.0, 127.0, 113.3, 113.2, 108.9, 87.3, 86.8, 86.2, 73.9, 70.9, 66.2, 63.3, 55.3, 12.5; MALDI-HRMS: m/z 613.2180 ($[M+Na]^+$, $C_{32}H_{34}N_2O_9Na^+$ calcd 613.2157).

7.1.28. 1-[2,5-Di-*O*-(*tert*-butyldimethylsilyl)-4-*C*-(4,4′-dimethoxytrityloxymethyl)-β-D-lyxofuranosyl]thymine (32) and 1-[3,5-di-*O*-(*tert*-butyldimethylsilyl)-4-*C*-(4,4′-dimethoxytrityloxymethyl)-β-D-lyxofuranosyl]thymine (33). *tert*-Butyldimethylsilyl chloride (1.21 g, 8.0 mmol) and imidazole (1.09 g, 16.0 mmol) were added to a stirred solution of nucleoside **31** (1.18 g, 2.0 mmol) in anhydrous pyridine (10 mL). The reaction mixture was stirred at room temperature for 12 h and MeOH (1.0 mL) was then added. After stirring for 30 min the reaction mixture was concentrated to dryness under reduced pressure. The residue was dissolved in EtOAc (100 mL) and washed with saturated aq $NaHCO_3$ (2×50 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated to dryness. The residue was coevaporated with toluene (2×5.0 mL) and purified by column chromatography [30–40% (v/v) EtOAc in light petroleum] to give nucleoside **32** (955 mg, 58%) and [45–50% (v/v) EtOAc in light petroleum] nucleoside **33** (384 mg, 23%) (both as white solid materials). R_f 0.26, 0.32 (MeOH/CH_2Cl_2 5:95, v/v); data for **32**: δ_H ($CDCl_3$) 8.74 (1H, s, NH), 7.43–7.39 (3H, m), 7.31–7.19 (7H, m), 6.82 (4H, d, J=8.7 Hz), 6.48 (1H, d, J=5.9 Hz, H1′), 4.77 (1H, dd, J=5.3, 5.5 Hz, H2′), 4.04–4.00 (2H, m, H3′ and H5′a), 3.77–3.74 (7H, m, H5′b and 2×OCH_3), 3.33 (1H, d, J=9.8 Hz, H5″a), 3.23 (1H, d, J=10.1 Hz, H5″b), 2.89 (1H, d, J=1.6 Hz, 3′-OH), 1.91 (3H, s, 5-CH_3), 0.80 and 0.76 (9H each, 2s, 2×$C(CH_3)_3$), 0.04, −0.02, −0.04 and −0.06 (3H each, 4s, 4×$SiCH_3$); δ_c ($CDCl_3$) 163.8 (C4), 158.6, 150.7 (C2), 144.5, 138.2, 135.8, 135.5, 130.1, 130.0, 128.1, 128.0, 127.0, 113.4, 113.3, 109.2 (C5), 87.2, 86.8 and 85.2 (C1′, C4′ and CAr_3), 73.0 and 72.7 (C2′ and C3′), 66.1 and 63.5 (C5′ and C5′), 55.3 (2×OCH_3), 25.8 and 25.6 (2×$C(CH_3)_3$), 18.2 and 18.0 (2×$C(CH_3)_3$), 12.6 (5-CH_3), −5.2, −5.3, −5.4 and −5.5 (4×$SiCH_3$); MALDI-HRMS: m/z 841.3900 ($[M+Na]^+$, $C_{44}H_{62}N_2O_9Si_2Na^+$ calcd 841.3886); data for **33**: δ_H ($CDCl_3$) 8.81 (1H, s, NH), 7.60 (1H, d, J=1.0 Hz, H6), 7.42 (2H, d, J=7.2 Hz), 7.33–7.21 (7H, m), 6.83 (4H, d, J=9.0 Hz), 6.10 (1H, d, J=2.7 Hz, H1′), 4.67 (1H, d, J=10.2 Hz, 2′-OH), 4.53 (1H, d, J=4.8 Hz, H3′), 4.12 (1H, ddd, J=2.7, 5.1, 10.2 Hz, H2′), 3.79 (6H, s, 2×OCH_3), 3.74 (1H, d, J=10.6 Hz, H5′a), 3.59 (1H, d, J=10.8 Hz, H5′b), 3.15 (1H, d, J=9.9 Hz, H5″a), 3.04 (1H, d, J=9.9 Hz, H5″b), 1.94 (3H, s, 5-CH_3), 0.95 and 0.81 (9H each, 2s, 2×$C(CH_3)_3$), 0.16, 0.14, 0.02 and −0.05 (3H each, 4s, 4×$SiCH_3$); δ_C ($CDCl_3$) 163.9, 158.6, 150.4, 144.4, 137.5, 135.6, 135.5, 130.1, 130.0, 128.1, 128.0, 127.0, 113.3, 108.8, 86.9, 86.6, 85.0, 74.4, 71.2, 65.3, 63.5, 55.3, 26.0, 25.8, 18.3, 18.1, 12.6, −4.7, −5.1, −5.4 and −5.5; MALDI-HRMS: m/z 841.3908 ($[M+Na]^+$, $C_{44}H_{62}N_2O_9Si_2Na^+$ calcd 841.3886).

7.1.29. 1-[3-*O*-(2-Cyanoethoxy(*N*,*N*-diisopropylamino)-phosphino)-2,5-di-*O*-(*tert*-butyldimethylsilyl)-4-*C*-(4,4′-dimethoxytrityloxymethyl)-β-D-lyxofuranosyl]thymine (34). 2-Cyanoethyl *N*,*N*-diisopropylphosphoramidochloridite (473 mg, 2.0 mmol) was added dropwise to a stirred solution of the nucleoside **32** (819 mg, 1.0 mmol) and *N*,*N*-diisopropylethylamine (1.0 mL) in anhydrous CH_2Cl_2 (10 mL). After stirring the resulting mixture for 12 h at room temperature, the reaction mixture was diluted with EtOAc (50 mL). Washing was performed with saturated aq $NaHCO_3$ (2×25 mL). The separated organic phase was dried (Na_2SO_4), filtered and concentrated to dryness under reduced pressure. The residue obtained was purified by column chromatography [33–40% EtOAc in *n*-hexane containing 0.5% Et_3N (v/v/v)] to give amidite **34** as a white solid material (723 mg, 71%). R_f 0.31, 0.32 (MeOH/CH_2Cl_2 5:95, v/v); δ_P 153.9 and 151.6; δ_H ($CDCl_3$, major isomer) 8.13 (br s, NH), 7.52 (s, H6), 7.42 (d, J=7.7 Hz), 7.32 (d, J=8.8 Hz), 7.27–7.21 (m), 6.84 (d, J=8.7 Hz), 6.35 (d, J=5.7 Hz, H1′), 4.59 (dd, J=5.1, 5.7 Hz, H2′), 4.45 (dd, J=5.1, 13.7 Hz, H3′), 4.02 (d, J=11.3 Hz, H5′a), 3.84 (d, J=11.6 Hz, H5′b), 3.79 (s, 2×OCH_3), 3.75–3.56 (m, OCH_2 and 2×$CH(CH_3)_2$), 3.44 (d, J=9.9 Hz, H5″a), 3.22 (d, J=9.8 Hz, H5″b), 2.34 (dd, J=6.5, 11.4 Hz, CH_2CN), 1.90 (s, 5-CH_3), 1.19 (d, J=6.3 Hz, $C(CH_3)_2$), 1.18 (d, J=6.4 Hz, $C(CH_3)_2$), 0.81 (s, 2×$C(CH_3)_3$), 0.06,

−0.05, −0.06 and −0.10 (4s, 4×$SiCH_3$); MALDI-HRMS: *m/z* 1041.4963 ($[M+Na]^+$, $C_{53}H_{79}N_4O_{10}PSi_2Na^+$ calcd 1041.4965).

7.1.30. 1-[2-*O*-Acetyl-5-*O*-benzoyl-3-*O*-(*tert*-butyldimethylsilyl)-4-*C*-(4,4′-dimethoxytrityloxymethyl)-α-L-arabinofuranosyl]thymine (36). *tert*-Butyldimethylsilyl chloride (2.0 g, 13.3 mmol), imidazole (1.82 g, 26.7 mmol) and DMAP (100 mg, 0.82 mmol) were added to a stirred solution of 1-[2-*O*-acetyl-5-*O*-benzoyl-4-*C*-(4,4′-dimethoxytrityloxymethyl)-α-L-arabinofuranosyl]thymine (**35**[28], 3.28 g, 4.45 mmol) dissolved in anhydrous DMF (10 mL). The reaction mixture was allowed to stir at 36 °C for 12 h and was then partitioned between CH_2Cl_2 (100 mL) and saturated aq $KHSO_4$ (100 mL). The separated organic phase was washed with saturated aq $NaHCO_3$ (50 mL), then dried (Na_2SO_4), concentrated and coevaporated with toluene (3×5.0 mL). The crude product was purified by column chromatography [45–50% (v/v) EtOAc in light petroleum] to give nucleoside **36** as white solid material (3.33 g). R_f 0.2 (MeOH/CH_2Cl_2 5:95, v/v); δ_H ($CDCl_3$) 8.79 (1H, s, NH), 7.83 (2H, d, *J*=7.8 Hz), 7.58 (1H, dd, *J*=7.4, 7.6 Hz), 7.47–7.39 (6H, m), 7.34 (4H, d, *J*=8.5 Hz), 7.28–7.21 (2H, m), 6.78 (4H, d, *J*=8.7 Hz), 6.30 (1H, d, *J*=3.5 Hz, H1′), 5.26 (1H, dd, *J*=3.3, 3.7 Hz, H2′), 4.65 (1H, d, *J*=10.8 Hz, H5″a), 4.56 (1H, d, *J*=10.9 Hz, H5″b), 4.28 (1H, d, *J*=3.2 Hz, H3′), 3.76 (6H, s, 2×OCH_3), 3.64 (1H, d, *J*=10.2 Hz, H5′a), 3.35 (1H, d, *J*=10.1 Hz, H5′b), 2.13 (3H, s, $COCH_3$), 1.57 (3H, s, 5-CH_3), 0.70 (9H, s, $C(CH_3)_3$), −0.01 (3H, s, $SiCH_3$), −0.19 (3H, s, $SiCH_3$); δ_C ($CDCl_3$) 169.7, 165.7, 163.6, 158.7, 158.6, 150.4, 144.3, 136.0, 135.7, 135.3, 133.4, 130.3, 130.2, 129.8, 129.4, 128.5, 128.4, 128.0, 127.1, 113.3, 111.1, 88.1, 87.4, 86.8, 82.0, 76.3, 63.1, 55.3, 25.6, 20.9, 17.8, 12.2, −4.9, −5.5. NMR spectroscopic data revealed the compound to be contaminated with traces of DMF; MALDI-HRMS: *m/z* 873.3393 ($[M+Na]^+$, $C_{47}H_{54}N_2O_{11}SiNa^+$ calcd 873.3389).

7.1.31. 1-[5-*O*-Benzoyl-3-*O*-(*tert*-butyldimethylsilyl)-4-*C*-(4,4′-dimethoxytrityloxymethyl)-α-L-arabinofuranosyl]-thymine (37). To a stirred solution of nucleoside **36** (3.0 g, 3.53 mmol) in MeOH (50 mL) was added methanol saturated with ammonia (10 mL) and the resulting mixture was stirred at room temperature for 5 h. The reaction mixture was concentrated to dryness under reduced pressure and the residue obtained was coevaporated with toluene (2×2 mL). The crude product was purified by column chromatography [50–60% (v/v) EtOAc in light petroleum] furnishing nucleoside **37** as a white solid material (2.6 g, 80% from **35**). R_f 0.13 (MeOH/CH_2Cl_2 5:95, v/v); δ_H ($CDCl_3$) 10.50 (1H, s, NH), 7.82–7.80 (2H, m), 7.53–7.47 (5H, m), 7.45–7.31 (6H, m), 7.23–7.19 (2H, m), 6.75–6.71 (4H, m), 6.12 (1H, s, H1′), 5.41 (1H, d, *J*=3.5 Hz, 2′-OH), 4.92 (1H, d, *J*=10.3 Hz, H5′a), 4.74 (1H, d, *J*=10.8 Hz, H5′b), 4.32 (1H, br s, H3′), 4.17 (1H, br s, H2′), 3.73 and 3.72 (3H each, 2s, 2×OCH_3), 3.63 (1H, d, *J*=10.7 Hz, H5″a), 3.31 (1H, d, *J*=10.8 Hz, H5″b), 1.57 (3H, s, 5-CH_3), 0.66 (9H, s, $C(CH_3)_3$), −0.03 (3H, s, $SiCH_3$), −0.15 (3H, s, $SiCH_3$); δ_C ($CDCl_3$) 165.6 (COPh), 164.6 (C4), 158.6, 158.5, 151.0 (C2), 144.6, 136.5, 135.9, 135.5, 133.0, 130.2, 130.0, 129.9, 129.7, 128.3, 128.2, 128.0, 126.9, 113.3, 113.2, 110.1 (C5), 93.3 (C1′), 90.3 (C4′), 86.3 (CAr_3), 83.5 (C2′), 78.2 (C3′), 63.3 and 63.1 (C5′ and C5″), 55.2 (2×OCH_3), 25.4 ($C(CH_3)_3$), 17.7 ($C(CH_3)_3$), 12.5 (5-CH_3), −5.1 ($SiCH_3$), −5.6 ($SiCH_3$); MALDI-HRMS: *m/z* 831.3273 ($[M+Na]^+$, $C_{45}H_{52}N_2O_{10}SiNa^+$ calcd 831.3283).

7.1.32. 1-[5-*O*-Benzoyl-3-*O*-(*tert*-butyldimethylsilyl)-4-*C*-(4,4′-dimethoxytrityloxymethyl)-2-*O*-methanesulfonyl)-α-L-arabinofuranosyl]thymine (38). Nucleoside **37** (2.56 g, 3.16 mmol) was dissolved in a 3:1 mixture of anhydrous CH_2Cl_2 and Et_3N (20 mL), and DMAP (580 mg, 4.75 mmol) was added. Methanesulfonyl chloride (544 mg, 4.75 mmol) was added dropwise and the reaction mixture was stirred at room temperature. After 4 h analytical TLC showed the formation of two products. Saturated aq $NaHCO_3$ (50 mL) was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2×50 mL) and the combined organic phase was washed first with aq HCl (1 M, 2×50 mL) and then with saturated aq $NaHCO_3$ (50 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated to dryness under reduced pressure. The crude product was coevaporated with toluene affording a white foam. An analytical sample was obtained by quick fractionation through silica gel [50–60% (v/v) EtOAc in light petroleum] affording the major product nucleoside **38** as a white solid material. R_f 0.23 (MeOH/CH_2Cl_2 5:95, v/v); δ_H ($CDCl_3$) 9.51 (1H, s, NH), 7.85–7.82 (2H, m), 7.58 (1H, m), 7.45–7.38 (6H, m), 7.33–7.29 (4H, m), 7.24–7.22 (2H, m), 6.78–6.74 (4H, m), 6.29 (1H, d, *J*=3.1 Hz, H1′), 5.08 (1H, dd, *J*=2.6, 2.8 Hz, H2′), 4.84 (1H, d, *J*=11.3 Hz, H5′a), 4.49 (1H, d, *J*=2.8 Hz, H3′), 4.41 (1H, d, *J*=10.9 Hz, H5′b), 3.75 and 3.74 (3H each, 2s, 2×OCH_3), 3.65 (1H, d, *J*=10.4 Hz, H5″a), 3.37 (1H, d, *J*=10.7 Hz, H5″b), 3.20 (3H, s, SO_2CH_3), 1.54 (3H, s, 5-CH_3), 0.69 (9H, s, $C(CH_3)_3$), −0.02 (3H, s, $SiCH_3$), −0.13 (3H, s, $SiCH_3$); δ_C ($CDCl_3$) 165.5 (COPh), 163.7 (C4), 158.7, 158.6, 150.7 (C2), 144.1, 135.5, 135.4, 135.1, 133.4, 130.3, 130.2, 130.1, 129.8, 129.4, 128.5, 128.4, 128.1, 127.1, 113.4, 113.3, 111.3 (C5), 89.3 (C4′), 88.1 (C1′), 86.8 and 86.6 (C2′ and CAr_3), 76.6 (C3′), 62.9 and 62.8 (C5′ and C5″), 55.3 (2×OCH_3), 39.0 (SO_2CH_3), 25.5 ($C(CH_3)_3$), 17.7 ($C(CH_3)_3$), 12.3 (5-CH_3), −4.8 ($SiCH_3$), −5.6 ($SiCH_3$); MALDI-HRMS: *m/z* 909.3040 ($[M+Na]^+$, $C_{46}H_{54}N_2O_{12}SSiNa^+$ calcd 909.3059).

7.1.33. 2,2′-Anhydro-1-[5-*O*-benzoyl-3-*O*-(*tert*-butyldimethylsilyl)-4-*C*-(4,4′-dimethoxytrityloxymethyl)-α-L-ribofuranosyl]thymine (39). The crude product obtained after mesylation of nucleoside **37** was coevaporated with anhydrous CH_3CN (2×5 mL) and then dissolved in CH_3CN (10 mL), and DBU (609 mg, 4 mmol) was added. The resulting mixture was stirred 12 h at room temperature and then evaporated to dryness under reduced pressure. $CHCl_3$ (50 mL) was added whereupon washing was performed with saturated aq $NaHCO_3$ (2×50 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated to dryness under reduced pressure. The residue was purified by column chromatography [4% (v/v) MeOH in CH_2Cl_2] to give nucleoside **39** as a white solid material (2.08 g, 83% from **37**). R_f 0.11 (MeOH/CH_2Cl_2 5:95, v/v); δ_H ($CDCl_3$) 7.91–7.89 (2H, m), 7.60 (1H, dd, *J*=7.3, 7.6 Hz), 7.44 (2H, dd, *J*=7.4, 7.9 Hz), 7.36–7.33 (2H, m), 7.27–7.12 (8H, m), 6.77–6.72 (4H, m), 6.15 (1H, d, *J*=5.8 Hz), 5.23 (1H, dd,

J=5.9, 6.0 Hz), 4.80 (1H, d, J=12.1 Hz), 4.49 (1H, d, J=6.2 Hz), 4.29 (1H, d, J=11.8 Hz), 3.76 (3H, s), 3.75 (3H, s), 3.34 (1H, d, J=11.3 Hz), 3.21 (1H, d, J=11.3 Hz), 1.97 (3H, s), 0.67 (9H, s), 0.04 (3H, s), −0.15 (3H, s); δ_C ($CDCl_3$) 172.1, 165.9, 159.9, 158.6, 144.5, 135.7, 135.2, 133.6, 130.2, 130.0, 129.9, 129.7, 129.4, 128.7, 128.0, 127.9, 127.0, 118.9, 113.3, 113.2, 89.2, 88.9, 86.3, 81.5, 73.5, 64.5, 63.3, 55.3, 25.6, 17.9, 14.3, −4.6, −5.6; MALDI-HRMS: m/z 813.3160 ($[M+Na]^+$, $C_{45}H_{50}N_2O_9SiNa^+$ calcd 813.3178).

7.1.34. 1-[5-*O*-(4,4′-Dimethoxytrityl)-4-*C*-hydroxymethyl-β-D-lyxofuranosyl]thymine (40). To a suspension of nucleoside **39** (1.7 g, 2.15 mmol) in a 1:1 mixture of EtOH and H_2O (20 mL) was added 2 M aqueous sodium hydroxide (1.5 mL), and the reaction mixture was heated under reflux for 6 h, then cooled and evaporated to approximately half of the original volume. The residue was partitioned between EtOAc (100 mL) and $NaHCO_3$ (50 mL). The separated organic phase was dried (Na_2SO_4), filtered and concentrated to dryness under reduced pressure. The crude product was purified by column chromatography [6–7% (v/v) MeOH in CH_2Cl_2] to give nucleoside **40** as a white solid material (935 mg, 74%). R_f 0.21 (MeOH/CH_2Cl_2 10:90, v/v); δ_H ($CDCl_3$) 10.30 (1H, s), 7.49 (1H, s), 7.45 (2H, d, J=7.3 Hz), 7.33 (4H, d, J=7.7 Hz), 7.25–7.15 (3H, m), 6.79 (4H, d, J=8.3 Hz), 6.28 (1H, d, J=5.2 Hz), 5.17 (1H, d, J=4.9 Hz), 4.75 (1H, m), 4.32 (1H, dd, J=4.3, 4.4 Hz), 3.79 (1H, m), 3.74–3.62 (7H, m), 3.58 (1H, d, J=2.9 Hz), 3.53 (1H, d, J=10.3 Hz), 3.38 (1H, d, J=10.4 Hz), 3.34 (1H, br s), 1.64 (3H, s); δ_C ($CDCl_3$) 165.4, 158.6, 151.3, 144.6, 139.0, 135.7, 135.5, 130.2, 130.1, 128.2, 128.0, 127.0, 113.3, 109.0, 88.1, 86.8, 85.8, 72.5, 71.3, 65.5, 63.5, 55.3, 12.4.

7.1.35. 1-[2,5-Di-*O*-(*tert*-butyldimethylsilyl)-4-*C*-(4,4′-dimethoxytrityloxymethyl)-α-L-ribofuranosyl]thymine (41) and 1-[3,5-di-*O*-(*tert*-butyldimethylsilyl)-4-*C*-(4,4′-dimethoxytrityloxymethyl)-α-L-ribofuranosyl]thymine (42). *tert*-Butyldimethylsilyl chloride (816 mg, 5.42 mmol) and imidazole (740 mg, 10.9 mmol) were added to a stirred solution of nucleoside **40** (800 mg, 1.35 mmol) dissolved in anhydrous pyridine (8 mL). The reaction mixture was stirred at room temperature for 12 h whereupon MeOH (1.0 mL) was added. After stirring for 30 min the resulting mixture was concentrated to dryness under reduced pressure. The residue was dissolved in EtOAc (100 mL) and washed with saturated aq $NaHCO_3$ (2×50 mL). The organic phase was dried (Na_2SO_4), filtered, concentrated to dryness under reduced pressure and coevaporated with toluene (2×5 mL). The crude product was purified by column chromatography [30–35% (v/v) EtOAc in light petroleum] yielding nucleoside **41** (395 mg, 36%) and [35–45% (v/v) EtOAc in light petroleum] nucleoside **42** (590 mg, 53%), both as white solid materials. R_f 0.24, 0.34 (MeOH/CH_2Cl_2 5:95, v/v); data for **41**: δ_H ($CDCl_3$) 8.45 (1H, s, NH), 7.47–7.44 (2H, m), 7.33 (4H, dd, J=1.8, 8.9 Hz), 7.27–7.18 (4H, m), 6.80 (4H, dd, J=1.8, 8.9 Hz), 6.39 (1H, d, J=6.2 Hz, H1′), 4.76 (1H, dd, J=5.4, 6.1 Hz, H2′), 4.11 (1H, dd, J=2.2, 5.5 Hz, H3′), 3.87 (1H, d, J=10.7 Hz, H5′a), 3.76 (6H, s, 2×OCH_3), 3.70 (1H, d, J=10.8 Hz, H5′b), 3.49 (1H, d, J=9.9 Hz, H5″a), 3.33 (1H, d, J=10.1 Hz, H5″b), 2.67 (1H, br s, 3′-OH), 1.80 (3H, s, 5-CH_3), 0.91 and 0.78 (9H each, 2s, 2×$C(CH_3)_3$), 0.10 (3H, s, $SiCH_3$), 0.07 (6H, s, 2×$SiCH_3$), −0.01 (3H, s, $SiCH_3$); δ_C ($CDCl_3$) 163.8 (C4), 158.7, 158.6, 150.5 (C2), 144.8, 138.3, 136.0, 135.7, 130.3, 130.2, 128.3, 128.0, 126.9, 113.2, 109.1 (C5), 88.4 (C4′), 86.4 (CAr_3), 85.6 (C1′), 72.9 (C2′ and C3′), 67.3 (C5′), 63.7 (C5″), 55.3 (2×OCH_3), 26.1 and 25.6 (2×$C(CH_3)_3$), 18.4 and 18.0 (2×$C(CH_3)_3$), 12.6 (5-CH_3), −5.2, −5.3, −5.4 and −5.5 (4×$SiCH_3$); MALDI-HRMS: m/z 841.3859 ($[M+Na]^+$, $C_{44}H_{62}N_2O_9Si_2Na^+$ calcd 841.3886); data for **42**: δ_H ($CDCl_3$) 8.83 (1H, s, NH), 7.54 (1H, s, H6), 7.46–7.44 (2H, m), 7.36–7.22 (7H, m), 6.81 (4H, d, J=9.0 Hz), 6.23 (1H, d, J=4.1 Hz, H1′), 4.52 (1H, d, J=5.4 Hz, H3′), 4.39 (1H, m, H2′), 3.78 (6H, s, 2×OCH_3), 3.73 (1H, d, J=10.6 Hz, H5′a), 3.68 (1H, d, J=10.7 Hz, H5′b), 3.47 (1H, d, J=10.4 Hz, H5″a), 3.24 (1H, d, J=6.6 Hz, 2′-OH), 3.16 (1H, d, J=10.5 Hz, H5″b), 1.69 (3H, s, 5-CH_3), 0.87 and 0.76 (9H each, 2s, 2×$C(CH_3)_3$), 0.07, 0.03, 0.01 and −0.11 (3H each, 4s, 4×$SiCH_3$); δ_C ($CDCl_3$) 164.0 (C4), 158.7, 158.6, 150.7 (C2), 144.5, 138.0, 135.9, 135.6, 130.3, 130.2, 128.4, 128.0, 127.1, 113.3, 113.2, 109.1 (C5), 87.5 (C4′), 87.1 (CAr_3), 85.4 (C1′), 73.4 (C3′), 71.7 (C2′), 64.7 and 64.1 (C5′ and C5″), 55.3 (2×OCH_3), 25.9 and 25.7 (2×$C(CH_3)_3$), 18.3 and 18.2 (2×$C(CH_3)_3$), 12.6 (5-CH_3), −5.0, −5.2, −5.3 and −5.4 (4×$SiCH_3$); MALDI-HRMS: m/z 841.3891 ($[M+Na]^+$, $C_{44}H_{62}N_2O_9Si_2Na^+$ calcd 841.3886).

7.1.36. 1-[3-*O*-(2-Cyanoethoxy(diisopropylamino)-phosphino)-2,5-di-*O*-(*tert*-butyldimethylsilyl)-4-*C*-(4,4′-dimethoxytrityloxymethyl)-α-L-ribofuranosyl]thymine (43). Cyanoethyl *N*,*N*′-diisopropylphosphoramidochloridite (170 mg, 0.72 mmol) was added dropwise to a stirred solution of nucleoside **41** (295 mg, 0.36 mmol) and *N*,*N*′-diisopropylethylamine (0.5 mL) in anhydrous CH_2Cl_2 (5 mL). After stirring for 12 h at room temperature, the reaction mixture was diluted with EtOAc (50 mL). Washing was performed with saturated aq $NaHCO_3$ (2×25 mL). The separated organic phase was dried (Na_2SO_4), filtered and concentrated to dryness under reduced pressure. The residue obtained was purified by column chromatography [30–35% EtOAc in *n*-hexane containing 0.5% Et_3N (v/v/v)] to give amidite **43** as a white solid material (242 mg, 66%). R_f 0.32, 0.35 (MeOH/CH_2Cl_2 5:95, v/v); δ_P 152.9 and 150.7; δ_H ($CDCl_3$, major isomer) 8.20 (br s, NH), 7.41 (d, J=8.1 Hz), 7.40 (s, H6), 7.32–7.16 (m), 6.78 (d, J=8.7 Hz), 6.20 (d, J=4.1 Hz, H1′), 4.69 (dd, J=4.8, 13.6 Hz, H3′), 4.40 (dd, J=4.3, 4.5 Hz, H2′), 4.22 (d, J=10.8 Hz, H5′a), 3.77 (s, 2×OCH_3), 3.74–3.68 (m, H5″a and OCH_2), 3.54 (d, J=10.8 Hz, H5′b), 3.44–3.41 (m, 2×$CH(CH_3)_2$), 3.17 (d, J=10.5 Hz, H5″b), 2.56 (t, J=6.4 Hz, CH_2CN), 1.78 (s, 5-CH_3), 1.11 (d, J=6.6 Hz, $C(CH_3)_2$), 0.93 (s, $C(CH_3)_3$), 0.87 (d, J=6.7 Hz, $C(CH_3)_2$), 0.71 (s, $C(CH_3)_3$), 0.12, 0.11, 0.04 and −0.17 (4s, 4×$SiCH_3$); δ_C ($CDCl_3$) 163.6, 158.5, 150.4, 145.1, 139.3, 136.2, 136.0, 130.2, 130.1, 128.2, 128.0, 126.8, 117.3, 113.3, 113.2, 108.9, 86.8 (d, J=4.6 Hz), 85.9, 85.4, 73.5 (d, J=16.9 Hz), 72.6 (d, J=2.2 Hz), 64.8, 64.4, 58.3 (d, J=21.8 Hz), 55.3, 43.2, 43.1, 26.1, 25.8, 24.8, 24.7, 24.6, 24.5, 20.4 (d, J=8.0 Hz), 18.5, 17.9, 12.7, −4.7, −4.8, −5.1, −5.2; MALDI-HRMS: m/z 1041.4926 ($[M+Na]^+$, $C_{53}H_{79}N_4O_{10}PSi_2Na^+$ calcd 1041.4965).

Synthesis and purification of modified oligonucleotides. The oligomers **ON5–ON10**, **ON15**, **ON17–ON19**, **ON21**,

ON23 and **ON24** (Table 1 and 2) were synthesized in 0.2 μmol scale on CPG solid support on an automated DNA-synthesizer using the phosphoramidite approach.[30] The stepwise coupling yield for the α-L-RNA phosphoramidites (T-monomer,[6] **6**, **12** and **25**) was above 90% (1*H*-tetrazole as activator, 20 min coupling time), for the phosphoramidite **34** approximately 88% (1*H*-tetrazole as activator, 60 min pre-activation by mixing **34** and activator, 120 min coupling time), and for phosphoramidite **43** approximately 95% (pyridinium chloride as activator, 10–16 min coupling time). After detritylation with 80% aq acetic acid, cleavage from the solid support and deacylations were effected using 40% aqueous methylamine (10 min, 55 °C). After cooling to −18 °C, the solid support was removed (centrifugation), washed [2×0.25 cm^3; EtOH–CH_3CN–H_2O (3/1/1, v/v/v)], and the combined liquid phase evaporated to dryness under reduced pressure. Desilylation of the oligomers was accomplished using a method described earlier[31] for 20 h (at 55 °C) and precipitation was then performed from *t*-BuOH. Standard conditions of the synthesizer were used for incorporation of DNA monomers whereas the incorporation of α-L-LNA monomers followed procedures described earlier.[2,3] The composition of the ONs was verified by MALDI-MS (negative ion mode) on a Micromass Tof Spec E mass spectrometer using a matrix of diammonium citrate and 2,6-dihydroxyacetophenone. Analysis by capillary gel electrophoresis verified the purity of the oligomers as being >80%. MALDI-MS of selected ONs *m/z* ($[M-H]^-$, found/calcd): **ON5**, 2800/2799; **ON6**, 2894/2891; **ON7**, 2800/2799; **ON8**, 2893/2891; **ON9**, 2900/2899; **ON10**, 2992/2987; **ON17**, 4238/4231; **ON18**, 4235/4231; **ON19**, 4237/4231; **ON24**, 4241/4242.

Thermal denaturation studies. Melting temperatures (T_m values, °C) were determined by measuring the absorbance at 260 nm against increasing temperature (1.0 °C/min) on equimolar mixtures (1.0 or 1.5 μM in each strand) of modified ONs and their complementary DNA/RNA strand in 10 mM phosphate buffers with different NaCl concentration (see captions to Tables 2 and 3) and were performed on a Perkin-Elmer UV–vis spectrometer fitted with a PTP-6 temperature programmer.

Molecular modelling. A DNA duplex of sequence 5′-d(GTGATATGC) and a DNA:RNA hybrid NMR solution structure[32] were used as template and further modified within the MacroModel V8.0 program suite.[33] The modified residue was first partially optimized (MMFF94s force field, 1000 cycles) and subsequently submitted to a 5 ns stochastic dynamics (300 K, 2 fs timestep, 1000 structures were sampled and minimized) using the SHAKE algorithm to keep X–H bond lengths fixed during the simulation. The non-bonded cut-off was 9 Å and a dielectric constant of 80 was applied. The residues neighbouring the modified residue were constrained whereas all other residues were frozen during stochastic dynamics.

RNase H assay. The 5′-r(AGGUCCAUAGAGAC) RNA target sequence was [^{32}P]-labelled at the 5-end with T4 kinase and the radioactive RNA was mixed with unlabelled RNA. 0.2 μM RNA (1 pmol/final sample) was incubated in the presence of a four-fold excess of complementary **ON16**, **ON17**, **ON18** or **ON19** in hybridization buffer (20 mM Tris–HCl, pH 7.5, 100 mM KCl) at 65 °C for 2 min followed by slow cooling to 37 °C. The RNase H digest was performed in 20 mM Tris–HCl, pH 7.5, 100 mM KCl, 10 mM $MgCl_2$, 1 mM with 0.01 U of *E. coli* RNase H (Amersham) enzyme at 37 °C. Aliquots of 10 μL samples were withdrawn and mixed with 5 μL formamide loading dye with 10 mM EDTA on ice at the time points 2, 10 and 60 min after RNase H addition. A basic hydrolysis of labelled RNA was performed by heating to 90 °C for 15 min in 100 mM Na_2CO_3 (pH 9.0, 2 mM EDTA) followed by cooling on ice and addition of formamide dye. All reaction products were analyzed by PAGE (20% polyacrylamide containing 8.3 M urea). The radioactive RNA bands were visualized by autoradiography of the dried gels.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.12.007. H contains copies of ^{13}C NMR spectra of compounds **1–3**, **5**, **7–11**, **14–20**, **22–24**, **27–33**, **36–42** and **43** (major isomer) and ^{31}P NMR spectra of compounds **6**, **12**, **25**, **34** (major isomer), **34** (minor isomer), **43** (major isomer) and **43** (minor isomer).

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A new approach towards 2-amino-1-aryloxy-3-methoxypropanes from 1-arylmethyl-2-(bromomethyl)aziridines

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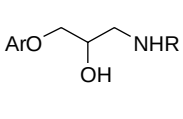
Abstract—1-Arylmethyl-2-(bromomethyl)azirdines were converted into the corresponding 2-(aryloxymethyl)aziridines upon treatment with the appropriate potassium phenoxides in DMF/acetone in excellent yields, followed by regioselective ring opening towards *N*,*N*-di(arylmethyl)-*N*-(2-bromo-3-aryloxypropyl)amines using benzyl bromide in acetonitrile. Treatment of the latter β-bromoamines with sodium methoxide afforded the desired 2-amino-1-aryloxy-3-methoxypropanes as the major compounds (49–58%) besides the isomeric 3-amino-1-aryloxy-2-methoxypropanes in minor quantities (9–15%).

1. Introduction

Many important pharmaceutical compounds contain a 1,2,3-trisubstituted three-carbon unit in their structure, and the synthesis of drugs based on this moiety has become a key issue in academic research as well as in pharmaceutical industry. Especially aryloxypropanolamines **1** constitute a very popular class of target compounds in organic synthesis due to the pronounced physiological activities ascribed to many representatives of this class of compounds. Propranolol, atenolol and metoprolol are frequently cited β-blockers containing an aryloxypropanolamine moiety **1**, used for the treatment of hypertension, angina pectoris, glaucoma, obesity, and arrhythmia.[1] Furthermore, aryloxypropanolamines with a 4-aminopiperidine scaffold exhibit antidiabetic activity[2] and those containing a xanthone unit have been reported as antihypertensive and vasorelaxing agents.[3] Synthetic efforts towards 2-amino-1,3-dioxypropane derivatives, however, are much more scarce then those towards the structurally related aryloxypropanolamines, despite of the biological relevance of the former class of compounds. Sphingolipids **2**, membrane compounds of essentially all eukaryotic cells, comprise a 2-amino-1,3-dihydroxypropane subunit as a part of a longer (unsaturated) carbon chain.[4] Also 2-[*N*-(arylmethyl)amino]propane-1,3-diols **3** (AMAP's) have been reported as new antitumor DNA intercalators with promising prospects in medicine.[5] Moreover, compounds containing a 2-amino-1,3-propanediol subunit are important constituents of broad-spectrum antibiotics such as thiamphenicol and the fluorine-containing florfenicol.[6]



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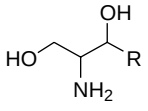

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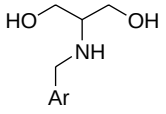

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Due to the general biological interest in 2-amino-1,3-dioxypropanes and the lack of synthetic methods for the preparation of 2-amino-1-aryloxy-3-alkoxypropanes, a new approach towards derivatives containing this moiety is reported here. This communication comprises the first report of the synthesis of 2-(di(arylmethyl)amino)-1-aryloxy-3-methoxypropanes as a new class of 1,2,3-trisubstituted propane derivatives with promising potential in medicinal chemistry, starting from 1-arylmethyl-2-(bromomethyl)aziridines.

Although several examples of the synthesis of 2-amino-1,3-propanediols are known,[7] these strategies are less suitable when aryloxypropane derivatives are contemplated, since an additional transformation of a hydroxyl group into an aryloxy group is required. Ring opening reactions of aziridines bearing an electron-withdrawing group at nitrogen (activated aziridines) have been well-covered in the literature, but only a minor part are dealing with the synthesis of 2-amino-1,3-dioxypropane derivatives,[8] for example, the synthesis of 2-amino-1,3-diaryloxypropane

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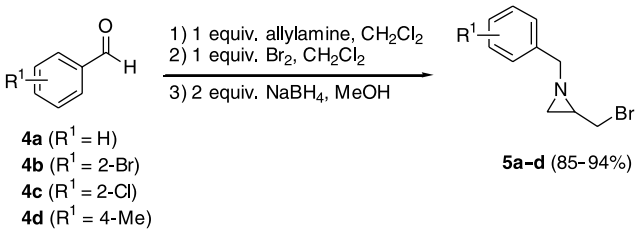
derivatives from 1-arenesulfonyl-2-(bromomethyl)aziridines upon treatment with a substituted phenol in water in the presence of potassium carbonate and silica.[8k] These procedures require the removal of the *N*-activating group in a final stage of the synthesis in order to obtain the corresponding amines. Up to now, only one type of ring opening reaction of unactivated aziridines, namely 1-alkyl-2-(alkoxymethyl)aziridines, towards 2-amino-1,3-dioxypropanes has been reported in the literature.[9] This transformation involves activation of the aziridine ring by means of an organic acid (e.g., AcOH or TFA), followed by ring opening of the aziridinium ion by the nucleophilic carboxylate anion. Hydrolysis of the resulting ester then affords the desired 2-amino-1-alkoxy-3-hydroxypropanes.

2. Results and discussion

1-Arylmethyl-2-(bromomethyl)aziridines **5** are very easily accessible substrates suitable for various applications in organic synthesis, although the synthetic potential of these β-haloamines has been scarcely evaluated in the literature. Condensation of benzaldehydes **4a–d** with 1 equiv of allylamine in dichloromethane in the presence of magnesium sulfate afforded the corresponding *N*-allylimines, which were subsequently brominated by bromine in dichloromethane to give *N*-(arylidene)-2,3-dibromopropylamines in a quantitative yield. The latter dibromoimines were used as such because of their instability and hence treated with sodium borohydride in methanol under reflux, furnishing 1-arylmethyl-2-(bromomethyl)aziridines **5a–d** in high overall yields (Scheme 1).[10] These 2-(bromomethyl)aziridines **5** are excellent substrates for the synthesis of 1,2,3-trisubstituted propane derivatives since their structure comprises a three-carbon unit in which the three electrophilic carbon atoms are structurally differentiated from each other, allowing the selective preparation of different substituted amines.



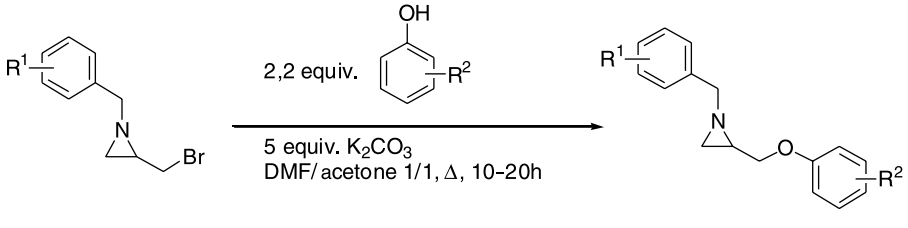
Scheme 1.

The incorporation of an aryloxy moiety into the desired three-carbon units can be very efficiently established by means of a nucleophilic substitution of the bromo atom of the aziridines **5** using a phenolate anion as a nucleophile (Scheme 2). It has already been demonstrated that 1-alkyl-2-(bromomethyl)aziridines can be easily transformed into the corresponding 2-(alkoxymethyl)aziridines upon treatment with alkoxides in alcohol via a direct substitution of the bromo atom (instead of ring opening ring closure, which occurs when *N*-activated aziridines are used).[11] Treatment of aziridines **5** with 2.2 equiv of phenol or, alternatively, a substituted bromo- or chlorophenol, and 5 equiv of K_2CO_3 in a mixture of DMF and acetone (1/1) afforded the corresponding 2-(aryloxymethyl)aziridines **6** in excellent yields and high purity after reflux for 10–20 h (Scheme 2, Table 1). These 2-(aryloxymethyl)aziridines **6** can be considered as synthetic precursors of 2-amino-1-aryloxypropanes at the one hand and 3-amino-1-aryloxypropanes at the other hand, depending on whether ring opening occurs at the less hindered or the more hindered carbon atom of the aziridine ring, respectively.

1-Arylmethyl-2-(bromomethyl)aziridines **5** can be transformed regioselectively into *N*-(2,3-dibromopropyl)amines upon treatment with benzyl bromide in acetonitrile in a straightforward reaction.[12] When this methodology was applied to 1-arylmethyl-2-(aryloxymethyl)aziridines **6**, *N*,*N*-di(arylmethyl)-*N*-(2-bromo-3-aryloxypropyl)amines **7** were isolated in high yields and high purity upon treatment with 1 equiv of a benzyl bromide in acetonitrile and reflux for 5 h (Scheme 3, Table 2). Detailed spectral analysis confirmed the structural identity of these *N*-(2-bromo-3-aryloxypropyl)amines **7**, excluding the formation of the corresponding regioisomers. These results confirm the general regioselectivity with which 2-substituted 1-(arylmethyl)aziridines are transformed into *N*-(2-bromopropyl)-amines upon ring opening with an arylmethyl bromide. *N*-(2-Halo-3-aryloxypropyl)amines such as compounds **7** might be of interest due to their potential biological activities, since some 2-bromo-1-oxypropane-3-amines have already been reported as potential antitumor, antimicrobial and antifungal agents,[13] as well as inhibitors of cytokinine production and secretion.[14]

β-Bromoamines **7** are suitable substrates for the synthesis of different 1,2,3-triheteroatom substituted propane derivatives, since only a nucleophilic substitution of the bromo atom by a heteroatom-centered nucleophile is required.

Consequently, *N*,*N*-di(arylmethyl)-*N*-(2-bromo-3-aryloxypropyl)amines **7** were treated with 2 equiv of sodium methoxide (0.2 N in methanol), yielding a mixture of 2-amino-1-aryloxy-3-methoxypropanes **8** as the major



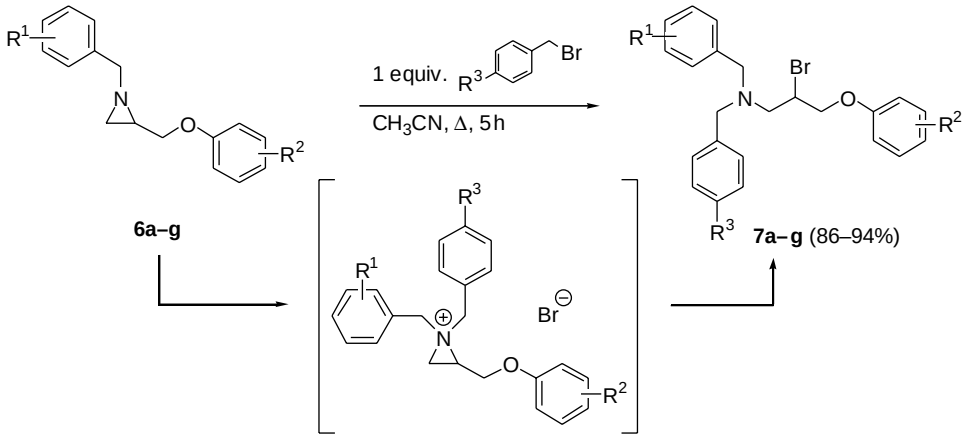
Scheme 2.

Table 1. Synthesis of 2-(aryloxymethyl)aziridines **6**

Entry	R^1	R^2	Compound (% yield)
1	H	3-Cl	**6a** (92)
2	2-Br	H	**6b** (95)
3	2-Cl	H	**6c** (91)
4	2-Br	2-Br	**6d** (90)
5	2-Cl	2-Cl	**6e** (90)
6	2-Cl	2-Br	**6f** (93)
7	4-Me	4-Cl	**6g** (93)

compounds (79–86%) and 3-amino-1-aryloxy-2-methoxypropanes **9** as the minor constituents (14–21%) after reflux for 2 h (Scheme 4, Table 3).

In order to obtain analytically pure samples for detailed spectroscopical analysis, the regioisomers **8** and **9** were separated by means of column chromatography on silica gel (hexane/ethyl acetate 98:2), affording the pure major isomers. The spectral data, thus obtained, confirmed that the major isomers formed in this reaction were 2-amino-1-



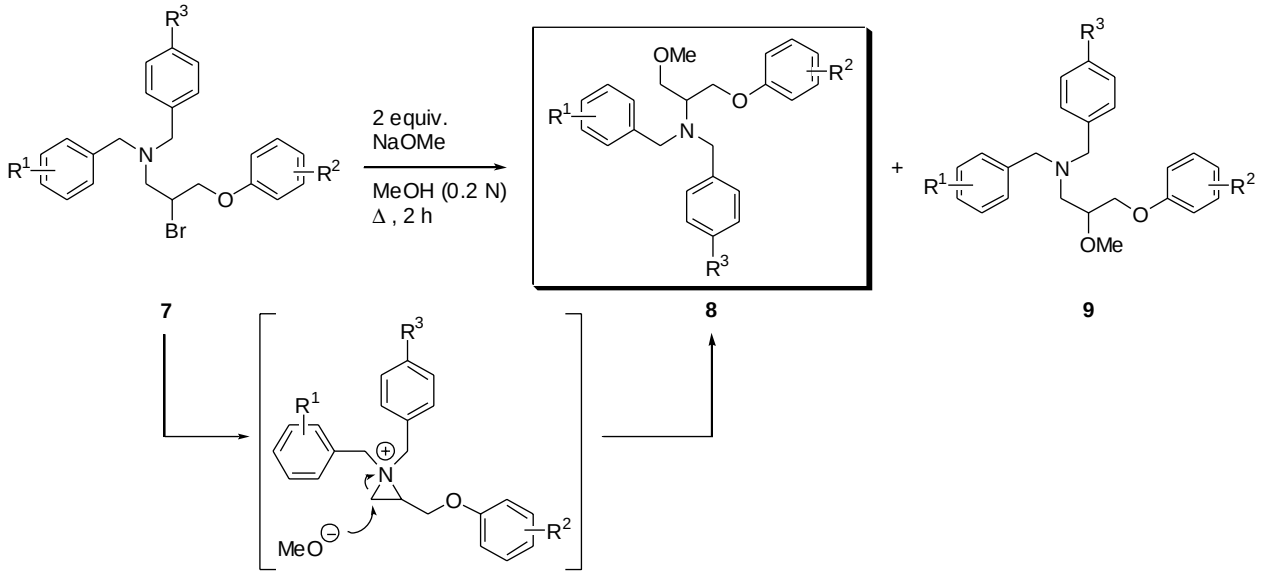
Scheme 3.

Table 2. Synthesis of *N*-(2-bromo-3-aryloxypropyl)amines **7**

Entry	R^1	R^2	R^3	Compound (% yield)
1	H	3-Cl	H	**7a** (89)
2	2-Br	H	H	**7b** (90)
3	2-Cl	H	H	**7c** (89)
4	2-Br	2-Br	H	**7d** (94)
5	2-Cl	2-Cl	H	**7e** (86)
6	2-Cl	2-Br	H	**7f** (91)
7	4-Me	4-Cl	Me	**7g** (89)

aryloxy-3-methoxypropanes **8**, whereas 3-amino-1-aryloxy-2-methoxypropanes **9** were present as the minor isomers. It should be noted that the ratio of major versus minor isomer slightly changes in the benefit of the major regioisomer when the aryloxy moiety is substituted with a halogen atom (Table 3).

The presence of both regioisomers can be rationalized considering the formation of an intermediate aziridinium ion upon heating, which is then attacked by methoxide at the least hindered carbon atom of the aziridine ring furnishing



Scheme 4.

Table 3. Formation of regio-isomers **8** and **9** upon treatment of *N*,*N*-di(arylmethyl)-*N*-(2-bromo-3-aryloxypropyl)amines **7** with sodium methoxide

Entry	R^1	R^2	R^3	Ratio **8/9**[a]	**8** (%)[b]	**9** (%)[b]
1	2-Br	H	H	79/21	**8a** (56)	**9a** (15)
2	2-Cl	H	H	80/20	**8b** (58)	**9b** (15)
3	2-Br	2-Br	H	85/15	**8c** (55)	**9c** (10)
4	2-Cl	2-Br	H	86/14	**8d** (57)	**9d** (9)
5	2-Cl	2-Cl	H	86/14	**8e** (54)	**9e** (9)
6	H	3-Cl	H	86/14	**8f** (49)	**9f** (—)
7	4-Me	4-Cl	Me	87/13	**8g** (55)	**9g** (—)

[a] Based on ^{1}H NMR.
[b] Yield after column chromatography.

the major isomers **8**, in which the amino moiety has moved from the terminus of the propane skeleton towards the central carbon atom. The formation of the minor isomers **9** can be the result of the attack of methoxide at the more hindered carbon atom of the aziridinium ion or, alternatively, the result of a S_N2 substitution reaction of methoxide at CHBr in bromoamines **7**.

In order to study the effect of the concentration of sodium methoxide in this transformation, 2-bromoamine **7g** was treated with a 0.2, 1.0, 1.5 and 2.0 N solution of 2 equiv of sodium methoxide in methanol, respectively. In all cases, the same ratio of isomers **8g** versus **9g** was observed after reaction (87/13). Apparently, the concentration of methoxide has no influence on the reaction outcome. When *N*-(2-bromo-3-aryloxypropyl)amines **7** were heated under reflux in methanol or ethanol, a mixture of the corresponding 2-amino-1-aryloxy-3-alkoxypropanes and 3-amino-1-aryloxy-2-alkoxypropanes was obtained, although in these cases the ratio of both isomers was almost in equilibrium (55/45 and 54/46, respectively). In isopropanol, however, no reaction occurred and the starting material was recovered. Attempts to introduce a hydroxyl group instead of a methoxy group using sodium hydroxide (3 N in H_2O) in CH_2Cl_2–H_2O (1/1) or in DMF–H_2O (3/1) (rt or 80 °C, 30 min–5 h), or using KOH in Et_2O (rt, 6 h) were unsuccessful and the starting material was recovered.

In conclusion, a new and attractive synthetic approach towards 2-amino-1-aryloxy-3-methoxypropanes, valuable compounds with diverse biological activities, has been developed in three efficient steps starting from 1-arylmethyl-2-(bromomethyl)aziridines. The latter aziridines were converted into the corresponding 2-(aryloxymethyl)-aziridines upon treatment with the appropriate phenoxide, followed by regioselective ring opening using benzyl bromide towards *N*,*N*-di(arylmethyl)-*N*-(2-bromo-3-aryloxypropyl)amines. Treatment of the latter amines with sodium methoxide in methanol afforded the desired 2-amino-1-aryloxy-3-methoxypropanes as the major compounds (49–58%) besides the isomeric 3-amino-1-aryloxy-2-methoxypropanes in minor quantities (9–15%).

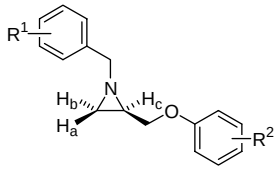
3. Experimental

3.1. General

^{1}H NMR spectra were recorded at 270 MHz (JEOL JNM-EX 270) or at 300 MHz (JEOL ECLIPSE+) with $CDCl_3$ as solvent and tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded at 68 MHz (JEOL JNM-EX 270) or at 75 MHz (JEOL ECLIPSE+) with $CDCl_3$ as solvent. Mass spectra were obtained with a mass spectrometer VARIAN MAT 112, 70 eV using a GC–MS coupling (RSL 200, 20 m glass capillary column, i.d. 0.53 mm, He carrier gas) or AGILENT 1100, 70 eV. IR spectra were measured with a Spectrum One FT-IR spectrophotometer. Melting points were measured using a Büchi B-540 apparatus and are uncorrected. Dichloromethane was distilled over calcium hydride, other solvents were used as received from the supplier.

3.2. Synthesis of 1-arylmethyl-2-(aryloxymethyl)aziridines 6

As a representative example, the synthesis of 1-(2-chlorophenyl)methyl-2-(phenoxymethyl)aziridine **6c** is described here. 1-(2-Chlorophenyl)methyl-2-(bromomethyl)aziridine **5c** (1.30 g, 5 mmol) was added to a mixture of phenol (1.04 g, 2.2 equiv) and K_2CO_3 (3.46 g, 5 equiv) dissolved in 50 mL of a solvent mixture containing acetone and DMF (1/1 on volumetric basis) and heated under reflux for 10 h. The reaction mixture was poured into brine and extracted with Et_2O (3×50 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 1-(2-chlorophenyl)methyl-2-(phenoxymethyl)aziridine **6c** (1.24 g, 91%), which was purified by means of column chromatography (hexane/ethyl acetate 4:1) in order to obtain an analytically pure sample.



3.2.1. 1-Phenylmethyl-2-(3-chlorophenoxymethyl)aziridine 6a. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.51 (1H, d, J=6.6 Hz, H_b); 1.79 (1H, d, J=3.6 Hz, H_a); 1.87–1.93 (1H, m, NCH); 3.42 and 3.47 (2H, 2×d, J=13.2 Hz, $C_6H_4CH_2$); 3.82 and 3.93 (2H, 2×d×d, J=10.6, 6.6, 4.6 Hz, CH_2O); 6.70–6.74, 6.86–6.88, 7.07–7.13 and 7.23–7.36 (1H, 2H, 1H and 5H, 5×m, CH_{arom}). ^{13}C NMR (68 MHz, $CDCl_3$): δ 31.72 (NCH_2CH); 37.65 (NCH); 64.22 ($PhCH_2$); 70.40 (CH_2O); 113.12 and 115.13 (2×CH_2OHC_{ortho}); 120.93, 127.17, 128.07, 128.37 and 130.13 (CH_2OHC_{para}, CH_2OHC_{meta}, 2×NCH_2HC_{ortho}, 2×NCH_2HC_{meta} and NCH_2HC_{para}); 134.79 and 138.76 (NCH_2C and CCl); 159.44 (CH_2OC). IR (NaCl, cm^{-1}): ν_{max}=3063; 3029; 2986; 2925; 2831; 1594; 1579; 1480; 1230; 1028; 733. MS

(70 eV): *m/z* (%): 274/276 ($M^+ + 1$, 100), 91 (10). Light-yellow oil. Anal. Calcd for $C_{16}H_{16}ClNO$: C 70.20, H 5.89, N 5.12. Found: C 70.39, H 6.06, N 4.98.

3.2.2. 1-(2-Bromophenyl)methyl-2-(phenoxymethyl)-aziridine 6b. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.66 (1H, d, J=6.6 Hz, H_b); 1.96 (1H, d, J=3.3 Hz, H_a); 2.05–2.10 (1H, m, H_c); 3.58 and 3.66 (2H, 2×d, J=15.2 Hz, $C_6H_4CH_2$); 3.97 and 4.07 (2H, 2×d×d, J=10.4, 6.6, 4.6 Hz, CH_2O); 6.80–6.83, 6.88–6.94, 7.13–7.36, 7.51–7.54 and 7.74–7.77 (2H, 3H, 2H and 2×1H, 5×m, CH_{arom}). ^{13}C NMR (68 MHz, $CDCl_3$): δ 31.52 (NCH_2CH); 38.62 (NCH); 62.60 ($PhCH_2$); 69.06 (CH_2O); 114.43 (2×CH_2OHC_{ortho}); 120.90 (CH_2OHC_{para}); 123.16 (CBr); 127.49; 128.64 and 129.38 (2×$BrHC_{meta}$, $BrHC_{para}$ and 2×CH_2OHC_{meta}); 132.33 ($BrHC_{ortho}$); 137.19 (NCH_2C); 158.27 (CH_2OC). IR (NaCl, cm^{-1}): ν_{max}=3064; 1664; 1594; 1496; 1472; 1242; 1027; 910; 751; 692. MS (70 eV): *m/z* (%): 318/20 ($M^+ + 1$, 100); 277/9 (55), 256/8 (8), 169/71 (15), 121 (16). R_f=0.18; hexane/ethyl acetate 4:1. Light-yellow oil. Anal. Calcd for $C_{16}H_{16}BrNO$: C 60.39, H 5.07, N 4.40. Found: C 60.53, H 5.20, N 4.27.

3.2.3. 1-(2-Chlorophenyl)methyl-2-(phenoxymethyl)-aziridine 6c. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.65 (1H, d, J=6.6 Hz, H_b); 1.94 (1H, d, J=3.3 Hz, H_a); 2.04–2.07 (1H, m, H_c); 3.60 and 3.37 (2H, 2×d, J=15.0 Hz, $C_6H_4CH_2$); 3.96 and 4.06 (2H, 2×d×d, J=10.3, 6.6, 4.8 Hz, CH_2O); 6.80–6.97; 7.17–7.36 and 7.72–7.75 (5H, 3H and 1H, 3×m, CH_{arom}). ^{13}C NMR (68 MHz, $CDCl_3$): δ 31.59 (NCH_2CH); 38.41 (NCH); 60.39 ($PhCH_2$); 69.38 (CH_2O); 114.46 (2×CH_2OHC_{ortho}); 120.84 (CH_2OHC_{para}); 126.84, 128.26, 129.00 and 129.36 ($ClHC_{para}$, 2×$ClHC_{meta}$, $ClHC_{ortho}$ and 2×CH_2OHC_{meta}); 132.84 and 135.99 (CCl and CCH_2N); 158.42 (CH_2OC). IR (NaCl, cm^{-1}): ν_{max}=3063; 2991; 2925; 1599; 1496; 1472; 1242; 1038; 910; 751; 692. MS (70 eV): *m/z* (%): 274/6 ($M^+ + 1$, 100); 231/3 (20). R_f=0.21; hexane/ethyl acetate 4:1. Light-yellow oil. Anal. Calcd for $C_{16}H_{16}ClNO$: C 70.20, H 5.89, N 5.12. Found: C 70.42, H 6.03, N 5.26.

3.2.4. 2-[(2-Bromophenoxy)methyl]-1-(2-bromophenyl)-methylaziridine 6d. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.66 (1H, d, J=6.6 Hz, H_b); 1.95 (1H, d, J=3.3 Hz, H_a); 2.10–2.16 (1H, m, H_c); 3.55 and 3.65 (2H, 2×d, J=15.1 Hz, $C_6H_4CH_2$); 3.98 and 4.17 (2H, 2×d×d, J=10.6, 6.9, 4.1 Hz, CH_2O); 6.80–6.86, 6.93–6.96, 7.09–7.37, 7.50–7.55 and 7.73–7.76 (2×1H, 3H, 2H and 1H, 5×m, CH_{arom}). ^{13}C NMR (68 MHz, $CDCl_3$): δ 31.77 (NCH_2CH); 38.12 (NCH); 63.56 ($PhCH_2$); 71.61 (CH_2O); 112.34 and 113.74 (2×CH_2OHC_{ortho}); 122.18, 123.22, 127.81, 129.56, 132.40 and 133.48 (7×HC_{arom} and NCH_2CCBr); 138.32 (CCH_2N); 155.22 (CH_2OC). IR (KBr, cm^{-1}): ν_{max}=2892; 1587; 1484; 1461; 1441; 1284; 1249; 1015; 742; 670. MS (70 eV): *m/z* (%): 396/8/400 ($M^+ + 1$, 100). R_f=0.20; hexane/ethyl acetate 4:1. White crystals; mp=82.4–82.6 °C. Anal. Calcd for $C_{16}H_{15}Br_2NO$: C 48.39, H 3.81, N 3.53. Found: C 48.21, H 4.11, N 3.37.

3.2.5. 2-[(2-Chlorophenoxy)methyl]-1-(2-chlorophenyl)-methylaziridine 6e. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.67 (1H, d, J=6.3 Hz, H_b); 1.95 (1H, d, J=3.6 Hz, H_a); 2.04–2.18 (1H, m, H_c); 3.54 and 3.72 (2H, 2×d, J=15.0 Hz, $C_6H_4CH_2$); 3.96 and 4.17 (2H, 2×d×d, J=10.5, 7.2, 4.3 Hz, CH_2O); 6.80–6.98, 7.10–7.36 and 7.73–7.76 (3H; 4H and 1H, 3×m, CH_{arom}). ^{13}C NMR (68 MHz, $CDCl_3$): δ 31.57 (NCH_2CH); 38.20 (NCH); 60.70 ($PhCH_2$); 71.07 (CH_2O); 113.62 (CH_2OHC_{ortho}); 120.82 and 122.86 (CH_2OCCC and CH_2OHC_{para}); 127.06, 127.65, 128.23, 129.29, 129.49, 130.22 (4×NCH_2HC_{arom} and 2×CH_2OHC_{meta}); 132.84 and 135.99 ($CClCCH_2N$ and CCH_2N); 158.42 (CH_2OC). IR (KBr, cm^{-1}): ν_{max}=2896; 1591; 1489; 1446; 1250; 1061; 742; 698. MS (70 eV): *m/z* (%): 308/10/12 ($M^+ + 1$, 100). R_f=0.20; hexane/ethyl acetate 4:1. Light-yellow crystals; mp=57.5–58.6 °C. Anal. Calcd for $C_{16}H_{15}Cl_2NO$: C 62.35, H 4.91, N 4.54. Found: C 62.51, H 5.12, N 4.35.

3.2.6. 2-[(2-Bromophenoxy)methyl]-1-(2-chlorophenyl)-methylaziridine 6f. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.66 (1H, d, J=6.6 Hz, H_b); 1.95 (1H, d, J=3.3 Hz, H_a); 2.05–2.16 (1H, m, H_c); 3.57 and 3.67 (2H, 2×d, J=15.0 Hz, $C_6H_4CH_2$); 3.98 and 4.16 (2H, 2×d×d, J=10.5, 6.9, 4.1 Hz, CH_2O); 6.80–6.85, 6.93–6.96, 7.17–7.35, 7.51–7.54 and 7.71–7.74 (2×1H, 4H and 2×1H, 5×m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.82 (NCH_2CH); 38.12 (NCH); 61.09 ($PhCH_2$); 71.60 (CH_2O); 112.33 and 113.73 (2×CH_2OHC_{ortho}); 122.16, 127.18, 128.24, 128.54, 129.14, 133.00 and 133.47 (7×HC_{arom} and CCl); 136.68 (CCH_2N); 155.22 (CH_2OC). IR (KBr, cm^{-1}): ν_{max}=2894; 1586; 1484; 1442; 1249; 1033; 743. MS (70 eV): *m/z* (%): 352/4/6 ($M^+ + 1$, 100). R_f=0.17; hexane/ethyl acetate 4:1. White crystals; mp=78.8–79.7 °C. Anal. Calcd for $C_{16}H_{15}BrClNO$: C 54.49, H 4.29, N 3.97. Found: C 54.66, H 4.52, N 3.81.

3.2.7. 1-(4-Methylphenyl)methyl-2-(4-chlorophenoxymethyl)aziridine 6g. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55 (1H, d, J=6.6 Hz, H_b); 1.81 (1H, d, J=3.6 Hz, H_a); 1.91–1.98 (1H, m, NCH); 2.33 (3H, s, $PhCH_3$); 3.47 and 3.42 (2H, d×d, J=13.2, 3.9 Hz, $ArCH_2$); 3.86 and 3.93 (2H, 2×d×d, J=10.4, 6.3, 4.8 Hz, $HCHO$); 6.76–6.81 and 7.11–7.25 (2H and 6H, 2×m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.09 ($PhCH_3$); 31.70 (NCH_2CH); 37.67 (NCH); 64.00 ($ArCH_2$); 70.46 (CH_2O); 115.88 ($OCCH_{ortho}$); 125.56 (CCl); 128.04, 129.03 and 129.20 (CH_{arom}); 135.67 and 136.71 (CCH_3 and CCH_2N); 157.28 (CH_2OC_{quat}). IR (NaCl, cm^{-1}): ν_{max}=2922; 1757; 1675; 1595; 1581; 1491; 1347; 1286; 1243; 1171; 1094; 1064; 1022; 824; 666. MS (70 eV): *m/z* (%): 288/90 ($M^+ + 1$, 100). R_f=0.24; hexane/ethyl acetate 7:3. Light-yellow oil. Anal. Calcd for $C_{17}H_{18}ClNO$: C 70.95, H 6.30, N 4.87. Found: C 71.18, H 6.51, N 4.72.

3.3. Synthesis of *N*-(2-bromo-3-aryloxypropyl)amines 7

As a representative example, the synthesis of *N*-benzyl-*N*-(2-chlorobenzyl)-*N*-(2-bromo-3-phenoxypropyl)amine **7c** is described here. To a solution of 1-(2-chlorophenyl)methyl-2-(phenoxymethyl)aziridine **6c** (2.73 g, 10 mmol) in 50 mL acetonitrile was added benzyl bromide (1.71 g, 1 equiv) under stirring and the resulting mixture was heated for 5 h under reflux. Evaporation of the solvent afforded *N*-benzyl-*N*-(2-chlorobenzyl)-*N*-(2-bromo-3-phenoxypropyl)amine **7c** (3.95 g, 89%), which was purified by means of column chromatography (hexane/ethyl acetate 1:1) in order to obtain an analytically pure sample.

3.3.1. *N*,*N*-Di(phenylmethyl)-*N*-(2-bromo-3-(3-chlorophenoxy)propyl)amine 7a. ^{1}H NMR (270 MHz, $CDCl_3$):

δ 2.91 and 3.08 (2H, 2×d×d, J=13.5, 8.7, 5.1 Hz, N(*HCH*)CH); 3.56 and 3.72 (4H, 2×d, J=13.2 Hz, 2×PhCH_2N); 3.93–3.99 and 4.07–4.19 (1H and 2H, 2×m, BrCH and (HCH)O); 6.64–6.68, 6.73–6.74, 6.88–6.96 and 7.13–7.43 (1H, 1H, 2H and 10H, 4×m, CH_{arom}). ^{13}C NMR (68 MHz): δ 48.57 (CHBr); 57.50 (NCH_2CH); 59.37 (2×NCH_2Ar); 70.06 (CH_2O); 113.08 and 114.98 (2×OHC_{ortho}), 121.18, 127.28, 128.34, 128.96, 130.10 (OHC_{meta}, OHC_{para}, 4×NCH_2HC_{ortho}, 4×NCH_2HC_{meta} and 2×NCH_2HC_{para}); 134.71 (CCl); 138.63 (2×NCH_2C); 158.85 (OC_{quat}). IR (NaCl, cm^{-1}): ν_{max}=3064; 3029; 2928; 2805; 1595; 1480; 1454; 1247; 1229; 749; 697. MS (70 eV): *m/z* (%): 444/46/48 (M^++1, 12), 396/8 (90), 364/6 (100). Colorless oil. Anal. Calcd for $C_{23}H_{23}BrClNO$: C 62.11, H 5.21, N 3.15. Found: C 62.26, H 5.42, N 3.02.

3.3.2. *N*-Benzyl-*N*-(2-bromobenzyl)-*N*-(2-bromo-3-phenoxypropylamine 7b. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.97 and 3.14 (2H, 2×d×d, J=13.8, 8.3, 5.9 Hz, N(*HCH*)CH); 3.75 (2H, d, J=13.8 Hz, PhCH_2N); 3.64 and 3.83 (2H, 2×d, J=13.6 Hz, PhCH_2N); 3.99–4.06 and 4.13–4.27 (1H and 2H, 2×m, BrCH and (HCH)O); 6.76–6.79, 6.93–6.98, 7.06–7.12, 7.17–7.45 and 7.49–7.68 (2H, 1H, 1H, 8H and 2H; 5×m, CH_{arom}). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 48.10 (CHBr); 57.99, 59.10 and 59.63 (3×NCH_2); 70.09 (CH_2O); 114.78, 121.22, 124.66, 127.48, 128.48, 128.86, 129.26, 129.52, 131.27 and 132.99 (14×CH_{arom} and CBr); 138.03 and 138.52 (2×NCH_2C); 158.29 ($COCH_2$). IR (NaCl, cm^{-1}): ν_{max}=3062; 3029; 2926; 2832; 1599; 1496; 1243; 1027; 753; 692. MS (70 eV): *m/z* (%): 488/90/92 (M^++1, 10); 409/11 (25); 408/10 (100); 365/7/9 (65). R_f=0.60; hexane/ethyl acetate 4:1. Anal. Calcd for $C_{23}H_{23}Br_2NO$: C 56.46, H 4.74, N 2.86. Colorless oil. Found: C 56.62, H 4.95, N 2.97.

3.3.3. *N*-Benzyl-*N*-(2-chlorobenzyl)-*N*-(2-bromo-3-phenoxypropyl)amine 7c. ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.96 and 3.13 (2H, 2×d×d, J=13.9, 8.3, 5.6 Hz, N(*HCH*)CH); 3.74 (2H, d, J=14.8 Hz, PhCH_2N); 3.62 and 3.84 (2H, 2×d, J=13.5 Hz, PhCH_2N); 3.99–4.06 and 4.13–4.23 (1H and 2H, 2×m, BrCH and (HCH)O); 6.76–6.98, 7.12–7.41 and 7.51–7.55 (5H, 8H and 1H; 3×m, CH_{arom}). ^{13}C NMR (68 MHz, $CDCl_3$): δ 48.97 (CHBr); 56.06, 57.52 and 59.14 (3×NCH_2); 69.61 (CH_2O); 114.46, 120.95, 126.56, 128.14, 128.53, 128.82, 128.89, 129.23, 129.38, 130.85, 133.92 (14×CH_{arom} and CCl); 136.04 and 138.22 (2×NCH_2C); 157.91 ($COCH_2$). IR (NaCl, cm^{-1}): ν_{max}=3063; 3030; 2832; 1598; 1497; 1243; 909; 754; 735; 692. MS (70 eV): *m/z* (%): 444/6 (M^++1, 10); 364/6 (100); 321 (23); 323 (21). R_f=0.85; hexane/ethyl acetate 1:1. Colorless oil. Anal. Calcd for $C_{23}H_{23}BrClNO$: C 62.11, H 5.21, N 3.15. Found: C 62.32, H 5.38, N 2.96.

3.3.4. *N*-Benzyl-*N*-(2-bromobenzyl)-*N*-(2-bromo-3-(2-bromophenoxy)propyl)amine 7d. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.01 and 3.24 (2H, 2×d×d, J=13.8, 7.6, 5.8 Hz, N(*HCH*)CH); 3.69 and 3.73 (2H, 2×d, J=13.6 Hz, PhCH_2N); 3.78 and 3.83 (2H, 2×d, J=14.2 Hz, PhCH_2N); 4.10–4.21 (3H, m, BrCH and (HCH)O); 6.71 (1H, d×d, J=8.0, 1.4 Hz, CH_{arom}); 6.83 (1H, d×t, J=7.4, 1.4 Hz, CH_{arom}); 7.06 (1H, d×t, J=7.7, 1.7 Hz, CH_{arom}); 7.19–7.34 (10H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 48.62 (CHBr); 58.00, 59.22 and 59.71 (3×NCH_2); 70.81 (CH_2O); 112.58, 113.43, 122.34, 127.44, 128.43, 128.80, 128.89, 129.14, 129.27, 131.31, 132.97 and 133.50 (13×CH_{arom} and 2×CBr); 138.06 and 138.54 (2×NCH_2C); 154.68 ($COCH_2$). IR (NaCl, cm^{-1}): ν_{max}=3062; 3028; 2930; 2833; 1586; 1481; 1442; 1278; 1248; 1030; 749; 698. MS (70 eV): *m/z* (%): 566/68/70/72 (M^++1, 5); 486/88/90 (100). R_f=0.88; hexane/ethyl acetate 1:1. Colorless oil. Anal. Calcd for $C_{23}H_{22}Br_3NO$: C 48.62, H 3.90, N 2.47. Found: C 48.79, H 4.03, N 2.30.

3.3.5. *N*-Benzyl-*N*-(2-chlorobenzyl)-*N*-(2-bromo-3-(2-chlorophenoxy)propyl)amine 7e. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.99 and 3.21 (2H, 2×d×d, J=13.8, 7.6, 5.4 Hz, N(*HCH*)CH); 3.62-3.92 (4H, m, 2×PhCH_2N); 4.19-4.23 (3H, m, BrCH and (HCH)O); 6.74 (1H, d×d, J=8.1, 1.0 Hz, CH_{arom}); 6.86-6.91 and 7.10-7.34 (1H and 10H, 2×m, CH_{arom}); 7.52 (1H, d, J=7.2 Hz, CH_{arom}). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 48.91 (CHBr); 56.39, 58.07 and 59.78 (3×NCH_2); 70.88 (CH_2O); 113.81, 122.05, 123.44, 127.00, 127.56, 127.84, 128.59, 128.70, 129.38, 129.81, 130.57, 131.38, 134.48 (13×CH_{arom} and 2×CCl); 136.55 and 138.72 (2×NCH_2C); 154.00 ($COCH_2$). IR (NaCl, cm^{-1}): ν_{max}=3064; 3028; 2931; 2833; 1590; 1486; 1445; 1278; 1249; 748; 699. MS (70 eV): m/z (%): 478/80/82/84 (M^++1; 5); 399/401/403 (65); 398/400/402 (100). R_f = 0.62; hexane/ethyl acetate 4/1. Colorless oil. Anal. Calcd for $C_{23}H_{22}BrCl_2NO$: C 57.64, H 4.63, N 2.92. Found: C 57.84, H 4.75, N 2.76.

3.3.6. *N*-Benzyl-*N*-(2-chlorobenzyl)-*N*-(2-bromo-3-(2-bromophenoxy)propyl)amine 7f. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.98 and 3.23 (2H, 2×d×d, J=11.1, 7.7, 5.5 Hz, N(*HCH*)CH); 3.63–3.86 (4H, m, 2×PhCH_2N); 4.11–4.20 (3H, m, BrCH and (HCH)O); 6.70 (1H, d×d, J=8.3, 1.4 Hz, CH_{arom}); 6.82 (1H, d×t, J=7.43, 1.38 Hz, CH_{arom}); 7.19–7.33 and 7.47–7.53 (10H and 1H, 2×m, CH_{arom}). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 48.65 (CHBr); 56.65, 58.04 and 59.72 (3×NCH_2); 70.74 (CH_2O); 112.57, 113.38, 122.34, 126.84, 127.41, 128.44, 129.23, 129.68, 131.22, 133.51 and 134.37 (13×CH_{arom}, CCl and CBr); 136.45 and 138.63 (2×NCH_2C); 154.68 ($COCH_2$). IR (NaCl, cm^{-1}): ν_{max}=3063; 3028; 2929; 2833; 1586; 1481; 1443; 1278; 1247; 1052; 1031; 749; 698. MS (70 eV): *m/z* (%): 522/4/6/8 (M^++1, 5); 443/5/7(20); 442/4/6(100). R_f=0.59; hexane/ethyl acetate 4:1. Colorless oil. Anal. Calcd for $C_{23}H_{22}Br_2ClNO$: C 52.75, H 4.23, N 2.67. Found: C 52.88, H 4.47, N 2.74.

3.3.7. *N*,*N*-Di[(4-methylbenzyl)methyl]-*N*-[2-bromo-3-(4-chlorophenoxy)propyl]amine 7g. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.31 (6H, s, 2×CH_3); 2.88 and 3.06 (2H, 2×d×d, J=13.6, 8.7, 5.4 Hz, N(*HCH*)CH); 3.50 and 3.66 (4H, 2×2×d, J=13.4 Hz, 2×Ar(*HCH*)N); 3.95–4.00 and 4.10–4.17 (1H and 2H, 2×m, CHBr and (HCH)O); 6.65–6.70 and 7.07–7.29 (2H and 10H, 2×m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.10 (2×CH_3); 48.92 (CHBr); 57.52 and 59.12 (2×NCH_2Ar); 70.22 (CH_2O); 115.93, 128.96, 129.02 and 129.22 (CH_{arom}); 129.47 (CCl); 135.69 and 136.79 (2×CH_3C and 2×NCH_2C_{quat}); 156.88 (OC_{quat}). IR (NaCl, cm^{-1}): ν_{max}=3021; 2922; 2823; 1596; 1582; 1514; 1491; 1454; 1370; 1286; 1244; 1171; 1092; 1021; 823; 808. MS (70 eV): *m/z* (%): 392/4 (M^+−Br, 100). R_f=0.53; hexane/ethyl acetate 4:1.

White crystals; mp = 54.4 °C. Anal. Calcd for $C_{25}H_{27}BrClNO$: C 63.50, H 5.76, N 2.96. Found: C 63.66, H 5.88, N 2.78.

3.4. Synthesis of 2-amino-1-aryloxy-3-methoxypropanes 8

As a representative example, the synthesis of 2-[*N*-benzyl-*N*-(2-chlorobenzyl)]amino-1-phenoxy-3-methoxypropane **8b** is described here. To *N*-benzyl-*N*-(2-chlorobenzyl)-*N*-(2-bromo-3-phenoxypropyl)amine **7c** (1.19 g, 3 mmol) was added slowly under stirring a solution of sodium methoxide in methanol (60 mL, 0.2 N, 12 mmol), and the resulting solution was heated under reflux for 2 h. The resulting reaction mixture was poured into brine (50 mL) and extracted with CH_2Cl_2 (3×50 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded a mixture of 2-[*N*-benzyl-*N*-(2-chlorobenzyl)]-amino-1-phenoxy-3-methoxypropane **8b** and *N*-benzyl-*N*-(2-chloorbenzyl)-*N*-(2-methoxy-3-phenoxypropyl)amine **9b** (4/1). Isolation of the major isomer was realized by means of column chromatography (SiO_2) (hexane/EtOAc 49:1).

3.4.1. 2-[*N*-Benzyl-*N*-(2-bromoarylmethyl)]amino-1-phenoxy-3-methoxypropane 8a. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.28–3.34 (1H, m, NCH); 3.32 (3H, s, CH_3O); 3.63–3.73 (2H, m, CH_2OMe); 3.88 (2H, s, NCH_2); 3.97 (2H, d, J=3.3 Hz, NCH_2); 4.11–4.21 (2H, m, CH_2OPh); 6.89–6.95 (3H, m, CH_{arom}); 7.03 (1H, d×t, J=7.7, 1.7 Hz, CH_{arom}); 7.16–7.29 and 7.37–7.40 (6H and 2H, 2×m, CH_{arom}); 7.46 (1H, d×d, J=8.0, 1.1 Hz, CH_{arom}); 7.68 (1H, d×d, J=7.7, 1.7 Hz, CH_{arom}). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 55.03 and 55.70 (2×NCH_2); 57.09 (NCH); 59.20 (OCH_3); 66.76 (*C*H_2OPh); 71.69 (*C*H_2OCH_3); 114.70, 120.83, 124.31, 127.03, 127.44, 128.36, 128.86, 129.59, 130.79, 132.68 (14×CH_{arom} and CBr); 139.41 and 140.28 (2×*C*CH_2N); 159.00 (*C*OCH_2). IR (NaCl, cm^{-1}): ν_{max}=3063; 3029; 2926; 2876; 1600; 1496; 1244; 909; 753; 734; 693. MS (70 eV): *m*/*z* (%): 440/2 (M^++1; 100). R_f=0.11; hexane/ethyl acetate 98:2. Colorless oil. Anal. Calcd for $C_{24}H_{26}BrNO_2$: C 65.46, H 5.95, N 3.18. Found: C 65.62, H 6.14, N 3.08.

3.4.2. 2-[*N*-Benzyl-*N*-(2-chlorobenzyl)]amino-1-phenoxy-3-methoxypropane 8b. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.28–3.39 (1H, m, NCH); 3.33 (3H, s, CH_3O); 3.64–3.72 (2H, m, CH_2OMe); 3.88 (2H, s, NCH_2); 3.98 and 4.04 (2×1H, 2×d, J=15.4 Hz, NCH_2); 4.14–4.22 (2H, m, CH_2OPh); 6.89–6.96, 7.11–7.39 and 7.67–7.69 (3H, 10H and 1H, 3×m, CH_{arom}). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 52.26 and 55.62 (2×NCH_2); 56.90 (NCH); 59.15 (OCH_3); 66.65 (*C*H_2OPh); 71.60 (*C*H_2OCH_3); 114.58, 120.73, 126.73, 126.94, 127.91, 128.28, 128.76, 129.33, 129.52, 130.57 and 133.96 (14×CH_{arom} and CCl); 137.75 and 140.25 (2×*C*CH_2N); 158.90 (*C*OCH_2). IR (NaCl, cm^{-1}): ν_{max}=3063; 3029; 2925; 2876; 1600; 1496; 1244; 1037; 753; 692. MS (70 eV): *m*/*z* (%): 396/98 (M^++1, 100). R_f=0.10; hexane/ethyl acetate 98:2. Colorless oil. Anal. Calcd for $C_{24}H_{26}ClNO_2$: C 72.81, H 6.62, N 3.54. Found: C 72.96, H 6.80, N 3.39.

3.4.3. 2-[*N*-Benzyl-*N*-(2-bromobenzyl)]amino-1-(2-bromophenoxy)-3-methoxypropane 8c. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.30–3.39 (1H, m, NCH); 3.33 (3H, s, CH_3O); 3.75 (2H, d, J=6.1 Hz, CH_2OMe); 3.90 and 3.97 (2H, 2×d, J=14.2 Hz, N(HCH)); 4.01–4.09 (2H, m, NCH_2); 4.18–4.27 (2H, m, CH_2OPh); 6.78–6.90 (2H, m, CH_{arom}); 7.06 (1H, d×t, J=7.6, 1.7 Hz, CH_{arom}); 7.16–7.33 (5H, m, CH_{arom}); 7.40–7.60 (4H, m, CH_{arom}); 7.72 (1H, d×d, J=7.7, 1.7 Hz, CH_{arom}). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 54.90 and 55.64 (2×NCH_2); 56.75 (NCH); 59.22 (OCH_3); 67.43 (*C*H_2OPh); 71.25 (*C*H_2OCH_3); 112.15, 112.80, 121.84, 124.24, 126.96, 127.44, 128.31, 128.52, 128.80, 130.83, 132.62, 133.44 (13×CH_{arom} and 2×CBr); 139.29 and 140.25 (2×*C*CH_2N); 155.35 (*C*OCH_2). IR (NaCl, cm^{-1}): ν_{max}=3062; 2925; 2875; 1587; 1481; 1442; 1277; 1248; 1121; 1030; 961. MS (70 eV): *m*/*z* (%): 518/20/22 (M^++1, 100). R_f=0.04; hexane/ethyl acetate 98:2. Colorless oil. Anal. Calcd for $C_{24}H_{25}Br_2NO_2$: C 55.51, H 4.85, N 2.70. Found: C 55.39, H 5.05, N 2.59.

3.4.4. 2-[*N*-Benzyl-*N*-(2-chlorobenzyl)]amino-1-(2-bromophenoxy)-3-methoxypropane 8d. ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.32-3.36 (1H, m, NCH); 3.33 (3H, s, CH3O); 3.75 (2H, d, J=5.9 Hz, CH_2OMe); 3.89 and 3.97 (2×1H, 2×d, J=14.2 Hz, NCH_2); 4.01 and 4.07 (2×1H, 2×d, J=15.0 Hz, NCH_2); 4.20-4.24 (2H, m, CH_2OPh); 6.79-6.88 and 7.09-7.30 (2H and 7H, 2×m, CH_{arom}); 7.40 (1H, d, J=7.3 Hz, CH_{arom}); 7.54 (1H, d×d, J=7.7, 1.5 Hz, CH_{arom}); 7.70 (1H, d, J=7.6 Hz, CH_{arom}). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 52.19 and 55.56 (2×NCH_2); 56.68 (NCH); 58.94 (OCH_3); 67.37 (*C*H_2OPh); 71.14 (*C*H_2OCH_3); 112.02, 112.69, 121.67, 126.60, 126.77, 127.76, 128.12, 128.32, 128.61, 129.16, 130.55, 133.24 and 133.82 (13×HC_{arom}, CBr and CCl); 137.59 and 140.09 (2×*C*CH_2N); 155.20 (*C*OCH_2). IR (NaCl, cm^{-1}): ν_{max}=3063; 3027; 2926; 2926; 2877; 1587; 1481; 1442; 1248; 1031; 749; 699. MS (70 eV): m/z (%): 472/4/6 (M^+-1; 100). R_f=0.04; hexane/ethyl acetate 98/2. Colorless oil. Anal. Calcd for $C_{24}H_{25}BrClNO_2$: C 60.71, H 5.31, N 2.95. Found: C 60.93, H 5.43, N 3.05.

3.4.5. 2-[*N*-Benzyl-*N*-(2-chlorobenzyl)]amino-1-(2-chlorophenoxy)-3-methoxypropane 8e. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.31–3.90 (1H, m, NCH); 3.33 (3H, s, CH_3O); 3.73 (2H, d, J=6.1 Hz, CH_2OMe); 3.88 and 3.96 (2×1H, 2×d, J=14.0 Hz, NCH_2); 4.01 and 4.05 (2×1H, 2×d, J=15.1 Hz, NCH_2); 4.22 (2H, d, J=5.5 Hz, CH_2OPh); 6.84–6.90 and 7.10–7.42 (2H and 10H, 2×m, CH_{arom}); 7.72 (1H, d×d, J=7.7, 1.7 Hz, CH_{arom}). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 52.24 and 55.62 (2×NCH_2); 56.71 (NCH); 59.20 (OCH_3); 67.46 (*C*H_2OPh); 71.33 (*C*H_2OCH_3); 112.96, 121.33, 122.91, 126.81, 126.96, 127.77, 127.95, 128.32, 128.32, 128.79, 129.35, 130.35, 130.68 and 133.99 (13×HC_{arom} and 2×CCl); 137.75 and 140.28 (2×CCH_2N); 154.53 (*C*OCH_2). IR (NaCl, cm^{-1}): ν_{max}=3064; 3027; 2926; 2877; 1590; 1486; 1446; 1249; 1062; 748; 698. MS (70 eV): *m*/*z* (%): 428/30/32 (M^+−1, 100). R_f=0.08; hexane/ethyl acetate 49:1. Colorless oil. Anal. Calcd for $C_{24}H_{25}Cl_2NO_2$: C 66.98, H 5.86, N 3.25. Found: C 67.13, H 6.02, N 3.11.

3.4.6. 2-(*N*,*N*-Dibenzyl)amino-1-(3-chlorophenoxy)-3-methoxypropane 8f. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.27–3.32 (1H, m, CHN); 3.31 (3H, s, OCH_3); 3.62 and 3.65 (2H, 2×d×d, J=9.9, 6.1, 5.8 Hz, (HCH)OCH_3); 3.78–3.87 (4H, m, 2×NCH_2); 4.10 and 4.13 (2H, 2×d×d, J=9.6, 6.3, 5.5 Hz, (*HCH*)OAr); 6.74–6.78, 6.89–6.93 and

7.13–7.39 (1H, 2H and 11H, 3×m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.42 (2×NCH_2); 55.96 (NCH); 58.92 (OCH_3); 67.21 (CH_2OAr); 71.64 (CH_2OCH_3); 112.97, 115.05, 120.88, 126.94, 128.25, 128.74, 129.21, 130.15 and 130.77 (HC_{arom}); 134.96 (CCl); 140.36 (2×NCH_2C_{quat}) 159.72 (OC_{quat}). IR (NaCl, cm^{-1}): ν_{max}= 3063; 3028; 2925; 1595; 1454; 1099; 1072; 745; 698. MS (70 eV): *m/z* (%): 396/8 (M^++1, 100). R_f=0.14; hexane/ethyl acetate 97:3. Colorless oil. Anal. Calcd for $C_{24}H_{26}ClNO_2$: C 72.81, H 6.62, N 3.54. Found: C 73.01, H 6.84, N 3.41.

3.4.7. 2-*N*,*N*-Di[(4-methylbenzyl)methyl]amino-1-(4-chlorophenoxy)-3-methoxypropane 8g. ^1H NMR (300 MHz, $CDCl_3$): δ 2.30 (6H, s, 2×CH_3); 3.25–3.30 (1H, m, CHN); 3.30 (3H, s, CH_3O); 3.59–3.66 (2H, m, CH_2OMe); 3.75 and 3.77 (4H, 2×2×d, *J*=14.3 Hz, 2×N(HCH)); 4.06 and 4.08 (2H, 2×d×d, *J*=9.9, 6.1, 5.5 Hz, (*HCH*)OAr); 6.74–6.81 and 6.97–7.28 (2H and 10H, 2×m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.08 (2×CH_3); 54.87 (2×NCH_2); 55.64 (NCH); 59.00 (OCH_3); 67.33 (CH_2OAr); 71.53 (CH_2OCH_3); 115.79 (2×HC_{ortho}); 125.38 (CCl); 128.59, 128.86 and 129.21 (CH_{arom}); 136.28 and 137.29 (2×CH_3C and 2×NCH_2C); 157.48 (OC_{quat}). IR (NaCl, cm^{-1}): ν_{max}=2923; 1596; 1513; 1491; 1242; 1207; 1094; 1019; 910; 823; 734. MS (70 eV): *m/z* (%): 424/6 (M^++1; 100); 307 (62). R_f=0.15; hexane/ethyl acetate 97:3. Colorless oil. Anal. Calcd for $C_{26}H_{30}ClNO_2$: C 73.65, H 7.13, N 3.30. Found: C 73.84, H 7.30, N 3.16.

3.5. Detectable signals derived from the minor constituents 9

3.5.1. *N*-Benzyl-*N*-(2-bromobenzyl)-*N*-(2-methoxy-3-phenoxypropyl)amine 9a. ^1H NMR (300 MHz, $CDCl_3$): δ 2.70 and 2.77 (2H, 2×d×d, *J*=13.5, 6.6, 5.2 Hz, CH(*HCH*)N); 3.44 (3H, s, CH_3O); 3.56–3.79 (5H, m, OCH and 2×NCH_2Ph); 3.85 and 4.01 (2H, 2×d×d, *J*=10.0, 5.6, 3.7 Hz, (HCH)OPh); 6.79–7.57 (14H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 54.37 (CH_2N); 58.50 (OCH_3); 59.17 and 59.95 (2×NCH_2Ph); 68.64 (CH_2O); 78.55 (OCH); 114.67, 120.77, 120.88, 124.60, 127.23, 127.40, 128.38, 128.57, 129.19, 129.42, 129.51, 131.07 and 132.87 (14×CH_{arom} and CBr); 138.64 and 139.15 (2×CCH_2N); 158.90 ($COCH_2$). IR (NaCl, cm^{-1}): ν_{max}=3063; 3029; 2928; 2827; 1600; 1496; 1244; 1027; 752; 734; 692. MS (70 eV): *m/z* (%): 440/2 (M^++1, 100). R_f=0.10; hexane/ethyl acetate 49:1. Colorless oil.

3.5.2. *N*-Benzyl-*N*-(2-chlorobenzyl)-*N*-(2-methoxy-3-phenoxypropyl)amine 9b. ^1H NMR (300 MHz, $CDCl_3$): δ 2.69 and 2.77 (1H, 2×d×d, *J*=13.5, 6.6, 5.2 Hz, CH(*HCH*)N); 3.45 (3H, s, CH_3O); 3.58–3.68 and 3.73–3.85 (3H and 2H, 2×m, OCH and 2×NCH_2Ph); 3.86 and 4.02 (H, 2×d×d, *J*=11.6, 5.6, 3.6 Hz, CH_2OPh); 6.81–7.59 (14H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 54.34 (CH_2N); 56.57 (OCH_3); 58.04 and 59.97 (2×NCH_2Ph); 68.58 (CH_2O); 78.53 (OCH); 114.63, 120.75, 126.77, 127.20, 128.26, 128.37, 129.13, 129.41, 129.56, 129.56, 130.94 and 134.28 (14×CH_{arom} and CCl); 137.00 and 139.19 (2×CCH_2N); 158.87 ($COCH_2$). IR (NaCl, cm^{-1}): ν_{max}=2928; 1600; 1496; 1245; 752; 692. MS (70 eV): *m/z* (%): 396/8 (M^++1, 100). R_f=0.07; hexane/ethyl acetate 49:1. Colorless oil.

3.5.3. *N*-Benzyl-*N*-(2-bromobenzyl)-*N*-[2-methoxy-3-(2-bromophenoxy)propyl]amine 9c. ^1H NMR (300 MHz, $CDCl_3$): δ 2.72 and 2.79 (2H, 2×d×d, *J*=13.6, 6.5, 5.5 Hz, CH(*HCH*)N); 3.50 (3H, s, CH_3O); 3.65–4.10 (7H, m, OCH, 2×NCH_2Ph and CH_2OPh); 6.74–7.75 (14H, m, CH_{arom}). ^{13}C NMR (68 MHz, $CDCl_3$): δ 54.64 (CH_2N); 58.51 (OCH_3); 59.03 and 59.82 (2×NCH_2Ph); 70.33 (CH_2O); 78.47 (OCH); aromatic signals could not be seen separately. R_f=0.03; hexane/ethyl acetate 49:1. Colorless oil.

3.5.4. *N*-Benzyl-*N*-(2-chlorobenzyl)-*N*-[2-methoxy-3-(2-bromophenoxy)propyl]amine 9d. ^1H NMR (270 MHz, $CDCl_3$): δ 2.70 and 2.78 (2H, 2×d×d, *J*=13.6, 6.4, 5.3 Hz, CH(*HCH*)N); 3.50 (3H, s, CH_3O); 3.62–4.06 (7H, m, OCH, 2×NCH_2Ph and CH_2OPh); 6.73–3.83, 7.10–7.35 and 7.47–7.55 (14H, 3×m, CH_{arom}). ^{13}C NMR (68 MHz, $CDCl_3$): δ 54.75 (CH_2N); 56.60 (OCH_3); 58.51 and 59.91 (2×NCH_2Ph); 70.37 (CH_2O); 78.54 (OCH); aromatic signals could not be seen separately. R_f=0.03; hexane/ethyl acetate 49:1. Colorless oil.

3.5.5. *N*-Benzyl-*N*-(2-chlorobenzyl)-*N*-[2-methoxy-3-(2-chlorophenoxy)propyl]amine 9e. ^1H NMR (300 MHz, $CDCl_3$): δ 2.67 and 2.75 (2H, 2×d×d, *J*=13.7, 6.5, 5.5 Hz, CH(*HCH*)N); 3.47 (3H, s, CH_3O); 3.53–4.12 (7H, m, OCH, 2×NCH_2Ph and CH_2OPh); 6.58–7.52 (14H, m, CH_{arom}). ^{13}C NMR (68 MHz, $CDCl_3$): δ 54.63 (CH_2N); 56.59 (OCH_3); 58.45 and 59.89 (2×NCH_2Ph); 70.37 (CH_2O); 78.54 (OCH); aromatic signals could not be observed separately. R_f=0.06; hexane/ethyl acetate 49:1. Colorless oil.

3.5.6. *N*,*N*-Dibenzyl-*N*-[2-methoxy-3-(3-chlorophenoxy)-propyl]amine 9f. MS (70 eV): *m/z* (%): no M^+; 350 (10); 254 (10); 210 (100); 181 (7); 91 (90).

3.5.7. *N*,*N*-Di[(4-methylbenzyl)methyl]-*N*-[2-methoxy-3-(4-chlorophenoxy)propyl]amine 9g. ^1H NMR (300 MHz, $CDCl_3$): δ 2.34 (6H, s, 2×CH_3); 2.58 and 2.70 (2H, 2×d×d, *J*=13.5, 7.4, 4.7 Hz, N(*HCH*)CH); 3.36 (3H, s, OCH_3); 3.57–4.05 (7H, m, C*H*OMe, 2×NCH_2Ar and 2×CH_2OAr); 6.69–6.72 and 6.97–7.28 (2H and 10H, 2×m, CH_{arom}). MS (70 eV): *m/z* (%): no M^+; 378/80 (34); 282 (34); 238 (19); 105 (100). Colorless oil.

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An efficient solid-phase synthesis of 2-alkyl-4,6-diaminopyrimidines and 2,4,6-triaminopyrimidines

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Abstract—An efficient and simple approach for the solid-phase synthesis of 2,4,6-triaminopyrimidines and 2-alkyl-4,6-diaminopyrimidines is described. Primary amines were immobilized on 2-(4-formyl-3-methoxyphenoxy)ethyl polystyrene resin via reductive amination. Attachment of two different 4,6-dichloropyrimidines led to the corresponding 4-chloro-6-aminopyrimidine intermediates. Aromatic nucleophilic substitution with various aliphatic amines or the corresponding lithium amides afforded the desired aminopyrimidines in high yield and excellent purity after acidic cleavage from the resin. The products were characterized by LC–MS, ^{1}H and ^{13}C NMR spectroscopy. Deuterium exchange experiments revealed that the investigated aminopyrimidines have a general tendency toward C-5 protonation.

1. Introduction

Di- and triaminopyrimidines are reported to exhibit diverse biological and pharmacological activities including acting as tyrosine kinase[1] and dihydrofolate reductase[2] inhibitors, as well as antibacterial,[3] antiallergenic[4] and antimalarial[5] agents. Antiviral,[6] antidepressant[7] and antiprotozoan[8] activities of diaminopyrimidines have been disclosed as well. With the potent biological and pharmacological activities of aminopyrimidines in mind, the development of an efficient solid-phase strategy for the synthesis of these compounds was explored.

In addition to a number of reports describing the solution-phase syntheses of aminopyrimidines[9] examples of solid-phase syntheses of these compounds can be found in the literature. Thus, various aminopyrimidines have been prepared on solid support starting either by de novo synthesis of the pyrimidine core onto the resin,[10,11] or by initial attachment of the pyrimidine to the resin and subsequent modification.[12–18] Most of the known methods couple the pyrimidine core to the resin either via an alkylsulfinyl group[10,11,15] or via the amino group of a Rink amide linker (Scheme 1).[12,13] Attachment to the solid support via an amino group using a carbamate bond has been reported as well.[14,17,18] There are two disadvantages of using an alkylsulfenyl group as a linker. Firstly, for substitution by amines the sulfide has to be oxidized to sulfone or sulfoxide, which can result in formation of undesired by-products (*N*-oxides). Secondly, removing of the excess of amine used in the last step requires an extra chemical step. The drawback of using methods based on a Rink amide linker is that they afford aminopyrimidines that are not substituted at one of the amino groups. Moreover, a general problem originates from the introduction of the third amino group, which requires very harsh conditions limiting the field of amines that can be used in this step. Although trimethyl aluminium catalyzed substitution of the sulfone group at the C-2-position by aromatic amines under mild conditions has been published recently, the method was used only for the synthesis of 2,4-diaminopyrimidines.[16]

Our aim was to develop a simple, efficient and robust synthetic strategy for the synthesis of 2-alkyl-4,6-diamino-pyrimidines and 2,4,6-triaminopyrimidines that would not only allow the use of a wide range of primary and secondary aliphatic amines but would easily be automated and would also be amenable to either large or small focused library synthesis. Our approach differs from previous ones by using solid-phase supported amines instead of the Rink linker and by using strongly nucleophilic lithium amides, generated from the amines, for the introduction of the third amino group.

Keywords: Solid-phase; Aliphatic amines; 4,6-Dichloropyrimidines.
Abbreviations: DCM, dichloromethane; DMF, *N*,*N*-dimethylformamide; DMAC, *N*,*N*-dimethylacetamide; THF, tetrahydrofuran; TFA, trifluoroacetic acid; TEA, triethylamine; DIEA, *N*,*N*-diisopropylethylamine; *m*-CPBA, 3-chloroperbenzoic acid; Pip, piperidine; Pyr, pyrrolidine; Pip-C(2,6), carbon atoms of piperidine at 2- and 6-positions; Pip-H(2,6), hydrogen atoms connected to Pip-C(2,6); eq, equatorial; ax, axial; ^{x}H and ^{y}H, chemically nonequivalent hydrogen atoms.
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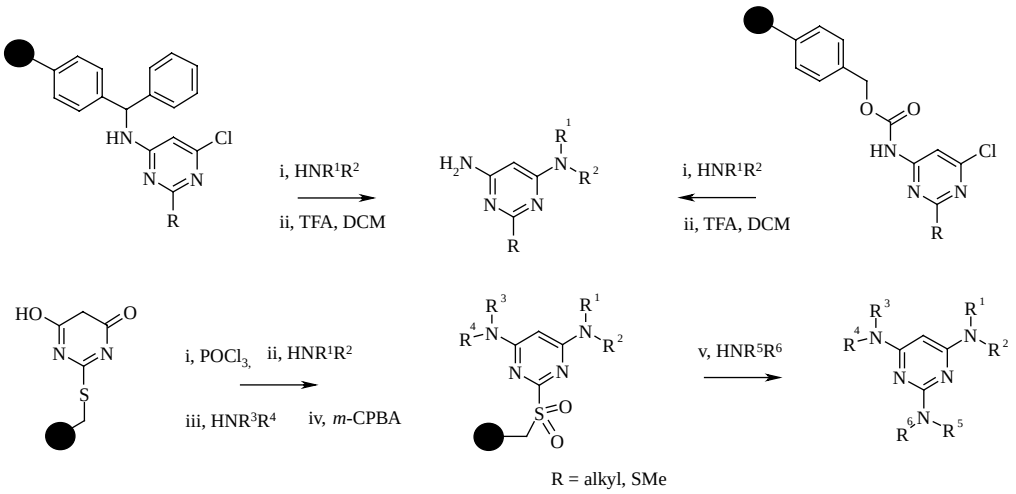


Scheme 1. Linkage strategies for aminopyrimidines.

2. Results and discussion

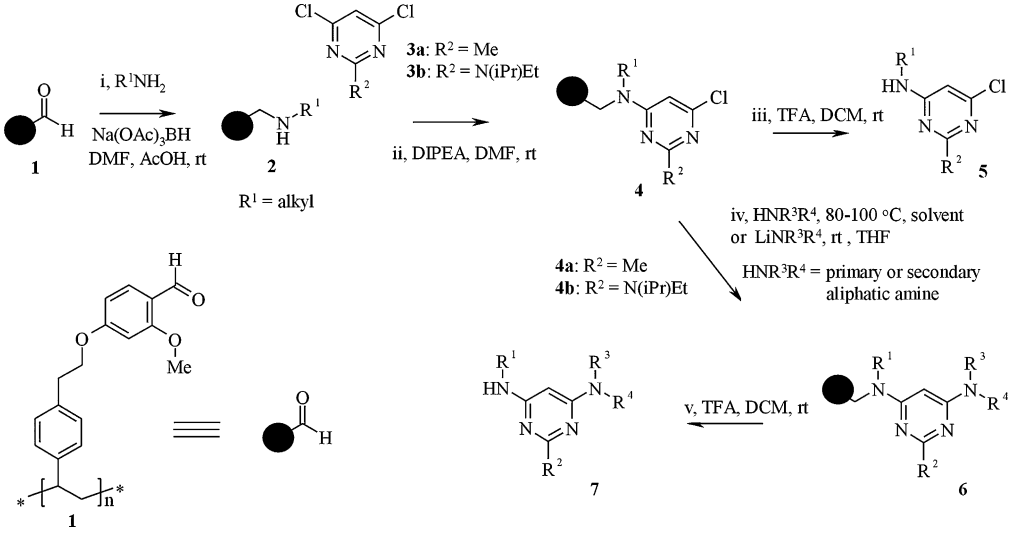
Herein, we report an efficient solid-phase synthesis of 2,4,6-triaminopyrimidines and 2-alkyl-4,6-diaminopyrimidines from acid labile 2-(4-formyl-3-methoxyphenoxy)ethyl polystyrene **1** in which sequential aromatic nucleophilic substitutions of the chlorines of 4,6-dichloropyrimidines are employed as key steps (Scheme 2).

Although the use of 2-(4-formyl-3-methoxyphenoxy)ethyl linker for the synthesis of aminopyrimidines had not been demonstrated before, it was successfully employed for solid-phase synthesis of diaminoquinazolines.[19] For the synthesis of aminopyrimidines the more acid sensitive 4-formyl-3,5-dimethoxyphenoxy linker was employed by Arvanitis et al.[16]

In the first step, 2-(4-formyl-3-methoxyphenoxy)ethyl polystyrene resin **1** was loaded with various primary aliphatic amines by reductive amination (Scheme 2).[20] The conversion proved to be quantitative, as checked by elemental analysis (N content). Primary amines branched at the α-position were also applied successfully in this step.

We chose to make use of two different 4,6-dichloropyrimidines (**3a**, **3b**) in order to explore the chemistry outlined in Scheme 2. Both 2-alkyl- and 2-aminopyrimidines can easily be synthesized: **3a** was prepared in one step from 2-methyl-4,6-pyrimidinedione,[21] **3b** from 2,4,6-trichloropyrimidine.[22]

Attachment of the two pyrimidines (**3a**, **3b**) to a supported secondary amine **2** was achieved in the presence of *N*,*N*-diisopropylethylamine (DIEA) in *N*,*N*-dimethylformamide (DMF) at room temperature. Quantitative attachment was obtained for a pyrimidine concentration of 1.5 M for 100 h at room temperature. Resin loadings were verified by the N content of the resin. At this point, it was checked whether the *o*-methoxybenzyl group of aminopyrimidine intermediate **4** can be cleaved by TFA/DCM mixture. Treatment of **4** with 10% TFA in DCM resulted in the formation of the expected 4-chloro-6-amino derivatives **5** in nearly



Scheme 2. Solid-phase synthesis of aminopyrimidines.

Table 1. Purities and yields of 6-amino-4-chloropyrimidines (**5**)

	Product	R^1	R^2	Yield (%)[a]	Purity (%)[b]
1	**5/1**	*n*-Hexyl	*N*-Isopropylethylamino	96	98
2	**5/2**	2-Methylbutyl	*N*-Isopropylethylamino	91	99
3	**5/3**	2-Heptyl	*N*-Isopropylethylamino	92	98
4	**5/4**	*n*-Hexyl	Methyl	94	99
5	**5/5**	2-Methylbutyl	Methyl	96	97
6	**5/6**	2-Heptyl	Methyl	98	98

[a] The yields were determined by weight based on the loading of **4**.
[b] The purities were determined by HPLC–MS at 254 nm.

quantitative yields and excellent purities (Table 1). The structures of these products was confirmed by NMR and mass spectrometry as well. Yields obtained from the N content of **4** are equal, within experimental error, to those calculated from the weight of **5**.

In the next step, aromatic nucleophilic substitution reaction of solid-phase bound 4-chloro-6-aminopyrimidine derivatives **4** with various aliphatic amines was studied. Release from the resin was achieved by treating **6** with 10% TFA in DCM to yield the desired product **7**. Formation of **7** in high purity was proven by HPLC, ^{1}H and ^{13}C NMR analysis of the unpurified material.

Reactions of 2-methyl- and 2-(*N*-isopropylethylamino)pyrimidine derivatives **4** with primary and secondary aliphatic amines, branched and unbranched four to six-membered cyclic amines were investigated in different solvents (*N*,*N*-dimethylacetamide (DMAC), *n*-BuOH, $MeNO_2$) using 20 fold excess of amines. Because in the course of our former experiments DMAC was found to be the best solvent of amines, it was tried first. While in the case of using unbranched four to six-membered cyclic amines the reaction was complete in 140 h in DMAC at 100 °C (Table 2, entries 1–11), primary and acyclic secondary aliphatic amines did not give pure products under these conditions. In the latter cases, in addition to the desired aminopyrimidines, 6-amino-4-dimethylaminopyrimidine side products were observed up to 15–45% of the product.

Formation of this type of side product in reaction of chloropyrimidines and amines in DMF was reported by Load[23] previously. Cyclic amines branched at α-position did not give pure product with **4a**, probably because of steric effects (Table 2, entries 12 and 13). While reactions of 2-methyl derivatives **4a** with primary and secondary aliphatic amines in *n*-BuOH or $MeNO_2$ afforded the desired products in high yield and purity (Table 2, entries 14–19), 2-amino derivatives **4b** did not give pure products under the same conditions. This is probably due to the fact that the chlorine in **4b** is less reactive than it is in **4a** because of the stronger electron donating effect of the *N*-isopropylethylamino group compared to the methyl group.

To replace the chlorine of **4b** by aliphatic amines under mild conditions a new approach was examined. Since we could not achieve high conversion neither by prolonged reaction times nor by higher concentrations of the amines we tried to increase the nucleophilic character of the reagent. Amines were deprotonated by *n*-BuLi, forming lithium amides, before adding resin to the solution. The reaction conducted at room temperature afforded the desired triaminopyrimidines in moderate yield and high purity after acidic cleavage from the resin (Table 2, entries 20 and 21).

Table 2. Purities and yields of 4,6-diaminopyrimidines (**7**)

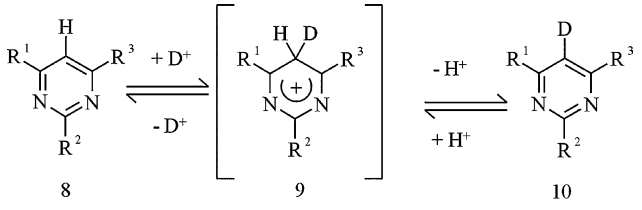
	Product	R^1	R^2	HNR^3R^4	Solvent	Yield (%)[a]	Purity (%)[b]
1	**7/1**	*n*-Hexyl	*N*-Isopropylethylamino	4-Methylpiperidin-1-yl	DMAC	89	95
2	**7/2**	2-Methylbutyl	*N*-Isopropylethylamino	4-Methylpiperidin-1-yl	DMAC	84	98
3	**7/3**	2-Methylbutyl	*N*-Isopropylethylamino	Pyrrolidin-1-yl	DMAC	89	99
4	**7/4**	2-Methylbutyl	*N*-Isopropylethylamino	Azetidin-1-yl	DMAC	87	81
5	**7/5**	*n*-Hexyl	Methyl	4-Methylpiperidin-1-yl	DMAC	95	99
6	**7/6**	2-Methylbutyl	Methyl	4-Methylpiperidin-1-yl	DMAC	94	99
7	**7/7**	2-Heptyl	Methyl	4-Methylpiperidin-1-yl	DMAC	93	99
8	**7/8**	2-Methylbutyl	Methyl	4-Phenylpiperazin-1-yl	DMAC	86	99
9	**7/9**	2-Methylbutyl	Methyl	Pyrrolidin-1-yl	DMAC	77	99
10	**7/10**	2-Heptyl	Methyl	Pyrrolidin-1-yl	DMAC	96	99
11	**7/11**	2-Methylbutyl	Methyl	Azetidin-1-yl	DMAC	84	99
12	**7/12**	2-Methylbutyl	Methyl	2-Ethylpiperidin-1-yl	DMAC	—	28
13	**7/13**	2-Methylbutyl	Methyl	2,6-Dimethylpiperidin-1-yl	DMAC	—	0
14	**7/14**	2-Methylbutyl	Methyl	Bis(*n*-butyl)amino	*n*-BuOH	82	95
15	**7/14**	2-Methylbutyl	Methyl	Bis(*n*-butyl)amino	$MeNO_2$	79	91
16	**7/15**	*n*-Hexyl	Methyl	*n*-Hexylamino	*n*-BuOH	87	98
17	**7/15**	*n*-Hexyl	Methyl	*n*-Hexylamino	$MeNO_2$	85	80
18	**7/16**	2-Methylbutyl	Methyl	*n*-Hexylamino	*n*-BuOH	85	98
19	**7/17**	2-Heptyl	Methyl	*n*-Hexylamino	*n*-BuOH	87	98
20	**7/18**	*n*-Hexyl	*N*-Isopropylethylamino	Bis(*n*-butyl)amino	THF	61	91
21	**7/19**	*n*-Hexyl	*N*-Isopropylethylamino	*n*-Hexylamino	THF	57	93

[a] The yields were determined by weight based on the loading of **4**.
[b] The purities were determined by HPLC–MS at 254 nm.

In summary, the next conditions were found to be optimal for the synthesis of **7**:

1. DMAC, 100 °C, 140 h, $c_{amine}=1.8$ mmol/1 mL solvent, for the introduction of four to six-membered unbranched cyclic aliphatic amines.
2. *n*-BuOH, 100 °C, 140 h, $c_{amine}=1.8$ mmol/1 mL solvent, for the introduction of unbranched primary and secondary aliphatic amines into 2-alkylpyrimidines.
3. Lithium amide salt of the amine, room temperature, THF, 24 h, $c_{Li-amide}=0.5$ M for the introduction of unbranched primary and secondary aliphatic amines into 2-aminopyrimidines.

We have recently showed that *N*,*N*,*N*′,*N*′,*N*″,*N*″-hexamethyl-2,4,6-pyrimidinetriamine (**8**, $R^1=R^2=R^3=NMe_2$, Fig. 1) could be carbon-protonated at the C(5) position in addition to the expected N(1) protonation.[22] We also described the synthesis of the first stable cationic sigma complex in the pyrimidine series.[24] In a forthcoming paper, we gave detailed account of the structure determination aspect of that work.[25] In the case of compound **8** ($R^1=R^2=R^3=NMe_2$) the C(5) and N(1) protonated forms could be detected simultaneously, showing that the exchange between the two protonated forms is slow on the NMR chemical shift timescale. Keeping on this track, in this paper we investigated the generality of carbon protonation of aminopyrimidines on aminopyrimidine derivatives (**5** and **7**). The C(5) protonated forms of the investigated compounds could not be detected directly due to their small population. An indirect proof, however, was observed via deuterium exchange NMR experiments (Fig. 1).



R^1: primary aliphatic amino group
R^2 : Me or -N(iPr)Et
R^3: Cl, primary or secondary aliphatic amino group

Figure 1. Deuterium exchange via the C(5) protonated sigma complex.

D_2O (5%) was added to the DMSO-d_6 solutions of selected derivatives prepared as TFA salts, and their ^1H NMR spectra were recorded at 30 °C immediately after addition of D_2O and again several hours later.

We observed nearly complete deuterium exchange of the H(5) proton for **7/1**, **7/2**, **7/3** within 1–3 h. Deuterium exchange of H(5) proceeded on a somewhat slower timescale (3–24 h) for **7/6–10**. After 2 days 70, 50 and 80% deuterium exchange was observed on the H(5) signal of **7/14**, **7/16** and **7/17**, respectively. It is interesting to note that **7/11** did not show considerable deuterium exchange, which is attributed to the presence of the strained azetidine ring. For the 4-chloro derivatives, deuterium exchange at H(5) was nearly complete for **5/2**, while **5/5** and **5/6** did not show exchange after 2 days.

The observed deuterium exchange proves the ongoing C(5) protonation indirectly, since the exchange process involves the presence of the C(5) protonated sigma complex form (**9**). The observed deuterium exchange characteristic of the investigated compounds, that is, the rate of exchange, qualitatively seems to show correlation with the electron donating effect of amino substituents. However, further investigations (precise exchange rate measurements) are required to prove this correlation.

3. Conclusion

A simple and efficient four-step strategy has been described for the solid-phase synthesis of 2,4,6-triaminopyrimidines and 2-alkyl-4,6-diaminopyrimidines. The synthetic approach provides convenient access to pharmacologically interesting aminopyrimidine derivatives in good yields and excellent purities. To the best of our knowledge, this is the first example of using 2-(4-formyl-3-methoxyphenoxy)ethyl linker for the synthesis of aminopyrimidines and the first solid-phase method applying lithium amide as nucleophile for displacing the chlorine of chloropyrimidines. Deuterium exchange experiments proved that 2,4,6-triaminopyrimidines and 2-alkyl-4,6-diaminopyrimidines have a general tendency toward C(5) protonation.

Further investigation to assess the applicability of the synthetic strategy to the automated synthesis of large aminopyrimidine libraries as well as a detailed study of C-5 protonation of aminopyrimidines are in progress.

4. Experimental

4.1. General

Reagents were obtained from Sigma-Aldrich. 2-(4-Formyl-3-methoxyphenoxy)ethyl polystyrene resin was purchased from Novabiochem (cat number: 01-64-0399, batch number: A26869, 100–200 mesh, 1% cross-linked, 1.2 mmol/g). Solvents were obtained from Merck and were used as received. Small scale parallel solid-phase reactions were performed using an Advanced ChemTech PLS 4×6 system in 8 mL glass reaction vials (1.5×5 cm) with Teflon-lined screw-cap. Cleavage and washing of the resin were performed in 8 mL Teflon vials (1.5×5 cm) equipped with a filter at the bottom.

Purity was determined by HPLC (Hewlett-Packard HP 1100) using an acetonitrile/water gradient (100% water to 95% acetonitrile v/v, with 0.1% TFA with a run time of 20 min) on a Discovery RP C_{16}–amide column (5 cm× 4.6 mm, 5 μm) operating at a flow rate of 1 mL/min; analysis was conducted at 254 nm wavelength, and retention times were recorded. The sample concentration was 1.0 mg/mL. Molecular parent ion identity was confirmed via mass spectrometry using electrospray ionization and a probe voltage of 4.0 kV.

The structures of compounds having at least 80% purity were confirmed by nuclear magnetic resonance (NMR)

spectroscopy. NMR spectra were recorded either at 300 or 500 MHz for ^{1}H and 125 or 75 MHz for ^{13}C on a Varian INOVA spectrometer. The chemical shifts are reported in ppm relative to TMS in $CDCl_3$ or in DMSO-d_6 at 30 °C. HRMS were performed on a FinninganMAT 95XP apparatus (EI, 70 eV, resolution: 10,000).

Melting points are uncorrected.

4.1.1. Resin-bound amines (2). Resin (3.0 g, 3.6 mmol) was added to a mixture of DMF (30 mL) and DCM (20 mL). Aliphatic primary amine (36 mmol) and acetic acid (36 mmol, 2.2 mL) were added dropwise. The resulting mixture was shaken for 2 h and then $NaBH(OAc)_3$ (3.68 g, 17 mmol) was added in 4 portions. After 24 h reaction at room temperature the resin was washed [3×30 mL DMF, 3×30 mL MeOH, 3×30 mL DCM, 3×30 mL DMF (5% TEA), 3×30 mL DCM (5% TEA), 3×30 mL MeOH (5% TEA), 4×30 mL MeOH, 4×30 mL DCM] and dried under vacuo for 48 h. The loading of the resin was determined by N content: **2a** (*N*-hexyl): 1.06 mmol/g (conversion=97%); **2b** (*N*-2-methylbutyl): 1.08 mmol/g (conversion=98%); **2c** (*N*-2-heptyl): 1.04 mmol/g (conversion=95%).

4.1.2. 4,6-Dichloro-2-methylpyrimidine (3a).[21] 4,6-Dihydroxy-2-methylpyrimidine (5.0 g, 0.04 mol) was stirred in $POCl_3$ (30 mL) at 140 °C for 3 h. The excess of $POCl_3$ was distilled off and the residue was poured onto crushed ice (50 g). The precipitate was filtered off and purified by silica gel column chromatography (50 g silica gel, $CHCl_3$) to give 5.4 g product (colourless crystal). Yield: 84%. Mp 46–47 °C. Mp published:[21] 49 °C. HPLC–MS: $M^+=162$ (EI); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.64 (s, 3H, CH_3), 7.18 [s, 1H, H(5)]. ^{13}C NMR ($CDCl_3$, 125 MHz, 30 °C): δ 25.7 CH_3, 118.4 C(5), 161.6, 169.8 C(4, 6), C(2).

4.1.3. 4,6-Dichloro-2-(*N*-isopropylethylamino)-pyrimidine (3b). A solution of 2,4,6-trichloropyrimidine (6.6 g, 0.036 mol) in DCM (100 mL) was cooled to −40 °C under a N_2 atmosphere. A solution of *N*,*N*-diisopropylethylamine (7.26 mL, 0.04 mol) and *N*-isopropylethylamine (4.84 mL, 0.04 mol) in DCM (100 mL) was added dropwise to the solution of trichloropyrimidine over 30 min. The reaction was allowed to warm up to room temperature over 2 h and was refluxed for 6 h. The solution was washed with water (2×200 mL), dried over Na_2SO_4, following which solvent removal was performed at reduced pressure and at temperature less than 40 °C. The 2-amino isomer was separated from its regioisomer by column chromatography (450 g silica gel, hexane/ethyl acetate=98:2). $m=3.0$ g (colourless oil). Yield=38%. HPLC–MS: $M^+=233$ (EI); ^{1}H NMR (DMSO-d_6, 500 MHz, 30 °C): δ 1.13 (t, 3H, $J=7$ Hz, CH_3CH_2N–), 1.14 (d, 6H, $J=6.5$ Hz, $(CH_3)_2CHN$–), 3.39 (q, 2H, $J=7$ Hz, CH_3CH_2N–), 4.79–4.88 [m, 1H, $(CH_3)_2CHN$–], 6.40 [s, 1H, H(5)]. ^{13}C NMR (DMSO-d_6, 125 MHz, 50 °C): δ 14.3, 20.3 [$(CH_3)_2CHN$–, CH_3CH_2N–], 37.4 CH_3CH_2N–, 47.1 $(CH_3)_2CHN$–, 107.0 C(5), 160.3, 161.2 C(2, 4, 6). Anal. Calcd for: $C_9H_{13}Cl_2N_3$; C, 46.17%; H, 5.60%; Cl, 30.28%; N, 17.95%. Found: C, 46.25%; H, 5.58%; Cl, 30.35%; N, 18.01%.

4.2. General procedure for the preparation of polymer-bound 4-chloropyrimidines (4)

To a suspension of polymer-bound amine (1.3 g, ≅1.4 mmol) **2** in DMF (4 mL) was added 4,6-dichloropyrimidine derivative **3** (20.7 mmol) and DIEA (1.25 mL, 7 mmol). The mixture was shaken for 120 h at room temperature. The polymer was filtered off, washed (3×20 mL DMF, 3×20 mL MeOH, 3×20 mL DCM, 3×20 mL MeOH, 3×20 mL DCM, 3×20 mL MeOH, 3×20 mL DCM), and dried in vacuo for 48 h to give resin **4**. Capacities of the resins ranged from 0.85 to 0.94 mmol/g based on a N content ranging from 2.7 to 3.5 mmol/g. Conversions calculated from the N content were 95–98%.

4.3. Cleavage of 4 from the resin: preparation of 6-amino-4-chloropyrimidines 5

Resin **4** (50 mg, 0.042–0.048 mmol) was shaken in DCM–TFA (9/1) (2 mL) for 2 h, then it was filtered off. The filtrate was combined with washes of DCM (2×1 mL) and MeOH (2×1 mL), the solvent was evaporated then the residue was dried under vacuo overnight to give **5**. The products as trifluoroacetate salts were obtained as glassy colourless or yellowish oils or semisolids. The weight of the products ranged from 14 to 17 mg. The yields were calculated from weight of **5** based on the loading of **4**, and ranged from 91 to 99%.

4.3.1. 6-(*n*-Hexylamino)-2-(*N*-isopropylethylamino)-4-chloropyrimidine (5/1). Yield: 96%. Glassy yellowish oil. ^{1}H NMR (DMSO-d_6, 500 MHz, 30 °C): δ 0.86 (t, 3H, $J=7$ Hz, $CH_3(CH_2)_3CH_2CH_2NH$–), 1.11 (t, 3H, $J=7$ Hz, CH_3CH_2N–), 1.12 [d, 6H, $J=7$ Hz, $(CH_3)_2CHN$–], 1.22–1.34 [m, 6H, $CH_3(CH_2)_3CH_2CH_2NH$–], 1.44–1.53 [m, 2H, $CH_3(CH_2)_3CH_2CH_2NH$–], 3.15–3.45 [br m, 4H, $CH_3(CH_2)_3CH_2CH_2NH$–, CH_3CH_2N–], 4.78 [m, 1H, $J=7$ Hz, –N$CH(CH_3)_2$], 5.70 [s, 1H, H(5)], 7.13 [br s, 1H, $CH_3(CH_2)_3CH_2CH_2NH$–]. ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.8 $CH_3(CH_2)_5NH$–, 14.9 CH_3CH_2N–, 20.1 $(CH_3)_2CHN$–, 22.0 $CH_3CH_2(CH_2)_3CH_2NH$–, 26.1 $CH_3(CH_2)_2CH_2(CH_2)_2NH$–, 28.9 $CH_3(CH_2)_3CH_2CH_2NH$–, 30.9 $CH_3CH_2CH_2(CH_2)_3NH$–, 36.1 CH_3CH_2N–, 40.4 $CH_3(CH_2)_5CH_2NH$–, 45.4 $(CH_3)_2CHN$–, 91.8 C(5), 156.7 C(6), 160.0 C(2), 163.4 C(4); HPLC–MS: $M^+=298$ (EI); Purity: 98%. HRMS: (EI), *m*/*z* [M^+] found: 298.1931, calcd for $C_{15}H_{27}^{35}ClN_4$: 298.1924.

4.3.2. 4-Chloro-2-(*N*-isopropylethylamino)-6-(2-methyl-*n*-butylamino)pyrimidine (5/2). Yield: 91%. Glassy yellowish oil. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.85 [d, 3H, $J=7$ Hz, $CH_3CH_2(CH_3)CHCH_2NH$–], 0.87 [t, 3H, $J=7$ Hz, $CH_3CH_2(CH_3)CHCH_2NH$–], 1.11 (t, $J=7$ Hz, 3H, CH_3CH_2N–), 1.12 [d, 6H, $J=7$ Hz, $(CH_3)_2CHN$–], 1.14–1.25 [m, 1H, $CH_3CH^xH^y(CH_3)CHCH_2NH$–], 1.25–1.50 [m, 1H, $CH_3CH^xH^y(CH_3)CHCH_2NH$–] 1.50–1.70 [m, 1H, $CH_3CH_2(CH_3)CHCH_2NH$–], 2.9–3.1 [m, 1H, $CH_3CH_2(CH_3)CHCH^xH^yNH$–], 3.15–3.35 [br m, 1H, $CH_3CH_2(CH_3)$- $CHCH^xH^yNH$–], 3.36 [q, 2H, $J=7$ Hz, CH_3CH_2N–], 4.78 [heptett, 1H, $J=7$ Hz, $CH_3CH_2(N$–$)CH(CH_3)_2$], 5.73 [s, 1H, H(5)], 7.21 [br s, 1H, $CH_3(CH_2)_3CH_2CH_2NH$–]. HPLC–MS: $M^+=284$ (EI); Purity: 99%. HRMS: (EI), *m*/*z* [M^+] found: 284.1774, calcd for $C_{14}H_{25}^{35}ClN_4$: 284.1768.

4.3.3. 4-Chloro-6-(2-heptylamino)-2-(*N*-isopropylethylamino)pyrimidine (5/3). Yield: 92%. Glassy yellowish oil. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.82 [t, 3H, $CH_3CH(NH–)(CH_2)_4CH_3$], 1.05–1.20 [m, 12H, $CH_3CH_2N–$, $(CH_3)_2CHN–$, $CH_3CH(NH–)(CH_2)_4CH_3$], 1.20–1.35 [m, 6H, $CH_3CH(NH–)CH_2(CH_2)_3CH_3$], 1.35–1.40 [m, 1H, $CH_3CH(NH–)CH^xH^y(CH_2)_3CH_3$], 1.40–1.55 [m, 1H, $CH_3CH(NH–)CH^xH^y(CH_2)_3CH_3$], 3.35–3.50 [q, 2H, $CH_3CH_2N–$], 4.00–4.15 [m, 1H, $CH_3CH(NH)(CH_2)_4CH_3$], 4.65–4.85 [m, 1H, $–NCH(CH_3)_2$], 5.69 [s, 1H, H(5)], 6.95 [br m, 1H, $CH_3CH(NH)(CH_2)_4CH_3$], 8.9–9.0 [br s, 1H, CF_3COOH]. HPLC–MS: $M^+=312$ (EI); Purity: 98%. HRMS: (EI), *m/z* [M^+] found: 312.2092, calcd for $C_{16}H_{29}^{35}ClN_4$: 312.2081.

4.3.4. 6-(*n*-Hexylamino)-4-chloro-2-methylpyrimidine (5/4). Yield: 94%. Glassy colourless oil. NMR (DMSO-d_6, 500 MHz): δ 0.87 [t, 3H, $J=7$ Hz, $CH_3(CH_2)_3CH_2CH_2NH–$], 1.22–1.34 [m, 6H, $CH_3(CH_2)_3CH_2CH_2NH–$], 1.50 [p, 2H, $J=7$ Hz, $CH_3(CH_2)_3CH_2CH_2NH–$], 2.32 [s, 3H, Me(C2)], 3.0–3.4 [br m, 2H, $CH_3(CH_2)_3CH_2CH_2NH–$], 6.35 [s, 1H, H(5)], 7.4–8.1 [br m, 1H, $CH_3(CH_2)_3CH_2CH_2NH–$], ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.8 $CH_3(CH_2)_4CH_2NH–$, 22.0 $CH_3CH_2(CH_2)_3CH_2NH–$, 25.2 $CH_3C(2)$, 25.9 $CH_3(CH_2)_2CH_2CH_2CH_2NH–$, 28.51 $CH_3(CH_2)_3CH_2CH_2NH–$, 30.9 $CH_3CH_2CH_2(CH_2)_3NH–$, 40.9 $CH_3(CH_2)_3CH_2CH_2NH–$, 100.6 C(5), 163.2 C(4), 167.4 C(2), The C(6) signal is broadened to the extent that it escapes detection. HPLC–MS: $M^+=227$ (EI); Purity: 99%. HRMS: (EI), *m/z* [M^+] found: 227.1178, calcd for $C_{11}H_{18}^{35}ClN_3$: 227.1189.

4.3.5. 4-Chloro-2-methyl-6-(2-methyl-*n*-butylamino)pyrimidine (5/5). Yield: 96%. Glassy colourless oil. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.86 (d, 3H, $J=6.9$ Hz, $CH_3CH_2(CH_3)CHCH_2NH–$), 0.87 (t, 3H, $CH_3CH_2(CH_3)CHCH_2NH–$), 1.05–1.20 (m, 1H, $CH_3CH^xH^y(CH_3)CHCH_2NH–$), 1.25–1.50 (m, 1H, $CH_3CH^xH^y(CH_3)CHCH_2NH–$), 1.50–1.68 (m, 1H, $CH_3CH_2(CH_3)CHCH_2NH–$), 2.31 [s, 3H, $CH_3(C2)$], 2.80–3.35 [m, 2×1H, $CH_3CH_2(CH_3)CHCH^xH^yNH–$], 6.37 [s, 1H, H(5)], 7.60 (br s, 1H, $CH_3CH_2(CH_3)CHCH_2NH–$). HPLC–MS: $M^+=213$ (EI); Purity: 97%. HRMS: (EI), *m/z* [M^+] found: 213.1039, calcd for $C_{10}H_{16}^{35}ClN_3$: 213.1033.

4.3.6. 4-Chloro-6-(2-heptylamino)-2-methylpyrimidine (5/6). Yield: 98%. Glassy colourless oil. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.85 [t, 3H, $J=6.6$ Hz, $CH_3CH(NH–)(CH_2)_4CH_3$], 1.09 [d, 3H, $J=6.6$ Hz, $CH_3CH(NH–)(CH_2)_4CH_3$], 1.18–1.35 [m, 6H, $CH_3CH(NH–)CH_2(CH_2)_3CH_3$], 1.35–1.55 [m, 2H, $CH_3CH(NH–)CH_2(CH_2)_3CH_3$], 2.31 [s, 3H, $CH_3(2)$], 4.0–4.3 [br m, 1H, $CH_3CH(NH)(CH_2)_4CH_3$], 6.2–6.4 [br s, 1H, H(5)], 7.5–7.7 [br m, 1H, $CH_3CH(NH)(CH_2)_4CH_3$]. HPLC–MS: $M^+=241$ (EI); Purity: 98%. HRMS: (EI), *m/z* [M^+] found: 241.1360, calcd for $C_{12}H_{20}^{35}ClN_3$: 241.1346.

4.4. Preparation of resin-bound 4,6-diamino- and 2,4,6-triaminopyrimidines (6)

Method A. Resin **4** (100 mg, ≅0.085–0.094 mmol) was swollen in DMAC (for reaction with four to six member cyclic amines) or in *n*-BuOH (for reaction of acyclic primary and secondary amines with 2-alkylpyrimidines) (1.0 mL), and the amine (1.7–1.84 mmol) was added. The mixture was shaken for 140 h at 100 °C. The resin was filtered off and washed (3×2 mL DMF, 3×2 mL MeOH, 3×2 mL DCM, 3×2 mL DMF, 3×2 mL MeOH, 3×2 mL DCM) to give **6**. *Method B*. (For reaction of 2,6-diamino-4-chloropyrimidines with acyclic aliphatic amines): to a solution of amine (0.85–0.94 mmol) in THF (4 mL, water content <0.01% v/v) *n*-BuLi (0.76 mmol, 0.48 mL 15% solution m/m in *n*-hexane) was added dropwise. (The vials had been dried and purged with argon previously). The reaction mixture was shaken for 20 min at room temperature. Resin **4** (0.085–0.094 mmol, 100 mg) was washed with dry THF (3×3 mL), then it was added to the solution of lithium amide. The mixture was shaken for 24 h at room temperature, and then the resin was filtered off and washed (3×4 mL MeOH, 3×4 mL THF, 3×4 mL DCM, 3×4 mL MeOH, 3×4 mL DCM).

4.5. Cleavage of 6 from the resin: preparation of 2-alkyl-4,6-diaminopyrimidines and 2,4,6-triaminopyrimidines (7)

The same procedure was followed as in the case of 6-amino-4-chloropyrimidines (**5**).

4.5.1. 6-(*n*-Hexylamino)-2-(*N*-isopropylethylamino)-4-(4-methylpiperidin-1-yl)pyrimidine (7/1). Yield: 89%. Yellowish semisolid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.88 (t, 3H, $J=7$ Hz, $CH_3(CH_2)_3CH_2CH_2NH–$), 0.92 (d, 3H, $J=6$ Hz, Pip-CH_3), 0.98–1.1 [m, 2H, Pip-H_{ax}(3, 5)], 1.15 (t, 3H, $J=7$ Hz, $CH_3CH_2N–$), 1.20 [d, 6H, $J=7$ Hz, $(CH_3)_2CHN–$], 1.22–1.40 [m, 6H, $CH_3(CH_2)_3CH_2CH_2NH–$], 1.49–1.60 [m, 2H, $CH_3(CH_2)_3CH_2CH_2NH–$], 1.64–1.74 [m, 3H, Pip-H_{eq}(3, 5), Pip-H(4)], 2.82–3.0 [m, 2H, Pip-H_{ax}(2,6)], 3.15–3.25 (br m, 2H, $CH_3(CH_2)_3CH_2CH_2NH–$), 3.35–3.42 [q, 2H, $CH_3CH_2(N–)CH(CH_3)_2$,], 4.0–4.2 [br m, 2H, Pip-H_{eq}(2,6)], 4.51 [m, 1H, $CH_3CH_2(N–)CH(CH_3)_2$], 5.35 [s, 1H, H(5)], 7.14 (br t, 1H, $CH_3(CH_2)_3CH_2CH_2NH–$), 10.54 (br s, 1H, CF_3COOH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.6, $CH_3(CH_2)_3CH_2CH_2NH–$, 14.0 $CH_3CH_2N–$, 19.6 $(CH_3)_2CHN–$, 21.2 Pip-CH_3, 21.7 $CH_3CH_2(CH_2)_4NH–$, 25.7 $CH_3(CH_2)_2CH_2(CH_2)_2NH–$, 27.6 $CH_3(CH_2)_3CH_2CH_2NH–$, 30.2 Pip-C(4), 30.7 $CH_3CH_2CH_2(CH_2)_3NH–$, 33.2 Pip-C(3, 5) 36.3 $CH_3CH_2N–$, 41.0 $CH_3(CH_2)_3CH_2CH_2NH–$, 44.3 Pip-C(2,6), 47.1 $(CH_3)_2CHN–$, 69.0 C(5), 150.4 C(2), 154.4 160.1 C(4). HPLC–MS: $M^+=361$ (EI); Purity: 95%. HRMS: (EI), *m/z* [M^+] found: 361.3211, calcd for $C_{21}H_{39}N_5$ 361.3205.

4.5.2. 6-(2-Methyl-*n*-butylamino)-4-(4-methylpiperidin-1-yl)-2-(*N*-isopropylethylamino)pyrimidine (7/2). Yield: 84%. Yellowish semisolid. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.89 [t, 3H, $J=6.3$ Hz, $CH_3CH_2CH(CH_3)CH_2NH–$], 0.91 (d, 3H, $J=5.1$ Hz, Pip-*Me*), 0.92 (d, 3H, $J=6.6$ Hz, $CH_3CH_2CH(CH_3)CH_2NH–$), 0.98–1.1 [m, 2H, Pip-H_{ax}(3, 5)], 1.1–1.3 [m, 1H, $CH_3CH^xH^yCH(CH_3)CH_2NH–$], 1.15 (t, 3H, $J=6.9$ Hz, $CH_3CH_2N–$), 1.20 [d, 6H, $J=6.9$ Hz, $(CH_3)_2CHN–$], 1.34–1.52 (br m, 1H, $CH_3CH^xH^yCH(CH_3)CH_2NH–$), 1.55–1.78 [m, 4H, Pip-H_{eq}(3, 5), Pip-H(4), $CH_3CH_2CH(CH_3)CH_2NH–$], 2.8–3.0 [br m, 2H, Pip-H_{ax}(2,6)], 3.0–3.2 [br m, 2H $CH_3CH_2CH(CH_3)CH_2NH–$], 3.37 (q, 2H, $CH_3CH_2N–$), 4.0–4.3 [br m, 2H, Pip-H_{eq}(2,6)], 4.3–4.5 [br m, 1H, $(CH_3)_2CHN–$], 5.37 [s, 1H, H(5)],

7.0–7.4 (br s, 1H, NH), 10.4–10.7 [br s, 1H, CF_3COOH]. HPLC–MS: $M^+=347$ (EI); Purity: 98%. HRMS: (EI), *m/z* [M^+] found: 347.3040, calcd for $C_{20}H_{37}N_5$: 347.3049.

4.5.3. 2-(*N*-Isopropylethylamino)-6-(2-methyl-*n*-butylamino)-4-(pyrrolidin-1-yl)pyrimidine (7/3). Yield: 89%. Yellowish foam. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.90 [t, 3H, $J=7.5$ Hz, $CH_3CH_2CH(CH_3)CH_2NH$–], 0.92 [d, 3H, $J=6.6$ Hz, $CH_3CH_2CH(CH_3)CH_2NH$–], 1.15 [t, 3H, $J=6.9$ Hz, CH_3CH_2N–], 1.10–1.18 [m, 1H, $CH_3CH^xH^yCH(CH_3)CH_2NH$–], 1.20 [d, 6H, $J=6.6$ Hz, $(CH_3)_2CHN$–], 1.30–1.50 [br m, 1H, $CH_3CH^xH^yCH(CH_3)CH_2NH$–], 1.50–1.75 [br m, 1H, $CH_3CH_2CH(CH_3)CH_2NH$–], 1.75–2.0 [m, 4H, Pyr-H(3, 4)], 2.90–3.20 [m, 2H, $CH_3CH_2CH(CH_3)CH^xH^yNH$–], 3.30–3.70 [m, 6H, CH_3CH_2N–, Pyr-H(2, 5)], 4.4–4.8 [br m, 1H, $(CH_3)_2CHN$–], 5.04 [s, 1H, H(5)], 7.1–7.3 [br s, 1H, $CH_3CH_2CH(CH_3)CH_2NH$–], 10.4–10.7 (br s, 1H, CF_3COOH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 10.7 $CH_3CH_2CH(CH_3)CH_2NH$–, 14.1 CH_3CH_2N–, 16.9 $CH_3CH_2CH(CH_3)CH_2NH$, 19.8 $(CH_3)_2CHN$–, 22.0 Pyr-C(3, 4), 27.0 $CH_3CH_2CH(CH_3)CH_2NH$–, 33.8 $CH_3CH_2CH(CH_3)CH_2NH$–, 36.1 CH_3CH_2N–, 46.5 Pyr-C(1, 5), 46.9 $CH_3CH_2CH(CH_3)CH_2NH$–, 47.5 $(CH_3)_2CHN$–, 69.9 C(5), 150.0 C(2), 153.5 C(6), 153.7 C(4). HPLC–MS: $M^+=319$ (EI); Purity: 99%. HRMS: (EI), *m/z* [M^+] found: 319.2742, calcd for $C_{18}H_{33}N_5$: 319.2736.

4.5.4. 4-(Azetidin-1-yl)-2-(*N*-isopropylethylamino)-6-(2-methyl-*n*-butylamino)pyrimidine (7/4). Yellowish semisolid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.89 [t, 3H, $J=7.5$ Hz, $CH_3CH_2CH(CH_3)CH_2NH$–], 0.92 [d, 3H, $J=7.0$ Hz, $CH_3CH_2CH(CH_3)CH_2NH$–], 1.10–1.22 [m, 1H, $CH_3CH^xH^yCH(CH_3)CH_2NH$–], 1.14 [t, 3H, $J=7$ Hz, CH_3CH_2N–], 1.19 [d, 6H, $J=7$ Hz, $(CH_3)_2CHN$–], 1.38–1.48 [br m, 1H, $CH_3CH^xH^yCH(CH_3)CH_2NH$–], 1.58–1.68 [br m, 1H, $CH_3CH_2CH(CH_3)CH_2NH$–], 2.28–2.38 [m, 2H, azetidine–H(3)], 2.90–3.20 [m, 2H, $CH_3CH_2CH(CH_3)CH^xH^yNH$–], 3.35–3.50 [m, 2H, CH_3CH_2N–], 4.00–4.15 [m, 4H, azetidine–H(2, 4)], 4.50–4.70 [br m, 1H, $(CH_3)_2CHN$–], 4.90 [s, 1H, H(5)], 7.34 [br s, 1H, $CH_3CH_2CH(CH_3)CH_2NH$–], 10.4–10.9 (br s, 1H, CF_3COOH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 10.9 $CH_3CH_2CH(CH_3)CH_2NH$–, 14.2 CH_3CH_2N–, 15.5 azetidine–C(3), 16.9 $CH_3CH_2CH(CH_3)CH_2NH$–, 19.7 $(CH_3)_2CHN$–, 26.2 $CH_3CH_2CH(CH_3)CH_2NH$–, 33.5 $CH_3CH_2CH(CH_3)CH_2NH$–, 36.3 CH_3CH_2N–, 47.0 $(CH_3)_2CHN$–, 47.3 $CH_3CH_2CH(CH_3)CH_2NH$–, 49.7 azetidine–C(2, 4), 67.9 C(5), 150.6 C(2), 153.6 C(6), 161.6 C(4). HPLC–MS: $M^+=305$ (EI); Purity: 81%. HRMS: (EI), *m/z* [M^+] found: 305.2567, calcd for $C_{17}H_{31}N_5$: 305.2579.

4.5.5. 6-(*n*-Hexylamino)-4-(4-methylpiperidin-1-yl)-2-methylpyrimidine (7/5). Yield: 95%. Colourless semisolid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.87 [t, 3H, $J=7$ Hz, $CH_3(CH_2)_3CH_2CH_2NH$–], 0.92 [d, 3H, $J=6$ Hz, *Me*-Pip], 0.98–1.12 [m, 2H, Pip-H_{ax}(3, 5)], 1.24–1.38 [m, 6H, $CH_3(CH_2)_3CH_2CH_2NH$–], 1.54 [p, 2H, $J=7$ Hz, $CH_3(CH_2)_3CH_2CH_2NH$–], 1.64–1.76 [m, 3H, Pip-H_{eq}(3, 5), Pip-H(4)], 2.36 [s, 3H, Me(C2)], 2.90–3.10 [m, 2H, Pip-H_{ax}(2,6)], 3.20–3.30 [m, 2H, $CH_3(CH_2)_3CH_2CH_2NH$–], 3.90–4.80 [br m, 2H, Pip-H_{eq}(2,6)], 5.74 [s, 1H, H(5)], 8.31 [m, 1H, $CH_3(CH_2)_3CH_2CH_2NH$–]. ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.7 $CH_3(CH_2)_3CH_2CH_2NH$–, 21.3 Pip-CH_3, Me(C2), 21.9 $CH_3CH_2(CH_2)_3CH_2NH$–, 25.8 $CH_3(CH_2)_2CH_2(CH_2)_2NH$–, 27.9 $CH_3(CH_2)_3CH_2CH_2NH$–, 30.1 Pip-C(4), 30.8 $CH_3CH_2CH_2(CH_2)_3NH$–, 33.3 Pip-C(3, 5), 41.2 $CH_3(CH_2)_3CH_2CH_2NH$–, 44.7 Pip-C(2,6), 75.6 C(5), 154.7 C(6), 158.5 C(2), 159.7 C(4). HPLC–MS: $M^+=290$ (EI); Purity: 99%. HRMS: (EI), *m/z* [M^+] found: 290.2479, calcd for $C_{17}H_{30}N_4$: 290.2470.

4.5.6. 2-Methyl-6-(2-methyl-*n*-butylamino)-4-(4-methylpiperidin-1-yl)pyrimidine (7/6). Yield: 94%. Yellowish semisolid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.87 [t, 3H, $J=7.5$ Hz, $CH_3CH_2CH(CH_3)CH_2NH$–], 0.90 [d, 3H, $J=7.5$ Hz, $CH_3CH_2CH(CH_3)CH_2NH$–], 0.92 [d, 3H, $J=7$ Hz, Pyp-CH_3], 0.98–1.12 [br m, 2H, Pip-H_{ax}(3, 5)], 1.12–1.22 [m, 1H $CH_3CH_xH_yCH(CH_3)CH_2NH$–], 1.38–1.48 [m, 1H, CH_3CH_x-$H_y$$CH(CH_3)CH_2NH$–], 1.60–1.76 [br m, 4H, Pip-H_{eq}(3, 5), Pip-H(4), $CH_3CH_2CH(CH_3)CH_2NH$–], 2.36 [s, 3H, Me-C(2)], 2.8–3.04 [m, 2H, Pip-H_{ax}(2,6)], 3.05–3.13 [m, 1H, $CH_3CH_2CH(CH_3)CH_xH_yNH$–], 3.14–3.22 [m, 1H, CH_3CH_2-$CH(CH_3)CH_xH_yNH$–], 3.9–4.6 [br m, 2H, Pip-H_{eq}(2,6)], 5.75 [s, 1H, H(5)], 8.15 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 10.9 $CH_3CH_2CH(CH_3)CH_2NH$–, 16.8 CH_3-$CH_2CH(CH_3)CH_2NH$–, 21.3 Me-C(2), Pip-CH_3, 26.2 CH_3-$CH_2CH(CH_3)CH_2NH$–, 30.1 Pip-C(4), 33.3 Pip-C(3, 5), 33.7 $CH_3CH_2CH(CH_3)CH_2NH$–, 44.7 Pip-C(2,6), 46.8 CH_3CH_2-$CH(CH_3)CH_2NH$–, 75.6 C(5), 154.6 C(6), 158.4, 158.8 C(2, 4). HPLC–MS: $M^+=276$ (EI); Purity: 99%. HRMS: (EI), *m/z* [M^+] found: 276.2325, calcd for $C_{16}H_{28}N_4$: 276.2309.

4.5.7. 6-(2-Heptylamino)-2-methyl-4-(4-methylpiperidin-1-yl)pyrimidine (7/7). Yield: 93%. Yellowish semisolid. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.86 [t, 3H, $J=6.9$ Hz, $CH_3CH(NH$–$)(CH_2)_4CH_3$], 0.92 (d, 3H, $J=6.3$ Hz, Pip-*Me*), 0.98–1.10 [m, 2H, Pip-H_{ax}(3, 5)], 1.13 [d, 3H, $J=6.3$ Hz, $CH_3CH(NH$–$)(CH_2)_4CH_3$], 1.18–1.40 [m, 6H, CH_3-$CH(NH$–$)CH_2(CH_2)_3CH_3$], 1.40–1.58 [m, 2H, $CH_3CH(NH$–$)$ $CH_2(CH_2)_3CH_3$], 1.60–1.78 [m, 3H, Pip-H_{eq}(3, 5), Pip-H(4)], 2.36 [s, 3H, Me-C(2)], 2.85–3.20 [m, 2H, Pip-H_{ax}(2,6)], 3.70–3.90 [m, 2H, Pip-H_{eq}(2,6)], 4.0–4.60 [br m, 1H, $CH_3CH(NH$–$)(CH_2)_4CH_3$], 5.76 [s, 1H, H(5)], 8.01 (d, 1H, $J=8.4$ Hz, NH). HPLC–MS: $M^+=304$ (EI); Purity: 99%. HRMS: (EI), *m/z* [M^+] found: 304.2622, calcd for $C_{18}H_{32}N_4$: 304.2627.

4.5.8. 2-Methyl-4-(4-phenylpiperazin-1-yl)-6-(2-methyl-*n*-butylamino)pyrimidine (7/8). Yield: 86%. Red glassy oil. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.89 [t, 3H, $J=7.2$ Hz, $CH_3CH_2CH(CH_3)CH_2NH$–], 0.91 [d, 3H, $J=6.9$ Hz, $CH_3CH_2CH(CH_3)CH_2NH$–], 1.10–1.30 [m, 1H, $CH_3CH^xH^yCH(CH_3)CH_2NH$–], 1.36–1.54 [m, 1H, $CH_3CH^xH^yCH(CH_3)CH_2NH$–], 1.59–1.75 [m, 1H, CH_3-$CH_2CH(CH_3)CH_2NH$–], 2.39 [s, 3H, Me-C(2)], 3.0–3.30 [m, 2H, $CH_3CH_2CH(CH_3)CH^xH^yNH$–], 3.70–4.0 [m, 8H, piperazine,], 5.85 [s, 1H, H(pyrimidin–C5)], 6.78–6.86 (m, 1H), 6.95–7.04 (m, 2H), 7.20–7.30 (m, 2H) (phenyl-H), 8.0–8.20 (br s, 1H, NH). HPLC–MS: $M^+=339$ (EI); Purity: 99%. HRMS: (EI), *m/z* [M^+] found: 339.2410, calcd for $C_{20}H_{29}N_5$: 339.2423.

4.5.9. 2-Methyl-6-(2-methyl-*n*-butylamino)-4-(pyrrolidin-1-yl)pyrimidine (7/9). Yield: 77%. Yellowish semisolid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.88 (t, 3H, $J=7.5$ Hz, $CH_3CH_2(CH_3)CHCH_2NH$–), 0.90 (d, 3H,

J=6.5 Hz, $CH_3CH_2(CH_3)CHCH_2NH$–), 1.11–1.21 [m, 1H, $CH_3CH^xH^y(CH_3)CHCH_2NH$–], 1.37–1.47 [m, 1H, $CH_3CH^xH^y(CH_3)CHCH_2NH$–], 1.60–1.70 [m, 1H, $CH_3CH_2(CH_3)CHCH_2NH$–], 1.84–2.06 [m, 4H, Pyr-H(3, 4)], 2.38 [s, 3H, Me-C(2)], 3.0–3.3 [br m, 2H, $CH_3CH_2(CH_3)CHCH^xH^yNH$–], 3.30–3.65 [br m, 4H, Pyr-H(2, 5)], 5.41 [s, 1H, H(5)], 7.99 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 10.9 $CH_3CH_2(CH_3)CHCH_2NH$–, 16.8 $CH_3CH_2(CH_3)CHCH_2NH$–, 21.3 CH_3(2), 24.5 Pyr-C(3, 4), 26.2 $CH_3CH_2(CH_3)CHCH_2NH$–, 33.7 $CH_3CH_2(CH_3)CHCH_2NH$–, 46.9 $CH_3CH_2(CH_3)CHCH_2NH$–, 47.2 Pyr-C(2, 4), 76.0 C(5), 158.4, 158.7, 159.0 C(2, 4, 6). HPLC–MS: M^+ = 248 (EI); Purity: 99%. HRMS: (EI), m/z [M^+] found: 248.2011, calcd for $C_{14}H_{24}N_4$: 248.2001.

4.5.10. 6-(2-Heptylamino)-2-methyl-4-(pyrrolidin-1-yl)pyrimidine (7/10). Yield: 96%. Yellowish foam. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.86 [t, 3H, J=6.6 Hz, $CH_3CH(NH$–$)(CH_2)_4CH_3$], 1.13 [d, 3H, J=6.6 Hz, $CH_3CH(NH$–$)(CH_2)_4CH_3$], 1.20–1.58 [br m, 8H, $CH_3CH(NH$–$)CH_2(CH_2)_3CH_3$], 1.84–2.08 [br m, 4H, Pyr-H(3, 4)], 2.38 [s, 3H, Me-C(2)], 3.20–3.60 [br m, 4H, Pyr-H(2, 5)], 4.20–5.20 [br m, 1H, $CH_3CH(NH$–$)(CH_2)_4CH_3$], 5.41 [s, 1H, H(5)], 8.05 (d, 1H, J=8.4 Hz, NH). HPLC–MS: M^+=276 (EI); Purity: 99%. HRMS: (EI), m/z [M^+] found: 276.2324, calcd for $C_{16}H_{28}N_4$: 276.2314.

4.5.11. 4-(Azetidin-1-yl)-2-methyl-6-(2-methyl-*n*-butylamino)pyrimidine (7/11). Yield: 84%. Yellowish glassy oil. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.86 [t, 3H, J=6.6 Hz, $CH_3CH_2CH(CH_3)CH_2NH$–], 0.88 [d, 3H, J=6.6 Hz, $CH_3CH_2CH(CH_3)CH_2NH$–], 1.08–1.24 [br m, 1H, $CH_3CH^xH^yCH(CH_3)CH_2NH$–], 1.32–1.50 [br m, 1H, $CH_3CH^xH^yCH(CH_3)CH_2NH$–], 1.54–1.74 [br m, 1H, $CH_3CH_2\ CH(CH_3)CH_2NH$–], 2.36 [s, 3H, Me-C(2)], 2.90–3.30 [br m, 2H, $CH_3CH_2CH(CH_3)CH^xH^yNH$–], 4.0–4.30 (m, 6H, azetidine–H), 5.26 [s, 1H, H(5)], 8.05–8.25 (br s, 1H, NH). HPLC–MS: M^+=234 (EI); Purity: 99%. HRMS: (EI), m/z [M^+] found: 234.1857, calcd for $C_{13}H_{22}N_4$: 234.1844.

4.5.12. 4-(2-Ethylpiperidin-1-yl)-2-methyl-6-(2-methyl-*n*-butylamino)pyrimidine (7/12). Yellowish oil. HPLC–MS: M^+=290 (EI); Purity: 28%. HRMS: (EI), m/z [M^+] found: 290.2478, calcd for $C_{17}H_{30}N_4$: 290.2470.

4.5.13. 4-Bis(*n*-butyl)amino-2-methyl-6-(2-methyl-*n*-butylamino)pyrimidine (7/14). Yield: 82% Yellowish semisolid. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.84–0.98 [m, 12H, $CH_3CH_2CH(CH_3)CH_2NH$–, $(CH_3(CH_2)_2CH_2)_2N$–], 1.08–1.72 [m, 11H, $CH_3CH^xH^yCH(CH_3)CH_2NH$–, $(CH_3(CH_2)_2CH_2)_2N$–], 2.35 [s, 3H, Me-C(2)], 2.90–3.20 [m, 2H, $CH_3CH_2CH(CH_3)CH^xH^yNH$–], 3.20–3.70 [br m, 4H, $(CH_3(CH_2)_2CH_2)_2N$–], 5.50 [s, 1H, H(5)], 7.86 (br s, 1H, NH). HPLC–MS: M^+=306 (EI); Purity: 95%. HRMS: (EI), m/z [M^+] found: 306.2771, calcd for $C_{18}H_{34}N_4$: 306.2783.

4.5.14. 4,6-Bis(*n*-hexylamino)-2-methylpyrimidine (7/15). Yield: 87%. Yellowish semisolid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.87 [t, 6H, J=7 Hz, $CH_3(CH_2)_4CH_2NH$–], 1.22–1.36 [m, 12H, $CH_3(CH_2)_3CH_2CH_2NH$–], 1.52 [p, 4H, J=7 Hz, $CH_3(CH_2)_3CH_2CH_2NH$–], 2.31 [s, 3H, Me(C2)], 3.10–3.30 [br m, 4H, $CH_3(CH_2)_3CH_2CH_2NH$–], 5.39 [s, 1H, H(5)], 7.82 [br m, 2H, $CH_3(CH_2)_3CH_2CH_2NH$–]. ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.8 $CH_3(CH_2)_4CH_2NH$–, 21.8 br, MeC(2), 22.0 $CH_3CH_2(CH_2)_3CH_2NH$–, 25.9 $CH_3(CH_2)_2CH_2CH_2CH_2NH$–, 28.1 $CH_3(CH_2)_3CH_2CH_2NH$–, 30.8 $CH_3CH_2CH_2(CH_2)_3NH$–, 40.9 $CH_3(CH_2)_3CH_2CH_2NH$–, 75.5 C(5), 156.0–162.0 br, C(2, 4, 6). HPLC–MS: M^+= 292 (EI); Purity: 98%. HRMS: (EI), m/z [M^+] found: 292.2622, calcd for $C_{17}H_{32}N_4$: 292.2627.

4.5.15. 6-(*n*-Hexylamino)-2-methyl-4-(2-methyl-*n*-butylamino)pyrimidine (7/16). Yield: 85%. Yellowish semisolid. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.80–0.96 [m, 9H, $CH_3(CH_2)_4CH_2NH$–, $CH_3CH_2CH(CH_3)CH_2NH$–], 1.08–1.70 [m, 11H, $CH_3(CH_2)_4CH_2NH$–, $CH_3CH_2CH(CH_3)CH_2NH$–], 2.36 [s, 3H, Me-C(2)], 2.80–3.40 [br m, 4H, $CH_3(CH_2)_4CH_2NH$–,$CH_3CH_2CH(CH_3)CH_2NH$–], 5.47 [s, 1H, H(5)], 7.7–8.4 (br s, 2H, NH). HPLC–MS: M^+=278 (EI); Purity: 98%. HRMS: (EI), m/z [M^+] found: 278.2461, calcd for $C_{16}H_{30}N_4$: 278.2470.

4.5.16. 4-(2-Heptylamino)-6-(*n*-hexylamino)-2-methylpyrimidine (7/17). Yield: 87%. Yellowish semisolid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.87 [q, 6H, J=7 Hz, $CH_3(CH_2)_4CH_2NH$–, $CH_3CH(NH$–$)(CH_2)_4CH_3$], 1.13 [d, 3H, J=6.5 Hz, $CH_3CH(NH$–$)(CH_2)_4CH_3$], 1.18–1.35 [m, 12H, $CH_3(CH_2)_3CH_2CH_2NH$–, $CH_3CH(NH$–$)CH_2(CH_2)_3CH_3$], 1.40–1.65 [m, 4H, $(CH_2)_3CH_2CH_2NH$–, $CH_3CH(NH$–$)CH_2(CH_2)_3CH_3$], 2.34 [s, 3H, Me-C(2)], 3.0–3.40 [br m, 2H, $CH_3(CH_2)_3CH_2CH_2NH$–], 3.50–4.00 [br m, 1H, $CH_3CH(NH$–$)(CH_2)_4CH_3$], 5.46 [s, 1H, H(5)], 8.14 (br m, 2H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.7 $CH_3(CH_2)_4CH_2NH$–, $CH_3CH(NH$–$)(CH_2)_4CH_3$, 19.9 $CH_3CH(NH$–$)(CH_2)_4CH_3$, 21.1 Me(C2), 21.9 $CH_3CH_2(CH_2)_4NH$–, $CH_3CH(NH$–$)(CH_2)_3CH_2CH_3$, 25.0 $CH_3CH(NH$–$)CH_2CH_2(CH_2)_2CH_3$, 25.9 $CH_3(CH_2)_2CH_2(CH_2)_2NH$–, 27.9 $CH_3(CH_2)_3CH_2CH_2NH$–, 30.8 $CH_3CH_2CH_2(CH_2)_3NH$–, 31.0 $CH_3CH(NH$–$)(CH_2)_2CH_2CH_2CH_3$, 35.6 $CH_3CH(NH$–$)CH_2(CH_2)_3CH_3$, 41.1 $CH_3(CH_2)_3CH_2CH_2NH$–, 47.0 $CH_3CH(NH$–$)(CH_2)_4CH_3$, 73.5–76.8 br, C(5), 156–163 br, C(2, 4, 6). HPLC–MS: M^+=306 (EI); Purity: 98%. HRMS: (EI), m/z [M^+] found: 306.2795, calcd for $C_{18}H_{34}N_4$: 306.2783.

4.5.17. 4-Bis(*n*-butyl)amino-6-(*n*-hexylamino)-2-(*N*-isopropylethylamino)pyrimidine (7/18). Yield: 61%. Yellowish semisolid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.88 [t, 3H, J=7 Hz, $CH_3(CH_2)_4CH_2NH$–], 0.90 [m, 6H, (CH_3 $(CH_2)_2CH_2)_2N$–], 1.14 (t, 3H, J=7 Hz, CH_3CH_2N–), 1.19 [d, 6H, J=7 Hz, $(CH_3)_2CHN$–], 1.22–1.37 [m, 10H, $CH_3(CH_2)_3CH_2CH_2NH$–, $(CH_3CH_2CH_2CH_2)_2N$–], 1.48–1.60 [m, 6H, $CH_3(CH_2)_3CH_2CH_2NH$–, $(CH_3CH_2CH_2CH_2)_2N$–], 3.18 [m, 2H, $CH_3(CH_2)_4CH_2NH$–], 3.36 [m, 2H, $CH_3(CH_2)_2CH_2^xN(-)CH_2^y(CH_2)_2CH_3$], 3.42 [q, 2H, J=7 Hz, CH_3CH_2N–], 3.51 [m, 2H, $CH_3(CH_2)_2CH_2^xN(-)CH_2^y(CH_2)_2CH_3$], 4.55 [br m, 1H, $(CH_3)_2CHN$–], 5.08 [s, 1H, H(5)], 7.28 (s, 1H, NH), 10.70 (br s, 1H, CF_3COOH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.6 ($CH_3(CH_2)_2CH_2)_2N$–, 13.8 $CH_3(CH_2)_4CH_2NH$–, 14.4 CH_3CH_2N–, 19.4 $(CH_3CH_2CH_2CH_2)_2N$–, 19.8 $(CH_3)_2CHN$–, 21.9 $CH_3CH_2(CH_2)_3CH_2N$–, 25.9 $CH_3(CH_2)_2CH_2CH_2CH_2N$–, 27.9 $CH_3(CH_2)_3CH_2CH_2N$–, 29.2 $CH_3CH_2CH_2^XCH_2N(-)CH_2CH_2^yCH_2CH_3$, 29.7 $CH_3CH_2CH_2^xCH_2N(-)CH_2CH_2^yCH_2CH_3$, 30.8 $CH_3CH_2CH_2(CH_2)_3N$–, 36.2 CH_3CH_2N–, 41.2

$CH_3(CH_2)_4CH_2N$–, 47.2 $(CH_3)_2CHN$–, 47.8 $(CH_3CH_2CH_2$-$CH_2)_2N$–, 69.1 C(5), 150.15 C(2), 153.8 C(6), 158.20 br, C(4). HPLC–MS: $M^+=391$ (EI); Purity: 91%. HRMS: (EI), *m/z* [M^+] found: 391.3668, calcd for $C_{23}H_{45}N_5$: 391.3675.

4.5.18. 4,6-Bis(*n*-hexylamino)-2-(*N*-isopropylethylamino)pyrimidine (7/19). Yield: 57%. Yellowish semisolid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.87 [t, 6H, $J=7$ Hz, $CH_3(CH_2)_4CH_2NH$–], 1.14 [t, 3H, $J=7$ Hz, CH_3CH_2N–], 1.19 [d, 6H, $J=6.5$ Hz, $(CH_3)_2CHN$–], 1.22–1.40 [br m, 12H, $CH_3(CH_2)_3CH_2CH_2NH$–], 1.44–1.62 [br m, 4H, $CH_3(CH_2)_3CH_2CH_2NH$–], 3.0–3.30 [br m, 4H, $CH_3(CH_2)_3CH_2CH_2NH$–], 3.30–3.50 [br m, 2H, CH_3CH_2N–], 4.45–4.70 [br m, 1H, $(CH_3)_2CHN$–], 5.03 [s, 1H, H(5)], 7.60–8.20 [br m, 2H, $CH_3(CH_2)_3CH_2CH_2NH$–], 10.72 [br m, 1H, CF_3COOH]. ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.8 $CH_3(CH_2)_4CH_2NH$–, 14.4 CH_3CH_2N–, 19.8 $(CH_3)_2CHN$–, 221.0 $CH_3CH_2(CH_2)_3CH_2NH$–, 26.0 $CH_3(CH_2)_2CH_2CH_2CH_2NH$–, 26.9 $CH_3(CH_2)_3CH_2CH_2$-NH–, 30.9 $CH_3CH_2CH_2(CH_2)_3NH$–, 38.8.CH_3CH_2N–, 41.3 $CH_3(CH_2)_3$ CH_2CH_2NH–, 47.4 $(CH_3)_2CHN$–, 70.8 C(5), Signals due to the C(2, 4, 6) carbons could not be detected. HPLC–MS: $M^+=363$ (EI); Purity: 93%. HRMS: (EI), *m/z* [M^+] found: 363.3369, calcd for $C_{21}H_{41}N_5$: 363.3362.

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Novel annulated products from aminonaphthyridinones

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Abstract—2-(4-Methoxyphenyl)-1-oxo-1,2-dihydro-1,6-naphthyridine-4-carboxamide (**4c**) underwent Hofmann rearrangement with iodobenzene diacetate in methanol to give the corresponding 4-amino compound (**6c**). This, when reacted with 2,4-pentanedione and then hot phosphoryl chloride (attempted Combes synthesis) gave a new heterocyclic system, 6-(4-methoxyphenyl)-2-methylpyrido[3,2-*c*]pyrrolo[2,3-*e*]azocin-7(6*H*)-one (**9c**). This showed typical pyrrole-type reactivity at the 3-position. Alternatively, an attempt to convert the 4-NH_2 in **6c** to 4-OH by diazotization gave, instead, a [1,2,3]triazolo[1,5-*a*]pyridine-3-carboxaldehyde (**16c**). The same series of reactions on a benzo analog, 2-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxamide (**4a**), gave the same results.

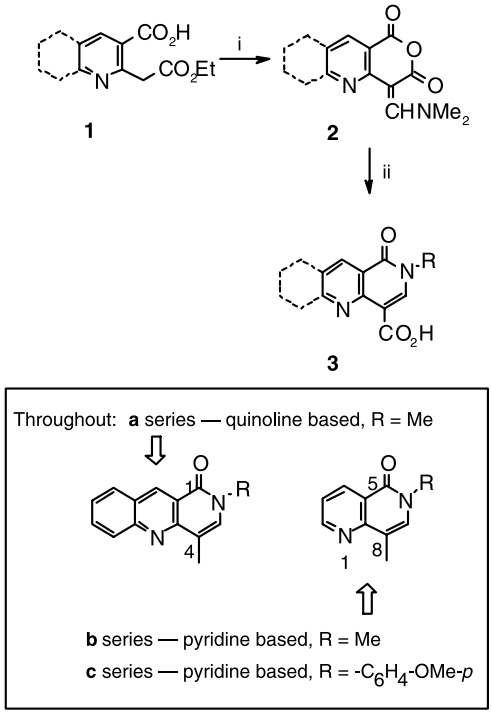
1. Introduction

We have previously demonstrated a useful transformation in which tricyclic dione **2a**, readily prepared by reaction of Vilsmeier reagent on the quinoline derivative **1a**, are converted to acids **3** by reaction with a range of primary amines (Scheme 1), and carboxamides derived from the tricyclic series have revealed potent antitumor activity.[1] As part of a continuing search for new heterocyclic systems as precursors of pharmacologically active derivatives, we sought to convert the carboxyl group in **3** (now extended to bicyclic, pyridine-based analogs) to amino and then build a further ring by any of various well known methods. This paper reports on success with the former and some unexpected findings during the latter.

2. Results and discussion

2.1. Preparation of the amino compounds

Classical methods for the change $-CO_2H \rightarrow -NH_2$ include the Hofmann[2a,3] and Curtius[4] rearrangements. We have concentrated on the former, and the necessary amide intermediates **4** were prepared by standard conversion to the acyl chloride followed by reaction with ammonia (Scheme 2). Many variations on the original bromine/aqueous sodium hydroxide rearrangement conditions have been reported. Of particular interest was a method which used iodobenzene diacetate in methanol under mild conditions.[5] In the present research, this worked well to give methyl carbamates **5**, which were hydrolyzed in alkali to liberate the amines **6**; the procedure was optimized so that it was not necessary to isolate the carbamates.



Scheme 1. (i) DMF–$POCl_3$/0 °C, then 20 °C/2 h; (ii) DMF+2.5 mol $MeNH_2$–THF for a, b; 3 mol anisidine+4 mol NEt_3 for c. All: 20 °C/16 h.

An interesting observation was that, for no obvious reason, the stability of **6** was quite variable. Amine **6b** was quite unstable;

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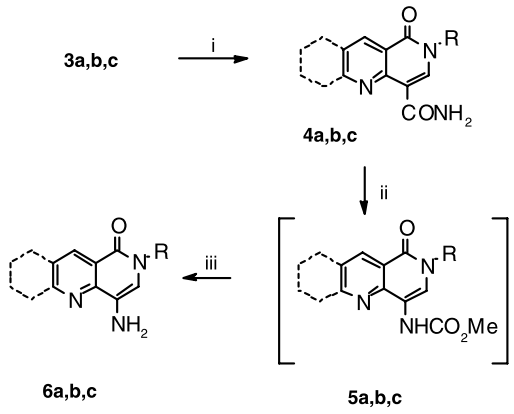
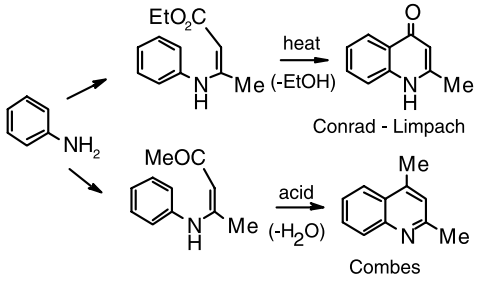


Scheme 2. (i) $SOCl_2$/reflux 0.5 h. Evap, add CH_2Cl_2. Bubble $NH_{3(g)}$; (ii) 1.1 mol $PhI(OAc)_2$/5 mol KOH/MeOH/5 °C, then 20 °C/0.5 h; (iii) Add 10 mol KOH/H_2O/reflux 3 h.

this compound had been previously reported by a different, longer sequence and noted to be unstable.[6] Some other examples not covered in the present paper were also unstable but, on the other hand, **6a** (same NR group as **6b**) and **6c** (same bicyclic system but different R group) were stable solids.

2.2. Attempted Combes synthesis

The construction of a further ring onto aniline is the basis of many classic syntheses of quinoline derivatives. In particular, β-keto esters (or ethoxymethylenemalonates) lead to quinolin-4-ones (Conrad–Limpach synthesis).[7a] The closely related Combes synthesis uses β-diketones as the 3-carbon source and acidic conditions for cyclization of the intermediate[7b] (Scheme 3), and these general pathways are applicable to many other aromatic amines.

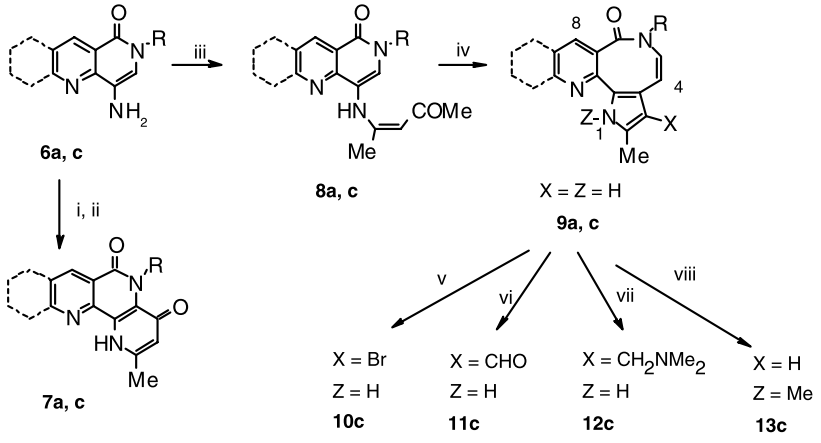


Scheme 3.

The Conrad–Limpach synthesis with ethyl acetoacetate proceeded as expected. By the standard route, a six-membered ring was added to the bicyclic **6c** and tricyclic **6a** to give **7c** and **7a**, respectively (Scheme 4).

The first step of the Combes synthesis, condensation with 2,4-pentanedione, gave the isolable intermediates **8**, sufficiently pure for direct further use. However, treatment with concentrated sulfuric acid or polyphosphoric acid at 100 °C failed to produce the desired cyclized product. The products were neither purified nor identified, but it was clear from ^{1}H NMR analysis that the sidechains had been lost.

At this point, we noted a literature report where sulfuric acid produced 'unsatisfactory results' but where hot phosphoryl chloride gave the desired product.[8] When applied to **8c**, a substantial amount of a fawn solid was isolated, but early NMR analysis showed this was not the expected product (see Scheme 3); while the carbon count was the same as in **8c**, there was only one methyl signal, and there were three single proton signals in the region 5.9–6.3 ppm, not expected for a fully aromatic product. Elemental analysis was in accord with a formula equivalent to a loss of water from **8c** (giving a yield of 77%), and the novel structure **9c** was assigned from analysis of data from various NMR experiments. Particularly informative were data for these three protons showing in the alkene region of the ^{1}H NMR spectrum, now assigned as H-3 (δ 5.85, s), H-4 (δ 6.27, d, J=8.1 Hz), and H-5 (δ 6.13, d, J=8.1 Hz). $^3J_{CH}$ couplings were crucial; from H–Me to C-3, from H-5 to the low field C-7 (these fixed both ends of the 6 carbon sequence C–Me–C-5), from both H-3 and H-4 to the same quaternary carbon, C-11b. The absence of coupling between H-3 and H-4 was consistent with the intermediacy of the quaternary carbon, C-3a, which did show $^3J_{CH}$ coupling to H-1 and H-5. The mechanism of this overall dehydration reaction, and the reason why the conventional six-membered annulation did not occur, is unclear. The enol form of the side chain, probably as a phosphorus-containing derivative, is a likely initiator of a sequence of ring forming and ring opening steps to create the five- and eight-membered rings.



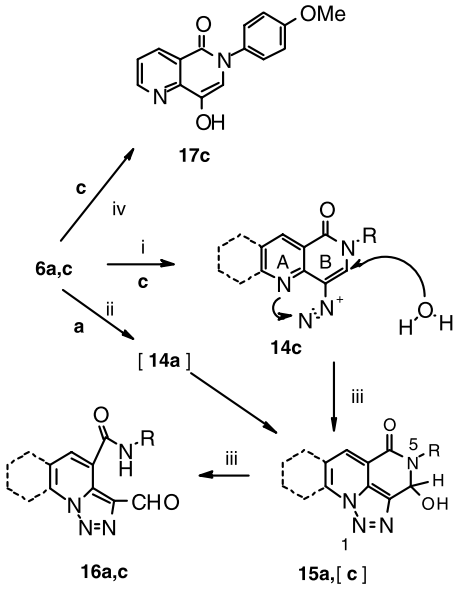
Scheme 4. (i) $AcCH_2CO_2Et/CaSO_4$/HOAc/EtOH/reflux 3.5 h; (ii) Ph_2O/250 °C/15 min; (iii) acac/$CaSO_4$/HOAc/EtOH/reflux 3.5 h, (iv) $POCl_3$/reflux 1 h; (v) Br_2/CH_2Cl_2/20 °C/10 min; (vi) 35 equiv $POCl_3$–DMF/DMF/0 °C/1 h; (vii) $Me_2NH_2^+Cl^-/(CH_2O)n$/EtOH/50 °C/4 h; (viii) MeI/C_6H_6–25%NaOH/TBAHS/stir vigorously 20 °C/24 h.

The tetracyclic analogue **9a** (64%) was formed in the same way from **6a**.

The ready availability of this new system prompted some further chemistry to check out the potential reactivity of the azocine and/or pyrrole rings. It appears that the 4,5-double bond in the former is reasonably stable while the latter readily undergoes typical pyrrole reactions at the available 1- and 3-positions (the work was confined to the more accessible **9c**). Thus, bromination with bromine in chloroform was immediate to give **10c** (92%), Vilsmeier reaction gave the aldehyde **11c** (83%), the Mannich reaction with dimethylamine hydrochloride and paraformaldehyde gave a 64% yield of **12c**, while reaction with methyl iodide under phase transfer conditions, as for indole,[9] gave the anticipated *N*-methyl product **13c** (88%). The ability to readily attach reactive functionalities to the 3-position potentially opens the way to further derivatization, and hence to interesting compounds for pharmacological testing.

2.3. Diazotization of the amines

A second, quite different type of reaction on the amino compounds **6a**, **6c** also led to unexpected annulation products (Scheme 5).



Scheme 5. (i) $NaNO_2$/43% HBF_4/H_2O/0 °C/1 h; (ii) $NaNO_2$/43% HBF_4/H_2O/20 °C/1 h, then MeCN/H_2O/5 min; (iii) 1% NaOH/20 °C/1 h; (iv) 5 mol $Na_2S_2O_5$/H_2O/reflux 4 h, then 10 mol NaOH/reflux 24 h.

The aim was to convert the amino to a hydroxy function, to prepare analogues of 8-hydroxyquinoline. A traditional way of achieving this conversion for aromatic amines is by hydrolysis of an intermediate diazonium salt.[2b] When **6c** in fluoroboric acid at 0 °C was treated with aqueous sodium nitrite,[10] a solid was precipitated. This was unstable in most solvents, for example, DMSO (immediate bubbling) but a ^{1}H NMR spectrum was obtained in acetone. Its general form suggested that the bicyclic system was intact and the compound was most likely the anticipated diazonium salt **14c**. The IR spectrum contained a strong band at 2228 cm^{-1}, consistent with the presence of the N≡N group.[11] When this salt was suspended in water and treated with 10% sodium hydroxide, a white solid resulted, which was not the target hydroxy compound but, rather, the triazolopyrido aldehyde **16c**. The formation of the triazole ring was indirectly suggested by a characteristic change in chemical shifts (proton and carbon) and coupling constants (proton) of the A ring atoms compared with **6c** and **14c**. Cleavage of the B ring was clear from characteristic NMR aldehyde signals [δ 10.22 (^{1}H), 183.3 (^{13}C) ppm], while assignment of the singlet at δ 10.48 ppm as the NH proton was based on its exchange with D_2O and $^3J_{CH}$ coupling with *ortho* protons in the R group (–C_6H_4–OMe-*p*) in the HMBC spectrum.

While the triazolopyridine system is not new, this method of formation is novel. The best standard synthesis appears to be by heating the tosylhydrazone of a pyridine-2-carboxaldehyde in morpholine at 95–100 °C.[12] A plausible mechanism in the present case requires that, reasonably, position 7 in **14c** is more electron deficient than position 8 and hydrolysis occurs here as shown in Scheme 5. In this case, the presumed intermediate **15c** was not isolated. There is precedence for water attack at an alternative highly electron deficient centre in a diazonium derivative of a quinolizinium ion.[13] It is noteworthy that in the sequence of Scheme 5, in contrast to the formation of compounds **9** earlier, cleavage of the naphthyridinone ring occurs at the N-6–C-7 bond.

While the same final result was obtained from the tricyclic **14a**, some interesting differences emerged. For solubility reasons, the diazotization reaction had to be carried out at room temperature. A pink solid separated immediately but, in this case, it was not the diazonium salt. The NMR resolution was improved following precipitation of a white solid by water addition to an acetonitrile solution. For this compound, the ^{1}H NMR spectrum was able to be obtained in DMSO and contained, in addition to the expected aromatic proton signals, two doublets at δ 6.35 and 7.11 ppm (J= 9.5 Hz). The latter disappeared on addition of D_2O while the former became a singlet. This compound was therefore assigned structure **15a**, the proposed immediate hydrolysis product of the diazonium salt, and apparently more stable in the tricyclic than bicyclic case. Rapid isomerization to the ring-open aldehyde **16a** was brought about by treatment with 1% aqueous NaOH. In this case where R=Me, the methyl signal in the NMR spectrum occurred as a doublet (J=4.4 Hz), providing further evidence for the ring cleavage having resulted in formation of the NH group. Interestingly, the above DMSO/D_2O NMR sample of **15a** quite rapidly changed to a mixture of **15a** and **16a**.

2.4. Corollary

The synthesis of the hydroxy compound **17c** has been achieved by reaction of **6c** with aqueous bisulfite, the Bucherer reaction[14] (Scheme 5). This was interesting as the Bucherer reaction is of limited scope and is typically applied to naphthalene derivatives. However, the yield of **17c** was unaccountably variable, while low yields of unidentified products resulted when the same conditions were applied to some analogs of **6c**.

3. Experimental

3.1. General

NMR spectra were recorded at 300.13 MHz (^{1}H) and 75.47 MHz (^{13}C) on a Bruker Avance 300 spectrometer. Chemical shifts are reported as δ values (ppm) relative to Me_4Si. Standard PENDANT, HSQC, and HMBC spectra were used in making the NMR assignments. Melting points are uncorrected. Microanalyses were performed at the Campbell Microanalytical Laboratory, University of Otago, New Zealand.

3.2. Precursors

Diones **2**[1a,15] and acid **3a**[1a] were prepared as previously reported. Acid **3b**, earlier synthesized from the dione by reaction with hot $POCl_3$,[15] was better prepared by reaction with methylamine,[16] as for **3a**.

3.2.1. 6-(4-Methoxyphenyl)-5-oxo-5,6-dihydro-1,6-naphthyridine-8-carboxylic acid (3c). To a suspension of dione **2b**,**c** (2.26 g, 10.37 mmol) in DMF (34 mL) was added Et_3N (5.65 mL) followed by *p*-anisidine (3.83 g, 31.10 mmol), and the whole was stirred for 16 h. Ice/water (ca. 100 mL) was added and the mixture was taken to pH 1 with 3.3% HCl. The resultant precipitate was filtered and washed with water to give carboxylic acid **3c** (1.86 g, 61%) as a beige solid, mp 245–246 °C, which was used without further purification. ^{1}H NMR (DMSO-d_6): δ 3.80 (s, 3H, O–CH_3), 7.07 (d, J=8.9 Hz, 2H, H-3′, H-5′), 7.44 (d, J=8.9 Hz, 2H, H-2′, H-6′), 7.76 (dd, J=8.1, 4.8 Hz, 1H, H-3), 8.35 (s, 1H, H-7), 8.74 (dd, J=8.1, 1.4 Hz, 1H, H-4), 9.07 (dd, J=4.8, 1.4 Hz, 1H, H-2), 15.18 (br s, 1H, CO_2H). ^{13}C NMR (DMSO-d_6): δ 55.6 (O–CH_3), 104.6 (C-8), 114.5 (C-3′, C-5′), 121.1 (C-4*a*), 123.3 (C-3), 128.2 (C-2′, C-6′), 132.7 (C-1′), 138.8 (C-4), 145.2 (C-7), 150.2 (C-8*a*), 152.6 (C-2), 159.4 (C-4′), 161.1 (C-5), 164.8 (CO_2H).

3.3. Preparation of amides

3.3.1. 2-Methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxamide (4a). Acid **3a** (2.41 g, 9.49 mmol) in $SOCl_2$ (24 mL) was heated under reflux for 30 min. The excess $SOCl_2$ was removed in vacuo and CH_2Cl_2 (40 mL) was added to the residue. Ammonia gas was bubbled through the mixture for 5 min, which was then evaporated at reduced pressure. Water was added and the mixture was filtered to give **4a** as a pale yellow solid (2.31 g, 96%), mp >300 °C (from 1,4-dioxane). ^{1}H NMR (DMSO-d_6): δ 3.60 (s, 3H, N–CH_3), 7.66 (t, J=7.4 Hz, 1H, H-8), 7.77 (br s, 1H, NH), 7.94 (t, J=7.7 Hz, 1H, H-7), 8.16 (d, J=8.6 Hz, 1H, H-6), 8.27 (d, J=8.3 Hz, 1H, H-9), 8.62 (s, 1H, H-3), 9.37 (s, 1H, H-10), 10.09 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6), 100 °C: δ 36.5 (N–CH_3), 109.1 (C-10*a*), 119.5 (C-4), 125.7 (C-9*a*), 126.8 (C-8), 128.1 (C-6), 129.6 (C-9), 133.2 (C-7), 139.3 (C-10), 144.9 (C-3), 148.7 (C-5*a*), 149.8 (C-4*a*), 162.2 (C-1), 164.9 ($CONH_2$). Anal. Calcd for $C_{14}H_{11}N_3O_2\cdot 0.1H_2O$: C, 65.93; H, 4.43; N, 16.47. Found: C, 65.82; H, 4.51; N, 16.30%.

3.3.2. 6-Methyl-5-oxo-5,6-dihydro-1,6-naphthyridine-8-carboxamide (4b). This was prepared from acid **3b**, as for **4a**, and obtained as a white solid (89%), mp 276–278 °C (from 1,4-dioxane). ^{1}H NMR (DMSO-d_6): δ 3.59 (s, 3H, N–CH_3), 7.59 (dd, J=8.1, 4.5 Hz, 1H, H-3), 7.68 (br s, 1H, NH), 8.57 (s, 1H, H-7), 8.62 (dd, J=8.1, 1.8 Hz, 1H, H-4), 8.98 (dd, J=4.5, 1.8 Hz, 1H, H-2), 9.71 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6), 100 °C: δ 36.7 (N–CH_3), 109.2 (C-8), 120.5 (C-4*a*), 121.9 (C-3), 136.9 (C-4), 143.8 (C-7), 150.7 (C-8*a*), 153.2 (C-2), 161.7 (C-5), 164.7 ($CONH_2$). Anal. Calcd for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.46; N, 20.68. Found: C, 59.11; H, 4.62; N, 20.76%.

3.3.3. 6-(4-Methoxyphenyl)-5-oxo-5,6-dihydro-1,6-naphthyridine-8-carboxamide (4c). This was prepared from acid **3c**, as for **4a**, and obtained as white needles (98%), mp 285–286 °C (from 1,4-dioxane). ^{1}H NMR (DMSO-d_6): δ 3.80 (s, 3H, O–CH_3), 7.06 (d, J=8.6 Hz, 2H, H-3′, H-5′), 7.43 (d, J=8.6 Hz, 2H, H-2′, H-6′), 7.65 (dd, J=8.0, 4.6 Hz, 1H, H-3), 7.79 (br s, 1H, NH), 8.31 (s, 1H, H-7), 8.65 (d, J=8.0 Hz, 1H, H-4), 9.03 (d, J=4.6 Hz, 1H, H-2), 9.73 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 55.6 (O–CH_3), 109.1 (C-8), 114.5 (C-3′, C-5′), 121.2 (C-4*a*), 122.5 (C-3), 128.2 (C-2′, C-6′), 133.1 (C-1′), 137.6 (C-4), 143.2 (C-7), 150.6 (C-8*a*), 153.7 (C-2), 159.3 (C-4′), 161.5 (C-5), 164.5 ($CONH_2$). Anal. Calcd for $C_{16}H_{13}N_3O_3$: C, 65.08; H, 4.44; N, 14.23. Found: C, 64.84; H, 4.49; N, 14.20%.

3.4. Hofmann rearrangement

3.4.1. 4-Amino-2-methylbenzo[*b*][1,6]naphthyridin-1(2*H*)-one (6a). A solution of KOH (1.11 g, 19.78 mmol) in MeOH (10 mL) was cooled to approximately 5 °C. To this mixture was added iodobenzene diacetate (1.40 g, 4.35 mmol) and carboxamide **4a** (1.00 g, 3.95 mmol). The mixture was allowed to warm to room temperature and was then stirred vigorously for 30 min to make the intermediate carbamate **5a**. A solution of KOH (2.22 g, 39.57 mmol) in MeOH (10 mL) and water (2 mL) was added, and the whole was heated under reflux for 3 h. The dark red solution was cooled, and the solid, which separated was collected by filtration and washed with water to give amine **6a** as orange needles (0.54 g, 61%), mp 197–199 °C (dec) (from EtOH). Extraction of the filtrate with CH_2Cl_2 (2×20 mL) gave a further 0.08 g. ^{1}H NMR (DMSO-d_6): δ 3.44 (s, 3H, N–CH_3), 4.76 (br s, 2H, NH_2), 6.96 (s, 1H, H-3), 7.63 (t, J=7.4 Hz, 1H, H-8), 7.91 (t, J=7.7 Hz, 1H, H-7), 8.10 (d, J=8.6 Hz, 1H, H-6), 8.25 (d, J=8.4 Hz, 1H, H-9), 9.27 (s, 1H, H-10). ^{13}C NMR (DMSO-d_6): δ 35.8 (N–CH_3), 116.4 (C-3), 120.0 (C-10*a*), 126.0 (C-4), 126.3 (C-9*a*), 126.4 (C-8), 128.4 (C-6), 129.8 (C-9), 132.5 (C-7), 138.3 (C-10), 146.7 (C-4*a*), 149.1 (C-5*a*), 159.1 (C-1). Anal. Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.65. Found: C, 69.04; H, 5.12; N, 18.48%.

3.4.2. 8-Amino-6-methyl-1,6-naphthyridin-5(6*H*)-one (6b). This was prepared from **4b**, as for **6a**. Water was added to the red reaction solution, which was then neutralized with AcOH and evaporated to dryness at reduced pressure. The residue was boiled with chloroform and filtered. Evaporation of the chloroform from the filtrate gave amine **6b** as a brown solid (86%), which was unstable and rapidly decomposed. ^{1}H NMR (DMSO-d_6): δ 3.42 (s, 3H, N–CH_3), 4.68 (br s, 2H, NH_2), 6.93 (s, 1H, H-7), 7.52

(dd, J=8.0, 4.5 Hz, 1H, H-3), 8.51 (dd, J=8.0, 1.7 Hz, 1H, H-4), 8.90 (dd, J=4.5, 1.7 Hz, 1H, H-2). ^{13}C NMR (DMSO-d_6): δ 36.1 (CH_3), 116.2 (C-7), 120.9 (C-4*a*), 122.1 (C-3), 126.3 (C-8), 136.0 (C-4), 147.0 (C-8*a*), 153.1 (C-2), 158.5 (C-5).

3.4.3. 8-Amino-6-(4-methoxyphenyl)-1,6-naphthyridin-5(6*H*)-one (6c). This was prepared from **4c**, as for **6a**, and obtained as yellow needles (68%), mp 164–165 °C (from EtOH). ^{1}H NMR (DMSO-d_6): δ 3.78 (s, 3H, O–CH_3), 4.72 (br s, 2H, NH_2), 6.91 (s, 1H, H-7), 7.02 (d, J=8.8 Hz, 2H, H-3′, H-5′), 7.35 (d, J=8.8 Hz, 2H, H-2′, H-6′), 7.58 (dd, J=8.0, 4.5 Hz, 1H, H-3), 8.55 (d, J=8.0 Hz, 1H, H-4), 8.96 (d, J=4.5 Hz, 1H, H-2). ^{13}C NMR (DMSO-d_6): δ 55.5 (O–CH_3), 114.3 (C-3′, C-5′), 115.9 (C-7), 121.5 (C-4*a*), 122.5 (C-3), 126.6 (C-8), 128.0 (C-2′, C-6′), 134.3 (C-1′), 136.5 (C-4), 147.4 (C-8*a*), 153.5 (C-2), 158.4 (C-4′), 158.5 (C-5). Anal. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.41; H, 4.90; N, 15.72. Found: C, 67.10; H, 5.07; N, 15.45%.

3.5. Conrad–Limpach synthesis

3.5.1. 2,5-Dimethylquinolino[3,2-*c*][1,6]naphthyridine-4,6(1*H*,5*H*)-dione (7a). To a warm solution of amine **6a** (0.34 g, 1.51 mmol) in EtOH (35 mL) was added ethyl acetoacetate (0.26 g, 1.96 mmol), $CaSO_4$ (1.03 g, 7.56 mmol) and AcOH (3.5 mL). This mixture was heated under reflux for 3.5 h, then filtered while hot and the filtrate was evaporated under reduced pressure to give the crotonate intermediate as an orange solid (0.46 g, 90%). A sample (0.26 g, 0.77 mmol) was added in portions to Ph_2O (2 mL) heated at 250 °C, and the solution was heated for a further 15 min. After being cooling to room temperature, the solution was poured onto Et_2O (50 mL) and the resultant precipitate was filtered and washed thoroughly with hot Et_2O to give **7a** as a brown solid (0.20 g, 89%), mp 159–162 °C [from CH_2Cl_2/petroleum spirit (bp 80–110 °C)]. ^{1}H NMR (DMSO-d_6): δ 2.43 (s, 3H, C–CH_3), 4.01 (s, 3H, N–CH_3), 6.17 (s, 1H, H-3), 7.76 (t, J=7.5 Hz, 1H, H-9), 8.03 (t, J=7.8 Hz, 1H, H-10), 8.30 (d, J=8.7 Hz, 1H, H-11), 8.36 (d, J=8.4 Hz, 1H, H-8), 9.40 (s, 1H, H-7), 11.61 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 18.7 (C–*C*H_3), 33.2 (N–CH_3), 116.1 (C-3), 119.7 (C), 126.8 (C), 127.6 (C-7*a*), 127.7 (C-9), 128.4 (C-4*a*, C-11), 129.9 (C-8), 133.3 (C-10), 138.9 (C-7), 143.7 (C-12*a*), 146.1 (C-2), 149.0 (C-11*a*), 160.4 (C-6), 171.7 (C-4). Anal. Calcd for $C_{17}H_{13}N_3O_2\cdot 0.5H_2O$: C, 67.99; H, 4.70; N, 13.99. Found: C, 68.08; H, 4.73; N, 13.60%.

3.5.2. 5-(4-Methoxyphenyl)-2-methylpyrido[3,2-*h*]-[1,6]naphthyridine-4,6(1*H*,5*H*)-dione (7c). This was prepared from amine **6c**, as for **7a**, and obtained as a light brown solid (71%). For microanalysis, a sample on a short bed of silica was washed with EtOAc, then eluted with MeCN. The residue after evaporation of the MeCN was recrystallized from MeCN to give **7c** as a fawn solid, mp 298–300 °C. ^{1}H NMR (DMSO-d_6): δ 2.35 (s, 3H, C–CH_3), 3.76 (s, 3H, O–CH_3), 5.92 (s, 1H, H-3), 6.85 (d, J=8.9 Hz, 2H, H-3′, H-5′), 7.05 (d, J=8.9 Hz, 2H, H-2′, H-6′), 7.81 (dd, J=8.0, 4.5 Hz, 1H, H-8), 8.62 (dd, J=8.0, 1.7 Hz, 1H, H-7), 9.14 (dd, J=4.5, 1.7 Hz, 1H, H-9), 11.80 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 18.6 (C–*C*H_3), 55.3 (O–CH_3), 112.9 (C-3′, C-5′), 115.5 (C-3), 122.4 (C-6*a*), 125.4 (C-8), 126.6 (C-10*b*), 128.2 (C-4*a*), 128.6 (C-2′, C-6′), 133.4 (C-1′), 137.0 (C-7), 145.2 (C-10*a*), 146.1 (C-2), 154.2 (C-9), 157.9 (C-4′), 160.2 (C-6), 169.5 (C-4). Anal. Calcd for $C_{19}H_{15}N_3O_3$: C, 68.46; H, 4.54; N, 12.61. Found: C, 68.04; H, 4.66; N, 12.79%.

3.6. Attempted Combes synthesis

3.6.1. 4-[2-Methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridin-4-yl]aminopent-3-en-2-one (8a). To a solution of **6a** (0.25 g, 1.11 mmol) in EtOH (25 mL), was added 2,4-pentanedione (0.14 g, 1.44 mmol), $CaSO_4$ (0.76 g, 5.56 mmol) and AcOH (2.5 mL). The red mixture was heated under reflux for 3.5 h, then filtered and the filtrate was evaporated under reduced pressure to give **8a** as a red solid (0.33 g, 97%), used in this state in the next reaction. ^{1}H NMR (DMSO-d_6): δ 1.98 (s, 3H, CH_3-5), 2.01 (s, 3H, CH_3-1), 3.52 (s, 3H, N–CH_3), 5.28 (s, 1H, H-3), 7.65 (t, J=7.5 Hz, 1H, H-8′), 7.87 (s, 1H, H-3′), 7.91 (t, J=7.7 Hz, 1H, H-7′), 8.04 (d, J=8.6 Hz, 1H, H-6′), 8.27 (d, J=8.3 Hz, 1H, H-9′), 9.31 (s, 1H, H-10′), 12.25 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 19.6 (CH_3-5), 29.1 (CH_3-1), 36.2 (N–CH_3), 97.6 (C-3), 116.6 (C), 119.6 (C), 126.3 (C-9*a*′), 126.7 (C-8′), 128.6 (C-6′), 129.8 (C-9′), 132.9 (C-7′), 133.3 (C-3′), 138.5 (C-10′), 148.4 (C-4*a*′), 149.5 (C-5*a*′), 160.9 (C-1′), 161.2 (C-4), 194.7 (C-2).

3.6.2. 8-[6-(4-Methoxyphenyl)-5-oxo-5,6-dihydro-1,6-naphthyridin-8-yl]aminopent-3-en-2-one (8c). This was prepared from **6c**, as for **8a**, and obtained as a red solid (87%), used in this state in the next reaction. ^{1}H NMR (DMSO-d_6): δ 1.95 (s, 3H, CH_3-5), 1.96 (s, 3H, CH_3-1), 3.79 (s, 3H, O–CH_3), 5.22 (s, 1H, H-3), 7.02 (d, J=8.8 Hz, 2H, H-3″, H-5″), 7.35 (d, J=8.8 Hz, 2H, H-2″, H-6″), 7.58 (dd, J=8.0, 4.5 Hz, 1H, H-3′), 7.75 (s, 1H, H-7′), 8.55 (d, J=8.0 Hz, 1H, H-4′), 8.99 (dd, J=4.5 Hz, 1H, H-2′). ^{13}C NMR (DMSO-d_6): δ 19.4 (C-5), 29.1 (C-1), 55.6 (O–CH_3), 97.6 (C-3), 114.3 (C-3″, C-5″), 117.2 (C-8′), 121.4 (C-4*a*′), 123.0 (C-3′), 128.3 (C-2″, C-6″), 132.4 (C-7′), 133.3 (C-1″), 136.5 (C-4′), 149.6 (C-8*a*′), 154.6 (C-2′), 158.9 (C-4″), 160.2 (C-5′), 161.3 (C-4) 194.8 (C-2).

3.6.3. 2,6-Dimethylpyrrolo[2′,3′:5,6]azocino[4,3-*b*]-quinolin-7(6*H*)-one (9a). Compound **8a** (0.33 g, 1.07 mmol) was added to $POCl_3$ (10 mL) and the whole was heated under reflux for 1 h. The solvent was evaporated under reduced pressure and water (30 mL) was added. The brown mixture was filtered, and the filtrate was basified with 10% NaOH. The solid, which separated was filtered and washed with water to give **9a** (0.20 g, 64%) as a light brown solid. For microanalysis, a sample on a short bed of silica was eluted with EtOAc–hexane (1/1). The residue after evaporation of the solvents was recrystallized from MeCN to give **9a** as a mustard solid, mp 294–296 °C (after darkening >270 °C). ^{1}H NMR (DMSO-d_6): δ 2.25 (s, 3H, C–CH_3), 3.00 (s, 3H, N–CH_3), 5.78 (d, J=2.0 Hz, 1H, H-3), 6.12 (d, J=8.3 Hz, 1H, H-4), 6.16 (d, J=8.3 Hz, 1H, H-5), 7.53 (t, J=7.5 Hz, 1H, H-10), 7.75 (t, J=7.7 Hz, 1H, H-11), 7.91–7.98 (m, 2H, H-9, H-12), 8.32 (s, 1H, H-8), 11.57 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 12.7 (C–*C*H_3), 35.4 (N–CH_3), 106.9 (C-3), 119.2 (C-3*a*), 120.5 (C-4), 125.7 (C-8*a*), 126.3 (C-10), 128.2 (C-12), 128.3 (C-9), 128.6 (C-5), 128.9 (C-13*b*), 130.8 (C-11), 132.0

(C-2), 132.2 (C-7*a*), 136.1 (C-8), 147.3 (C-12*a*), 148.8 (C-13*a*), 167.3 (C-7). Anal. Calcd for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.50; H, 5.29; N, 14.60%.

3.6.4. 6-(4-Methoxyphenyl)-2-methylpyrido[3,2-*c*]-pyrrolo[2,3-*e*]azocin-7(6*H*)-one (9c). This was prepared from **8c**, as for **9a**, and **9c** (77%) was purified in the same way (elution with acetone) and obtained as a fawn solid, mp 244–246 °C after recrystallization from toluene. ^{1}H NMR (DMSO-d_6): δ 2.24 (s, 3H, C–CH_3), 3.73 (s, 3H, O–CH_3), 5.85 (s, 1H, H-3), 6.13 (d, J=8.1 Hz, 1H, H-5), 6.27 (d, J=8.1 Hz, 1H, H-4), 6.94 (d, J=8.7 Hz, 2H, H-3′, H-5′), 7.16 (d, J=8.7 Hz, 2H, H-2′, H-6′), 7.32 (dd, J=7.7, 4.4 Hz, 1H, H-9), 7.91 (d, J=7.7 Hz, 1H, H-8), 8.59 (d, J=4.4 Hz, 1H, H-10), 11.46 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 12.7 (C–*C*H$_3$), 55.4 (O–*C*H$_3$), 106.4 (C-3), 114.2 (C-3′, C-5′), 118.5 (C-3*a*), 121.2 (C-9), 122.2 (C-4), 127.8 (C-2′, C-6′), 127.9 (C-5), 129.0 (C-11*b*), 130.3 (C-2), 133.1 (C-7*a*), 133.3 (C-1′), 136.1 (C-8), 147.3 (C-11*a*), 149.6 (C-10), 158.1 (C-4′), 167.5 (C-7). Anal. Calcd for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.57; H, 5.00; N, 12.71%.

3.7. Bromination

3.7.1. 3-Bromo-6-(4-methoxyphenyl)-2-methylpyrido-[3,2-*c*]pyrrolo[2,3-*e*]azocin-7(6*H*)-one (10c). To a solution of **9c** (0.14 g, 0.42 mmol) in CH_2Cl_2 (30 mL) was added bromine (0.11 g, 0.69 mmol). The solution was stirred for 10 min, washed with 10% K_2CO_3 (2×20 mL), and the organic phase was dried with $MgSO_4$ and evaporated to give **10c** (0.16 g, 92%) as a fawn solid, mp 227–230 °C [from CH_2Cl_2/petroleum spirit (bp 80–110 °C)]. ^{1}H NMR (DMSO-d_6): δ 2.22 (s, 3H, C–CH_3), 3.73 (s, 3H, O–CH_3), 6.13 (d, J=8.0 Hz, 1H, H-4), 6.27 (d, J=8.0 Hz, 1H, H-5), 6.97 (d, J=8.9 Hz, 2H, H-3′, H-5′), 7.15 (d, J=8.9 Hz, 2H, H-2′, H-6′), 7.40 (dd, J=7.8, 4.8 Hz, 1H, H-9), 7.98 (dd, J=7.8, 1.6 Hz, 1H, H-8), 8.63 (dd, J=4.8, 1.6 Hz, 1H, H-10), 12.05 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 11.5 (C–*C*H$_3$), 55.5 (O–*C*H$_3$), 94.8 (C-3), 114.3 (C-3′, C-5′), 117.7 (C-3*a*), 120.4 (C-4), 122.0 (C-9), 127.6 (C-2′, C-6′), 128.8 (C-11*b*), 129.5 (C-2), 129.7 (C-5), 132.8 (C-1′), 133.4 (C-7*a*), 136.5 (C-8), 146.4 (C-11*a*), 149.8 (C-10), 158.2 (C-4′), 167.0 (C-7). Anal. Calcd for $C_{20}H_{16}BrN_3O_2\cdot 0.5H_2O$: C, 57.29; H, 4.09; N, 10.02. Found: C, 57.70; H, 4.09; N, 10.00%.

3.8. Vilsmeier–Haack formylation

3.8.1. 3-Formyl-6-(4-methoxyphenyl)-2-methylpyrido-[3,2-*c*]pyrrolo[2,3-*e*]azocin-7(6*H*)-one (11c). To DMF (2 mL) at 0 °C was added $POCl_3$ (1 mL), dropwise and with stirring. Azocine **9c** (0.10 g, 0.30 mmol) in DMF (2 mL) was added. The cold solution was stirred for 1 h, then poured onto ice/water (30 mL) and basified to pH 9 with 10% NaOH solution. The resultant brown precipitate was filtered and washed with water to give aldehyde **11c** (0.09 g, 83%) as a brown solid, mp 257–259 °C (from toluene). ^{1}H NMR (DMSO-d_6): δ 2.54 (s, 3H, C–CH_3), 3.73 (s, 3H, O–CH_3), 6.27 (d, J=8.1 Hz, 1H, H-5), 6.51 (d, J=8.1 Hz, 1H, H-4), 6.94 (d, J=8.9 Hz, 2H, H-3′, H-5′), 7.17 (d, J=8.9 Hz, 2H, H-2′, H-6′), 7.45 (dd, J=7.8, 4.8 Hz, 1H, H-9), 8.01 (dd, J=7.8, 1.5 Hz, 1H, H-8), 8.68 (dd, J=4.8, 1.5 Hz, 1H, H-10), 9.91 (s, 1H, CHO), 12.40 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 11.2 (C–*C*H$_3$), 55.4 (O–*C*H$_3$), 114.2 (C-3′, C-5′), 117.6 (C-3*a*), 119.6 (C-3), 121.8 (C-4), 122.4 (C-9), 127.6 (C-2′, C-6′), 128.9 (C-5), 130.2 (C-11*b*), 132.9 (C-1′), 133.8 (C-7*a*), 136.4 (C-8), 142.0 (C-2), 145.6 (C-11*a*), 150.0 (C-10), 158.1 (C-4′), 167.0 (C-7), 185.1 (CHO). Anal. Calcd for $C_{21}H_{17}N_3O_3$: C, 70.18; H, 4.77; N, 11.69. Found: C, 70.59; H, 4.89; N, 11.67%.

3.9. Mannich reaction

3.9.1. 3-(Dimethylamino)methyl-6-(4-methoxyphenyl)-2-methylpyrido[3,2-*c*]pyrrolo[2,3-*e*]azocin-7(6*H*)-one (12c). To a mixture of dimethylamine hydrochloride (0.96 g) and paraformaldehyde (0.48 g) in EtOH (15 mL) was added azocine **9c** (0.12 g, 0.36 mmol) and the whole was heated at 50 °C for 4 h. The mixture was evaporated at reduced pressure and water (30 mL) was added. The solution was basified with 10% NaOH solution and extracted with CH_2Cl_2 (3×10 mL). The combined extracts were washed with water (2×20 mL), dried over $MgSO_4$ and evaporated under reduced pressure to give **12c** (0.09 g, 64%) as a light brown solid, mp 112–114 °C (from toluene). ^{1}H NMR (DMSO-d_6): δ 2.10 [s, 6H, N(CH$_3$)$_2$], 2.21 (s, 3H, C–CH_3), 3.17 (d, J=4.9 Hz, 2H, CH_2), 3.73 (s, 3H, O–CH_3), 6.14 (d, J=8.2 Hz, 1H, H-5), 6.32 (d, J=8.2 Hz, 1H, H-4), 6.92 (d, J=8.9 Hz, 2H, H-3′, H-5′), 7.23 (d, J=8.9 Hz, 2H, H-2′, H-6′), 7.32 (dd, J=7.8, 4.7 Hz, 1H, H-9), 7.90 (dd, J=7.8, 1.5 Hz, 1H, H-8), 8.59 (dd, J=4.7, 1.5 Hz, 1H, H-10), 11.39 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 10.9 (C–*C*H$_3$), 45.0 [N(CH$_3$)$_2$], 53.8 (CH_2), 55.4 (O–*C*H$_3$), 114.0 (C-3′, C-5′), 115.5 (C-3), 118.7 (C-3*a*), 121.1 (C-9), 122.1 (C-4), 127.8 (C-2′, C-6′, C-5), 128.1 (C-11*b*), 129.9 (C-2), 133.2 (C-7*a*, C-1′), 136.0 (C-8), 147.4 (C-11*a*), 149.6 (C-10), 158.0 (C-4′), 167.3 (C-7). Anal. Calcd for $C_{23}H_{24}N_4O_2\cdot 0.25H_2O$: C, 70.29; H, 6.28; N, 14.26. Found: C, 70.32; H, 6.17; N, 14.11%.

3.10. *N*-Methylation

3.10.1. 1-Methyl-6-(4-methoxyphenyl)-2-methylpyrido-[3,2-*c*]pyrrolo[2,3-*e*]azocin-7(6*H*)-one (13c). To a stirred solution of azocine **9c** (0.24 g, 0.73 mmol) in C_6H_6 (20 mL), was added 25% NaOH solution (15 mL), tetra-*n*-butylammonium hydrogen sulfate (0.27 g, 0.80 mmol) and methyl iodide (1 mL). The biphasic mixture was stirred vigorously for 24 h. Water (20 mL) was added and the organic phase was separated, washed with water (3× 20 mL), dried over $MgSO_4$ and evaporated under reduced pressure to give **13c** as a brown solid (0.22 g, 88%), mp 157–160 °C [from petroleum spirit (bp 80–110 °C)]. ^{1}H NMR (DMSO-d_6): δ 2.25 (s, 3H, C–CH_3), 3.60 (s, 3H, N–CH_3), 3.73 (s, 3H, O–CH_3), 5.92 (s, 1H, H-3), 6.13 (d, J=8.1 Hz, 1H, H-5), 6.26 (d, J=8.1 Hz, 1H, H-4), 6.94 (d, J=8.9 Hz, 2H, H-3′, H-5′), 7.17 (d, J=8.9 Hz, 2H, H-2′, H-6′), 7.36 (dd, J=7.8, 4.8 Hz, 1H, H-9), 7.96 (dd, J=7.8, 1.5 Hz, 1H, H-8), 8.65 (dd, J=4.8, 1.5 Hz, 1H, H-10). ^{13}C NMR (DMSO-d_6): δ 12.0 (C–*C*H$_3$), 31.7 (N–*C*H$_3$), 55.4 (CH_3, O–*C*H$_3$), 106.0 (C-3), 114.2 (C-3′, C-5′), 118.3 (C-3*a*), 121.3 (C-9), 122.1 (C-4), 127.7 (C-2′, C-6′), 128.7 (C-5), 129.9 (C-11*b*), 132.9 (C-1′), 133.4 (C-2), 134.7 (C-7*a*), 135.7 (C-8), 146.9 (C-11*a*), 149.4 (C-10), 158.1

(C-4′), 167.0 (C-7). Anal. Calcd for $C_{21}H_{19}N_3O_2$: C, 73.03; H, 5.54; N, 12.17. Found: C, 72.95; H, 5.66; N, 12.12%.

3.11. Diazotization

3.11.1. 6-(4-Methoxyphenyl)-5-oxo-5,6-dihydro-1,6-naphthyridine-8-diazonium tetrafluoroborate (14c). To a solution of amine **6c** (0.20 g, 0.75 mmol) in 43% HBF_4 (2 mL) at 0 °C was added, dropwise, $NaNO_2$ (0.06 g, 0.90 mmol) in water (1 mL). The orange mixture was stirred for 1 h at 0 °C. The yellow solid was filtered and washed with Et_2O to give **14c** (0.20 g, 73%), mp 148–151 °C (dec). ^{1}H NMR (acetone-d_6): δ 3.88 (s, 3H, O–CH_3), 7.13 (d, J=8.9 Hz, 2H, H-3′, H-5′), 7.58 (d, J=8.9 Hz, 2H, H-2′, H-6′), 7.92 (dd, J=8.0, 4.7 Hz, 1H, H-3), 8.76 (dd, J=8.0, 1.0 Hz, 1H, H-4), 9.18 (dd, J=4.7, 1.0 Hz, 1H, H-2), 9.97 (s, 1H, H-7). ^{13}C NMR (acetone-d_6): δ 54.9 (O–CH_3), 90.5 (C-8), 114.3 (C-3′, C-5′), 120.9 (C-4*a*), 125.4 (C-3), 127.7 (C-2′, C-6′), 130.8 (C-1′), 137.5 (C-4), 143.9 (C-8*a*), 156.0 (C-2), 156.5 (C-7), 159.7 (C-5), 160.7 (C-4′). IR (nujol): 2227.7 cm^{-1}.

3.11.2. 3-Formyl[1,2,3]triazolo[1,5-*a*]pyridine-4-(4-methoxyphenyl)carboxamide (16c). Diazonium salt **14c** (0.15 g, 0.41 mmol) was suspended in water (10 mL) and 10% NaOH (1 mL) was added. The mixture was stirred for 1 h, at which time the white solid was filtered and washed with water to give **16c** (0.10 g, 82%), mp 184–185 °C (from MeCN). ^{1}H NMR (DMSO-d_6): δ 3.73 (s, 3H, O–CH_3), 6.93 (d, J=8.8 Hz, 2H, H-3′, H-5′), 7.51 (t, J=7.2 Hz, 1H, H-6), 7.62 (d, J=8.8 Hz, 2H, H-2′, H-6′), 8.02 (d, J=7.2 Hz, 1H, H-5), 9.42 (d, J=7.0 Hz, 1H, H-7), 10.22 (s, 1H, CHO), 10.48 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 55.3 (O–CH_3), 114.0 (C-3′, C-5′), 117.2 (C-6), 121.9 (C-2′, C-6′), 128.2 (C-4), 128.4 (C-7), 130.9 (C-3*a*), 130.9 (C-5), 131.8 (C-1′), 136.9 (C-3), 156.0 (C-4′), 162.8 (CO), 183.3 (CHO). Anal. Calcd for $C_{15}H_{12}N_4O_3$: C, 60.81; H, 4.08; N, 18.91. Found: C, 60.61; H, 4.18; N, 18.89%.

3.11.3. 4-Methyl-5-oxo-5,6-dihydro-3*H*-benzo[*b*][1,2,3]-triazolo[4,5,1-*ij*][1,6]naphthyridin-3-ol (15a). To a solution of amine **6a** (0.36 g, 1.60 mmol) in 43% HBF_4 (5 mL) at room temperature was added, dropwise, a solution of $NaNO_2$ (0.13 g, 1.92 mmol) in water (3 mL). The resultant mixture was stirred for 1 h, then filtered and washed with Et_2O to give a pink solid. This was suspended in MeCN (10 mL) and water was added (1 mL). The mixture was stirred for 5 min, during which time the color changed from pink to white, and filtration gave **15a** as a white solid (0.24 g, 59%), mp 235–239 °C (after darkening >187 °C), which partially changed to **16a** on standing or during attempted recrystallization. ^{1}H NMR (DMSO-d_6): δ 3.14 (s, 3H, N–CH_3), 6.35 (d, J=9.5 Hz, 1H, H-3), 7.11 (d, J=9.5 Hz, 1H, OH), 7.76 (t, J=7.7 Hz, 1H, H-9), 7.96 (t, J=7.5 Hz, 1H, H-8), 8.29 (s, 1H, H-6), 8.33 (d, J=7.8 Hz, 1H, H-10), 8.61 (d, J=8.2 Hz, 1H, H-7). ^{13}C NMR (DMSO-d_6): δ 32.2 (N–CH_3), 80.0 (C-3), 115.5 (C-7), 117.1 (C-5*a*), 125.0 (C-10*a*), 125.9 (C-6), 128.0 (C-9), 128.5 (C-11*a*), 131.7 (C-6*a*), 131.9 (C-10), 132.2 (C-8), 135.3 (C-2*a*), 159.2 (C-5).

3.11.4. *N*-Methyl-3-formyl[1,2,3]triazolo[1,5-*a*]quinoline-4-carboxamide (16a). A suspension of **15a** (0.18 g, 7.09 mmol) in water (10 mL) and 10% NaOH (1 mL) was stirred for 1 h. A white solid was filtered to give aldehyde **16a** (0.16 g, 89%), mp 241–243 °C (after darkening >205 °C) [from 1,4-dioxane–DMF (9/1)]. ^{1}H NMR (DMSO-d_6): δ 2.86 (d, J=4.4 Hz, 3H, N–CH_3), 7.83 (t, J=7.4 Hz, 1H, H-7), 8.01 (t, J=7.8 Hz, 1H, H-8), 8.22 (d, J=8.0 Hz, 1H, H-6), 8.35 (s, 1H, H-5), 8.78 (d, 1H, J=8.3 Hz, H-9), 8.83 (br s, 1H, NH), 10.31 (s, 1H, CHO). ^{13}C NMR (DMSO-d_6): δ 26.4 (N–CH_3), 116.1 (C-9), 123.0 (C-5*a*), 124.5 (C-4), 128.7 (C-7), 130.0 (C-6), 130.5 (C-3*a*), 130.8 (C-5), 130.9 (C-9*a*), 132.8 (C-8), 138.5 (C-3), 165.3 (CO), 184.2 (CHO). Anal. Calcd for $C_{13}H_{10}N_4O_2$: C, 61.41; H, 3.96; N, 22.04. Found: C, 61.25; H, 4.16; N, 22.30%.

3.12. Bucherer reaction

3.12.1. 8-Hydroxy-6-(4-methoxyphenyl)-1,6-naphthyridin-5(6*H*)-one (17c). To a solution of sodium metabisulfite (0.85 g, 4.49 mmol) in water (15 mL) was added amine **6c** (0.24 g, 0.90 mmol) and the yellow mixture was heated under reflux for 24 h. After this time, the ensuing orange solution was cooled to room temperature, whereby a yellow solid separated. KOH (0.50 g, 8.99 mmol) was added and the mixture was heated under reflux for 24 h. The solution was then cooled until a yellow precipitate formed, which was collected by filtration to give unreacted **6c** (0.10 g). The filtrate was neutralized with concentrated HCl and the green solid, which separated was filtered and washed with water (0.45 g). Recrystallization from MeCN gave **17c** (0.11 g, 46%) as a yellow solid (which rapidly turned green), mp 174–175 °C. ^{1}H NMR (DMSO-d_6): δ 3.79 (s, 3H, O–CH_3), 7.02 (dd, J=6.8, 2.2 Hz, 2H, H-3′, H-5′), 7.11 (s, 1H, H-7), 7.36 (dd, J=6.8, 2.2 Hz, 2H, H-2′, H-6′), 7.60 (dd, J=8.1, 4.6 Hz, 1H, H-3), 8.55 (dd, J=8.1, 1.7 Hz, 1H, H-4), 8.99 (dd, J=4.6, 1.7 Hz, 1H, H-2), 9.01 (br s, 1H, OH). ^{13}C NMR (DMSO-d_6): δ 55.5 (O–CH_3), 114.3 (C-3′, C-5′), 119.2 (C-7), 121.4 (C-4*a*), 122.8 (C-3), 128.1 (C-2′, C-6′), 133.9 (C-1′), 136.2 (C-8), 136.6 (C-4), 148.0 (C-8*a*), 153.8 (C-2), 158.6 (C-4′), 158.9 (C-5). Anal. Calcd for $C_{15}H_{12}N_2O_3\cdot 0.75H_2O$: C, 63.94; H, 4.83; N, 9.94. Found: C, 63.98; H, 4.36; N, 9.97%.

A yellow solution in EtOH gave an intense green color on addition of Fe^{3+}.

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Backbone extended pyrrolidine PNA (*bep*PNA): a chiral PNA for selective RNA recognition

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Abstract—Synthesis of cationic, chiral PNA analogues with an extra atom in the backbone (*bep*PNA) is reported. The (2*S*,4*S*) geometry of the pyrrolidine ring, and an additional carbon atom in the backbone of homopyrimidine-*bep*PNAs resulted in the optimization of the inter-nucleobase distance, such that selective binding to complementary RNA over DNA was observed in the triplex mode. It was evident from circular dichroism studies that oligomers with mixed aminoethylglycyl–bep (*aeg–bep*) repeating units, and also *bep*PNA with homogeneous backbone attained structures quite different from those of *aeg*PNA$_2$:RNA/DNA complexes. The *bep*PNA, when incorporated in a duplex forming mixed purine–pyrimidine sequence, also showed a preference for binding complementary RNA over DNA.

1. Introduction

Synthetic oligonucleotides (Fig. 1, DNA/RNA **I**) have been considered as potential gene targeted therapeutic agents (antisense and antigene).[1] However, the unmodified oligonucleotides are rapidly identified and cleaved by the action of nucleases that hydrolyze the inter-nucleoside phosphodiester linkage of the backbone.[1] Among the known oligonucleotides analogues,[2,3] acyclic *N*-(2-aminoethyl)-glycyl peptide nucleic acids (Fig. 1, *aeg*PNA **II**), are found to be very good mimics of DNA/RNA.[3] Because of the higher thermal stability of PNA:DNA/RNA hybrids and their stability toward proteases and nucleases, PNA has generated interest in medicinal chemistry, having potential for the development as gene targeted drugs and as reagents in molecular biology and diagnostics.[3] The ability of the negatively charged DNA, as well as that of uncharged *aeg*PNA, to cross the cell membrane is poor. Additionally, PNA suffers from drawbacks such as poor aqueous solubility, cell permeability, and ambiguity in binding complementary DNA/RNA in both parallel and antiparallel orientations. To overcome these obstacles and to facilitate their use as antisense therapeutic agents in biological systems, several rational modifications have been reported to-date.[4] Editing at the molecular level of designed backbones is translated in imparting selectivity of binding with DNA or RNA, due to the intrinsic structural differences at duplex/triplex level of the natural nucleic acids.[5] Neutral

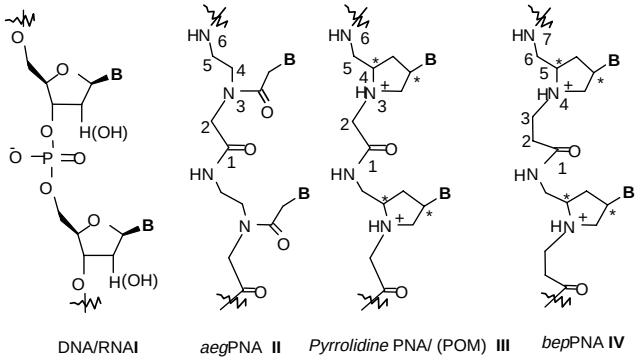

Figure 1. Structure of DNA, PNA, and modified PNAs.

pyrrolidinone and cationic pyrrolidine PNAs (Fig. 1, **III**) belong to this class of modifications. (3*S*,5*R*)-Pyrrolidinone PNA destabilized both DNA and RNA complexes[6] whereas *aepone*-PNA (2*S*,4*S*) stabilized complex with DNA over RNA.[7] A pentameric (2*R*,4*R*) pyrrolidine-amide oligonucleotide mimic (Fig. 1, POM **III**), showed kinetic binding preference to RNA over DNA.[8] Pyrrolidine PNA (Fig. 1, **III**) having one (2*R*,4*S*)-modified unit, showed destabilization with DNA and RNA, but bound strongly when fully modified.[9] (2*S*,4*S*)-Pyrrolidine PNA destabilized complexation with both DNA and RNA.[10] Previous studies on DNA/RNA analogues have shown that the length of the linkage in the repetitive DNA/RNA backbone can be varied from five to seven.[11] An example of the five-bond contracted backbone is TNA, an extraordinary oligonucleotide system introduced by Eschenmoser et al. TNA cross-paired

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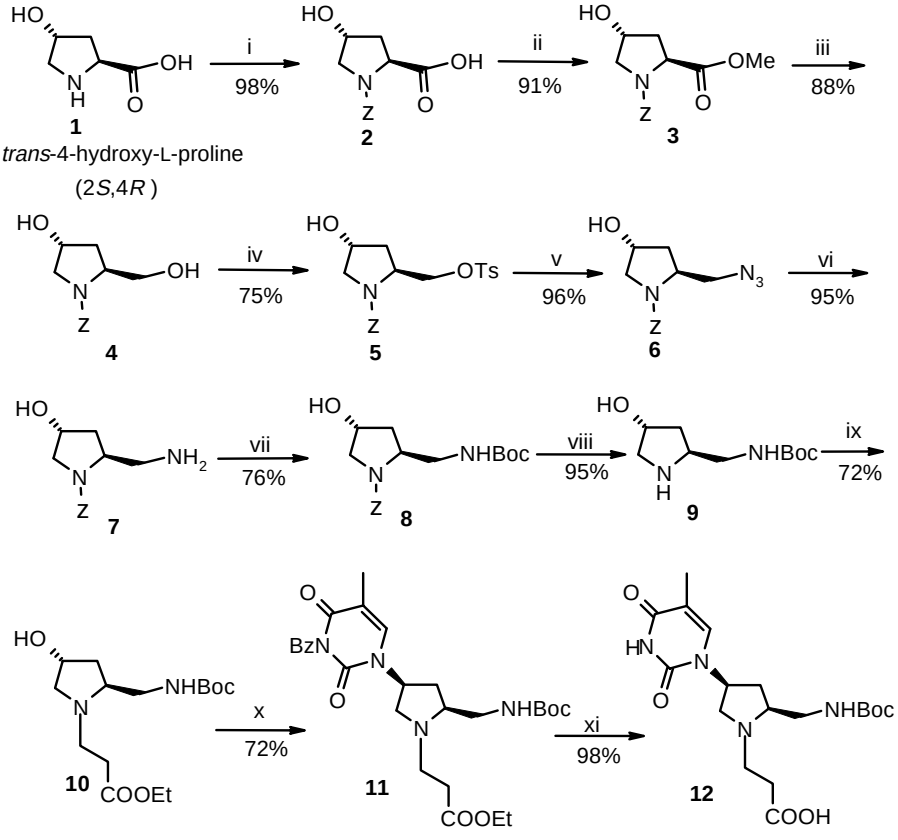
efficiently with complementary DNA and RNA, and showed relatively high affinity to RNA over DNA.[11] Matsuda et al. studied oligonucleotides containing oxetanocin A,[12] an isomer of deoxyadenosine with an oxetane sugar moiety, and a higher analogue. These analogues with extended seven-bond backbones cross-pair with RNA with high affinity compared to DNA. A carbocyclic analogue of the oxetanocin A oligonucleotide system also showed a tendency to form stronger complexes with RNA rather than with deoxyribonucleotide.[13] Many examples in the literature suggest that a five-atom amide leading to a seven-atom repeating backbone may be more useful, because of the reduced conformational flexibility of the amide relative to phosphodiester backbone.[14] This postulate has been supported by X-ray studies. X-ray data confirms that the amide backbone has a trans conformation, and that the distance between neighboring base pairs is not affected by incorporation of a longer backbone.[14a,e] On the contrary, Lowe et al. very effectively accomplished preferential DNA binding by replacing glycine with one-atom extended β-amino acids in his prolyl-glycyl PNA analogues.[15] Our preliminary results on the chimeric phosphate-amide extended backbone revealed that 2*R*,4*R* pyrrolidine–amide chimera were accommodated better in triplex forming sequences.[16]

In view of the above reports, we recently presented preliminary results on the backbone extended pyrrolidine PNA (Fig. 1, *bep*PNA **IV**).[17] In this paper, we present detailed studies on the hybridization properties of *bep*PNA using UV–T_m measurements, gel electrophoretic shift assay, and circular dichroism analysis of the *bep*PNA hybrids that address binding properties in both triplex and duplex modes, using either homopyrimidine or mixed purine–pyrimidine base sequences, respectively.

1.1. Synthesis of *bep*PNA monomer [(2*S*,4*S*)-2-(*tert*-butyloxycarbonylaminomethyl)-4-(thymin-1-yl) pyrolidin-1-yl] propanoic acid

The ring nitrogen of the naturally occurring *trans*-4-hydroxy-L-proline **1** was protected as the carbamate to give compound **2**, which was then converted into its methyl ester **3** on treatment with MeOH/$SOCl_2$.[12] Methyl ester **3** was reduced using LiCl/$NaBH_4$ to yield diol **4** (Scheme 1). Selective tosylation of the primary hydroxy group by controlled dropwise addition of *p*-TsCl (freshly crystallized from chloroform and petroleum ether) in pyridine gave monotosylate **5** (some ditosylate formed was removed by column chromatography). The monotosylate **5** was treated with NaN_3 to obtain azido compound **6**, and selective reduction of azide functionality using Raney Ni in methanol gave free amine **7**. Protection of free amine **7** using $BocN_3$ in DMSO yielded compound **8**. Compound **8** was subjected to hydrogenation using Pd–C catalyst to remove the benzyloxycarbonyl group to get free amine **9**. The free ring nitrogen was subsequently alkylated using ethyl acrylate in methanol as solvent, giving alkylated product **10**.



Scheme 1. Reagents and conditions: (i) Z–Cl (50% toluene soln), Et_3N, $NaHCO_3$, water, rt, 8 h; (ii) $SOCl_2$, Et_3N, MeOH, rt, 7 h; (iii) LiCl, $NaBH_4$, ethanol–THF (4/3), rt, 7 h; (iv) TsCl, pyridine, rt, 7 h; (v) NaN_3, DMF, 70 °C, 8 h; (vi) Raney Ni, H_2, MeOH, 35 psi, rt, 3 h; (vii) $BocN_3$, DMSO, 50 °C, 5 h; (viii) H_2/Pd–C, MeOH, 60 psi, rt, 7 h; (ix) ethyl acrylate, MeOH, rt, 2.5 h; (x) *N*3-benzoylthymine, DEAD, PPh_3, benzene, rt, 4 h; (xi) 2 M aqueous NaOH, rt, 5 h, Dowex-H^+.

No external base was required, as the amine **8** itself acted as a base, and the inclusion of an extra atom in the backbone was easily achieved by using conjugate addition to ethyl acrylate as compared to cumbersome methods in extended sugar-phosphate backbone.[14] Secondary alcohol **10** was converted to protected monomer ethyl ester **11** on treating with *N*3-benzoyl thymine under Mitsunobu conditions.[18] Hydrolysis of ethyl ester **11** and simultaneous deprotection of *N*3 of thymine was achieved using 2 M NaOH in aqueous methanol. The aqueous layer was washed with DCM to remove benzoic acid, and was then neutralized with a cation exchange resin (Dowex-H^+) by careful acidification of the reaction mixture to pH 7.0. The neutral aqueous layer was filtered and concentrated under reduced pressure to yield required monomer [(2*S*,4*S*)-2-(*tert*-butoxycarbonylamino-methyl)-4-(thymin-1-yl) pyrolidin-1-yl] propanoic acid (**12**) in good yield (Scheme 1). All new compounds were characterized by NMR, mass spectroscopy and elemental analysis. One-step conversion of the 4-OH in **10** to the corresponding thymin-1-yl derivative with an inversion of configuration can be achieved under Mitsunobu conditions. As the reactivity of *N*1 and *N*3 of thymine are comparable towards alkylation, this reaction results in both *N*1-alkylated and *N*1,*N*3-dialkylated products. Hence, *N*3 of the thymine was first protected as its benzoyl derivative.[19] The aminoethylglycyl PNA (A/G/C/T) monomers were synthesized following the literature procedure,[20] and these monomers were used for the synthesis of *aeg*PNA T_8 octamer (**13**) and *aeg*PNA **19** mixed decamer for the control studies and to synthesize *bep*PNA–*aeg*PNA chimeras.

1.2. Determination of the pK_a of the pyrrolidine ring nitrogen (*N*1) of the *bep*PNA thymine monomer 12

The *bep*PNA monomer has a tertiary amino group in the pyrrolidine ring that can be protonated. pH titration experiment was carried out with NaOH to determine the approximate pK_a of this nitrogen atom. A plot of pH versus volume of NaOH-added gave three transitions; the first one corresponding to the carboxylic acid, second corresponding to the tertiary ring nitrogen. The third transition could correspond to the free amine group of the deprotected monomer and the N3–H of thymine (Fig. 2). This transition is not very well resolved under the present conditions. The Boc protected monomer **12** was deprotected using trifluoro-acetic acid, and the product titrated against 0.2 M NaOH to find out the approximate pK_a value of pyrrolidine ring nitrogen. The pK_a values for free –COOH was found to be in the range of 3–4 and those of $-NH_2$ and N3–H of thymine overlapped at ~10. The pK_a of the ring nitrogen was found to be ~7.7 (Fig. 2). The pyrrolidine ring nitrogen in the monomer could partially be protonated under physiological conditions (pH). This pK_a (7.7) of the ring nitrogen is higher than any other pyrrolidine PNAs, and can be attributed to the fact that the additional methylene group in the backbone increases the basic character of the ring nitrogen.

1.3. Synthesis of cationic backbone extended pyrrolidine peptide nucleic acids (*bep*PNA) and UV-melting studies of *bep*PNA:DNA/RNA complexes

The modified *cis*-(2*S*,4*S*)-*bep*PNA thymine monomer **12** was incorporated into PNA sequences using Boc-chemistry on L-lysine-derivatized (4-methylbenzhydryl)amine (MBHA) resin as reported before, using HBTU/HOBt/DIEA in DMF as the coupling reagent. Various homo-thymine PNA oligomers (**13**–**18**, Tables 1 and 2) incorporating modified monomers at the middle (**15**), N-terminus (**16**), C-terminus (**14**), at alternative positions (**17**), and through the entire sequence (homo-oligomer **18**) were synthesized in order to study their triplex formation and stability with DNA/RNA. Octamer *aeg*PNA T_8 (**13**) sequence was also synthesized, incorporating *aeg*PNA thymine monomer for the use of control studies. In order to study the duplex formation potential, and in particular DNA/RNA discrimination of the *bep*PNA monomeric units, it was imperative to synthesize mixed sequences, incorporating both purines and pyrimidines. Mixed sequences *aeg*PNA **19** and *bep*PNA **20** were also synthesized by incorporating *aeg*PNA (A/G/C/T) monomers and *bep*PNA (T) monomers (Table 3). The oligomers were cleaved from the resin using a 'low–high TFA–TFMSA' procedure,[21] followed by RP-HPLC purification and characterization by mass spectrometry (LC-TOF-MS). The complementary DNA oligonucleotides **21**, **23**, **24** were synthesized on Applied Biosystems ABI 3900 High Throughput DNA Synthesizer using standard β-cyanoethyl phosphoramidite chemistry. The oligomers were synthesized in the 3′–5′ direction on polystyrene solid support, followed by ammonia treatment.[22] The oligonucleotides were desalted by gel filtration, their purity ascertained by RP-HPLC on a C18 column to be more than 98%, and were used without further purification in the biophysical studies of PNAs. The RNA oligonucleotides **22**, **25**, and **26** were obtained commercially.

The T_m values of homopyrimidine PNAs **13**–**18**, hybridized with complementary DNA and RNA were obtained from

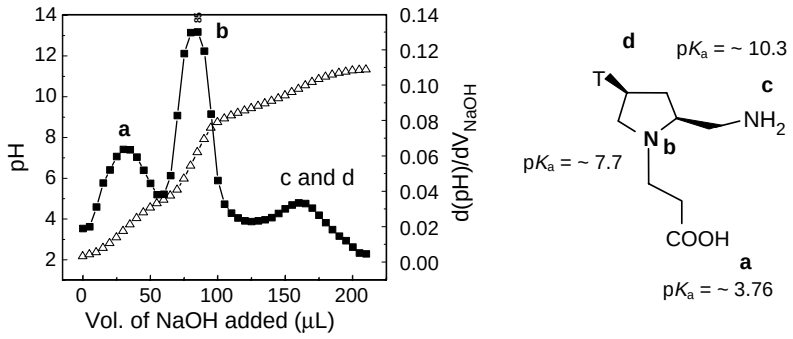


Figure 2. pH titration curve of (2*S*,4*S*)-*bep*PNA monomer (free amine) with NaOH (empty triangles) and change in pH with volume of NaOH (filled squares).

Table 1. HPLC and mass spectral analysis of synthesized PNAs

Entry	PNA	HPLC (RT, in min)	M_W (calcd)	M_W (found)[a]
1	*aeg*PNA **13**	7.536	2274.00 ($C_{96}H_{132}N_{35}O_{32}$)	2275.90
2	*bep*PNA **14**	7.596	2286.00 ($C_{96}H_{132}N_{35}O_{32}$)	2288.00
3	*bep*PNA **15**	7.270	2286.00 ($C_{96}H_{132}N_{35}O_{32}$)	2288.00
4	*bep*PNA **16**	7.359	2286.00 ($C_{96}H_{132}N_{35}O_{32}$)	2288.04
5	*bep*PNA **17**	9.562	2323.00 ($C_{102}H_{144}N_{35}O_{29}$)	2326.06
6	*bep*PNA **18**	8.246	2370.00 ($C_{110}H_{160}N_{35}O_{25}$)	2374.43
7	*aeg*PNA **19**	10.505	2852.00 ($C_{114}H_{147}N_{60}O_{31}$)	2853.00
8	*bep*PNA **20**	7.852	2887.00 ($C_{120}H_{159}N_{60}O_{28}$)	2891.36

[a] LC-TOF-MS, RT=retention time.

Table 2. Melting temperatures (T_m) of PNA_2:DNA/RNA triplexes[a]

No.	Homopyrimidine PNA sequence	DNA	RNA
1	**13**, H-TTTTTTTT-$LysNH_2$	51.5	65.8
2	**14**, H-TTTTTTT**t**-$LysNH_2$	49.0	59.9
3	**15**, H-TTT**t**TTTT-$LysNH_2$	nd	59.2
4	**16**, H-**t**TTTTTTT-$LysNH_2$	53.0	59.0
5	**17**, H-T**t**T**t**T**t**T**t**-$LysNH_2$	nd	84.4
6	**18**, H-**tttttttt**-$LysNH_2$	nd	58.9

[a] T_m=melting temperature (measured in buffer 10 mM sodium phosphate, pH 7.0 with 100 mM NaCl and 0.1 mM EDTA). Measured from 10 to 90 °C at ramp 0.2 °C/min. UV-absorbance measured at 260 nm. All values are an average of three independent experiments and accurate to within ±0.5 °C. DNA **21**=dCGCA_8CGC; RNA **22**=poly rA; nd=not detected.

temperature dependent UV-absorbance data (Fig. 4, Table 2). The UV and CD Job's plots[23] suggest the formation of 2:1 *bep*PNA_2/DNA and *bep*PNA_2/RNA triplexes (Fig. 3) and hence all the complementation studies were performed with 2:1 PNA/DNA stoichiometry. The UV–T_m values were obtained from the first derivatives of the normalized absorbance-temperature plots of the corresponding PNA:DNA complexes (Fig. 4A, Table 2). The C-terminal modified *bep*PNA **14** binds to DNA with slight decrease in T_m ($\Delta T_m=-1$ °C) where as *bep*PNA **16** modified at N-terminal stabilizes the complex ($\Delta T_m=+2$ °C) compare to the control *aeg*PNA **13**. Surprisingly, *bep*PNA **15**, with a modified unit at the center did not show any complexation with DNA. Alternate and homooligomeric *bep*PNAs (**17** and **18**) also did not form

Table 3. UV–T_m (°C) of PNA:DNA/RNA duplexes[a]

Mix PNA sequence	DNA **23**	RNA **25**
19, H-GTAGATCACT-$LysNH_2$	55.0 (40.0)[b]	55.4
20, H-G**t**AGA**t**CAC**t**-$LysNH_2$	nd	81.0 (74)

[a] T_m=melting temperature (measured in buffer 10 mM sodium phosphate, pH 7.0 with 100 mM NaCl and 0.1 mM EDTA). Measured from 10 to 90 °C at ramp 0.2 °C/min. UV-absorbance measured at 260 nm. DNA **23**=5′AGTGATCTAC (ap); DNA **24**, 5′-CATCTAGTGA-3′(p); RNA **25**=5′ AGUGAUCUAC (ap); RNA **26**, 5′-CAUCUAGUGA-3′ (p).

[b] Measured by CD to avoid interference from thermal transitions of single stranded PNAs. nd=not detected. Values in brackets are T_m for parallel duplexes with DNA **24** and RNA **26**.

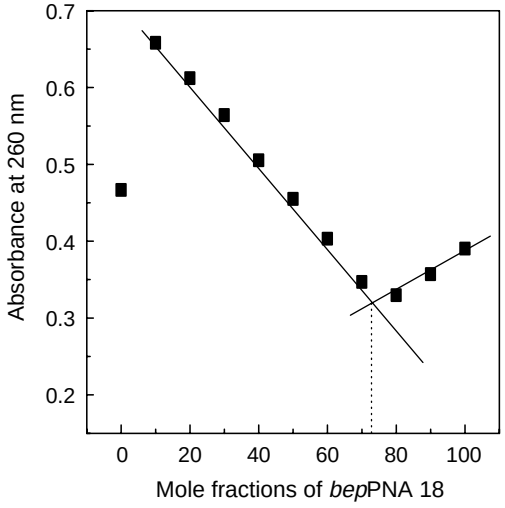


Figure 3. UV–Job's plot for *bep*PNA **18** and the complementary RNA (poly rA) mixtures in the molar ratios of 0:100, 10:90, 20:80, 30:70, 40:60, 50:50, 60:40, 70:30, 80:20, 90:10, 100:0 at 260 nm (buffer, 10 mM sodium phosphate pH 7.0, 100 mM NaCl, 0.1 mM EDTA).

complex with DNA as shown in UV-melting curves. When the complexation studies were performed with RNA, chimeric PNAs with a single *bep*PNA unit were found to bind with approximately same T_m, but slightly lower than that of control *aeg*PNA **13**. *bep*PNA **17**, with alternating *aeg–bep* units exhibiting a very high binding affinity ($\Delta T_m=+4.5$ °C/mod) (Fig. 4B, Table 2). The observed transitions were very sharp with RNA compared to that with DNA. The sequence **18** comprised only of a *bep*PNA backbone also recognized only RNA, but with reduced strength compared to the alternating *aeg–bep*PNA. These results suggest that *bep*PNA monomer in chimeric and homooligomeric PNAs introduced binding selectivity for RNA over DNA. Incorporation of the modified units at the terminals (C-/N-) seems to exert very weak effective preorganized conformation, and allowed binding with DNA as well as RNA. When in the center of the sequence, the induced conformation allows recognition of RNA but that of DNA is suppressed. The high affinity binding of alternating *aeg–bep*PNA **17** with RNA suggests that the alternating *aeg–bep* units are uniformly spaced, such that a balanced optimum conformation may be reached for recognition of RNA. The fully modified backbone in **18** binds to RNA but with reduced strength compared with the alternating sequence **17**. This could be because of over-organization of single strand as suggested for fully modified LNA,[14b,d] or high positive charge concentration of two *bep*-homooligomers in 2:1 binding mode. The 2:1 binding stoichiometry for:**18**:RNA was confirmed by UV–Job's plot (Fig. 3). The charge–charge repulsions could therefore be the possible reason for the observed reduced T_m. To study the RNA binding selectivity of *bep*PNA in duplex formation, purine–pyrimidine-mix *bep*PNA decamer **20** was synthesized incorporating the *bep*PNA-T monomer at three thymine positions in control *aeg*PNA **19**. The UV and CD-thermal denaturation[24] studies of *bep*PNA **20** with DNA and RNA were carried out (Fig. 5 and Supplementary information). Data in Table 3 shows that the reference *aeg*PNA **19** forms ap-duplexes with complementary DNA **23** and RNA **25** with equal stability. Mixed *bep*PNA **20** did

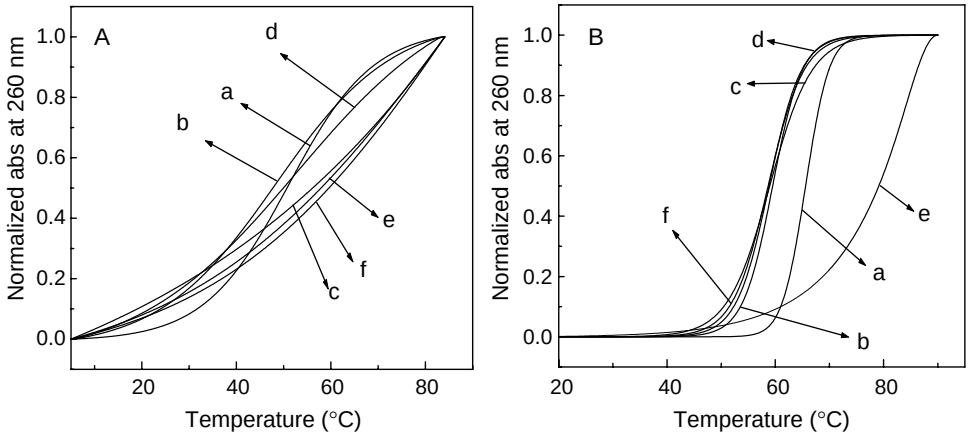


Figure 4. UV–T_m curves of A. (a) *aeg*PNA **13**, (b) *bep*PNA **14**, (c) *bep*PNA **15**, (d) *bep*PNA **16**, (e) *bep*PNA **17** and (f) *bep*PNA **18** with DNA **21**. B. (a) *aeg*PNA **13**, (b) *bep*PNA **14**, (c) *bep*PNA **15**, (d) *bep*PNA **16**, (e) *bep*PNA **17** and (f) *bep*PNA **18** with RNA **22** (buffer, 10 mM sodium phosphate pH 7.0, 100 mM NaCl, 0.1 mM EDTA).

not bind to DNA (antiparallel and parallel), as there was no transition detected in the UV melting experiment, whereas high affinity binding was observed with RNA (antiparallel, $\Delta T_m = 26\ ^\circ C$). Destabilization of ($\Delta T_m \sim 7\ ^\circ C$) was observed for the parallel *bep*PNA **20**:RNA duplex indicating the preference for antiparallel mode of binding.

1.4. CD spectroscopic studies of *bep*PNA:DNA and *bep*PNA:RNA complexes

Achiral *aeg*PNAs show very weak CD signatures due to the presence of chiral linker amino acid L-lysine. However, PNA:DNA complexes exhibit characteristic CD signatures due to chirality induced by the DNA component. It is known that the formation of PNA_2:DNA triplexes[25] accompanied by the appearance of positive CD bands at 260 and 285 nm that are not present in DNA (Supplementary information). Unlike *aeg*PNA **13**, the single stranded *bep*PNAs (**14**–**18**), showed distinct CD patterns depending on the number and position of modified units present (Supplementary information). Alternating *aeg*–*bep*PNA **17** showed a positive lower intensity bands at 245 nm, high intensity band at 260 nm and negative intensity bands at around 225 and 275 nm region (Fig. 6B, a). The fully modified *bep*PNA homo-oligomer (**18**) gave a CD signature with a maximum intensity positive band at around 235 nm, and a negative intensity band at 265 nm (Fig. 6B, c). Interestingly, the CD signature of the *bep*PNA **18** is more pronounced than that of DNA **21** (Supplementary information). As expected, the C- and N-terminus modified *bep*PNAs **14** and **16** with DNA showed CD signatures similar to the control *aeg*PNA_2:DNA triplex (Fig. 6A, a and c), whereas the CD signature of *bep*PNA **15** with DNA showed broad band from 260–285 nm (Fig. 6A, b) due to weak binding interaction as shown by gel electrophoresis assay. CD patterns of the alternating *aeg*–*bep*PNA **17** and *bep*PNA **18** with DNA **21** (Fig. 6A, d and e) were found to be additive spectra of corresponding CD signals of single stranded *bep*PNA and DNA **21**. Subtraction of the CD spectra of single stranded *bep*PNA **17** and **18** from the CD spectra of [*bep*PNA **17**+DNA **21**] and [*bep*PNA **18**+DNA **21**], respectively, gave the CD spectrum corresponding to single strand DNA **21**(Fig. 6B, b and d). These CD results are in complete agreement with the results obtained by UV measurements and gel shift assay.[17] CD spectra of *bep*PNA–poly rA complexes were recorded to study the structural changes after complexation in comparison with control *aeg*PNA **13**:poly rA complex (Fig. 6C, a). The CD signatures of singly modified *bep*PNAs **14**, **15**, and **16** with poly rA (Fig. 6C, b–d, respectively) gave different pattern compared to the control *aeg*PNA **13**–poly rA that was similar to (*aeg*PNA **13**)$_2$–DNA **21** triplex; CD profile with two characteristic bands at 260 and 285 nm. As expected from the UV–T_m data of *aeg*–*bep*PNA **17** and *bep*PNA **18**, the CD patterns were quite similar to each other as well as to that of control *aeg*PNA **13**–poly rA (Fig. 6C, e and f and a, respectively). The *aeg*–*bep*PNA–poly rA complexation was accompanied by the appearance of strong positive bands at 225 and 265 nm and a low negative intensity band at 245 nm compare to control with slight similarity. However, *bep*PNA **18**–poly rA showed presence of single strand *bep*PNA **18** and strong positive band at 235 nm was also observed. Thus, the CD spectral studies also demonstrated RNA selectivity of *bep*PNAs.

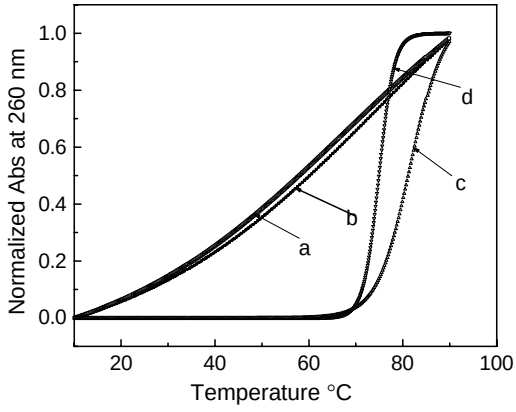


Figure 5. Melting curves of *bep*PNA **20** with A: (a) DNA **23** (antiparallel), (b) DNA **24** (parallel), (c) RNA **25** (antiparallel), and (d) RNA **26** (parallel).

1.5. Electrophoretic gel shift assay

An electrophoretic gel shift experiment was carried out to prove the results obtained from UV-thermal denaturation studies of *bep*PNAs with complementary DNA **21**

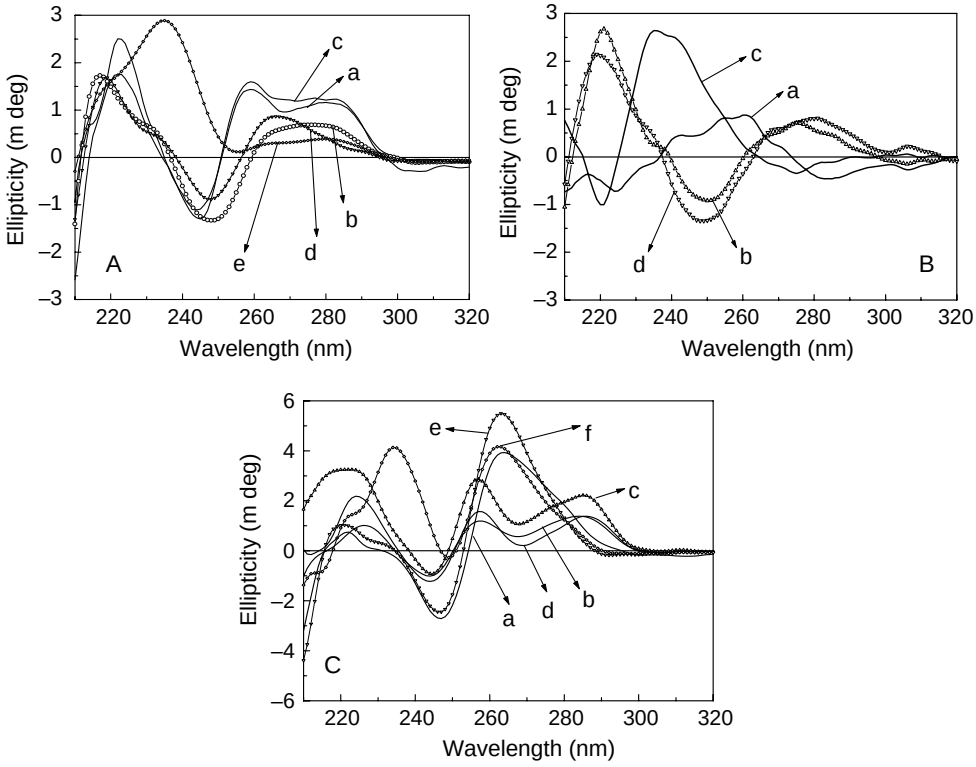


Figure 6. A. CD spectra of PNA_2:DNA (a) *bep*PNA **14**, (b) *bep*PNA **15**, (c) *bep*PNA **16**, (d) *bep*PNA **17** and (e) *bep*PNA **18** with DNA **21**; B. CD spectra of single stranded (a) *bep*PNA **17** and (c) *bep*PNA **18**; subtraction spectra (b) [*bep*PNA **17**:DNA **21**–*bep*PNA **17**] and (d) [*bep*PNA **18**:DNA **21**–*bep*PNA **18**]; C. CD spectra of PNA_2:RNA (a) *aeg*PNA **13**, (b) *bep*PNA **14**, (c) *bep*PNA **15**, (d) *bep*PNA **16**, (e) *bep*PNA **17** and (f) *bep*PNA **18** with RNA **22** (buffer, 10 mM sodium phosphate pH 7.0, 100 mM NaCl, 0.1 mM EDTA).

(Supplementary information). The various PNAs were individually mixed with DNA **21** in buffer, and subjected to non-denaturing gel electrophoresis[26] at 10 °C. The bands were visualized on a fluorescent TLC background. The formation of a PNA:DNA complex was accompanied by disappearance of the band due to single stranded DNA **21** and appearance of a lower migrating band of complex. The terminally modified *bep*PNAs **14** and **16**, upon mixing with DNA migrated about the same as the control *aeg*PNA **13**:DNA complex (Fig. SI, lane 1) and much lower than that of DNA (Fig. SI, lanes 5 and 7). The *bep*PNA **15** exhibited very weak binding interaction at lower temperature, though it was not seen during UV–T_m thermal denaturation (Fig. SI, lane 6). Under the conditions used, the single stranded PNAs carrying positive charge do not migrate from the well. No complexation was observed in case of alternating *aeg*–*bep*PNA **17** and *bep*PNA **18** with DNA as it can be seen from faster moving band due to unbound single strand DNA and hence clearly support the data obtained from UV–T_m experiments.

2. Summary

We have reported the design and synthesis of a novel class of cationic pyrrolidine PNAs with extended backbone that show improved binding affinity and selectivity towards DNA/RNA recognition. The complementation studies with DNA/RNA reveal that these *bep*PNAs bring in unprecedented RNA binding selectivity in triplex as well as duplex modes. From the application perspective, this chiral, cationic PNA analogue is shown to have very important properties essential for development into a therapeutic drug. Further studies on the mixed purine–pyrimidine sequences with *bep*PNA A/G/C/T units and other diastereomeric *bep*PNAs are underway.

3. Experimental

3.1. General experimental and spectroscopic data

Melting points of samples were determined in open capillary tubes using Buchi Melting point B-540 apparatus and are uncorrected. IR spectra were recorded on an infrared Fourier Transform spectrophotometer using KBr pellets. Column chromatographic separations were performed using silica gel 60–120 mesh, solvent systems gradient EtOAc/pet ether and pure DCM to 3% MeOH/DCM. ^1H and ^{13}C spectra were obtained using Bruker AC-200 (200 MHz) and 500 MHz NMR spectrometers. The chemical shifts are reported in delta (δ) values. The optical rotation values were measured on Bellingham-Stanley Ltd, ADP220 polarimeter. CD spectra were recorded on JASCO-715 Spectropolarimeter. Mass spectra were obtained either by LCMS techniques or by LC-TOF-MS mass spectrometry. Oligomers were characterized by RP-HPLC, C18 column and LC-TOF-MS mass spectrometry.

3.1.1. (2*S*,4*R*)-*N*1-(Benzyloxycarbonyl)-4-hydroxy-2-(hydroxymethyl)-pyrrolidine (4). To an ice cooled solvent mixture of dry THF (175 ml) and absolute ethanol (250 ml) containing $NaBH_4$ (3.192 g, 84.3 mmol) in a three-necked flask, LiCl (3.58 g, 84.3 mmol) was added slowly from a

solid addition funnel over 30 min. The above solution was stirred for 1.0 h and the appearance of a milky solution indicates the formation of $LiBH_4$ in situ. To the above ice-cooled milky solution, (2*S*,4*R*)-*N*1-(benzyloxycarbonyl)-4-hydroxyproline methyl ester (**3**) (9.45 g, 33.75 mmol) dissolved in absolute ethanol (50 ml) was added from a dropping funnel over a period of 30 min under nitrogen atmosphere, and the reaction mixture was stirred over night at rt. Then the pH of the reaction mixture was adjusted to 7.0 by adding saturated NH_4Cl. The solvent mixture was removed under vacuum and the residue was extracted into ethyl acetate (25 ml×3). The organic layer was washed with water, brine solution, dried over anhydrous Na_2SO_4 and concentrated to afford oily product diol **4** (7.5 g, yield 88%, R_f=0.3, ethyl acetate/petroleum ether-1:1). $[\alpha]_D^{20}$ +16.8 (*c* 3.26, CH_2Cl_2); IR (neat) (ν) cm^{-1}. 3410, 3021, 1699, 1470, 1415. ^1H NMR ($CHCl_3$-*d*, 200 MHz); δ: 1.55–1.8 (m, 1H), 1.9–2.2 (m, 1H), 3.25–3.8 (m, 4H), 3.8–4.25 (m, 2H), 4.25–4.5 (br d, 1H), 5.12 (s, 2H), 7.4 (s, 5H). ^{13}C NMR ($CHCl_3$-*d*, 200 MHz); δ: 37.1, 55.4, 58.9, 65.5, 87.2, 89.0, 127.7, 128.3, 136.2, 159.5. Anal. Calcd (%) for $C_{13}H_{17}NO_4$: C, 62.15; H, 10.75; N, 5.57. Found C, 61.83; H, 10.91; N, 5.53; LCMS; 252.07 $[M+1]^+$.

3.1.2. (2*S*,4*R*)-*N*1-(Benzyloxycarbonyl)-4-hydroxy-2-(*p*-toluenesulfonyloxymethyl)-pyrrolidine (5). The diol **4** (7.12 g, 28.36 mmol) was dissolved in dry pyridine (200 ml) and cooled to 0 °C. To this ice cooled solution, freshly crystallized *p*-toluenesulfonyl chloride (5.95 g, 31.2 mmol) in pyridine was added from a dropping funnel over a period of 1.5 h under nitrogen atmosphere. The reaction mixture was stirred for 8 h at rt. Pyridine was removed under reduced pressure and co-evaporated with toluene (twice). The residue was extracted into ethyl acetate (50 ml×2), washed with water, dried over Na_2SO_4 and concentrated to yield crude oily residue. The residue was purfied by column chromatography to get monotosylate **5** as a thick oil. (8.6 g, yield 75%, R_f=0.36, ethyl acetate/petroleum ether-1:1). $[\alpha]_D^{20}$ +27.7 (*c* 4.43, CH_2Cl_2); IR (neat) (ν) cm^{-1}. 3011, 1699,1550, 1500, 1470, 1415. ^1H NMR ($CHCl_3$-*d*, 200 MHz); δ:1.7–2.15 (2H, C2H, C3H), 2.2–2.5 (s, 3H, OCH_3), 3.1–3.6 (m, 2H, C5H_2), 3.7–4.2 (m, 3H, CH_3), 4.25–4.65 (m, 2H, CH_2-OTs), 4.7–5.5 (br d, 4H, C4H, $COOCH_2$, OH), 7.26–7.4 (s, 7H, C_6H_5, two CH-Ts), 7.5–7.8 (m, 2H, two CH-Ts). ^{13}C NMR ($CHCl_3$-*d*, 200 MHz); δ: 21.0, 35.9, 54.5, 54.8, 66.4, 68.7, 69.8, 127.3, 128.0, 129.5, 132.3, 136.0, 144.5, 154.6. Anal. Calcd (%) for $C_{20}H_{23}NO_6S$: C, 59.25; H, 5.67; N, 3.45; S, 7.90. Found C, 58.92; H, 5.77; N, 3.37; S, 7.67; MS LCMS; 405.00 $[M]^+$.

3.1.3. (2*S*,4*R*)-*N*1-(Benzyloxycarbonyl)-4-hydroxy-2-(azidomethyl)-pyrrolidine (6). To the solution of monotosylate **5** (6.0 g, 14.8 mmol) in DMF (50 ml), NaN_3 (7.7 g, 118.4 mmol) was added. The reaction mixture was stirred at 55 °C for 8 h. The solvent was removed under reduced pressure and the residue was extracted into ethyl acetate (25 ml×3). The combined organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and then concentrated to yield azide **6** as thick oil. (3.9 g, yield 96%, R_f=ethyl acetate/petroleum ether-1:1). $[\alpha]_D^{20}$ +19.3 (*c* 2.15, CH_2Cl_2); IR (neat) (ν) cm^{-1}. 3016, 2360, 2106, 1697, 1419. ^1H NMR ($CHCl_3$-*d*, 200 MHz); δ: 1.95–2.02 (m, 2H, C3H), 3.07–3.85 (m, 4H, 2×C5H, CH_2N_3, OH), 3.97–4.45 (m, 2H, C2H, C4H), 5.09 (s, 2H, OCH_2), 7.31 (s, 5H, C_6H_5). ^{13}C NMR ($CHCl_3$-*d*, 200 MHz); δ: 36.9, 37.5, 51.9, 53.2, 55.2, 54.8, 5, 66.6, 67.0, 68.4, 68.8, 127.2, 127.5, 128.1, 136.2, 162.5; LCMS; 277.00 $[M+1]^+$.

3.1.4. (2*S*,4*R*)-*N*1-(Benzyloxycarbonyl)-4-hydroxy-2-(aminomethyl)-pyrrolidine (7). To a solution of the azide **6** (3.5 g, 12.7 mmol) in methanol (5 ml) taken in hydrogenation flask was added Raney Ni (1.5 ml). The reaction mixture was hydrogenated in a Parr apparatus for 3.5 h at rt and H_2 of pressure 35–40 psi. The catalyst was filtered off and then solvent was removed under reduced pressure to yield a residue of the amine **7** as colorless oil. Yield (3.0 g, 95.0%); this compound was used for the further reaction without any purification.

3.1.5. (2*S*,4*R*)-*N*1-(Benzyloxycarbonyl)-2-(*tert*-butyloxycarbonylaminomethyl)-4-hydroxy pyrrolidine (8). The amine **7** (3.0 g, 12.0 mmol) was taken in DMSO (10 ml), triethylamine (1.58 g, 15.6 mmol) and $BocN_3$ (2.05 g, 14.4 mmol) were added. The reaction mixture was heated to 50 °C for 8 h. The reaction mixture was poured into 150 ml of ice-cold water and the product extracted into ether (20 ml×8). The combined ether layer was washed with water, brine and then concentrated to give Boc protected amine **8** as light yellow oil. (3.2 g, yield 76%, R_f=0.6, ethyl acetate:petroleum ether). $[\alpha]_D^{20}$ −12.7 (*c* 0.7, CH_2Cl_2); IR (neat) (ν) cm^{-1}. 3310, 3121, 1689, 1570. ^1H NMR ($CHCl_3$-*d*, 200 MHz); δ: 1.41 (s, 9H, Boc), 1.6–2.3 (m, 3H, C2H, C3H_2), 3.15–3.75 (m, 4H, C5H_2, CH_2NH), 3.9–4.2 (m, 1H, C4–OH), 4.3–4.5 (m, 1H, C4H), 5.11 (s, 2H, OCH_2), 5.4–5.6 (br d, 1H, carbamate NH), 7.33 (s, 5H, C_6H_5). ^{13}C NMR ($CHCl_3$-*d*, 200 MHz); δ: 28.3, 38.04, 44.1, 54.9, 56.6, 67.0, 69.2, 79.2, 128.4, 136.4, 156.3, 159.6. Anal. Calcd (%) for $C_{18}H_{26}N_2O_5$: C, 61.71; H, 7.42; N, 8.00. Found C, 61.68; H, 7.64; N, 7.78; LCMS; 351.21 $[M+1]^+$.

3.1.6. [(2*S*,4*R*)-2-(*tert*-Butyloxycarbonylaminomethyl)-4-hydroxypyrrolidine (9). To a solution of the ester **8** (3.2 g, 9.5 mmol) in methanol (5 ml) in a hydrogenation flask was added 10% Pd–C (0.32 g). The reaction mixture was hydrogenated in a Parr apparatus for 7 h at rt and H_2 at 60 psi pressure. The catalyst was filtered off and then solvent was removed under reduced pressure to yield a residue of the amine **9** as colorless oil. Yield (1.9 g, 95%); this compound was used for the further reaction without any purification.

3.1.7. Ethyl [(2*S*,4*R*)-2-(*tert*-butyloxycarbonylaminomethyl)-4-hydroxypyrrolidin-1-yl]-propanoate (10). To the cyclic amine **9** (1.9 g, 8.8 mmol) in methanol (20 ml), was added ethyl acrylate (0.97 g, 9.68 mmol) and stirred for 3 h at rt. The reaction mixture was evaporated to dryness and was extracted into ethyl acetate (25 ml×3). The organic layer was dried over Na_2SO_4 and concentrated to give crude residue, which on column chromatography afford ester **10** as thick colorless oil. (2.0 g, yield 72%, R_f=0.6, MeOH/CH_2Cl_2-1:9). $[\alpha]_D^{20}$ −7.7 (*c* 3.23, CH_2Cl_2); IR (neat) (ν) cm^{-1}. 3410, 1730, 1697, 1410. ^1H NMR ($CHCl_3$-*d*, 200 MHz); δ: 1.24 (t, 3H, ester CH_3), 1.41 (s, 9H, Boc), 1.52–1.9 (m, 2H, C3H_2), 1.95–2.6 (m, 5H, –CH_2–CH_2–, C2H), 2.7–3.5 (m, 5H, C5H_2, CH_2NH, OH), 3.7–4.2 (m, 2H, ester CH_2), 4.25–4.4 (m, 1H, C4H), 4.75–5.45 (br d, 1H, NH). ^{13}C NMR ($CHCl_3$-*d*,

200 MHz); δ:13.9, 28.1, 33.7, 37.7, 40.7, 49.1, 60.2, 61.3, 61.6, 69.2, 78.7, 156.3, 172.4. Anal. Calcd (%) for $C_{15}H_{28}N_2O_5$: C, 56.96; H, 8.86; N, 8.86. Found C, 56.65; H, 8.95; N, 8.71; LCMS; 317.00 $[M+1]^+$.

3.1.8. Ethyl [(2*S*,4*S*)-2-(*tert*-butyloxycarbonylaminomethyl)-4-(*N*3-benzoylthymin-1-yl)-pyrrolidin-1-yl]-propanoate (11). To a solution of alcohol **10** (1.5 g, 4.74 mmol), *N*3-benzoylthymine and triphenylphosphine in dry benzene cooled to 4 °C, was added DIAD dropwise by a syringe under nitrogen atmosphere. The reaction mixture was stirred for another 5 h at rt. The reaction mixture was evaporated to dryness and the residue was purified by column chromatography to obtain monomer ethyl ester **11** as foam. (1.8 g, yield 72%, R_f=0.76, MeOH/CH_2Cl_2-1:9). $[\alpha]_D^{20}$ −69.16 (*c* 0.50, CH_2Cl_2); IR (Nujol) (ν) cm^{-1}. 3019, 1730, 1710, 1697, 1550, 1415. ^1H NMR ($CHCl_3$-*d*, 500 MHz); δ_H 1.29 (t, 3H, ester CH_3), 1.41 (s, 9H, Boc), 1.55–1.8 (m, 1H, C3H′), 1.96 (s, 3H, thymine-CH_3), 2.15–2.3 (m, 1H, C3H), 2.35–2.7 (m, 5H, –CH_2–CH_2–, C2H), 3.0–3.2 (m, 3H, C5H′, CH_2NH), 3.25–3.4 (m, 1H, C5H), 3.95–4.15 (m, 2H, ester CH_2), 4.95–5.15 (m, 1H, C4H), 5.2–5.3 (br d, 1H, NH), 7.15–7.25 (m, 2H, Ar), 7.25–7.35 (m, 1H, Ar), 7.35–8.00 (m, 3H, thy CH, Ar). ^{13}C NMR ($CHCl_3$-*d*, 500 MHz); δ_C 12.1, 13.9, 28.0, 33.2, 35.5, 39.5, 47.5, 57.3, 58.5, 60.4, 63.0, 79.0, 110.6, 128.8, 130.0, 131.6, 134.5 and 135.4, 149.6, 156 .0, 162.2, 168.9, 172.2. Anal. Calcd (%) for $C_{27}H_{36}N_4O_7$: C, 61.36; H, 6.81; N, 10.60. Found C, 61.13; H, 6.97; N, 10.43; MS LCMS; 528.01 $[M]^+$, 428.01 $[M-t\text{Boc}]^+$.

3.1.9. [(2*S*,4*S*)-2-(*tert*-Butyloxycarbonylaminomethyl)-4-(thymin-1-yl)-pyrrolidin-1-yl]-propaonic acid (12). The monomer ethyl ester **11** (1.2 g, 2.8 mmol) was dissolved in methanol (6 ml), 2 M NaOH (6 ml) was added and the reaction stirred for 7 h. The aqueous layer was then neutralized with cation exchange resin (Dowex-H^+). The reaction mixture was filtered to remove the resin. The aqueous layer was washed with ethyl acetate to remove benzoic acid. The aqueous layer was concentrated to a residue that on co-evaporation with dichloromethane (10 ml×2) afforded monomer **12** as foam. (1.1 g, yield 98%), mp, 119–121 °C; $[\alpha]_D^{20}$ −78.0 ° (*c* 0.5, CH_2Cl_2); IR (neat) (ν) cm^{-1}. 3016, 1705, 1699. ^1H NMR (D_2O, 500 MHz); δ_H 1.39 (s, 9H, Boc), 1.82 (s, 3H, thy CH_3), 2.1–2.3 (m, 1H, C3H′), 2.45–2.75 (m, 2H, N–CH_2–CH_2–CO), 2.8–2.9 (m, 1H, C3H), 2.95–3.15 (m, 1H, C2H), 3.4–3.8 (m, 5H, COCH_2–CH_2–N, CH_2NH, C5H), 3.95–4.15 (m, 1H, C5H′) 4.8 (m, 1H, C4H), 7.44 (s, 1H, thy CH). ^{13}C NMR (D_2O, 500 MHz); δ_C 11.0, 27.45, 31.9, 32.4, 38.0, 50.3, 56.7, 57.5, 66.8, 81.4, 110.4, 142.6, 157.6, 158.0, 168.5, 177.7. Anal. Calcd (%) for $C_{18}H_{28}N_4O_6$: C, 54.54; H, 7.07; N, 14.14. Found C, 54.23; H, 7.29; N, 13.97; MS LCMS; 397.05 $[M+H]^+$, 297.05 $[M+1-t\text{Boc}]^+$.

3.2. Hydrolysis of the ethyl ester functions of *aeg*PNA monomers (general method)

The ethyl esters were hydrolyzed using 2 M aqueous NaOH in methanol and the resulting acid was neutralized with activated Dowex-H^+ until the pH of the solution was 7.0. The resin was removed by filtration and the filtrate was concentrated to obtain the resulting Boc-protected acids in excellent yield (>85%). In case of cytosine monomer ethyl ester, mild base 0.5 M LiOH was used to avoid deprotection of the exocyclic amine-protecting group.

3.3. Synthesis of PNA oligomers, incorporating *bep*PNA monomers

The modified PNA monomers were built into PNA oligomers using standard procedure on a L-lysine derivatized (4-methylbenzhydryl)amine (MBHA) resin (initial loading 0.25 meq g^{-1}) with HBTU/HOBt/DIEA in DMF/DMSO as a coupling reagent.

3.4. Cleavage of the PNA oligomers from the resin

The PNA oligomers were cleaved from the resin with TFMSA. The oligomrs were purified by RP-HPLC (C18 column) and characterized by LC-TOF-MS mass spectrometry. The overall yields of the raw products were 35–65%. The normal PNAs were prepared similarly as discussed above. The oligomer attached MBHA resin (20 mg) was stirred with thioanisole (40 μl) and 1, 2-ethanedithiol (32 μl) in an ice bath for 10 min. TFA (240 μl) was added, and after equilibration for 10 min, TFMSA (32 μl) was added slowly. The reaction mixture stirred for 2.5 h at rt, filtered and concentrated under vacuum. The product was precipitated with dry ether from methanol and the precipitate was dissolved in water (200 μl) and loaded over Sephadex G25 column. Fractions of 0.5 ml were collected and the presence of oligomer was detected by measuring the absorbance at 260 nm. Fractions containing oligomer were freeze-dried and the purity of the fractions was assessed by analytical RP-HPLC. If the purity is less than 90%, oligomers were purified by preparative HPLC.

3.5. Gel filtration

The crude PNA oligomer obtained after ether precipitation was dissolved in water (200 μl) and loaded on a gel filtration column. This column consisted of G25 Sephadex and had a void volume of 1 ml. The oligomer was eluted with water and ten fractions of 1 ml volume each were collected. The presence of the PNA oligomer was detected by measuring the absorbance at 260 nm. The fractions containing the oligomer were freeze-dried. The purity of the cleaved crude PNA oligomer was determined by RP-HPLC on a C18 column. If the purity of the oligomers found to be above 96%, the oligomers were used as such for experiments without further purification. If the purity was not satisfactory, the oligomers were purified by HPLC.

3.6. HPLC (high performance liquid chromatography) purification of PNA oligomers

Peptide purifications were performed on a Waters DELTA-PAK-RP semi preparative C18 column attached to a Hewlett Packard 1050 HPLC system equipped with an auto sampler and Jasco-UV970 variable-wavelength detector. An isocratic elution method with 10% CH_3CN in 0.1% TFA/H_2O was used with flow rate 1.5 ml/min and the eluent was monitored at 260 nm. The purity of the oligomers was further assessed by RP-C18 analytical HPLC column (25× 0.2 cm, 5 μm) with gradient elution: *A* to 50% *B* in 30 min,

$A=0.1\%$ TFA in H_2O, $B=0.1\%$ TFA in CH_3CN/H_2O 1:1 with flow rate 1 ml/min. The purities of the purified oligomers were found to be $>98\%$.

3.7. LC-TOF-MS

Purity and the integrity of all PNAs synthesized were ascertained by HPLC/LC-TOF-MS mass spectrometry employing electrospray ionization technique. Neat samples were dissolved in methanol and are injected through HPLC system. The TOF (time of flight) detector was used to analyze the molecular ion peaks.

3.8. Binding stoichiometry

Eleven mixtures of PNA:DNA with different ratios to each other such as 0:100, 10:90, 20:80, 30:70, 40:60, 50:50, 60:40, 70:30, 80:20, 90:10 and 100:0; all of the same total strand concentration (2 mM) in sodium phosphate buffer (100 mM NaCl, 0.1 mM EDTA, pH 7.0). The samples are heated to 85 °C in water bath for 5 min, allowed to cool to rt and then cooled further in a refrigerator overnight. CD spectra for all the samples were recorded at 10 °C with wavelength range from 350–190 nm with scan speed 100 nm/min, accumulation-8, response time-4 s, band width-1 nm and sensitivity-10 mdeg. CD cell for all the studies was of 10 mm path length. Baseline was subtracted from all the CD spectra.

3.9. UV–T_m measurements

The concentration was calculated on the basis of absorbance from the molar extinction coefficients of the corresponding nucleobases (i.e., T, 8.8 $cm^2/\mu mol$; C, 7.3 $cm^2/\mu mol$; G, 11.7 $cm^2/\mu mol$ and A, 15.4 $cm^2/\mu mol$). The complexes were prepared in 10 mM sodium phosphate buffer, pH 7.0 containing NaCl (100 mM) and EDTA (0.1 mM) and were annealed by keeping the samples at 85 °C for 5 min followed by slow cooling to rt (annealing). Absorbance versus temperature profiles were obtained by monitoring at 260 nm with Perkin-Elmer Lambda 35 UV–vis spectrophotometer scanning from 5 to 85/90 °C at a ramp rate of 0.2 °C per min. The data were processed using Microcal Origin 5.0 and T_m values derived from the first derivative curves.

3.10. Circular dichroism

CD spectra were recorded on a JASCO J-715 spectropolarimeter. The CD spectra of the PNA:DNA complexes and the relevant single strands were recorded in 10 mM sodium phosphate buffer, 100 mM NaCl, 0.1 mM EDTA, pH 7.0. The temperature of the circulating water was kept below the melting temperature of the PNA:DNA complexes, that is, at 10 °C. The CD spectra of the homothymine T_8 single strands were recorded as an accumulation of 10 scans from 320 to 195 nm using a 1 cm cell, a resolution of 0.1 nm, band width of 1.0 nm, sensitivity of 2 mdeg, response 2 s and a scan speed of 50 nm/min for the PNA_2:DNA complexes, spectra were recorded as an accumulation of 8 scans, response of 1 s and a scan speed of 200 nm/min.

3.11. Gel mobility shift assay

The PNAs (**13–18**, Table 2) were individually mixed with DNA **21** in 2:1 ratio (PNA strand, 0.4 mM and DNA **21**, 0.2 mM) in water. The samples were lyophilized to dryness and re-suspended in sodium phosphate buffer (10 mM, pH 7.0, 10 µl) containing EDTA (0.1 mM). The samples were annealed by heating to 85 °C for 5 min followed by slow cooling to rt and refrigeration at 4 °C overnight. To this, 10 µl of 40% sucrose in TBE buffer pH 8.0 was added and the sample was loaded on the gel. Bromophenol blue (BPB) was used as the tracer dye separately in an adjacent well. Gel-electrophoresis was performed on a 15% non-denaturing polyacrylamide gel (acrylamide/bis-acrylamide, 29:1) at constant power supply of 200 V and 10 mA, until the BPB migrated to three-fourth of the gel length. During electrophoresis the temperature was maintained at 10 °C. The spots were visualized through UV shadowing by illuminating the gel placed on a fluorescent silica gel plate, GF_{254} using UV-light.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.12.002. ^1H and ^{13}C NMR Spectra, Mass spectra of selected compounds, HPLC profiles and LC-TOF-MS spectra of bepPNAs and UV–T_m curves, CD curves.

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1-Iodo-1-selenoalkenes as versatile alkene 1,1-dianion equivalents. Novel connective approach towards the tetrahydropyran subunit of polycavernoside A

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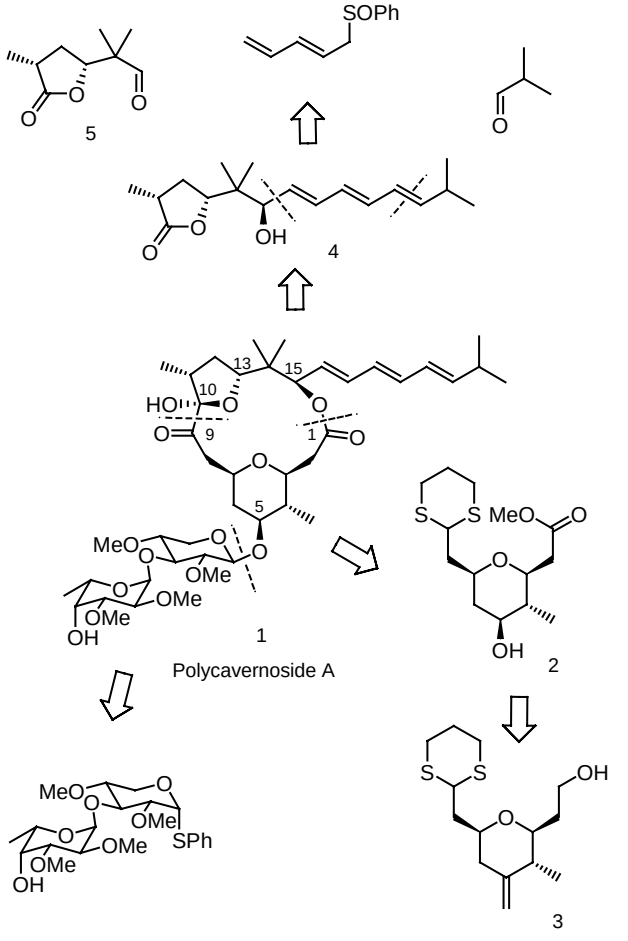
Abstract—*syn*-Hydroalumination of 2,4,6-triisopropylphenylselanyl-1-alkynes with DIBAL-H followed by Al/I exchange with I_2 afforded exclusively (*E*)-1-iodo-1-selenoalkenes in good yields. 1-Iodo-1-selenopropene **10** proved to be a convenient 1,1 dianion equivalent, leading to the stereodivergent synthesis of allylsilanes (*Z*)-**6** and (*E*)-**6**. Adduct **3**, an intermediate in the synthesis of the tetrahydropyran subunit of polycavernoside A, was efficiently synthesised from allylsilane (*Z*)-**6** and aldehyde **7** via an intramolecular Sakurai cyclisation.

1. Introduction

In April 1991, the ingestion of the red alga *gracilaria tsudae* caused a severe human intoxication in the island of Guam. Thirteen people were affected; three of them died.[1] This alga, documented only from the west coast of Guam, is a local gastronomic speciality that develops seasonal toxic properties for still unknown reasons. In 1993, Yasumoto and co-workers reported the isolation, from the causative alga, of polycavernosides A and B, which were identified as the responsible toxins for fatal poisoning.[2] Three other analogs (A2, A3, B2) were reported by Yasumoto in 1995.[3] Polycavernoside A **1** is the main member of a growing family of polycavernoside congeners. Since the elucidation of its planar structure, **1** has attracted the attention of several synthetic groups, undoubtedly due to its challenging architectural features and its biological activities. Polycavernoside A possesses an unusual 13-membered keto-lactone ring and an interesting five-membered hemiketal function connected to the C_9 ketone group. Moreover, a labile triene moiety is linked to C_{15} (Scheme 1). The first total synthesis of **1** was reported by Murai and co-workers in 1998. They established at the same time its absolute stereochemistry.[4] Two other total synthesis have been reported so far.[5]

Our retrosynthetic analysis of **1** is depicted in Scheme 1. Disconnection of the C_1–O and C_9–C_{10} bonds leads to three fragments of approximately the same molecular complexity.



Scheme 1. Retrosynthetic analysis of polycavernoside A.

Keywords: Alkenes; Carbanions; Polycavernoside A; Sakurai cyclisation; Selenium.
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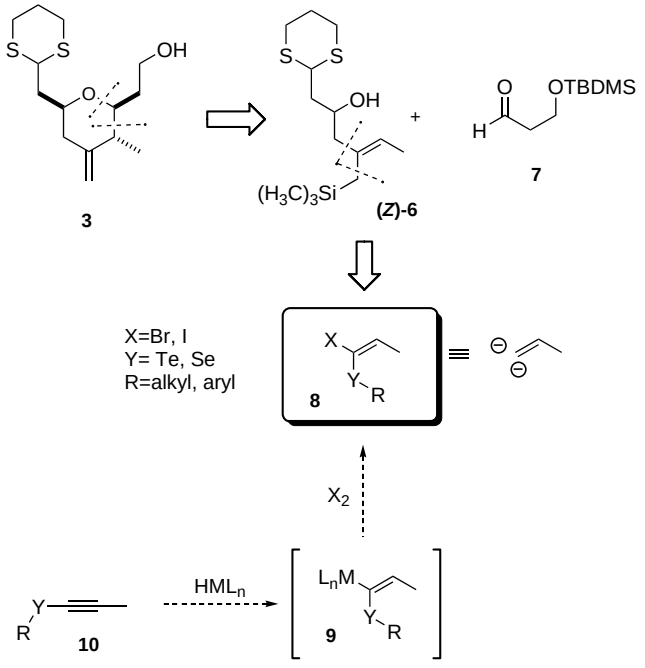
The northern subunit consists of the five-membered lactone **4**, bearing the trienyl side chain, and the southern moiety **2** embodies a tetrasubstituted tetrahydropyran core. The disaccharide residue has already been efficiently prepared by Murai et al.[6] Our laboratory has previously disclosed an expedient synthesis of **4** from the readily available γ-butyrolactone subunit **5**.[7] Recently, we have reported our preliminary results on a stereocontrolled approach to the tetrahydropyran subunit **2**, via an intramolecular Sakurai cyclisation (IMSC).[8] In this article, we wish to present a full account of our investigations directed towards a connective and efficient synthesis of the tetrahydropyran subunit of polycavernoside A, using as a key intermediate, a novel alkene 1,1-dianion equivalent.

According to our strategy, the southern subunit **2** could be derived from the tetrahydropyran **3** by a few functional group transformations. Thus, the stereocontrolled preparation of **3** became our prime objective. Our antithetic analysis of **3** is shown in Scheme 2. Application of the IMSC retron to **3** leads to the generation of two simple fragments: the allylsilane **6** and the β-hydroxy aldehyde **7**. The condensation of these two fragments should afford stereoselectively the requisite *exo*-methylene tetrahydropyran **3**. The intramolecular Sakurai cyclisation is believed to proceed via a two-step mechanism. The coupling between an allylsilane such as **6** and an aldehyde such as **7**, in the presence of a Lewis acid, generates initially an oxocarbenium cation intermediate, which undergoes subsequent ring closure by intramolecular nucleophilic addition of the pendant allylsilane function, to give a tetrahydropyran ring possessing an exocyclic C–C double bond. The relative configuration of the three stereogenic centres in the final product is governed by the preference of the substituents to occupy pseudoequatorial positions in the chair-like transition-state during the ring closure step.[9] An important parameter in the control of the relative orientation of the substituents in the final adduct is the geometry of the C–C double bond of the allylsilane. According to this model, the (*Z*)-allylsilane **6** is required to obtain the tetrahydropyran possessing the correct stereochemistry present in polycavernoside A.



Scheme 2. Strategy for the synthesis of tetrahydropyran **3**.

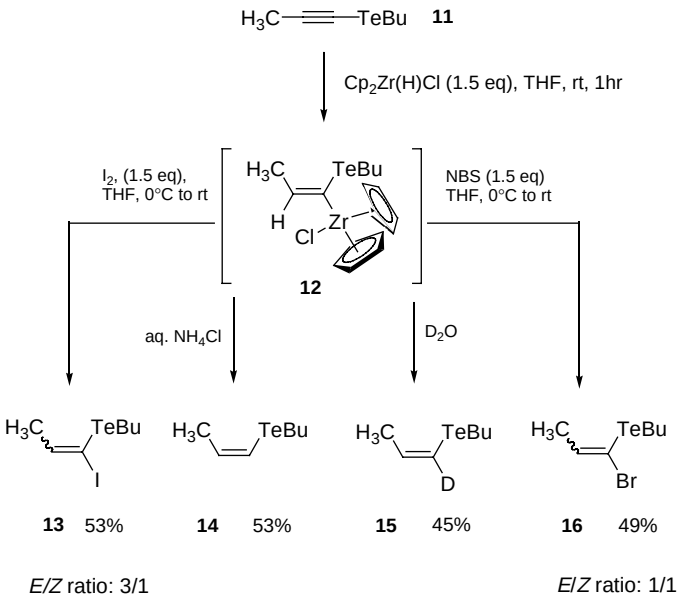
Despite the number of procedures described in the literature for the synthesis of alkenes, there are few, simple and general methodologies that lead to the preparation of trisubstituted allylsilanes with good stereocontrol of the olefin geometry.[10] In order to explore new strategies in this field, we decided to prepare allylsilane **6** from a synthetic equivalent of an alkene 1,1-dianion. Several reports describe the synthesis of alkene 1,1-bismetallic species.[11] Unfortunately, most of these reagents were found to suffer from serious shortcomings, such as lack of reactivity, difficulty in handling and, often, tedious preparation. Therefore, it was deemed interesting to investigate the reactivity of 1-halo-1-chalcogeno-alkenes **8** as equivalents of alkene 1,1-dianions. Compounds such as **8** can be handled without special precautions and can be transformed easily into a variety of di- and tri-substituted olefins via a sequential functionalisation of both hetereoatom positions. Interestingly, by inverting the sequence, the same precursor **8** should afford the opposite *E*/*Z* isomer of **6**.

The stereoselective synthesis of 1-halo-1-chalcogeno-alkenes **8** was envisaged to be accomplished by the hydrometallation of the C–C triple bond of 1-alkynyl chalcogenides **10**, followed by metal/halogen exchange of the in situ generated 1-metallo-1-chalcogeno alkene species **9**. Hydrometallation of hetero-substituted alkynes is usually a highly regio- and stereoselective reaction and, in most cases, the addition can be controlled to take place in a *syn* manner. The C–C triple bond of 1-alkynyl chalcogenides is polarized in such a way that the metal residue is typically positioned on the carbon bearing the chalcogen substituent. The most common hydrometallating agents are boron, aluminium and zirconium mono hydrides. Among these, $Cp_2Zr(H)Cl$ is the most tolerant with regard to other functional groups.

2. Results and discussion

2.1. Synthesis of 1-halogeno-1-chalcogeno-alkenes

2.1.1. 1-Telluro-1-halogeno propenes. Attracted by the broad range of interesting potential transformations that organotellurides can undergo,[12] we began our investigations by the preparation of 1-halo-1-telluro propenes, according to the procedure described by Dabdoud et al.[13] Hydrozirconation of 1-butyltellanyl-propyne **11** with $Cp_2Zr(H)Cl$ generated in situ the 1-telluro-1-zircono alkene species **12**,[14,15] which was subsequently trapped with different electrophiles giving the corresponding 1-alkenyl tellurides **13**–**16** (Scheme 3). In our hands, hydrozirconation of **11** afforded the 1-alkenyl tellurides in only moderate yields. Besides the desired products, and in all cases, a considerable amount of dibutyl ditelluride was formed. It has been reported that 1-butyltellanyl alkynes undergo easy tellurium–spC bond cleavage by treatment with hydrides, such as DIBAL-H, $LiAlH_4$ or $NaBH_4$, affording the tellurium free alkyne and dibutyl ditelluride. It is believed that hydride addition on the tellurium moiety generates

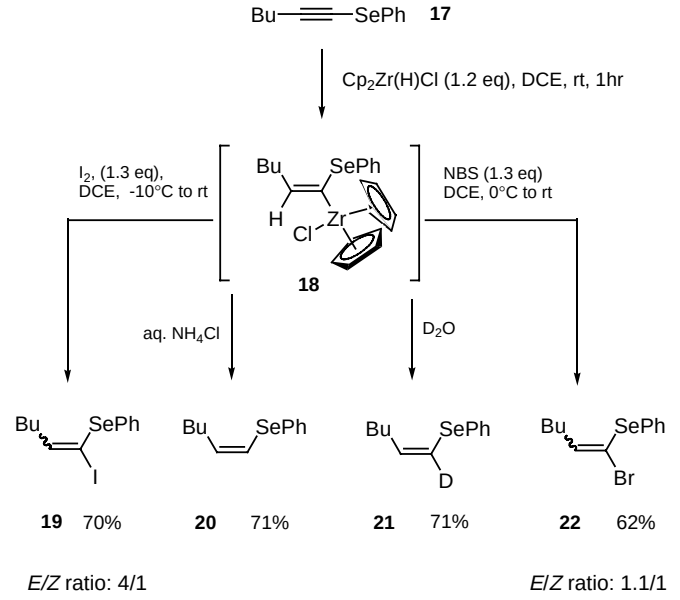


Scheme 3. Hydrozirconation–halogenation of telluroalkyne **11**.

butyltellurol and an acetylide anion. Butyltellurol is deprotonated by the hydride to give butyltellurate, which rapidly oxidises to dibutyl ditelluride in the presence of oxygen, during the work-up.[15] Our results indicate that the hydrozirconation of **11** leads to the competitive formation of dibutyl ditelluride via an analogous pathway.

In our case, the optimised conditions for the hydrozirconation of **11** were found to require 1.5 equiv of freshly prepared $Cp_2Zr(H)Cl$. However, other groups reported the use of 1.1[13b] and 2.0[13a] equiv as the optimal number of $Cp_2Zr(H)Cl$ equivalents. The isolated yields of 1-alkenyl tellurides also differ significantly from one group to another, indicating that the hydrozirconation of 1-alkynyl tellurides is highly dependent upon the quality and the mode of preparation of $Cp_2Zr(H)Cl$.[16] These results are thus difficult to reproduce and it was decided to investigate the hydrozirconation of other, more ameanable precursors. Moreover, 1-iodo-1-butyltellanyl-propene **13** and 1-bromo-1-butyltellanyl propene **16** were always obtained as an inseparable mixture of *E*/*Z* isomers.

2.1.2. 1-Seleno-1-halogeno alkenes. Searching for substrates less prone to undergo heteroatom-spC cleavage during the hydrozirconation step, and aware that the C–Se bond is stronger than the C–Te bond, we elected to study the hydrometallation of the corresponding alkynyl selenides. As a model compound, hex-1-ynylselanyl-benzene **17** was hydrozirconated with $Cp_2Zr(H)Cl$ and the in situ generated 1-seleno-1-zircono-alkene intermediate **18** was quenched with various electrophiles (Scheme 4).[17,18] As expected, the corresponding 1-alkenyl selenides **19**–**22** were obtained in better yields (around 70%) as compared to the 1-alkenyl tellurides. However, diphenyl diselenide was formed as

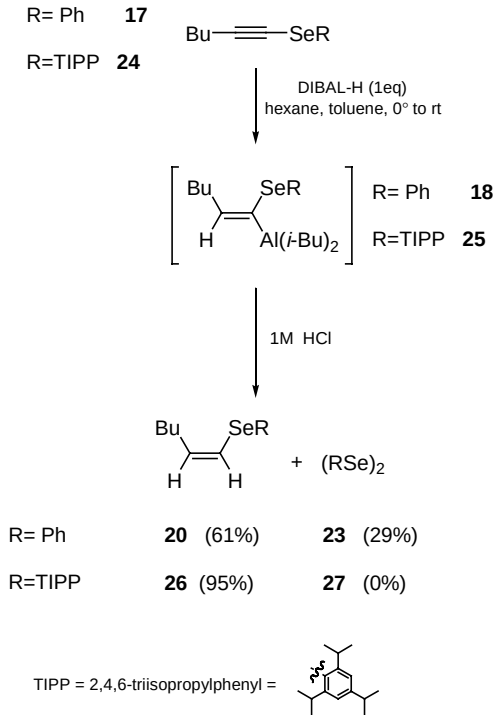


Scheme 4. Hydrozirconation–halogenation of selenoalkyne **17**.

the main by-product, indicating that the competitive Se–spC cleavage could not be completely prevented. Trapping **18** with I_2 or NBS, at low temperature, provided an inseparable mixture of (*E*)- and (*Z*)-isomers of the corresponding 1-halo-1-selenoalkenes **19** and **22**. Though the iodoalkene **19** was obtained in a fairly good yield, and a reasonable *E*/*Z* ratio of 4:1, such a selectivity is clearly not adequate for synthetic purposes.

In order for our methodology to embrace broad synthetic interest, it proved imperative to overcome three main drawbacks; (i) to prevent completely the competitive Se–spC bond cleavage; (ii) to avoid the isomerisation during the metal/halogen exchange and (iii) if possible, to replace the expensive and sensitive $Cp_2Zr(H)Cl$ by another, cheaper and easier to handle, hydrometallating agent.

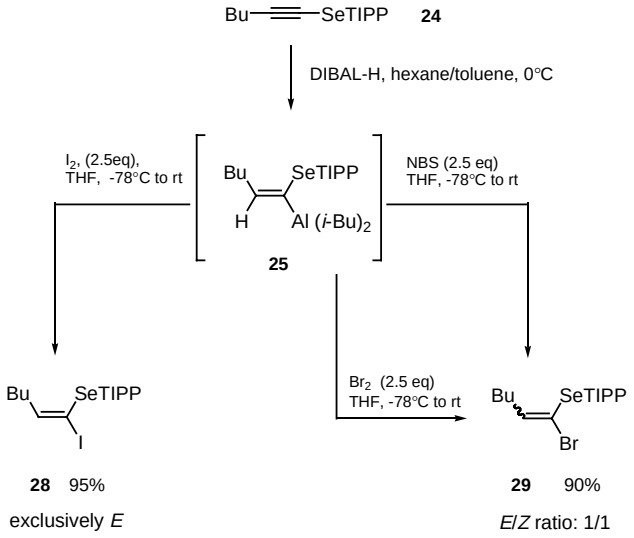
Hydroalumination of hex-1-ynylselanyl-benzene **17** with DIBAL-H,[19] followed by quenching with dilute HCl, provided a mixture of 1-hexenyl selenide **20** (61% yield) and diphenyl diselenide **23** (39% yield, Scheme 5). Although DIBAL-H produced more diphenyl diselenide than $Cp_2Zr(H)Cl$, it was envisioned that the competitive spC–Se bond cleavage could probably be suppressed by selectively hindering the selenium atom, thereby impeding the coordination between the selenium substituent and the aluminium reagent and hence, thwarting the delivery of hydride on selenium. In order to verify our hypothesis, 1-(2,4,6)-triisopropylphenyl-selenyl-hex-1-yne **24**, bearing the voluminous 2,4,6-triisopropylphenyl (TIPP) substituent instead of the phenyl group, was prepared.[20] When **24** was treated with DIBAL-H, followed by quenching of the intermediate vinyl alane **25** with dilute HCl (under the same conditions than **18**), we were delighted to observe the exclusive formation of the (*Z*)-alkenyl selenide **26**, which



Scheme 5. Effect of the TIPP group on the hydroalumination of selenoalkynes.

was isolated in 95% yield. Diselenide **27** could not be detected in the crude reaction mixture (Scheme 5). It thus transpires that the steric hindrance of the TIPP group dramatically influences the selectivity of the hydroalumination reaction by suppressing the competitive C–Se bond cleavage. The formation of the diselenide by-product **27** is prevented and the hydrometallation of the C–C triple bond becomes essentially quantitative.

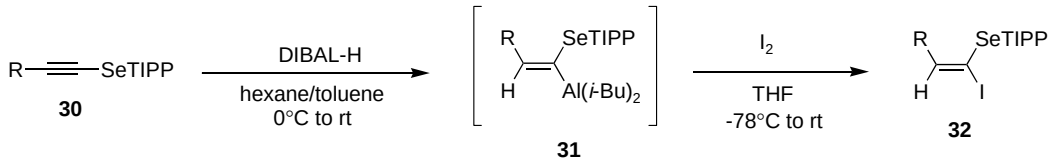
Having discovered that the use of the TIPP group enabled the efficient hydroalumination of **24**, we next turned our attention to the metal/halogen exchange reaction. To our delight, trapping of **25** with I_2, at low temperature, afforded the corresponding 1-iodo-1-selenoalkene **28** in 95% yield. Even more gratifyingly, only the (*E*)-isomer was isolated, indicating that the replacement of Al by I took place with retention of configuration of the C–C double bond (Scheme 6). In sharp contrast, bromination of **25**, either with Br_2 or NBS, afforded a 1/1 mixture of (*E*)- and (*Z*)-1-bromo-1-selenoalkenes **29**. Although the yields were good, the replacement of Al by Br occurred with complete scrambling of the configuration of the C–C double bond, even under carefully controlled reaction conditions. These observations suggest that bromination and iodination of **25** might follow different mechanistic pathways.

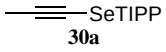
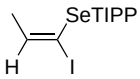
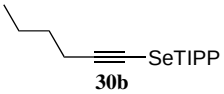
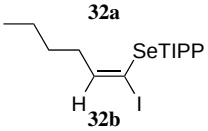
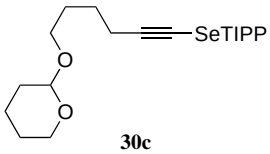
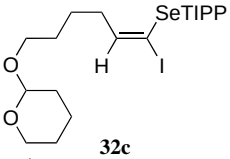
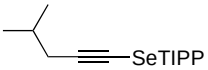
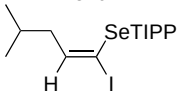
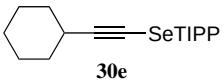
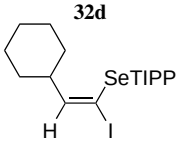
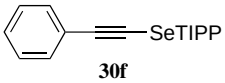


Scheme 6. Hydroalumination–halogenation of selenoalkyne **24**.

In order to verify that this sequence could constitute a new method for the synthesis of (*E*)-1-iodo-1-selenoalkenes, this procedure was applied to other 1-alkynyl selenides bearing the TIPP group. The results of our investigations are shown in Table 1. In all cases, the corresponding (*E*)-1-iodo-1-selenoalkenes **32** were obtained in good to excellent yields and as a single isomer. Only the phenyl acetylene derivative **30f** refused to react (entry 6). In this case, the addition of DIBAL-H to the triple bond did not occur, even when the reaction was attempted in hexane at reflux. This lack of reactivity could be due to prohibitive steric repulsions that gradually build up between the phenyl and the SeTIPP groups during the addition of the aluminium hydride.

Table 1. Synthesis of (*E*)-1-iodo-1-selenoalkenes via hydroalumination–iodination



Entry	Substrate	Product	Yield (%)[a]
1	 **30a**	 **32a**	92
2	 **30b**	 **32b**	95
3	 **30c**	 **32c**	96
4	 **30d**	 **32d**	82
5	 **30e**	 **32e**	91
6	 **30f**	—	0

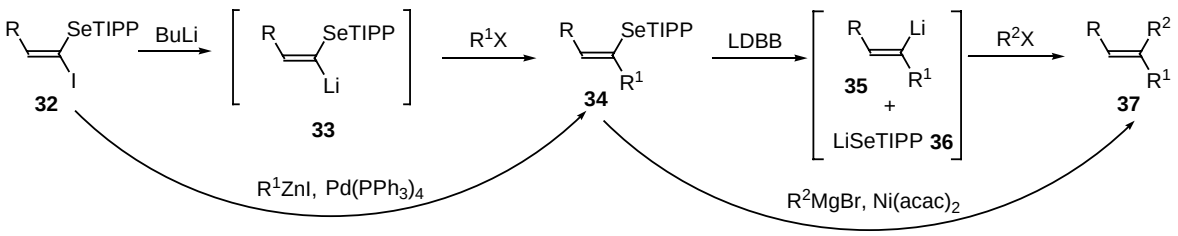
[a] Isolated yield after purification by column chromatography.

The Al/I exchange requires a careful control of the reaction conditions in order for the iodination to be complete. If the reaction mixture is stirred longer than 1 h at room temperature, some degradation occur, accompanied by the appearance of the (*Z*)-isomer.

It did not escape us that the 1-alumino-1-seleno-alkene intermediate **25** (Scheme 6) could be an interesting precursor for the stereodefined synthesis of alkenes, since it is readily accessible from **24** via a simple and selective hydroalumination. Unfortunately, **25** proved to be rather unreactive towards various carbon electrophiles.

2.1.3. Functionalisation of 1-iodo-1-selenoalkenes. With an efficient access to (*E*)-1-iodo-1-selenoalkenes in hand, we turned our attention to the sequential functionalisation of both heteroatom positions (Scheme 7). Initially, the more labile C–I bond was selectively replaced by a C–C bond, either via the intermediacy of the 1-seleno-1-lithio-alkene species **33** or via a palladium-catalysed cross-coupling with organozinc derivatives. Subsequently, the selenium substituent was replaced by a second C–C bond, either via the generation of the disubstituted 1-alkenyl lithium species **35** or via nickel-catalysed cross-coupling with Grignard reagents. No loss of the C–C double bond integrity was observed in this overall process, indicating that 1-iodo-1-selenoalkenes **32** are convenient 1,1-dianion equivalents for the stereoselective synthesis of trisubstituted alkenes.

2.1.4. Functionalisation of the iodo position. 1-Iodo-1-selenoalkene **32a** underwent smooth I/Li exchange when reacted with *n*-BuLi or *t*-BuLi, to give the 1-seleno-1-alkenyllithium intermediate **33a**.[21] Subsequent treatment with various electrophiles, including acylating agents,



Scheme 7. Functionalisation of 1-iodo-1-selenoalkenes.

aldehydes, epoxides or alkyl halides, afforded the corresponding functionalised 1-alkenyl selenides **34** in good yields (Table 2). The I/Li exchange was carried out with 1 equiv of *n*-BuLi, either in THF at −78 °C or in hexane at room temperature. The choice of the best conditions depends strongly upon the electrophile. In the case of valeraldehyde (entry 7), better yields were obtained when the I/Li exchange was performed in hexane, at room temperature.[22] On the contrary, benzoyl chloride (entry 4) gave better results when the metallation was performed in THF, at −78 °C. In order to prevent the formation of butylated by-products, when alkyl halides (entries 10 and 11) were used as electrophiles, the exchange was performed with 2 equiv of *t*-BuLi in THF, at −78 °C. In the case of the allysilane **34k** (entry 11), an interesting improvement was observed when the alkenyl lithium intermediate **33a** was generated by reverse addition, that is, by adding 1-iodo-1-selenoalkene **32a** to a solution of *t*-BuLi in THF, cooled at −78 °C. Subsequent treatment of **33a** with iodomethyltrimethylsilane afforded **34k** in 78% yield. Normal addition (*t*-BuLi added to a THF solution of **33a** at −78 °C) gave **34k** in only 41% yield.

Treatment of **32a** with 2 equiv of isopropylmagnesium chloride, in THF, at room temperature led to the I/Mg exchange.[23] However, the resulting 1-seleno-1-alkenyl magnesium chloride intermediate did not react with carbon electrophiles. This Grignard reagent only underwent protonolysis and deuterolysis.

The palladium-catalysed cross coupling of 1-iodo-1-selenoalkene **32b** with organozinc species (Scheme 8) enabled the direct formation of a C–C bond from the C–I bond. However, only moderate yields were obtained so far.

2.1.5. Functionalisation of the seleno position. The vinylic C–Se bond of several functionalised 1-alkenyl selenides was reductively cleaved in the presence of 2 equiv of LDBB (lithium 4,4′-di-*tert*-butylbiphenyl),[24] generating in situ lithium 2,4,6-triisopropylphenylselenoate **36** and the corresponding 1-alkenyl lithium **35** (Scheme 7).[25] Trapping of the 1-alkenyl lithium derivatives with various electrophiles, at low temperature, afforded the expected trisubstituted alkenes **37–42** in good yields and with complete retention of the C–C double bond geometry (Table 3). The selenoate **36**, generated as a by-product, proved to be a better nucleophile than the 1-alkenyl lithium species. In the reactions of **35** with alkylating agents, the selective quenching of selenoate **36** with 1 equiv of MeI (to give 1 equiv of 2,4,6-triisopropylphenyl methyl selenide), was routinely performed prior to the addition of the electrophile.

It has been described that the vinyl C–Se bond of 1-alkenyl selenides undergoes cross-coupling with organomagnesium derivatives in the presence of nickel complexes as catalyst.[26] This coupling led to a straightforward construction of tri- and tetrasubstituted allylsilanes.[27] In our case, probably due to the steric hindrance of the TIPPSe group, only methylmagnesium bromide could be coupled to **34** (Table 3, entries 5 and 6) using $Ni(acac)_2$ as catalyst. When nickel complexes bearing phosphino ligands were employed, only the starting material was recovered. This observation indicates that only ligandless Ni(0) species are able to insert into the sterically hindered C–Se bond. More encumbered organomagnesium derivatives, such as phenylmagnesium bromide or (trimethylsilylmethyl)magnesium chloride, in the presence of $Ni(acac)_2$, did not afford the expected products.

2.1.6. Synthesis of the (*Z*)- and (*E*)-allylsilanes 6. As previously discussed, the construction of the tetrahydropyran core of polycavernoside A was envisioned from the (*Z*)-allylsilane **6** and the aldehyde **7**, via an IMSC condensation. The (*Z*)-allylsilane **6** was readily assembled from the (*E*)-1-iodo-propenyl selenide **32a** by sequential replacement of the heteroatom substituents (Scheme 9).

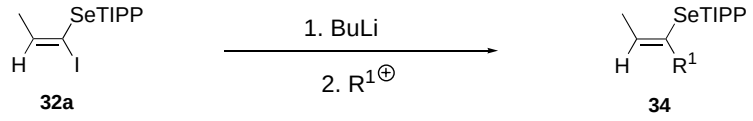
Opening of the dithianylmethyl oxirane **43**, by the vinylic anion derived from **32a** by I/Li exchange with *n*-BuLi, in the presence of $BF_3{\cdot}OEt_2$, resulted in the formation of the homoallylic alcohol **34i** in 50% yield based upon **32a** (100% based upon oxirane **43**). In the absence of the Lewis acid, this vinyl lithium species proved to be rather unreactive towards oxirane **43**. The moderate yield in the presence of $BF_3{\cdot}OEt_2$ is due to the concomitant formation of an unreactive vinyl fluoroborate intermediate,[28] which consumes 50% of the vinyl lithium reagent. By employing two equivalents of vinylselenide **32a**, a quantitative yield of adduct **34i** was obtained.

After treatment of **34i** with methylmagnesium bromide, in order to deprotonate the homoallylic hydroxy function, the alkenyl C–Se bond was reductively cleaved with LDBB, generating the carbanion **45** and lithium selenoate **36** (Scheme 7). Whilst it is reasonable to assume that the lithium salt **45** is initially formed under these reductive conditions, it is quite plausible that metal exchange might take place under the reaction conditions, leading either to **46** or an equilibrating mixture of **45** and **46**, with the latter reagent being the active species in the subsequent coupling step. In this regard, using *n*-BuLi to perform the deprotonation of alcohol **34i**, followed by LDBB treatment, led to significant erosion in the yields of **44** (Scheme 10).

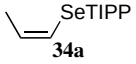
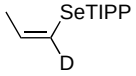
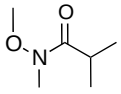
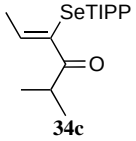
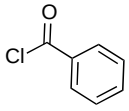
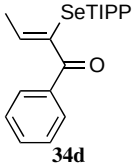
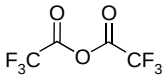
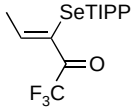
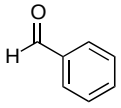
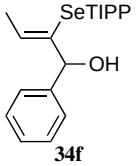
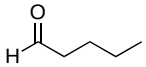
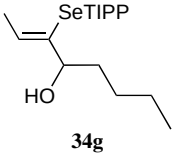
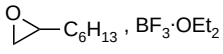
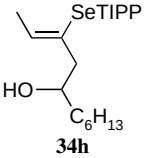
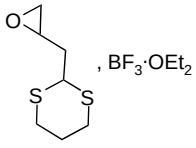
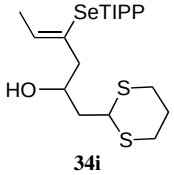
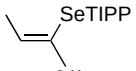
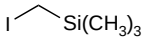
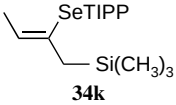
Attempts to react the organometallic derivatives **45/46** with various alkylating agents, in order to introduce directly the CH_2TMS moiety failed, probably owing to the lack of reactivity of these silyl-containing electrophiles. Quenching of **45/46** with I_2 led to the vinyl iodide **44** in excellent yield. It is noteworthy that 1 equiv of MeI has to be added to the lithiated species **45/46**, before the iodine quench, in order to obtain good yields of **44**. Cross-coupling of **44** with trimethylsilylmethyl magnesium chloride, catalysed by $Pd(PPh_3)_4$, ultimately generated the requisite (*Z*)-allylsilane **6** in 55% overall yield from **34i** (Scheme 6). The (*Z*)-configuration of the C–C double bond was established by NOE experiments and subsequently confirmed by the independent synthesis of the (*E*)-isomer, indicating that the transformation of **32a** to (*Z*)-**6** took place with retention of configuration.

To demonstrate the versatility of our methodology, the opposite (*E*)-allylsilane **6** was synthesised from the same precursor **32a** by simply inverting the heteroatom exchange/alkylation sequence. Thus, vinyl selenide **34k** was obtained in 78% yield by alkylation of the vinyl anion, derived from

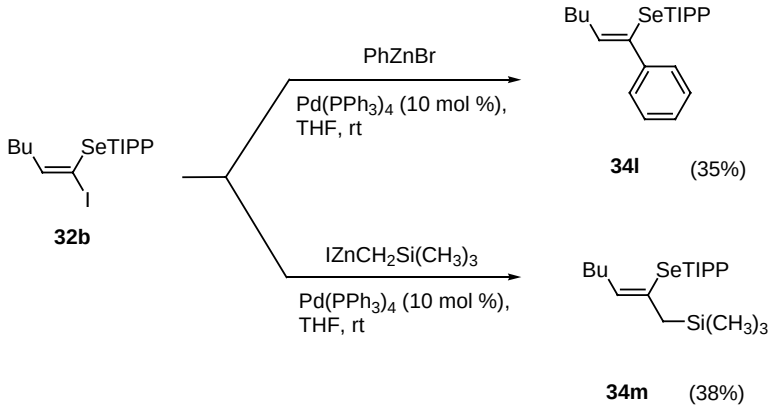
Table 2. Stereocontrolled iodine replacement in **32a**



32a **34**

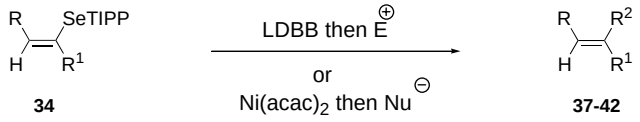
Entry	Conditions	Electrophile	Product	Yield (%)[a]
1	*n*-BuLi (1 equiv), THF, −78 °C	H_2O	 **34a**	91
2	*n*-BuLi (1 equiv), hexane, rt	D_2O	 **34b**	92
3	*n*-BuLi (1 equiv), THF, −78 °C		 **34c**	67
4	*n*-BuLi (1 equiv), THF, −78 °C		 **34d**	72
5	*n*-BuLi (1 equiv), THF, −78 °C		 **34e**	78
6	*t*-BuLi (2 equiv), THF, −78 °C		 **34f**	82
7	*n*-BuLi (1 equiv), hexane, rt		 **34g**	65
8	*n*-BuLi (1 equiv), THF, −78 °C		 **34h**	50
9	*n*-BuLi (1 equiv), THF, −78 °C		 **34i**	50
10	*t*-BuLi (2 equiv), THF, −78 °C	MeI	 **34j**	93
11	*t*-BuLi (2 equiv), THF, −78 °C, reverse addition		 **34k**	78

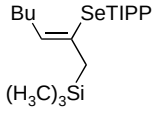
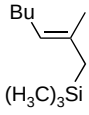
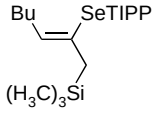
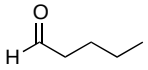
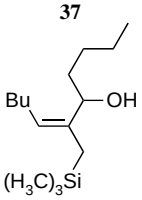
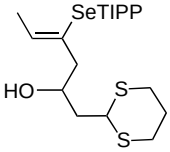
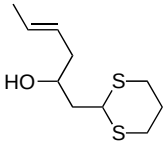
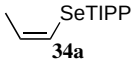
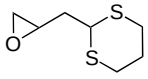
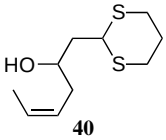
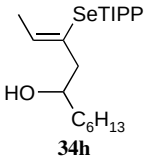
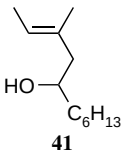
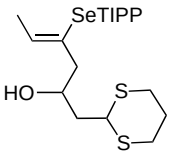
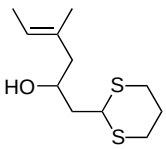
[a] Isolated yield after purification by column chromatography.



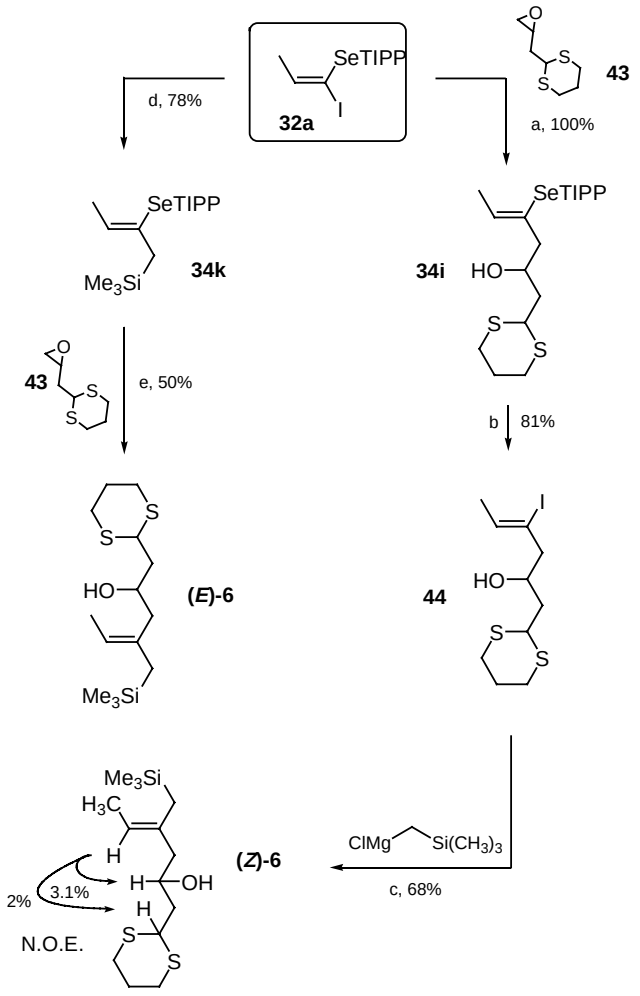
Scheme 8. Negishi coupling of **32b**.

Table 3. Stereocontrolled selenium substitution in **34**

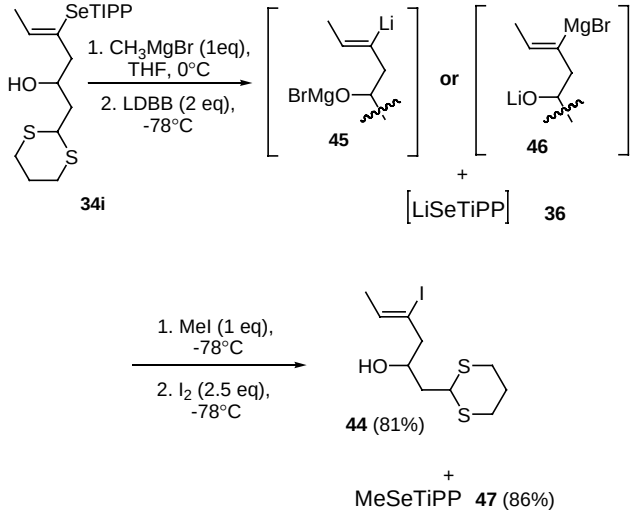


Entry	Sustrate	Conditions	Electrophile/ nucleophile	Product	Yield (%)[a]
1	 **34m**	LDBB (2 equiv), THF, −78 °C	MeI	 **37**	67
2	 **34m**	LDBB (2 equiv), THF, −78 °C		 **38**	62
3	 **34i**	(1) *n*-BuLi (1 equiv), THF, −78 °C (2) LDBB (2 equiv)	H_2O	 **39**	92
4	 **34a**	LDBB (2 equiv), THF, −78 °C	 $BF_3 \cdot OEt_2$	 **40**	85
5	 **34h**	$Ni(acac)_2$ (1 mol%), THF, room temperature	MeMgBr	 **41**	60
6	 **34i**	$Ni(acac)_2$ (1 mol%), THF, room temperature	MeMgBr	 **42**	64

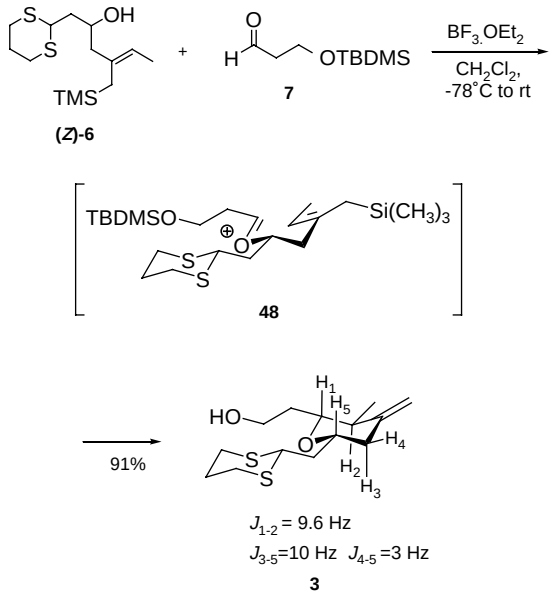
[a] Isolated yield after purification by column chromatography.



Scheme 9. Preparation of (*Z*)- and (*E*)-allysilanes **6**. Conditions: (a) *n*-BuLi, THF, −78 °C, 30 min, $BF_3\cdot OEt_2$, then (±)-**43**, THF, −78 °C, 1 h; (b) CH_3MgBr, THF, 0 °C, 15 min, LDBB (2 equiv), −78 °C, 30 min, MeI, −78 °C, 15 min, then I_2, −78 °C, 1 h; (c) $ClMgCH_2Si(CH_3)_3$, $Pd(PPh_3)_4$, THF, rt, 9 h; (d) *t*-BuLi (2 equiv), THF, −78 °C, 10 min, then iodomethyltrimethylsilane, THF, −78 °C to rt; (e) LDBB (2 equiv), THF, −78 °C, 30 min, MeI, −78 °C, 15 min, $BF_3\cdot OEt_2$ then (±)-**43**, THF, −78 °C, 1 h.



Scheme 10. Selenium replacement in **34i**.



Scheme 11. The IMSC condensation.

32a by I/Li exchange with *t*-BuLi, with iodomethyltrimethylsilane. Reductive lithiation of **34k** with LDBB generated in situ the corresponding 1-alkenyl lithium species, which opened oxirane **43** in the presence of $BF_3\cdot OEt_2$, to give the (*E*)-allylsilane **6** in 39% overall yield from **32a**.

2.1.7. Intramolecular Sakurai cyclisation. With a ready supply of allylsilane (*Z*)-**6** in hand, we next turned our attention to the crucial intramolecular Sakurai cyclisation. We were delighted to observe that the tetrahydropyran **3** could be readily obtained, in a 91% yield, when (*Z*)-**6** and aldehyde **7** were treated with 1 equiv of $BF_3\cdot OEt_2$, at low temperature. Interestingly, it was found that smooth deprotection of the TBDMS group occurred concomitantly, when the reaction mixture was allowed to warm up to room temperature, affording in a single operation the free alcohol **3**. The relative stereochemistry of **3** was unambiguously established by careful analysis of its ^1H NMR spectrum. The coupling constant values of 9.6 and 10 Hz for the H^1–H^2 and H^5–H^3 hydrogen pairs clearly indicate that the three substituents occupy equatorial positions on the tetrahydropyran ring system (Scheme 11).

The relative stereochemistry of adduct **3** can be easily rationalised by examining the transition state invoked in the final cyclisation of the allylsilane residue onto the oxocarbenium cation **48**. In order to minimise steric interactions, the substituents occupy pseudoequatorial positions. The geometry of the allylsilane double bond controls the C_2 configuration.

3. Conclusions

In summary, we have shown that racemic tetrahydropyran **3** could be efficiently synthesised from allylsilane (*Z*)-**6** and aldehyde **7**, using the IMSC condensation as a key step. By the judicious control of the allylsilane C–C double bond, the relative stereochemistry of three stereogenic centres could be

established in a single operation. We have also developed a simple and efficient procedure for the stereocontrolled preparation of a range of 1-iodo-1-selenoalkenes and demonstrated that they are useful precursors for the synthesis of stereodefined di- and tri-substituted alkenes, including the important allylsilane **6**. These interesting vinylselenides can be considered as alkene-1,1-dianion equivalents.

4. Experimental

4.1. Generalities

Unless otherwise stated all the reactions were carried out using anhydrous conditions and under an atmosphere of argon. ^{1}H and ^{13}C NMR spectra were recorded on Varian Gemini 200 and 300 instruments. Chemical shifts are expressed as parts per million (ppm) downfield from tetramethylsilane or calibrated from $CDCl_3$. Mass spectra were obtained using Varian MAT-44 and Finnigan MAT-TSQ 70 spectrometers with electron impact (70 eV) and chemical ionization (100 eV, ionization gas, isobutene). IR spectra were taken with a BIO-RAD FTS 135 spectrometer. Microanalysis were performed in Professor V. Jäger's analytical laboratory (Institut für Organishe Chemie, Universität Stuttgart, Germany). High resolution mass spectra were recorded in Professor R. Flamant's laboratory (Université de Mons, Belgium).

4.1.1. 1-Butyltellanyl-propyne (11). Methylacetylene was bubbled through a stirred solution of *n*-BuLi (6.25 mL, 10 mmol, 1.6 M in hexanes) in THF (7 mL) cooled at 0 °C, until the initial yellow solution becomes a milky suspension. Tellurium (1.3 g, 10 mmol) was added and the suspension heated for 1 h at reflux. The heat source was removed, 1-iodobutane (1.1 mL, 10 mmol) was added and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with petroleum ether (30 mL), washed with brine (30 mL), dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude material was purified by flash chromatography (petroleum ether) affording 1.63 g (73%) of the title compound as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=2.79$ (t, $J=7.4$ Hz, 2H), 2.16 (s, 3H), 1.85 (m, 2H), 1.42 (d, $J=6.9$ Hz, 2H), 0.94 (t, $J=7.3$ Hz, 3H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=$ 189.3, 125.7, 33.7, 24.7, 13.3, 8.6, 5.8 ppm. IR (neat, NaCl): $\nu=3027$, 2936, 2197, 1423, 1030, 1011 cm^{-1}. MS (EI): *m/z* (%): 224 [$M^{+\cdot}$] (76), 168 [$M^{+\cdot}-C_4H_9$] (41). Elemental analysis calcd for $C_7H_{12}Te$ (223.77): C, 37.57; H, 5.41. Found C, 38.02; H, 5.63.

4.1.2. (*Z*/*E*)-1-Butyltellanyl-1-iodo-propene (13). To a suspension of $Cp_2Zr(H)Cl$ (348 mg, 1.35 mmol) in THF (1.5 mL) under argon was added a solution of 1-butyltellanyl-propyne **11** (201 mg, 0.9 mmol) in THF (2 mL). The mixture was stirred at room temperature until a red solution was obtained (ca. 15 min). The solution was cooled to 0 °C and a solution of I_2 (343 mg, 1.35 mmol) in THF (0.5 mL) was added. The mixture was stirred for 1 h at 0 °C and was then allowed to slowly reach room temperature. It was diluted with hexane (10 mL), washed with a saturated aqueous solution of $Na_2S_2O_3$ (10 mL) and then with brine (8 mL). The organic layer was dried over Na_2SO_4 and the solvents were removed under reduced pressure. The crude material was purified by flash chromatography (hexane as eluent) affording 168 mg (53% yield) of the title compound as an inseparable mixture of isomers (*E*/*Z*:3/1; brown oil). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=7.08$ (q, $J=6.8$ Hz, 1H), 6.70 (q, $J=6.4$ Hz, 1H), 2.92 (t, $J=7.4$ Hz, 2H), 2.88 (t, $J=$ 7.4 Hz, 2H), 1.90–1.72 (m, 4H), 1.75 (d, $J=6.3$ Hz, 3H), 1.67 (d, $J=7.4$ Hz, 3H), 1.50–1.33 (m, 4H), 0.94 (t, $J=$ 7.2 Hz, 6H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=150.6$, 149.2, 78.6, 74.6, 34.0, 24.8, 20.8, 14.9, 14.1, 13.5, 6.9 ppm.

4.1.3. (*Z*)-1-Butyltellanyl-propene (14). To a suspension of $Cp_2Zr(H)Cl$ (198 mg, 0.76 mmol, 1.2 equiv) under argon in THF (1.5 mL) was added a solution of 1-butyltellanyl-propyne **11** (143 mg, 0.64 mmol) in THF (2 mL). The yellow suspension was stirred at room temperature for 20 min until a clear red solution was obtained. H_2O (2 μL) was added and the mixture was stirred for a further 15 min. Hexane was added until a white precipitate was formed. It was filtered through a short path of silica and the solvents were removed under reduced pressure. The crude material was purified by column chromatography (hexane as eluent) affording 56 mg (53% yield) of the title compound as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=6.58$ (dd, $J=$ 9.3, 1.2 Hz, 1H), 6.24 (dq, $J=9.3$, 6.4 Hz, 1H), 2.68 (t, $J=$ 7.4 Hz, 2H), 1.84–1.68 (m, 2H), 1.71 (dd, $J=6.4$, 1.2 Hz, 2H), 1.45–1.30 (m, 2H), 0.92 (t, $J=7.3$ Hz, 3H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=142.4$, 100.2, 34.1, 24.9, 13.9, 13.6, 9.9 ppm. IR (neat, NaCl): $\nu=3025$, 2940, 2923, 2201, 1424, 1031, 1011 cm^{-1}. MS (EI): *m/z* (%): 226 [$M^{+\cdot}$] (85). Elemental analysis calcd for $C_7H_{14}Te$ (225.78): C, 37.24; H, 6.25. Found C, 37.69; H, 6.47.

4.1.4. (*Z*/*E*)-1-Bromo-1-butyltellanyl-propene (16). To a suspension of $Cp_2Zr(H)Cl$ (240 mg, 0.93 mmol) in THF (1 mL) under argon was added a solution of 1-butyltellanyl-propyne **11** (137 mg, 0.62 mmol) in THF (1.5 mL). The mixture was stirred at room temperature until a red solution was obtained (ca. 15 min). The solution was cooled to −40 °C and neat NBS (166 mg, 0.93 mmol) was added. The mixture was stirred for 1 h at −40 °C and then it was allowed to slowly reach −10 °C. Hexane (6 mL) was added in order to precipitate the zirconium salts. The solids were removed by filtration through a path of silica and the solvents were removed under reduced pressure. The crude material was purified by flash chromatography (hexane as eluent) affording 92 mg (49% yield) of the title compound as an inseparable mixture of isomers (*Z*/*E*:1/1; brownish oil). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=6.74$ (q, $J=6.5$ Hz, 1H), 6.59 (q, $J=6.9$ Hz, 1H), 2.95 (t, $J=7.5$ Hz, 4H), 1.94–1.76 (m, 4H), 1.81 (d, $J=6.5$ Hz, 3H), 1.72 (d, $J=6.9$ Hz, 3H), 1.51–1.32 (m, 4H), 0.94 (t, $J=7.2$ Hz, 6H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=144.5$, 138.2, 109.2, 106.5, 33.9, 24.7, 13.3, 12.5, 12.0, 7.0 ppm.

4.1.5. Hex-1-ynylselanyl-benzene (17). To a solution of 1-hexyne (2.3 g, 27.5 mmol) in dry THF (35 mL) at 0 °C was added dropwise *n*-BuLi (12.1 mL, 30.3 mmol, 2.5 M in hexanes), and the mixture was stirred for 10 min at 0 °C. A solution of phenyl selenyl bromide (6.5 g, 27.5 mmol) in THF (16 mL) was added dropwise over a 5 min period. The reaction mixture was then allowed to reach slowly room temperature and was stirred overnight. It was poured into

a saturated NH_4Cl solution (100 mL) and extracted with petroleum ether (3×75 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether as eluent) affording 6.3 g (92% yield) of the title compound as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$): δ=7.55–7.45 (m, 2H), 7.35–7.15 (m, 3H), 2.45 (t, J=7.0 Hz, 2H), 1.65–1.40 (m, 4H), 0.93 (t, J=7.1 Hz, 3H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ= 129.3, 128.6, 126.6, 104.6, 67.4, 30.8, 21.9, 20.2, 13.6 ppm. IR (neat, NaCl): ν=3059, 2957, 2931, 2871, 2180, 1578, 1477, 1439, 1325 cm^{-1}. MS (EI): m/z (%): 238 [$M^{+\cdot}$] (94), 194[$M^{+\cdot}-C_3H_8$] (24). Elemental analysis calcd for $C_{12}H_{14}Se$ (237.19): C, 60.76; H, 5.95. Found C, 61.23; H, 6.03.

4.1.6. (*Z*/*E*)-(1-Iodo-hex-1-enylselanyl)-benzene (19). To a flask containing $Cp_2Zr(H)Cl$ (274 mg, 1.06 mmol) under argon was added 1,2-dichloroethane (2 mL). To this suspension was added a solution of hex-1-ynylselanyl-benzene **17** (210 mg, 0.88 mmol) in 1,2-dichloroethane (1.5 mL) via syringe. The suspension was stirred for 20 min until a clear red solution was obtained. The solution was cooled to −10 °C and a solution of I_2 (290 mg, 1.14 mmol) in 1,2-dichloroethane (1.5 mL) was added dropwise. The reaction mixture was stirred at −10 °C for 30 min and then it was allowed to slowly reach room temperature. It was diluted with petroleum ether (15 mL), washed with a saturated $Na_2S_2O_3$ solution (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash chromatography (petroleum ether as eluent) affording 225 mg (70% yield) of the title compound as an inseparable mixture of isomers (*E*/*Z*:4/1; brownish oil). ^1H NMR (300 MHz, $CDCl_3$): δ=7.60–7.30 (m, 10H), 7.03 (t, J= 7.4 Hz, 1H), 6.40 (t, J=6.9 Hz, 1H), 2.30–2.10 (m, 4H), 1.50–1.30 (m, 8H), 0.95 (t, J=7.1 Hz, 6H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=153.3, 148.5, 132.6, 132.4, 129.3, 129.2, 128.8, 127.6, 79.4, 74.5, 38.2, 35.1, 35.0, 30.6, 22.2, 13.9 ppm. IR (neat, NaCl): ν=3030, 2936, 1480, 1427, 1027, 1010 cm^{-1}. MS (EI): m/z (%): 366 [$M^{+\cdot}$] (26), 239 [$M^{+\cdot}-I$] (5).

4.1.7. (*Z*)-Hex-1-enylselanybenzene (20). To a 10 mL round bottomed flask, containing $Cp_2Zr(H)Cl$ (286 mg, 1.1 mmol) under argon, was added freshly distilled 1,2-dichloroethane (1.5 mL). To this suspension was added via cannula a solution of hex-1-ynylselanyl-benzene **17** (219 mg, 0.92 mmol) in 1,2-dichloroethane (1.5 mL). The mixture was stirred for 20 min at room temperature and quenched by the addition of a saturated NH_4Cl solution (0.5 mL). Petroleum ether was added dropwise until a white precipitate was formed. The precipitate was removed by filtration over florisil and washed with petroleum ether. The crude material was purified by column chromatography (petroleum ether as eluent) affording 157 mg (71% yield) of the title compound as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$): δ=7.55–7.40 (m, 2H), 7.35–7.20 (m, 3H), 6.43 (dt, J=8.9, 1.2 Hz, 1H), 6.05 (dt, J=8.9, 7.1 Hz, 1H), 2.19 (qd, J=7.2, 7.1 Hz, 2H), 1.50–1.25 (m, 4H), 0.92 (t, J=7.1 Hz, 3H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=135.4, 131.7, 129.2, 126.8, 120.1, 31.1, 22.3, 13.9 ppm. IR (neat, NaCl): ν=3043, 2960, 2870, 2850, 1579, 1456 cm^{-1}. MS (EI): m/z (%): 240 [$M^{+\cdot}$] (100), 197 [$M^{+\cdot}-C_3H_8$] (18). Elemental analysis calcd for $C_{12}H_{16}Se$ (239.22): C, 60.25; H, 6.74. Found C, 60.41; H, 6.87.

4.1.8. (*Z*/*E*)-(1-Bromo-hex-1-enylselanyl)-benzene (22). To a 10 mL round bottomed flask containing $Cp_2Zr(H)Cl$ (304 mg, 1.17 mmol) under argon was added 1,2-dichloroethane (2 mL). To this suspension was added a solution of hex-1-ynylselanyl-benzene **17** (233 mg, 0.98 mmol) in 1,2-dichloroethane (1.5 mL) via syringe. The suspension was stirred for 20 min until a clear red solution was obtained. This solution was transferred via cannula to a flask containing a suspension of NBS (227 mg, 1.27 mmol) in 1,2-dichloroethane (2 mL) cooled to 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then it was allowed to slowly reach room temperature. Petroleum ether was added until a white precipitate was formed. The precipitate was removed by filtration through a short path of florisil and the filtrate was concentrated in vacuo. The crude material was purified by flash chromatography (petroleum ether as eluent) affording 189 mg (61% yield) of the title compound as an inseparable mixture of isomers (*E*/*Z*:1.1/1; colourless oil). ^1H NMR (300 MHz, $CDCl_3$): δ=7.54–7.47 (m, 4H), 7.36–7.28 (m, 6H), 6.61 (t, J=7.2 Hz, 1H), 6.52 (t, J=7.1 Hz, 1H), 2.28 (q, J=7.2 Hz, 2H), 2.23 (q, J=7.1 Hz, 2H), 1.50–1.28 (m, 8H), 0.92 (t, J=7.0 Hz, 3H), 0.91 (t, J=7.1 Hz, 3H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=145.7, 143.8, 132.4, 132.3, 129.3, 127.8, 127.6, 107.1, 105.8, 33.5, 33.1, 30.8, 30.1, 22.2, 22.1, 13.8 ppm. IR (neat, NaCl): ν=3023, 2957, 2871, 2858, 1578, 1477, 1439, 1022 cm^{-1}. MS (EI): m/z (%): 318 [$M^{+\cdot}$] (14), 81 [Bu–C≡$C^{+\cdot}$] (100). HRMS (EI+, M+) calcd for $C_{12}H_{15}BrSe$, 317.9522; found 317.9699.

4.1.9. 2,4,6-Ditriisopropylphenyl diselenide. To a solution of 1-bromo-2,4,6-triisopropylbenzene (11.67 g, 41.23 mmol) in THF (134 mL) cooled at −78 °C was added *t*-butyllithium (48 mL, 82.47 mmol, 1.7 M in pentane) dropwise. The mixture was stirred for 15 min at −78 °C until a yellow milky solution was formed. Selenium (3.58 g, 45.35 mmol) was added. The reaction mixture was allowed to reach room temperature slowly and was stirred overnight. A saturated aqueous NH_4Cl solution (40 mL) was added and the whole was stirred in the presence of atmospheric oxygen for 15 min. The reaction mixture was extracted with Et_2O (3×75 mL). The combined organic layers were washed with brine (75 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude material was recrystalized from ethanol/petroleum ether to yield 9.76 g (84%) of the title compound as an orange crystalline solid. ^1H NMR (300 MHz, $CDCl_3$): δ=6.89 (s, 4H), 3.53 (hep, J=6.9 Hz, 4H), 2.82 (hep, J=6.9 Hz, 2H), 1.19 (d, J= 6.9 Hz, 12H), 0.99 (d, J=6.9 Hz, 24H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ_C=153.6, 150.3, 129.0, 121.6, 34.4, 34.0, 23.9, 23.8 ppm. IR (neat, NaCl): ν=3043, 2958, 2926, 2866, 1594, 1382, 1361, 1166, 1154 cm^{-1}. MS (EI): m/z (%): 564 [$M^{+\cdot}$] (100), 282 [SeTIPP$^+$] (16). Elemental analysis calcd for $C_{30}H_{46}Se_2$ (564.61): C, 63.82; H, 8.21. Found C, 63.96; H, 8.16.

4.2. General procedure for the preparation of 1-(2,4,6)-triisopropylphenyl-1-alkynyl selenides

To a solution of di-2,4,6-triisopropyldiselenide (23.7 mmol) in THF (400 mL) at 0 °C was added a solution of Br_2

(24.9 mmol) in benzene (23 mL) over a period of 15 min, using an addition funnel. The dark brown solution was allowed to reach room temperature and was stirred for a further 30 min. In parallel, to a solution of the corresponding terminal alkyne (49.8 mmol) in THF (60 mL) at 0 °C was added *n*-BuLi (49.7 mmol, 1.6 M in hexanes). This solution was transferred via cannula to the solution of selenyl bromide cooled to 0 °C. The clear solution obtained was stirred for 2 h at room temperature. The reaction mixture was diluted with petroleum ether (300 mL) and washed with H_2O (300 mL) and brine (300 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by column chromatography to give pure 1-TIPP-1-alkynyl selenides.

4.2.1. (1,3,5)-Triisopropyl-2-prop-1-ynylselanyl-benzene (30a). The title compound was obtained as a light yellow oil in 87% yield following the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.04 (s, 2H), 3.88 (hep, J=6.9 Hz, 2H), 2.89 (hep, J=6.9 Hz, 1H), 1.90 (s, 3H), 1.27 (d, J=6.9 Hz, 12H), 1.25 (d, J=6.9 Hz, 6H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=152.2, 150.3, 125.7, 122.1, 92.8, 60.1, 34.3, 34.2, 24.2, 23.9, 5.2 ppm. IR (neat, NaCl): ν=3043, 2960, 2926, 2867, 2243, 1594, 1383, 1314, 1168 cm^{-1}. MS (EI): *m*/*z* (%): 322 [$M^{+\cdot}$] (100), 280 [$M^{+\cdot}-C_3H_7$] (16). Elemental analysis calcd for $C_{18}H_{26}Se$ (321.36): C, 67.36; H, 8.11. Found C, 67.28; H, 8.16.

4.2.2. 2-Hex-1-ynylselanyl-(1,3,5)-triisopropyl-benzene (30b). The title compound was obtained as a colourless oil in 93% yield following the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.03 (s, 2H), 3.88 (hep, J=6.9 Hz, 2H), 2.88 (hep, J=6.9 Hz, 1H), 2.24 (t, J=7.0 Hz, 2H), 1.50–1.30 (m, 4H), 1.26 (d, J=6.9 Hz, 12H), 1.25 (d, J=6.9 Hz, 6H), 0.85 (t, J=7.1 Hz, 3H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=152.2, 150.4, 126.0, 122.2, 97.8, 61.1, 34.6, 34.5, 31.0, 24.5, 24.2, 22.2, 20.4, 13.9 ppm. IR (neat, NaCl): ν=2960, 2931, 2869, 2346, 1653, 1560, 1472, 1104 cm^{-1}. MS (EI): *m*/*z* (%): 364 [$M^{+\cdot}$] (34), 349 [$M^{+\cdot}-CH_3$] (13). Elemental analysis calcd for $C_{21}H_{32}Se$ (363.44): C, 69.51; H, 8.89. Found C, 69.32; H, 8.86.

4.2.3. 2-[6-(2,4,6-Triisopropyl-phenylselanyl)-hex-5-ynyloxyl]-tetrahydro-pyrane (30c). The title compound was obtained as a light yellow oil in 76% yield following the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.03 (s, 2H), 4.55 (t, J=3.4 Hz, 1H), 3.89 (hep, J=6.6 Hz, 2H), 3.87–3.79 (m, 1H), 3.71 (dt, J=10.0, 6.0 Hz, 1H), 3.52–3.44 (m, 1H), 3.36 (dt, J=10.0, 6.0 Hz, 1H), 2.89 (hep, J=6.6 Hz, 1H), 2.29 (t, J=7.0 Hz, 2H), 1.85–1.46 (m, 10H), 1.26 (d, J=6.6 Hz, 12H), 1.25 (d, J=6.6 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=152.3, 150.4, 125.9, 122.3, 98.9, 97.4, 67.1, 62.4, 61.6, 34.6, 34.5, 30.9, 29.1, 25.8, 25.7, 24.5, 24.2, 20.5, 19.8 ppm. IR (neat, NaCl): ν=3043, 2959, 2867, 2655, 1593, 1463, 1382, 1361 cm^{-1}. MS (EI): *m*/*z* (%): 464 [$M^{+\cdot}$] (2), 384 [$M^{+\cdot}-$THP] (2). Elemental analysis calcd for $C_{26}H_{40}O_2Se$ (463.55): C, 67.37; H, 8.70. Found C, 66.64; H, 8.47.

4.2.4. 1,3,5-Triisopropyl-2-(4-methyl-pent-1-ynylselanyl)-benzene (30d). The title compound was obtained as a light yellow oil in 91% yield following the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.05 (s, 2H), 3.92 (hep, J=6.9 Hz, 2H), 2.89 (hep, J=6.9 Hz, 1H), 2.15 (d, J=6.9 Hz, 2H), 1.76 (non, J=6.9 Hz, 1H), 1.28 (d, J=6.9 Hz, 6H), 1.27 (d, J=6.9 Hz, 12H), 0.93 (d, J=6.9 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=152.5, 150.2, 126.2, 122.4, 107. 3, 62.2, 34.9, 34.7, 30.1, 28.7, 24.8, 24.5, 22.5 ppm. IR (neat, NaCl): ν=2999, 2943, 2860, 2246, 1657, 1562, 1471, 1112 cm^{-1}. MS (EI): *m*/*z* (%): 364 [$M^{+\cdot}$] (34), 349 [$M^{+\cdot}-CH_3$] (13), 321 [$M^{+\cdot}-C_3H_7$] (12). Elemental analysis calcd for $C_{21}H_{32}Se$ (363.44): C, 69.40; H, 8.87. Found C, 69.52; H, 8.63.

4.2.5. 2-Cyclohexylethynylselanyl-1,3,5-triisopropyl-benzene (30e). The title compound was obtained as a yellow oil in 86% yield following the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.02 (s, 2H), 3.90 (hep, J=6.6 Hz, 2H), 2.88 (hep, J=6.6 Hz, 1H), 2.90–2.79 (m, 1H), 1.80–1.23 (m, 10H), 1.26 (d, J=6.6 Hz, 6H), 1.25 (d, J=6.6 Hz, 12H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=152.1, 150.1, 125.9, 122.0, 101. 5, 61.0, 34.3, 34.2, 32.7, 30.7, 25.9, 24.9, 24.3, 24.0 ppm. IR (neat, NaCl): ν=2997, 2953, 2898, 2546, 1653, 1565, 1476 cm^{-1}. MS (APCI): *m*/*z* (%): 390 [$M^{+\cdot}$] (97). Elemental analysis calcd for $C_{23}H_{34}Se$ (389.48): C, 70.93; H, 8.80. Found C, 70.99; H, 8.54.

4.2.6. 1-(2,4,6)-Triisopropylphenylselenyl-1-phenyl-acetylene (30f). The title compound was obtained as a yellow crystalline solid in 95% yield following the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.41–7.31 (m, 2H), 7.27–7.23 (m, 5H), 7.06 (s, 2H), 3.89 (hep, J=6.6 Hz, 2H), 3.87–3.79 (m, 1H), 3.95 (hep, J=6.6 Hz, 2H), 2.88 (hep, J=7.2 Hz, 1H), 1.30 (d, J=6.6 Hz, 12H), 1.26 (d, J=7.2 Hz, 6H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=152.6, 150.9, 131.7, 128.4, 128.4, 125.6, 123.8, 122.5, 96.7, 73.3, 34.7, 34.4, 24.5, 24.1 ppm. IR (neat, NaCl): ν=3057, 2963, 2932, 2866, 2240, 1567, 1383, 1321, 1163 cm^{-1}. MS (EI): *m*/*z* (%): molecular peak not observed, 204 [$TIPP^+$]. Elemental analysis calcd for $C_{23}H_{28}Se$ (383.43): C, 71.92; H, 7.35. Found C, 71.80; H, 7.36.

4.3. General procedure for the preparation of (*E*)-1-iodo-1-selenoalkenes

To a solution of the corresponding 1-alkynyl selenide (37.8 mmol) in hexane (80 mL) at 0 °C was added dropwise DIBAL-H (39.6 mmol, 1.5 M in toluene). The colourless solution was stirred at 0 °C for 1 h and then for 3 h at room temperature. The mixture was cooled to −78 °C and a solution of I_2 (94.5 mmol) in THF (45 mL) was added dropwise via cannula. The reaction was stirred at −78 °C for 30 min, then it was allowed to slowly reach 0 °C and finally it was stirred during 45 min at room temperature. It was poured in a mixture of EtOH (215 mL)/EtOAc (215 mL)/H_2O (108 mL) and treated with $NaBH_4$ until the solution became colourless or slightly yellow. The resulting solution was washed with aqueous 1 M HCl (120 mL), a saturated aqueous $Na_2S_2O_3$ solution (100 mL), brine (130 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash chromatography to give pure 1-iodo-1-selenoalkenes.

4.3.1. (*E*)-2-(Iodo-propenylselanyl)-1,3,5-triisopropyl-benzene (32a). The title compound was obtained as a red-brown oil in 92% yield following the general procedure. ^{1}H

NMR (300 MHz, $CDCl_3$): δ=7.04 (s, 2H), 6.83 (q, J=6.9 Hz, 1H), 3.67 (hep, J=6.9 Hz, 2H), 2.91 (hep, J=7.0 Hz, 1H), 2.75 (d, J=6.9 Hz, 3H), 1.27 (d, J=7.0 Hz, 6H), 1.25 (d, J=6.9 Hz, 12H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=153.0, 150.7, 140.7, 125.8, 121.9, 82.1, 34.2, 33.9, 24.2, 23.8, 20.2 ppm. IR (neat, NaCl): ν=3041, 2959, 2926, 1701, 1462, 1382, 1361, 1168, 1069 cm^{-1}. MS (EI): m/z (%): 450 [$M^{+\cdot}$] (62), 324 [$M^{+\cdot}-I$] (73). Elemental analysis calcd for $C_{18}H_{27}ISe$ (449.27): C, 48.12; H, 6.06. Found C, 49.45; H, 6.23.

4.3.2. (*E*)-2-(1-Iodo-hex-1-enylselanyl)-1,3,5-triisopropyl-benzene (32b). The title compound was obtained as a brown oil in 95% yield following the general procedure. ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.03 (s, 2H), 6.78 (t, J=6.9 Hz, 1H), 3.68 (hep, J=6.9 Hz, 2H), 2.91 (hep, J=7.0 Hz, 1H), 2.27 (m, 2H), 1.50–1.32 (m, 4H), 1.27 (d, J=7.3 Hz, 6H), 1.23 (d, J=7.3 Hz, 12H), 0.94 (t, J=7.0 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=152.9, 150.8, 146.7, 125.8, 122.0, 81.2, 34.6, 34.3, 33.9, 30.7, 24.3, 23.9, 22.2, 13.9 ppm. IR (neat, NaCl): ν=3043, 2960, 2927, 1701, 1594, 1382, 1361, 1154 cm^{-1}. MS (EI): m/z (%): 492 [$M^{+\cdot}$] (100), 365 [$M^{+\cdot}-I$] (55). Elemental analysis calcd for $C_{21}H_{33}ISe$ (491.35): C, 51.33; H, 6.77. Found C, 52.17; H, 6.71.

4.3.3. 2-[6-Iodo-6-(2,4,6)-triisopropyl-phenylselanyl)-hex-5-enyloxy]-tetrahydropyran (32c). The title compound was obtained as a yellow oil in 96% yield following the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.03 (s, 2H), 6.78 (t, J=7.2 Hz, 1H), 4.60 (dd, J=6.0, 2.7 Hz, 1H), 3.94–3.81 (m, 1H), 3.77 (dt, J=9.4, 6.0 Hz, 1H), 3.66 (hep, J=6.7 Hz, 2H), 3.58–3.42 (m, 1H), 3.42 (dt, J=9.4, 6.0 Hz, 1H), 2.91 (hep, J=6.6 Hz, 1H), 2.30 (q, J=7.2 Hz, 2H), 1.90–1.45 (m, 10H), 1.26 (d, J=6.7 Hz, 6H), 1.22 (d, J=6.6 Hz, 12H), 0.94 (t, J=7.0 Hz, 3H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=153.0, 150.8, 146.3, 125.7, 122.1, 98.9, 81.9, 67.4, 62.5, 34.9, 34.5, 34.1, 31.0, 29.5, 25.7, 25.5, 24.5, 24.2, 19.9 ppm. IR (neat, NaCl): ν=3043, 2960, 2868, 2667, 1708, 1576, 1364, 1361, 1154 cm^{-1}. MS (EI): m/z (%): 592 [$M^{+\cdot}$] (100), 465 [$M^{+\cdot}-I$] (61). HRMS (EI+, M+) calcd for C_{26} $H_{41}IO_2Se$, 592.1316; found 592.1319.

4.3.4. 2-(1-Iodo-4-methyl-pent-1-enylselanyl)-1,3,5-triisopropyl-benzene (32d). The title compound was obtained as a yellow oil in 82% yield following the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.02 (s, 2H), 6.79 (t, J=6.9 Hz, 1H), 3.66 (hep, J=6.6 Hz, 2H), 2.90 (hep, J=6.9 Hz, 1H), 2.16 (t, J=6.6 Hz, 2H), 1.76 (non, J=6.9 Hz, 1H), 1.26 (d, J=6.9 Hz, 6H), 1.22 (d, J=6.6 Hz, 6H), 0.96 (d, J=6.6 Hz, 6H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=153.3, 151.1, 145.9, 130.6, 122.4, 82.5, 44.4, 34.8, 34.4, 28.8, 24.9, 24.5, 22.9 ppm. IR (neat, NaCl): ν=2958, 2959, 2920, 1594, 1463, 1382, 1168, 1061 cm^{-1}. MS (APCI): m/z (%): 492 [$M^{+\cdot}$] (76), 365 [$M^{+\cdot}-I$] (100). HRMS (CI+, M+) calcd for $C_{21}H_{33}ISe$, 492.0792; found 492.0799.

4.3.5. 2-(2-Cyclohexyl-1-iodo-vinylselanyl)-1,3,5-triisopropyl-benzene (32e). The title compound was obtained as a yellow oil in 91% yield following the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.02 (s, 2H), 6.79 (t, J=6.9 Hz, 1H), 3.66 (hep, J=6.6 Hz, 2H), 2.90 (hep, J=6.9 Hz, 1H), 2.16 (t, J=6.6 Hz, 2H), 1.76 (non, J=6.9 Hz, 1H), 1.26 (d, J=6.9 Hz, 6H), 1.22 (d, J=6.6 Hz, 6H), 0.96 (d, J=6.6 Hz, 6H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=152.8, 152.0, 150.6, 130.3, 121.9, 79.5, 44.4, 34.3, 33.9, 32.1, 25.9, 25.7, 24.4, 24.0 ppm. IR (neat, NaCl): ν=2958, 2959, 2920, 1594, 1463, 1382, 1168, 1061 cm^{-1}. MS (APCI): m/z (%): 518 [$M^{+\cdot}$] (34), 391 [$M^{+\cdot}-I$] (100). HRMS (CI+, M+) calcd for $C_{23}H_{35}ISe$, 518.0949; found 518.0943.

4.3.6. (*Z*)-1,3,5-Triisopropyl-2-propenylselanyl-benzene (34a). To a solution of the vinyl iodide **32a** (325 mg, 0.72 mmol) in THF (10 mL) at −78 °C was added *n*-BuLi (470 μL, 0.75 mmol, 1.6 M in hexanes) dropwise. The solution was stirred for 20 min at −78 °C and then it was poured into a saturated aqueous solution of NH_4Cl (8 mL) and extracted with petroleum ether (3×10 mL). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash chromatography (PE) to afford 212 mg (91% yield) of the title compound as a slightly yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.04 (s, 2H), 6.09 (dd, J=8.8, 1.3 Hz, 1H), 5.90 (dq, J=8.8, 6.6 Hz, 1H), 3.82 (hep, J=6.9 Hz, 2H), 2.90 (hep, J=6.9 Hz, 1H), 1.80 (dd, J=6.6, 1.3 Hz, 3H), 1.25 (d, J=6.9 Hz, 6H), 1.23 (d, J=6.9 Hz, 12H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=152.8, 149.3, 127.5, 125.3, 121.8, 121.6, 34.2, 34.1, 24.3, 23.9, 16.2 ppm. IR (neat, NaCl): ν=3041, 2962, 2860, 1685, 1762, 1595, 1381 cm^{-1}. MS (EI): m/z (%): 324 [$M^{+\cdot}$] (100), 309 (27). Elemental analysis calcd for $C_{18}H_{28}Se$ (323.37): C, 66.86; H, 8.73. Found C, 66.89; H, 8.79.

4.3.7. (*E*)-4-(2,4,6 Triisopropylphenyl)seleno-2-methyl hex-4-en-3-one (34c). To a solution of the vinyl iodide **32a** (195 mg, 0.43 mmol) in THF (5 mL) at −78 °C was added *n*-BuLi (282 μL, 0.45 mmol, 1.6 M in hexanes) dropwise. The solution was stirred for 20 min at −78 °C and then neat *N*-methoxy-*N*-methylamide (56 mg, 0.48 mmol) was added at once. The reaction mixture was allowed to reach slowly room temperature. It was poured into a saturated aqueous solution of NH_4Cl (5 mL) and extracted with petroleum ether (3×10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash chromatography (PE/Et_2O:30/1 as eluent) to afford 110 mg (67% yield) of the title compound as a yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.88 (s, 2H), 6.69 (q, J=6.6 Hz, 1H), 3.64 (hep, J=6.9 Hz, 2H), 2.98 (hep, J=6.9 Hz, 1H), 2.76 (hep, J=6.9 Hz, 1H), 1.66 (d, J=6.9 Hz, 3H), 1.13 (d, J=6.9 Hz, 6H), 1.11 (d, J=6.9 Hz, 12H), 0.77 (d, J=6.9 Hz, 6H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=202.8, 153.7, 150.6, 139.8, 137.7, 127.1, 122.5, 36.6, 34.9, 34.8, 24.9, 24.5, 19.4, 17.6 ppm. IR (neat, NaCl): ν=3045, 2962, 2869, 1685, 1595, 1463, 1361 cm^{-1}. MS (EI): m/z (%): 394 [$M^{+\cdot}$] (45), 323 [$M^{+\cdot}-COC_3H_7$] (12). Elemental analysis calcd for $C_{22}H_{34}OSe$ (393.46): C, 67.16; H, 8.71. Found C, 67.19; H, 8.65.

4.3.8. (*Z*)-1-Phenyl-2-(2,4,6-triisopropyl-phenylselanyl)-but-2-en-1-one (34d). To a solution of the vinyl iodide **32a** (250 mg, 0.55 mmol) in THF (6 mL) at −78 °C was added

n-BuLi (362 μL, 0.58 mmol, 1.6 M in hexanes) dropwise. The solution was stirred for 20 min at −78 °C and then a solution of benzoyl chloride (67 μL, 0.58 mmol) in THF (2 mL) was added dropwise. The reaction mixture was allowed to slowly reach room temperature. It was poured into a saturated aqueous solution of $NaHCO_3$ (5 mL) and extracted with petroleum ether (3×10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash chromatography (PE/Et_2O:25/1 as eluent) to afford 169 mg (72% yield) of the title compound as a yellowish oil. ^1H NMR (300 MHz, $CDCl_3$): δ=7.70–7.65 (m, 2H), 7.03 (s, 2H), 7.01–6.90 (m, 3H), 6.15 (q, J=6.8 Hz, 3H), 3.97 (hep, J=6.9 Hz, 2H), 2.68 (hep, J=6.9 Hz, 1H), 1.73 (d, J=6.8 Hz, 3H), 1.28 (d, J=6.9 Hz, 12H), 1.11 (d, J=6.9 Hz, 6H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=194.0, 153.5, 152.7, 149.7, 137.3, 136.9, 132.1, 129.2, 128.4, 127.8, 121.5, 34.1, 33.9, 24.3, 24.0, 17.2 ppm. IR (neat, NaCl): ν=3045, 2961, 2869, 1722, 1662, 1596, 1382 cm^{-1}. MS (EI): *m*/*z* (%): 428 [$M^{+\cdot}$] (12). HRMS (EI+, M+) calcd for $C_{25}H_{32}OSe$, 428.1618; found 428.1614.

4.3.9. (*Z*)-1,1,1-Trifluoro-3-(2,4,6-triisopropyl-phenylselanyl)-pent-3en-2one (34e). To a solution of the vinyl iodide **32a** (200 mg, 0.45 mmol) in THF (5 mL) at −78 °C was added *n*-BuLi (292 μL, 0.47 mmol, 1.6 M in hexanes) dropwise. The solution was stirred for 20 min at −78 °C and then a solution of trifluoroacetic anhydride (103 mg, 0.49 mmol) in THF (1 mL) was added. The reaction mixture was allowed to slowly reach room temperature. It was poured into a saturated aqueous solution of $NaHCO_3$ (4 mL) and extracted with petroleum ether (3×10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated. The crude material was purified by flash chromatography (pure PE as eluent) to afford 147 mg (78% yield) of the title compound as a colourless oil. ^1H NMR (200 MHz, $CDCl_3$): δ=7.12 (s, 2H), 6.87 (qq, J=6.9, 1.3 Hz, 1H), 4.01 (hep, J=6.9 Hz, 2H), 2.70 (hep, J=6.9 Hz, 1H), 1.58 (d, J=6.9 Hz, 3H), 1.28 (d, J=6.9 Hz, 12H), 1.12 (d, J=6.9 Hz, 6H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=200.8, 154.2, 151.1, 139.8, 137.7, 132.5, 127.1, 122.5, 34.9, 34.8, 24.8, 24.3, 19.4 ppm. IR (neat, NaCl): ν=3043, 2962, 2871, 1716, 1594, 1463, 1383 cm^{-1}. MS (EI): *m*/*z* (%): 420 [$M^{+\cdot}$] (100), 377 [$M^{+\cdot}-C_3H_7$] (25). Elemental analysis calcd for $C_{20}H_{27}F_3OSe$ (419.38): C, 57.28; H, 6.49. Found C, 57.74; H, 6.61.

4.3.10. (*E*)-2-(2,4,6-Triisopropylphenyl)seleno-1-phenyl-but-2-ene-1-ol (34f). To a solution of the vinyl iodide **32a** (490 mg, 1.1 mmol) in THF (15 mL) at −78 °C was added *t*-BuLi (750 μL, 2.3 mmol, 1.5 M in pentane). The solution was stirred at −78 °C for 15 min and neat benzaldehyde (122 μL, 1.2 mmol) was added. The mixture was stirred for 1 h at −78 °C and then it was allowed to slowly room temperature. The reaction was quenched by the addition of deuterated methanol (500 μL) and stirred for further 15 min. It was diluted with petroleum ether (15 mL) and then poured into a saturated aqueous solution of NH_4Cl (20 mL). It was extracted with petroleum ether (3×15 mL) and the combined organic layers were washed with brine (40 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash chromatography (PE/Et_2O:4/1 as eluent) to afford 335 mg (82% yield) of the allylic alcohol as a yellowish oil. ^1H NMR (300 MHz, $CDCl_3$): δ=7.37–7.15– (m, 5H), 7.00 (s, 2H), 5.92 (qt, J=6.6, 0.9 Hz, 1H), 4.87 (s, 1H), 3.62 (hep, J=6.9 Hz, 2H), 2.88 (hep, J=6.9 Hz, 1H), 1.88 (dd, J=6.6, 0.9 Hz, 3H), 1.26 (d, J=6.9 Hz, 6H), 1.18 (d, J=6.9 Hz, 6H), 1.16 (d, J=6.9 Hz, 6H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=153.4, 150.1, 141.7, 138.3, 128.3, 127.7, 127.1, 126.9, 125.1, 122.0, 76.2, 34.4, 33.9, 24.6, 24.3, 24.1, 16.8 ppm. IR (neat, NaCl): ν=3414, 3030, 3031, 2960, 1632, 1595, 1462, 1312 cm^{-1}. MS (EI): *m*/*z* (%): 430 [$M^{+\cdot}$] (100), 323 [$M^{+\cdot}-CH(OH)Ph$] (89). Elemental analysis calcd for $C_{25}H_{34}OSe$ (429.50): C, 70.07; H, 8.04. Found C, 70.00; H, 7.99.

4.3.11. (*Z*)-3-(2,4,6-Triisopropyl-phenylselanyl-oct-2-en-4-ol (34g). To a solution of the vinyl iodide **32a** (325 mg, 0.72 mmol) in hexane (10 mL) at room temperature was added *n*-BuLi (470 μL, 0.75 mmol, 1.6 M in hexanes) dropwise. The solution was stirred at room temperature for 10 min and neat valeraldehyde (92 μL, 0.86 mmol) was added. The mixture was stirred for 1.5 h at room temperature and then poured into a saturated aqueous solution of NH_4Cl (8 mL). It was extracted with petroleum ether (3×10 mL) and the combined organic layers were washed with brine (25 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash chromatography (PE/Et_2O:2/1 as eluent) to afford 191 mg (65% yield) of the title compound as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$): δ=7.00 (s, 2H), 6.05 (qd, J=6.6, 0.9 Hz, 1H), 3.78 (hep, J=6.9 Hz, 2H), 3.84–3.70 (m, 1H), 2.87 (hep, J=6.9 Hz, 1H) 1.89 (dd, J=6.6, 0.9 Hz, 3H), 1.60–1.10 (m, 6H), 1.24 (d, J=6.9 Hz, 12H), 1.20 (d, J=6.9 Hz, 6H), 0.87 (t, J=6.9 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=153.1, 149.9, 139.2, 125.5, 124.8, 122.0, 75.2, 36.5, 34.5, 34.2, 28.3, 24.7, 24.2, 22.8, 16.8, 14.3 ppm. IR (neat, NaCl): ν=3396, 3042, 2960, 2929, 1632, 1595, 1462, 1362 cm^{-1}. MS (EI): *m*/*z* (%): 409 [$M^{+\cdot}$] (35). Elemental analysis calcd for $C_{23}H_{38}OSe$ (409.50): C, 67.46; H, 9.35. Found C, 67.17; H, 9.04.

4.3.12. (*Z*)-3-(2,4,6-Triisopropyl-phenylselanyl)-undec-2-en-5-ol (34h). To a solution of the vinyl iodide **32a** (660 mg, 1.47 mmol) in THF (15 mL) at −78 °C was added *n*-BuLi (920 μL, 1.47 mmol, 1.6 M in hexanes) dropwise. The solution was stirred for 20 min at −78 °C and neat epoxide (225 μL, 1.47 mmol) and then neat $BF_3\cdot OEt_2$ (144 μL, 1.47 mmol) were added. The solution was stirred at −78 °C for 30 min and then it was allowed to slowly reach 0 °C. At this temperature a saturated aqueous solution of $NaHCO_3$ (8 mL) was added and the mixture was allowed to warm up to room temperature. It was extracted with EtOAc (3×10 mL), the combined organic layers were washed with brine (25 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash chromatography (PE/Et_2O:2/1 as eluent) to afford 332 mg (50% yield) of the title compound as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$): δ=7.00 (s, 2H), 5.79 (q, J=6.6 Hz, 1H), 3.70 (hep, J=6.9 Hz, 2H), 3.46 (m, 1H), 2.88 (hep, J=6.9 Hz, 1H), 2.05 (d, J=14.1 Hz, 1H), 1.94 (dd, J=14.1, 9.0 Hz, 1H), 1.90 (d, J=6.6 Hz, 3H), 1.70 (m, 1H), 1.24 (d, J=6.9 Hz, 6H), 1.22 (d, J=6.9 Hz, 6H), 1.17

(d, J=6.9 Hz, 3H), 1.39–098 (m, 10H), 0.85 (t, J=6.9 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=153.1, 149.9, 133.4, 126.5, 125.7, 121.9, 69.2, 46.0, 36.6, 34.4, 34.2, 32.0, 29.6, 25.7, 24.8, 24.2, 23.0, 17.1, 14.3 ppm. IR (neat, NaCl): ν=3410, 3043, 2960, 2868, 1630, 1595, 1462, 1361 cm^{-1}. MS (EI): *m/z* (%): 452 [$M^{+\cdot}$] (100), 323 (11). Elemental analysis calcd for $C_{26}H_{44}OSe$ (451.59): C, 69.15; H, 9.82. Found C, 69.05; H, 9.88.

4.3.13. (*Z*)-1,3,5-Triisopropyl-2-(1-methyl-propenyl-selanyl)-benzene (34j). To a solution of vinyl iodide **32a** (355 mg, 0.79 mmol) in THF (4 mL) at −78 °C was added *t*-BuLi (1.0 mL, 1.5 M in pentane, 1.58 mmol) dropwise. It was stirred at −78 °C for 15 min and neat methyl iodide (74 μL, 1.2 mmol) was added in three portions. The mixture was stirred at −78 °C for 1 h, then it was allowed to slowly reach room temperature It was diluted with petroleum ether (10 mL), washed with H_2O, dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. The crude material was purified by flash chromatography (pure petroleum ether as eluent) to afford 251 mg of the title compound (93% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.01 (s, 2H), 5.65 (qq, J=6.6, 1.5 Hz, 1H), 3.79 (hep, J=6.9 Hz, 2H), 2.88 (hep, J=6.9 Hz, 1H), 1.82 (dq, J=6.6, 1.5 Hz, 3H), 1.67 (m, 3H), 1.25 (d, J=6.9 Hz, 6H), 1.20 (d, J=6.9 Hz, 12H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=153.5, 149.8, 131.2, 125.3, 122.3, 121.7, 34.4, 34.3, 25.2, 24.4, 24.2, 16.8 ppm. IR (neat, NaCl): ν=2960, 2868, 1640, 1595, 1461, 1424, 1143 cm^{-1}. MS (EI): *m/z* (%): 338 [$M^{+\cdot}$] (100), 323 [$M^{+\cdot}-CH_3$] (28). Elemental analysis calcd for $C_{19}H_{30}Se$ (337.40): C, 67.64; H, 8.96. Found C, 68.08; H, 9.20.

4.3.14. (*Z*)-Trimethyl-[2-(2,4,6-triisopropyl-phenylselanyl)-but-2-enyl]-silane (34k). To a 25 mL round bottomed flask, containing THF (2 mL) at −78 °C were added *t*-BuLi (1.0 mL, 1.77 mmol, 1.7 M in pentane) and immediately after, a solution of vinyl iodide **32a** (361 mg, 0.8 mmol) in THF (1 mL). The mixture was stirred for 5 min at −78 °C, meanwhile the formation of a white precipitate was observed. Neat iodomethyltrimethylsilane (275 μL, 1.9 mmol) was added and the mixture was stirred for 1 h at −78 °C and then allowed to slowly reach room temperature. It was poured into a mixture of PE (10 mL)/H_2O (10 mL) and extracted with petroleum ether (3× 8 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated. The crude material was purified by flash chromatography (pure PE as eluent) to afford 256 mg (78% yield) of the title compound as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.18 (s, 2H), 5.45 (q, J=6.6 Hz, 1H), 4.12 (hep, J=6.9 Hz, 2H), 2.76 (hep, J=6.9 Hz, 1H), 1.93 (d, J=6.6 Hz, 3H), 1.61 (m, 2H), 1.32 (d, J=6.9 Hz, 12H), 1.18 (d, J=6.9 Hz, 6H), 0.05 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=153.6, 149.6, 133.1, 127.2, 123.0, 122.0, 34.6, 34.3, 27.8, 24.8, 24.6, 17.7, −0.8 ppm. IR (neat, NaCl): ν=3043, 2961, 2929, 2870, 1624, 1595, 1562, 1462, 1422, 1382, 1248 cm^{-1}. MS (EI): *m/z* (%): 410 [$M^{+\cdot}$] (37), 395 [$M^{+\cdot}-CH_3$] (12). Elemental analysis calcd for $C_{22}H_{38}SeSi$ (409.58): C, 64.51; H, 9.35. Found C, 64.03; H, 9.25.

4.3.15. (*Z*)-Trimethyl-[2-(2,4,6-triisopropyl-phenylselanyl)-hept-2-enyl]-silane (34m). To a solution of vinyl iodide **32a** (225 mg, 0.46 mmol) and $Pd(PPh_3)_4$ (53 mg, 0.046 mmol) in THF (4 mL) at room temperature was added trimethylsilylzinc iodide[29] (500 μL, 0.55 mmol, 1.0 M in THF). The yellow solution thus obtained was stirred at reflux for 10 h. It was diluted with petroleum ether (10 mL), washed with aqueous 0.5 M HCl (8 mL) and extracted several times with PE. The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$ and concentrated. The crude material was purified by flash chromatography (PE) affording 79 mg (38% yield) of the title compound as a yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.99 (s, 2H), 5.42 (t, J=7.0 Hz, 1H), 3.79 (hep, J=6.9 Hz, 2H), 2.88 (hep, J=6.9 Hz, 1H), 2.32 (dd, J=7.0, 7.0 Hz, 2H), 1.49 (s, 2H), 1.45–1.30 (m, 4H), 1.26 (d, J=6.9 Hz, 6H), 1.18 (d, J=6.9 Hz, 12H), 0.93 (t, J=7.0 Hz, 3H), 0.03 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=153.2, 149.3, 131.7, 128.8, 126.0, 121.6, 34.1, 33.6, 32.0, 31.5, 27.2, 24.2, 23.9, 22.4, 14.0, −1.4 ppm. IR (neat, NaCl): ν=3042, 2959, 2927, 2870, 1762, 1595, 1562, 1462, 1422, 1382, 1247 cm^{-1}. MS (EI): *m/z* (%): 452 [$M^{+\cdot}$] (92), 437 [$M^{+\cdot}-CH_3$] (19), 379 [$M^{+\cdot}-Si(CH_3)_3$] (20). Elemental analysis calcd for $C_{25}H_{44}SeSi$ (451.66): C, 66.48; H, 9.82. Found C, 66.73; H, 9.64.

4.4. Preparation of Lithium 4,4′-di-*tert*-butyl biphenylide (LDBB)

To a flame-dried two necked flask, equipped with a glass-coated stirring bar, rubber septum and Ar inlet, were added 4,4′-di-*tert*-butyl-biphenyl (DBB) (1.6 g, 6.02 mmol) and THF (20 mL). Lithium ribbon was prepared by scraping the dark oxide coating off the surface while it was immersed in mineral oil. The shiny metal was dipped in hexane in order to remove the oil and then weighed (50 mg, 7.13 mmol) in a tared beaker containing mineral oil. The metal was sliced into small pieces while it was still immersed in mineral oil. The lithium pieces were dipped again in hexane prior to addition to the solution of DBB in THF, while the flask was rapidly being purged with Ar. The reaction mixture was stirred at room temperature for 5 min until a dark green colour appeared on the lithium surface, then it was cooled down to 0 °C and stirred for 4–5 h. The resulting dark green LDBB solution (6.02 mmol, 0.3 M in THF) was ready for use in reductive lithiation. The actual amount of LDBB is usually less than indicated due to impurities on the lithium ribbon and decomposition of LDBB. The real concentration can be calculated by titration with $PhSCH_2Si(CH_3)_3$. A solution of this phenylthio ether in THF was added dropwise to a known volume of solution of LDBB at −78 °C until the colour of the solution changed from dark green to yellow-red. The concentration of the LDBB solution was calculated from the amount of phenylthio ether added.

4.4.1. (*E*)-Trimethyl-(2-methyl-hept-2-enyl)-silane (35). To a freshly prepared solution of LDBB (4.3 mL, 1.3 mmol, 0.3 M in THF) at −78 °C was added a solution of selenide **34m** (275 mg, 0.6 mmol) in THF (10 mL) dropwise. At the end of the addition the dark green solution changed to pale red. It was stirred for further 10 min at −78 °C and neat methyl iodide (50 μL, 1.3 mmol) was added. The reaction mixture was stirred for 30 min at −78 °C and then was allowed to reach slowly 0 °C. It was diluted with petroleum ether (10 mL), washed with aqueous 1 M HCl (10 mL)

and extracted with PE (3×10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash chromatography (pure PE as eluent) to afford 74 mg (67% yield) of the title compound as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.16 (tt, J=7.0, 1.0 Hz, 1H), 2.32 (d, J=1.0 Hz, 2H), 2.07 (q, J=7.0 Hz, 2H), 1.35 (s, 3H), 1.40–1.20 (m, 4H), 0.90 (t, J=7.0 Hz, 3H), 0.08 (s, 9H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=132.6, 102.5, 36.8, 36.7, 30.8, 24.1, 22.3, 13.9, −1.3 ppm. IR (neat, NaCl): ν=3417, 2959, 2985, 2870, 1595, 1562, 1462, 1422, 1382, 1247 cm^{-1}. MS (EI): m/z (%): 184 [$M^{+\cdot}$] (63). HRMS (EI+, M+) calcd for $C_{11}H_{24}Si$, 184.1647; found 184.1642.

4.4.2. (*E*)-6-Trimethylsilanylmethyl-undec-6-en-5-ol (36). To a freshly prepared solution of LDBB (1.1 mL, 0.32 mmol, 0.3 M in THF) at −78 °C was added a solution of selenide **34m** (71 mg, 0.16 mmol) in THF (2.5 mL) dropwise. At the end of the addition the dark green solution changed to pale red. It was stirred for a further 10 min at −78 °C and neat valeraldehyde (50 μL, 0.47 mmol) was added. The reaction mixture was stirred for 30 min at −78 °C and then was allowed to slowly reach 0 °C. It was diluted with petroleum ether (10 mL), washed with aqueous 1 M HCl (10 mL) and extracted with PE (3×8 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash chromatography (PE/EtOAc:30/1) to afford 25 mg (62% yield) of the title compound as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.08 (t, J=7.4 Hz, 1H), 4.49 (t, J=6.9 Hz, 1H), 2.15–1.90 (m, 4H), 1.63–1.15 (m, 10H), 0.90 (t, J=6.9 Hz, 3H), 0.89 (t, J=6.9 Hz, 3H), 0.03 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=138.5, 126.0, 70.5, 35.3, 32.7, 28.2, 27.2, 22.7, 22.3, 19.9, 14.0, 13.9, −0.7 ppm. IR (neat, NaCl): ν=3415, 2960, 2920, 2860, 1638, 1457, 1379, 1248 cm^{-1}. MS (EI): m/z (%): 256 [$M^{+\cdot}$] (41). HRMS (EI+, M+) calcd for $C_{15}H_{32}OSi$, 256.2222; found 256.2223.

4.4.3. (*E*)-1-[1,3]Dithian-2-yl-1-hex-4-en-2-ol (37). To a solution of selenide **34i** (275 mg, 0.55 mmol) in THF (6 mL) at −78 °C was added *n*-BuLi (343 μL, 0.55 mmol, 1.6 M in hexanes) dropwise and then the solution was allowed to warm up slowly to 0 °C. This solution was added via cannula to a freshly prepared solution of LDBB (4.3 mL, 1.3 mmol, 0.3 M in THF). At the end of the addition the dark green solution changed to pale red. It was stirred for a further 10 min at −78 °C and neat methanol (1.5 mL) was added. The reaction mixture was allowed to slowly reach room temperature. It was diluted with petroleum ether (15 mL), washed with aqueous 1 N HCl (10 mL) and extracted with PE (3×10 mL). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash chromatography (PE/Et_2O:1/1 as eluent) to afford 110 mg (92% yield) of the title compound as a coulorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.53 (dqt, J=15.2, 6.2, 1.1 Hz, 1H), 5.39 (dqt, J=15.2, 7.5, 1.2 Hz, 1H), 4.25 (dd, J=6.8, 6.7 Hz, 1H), 3.89 (m, 1H), 2.94–2.75 (m, 4H), 2.30–2.08 (m, 3H), 1.96–1.81 (m, 4H), 1.67 (dd, J=6.2, 1.2 Hz, 3H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ=129.3, 126.3, 67.7, 44.2, 42.0, 40.7, 30.3, 29.9, 25.9, 17.9 ppm. IR (neat, NaCl): ν=3416, 3021, 2933, 2903, 2858, 1635, 1423, 1275 cm^{-1}. MS (EI): m/z (%): 219 [$M^{+\cdot}$] (25). Elemental analysis calcd for $C_{10}H_{18}OS_2$ (218.38): C, 55.00; H, 8.31, S, 29.36. Found C, 55.00; H, 8.29; S, 29.36.

4.4.4. (*Z*)-1-[1,3]Dithian-2-yl-1-hex-4-en-2-ol (38). To a freshly prepared solution of LDBB (32 mL, 9.52 mmol, 0.3 M in THF) at −78 °C was added a solution of selenide **34a** (1.53 g, 4.76 mmol) in THF (3 mL) dropwise. At the end of the addition the dark green solution changed to pale red. It was stirred for a further 10 min at −78 °C and neat methyl iodide (100 μL, 4.76 mmol) was added. The reaction mixture was stirred for 30 min at −78 °C and then a solution of oxirane **41** (418 mg, 2.38 mmol) in THF (1.5 mL) and neat $BF_3\cdot OEt_2$ (150 μL, 2.38 mmol) were added. The reaction mixture was stirred for 2 h at −78 °C and then quenched by addition of a saturated aqueous solution of $NaHCO_3$ (2 mL). The mixture was allowed to reach room temperature and poured into a mixture PE (40 mL)/H_2O (40 mL). It was extracted with petroleum ether (2×40 mL) and the combined organic layers were washed with brine (60 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash chromatography (PE/Et_2O:2/1 as eluent) to afford 441 mg (85% yield) of the title compound as a crystalline white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.22 (dq, J=9.1, 1.4 Hz, 1H), 5.99 (m, 1H), 4.25 (dd, J=6.8, 6.7 Hz, 1H), 3.89 (m, 1H), 4.05 (m, 1H), 3.10–2.79 (m, 5H), 2.53 (dd, J=12.9, 5.1 Hz, 1H), 2.30–2.02 (m, 4H), 1.72 (dd, J=6.2, 1.4 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=129.3, 106.6, 67.5, 44.2, 42.1, 34.9, 30.5, 30.2, 26.1, 18.5 ppm. IR (neat, NaCl): ν=3410, 3021, 2936, 2858, 1636, 1423, 1275 cm^{-1}. MS (EI): m/z (%): 219 [$M^{+\cdot}$] (25). Elemental analysis calcd for $C_{10}H_{18}OS_2$ (218.38): C, 55.00; H, 8.31, S, 29.36. Found C, 54.98; H, 8.34; S, 29.36.

4.4.5. (*E*)-Methyl-undec-2-en-5-ol (39). To a round bottomed flask containing $Ni(acac)_2$ (10 mg, 0.03 mmol), under argon, was added a solution of alcohol **34h** (250 mg, 0.55 mmol) in THF (9 mL). The suspension was cooled down to 0 °C and methylmagnesium bromide (424 μL, 1.28 mmol, 3.0 M in ether) was added dropwise. At the end of the addition, the solution changed from green to red. The reaction mixture was stirred 16 h at room temperature. It was diluted with EtOAc (5 mL) and poured into a saturated aqueous solution of NH_4Cl (10 mL). The aqueous phase was extracted with EtOAc (3×8 mL) and the combined organic layers were washed with brine (25 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash chromatography (PE/EtOAc:10/1 as eluent) to afford 61 mg (60% yield) of the title compound as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.32 (q, J=6.9 Hz, 1H), 3.74–3.60 (m, 1H), 2.19 (d, J=13.2 Hz, 1H), 1.98 (dd, J=13.2, 9.6 Hz, 1H), 1.67 (s, 1H), 1.63 (s, 3H), 1.61 (d, J=6.9 Hz, 3H), 1.52–1.14 (m, 10H), 0.88 (t, J=6.6 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=133.5, 122.6, 68.7, 48.3, 37.3, 32.1, 29.7, 26.0, 22.9, 16.0, 14.4, 13.8 ppm. IR (neat, NaCl): ν=3411, 2958, 2928, 2858, 1638, 1457, 1379, 1125 cm^{-1}. MS (EI): m/z (%): 184 [$M^{+\cdot}$] (4), 96 [$M^{+\cdot}-C_6H_{15}$] (24). HRMS (EI+, M+) calcd for $C_{12}H_{24}O$, 184.1827; found 184.1830.

4.4.6. (*E*)-1-[1,3]Dithian-2-yl-4-methyl-hex-4-en-2-ol (40). To a round bottomed flask containing $Ni(acac)_2$ (2 mg, 0.008 mmol), under argon, was added a solution of alcohol **34i** (134 mg, 0.27 mmol) in THF (2.5 mL). The suspension was cooled down to 0 °C and methylmagnesium bromide (270 μL, 0.8 mmol, 3.0 M in ether) was added dropwise. At the end of the addition, the solution changed from green to red. The reaction mixture was stirred 20 h at room temperature. It was diluted with EtOAc (5 mL) and poured into a saturated aqueous solution of NH_4Cl (8 mL). The aqueous phase was extracted with EtOAc (3×10 mL) and the combined organic layers were washed with brine (25 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash chromatography (PE/EtOAc:10/1 as eluent) to afford 40 mg (64% yield) of the title compound as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.33 (qq, J=6.6, 1.2 Hz, 1H), 4.30 (dd, J=8.6, 6.9 Hz, 1H), 4.01 (m, 1H), 3.00–2.78 (m, 4H), 2.18 (dd, J=13.2, 4.5 Hz, 1H), 2.08 (dd, J=13.2, 8.7 Hz, 1H), 2.20–2.08 (m, 1H), 1.96–1.81 (m, 4H), 1.63 (s, 3H), 1.61 (d, J=6.6 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=132.5, 123.1, 65.5, 48.2, 44.5, 42.6, 30.6, 30.3, 26.2, 15.9, 13.7 ppm. IR (neat, NaCl): ν=3413, 2929, 2905, 2858, 1668, 1497, 1382, 1275 cm^{-1}. MS (EI): *m*/*z* (%): 232 [$M^{+\cdot}$] (29), 161 [$M^{+\cdot}-C_5H_9S_2$] (19). Elemental analysis calcd for $C_{11}H_{20}OS_2$ (232.40): C, 56.85; H, 8.67, S, 27.59. Found C, 56.89; H, 8.44; S, 28.36.

4.4.7. (*rac*)-2-[1,3]Dithian-2-ylmethyl-oxirane (41). To a solution of 1,3 dithiane (5.0 g, 41.6 mmol) in THF (100 mL) at −78 °C was added *n*-BuLi (30 mL, 41.6 mmol, 1.6 M in hexanes) dropwise via syringe. The reaction mixture was warmed to −20 °C and stirred at that temperature for 2 h. It was then cooled down to −78 °C and neat (±)-epichlorohydrin (3.3 mL, 41.6 mmol) was added. The mixture was allowed to slowly reach room temperature and was stirred overnight at that temperature. The solution was concentrated under reduced pressure to 75 mL, then washed with H_2O and extracted with petroleum ether (4×40 mL). The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash chromatography (PE/Et_2O:2/1) to afford 6.68 g (92% yield) of the title compound as a yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.26 (t, J=7.0 Hz, 1H), 3.20–3.12 (m, 1H), 3.10–2.80 (m, 5H), 2.55 (dd, J=5.1, 2.7 Hz, 1H), 2.20–2.08 (m, 1H), 1.97 (dd, J=6.9, 6.0 Hz, 2H), 1.94–1.80 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=49.9, 47.3, 45.0, 38.9, 30.8, 30.6, 26.0 ppm. IR (neat, NaCl): ν=3348, 2992, 2901, 2827, 1687, 1480, 1277, 1258 cm^{-1}. MS (EI): *m*/*z* (%): 176 [$M^{+\cdot}$] (84). Elemental analysis calcd for $C_7H_{12}OS_2$ (176.30): C, 47.69; H, 6.86, S, 36.37. Found C, 47.61; H, 6.88; S, 36.07.

4.4.8. (*Z*)-1-[1,3]Dithian-2-yl-4-(2,4,6-triisopropyl-phenylselanyl)-hex-4-en-2-ol (34i). To a solution of iodide **32a** (23.2 g, 51.6 mmol) in THF (500 mL) at −78 °C was added *n*-BuLi (34 mL, 51.6 mmol, 1.6 M in hexanes) dropwise and the mixture was stirred for 15 min at −78 °C. Neat $BF_3\cdot OEt_2$ (3.27 mL, 25.8 mmol) was added and immediately after, a solution of the oxirane **41** (4.5 g, 28.5 mmol) in THF (10 mL) was added all at once. The reaction mixture was stirred at −78 °C for 1 h and then quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (15 mL). The mixture was allowed to slowly reach room temperature. It was diluted with petroleum ether (300 mL), washed with H_2O and extracted several times with petroleum ether. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash chromatography (PE/Et_2O:2/1 as eluent) to afford 6.45 g (100% yield, based upon oxirane) of the title compound as a white crystalline solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.99 (s, 2H), 5.81 (q, J=6.6 Hz, 1H), 4.26 (dd, J=9.4, 4.8 Hz, 1H), 3.95–3.80 (m, 1H), 3.70 (hep, J=6.8 Hz, 2H), 2.90–2.78 (m, 5H), 2.05 (d, J=6.5 Hz, 2H), 1.91 (d, J=6.6 Hz, 3H), 2.15–1.72 (m, 2H), 1.70–1.55 (m, 2H), 1.25 (d, J=6.8 Hz, 6H), 1.22 (d, J=6.8 Hz, 6H), 1.17 (d, J=6.8 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=152.9, 149.4, 132.1, 127.2, 125.0, 121.5, 65.8, 45.6, 43.8, 41.7, 33.9, 33.7, 30.2, 29.7, 25.7, 24.3, 24.1, 23.8, 16.4 ppm. IR (neat, NaCl): ν=3347, 3042, 2959, 2907, 2867, 1594, 1560, 1462, 1382 cm^{-1}. MS (EI): *m*/*z* (%): 499 [$M^{+\cdot}$] (10), 217 [$M^{+\cdot}-$SeTIPP] (100). Elemental analysis calcd for $C_{25}H_{40}OS_2Se$ (499.68): C, 60.10; H, 8.07; S, 12.83. Found C, 59.97; H, 8.04; S, 13.59.

4.4.9. 1-[1,3]Dithian-2-yl-4-iodo-hex-4-en-2-ol (42). To a solution of selenide **34i** (130 mg, 0.26 mmol) in THF at 0 °C under argon was added dropwise CH_3MgBr (130 μL, 0.39 mmol, 3.0 M in Et_2O). The reaction mixture was stirred for 15 min at 0 °C. This solution was added to a LDBB solution (2.5 mL, 0.3 M in THF) at −78 °C via syringe. At the end of the addition, the solution colour changed from dark green to clear red. It was stirred for 30 min at −78 °C, neat MeI (16 μL, 0.26 mmol) was added and the mixture was stirred for a further 10 min. After the addition, the solution became colourless. A solution of I_2 (165 mg, 0.65 mmol) in THF (2 mL) was added dropwise and the reaction mixture was stirred for 1 h to −78 °C. It was quenched by the addition of ethanol (2 mL) at −78 °C and then it was allowed to reach room temperature. It was diluted with petroleum ether (5 mL), washed with a saturated aqueous solution of $Na_2S_2O_3$ (5 mL) and the aqueous layer extracted several times with petroleum ether. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash chromatography (PE/Et_2O:1/1 as eluent) to afford 73 mg (81% yield) of the title compound as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.73 (qt, J=6.3, 1.1 Hz, 1H), 4.28 (dd, J=8.4, 6.0 Hz, 1H), 4.35–4.20 (m, 1H), 2.99–2.80 (m, 4H), 2.62 (d, J=6.5 Hz, 2H), 2.25–1.80 (m, 4H), 1.77 (d, J=6.3 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=128.4, 106.3, 67.3, 53.3, 44.7, 42.4, 30.6, 30.2, 26.4, 22.5 ppm. IR (neat, NaCl): ν=3348, 2938, 2900, 2827, 1647, 1422, 1275, 1164, 1072 cm^{-1}. MS (EI): *m*/*z* (%): 219 [$M^{+\cdot}-$I] (15), 205 (29), 188 (22), 145 (24). HRMS (CI+, M+) calcd for $C_{10}H_{17}IOS_2$, 344.9765; found 344.9769.

4.4.10. (*Z*)-1-[1,3]Dithian-2-yl-trimethylsilanylmethyl-hex-4-en-2-ol ((*Z*)-6). To a solution of vinyl iodide **42** (462 mg, 1.35 mmol) and $Pd(PPh_3)_4$ (80 mg, 0.07 mmol) in THF (5 mL) was added trimethylsilylmagnesium chloride (1.7 mL, 4.05 mmol, 2.3 M in THF) dropwise. The mixture was stirred overnight at room temperature. It was then poured into a saturated aqueous solution of NH_4Cl (10 mL) and the aqueous layer extracted with EtOAc (4×10 mL).

The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash chromatography (PE/Et_2O:1.5/1 as eluent) to afford 279 mg (68% yield) of the title compound as a colourless oil. ^1H NMR (500 MHz, $CDCl_3$): $\delta=5.20$ (q, $J=7.0$ Hz, 1H), 4.29 (dd, $J=9.2$, 5.2 Hz, 1H), 3.98 (m, 1H), 2.86 (m, 4H), 2.11 (m, 2H), 2.01 (d, $J=2.4$ Hz, 1H), 1.97 (dd, $J=13.1$, 9.2 Hz, 1H), 1.88 (m, 1H), 1.82 (m, 2H), 1.62 (d, $J=14.4$ Hz, 1H), 1.54 (d, $J=7.0$ Hz, 3H), 1.40 (d, $J=14.4$ Hz, 1H), 0.02 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=134.3$, 119.3, 65.1, 47.3, 44.2, 42.3, 30.3, 30.0, 25.9, 20.8, 13.9, −0.8 ppm. IR (neat, NaCl): $\nu=3321$, 2958, 2931, 2902, 1637, 1561, 1461, 1422, 1382, 1056 cm^{-1}. MS (EI): *m/z* (%): 304 [$M^{+\cdot}$] (25), 233 [$M^{+\cdot}-Si(CH_3)_3$] (39). Elemental analysis calcd for $C_{14}H_{28}OS_2Si$ (304.59): C, 55.31; H, 9.28, S, 21.09. Found C, 55.59; H, 9.10; S, 21.14.

4.4.11. (*E*)-1-[1,3]Dithian-2-yl-trimethylsilanylmethyl-hex-4-en-2-ol ((*E*)-6). To a freshly prepared solution of LDBB (11.2 mL, 3.15 mmol, 0.28 M in THF) at −78 °C was added a solution of allylsilane **34k** (645 mg, 1.58 mmol) in THF (1 mL) dropwise. At the end of the addition the dark green solution turned to pale red. It was stirred for a further 10 min at −78 °C and neat methyl iodide (98 μL, 1.58 mmol) was added. The reaction mixture was stirred for 30 min at −78 °C and then a solution of oxirane **41** (280 mg, 1.58 mmol) in THF (1 mL) and neat $BF_3\cdot OEt_2$ (198 μL, 1.58 mmol) were added. The reaction mixture was stirred for 2 h at −78 °C and then quenched by the addition of a saturated $NaHCO_3$ aqueous solution (2 mL). It was allowed to reach room temperarture and was poured into a mixture of PE (40 mL)/H_2O (40 mL). The aqueous layer was extracted with petroleum ether (2×40 mL) and the combined organic layers were washed with brine (60 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by HPLC using a reverse phase column (hexane/isopropanol:99/1) affording 240 mg (50% yield) of the title compound as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$): $\delta=5.54$ (q, $J=6.6$ Hz, 1H), 4.27 (t, $J=7.0$ Hz, 1H), 3.95 (m, 1H), 2.86 (m, 4H), 2.56 (d, $J=3.3$ Hz, 1H), 2.11 (m, 2H), 2.18–2.05 (m, 2H), 1.96–1.85 (m, 2H), 1.88 (s, 2H), 1.81 (d, $J=6.6$ Hz, 3H), 0.05 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=132.3$, 126.7, 67.5, 59.31, 44.3, 42.2, 33.3, 30.3, 29.4, 26.2, 17.9, 0.9 ppm. IR (neat, NaCl): $\nu=3321$, 2957, 2929, 2902, 1640, 1459, 1422, 1164, 1072 cm^{-1}. MS (EI): *m/z* (%): 304 [$M^{+\cdot}-I$] (15), 233 ($M^{+\cdot}-Si(CH_3)_3$, 53), 214 (63). Elemental analysis calcd for $C_{14}H_{28}OS_2Si$ (304.59): C, 55.31; H, 9.28, S, 21.09. Found C, 55.49; H, 9.18; S, 21.06.

4.4.12. 2-(6-[1,3]Dithian-2-ylmethyl-3-methyl-4-methylene)-tetrahydro-pyran-2-yl-ethanol (3). To a solution of (*Z*)-allylsilane **6** (65 mg, 0.21 mmol) and aldehyde **7** (60 μL, 0.32 mmol) in CH_2Cl_2 (2 mL), at −78 °C, was added neat $BF_3\cdot OEt_2$ (41 μL, 0.32 mmol) dropwise. The reaction mixture was allowed to warm up slowly to −30 °C and the disappearance of the starting material was monitored by TLC. The solution was then allowed to slowly reach room temperature. It was poured into a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (4×5 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash chromatography (PE/Et_2O:2/1) affording 55 mg (91% yield) of the title compound as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$): $\delta=4.80$ (d, $J=1.5$ Hz, 1H), 4.73 (d, $J=1.5$ Hz, 1H), 4.23 (dd, $J=9.3$, 4.8 Hz, 1H), 3.92–3.82 (m, 2H), 3.62 (tt, $J=10.0$, 3.0 Hz, 1H), 3.18 (td, $J=9.6$, 3.0 Hz, 1H), 3.00–2.66 (m, 4H), 2.30–1.60 (m, 9H), 1.99 (d, $J=6.9$ Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=$ 148.3, 107.3, 83.2, 75.2, 60.9, 44.4, 42.5, 41.5, 41.4, 35.6, 30.8, 30.5, 26.1, 12.7 ppm. IR (neat, NaCl): $\nu=3332$, 3084, 2935, 2899, 2859, 1647, 1423, 1364, 1324, 1191 cm^{-1}. MS (EI): *m/z* (%): 288 [$M^{+\cdot}$] (89). Elemental analysis calcd for $C_{14}H_{24}O_2S_2$ (288.47): C, 58.29; H, 8.39. Found C, 57.54; H, 8.35.

Acknowledgements

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Brønsted acidity of ceric ammonium nitrate in anhydrous DMF. The role of salt and solvent in sucrose cleavage

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Dedicated to the memory of Professor Gaspare Barone

Abstract—The generation of an unexpected Brønsted acidity in anhydrous DMF at 50 °C was evidenced by NMR measurements during the investigation on the course of sucrose cleavage by ceric ammonium nitrate (CAN). The formation of a nitrooxy derivative of DMF by reaction with CAN is responsible for this acidity. The reactivity of CAN at 50 °C with several solvents was evaluated by voltammetric and potentiometric measurements. The possible release of protons from these reactions, particularly when aqueous solvent mixtures are used, should always be taken into account in the mechanistic interpretation of CAN synthetic applications.

1. Introduction

Ceric ammonium nitrate is widely utilised to accomplish a variety of oxidative transformations.[1–4] In the carbohydrate field it has been used to perform oxidation reactions under strongly acidic aqueous conditions;[5–8] recently, its ability to induce formation[9] and cleavage[10,11] of ketals on many types of derivatives has also been reported. In addition, the possibility of accomplishing hydrolyses of glycoside linkages with CAN under buffered neutral conditions was reported.[12] Given our interest in the research of new protocols for glycosidic bond cleavage in polysaccharides, we investigated this reaction in-depth. In this regard, we found that ceric ammonium nitrate in anhydrous DMF can be used to cleave selectively the glycosidic linkages of Ko and Kdo in lipopolysaccharides.[13] In that paper, we quoted the development of this method to cleave the glycosidic bond of sucrose: the description of the course of this reaction at 50 °C is now reported. In addition the investigation on the stability at 50 °C of CAN in several solvents, commonly used to perform reactions with CAN, is addressed by NMR analysis and voltammetric and potentiometric measurements.

2. Results and discussion

The first report on sucrose cleavage by CAN was by Ishida,[12] who claimed the glycosidic linkage cleaved at pH = 7 using 5.0 mmol dm^{-3} of CAN with 50 mmol dm^{-3} of Tris buffer at 40–100 °C. In our hands these conditions gave a pH of about 2 instead of 7, on the other hand no disaccharide hydrolysis occurred when, increasing 10-fold the amount of Tris buffer (0.5 mol dm^{-3}), the solution showed a pH of 6.7. Analogously, no reaction occurred when pH = 7 was reached by adding 8 M HCl to a Tris solution of CAN and sucrose. The non-neutral conditions of Ishida reaction was supported by the fact that in no case was reported the precipitation of cerium hydroxide, which occurs under neutral conditions.[14] Accordingly, when we worked under carefully checked neutral conditions, cerium hydroxide precipitated. We think that the deceptive neutral conditions might be due to a deficient buffer concentration, whose amount should not be enough to buffer the acidity determined by CAN hydrolysis. In addition, this acidity should be further increased if it is taken into account that Ishida's reactions are performed at 40–100 °C and that the pH value decreases with the increase of the temperature. Therefore, in our opinion, protic acid hydrolysis is occurring under Ishida's conditions, suggesting a Lewis acid catalysis of Ce(IV) at pH = 2.

However, the possibility that CAN could cleave the sucrose glycoside linkage under non-aqueous conditions was suggested by the finding that in the procedure of

Keywords: Ceric ammonium nitrate; Brønsted acidity; DMF; Sucrose.
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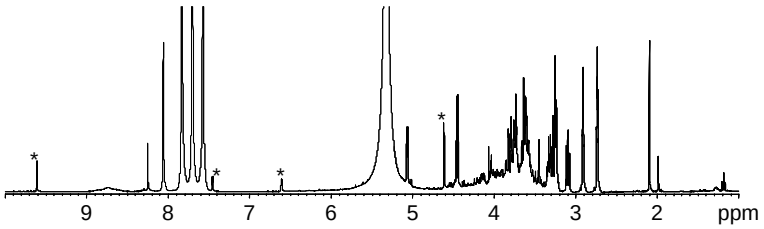


Figure 1. ^{1}H NMR at 400 MHz of the crude CAN sucrose reaction in DMF-d_7 after 2 h at 50 °C (HMF peaks are marked with an asterisk).

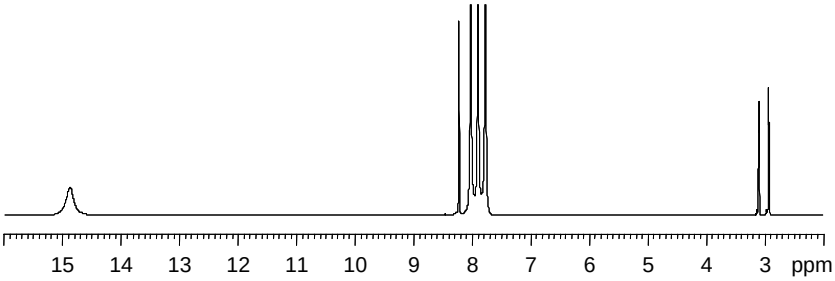


Figure 2. ^{1}H NMR at 400 MHz of the red CAN DMF-d_7 solution at 50 °C.

isopropylidene closure on sucrose at 60 °C by CAN in DMF,[9] the use of a molar ratio of CAN/substrate higher than 0.2 seemed to produce glucose. Actually, we have realized the complete cleavage of the glycosidic linkage of sucrose with CAN in a 1:1 molar ratio in anhydrous DMF under mild temperature conditions (50 °C), obtaining quantitative amounts of glucose and several products arising from the fructose moiety, among which 5-(hydroxymethyl)furfural (HMF) was the most abundant.

In order to gain insight into the course of the reaction we monitored it by NMR measurements. In the first experiment, equimolar solutions of CAN and sucrose in DMF-d_7, both equilibrated at 50 °C, were mixed in a NMR tube and spectra were measured at this temperature every 5 min. The initially red solution of CAN, became colourless after adding sucrose within 15 min. After 2 h the solution appeared slightly yellow and the ^{1}H NMR spectum (Fig. 1) showed the complete disappearance of sucrose signals and the presence of glucose α- and β-anomer signals at 5.04 and 4.43 ppm, respectively, those of HMF at 9.60, 7.50, 6.60 and 4.60 ppm and the triplet signal of the ammonium ion at 7.92 ppm. The ^{13}C NMR spectrum, in addition to glucose and HMF signals, showed in the range between 83–86 ppm at least four minor signals suggesting the presence of several furanic products, among which we were able to identify the 2,6-anhydro-α-D-fructo-furanose and traces of fructose. From a quantitative point of view, HPLC analysis of the crude reaction allowed us to estimate only the amounts of glucose (100% molar yield) and HMF (13% molar yield). A confirmation of HMF molar yield was obtained by integration of its hydroxymethylene signal at 4.60 ppm with respect to the sum of the anomeric glucose signals in the ^{1}H NMR spectrum. The total yield of the other identified minor products was estimated to be about 15%. These results indicated that the fructose moiety of sucrose underwent an extended decomposition whereas the glucose part was stable under the reaction conditions.

When the reaction was performed in the presence of an excess of an acid scavenger (potassium carbonate or pyridine),[15] it did not proceed at all indicating the involvement of an acid reagent in the sucrose degradation. Indeed the ^{1}H NMR spectrum at 50 °C of the red CAN DMF-d_7 solution showed a broad singlet at 14.8 ppm (Fig. 2), suggesting unexpected Brønsted acidity.

An acidic signal at 14.2 ppm was also found in the ^{1}H NMR spectrum of a colourless CAN solution, without sucrose, obtained by standing at 50 °C for about 30 min. This signal was detected even after that the NMR tube was kept at 4 °C for 20 days. The decolourization of the red CAN solution suggested the reduction of Ce(IV) to Ce(III) by DMF. Indeed the oxidation of amides by ceric ion has already been reported, albeit under strongly acidic aqueous conditions.[16,17] Differential pulse voltammetric measures (Fig. 3) confirmed

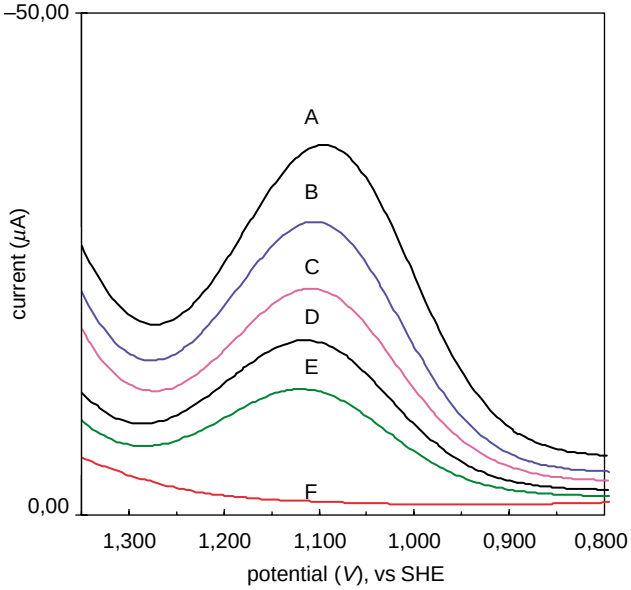


Figure 3. Differential pulse voltammetry for the reduction of CAN at glassy carbon electrode in DMF versus standard hydrogen reference electrode (SHE). The different traces show the decay of Ce(IV) concentration at 20 °C with time: (A) 1 min, (B) 2 min, (C) 4 min, (D) 6 min, (E) 9 min, (F) 20 min.

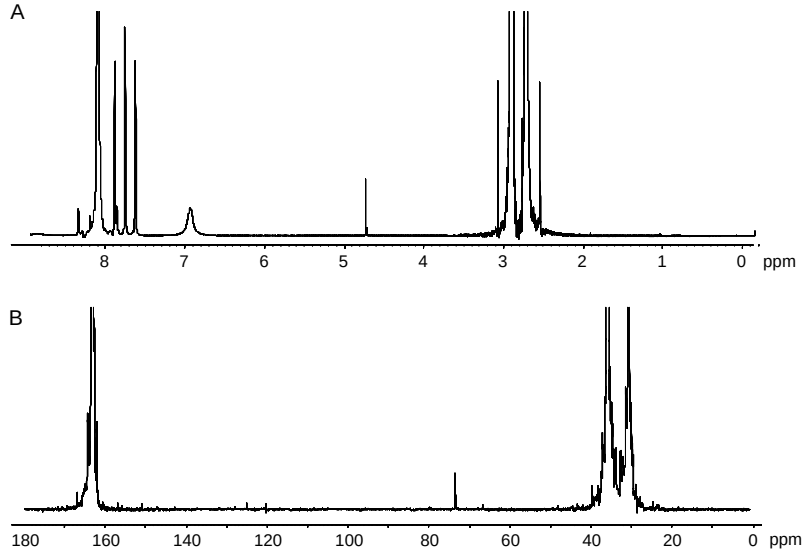


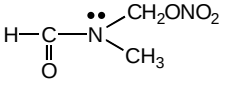
Figure 4. ^{1}H (400 MHz) (A) and ^{13}C NMR (100 MHz) (B) at 50 °C of a 9:1 DMF/DMF-d_7 0.10 M CAN solution.

the reduction of Ce(IV) to Ce(III) in anhydrous DMF within a few minutes at 50 °C, which proceeded in parallel with the decolourization of the solution. When sucrose was added to the colourless CAN solution, the ^{1}H NMR spectrum, measured after 2 h at 50 °C, was very similar to that obtained when sucrose was added to the red CAN solution except for the lack of HMF signals. This suggested that sucrose cleavage was mainly due to the Brønsted acidity and the absence of HMF could be due to the lack of Ce(IV) in the colourless CAN solution.[18]

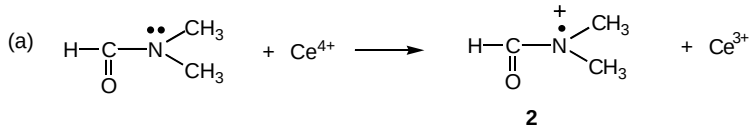
Support for this hypothesis was obtained by observing that a DMF-d_7 solution of sucrose and cereous ammonium nitrate, $Ce(NH_4)_2(NO_3)_5 \cdot 4H_2O$ [CAN(III)], remained unalterated for at least 16 h at 50 °C, confirming that sucrose cleavage in the colourless CAN solution did not depend on Ce(III) ion but, evidently, on the high Brønsted acidity of the solution. In fact, the ^{1}H NMR spectrum of a CAN(III) DMF-d_7 solution at 50 °C showed a singlet signal at 3.8 ppm,[19] indicating a lower acidity than that of colourless CAN solution, salt concentration being equal. In the light of these results the presence of the proton signal at 14.8 ppm in the perdeuterated solvent DMF-d_7 (Fig. 2) must be ascribed to the exchange of deuterium cation with the protons of the ammonium ion of CAN.

To confirm this suggestion we replaced CAN with ceric tetrabutylammonium nitrate (CTAN).[20] When this salt was dissolved in DMF-d_7 at 50 °C, we observed that the red colour of the solution survived longer with respect to the CAN solution and both the red coloured and colourless solution of CTAN showed a ^{1}H NMR spectrum without proton signals excepting the aliphatic ones. However, adding sucrose to the red CTAN solution, the ^{1}H NMR spectrum, after 5 h at 50 °C, was very similar to that obtained from sucrose in the CAN red solution indicating the same product composition in both cases. This strongly suggested that also CTAN produced Brønsted acidity by oxidation of DMF. The main difference was the known slow rate of the CTAN reaction[20] with respect to the CAN one.

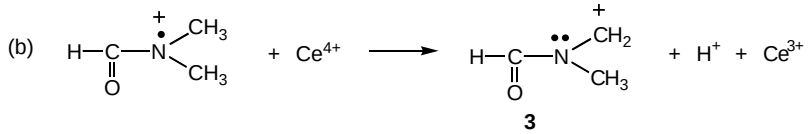
In order to explain the origin of this Brønsted acidity, NMR spectra were measured in a 0.1 M 9:1 DMF/DMF-d_7 CAN solution at 50 °C. Together with the very intense signals due to



1



2



3

$$2Ce^{4+} + H(C{=}O)N(Me)_2 + NO_3^- = 2Ce^{3+} + H(C{=}O)N(Me)CH_2ONO_2 + H^+$$

Scheme 1. Suggested mechanism of oxidation of DMF by CAN.

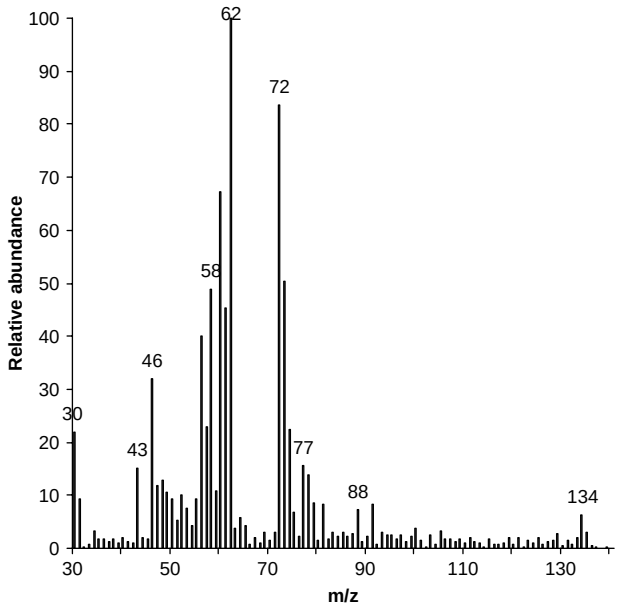


Figure 5. Mass spectrum of **1**, recorded with a ThermoQuest Finnigan ion-trap mass spectrometer Mod. Polaris from 30 to 140 mass units. This MS has been recorded after chromatography carried out on RTX Restek column (30 m×0.25 mmID) mounted in the oven of a ThermoQuest GC Series Trace 2000.

DMF, a strong signal appeared in the ^{1}H NMR spectrum (Fig. 4A) at 4.70 ppm,[21] which was correlated to the carbon signal at 73.4 ppm (Fig.4B), assigned to a methylene carbon on the basis of a DEPT experiment. This signal suggested a product with structure **1** (Scheme 1) by analogy with the mechanism reported for the anodic oxidation of DMF in methanol and acetic acid,[22] or acetonitrile[23] which involves the formation of radical cation **2** in a rate-determining step followed by the formation of cation **3** by loss of another electron and a proton, according to equations (a) and (b) shown in Scheme 1. Finally, cation **3** reacted with the nucleophilic solvent to give an adduct. In our case, **3** should react with the nitrate ion. Unfortunately we were unable to identify the other NMR signals of compound **1**, that is formyl and *N*-methyl protons and the corresponding carbon signals, due to overlap with the corresponding intense signals of DMF. However, confirmatory evidence of the formation of **1** was obtained by GC–MS mass spectrum which showed, in addition to DMF, another product with a molecular ion at *m/z* 134 and fragments at *m/z* 46, 62 and 72, 88 (Fig. 5). The fragment at *m/z* 72 is in agreement with the formation of ion **3**, whereas that one at *m/z* 46 (NO_2^+) is indicative of the nitro-group. This latter is also confirmed by the ion at *m/z* 88, assignable to an ion at M-46. Less immediate is the identification of the ion at *m/z* 62, probably it might correspond to the ion $CH_3N^+(O)OH$, arising from a rearrangement. In agreement with structure **1** was also the IR spectrum, which showed the typical signals of a nitric ester at 1640, 1260 and 870 cm^{-1}. In conclusion, DMF oxidation by CAN involves the production of protons according to the total equation shown in Scheme 1. An acid titration was in a good agreement with a 2:1 Ce ion/H^+ stoichiometry ratio. However, it cannot be excluded that other minor species could be formed, because, when α-2,3-epoxy-5α-cholestane **4** was added to the colourless CAN solution, 2β-formoxy-3α-hydroxy-5α-cholestane **5** was found together with the expected 3α-hydroxy-2β-nitrooxy-5α-cholestane **6** and other unidentified products (Scheme 2).[24] Probably the radical cation **2** can cleave to give a formyl cation,[17] which reacts with the nitrate ion to give a reacting anhydride able to give formates.

On the basis of these results, the involvement of Brønsted acidity in reactions with CAN in anhydrous DMF at 50 °C can be suggested; in particular, in the case of sucrose, the reaction proceeds mainly by protic cleavage of the glycosidic linkage to give glucose and fructofuranosyl cation (Scheme 3) which, in turn, is responsible for all other products. The formation of HMF, which occurs only when Ce(IV) is present, can be ascribed to the strong dehydrating action of Ce(IV) due to its high hardness and oxophilicity. As for 2,6-anhydro-α-D-fructofuranose **7** it arises from the intramolecular cyclization of 6-hydroxymethylene group.

In conclusion, the detected Brønsted acidity of CAN in anhydrous DMF indicates a low stability of CAN at 50 °C in this solvent, which is confirmed by potentiometric titration. In agreement with the procedure of Torii et al.[25] we reported

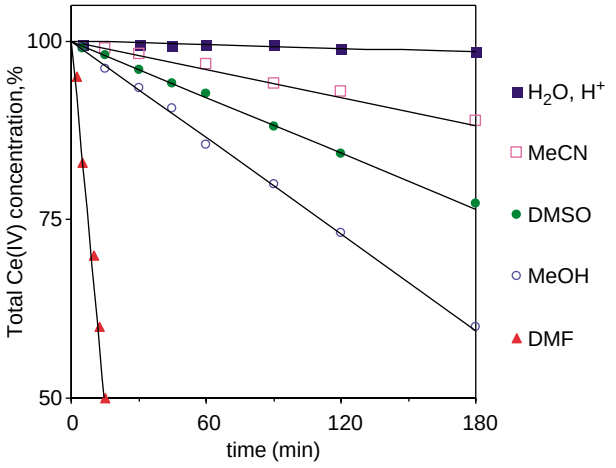
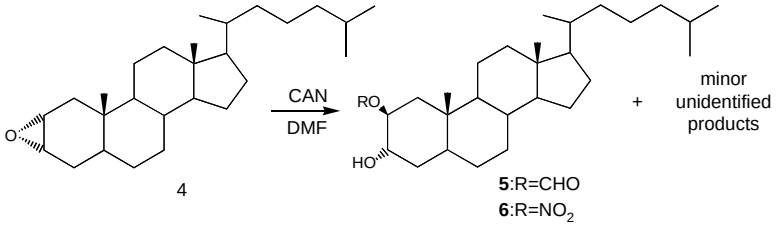
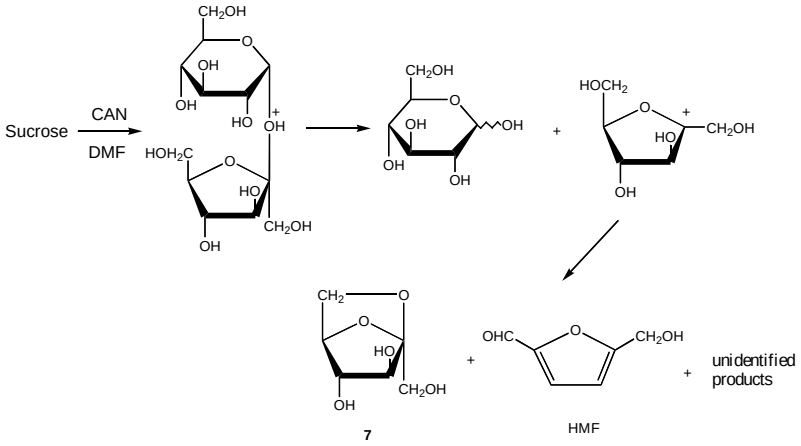


Figure 6. Relationship between the total concentration of Ce(IV) versus time. A 15 mM solution of CAN in different solvents was allowed to stand at 50 °C under N_2 flow. The slope of straight lines is very dependent upon the temperature.



Scheme 2. Cleavage of α-2,3-epoxy-5α-cholestane with CAN in DMF.



Scheme 3. Mechanism of sucrose cleavage by CAN in DMF.

in Figure 6 the relationship between the variation of the total concentration of CAN versus the time indicating the relative CAN stability in several solvents. This figure reports the stability order of CAN in DMF, DMSO, MeOH, MeCN and H_2O. In particular, it is interesting to observe that CAN is very stable[26] only in H_2O/H^+; as for the organic solvents commonly used to perform reactions with CAN, it is rather stable in MeCN but it degrades rather easily in MeOH[27] and DMF.

3. Conclusion

We have shown that, in spite of an expected Lewis acidity, CAN in anhydrous DMF at 50 °C also produces a Brønsted acidity giving Ce(III) ion and a nitrooxy derivative of DMF. This protic acidity is responsible for sucrose cleavage to give quantitative glucose and fructofuranosyl cation, from which arises the formation of HMF, **7**, fructose and other minor unidentified products. A valuable result is that our data stress the high reactivity at 50 °C of CAN with some common solvents (Fig. 6) with possible concomitant release of protons,[27] particularly when aqueous solvent mixtures are used.[10]

4. Experimental

4.1. General methods

^1H and ^{13}C NMR spectra were obtained at 400 and 100 MHz, respectively, with a Bruker AM 400 spectrometer equipped with a reverse probe, in the FT mode at 50 °C. ^{13}C and ^1H chemical shifts are expressed in ppm relative to DMF (^1H 8.02, ^{13}C 162.6 ppm in DMF-d_7) or $CHCl_3$ (^1H 7.26, ^{13}C 77.0 ppm in $CDCl_3$). Two-dimensional spectra (COSY, HSQC and HMBC) were measured using standard Bruker software. HPLC analysis was performed by using a SUPELCO RP-18 column (4×25 mm) with water as eluent at a 0.7 mL/min flow and a double detector (refractive index and $UV_{\lambda=290\ nm}$). Optical rotations were measured on a JASCO P-1010 polarimeter. Melting points were measured on a Reichert Thermovar apparatus. IR spectral measurements were carried out using a Brucker Vector22 FT-IR spectrometer. Elementar analysis were performed on a Carlo Erba 1108 instrument. Positive ESI-MS spectra were recorded on a Finnigan LCQ-DECA ion trap mass spectrometer.

4.2. Electrochemistry: instrumentation and software

Voltammetric experiments were performed using a Metrohm electroanalyser (model 757 VA Computrace) connected to a PC. The system was operated and measurements were recorded using VA Computrace version 2.0 run under Windows 98SE. The three-electrode system consisted of the rotating disk glassy carbon electrode as working electrode, Ag/AgCl/3 M KCl as reference electrode and a platinum wire as auxiliary electrode purchased from Metrohm. All chemicals were electrochemical or spectrophotometric grade. The electrolyte employed in all experiments was potassium perchlorate 0.5 M, while the concentration of CAN was 15 mM. Voltammograms were recorded at room temperature at a scan rate of 50 mV/s. All solutions were degassed with high-purity nitrogen prior to undertake voltammetric experiments. Since there is always a question as to the effect of junction-potential variations on electrochemical measurements, the redox potentials for

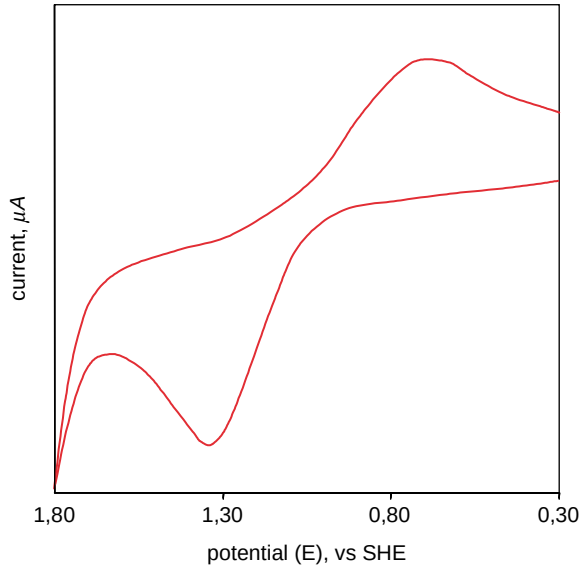


Figure 7. Cyclic voltammetric response of CAN at glassy carbon electrode DMF 0.5 M $KClO_4$ versus standard hydrogen reference electrode (SHE).

the $Fe(CN)_6^{3-}/Fe(CN)_6^{4-}$ couple in the organic solvents have been measured by cyclic voltammetry under the same conditions. Then, the value for the reduction of Ce(IV) to Ce(III) in DMF was determinated to be +0.72 V, while the oxidation peak at about +1.37 V was due to Ce(III) to Ce(IV) oxidation versus standard hydrogen electrode (SHE) (Fig. 7).

4.3. Measure of the stability of Ce(IV)

The stability of the Ce(IV) solutions in the study solvents (DMF, DMSO, MeCN, MeOH, H_2O) was evaluated by measuring at 50 °C during the time the decrease of Ce(IV) total concentration that was determined by titration with a standard solution of Fe(II) ammonium sulfate (FAS). Samples (10 mL) were withdrawn at a recorded time, quenched with an excess of 10 mM FAS in 0.5 M sulphuric acid, and the excess ferrous salt was back-titrated with 10 mM CAN, using *o*-phenanthroline–Fe(II) as indicator. The biamperometric method was used for more accurate determinations with a double platinum sheet electrode (0.2×8×8 mm, Metrohm) in conjunction with an Amel potentiostat (Model 2051). The decay of Ce(IV) concentration was also followed by a potentiometric method. Potentiometric measurements were performed by using two electrodes in conjunction with a high-impedance electrometer (Keithley Model 197A). A platinum wire served as the indicating electrode, and the reference electrode with double junction was used (Ag/AgCl with sleeve diaphragm and bridge electrolyte, purchased from Metrohm).

4.4. Determination of H^+ concentration

The H^+ concentration of a solution in which all Ce(IV) it has been reduced to Ce(III) has been determined by potentiometric titration using a sodium methoxide organic solution as titrant. This solution is standardized against pure benzoic acid. The endpoint has been determined using the Gran plot.[28]

4.5. Hydrolysis of the glycoside linkage of sucrose

(i) Conditions as reported in the literature (Ref. 12): Tris (303 mg, 2.5 mmol) was dissolved in H_2O (43 mL) and 8 M HCl was added up until pH=7 was reached. To this solution CAN (137 mg, 0.25 mmol) was added and the mixture was diluted to 50 mL in order to obtain a final solution, which was 50 mM in Tris and 4.8 mM in CAN. The final pH was 1.9. Sucrose (85 mg, 0.201 mmol) was dissolved in 2 mL of this solution and the mixture was kept at 100 °C. After 30 min the complete hydrolysis of sucrose to glucose and fructose was evidenced by TLC analysis. (ii) Conditions using 10 times of the reported amount of buffer: using identical reagent amounts as above, except for Tris (3.030 g, 25 mmol), the final solution was cloudy and at pH=6.7. Sucrose was found to be unaltered in this solution after 3 h at 100 °C. (iii) Our neutral conditions: Tris (303 mg, 2.5 mmol) and CAN (137 mg, 0.25 mmol) were dissolved in H_2O (43 mL) and 8 M HCl was added until reaching pH=7 and the whole mixture diluted to 50 mL. Also in this case, the solution was cloudy and sucrose was recovered unaltered after 3 h at 100 °C.

4.6. Reaction of sucrose with CAN in DMF-d_7

Sucrose (20 mg, 0.058 mmol) was dissolved in DMF-d_7 (250 μL) under stirring at T=50 °C for about 30 min. A CAN (32 mg, 0.058 mmol) solution in DMF-d_7 (500 μL) was then added, after that ^{1}H NMR spectra were recorded at T=50 °C every 5 min. Analogous reactions were conducted in DMF in order to perform HPLC analyses of the mixtures.

4.7. Reaction of sucrose with CAN in DMF-d_7 in presence of acid scavenger

Sucrose (20 mg, 0.058 mmol) was dissolved in DMF-d_7 (250 μL) under stirring at T=50 °C for about 30 min and then K_2CO_3 (40 mg, 0.290 mmol) or pyridine (23 μL, 0.290 mmol) was added. A CAN (32 mg, 0.058 mmol) solution in DMF-d_7 (500 μL) was then added, after that ^{1}H NMR spectra were recorded at T=50 °C every 5 min.

4.8. Reaction of sucrose with $Ce(NH_4)_2(NO_3)_5$ in DMF-d_7

Sucrose (20 mg, 0.058 mmol) was dissolved in DMF-d_7 (250 μL) under stirring at T=50 °C for about 30 min. $Ce(III)(NH_4)_2(NO_3)_5$ was oven-dried at 85 °C for 8 h, then cooled under an argon flow and dissolved in DMF-d_7 (500 μL). The cereous mixture was added to the sucrose solution, after that ^{1}H NMR spectra were recorded at T=50 °C every 5 min.

4.9. Reaction of sucrose with CTAN in DMF-d_7

Sucrose (20 mg, 0.058 mmol) was dissolved in DMF-d_7 (250 μL) with stirring at T=50 °C for about 30 min. A CTAN (58 mg, 0.058 mmol) solution in DMF-d_7 (500 μL) was then added, after that ^{1}H NMR spectra were recorded at T=50 °C every 5 min.

4.10. Reaction of α-2,3-epoxy-5α-cholestane with CAN in DMF

α-2,3-Epoxy-5α-cholestane **4** (30 mg, 0.078 mmol) was dissolved in DMF (700 μL) and then a CAN (47 mg, 0.086 mmol) solution in DMF (300 μL) was added. Additional aliquots (150 μL) of the CAN solution were then added after 2 and 4 h. After 5 h, TLC showed complete disappearance of the starting compound, therefore the reaction was quenched by addition of solid $NaHCO_3$ to reach pH=6. The mixture was filtered and concentrated by co-evaporation with toluene (×5, 1 mL). The residue was then suspended in CH_2Cl_2 (25 mL) and washed with 5 M NaCl (25 mL). The organic layer was collected, dried and concentrated to give a residue, which, after chromatography (3:1 cyclohexane/ethyl acetate) gave several fractions, the main ones being pure 2-β-formoxy-3-α-hydroxy-5α-cholestane **5** (9 mg) as a white solid and pure 3-α-hydroxy-2-β-nitrooxy-5α-cholestane **6** (9 mg) as a white solid.

Compound **5**. $[\alpha]_D$ +32 (*c* 0.3, CH_2Cl_2). Mp=100–101 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (s, 1H, *H*CO), 5.02 (br s, 1H, H-2), 3.97 (br s, 1H, H-3), 1.94 (m, 1H, H-1), 1.83 (m, 1H, H-4), 1.70–1.46 (m, 8H), 1.41–1.25 (m, 13H), 1.17–1.05 (m, 7H), 1.02 (s, 3H, H-19), 0.91 (d, 3H, J=6.0 Hz, H-21), 0.88 (2d, 6H, J=6.0 Hz, H-26, H-27), 0.66 (s, 3H,

H-18); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.3 (H*C*O), 72.8 (C-2), 68.8 (C-3), 56.5, 56.4, 55.1, 42.7, 40.7, 40.1, 39.9, 39.6, 36.2, 35.8, 35.4, 34.9, 31.9, 29.7, 28.7, 28.2, 28.0, 24.2, 23.9, 22.8, 22.6, 20.9, 18.7, 14.4, 12.1; IR ($CHCl_3$): 1720 cm^{-1} (formate ester signal). ESI-MS for $C_{28}H_{48}O_3$ (*m*/*z*): M_r (calcd) 432.36, M_r (found) 455.19 $(M+Na)^+$. Anal. Calcd: C 77.72, H 11.18. Found: C 77.40, H 11.09.

Compound **6**. $[\alpha]_D$ +16 (*c* 0.7, CH_2Cl_2). Mp=90–91 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.08 (br s, 1H, H-2), 4.02 (br s, 1H, H-3), 1.92 (m, 1H, H-1), 1.73 (m, 1H, H-4), 1.70–1.47 (m, 8H), 1.45–1.19 (m, 8H), 1.15–0.95 (m, 12H), 0.90 (m, 6H, H-19, H-21), 0.87 (2d, 6H, J=6.0 Hz, H-26, H-27), 0.65 (s, 3H, H-18); ^{13}C NMR (100 MHz, $CDCl_3$): δ 82.0 (C-2), 66.1 (C-3), 56.4, 56.2, 54.8, 42.6, 39.9, 39.5, 38.4, 36.4, 36.2, 35.8, 35.4, 35.0, 32.2, 31.8, 29.7, 28.2, 28.0, 24.1, 23.8, 22.8, 22.5, 20.8, 18.7, 13.4, 12.1; IR ($CHCl_3$): 1629 and 1263 cm^{-1} (nitrate ester signals). ESI-MS for $C_{27}H_{47}NO_4$ (*m*/*z*): M_r (calcd) 449.35, M_r (found) 472.27 $(M+Na)^+$. Anal. Calcd: C 72.12, H 10.54, N 3.11. Found: C 72.17, H 10.51, N 3.08.

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Nucleophilic aromatic substitution reaction of nitroarenes with alkyl- or arylthio groups in dimethyl sulfoxide by means of cesium carbonate

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Abstract—Treatment of nitroarenes having electron-withdrawing groups at the *ortho* or *para* position with alkanethiol in the presence of cesium carbonate in dimethyl sulfoxide at 25 °C leads to nucleophilic displacement of the nitro group with the alkylthio group. Cesium carbonate is superior to other bases such as potassium carbonate, sodium carbonate, and triethylamine. The cesium-mediated nucleophilic aromatic substitution reaction provides a mild yet powerful and user-friendly protocol for the synthesis of aryl sulfides.

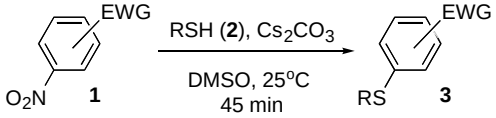
1. Introduction

Nucleophilic aromatic substitution reactions (S_NAr reactions) of nitroarenes that have strong electron-withdrawing groups at the *ortho* or *para* positions are well-known processes.[1] Here, we report an improved method for S_NAr reactions of activated nitroarenes with thiols. We have been interested in the excellent nucleophilicity of thiols in combination with cesium base,[2] since the development of truly powerful and highly reliable bond-forming reactions have attracted increasing attention.[3,4] The present cesium-mediated reaction is high-yielding and rapid, compared with similar reactions mediated by other bases,[1,5] and will be an extremely useful tool for conjugation chemistry through the formation of an sp^2-carbon–sulfur covalent bond.

2. Results and discussions

The reaction of 4-nitrobenzaldehyde (**1a**) with odorless 1-dodecanethiol (**2a**)[6] was chosen as a model reaction. Treatment of **1a** (0.50 mmol) with **2a** (0.60 mmol) in dimethyl sulfoxide (DMSO, 3 mL) in the presence of cesium carbonate (0.60 mmol) at 25 °C for 45 min provided the corresponding sulfide **3a** in 97% yield (Table 1, entry 1). Cesium carbonate[7] proved to be most powerful among bases we tested. Use of potassium carbonate and sodium carbonate resulted in lower yields, 46 and 11%, respectively. Organic bases such as triethylamine were far less effective. In the previous report,[1b] the success of the displacement is crucially due to the use of

Table 1. Cesium-mediated S_NAr reactions of nitroarenes with thiols



Entry	EWG	R	Yield (%)
1	4-CHO (**1a**)	$^nC_{12}H_{25}$ (**2a**)	97 (**3a**)
2	2-CHO (**1b**)	$^nC_{12}H_{25}$ (**2a**)	98 (**3b**)
3	4-NO_2 (**1c**)	$^nC_{12}H_{25}$ (**2a**)	88 (**3c**)
4	4-$COCH_3$ (**1d**)	$^nC_{12}H_{25}$ (**2a**)	88 (**3d**)
5	4-$COOCH_3$ (**1e**)	$^nC_{12}H_{25}$ (**2a**)	93 (**3e**)
6	4-CN (**1f**)	$^nC_{12}H_{25}$ (**2a**)	87 (**3f**)
7	4-F (**1g**)	$^nC_{12}H_{25}$ (**2a**)	—[a]
8	4-CHO (**1a**)	Ph (**2b**)	91 (**3g**)
9	4-CHO (**1a**)	CH_2=$CHCH_2$ (**2c**)	69 (**3h**)
10	4-CHO (**1a**)	PhCH=$CHCH_2$ (**2d**)	84 (**3i**)
11	4-CHO (**1a**)	$^tC_4H_9$ (**2e**)	89 (**3j**)
12	4-CHO (**1a**)	$HOCH_2CH_2$ (**2f**)	99 (**3k**)
13	H	$^nC_{12}H_{25}$ (**2a**)	<1 (**3l**)[b]

[a] 4-(Dodecylthio)nitrobenzene was obtained in 100% yield.
[b] The reaction was performed at 90 °C for 4 h.

Keywords: Cesium; Thiol; Sulfide; Nitroarene; Nucleophilic aromatic substitution reaction.
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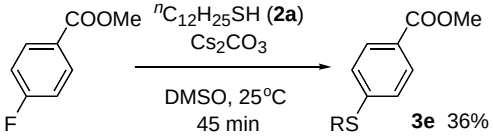
hexamethylphosphoramide (HMPA) and the use of DMSO resulted in lower efficiency. We chose DMSO as a solvent to avoid using carcinogenic HMPA.[8] Fortunately, the cesium-mediated displacement went to completion within 45 min at 25 °C. While 0.50 equiv of cesium carbonate effected the S_NAr reaction to yield **3a** in 87% yield, a stoichiometric amount of cesium carbonate is essential to attain quantitative reactions. Catalytic amounts of cesium carbonate resulted in poor conversions even with prolonged reaction time (20 mol%, 36%; 10 mol%, 17%; 5 mol%, 4% after 24 h).

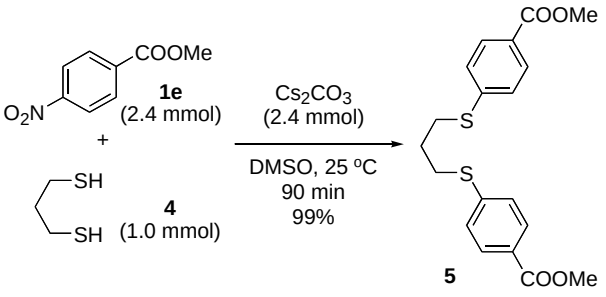
The reaction of 2-nitrobenzaldehyde (**1b**) proceeded almost quantitatively (entry 2). Not only a formyl group but also other electron-withdrawing groups such as acetyl and cyano groups enhanced the displacement reaction (entries 3–6). It is worth noting that the S_NAr reaction of methyl ester **1e** predominated over possible cleavage of the methyl ester linkage.[9] Fluoronitrobenzene **1g** underwent an S_NAr reaction at the fluorinated carbon to furnish 4-(dodecylthio)-nitrobenzene (entry 7). Nitrobenzene itself and 3-nitrobenzaldehyde resisted the S_NAr sulfidation under the same conditions. Aromatic thiol **2b**, allylic thiols **2c** and **2d**, and sterically demanding **2e** underwent the S_NAr displacement smoothly (entries 8–11). The hydroxy group of **2f** did not retard the reaction (entry 12). An additional electron-withdrawing group on nitrobenzene is essential. The reaction of nitrobenzene with **2a** failed to afford the corresponding product even at an elevated temperature (entry 13).

Nitroarenes are the better substrates for the S_NAr sulfidation reaction than the corresponding fluoroarenes that are recognized to be the standard substrates.[10] For instance, the reaction of methyl 4-fluorobenzoate with **2a** for 45 min provided **3e** in only 36% yield, leaving 60% of methyl 4-fluorobenzoate untouched (Eq. 1). It is worth noting that the chromatographic separation of **3e** and the starting fluoroarene on silica gel was quite difficult due to their comparable R_f values. The S_NAr sulfidation reaction with nitroarenes is thus advantageous with regard to facile purification procedure when needed as well as the superb efficiency.

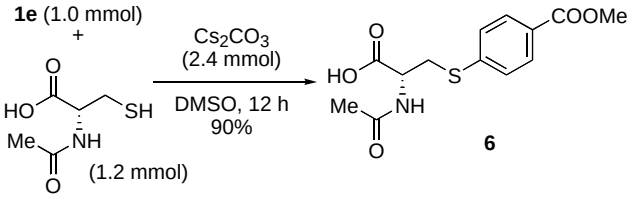


(1)

The reaction was efficient enough to allow multiple carbon–sulfur bond formations in one pot. Dithiol **4** underwent the S_NAr reactions with 2.4 equiv of nitro ester **1e** and cesium carbonate to provide **5** quantitatively (Eq. 2). Selective arylation at sulfur was also observed in the reaction of *N*-acetyl-L-cysteine, albeit a longer reaction time was necessary (Eq. 3). The longer reaction time would be due to the carboxy group. No observable racemization took place. The perfect reactivity of the sulfur moieties demonstrates that the present carbon–sulfur bond formation reaction is applicable to conjugation chemistry.



(2)



(3)

3. Summary

We have disclosed extremely powerful conditions for S_NAr reactions of activated nitroarenes with thiols. Cesium carbonate serves quite effectively in DMSO, which will allow us to use an sp^2-carbon–sulfur bond formation as a useful tool for conjugation chemistry.

4. Experimental

4.1. Cesium-mediated S_NAr reaction of nitroarenes with thiols

The reaction of dodecanethiol with 4-nitrobenzaldehyde is representative (Table 1, entry 1). Cesium carbonate (0.20 g, 0.60 mmol) was placed in a 20-mL reaction flask under argon. Dimethyl sulfoxide (3.0 mL), 4-nitrobenzaldehyde (**1a**, 0.076 g, 0.50 mmol), and dodecanethiol (**2a**, 0.12 g, 0.60 mmol) were added at 25 °C. The mixture was stirred for 45 min. Water (10 mL) was added, and the product was extracted with hexane–ethyl acetate (10/1, 10 mL×3). The combined organic layer was dried over sodium sulfate. Concentration followed by purification on silica gel afforded 4-dodecylthiobenzaldehyde (**3a**, 0.15 g, 0.49 mmol, 97%) as a yellow solid.

4.2. Characterization data

4.2.1. 4-Dodecylthiobenzaldehyde (3a). IR (Nujol) 2924, 2853, 2731, 2345, 1701, 1591, 1560, 1466, 1383, 1261, 1213, 1169, 1090, 1049, 837, 810 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, J=7.0 Hz, 3H), 1.09–1.37 (m, 16H), 1.46 (tt, J=7.0, 7.5 Hz, 2H), 1.71 (tt, J=7.0, 7.5 Hz, 2H), 3.00 (t, J=7.5 Hz, 2H), 7.35 (d, J=8.5 Hz, 2H), 7.76 (d, J=8.5 Hz, 2H), 9.92 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.09, 22.66, 28.62, 28.88, 29.12, 29.32, 29.45, 29.54, 29.60, 29.61, 31.80, 31.89, 126.27, 129.98, 133.08, 147.15, 191.19. Found: C, 74.22; H, 10.05%. Calcd for $C_{19}H_{30}OS$: C, 74.45; H, 9.86%. Mp 33.3–34.0 °C.

4.2.2. 2-Dodecylthiobenzaldehyde (3b). IR (neat) 2924, 2853, 2731, 1695, 1587, 1560, 1460, 1439, 1396, 1261, 1196, 1128, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, J=7.0 Hz, 3H), 1.21–1.35 (m, 16H), 1.45 (tt, J=7.5, 7.5 Hz, 2H), 1.70 (tt, J=7.5, 7.5 Hz, 2H), 2.95 (t, J=7.5 Hz, 2H), 7.30 (dd, J=7.0, 7.5 Hz, 1H), 7.42 (d, J=8.0 Hz, 1H), 7.51 (dd, J=7.0, 8.0 Hz, 1H), 7.84 (d, J=7.5 Hz, 1H), 10.39 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.09, 22.64, 28.48, 28.93, 29.12, 29.30, 29.43, 29.53, 29.57, 29.59, 31.86, 33.18, 125.09, 127.97, 131.98, 133.82, 133.83, 142.30, 191.50. Found: C, 74.55; H, 9.95%. Calcd for $C_{19}H_{30}OS$: C, 74.45; H, 9.86%.

4.2.3. 1-Dodecylthio-4-nitrobenzene (3c). IR (Nujol) 2224, 2853, 2332, 2235, 1578, 1508, 1466, 1337, 1082, 962, 851, 837, 745, 723, 669, 617 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, J=7.0 Hz, 3H), 1.20–1.38 (m, 16H), 1.46 (tt, J=7.5, 7.5 Hz, 2H), 1.72 (tt, J=7.5, 7.5 Hz, 2H), 3.01 (t, J=7.5 Hz, 2H), 7.31 (d, J=9.5 Hz, 2H), 8.12 (d, J=9.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.11, 22.67, 28.44, 28.86, 29.09, 29.32, 29.44, 29.53, 29.60, 29.61, 31.89, 31.90, 123.91, 125.93, 144.79, 148.17. Found: C, 66.68; H, 8.96%. Calcd for $C_{18}H_{29}NO_2S$: C, 66.83; H, 9.04%. Mp 49.5–50.5 °C.

4.2.4. 4-Dodecylthioacetophenone (3d). IR (Nujol) 2920, 2851, 2345, 1678, 1591, 1462, 1377, 1364, 1053, 976, 816, 719, 590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, J=7.0 Hz, 3H), 1.20–1.36 (m, 16H), 1.45 (tt, J=7.5, 7.5 Hz, 2H), 1.70 (tt, J=7.5, 7.5 Hz, 2H), 2.57 (s, 3H), 2.99 (t, J=7.5 Hz, 2H), 7.30 (d, J=9.0 Hz, 2H), 7.86 (d, J=9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.12, 22.68, 26.44, 28.70, 28.89, 29.13, 29.33, 29.46, 29.55, 29.61, 29.62, 31.89, 31.90, 126.16, 128.72, 133.63, 145.01, 197.21. Found: C, 74.76; H, 9.87%. Calcd for $C_{20}H_{32}OS$: C, 74.94; H, 10.06%. Mp 69.5–70.2 °C.

4.2.5. Methyl 4-dodecylthiobenzoate (3e). IR (Nujol) 2918, 2851, 1724, 1678, 1599, 1462, 1398, 1366, 1290, 1196, 1115, 1092, 831, 816, 754, 719, 691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, J=7.0 Hz, 3H), 1.20–1.35 (m, 16H), 1.44 (tt, J=7.0, 7.5 Hz, 2H), 1.69 (tt, J=7.0, 7.5 Hz, 2H), 2.98 (t, J=7.5 Hz, 2H), 3.90 (s, 3H), 7.28 (d, J=8.5 Hz, 2H), 7.92 (d, J=8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.12, 22.68, 28.70, 28.88, 29.13, 29.33, 29.46, 29.55, 29.61, 29.62, 31.90, 31.99, 52.02, 126.18, 126.43, 129.86, 144.51, 166.85. Found: C, 71.27; H, 9.41%. Calcd for $C_{20}H_{32}O_2S$: C, 71.38; H, 9.58%. Mp 64.5–65.2 °C.

4.2.6. 4-Dodecylthiobenzonitrile (3f). IR (Nujol) 2918, 2851, 2230, 1919, 1593, 1547, 1487, 1470, 1431, 1402, 1379, 1346, 1302, 1244, 1182, 1126, 1089, 1070, 1015, 824, 779, 762, 719, 592, 544 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, J=7.0 Hz, 3H), 1.21–1.36 (m, 16H), 1.44 (tt, J=7.0, 7.5 Hz, 2H), 1.69 (t, J=7.5, 7.5 Hz, 2H), 2.97 (t, J=7.5 Hz, 2H), 7.29 (d, J=8.5 Hz, 2H), 7.52 (d, J=8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.11, 22.67, 28.51, 28.84, 29.09, 29.32, 29.44, 29.53, 29.59, 29.61, 31.82, 31.88, 107.80, 118.98, 126.57, 132.16, 145.31. Found: C, 75.12; H, 9.50%. Calcd for $C_{19}H_{29}NS$: C, 75.19; H, 9.63%. Mp 50.0–50.5 °C.

4.2.7. 4-Phenylthiobenzaldehyde (3g). IR (neat) 3059, 2831, 2735, 1699, 1670, 1593, 1562, 1475, 1441, 1387, 1358, 1302, 1285, 1211, 1169, 1078, 1024, 1013, 1001, 920, 837, 816, 750, 692, 507, 478 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.24 (d, J=8.0 Hz, 2H), 7.41–7.46 (m, 3H), 7.51–7.56 (m, 2H), 7.72 (d, J=8.0 Hz, 2H), 9.91 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 127.10, 129.14, 129.77, 130.09, 131.16, 133.59, 134.34, 147.23, 191.18. Found: C, 72.64; H, 4.83%. Calcd for $C_{13}H_{10}OS$: C, 72.87; H, 4.70%.

4.2.8. 4-(2-Propenylthio)benzaldehyde (3h). IR (neat) 2922, 2833, 2736, 1697, 1672, 1637, 1591, 1562, 1489, 1410, 1387, 1306, 1285, 1215, 1171, 1090, 989, 926, 837, 812, 739, 696, 536, 486 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.68 (d, J=6.5 Hz, 2H), 5.19 (d, J=9.0 Hz, 1H), 5.31 (d, J=15.5 Hz, 1H), 5.91 (ddd, J=6.5, 9.0, 15.5 Hz, 1H), 7.38 (d, J=6.5 Hz, 2H), 7.77 (d, J=6.5 Hz, 2H), 9.93 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 35.02, 118.68, 126.90, 129.91, 132.28, 133.34, 145.82, 191.24. Found: C, 67.26; H, 5.67%. Calcd for $C_{10}H_{10}OS$: C, 67.38; H, 5.65%.

4.2.9. 4-[(*E*)-3-Phenyl-2-propenylthio]benzaldehyde (3i). IR (Nujol) 2924, 2855, 2731, 1696, 1589, 1560, 1460, 1377, 1084, 1028, 966, 837, 814, 762, 745, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.85 (d, J=7.0 Hz, 2H), 6.26 (dt, J=16.0, 7.0 Hz, 1H), 6.62 (d, J=16.0 Hz, 1H), 7.22–7.37 (m, 5H), 7.42 (d, J=8.0 Hz, 2H), 7.77 (d, J=8.0 Hz, 2H), 9.93 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 34.95, 123.56, 126.38, 127.16, 127.90, 128.60, 130.01, 133.47, 133.73, 136.25, 145.81, 191.27. Found: C, 75.29; H, 5.53%. Calcd for $C_{16}H_{14}OS$: C, 75.56; H, 5.55%. mp 91.0–92.5 °C.

4.2.10. 4-(1,1-Dimethylethylthio)benzaldehyde (3j). IR (neat) 2963, 2924, 2899, 2862, 2831, 2729, 1705, 1593, 1562, 1474, 1458, 1366, 1298, 1281, 1205, 1167, 1086, 1016, 826, 718, 698, 503 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (s, 9H), 7.69 (d, J=8.0 Hz, 2H), 7.83 (d, J=8.0 Hz, 2H), 10.04 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 31.05, 47.10, 129.37, 135.77, 136.97, 141.20, 191.66. Found: C, 68.28; H, 7.31%. Calcd for $C_{11}H_{14}OS$: C, 68.00; H, 7.26%.

4.2.11. Methyl 4-(2-hydroxyethylthio)benzoate (3k). IR (Nujol) 3344, 2924, 2855, 1720, 1597, 1460, 1377, 1281, 1115, 1057, 1013, 959, 758 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.11 (s, 1H), 3.20 (t, J=6.5 Hz, 2H), 3.82 (t, J=6.5 Hz, 2H), 3.89 (s, 3H), 7.34 (d, J=9.0 Hz, 2H), 7.92 (d, J=9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 35.37, 52.10, 60.40, 127.20, 127.30, 130.01, 142.40, 166.67. Found: C, 56.44; H, 5.67%. Calcd for $C_{10}H_{12}O_3S$: C, 56.58; H, 5.70%. Mp 58.0–59.5 °C.

4.2.12. 1,3-Di(4-methoxycarbonylphenylthio)propane (5). IR (Nujol) 2924, 2853, 1722, 1595, 1435, 1377, 1277, 1250, 1192, 1113, 1015, 961, 847, 829, 756, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.06 (quint, J=7.0 Hz, 2H), 3.14 (t, J=7.0 Hz, 4H), 3.90 (s, 6H), 7.29 (d, J=9.0 Hz, 4H), 7.91 (d, J=9.0 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 27.89, 31.05, 52.34, 127.02, 127.32, 130.26, 143.30, 166.94. Found: C, 60.36; H, 5.38%. Calcd for $C_{19}H_{20}O_4S_2$: C, 60.61; H, 5.35%. Mp 98.5–100.0 °C.

4.2.13. *N*-Acetyl-*S*-(4-methoxycarbonylphenyl)-L-cysteine (6). IR (Nujol) 3337, 2924, 2855, 2532, 2104, 1715, 1618, 1597, 1560, 1491, 1458, 1439, 1377, 1277, 1232, 1186, 1109, 1013, 758 cm^{-1}; ^1H NMR (CD_3OD) δ 1.90 (s, 3H), 3.26–3.36 (m, 1H), 3.54–3.64 (m, 1H), 3.88 (s, 3H), 4.60–4.66 (m, 1H), 7.43 (d, J=8.7 Hz, 2H), 7.91 (d, J=8.7 Hz, 2H); ^{13}C NMR (CD_3OD) δ 22.35, 34.84, 52.60, 53.37, 128.40, 128.48, 130.81, 144.11, 167.88, 172.82, 173.05. Found: C, 52.37; H,

5.08%. Calcd for $C_{13}H_{15}NO_5S$: C, 52.52; H, 5.08%. Mp 158.5–159.5 °C. Retention time: 7.5 min (CHIRALCEL® OJ-H column, 4.6×250 mm, Daicel Chemical Industries, hexane/2-propanol = 80:20, 1.3 mL/min, 40 °C, 254 nm UV detector, retention time of minor isomer: 9.2 min).

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Regioselectivity in acylation of oligosaccharides catalyzed by the metalloprotease thermolysin

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Abstract—Investigation of the acylation scope of carbohydrates by metalloprotease thermolysin immobilized on Celite as biocatalyst has been carried out. The reactions were performed in DMSO, a good solvent for carbohydrates, where the enzyme has previously shown its activity in transesterifications of sucrose, maltose and maltose-containing oligosaccharides. Surprisingly, no reaction was observed for glucose or the glucose-containing disaccharides, trehalose and lactose. In contrast, laurate monoesters of several sucrose-containing tri- and tetrasaccharides were synthetized through a one step transesterification using vinyl laurate as the acylating agent. Enzyme regioselectivity was accurately determined by HPLC/MS and the structure of the main regioisomers was established by a combination of NMR experiments. The preferred position of acylation in all cases was the 2-OH of the α-D-glucopyranose moiety linked 1→2 to the β-D-fructofuranose unit. These results correlate with the regioselectivity observed in the case of the disaccharide sucrose. A general carbohydrate binding motif for catalysis by thermolysin is proposed.

1. Introduction

Carbohydrate fatty acid esters are an important class of biodegradable and non-toxic surfactants with broad applications in food, cosmetic and pharmaceutical industries.[1] Their emulsifying and surfactant properties[2] may be modulated by the type of fatty acid and the sugar moiety. Actually, the degree of substitution and the position of attachment to the fatty acid is also important as shown by the different CMC values found for regioisomeric sucrose monoesters.[3] Moreover, this type of compounds also present interesting biological properties like the recently reported antibacterial[4] and antitumoral[5] activities of maltotriose fatty acid esters.

Regioselective chemical monoacylation of carbohydrates is not easy due to their multifunctionality[6] and frequently, protection/deprotection sequences are needed.[7] On the other hand, enzymatically catalyzed sugar fatty acid esterification reactions are, in general, reasonably specific and the regioselective acylation of several carbohydrates with both lipases[8] and proteases[9] has been reported.[10] The hydrolases used in these processes share in common a similar mechanism, which involves the formation of an acyl enzyme intermediate and the acylation takes place on the less hindered primary hydroxyls.

We have recently reported on the enzymatic preparation of oligosaccharide fatty acid esters showing how different regioisomers substituted on primary hydroxyls can be prepared by selecting the appropriate hydrolase preparation.[11] We were also interested in investigating enzymes that could provide regioselective esterification on secondary hydroxyl groups. Lipases are able to acylate secondary hydroxyls groups in sugars solely when the primary hydroxyls are blocked (with a protecting group)[12] and there are only two examples of serine proteases, which have shown regioselectivity towards secondary hydroxyls in unprotected carbohydrates.[13–15] A very promising enzyme employed to date for secondary hydroxyl acylation in carbohydrates is thermolysin, the thermostable neutral metalloprotease from *Bacillus thermoproteolyticus*. This enzyme was first used by Pedersen et al.[16] to catalyze the transesterification of sucrose with vinyl laurate in DMSO with selectivity towards the 2-OH of the glucose moiety. Recently, the same authors have extended the use of this enzyme to prepare cyclodextrin esters.[17]

In this work, we study the transesterification of carbohydrates catalyzed by thermolysin. Acylation of the sucrose-containing oligosaccharides raffinose, melezitose, 1-kestose and stachyose with vinyl laurate in DMSO is described (Scheme 1).

Keywords: Oligosaccharide acylation; Thermolysin; Carbohydrate fatty acid esters; Transesterification; Regioselectivity.
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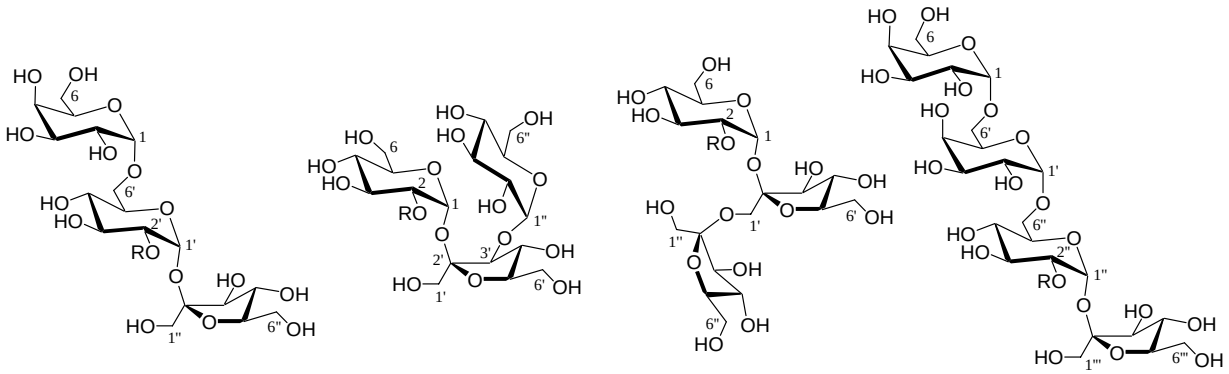


1 :R = H (raffinose) **2** : R = H (melezitose) **3** : R = H (1-kestose) **4** : R = H (stachyose)
1a: R = $CO(CH_2)_{10}CH_3$ **2a**: R = $CO(CH_2)_{10}CH_3$ **3a**: R = $CO(CH_2)_{10}CH_3$ **4a**: R = $CO(CH_2)_{10}CH_3$

Scheme 1. Oligosaccharides used in this study and their corresponding main acylated regioisomers found after thermolysin catalysis.

The results obtained allow us to suggest a possible reaction-mechanism for carbohydrate acylation by thermolysin.

2. Results

Our investigation on the acylation capacity of thermolysin over a range of carbohydrates used the reaction conditions previously described for sucrose.[16] We decided to employ the amorphous form of each oligosaccharide obtained by lyophilization in order to remove most of the crystallization water[18] and thus avoid the formation of fatty acid (by thermolysin-catalyzed hydrolysis of the vinyl ester). The amorphous form also has the additional advantage of being dissolved much more rapidly in DMSO than the crystalline carbohydrate. The enzyme was immobilized onto Celite as previously described[16] but the preparation was dried by lyophilization instead of overnight vacuum drying.

First, we tried transesterification of monosaccharide glucose since sucrose is acylated at the 2-OH of the glucose unit by thermolysin. Suprisingly, no reaction was observed by TLC after 24 h (Fig. 1). Furthermore, neither trehalose or lactose, two disaccharides that contain glucose in their structures, showed acylation by the metalloprotease. Although maltose and sucrose, both containing glucose in their structures, are acylated at secondary hydroxyl groups, it seems that other structural or electrostatic features are needed in the carbohydrate to interact with thermolysin and allow catalysis to take place.

Next, we investigated the acylation of raffinose (**1**) that can be considered a sucrose molecule substituted at the C-6 hydroxyl group with a galactose unit. After 24 h, a mono-acylated product was observed by TLC (Fig. 1). The reaction was stopped after 72 h, when traces of diester were observed although some starting material remained unreacted. No reaction was observed with the Celite control prepared in the same manner as the immobilized enzyme. The reaction mixture of the enzyme-catalyzed transesterification was processed and finally subjected to flash chromatography. The monoester fraction was separated from remaining starting material and minor amounts of

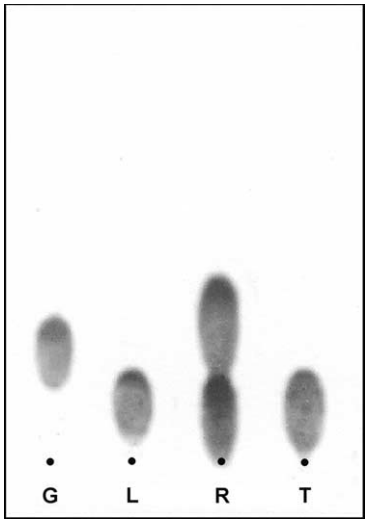


Figure 1. TLC of reaction after 24 h with the saccharides G = glucose; L = lactose; R = raffinose and T = trehalose. Only product formation is observed in the raffinose reaction. Alliquots were extracted with *n*-hexane to remove excess of vinyl laurate and diluted with methanol prior to analysis. Eluent: chloroform–methanol (2.5/1, v/v)

Table 1. HRMS [FAB (+)] of the oligosaccharide monoesters. R_f and yields are also indicated

Carbohydrate	Monolaurate[a] Isolated yield (%)[c]	R_f[b]	Formula	M_W (M+Na) Calculated	Found
Raffinose	27	0.31	$C_{30}H_{54}O_{17}Na$	709.3259	709.3246
Melezitose	22	0.32	$C_{30}H_{54}O_{17}Na$	709.3259	709.3263
1-Kestose	32	0.32	$C_{30}H_{54}O_{17}Na$	709.3259	709.3248
Stachyose	12	0.63	$C_{36}H_{64}O_{22}Na$	871.3787	871.3785

[a] As a mixture of regioisomers.
[b] See TLC solvent in Section 4.
[c] See Section 4 for yield calculation.

diacylated compounds. The FTIR analysis of the isolated monoester (as a mixture of regioisomers) showed the presence of the ester carbonyl group signal at 1730 cm^{-1} and HRMS analysis gave the expected molecular weight (Table 1). The isolated yield obtained is slightly lower than for sucrose.[16]

Then, we extended the reaction to other sucrose-containing oligosaccharides to check the possible influence of other sugar substituents in the structure of sucrose on acylation with themolysin. Two trisaccharides and a tetrasaccharide were examined: melezitose (**2**) and 1-kestose (**3**), that can be considered as a C-3′ hydroxyl-glucosylated sucrose and a C-1′ hydroxyl-fructosylated sucrose, respectively, and stachyose (**4**), that can be considered a raffinose extended on C-6 with galactose. All reactions showed some diester formation and remaining starting sugar by TLC after 72 h, similarly to the raffinose case. After processing and purification, monoacylated compounds were isolated (as a mixture of regioisomers) with the yields shown in Table 1.

In order to study the regioselectivity of the acylation by thermolysin, the purified monoester fraction for each reaction was analyzed by HPLC/MS (see Section 4).[11] The regioisomeric distribution obtained by this method is much more accurate than the typically reported based on ^{13}C NMR. The high chromatographic sensitivity achieved by acquisition in SIR mode (selected-ion recording mode) allows the detection of regioisomers present in the sample in very small quantities; on the other hand, the intensities observed in the routine ^{13}C NMR spectrum are highly dependent on the number of acquisition scans (minor regioisomers may not even appear in the spectrum) and a particular carbon in different regioisomers may present different relaxation times. HPLC/MS chromatograms in Figure 2 show the substitution pattern obtained for each oligosaccharide. It is clear the presence of a major regioisomer in all cases, although the selectivity is not the same, decreasing in the order: raffinose ≈ stachyose > melezitose > 1-kestose.

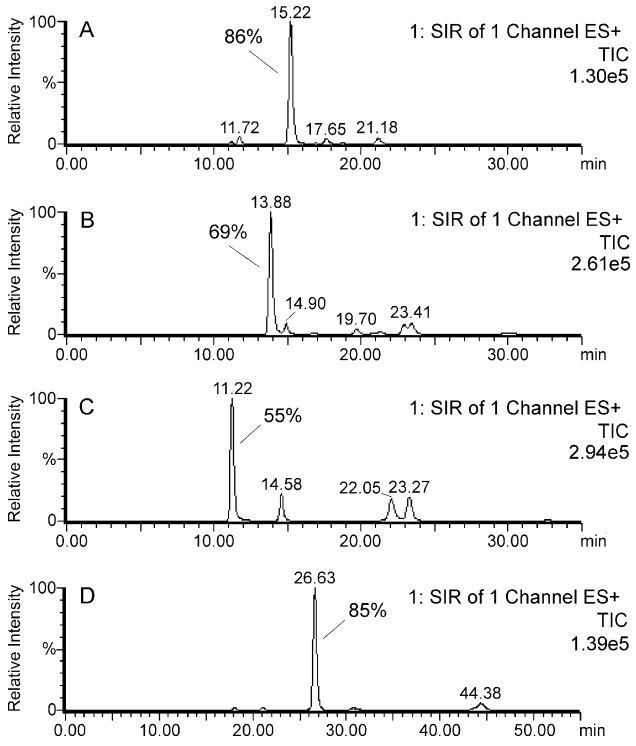


Figure 2. HPLC/MS chromatograms showing the regioisomeric distribution in the isolated monoesters. (A) Raffinose monolaurate regioisomers. (B) Melezitose monolaurate regioisomers. (C) 1-Kestose monolaurate regioisomers. (D) Stachyose monolaurate regioisomers. The percentage of the main regioisomer in each mixture is also indicated.

A combination of one and two-dimensional NMR experiments was then used to establish the position of acylation in the main regioisomer. Using raffinose monolaurate as example, the HMBC spectrum shows the correlation between the carbon peak of the carbonyl of the newly created ester linkage with the proton of the carbon bearing the oxygen atom of the ester function (Fig. 3A). The edited-HSQC spectrum corroborates that this carbon is a methine and thus acylation has taken

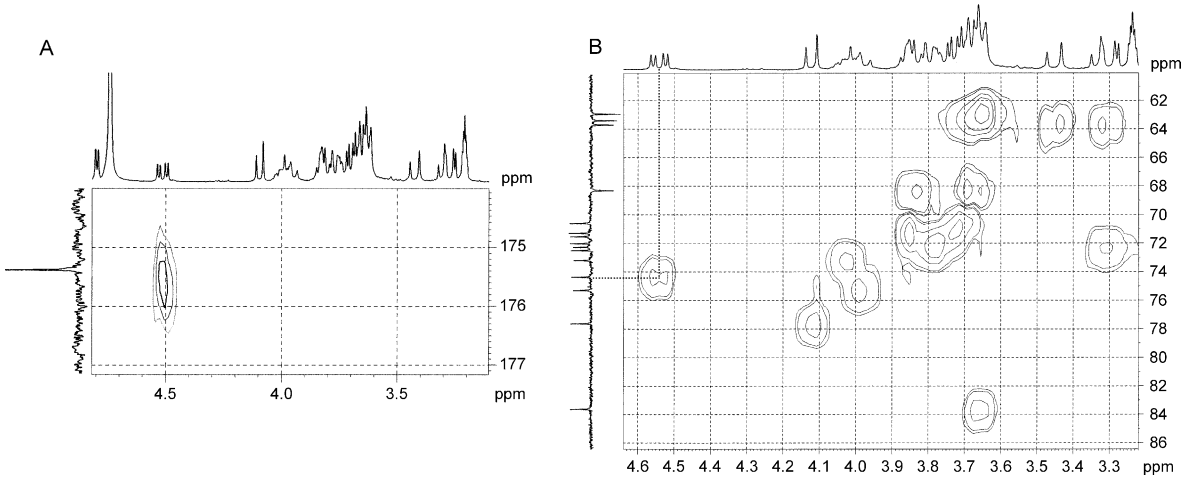


Figure 3. (A) Amplification of the HMBC spectrum of isolated 2′-*O*-lauroylraffinose (**1a**) (86% regioisomeric purity) showing the key cross peak involving the carbonyl ester signal. (B) Part of the edited-HSQC spectrum of the same product. The correlation between the acylated carbon of raffinose (a methine) and its corresponding proton is indicated.

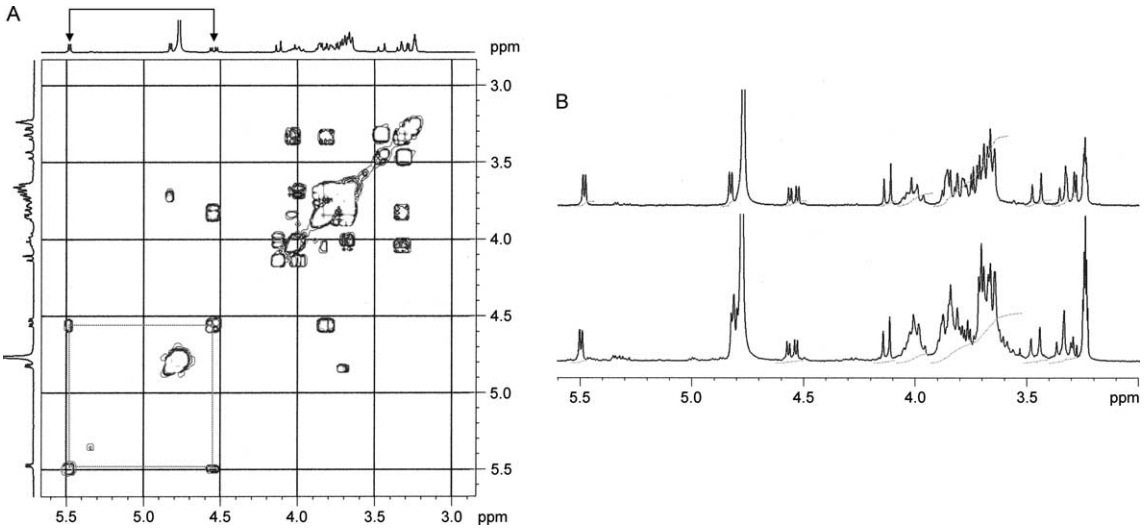


Figure 4. (A) Part of the COSY spectrum (carbohydrate region) of 2′-*O*-lauroylraffinose (**1a**) (86% regioisomeric purity) with indication of the vicinal coupling between the anomeric glucose proton and the proton of the acylated position. (B) Comparison between the proton spectra (carbohydrate region) of 2′-*O*-lauroylraffinose (**1a**) (86% regioisomeric purity) (upper spectrum) and 2″-*O*-lauroylstachyose (**4a**) (85% regioisomeric purity) (lower spectrum).

place in a secondary hydroxyl (Fig. 3B). Finally, a COSY experiment reveals vicinal scalar coupling between the proton of this methine and the anomeric proton of the glucose moiety (Fig. 4A) providing the final evidence that acylation has taken place in the 2-OH of the glucose moiety in raffinose. A similar approach was used for the other oligosaccharide monolaurates. In the case of the stachyose derivative a simple comparison between its 1D proton spectrum and that of the acylated raffinose (Fig. 4B) proves at a glance that acylation has also taken place in the 2-OH of the glucose moiety in stachyose. In the cases of melezitose and 1-kestose, where a more complex regioisomeric mixture was observed, selective 1D-TOCSY experiments were very helpful. Comparison between the spectrum obtained by selective excitation of the anomeric glucose proton in both 1-kestose and its derivative clearly shows that the 2-OH of this (spin system) residue was acylated (Fig. 5A). In the case of melezitose the same approach shows that acylation has taken place in the 2-OH of the α-D-glucopyranose moiety linked 1→2 to the β-D-fructofuranose unit (Fig. 5B). When compared with the parent carbohydrate, the ^{13}C NMR spectra of all new derivatives (Table 2) showed the expected downfield shift of the peak corresponding to the acylated glucosyl C-2 and a similar upfield shift of the peaks corresponding to the neighboring glucosyl C-1 and C-3, in agreement with the general trend observed by Yoshimoto et al.[19] In all these sucrose-containing oligosaccharides acylation occurred preferentially at the 2-OH of the α-D-glucopyranose moiety linked 1→2 to β-D-fructofuranose, which is in agreement with the regioselectivity reported in the case of sucrose acylation catalyzed by the same enzyme[16] (see structures **1a**–**4a** in Scheme 1).

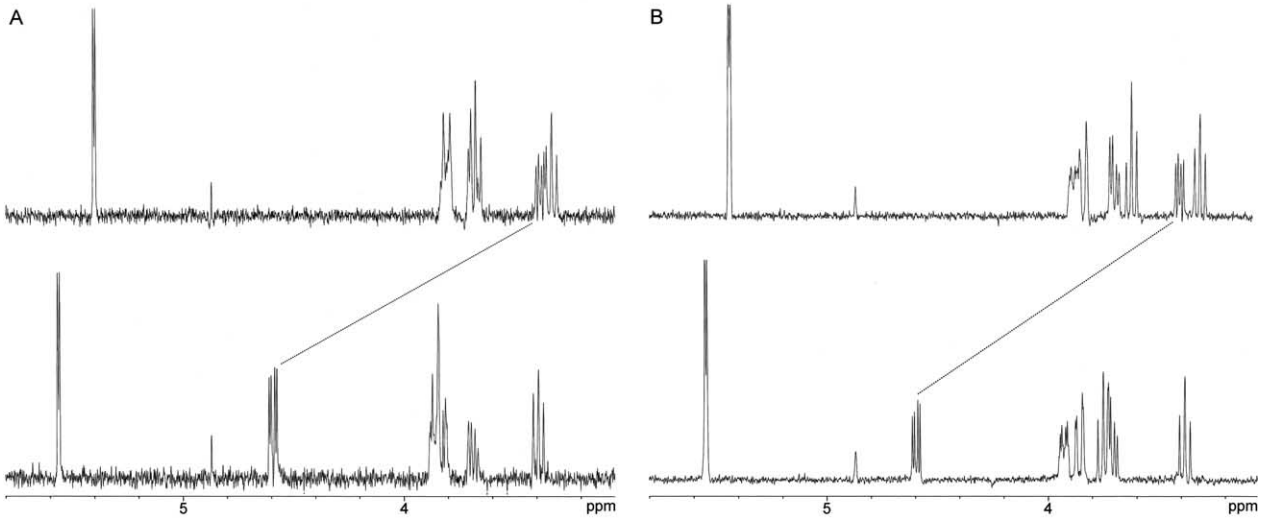


Figure 5. Comparison of 1D TOCSY spectra obtained after selective excitation of the anomeric proton of α-D-glucopyranose moiety linked 1→2 to β-D-fructofuranose in: (A) 1-kestose (upper) and its monolauroyl ester (lower); (B) melezitose (upper) and its monolauroyl ester (lower). Deshielding of the 2-H of the glucose residue consequence of esterification is evident as shown in the figure.

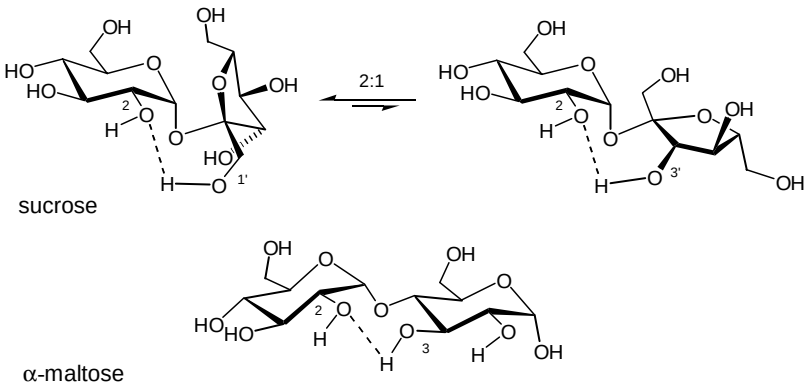
Table 2. ^{13}C NMR chemical shifts (ppm) of compounds **1a**, **2a**, **3a**, **4a** and their parent carbohydrates **1**, **2**, **3** and **4**

Compound		C-1	C-2	C-3	C-4	C-5	C-6
α-Galactopyranosyl-(1→6)-	**1**	100.5	70.5	71.4	71.0	72.4	62.8
α-Glucopyranosyl-(1→2)-		**93.4**	**73.0**	74.4	72.0	73.3	68.3
β-Fructofuranose		64.2	105.3	79.2	75.3	83.4	63.2
α-Galactopyranosyl-(1→6)-	**1a**	100.6	70.5	71.4	71.2	72.3	62.8
α-Glucopyranosyl-(1→2)-		**90.7**	**74.2**	**72.1**	71.9	73.0	68.2
β-Fructofuranose		63.6	105.8	77.5	75.2	83.4	63.2
Laurate		175.4 (C=O)	35.1 (–*C*H$_2$–CO–)	33.0–23.7 (–*C*H$_2$– chain)	14.4 (*C*H$_3$–)		
α-Glucopyranosyl-(1→2)-	**2**	**93.3**	**73.2**	**75.1**	71.7	74.1	62.4
β-Fructofuranosyl-(3→1)-		64.2	105.3	85.8	74.4	83.4	63.3
α-Glucopyranose		101.9	73.8	74.9	72.2	74.0	62.9
α-Glucopyranosyl-(1→2)-	**2a**	**90.3**	**74.3**	**72.4**	71.4	74.1	62.3
β-Fructofuranosyl-(3→1)-		63.9	105.0	85.2	74.3	83.2	63.3
α-Glucopyranose		102.7	73.7	74.8	71.8	74.0	62.4
Laurate		175.2 (C=O)	35.1 (–*C*H$_2$–CO–)	33.0–23.7 (–*C*H$_2$– chain)	14.4 (*C*H$_3$–)		
α-Glucopyranosyl-(1→2)-	**3**	**94.1**	**73.4**	**74.7**	71.5	74.4	62.4
β-Fructofuranosyl-(1→2)-		63.0	105.3	79.9	75.6	83.6	63.2
β-Fructofuranose		62.4	105.0	78.9	76.4	83.5	63.8
α-Glucopyranosyl-(1→2)-	**3a**	**91.1**	**74.3**	**72.0**	71.6	74.3	62.2
β-Fructofuranosyl-(1→2)-		63.2	105.5	77.8	75.0	83.6	63.2
β-Fructofuranose		63.0	105.2	78.9	76.4	83.4	63.5
Laurate		175.5 (C=O)	35.1 (–*C*H$_2$–CO–)	33.1–23.7 (–*C*H$_2$– chain)	14.5 (*C*H$_3$–)		
α-Galactopyranosyl-(1→6)-	**4**[a]	99.8	70.2[b]	71.3[b]	70.8	72.3	62.5
α-Galactopyranosyl-(1→6)-		100.1	70.1[b]	71.1[b]	70.8	70.3[b]	67.7
α-Glucopyranosyl-(1→2)-		**93.4**	**72.8**	**74.4**	71.5	72.9	67.7
β-Fructofuranose		63.8	105.2	78.7	75.3	83.3	63.4
α-Galactopyranosyl-(1→6)-	**4a**	100.1	70.3[b]	71.5[b]	71.1[b]	72.4	62.7
α-Galactopyranosyl-(1→6)-		100.4	70.2[b]	71.3[b]	71.0[b]	70.3[b]	67.9
α-Glucopyranosyl-(1→2)-		**90.7**	**74.2**	**72.1**	71.9	72.9	68.1
β-Fructofuranose		63.6	105.9	77.5	75.2	83.5	63.3
Laurate		175.4 (C=O)	35.1 (–*C*H$_2$–CO–)	33.0–23.7 (–*C*H$_2$– chain)	14.4 (*C*H$_3$–)		

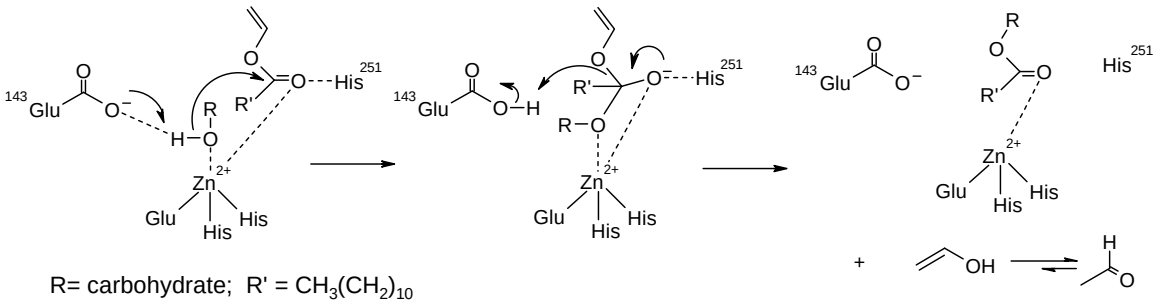
All spectra were acquired in CD_3OD. The carbons where the induced shift effect due to acylation is observed are indicated in bold.
[a] Solvent CD_3OD–D_2O (7.5/1).
[b] Assignments marked with the same letter may be reversed.

3. Discussion

Acylation of a number of carbohydrates using metalloprotease thermolysin has been investigated. In this work, sucrose-containing oligosaccharides have been esterified with vinyl laurate. At the same time, transesterification of sucrose, maltose, maltotetraose, maltoheptaose and cyclodextrins has been reported by Pedersen et al.[16,17] The major regioisomer obtained for sucrose and cyclodextrins has shown acylation at the secondary hydroxyl group in position 2 of glucose whereas no regioselectivity has been reported for maltose and maltose-containing oligosaccharides. It is important to note that monosaccharide glucose and disaccharides trehalose and lactose, both containing glucose in their structure, gave no acylation on the same reaction conditions. It seems that a common structural motif is necessary for a proper binding of the carbohydrate with the enzyme so that catalysis occurs. In fact, an inter-residue H-bond is present in sucrose,[20] (1′-OH···O-2 or 3′-OH···O-2) maltose and cyclodextrins[21] (3-OH···O-2′), where glucose OH-2 participates as hydrogen bond acceptor (Scheme 2).



Scheme 2. Inter-residual hydrogen bond found in DMSO-d_6 for sucrose (equilibrium of two conformations) and α-maltose.



Scheme 3. Proposed reaction mechanism for transesterification of carbohydrates with vinyl laurate by metalloprotease thermolysin.

It is important to note that this hydrogen bond organizes both involved hydroxyl groups in a very similar spatial position for both disaccharides. This motif is not possible in glucose, trehalose or lactose, and may arrange the sucrose- or maltose-containing saccharides in a specific way that allows appropriate interaction with the metalloprotease for catalysis to take place. In fact, sucrose is able to act as a bidentade ligand towards heavy atoms yielding isolable complexes like Δ-$[Co(III)(phen)_2(sucrose)]^{3+}$ in which coordination takes place at the 2-OH of the glucose unit and the 1′-OH of the fructose unit, but no complex is formed with the monosaccharide glucose in such a case, probably because the specific spatial placement of the OHs achieved by sucrose is needed.[22] On the other hand, the hydroxamate moiety of some inhibitors of thermolysin form a bidentade complex with the active site's zinc.[23] Thus, it would be reasonable to think that the carbohydrate binding to the zinc cation in the active site follows a similar bidentade approach, that would be possible for sucrose- or maltose-containing saccharides, but not for glucose, trehalose or lactose.

When we compared the regioselectivity found in the transesterification of the sucrose-containing oligosaccharides with the obtained for sucrose, a decrease is observed in the order sucrose ≈ rafinnose ≈ stachyose > melezitose > 1-kestose. Actually, from the hydrolytic mechanism accepted for thermolysin,[24] a putative mechanism for the carbohydrate transesterification may be proposed to help understand the regioselectivity obtained. In this mechanism (Scheme 3) the nucleophilicity of the attacking hydroxyl is enhanced by aminoacid Glu143, which functions as a general-basic catalyst (GBC) in the reaction. A possible explanation for the regioselectivity observed could be related with the relative acidity of this hydroxyl in the different carbohydrates, bearing in mind the GBC role of Glu143. ^{1}H NMR experiments have shown the presence of two intramolecular hydrogen-bond conformations for sucrose in DMSO-d_6, in which the glucosyl 2-OH acts as acceptor for 1′-OH or 3′-OH of the fructofuranosyl residue. The two hydrogen-bond conformations exist in a competitive equilibrium with the 1′-OH···O-2 hydrogen bond favoured over the 3′-OH···O-2 hydrogen bond in a ratio ~2:1, assuming that the magnitudes of the isotope effects reflect the relative 'strengths' of the hydrogen bonds (Scheme 2).[20] Semiempirical calculations based on these hydrogen bond conformations clearly establish that the glucosyl 2-OH is the most acidic position of the sucrose molecule.[25] This is also corroborated experimentally in the base-catalyzed acylation of sucrose with vinyl laurate in DMSO, which produces 2-O-lauroylsucrose as the main regioisomer.[26] Similar NMR experiments have shown that the same competitive hydrogen-bond equilibrium found in sucrose also occurs in raffinose and stachyose[27] and thus a similar acidity of the corresponding glucosyl 2-OH should be expected. Both melezitose and 1-kestose have one of the possible interresidue H-bonds excluded in their sucrose moiety due to substitution with a sugar unit. The other possible inter-residual H-bond, the 1′-OH···O-2 hydrogen bond for melezitose and the 3′-OH···O-2 hydrogen bond for 1-kestose may take place, since O-3′ sucrose derivatives and 1′-sucrose derivatives with similar structures have showed its presence in DMSO-d_6.[28,29] It is important to note that missing one of the two-possible hydrogen-bonds may reduce the actual acidity of the OH-2, and also that the 3′-OH···O-2 hydrogen bond is weaker than the 1′-OH···O-2.[20] This takes us to the following order of relative acidity of the glucosyl 2-OH for each carbohydrate: sucrose ≈ rafinnose ≈ stachyose > melezitose > 1-kestose, which correlates quite well with the substitution pattern observed.

In summary, we have extended the study of acylation with the metalloprotease thermolysin to several mono-, di-, tri- and tetrasaccharides. It seems that a common structural motif in the carbohydrate is needed for proper binding so that catalysis may take place. This motif may locate the two hydroxyl groups involved in an inter-residual H-bond in a position where they are able to bind the zinc ion via a bidentade mode. Accurate HPLC/MS analysis along with NMR spectroscopic studies show that the acylation occurs preferentially in the 2-OH of the glucose moiety involved in an inter-residue H-bond with the vicinal sugar moiety. Moreover, it is the first time that sucrose containing tri- and tetrasaccharides are acylated enzymatically in a secondary hydroxyl group. Studies of the biological and physical properties of these new non-ionic surfactants are in progress.

4. Experimental

4.1. Chemicals

Anhydrous dimethyl sulfoxide (DMSO) and vinyl laurate were supplied by Fluka; raffinose and melezitose from Sigma and stachyose and 1-kestose from TCI Chemicals. All the carbohydrates were used in their amorphous form prepared by lyophilization of the corresponding aqueous solutions. Thermolysin from *Bacillus thermoproteolyticus*

rokko (Type X, lyophilized powder, 50–100 units/mg protein) and acid-washed Celite were from Sigma.

4.2. Enzyme immobilization

Enzyme adsorption onto Celite was done essentially as previously described.[16] Basically, thermolysin (100 mg) was dissolved in 3.33 ml of 50 mM 3-morpholinopropanesulfonic acid (Na-MOPS) buffer at pH 7.5. The enzyme solution was mixed thoroughly with 3.33 g of acid-washed Celite and subsequently lyophilized to ensure complete drying of the preparation. Celite control was prepared as the immobilized enzyme.

4.3. General procedure for ester synthesis and product isolation

In a typical experiment a solution of raffinose, melezitose, 1-kestose (150 mg, 0.30 mmol) or stachyose (200 mg, 0.30 mmol) in anhydrous DMSO (8.5 ml) and vinyl laurate (228 mg, 1 mmol) were shaken with orbitalic stirring (325 rpm) at 45 °C in the presence of immobilized enzyme (1500 mg). When traces of diester were observed by TLC, the mixture was cooled and filtered. Then, *n*-hexane was added (5 ml) and the mixture vigorously stirred and then cooled to −20 °C. The *n*-hexane, which took up residual vinyl laurate, was decanted. The DMSO reaction solution was allowed to warm at room temperature and then mixed with 10 ml of water. The mixture was extracted with *n*-butanol–cylohexane (3/1 v/v for trisaccharide reactions and 4:1 v/v for the stachyose reaction) (3×40 ml). The organic phases were pooled and washed with 15 ml of brine to remove residual DMSO, and solvents were evaporated off. The remaining residue was subjected to flash chromatography. Concentration of pure fractions in vacuo afforded the monolaurates (mixture of regioisomers) as amorphous white solids. Yields of oligosaccharide monolaurates (Table 1) are based on weight of the isolated fraction containing the monoesters.

All reactions were monitored by TLC on precoated Silica-Gel 60 plates (Alugram Sil G/UV_{254} supplied by Macherey-Nagel), and detected by heating with Mostain (500 ml of 10% H_2SO_4, 25 g of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, 1 g $Ce(SO_4)_2\cdot 4H_2O$). The elution system was $CHCl_3$–MeOH (2.5/1) for the reactions involving trisaccharides and EtOAc–MeOH–H_2O (7/5/1) for the reactions with stachyose. Flash chromatography was performed with Aldrich Silica gel 60 (200–400 mesh) using a gradient of chloroform/methanol 5:1–2:1 (v/v) for the trisaccharides monolaurates and 5:1 to 1:1 v/v for stachyose monolaurate.

4.4. HPLC/MS analysis

Analysis of the regioisomeric distribution of the isolated monoesters was carried out by HPLC/MS.[11] A Waters Alliance 2695 separation module was employed with a Waters Spherisorb 3 μm ODS2 column (4.6×250 mm) and a Waters Micromass ZQ mass spectrometer detector. The temperature of the column was set to 40 °C. Flow rate was 1.1 ml/min with splitting before the detection module (so that 0.20 ml/min enters the detector). Mobile phases were acetonitrile:water mixtures in isocratic conditions. The ratio changed depending on the compounds as follows: for the analysis of the regioisomeric distribution of trisaccharide monolaurates, acetonitrile/water 35:65 (v:v) and for the more polar stachyose monolaurate, 30:70 (v:v). Detection was done with positive ESI ionization in both Scan and SIR (selecting the mass of the Na^+ adduct, i.e., M+Na) modes. Cone voltage was set to 40 V to have the maximum possible intensity for the molecular ion and no fragmentation. Samples were prepared as water solutions (ca. 1 ppm) and immediately analyzed. Percentage of main regioisomer in each mixture was calculated by integration (using MassLynx version 3.5 software) of the corresponding SIR chromatogram (Fig. 2) as follows: [(Area peak mean regioisomer)/(ΣArea all peaks)]×100%. This calculation assumes that all regioisomers in the sample have the same response in the detector, that is, all of them ionize equally in the ESI source. The chromatographic conditions we have employed (constant flow rate, isocratic eluent, absence of additives in the mobile phase, sample diluted enough to avoid signal saturation, etc.) and the obvious structural similarity between all regioisomers (all of them have the same hydrophilic–lipophilic balance and are polar enough to form stable adducts with Na^+ in the source) ensure that the equal response requirement is met.

4.5. Spectroscopic analysis

NMR spectra of the parent oligosaccharides and their corresponding isolated monolaurates were recorded on either a Bruker AVANCE 300 or ARX 400 [300 or 400 MHz (^{1}H) and 75 or 100 (^{13}C)] at room temperature for solutions in CD_3OD. Chemical shifts are referred to the methanol multiplet, centered at 3.31 ppm for ^{1}H NMR and 49.0 ppm for ^{13}C NMR. All spectra were acquired using standard pulse sequences, instrument settings and procedures (selective excitation in 1D selective TOCSY spectra was achieved by excitation sculpting with a PFGSE sequence). High resolution FAB (+) mass spectral analyses were obtained on a Micromass AutoSpec-Q spectrometer. Infrared spectra (KBr disks) were recorded using a Nicolet 20SXB FTIR spectrophotometer.

4.5.1. 2′-*O*-Lauroylraffinose (1a). The general procedure outlined above was followed. After 72 h the reaction was stopped and the monoester fraction isolated (56 mg, 27%). R_f=0.31, ν_{max} (cm^{-1}) (KBr disks): 3410 br (O–H), 1730 (C=O); HRMS (FAB+): calcd for $C_{30}H_{54}O_{17}Na$ (M+Na) 709.3259, found 709.3246. Compound **1a** was obtained with 86% regioisomeric purity (HPLC/MS). NMR assignments of main regioisomer **1a**: ^{1}H NMR (CD_3OD, 300 MHz): δ 5.55 (d, 1H, $J_{1'-2'}$=3.7 Hz, H-1′), 4.90 (d, 1H, J_{1-2}=3.4 Hz, H-1), 4.61 (dd, 1H, $J_{2'-3'}$=9.7 Hz, $J_{1'-2'}$=3.7 Hz, H-2′), 4.19 (d, 1H, $J_{3''-4''}$=8.8 Hz, H-3″), 4.10 (m, 1H, H-5′), 4.06 (t, 1H, $J_{3''-4''}=J_{4''-5''}$=8.8 Hz, H-4″), 3.93 (m, 1H, H-3), 3.93 (dd, 1H, $J_{6'a-b}$=11.2 Hz, $J_{6'a-5'}$=5.7 Hz, H-6′a), 3.88 (t, 1H, $J_{2'-3'}=J_{3'-4'}$=9.7 Hz, H-3′), 3.85 (m, 1H, H-5), 3.80 (m, 1H, H-4), ca. 3.77 (m, 1H, H-2), 3.75 (m, 1H, H-6′b), ca. 3.73 (m, 3H, H-5″, H-6″a, H-6″b), ca. 3.71 (m, 2H, H-6a, H-6b), 3.53 (d, 1H, $J_{1''a-b}$=11.9 Hz, H-1″a), 3.39 (t, 1H, $J_{3'-4'}=J_{4'-5'}$=9.7 Hz, H-4′), 3.38 (d, 1H, $J_{1''a-b}$=11.9 Hz, H-1″b), 2.38 (t, 2H, J=7.4 Hz, –CH_2–CO–), 1.63 (m, 2H, CH_2–CH_2–CO–),

1.29 (m, 16H, –CH_2– chain), 0.90 (t, 3H, J=6.7 Hz, CH_3–); ^{13}C NMR (CD_3OD, 75 MHz): see assignment in Table 2.

4.5.2. 2-*O*-Lauroylmelezitose (2a). The general procedure outlined above was followed. After 72 h the reaction was stopped and the monoester fraction isolated (45 mg, 22%). R_f=0.32, ν_{max} (cm^{-1}) (KBr disks): 3400 br (O–H), 1725 (C=O); HRMS (FAB+): calcd for $C_{30}H_{54}O_{17}Na$ (M+Na) 709.3259, found 709.3263. Compound **2a** was obtained with 69% regioisomeric purity (HPLC/MS). NMR assignments of main regioisomer **2a**: ^{1}H NMR (CD_3OD, 300 MHz): δ 5.55 (d, 1H, J_{1-2}=3.7 Hz, H-1), 5.07 (d, 1H, $J_{1''-2''}$=3.7 Hz, H-1″), 4.61 (dd, 1H, J_{2-3}=9.7 Hz, J_{1-2}= 3.7 Hz, H-2), ca. 4.26 (m, 2H, H-3′, H-4′), 3.94 (m, 1H, H-5), 3.88 (m, 1H, H-5″), 3.87 (dd, 1H, J_{6a-b}=12.1 Hz, J_{6a-5}=2.1 Hz, H-6a), ca. 3.82 (m, 2H, H-6″a, H-6″b), ca. 3.78 (m, 3H, H-5′, H-6′a, H-6′b), 3.76 (t, 1H, J_{2-3}=J_{3-4}= 9.7 Hz, H-3), 3.72 (dd, 1H, J_{6a-b}=12.1 Hz, J_{6b-5}=6.1 Hz, H-6b), 3.70 (t, 1H, $J_{2''-3''}$=$J_{3''-4''}$=9.6 Hz, H-3″), 3.67 (d, 1H, $J_{1'a-b}$=11.9 Hz, H-1′a), 3.44 ((dd, 1H, $J_{2''-3''}$=9.6 Hz, $J_{1''-2''}$=3.7 Hz, H-2″), 3.43 (t, 1H, $J_{3''-4''}$=$J_{4''-5''}$=9.6 Hz, H-4″), 3.39 (t, 1H, J_{3-4}=J_{4-5}=9.7 Hz, H-4), 3.28 (d, 1H, $J_{1'a-b}$=11.9 Hz, H-1′b), 2.38 (t, 2H, J=7.5 Hz, –CH_2–CO–), 1.63 (m, 2H, CH_2–CH_2–CO–), 1.29 (m, 16H, –CH_2– chain), 0.89 (t, 3H, J=6.8 Hz, CH_3–); ^{13}C NMR (CD_3OD, 75 MHz): see assignment in Table 2.

4.5.3. 2-*O*-Lauroyl(1-kestose) (3a). The general procedure outlined above was followed. After 72 h the reaction was stopped and the monoester fraction isolated (66 mg, 32%). R_f=0.32, ν_{max} (cm^{-1}) (KBr disks): 3400 br (O–H), 1730 (C=O); HRMS (FAB+): calcd for $C_{30}H_{54}O_{17}Na$ (M+Na) 709.3259, found 709.3248. Compound **3a** was obtained with 55% regioisomeric purity (HPLC/MS). NMR assignments of main regioisomer **3a**: ^{1}H NMR (CD_3OD, 400 MHz): δ 5.57 (d, 1H, J_{1-2}=3.7 Hz, H-1), 4.61 (dd, 1H, J_{2-3}=9.7 Hz, J_{1-2}=3.7 Hz, H-2), 4.27 (d, 1H, $J_{3'-4'}$= 8.4 Hz, H-3′), 4.15 (d, 1H, $J_{3''-4''}$=8.3 Hz, H-3″), ca. 4.04 (m, 2H, H-4′, H-4″), 3.87 (m, 1H, H-5), 3.86 (m, 1H, H-3), ca. 3.84 (m, 1H, H-6a), ca. 3.84-3.77 (m, 2H, H-1′a, H-1′b), ca. 3.77–3.72 (6H, H-5′, H-5″, H-6′a, H-6′b, H-6″a, H-6″b), 3.70 (dd, 1H, J_{6a-b}=12.0 Hz, J_{6b-5}=5.2 Hz, H-6b), ca. 3.64–3.60 (2H, H-1″a, H-1″b), 3.41 (t, 1H, J_{3-4}=J_{4-5}= 9.7 Hz, H-4), 2.38 (t, 2H, J=7.5 Hz, –CH_2–CO–), 1.63 (m, 2H, CH_2–CH_2–CO–), 1.29 (m, 16H, –CH_2– chain), 0.90 (t, 3H, J=6.8 Hz, CH_3–); ^{13}C NMR (CD_3OD, 100 MHz): see assignment in Table 2.

4.5.4. 2″-*O*-Lauroylstachyose (4a). The general procedure outlined above was followed. After 72 h the reaction was stopped and the monoester fraction isolated (31 mg, 12%). R_f=0.63, ν_{max} (cm^{-1}) (KBr disks): 3410 br (O–H), 1730 (C=O); HRMS (FAB+): calcd for $C_{36}H_{64}O_{22}Na$ (M+Na) 871.3787, found 871.3785. Compound **4a** was obtained with 85% regioisomeric purity (HPLC/MS). NMR assignments of main regioisomer **4a**: ^{1}H NMR (CD_3OD, 300 MHz): δ 5.55 (d, 1H, $J_{1''-2''}$=3.7 Hz, H-1″), 4.89 (d, 1H, H-1), 4.88 (d, 1H, $J_{1'-2'}$=3.6 Hz, H-1′), 4.61 (dd, 1H, $J_{2''-3''}$=9.7 Hz, $J_{1''-2''}$=3.7 Hz, H-2″), 4.20 (d, 1H, $J_{3'''-4'''}$= 8.6 Hz, H-3‴), 4.08 (m, 1H, H-5″), 4.07 (m, 1H, H-5′), 4.05 (t, 1H, $J_{3'''-4'''}$=$J_{4'''-5'''}$=8.6 Hz, H-4‴), 3.93 (m, 1H, H-3′), 3.93 (dd, 1H, $J_{6''a-b}$=11.1 Hz, $J_{6''a-5''}$=5.6 Hz, H-6″a), ca. 3.89 (m, 1H, H-3), 3.87 (t, 1H, $J_{2''-3''}$=$J_{3''-4''}$=9.7 Hz, H-3″), ca. 3.85 (m, 1H, H-6′a), ca. 3.83 (m, 1H, H-5), ca. 3.80 (m, 1H, H-4), ca. 3.76 (m, 2H, H-2, H-2′), ca. 3.73 (m, 4H, H-4′, H-5‴, H-6‴a, H-6‴b), ca. 3.71 (m, 2H, H-6a, H-6b), 3.70 (m, 1H, H-6″b), ca. 3.65 (m, 1H, H-6′b), 3.53 (d, 1H, $J_{1'''a-b}$=11.9 Hz, H-1‴a), 3.39 (t, 1H, $J_{3''-4''}$= $J_{4''-5''}$=9.7 Hz, H-4″), 3.38 (d, 1H, $J_{1'''a-b}$=11.9 Hz, H-1‴b), 2.38 (t, 2H, J=7.4 Hz, –CH_2–CO–), 1.63 (m, 2H, CH_2–CH_2–CO–), 1.29 (m, 16H, –CH_2– chain), 0.90 (t, 3H, J=6.7 Hz, CH_3–); ^{13}C NMR (CD_3OD, 75 MHz): see assignment in Table 2.

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Correct structures of Diels–Alder adducts from the natural cyclolignan thuriferic acid and its 8-epimer

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Abstract—A detailed analysis of one- and two-dimensional ^{1}H and ^{13}C NMR data for the *endo* and the *exo* adducts, obtained by Diels–Alder reaction of thuriferic and epithuriferic acids with cyclopentadiene is described. The unequivocal spectral data assignment of the *endo* and *exo* structures was complemented with molecular modelling studies and confirmed through X-ray diffraction studies.

1. Introduction

Thuriferic acid **1**, a lignan isolated from *Juniperus thurifera L*[1] and its 8′-epimer, epithuriferic acid **2**[2] (Fig. 1), are two non-lactonic cyclolignans, related to podophyllotoxin **3**. Podophyllotoxin is a well-known naturally occurring lignan endowed with potent cytotoxicity, acting as a potent inhibitor of microtubule assembly.[3] In spite of its initial use as an anticancer drug, human clinical trials were soon abandoned due to its toxicity. An extensive semi-synthetic

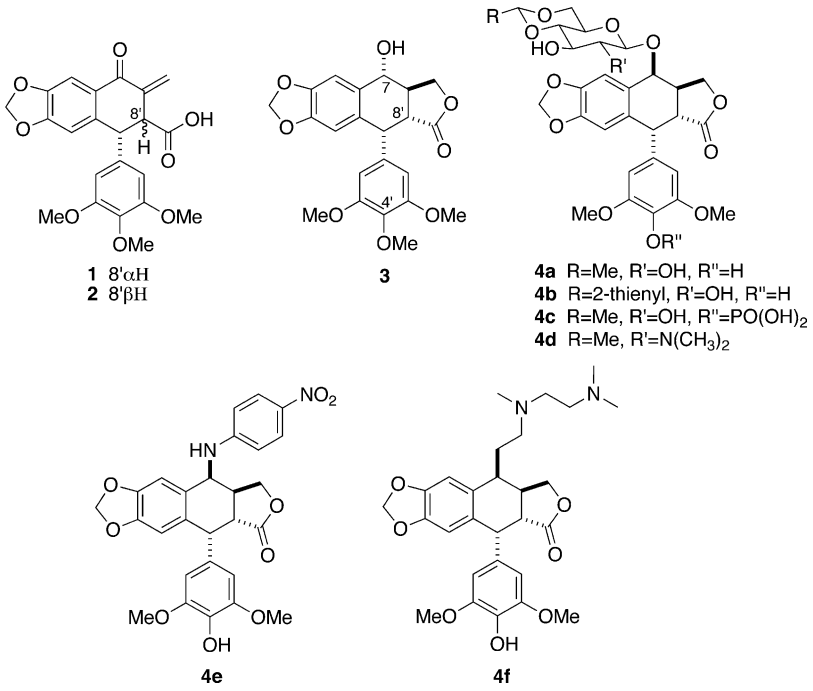

Figure 1. Compounds **1**, **2** and **3**, lignans in the market and some of those under clinical trials.

Keywords: Lignans; Podophyllotoxin; Thuriferic acid; Epithuriferic acid; Diels–Alder.
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programme at Sandoz resulted in the development of etoposide **4a** and teniposide **4b**, two glycoside derivatives of 4′-demethylepipodophyllotoxin,[4] which did not interact significantly with tubulin, but caused extensive DNA breaking, as a consequence of their interaction with DNA–topoisomerase II. Etoposide is currently one of the most prescribed anticancer drugs, with good clinical prognosis against several types of cancer.[5] Continuous efforts have led to the synthesis of new related compounds, displaying decreased toxicity and side effects, metabolic inactivation, drug resistance, and increased water solubility. Etopophos **4c** is the etoposide phosphate designed to overcome the limitations associated with the poor solubility of etoposide.[6] NK611[7] **4d**, GL331 **4e** and TOP-53 **4f** (Fig. 1) are three related derivatives, which are currently under clinical trials.[8] GL331 presents a promising potential in the treatment of gastric carcinoma, colon cancer and non-small cell lung cancer[9] and it is more potent than etoposide.[10] NK611 can be administered orally.[11] TOP-53 is active against neoplasms resistant to etoposide.[12] Other related compounds have shown antiviral[13] and immunosuppressive activities.[14] Podophyllotoxin itself is actually prescribed for removing condiloma and other venereal warts.

The structures of thuriferic and epithuriferic acids are well established[15] and reconfirmed by total synthesis.[16] Their α,β-unsaturated ketone fragment has attracted our attention, because it may act as a dienophile and undergo cycloaddition reactions, which could lead to novel structures with enhanced bioactivity. Previously, we have prepared diverse norbornenecarboxylate esters of podophyllotoxin and its epimers and diastereoisomers through Diels–Alder cycloaddition, by treating the dienophilic acrylates of these cyclolignans with cyclopentadiene.[17] Some of the resulting adducts showed a one-fold increase in their cytotoxicity when compared to that of the natural product **3**.

Presently, we have studied the Diels–Alder cyclocondensations of thuriferic and epithuriferic acids with cyclopentadiene, that afford complex mixtures containing not only the expected *endo*/*exo* adducts, but also other structurally indeterminate compounds. The structures of these adducts have been established on the basis of 2D NMR spectral data, modelling studies and X-ray diffraction data. Their antineoplastic cytotoxicities have been evaluated and the results will be published elsewhere.

In a paper published by Höfert and Matusch[18] two adducts, obtained by cycloaddition of thuriferic acid methyl ester with cyclopentadiene, were reported. These authors proposed for thuriferic acid **1** the erroneous opposite configuration at the C-8′ position. As a consequence, the configuration of the corresponding position in the cycloadducts was also erroneous. Besides, the authors did not justify satisfactorily the configuration of the new stereocenter C-8, generated in the course of the reaction. This induced us to carry out the same cycloaddition and to extend the study to epithuriferic acid, in order to clarify the configuration of the adducts at C-8 and C-8′. We used the free acids instead the methyl esters, to avoid additional steric hindrance and to facilitate the formation of other minor stereoisomers.

2. Results and discussion

The starting podophyllotoxin **3** was isolated from commercial *podophyllum* resin and transformed into thuriferic **1** and epithuriferic acids **2** through reported procedures[1,2] (Fig. 2). These acids contain an α,β-unsaturated ketone fragment, which may undergo the cycloaddition reaction. Therefore, lignans **1** and **2** were treated with cyclopentadiene in order to obtain the corresponding adducts. Cyclopentadiene was prepared by cracking of dicyclopentadiene and used immediately after its preparation. The best results were obtained when dicyclopentadiene was dropped slowly over hot paraffin, with stirring at temperatures under 240 °C. Cyclopentadiene distilled at 40–42 °C. Initially, the reactions were performed at −18 °C, in absence of a catalyst, and needed about 4 weeks to go to completion in the case of thuriferic acid (α and β faces hindered by the trimethoxyphenyl and the carboxyl groups, respectively) and 3 days in that of epithuriferic acid. When $AlCl_3$ was added as catalyst, thuriferic acid needed only 4 days for completion, while the *endo*/*exo* ratio was practically maintained. For epithuriferic acid, the reaction time was not substantially modified, but the *endo*/*exo* ratio changed significantly due to the influence of the catalyst on the

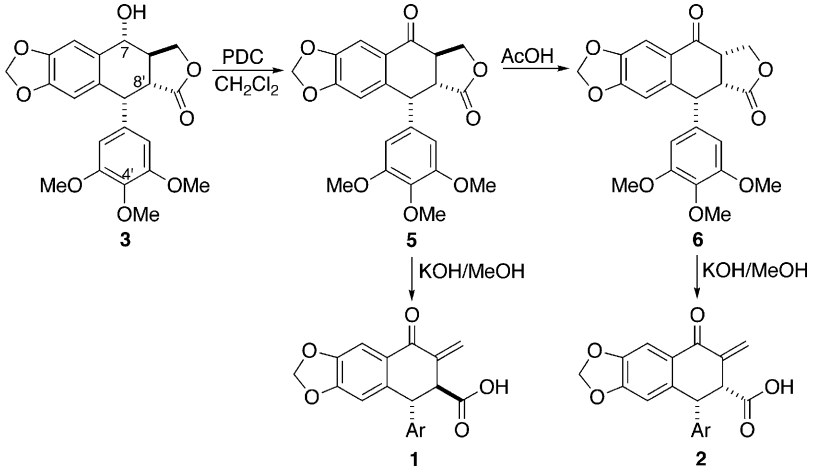

Figure 2. Preparation of thuriferic and epithuriferic acids from podophyllotoxin.

transition state conformation,[19] leading to a decrease in the proportion of the *exo* attack. In fact, in absence of catalyst, the *endo*/*exo* ratio was 1:5 whereas in its presence was 1:3. Analysis of the reaction mixtures by TLC, after treating the crude reaction product with diazomethane, showed that the four possible diastereoisomeric norbornene adducts from thuriferic acid (**1**β-*en*, **1**α-*ex*, **1**α-*en*, and **1**β-*ex*) (Fig. 3) were formed. On the other hand, in the case of epithuriferic acid only two adducts (**2**β-*ex*, **2**β-*en*) were detected (Fig. 6). The α/β codes used here to denominate the adducts, indicate the attacked face of the lignan considered as the substrate and the *en*/*ex* codes represent the *endo*/*exo* orientation of the approach. The determination of the diastereomeric excess of the four Diels–Alder reactions was performed by HPLC analysis (Figs. 3 and 6). The identification of the methyl esters of the resulting adducts was achieved through the analysis of ^{1}H, ^{13}C NMR and 2D NMR spectroscopic data. The ^{1}H and ^{13}C chemical shifts of these compounds were fully assigned using COSY, HMQC, and HMBC NMR correlations. Apart from the cross-peak correlations corresponding to the lignan fragment in the HMBC spectra, some other diagnostic connectivities were observed between the bicycloheptene and the lignan fragments. Indeed, correlations between the C-8 and the protons H-7′, H-8′, H-8e and H-9 were observed for all the adducts. Besides, the signal of H-8a correlated with those of carbons 8b, 8c, 8d, 8e and 9. All the correlations allowed the unambiguous assignment of the ^{1}H and ^{13}C NMR spectral signals. Nevertheless, the chemical shift differences observed for the norbornene signals of each adduct were not sufficient to establish unambiguously the configuration of the C-8a and C-8d stereocenters generated during the cyclocondensation. Similarly, the analysis of the possible influence of the lignan fragment did not allow the satisfactory comparison of chemical shifts of the adducts with those of related norbornenes reported in the literature.[20] Because of this, we carried out some molecular modelling studies for the methyl esters of the adducts. A conformational search[21] for each methylated adduct from thuriferic and epithuriferic acids allowed us to find two main conformers for each adduct. In the case of methylated adducts from thuriferic acid (Fig. 4), the trimethoxyphenyl ring and the methoxycarbonyl groups are placed in a pseudodiaxial disposition in one conformer, and in a pseudodiequatorial disposition in the other. However, in the case of methylated adducts from epithuriferic acid, one of these moieties is oriented pseudoaxially and the other pseudoequatorially, alternatively, for both conformers of each adduct. All of the compounds were later subjected to ab initio calculations at the HF/6-31G* level.[22] The results of calculations appear in Figures 4 and 7 and are in excellent agreement with those found experimentally by NMR. The use of ROESY correlations and the distance values derived from theoretical models (Tables 1 and 2) enabled the definitive stereochemical determinations.

In the adduct **1**α-*ex*, the ROE observed between H-8′ and H-8b indicated that this compound came through the *exo* approach. Besides, other ROE between H-8′ and H-9a clearly indicated that the attack of the cyclopentadiene took place from the alpha face of thuriferic acid. This finding was corroborated by the observed broadening of the two singlets corresponding to the aromatic protons (6.30 ppm) and to the two symmetric methoxyls (3.77 ppm) of the trimethoxyphenyl group, thus indicating the existence of a rotational restriction due to steric hindrance provoked by their close proximity to the olefinic proton H-8b of the norbornene fragment. Additionally, the ^{1}H NMR spectrum of the adduct **1**α-*ex* showed a coupling constant H7′–H8′ of 1.5 Hz, indicating a 1,2-pseudodiaxial arrangement of those trimethoxyphenyl and methoxycarbonyl groups,[2] in agreement with theoretical results (see conformation of **1**α-*ex*-*ax* in Fig. 4). Finally, the structure was confirmed unambiguously by X-ray diffraction (Fig. 5). Interestingly, the conformation of **1**α-*ex* in the crystal resulted different from that deduced by NMR in solution, showing a trans-pseudodiequatorial disposition for both trimethoxyphenyl and methoxycarbonyl residues (conformation **1**α-*ex*-*eq*). Nevertheless, this X-ray conformation could not explain neither the coupling constant H7′-H8′ (1.5 Hz) nor the ROE

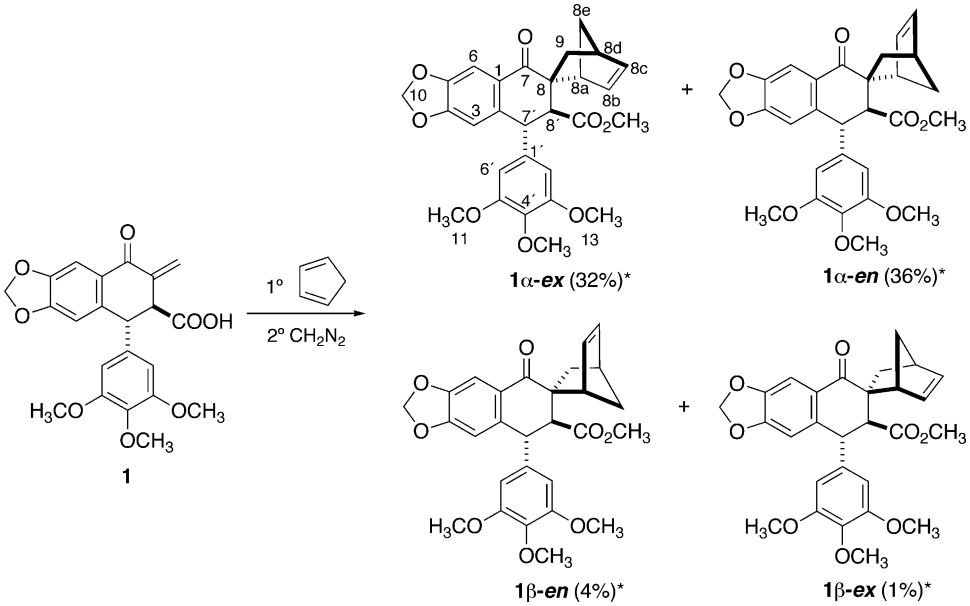

Figure 3. Adducts from thuriferic acid **1**. (*) Yields from HPLC analysis.

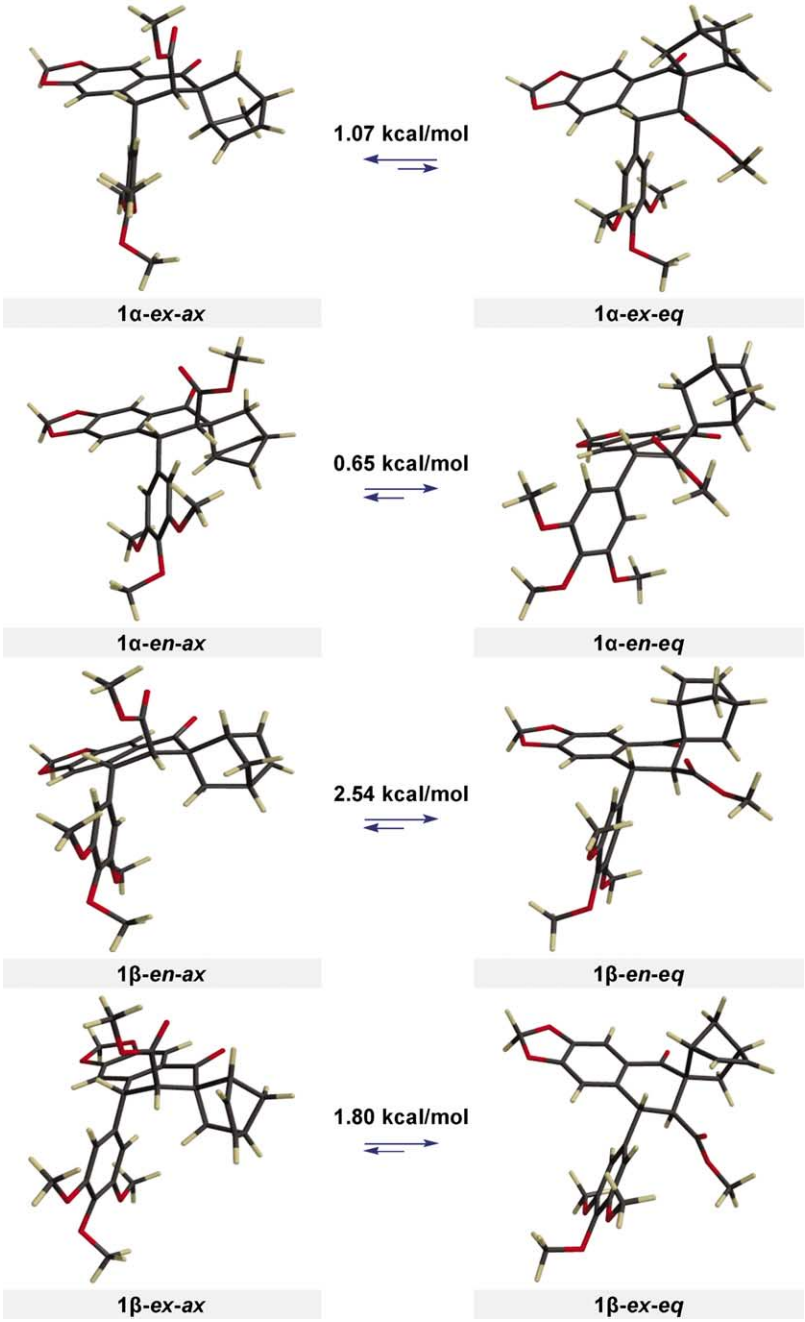

Figure 4. Theoretical model of the four adducts from thuriferic acid **1** and cyclopentadiene and the energies (kcal/mol) obtained by ab initio method at HF/6-31G* level. The energy differences are expressed in kcal/mol.

Table 1. Significant interprotonic distances (Å) in theoretical models for the two main conformers of each adduct from thuriferic acid

Conformer/H		**8′–8b**	**8′–8e$_a$**	**8′–8e$_b$**	**7′–8a**	**8′–9a**	**8′–9b**
1α-*ex*	*ax*	**2.75**[a]	4.81	4.61	4.24	**2.57**[a]	3.73
	eq	3.64	4.55	5.07	4.99	3.71	4.17
1α-*en*	*ax*	5.04	**2.12**[a]	3.77	3.99	**2.53**	3.73
	eq	6.61	3.73	4.73	4.79	3.70	4.15
1β-*en*	*ax*	5.06	**2.17**	3.74	4.77	**2.52**	3.74
	eq	5.26	3.90	5.20	**2.31**[a]	**2.70**[a]	3.23
1β-*ex*[b]	*ax*	3.09	4.79	4.62	5.00	**2.51**	3.71
	eq	4.51	4.67	5.53	**2.60**	4.53	5.06

In bold: calculated distances, for which a ROE could be expected.
[a] Experimentally observed ROEs.
[b] Experiment not performed for this compound.

Table 2. Significant interprotonic distances (Å) in theoretical models for the two main conformers of each possible adduct from epithuriferic acid

Conformer/H		7′–8a	7′–8b	8′–8b	8′–8e	8′–9a	8′–9b
2α-*ex*[a]	*ax*	4.21	4.62	5.53	5.53	2.75	3.14
	eq	4.91	4.89	**2.64**	4.72	**2.42**	3.69
2α-*en*[a]	*ax*	3.98	6.06	5.31	3.71	**2.42**	3.15
	eq	4.74	6.01	5.00	**2.04**	**2.44**	3.72
2β-*en*	*ax*	4.64	6.47	4.45	3.18	3.68	4.27
	eq	**2.06**[b]	4.49	**2.93**	**2.05**	3.75	**2.50**[b]
2β-*ex*	*ax*	4.88	4.99	**2.94**	4.49	4.27	3.70
	eq	**2.32**[b]	**2.73**[b]	4.57	4.57	3.74	**2.49**

In bold: calculated distances, for which a ROE could be expected.
[a] Compound not found.
[b] Experimentally observed ROEs.

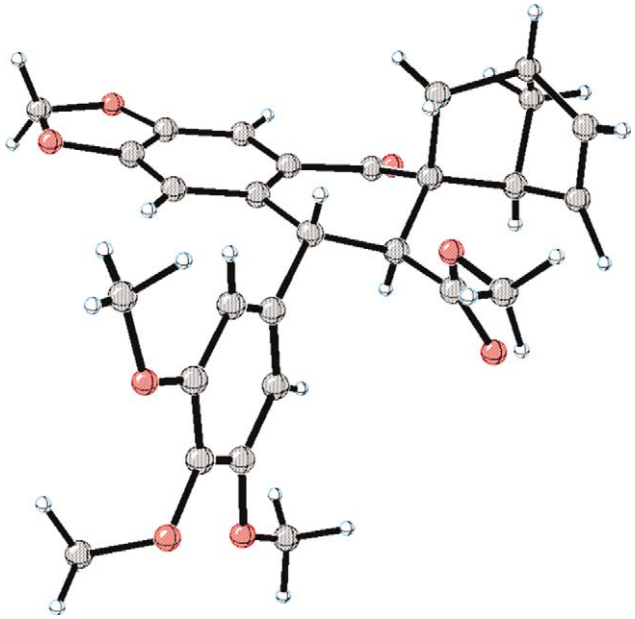

Figure 5. Diagram showing the crystal structure of compound **1**α-*ex*-*eq*.

observed between the H-8′ and H-8 signals, because in the ordinarily used NMR experimental conditions, the distance between these two protons (3.6 Å, in the crystal structure) would be too large for the ROE being observed, thus indicating a conformational change with the change of aggregation state. This change can be justified because the energy difference between both conformations is small (0.6 Kcal/mol) (Fig. 4). The spectral data of this adduct are identical to those described by Höfert and Matusch[18] for the adduct formed by the beta-*endo* approach of cyclopentadiene to epithuriferic acid **2**. In consequence, C-8 and C-8′ have the opposite configurations to those published by these authors. In addition, the HMBC NMR correlations allowed us to reassign some previous incorrect assingments.

The ^{1}H NMR spectrum of adduct **1**β-*en* shows a coupling constant between the H-7′ and H-8′ of 10.8 Hz, indicating a pseudodiequatorial arrangement for those trimethoxyphenyl and carboxyl groups.[2] The ROE observed between H-7′ and H-8a indicated that this adduct came through the approach of the cyclopentadiene from the beta face of the lignan. Besides, another important ROE was observed between H-8′ and one of the hydrogen atoms of the methylene 9, indicating the *endo* orientation of the approach. The comparison of data derived from this ROE, along with the distances measured on the theoretical models, proved that this compound is compatible only with the structure **1**β-*en*. All this data are in complete agreement with the energy values found in the theoretical calculations, demonstrating a greater stability for the pseudodiequatorial conformation of this **1**β-*en* adduct.

The ^{1}H NMR spectrum of the **1**α-*en* adduct shows a coupling constant between the H-7′ and H-8′ of 3.5 Hz, slightly larger than that of the **1**α-*ex* adduct, that could be explained by the smaller energy difference between the two mayor conformers of this adduct, in comparison with that of the **1**α-*ex* adduct (Fig. 4). The ROE observed between H-8′ and H-8e indicated that this adduct came from the *endo* approach of the cyclopentadiene as in the case of compound **1**β-*en*; in consequence, this must be the alpha-*endo* adduct. Spectral data of this adduct were almost identical to those described by Höfert and Matusch[18] for the adduct formed by the beta-*exo* approach to epithuriferic acid **2**. Finally, the **1**β-*ex* structure must correspond to the beta-*exo* adduct. Its ^{1}H NMR spectrum shows a coupling constant of 6.0 Hz between H-7′ and H-8′, a value in-between that of the adducts **1**α-*ex* and **1**β-*en*, indicating similar populations of both extreme conformers, due to the small energy difference existing between them.

As in the case of thuriferic acid, in the molecular modelling studies on the methylated adducts from epithuriferic acid, two main conformers were found for every adduct (Figs. 6 and 7). Nevertheless, the energy differences between the pairs of conformers were greater in this case, over 7–9 Kcal/mol. This difference means that the conformational equilibrium is displaced almost completely to the preferred conformation, in which the trimethoxyphenyl group is placed in a pseudoequatorial arrangement forcing the methoxycarbonyl group to adopt a pseudoaxial disposition. The theoretical coupling constant between H-7′ and H-8′ in the lower energy conformations, over 6 Hz, is close to the experimental values (6.2 Hz in **2**β-*ex* and 5.6 Hz in **2**β-*en*).

In the two adducts obtained from epithuriferic acid, **2**β-*ex* and **2**β-*en*, the strong ROE correlation observed between the benzylic proton H-7′ and the olefinic proton H-8a of the norbornene, clearly indicates that both compounds came from the beta approach of cyclopentadiene to the lignan (Table 2). Additionally, in the **2**β-*ex* adduct, another ROE between H-7′ and the olefinic H-8b indicated the *exo* aproach. This adduct was the major reaction product, in

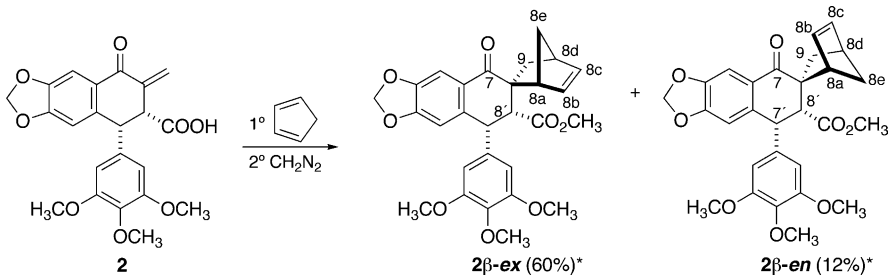

Figure 6. Adducts from epithuriferic acid **2**. (*) Yields from HPLC analysis.

contrast with the case of thuriferic acid cycloaddition. This results clearly indicate that the steric hindrance of the methoxycarbonyl plays a determinant role on regulating the reaction pathway and the configuration of the resulting adducts.

In the ROE experiment of the **2**β-*en* adduct, one additional correlation between H-8′ and one of the methylenic protons H-9 was observed, indicating that this adduct comes through the *endo* approach from the beta face of the lignan.

To resume, thuriferic acid, with both alpha and beta faces highly hindered for the diene attack, reacts very slowly, but gives all the four possible stereoisomeric adducts, with predominance of those resulting from the alpha approach,

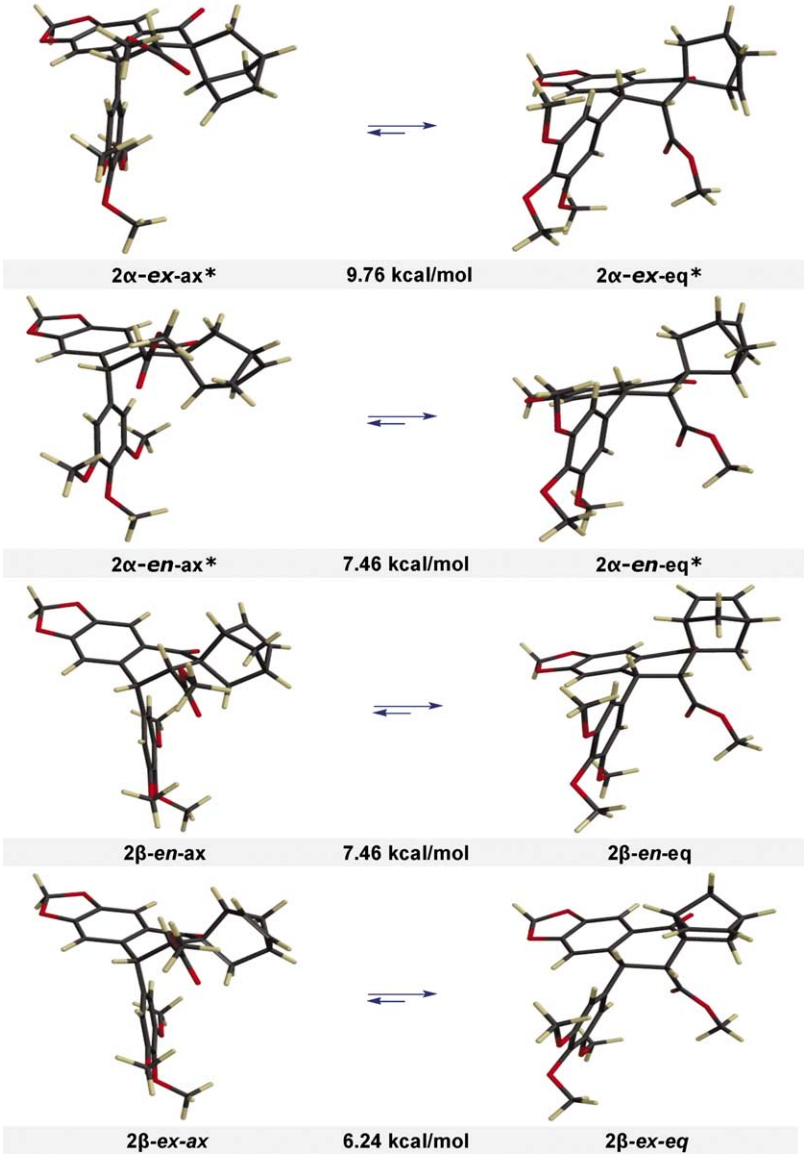

Figure 7. Theoretical model of the four possible adducts formed from epthuriferic acid **2** and cyclopentadiene obtained by ab initio method at HF/6-31G* level. The energy differences are expressed in kcal/mol. *Not formed in the cycloaddition conditions.

independently of the presence or absence of the catalyst. On the other hand, in the case of epithuriferic acid, with a much less hindered beta face, reacts faster and only the two adducts resulting from the beta approach of the diene were detected. Nevertheless, it must be considered that the beta adducts of thuriferic acid were always formed in a very low proportion (1–4% within all the experiments performed) and their scarcity, probably, could be the reason for which, they were not detected previously in the research of Höfert and Matusch.[18]

In the thuriferic acid cycloaddition, the major alpha adduct and the major beta adduct, resulted from an *endo* approach, in agreement with the frontier molecular orbitals theory. On the contrary, in the epithuriferic acid cycloaddition, the relative stability of its conformers governed the approach and the major product was the *exo* adduct, as it is proven by the broadening of the trimethoxyphenyl NMR signals as stated above. All these results are in agreement with the conformational study on both epimers, previously reported by us.[15]

3. Experimental

3.1. General methods

Purification and drying according to accepted general procedures.[23] If not otherwise stated, commercially available solvents of the highest purity were used. Melting points were determined on a Büchi 510-K melting point apparatus and are uncorrected. Optical rotations were recorded on a Perkin Elmer 241 polarimeter in chloroform solution. IR spectra were recorded in a Nicolet Impact 410 spectrophotometer. NMR spectra were measured using Bruker AC 200 (200 MHz) and Bruker DRX 400 (400 MHz) instruments. The chemical shifts are in δ values (ppm) relative to the internal standard TMS. Reported as: chemical shift (multiplicity, coupling constant, assignment). Reported assignments were determined with the help of COSY, HMQC, HMBC, and NOESY 2D-Spectra. For EIMS and HRFABMS analysis, a VG-TS250 mass spectrometer (70 eV) was used. X-ray diffraction data were collected on a four-circle Seifert XRD 3003 SC diffractometer (CuF_α, $\lambda=1.5418$ Å), graphite monochromator, room temperature, ω–2θ scans. Scattering factors for neutral atoms and anomalous dispersion correction for C and O were taken from 'International Tables for X ray Crystallography'.[24] Full matrix least-squares refinement with anisotropic thermal parameters for non-H atoms was carried out by minimizing $w(F_o^2-F_c^2)^2$. Refinement on F^2 for all reflections, weighted R factors (R_w), and all goodness of fit S are based on F^2, while conventional R factors (R) are based on F; R factors based on F^2 are statistically about twice as large those based on F, and R factors based on all data will be even larger. All calculations were performed using CRYSOM[25] software for data collection, XRAY80[26] for data reduction, SHELXTLTM[27] to resolve and refine the structure and to prepare figures for publication. Silica gel 60 (Merck, 230–400 mesh) was used for flash chromatography; precoated silica gel plates (Merck, Kieselgel 60 F254, 0.25 mm) were used for TLC analysis.

3.2. HPLC

HPLC analyses were carried out using a Waters Delta 600 with a Chromolith RP-18e 100–4.6 column. Wavelength 220–400 nm; column temperature 30 °C; injection volume 50 ml; acetonitrile and water buffered at pH 2.6 served as solvents.

3.3. Sources of precursors and synthesis of compounds

3.3.1. Podophyllotoxin (3). The title compound was obtained in pure form by recrystalization from the ethyl acetate extract of *Podophyllum emodi* resin.

3.3.2. Podophyllotoxone (5). Compound **3** (1.5 g) in 35 ml of dry CH_2Cl_2 was treated with 1.5 g of PDC. The suspension was stirred for 3 h at room temperature. Usual work up afforded after flash chromatography (CH_2Cl_2/EtOAc 1:1) 1.26 g (84%) of **5**. Spectroscopic and physical data were identical to those reported.[28]

3.3.3. Isopicropodophyllone (6). Compound **5** (400 mg) in 28 ml of acetic acid were refluxed for 1 h. After addition of H_2O, extraction with EtOAc and usual work up, the reaction crude was chromatographied (CH_2Cl_2/EtOAc 95:5) yielding 280 mg (70%) of **6** and 88 mg of **5**. Spectroscopic and physical data of **6** were identical to those reported.[28]

3.3.4. Thuriferic acid (1). Compound **5** (700 mg) was treated with 15 ml of 1% KOH/MeOH. The mixture was left 30 min at room temperature yielding, after usual work up and flash chromatography on Si gel, 670 mg of **1**. Mp = 92–96 °C (Et_2O). Spectroscopic and physical data were identical to those reported.[2]

3.3.5. Epithuriferic acid (2). Compound **6** (200 mg) was treated with 5 ml of 1% KOH/MeOH. The mixture was left 10 min at room temperature yielding, after usual work up and flash chromatography on Si gel, 50 mg of junaphtoic acid[29] and 110 mg of **2**. Mp = 92–96 °C (Et_2O). Spectroscopic and physical data were identical to those reported.[2]

3.3.6. Adducts of Diels–Alder reaction from 1. To a solution of thuriferic acid (600 mg, 1.42 mmol) in anhydrous CH_2Cl_2 (30 mL) at −18 °C under nitrogen atmosphere, freshly distilled cyclopentadiene (0.2 mL, 2.7 mmol) was added dropwise. After 27 days, HPLC control showed that the reaction was over. The reaction mixture was concentrated in vacuo followed by dilution with EtOAc (20 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (100 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. After methylation of the crude reaction product with diazomethane in ethereal solution, purification was carried out by flash chromatography eluting with *n*-hexane–ethyl acetate (2/1.2) to give the corresponding adducts **1**β-*en* (15 mg; hexane/AcOEt 2:1) (2.1%), **1**α-*ex* (135 mg, hexane/AcOEt 1:1) (18.9%), **1**α-*en* (145 mg; hexane/AcOEt 1:1.5) (20.3%), and **1**β-*ex* (4 mg; hexane/AcOEt 1:2) (0.6%).

3.3.6.1. Adduct (1β-*en*). Mp 146–149 °C (white solid); $[\alpha]^{22}$ −163 (Na 589), −170 (Hg 578), −217 (546) (*c* 1%, $CDCl_3$); IR (film) γ_{max}: 3025, 2960, 2840, 1733, 1680,

1617, 1588, 1506, 1480, 1463, 1245, 1127, 1037, 1008, 935 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.40 (d, J= 8.0 Hz, H-8ea), 1.50 (d, J=8.0 Hz, H-8eb), 1.70 (dd, J= 3.6, 12.0 Hz, H-9a), 2.86 (s, H-8d), 3.00 (dd, J=2.4, 12.0 Hz, H-9b), 3.19 (s, H-8a), 3.46 (d, J=10.8 Hz, H-8′), 3.57 (s, COOMe), 3.77 (s, H-11, H-13), 3.83 (s, H-12), 4.84 (d, J=10.8 Hz, H-7′), 5.60 (dd, J=3.0, 5.5 Hz, H-8b), 5.98 (dd, J=1.0, 4.8 Hz, H-10), 6.25 (dd, J=3.0, 5.6 Hz, H-8c), 6.30 (s, H-2′, H-6′), 6.32 (s, H-3), 7.22 (s, H-6). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.00 (C-9), 42.26 (C-8d), 46.51 (C-8a), 46.78 (C-7′), 48.42 (C-8e), 51.80 (COOMe), 55.98 (C-8′), 56.13 (C-8), 56.13 (C-11, C-13), 60.79 (C-12), 101.64 (C-10), 105.71 (C-6), 106.36 (C-2′, C-6′), 108.67 (C-3), 127.82 (C-1), 132.91 (C-8b), 137.01 (C-4′), 139.01 (C-1′), 139.54 (C-2), 139.68 (C-8c), 147.16 (C-4), 151.95 (C-5), 153.16 (C-3′, C-5′), 172.23 (C-9′), 197.23 (C-7). HRFABMS *m/z* 492.1792 (calcd For $C_{28}H_{28}O_8$, 492.1784).

3.3.6.2. Adduct (1α-*ex*). Mp 150–152 °C (colourless crystals); $[\alpha]^{22}$ +54 (Na 589), +59 (Hg 578), +62 (546), +106 (436) (*c* 1%, $CDCl_3$); IR (film) γ_{max}: 3057, 2958, 2836, 1734, 1680, 1617, 1589, 1505, 1481, 1463, 1246, 1126, 1037, 1009, 935 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.60 (dd, J=3.0, 6.0 Hz, H-9a), 1.10 (d, J=8.5 Hz, H-8ea), 1.70 (d, J=8.6 Hz, H-8eb), 2.70 (s, H-8d), 2.74 (d, J=3.8 Hz, H-8a), 2.80 (dd, J=4.0, 8.0 Hz, H-9b), 3.08 (d, J=1.5 Hz, H-8′), 3.59 (s, COOMe), 3.77–3.82 (br s, H-11, H-13), 3.83 (s, H-12), 4.46 (d, J=1.5 Hz, H-7′), 4.60 (dd, J=3.0, 4.0 Hz, H-8b), 5.96 (d, J=1.1 Hz, H-10), 5.96 (dd, J=3.0, 4.0 Hz, H-8c), 6.30–6.45 (br s, H-2′, H-6′), 6.51 (s, H-3), 7.62 (s, H-6). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 35.45 (C-9), 41.34 (C-8a), 46.00 (C-8e), 46.18 (C-7′), 50.99 (C-8d), 52.03 (COOMe), 53.44 (C-8), 56.42 (C-11, C-13), 58.07 (C-8′), 60.97 (C-12), 101.70 (C-10), 106.75 (C-3), 107.08 (C-2′, C-6′), 109.33 (C-6), 127.94 (C-1), 135.34 (C-2), 135.59 (C-8b), 137.29 (C-4′), 138.92 (C-1′), 139.12 (C-8c), 147.69 (C-4), 151.63 (C-5), 153.03 (C-3′, C-5′), 174.43 (C-9′), 197.01 (C-7). HRFABMS *m/z* 492.1786 (calcd for $C_{28}H_{28}O_8$, 492.1784).

3.3.6.3. Adduct (1α-*en*). Mp 156–158 °C (white solid); $[\alpha]^{22}$ +106 (Na 589), +109 (Hg 578), +126 (546), +236 (436) (*c* 1%, $CDCl_3$); IR (film) γ_{max}: 3059, 2953, 1734, 1681, 1617, 1589, 1505, 1480, 1463, 1246, 1128, 1037, 1009, 935 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.30 (d, J=8.8 Hz, H-8e-b), 1.50 (dd, J=3.0, 12.0 Hz, H-9a), 1.70 (d, J=8.5 Hz, H-8e-a), 1.98 (d, J=12 Hz, H-9b), 2.70 (s, H-8d), 2.90 (s, H-8a), 3.54 (d, J=3.5 Hz, H-8′), 3.60 (s, COOMe), 3.77 (s, H-11, H-13), 3.83 (s, H-12), 4.54 (d, J= 3.5 Hz, H-7′), 5.70 (dd, J=2.8, 5.0 Hz, H-8b), 5.9 (dd, J= 3.4 Hz, H-10), 6.13 (dd, J=3.0, 5.0 Hz, H-8c), 6.41 (s, H-2′, H-6′), 6.48 (s, H-3), 7.39 (s, H-6). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 35.65 (C-9), 42.77 (C-8d), 46.18 (C-7′), 47.33 (C-8e), 48.50 (C-8a), 52.07 (COOMe), 54.58 (C-8), 56.42 (C-11, C-13), 58.06 (C-8′), 60.97 (C-12), 101.65 (C-10), 106.31 (C-2′, C-6′), 106.38 (C-6), 109.30 (C-3), 128.55 (C-1), 133.40 (C-8b), 135.90 (C-2), 137.10 (C-4′), 137.76 (C-8c), 139.79 (C-1′), 147.43 (C-4), 151.40 (C-5), 153.21 (C-3′, C-5′), 173.91 (C-9′), 196.48 (C-7). HRFABMS *m/z* 492.1788 (calcd for $C_{28}H_{28}O_8$, 492.1784).

3.3.6.4. Adduct (1β-*ex*). (Amorphous white solid); IR (film) γ_{max}: 3061, 2954, 1736, 1680, 1614, 1588, 1503, 1478, 1460, 1245, 1128, 1036, 1009, 937 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.73 (m, H-8a), 3.06 (d, J=6.0 Hz, H-8′), 3.58 (s, H-14), 3.74 (s, H-11, H-13), 3.82 (s, H-12), 4.49 (d, J=6.0 Hz, H-7′), 5.62 (sa, H-10), 5.97 (dd, J=3.0, 5.0 Hz, H-8b), 6.24 (dd, J=3.0, 5.0 Hz, H-8c), 6.31 (s, H-2′, H-6′), 6.41 (s, H-3), 7.53 (s, H-6). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 35.50 (C-9), 42.56 (C-8d), 46.53 (C-8a), 46.78 (C-7′), 48.11 (C-8e), 51.8 (C-14), 51.86 (C-8), 56.12 (C-11 13), 56.12 (C-8′), 60.83 (C-12), 101.70 (C-10), 105.74 (C-6), 106.29 (C-2′ 6′), 108.97 (C-3), 127.79 (C-1), 134.70 (C-8b), 136.94 (C-4′), 139.0 (C-1′), 139.29 (C-8c), 139.3 (C-2), 147.49 (C-4), 151.82 (C-5), 153.19 (C-3′ 5′), 173.15 (C-9′), 198.91 (C-7). HRFABMS *m/z* 492.1788 (calcd for $C_{28}H_{28}O_8$, 492.1784).

3.3.7. Adducts of Diels–Alder reaction from 1 in presence of $AlCl_3$. To a solution of thuriferic acid (50 mg, 0.12 mmol) in anhydrous CH_2Cl_2 (10 mL) at −78 °C under nitrogen atmosphere, 5 mg of $AlCl_3$ and freshly cracked distilled ciclopentadiene (0.1 mL, 1.3 mmol) was added dropwise. After 4 days the reaction was over and HPLC analysis showed that the reaction products were the same in a similar proportion to that observed without catalyst.

3.3.8. Adducts of Diels–Alder reaction from 2. To a solution of epithuriferic acid (200 mg, 0.49 mmol) in anhydrous CH_2Cl_2 (20 mL) at −18 °C under nitrogen atmosphere, freshly distilled cyclopentadiene (0.1 mL, 1.3 mmol) was added dropwise. After 3 days, HPLC showed that the reaction was over. The reaction mixture was concentrated in vacuo and diluted with EtOAc (20 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (100 mL), dried with anhydrous Na_2SO_4, and evaporated under reduced pressure. The reaction crude was trated with diazomethane and then chromatograpied eluting with hexane/ethyl acetate to give the adducts **2**β-*ex* (98 mg; hexane/AcOEt 2:1) (41.2%) and **2**β-*en* (7 mg; hexane/AcOEt 1:2) (3.0%).

3.3.8.1. Adduct (2β-*ex*). (Yellow oil); $[\alpha]^{22}$ +106 (Na 589), +109 (Hg 578), +126 (546), +236 (436) (*c* 1%, $CDCl_3$); IR (film) γ_{max}: 2970, 2945, 2839, 1731, 1675, 1616, 1590, 1504, 1481, 1461, 1423, 1253, 1126, 1037, 1007, 935, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.20 (dd, J=3.6, 12.0 Hz, H-9b), 1.60 (dd, J=1.0, 8.7 Hz, H-8eb), 1.80 (dd, J=1.0, 8.7 Hz, H-8ea), 2.30 (dd, J=2.5, 12.0 Hz, H-9b), 2.96 (br s, H-8d), 3.13 (br s, H-8a), 3.32 (s, COOMe), 3.36 (d, J=6.2 Hz, H-8′), 3.60–3.85 (br s, H-11, H-13), 3.85 (s, H-12), 4.80 (d, J=6.2 Hz, H-7′), 5.6 (dd, J= 2.9, 5.8 Hz, H-8b), 5.99 (d, J=1.82 Hz, H-10), 6.20–6.40 (br s, H-2′, H-6′), 6.30 (dd, J=2.6, 5.5 Hz, H-8c), 6.43 (s, H-3), 7.44 (s, H-6). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 32.39 (C-9), 42.55 (C-8d), 45.23 (C-8e), 46.86 (C-7′), 49.52 (C-8a), 51.25 (COOMe), 56.17 (C-11, C-13), 56.84 (C-8), 59.14 (C-8′), 60.81 (C-12), 101.57 (C-10), 106.42 (C-3), 108.46 (C-6), 128.24 (C-1), 132.53 (C-8b), 135.96 (C-2), 137.17 (C-1′), 137.39 (C-4′), 141.06 (C-8c), 147.43 (C-5), 151.39 (C-4), 153.32 (C-3′, C-5′), 173.22 (C-9′), 196.84 (C-7), 106.42 br s (C-2′, C-6′). HRFABMS *m/z* 492.1779 (calcd for $C_{28}H_{28}O_8$, 492.1784).

3.3.8.2. Adduct (2β-*en*). (Yellow oil); $[\alpha]^{22}$ +106 (Na 589), +109 (Hg 578), +126 (546), +236 (436) (*c* 1%,

$CDCl_3$); IR (film) γ_{max}: 2984, 2949, 2841, 1732, 1676, 1616, 1590, 1504, 1478, 1462, 1419, 1250, 1127, 1037, 1008, 935, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.61 (dd, $J=2.0$, 11.6 Hz, H-9b), 1.34 (dd, $J=2.0$, 8.4 Hz, H-8ea), 1.68 (d, $J=8.8$ Hz, H-8eb), 2.84 (d, $J=3.6$, 12.0 Hz, H-9b), 2.90 (ba, H-8a), 2.93 (d, $J=5.6$ Hz, H-8′), 2.95 (br s, H-8d), 3.31 (s, COOMe), 3.40–3.84 (br s, H-11, H-13), 3.86 (s, H-12), 4.50 (d, $J=5.6$ Hz, H-7′), 5.70 (dd, $J=2.8$, 5.6 Hz, H-8b), 5.99 (dd, $J=1.2$, 7.0 Hz, H-10), 6.30–6.42 (br s, H-2′, H-6′), 6.40 (dd, $J=2.8$, 5.6 Hz, H-8c), 6.42 (s, H-3), 7.60 (s, H-6). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 33.74 (C-9), 43.37 (C-8d), 46.2 (C-8a), 47.87 (C-8e), 47.89 (C-7′), 51.45 (COOMe), 55.35 (C-8), 56.23 (C-11, C-13), 59.98 (C-8′), 60.9 (C-12), 101.66 (C-10), 105.99 (C-3), 108.72 (C-6), 129.08 (C-1), 131.17 (C-8b), 136.76 (C-2), 137.35 (C-1′), 137.35 (C-4′), 139.26 (C-8c), 147.2 (C-5), 151.46 (C-4), 153.33 (C-3′, C-5′), 173.11 (C-9′), 195.67 (C-7), 105.99 br s (C-2′, C-6′). HRFABMS *m/z* 492.1779 (calcd for $C_{28}H_{28}O_8$, 492.1784).

3.3.9. Adducts of Diels–Alder reaction from 2 in presence of $AlCl_3$. To a solution of epithuriferic acid (50 mg, 0.12 mmol) in anhydrous CH_2Cl_2 (10 mL) at −78 °C under nitrogen atmosphere, 5 mg of $AlCl_3$ and freshly cracked distilled ciclopentadiene (0.1 mL, 1.3 mmol) was added dropwise. After 2 days the reaction was over and HPLC analysis showed a rate between **2**β-*ex*/**2**β-*en* of 3:1.

3.4. X-ray analysis of compound 1α-*ex*

Compound **1**α-*ex*, $C_{28}H_{28}O_8$. Crystal dimensions 0.30×0.40×0.70 nm; crystallizes in monoclinic space group $P2_1$, with $Z=2$, and unit cell parameters, $a=6.7220(13)$ Å, $b=16.706(3)$ Å, $c=11.047(2)$ Å, $\langle=90°$, $\beta=106.51°$ (3), $\gamma=90°$. The unit cell parameters were determined by least squares refinement on the 2θ values of 25 strong well centred reflections in the range 4.17–60.00°. The structure of $C_{28}H_{28}O_8$ was resolved by direct methods and refined in the space group $P2_1$. Resulting absolute structure parameter: 0.09(28). Full crystallographic details have been deposited at the Cambridge Crystallographic Data Centre No. CCDC 286044.

3.5. Molecular modelling

Calculations were performed initially on a Silicon Graphics Indigo computer. Compounds were built using Macromodel V.4.[21] Conformational analysis was performed by a Monte Carlo random search. All freely rotating bonds were searched with MM2[30] minimization to a gradient of less than 0.001 Kcal/mol. Full geometry optimization of the two main conformers of each compound was performed using a molecular orbital ab initio method at the Hartree–Fock level of theory with the 6-31G* basis set using the SPARTAN 04′ Macintosh program distributed by Wavefunction Inc.

Acknowledgements

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Synthesis of analogs of the phenylamino-pyrimidine type protein kinase C inhibitor CGP 60474 utilizing a Negishi cross-coupling strategy

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Abstract—Analogs of 3-{4-[2-(3-chlorophenylamino)-pyrimidin-4-yl]-pyridin-2-yl-amino}-propanol (CGP 60474) were synthesized as useful models for the evaluation of structure–activity relationships of phenylamino-pyrimidine-type protein kinase C inhibitors. The approach involved Pd-assisted cross-coupling as the key step. Negishi-type coupling was performed both with free amino functionalities and Boc-protected amines present and showed that the protection–cross-coupling–deprotection sequence leads to significantly higher yields.

1. Introduction

Protein kinase C (PKC) plays a crucial role in signal transductions, cellular proliferation, and differentiation.[1] PKC is the term for a whole family of cytosolic serine/threonine kinases. The individual PKC subtypes show differences in the mode of activation and in the specificity with respect to protein substrates.[2,3] It has already been shown in animal tumor models, that different inhibitors of PKC show cytostatic activity.[4,5] Therefore, the discovery and the development of specific protein kinase inhibitors will have the potential to define more clearly the respective functional roles of every protein kinase in cells.

Phenylamino-pyrimidines like 3-{4-[2-(3-chlorophenyl-amino)-pyrimidin-4-yl]-pyridin-2-yl-amino}-propanol (CGP 60474)[6] represent a promising class of inhibitors of PKC with a high degree of selectivity versus other serine/threonine and tyrosine kinases and show competitive kinetics relative to ATP. Imatinib (Glivec™),[7] a tyrosine kinase inhibitor with high activity against chronic myeloid leukemia (CML), was introduced as the first commercial product of this type to the pharmaceutical market recently by Novartis (Fig. 1).[8,9]

The preparation of the title compounds was based on a recently published strategy.[10] The scaffold of CGP 60474 and its isomer **I** were prepared in that course via Negishi cross-coupling from the organozinc **1a** as key intermediate (Scheme 1). This method was now extended to the preparation of a series of other analogs. With respect to CGP 60474 one or both of the present heterocycles (pyrimidine and pyridine) were substituted by other ring systems (phenyl or pyridine).

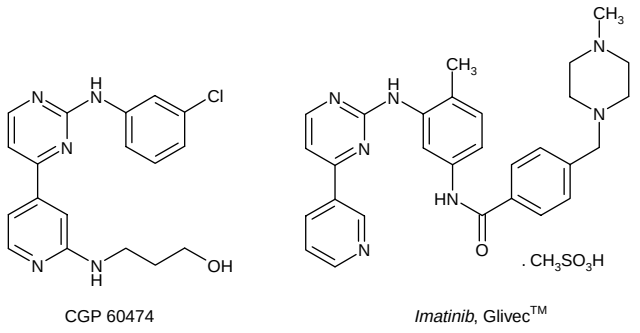

Figure 1. Significant Phenylamino-pyrimidines.

2. Results and discussion

The envisioned target compounds are presented in Figure 2. From the original pyridinyl-pyrimidine motif in CGP 60474 variations of the pyrimidine and pyridine ring were undertaken. The target compounds contain therefore a pyridine–phenyl (**2**), a pyridine–pyridine (**3**), and a pyrimidine–phenyl (**4**) connection.

Keywords: Negishi cross-coupling; Protein kinase inhibitors; Nucleophilic displacement; Phenylamino-pyrimidines.
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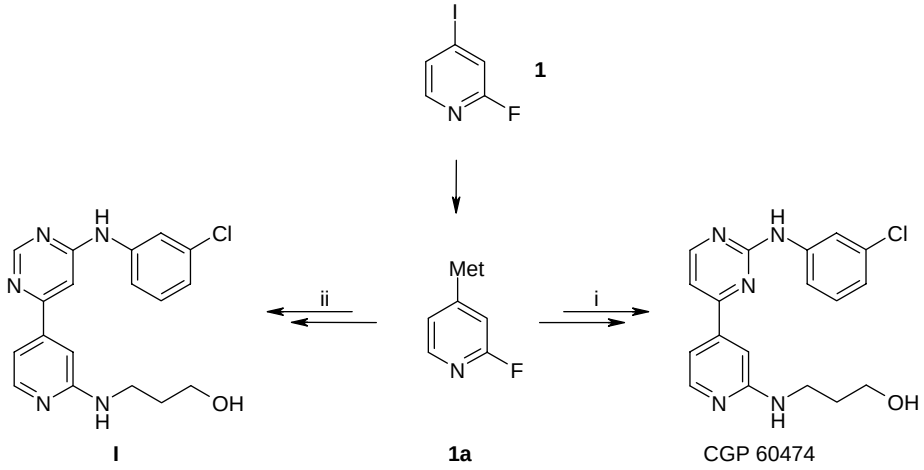


Scheme 1. (i) Three steps, 70% overall yield. (ii) three steps, 33% overall yield.

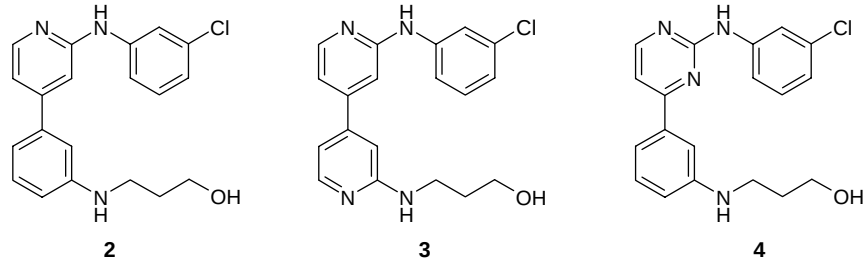
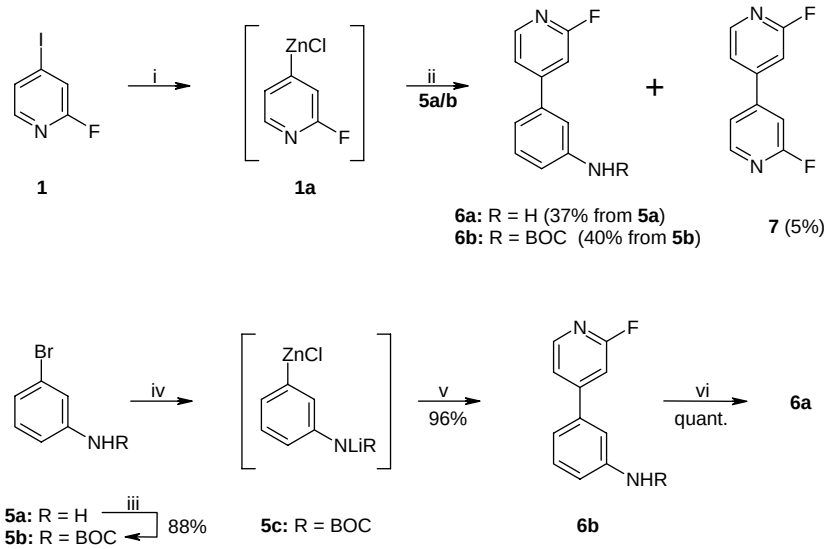


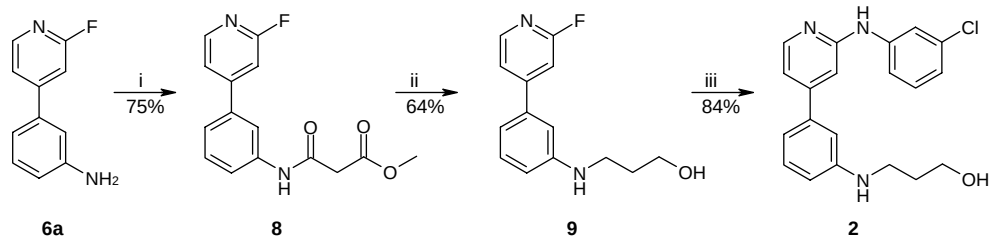
Figure 2. Target compounds **2**, **3**, and **4**.

Compounds **2** and **3** should again be prepared from key intermediate **1a** via a Negishi cross-coupling reaction.[11] For preparation of compound **2**, **1a** was initially reacted with 3-bromoaniline (**5a**) under $Pd(PPh_3)_4$ catalysis. Since in this reaction only 37% of the desired cross-coupling product **6a** were obtained (besides 5% of homo-coupling by-product **7**), suitable protection of the amine function was required. Substrate **5a** was Boc-protected via a standard method[12] in 88% yield to give **5b**. Cross-coupling reaction of this compound yielded again only 40% of the desired product. A possible hydrolysis of **1a** by the NH proton of carbamate **5b** was excluded by initial deprotonation with NaH at room temperature. This led to no improvement in the cross-coupling process but *N*-alkylation of the cross-coupling product by iodobutane was observed to some extent.

Consequently, the cross-coupling strategy was 'inverted' utilizing the organozinc species derived from the Boc-protected aniline **5b** (Scheme 2). The NH-proton of **5b** was removed with MeLi at 15 °C before the metal–halogen



Scheme 2. (i) *n*-BuLi, $ZnCl_2$, THF, −75 °C to rt; (ii) $Pd(PPh_3)_4$, **5a/b**, THF, reflux; (iii) $(Boc)_2O$, THF, reflux; (iv) MeLi, *t*-BuLi, $ZnCl_2$, THF; (v) $Pd(PPh_3)_4$, **1**, THF, reflux; (vi) TFA, CH_2Cl_2, rt.



Scheme 3. (i) $ClCOCH_2COOMe$, NEt_3, THF, 0 °C; (ii) BH_3–THF, THF, 0 °C; (iii) HCl, 3-chloroaniline, water/dioxane 4:1, reflux.

exchange was performed at −75 °C with *n*-BuLi. Subsequent addition of an excess of $ZnCl_2$ gave the desired organozinc derivative, which was then submitted to the cross-coupling reaction. Again, some *N*-alkylated coupling product was detected. This could be avoided by replacing *n*-BuLi with *t*-BuLi. With these modifications the yield of **6b** was optimized to 96%. Subsequent deprotection with TFA gave **6a** quantitatively.

The aminopropanol side chain was introduced via acylation of **6a** in the presence of NEt_3 with methyl chlorocarbonylacetate in dry THF to yield 75% of **8**. Subsequent reduction with BH_3–THF gave **9** in 64% yield (Scheme 3).

The nucleophilic displacement of the fluorine moiety was initially performed by heating **9** in an excess of 3-chloroaniline to 210–230 °C for 17 h to give **2** in 51% yield. Optimized yields were obtained performing the reaction with equimolar amounts of HCl under reflux in a water–dioxane (4/1) mixture for 48 h providing **2** in 84% yield.

2.1. Synthesis of target compound 3

In the case of the target bipyridinyl **3**, a different strategy had to be employed since an immediate cross-coupling reaction of intermediate **1a** with **1** would lead to the symmetric compound **7** with no selectivity for the nucleophilic displacements of the two fluoro atoms. Hence, one nucleophilic displacement had to be performed before the cross-coupling step. The challenge of this approach lies in the similar reactivity of positions 2 and 4 in the halogenated pyridine substrate. Indeed, when the reaction was carried out under standard reaction conditions[13] we did not observe selectivity between these two positions. Instead of the desired mono substituted **10**, di-substituted compound **11** was obtained as the major product only accompanied by starting material. Milder reaction conditions did not give any conversion. An option to overcome this problem is proton catalyzed activation of the pyridine system, which activates the 2-position.[14,15] In an optimization approach aqueous reaction conditions proved to be crucial and compound **10** was obtained in 66% yield only accompanied by small amounts of by-product **11** (9%).

The Negishi reaction was performed with coupling partner **10** and gave an optimized 37% of **13a** besides starting material **10**. Boc-protection of the amine (**12**, 80%) improved substantially the yield in the cross-coupling step giving **13b** in 73%. Cleavage of the Boc group via a standard protocol yielded **13a** quantitatively (Scheme 4).

The aminopropanol side chain was introduced by refluxing **13a** in 3-aminopropanol[10] to give 84% of **3**. We found that **3** can be accessed directly from **13b** under the conditions of the nucleophilic displacement in 92% yield due to the thermal instability of the Boc group.

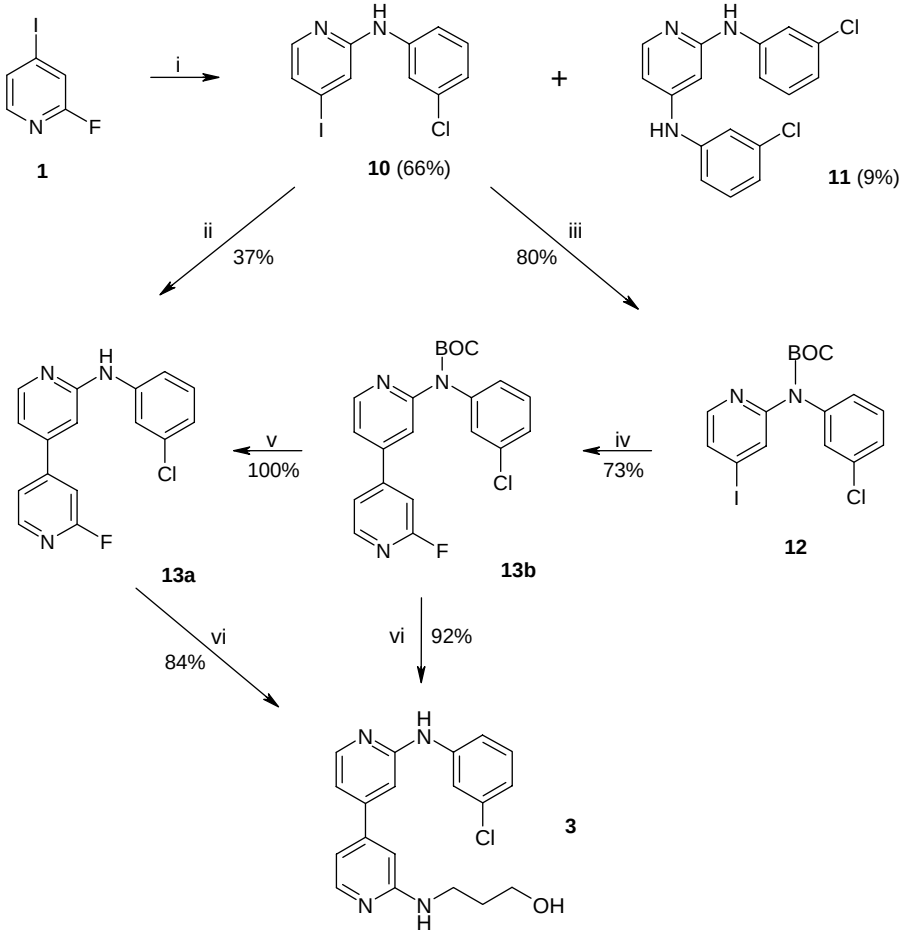
2.2. Synthesis of target compound 4

The synthesis of **4** is very similar to the route finally applied to the preparation of target compound **2**. In this case, 2,4-dichloropyrimidine was cross-coupled with **5c** under Negishi conditions to give 75% of desired product **14** and 9% of by-product **15**, which is formed in a follow-up reaction of **14**. In contrast to aromatic organozinc species,[16,17] aliphatic organozinc compounds can undergo a cross-coupling reaction in the 2-position of the pyrimidine system under thermal conditions. The formation of **15** can therefore be explained by a cross-coupling reaction of methylzinc chloride (from excess of MeLi and $ZnCl_2$) with **14**. The structure of **14** was confirmed via 2D NMR experiments (NOE, NOESY). Recently, we have demonstrated that the 2-position is accessible for cross-coupling also with aromatic organozincs under microwave conditions.[18]

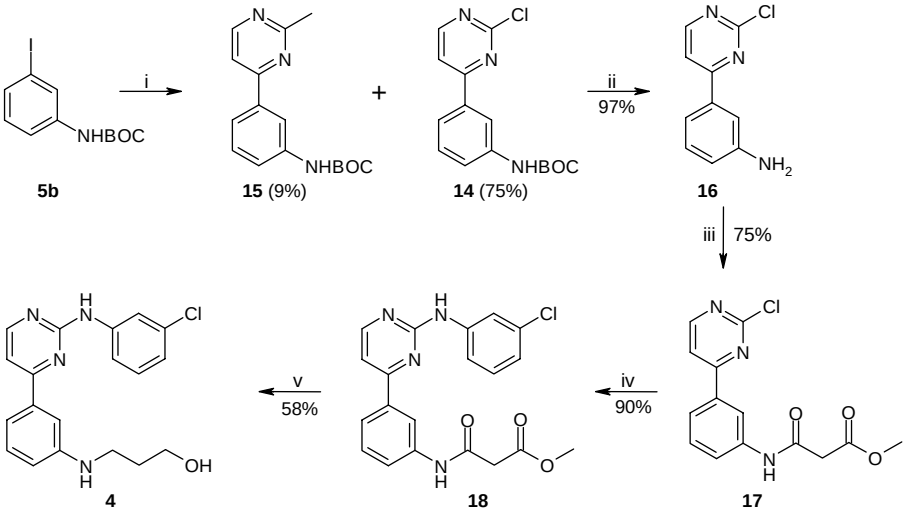
The Boc group was then cleaved to give **16** (97%), followed by introduction of the side chain as already described for the synthesis of **2**. Acylation of the amine function gave 75% of **17**. Reduction of **17** with BH_3–THF failed to give the desired compound even under very mild reaction conditions (ice cooling) only leading to decomposition of the heterocyclic system. In order to decrease the high reactivity of the 2-position in the pyrimidine part 3-chloroaniline was introduced prior to the reduction of the side chain in this series. The nucleophilic displacement was performed in dry dioxane under *p*-TSA-catalysis at reflux and yielded **18** in 90%. The reduction with BH_3–THF at this stage finally gave **4** in a satisfactory 58% yield (Scheme 5).

3. Conclusion

Based on the synthesis of CGP 60474 we developed suitable reaction sequences for the formation of all three target compounds (**2**, **3**, and **4**). Compound **2** was synthesized starting from 3-bromoaniline and 2-fluoro-4-iodopyridine (**1**, prepared from commercially available 2-fluoropyridine in two steps and improved 88% yield compared to the literature[19,20]) in six steps with 34% overall yield, compound **4** was obtained in five steps from



Scheme 4. (i) HCl, 3-chloroaniline, water/dioxane 4:1, reflux; (ii) (1) *n*-BuLi, $ZnCl_2$, THF, −75 °C to rt; than $Pd(PPh_3)_4$, **10**, THF, reflux; (iii) NaH, $(Boc)_2O$, THF, reflux; (iv) **1**, *n*-BuLi, $ZnCl_2$, THF, −75 °C to rt; (2) $Pd(PPh_3)_4$, **12**, THF, reflux; (v) TFA, CH_2Cl_2, rt; (vi) 3-aminopropanol, reflux.



Scheme 5. (i) (1) *n*-BuLi, $ZnCl_2$, THF, −75 °C to rt; (2) 2,4-dichloropyrimidine, $Pd(PPh_3)_4$, THF, reflux; (ii) TFA, CH_2Cl_2, rt; (iii) $ClCOCH_2COOMe$, NEt_3, THF, 0 °C; (iv) 3-chloroaniline, *p*-TSA·H_2O, dioxane, reflux; (v) BH_3–THF, THF, 0 °C.

3-bromoaniline and 2,4-dichloropyrimidine with 26% overall yield, and compound **3** was formed starting from **1** in four steps and 35% overall yield. The results of the biological screening of the title compounds showed no improved fungicidal activity compared to CGP 60474 and will be published elsewhere.

4. Experimental

4.1. General

Melting points were determined using a Kofler-type Leica Galen III micro hot stage microscope and are uncorrected.

Combustion analysis was carried out in the Microanalytical Laboratory, Institute of Physical Chemistry, University of Vienna. Flash column chromatography was performed on silica gel 60 from Merck 40–63 μm). NMR-spectra were recorded from $CDCl_3$ or d_6-DMSO solutions on a Bruker AC 200 (200 MHz) or Bruker Avance UltraShield 400 (400 MHz) spectrometer and chemical shifts are reported in ppm using TMS as internal standard.

4.1.1. 3-{3-[2-(3-Chlorophenylamino)-pyridin-4-yl]-phenylamino}-propanol (2). Substrate **9** (0.50 g, 2.03 mmol, 1 equiv), 1.6 N HCl (1.3 mL, 2.03 mmol, 1 equiv) and 3-chloroaniline (1.5 mL, 14.2 mmol, 7 equiv) were dissolved in 20 mL of a water–dioxane mixture (4/1) and refluxed for 48 h. The solution was poured onto water, adjusted to basic pH with saturated aqueous Na_2CO_3 solution, and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (LP/EtOAc 2:1→1:2) to give **2** as a brown oil (0.60 g, 1.70 mmol, 84%); ^{1}H NMR (d_6-DMSO, 200 MHz): δ 1.79 (quin, ^3J=6.6 Hz, 2H), 3.14 (m, 2H), 3.55 (m, 2H), 4.58 (br s, 1H), 5.73 (br s, 1H), 6.68 (d, ^3J=7.6 Hz, 1H), 6.75–6.95 (m, 3H), 7.02 (d, ^3J=5.5 Hz, 1H), 7.08 (s, 1H), 7.20 (t, ^3J=7.6 Hz, 1H), 7.27 (t, ^3J=8.5 Hz, 1H,), 7.56 (d, 1H), 8.09 (s, 1H), 8.24 (d, 1H), 9.37 (s, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz): δ 32.0 (t), 40.0 (t), 58.8 (t), 108.3 (d), 109.6 (d), 112.9 (d), 113.2 (d), 113.8 (d), 116.2 (d), 117.0 (d), 119.7 (d), 129.7 (d), 130.1 (d), 133.2 (s), 138.6 (s), 143.4 (s), 147.7 (d), 149.7 (s, 2C), 156.1 (s).

4.1.2. 3-{[2′-(3-Chlorophenylamino)-[4,4′]-bipyridinyl-2-yl]-amino}-propanol (3). Substrate **13b** (0.50 g, 1.25 mmol) or **13a** (0.20 g, 0.67 mmol) were refluxed in an excess of 3-aminopropanol (20 mL) for 3 h. The mixture was cooled with ice and water was added (80 mL). The crude product, precipitated as sticky oil, was dissolved in ethyl acetate and subsequently washed with water (2×) and brine. The organic solution was dried over Na_2SO_4 and the solvent removed in vacuo to afford **3** as yellow crystals (0.41 g, 1.16 mmol, 92% in the case of starting material **13b**; 0.20 g, 0.56 mmol, 84% in the case of starting material **13a**); mp 138–140 °C (EtOAc); ^{1}H NMR (d_6-DMSO, 200 MHz): δ 1.70 (quin, ^3J=6.6 Hz, 2H), 3.35 (m, 2H), 3.50 (q, ^3J=6.6 Hz, 1H), 4.53 (t, ^3J=6.6 Hz, 1H), 6.63–6.80 (m, 3H), 6.91 (m, 1H), 7.02 (dd, ^3J=5.3 Hz, ^4J=1.1 Hz, 1H), 7.09 (s, 1H), 7.27 (t, ^3J=8.0 Hz, 1H), 7.52 (m, 1H), 8.00–8.13 (m, 2H), 8.28 (d, ^3J=5.5 Hz, 1H), 9.40 (s, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz): δ 32.4 (t), 38.1 (t), 58.7 (t), 104.9 (d), 108.3 (d), 109.0 (d), 112.6 (d), 116.3 (d), 117.1 (d), 119.9 (d), 130.1 (d), 133.2 (s), 143.2 (s), 145.8 (s), 147.2 (s), 148.1 (d), 148.7 (d), 156.1 (s), 159.8 (s). Anal. Calcd for $C_{19}H_{19}ClN_4O$ (354.84): C, 64.31; H, 5.40; N, 15.79. Found: C, 64.18; H, 5.30; N, 15.53.

4.1.3. 3-{3-[2-(3-Chlorophenylamino)-pyrimidin-4-yl]-phenylamino}-propanol (4). BH_3–THF complex (23.5 mL, 1 M in THF, 23.5 mmol, 10.7 equiv) was cooled to 0 °C and **18** (1.00 g, 2.52 mmol, 1 equiv) in dry THF (20 mL) was added dropwise within 15 min. The mixture was stirred for 15 min at 0 °C and for 5 h at room temperature. 6 N HCl (20 mL) was added and the mixture was boiled for 5 min. After cooling to room temperature, water was added and the solution was adjusted to basic pH with saturated aqueous Na_2CO_3 solution. The mixture was extracted with ethyl acetate, the combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude material was purified by column chromatography (LP/EtOAc 1:1→1:2) to give **4** as yellow crystals (0.52 g, 1.47 mmol, 58%); mp 100–102 °C (DIPE); ^{1}H NMR (d_6-DMSO, 200 MHz): δ 1.78 (quin, ^3J=6.6 Hz, 2H), 3.18 (m, 2H), 3.59 (t, ^3J=6.6 Hz, 2H), 4.52 (br s, 1H), 5.73 (t, ^3J=6.6 Hz, 1H), 6.78 (m, 1H), 6.99 (m, 1H), 7.15–7.45 (m, 5H), 7.78 (m, 1H), 8.11 (m, 1H), 8.56 (d, ^3J=5.6 Hz, 1H), 9.84 (s, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz): δ=31.9 (t), 40.0 (t), 58.7 (t), 108.6 (d), 109.2 (d), 114.3 (d), 115.3 (d), 117.0 (d), 117.8 (d), 120.6 (d), 129.2 (d), 130.0 (d), 133.0 (s), 137.2 (s), 142.7 (s), 149.5 (s), 158.7 (d), 159.8 (s), 164.6 (s). Anal. Calcd for $C_{19}H_{19}ClN_4O$ (354.84): C, 64.31; H, 5.40; N, 15.79. Found: C, 64.06; H, 5.60; N, 15.66.

4.1.4. *N*-(3-Bromophenyl)-carbamic acid 1,1-dimethylethyl ester (5b). 3-Bromoaniline (7.00 g, 40.7 mmol, 1 equiv) and $(Boc)_2O$ (9.16 g, 40.7 mmol, 1 equiv) were refluxed in dry THF (120 mL) for 65 h. The solvent was evaporated in vacuo and the crude product was washed twice with cold LP to afford **8** as colorless crystals (9.72 g, 35.7 mmol, 88%); mp 85–86 °C (LP); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.51 (s, 9H), 6.54 (br s, 1H), 7.06–7.26 (m, 3H), 7.66 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 28.2 (q), 80.9 (*s*), 116.9 (d), 121.3 (d), 122.6 (s), 125.8 (d), 130.1 (d), 139.7 (s), 152.4 (s).

4.1.5. 3-(2-Fluoropyridin-4-yl)-phenylamine (6a). *Method A*. Compound **6b** (6.17 g, 21.4 mmol, 1 equiv) was suspended in dry dichloromethane (80 mL) and trifluoroacetic acid (25 mL, 15.7 equiv) was added. The mixture was stirred for 2 h at room temperature. The solution was poured onto water, adjusted to basic pH with saturated aqueous Na_2CO_3 solution, and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to afford **6a** as yellow crystals (4.02 g, 21.4 mmol, 100%);

Method B. 2-Fluoro-4-iodo-pyridine **1** (0.97 g, 4.36 mmol, 1.5 equiv) was dissolved in dry THF (30 mL) and *n*-BuLi in hexane (2.1 mL, 2.29 M, 4.80 mmol, 1.65 equiv) was added at −75 °C. After stirring for 30 min, freshly dried $ZnCl_2$ (0.59 g, 4.36 mmol, 1.5 equiv) in dry THF (5 mL) was added. The mixture was allowed to warm to room temperature. $Pd(PPh_3)_4$ (0.03 g, 0.03 mmol, 0.01 equiv) and 3-bromoaniline (0.50 g, 2.91 mmol, 1 equiv) in dry THF (10 mL) were added and the mixture was refluxed for 4 h. The mixture was poured onto water, adjusted to basic pH with 2 N NaOH solution, and extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was subjected to column chromatography (LP/EtOAc 7:1) to afford **6a** as yellow crystals (0.20 g, 1.06 mmol, 37%); mp 110–112 °C (methanol); ^{1}H NMR (d_6-DMSO, 200 MHz): δ 5.32 (br s, 2H), 6.68–6.75 (m, 1H), 6.88–6.93 (m, 1H), 6.98 (t, ^4J=1.8 Hz, 1H), 7.17 (t, ^3J=8.0 Hz, 1H), 7.32 (s, 1H), 7.47–7.52 (m, 1H), 8.25 (d, ^3J=5.6 Hz 1H); ^{13}C NMR (d_6-DMSO, 50 MHz): δ 106.2 (d, $^2J_{CF}$=38 Hz), 112.0 (d),

114.5 (d), 115.5 (d), 119.4 (d, $^4J_{CF}=4$ Hz), 129.8 (d), 136.7 (s, $^4J_{CF}=3$ Hz), 147.9 (d, $^3J_{CF}=16$ Hz), 149.4 (s), 154.2 (s, $^3J_{CF}=8$ Hz), 164.0 (s, $^1J_{CF}=234$ Hz). Anal. Calcd for $C_{11}H_9FN_2$ (188.20): C, 70.20; H, 4.82; N, 14.88. Found: C, 69.91; H, 4.74; N, 14.81.

4.1.6. *N*-[3-(2-Fluoropyridin-4-yl)-phenyl]-carbamic acid 1,1-dimethylethyl ester (6b). Substrate **5b** (6.10 g, 22.4 mmol, 1 equiv) was dissolved in dry THF (200 mL) and MeLi in diethyl ether (17.1 mL, 1.44 M, 24.7 mmol, 1.1 equiv) was added at room temperature. After 30 min the mixture was cooled to −85 °C and *t*-BuLi in pentane (37.1 mL, 1.33 M, 49.3 mmol, 2.2 equiv) was added. The solution was stirred at −85 °C for 30 min. Then freshly dried $ZnCl_2$ (10.1 g, 74.0 mmol, 3.3 equiv) in dry THF (80 mL) was added. After 30 min the reaction mixture was allowed to warm to room temperature. $Pd(PPh_3)_4$ (0.25 g, 0.22 mmol) and **1** (5.00 g, 22.4 mmol, 1 equiv) in dry THF (25 mL) were added and the mixture was refluxed for 1 h. The cooled solution was poured onto a solution of EDTA (22 g) in water (300 mL), and adjusted to basic pH with saturated aqueous Na_2CO_3 solution. The mixture was extracted with diethyl ether, the combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure to give **9** as yellow crystals (6.18 g, 21.4 mmol, 96%); mp 181–184 °C (DIPE); ^{1}H NMR (d_6-DMSO, 200 MHz): δ 1.52 (s, 9H), 7.30–7.65 (m, 3H), 7.48–7.65 (m, 2H), 7.92 (s, 1H), 8.30 (d, $^3J=5.3$ Hz, 1H), 9.52 (s, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz): δ 28.1 (q), 79.3 (*s*), 106.4 (d, $^2J_{CF}=39$ Hz), 116.4 (d), 119.5 (d), 119.6 (d, $^4J_{CF}=4$ Hz), 120.7 (d), 129.6 (d), 136.5 (s, $^4J_{CF}=4$ Hz), 140.4 (s), 148.1 (d, $^3J_{CF}=16$ Hz), 152.8 (s), 153.4 (s, $^3J_{CF}=8$ Hz), 164.0 (s, $^1J_{CF}=235$ Hz). Anal. Calcd for $C_{16}H_{17}FN_2O_2$ (288.32): C, 66.65; H, 5.94; N, 9.72. Found: C, 66.52; H, 5.78; N, 9.56.

4.1.7. 2,2′-Difluoro-[4,4′]-bipyridinyl (7).[21] Compound **7** was formed as by-product during the formation of **6a** according to method B. Colorless crystals (20 mg, 0.10 mmol, 5%); R_f 0.60 (LP/EtOAc 2:1). Anal. Calcd for $C_{10}H_6F_2N_2$ (192.17): C, 62.50; H, 3.15; N, 14.58. Found: C, 62.21; H, 3.29; N, 14.33.

4.1.8. 3-{[3-(2-Fluoropyridin-4-yl)-phenyl]-amino}-3-oxopropanoic acid methyl ester (8). Substrate **6a** (2.00 g, 10.6 mmol, 1 equiv) and triethylamine (1.18 g, 11.7 mmol, 1.1 equiv) were dissolved in dry THF (30 mL) and cooled to 0 °C. 3-Chloro-3-oxopropanoic acid methyl ester (1.60 g, 11.7 mmol, 1.1 equiv) in dry THF (3 mL) was added dropwise within 10 min. After stirring for 2 h at 0 °C the mixture was poured onto water and extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product was purified by column chromatography (LP/EtOAc 1:1) to yield **8** as orange crystals (2.31 g, 8.01 mmol, 75%); mp 72–75 °C (EtOAc); ^{1}H NMR (d_6-DMSO, 200 MHz): δ 3.55 (s, 2H), 3.68 (s, 3H), 7.40 (s, 1H), 7.47–7.56 (m, 2H), 7.56–7.63 (m, 1H), 7.64–7.72 (m, 1H), 8.03 (s, 1H), 8.32 (d, $^3J=5.1$ Hz, 1H), 10.4 (s, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz): δ 43.5 (t), 52.0 (q), 106.6 (d, $^2J_{CF}=39$ Hz), 117.5 (d), 119.6 (d, $^4J_{CF}=4$ Hz), 120.5 (d), 122.3 (d), 129.8 (d), 136.7 (s, $^4J_{CF}=3$ Hz), 139.6 (s), 148.2 (d, $^3J_{CF}=16$ Hz), 153.1 (s, $^3J_{CF}=8$ Hz), 164.0 (s, $^1J_{CF}=235$ Hz), 164.4 (s), 168.1 (s). Anal. Calcd for $C_{15}H_{13}FN_2O_3$ (288.28): C, 62.50; H, 4.55; N, 9.72. Found: C, 62.27; H, 4.64; N, 9.64.

4.1.9. 3-[3-(2-Fluoropyridin-4-yl)-phenylamino]-propanol (9). BH_3–THF complex (25.5 mL, 1 M in THF, 25.5 mmol, 3.67 equiv) was cooled to 0 °C and **8** (2.00 g, 6.94 mmol, 1 equiv) in dry THF (30 mL) was added dropwise within 15 min. After additional stirring for 15 min at 0 °C, the mixture was refluxed for 2 h. After cooling to room temperature water was added and the mixture was stirred for 1 h. The solution was adjusted to basic pH with saturated aqueous Na_2CO_3 solution. The mixture was extracted with diethyl ether, the combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (LP/EtOAc 1:1 → 1:2) to give **9** as yellow crystals (1.10 g, 4.47 mmol, 64%); mp 88–90 °C (DIPE); ^{1}H NMR (d_6-DMSO, 200 MHz): δ 1.75 (quin, $^3J=6.6$ Hz, 2H), 3.18 (q, $^3J=6.6$ Hz, 2H), 3.58 (q, $^3J=6.6$ Hz, 2H), 4.52 (t, $^3J=6.6$ Hz, 1H), 5.76 (t, $^3J=6.6$ Hz, 1H), 6.70 (d, $^3J=8.2$ Hz, 1H), 6.90–7.00 (m, 2H), 7.22 (t, $^3J=8.2$ Hz, 1H), 7.38 (s, 1H), 7.55–7.60 (m, $^3J=5.1$ Hz, $^5J=1.5$ Hz, 1H), 8.25 (d, $J=5.1$ Hz, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz): δ 32.0 (t), 39.8 (t), 58.7 (t), 106.3 (d, $^2J_{CF}=38$ Hz), 109.7 (d), 113.7 (d), 114.1 (d), 119.6 (d, $^4J_{CF}=4$ Hz), 129.7 (d), 136.8 (s, $^4J_{CF}=3$ Hz), 147.9 (d, $^3J_{CF}=16$ Hz), 149.8 (s), 154.3 (s, $^3J_{CF}=8.4$ Hz), 164.0 (s, $^1J_{CF}=234$ Hz). Anal. Calcd for $C_{14}H_{15}FN_2O$ (246.28): C, 68.28; H, 6.14; N, 11.37. Found: C, 68.08; H, 6.24; N, 11.26.

4.1.10. *N*-(3-Chlorophenyl)-4-iodo-2-pyridinamine (10). Substrate **1** (4.00 g, 17.9 mmol, 1.2 equiv), 3-chloroaniline (1.91 g, 14.9 mmol, 1 equiv) and 1.6 N HCl (9.3 mL, 14.9 mmol, 1 equiv) were dissolved in a water–dioxane mixture (9/1, 250 mL) and refluxed for 22 h. Dioxane (30 mL) was added and the mixture was refluxed for further 24 h. The solvents were evaporated and the residue was suspended in a saturated aqueous Na_2CO_3 solution (150 mL). After extraction with diethyl ether, the combined organic layers were dried over Na_2SO_4 and concentrated. The crude material was triturated with LP–EtOAc (4/1) to give crystalline **10** (2.85 g), which was dried in vacuo. The mother liquor was concentrated and the residue was purified by column chromatography (LP/EtOAc 4:1 → 1:1) to obtain a second fraction of **10** (0.40 g). Total yield: 3.25 g (9.83 mmol, 66%) of **10** as colorless crystals; mp 127–129 °C (LP); R_f 0.40 (LP/EtOAc 4:1); ^{1}H NMR (d_6-DMSO, 400 MHz): δ 6.94 (ddd, $^3J=8.1$ Hz, $^4J=1.8$, 1.2 Hz, 1H), 7.16 (dd, $^3J=5.5$ Hz, $^4J=1.5$ Hz, 1H), 7.23–7.34 (m, 2H), 7.45 (ddd, $^3J=8.1$ Hz, $^4J=1.8$, 1.2 Hz, 1H), 7.91 (d, $J=5.5$ Hz, 1H), 7.96 (t, $J=1.8$ Hz, 1H), 9.32 (s, 1H); ^{13}C NMR (d_6-DMSO, 100 MHz): δ 106.3 (s), 116.5 (d), 117.3 (d), 119.5 (d), 120.3 (d), 123.2 (d), 130.1 (d), 133.1 (s), 142.5 (s), 147.8 (d), 155.7 (s). Anal. Calcd for $C_{11}H_8ClIN_2$ (330.56): C, 39.97; H, 2.44; N, 8.47. Found: C, 40.25; H, 2.61; N, 8.31.

4.1.11. *N*2,*N*4-Bis-(3-chlorophenyl)-pyridine-2,4-diamine (11). Formed as by-product during the formation of **10**. 0.22 g (0.60 mmol, 9%); ^{1}H NMR (d_6-DMSO, 400 MHz): δ 6.43 (dd, 1H, $^3J=6.0$ Hz, $^4J=1.8$ Hz), 6.51 (d, $J=1.8$ Hz, 1H), 6.85 (ddd, 1H, $^3J=8.2$ Hz, $^4J=2.4$,

1.4 Hz), 7.03 (ddd, 1H, ^3J=8.2 Hz, ^4J=2.4, 1.4 Hz), 7.13–7.28 (m, 3H), 7.35 (t, 1H, ^3J=8.2 Hz), 7.40–1.48 (m, 1H), 7.95 (d, ^3J=6.0 Hz, 1H), 8.02 (t, ^4J=2.4 Hz, 1H), 8.82 (s, 1H), 9.02 (s, 1H); ^{13}C NMR (d_6-DMSO, 100 MHz): δ 94.3 (d), 104.5 (d), 116.0 (d), 116.9 (d), 117.8 (d), 118.8 (d), 119.2 (d), 119.9 (d), 129.8 (d), 130.7 (d), 133.1 (s), 133.7 (s), 142.6 (s), 143.6 (s), 147.9 (s), 150.3 (s), 156.6 (d). Anal. Calcd for $C_{17}H_{13}Cl_2N_3\cdot HCl$ (366.68): C, 55.69; H, 3.85; N, 11.46. Found: C, 55.83; H, 3.87; N, 11.17.

4.1.12. *N*-(3-Chlorophenyl)-*N*-(4-iodopyridin-2-yl)-carbamic acid 1,1-dimethylethyl ester (12). Substrate **10** (3.50 g, 10.6 mmol, 1 equiv) was dissolved in dry THF (50 mL), deprotonated with NaH (0.30 g, 12.7 mmol, 1.2 equiv) and treated with $(Boc)_2O$ (2.86 g, 12.7 mmol, 1.2 equiv) in dry THF (10 mL). The mixture was refluxed for 3 h, poured onto water, and extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (LP/EtOAc 8:1) to give **12** as colorless crystals (3.65 g, 8.48 mmol, 80%); mp 91–94 °C (EtOAc); ^{1}H NMR (d_6-DMSO, 200 MHz): δ 1.39 (s, 9H), 7.11–7.19 (m, 1H), 7.28–7.40 (m, 3H), 7.63 (dd, 1H, ^3J=5.1 Hz, ^4J=1.3 Hz), 8.01 (d, ^3J=5.1 Hz, 1H), 8.08 (m, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz): δ 27.6 (q), 81.7 (*s*), 107.0 (s), 126.4 (d), 126.6 (d), 127.7 (d), 129.2 (d), 129.6 (d), 130.2 (d), 132.7 (s), 142.4 (s), 148.5 (d), 152.2 (s), 154.5 (s). Anal. Calcd for $C_{16}H_{16}ClIN_2O_2$ (430.67): C, 44.62; H, 3.74; N, 6.50. Found: C, 44.80; H, 3.79; N, 6.40.

4.1.13. *N*-(3-Chlorophenyl)-*N*-(2′-fluoro-[4,4′]-bipyridinyl-2-yl)amine (13a). *Method A*. Substrate **13b** (0.80 g, 2.00 mmol, 1 equiv) was suspended in dry dichloromethane (30 mL) and trifluoroacetic acid (1.5 mL, 2.02 mmol, 1.01 equiv) was added. The mixture was stirred at room temperature for 3 h, poured onto water, adjusted to basic pH with saturated aqueous Na_2CO_3 solution and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give **6** as yellow crystals (0.60 g, 100%).

Method B. *n*-BuLi in hexane (0.85 mL, 2.13 M, 1.81 mmol, 2 equiv) was added to **1** (0.40 g, 1.81 mmol, 2 equiv) in dry THF (100 mL) at −75 °C within 10 min. After 30 min freshly dried $ZnCl_2$ (0.25 g, 1.81 mmol, 2 equiv) in dry THF (5 mL) was added. The reaction mixture was warmed to room temperature and $Pd(PPh_3)_4$ (0.06 g, 0.05 mmol, 0.055 equiv) and **10** (0.30 g, 0.91 mmol, 1 equiv) in dry THF (15 mL) were added. After refluxing for 3 h, the mixture was stirred another 48 h at room temperature. More $Pd(PPh_3)_4$ (0.05 g, 0.04 mmol, 0.05 equiv) was added and the solution was refluxed for 2 h. The mixture was poured onto water, adjusted to basic pH with saturated aqueous Na_2CO_3 solution, and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by column chromatography (LP/EtOAc 7:1) to afford **13a** as yellow crystals (0.10 g, 0.33 mmol, 37%); mp 158–160 °C (methanol); ^{1}H NMR (d_6-DMSO, 200 MHz): δ 6.90–6.96 (m, 1H), 7.17 (s, 1H), 7.21 (dd, ^3J=5.5 Hz, ^4J=1.4 Hz, 1H), 7.28 (t, ^3J=8.2 Hz, 1H), 7.47–7.57 (m, 2H), 7.67 (dt, ^3J=5.5 Hz, ^4J=1.4 Hz, 1H), 8.03 (t, ^4J=2.1 Hz, 1H), 8.34 (d, ^3J=5.5 Hz, 1H), 8.38 (d, ^3J=5.5 Hz, 1H), 9.48 (s, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz): δ 107.0 (d, $^2J_{CF}$=39 Hz), 108.8 (d), 112.6 (d), 116.4 (d), 117.2 (d), 119.6 (d, $^4J_{CF}$=4 Hz), 120.1 (d), 130.1 (d), 133.1 (s), 142.9 (s), 144.6 (s, $^4J_{CF}$=3 Hz), 148.4 (d), 148.5 (d, $^3J_{CF}$=15 Hz), 151.1 (s, $^3J_{CF}$=8 Hz), 156.2 (s), 164.0 (s, $^1J_{CF}$=235 Hz). Anal. Calcd for $C_{16}H_{11}ClFN_3$ (299.74): C, 64.12; H, 3.70; N, 14.02. Found: C, 63.97; H, 3.68; N, 13.84.

4.1.14. *N*-(3-Chlorophenyl)-*N*-(2′-fluoro-[4,4′]-bipyridinyl-2-yl)-carbamic acid 1,1-dimethylethyl ester (13b). *n*-BuLi in hexane (4.2 mL, 2.29 M, 9.54 mmol, 1.48 equiv) was added to 2-fluoro-4-iodo-pyridine (1.93 g, 8.67 mmol, 1.33 equiv) in dry THF (100 mL) at −75 °C within 10 min. After 30 min freshly dried $ZnCl_2$ (1.18 g, 9.54 mmol, 1.48 equiv) in dry THF (10 mL) was added. The reaction mixture was warmed to room temperature and $Pd(PPh_3)_4$ (0.04 g, 0.003 mmol, 0.0005 equiv) and **12** (2.80 g, 6.50 mmol, 1 equiv) in dry THF (15 mL) were added. After refluxing for 1.5 h the solution was poured onto water, adjusted to basic pH with saturated aqueous Na_2CO_3 solution, and extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was recrystallized from EtOAc to afford **13b** as colorless crystals (1.90 g, 4.75 mmol, 73%); mp 172–175 °C (EtOAc); ^{1}H NMR (d_6-DMSO, 200 MHz): δ 1.40 (s, 9H), 7.19 (dt, ^3J=8.2 Hz, ^4J=2.0 Hz, 1H), 7.26–7.42 (m, 3H), 7.68 (s, 1H), 7.72 (dd, ^3J=5.2 Hz, ^4J=1.5 Hz, 1H), 7.77–7.83 (m, 1H), 8.07 (s, 1H), 8.41 (d, ^3J=5.2 Hz, 1H), 8.49 (d, ^3J=5.2 Hz, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz): δ 27.8 (q), 81.7 (s), 107.4 (d, $^2J_{CF}$=39 Hz), 119.1 (d), 119.3 (d), 119.9 (d, $^4J_{CF}$=4 Hz), 126.3 (d), 126.4 (d), 127.4 (d), 130.3 (d), 132.8 (s), 142.8 (s), 145.3 (s), 148.8 (d, $^3J_{CF}$=16 Hz), 149.4 (d), 150.1 (s, $^3J_{CF}$=8 Hz), 152.5 (s), 155.5 (s), 164.0 (s, $^1J_{CF}$=239 Hz). Anal. Calcd for $C_{21}H_{19}ClFN_3O_2$ (399.85): C, 63.08; H, 4.79; N, 10.51. Found: C, 62.82; H, 4.78; N, 10.41.

4.1.15. *N*-[3-(2-Chloropyrimidin-4-yl)-phenyl]-carbamic acid 1,1-dimethylethyl ester (14). Substrate **5b** (4.57 g, 16.8 mmol, 1 equiv) was dissolved in dry THF (120 mL) and MeLi in diethyl ether (12.8 mL, 1.44 M, 18.5 mmol, 1.1 equiv) was added dropwise at +15 °C. After stirring for 30 min, the mixture was cooled to −85 °C and *t*-BuLi in pentane (27.6 mL, 1.34 M, 37.0 mmol, 2.2 equiv) was added dropwise. The solution was stirred for 30 min at −75 °C and freshly dried $ZnCl_2$ (7.55 g, 55.4 mmol, 3.3 equiv) in dry THF (80 mL) was added. The mixture was stirred for further 30 min and then allowed to warm to room temperature. $Pd(PPh_3)_4$ (0.19 g, 0.16 mmol, 0.01 equiv) and 2,4-dichloropyrimidine (2.50 g, 16.8 mmol, 1 equiv) in dry THF (15 mL) were added, and the mixture was refluxed for 1 h. The solution was poured onto a solution of EDTA (17 g) in water (200 mL), which was adjusted to basic pH with saturated aqueous Na_2CO_3 solution, and extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (LP/EtOAc 3:1→1:1) to give **14** as yellow crystals (3.87 g, 12.7 mmol, 75%); mp 155–157 °C (DIPE); ^{1}H NMR (d_6-DMSO, 200 MHz): δ 1.24 (s, 9H), 7.19 (t, ^3J=8.5 Hz, 1H), 7.38 (d, ^3J=8.5 Hz, 1H), 7.50 (d, ^3J=8.5 Hz, 1H), 7.75 (d, ^3J=5.5 Hz, 1H), 8.10 (s, 1H), 8.54 (d, ^3J=5.5 Hz, 1H), 9.32 (s, 1H); ^{13}C

NMR (d_6-DMSO, 50 MHz): δ 28.1 (q), 79.4 (*s*), 116.1 (d), 116.6 (d), 121.2 (d), 121.7 (d), 129.5 (d), 135.1 (s), 140.5 (s), 152.8 (s), 160.5 (s), 161.2 (d), 166.3 (s). Anal. Calcd for $C_{15}H_{16}ClN_3O_2$ (305.76): C, 58.92; H, 5.27; N, 13.74. Found: C, 58.71; H, 5.38; N, 13.53.

4.1.16. *N*-[3-(2-Methylpyrimidin-4-yl)-phenyl]-carbamic acid 1,1-dimethylethyl ester (15). The title compound formed as by-product during the formation of **14**. (LP/EtOAc 3:1). Yellow crystals (0.42 g, 1.47 mmol, 9%); mp 156–159 °C (EtOAc); ^{1}H NMR (d_6-DMSO, 200 MHz): δ 1.49 (s, 9H), 2.67 (s, 3H), 7.40 (t, ^3J=8.4 Hz, 1H), 7.60 (d, ^3J=8.5 Hz, 1H), 7.65–7.85 (m, 2H), 8.34 (s, 1H), 8.73 (d, ^3J=5.5 Hz, 1H), 9.51 (s, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz): δ 25.9 (q), 28.1 (q), 79.2 (*s*), 114.0 (d), 116.5 (d), 120.7 (d), 120.8 (d), 129.2 (d), 136.8 (s), 140.2 (s), 152.8 (s), 158.1 (d), 162.8 (s), 167.4 (s). Anal. Calcd for $C_{16}H_{19}N_3O_2$ (285.34): C, 67.35; H, 6.71; N, 14.73. Found: C, 67.10; H, 6.75; N, 14.52.

4.1.17. 2-Chloro-4-(3-aminophenyl)-pyrimidine (16). Substrate **14** (4.43 g, 14.5 mmol, 1 equiv) was suspended in dry dichloromethane (20 mL) and treated with trifluoroacetic acid (10 mL, 135 mmol, 9.3 equiv). The mixture was stirred at room temperature for 3 h, poured onto water, adjusted to basic pH with saturated aqueous Na_2CO_3 solution and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to yield **16** as yellow crystals (2.93 g, 14.2 mmol, 98%); mp 137–138 °C (MeOH); ^{1}H NMR (d_6-DMSO, 200 MHz): δ 5.40 (br s, 2H), 6.79 (dt, ^3J=8.0 Hz, ^4J=2.3 Hz, 1H), 7.19 (dd, ^3J=8.0 Hz, 1H), 7.28 (d, J=8.0 Hz, 1H), 7.42 (t, ^4J=2.3 Hz, 1H), 7.93 (d, ^3J=5.3 Hz, 1H), 8.74 (d, J=5.3 Hz, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz): δ 112.1 (d), 114.9 (d), 115.8 (d), 117.6 (d), 129.7 (d), 135.1 (s), 149.4 (s), 160.5 (s), 160.7 (d), 167.0 (s). Anal. Calcd for $C_{10}H_8ClN_3$ (205.65): C, 58.41; H, 3.92; N, 20.43. Found: C, 58.25; H, 4.19; N, 20.14.

4.1.18. 3-{[3-(2-Chloropyrimidin-4-yl)-phenyl]-amino}-3-oxopropanoic acid methyl ester (17). Substrate **16** (2.50 g, 12.2 mmol, 1 equiv) and triethylamine (1.35 g, 13.4 mmol, 1.1 equiv) were dissolved in dry THF (50 mL) and cooled to 0 °C. 3-Chloro-3-oxopropanoic acid methyl ester (1.83 g, 13.4 mmol, 1.1 equiv) in dry THF (5 mL) was added dropwise within 10 min. After stirring for 2 h at 0 °C the mixture was poured onto water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product was purified by column chromatography (LP/EtOAc 1:1) to yield **17** as colorless crystals (2.80 g, 9.16 mmol, 75%); mp 117–119 °C (DIPE); ^{1}H NMR (d_6-DMSO, 200 MHz): δ 3.52 (s, 2H), 3.67 (s, 3H), 7.52 (t, ^3J=8.3 Hz, 1H), 7.84–7.93 (m, 2H), 8.07 (d, ^3J=5.5 Hz, 1H), 8.38 (t, ^4J=2.2 Hz, 1H), 8.82 (d, ^3J=5.5 Hz, 1H), 10.48 (s, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz): δ 43.5 (t), 52.0 (q), 116.0 (d), 117.5 (d), 122.4 (d), 122.5 (d), 129.7 (d), 135.0 (s), 139.6 (s), 160.5 (s), 161.2 (d), 164.3 (s), 165.8 (s), 168.0 (s). Anal. Calcd for $C_{14}H_{12}ClN_3O_3$ (305.72): C, 55.00; H, 3.96; N, 13.74. Found: C, 54.74; H, 4.12; N, 13.48.

4.1.19. 3-{[3-[2-(3-Chlorophenylamino)-pyrimidin-4-yl]-phenyl]-amino}-3-oxopropanoic acid methyl ester (18). Substrate **17** (2.00 g, 6.54 mmol, 1 equiv), 3-chloroaniline (1.25 g, 9.81 mmol, 1.5 equiv), and *p*-TSA·H_2O (1.06 g, 5.56 mmol, 0.85 equiv) were dissolved in dry dioxane (40 mL) and refluxed for 4 h. The solvent was removed in vacuo and the residue was suspended in water. The suspension was adjusted to basic pH with saturated aqueous Na_2CO_3 solution and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product was purified by column chromatography ((LP/EtOAc 1:1 → 1:3) to yield **18** as yellow crystals (2.34 g, 5.90 mmol, 90%); mp 173–176 °C (EtOAc); ^{1}H NMR (d_6-DMSO, 200 MHz): δ 3.54 (s, 2H), 3.68 (s, 3H), 7.00 (d, ^3J=8.2 Hz, 1H), 7.28–7.43 (m, 2H), 7.50 (t, ^3J=7.6 Hz, 1H), 7.68 (d, ^3J=8.2 Hz, 1H), 7.80–7.95 (m, 2H), 7.99 (t, ^4J=2.2 Hz, 1H), 8.48 (s, 1H), 8.62 (d, ^3J=5.5 Hz, 1H), 9.92 (s, 1H), 10.39 (s, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz): δ 43.5 (t), 52.0 (q), 108.6 (d), 117.1 (d), 117.8 (d), 118.0 (d), 120.8 (d), 121.6 (d), 122.2 (d), 129.4 (d), 130.3 (d), 133.0 (s), 137.3 (s), 139.4 (s), 142.2 (s), 159.1 (d), 159.9 (s), 163.7 (s), 164.3 (s), 168.1 (s). Anal. Calcd for $C_{20}H_{17}ClN_4O_3$ (396.83): C, 60.53; H, 4.32; N, 14.12. Found: C, 60.59; H, 4.60; N, 13.96.

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Enantioselective diethylzinc addition to aromatic and aliphatic aldehydes using (3*R*,5*R*)-dihydroxypiperidine derivatives catalyst

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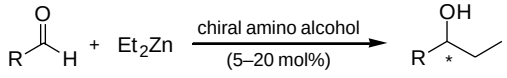
Abstract—A series of chiral (3*R*,5*R*)-dihydroxypiperidine derivatives **3a–f** were conveniently prepared from *trans*-4-hydroxy-L-proline and applied to the catalytic enantioselective addition of diethylzinc to benzaldehyde and heptanal. Among them, **3d** was found to show the best asymmetric induction in promoting the addition of Et_2Zn to various aldehydes, providing (*R*)-secondary alcohols in up to 98% ee.

1. Introduction

Among asymmetric catalysis of C–C bond formation, the enantioselective addition of diorganozinc reagents to aldehydes in the presence of a catalytic amount of a chiral ligand is a convenient method for the preparation of optically active secondary alcohols.[1] Among the numerous chiral catalysts developed for asymmetric organozinc additions, β-amino alcohols hold a prominent position.[1e,2] The use of these catalysts for the addition of diethylzinc to aromatic aldehydes produces 1-aryl-1-ethanols in both excellent chemical yield and enantioselectivity[3,4] (Scheme 1). In contrast, the enantioselectivity for aliphatic aldehydes is usually considerably lower.[5]



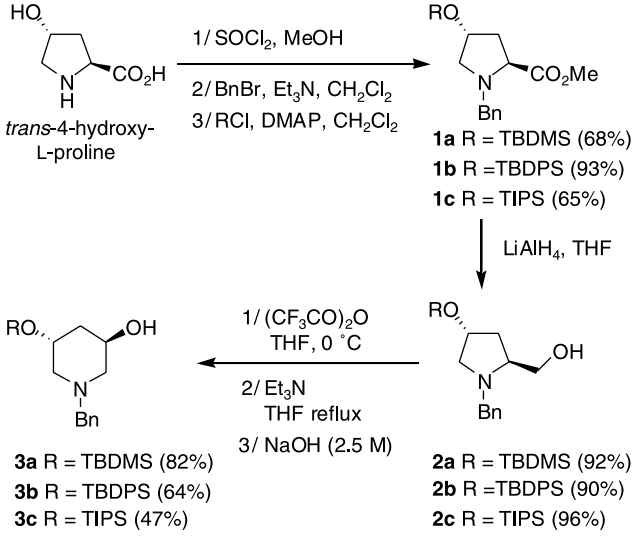
Scheme 1. Enantioselective addition of diethylzinc to aldehydes catalyzed by chiral amino alcohols.

2. Results

In the course of our studies on the synthesis and applications of optically active 3,5-dihydroxy-piperidines,[6] we would like to report here the use of (3*R*,5*R*)-dihydroxypiperidine derivatives on the enantioselective addition of diethylzinc to aryl aldehydes as well as to aliphatic aldehydes.

Ligands **3a–f** were prepared from the commercially available *trans*-4-hydroxy-L-proline by utilizing a ring expansion[7,8] that we have devised previously to synthesize (3*R*,5*R*)-dihydroxypiperidine derivatives.

Compounds **3a**,[7g] **3b**, and **3c** were prepared from the corresponding prolinols **2** by treatment with trifluoroacetic anhydride followed by the addition of triethylamine and then by treatment with sodium hydroxide.[7g] The (3*R*,5*R*)-dihydroxypiperidine derivatives **3a**, **3b**, and **3c** were obtained in 82, 64, and 47% yield, respectively, (Scheme 2). Compound **3a** was then transformed into **3d–f**.



Scheme 2.

Keywords: Enantioselective addition; Aliphatic aldehydes; Chiral ligands.
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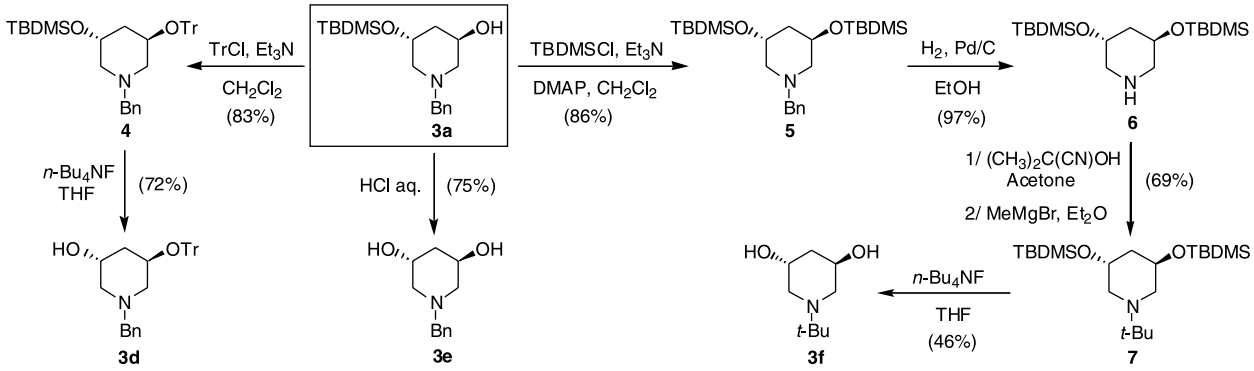


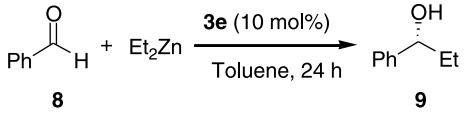
Scheme 3.

For obtaining **3d**, the hydroxypiperidine **3a** was treated with triphenylmethane chloride (CH_2Cl_2, Et_3N, 0 °C) and the resulting piperidine **4** was mono-deprotected with *n*-Bu_4NF (THF, rt) to produce **3d** with an overall yield of 60%. The 3,5-dihydroxypiperidine **3e**[7g] was obtained in 75% yield by deprotection of **3a** using HCl (1.2 N) (Scheme 3).

The synthesis of *N*-*t*-butyl-3,5-dihydoxypiperidine **3f** was achieved from **3a** in four steps. After protection of the hydroxyl group (TBDMSCl, DMAP, Et_3N) and deprotection of the nitrogen (H_2, Pd/C), the amine **6** was treated with acetone cyanohydrin followed by the addition of methylmagnesium bromide[9] and, after addition of *n*-Bu_4NF to the resulting *N*-*t*-butylpiperidine **7** (THF, rt), compound **3f** was isolated with an overall yield of 26% (Scheme 3). It is worth noting that by using this synthetic pathway, a library of chiral ligands should be easily prepared. The novel chiral ligands **3a–f** were then evaluated in the asymmetric induction efficiency of diethylzinc addition to aryl aldehydes and aliphatic aldehydes.

The first test was performed on benzaldehyde using ligand **3e** under standard conditions. The reaction was carried out in dry toluene in the presence of 10 mol% of the chiral ligand **3e** and 2.2 equiv of Et_2Zn at rt for 24 h. The reaction was quenched with HCl (1.2 N) and after extraction and purification by chromatography over silica gel 1-phenylpropan-1-ol **9**[41] was isolated in 84% yield and 89% ee with the (*R*) configuration (Table 1, entry 1). When the temperature was lowered to 0 °C, the yield in **9** was decreased to 73% and the ee remained similar (Table 1, entry 2). By decreasing the number of equivalents of Et_2Zn, from 2.2 to 1.5 or 1.2 equiv, the yield in **9** was increased in the range of 93–99% and the ee was similar and reproducible 87–92%.

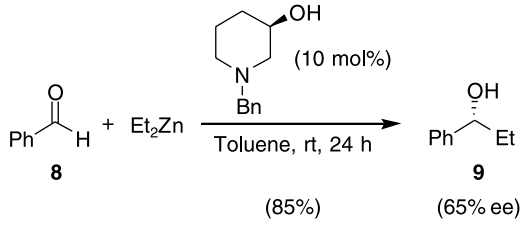
Table 1. Enantioselective addition of diethylzinc to benzaldehyde catalyzed by ligand **3e**



Entry	Et_2Zn (equiv)	*T* (°C)	Yield (%)	ee (%)[a]	Conf.[b]
1	2.2	rt	84	89	*R*
2	2.2	0	73	87	*R*
3	1.5	rt	93	87	*R*
4	1.2	rt	99	92	*R*

[a] Determined by using a Chiralcel OD-H column and eluting with hexane–*i*PrOH (99/1) at the flow rate of 1 mL/min.
[b] Determined by comparison with the absolute optical rotation reported in the literature.

We have to point out that the use of (*R*)-*N*-benzyl-3-hydroxypiperidine[7g] led to **9** in 85% yield but the ee was only 65%, which means that 3,5-dihydroxypiperidines were promising (Scheme 4).

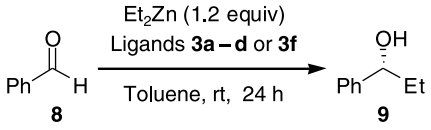


Scheme 4.

Due to these results, ligands **3a–e** were then evaluated to check their asymmetric induction in the addition of diethylzinc to benzaldehyde **8**.

N-Benzyl monoprotected 3,5-dihydroxypiperidine **3a–d** were tested as well as the *N*-*t*-butyl non-protected dihydroxypiperidine **3f**. As reported in Table 2, **3d** shows the best asymmetric induction as 1-phenylpropanol **9** was obtained with 98% ee using 2 mol% of **3d** as catalyst

Table 2. Enantioselective addition of diethylzinc to benzaldehyde catalyzed by ligands **3a–d** and **3f**

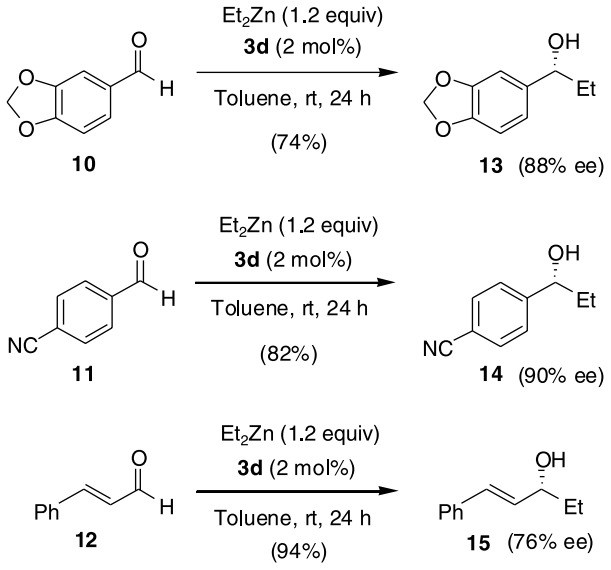


Entry	Ligand	mol%	Yield (%)	ee (%) (conf.)[a]
1	**3a**	10	76	80 (*R*)
2	**3b**	2	94	89 (*R*)
3	**3c**	10	85	88 (*R*)
4	**3d**	2	74	98 (*R*)
5	**3f**	2	77	91 (*R*)

[a] Determined by using a Chiralcel OD-H column and eluting with hexane–*i*PrOH (99/1) at the flow rate of 1 mL/min; the absolute configuration was determined by comparison with the absolute optical rotation given in the literature.

(Table 2, entry 4). Obviously, the presence of a bulky trityl substituent at C3 is crucial to obtain the best asymmetric induction. It is interesting to note that the *N*-*t*-butyl substituent in **3f** also plays an important role in the enantioselectivity (Table 2, entry 5) as **9** was obtained with an ee of 91%.

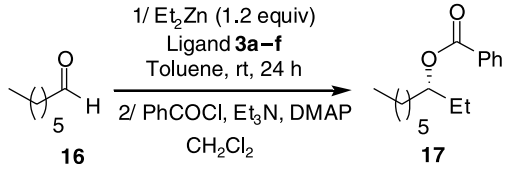
By using **3d** as the catalyst, ethyl alcohol **13**[10] (88% ee), **14**[11] (90% ee) and **15**[3e,12] (76% ee) were obtained with good ee and in good yield from aldehydes **10**, **11**, and **12**, respectively, (Scheme 5).



Scheme 5.

Chiral ligand **3d** was then examined for the asymmetric addition of diethylzinc to the aliphatic aldehyde **16**. In order to facilitate the ee determination by chiral HPLC, the alcohol obtained after the addition of Et_2Zn was benzoylated to produce **17**. The benzoate **17**[13] was obtained with an overall yield of 57% with an ee of 69% (Table 3, entry 4). In the aim of increasing the ee, the chiral ligands **3a**–**c**, **3e**, and **3f** were tested (Table 3). The best ligand for aliphatic aldehydes seems to be the *N*-*t*-butyl-3,5-dihydroxypiperidine **3f** as **17** was obtained with an overall yield of 57% and with an ee of 81% (Table 3, entry 6).

Table 3. Enantioselective addition of diethylzinc to heptanal catalyzed by ligand **3a**–**f**



Entry	Ligand	mol%	Yield (%)[a]	ee (%) (conf.)[b]
1	**3a**	10	34	35 (*R*)
2	**3b**	10	39	59 (*R*)
3	**3c**	10	42	62 (*R*)
4	**3d**	2	57	69 (*R*)
5	**3e**	10	25	60 (*R*)
6	**3f**	2	57	81 (*R*)

[a] Overall yield for addition and benzoylation.
[b] Determined by using a Chiralcel OD-H column and eluting with hexane–*i*PrOH (99/1) at the flow rate of 1 mL/min; the absolute configuration was determined by comparison with the absolute optical rotation given in the literature.

In conclusion, a series of new chiral ligands **3a–f** for the addition of dialkylzinc to aldehydes have been prepared from *trans*-4-hydroxy-L-proline. Compound **3d** was found to be highly efficient for the enantioselective addition of diethylzinc to aromatic aldehydes and good for the enantioselective addition of diethylzinc to aliphatic aldehydes. In the case of aliphatic aldehydes a better ee was obtained with **3f**.

The chiral ligands described in this study might be used in other asymmetric catalytic transformations. Such as for example, the enantioselective Henry reaction of nitromethane with aldehydes.[14]

3. Experimental

3.1. General

All reactions were carried out under argon atmosphere. Commercially available reagents and solvents were used as received. Anhydrous solvents were distilled: tetrahydrofuran and diethyl ether were purified by distillation from sodium and benzophenone, methylene chloride, and toluene were dried by distillation from CaH_2. Flash column chromatography was performed on silica gel (Merck-Kieselgel 60, 230–400 mesh).

Melting points (mp) were not corrected. ^1H and ^{13}C NMR spectra were, respectively, recorded on a Bruker AC 300 at 300 and 75 MHz. Spectra were recorder in $CDCl_3$ as solvent, and chemical shifts (δ) were expressed in ppm relative to residual $CHCl_3$ at $\delta=7.27$ ppm for ^1H and to $CDCl_3$ at $\delta=77.1$ ppm for ^{13}C. ^1H NMR *J* values given in Hz. IR spectra were recorded as neat films (NaCl cell) and KBr pellets for solids on a Perkin-Elmer 298. Mass spectra were obtained by GC/MS with electron impact (EI) ionization by using a 5971 Hewlett Packard instrument at 70 eV: only selected ions are reported. HRMS were performed at the Laboratoire de Spectrochimie de l'Ecole Normale Supérieure in Paris. Optical rotations were measured on a Perkin-Elmer 343 polarimeter in a 10 cm cell. Analytical HPLC was carried out using a Waters 515 solvent-delivery system and a Waters 2487 variable-wavelength absorbance detector operating at 254 nm. The ee of the products were determined using a Chiralcel OD-H column and eluting with hexane–*i*PrOH (99/1) at the flow rate of 1 mL/min. Elemental analysis were performed by the Centre Régional de Microanalyses (Université Pierre et Marie Curie, Paris VI).

3.1.1. (2*S*,4*R*)-1-Benzyl-4-[(*tert*-butyldimethylsilyl)oxy]-2-methoxycarbonylpyrrolidine (1a);[15] typical procedure

To a stirred suspension of (2*R*,4*R*)-4-hydroxy-2-methoxycarbonylpyrrolidine (5.0 g, 38.1 mmol, 1.0 equiv) in MeOH (150 mL) at 0 °C thionyl chloride (3.4 mL, 45.7 mmol, 1.2 equiv) was added dropwise. After 72 h at rt, the organic solvent was removed in vacuo to afford a white solid.

To a stirred suspension of the resulting white solid in CH_2Cl_2 (40 mL) at rt was added Et_3N (21.4 mL, 152.4 mmol, 4 equiv), followed by BnBr (5.5 mL, 45.7 mmol, 1.2 equiv). After 10 min at rt, the reaction mixture was heated at reflux for 5 h and cooled to rt. DMAP (0.5 g, 3.8 mmol, 0.1 equiv) and TBDMSCl (6.9 g, 45.7 mmol, 1.2 equiv) were added. After 12 h at rt, the reaction mixture was quenched with a saturated aqueous Na_2CO_3 solution until pH ~ 10. The aqueous layer was extracted with CH_2Cl_2 and EtOAc and the combined organic phases were dried over $MgSO_4$ and filtered. The solvent was removed in vacuo to afford an oil, which was purified by flash column chromatography on silica gel (EtOAc/cyclohexane 30:70) to give **1a** (9.0 g, 25.8 mmol, 68% yield) as a colorless oil; $[\alpha]_D^{20}$ −49.6 (*c* 3.65, $CHCl_3$); IR (neat): 1740, 1375, 780, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.35–7.21 (5H), 4.41 (m, 1H), 3.91 (d, J=12.5 Hz, 1H), 3.65 (s, 3H), 3.60 (d, J=12.5 Hz, 1H), 3.53 (t, J=8.1 Hz, 1H), 3.27 (dd, J=9.6, 5.7 Hz, 1H), 2.37 (dd, J=9.6, 5.2 Hz, 1H), 2.19 (ddd, J=13.1, 7.5, 7.3 Hz, 1H), 2.03 (ddd, J=12.8, 8.5, 4.0 Hz, 1H), 0.8 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 174.1 (s), 138.0 (s), 129.0 (d), 128.1 (d), 127.0 (d), 70.3 (d), 64.2 (d), 61.5 (t), 59.3 (t), 51.7 (q), 39.4 (t), 25.6 (q), 17.8 (s), −5.0 (q); EI MS *m/z* (relative intensity) 349 ($M^{+\cdot}$, 1), 292 (10), 291 (27), 290 (100), 158 (14), 91 (41).

3.1.2. (2*S*,4*R*)-1-Benzyl-4-[(*tert*-butyldiphenylsilyl)oxy]-2-methoxycarbonylpyrrolidine (1b). Yield: 93% from (2*R*,4*R*)-4-hydroxy-2-methoxycarbonylpyrrolidine; colorless oil; $[\alpha]_D^{20}$ −20.8 (*c* 3.65, $CHCl_3$); IR (neat): 1740, 1375, 740, 710, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.78–7.73 (1H), 7.68–7.60 (4H), 7.48–7.23 (10H), 4.46 (m, 1H), 3.92 (d, J=12.9 Hz, 1H), 3.66 (d, J=12.9 Hz, 1H), 3.62 (s, 3H), 3.61 (dd, J=8.1, 8.1 Hz, 1H), 3.19 (dd, J=9.9, 5.9 Hz, 1H), 2.53 (dd, J=9.9, 4.8 Hz, 1H), 2.13 (m, 1H), 2.04 (m, 1H), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$) δ: 174.0 (s), 138.0 (s), 135.5 (d), 134.7 (d), 133.7 (s), 133.6 (s), 129.7 (d), 129.6 (d), 129.0 (d), 128.1 (d), 127.6 (d), 127.5 (d), 127.0 (d), 71.4 (d), 64.3 (d), 61.5 (t), 59.1 (t), 51.6 (q), 39.4 (t), 26.8 (q), 18.9 (s); EI MS *m/z* (relative intensity) 473 ($M^{+\cdot}$, 1), 458 (1), 414 (100) 199 (11), 183 (6), 158 (11), 135 (5), 91 (49).

3.1.3. (2*S*,4*R*)-1-Benzyl-4-[(triisopropylsilyl)oxy]-2-methoxycarbonylpyrrolidine (1c). Yield: 65% from (2*R*,4*R*)-4-hydroxy-2-methoxycarbonylpyrrolidine; colorless oil; $[\alpha]_D^{20}$ −17.3 (*c* 1.54, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 7.36–7.22 (5H), 4.51 (m, 1H), 3.91 (d, J=12.9 Hz, 1H), 3.64 (s, 3H), 3.62 (d, J=12.9 Hz, 1H), 3.55 (dd, J=8.1, 8.1 Hz, 1H), 3.33 (dd, J=9.7, 5.7 Hz, 1H), 2.43 (dd, J=9.7, 5.0 Hz, 1H), 2.23 (ddd, J=12.9, 8.1, 7.0 Hz, 1H), 2.09 (ddd, J=12.7, 8.7, 4.1 Hz, 1H), 1.06–1.03 (21H); ^{13}C NMR ($CDCl_3$) δ: 174.0 (s), 138.0 (s), 129.0 (d), 128.1 (d), 127.0 (d), 70.5 (d), 64.3 (d), 62.0 (t), 59.1 (t), 51.7 (q), 39.9 (t), 17.8 (q), 17.6 (q), 12.1 (d), 11.8 (d); EI MS *m/z* (relative intensity) 387 (13), 344 (11), 332 ($M^{+\cdot}$−COOMe, 100), 316 (5), 288 (5), 215 (6), 183 (4), 158 (11), 131 (7), 103 (6), 91 (77), 75 (11), 61 (5).

3.1.4. (2*S*,4*R*)-2-{1-Benzyl-4-[(*tert*-butyldimethylsilyl)-oxy]-pyrrolidinyl}methanol (2a);[16] typical procedure To a suspension of $LiAlH_4$ (0.87 g; 23.0 mmol, 2.0 equiv) in THF (15 mL) at 0 °C, a solution of pyrrolidine **1a** (4.0 g, 11.5 mmol, 1.0 equiv) in THF (15 mL) was added dropwise. After stirring at 0 °C for 10 min, the reaction mixture was heated at reflux for 2 h and then cooled to 0 °C. Water (0.09 mL), an aqueous 3.75 M NaOH solution (0.89 mL), and water (2.7 mL) were successively added. The obtained precipitate was collected on a Celite pad and washed with THF. The organic solvent was removed in vacuo to give **2a** (3.4 g, 10.6 mmol, 92% yield) as a colorless oil; $[\alpha]_D^{20}$ −43.4 (*c* 1.00, $CHCl_3$), IR (neat): 3400, 1375, 780, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.37–7.27 (5H), 4.27 (m, 1H), 3.97 (d, J=13.2 Hz, 1H), 3.67 (dd, J=11.0, 3.3 Hz, 1H), 3.47 (d, J=13.2 Hz, 1H), 3.39 (d, J=11.0 Hz, 1H), 3.14 (dd, J=9.9, 5.5 Hz, 1H), 3.07 (m, 1H), 2.65 (s, 1H), 2.37 (dd, J=9.9, 5.7 Hz, 1H), 2.09 (ddd, J=12.9, 7.4, 7.4 Hz, 1H), 1.84 (ddd, J=13.0, 8.6, 4.6 Hz, 1H), 0.8 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 139.0 (s), 128.5 (d), 128.3 (d), 126.9 (d), 70.6 (d), 63.3 (d), 62.1 (t), 60.9 (t), 58.6 (t), 37.7 (t), 25.7 (q), 17.9 (s), −4.9 (q); EI MS *m/z* (relative intensity) 306 ($M^{+\cdot}$−CH3, 3), 292 (7), 291 (24), 290 (100), 158 (14), 91 (61), 75 (7).

3.1.5. (2*S*,4*R*)-2-{1-Benzyl-4-[(*tert*-butyldiphenylsilyl)-oxy]-pyrrolidinyl}methanol (2b). Yield: 90% from **1b**; colorless oil; $[\alpha]_D^{20}$ −1.2 (*c* 2.40, $CHCl_3$); IR (neat): 3350, 1425, 1375, 735, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.73–7.63 (4H), 7.53–7.23 (11H), 4.34 (m, 1H), 3.99 (d, J=12.9 Hz, 1H), 3.63 (dd, J=11.0, 3.7 Hz, 1H), 3.54 (d, J=13.2 Hz, 1H), 3.36 (dd, J=11.0, 1.8 Hz, 1H), 3.14 (tdd, J=8.1, 3.3, 1.8 Hz, 1H), 3.06 (dd, J=10.3, 5.5 Hz, 1H), 2.52 (dd, J=10.1, 4.9 Hz, 1H), 2.48 (br s, 1H), 1.90–1.98 (2H), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$) δ: 139.0 (s), 135.5 (d), 134.4 (s), 129.6 (d), 129.5 (d), 128.5 (d), 128.2 (d), 127.5 (d), 127.4 (d), 126.9 (d), 71.7 (d), 63.4 (d), 62.1 (t), 60.8 (t), 58.7 (t), 37.5 (t), 26.8 (q), 18.9 (s); EI MS *m/z* (relative intensity) 445 ($M^{+\cdot}$, 1), 414 (100), 199 (14), 183 (5), 158 (12), 91 (49); HRMS (CI) calcd for $C_{28}H_{36}O_2NSi$ ($M+H^+$) 446.2515, found 446.2508.

3.1.6. (2*S*,4*R*)-2-{1-Benzyl-4-[(triisopropylsilyl)oxy]-pyrrolidinyl}methanol (2c). Yield: 96% from **1c**; colorless oil; $[\alpha]_D^{20}$ −9.9 (*c* 1.06, $CHCl_3$); IR (neat): 3390, 1460, 1380, 735, 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.38–7.24 (5H), 4.37 (m, 1H), 3.97 (d, J=12.9 Hz, 1H), 3.65 (dd, J=10.8, 3.3 Hz, 1H), 3.51 (d, J=13.2 Hz, 1H), 3.40 (d, J=10.7 Hz, 1H), 3.19 (dd, J=8.1, 5.5 Hz, 1H), 3.11 (tdd, J=8.1, 3.3, 1.8 Hz, 1H), 2.91 (br s, 1H), 2.43 (dd, J=9.9, 5.1 Hz, 1H), 2.11 (dt, J=12.9, 7.4 Hz, 1H), 1.88 (ddd, J=12.8, 8.3, 4.1 Hz, 1H), 1.07–1.05 (21H); ^{13}C NMR ($CDCl_3$) δ: 139.0 (s), 128.5 (d), 128.3 (d), 126.9 (d), 70.8 (d), 63.3 (d), 62.6 (t), 60.1 (t), 58.7 (t), 38.0 (t), 17.8 (q), 17.6 (q), 12.2 (d), 11.9 (d); EI MS *m/z* (relative intensity) 332 ($M^{+\cdot}$−CH_2OH, 100), 207 (19), 158 (15), 91 (60), 75 (8), 61 (5); HRMS (CI) calcd for $C_{21}H_{38}O_2NSi$ ($M+H^+$) 364.2672, found 364.2665.

3.1.7. (3*R*,5*R*)-1-Benzyl-5-[(*tert*-butyldimethylsilyl)oxy]-piperidin-3-ol (3a);[6] typical procedure Trifluoroacetic anhydride (1.1 mL, 7.5 mmol, 1.2 equiv) was added dropwise to a solution of pyrrolidine **2a** (2.0 g, 6.2 mmol, 1.0 equiv) in THF (60 mL), cooled to 0 °C. After 1 h, Et_3N (3.5 mL, 24.8 mmol, 4.0 equiv) was added dropwise. The reaction mixture was stirred for 20 min at 0 °C and then heated at reflux for 72 h. After addition of an aqueous 2.5 M NaOH solution (15 mL), the mixture was stirred for 2 h at rt

and then extracted with EtOAc, dried with $MgSO_4$, and evaporated to dryness in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/cyclohexane 30:70) to give **3a** (1.65 g, 5.1 mmol, 82% yield) as an oil; $[\alpha]_D^{20}$ +25.3 (*c* 1.75, EtOH); IR (neat): 3450, 1460, 1250, 1150, 1090, 840, 775, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.37–7.24 (5H), 4.05 (h, J=4.8 Hz, 1H), 3.96 (s, 1H), 3.63 (d, J=13.2 Hz, 1H), 3.53 (d, J=13.2 Hz, 1H), 2.90 (m, 1H), 2.75 (m, 1H), 2.50 (br s, 1H), 2.19 (dd, J=11.4, 1.84 Hz, 1H), 2.09 (m, 1H), 1.97 (t, J=10.1 Hz, 1H), 1.38 (ddd, J=13.0, 10.3, 2.6 Hz, 1H), 0.88 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 137.7 (s), 128.8 (d), 128.1 (d), 127.0 (d), 65.8 (d), 65.2 (d), 62.1 (t), 61.0 (t), 58.5 (t), 40.8 (t), 25.7 (q), 18.0 (s), −4.8 (q), −4.9 (q); EI MS *m/z* (relative intensity) 321 ($M^{+\cdot}$, 5), 304 (2), 264 (39), 246 (7), 134 (23), 120 (10), 101 (10), 91 (100), 73 (11).

3.1.8. (3*R*,5*R*)-1-Benzyl-5-[(*tert*-butyldiphenylsilyl)oxy]-piperidin-3-ol (3b). Yield: 64% from **2b**; oil; $[\alpha]_D^{20}$ +46.8 (*c* 1.57, EtOH); IR (neat): 3350, 1420, 1100, 900, 820, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.69–7.61 (4H), 7.48–7.18 (11H), 4.08 (m, 1H), 3.95 (s, 1H), 3.49 (s, 2H), 2.80–2.59 (2H), 2.33–2.23 (2H), 2.10–1.98 (2H), 1.55 (ddd, J=12.9, 9.9, 2.9 Hz, 1H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$) δ: 137.7 (s), 135.6 (d), 135.5 (d), 134.2 (s), 133.9 (s), 129.5 (d), 129.4 (d), 128.7 (d), 128.1 (d), 127.5 (d), 127.4 (d), 127.0 (d), 66.2 (d), 65.8 (d), 62.0 (t), 60.4 (t), 58.9 (t), 53.3 (t), 40.7 (t), 26.8 (q), 19.0 (s); EI MS *m/z* (relative intensity) 445 ($M^{+\cdot}$, 2), 388 (45), 310 (43), 199 (18), 183 (15), 134 (10), 91 (100); HRMS (CI) calcd for $C_{28}H_{36}O_2NSi$ ($M+H^+$) 446.2515, found 446.2514.

3.1.9. (3*R*,5*R*)-1-Benzyl-5-[(triisopropylsilyl)oxy]-piperidin-3-ol (3c). Yield: 47% from **2c**; oil; $[\alpha]_D^{20}$ +17.9 (*c* 2.00, EtOH); IR (neat): 3460, 1450, 1150, 1100, 910, 880, 800, 735, 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.36–7.23 (5H), 4.10 (m, 1H), 3.97 (s, 1H), 3.60 (d, J=13.2 Hz, 1H), 3.55 (d, J=13.2 Hz, 1H), 2.96 (m, 1H), 2.77 (m, 1H), 2.53 (br s, 1H), 2.25–2.11 (2H), 1.95 (dd, J=10.3, 9.6 Hz, 1H), 1.40 (ddd, J=13.1, 10.3, 2.6 Hz, 1H), 1.05–1.00 (21H); ^{13}C NMR ($CDCl_3$) δ: 137.8 (s), 128.8 (d), 128.1 (d), 127.0 (d), 66.0 (d), 65.2 (d), 62.1 (t), 61.1 (t), 58.8 (t), 41.0 (t), 17.8 (q), 12.1 (d); EI MS *m/z* (relative intensity) 363 ($M^{+\cdot}$, 6), 320 (28), 190 (9), 172 (7), 134 (14), 120 (10), 91 (100). Anal. Calcd for $C_{21}H_{37}NO_2Si$: C, 69.37; H, 10.26; N, 3.85. Found C, 69.23; H, 10.42; N, 3.82.

3.1.10. (3*R*,5*R*)-1-Benzyl-5-[(*tert*-butyldimethylsilyl)-oxy]-5-trityloxypiperidine (4). To a stirred solution of piperidine **3a** (0.30 g, 0.93 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) at rt was added triphenylmethyl chloride (0.29 g, 1.0 mmol, 1.1 equiv), followed by the addition of Et_3N (0.26 mL, 1.9 mmol, 2.0 equiv). After stirring at rt for 48 h, the reaction was quenched with an aqueous 3.75 M NaOH solution (6 mL). After extraction with EtOAc, the combined organic layers were dried with $MgSO_4$ and filtered. The solvent was removed in vacuo to afford a yellow oil, which was purified by flash column chromatography on silica gel (EtOAc/petroleum ether 20:80) to give **4** (0.44 g, 0.78 mmol, 83% yield) as a amorphous solid. ^1H NMR ($CDCl_3$) δ: 7.54–7.47 (5H), 7.34–7.16 (15H), 4.16 (m, 1H), 3.89 (m, 1H), 3.53 (d, J=13.6 Hz, 1H), 3.33 (d, J=13.6 Hz, 1H), 2.65 (dd, J=10.6, 3.3 Hz, 1H), 2.17 (dd, J=11.6, 5.5 Hz, 1H), 2.12 (dd, J=10.8, 3.3 Hz, 1H), 1.86 (dd, J=11.4, 2.6 Hz, 1H), 1.42 (m, 1H), 1.19 (m, 1H), 0.85 (s, 9H), 0.00 (s, 3H), −0.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 146.8 (s), 145.1 (s), 138.7 (s), 128.9 (d), 128.8 (d), 128.7 (d), 127.9 (d), 127.8 (d), 127.5 (d), 127.1 (d), 126.7 (d), 126.6 (d), 86.7 (s), 67.7 (d), 66.2 (d), 62.1 (t), 60.2 (t), 57.7 (t), 40.0 (t), 25.8 (q), 18.0 (s), −4.8 (q), −4.9 (q); EI MS *m/z* (relative intensity) 548 ($M^{+\cdot}-CH_3$, 1), 320 (100), 243 (17), 165 (21), 91 (59), 73 (7).

3.1.11. (3*R*,5*R*)-1-Benzyl-5-trityloxypiperidin-3-ol (3d). To a stirred solution of piperidine **4** (0.38 g, 0.68 mmol, 1.0 equiv) in THF (1 mL) at rt was added a solution of tetrabutylammonium fluoride 1 M in THF (2.7 mL, 2.7 mmol, 4.0 equiv). After stirring at rt for 72 h, the reaction was quenched with water (6 mL). After extraction with EtOAc, the combined organic layers were dried with $MgSO_4$ and filtered. The solvent was removed in vacuo to afford a yellow gum, which was purified by flash column chromatography on silica gel (EtOAc/cyclohexane 30:70) to give **3d** (0.22 g, 0.49 mmol, 72% yield) as a white solid. Mp 76 °C; $[\alpha]_D^{20}$ +28.7 (*c* 1.23, $CHCl_3$); IR (KBr): 3300, 1440, 1150, 1020, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.52–7.44 (15H), 7.33–7.09 (5H), 3.95–3.82 (2H), 3.37 (d, J=12.9 Hz, 1H), 3.27 (d, J=13.2 Hz, 1H), 2.64 (m, 1H), 2.24–1.94 (4H), 1.84–1.69 (2H); ^{13}C NMR ($CDCl_3$) δ: 144.8 (s), 137.6 (s), 128.8 (d), 128.7 (d), 128.0 (d), 127.6 (d), 126.9 (d), 126.8 (d), 86.8 (s), 66.9 (d), 65.9 (d), 62.1 (t), 59.0 (t), 58.9 (t), 38.9 (t). Anal. Calcd for $C_{31}H_{31}NO_2$: C, 82.82; H, 6.95; N, 3.12. Found C, 82.68; H, 7.14; N, 3.13.

3.1.12. (3*R*,5*R*)-1-Benzylpiperidin-3,5-diol (3e).[7g] To a stirred solution of piperidine **3a** (0.52 g, 1.6 mmol, 1.0 equiv) in EtOAc (0.5 mL) at rt was added an aqueous 1.2 M solution of HCl (10.0 mL, 27.4 mmol, 17.1 equiv). After stirring at rt for 8 h, the reaction was quenched with an aqueous 3.75 M NaOH solution until pH ~ 11. After extraction with EtOAc, the combined organic layers were dried with $MgSO_4$ and filtered. The solvent was removed in vacuo to afford a colorless oil, which was purified by flash column chromatography on silica gel (EtOAc/MeOH 95:5) to give **3e** (0.25 g, 1.21 mmol, 75% yield) as a white solid. Mp 109 °C; $[\alpha]_D^{20}$ +15.2 (*c* 0.99, EtOH); IR (KBr): 3440, 1200, 1140, 1100, 1050, 1000, 960, 760 cm^{-1}; ^1H NMR (CD_3OD) δ: 7.60–7.40 (5H), 4.19 (m, 2H), 3.65 (s, 2H), 2.73 (dd, J=10.9, 1.7 Hz, 2H), 2.50 (dd, J=10.9, 6.8 Hz, 2H), 1.38 (t, J=5.5 Hz, 2H); ^{13}C NMR (CD_3OD) δ: 139.0 (s), 130.8 (d), 129.5 (d), 128.5 (d), 66.1 (t), 64.0 (t), 60.9 (t), 41.1 (t); EI MS *m/z* (relative intensity) 207 ($M^{+\cdot}$,14), 189 (2), 134 (12), 130 (10), 120 (14), 116 (27), 91 (100), 65 (8).

3.1.13. (3*R*,5*R*)-1-Benzyl-3,5-di[(*tert*-butyldimethylsilyl)-oxy]-piperidine (5).[6] To a stirred solution of piperidine **3a** (1.30 g, 4.0 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at rt were added TBDMSCl (1.2 g, 8.0 mmol, 2.0 equiv), Et_3N (0.68 mL, 4.8 mmol, 1.2 equiv) and DMAP (0.05 g, 0.4 mmol, 0.1 equiv). After 16 h at rt, the reaction mixture was quenched with a saturated aqueous Na_2CO_3 until pH ~ 10. The aqueous layer was extracted with EtOAc and the combined organic phases were dried over $MgSO_4$ and filtered. The solvent was removed in vacuo to afford a yellow oil, which was purified by flash column

chromatography on silica gel (EtOAc/petroleum ether 10:90) to give **5** (1.50 g, 3.45 mmol, 86% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 7.39–7.21 (5H), 4.11 (m, 2H), 3.73 (d, J=13.6 Hz, 1H), 3.45 (d, J=13.6 Hz, 1H), 2.47 (dd, J=11.0, 3.0 Hz, 2H), 2.33 (dd, J=11.0, 6.3 Hz, 2H), 1.66 (t, J=5.1 Hz, 2H), 0.91 (s, 18H), 0.06 (s, 6H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) δ: 138.6 (s), 128.7 (d), 128.0 (d), 126.7 (d), 66.1 (d), 62.2 (t), 59.9 (t), 42.0 (t), 25.8 (q), 18.1 (s), −4.8 (q), −4.9 (q); EI MS *m/z* (relative intensity) 435 ($M^{+\cdot}$, 9), 420 (10), 378 (61), 344 (11), 315 (11), 303 (17), 263 (13), 246 (20), 212 (21), 159 (17), 134 (48), 101 (25), 91 (100), 75 (10), 59 (8).

3.1.14. (3*R*,5*R*)-3,5-Di[(*tert*-butyldimethylsilyl)oxy]-piperidine (6)[6] To a solution of piperidine **5** (1.5 g, 3.45 mmol, 1.0 equiv) in absolute EtOH (10 mL) was added Pd/C (367 mg, 10%, 0.36 mmol, 0.1 equiv). The mixture was stirred under 4 atm of hydrogen at rt for 18 h and was filtered through silica gel. The filtrate was concentrated under reduced pressure to give **6** (1.16 g, 3.36 mmol, 97% yield) as a colorless gum. ^{1}H NMR ($CDCl_3$) δ: 3.95 (m, 2H), 2.97 (br s, 1H), 2.83 (dd, J=14.1, 3.1 Hz, 2H), 2.57 (dd, J=13.4, 6.4 Hz, 2H), 1.73 (t, J=5.3 Hz, 2H), 0.89 (s, 18H), 0.07 (s, 6H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$) δ: 66.3 (d), 52.4 (t), 41.6 (t), 25.7 (q), 18.0 (s), 5.0 (q); EI MS *m/z* (relative intensity) 345 ($M^{+\cdot}$, 1), 330 (6), 301 (23), 288 (100), 156 (34), 116 (10), 101 (10), 82 (40), 75 (15), 73 (32), 59 (7).

3.1.15. (3*R*,5*R*)-1-*tert*-Butyl-3,5-di[(*tert*-butyldimethylsilyl)oxy]-piperidine (7). To a stirred solution of piperidine **6** (0.40 g, 1.2 mmol, 1.0 equiv) in acetone (3 mL) at rt was added acetone cyanohydrin (0.11 mL, 1.2 mmol, 1.0 equiv). After stirring at rt for 16 h, the solvent was removed in vacuo to afford a colorless gum, which was dissolved in ether (2 mL). A 3 M solution of MeMgBr in ether (3.5 mL, 10.5 mmol, 8.75 equiv) was added dropwise to the previously prepared α-aminonitrile solution at 0 °C. After stirring at rt for 20 h, the reaction was quenched with ice. After extraction with EtOAc, the combined organic layers were dried with $MgSO_4$ and filtered. The solvent was removed in vacuo to afford a yellow oil, which was purified by flash column chromatography on silica gel (CH_2Cl_2/petroleum ether/Et_3N 50:50:1) to give **7** (0.32 g, 0.8 mmol, 67% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 4.02 (m, 2H), 2.59 (dd, J=11.0, 2.9 Hz, 2H), 2.34 (dd, J=10.7, 6.3 Hz, 2H), 1.61 (t, J=5.5 Hz, 2H), 1.04 (s, 9H), 0.90 (s, 18H), 0.07 (s, 12H); ^{13}C NMR ($CDCl_3$) δ: 66.9 (d), 53.1 (t), 53.0 (s), 42.1 (t), 26.0 (q), 25.8 (q), 18.0 (s), −4.9 (q), −4.8 (q); EI MS *m/z* (relative intensity) 401 ($M^{+\cdot}$, 1), 386 (100), 82 (4), 73 (13), 57 (4).

3.1.16. (3*R*,5*R*)-1-*tert*-Butylpiperidin-3,5-diol (3f). To a stirred solution of piperidine **7** (0.27 g, 0.67 mmol, 1.0 equiv) in THF (2 mL) at rt was added a solution of tetrabutylammonium fluoride 1 M in THF (3.8 mL, 3.8 mmol, 5.6 equiv). After stirring at rt for 72 h, the reaction was quenched with water (6 mL). After extraction with EtOAc, the combined organic layers were dried with $MgSO_4$ and filtered. The solvent was removed in vacuo to afford a yellow oil, which was purified by flash column chromatography on silica gel (EtOAc/MeOH/Et_3N 95:5:1) to give **3f** (54.0 mg, 0.31 mmol, 46% yield) as a white solid. Mp 112 °C; $[\alpha]_D^{20}$ +21.3 (*c* 0.94, CH_3OH); IR (KBr): 3300, 1320, 1200, 1060, 960, 830 cm^{-1}; ^{1}H NMR (CD_3OD) δ: 4.14 (m, 2H), 2.88 (dd, J=11.0, 2.9 Hz, 2H), 2.63 (dd, J=11.0, 6.6 Hz, 2H), 1.88 (t, J=5.5 Hz, 2H), 1.29 (s, 9H); ^{13}C NMR (CD_3OD) δ: 66.7 (t), 55.0 (s), 54.3 (t), 41.4 (t), 26.6 (q); HRMS (CI) calcd for $C_9H_{20}O_2N$ ($M+H^+$) 174.1494, found 174.1490.

3.2. Asymmetric addition of diethylzinc to aldehydes; general procedure

Diethylzinc (1.1 M in toluene, 1.2 equiv) was added to ligand **3** in toluene under argon at 0 °C and the mixture was stirred for 0.5 h at 0 °C. After the addition of aldehyde (1.0 equiv) at 0 °C, the mixture was stirred at rt and after 24 h an aqueous 1.2 M solution of HCl was added. After usual work-up, pure alcohols were obtained by flash column chromatography. The ee and the absolute configuration of the resulting alcohol were determined by using HPLC.

3.3. Asymmetric addition of diethylzinc to aldehydes and benzoylation; general procedure

Diethylzinc (1.1 M in toluene, 1.2 equiv) was added to ligand **3** in toluene under argon at 0 °C and the mixture was stirred for 0.5 h at 0 °C. After addition of heptanal (1.0 equiv) at 0 °C, the mixture was stirred at rt and after 24 h an aqueous 1.2 M solution of HCl was added. After extraction with EtOAc, the combined organic layers were dried with $MgSO_4$ and filtered. The solvent was removed in vacuo to afford the crude nonan-3-ol, which was dissolved in CH_2Cl_2. Benzoyl chloride (1.5 equiv), followed by Et_3N (2 equiv) and DMAP (1 equiv) were added to the previously prepared alcohol solution. After stirring at rt for 18 h, the reaction was quenched with an aqueous 1.2 M solution of HCl. After usual work-up, the pure esters were obtained by flash column chromatography. The ee and the absolute configuration of the resulting ester were determined by using HPLC.

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Direct synthesis of 4,4-disubstituted *N*-silyl-1,4-dihydropyridines

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Abstract—An unprecedented method for the preparation of 4,4-disubstituted 1,4-dihydropyridines is presented. It is based on the trapping reaction of 4-substitued *N*-silylpyridinium ions. When performed with dialkylmagnesium reagents, such as $i\mathrm{Pr}_2\mathrm{Mg}$, silyl protected 4,4-disubstituted 1,4-dihydropyridines were obtained in up to quantitative yields. High 1,4-selectivity was found for sterically demanding nucleophiles, whereas small nucleophiles ($\mathrm{Me}_2\mathrm{Mg}$) tend to yield 1,2-addition-products. Grignard, dialkylzinc and organocopper reagents were found to give either no addition products or less favorable results. Reduction of the obtained 1,4-dihydropyridine with NaCNBH_3 in the presence of HCl, followed by treatment with *tert*-butyl dicarbonate provided the corresponding *N*-Boc protected piperidines with high yields.

1. Introduction

1,4-Dihydropyridines (DHP) constitute important classes of compounds, with many derivatives being found especially among natural products and bioactive agents.[1] Regioselective addition of nucleophilic reagents to *N*-acylpyridinium ions is a common method in the preparation of 1,2- and 1,4-dihydropyridines. When Grignard[2] or organotin[3] reagents are used mainly 2-substituted 1,2-dihydropyridines are formed. In contrast, the use of organotitanium[4] reagents and lithium–dialkylcuprates[5] leads almost exclusively to the formation of 4-substituted 1,4-dihydropyridines, which is also the case when Grignard and organozinc reagents admixed with copper(I) salts are employed.[6] The regioselectivity of the nucleophilic attack on the pyridinium cation is believed to follow the HSAB principle. According to this principle relatively hard nucleophiles are predicted to display a preference for the addition to the 2-position of the pyridine ring and relatively soft nucleophiles for the 4-position.[7] Whereas *N*-ayclpyridinium ions are widely used for nucleophilic addition reactions, related examples with *N*-silylpyridinium ions are scarce. According to the work of Akiba et al.[8] with *N*-silylpyridinium ions derived from pyridine, these intermediates are susceptible to nucleophilic addition reactions of Grignard reagents leading to 1,4-addition products with high regioselectivity. Similar results were found, for *N*-silylpyridinium ions derived methyl nicotinate.[9] Compared to *N*-silylpyridinium ions the 1,4-regioselectivity of related reactions of *N*-silylquinolinium[10] ions is poor, though it may be improved by increasing the bulk of the *N*-silyl moiety. It is well documented that the regioselectivity of addition reactions to *N*-acylpyridinium ions is strongly influenced by the substituents present on the pyridine ring: for example, when a substituent is present in the 4-position, nucleophiles almost exclusively add to the 2- and 6-position of the ring system.[11] However, corresponding data for *N*-silylpyridinium ions are still missing. So far, even the question whether 4-substituted *N*-silylpyridinium ions are susceptible to nucleophilic addition reactions at all has not been examined, although such trapping reactions might be synthetically quite useful. Actually, one would expect that the presence of a sterically demanding *N*-silyl group would shield the 2- and 6-position and thus force a nucleophile to add to the 4-position of the *N*-silylpyridinium ion even if a substituent is already present in this position. As a result 4,4-disubstituted *N*-silyl-1,4-dihydopyridines and finally, after desilylation, the parent compounds should be formed. So far, only a few scattered examples for the direct preparation of 4,4-disubstituted 1,4-dihydropyridines from activated pyridine derivatives are known. These are limited to *N*-alkyl- and *N*-acylpyridinium salts possessing an ester function in the 4-position, which when treated with alkyl or acyl halides and zinc give the 4,4-disubstituted products presumably by a radical process.[12] In addition to these examples 4-addition to 4-substituted pyridine derivatives has only been observed for intramolecular processes leading to spirocyclic compounds.[13] But usually multistep syntheses are required for the construction of 4,4-disubstituted 1,4-dihydropyridines.[14] We therefore thought it would be

Keywords: Dihydropyridines (DHP); Piperidines; Pyridinium salts; Dialkylmagnesium reagents.
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a highly rewarding endeavor to establish a method for the direct synthesis of 4,4-disubstituted 1,4-dihydropyridines from *N*-silylpyridinium ions. In the present paper, we report the successful implementation of this plan.

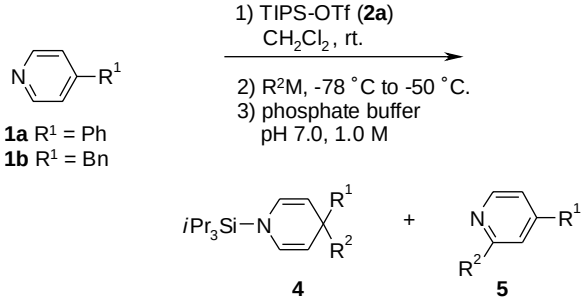
2. Results and discussion

Initial experiments were performed with pyridine **1a** (Table 1) and triisopropylsilyl triflate (TIPS triflate **2a**) as activating agent. The 4-phenyl group present in **1a** was chosen because of its inertness towards basic conditions and the TIPS group as it should efficiently shield the 2- and 6-position of the pyridine ring (Scheme 1). We were very pleased to find that upon treatment of **1a** with one equivalent of TIPS triflate at room temperature followed by 2 equiv of EtMgCl (2.0 M in Et_2O) at −78 °C the 4,4-disubstituted dihydropyridine **4a** was formed. Under optimized conditions the yield of **4a** amounted to 28%. Interestingly, **4a** was sufficiently stable for isolation, in contrast to the 1,2-addition product, which probably had already been oxidized during the quench reaction to give the aromatic species **5a**. But according to the ^{1}H NMR of the crude product only 1% of the latter was formed. Thus, the addition reaction had proceeded with a high regioselectivity in favor of the 1,4-addition. But unfortunately, even under optimized conditions 64% of the starting material **1a** were still present in the crude product (according to ^{1}H NMR).

When *n*BuMgCl (2.9 M in Et_2O) was used as a nucleophile, the corresponding 4-addition product **4b** was isolated in 34% (Table 1, entry 4). Interestingly, the reaction failed when Et_2O as solvent for the Grignard reagent (*n*BuMgCl) was replaced by THF. With BnMgCl, using again Et_2O as solvent (1.0 M) the reaction even came to completion and gave the 1,4-addition product **4c** in high yield (90%) and with good regioselectivity (Table 1, entry 7). Various other organometallic compounds as well as the pyridine derivative **1b** were checked for their suitability in this reaction. However, all of these reactions failed except for the ones employing higher order cuprates for which at least small amounts of the 1,4-addition products could be isolated or observed by ^{1}H NMR (Table 1, entries 10 and 11).

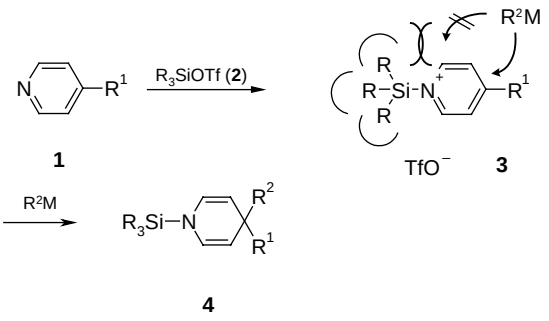
We speculated that the failure and the low yields observed for some of the trapping reactions of **3** using Grignard reagents were caused by the halide ions that had been introduced with the organometallic species. Due to their higher nucleophilicity compared to the triflate ion, the halide ion should shift the equilibrium between the *N*-silylpyridinium ion **3** and the free pyridine **1** towards the latter. This might hamper or even prevent trapping reactions of **3** especially when they are slow. To shed some light on this question we performed additional trapping reactions of **3** with ethyl and *n*-butyl Grignard reagents exhibiting bromide and iodide instead of chloride as counter ion. With EtMgBr the yield of **4a** improved to 44% (Table 1, entry 2) as compared to the addition reaction of EtMgCl

Table 1. Addition of various organometallic compounds to *N*-triisopropylsilylpyridinium ions



Entry	Start. mat.	R^2M[a]	Product	Yield **4** (%)[b]	Product ratio **4/5/1** (%)[c]
1	**1a** R^1=Ph	EtMgCl	**4a 5a**	28	35/1/64
2	**1a** R^1=Ph	EtMgBr	**4a 5a**	44	46/7/47
3	**1a** R^1=Ph	EtMgI	**4a 5a**	30	35/1/64
4	**1a** R^1=Ph	*n*BuMgCl[d]	**4b 5b**	34	36/11/53
5	**1a** R^1=Ph	*n*BuMgBr	**4b 5b**	20	27/4/69
6	**1a** R^1=Ph	*n*BuMgI	**4b 5b**	12	13/0/87
7	**1a** R^1=Ph	BnMgCl	**4c 5c**	90	90/10/0
8	**1a** R^1=Ph	PhMgBr	**4d 5d**	0	0/0/100
9	**1a** R^1=Ph	MeMgBr	**4e 5e**	0	0/0/100
10	**1a** R^1=Ph	$nBu_2CuCNLi_2$	**4b 5b**	11	nd[e]
11	**1a** R^1=Ph	$Me_2CuCNLi_2$	**4e 5e**	—[f]	3/0/97
12	**1a** R^1=Ph	Et_2Zn	**4a 5a**	0	0/0/100
13	**1a** R^1=Ph	*n*BuLi	**4b 5b**	0	0/0/100
14	**1b** R^1=Bn	EtMgBr	**4i 5i**	0	0/0/100
15	**1b** R^1=Bn	*n*BuMgCl	**4k 5k**	0	0/0/100

[a] In Et_2O.
[b] Isolated yield.
[c] According to ^{1}H NMR of the crude reaction product.
[d] With *n*BuMgCl in THF no reaction occurred.
[e] Not determined.
[f] Not isolated.



1 3 4

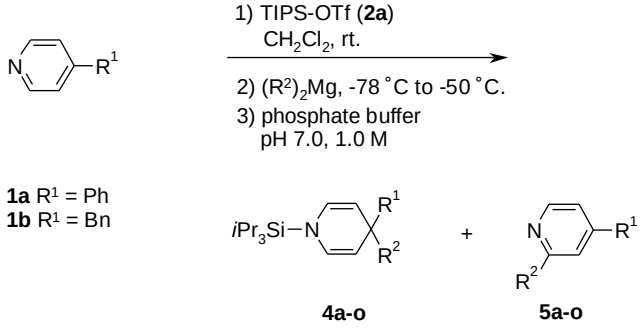
Scheme 1. Directing nucleophilic attack towards the 4-position of a pyridine nucleus.

(**4a**: 28%; Table 1, entry 1). However, using EtMgI a yield similar to the one of the addition reaction of EtMgCl was observed (30 vs 28%, compare Table 1, entries 3 and 1). In case of the addition of a *n*-butyl residue, the yield became distinctly lower when *n*BuMgBr instead of *n*BuMgCl was used, and showed a further drop when *n*BuMgI was employed (Table 1, entries 4–6). Although there was, obviously, no clear correlation between the yield of **4a** and the nucleophilicity of the counter ion of the Grignard reagent that could have supported our assumption, we thought it worth employing dialkylmagnesium derivatives as nucleophilic trapping reagents. The required magnesium compounds were prepared from Grignard reagents by precipitation of MgX_2.

When Et_2Mg (Table 2, entry 1) instead of ethyl Grignard reagents (Table 1, entry 1–3) was used the yield of the 4-addition product **4a** rose to 78%. Moreover, the regioselectivity was quite satisfactory (90/4; Table 2, entry 1). When using Bn_2Mg the yield, which had already been very high (Table 1, entry 7, 90%), remained more or less unaffected, while the regioselectivity (Table 2, entry 3; **4c/5c** 95/2) was significantly improved. Finally, employing iPr_2Mg the reaction proceeded with complete control of the regioselectivity providing the 4-addition product in 91% yield (Table 2, entry 6).

To uncover the impact of the *N*-silyl moiety on the outcome of the addition reactions experiments employing trimethylsilyl triflate **2b** and triphenylsilyl triflate **2c** as activating agents were performed. In case of trimethylsilyl triflate mediated trapping reactions employing Et_2Mg and Bn_2Mg as nucleophiles the results were far less satisfying both in respect to yield and regioselectivity (see Table 3, entries 1–2). But for the addition of iPr_2Mg regioselectivity and yield were only slightly diminished (see Table 3, entry 3). The most negative results had been yielded by the reaction of Et_2Mg. The addition products **4p** and **5a** were formed only in minute amounts and, interestingly, the regioselectivity had been inverted. In addition, all *N*-trimethylsilyl derivatives **4p–4r** were highly susceptible to hydrolysis and thus barley isolable. The use of the bulkier triphenylsilyl group gave some increased stability but for Et_2Mg and Bn_2Mg the yields of the desired product were distinctly

Table 2. Addition of various dialkylmagnesium reagents to *N*-triisopropylsilylpyridinium ions

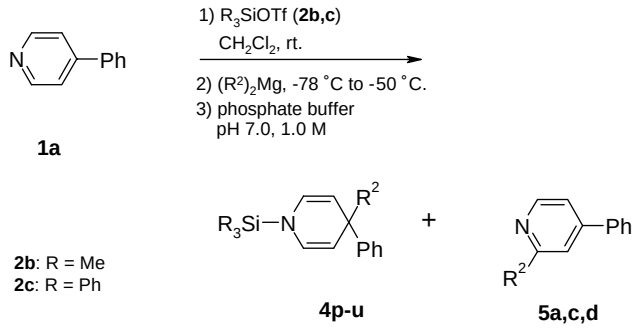


4a-o **5a-o**

Entry	Start. mat.	$(R^2)_2Mg$[a]	Product	Yield **4** (%)[b]	Product ratio **4/5/1** (%)[c]
1	**1a** R^1 = Ph	Et_2Mg	**4a 5a**	78	90/4/6
2	**1a** R^1 = Ph	nBu_2Mg	**4b 5b**	82	100/0/0
3	**1a** R^1 = Ph	Bn_2Mg	**4c 5c**	92	95/2/3
4	**1a** R^1 = Ph	Ph_2Mg	**4d 5d**	0	5/95[d]/0
5	**1a** R^1 = Ph	Me_2Mg	**4e 5e**	0	0/59/41
6	**1a** R^1 = Ph	iPr_2Mg	**4f 5f**	91	99/0/1
7	**1a** R^1 = Ph	tBu_2Mg	**4g 5g**	56	80/3/17[e]
8	**1a** R^1 = Ph	$Allyl_2Mg$	**4h 5h**	20	20/78[d]/2
9	**1b** R^1 = Bn	Et_2Mg	**4i 5i**	73	86/2/12
10	**1b** R^1 = Bn	nBu_2Mg	**4k 5k**	54	54/6/40
11	**1b** R^1 = Bn	Bn_2Mg	**4l 5l**	85	95/0/5
12	**1b** R^1 = Bn	iPr_2Mg	**4m 5m**	78	100/0/0
13	**1b** R^1 = Bn	tBu_2Mg	**4n 5n**	5	6/0/94[f]
14	**1b** R^1 = Bn	$Allyl_2Mg$	**4o 5o**	12	21/70/9

[a] After addition of the organomagnesium compound to the *N*-silylpyridinium ion at −78 °C the mixture was slowly warmed to −50 °C.
[b] Isolated yield.
[c] According to ^{1}H NMR of the crude reaction product.
[d] Sum of **5** and non oxidized 1,2-addition product, which were both present.
[e] Yield 63%, ratio 86/2/12 when addition performed by warming the mixture from −78 °C to room temperature.
[f] Yield 29%, ratio 32/0/68 when addition performed by warming the mixture from −78 °C to room temperature.

Table 3. Variation of the *N*-trialkylsilyl group in the trapping reactions of *N*-silylpyiridinium ions



Entry	R_3SiOTf	$(R^2)_2Mg$[a]	Product	Yield **4** (%)[b]	Product ratio **4/5/1** (%)[c]
1	Me_3SiOTf	Et_2Mg	**4p 5a**	0	1/4/95
2	Me_3SiOTf	Bn_2Mg	**4q 5c**	45	66/9/25
3	Me_3SiOTf	iPr_2Mg	**4r 5f**	90	91/2/7
4	Ph_3SiOTf	Et_2Mg	**4s 5a**	0	11/30/59
5	Ph_3SiOTf	Bn_2Mg	**4t 5c**	48	49/7/44
6	Ph_3SiOTf	iPr_2Mg	**4u 5f**	86	98/1/1

[a] After addition of the organomagnesium compound to the *N*-silylpyridinium ion at −78 °C the mixture was slowly warmed to −50 °C.
[b] Isolated yield.
[c] According to ^{1}H NMR of the crude reaction product.

lower than those obtained with TIPS triflate as activating agent (Table 3, entries 4–6). Additionally, with Et_2Mg a reversed selectivity in favor of **5a** was observed again (compare Table 2, entry 1 with Table 3, entry 4).

Consequently, for additional trapping reactions varying the diorganomagnesium compounds again, TIPS triflate was used for the activation of the pyridine moiety. In case of nBu_2Mg the 1,4-addition product **4b** was formed exclusively and in high yield (Table 2, entry 2). Even with tBu_2Mg the addition reaction proceeded smoothly providing **4g** in good yield and with high regioselectivity (Table 2, entry 7).

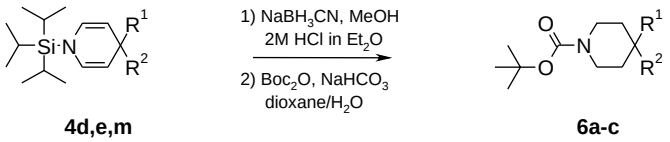
In contrast, Ph_2Mg, Me_2Mg and $allyl_2Mg$ with sterically less demanding residues reacted predominantly in the 2-position to yield the pyridine derivatives **5d**, **5e** and **5h** after aqueous workup as the major product (Table 2, entries 4, 5 and 8).

Additionally, a further set of experiments was performed with the pyridine derivative **1b**. The results of these trapping reactions closely paralleled those obtained for **1a**. The yield for the 4-addition product **4** obtained from **1b** was significantly lower only with tBu_2Mg (Table 2, entry 13, **4n**, 5%). But when the reaction was performed by increasing the temperature (from −78 °C) not only to −50 °C but to room temperature, the yield rose to 29% (ratio **4/5/1**=32/0/68). For the addition of tBu_2Mg to **1a** both the yield that had already been quite satisfying (from 56 to 63%) and the product ratio [from 80/3/17 to 86/2/12 (5/4/1)] improved slightly when the reaction temperature was allowed to reach room temperature. The insufficient outcome of the addition of tBu_2Mg to **1b** (yield 5%, see Table 2, entry 13) under standard conditions could be the result of a competing deprotonation reaction. It is obvious that the benzylic position of **1b** is highly acidic, which should be even more true for the *N*-silyl derivative of **1b**. Therefore, in case of the addition of tBu_2Mg to **1b** it also seems likely that a deprotonation reaction of the benzylic position occurs, which finally diminishes the yield of the addition product. Actually, it is quite intriguing that the reactivity of the benzylic position (in **1b**) had no or only a secondary effect on the other addition reactions performed with **1b**. The sharp drop in yield observed for the addition of tBu_2Mg is possibly due to its higher steric demand in addition to his higher basicity as compared to the other Grignard reagents.

At first sight one might be tempted to assume that the regioselectivity observed in the trapping reactions of **1a** and **1b** is a function of the softness, according to the HSAB principle, of the alkyl moiety of the organomagnesium compound used. Particularly, since relatively soft nucleophiles (such as Et_2Mg, nBu_2Mg, iPr_2Mg, tBu_2Mg) add preferentially to the 4-position of the pyridine ring, whereas harder nucleophiles ($allyl_2Mg$, Ph_2Mg) give mainly the respective 2-addition products. However, with Me_2Mg the 2-addition is more favored than with Ph_2Mg or $allyl_2Mg$ (see Table 2, entries 6–8), whereas according to the HSAB principle the opposite should be true. Therefore, it is more likely that the regioselectivity is dominated by the size and the steric demand of the nucleophile and depends only partly on the softness of the reagent. This is also indicated by the results of the trapping reaction with varying *N*-silyl groups according to which the size of the nucleophile as well as the steric demand of the *N*-silyl moiety play important roles for the regioselectivity.

The *N*-triisopropylsilyl-1,4-dihydropyridines prepared in this study were found to be sufficiently stable for isolation. Although, chromatography on standard silica gel columns caused considerable decomposition, the recovery of the materials was almost quantitative when aluminum oxide was used for purification (neutral, Brockmann activity III[15]).

Table 4.



4d,e,m **6a-c**

Entry	Start. mat.	Product	R^1	R^2	Yield **6** (%)[a]
1	**4f**	**6a**	Ph	*i*Pr	90
2	**4g**	**6b**	Ph	*t*Bu	95
3	**4m**	**6c**	Bn	*i*Pr	92

[a] Isolated yield.

Stored under nitrogen atmosphere at −20 °C the isolated *N*-triisopropylsilyl-1,4-dihydropyridines were stable for weeks.

Having established a highly efficient access to *N*-triisopropylsilyl-1,4-dihydropridines we set out to explore the utility of these compounds for the preparation of related 4,4-disubstituted piperidines. Interestingly, synthetic methods giving access to this class of compounds are still rare.[16]

It turned out that the desired transformation can be efficiently accomplished by treating the respective *N*-triisopropylsilyl-silyl-1,4-dihydropyridine in Et_2O with $NaCNBH_3$ and etheral HCl. Under these conditions not only a reduction of the double bonds but also, though not unexpected, a removal of the *N*-silyl group occurs. To allow for a more convenient isolation the formed amines were finally trapped with di-*tert*-butyl dicarbonate (Boc_2O) providing the corresponding Boc protected piperidine derivatives. Thus, from the *N*-silyl derivatives **4f**, **4g** and **4m** the corresponding piperidine derivatives **6a–c** were obtained in yields of ≥90%, which clearly demonstrates the efficiency of this approach (Table 4).

3. Conclusion

In summary, we have presented an easy and straightforward method for the preparation of 4,4-disubstituted 1,4-dihydropyridines with a wide variety of substituents. It is based on unprecedented trapping reactions of 4-substituted *N*-silylpyridinium ions with organomagnesium compounds. The obtained 4,4-disubstituted 1,4-dihydropyridines have been demonstrated to give rapid access to fully saturated 4,4-disubstituted piperidine derivatives, which adds a new method to the few existing for the preparation of piperidine derivatives with a quaternary carbon in 4-position. Further studies exploring the scope of the trapping reaction of *N*-silylpyridinum ions mentioned above for the synthesis of highly functionalized 1,4-dihydropyridines are in progress.

4. Experimental

4.1. General experimental

All reactions were performed using flame-dried glassware under N_2 atmosphere. All solvents were freshly dried using standard[17] procedures. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or CD_2Cl_2 at 500 and 125 MHz, respectively. Infrared spectra were obtained on a Perkin-Elmer Model 1600 FTIR spectrometer. Microanalytical data for carbon, hydrogen and nitrogen were determined on a Heraeus Rapid Analyser and on a Elementar Vario EL Analyser. Flash chromatography was performed with 50–150 mesh aluminium oxide (neutral Brockmann activity III).

4.2. General procedure for the preparation of dialkylmagnesium reagents[18] (GP1)

Commercially available alkylmagnesium halide solutions in Et_2O or THF were diluted with Et_2O to yield 1.0 M stock solutions. 1,4-Dioxane (1.1 equiv) was added slowly to the mechanically stirred Grignard solution at room temperature. The heterogeneous solution was stirred over night to complete precipitation. The resulting suspensions were centrifuged to yield clear colorless R_2Mg solutions. Complete precipitation of magnesium halide was verified by addition of a few drops of 1,4-dioxane. The clear R_2Mg solutions were kept under nitrogen at 4 °C.

4.3. General procedure for the preparation of 4,4-disubstituted *N*-silyl-1,4-dihydropyridines (GP2)

The corresponding 4-substituted pyridine was dissolved in CH_2Cl_2 and treated with 1.0 equiv TIPS triflate at room temperature. After stirring at ambient temperature for 15 min the colorless solution was cooled to −78 °C, followed by dropwise addition of a twofold excess of R_2Mg solution. The resulting yellow to deep red colored mixture was slowly warmed to −50 °C and quenched after the time given by addition of 2 ml phosphate buffer (pH 7, *c* 1.0 M). The aqueous layer was extracted with CH_2Cl_2 (4×7 ml). The combined organic layers were dried ($MgSO_4$), and concentrated in vacuo. Column chromatography at aluminum oxide (neutral, Brockmann activity III, pentane; addition of CH_2Cl_2 to dissolve side products was necessary in some cases) yielded the final product. The final compound was stored under N_2 atmosphere at −20 °C to avoid oxidation.

4.4. General procedure for the preparation of 4,4-disubstituted *N*-Boc protected piperidines (GP3)

The corresponding 4,4-disubstituted *N*-silyl-1,4-dihydropyridine was dissolved in CH_2Cl_2 and treated with 2.5 equiv of $NaBH_3CN$ in MeOH at room temperature. After addition of 5.0 equiv 2 M HCl in Et_2O the mixture was stirred for 1 h

at room temperature and subsequently quenched with aqueous 5 M KOH. The water phase was extracted with CH_2Cl_2. The raw material resulting from the combined organic layers was dissolved in a 1:1 mixture of dioxane and water containing $NaHCO_3$ and treated with 1.1 equiv of Boc_2O. After stirring over night the mixture was extracted with CH_2Cl_2. The organic extracts were concentrated and the resulting residue purified by CC on silica gel.

4.4.1. 4-Ethyl-4-phenyl-1-triisopropylsilyl-1,4-dihydropyridine (4a). According to GP2 from 4-phenylpyridine (**1a**, 38.8 mg, 0.25 mmol), TIPS triflate (76.6 mg, 67.4 µl, 0.25 mmol) in CH_2Cl_2 (2 ml) and Et_2Mg (1.0 ml, 0.5 M in Et_2O), reaction time 10 h.

Yield 66.6 mg (78%), colorless crystals, mp 59 °C. TLC R_f=0.69 (aluminum oxide 60 neutral, *n*-pentane). ^{1}H NMR ($CDCl_3$) δ=0.95 (t, J=7.5 Hz, 3H, CH_2CH_3), 1.11 (d, J=7.5 Hz, 18H, $CHCH_3$), 1.30 (sept, J=7.5 Hz, 3H, $CHCH_3$), 1.68 (q, J=7.5 Hz, 2H, CH_2CH_3), 4.36 (d, J=8.0 Hz, 2H, NCH=C*H*), 6.15 (d, J=8.0 Hz, 2H, NC*H*=CH), 7.12–7.16 (m, 1H, H_{aromat}), 7.30–7.34 (m, 2H, H_{aromat}), 7.40–7.43 (m, 2H, H_{aromat}). ^{13}C NMR ($CDCl_3$, DEPT) δ=10.0 (q), 11.4 (d), 17.9 (q), 35.0 (t), 42.2 (s), 106.1 (d, NC=*C*), 125.1 (d, C_{aromat}), 126.7 (d, N*C*=C), 128.0 (d, C_{aromat}), 128.2 (d, C_{aromat}), 152.6 (s, C_{aromat}). MS (CI, CH_5^+); *m*/*z* (%): 324 (100) $[M+1]^+$, 312 (33), 157 (4), 147 (4). IR (film): $\tilde{\nu}$= 3054 cm^{-1}, 2984, 2304, 1423, 1265, 895, 746. Anal. Calcd for $C_{22}H_{35}NSi$ (341.62): C 77.35, H 10.33, N 4.10. Found C 77.33, H 10.39, N 4.05.

4.4.2. 4-*n*-Butyl-4-phenyl-1-triisopropylsilyl-1,4-dihydropyridine (4b). (A) According to GP2 from 4-phenylpyridine (**1a**, 77.6 mg, 0.5 mmol), TIPS triflate (153.2 mg, 134.8 µl, 0.5 mmol) in CH_2Cl_2 (4 ml) and Bu_2Mg (2.0 ml, 0.5 M in Et_2O), reaction time 10 h.

Yield 151.6 mg (82%), colorless crystals, mp 85–86 °C. TLC R_f=0.76 (aluminum oxide 60 neutral, *n*-pentane). ^{1}H NMR ($CDCl_3$) δ=0.92 (t, J=7.2 Hz, 3H, CH_3), 1.11 (d, J=7.4 Hz, 18H, CH_3), 1.28 (sept, J=7.4 Hz, 3H, $CH(CH_3)_2$), 1.31–1.39 (m, 4H, CH_2), 1.65 (m, 2H, CH_2), 4.40 (d, J=8.3 Hz, 2H, NCH=C*H*), 6.12 (d, J=8.3 Hz, 2H, NC*H*=CH), 7.14 (tt, J=7.2/1.1 Hz, 1H, H_{aromat}), 7.33 (m, 2H, H_{aromat}), 7.42 (m, 2H, H_{aromat}). ^{13}C NMR ($CDCl_3$, DEPT) δ=11.4 (d), 12.3 (q), 17.9 (q), 23.3 (t), 28.3 (t), 41.6 (s), 42.9 (t), 106.7 (d, NC=*C*), 125.1 (d, C_{aromat}), 126.6 (d, N*C*=C), 127.8 (d, C_{aromat}), 128.0 (d, C_{aromat}), 152.7 (s, C_{aromat}). MS (CI, CH_5^+); *m*/*z* (%): 370 (100) $[M+1]^+$, 312 (53), 178 (7), 156 (6), 147 (5). IR (Film): $\tilde{\nu}$=3054 cm^{-1}, 2986, 2868, 2305, 1665, 1422, 1265, 895, 740, 705. Anal. Calcd for: $C_{27}H_{37}NSi$ (369.67): C 77.98, H 10.63, N 3.79. Found. C 77.98, H 10.73, N 3.79.

(B) A solution of 4-phenylpyridine (**1a**, 38.8 mg, 0.25 mmol) in CH_2Cl_2 (2 ml) was treated with TIPS triflate (76.6 mg, 67.4 µl, 0.25 mmol), and stirred for 15 min at room temperature. After cooling to −78 °C the mixture was transferred via cannula to a prior prepared solution of $Bu_2CuCNLi_2$[19] (2.0 equiv) in Et_2O kept at −78 °C. Then the resulting red colored mixture was allowed to warm up to 0 °C. After 4 h it was quenched and worked up as described above. Yield of **4b**: 11%.

4.4.3. 4-Benzyl-4-phenyl-1-triisopropylsilyl-1,4-dihydropyridine (4c). According to GP2 from 4-phenylpyridine (**1a**, 38.8 mg, 0.25 mmol), TIPS triflate (76.6 mg, 67.4 µl, 0.25 mmol) in CH_2Cl_2 (2 ml) and Bn_2Mg (1.0 ml, 0.5 M in Et_2O), reaction time 10 h.

Yield 92.8 mg (92%), colorless crystals, mp 81 °C. TLC R_f=0.37 (aluminum oxide 60 neutral, *n*-pentane). ^{1}H NMR ($CDCl_3$) δ=0.95 (d, J=7.5 Hz, 18H, CH_3), 1.15 (sept, J=7.5 Hz, 3H, $CH(CH_3)_2$), 3.03 (s, 2H, CH_2), 4.51 (d, J=8.0 Hz, 2H, NCH=C*H*), 5.96 (d, J=8.0 Hz, 2H, NCH=C*H*), 7.09–7.15 (m, 3H, H_{aromat}), 7.16–7.20 (m, 3H, H_{aromat}), 7.38 (t, J=7.5 Hz, 2H, H_{aromat}), 7.49 (d, J=7.5 Hz, 2H, H_{aromat}). ^{13}C NMR ($CDCl_3$, DEPT) δ=11.2 (d), 17.7 (q), 43.2 (s), 50.0 (t), 105.9 (d, NC=*C*), 125.3 (d, C_{aromat}), 125.5 (d, C_{aromat}), 126.7 (d, N*C*=C), 127.3 (d, C_{aromat}), 128.0 (d, C_{aromat}), 128.1 (d, C_{aromat}), 131.3 (d, C_{aromat}), 139.3 (s, C_{aromat}), 152.2 (s, C_{aromat}). MS (CI, CH_5^+); *m*/*z* (%): 404 (100) $[M+1]^+$, 312 (84), 287 (12), 195 (22), 187 (11), 183 (6), 157 (6), 141 (7). IR (film): $\tilde{\nu}$= 3053 cm^{-1}, 2985, 2305, 1422, 1264, 895, 746, 706. Anal. Calcd for $C_{27}H_{37}NSi$ (403.69): C 80.33, H 9.24, N 3.47. Found C 80.34, H 9.26, N 3.41.

4.4.4. 4-Isopropyl-4-phenyl-1-triisopropylsilyl-1,4-dihydropyridine (4f). According to GP2 from 4-phenylpyridine (**1a**, 38.8 mg, 0.25 mmol), TIPS triflate (76.6 mg, 67.4 µl, 0.25 mmol) in CH_2Cl_2 (2 ml) and *i*Pr_2Mg (1.0 ml, 0.5 M in Et_2O), reaction time 4 h.

Yield 81.0 mg (91%), colorless oil. TLC R_f=0.58 (aluminum oxide 60 neutral, *n*-pentane). ^{1}H NMR ($CDCl_3$) δ=0.82 (d, J=6.7 Hz, 6H, CH_3), 1.09 (d, J=7.4 Hz, 18H, $SiCH(CH_3)_2$), 1.26 (sept, J=7.4 Hz, 3H, $SiCH(CH_3)_2$), 2.07 (sept, J=6.7 Hz, 1H, $CH(CH_3)_2$), 4.97 (d, J=8.5 Hz, 2H, NCH=C*H*), 6.14 (d, J=8.5 Hz, 2H, NC*H*=CH), 7.13 (tt, J=7.2/1.4 Hz, 1H, H_{aromat}), 7.30–7.38 (m, 4H, H_{aromat}). ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ= 11.4 (d), 17.8 (q), 17.9 (q), 37.4 (d), 45.5 (s), 104.2 (d, NC=*C*), 124.7 (d, C_{aromat}), 126.7 (d, C_{aromat}), 128.1 (d, C_{aromat}), 128.5 (d, N*C*H=CH)., 151.5 (s). MS (CI, CH_5^+); *m*/*z* (%): 356 (100) $[M+1]^+$, 312 (48), 235 (9), 189 (5), 184 (5), 157 (7), 147 (9). IR (film): $\tilde{\nu}$=3054 cm^{-1}, 2985, 2868, 2305, 1666, 1423, 1265, 895, 739, 706. Anal. Calcd for $C_{23}H_{37}NSi$ (355.64): C 77.68, H 10.49, N 3.94. Found C 74.64, H 10.65, N 3.93.

4.4.5. 4-*tert*-Butyl-4-phenyl-1-triisopropylsilyl-1,4-dihydropyridine (4g). According to GP2 from 4-phenylpyridine (**1a**, 38.8 mg, 0.25 mmol), TIPS triflate (76.6 mg, 67.4 µl, 0.25 mmol) in CH_2Cl_2 (2 ml) and *t*Bu_2Mg (1.0 ml, 0.5 M in Et_2O). After addition of the organometallic reagent the mixture was slowly warmed to room temperature, reaction time 10 h.

Yield 58.6 mg (63%), colorless crystals, mp 74 °C. TLC R_f=0.64 (aluminum oxide 60 neutral, *n*-pentane). ^{1}H NMR ($CDCl_3$) δ=0.86 (s, 9H, CH_3), 1.04 (d, J=7.4 Hz, 18H, $HCH(CH_3)_2$), 1.24 (sept, J=7.4 Hz, 3H, $CH(CH_3)_2$), 5.12 (d, J=8.5 Hz, 2H, NCH=C*H*), 6.11 (d, J=8.5 Hz, 2H, NC*H*=CH), 7.10 (t, J=7.4 Hz, 1H, H_{aromat}), 7.23–7.26 (m, 2H, H_{aromat}), 7.29–7.31 (m, 2H, H_{aromat}). ^{13}C NMR ($CDCl_3$, DEPT) δ=11.3 (d), 17.8 (q), 25.9 (q), 38.6 (s), 45.9 (s),

103.0 (d, NC=*C*), 124.7 (d, C_{aromat}), 127.0 (d, N*C*=C), 127.4 (d, C_{aromat}), 128.4 (d, C_{aromat}), 149.1 (s, C_{aromat}). MS (CI, CH_5^+); *m/z* (%): 370 (100) $[M+1]^+$, 312 (67), 292 (5), 184 (8), 156(12), 147 (9), 119 (6). IR (film): $\tilde{\nu}=3054\ cm^{-1}$, 2984, 2868, 2305, 1666, 1422, 1265, 895, 740, 706. Anal. Calcd for $C_{27}H_{37}NSi$ (369.67): C 77.98, H 10.63, N 3.79. Found C 77.80, H 10.65, N 3.72.

4.4.6. 4-Allyl-4-phenyl-1-triisopropylsilyl-1,4-dihydropyridine (4h). According to GP2 from 4-phenylpyridine (**1a**, 38.8 mg, 0.25 mmol), TIPS triflate (76.6 mg, 67.4 µl, 0.25 mmol) in CH_2Cl_2 (2 ml) and $allyl_2Mg$ (1.0 ml, 0.5 M in Et_2O), reaction time 2 h.

Yield 17.9 mg (20%), colorless oil. TLC $R_f=0.61$ (aluminum oxide 60 neutral, *n*-pentane). ^1H NMR ($CDCl_3$) $\delta=$ 1.10 (d, $J=7.5$ Hz, 18H, SiCH(CH_3)$_2$), 1.26 (sept, $J=$ 7.5 Hz, 3H, SiC*H*(CH_3)$_2$), 2.53 (d, $J=7.0$ Hz, 2H, CH_2), 4.46 (d, $J=8.0$ Hz, 2H, NCH=C*H*), 5.01–5.05 (m, 2H, CH=CH_2), 5.79–5.88 (m, 1H, C*H*=CH_2), 5.96 (d, $J=$ 8.0 Hz, 2H, NC*H*=CH), 7.16 (t, $J=7.5$ Hz, 1H, H_{aromat}), 7.34 (t, $J=7.5$ Hz, 2H, H_{aromat}), 7.42 (d, $J=7.5$ Hz, 2H, H_{aromat}). ^{13}C NMR ($CDCl_3$, DEPT) $\delta=11.4$ (d), 17.9 (q), 41.5 (s), 48.1 (t), 106.4 (d, NC=*C*), 116.2 (t, CH=*C*H_2), 125.2 (d, C_{aromat}), 126.7 (d, N*C*=C), 127.9 (d, C_{aromat}), 128.1 (d, C_{aromat}), 136.4 (*C*H=CH_2), 152.7 (s, C_{aromat}). MS (CI, CH_5^+); *m/z* (%): 354 (98) $[M+1]^+$, 312 (100), 236 (20), 184 (6), 156 (16), 147 (11). IR (film): $\tilde{\nu}=3053\ cm^{-1}$, 2985, 2304, 1665, 1421, 1265, 895, 739, 705. Anal. Calcd for $C_{23}H_{35}NSi$ (353.63): C 78.12, H 9.98, N 3.96. Found C 78.02, H 10.07, N 3.89.

4.4.7. 4-Benzyl-4-ethyl-1-triisopropylsilyl-1,4-dihydropyridine (4i). According to GP2 from 4-benzylpyridine (**1b**, 81.2 mg, 76.4 µl, 0.5 mmol), TIPS triflate (153.2 mg, 134.8 µl, 0.5 mmol) in CH_2Cl_2 (4 ml) and Et_2Mg (2.0 ml, 0.5 M in Et_2O), reaction time 10 h.

Yield 129.8 mg (73%), colorless oil. TLC $R_f=0.67$ (aluminum oxide 60 neutral, *n*-pentane). ^1H NMR ($CDCl_3$) $\delta=0.87$ (t, $J=7.4$ Hz, 3H, CH_2CH_3), 0.98 (d, $J=7.4$ Hz, 18H; CH(CH_3)$_2$), 1.16 (sept, $J=7.4$ Hz, 3H, C*H*(CH_3)$_2$), 1.23 (q, $J=7.4$ Hz, 2H, CH_2CH_3), 2.52 (s, 2H, CH_2Ph), 4.06 (d, $J=8.3$ Hz, 2H, NC*H*=CH), 5.96 (d, $J=$ 8.3 Hz, 2H, NCH=C*H*), 7.11–7.14 (m, 3H, H_{aromat}), 7.19–7.22 (m, 2H, H_{aromat}). ^{13}C NMR ($CDCl_3$, DEPT) $\delta=$ 11.3 (d), 11.3 (q), 17.7 (q), 36.1 (t), 40.0 (s), 41.8 (t), 42.9 (t), 105.6 (d, NC=*C*), 125.3 (d, C_{aromat}), 127.2 (d, N*C*=C), 129.1 (d, C_{aromat}), 131.0 (d, C_{aromat}), 139.3 (s, C_{aromat}). MS (CI, CH_5^+); *m/z* (%): 356 (56) $[M+1]^+$, 264 (100), 147 (4). IR (film): $\tilde{\nu}=2958\ cm^{-1}$, 2867, 1671. Anal. Calcd for $C_{28}H_{39}NSi$ (355.64): C 77.68, H 10.49, N 3.94. Found C 77.58, H 10.63, N 3.89.

4.4.8. 4-Benzyl-4-*n*-butyl-1-triisopropylsilyl-1,4-dihydropyridine (4k). According to GP2 from 4-benzylpyridine (**1a**, 81.1 mg, 76.4 µl, 0.5 mmol), TIPS triflate (153.2 mg, 134.8 µl, 0.5 mmol) in CH_2Cl_2 (4 ml) and *n*Bu_2Mg (2.0 ml, 0.5 M in Et_2O), reaction time 5 h.

Yield 103.0 mg (54%), colorless crystals, mp 47 °C. TLC $R_f=0.68$ (aluminum oxide 60 neutral, *n*-pentane). ^1H NMR ($CDCl_3$) $\delta=0.89$ (t, $J=7.1$ Hz, 3H, CH_2CH_3), 0.98 (d, $J=7.3$ Hz, 18H, CH(CH_3)$_2$), 1.16 (sept, $J=7.6$ Hz, 3H, C*H*(CH_3)$_2$), 1.19–1.23 (m, 2H, CH_2), 1.27–1.34 (m, 4H, CH_2), 1.55 (s, 2H, CH_2Ph), 4.11 (d, $J=8.3$ Hz, 2H, NC*H*=CH), 5.92 (d, $J=8.3$ Hz, 2H, NCH=C*H*), 7.11–7.14 (m, 3H, H_{aromat}), 7.19–7.22 (m, 2H, H_{aromat}). ^{13}C NMR ($CDCl_3$, DEPT) $\delta=11.3$ (q), 14.2 (d), 17.7 (q), 23.3 (t), 28.6 (t), 39.5 (s), 43.9 (t), 52.0 (t), 106.3 (d, NC=*C*), 125.3 (d, C_{aromat}), 127.2 (d, N*C*=C), 128.7 (d, C_{aromat}), 131.0 (d, C_{aromat}), 139.3 (s, C_{aromat}). MS (CI, CH_5^+); *m/z* (%): 384 (70) $[M+1]^+$, 292 (100), 147 (5). IR (film): $\tilde{\nu}=3053\ cm^{-1}$, 2960, 2867, 1668, 1288, 1265, 895, 737, 705. Anal. Calcd for $C_{28}H_{39}NSi$ (383.70): C 78.26, H 10.77, N 3.65. Found C 77.96, H 10.77, N 3.61.

4.4.9. 4-Dibenzyl-1-triisopropylsilyl-1,4-dihydropyridine (4l). According to GP2 from 4-benzylpyridine (**1b**, 40.6 mg, 38.2 µl, 0.25 mmol), TIPS triflate (76.6 mg, 67.4 µl, 0.25 mmol) in CH_2Cl_2 (2 ml) and Bn_2Mg (1.0 ml, 0.5 M in Et_2O), reaction time 10 h.

Yield 88.8 mg (85%), colorless crystals, mp 101–102 °C. TLC $R_f=0.48$ (aluminum oxide 60 neutral, *n*-pentane). ^1H NMR ($CDCl_3$) $\delta=0.84$ (d, $J=7.4$ Hz, 18H, CH(CH_3)$_2$), 1.02 (sept, $J=7.4$ Hz, 3H, C*H*(CH_3)$_2$), 2.66 (s, 4H, CH_2), 4.18 (d, $J=8.3$ Hz, 2H, NCH=C*H*), 5.75 (d, $J=8.3$ Hz, 2H, NC*H*=CH), 7.11–7.16 (m, 6H, H_{aromat}), 7.19–7.22 (m, 4H, H_{aromat}). ^{13}C NMR ($CDCl_3$, DEPT) $\delta=11.3$ (d), 17.5 (q), 41.5 (s), 51.5 (t), 105.7 (d, NC=*C*), 125.4 (d, C_{aromat}), 127.3 (d, N*C*=C), 128.8 (d, C_{aromat}), 131.0 (d, C_{aromat}), 139.6 (s, C_{aromat}). MS (CI, CH_5^+); *m/z* (%): 418 (48) $[M+1]^+$, 326 (100), 170 (7), 147 (8), 119 (7), 105 (11). IR (film): $\tilde{\nu}=3055\ cm^{-1}$, 2986, 1422, 1265, 896, 741, 706. Anal. Calcd for $C_{28}H_{39}NSi$ (417.72): C 80.51, H 9.41, N 3.35. Found C 80.34, H 9.26, N 3.31.

4.4.10. 4-Benzyl-4-isopropyl-1-triisopropylsilyl-1,4-dihydropyridine (4m). According to GP2 from 4-benzylpyridine (**1b**, 40.6 mg, 38.2 µl, 0.25 mmol), TIPS triflate (76.6 mg, 67.4 µl, 0.25 mmol) in CH_2Cl_2 (2 ml) and *i*Pr_2Mg (1.0 ml, 0.5 M in Et_2O), reaction time 2 h.

Yield 71.8 mg (78%), colorless oil. TLC $R_f=0.70$ (aluminum oxide 60 neutral, *n*-pentane). ^1H NMR ($CDCl_3$) $\delta=$ 0.94 (d, $J=7.4$ Hz, 18H, SiCH(CH_3)$_2$), 0.95 (d, $J=6.9$ Hz, 6H, CH(CH_3)$_2$), 1.12 (sept, $J=7.4$ Hz, 3H, SiC*H*(CH_3)$_2$), 1.40 (sept, $J=6.9$ Hz, 1H, C*H*(CH_3)$_2$), 2.56 (s, 2H, CH_2Ph), 4.11 (d, $J=8.5$ Hz, 2H, NCH=C*H*), 5.89 (d, $J=8.3$ Hz, 2H, NC*H*=CH), 7.08–7.14 (m, 3H, H_{aromat}), 7.17–7.20 (m, 2H, H_{aromat}). ^{13}C NMR ($CDCl_3$, DEPT) $\delta=11.3$ (d), 17.7 (q), 18.0 (q), 38.5 (d), 43.0 (s), 48.3 (t), 104.1 (d, NC=*C*), 125.2 (d, C_{aromat}), 127.1 (d, C_{aromat}), 129.0 (d, C_{aromat}), 131.0 (d, N*C*=C), 140.4 (s, C_{aromat}). MS (CI, CH_5^+); *m/z* (%): 370 (65) $[M+1]^+$, 326 (10), 278 (100), 147 (7), 122 (7). IR (film): $\tilde{\nu}=3054\ cm^{-1}$, 2985, 2867, 2305, 1668, 1422, 1265, 895, 740, 706. Anal. Calcd for $C_{24}H_{39}NSi$ (369.67): C 77.98, H 10.63, N 3.79. Found C 78.02, H 10.70, N 3.76.

4.4.11. 4-Benzyl-4-*tert*-butyl-1-triisopropylsilyl-1,4-dihydropyridine (4n). According to GP2 from 4-benzylpyridine (**1b**, 40.6 mg, 38.2 µl, 0.25 mmol), TIPS triflate (76.6 mg, 67.4 µl, 0.25 mmol) in CH_2Cl_2 (2 ml) and *t*Bu_2Mg (1.0 ml, 0.5 M in Et_2O). After addition of the

organometallic reagents the mixture was slowly warmed to room temperature, reaction time 10 h.

Yield 28.1 mg (29%), colorless crystals, mp 74–75 °C. TLC R_f=0.69 (aluminum oxide 60 neutral, *n*-pentane). ^{1}H NMR ($CDCl_3$) δ=0.90 (d, J=7.3 Hz, 18H, SiCH(CH_3)$_2$), 0.97 (s, 9H, C(CH_3)$_3$), 1.08 (sept, J=7.6 Hz, 3H, SiC*H*(CH_3)$_2$), 2.54 (s, 2H, CH_2Ph), 4.26 (d, J=8.5 Hz, 2H, NCH=C*H*), 5.81 (d, J=8.5 Hz, 2H, NC*H*=CH), 7.05–7.10 (m, 3H, H_{aromat}), 7.14–7.18 (m, 2H, H_{aromat}). ^{13}C NMR ($CDCl_3$, DEPT) δ=11.2 (d), 17.6 (q), 25.3 (q), 38.4 (s), 43.4 (t), 45.4 (s), 103.3 (d, NC=*C*), 125.0 (d, C_{aromat}), 127.0 (d, C_{aromat}), 128.8 (d, C_{aromat}), 131.2 (d, N*C*=C), 141.6 (s, C_{aromat}). MS (CI, CH_5^+); *m*/*z* (%): 384 (92) $[M+1]^+$, 326 (51), 292 (100), 170 (9), 157 (8), 147 (15). IR (film): $\tilde{\nu}$=3054 cm^{-1}, 2985, 1422, 895, 740, 706. Anal. Calcd for $C_{24}H_{39}NSi$ (383.70): C 78.22, H 10.77, N 3.65. Found C 78.22, H 10.55, N 3.57.

4.4.12. 4-Allyl-4-benzyl-1-triisopropylsilyl-1,4-dihydropyridine (4o). According to GP2 from 4-benzylpyridine (**1b**, 40.6 mg, 38.2 µl, 0.25 mmol), TIPS triflate (76.6 mg, 67.4 µl, 0.25 mmol) in CH_2Cl_2 (2 ml) and allyl$_2$Mg (1.0 ml, 0.5 M in Et_2O), reaction time 10 h.

Yield 10.8 mg (12%), colorless oil. TLC R_f=0.62 (aluminum oxide 60 neutral, *n*-pentane) ^{1}H NMR ($CDCl_3$) δ=0.98 (d, J=7.3 Hz, 18H, CH(CH_3)$_2$), 1.36 (sept, J=7.3 Hz, 3H, C*H*(CH_3)$_2$), 2.09 (dt, J=7.1/1.4 Hz, 2H, CH_2CH=CH$_2$), 2.57 (s, 2H, CH_2Ph), 4.17 (d, J=8.3 Hz, 2H, NC*H*=CH), 4.97–5.05 (m, 2H, CH=CH_2), 5.88–5.97 (m, 3H, C*H*=CH$_2$, NCH=C*H*), 7.12–7.15 (m, 3H, H_{aromat}), 7.20–7.23 (m, 2H, H_{aromat}). ^{13}C NMR ($CDCl_3$, DEPT) δ=11.3 (d), 17.7 (q), 36.4 (s), 49.1 (t), 50.9 (t), 105.9 (d, NC=*C*), 115.8 (t, CH=*C*H$_2$), 125.5 (d), 127.3 (d), 128.8 (d), 130.9 (d), 136.7 (d), 139.0 (s). MS (CI, CH_5^+); *m*/*z* (%): 368 (92) $[M+1]^+$, 326 (49), 276 (100), 236 (5), 147 (6). IR (film): $\tilde{\nu}$=3027 cm^{-1}, 2944, 2866, 2350, 1670, 1464, 1287, 1057. HRMS (70 eV) calcd for $C_{24}H_{37}NSi$ [M^+]: 367.2701. Found 367.2695.

4.4.13. 4-Benzyl-4-phenyl-1-trimethylsilyl-1,4-dihydropyridine (4q). According to GP2 from 4-phenylpyridine (**1a**, 38.8 mg, 0.25 mmol), TMS triflate (55.6 mg, 45.2 µl, 0.25 mmol) in CH_2Cl_2 (2 ml) and Bn$_2$Mg (1.0 ml, 0.5 M in Et_2O), reaction time 3 h.

Yield 36.1 mg (45%), colorless crystals, mp 51–52 °C. TLC R_f=0.9 (aluminum oxide 60 neutral, *n*-pentane/CH_2Cl_2 9:1). ^{1}H NMR ($CDCl_3$) δ=0.06 (s, 9H, Si(CH_3)$_3$), 3.04 (s, 2H, CH_2), 4.59 (d, J=8.2 Hz, 2H, NCH=C*H*), 5.98 (d, J=8.2 Hz, 2H, NC*H*=CH), 7.01–7.03 (m, 2H, H_{aromat}), 7.14–7.20 (m, 4H, H_{aromat}), 7.34–7.37 (m, 2H, H_{aromat}) 7.42–7.45 (m, 2H, H_{aromat}). ^{13}C NMR ($CDCl_3$, DEPT) δ=−1.2 (q), 43.1 (s), 50.7 (t), 106.5 (d, NC=*C*), 125.3 (d), 125.5 (d), 126.5 (d), 126.7 (d), 127.1 (d), 128.2 (d), 131.1 (d), 138.7 (s, C_{aromat}), 151.6 (s, C_{aromat}). MS (CI, CH_5^+); *m*/*z* (%): 320 (88) $[M+1]^+$, 248 (19), 228 (100), 156 (28). IR (film): $\tilde{\nu}$=3024 cm^{-1}, 2952, 2359, 1666, 1598, 1293, 1253, 1098, 1036, 840, 735, 698. Anal. Calcd for $C_{17}H_{25}NSi$ (271.48): C 78.94, H 7.89, N 4.38. Found C 78.80, H 7.82, N 4.30.

4.4.14. 4-Isopropyl-4-phenyl-1-trimethylsilyl-1,4-dihydropyridine (4r). According to GP2 from 4-phenylpyridine (**1a**, 77.6 mg, 0.5 mmol), TMS triflate (111.2 mg, 90.4 µl, 0.5 mmol) in CH_2Cl_2 (2 ml) and *i*Pr$_2$Mg (2.0 ml, 0.5 M in Et_2O), reaction time 3 h.

Yield 122.1 mg (90%), colorless oil. TLC R_f=0.9 (aluminum oxide 60 neutral, *n*-pentane/CH_2Cl_2 9:1). ^{1}H NMR ($CDCl_3$) δ=0.19 (s, 9H, Si(CH_3)$_3$), 0.78 (d, J=6.6 Hz, 6H, CH(CH_3)$_2$), 2.01 (sept, J=6.6 Hz, 3H, C*H*(CH_3)$_2$), 4.55 (d, J=8.3 Hz, 2H, NCH=C*H*), 6.16 (d, J=8.5 Hz, 2H, NC*H*=CH), 7.08–7.12 (m, 1H, H_{aromat}), 7.28–7.33 (m, 4H, H_{aromat}). ^{13}C NMR ($CDCl_3$, DEPT) δ=−1.4 (q), 17.7 (q), 37.7 (d), 45.6 (s), 104.5 (d, NC=*C*), 124.8 (d, C_{aromat}), 126.6 (d, C_{aromat}), 127.3 (d, N*C*=C), 128.2 (d, C_{aromat}), 151.7 (s, C_{aromat}). MS (CI, CH_5^+); *m*/*z* (%): 272 (100) $[M+1]^+$, 228 (85), 204 (6), 200 (11), 194 (5), 181 (8), 156 (7), 105 (9). IR (film): $\tilde{\nu}$=3053 cm^{-1}, 2956, 1667, 1598, 1295, 1253, 1092, 997, 843, 759. Anal. Calcd for $C_{17}H_{25}NSi$ (271.48): C 75.21, H 9.28, N 5.16. Found C 74.97, H 9.43, N 5.38.

4.4.15. 4-Benzyl-4-phenyl-1-triphenylsilyl-1,4-dihydropyridine (4t). According to GP2 from 4-phenylpyridine (**1a**, 38.8 mg, 0.25 mmol), triphenylsilyl triflate (1.0 ml, 0.25 M in CH_2Cl_2) in CH_2Cl_2 (2 ml) and Bn$_2$Mg (1.0 ml, 0.5 M in Et_2O), reaction time 3 h.

Yield 61.3 mg (48%), colorless crystals, mp 133–134 °C. TLC R_f=0.64 (aluminum oxide 60 neutral, *n*-pentane/CH_2Cl_2 9:1). ^{1}H NMR (CD_2Cl_2) δ=3.04 (s, 2H, CH_2Ph), 4.62 (d, J=8.5 Hz, 2H, NCH=C*H*), 5.95 (d, J=8.5 Hz, 2H, NC*H*=CH), 7.13–7.15 (m, 2H, H_{aromat}), 7.18–7.21 (m, 1H, H_{aromat}), 7.29–7.30 (m, 3H, H_{aromat}), 7.35–7.38 (m, 8H, H_{aromat}), 7.41–7.50 (m, 11H, H_{aromat}). ^{13}C NMR (CD_2Cl_2, DEPT) δ=43.5 (s), 50.1 (t), 107.2 (d, NC=*C*), 125.5 (d, C_{aromat}), 125.8 (d, C_{aromat}), 126.6 (d, N*C*=C), 127.4 (d, C_{aromat}), 128.0 (d, C_{aromat}), 128.1 (d, C_{aromat}), 128.2 (d, C_{aromat}), 130.3 (d, C_{aromat}), 131.4 (d, C_{aromat}), 132.0 (s, C_{aromat}), 135.9 (d, C_{aromat}), 139.4 (s, C_{aromat}), 151.9 (s, C_{aromat}). MS (EI); *m*/*z* (%): 505 (1) $[M^+]$, 414 (100), 259 (86), 181 (14), 105 (6), 91 (5). IR (Film): $\tilde{\nu}$=3428 cm^{-1}, 3022, 2343, 1667, 1428, 1288, 1114, 697. HRMS (70 eV) calcd for $C_{36}H_{31}NSi$ [M^+]: 505.2226. Found 505.2227.

4.4.16. 4-Isopropyl-4-phenyl-1-triphenylsilyl-1,4-dihydropyridine (4u). According to GP2 from 4-phenylpyridine (**1a**, 38.8 mg, 0.25 mmol), triphenylsilyl triflate (1.0 ml, 0.25 M in CH_2Cl_2) in CH_2Cl_2 (2 ml) and *i*Pr$_2$Mg (1.0 ml, 0.5 M in Et_2O), reaction time 3 h.

Yield 98.9 mg (86%), colorless oil. TLC R_f=0.66 (aluminum oxide 60 neutral, *n*-pentane/CH_2Cl_2 9:1). ^{1}H NMR (CD_2Cl_2) δ=0.86 (d, J=6.9 Hz, 6H, CH(CH_3)$_2$), 2.09 (sept, J=6.9 Hz, 1H, C*H*(CH_3)$_2$), 4.62 (d, J=8.3 Hz, 2H, NCH=C*H*), 6.16 (d, J=8.3 Hz, 2H, NC*H*=CH), 7.13–7.16 (m, 1H, H_{aromat}), 7.33–7.37 (m, 4H, H_{aromat}), 7.40–7.43 (m, 6H, H_{aromat}), 7.46–7.50 (m, 3H, H_{aromat}), 7.62–7.64 (m, 6H, H_{aromat}). ^{13}C NMR (CD_2Cl_2, DEPT) δ=18.2 (q), 37.8 (d), 45.9 (s), 105.9 (d, NC=*C*), 125.3 (d, C_{aromat}), 126.9 (d, C_{aromat}), 128.4 (d, C_{aromat}), 128.5 (d, N*C*=C), 128.8 (d, C_{aromat}), 130.7 (d, C_{aromat}), 132.5 (s, C_{aromat}), 136.3 (d, C_{aromat}), 151.6 (s, C_{aromat}). MS (CI, CH_5^+); *m*/*z* (%): 458

(100) $[M+1]^+$, 414 (39), 380 (6), 259 (13). IR (film): $\tilde{\nu}=$ 3049 cm^{-1}, 2958, 1669, 1428, 1292, 1114, 699. HRMS (70 eV) calcd for $C_{32}H_{31}NSi$ $[M^+]$ 457.2226. Found 457.2231.

4.4.17. 2,4-Diphenyl-pyridine (5d). According to GP2 from 4-phenylpyridine (**1a**, 77.6 mg, 0.5 mmol), TIPS triflate (153.2 mg, 134.8 µl, 0.5 mmol) in CH_2Cl_2 (4 ml) and Ph_2Mg (4.0 ml, 0.25 M in Et_2O), the reaction mixture was warmed to room temperature during 12 h. The reaction was quenched by addition of 2 ml 2 M HCl. The mixture was stirred for 15 min, before adding 3 ml, 2 M NaOH solution and extraction with CH_2Cl_2. The crude product was purified by CC on silica gel.

Yield 47.9 mg (41%), colorless oil. TLC $R_f=0.24$ (SiO_2, *n*-pentane/EtOAc 95:5). ^1H NMR ($CDCl_3$) $\delta=7.43$–7.55 (m, 7H, H_{aromat}), 7.71 (d, $J=7.0$ Hz, 2H, H_{aromat}), 7.95 (s, 1H, H_{aromat}), 8.06 (d, $J=7.0$ Hz, 2H, H_{aromat}), 8.76 (d, $J=$ 5.3 Hz, 1H, NC*H*=CH). HRMS (70 eV) calcd for $C_{17}H_{13}N$ $[M^+]$ 231.1048. Found 231.1036. Spectroscopic data for ^1H, ^{13}C NMR and IR are in accordance with those previously published.[20]

4.4.18. 4-Isopropyl-4-phenyl-piperidine-1-carboxylic acid *tert*-butyl ester (6a). According to GP3 from **4d** (150.8 mg, 0.424 mmol), $NaBH_3CN$ (66.6 mg, 1.06 mmol) in MeOH (3 ml), HCl 2 M in Et_2O (2.12 ml) and Boc_2O (101.9 mg, 0.467 mmol).

Yield 115.3 mg (90%), colorless crystals, mp 83–84 °C. TLC $R_f=0.28$ (SiO_2, *n*-pentane/EtOAc 95:5). ^1H NMR (500 MHz, $C_2D_2Cl_4$, 80 °C) $\delta=0.75$ (d, $J=6.6$ Hz, 6H, $CH(CH_3)_2$), 1.46 (s, 9H, $C(CH_3)_3$), 1.66–1.72 (m, 3H, $CH(CH_3)_2$ and NCH_2CH_2), 2.28–231 (m, 2H, NCH_2CH_2), 2.79–2.84 (m, 2H, NCH_2), 3.85–3.88 (m, 2H, NCH_2), 7.23–7.28 (m, 3H, H_{aromat}), 7.35–7.38 (m, 2H, H_{aromat}). ^{13}C NMR (125 MHz, $C_2D_2Cl_4$, DEPT, 80 °C) $\delta=17.3$ (q, CH_3), 28.6 (q, CH_3), 32.7 (t, CH_2), 38.5 (d, *C*H), 40.7 (t, CH_2), 43.5 (s), 79.0 (s), 125.8 (d, C_{aromat}), 128.0 (d, C_{aromat}), 128.4 (d, C_{aromat}), 141.5 (s, C_{aromat}), 155.0 (s, CO). MS (CI, CH_5^+); *m*/*z* (%): 304 (6) $[M+1]^+$, 248 (100), 204 (13). IR (KBr): $\tilde{\nu}=2972$ cm^{-1}, 2867, 1685. Anal. Calcd for $C_{19}H_{29}NO_2$ (303.45): C 75.21, H 9.63, N 4.62. Found C 75.15, H 9.77, N 4.61.

4.4.19. 4-*tert*-Butyl-4-phenyl-piperidine-1-carboxylic acid *tert*-butyl ester (6b). According to GP3 from **4e** (91.9 mg, 0.249 mmol), $NaBH_3CN$ (39.1 mg, 0.622 mmol) in MeOH (2 ml), HCl 2 M in Et_2O (1.24 ml) and Boc_2O (59.8 mg, 0.274 mmol).

Yield 75.9 mg (95%), colorless crystals, mp 107 °C. TLC $R_f=0.28$ (SiO_2, *n*-pentane/EtOAc 95:5). ^1H NMR (500 MHz, $C_2D_2Cl_4$, 80 °C) $\delta=0.85$ (s, 9H, $C(CH_3)_3$), 1.45 (s, 9H, $OC(CH_3)_3$), 1.77–1.83 (m, 2H, NCH_2CH_2), 2.30–2.33 (m, 2H, NCH_2CH_2), 2.61–2.66 (m, 2H, NCH_2), 3.92–3.95 (m, 2H, NCH_2), 7.23–7.28 (m, 3H, H_{aromat}), 7.34–7.37 (m, 2H, H_{aromat}). ^{13}C NMR (125 MHz, $C_2D_2Cl_4$, DEPT, 80 °C) $\delta=26.1$ (q, CH_3), 28.6 (q, CH_3), 29.3 (t, CH_2), 36.1 (s), 40.9 (t, CH_2), 43.4 (s), 78.9 (s), 125.8 (d, C_{aromat}), 127.6 (d, C_{aromat}), 129.9 (d, C_{aromat}), 139.8 (s, C_{aromat}), 155.0 (s, CO). MS (CI, CH_5^+); *m*/*z* (%): 318 (12) $[M+1]^+$, 262 (100), 218 (13). IR (KBr): $\tilde{\nu}=2968$ cm^{-1}, 2872, 1689. Anal. Calcd for $C_{20}H_{31}NO_2$ (317.48): C 75.67, H 9.84, N 4.41. Found C 75.53, H 9.91, N 4.40.

4.4.20. 4-Benzyl-4-isopropyl-piperidine-1-carboxylic acid *tert*-butyl ester (6c). According to GP3 from **4m** (151.1 mg, 0.409 mmol), $NaBH_3CN$ (64.1 mg, 1.02 mmol) in MeOH (3 ml), HCl 2 M in Et_2O (1.28 ml) and Boc_2O (98.2 mg, 0.450 mmol).

Yield 120 mg (92%), colorless crystals, mp 84–85 °C. TLC $R_f=0.34$ (SiO_2, *n*-pentane/EtOAc 95:5). ^1H NMR (400 MHz, $C_2D_2Cl_4$, 100 °C) $\delta=0.96$ (d, $J=6.8$ Hz, 6H, $CH(CH_3)_2$), 1.34–1.39 (m, 2H, NCH_2CH_2), 1.46 (s, 9H, $C(CH_3)_3$), 1.57–1.62 (m, 2H, NCH_2CH_2), 1.97 (sept, $J=$ 6.8 Hz, 1H, $CH(CH_3)_2$), 2.69 (s, 2H, CH_2Ph), 3.38–3.50 (m, 4H, NCH_2), 7.15–7.32 (m, 5H, H_{aromat}). ^{13}C NMR (100 MHz, $C_2D_2Cl_4$, DEPT, 100 °C) $\delta=16.7$ (q, CH_3), 28.6 (q, CH_3), 30.1 (d, *C*H), 31.0 (t, CH_2), 37.3 (s), 38.8 (t, CH_2Ph), 39.8 (t, NCH_2), 79.0 (s), 126.0 (d, C_{aromat}), 127.9 (d, C_{aromat}), 130.9 (d, C_{aromat}), 138.8 (s, C_{aromat}), 155.2 (s, CO). MS (CI, CH_5^+); *m*/*z* (%): 318 (2) $[M+1]^+$, 262 (100), 218 (11). IR (KBr): $\tilde{\nu}=2973$ cm^{-1}, 1679, 1418, 1155. Anal. Calcd for $C_{20}H_{31}NO_2$ (317.48): C 75.50, H 9.89, N 4.42. Found C 75.23, H 9.96, N 4.42.

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Synthesis of substituted 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine as new scaffolds for potential bioactive compounds

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Abstract—The title compounds having different substituents on the heterocyclic framework were prepared by several methods from 2-acetamido-3-hydroxypyridine. The condensation of 2-protected-amino-3-hydroxypyridine with 2-chloroacrylonitrile or ethyl 2,3-dibromopropionate provided in several cases two isomeric pyrido-oxazines. Whereas the reaction of 2-acetamido-3-hydroxypyridine with methyl 2,3-dibromopropionate or with α-halocarbonyl compounds gave exclusively the 2-substituted pyrido-oxazine, in a one-step operation.

1. Introduction

3,4-Dihydro-2*H*-1,4-benzoxazine derivatives (**I**) have attracted considerable interest due to their presence in a number of biologically active compounds.[1] Bioisosteric replacement of the benzene by pyridine leads to pyrido-oxazines (**II**), which have rarely been described (Fig. 1).[2]

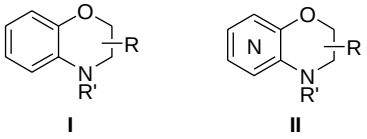

Figure 1.

The synthetic methods for obtaining 1,4-benzoxazines are not suitable for the pyridine derivatives. Whereas the pyrido[4,3-*b*][1,4]oxazine nucleus is well known,[3] the position isomer pyrido[3,2-*b*][1,4]oxazine is practically unknown. The first synthesis of the practically unknown 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine was carried out by reduction of 3,4-dihydro-2*H*-pyrido[3,2-*b*]oxazin-3-one.[4] Our investigation of this system forms part of an ongoing study of pyrido derivatives, initiated by the preparation of hydroxymethylpyrido[3,2-*b*]oxazines from chiral glycidyl tosylates.[5] In this communication, we report the synthesis of pyrido[3,2-*b*][1,4]oxazines-2- and 3-substituted.

2. Chemistry

In our first attempt to access to pyrido-oxazines, when the 2-amino-3-hydroxypyridine was condensed with 2-chloro-acrylonitrile in refluxing acetone, neither DMF nor acetonitrile gave the desired pyrido-oxazine and both yielded only the starting material or degradation products (Table 1, entries 1 and 2).

In the same way, the condensation of 2-amino-3-hydroxypyridine with 1,3-dichloropropanon-2-one yielded the 2-chloromethyl-8-hydroxyimidazo[1,2-*a*]pyridine **2** (Scheme 1). When toluene was used as solvent and PTSA (*p*-toluenesulfonic acid) as catalyst only the imidazopyridine **2** was obtained in 62% yield, whereas treatment with K_2CO_3 in acetonitrile led to the imidazopyridine in only 24% yield together with starting material. Under these acidic or basic conditions the pyrido-oxazine ring was not detected. The results can be explained if the nucleophilic attack of the *N*-pyridinic occurs more rapidly than the attack of the hydroxyl group placed at the C-3. The most common method for preparing imidazo[1,2-*a*]pyridines is that reported by Tschitschibabin, which involves the reaction of 2-aminopyridines with aldehydes or ketones in acidic media.[6]

Keywords: Pyrido-oxazines; α-Halocarbonyl compounds; Protected 2-aminopyridine.
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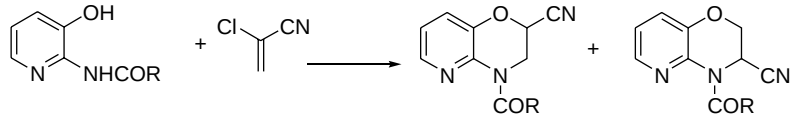
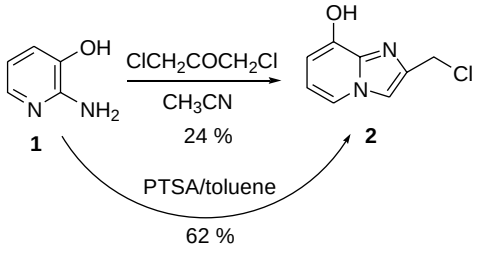
Table 1. Reagents and conditions for the preparation of pyrido-oxazines



1, 3-5 **6a-c** **7a,b**

Entry	R	Solvent	Base	*t* (h)	Compound (%)	Compound (%)
1	H (**1**)	Acetone	K_2CO_3	24	—	—
2	H (**1**)	Acetonitrile	K_2CO_3	2	—	—
3	–$COCH_3$ (**3**)	Acetone	K_2CO_3	24	**6a** (36)	**7a** (36)
4	–$COCH_3$ (**3**)	DMF	K_2CO_3	20	**6a** (26)	**7a** (24)
5	–$COCH_3$ (**3**)	Acetonitrile	K_2CO_3	2	**6a** (70)	—
6	–$COCH_3$ (**3**)	Acetonitrile	Cs_2CO_3	2	**6a** (68)	—
7	–$COCH_3$ (**3**)	Acetonitrile	DBU	2	**6a** (42)	—
8	–$COCH_3$ (**3**)	Acetonitrile	Et_3N	5	**6a** (23)	—
9	–$COOCH_2CH_3$ (**4**)	Acetonitrile	K_2CO_3	2	**6b** (40)	**7b** (40)
10	–$COOCH_2CH_3$ (**4**)	Acetone	K_2CO_3	2	**6b** (30)	**7b** (28)
11	–$COOCH_2CH_3$ (**4**)	Acetonitrile	Cs_2CO_3	2	**6b** (38)	**7b** (36)
12	–$COC(CH_3)_3$ (**5**)	Acetonitrile	K_2CO_3	2	**6c** (50)	—



Scheme 1.

The protection of the amino group at C-2 by conversion to acetylamino, ethoxycarbonylamino or *t*-butylcarbonylamino facilitates the condensation with alkylating reagents. The 2-acetamido-3-hydroxypyridine (**3**) was the best starting compound for the preparation of 2-substituted pyrido-oxazines, whereas the carbamate derivative (**4**) leads to a mixture 1:1 of 2-, and 3-substituted compounds (**6b**, **7b**). Both regioisomers were separated by SiO_2 column chromatography. The *t*-butyl carbonyl group hindered the condensation reaction, and the 2-substituted compound (**6c**) was isolated as the only regioisomeric product in 50% yield, when *t*-butyl amide (**5**) was condensed with 2-chloroacrylonitrile (Table 1, entry 12). This last protecting group was unstable and easily hydrolysed.

In order to find appropriate conditions for the pyrido-oxazine structure formation we carried out the reaction of protected 2-amino-3-hydroxypyridine with 2-chloroacrylonitrile varying: (a) solvent, (b) reaction time, and (c) base.

The condensation of **3** with 2-chloroacetonitrile (entry 5, Table 1) proceeded with acceptable yield, and so we considered this method as an effective procedure for pyrido-oxazine formation; moreover, the obtained compounds were easily purified. With this condensation, it is possible, in principle, to obtain two regioisomeric pyrido-oxazine compounds. These isomeric compounds can be easily distinguished on the basis of their ^{13}C NMR spectral data, and in this respect the signal of the methylene group of the oxazine moiety is the most indicative one with differences in chemical shifts of 40.9 and 61.2 ppm (CH_2–N, and CH_2–O, compounds **6a** and **7a**, respectively). In order to confirm the main isomer formed, we performed 2D NMR-experiments (HETCOR, HMQC, HMBC), and the results prove the proposed structure for **6a**. The signal (CH) at 63.5 ppm is assignable as the C-2 and this carbon shows a cross peak with H-2 (see HETCOR spectrum). The ^{13}C signal (CH_2) at 40.9 ppm shows two cross peaks. These results suggest that C-3 is bonded to two protons (CH_2), which are non-equivalent, having different chemical shifts. It is seen that the protons on C-3 appear at 3.95 ppm (H-3) and 4.93 ppm (H-3′) (Fig. 2).

Although it is difficult to correlate the regioselectivity of the oxazine ring formation from the same starting material with a particular solvent parameter, acetonitrile appears to be an appropriate solvent for this process when the amino at C-2 was protected with acetyl group (Table 1, entries 5 and 6). Whereas, the same reaction in acetone give a mixture of **6a** (36%) and **7a** (36%) (Table 1, entry 3), DMF also afforded mixture in a ratio 1:1 of **6a** and **7a** in a 26 and 24% yield, respectively (entry 4). The reaction in DMF required more time to completely react (20 h) and provided lower yields.

It should be noted that the *N*-substituent of the 2-amino-3-hydroxypyridine has a substantial effect on the regioselectivity of the reaction with 2-chloroacrilonitrile. Thus, while acetyl group of **3** in acetonitrile facilitates the 2-substituted isomer formation (Table 1, entries 5–8), when the carbamate (**4**) was used as starting material under reflux in acetone or acetonitrile it gave a mixture of isomers **6b** and **7b** without regioselectivity (Table 1, entries 9–11). As pointed at the beginning of this work, under the same conditions, the condensation of *t*-butylamide **5** and 2-chloroacrylonitrile gave only the 2-substituted isomer (Table 1, entry 12).

The experimental results demonstrate that K_2CO_3 (Table 1, entries 5 and 9) and Cs_2CO_3 (Table 1, entries 6 and 11) behaved similarly, whereas DBU and Et_3N afforded the same products in lower yields (Table 1, entries 7 and 8, respectively).

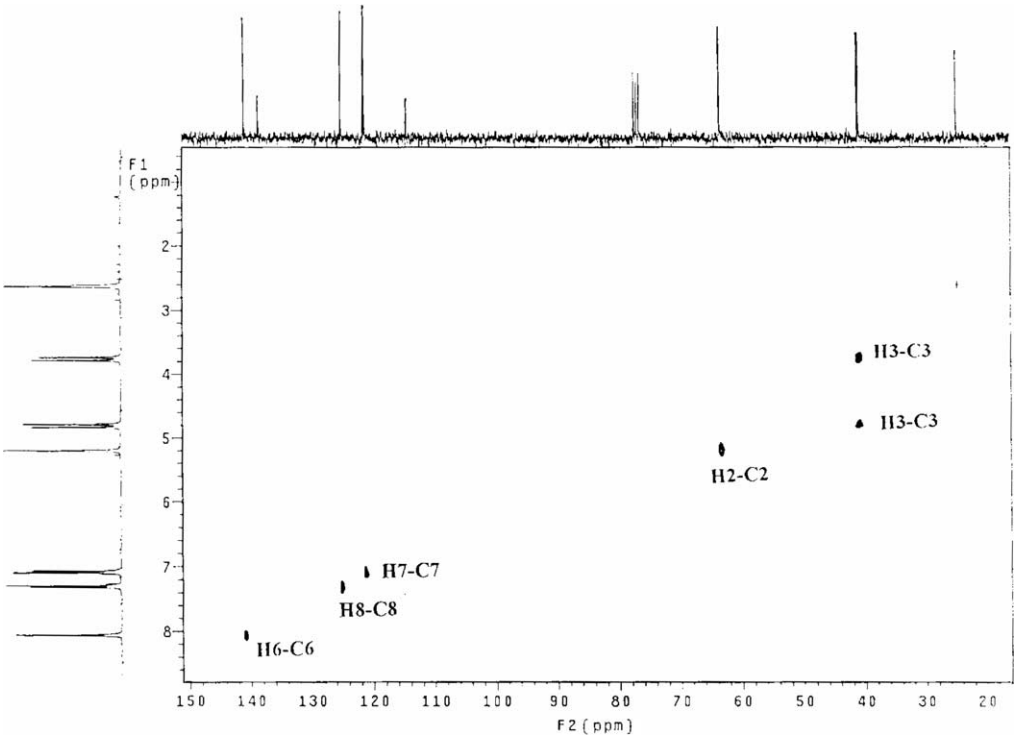
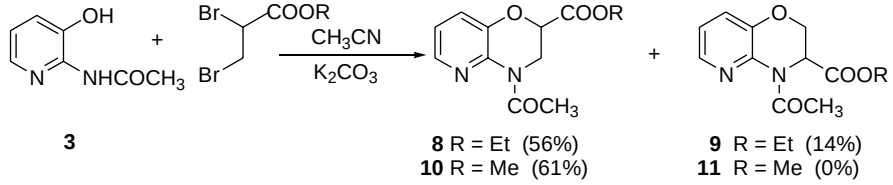


Figure 2. HETCOR spectrum of **6a** (300 MHz, $CDCl_3$). The horizontal axis of the spectrum corresponds to the ^{13}C spectrum and the vertical axis refers to the ^{1}H spectrum.

Having established a one pot two-component condensation method that operates under mild conditions, we next decided to investigate the scope of the reaction with respect to the nature and structure of the alkylating agent; thus, this methodology was applied to the synthesis of other pyrido-oxazines as **8**–**10**. The mixture of **8** and **9** was prepared by condensation of the acetamido **3** with ethyl 2,3-dibromo-propionate in the presence of K_2CO_3 and CH_3CN in 56% (**8**) and 14% (**9**) yield (Scheme 2). It seemed likely that under these conditions (K_2CO_3/CH_3CN/82 °C/24 h) elimination of hydrogen bromide from ethyl 2,3-dibromopropionate to give the α-bromoolefinic ester would occur more rapidly than nucleophilic displacement of bromide ion by the formed anion.[7] The same conditions of reaction, using methyl 2,3-dibromopropionate gave regioselectively the 2-substituted ester **10** in 61% yield, whereas the reaction of **3** with methyl 2,3-dichloropropionate gave the same ester **10** in only 35% yield (Scheme 2). The diminished yield can probably be attributed to the reduced reactivity of the chloro alkylating reagent in comparison with the bromo analogue. At this point, it is interesting to mark that the regioisomer in 2-position is nearly always predominant and it is in accord with other works related with 1,4-oxazines reported before.[8]

More recently, we investigated the formation of substituted ketones and aldehydes by the same condensation strategy, employing a reagent with a preformed α-halocarbonyl unit. The bromoderivative had been shown to be a suitable reagent for this purpose, whereas the chloroderivative was found to be less reactive (to see Table 2, entry 2 vs entry 1; entry 4 vs entry 3; entry 6 vs entry 5). When the acetamide **3** was reacted with a chloroketones tipus **B** only decomposition compounds were obtained (Table 2, entry 2), starting material was recovered (entry 6) or the expected product was obtained in poor yield (entry 4). Conjugated aldehydes did not react (entries 7 and 8, Table 2), and we believe that aldehydes are unstable under the tested conditions. The most efficient conditions were the treatment of **3** with the α-bromocarbonyl compound under reflux in acetonitrile in the presence of K_2CO_3 for 5 h (Table 2, entry 1). These conditions applied to the condensation of **3** with several α-halocarbonyl compounds provided only the 2-substituted isomer in respect of the chemical shift of N–CH_2 at 39.6/40.5 ppm (^{13}C NMR) (**12a**–**c**, Table 2). The quantity of alkylating reagent added is significant. Reactions of **3** with 5 equiv of haloalkenyl compounds did increase the yields of **12a** (Table 2, entry 1), and **12b** (Table 2, entry 4). Heating in



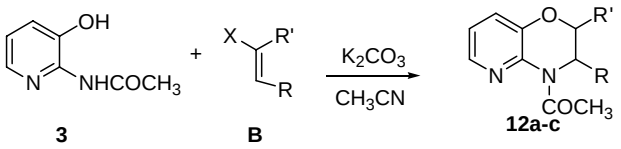
3

8 R = Et (56%)
10 R = Me (61%)

9 R = Et (14%)
11 R = Me (0%)

Scheme 2.

Table 2. Condensation of **3** with haloalkenyl compounds (**B**)



3 **B** **12a-c**

Entry	Compound **B**	Conditions	Product (% yield)
1	X=Br R=H R′=–CO–CH_3 (**13**)	Reflux, 24 h (1.5 equiv) Reflux, 24 h (2 equiv) Reflux, 5 h (5 equiv) Sealed tube, 60 °C, 2 h 30 (5 equiv)	**12a** (5) **12a** (24) **12a** (52) **12a** (26)
2	X=Cl R=H R′=–CO–CH_3 (**14**)	Reflux, 2 h (5 equiv) Sealed tube, 60 °C, 4 h	Decomposition Decomposition
3	X=Br R=H R′=–COC_6H_5 (**15**)	Reflux, 2 h 30 (5 equiv)	**12b** (48)
4	X=Cl R=H R′=–COC_6H_5 (**16**)	Reflux, 2 h 10 (5 equiv) Reflux, 2 h 10 (2 equiv)	**12b** (34) **12b** (16)
5	X=Br R′–R=$CO(CH_2)_3$– (**17**)	Reflux, 4 h (5 equiv)	**12c** (53)
6	X=Cl R′–R=$CO(CH_2)_3$– (**18**)	Reflux, 60 h (5 equiv)	—
7	X=Br R=–C_6H_5 R′=–COH (**19**)	Reflux, 5 h (5 equiv)	—
8	X=Cl R=–C_6H_5 R′=–COH (**20**)	Reflux, 5 h (5 equiv)	—

acetonitrile at reflux during 2–5 h was an appropriate detail. Stronger reaction conditions (<24 h, <5 equiv, reflux) were tested but only decomposed compounds were generated.

It is notable that the intermediate compounds types **B** are not commercially available, and were prepared previously from readily accessible starting materials in a one pot procedure. These compounds were isolated directly from the crude reaction mixture in high purity and in poor to moderate yields according to described methods for bromoketones **13** and **15**,[9] chloroketones **14** and **16**,[10] the bromocyclohexenone **17**,[11] chlorocyclohexenone **18**,[12] and the bromo- and chloroaldehydes **19** and **20**.[13]

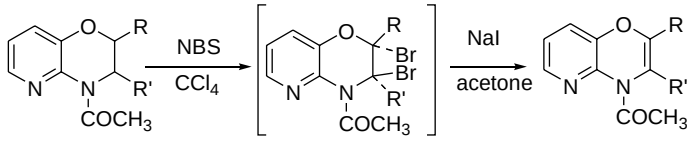
A possible mechanism for the formation of pyrido-oxazines 2-substituted involves Michael addition of the amide to the double bond, followed by ring-closure involving elimination of bromide.

The condensation of the acetamido **3** with 1,3-dichloropropanon-2-one, in the same conditions (K_2CO_3, CH_3CN, reflux) was unfruitful and gave degradation compounds or only starting material was recovered.

Antecedents of the reactivity of 1,4-benzodioxine were considered for the insaturation of the pyrido-oxazines **6a** and **7a**. First the dibromination of the saturated pyrido-oxazine with NBS (*N*-bromosuccinimide) in CCl_4 was performed. This unstable intermediate could be isolated and purified; however it could be easily transformed into a stable product by dehalogenation with NaI in acetone affording the unsaturated nitriles **21** and **22** in an acceptable yield in a single flask (Scheme 3). Using the same conditions the ester **10** and the ketone **12a** were transformed into the corresponding unsaturated analogues **23a**,**b** in isolated yields of 81 and 91%, respectively. Under these conditions, the acetamido protecting group was not affected.

3. Conclusion

Effective methods for the preparation of new pyrido-oxazines have been developed using commercially



6a R = CN, R' = H
7a R = H, R' = CN
10 R = $COOCH_3$, R' = H
12a R = $COCH_3$, R' = H

21 R = CN, R' = H (55%)
22 R = H, R' = CN (60%)
23a R = $COOCH_3$, R' = H (81%)
23b R= $COCH_3$, R' = H (91%)

Scheme 3.

available 2-amino-3-hydroxypyridine as starting compound. The procedure makes it possible to obtain pyridooxazines-2 or 3-substituted in one pot. Conversion of the 2-acetamido-3-hydroxypyridine to the corresponding pyrido-oxazine-2-nitrile was readily accomplished using 2-chloroacrylonitrile in acetonitrile at reflux. Protection of the amino group at C-2 as amide or carbamate is completely required. The steric nature of the *N*-substituent affected both the reaction rate and the yield. Our future investigations will aim to functionalize the pyrido-oxazine substructure in order to synthesize a new series of compounds.

4. Experimental

4.1. General

Melting points were determined on an MFB 595010 M Gallenkamp melting point apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 or Varian Gemini 300 spectrometer or on a Varian VXR-500 spectrometer or on a Brucker 250 MHz with tetramethylsilane as internal standard and using $CDCl_3$ as solvent or CD_3OD. Chemical shifts were expressed in ppm downfield from internal TMS or residual signal of deuterated solvent (δ). IR spectra were recorded on a FTIR Perkin Elmer 1600 spectrophotometer. Mass spectra were recorded on a Hewlett-Packard spectrometer 5988-A (70 eV). The chromatography was carried out on SiO_2 (silica gel 60, SDS, 60–200 (μm). Microanalyses were determined on a Carlo Erba 1106 Analyzer by Serveis Científico-Tècnics, Universitat de Barcelona, and analytical values obtained were within $\pm 0.4\%$ of the calculated values. All reagents were of commercial quality or were purified before use and the organic solvents were of analytical grade or purified by standard procedures.

4.1.1. 2-Chloromethyl-8-hydroxyimidazo [1,2-*a*]pyridine (2). To a solution of 2-amino-3-hydroxypyridine (200 mg, 1.82 mmol) in toluene (20 mL) was added dropwise 1,3-dichloropropan-2-one (350 mg, 2.73 mmol) and a catalyst amount of PTSA (*p*-toluenesulfonic acid monohydrate). The resulting mixture was refluxed for 3 h. The solvent was removed under vacuum and a solution of NaOH 2 N was added dropwise until pH basic, followed by extraction with ethyl acetate (3×15 mL). The combined organic layers were dried (Na_2SO_4), filtered off and the solvent removed, the resulting residue was purified by column chromatography (on silica gel hexane/ethyl acetate in a ratio 6:4) giving 210 mg of this compound as a colorless solid (62% yield). Mp 248–250 °C. IR (KBr) υ (cm^{-1}), 1567 (CN); 1210 (Ar–O); 723 (C–Cl). ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm), 3.39 (s, 2H, CH_2–Cl); 6.70–6.75 (m, 2H, H-6, H-7); 7.59 (s, 1H, H-3); 7.64–7.70 (m, 1H, H-5). Anal. Calcd for $C_8H_7ClN_2O$: C, 52.62%; H, 3.86%; N, 15.34%. Found: C, 52.38%; H, 3.98%; N, 15.01%.

4.1.2. 2-Acetamido-3-hydroxypyridine (3). To a solution of 2-amino-3-hydroxypyridine (400 mg, 3.64 mmol) in dry dichoromethane (20 mL), triethylamine (1 mL, 7.28 mmol) was added. Then the mixture was cooled to 0 °C and acetyl chloride (314 mg, 4 mmol) was added. Finally, the mixture was stirred at room temperature for 12 h (TLC: ethyl acetate/MeOH, 9:1), dichloromethane was evaporated and the residue was purified on a silica gel chromatography column, using ethyl acetate as eluent, to give 490 mg (89%) of a yellow solid. Mp 98–100 °C (hexane/ethyl acetate). IR (KBr) υ (cm^{-1}), 3214 (OH), 3014 (NH), 1661 (CO), 1228 (Ar–O). ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm), 2.30 (s, 3H, CH_3); 7.15 (dd, $J=3.0$, 5.0 Hz, 1H, H-5); 7.40 (dd, $J=1.0$, 5.0 Hz, 1H, H-4); 7.87 (dd, $J=1.0$, 3.0 Hz, 1H, H-6); 10.98 (s, 2H, OH, NH). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm), 23.3 (CH_3); 122.7 (CH, C-5); 128.5 (CH, C-4); 138.0 (CH, C-6); 140.6 (C, C-3); 145.3 (C, C-2); 172.0 (C, CO). Anal. Calcd for $C_7H_8N_2O_2$: C, 55.26%; H, 5.30%; N, 18.41%. Found: C, 55.58%; H, 5.74%; N, 18.12%. MS (*m*/*z*; IS) calcd for: $[C_7H_8N_2O_2]^+$: 152.15; found: 153 $[M+H]^+$.

4.1.3. 2-(Ethoxycarbonylamino)-3-hydroxypyridine (4). To a solution of 2-amino-3-hydroxypyridine (200 mg, 1.82 mmol) in dichloromethane (30 mL) was added triethylamine (0.5 mL, 3.64 mmol). Then the mixture was cooled to 0 °C and ethyl chloroformate (217 mg, 2 mmol) was added dropwise. The mixture was stirred at room temperature for 4 h (TLC: ethyl acetate). Finally, the solution was diluted with dichloromethane (20 mL) and water (20 mL), the organic phase was washed sequentially with $NaHCO_3$ (5% in water) and brine (20 mL), dried over $MgSO_4$ and evaporated to yield a residue, which was purified on silica gel chromatography column using ethyl acetate as eluent. The compound **3** (129 mg, 39%) was obtained as a white solid. Mp 102–104 °C. IR (NaCl) υ (cm^{-1}), 3310 (OH); 2980 (NH); 1686 (CO); 1262 (Ar–O); 1092 (C–O). ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm), 1.36 (t, $J=7.2$ Hz, 3H, –CH_3); 4.30 (q, $J=7.0$ Hz, 2H, –CH_2); 7.06 (dd, $J=4.8$, 8.2 Hz, 1H, H-5); 7.29 (dd, $J=1.8$, 8.2 Hz, 1H, H-4); 7.97 (dd, $J=1.8$, 4.8 Hz, 1H, H-6); 8.97 (br s, 1H; OH, NH). ^{13}C NMR ($CDCl_3$, $J=50.3$ Hz) δ (ppm), 14.5 (CH_3); 62.9 (CH_2); 121.3 (CH, C-5); 128.0 (CH, C-4); 138.6 (C, C-3); 140.2 (CH, C-6); 143.9 (C, C-2); 156.7 (C, CO). Anal. Calcd for $C_8H_{10}N_2O_3$: C, 52.74%; H, 5.53%; N, 15.38%. Found: C, 52.43%; H, 5.67%; N, 15.01%.

4.1.4. 2-(*tert*Butylcarbonyl)-3-hydroxypyridine (5). In a similar way to that described for 2-acetylamino-3-hydroxypyridine, starting from 2-amino-3-hydroxypyridine (150 mg, 1.36 mmol) and *tert*butyl acide chloride (327 mg, 1.27 mmol) was obtained the amide *tert*butyl in a 90% yield as a white solid. Mp 82–84 °C. IR (NaCl) ν (cm^{-1}), 3485 (OH); 3164 (NH); 1768 (CO); 1231 (Ar–O); 1100 (C–O). ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm), 1.54 (s, 9H, –CH_3); 4.54 (br s, 2H, -OH, NH); 6.69 (dd, $J=4.8$, 7.8 Hz, 1H, H-5); 7.39 (dd, $J=1.0$, 4.8 Hz, 1H, H-4); 7.97 (dd, $J=1.0$, 4.8 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm), 27.9 (CH_3); 42.8 (C, $C(CH_3)_3$); 122.0 (CH, C-5); 129.1 (CH, C-4); 138.2 (CH, C-6); 138.2 (C, C-3); 141.8 (C, C-2); 171.5 (C, CO). Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84%; H, 7.27%; N, 16.47%. Found: C, 62.03%; H, 7.65%; N, 16.23%.

4.2. Formation of [1,4]oxazine ring. General procedure

To a suspension of K_2CO_3 (454 mg, 3.29 mmol) in acetonitrile (20 mL) was added 3-protected-2-hydroxypyridine (0.66 mmol). The resulting mixture was stirred at room temperature for 15 min, then chloroacrilonitrile or

2,3-dibromopropionate ethyl ester (0.72 mmol) was added dropwise in a twice separated by 1 h. The mixture was stirred at reflux for 2–24 h. The solvent was evaporated, the residue was suspended in cold water (20 mL), and the aqueous solution was further extracted with CH_2Cl_2 (3× 15 mL). The combined organic phases were washed with 0.5% $NaHCO_3$, dried (Na_2SO_4), and concentrated to providing crude nitrile or ester. The residue was purified by column chromatography on silica gel eluting with mixtures of hexane/ethyl acetate. The yields reported correspond to analytically pure isolated compounds.

4.2.1. 4-Acetyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-2-nitrile (6a). Following the general procedure described above starting from 2-acetamido-3-hydroxypyridine (100 mg, 0.66 mmol) and 2-chloroacrylonitrile (63 mg, 0.72 mmol) a mixture of two isomeres was obtained. The 4-Acetyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-2-nitrile was obtained as a white solid in 70% yield. Mp 113–115 °C. IR (KBr) υ (cm^{-1}), 2230 (CN); 1671 (CO); 1580 (CN); 1268 (Ar–O); 1081 (C–O). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm), 2.66 (s, 3H, CH_3); 3.95 (dd, J=4.4, 14.2 Hz, 1H, CH_2N); 4.93 (dd, J=4.4, 14.2 Hz, 1H, CH_2N); 5.21 (dd, J=1.0, 6.8 Hz, 1H, H-2); 7.13 (dd, J=4.6, 7.9 Hz, 1H, H-7); 7.38 (dd, J=1.0, 7.9 Hz, 1H, H-8); 8.18 (dd, J=1.0, 4.6 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm), 24.8 (CH_3); 40.9 (CH_2); 63.5 (CH–O); 114.6 (C, CN); 121.5 (CH, C-7); 125.3 (CH, C-8); 138.8 (C, C-8a); 141.2 (C, C-8); 151.2 (C, C-4a); 170.1 (CO, amide). Anal. Calcd for $C_{10}H_9N_3O_2$: C, 59.11%; H, 4.46%; N, 20.68%. Found: C, 59.34%; H, 4.63%; N, 20.54%. The 4-Acetyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-3-nitrile (**7a**) was obtained as a white solid in 36% yield when acetone was used as a solvent (see Table 1). Mp 110–112 °C. IR (KBr) υ (cm^{-1}), 2236 (CN); 1675 (CO); 1567 (CN); 1243 (Ar–O); 1032 (C–O). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm), 3.67–3.78 (m, 1H, CHN); 3.80 (s, 3H, CH_3); 4.80–4.90 (m, 2H, H-2); 6.61 (dd, J=4.5, 8.0 Hz, 1H, H-7); 7.18 (dd, J=1.0, 8.0 Hz, 1H, H-8); 7.72 (dd, J=1.0, 8 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm), 27.2 (CH_3); 42.5 (CH_2); 61.2 (CH_2–O); 115.9 (C, CN); 122.3 (CH, C-7); 126.2 (CH, C-8); 137.5 (C, C-8a); 141.8 (C, CH-6); 150.8 (C, C-4a); 168.2 (CO, amide). Anal. Calcd for $C_{10}H_9N_3O_2$: C, 59.11%; H, 4.46%; N, 20.68%. Found: C, 59.02%; H, 4.72%; N, 20.72%.

4.2.2. 4-Ethoxycarbonyl-3,4-dihydro-2*H*-pyrido[3,2-*b*]-[1,4]oxazine-2-nitrile (6b). From 2-ethoxycarbonyl-3-hydroxypyridine (100 mg, 0.55 mmol) and 2-chloroacrylonitrile (53 mg, 0.60 mmol) a mixture of two isomers was obtained. The majority isomer 4-ethoxycarbonyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-2-nitrile was obtained as a yellow pale solid in 40% yield. Mp 103–104 °C. IR (KBr) υ (cm^{-1}), 2251 (CN); 1784 (CO); 1576 (CN); 1151 (Ar–O); 1080 (C–O). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm), 1.26 (s, 3H, CH_3); 2.20 (dd, J=1.0, 8.4 Hz, 1H, CHN); 2.73 (dd, J=1.0, 8.5 Hz, 1H, CHN); 4.07–4.19 (m, 2H, CH_2–O); 4.81 (dd, J=1.0, 9.1 Hz, 1H, H-2); 7.20 (dd, J=4.5, 8.0 Hz, 1H, H-7); 7.41 (dd, J=1.0, 8.0 Hz, 1H, H-8); 8.21 (dd, J=1.0, 8 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm), 14.4 (CH_3); 43.4 (CH_2); 62.8 (CH_2–O); 72.9 (CH, C-2); 119.2 (C, CN); 121.2 (CH, C-7); 124.6 (CH, C-8); 138.5 (C, C-8a); 140.6 (CH, C-6); 153.2 (C, C-4a); 168.4 (CO, amide). Anal. Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65%; H, 4.75%; N, 18.02%. Found: C, 56.34%; H, 4.43%; N, 17.69%. The minor isomer 4-ethoxycarbonyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-3-nitrile (**7b**) was obtained as a white solid in 40% yield. Mp 199–201 °C. IR (KBr) υ (cm^{-1}), 2280 (CN); 1784 (CO); 1556 (CN); 1210 (Ar–O); 1046 (C–O). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm), 1.26 (t, J=7 Hz, 3H, CH_3); 4.12 (m, 3H, CHN and CH_2–O); 4.72 (d, J=14.2 Hz, 1H, CH_2O); 7.08–7.12 (m, 1H, H-7); 7.41 (dd, J=1.0, 8.0 Hz, 1H, H-8); 8.18 (dd, J=1.0, 4.8 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm), 14.8 (CH_3); 40.8 (CH, CH–N); 62.8 (CH_2, CH_2–O); 63.5 (CH_2–O); 115.9 (C, CN); 121.8 (CH, C-7); 126.7 (CH, C-8); 138.5 (C, C-8a); 141.5 (C, C-8a); 153.2 (C, C-4a); 168.2 (CO, amide). Anal. Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65%; H, 4.75%; N, 18.02%. Found: C, 56.87%; H, 5.02%; N, 17.71%.

4.2.3. 4-*tert*Butylcarbonyl-2,3-dihydro-4*H*-pyrido[3,2-*b*]-[1,4]oxazine-2-nitrile (6c). From 2-*tert*butylcarbonyl-amino-3-hydroxypyridine (100 mg, 0.52 mmol) and 2-chloroacrylonitrile (50 mg, 0.57 mmol) the 2-substituted pyrido-oxazine was obtained with 50% yield as a yellow pale instable solid. IR (KBr) υ (cm^{-1}), 2242 (CN); 1717 (CO); 1568 (CN); 1254 (Ar–O); 1097 (C–O). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm), 1.55 (s, 9H, CH_3); 3.81–3.85 (m, 1H, H-3); 4.50–4.61 (m, 1H, H-3); 5.10–5.19 (m, 1H, H-2); 7.05–7.09 (m, 1H, H-7); 7.24–7.28 (m, 1H, H-8); 8.21 (dd, J=1.8, 4.8 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ(ppm), 28.1 (CH_3); 43.9 (CH_2, CH_2–N); 63.2 (CH, CH–O); 83.2 (C); 116.8 (C, CN); 121.2 (CH, C-7); 124.9 (CH, C-8); 138.9 (C, C-8a); 141.9 (CH, C-6); 150.0 (C, C-4a); 168.1 (C, CO). Anal. Calcd for $C_{13}H_{15}N_3O_2$: C, 63.66%; H, 6.16%; N, 17.13%. Found: C, 63.99%; H, 6.54%; N, 16.08%.

4.2.4. 4-Acetyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-2-carboxylic acid ethyl ester (8). Following the general procedure described above starting from 2-acetamido-3-hydroxypyridine (100 mg, 0.66 mmol) and 2,3-dibromo-propionate ethyl ester (188 mg, 0.72 mmol) the 4-acetyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-2-carboxylic acid ethyl ester was obtained in 56% yield. Colorless oil. IR (KBr) υ (cm^{-1}), 1745 (CO); 1653 (CO), 1228 (Ar–O); 1059 (C–O). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm), 1.28 (t, J=7.0 Hz, 3H, CH_3); 2.54 (s, 3H, CH_3); 3.98 (dd, J=4.0, 7.0 Hz, 2H, CH–N); 4.24 (q, J=7.0 Hz, 2H, CH_2–O); 4.94–4.99 (m, 1H, CH–O), 7.09 (dd, J=1.4, 4.7 Hz, 1H, H-7); 7.18 (dd, J=1.3, 8.0 Hz, 1H, H-8); 8.01 (dd, J=1.4, 4 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm), 14.1 (CH_3); 24.5 (CH_3); 40.3 (CH_2–N); 62.0 (CH_2–O); 73.1 (CH–O); 121.4 (CH, C-7); 124.6 (CH, C-8); 139.7 (CH, C-6); 141.1 (C, C-8a); 141.3 (C, C-4a); 168.1 (CO, ester); 170.1 (CO, amide). Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59%; H, 5.64%; N, 11.19%. Found: C, 57.78%; H, 5.89%; N, 11.40%. 4-Acetyl-3,4-dihydro-2*H*-pyrido[3,2-*b*]-[1,4]oxazine-3-carboxylic acid ethyl ester (**9**) the 4-acetyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-3-carboxylic acid ethyl ester was obtained in 14% yield. Colorless oil. IR (KBr) υ (cm^{-1}), 1756 (CO); 1667 (CO), 1232 (Ar–O); 1045 (C–O). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm), 1.30 (t, J=7.0 Hz, 3H, CH_3); 2.53 (s, 3H, CH_3); 3.97 (m, 1H, CH–N); 4.24 (q, J=7.0 Hz, 2H, CH_2–O); 4.87–4.95 (m, 2H, CH_2–O), 6.83 (m, 1H, H-7); 7.21 (dd, J=1.3, 8.0 Hz, 1H,

H-8); 7.87 (dd, J=1.5, 4.0 Hz, 1H, H-6). Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59%; H, 5.64%; N, 11.19%. Found: C, 57.82%; H, 5.43%; N, 11.45%.

4.2.5. 4-Acetyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-2-carboxylic acid methyl ester (10). Following the general procedure described above starting from 2-acetamido-3-hydroxypyridine (100 mg, 0.66 mmol) the title compound was obtained in 61% yield. Colorless oil. IR (NaCl) ν (cm^{-1}), 1755 (CO); 1673 (CO). ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm), 2.54 (s, 3H, CH_3); 3.76 (s, 3H, OCH_3); 3.82 (dd, J= 3.4, 13.8 Hz, 1H, CHN); 4.69 (dd, J=3.8, 13.8 Hz, 1H, CHN); 4.92 (t, J=3.8 Hz, 1H, H-2); 7.09 (dd, J=4.7, 8.1 Hz, 1H, H-7); 7.35 (dd, J=1.4, 8.1 Hz, 1H, H-8); 8.01 (dd, J=1.4, 4.7 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm), 24.6 (CH_3); 40.6 (CH_2); 52.9 (OCH_3); 73.3 (CH, C-2); 121.7 (CH, C-7); 124.9 (CH, C-8); 139.9 (C, C-8a); 140.1 (CH, C-6); 141.3 (C, C-4a); 168.9 (CO); 170.4 (CO). MS (IS) (m/z) calcd for: $[C_{11}H_{12}N_2O_4]^+$: 236.23; found: 237 $[M+H]^+$, 259.5 $[M+Na]^+$.

4.3. General procedure for the condensation of α-halo-vinylcarbonyl compounds

A solution of 2-acetamido-3-hydroxypyridine (100 mg, 0.66 mmol) and K_2CO_3 (454 mg, 3.29 mmol) in acetonitrile (5 mL) was stirred at room temperature for about 30 min. After addition of the α-haloene (3.29 mmol) the mixture was refluxed for 2 to 24 h (see in detail Table 2). After cooling to room temperature, the solution was filtered through a pad of Celite and the filtrate concentrated in vacuum. The residue was then purified by column chromatography on silica gel.

4.3.1. 2,4-Diacetyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]-oxazine (12a). Purification on silica gel (ethyl acetate/petrol ether, 6:4) yielded 75 mg (52%) of **12a** as a yellow solid. IR (NaCl) υ (cm^{-1}), 1729 (CO); 1669 (CO); 1456. ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm), 2.29 (s, 3H, CH_3); 2.54 (s, 3H, CH_3); 4.03 (dd, J=3.5, 13.8 Hz, 1H, N–CH_2); 4.46 (dd, J=5.0, 13.8 Hz, 1H, N–CH_2); 4.81 (dd, J=3.5, 5.0 Hz, 1H, O–CH); 7.08 (dd, J=4.7, 8.2 Hz, 1H, H-7); 7.35 (dd, J=1.6, 8.2 Hz, 1H, H-8); 7.99 (dd, J=1.6, 4.7 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm), 24.7 (CH_3); 26.5 (CH_3); 39.6 (CH_2, CH_2–N); 79.4 (CH, CH–O); 121.6 (CH, C-7); 124.7 (CH, C-8); 139.7 (C, C-8a); 139.9 (CH, C-6); 141.3 (C, C-4a); 170.3 (CO, amide); 203.4 (CO, ketone). HRMS (m/z; IS) calcd for $[C_{11}H_{12}N_2O_3]^+$: 220.08479; found: 220.0849.

4.3.2. 4-Acetyl-2-benzoyl-3,4-dihydro-2*H*-pyrido[3,2-*b*]-[1,4]oxazine (12b). Purification on silica gel (ethyl acetate/petrol ether, 6:4) yielded 89 mg (48%) of **12b** from B, X= Br or 63 mg (34%) from B, X=Cl as a yellow solid. IR (NaCl) υ (cm^{-1}), 3064 (Ar–H); 3015 (Ar–H); 1694 (CO); 1578; 1456. ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm), 2.54 (s, 3H, CH_3); 4.24 (dd, J=3.5, 13.8 Hz, 1H, N–CH_2); 4.42 (dd, J=5.3, 13.8 Hz, 1H, N–CH_2); 5.72 (dd, J=3.5, 5.0 Hz, 1H, O–CH); 7.09 (dd, J=4.7, 8.2 Hz, 1H, H-7); 7.36 (dd, J= 1.6, 8.2 Hz, 1H, H-8); 7.48 7.54 (m, 2H, Ar); 7.60–7.70 (m, 1H, Ar); 7.94–7.98 (m, 2H, Ar); 8.02 (dd, J=1.6, 4.7 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm), 24.5 (CH_3); 40.5 (CH_2, CH_2–N); 75.6 (CH, CH–O); 121.6 (CH, C-7); 124.8 (CH, C-8); 128.6 (CH, C-3′, C-5′); 129.2 (CH, C-2′, C-6′); 131.8 (C, C-8a); 134.2 (C, C-1′); 134.3 (CH, C-4′); 139.8 (CH, C-6); 141.9 (C, C-4a); 170.5 (CO, amide); 194.0 (CO, ketone). HRMS (m/z; IS) calcd for $[C_{16}H_{14}N_2O_3]^+$: 282.10044; found: 282.1007.

4.3.3. 10-Acetyl-8,9,9a,10-tetrahydro-7*H*-pyrido[3,2-*b*]-benzo[1,4]oxazin-6-one (12c). Purification on silica gel (ethyl acetate/petrol ether, 6:4) yielded 85 mg (53%) of **12c** as a colorless oil. IR (NaCl) υ (cm^{-1}), 1726 (CO); 1668 (CO); 1577, 1451. ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm), 1.57 (ddd, J=3.84, 12.63, 25.56 Hz, 1H, H-9); 1.70 (dddd, J=3.84, 3.84, 13.68, 27.39 Hz, 1H, H-8); 1.87–1.92 (m, 1H, H-9); 2.02–2.08 (m, 1H, H-8); 2.38–2.41 (m, 1H, H-7); 2.63 (s, 3H, CH_3); 2.76 (ddd, J=6.2, 13.7, 13.7 Hz, 1H, H-7); 4.29–4.30 (m, 1H, H-5a); 5.14 (ddd, J=2.7, 5.0, 12.7 Hz, 1H, H-9); 7.06 (dd, J=4.7, 8.2 Hz, 1H, H-3); 7.28 (dd, J= 1.6, 8.2 Hz, 1H, H-4); 8.03 (dd, J=1.6, 4.7 Hz, 1H, H-2). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm), 22.2 (CH_2, C-8); 24.0 (CH_2, C-9); 25.9 (CH_3) 36.8 (CH_2, C-7); 50.3 (CH, C-9a); 79.6 (CH, C-5a); 120.9 (CH, C-3); 124.5 (CH, C-4); 138.6 (C, C-4a); 139.8 (C, C-10a); 140.5 (CH, C-2); 141.3 (C, C-4a); 169.9 (CO, amide); 204.0 (CO, ketone). HRMS (m/z; IS) calcd for $[C_{13}H_{14}N_2O_3]^+$: 246.10044; found: 246.1007.

4.4. Unsatured compounds. General procedure

To a stirred solution of the pyrido-oxazine (0.50 mmol) in dry CCl_4 (15 mL) *N*-bromosuccinimide (3 equiv) and a catalytic amount of AIBN were added. The reaction mixture was stirred and heated with a bulb lamp (100 W) for 60 min and then allowed to cool to room temperature. Upon cooling to room temperature the NBS was filtered off, and the solvent was removed on vacuum. The oil obtained sufficiently pure was used directly in the next step. The crude of reaction was dissolved in acetone (20 mL). Then sodium iodide (1.23 mmol) was added and the resulting mixture was stirred at room temperature for 24 h. Finally, the solvent was evaporated to dryness in vacuum followed by addition of ethyl acetate (20 mL) and washed with water and after with 1 M solution of sodium thiosulfate. The organic phase was dried over $MgSO_4$. Evaporation of the solvent gave the desired compound, which was subjected to column chromatography of silica gel eluting with hexane/ethyl acetate.

4.4.1. 4-Acetyl-4*H*-pyrido[3,2-*b*][1,4]oxazine-2-nitrile (21). Following the general procedure the title compound was obtained with a 55% yield as a white solid. Mp 126–128 °C. IR (KBr) υ (cm^{-1}), 2227 (CN); 1724 (C=O); 1580 (C=N); 1230 (Ar–O); 1102 (C–O). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm), 2.67 (s, 3H, CH_3); 7.05–7.12 (m, 2H, H-7 and H-8); 7.54 (s, 1H, H-3); 7.99 (dd, J=1.8, 4.8 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm), 26.4 (CH_3); 112.4 (C, C-2); 116.4 (C, CN); 121.5 (CH, C-3); 122.8 (CH, C-7); 124.6 (CH, C-8); 139.9 (C, C-8a); 140.6 (CH, C-6); 153.2 (C, C-4a); 168.4 (CO, amide). Anal. Calcd for $C_{10}H_7N_3O_2$: C, 59.70%; H, 3.51%; N, 20.89%. Found: C, 59.92%; H, 3.81%; N, 20.58%.

4.4.2. 4-Acetyl-4*H*-pyrido[3,2-*b*][1,4]oxazine-3-nitrile (22). Following the general procedure the title compound

was obtained with a 60% yield as a colorless oil. IR (KBr) υ (cm^{-1}), 2229 (CN); 1735 (C=O); 1565 (C=N); 1260 (Ar–O); 1100 (C–O). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm), 2.69 (s, 3H, CH_3); 7.02–7.18 (m, 2H, H-7 and H-8); 7.42 (s, 1H, H-3); 8.18 (dd, $J=1.8$, 4.8 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm), 25.2 (CH_3); 116.6 (C, CN); 126.7 (CH, C-3); 122.8 (CH, C-7); 124.8 (CH, C-8); 140.3 (C, C-8a); 141.7 (CH, C-2); 142.8 (CH, C-6); 152.5 (C, C-4a); 166.9 (CO, amide). Anal. Calcd for $C_{10}H_7N_3O_2$: C, 59.70%; H, 3.51%; N, 20.89%. Found: C, 59.83%; H, 3.76%; N, 20.77%.

4.4.3. 4-Acetyl-4*H*-pyrido[3,2-*b*][1,4]oxazine-2-carboxylic acid methyl ester (23a). Following the general procedure described above starting from the corresponding saturated ester the title compound was obtained. After purification on silica gel (hexane/ethyl acetate) were obtained 48 mg (81%) as a yellow solid (mp=83–84 °C). IR (NaCl) υ (cm^{-1}), 1732 (CO), 1687 (CO). ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm), 2.68 (s, 3H, CH_3); 3.84 (s, 3H, OCH_3); 7.02 (dd, $J=4.7$, 7.9 Hz, 1H, H-7); 7.21 (dd, $J=1.6$, 7.9 Hz, 1H, H-8); 7.88 (s, 1H, H-3); 7.94 (dd, $J=1.6$, 4.7 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm), 26.6 (CH_3); 52.5 (OCH_3); 118.4 (CH, C-3); 119.2 (C, C-2); 122.6 (CH, C-7); 124.7 (CH, C-8); 131.3 (C, C-8a); 141 (C, C-4a); 142.2 (CH, C-6); 161.3 (CO, ester), 167.7 (CO, amide). MS (IS) (*m*/*z*) calcd for: $[C_{11}H_{10}N_2O_4]^+$: 234.21; found: 235.5 $[M+H]^+$, 257.5 $[M+Na]^+$.

4.4.4. 2,4-Diacetyl-4*H*-pyrido[3,2-*b*][1,4]oxazine (23b). After purification on silica gel (ethyl acetate/petrol ether, 1:1) were obtained 54 mg (91%) of **23b** as a yellow solid (mp 139–141 °C). IR (NaCl) ν (cm^{-1}), 1690 (CO); 1682 (CO). ^1H NMR ($CDCl_3$, 250 Hz): δ (ppm), 2.34 (s, 3H; CH_3); 2.70 (s, 3H; CH_3); 7.02 (dd, $J=5$, 8.2 Hz, 1H; H-7); 7.22 (dd, $J=1.6$, 8.2 Hz, H-8); 7.88 (s, 1H; H-3); 7.93 (dd, $J=1.6$, 5 Hz, 1H; H-6). ^{13}C NMR ($CDCl_3$, $J=62.9$ Hz): δ (ppm), 25.2 (*C*H_3); 26.7 (CH_3); 119.2 (*C*H); 122.7 (*C*H); 124.7 (*C*H); 138.2 (C); 140.8 (*C*); 142.1 (*C*H); 142.2 (*C*); 168 (*C*O, amide); 189.5 (*C*O, ketone). HRMS (*m*/*z*; IS) calcd for: $[C_{11}H_{10}N_2O_3]^+$: 218.06914; found: 218.0697.

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Greenish metal-lustrous organic crystals formed from 1-aryl-2-(2-thienyl)-5-(5-tricyanoethenyl-2-furyl)pyrroles

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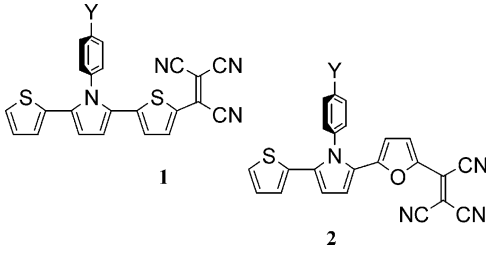
Abstract—On the treatment of 1-aryl-2-(2-furyl)-5-(2-thienyl)pyrroles with tetracyanoethylene, 1-aryl-2-(2-thienyl)-5-(5-tricyanoethenyl-2-furyl)pyrroles were produced. These compounds formed crystals with greenish metallic luster. In their solid-state UV–vis–NIR diffuse reflection–absorption spectra, absorption band corresponding to metallic reflection spreads in the range of 550–900 nm. Furthermore, strong absorption appeared below 520–540 nm. This absorption results in the appearance of green color. Single-crystal X-ray crystallographic analysis revealed the crystal structure of 1-(4-methoxyphenyl)-2-(2-thienyl)-5-(5-tricyanoethenyl-2-furyl)pyrrole (**2c**). The distinct features of the crystal structure are as follows: (1) the thiophene–pyrrole–furan–tricyanoethenyl π-system is approximately flat; (2) the conformational relation between the pyrrole ring and the furan ring is anti, that is, these rings are pointing in opposite directions and the dihedral angle of N–C–C–O = 180°; (3) as a result, the tricyanoethenyl group is far from the 4-methoxyphenyl group; (4) the molecules of **2c** are arranged in a ribbon structure; (5) the ribbons are assembled side-by-side to form a terraced layer; (6) the layers stack so that the π-orbitals of **2c** become close to each other.

1. Introduction

Chemical scientists have been developing metal-like organic materials such as electron-conducting polymers[1] that are represented by polythiophenes[2] and polyacetylenes,[3] molecular metals that require charge transfer between two different chemical species,[4–6] and highly conducting crystals consisting of single-component neutral nickel complexes.[7,8] Some organic π-conjugated molecules with relatively lower molecular weight are known to exhibit metallic luster such as furan- and pyrrole-containing analogues of α-quinquethiophene[9] and α,α′-bis(dithieno[3,2-*b*:2′,3′-*d*]thiophene) (BDT).[10] Recently, we also found novel organic compounds, 1-aryl-2-(2-thienyl)-5-(5-tricyanoethenyl-2-thienyl)pyrroles (**1**), which easily form crystals with gold-like, bronze-like, or red-violet metallic luster through the intermolecular side-by-side interaction between their π-molecular orbitals.[11–15] With these intriguing findings, we were interested in the role of the thiophene rings: how do they contribute to the appearance of the metallic luster? (Scheme 1).



Scheme 1.

Hence, our investigation was started on the synthesis of 1-aryl-2-(2-thienyl)-5-(5-tricyanoethenyl-2-furyl)pyrroles (**2**), which have a furan ring[16] instead of the inner thiophene ring of **1**. Here, we would like to report that these compounds (**2**) form crystals with greenish metallic luster.

2. Results and discussion

First of all, 1-aryl-2-(2-thienyl)-5-(5-tricyanoethenyl-2-furyl)pyrroles (**2**) were easily synthesized from 1-(2-furyl)-4-(2-thienyl)-1,4-butanedione (**3**).[17] The reaction of 1-aryl-2-(2-furyl)-5-(2-thienyl)pyrroles (**4**), which were prepared by the Paal–Knorr reaction of **3** with anilines, with tetracyanoethylene occurred at ambient temperature

Keywords: Metallic luster; Reflection; Organic Crystal; Furan; Pyrrole; Thiophene; Tricyanoethenyl.
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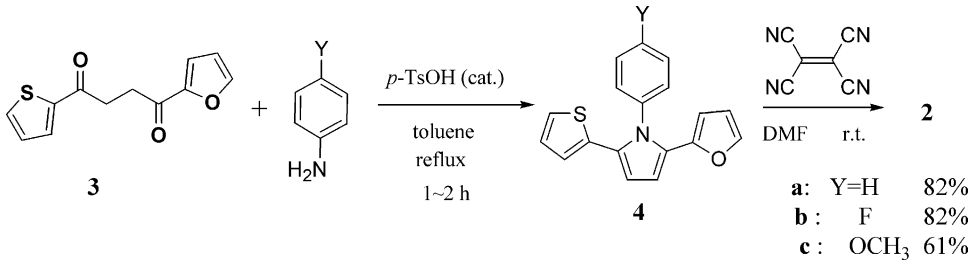

Scheme 2.

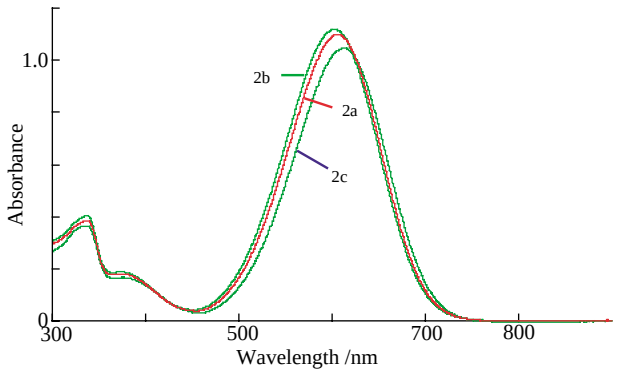

Figure 1. Solution UV–vis absorption spectra of **2** in THF (3.0×10^{-5} M). **2a**: λ_{max} 607 nm (ε 36,600), λ_{min} 455 nm (ε 1270); **2b**: 603 nm (ε 37,300), 453 nm (ε 1410); **2c**: 613 nm (ε 34,900), 457 nm (ε 1020).

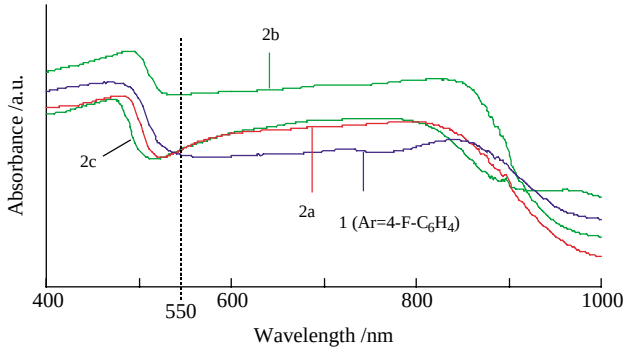

Figure 3. Solid state UV–vis NIR diffuse reflection–absorption spectra of **1** and **2**.

in *N*,*N*-dimethylformamide (DMF) to produce the corresponding **2** in good to high yields. Interestingly, an alternative product, 1-aryl-2-(2-furyl)-5-(5-tricyanoethenyl-2-thienyl)-pyrrole that is produced by the attack of tetracyanoethylene on the thiophene part of **4**, was not detected in the reaction mixture (Scheme 2).

They are soluble in regular organic solvents such as chloroform, acetone, and THF to give a deep blue solution because they absorb visible light around the wavelength of 600 nm (Fig. 1). It is noteworthy that their absorption maxima are shifted to the shorter wavelength compared with those of **1** (λ_{max} in THF: Y=H, 613 nm; *F*, 609 nm; CH_3O, 625 nm).

To our surprise, slow evaporation of the solvent gave crystals with greenish metallic luster, as shown in Figure 2. Their solid-state UV–vis–NIR diffuse reflection–absorption spectra are shown in Figure 3. Instead of the absorption band around 600 nm in a solution, a peculiar broadened absorption band was observed in a visible region of 500–1000 nm wavelength. This broad band contributes to the appearance of metallic luster: the appearance of a solid depends on the degree of absorption and reflectance in the visible region of the spectrum. With a band below 1.5 eV (800 nm), in the infrared, the solid may appear dark in color or shiny metallic, depending on the reflectivity.[18] The latter is the present case. Further, stronger absorption appeared below 520–540 nm with a maximum at 500–520 nm in the solid state spectra of **2**. This is the reason why the crystals of **2** exhibit greenish metallic luster.

Fortunately, crystals of sufficient quality for structural studies were obtained for the compound **2c**. The crystal structure of **2c** was shown in Figure 4. The molecule adopts a flat conformation, in which the pyrrole and furan rings are placed in an anti fashion. The anti fashion means the torsion angle of N–C–C–O is approximately 180°. The distance between the phenyl *ipso* carbon and the 3-hydrogen of

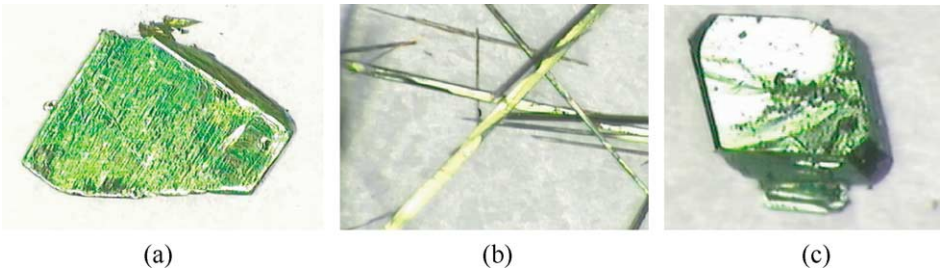

Figure 2. Crystal photographs. (a) A crystal of **2a** from acetone. (b) Crystals of **2b** from acetone. (c) A crystal of **2c** from chloroform.

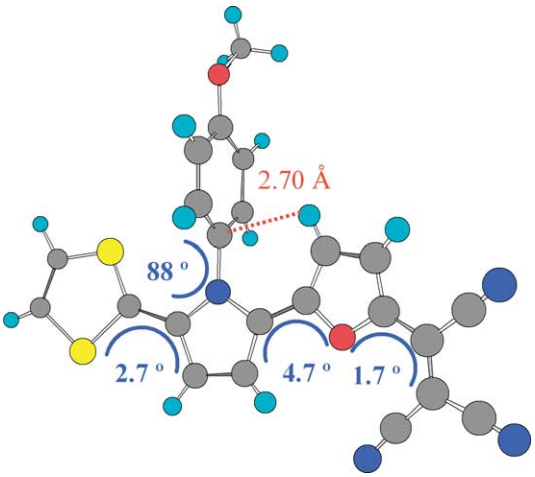

Figure 4. Crystal structure of **2c**. The thiopene ring is disordered: the sulfur that is located at the bottom of the above formula has a larger population (66%). Dihedral angles are shown with blue letters. The distance between the phenyl *ipso* carbon and the 3-hydrogen of the furan ring is shown with red letters.

the furan ring is 2.70 Å, meaning that a CH/π interaction[19] works in this system.

In a solution, this interaction seems to be valid, because, in the ^{1}H NMR spectrum ($CDCl_3$), the chemical shift of the 3-proton of the furan ring was observed at a higher field (δ 5.28) than those of the usual furan derivatives (furan δ 6.37; furfuryl acetate, δ 6.35; 2-furaldehyde, δ 6.63 and 7.28). This tendency was also observed in the ^{1}H NMR of **4** (Y = H, δ 5.17; CH_3O, 5.20; F, 5.28). Therefore, it seems to be general that, in 1-aryl-2-(2-furyl)-5-(2-thienyl)pyrroles, the CH/π interaction is effective in a solution and in crystalline state for settling the furan ring to be anti to the pyrrole ring. Thus, the tricyanoethenyl group is far from the 4-methoxyphenyl group. This anti conformation is in a sharp contrast with that of **1**, because the tricyanoethenyl group and the 1-aryl group are always pointed toward the same direction in the crystalline state of **1** investigated hitherto. Figure 5 summarizes the arrangement of the π-molecules in the crystal of **2c**.

The π-molecules are arranged in a ribbon. The ribbons are assembled in a side-by-side manner to form a terraced plane. The terraced planes stack vertically to form crystals. In the ribbon, the π-molecules are aligned side-by-side so that the cyano group is placed 3.97 Å from the pyrrole carbon of the neighboring π-molecule. This distance is longer than those observed in the crystal layer of **1**. It is likely that the 4-methoxyphenyl group interacts with the terminal thiophene ring through the CH/π interaction to maintain the ribbon structure. Interestingly, the close approach of π-molecules was observed between the terraced planes.

As shown in Figure 6, there are two types of stacking (Stacking A and Stacking B). These two stacking modes are alternatively arranged. In Stacking A, the furan ring and the pyrrole ring are very close to the tricyanoethenyl group of

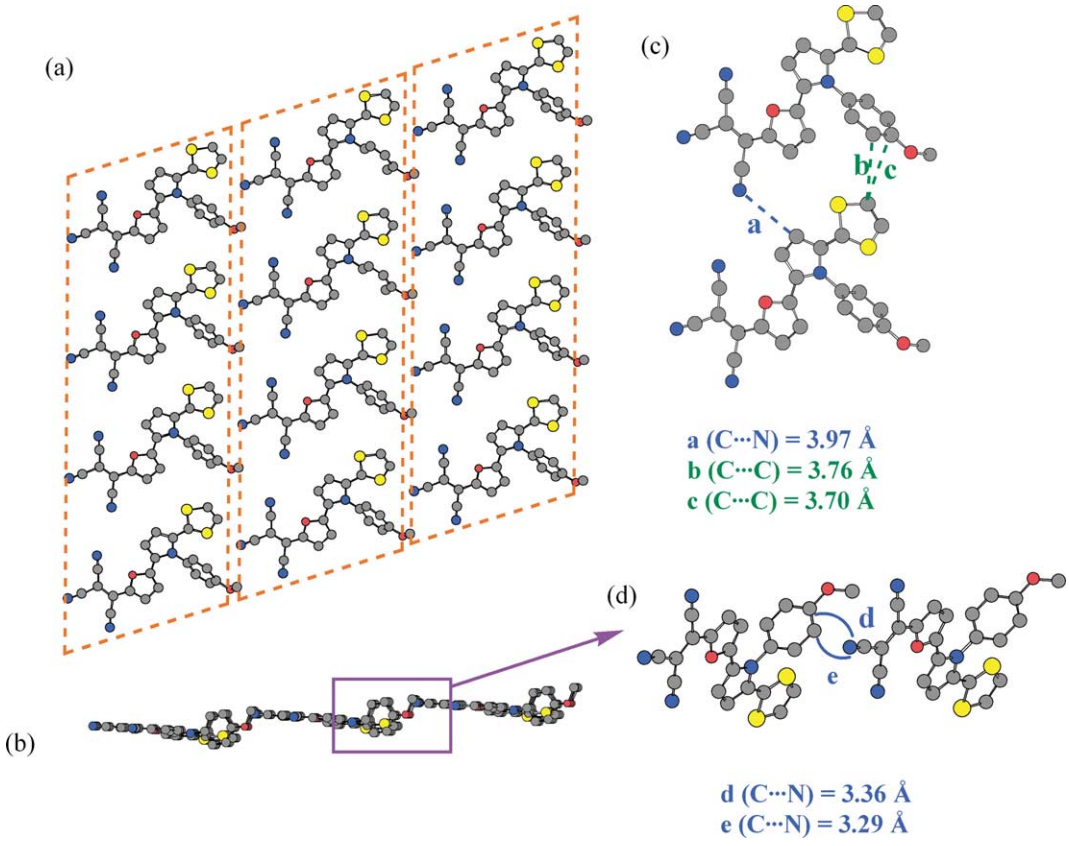

Figure 5. The terraced plane of the **2c** crystal. (a) Top view of the plane. The dashed lines depict the ribbon structures. (b) Side view of the plane. (c) The approach of two molecules in the ribbon. (d) The nearest molecules between the adjacent ribbons.

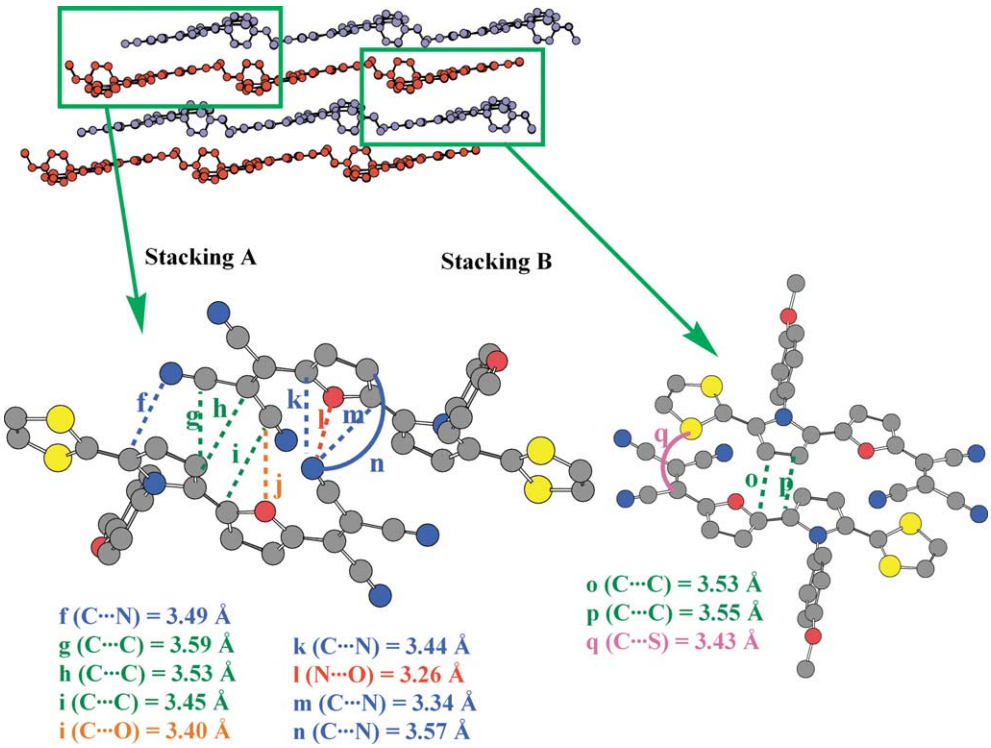

Figure 6. Interlayer interactions between the molecules in the crystal of **2c**.

the neighboring layer. The distances are in the range of 3.26–3.60 Å. In Stacking B, the pyrrole ring and the sulfur atom in the thiophene approach to the furan ring and the tricyanoethenyl group, respectively, of the adjacent layer. The thiopene ring is disordered, but the sulfur that can contact to the tricyanoethenyl group has a larger population (66%). These facts imply that the π-molecules interact to each other between the terraced planes. In the present crystals, the vertical continuous stacking of the π-molecules seems to play an important role in the appearance of metallic luster. Hence, we examined what oscillating direction of a plane-polarized light effectively contributes to the metallic luster, using the faces of the single crystal. The single crystal of **2c** (Fig. 2c) was used for this analysis. We selected three large faces [Miller indices: (001), (01−1), and (11−1)] and their reflection spectra were measured with microscopic UV–vis-NIR spectrophotometer (JASCO MSV-370) (Fig. 7). All of the faces reflect the incident light with the wavelength longer than 480 nm.

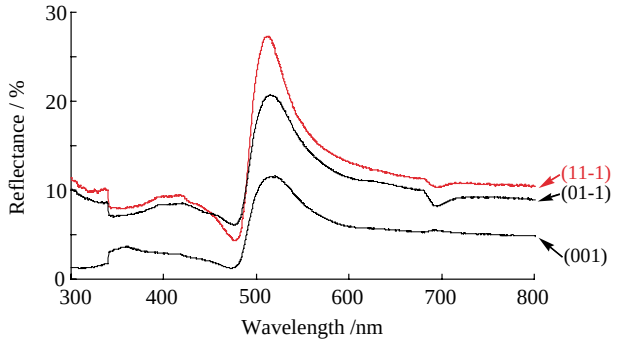

Figure 7. UV–vis-NIR reflection spectrum for each face of a single crystal of **2c**. The Miller indices of the face are shown at the right side.

Furthermore, we investigated the relationship between the arrangement of the π-systems of **2c** and the metallic luster. The (11−1) face of the single crystal was selected because this face made us view the arrangement of the molecules clearly. The plane-polarized light was incident vertically on the (11−1) surface to give a reflection spectrum. In Figure 8, the molecular arrangement is shown together with the (11−1) face. To our expectations, the reflective intensity is changeable according to the angle of the oscillation plane of the plane-polarized light, as summarized in Figure 9: the spectra were taken every 10 degrees of the oscillation plane. When the oscillation plane is approximately parallel to the layer (the angle of the oscillation plane=0° in Figure 9), the reflection is the weakest. In contrast, we obtained the strongest reflection in case the oscillation plane is at nearly right angles to the layer (the angle of the oscillation plane=90°). These results suggest that the interlayer movement of electrons contributes to the light reflection. This is consistent with the afore-mentioned fact that the π-orbitals of **2c** in the crystalline state are close between the layers.

3. Conclusion

Interestingly, 1-aryl-2-(2-thienyl)-5-(5-tricyanoethenyl-2-furyl)pyrroles formed crystals with green metallic luster. In their solid-state UV–vis–NIR diffuse reflection–absorption spectra, broad absorption bands appeared in the range of 550–900 nm, corresponding to the appearance of the metallic luster. Further, strong absorption was observed below 520–540 nm, resulting in the appearance of greenish color. From single-crystal X-ray crystallographic analysis of 1-(4-methoxyphenyl)-2-(2-thienyl)-5-(5-tricyanoethenyl-2-furyl)pyrrole (**2c**), it was shown that, in a crystalline state,

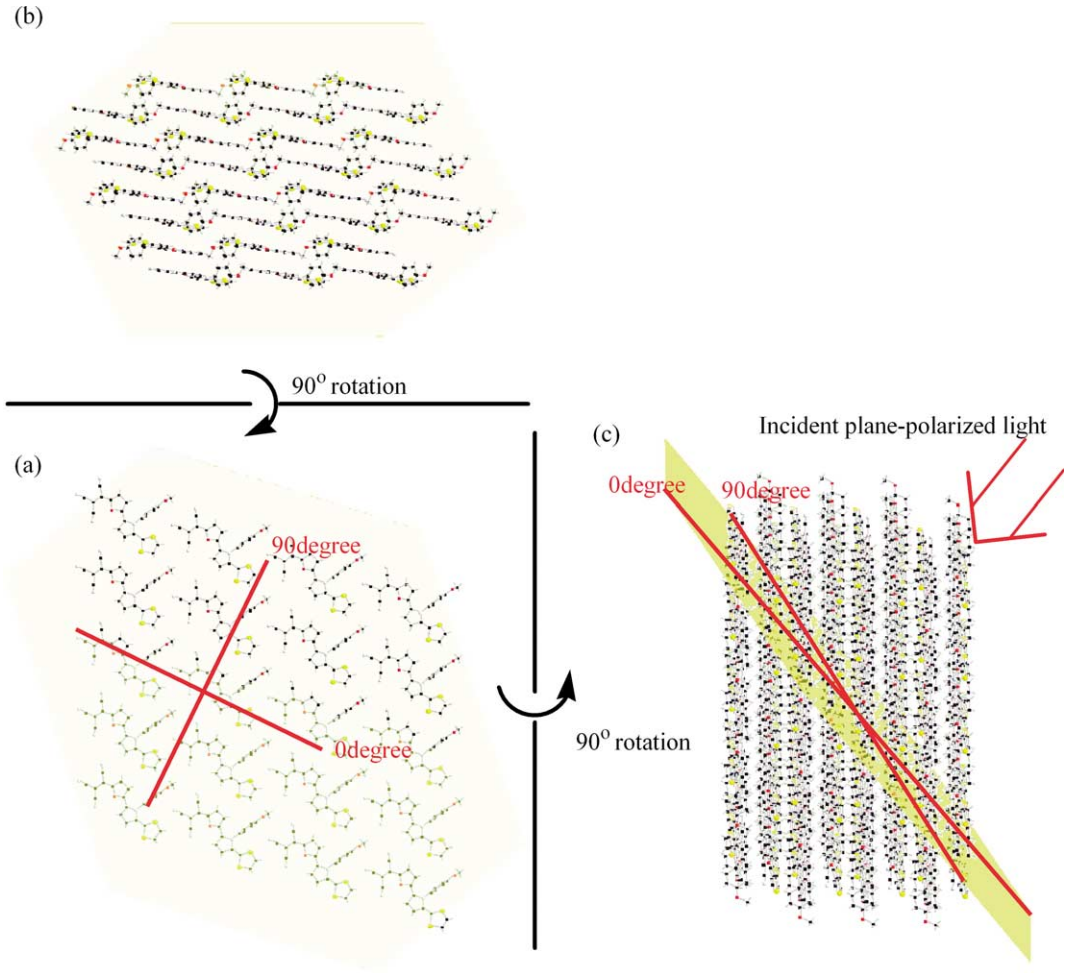

Figure 8. The terraced layers, the (11 − 1) face (yellow plane), and the plane-polarized light that is incident vertically to the (11 − 1) face. (a) The front view of one terraced layer and the (11 − 1) face. The red lines show the plane angle of the indient light. (b) The top view. Eight layers are shown. (c) The side view of eight layers.

the thiophene–pyrrole–furan–tricyanoethenyl π-system of **2c** is approximately flat and the flat molecules of **2c** are arranged in a ribbon structure. The ribbons are assembled side-by-side to form a terraced layer. The layers stack to form the crystal structure. The stacking of the layers makes that the π-orbitals of **2c** much close to each other. This seems to be related with the appearance of metallic luster.

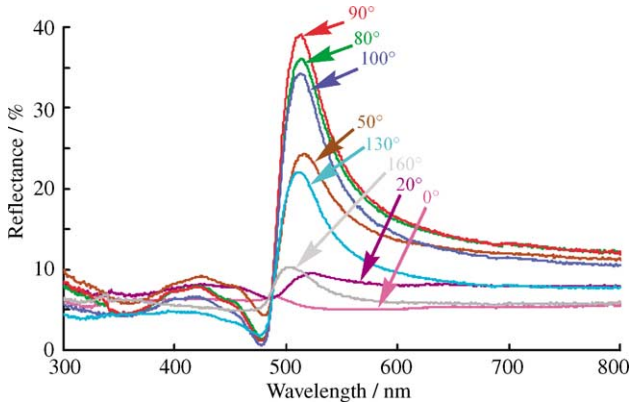

Figure 9. UV–vis–NIR Reflection spectra of the (11 − 1) face with plane-polarized light. Refer the angle of the oscillation plane of the incident light to Figure 8.

4. Experimental

Melting points are determined on a hot-stage microscope apparatus (Yanaco MP-500D) and uncorrected. All chemicals were obtained from commercial suppliers and used without further purification. ^{1}H NMR spectra were recorded at 300 MHz using a Varian Gemini-2000 NMR spectrometer and chemical shifts were referenced to TMS as internal standard. UV–vis–NIR absorption spectra were recorded on a JASCO V-570 spectrophotometer. Infrared spectra were measured on a JASCO FT/IR-350 spectrophotometer. Elemental analyses were performed by Chemical Analysis Center of Chiba University.

4.1. Preparation of 1-phenyl-2-(2-thienyl)-5-(5-tricyanoethenyl-2-furyl)pyrrole. A typical procedure

A solution of 1-(2-furyl)-4-(2-thienyl)-1,4-butanedione (0.500 g, 1.72 mmol), aniline (1.03 g, 11.0 mmol), and *p*-toluenesulfonic acid monohydrate (0.123 g, 0.647 mmol) in toluene (10 mL) was refluxed under occasionally removing the distillated toluene. The reaction progress was monitored with TLC, showing that the reaction completed after 2 h. The solution was subjected to column chromatography on silica gel (eluent: toluene) to give

2-(2-furyl)-1-phenyl-5-(2-thienyl)pyrrole (**4a**) as colorless solid (0.304 g: 60% yield). This product was too sensitive to air to be isolated in a completely pure form. From the following physical data, we confirmed its structure and subjected it to the next reaction.

Compound **4a**. Colorless solid; mp 130.4–131.4 °C; ^{1}H NMR ($CDCl_3$) δ 5.17 (dd, J=0.7, 3.4 Hz, 1H), 6.17 (dd, J=1.8, 3.4 Hz, 1H), 6.53 (dd, J=1.2, 3.6 Hz, 1H), 6.56 (d, J=3.8 Hz, 1H), 6.66 (d, J=3.8 Hz, 1H), 6.80 (dd, J=3.6, 5.2 Hz, 1H), 7.04 (dd, J=1.2, 5.2 Hz, 1H), 7.28 (dd, J=0.7, 1.7 Hz, 1H), 7.34–7.37 (m, 2H), 7.50–7.51 (m, 3H); IR (KBr) 1496, 1412, 1203, 1011, 773, 762, 742, 694, 679, 594 cm^{-1}; HRMS (FAB) calcd for $C_{18}H_{13}NOS$ 291.0718, found 291.0693.

A mixture of **4a** (0.253 g, 0.870 mmol, 1.00 equiv) and tetracyanoethylene (0.135 g, 1.05 mmol, 1.21 equiv) in anhydrous DMF (10 mL) was stirred for 1.5 h at room temperature. The reaction mixture was poured into brine (100 mL), and the resulting mixture was extracted with ethyl acetate (100 mL×3). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The dark blue residue was purified by column chromatography on silica gel using toluene as an eluent to give **2a** as greenish metal-lustrous crystals (0.279 g: 82% yield).

4.1.1. 1-Phenyl-2-(2-thienyl)-5-(5-tricyanoethenyl-2-furyl)pyrrole (2a). Greenish metal-lustrous crystals; mp 197.7–198.2 °C (from $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.21 (broad d, J=3.2 Hz, 1H) [this signal became a doublet (J=4.3 Hz) at −30 °C], 6.79 (d, J=4.3 Hz, 1H), 6.79 (dd, J=1.1, 3.8 Hz, 1H), 6.89 (dd, J=3.7, 5.1 Hz, 1H), 7.18 (dd, J=1.1, 5.1 Hz, 1H), 7.19 (broad s, 1H), 7.34 (d, J=4.3 Hz, 1H), 7.42 (d, J=7.4 Hz, 2H), 7.59–7.71 (m, 3H); IR (KBr) 2214, 1593, 1518, 1471, 1442, 1352, 1248, 1211, 1036, 978 cm^{-1}. UV–vis (THF, 3×10^{-5} M) λ_{max} (nm) (ε, M^{-1} cm^{-1}) 607 (36,600). Anal. Calcd for $C_{23}H_{12}N_4OS$: C, 70.39; H, 3.08; N, 14.28. Found: C, 70.47; H, 3.09; N, 14.32.

4.1.2. 1-(4-Flurophenyl)-2-(2-furyl)-5-(2-thienyl)pyrrole (4b). Pale yellow crystals (77% yield); mp 153.3–154.0 °C (from acetone); ^{1}H NMR ($CDCl_3$) δ 5.28 (d, J=3.5 Hz, 1H), 6.20 (dd, J=1.9, 3.2 Hz, 1H), 6.55 (d, J=3.8 Hz, 1H), 6.57 (d, J=3.8 Hz, 1H), 6.64 (dd, J=0.9, 3.5 Hz, 1H), 6.84 (dd, J=3.7, 5.2 Hz, 1H), 7.07 (dd, J=1.1, 5.1 Hz, 1H), 7.15–7.21 (m, 2H), 7.28–7.35 (m, 3H); IR (KBr) 3116, 3072, 1508, 1414, 1215, 841, 762, 735, 700, 681 cm^{-1}. Anal. Calcd for $C_{18}H_{12}FNOS$: C, 69.88; H, 3.91; N, 4.53. Found: C, 69.86; H, 3.96; N, 4.39.

4.1.3. 1-(4-Fluorophenyl)-2-(2-thienyl)-5-(5-tricyanoethenyl-2-furyl)pyrrole (2b). Greenish metal-lustrous crystals (82% yield); mp 177.4–177.9 °C (from ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 5.33 (broad s, 1H) [this signal became a doublet (J=4.3 Hz) at −30 °C], 6.75 (d, J=4.3 Hz, 1H), 6.83 (dd, J=1.2, 3.8 Hz, 1H), 6.92 (dd, J=3.8, 5.2 Hz, 1H), 7.20 (dd, J=1.1, 5.1 Hz, 1H), 7.24 (broad s, 1H), 7.31 (d, J=4.0 Hz, 1H), 7.31–7.33 (m, 2H), 7.40–7.44 (m, 2H); IR (KBr) 2216, 1520, 1510, 1473, 1442, 1358, 1252, 1211, 1038, 978 cm^{-1}. UV–vis (THF, 3×10^{-5} M) λ_{max} (nm) (ε, M^{-1} cm^{-1}) 603 (37,300). Anal. Calcd for $C_{23}H_{11}FN_4OS$: C, 67.31; H, 2.70; N, 13.65. Found: C, 67.26; H, 2.62; N, 13.57.

4.1.4. 2-(2-Furyl)-1-(4-methoxyphenyl)-5-(2-thienyl) pyrrole (4c). Pale yellow solid (41% yield; air-sensitive); mp 140.8–141.2 °C; ^{1}H NMR ($CDCl_3$) δ 3.89 (s, 3H), 5.20 (dd, J=0.6, 3.4 Hz, 1H), 6.18 (dd, J=1.8, 3.4 Hz, 1H), 6.56 (d, J=4.0 Hz, 1H), 6.60 (dd, J=1.1, 3.7 Hz, 1H), 6.64 (d, J=4.0 Hz, 1H), 6.82 (dd, J=3.6, 5.1 Hz, 1H), 7.00 (d, J=8.9 Hz, 2H), 7.04 (dd, J=1.1, 5.1 Hz, 1H), 7.24–7.29 (m, 3H); IR (KBr) 1516, 1412, 1296, 1250, 1203, 1026, 833, 762, 741, 702 cm^{-1}. HRMS (FAB) calcd for $C_{19}H_{15}NO_2S$ 321.0824, found 321.0805.

4.1.5. 1-(4-Methoxyphenyl)-2-(2-thienyl)-5-(5-tricyanoethenyl-2-furyl)pyrrole (2c). Greenish metal-lustrous crystals (61% yield); mp (from $CHCl_3$) 212.8–213.2 °C; ^{1}H NMR ($CDCl_3$) δ 3.95 (s, 3H), 5.28 (broad s, 1H) [this signal became a doublet (J=4.3 Hz) at −30 °C], 6.76 (d, J=4.3 Hz, 1H), 6.87 (dd, J=1.2, 3.7 Hz, 1H), 6.92 (dd, J=3.7, 5.0 Hz, 1H), 7.09 (d, J=8.9 Hz, 2H), 7.18 (dd, J=1.2, 5.1 Hz, 1H), 7.20 (broad s, 1H), 7.31 (d, J=4.3 Hz, 1H), 7.32 (d, J=8.9 Hz, 2H); IR (KBr) 2218, 1523, 1442, 1473, 1362, 1252, 1209, 1171, 1032, 980 cm^{-1}. UV–vis (THF, 3×10^{-5} M) λ_{max} (nm) (ε, M^{-1} cm^{-1}) 613 (34,900). Anal. Calcd for $C_{24}H_{14}N_4O_2S$: C, 68.23; H, 3.34; N, 13.26. Found: C, 68.00; H, 3.40; N, 13.22.

4.2. X-ray crystallographic analysis of a single crystal of 2c

Data collection was performed on a Mac Science MXC18 four-circle diffractometer with graphite monochromated Cu Kα radiation (λ=1.54178 Å) using the θ–2θ scan technique at 298 K. The structure was solved by direct methods and refined by full-matrix least-squares methods against F (SIR 92[20]) on a computer program package: maXus ver. 3.2.1 from MAC Science Co. Ltd). All non-hydrogen atoms were refined with anisotropic displacement parameters and hydrogen atoms were refined isotropically. Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 286697. 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].

Crystal data of **2c**. $C_{24}H_{14}N_4O_2S$, M_r=422.46, greenish metal-lustrous plates, triclinic, space group $P\bar{1}$, a=8.993(4) Å, b=10.023(5) Å, c=12.316(5) Å, α=99.25(4)°, β=99.40(3)°, γ=104.48(4)°, V=1036.4(8) Å^3, Z=2, D_{calcd}=1.354 g cm^{-3}, $F(000)$=436, μ=1.63 cm^{-1}, 4176 observed reflections($I>2.00\sigma(I)$), 334 parameters, R=0.071, wR=0.111.

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Selective syntheses of benzoxazoles and *N*-(2-hydroxyaryl)pyrrolidin-2-ones from the corresponding cyclopropyl amides with PPh_3/CX_4

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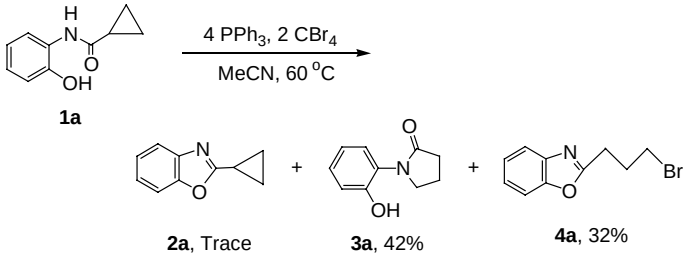
Abstract—Benzoxazoles **2** can be smoothly synthesized by treatment of starting materials of *N*-(2-hydroxyaryl) cyclopropyl amides **1** with PPh_3/CCl_4 in acetonitrile in good yields. When PPh_3/CBr_4/MS 4 Å was used in the reaction system, the corresponding ring-expanding products **3** were obtained in moderate to good yields in acetonitrile at 80 °C. Using DCE as a solvent in this reaction, the corresponding 2-(3-chloropropyl)benzoxazoles **5** were obtained as major products.

1. Introduction

It is well known that triphenylphosphine in the combination with a tetrahalomethane provides reagents that have manifold uses and are finding increasing application in preparative chemistry for halogenation, dehydration, and P–N linking reactions.[1] Of more general importance is tertiary phosphane/tetrachloromethane system, as chlorinating and dehydrating agent for sensitive substrates to the aggressive and readily hydrolyzed acid chlorides such as PCl_5, $P(O)Cl_3$, thionyl chloride and sulfonyl chloride. A great advantage can also be seen in the ability to the demands made by the various donor strengths of the substituents chosen for attachment to the phosphorus atom.[2] However, there are few reports about changing the halogen atom in the reaction by use of tetrahalomethane in the combination with tertiary phosphane system.[1a,3]

Recently, we reported a new preparation method for *N*-substituted pyrrolidin-2-ones from cyclopropyl amides in good yields in the presence of 2.0 equiv of PPh_3 and 1.0 equiv of CBr_4.[4] As it is well known, lactam rings are of important structures in a number of biologically and pharmaceutically active compounds as well as some alkaloids such as cotinine or mannolactam having lactam structures.[5] Among these lactam compounds, pyrrolidinones are often found in natural products and a variety of pharmacologically active compounds, for example, convultamides,[6] enzyme inhibitors[7] and various drugs.[8] Therefore, in order to extend the scope and limitations of this interesting ring-expanding reaction, we next carried out the reaction of *N*-(2-hydroxyphenyl)cyclopropyl amide **1a** in the presence of PPh_3/CBr_4 under the same reaction conditions. As shown in Scheme 1, *N*-(2-hydroxyphenyl)-pyrrolidin-2-one **3a** as a ring-expanding product was



Scheme 1. Reaction of *N*-(2-hydroxyphenyl) cyclopropyl amide **1a** with PPh_3/CBr_4.

Keywords: Cyclopropyl amide; Benzoxazole; Triphenylphosphine; Tetrahalomethane; Cyclopropane; Ring-expanding reaction; Ring-opening reaction; Pyrrolidin-2-one.
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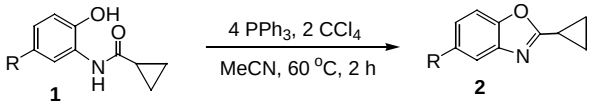
obtained in 42% yield along with a trace of benzoxazole product **2a** and 32% of 2-(3-bromopropyl)benzoxazole **4a**, which was determined as a ring-opening product of **2a** by Br^- (see Supporting information for spectroscopic data).

This result intrigued us to explore the precious reaction conditions to prepare benzoxazole products and *N*-(2-hydroxyaryl)pyrrolidin-2-one derivatives selectively from *N*-(2-hydroxyaryl) cyclopropyl amide **1** since highly selective synthesis beginning from the same starting materials is a formidable challenge in organic synthesis.[9]

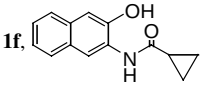
2. Results and discussion

After trial and error, we found that the dehydration reaction proceeded smoothly to give the desired benzoxazole product **2a** in 88% yield as a sole product in acetonitrile at 60 °C with 4.0 equiv of PPh_3 and 2.0 equiv of CCl_4 without ring-expanding product **3a** and ring-opening product **4a** (Table 1, entry 1). Moreover, the above reaction conditions were found to be quite general. Other *N*-(2-hydroxyaryl) cyclopropyl amides **1a–g** bearing a variety of substituted phenyl groups as well as cyclopropanecarboxylic acid (3-hydroxynaphthalen-2-yl) amide **1f** also underwent the dehydration and cyclization to give the corresponding benzoxazoles **2**, as a sole product, in excellent yields under the same reaction conditions within 2 h (Table 1, entries 2–6).

Table 1. Intramolecular dehydration reaction of **1** with PPh_3/CBr_4



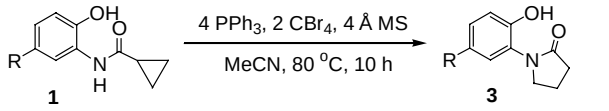
1 2

Entry	R	Yield (%)[a]
		2
1	**1a**, H	**2a**, 88
2	**1b**, Me	**2b**, 96
3	**1c**, OMe	**2c**, 95
4	**1d**, Cl	**2d**, 97
5	**1e**, F	**2e**, 85
6	**1f**, 	**2f**, 96

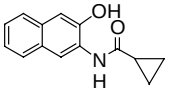
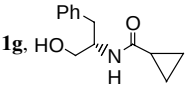
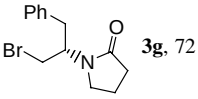
[a] Isolated yields.

Interestingly, we found that when CBr_4 was utilized to replace CCl_4 for this reaction, the corresponding ring-expanding product **3a** was formed in 87% yield in acetonitrile after the reaction solution was stirred for 10 h at 80 °C in the presence of molecular sieves 4 Å (100 mg for 0.3 mmol) (Table 2, entry 1). It should be noted that molecular sieves 4 Å was necessary for this reaction because three products were formed in the absence of MS 4 Å (Scheme 1). Next, under these optimized reaction conditions, the ring-expanding reactions of other substrates were also investigated in the presence of PPh_3/CBr_4/MS 4 Å in acetonitrile. The results are summarized in Table 2. The corresponding 1-(2-hydroxyphenyl)pyrrolidin-2-ones **3** were obtained in good yields for a variety of *N*-(2-hydroxyaryl) cyclopropyl amides **1** (Table 2, entries 2–4). However, for substrate **3e** bearing an electron-withdrawing fluoro group on the benzene ring, the reaction became sluggish and some of the starting materials (amide **1e**) can be recovered even if the reaction time was prolonged to 3 days (Table 2, entry 5). Using **1f** as substrate, no reaction occurred (Table 2, entry 6). As for aliphatic cyclopropyl amide **1g**, a L-2-amino-3-phenylpropanol derivative, the corresponding ring-expanding as well as brominated product **3g** was formed in 72% yield under identical conditions (Table 2, entry 7).

Table 2. Ring-expanding reaction of **1** with PPh_3/CBr_4/MS 4 Å in MeCN



1 3

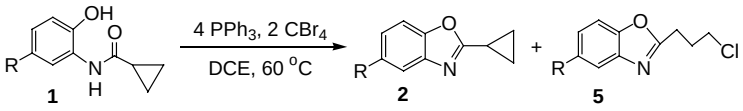
Entry	R	Yield (%)[a]
		3
1	**1a**, H	**3a**, 87
2	**1b**, Me	**3b**, 77
3	**1c**, OMe	**3c**, 50
4	**1d**, Cl	**3d**, 88
5	**1e**, F	**3e**, 51 (26)[b]
6	**1f**, 	NR
7	**1g**, 	 **3g**, 72

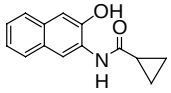
[a] Isolated yields.
[b] The reaction time was prolonged to 3 days, the yield in bracket is the recovered yield of starting materials **1e**.

The structures of benzoxazole products **2** and pyrrolidin-2-ones **3** were determined by NMR spectroscopic data, microanalyses and HRMS (see Supporting information).

The similar reaction was also investigated using 1,2-dichloroethane (DCE) instead of acetonitrile as a solvent. We found that *N*-(2-hydroxyaryl) cyclopropyl amides **1a–1f** could surprisingly undergo dehydration and subsequent chloride displacement to afford the corresponding 2-(3-chloropropyl)benzoxazole products **5a–5f** in moderate to good yields along with 2-cyclopropylbenzoxazoles **2** as minor constituents during a prolonged reaction time (Table 3, entries 1–6). The structure of **5d** was further determined by X-ray diffraction. The ORTEP draw of **5d** is shown in Figure 1.[10] The control experiment showed that after a prolonged reaction time, 2-(3-chloropropyl)benzoxazole product **5a** can be obtained from the corresponding 2-(3-bromopropyl)benzoxazole **4a** in 88% yield when the reaction was carried out in DCE, in addition, no reaction occurred when **2a** was treated with PPh_3 in DCE under identical conditions (Scheme 2). Therefore, we believe that products **5** were formed through the corresponding products **4** when DCE, containing Cl atom, was used as a solvent. Namely, although Cl^-, generated from PPh_3 and DCE,[11] cannot trigger the ring-opening reaction of benzoxazole products **2** bearing a cyclopropyl ring to take place presumably due to its weak nucleophilicity, nucleophilic displacement of bromo atom in compounds **4** by chloro

Table 3. Reaction of **1** with PPh_3/CBr_4 in DCE



Entry	R	Time (days)	Yield (%)[a]	Yield (%)[a]
			2	**5**
1	**1a**, H	3	**2a**, Trace	**5a**, 79
2	**1b**, Me	3	**2b**, Trace	**5b**, 64
3	**1c**, OMe	4	**2c**, Trace	**5c**, 89
4	**1d**, Cl	3	**2d**, Trace	**5d**, 84
5	**1e**, F	5	**2e**, 17	**5e**, 69
6	**1f**, 	5	**2f**, 20	**5f**, 73

[a] Isolated yields.

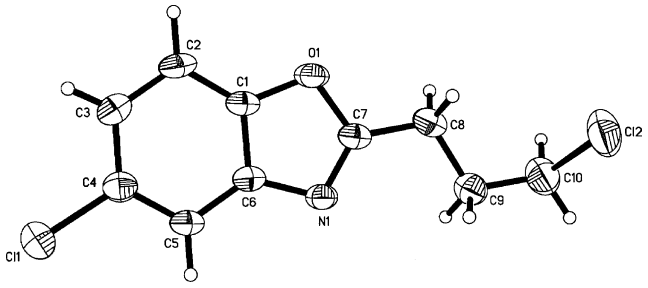
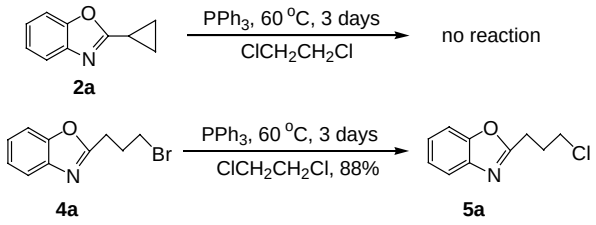


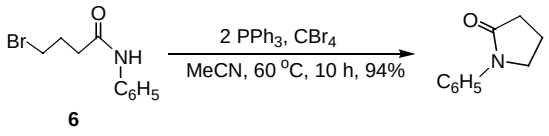
Figure 1. ORTEP drawing of **5d**.



Scheme 2. Control experiment of the formation of **5a**.

atom could occur to give the corresponding chlorinated products **5** at 60 °C.

Based on the above results and previous literature on the reaction of amide with PPh_3/CX_4[12] as well as our studies on the mechanism in the transformation of cyclopropyl amides to *N*-substituted pyrrolidin-2-ones in which we confirmed that the ring-expanding reaction proceeded through 4-bromo-butyramide intermediate **6** as shown in Scheme 3,[4] a plausible reaction mechanism is proposed in Scheme 4. At first, triphenylphosphine reacts with carbon tetrahalide to give the corresponding dihalogentriphenylphosphorane **7**

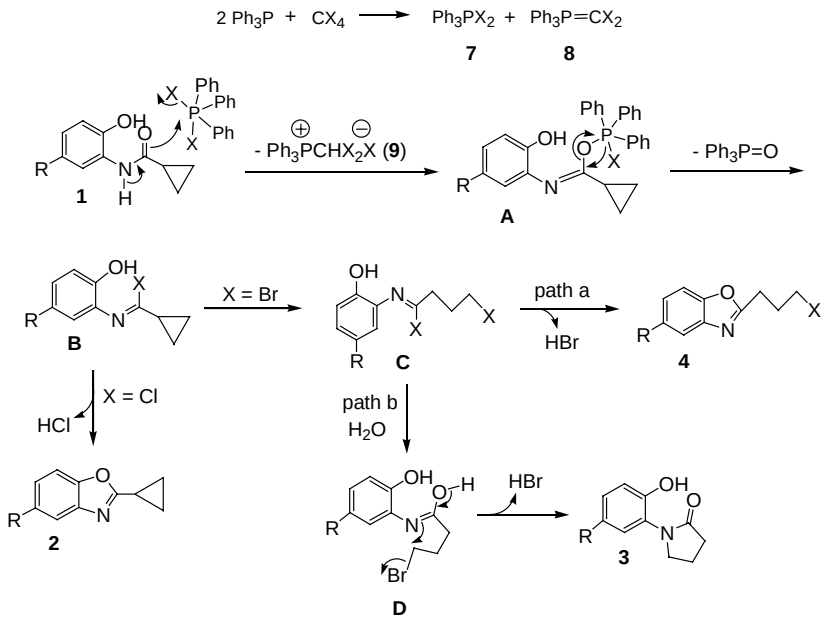


Scheme 3. Ring-closure reaction of 4-bromo-*N*-phenyl-butyramide **6** with PPh_3/CBr_4.

and dihalogenmethylene ylid **8**. Next, the intermediate **A** is formed by the reaction of *N*-(2-hydroxyaryl) cyclopropyl amide **1** with dihalogentriphenylphosphorane **7** to release a dihalogenmethyltriphenylphosphonium salt **9** as white precipitates, which is dissolved after the solution was heated.[1f,g] Thus, the corresponding *N*-substituted formimidoyl halogen **B** is formed along with the generation of triphenylphosphine oxide. When CCl_4 is used in the reaction, intramolecular ring-closure smoothly takes place to give the corresponding benzoxazoles bearing cyclopropyl group **2**. On the other hand, if CBr_4 is subjected into the reaction instead of CCl_4, the subsequent ring-opening process of *N*-substituted formimidoyl halogen **B** takes place, because of the comparatively stronger nucleophilicity of Br^- than Cl^-, to give another formimidoyl halogen **C**, which gives the ring-closure product **4** through intramolecuar substitution of Br atom by the phenolic OH group on the *ortho* position (path a). If the Br atom in formimidoyl halogen **C** is substituted by OH group of ambient H_2O in the reaction system, the corresponding pyrrolidin-2-one **3** can be obtained through intermediate **D** (path b). Though it is difficult to explain the exact role of molecular sieves 4 Å at present stage, experiment results indicate that molecular sieves 4 Å prevent the intramolecuar substitution of Br atom by the phenolic OH group on the *ortho* position and alternatively, intermolecular attack by ambient H_2O in reaction system takes place to give the corresponding pyrrolidin-2-one product **3**.

3. Conclusion

We succeeded in the preparation of intramolecular dehydration product benzoxazoles bearing cyclopropyl group **2** from the *N*-(2-hydroxyaryl) cyclopropyl amide **1** with PPh_3/CCl_4. When CBr_4 was used instead of CCl_4 in the reaction, 1-(2-hydroxyaryl)pyrrolidin-2-ones **3** can be obtained in moderate to good yield in the presence of molecular sieves 4 Å. Using DCE as a solvent for the reaction, the corresponding 2-(3-chloropropyl)benzoxazoles **5** were obtained as major products. Efforts are underway to elucidate the mechanistic details and to extend the scope of this reaction.



Scheme 4. A possible reaction mechanism.

4. Experimental

4.1. General methods

^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Mass spectra were recorded by EI and MALDI methods, and HRMS was measured on Kratos Analytical Concept mass spectrometer (EI), Bruker FT mass spectrometer (ESI), and IonSpec 4.7 T FTMS (MALDI). Organic solvents used were dried by standard methods when necessary. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with Yinlong GF254 silica gel coated plates. Flash column chromatography was carried out using 300–400 mesh silica gel at increased pressure.

4.2. General procedure for the preparation of *N*-(2-hydroxyaryl) cyclopropyl amide

Added dropwise cyclopropanecarbonyl chloride (261 mg, 2.5 mmol, 228 μL) to the mixture of 2-aminophenol (2.5 mmol) and pyridine (3.0 mmol) in ethyl acetate (EtOAc) (20 mL) at room temperature. After stirring for another 2 h, the reaction mixture was washed with 10% HCl (50 mL×2) and dried over anhydrous $MgSO_4$. The corresponding pure *N*-(2-hydroxyaryl) cyclopropyl amide can be obtained through a short column chromatography (SiO_2).

4.3. General procedure for the synthesis of benzoxazole from *N*-(2-hydroxyaryl) cyclopropyl amide

A mixture of *N*-(2-hydroxyaryl) cyclopropyl amide (0.3 mmol), PPh_3 (314 mg, 1.2 mmol) and CCl_4 (92 mg, 58 μL, 0.6 mmol) was dissolved in acetonitrile (3.0 mL). The solvent was evaporated after the reaction system was heated at 60 °C for 2 h. The residue was dissolved in CH_2Cl_2 (50 mL), washed with H_2O (50 mL×2), and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by a silica gel column chromatography to give the corresponding benzoxazole product.

4.4. General procedure for the synthesis of *N*-(2-hydroxyphenyl)pyrrolidin-2-one from *N*-(2-hydroxyaryl) cyclopropyl amide

Molecular sieves 4 Å (100 mg) was put into a glass vessel and the vessel was flame-dried under reduced pressure. Then, *N*-(2-hydroxyaryl) cyclopropyl amide (0.3 mmol), PPh_3 (314 mg, 1.2 mmol) and CBr_4 (200 mg, 0.6 mmol) and acetonitrile (3.0 mL) were added successively. Kept the reaction system at 80 °C for necessary time. After filtration, the solvent was evaporated and the residue was dissolved in CH_2Cl_2 (50 mL), washed with H_2O (50 mL×2), and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by a silica gel column chromatography to give the corresponding pyrrolidin-2-one product.

4.5. General procedure for the synthesis of 2-(3-chloropropyl)benzoxazole from *N*-(2-hydroxyaryl) cyclopropyl amide

A mixture of *N*-(2-hydroxyaryl) cyclopropyl amide (0.3 mmol), PPh_3 (314 mg, 1.2 mmol) and CBr_4 (200 mg, 0.6 mmol) was dissolved in DCE (3.0 mL). Then the reaction system was heated to 60 °C. The solvent was evaporated after the necessary reaction time, which can be monitored by ^{1}H NMR spectroscopy. The residue was dissolved in CH_2Cl_2 (50 mL), washed with H_2O (50 mL×2), and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by a silica gel column chromatography to give the corresponding 2-(3-chloropropyl)benzoxazole product.

4.5.1. Cyclopropanecarboxylic acid (2-hydroxyphenyl)-amide (1a). This compound was obtained as a white solid, yield: 92%, mp 125–126 °C. IR (CH_2Cl_2): ν 1098, 1136,

1178, 1200, 1247, 1311, 1384, 1455, 1498, 1533, 1601, 1656, 1753, 3285 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 0.91–0.95 (m, 2H, CH_2), 1.12–1.15 (m, 2H, CH_2), 1.62–1.70 (m, 1H, CH), 6.83–6.88 (m, 1H, Ar), 6.99–7.02 (m, 2H, Ar), 7.26–7.27 (m, 1H, Ar), 7.84 (br, 1H, NH), 9.01 (br, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 8.8, 15.3, 119.8, 120.3, 122.0, 125.8, 127.0, 148.7, 174.2; MS (EI) *m/z*: 177 (M^+, 51), 159 (4), 133 (1), 120 (1), 109 (100), 80 (14), 69 (93), 41 (54). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.25; N, 7.90%. Found: C, 67.51; H, 6.25; N, 7.83%.

4.5.2. Cyclopropanecarboxylic acid (2-hydroxy-5-methylphenyl)amide (1b). This compound was obtained as a white solid, yield: 86%, mp 110–112 °C. IR (CH_2Cl_2): ν 1215, 1242, 1273, 1316, 1383, 1439, 1505, 1537, 1602, 1653, 3284 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 0.86–0.92 (m, 2H, CH_2), 1.08–1.13 (m, 2H, CH_2), 1.60–1.65 (m, 1H, CH), 2.22 (s, 3H, CH_3), 6.85 (s, 1H, Ar), 6.88 (s, 2H, Ar), 8.00 (br, 1H, NH), 8.87 (br, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 8.6, 15.2, 20.3, 119.3, 122.4, 125.4, 127.5, 129.8, 146.1, 174.1; MS (EI) *m/z*: 191 (M^+, 40), 172 (1), 160 (3), 132 (1), 123 (100), 106 (3), 69 (26), 41 (18). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32%. Found: C, 68.89; H, 6.79; N, 7.07%.

4.5.3. Cyclopropanecarboxylic acid (2-hydroxy-5-methoxyphenyl)amide (1c). This compound was obtained as a white solid, yield: 87%, mp 124–126 °C. IR (CH_2Cl_2): ν 1039, 1102, 1151, 1198, 1219, 1273, 1307, 1376, 1431, 1453, 1508, 1540, 1600, 1650, 3182 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 0.86–0.89 (m, 2H, CH_2), 1.08–1.13 (m, 2H, CH_2), 1.60–1.65 (m, 1H, CH), 3.69 (s, 3H, OCH_3), 6.64 (d, J=7.2 Hz, 1H, Ar), 6.79 (s, 1H, Ar), 6.88 (d, J=7.2 Hz, 1H, Ar), 8.28 (br, 1H, NH), 8.46 (br, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 8.6, 15.2, 55.7, 107.3, 112.0, 119.4, 126.4, 141, 8, 153.3, 174.1; MS (EI) *m/z*: 207 (M^+, 19), 185 (10), 174 (4), 149 (6), 139 (100), 124 (6), 110 (9), 69 (58), 41 (64). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76%. Found: C, 63.47; H, 6.25; N, 6.59%.

4.5.4. Cyclopropanecarboxylic acid (5-chloro-2-hydroxyphenyl)amide (1d). This compound was obtained as a white solid, yield: 85%, mp 178–180 °C. IR (CH_2Cl_2): ν 1204, 1268, 1371, 1426, 1542, 1589, 1655, 3016 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 0.94–1.00 (m, 2H, CH_2), 1.14–1.19 (m, 2H, CH_2), 1.59–1.65 (m, 1H, CH), 6.91–6.95 (m, 1H, Ar), 7.06–7.09 (m, 2H, Ar), 7.65 (br, 1H, NH), 8.83 (s, 1H, OH); ^{13}C NMR (75 MHz, CD_3COCD_3): δ 7.0, 14.0, 116.8, 120.2, 123.0, 123.5, 127.7, 145.6, 172.8; MS (EI) *m/z*: 213 (16), 211 (M^+, 50), 193 (5), 167 (1), 154 (1), 145 (15), 143 (44), 114 (11), 99 (2), 69 (100), 41 (37). Anal. Calcd for $C_{10}H_{10}ClNO_2$: C, 56.75; H, 4.76; N, 6.62%. Found: C, 57.11; H, 4.72; N, 6.62%.

4.5.5. Cyclopropanecarboxylic acid (5-fluoro-2-hydroxyphenyl)amide (1e). This compound was obtained as a white solid, yield: 76%, mp 165–167 °C. IR (CH_2Cl_2): ν 1134, 1190, 1212, 1261, 1311, 1443, 1534, 1620, 1655 cm^{-1}; ^1H NMR (300 MHz, CD_3COCD_3): δ 0.80–0.88 (m, 2H, CH_2), 0.90–1.03 (m, 2H, CH_2), 1.98–2.03 (m, 1H, CH), 3.34 (br, 2H, OH, NH), 6.66–6.73 (m, 1H, Ar), 6.84–6.89 (m, 1H, Ar), 7.65–7.69 (m, 1H, Ar); ^{13}C NMR (75 MHz, CD_3SOCD_3): δ 7.5, 14.2, 108.1 (d, J_{C-F}=27.2 Hz), 109.4 (d, J_{C-F}=23.1 Hz), 115.3 (d, J_{C-F}=9.0 Hz), 127.4 (d, J_{C-F}=11.3 Hz), 143.3, 154.8 (d, J_{C-F}=230.8 Hz), 172.4; MS (EI) *m/z*: 195 (M^+, 14), 177 (2), 154 (1), 127 (19), 109 (1), 98 (5), 69 (100), 41 (43); HRMS (EI) Calcd for $(C_{10}H_{10}FNO_2)^+$: 195.0696, found: 195.0699.

4.5.6. Cyclopropanecarboxylic acid (3-hydroxynaphthalen-2-yl)amide (1f). This compound was obtained as a white solid, yield: 66%, mp 180–182 °C. IR (CH_2Cl_2): ν 1234, 1304, 1434, 1505, 1536, 1626, 3257 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 0.98–1.04 (m, 2H, CH_2), 1.20–1.28 (m, 2H, CH_2), 1.79–1.86 (m, 1H, CH), 7.26 (d, J=8.7 Hz, 1H, Ar), 7.39 (dt, J=1.2, 3.6 Hz, 1H, Ar), 7.53 (dt, J=1.5, 6.9 Hz, 1H, Ar), 7.69 (d, J=1.2 Hz, 1H, Ar), 7.80 (t, J=9.0 Hz, 2H, Ar), 7.94 (br, 1H, NH), 8.78 (br, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 9.0, 15.3, 117.1, 119.1, 121.6, 123.7, 126.9, 128.16, 128.2, 128.7, 129.0, 148.1, 174.5; MS (EI) *m/z*: 227 (M^+, 25), 209 (3), 180 (1), 159 (100), 149 (2), 130 (19), 103 (10), 69 (43), 41 (42); HRMS (ESI) Calcd for $(C_{14}H_{13}NO_2+Na)^+$: 250.0838, found: 250.0841.

4.5.7. Cyclopropanecarboxylic acid (1-benzyl-2-hydroxyethyl)amide (1g). This compound was obtained as a white solid, yield: 91%, mp 113–115 °C. IR (CH_2Cl_2): ν 1036, 1250, 1455, 1497, 1542, 1645, 3290, 3649 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 0.70–0.76 (m, 2H, CH_2), 0.93–0.97 (m, 2H, CH_2), 1.26–1.36 (m, 1H, CH), 2.88 (d, J=6.9 Hz, 2H, CH_2), 3.34 (br, 1H, OH), 3.57–3.71 (m, 2H, CH_2), 4.11–4.19 (m, 1H, CH), 6.10 (br, 1H, NH), 7.21–7.33 (m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 7.3, 7.4, 14.7, 37.0, 53.0, 63.9, 126.6, 128.6, 129.2, 137.7, 174.4; MS (EI) *m/z*: 219 (M^+, 1), 188 (3), 168 (1), 128 (39), 91 (32), 69 (100), 41 (41). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39%. Found: C, 71.08; H, 7.65; N, 6.32%.

4.5.8. 2-Cyclopropylbenzooxazole (2a). This compound was obtained as a pale oil,[13] yield: 42 mg, 88%. ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 1.13–1.21 (m, 2H, CH_2), 1.25–1.30 (m, 2H, CH_2), 2.16–2.25 (m, 1H, CH), 7.21–7.30 (m, 2H, Ar), 7.41–7.43 (m, 1H, Ar), 7.59–7.62 (m, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 9.1, 9.2, 109.9, 118.9, 123.9, 124.0, 141.5, 150.3, 168.5.

4.5.9. 2-Cyclopropyl-5-methylbenzooxazole (2b). This compound was obtained as a pale oil, yield: 50 mg, 96%. IR (CH_2Cl_2): ν 1029, 1044, 1083, 1158, 1180, 1260, 1456, 1483, 1576, 1615, 2856, 2924, 3015 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 1.10–1.19 (m, 2H, CH_2), 1.22–1.28 (m, 2H, CH_2), 2.13–2.22 (m, 1H, CH), 2.43 (s, 3H, CH_3), 7.04 (dd, J=8.4, 1.5 Hz, 1H, Ar), 7.28 (d, J=8.4 Hz, 1H, Ar), 7.38 (d, J=1.5 Hz, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 9.0, 9.3, 21.4, 109.3, 118.9, 124.8, 133.7, 141.7, 148.6, 168.6; MS (EI) *m/z*: 173 (M^+, 100), 158 (8), 154 (1), 147 (43), 144 (11), 130 (5), 117 (3), 106 (5), 78 (14); HRMS (MALDI) Calcd for $(C_{11}H_{11}NO+H)^+$: 174.0913, found: 174.0906.

4.5.10. 2-Cyclopropyl-5-methoxybenzooxazole (2c). This compound was obtained as a pale oil, yield: 54 mg, 95%. IR (CH_2Cl_2): ν 1028, 1153, 1174, 1195, 1288, 1441, 1483, 1574, 1615, 2834, 2939, 3011 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$, TMS): δ 1.11–1.16 (m, 2H, CH_2), 1.22–1.27 (m, 2H, CH_2), 2.12–2.20 (m, 1H, CH), 3.82 (s, 3H, OCH_3), 6.83 (dd, J=2.7, 8.7 Hz, 1H, Ar), 7.10 (d, J=2.7 Hz, 1H, Ar), 7.29 (d, J=8.7 Hz, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 9.0, 9.2, 55.7, 102.3, 109.9, 111.9, 142.3, 144.9, 156.9, 169.3; MS (EI) *m/z*: 189 (M^+, 100), 174 (57), 163 (26), 146 (6), 107 (57), 79 (75), 63 (13), 51 (43); HRMS (MALDI) Calcd for $(C_{11}H_{11}NO_2+H)^+$: 190.0863, found: 190.0868.

4.5.11. 5-Chloro-2-cyclopropylbenzooxazole (2d). This compound was obtained as a white solid, yield: 56 mg, 97%, mp 70–72 °C. IR (CH_2Cl_2): ν 1028, 1047, 1291, 1343, 1456, 1571, 1607, 2924, 3049, 3094 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 1.15–1.22 (m, 2H, CH_2), 1.23–1.30 (m, 2H, CH_2), 2.14–2.32 (m, 1H, CH), 7.20 (dd, J=1.8, 8.7 Hz, 1H, Ar), 7.32 (d, J=8.7 Hz, 1H, Ar), 7.56 (d, J=1.8 Hz, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 9.3, 9.4, 110.6, 118.9, 124.1, 129.4, 142.7, 148.9, 170.0; MS (EI) *m/z*: 195 (31), 193 (M^+, 100), 178 (8), 169 (18), 167 (63), 130 (14), 112 (4), 102 (12), 63 (53), 41 (19). Anal. Calcd for $C_{10}H_8ClNO$: C, 62.03; H, 4.16; N, 7.23%. Found: C, 62.09; H, 4.27; N, 7.15%.

4.5.12. 2-Cyclopropyl-5-fluorobenzooxazole (2e). This compound was obtained as a white solid, yield: 45 mg, 85%, mp 63–65 °C. IR (CH_2Cl_2): ν 1031, 1103, 1136, 1151, 1174, 1265, 1293, 1339, 1350, 1441, 1466, 1481, 1570, 1615, 2851, 2922, 3012, 3034 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 1.15–1.22 (m, 2H, CH_2), 1.23–1.30 (m, 2H, CH_2), 2.15–2.24 (m, 1H, CH), 6.93–7.00 (m, 1H, Ar), 7.26–7.36 (m, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 9.3, 9.4, 105.5 (d, J_{C-F}=25.7 Hz), 110.1 (d, J_{C-F}=9.8 Hz), 111.3 (d, J_{C-F}=25.7 Hz), 142.4 (d, J_{C-F}=13.2 Hz), 146.7, 159.9 (d, J_{C-F}=238.1 Hz), 170.5; MS (EI) *m/z*: 177 (M^+, 100), 162 (9), 151 (67), 122 (5), 109 (7), 82 (26), 63 (14), 41 (16); HRMS (EI) Calcd for $C_{10}H_8FNO$: 177.0590, found: 177.0576.

4.5.13. 2-Cyclopropylnaphtho[2,3-*d*]oxazole (2f). This compound was obtained as a pale yellow oil, yield: 60 mg, 96%. IR (CH_2Cl_2): ν 1005, 1027, 1099, 1161, 1198, 1236, 1261, 1274, 1372, 1569, 1591, 1641, 2924, 3013, 3064 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 1.15–1.21 (m, 2H, CH_2), 1.25–1.34 (m, 2H, CH_2), 1.29–2.35 (m, 1H, CH), 7.47–7.64 (m, 3H, Ar), 7.69 (d, J=8.7 Hz, 1H, Ar), 7.92 (d, J=8.4 Hz, 1H, Ar), 8.45 (dd, J=8.1, 0.3 Hz, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 9.0, 9.5, 110.5, 121.9, 124.7, 124.9, 126.0, 126.6, 128.4, 130.9, 136.6, 147.4, 167.5; MS (EI) *m/z*: 209 (M^+, 100), 192 (3), 180 (19), 153 (6), 140 (6), 128 (5), 114 (22), 88 (10), 63 (10); HRMS (ESI) Calcd for $(C_{14}H_{12}NO+Na)^+$: 210.0913, found: 210.0915.

4.5.14. 1-(2-Hydroxyphenyl)pyrrolidin-2-one (3a). This compound was obtained as a white solid,[14] yield: 44 mg, 87%, mp 136–138 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 2.28 (tt, J=8.1, 7.2 Hz, 2H, CH_2), 2.68 (t, J=8.1 Hz, 2H, CH_2), 3.96 (t, J=7.2 Hz, 2H, CH_2), 6.92 (dt, J=0.6, 7.5 Hz, 1H, Ar), 7.06 (dd, J=0.6, 8.4 Hz, 2H, Ar), 7.18 (dt, J=0.9, 7.8 Hz, 1H, Ar), 8.58 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 19.5, 32.2, 50.9, 109.7, 120.5, 120.7, 121.2, 127.7, 150.1, 176.2.

4.5.15. 1-(2-Hydroxy-5-methylphenyl)pyrrolidin-2-one (3b). This compound was obtained as a white solid, yield: 44 mg, 77%, mp 177–179 °C. IR (CH_2Cl_2): ν 1106, 1135, 1186, 1261, 1308, 1420, 1439, 1461, 1510, 1601, 1656, 2851, 2922 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 2.24 (tt, J=8.1, 6.6 Hz, 2H, CH_2), 2.27 (s, 3H, CH_3), 2.64 (t, J=8.1 Hz, 2H, CH_2), 3.93 (t, J=6.6 Hz, 2H, CH_2), 6.85 (d, J=0.6 Hz, 1H, Ar), 6.92–6.99 (m, 2H, Ar), 8.32 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 19.4, 20.5, 32.1, 50.7, 120.3, 121.6, 127.2, 128.2, 129.8, 147.7, 176.0; MS (EI) *m/z*: 191 (M^+, 69), 174 (2), 162 (3), 148 (4), 136 (100), 120 (2), 109 (37), 91 (12), 77 (16). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32%. Found: C, 68.83; H, 6.64; N, 7.07%.

4.5.16. 1-(2-Hydroxy-5-methoxyphenyl)pyrrolidin-2-one (3c). This compound was obtained as a white solid, yield: 31 mg, 50%, mp 83–85 °C. IR (CH_2Cl_2): ν 1038, 1176, 1212, 1261, 1416, 1461, 1509, 1612, 1662, 2959, 3919 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 2.29 (tt, J=8.1, 6.6 Hz, 2H, CH_2), 2.69 (t, J=8.1 Hz, 2H, CH_2), 3.77 (s, 3H, OCH_3), 3.95 (t, J=6.6 Hz, 2H, CH_2), 6.61 (d, J=3.0 Hz, 1H, Ar), 6.76 (dd, J=9.0, 3.0 Hz, 1H, Ar), 7.00 (d, J=9.0 Hz, 1H, Ar), 7.97 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 19.4, 32.2, 50.8, 55.8, 107.4, 112.45, 121.2, 128.2, 143.9, 153.4, 176.0; MS (EI) *m/z*: 207 (M^+, 100), 192 (9), 179 (3), 164 (10), 152 (78), 136 (11), 125 (14), 69 (9); HRMS (EI) Calcd for $(C_{11}H_{13}NO_3)^+$: 207.0895, found: 207.0908.

4.5.17. 1-(5-Chloro-2-hydroxy-phenyl)pyrrolidin-2-one (3d). This compound was obtained as a white solid, yield: 56 mg, 88%, mp 213–215 °C. IR (CH_2Cl_2): ν 1024, 1117, 1191, 1282, 1302, 1418, 1464, 1504, 1657, 2852, 2924 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 2.31 (tt, J=7.8, 6.9 Hz, 2H, CH_2), 2.71 (t, J=7.8 Hz, 2H, CH_2), 3.95 (t, J=6.9 Hz, 2H, CH_2), 6.99 (d, J=8.4 Hz, 1H, Ar), 7.04 (d, J=2.4 Hz, 1H, Ar), 7.14 (d, J=2.4, 8.4 Hz, 1H, Ar), 8.57 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 19.5, 32.2, 50.9, 121.0, 121.9, 125.1, 127.5, 148.8, 176.5; MS (EI) *m/z*: 213 (18), 211 (M^+, 64), 194 (2), 183 (4), 169 (2), 156 (100), 148 (3), 129 (23), 93 (16). Anal. Calcd for $C_{10}H_{10}ClNO_2$: C, 56.75; H, 4.76; N, 6.62%. Found: C, 56.62; H, 4.52; N, 6.41%.

4.5.18. 1-(5-Fluoro-2-hydroxyphenyl)pyrrolidin-2-one (3e). This compound was obtained as a white solid, yield: 30 mg, 51%, mp 158–160 °C. IR (CH_2Cl_2): ν 1178, 1270, 1419, 1445, 1519, 1622, 1663, 2962, 3103 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 2.30 (tt, J=7.8, 6.9 Hz, 2H, CH_2), 2.69 (t, J=7.8 Hz, 2H, CH_2), 3.93 (t, J=6.9 Hz, 2H, CH_2), 6.76–6.80 (m, 1H, Ar), 6.86–6.92 (m, 1H, Ar), 6.98–7.03 (m, 1H, Ar), 8.29 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 19.4, 32.2, 50.8, 107.9 (J_{C-F}=25.8 Hz), 114.1 (J_{C-F}=22.3 Hz), 121.4 (J_{C-F}=9.2 Hz), 128.2, 146.1, 156.4 (J_{C-F}=237.6 Hz), 176.4; MS (EI) *m/z*: 195 (M^+, 57), 174 (12), 149 (28), 140 (100), 129 (25), 113 (51), 91 (60), 57 (52); HRMS (EI) Calcd for $(C_{10}H_{10}FNO_2)^+$: 195.0696, found: 195.0692.

4.5.19. 1-(1-Benzyl-2-hydroxyethyl)pyrrolidin-2-one (3g). This compound was obtained as a pale red oil, yield: 61 mg, 72%. IR (CH_2Cl_2): ν 1290, 1462, 1495, 1658, 1729,

2854, 2922 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 1.89–1.99 (m, 2H, CH_2), 2.29–2.38 (m, 2H, CH_2), 2.98 (d, $J=7.8$ Hz, 2H, CH_2), 3.32 (t, $J=6.9$ Hz, 2H, CH_2), 3.57 (d, $J=7.5$ Hz, 2H, CH_2), 4.47 (tt, $J=7.8$, 7.5 Hz, 1H, CH), 7.20–7.32 (m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 18.4, 31.2, 33.3, 36.8, 44.7, 54.3, 126.7, 128.5, 128.7, 136.9, 175.3; MS (MALDI) *m/z*: 284 [$(M+3)^+$, 100], 282 [$(M+1)^+$, 100]; HRMS (MALDI) Calcd for $(C_{13}H_{16}BrNO+H)^+$: 282.0488, found: 282.0494.

4.5.20. 2-(3-Bromopropyl)benzooxazole (4a). This compound was obtained as a pale oil, yield: 23 mg, 32%. IR (CH_2Cl_2): ν 1003, 1104, 1155, 1167, 1243, 1455, 1572, 1615, 2853, 2924, 2956 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 2.46 (tt, $J=7.2$, 6.3 Hz, 2H, CH_2), 3.14 (t, $J=7.2$ Hz, 2H, CH_2), 3.58 (t, $J=6.3$ Hz, 2H, CH_2), 7.30–7.34 (m, 2H, Ar), 7.48–7.51 (m, 1H, Ar), 7.66–7.69 (m, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 26.9, 29.3, 32.3, 110.3, 119.6, 124.2, 124.7, 141.1, 150.7, 165.5; MS (EI) *m/z*: 241 (6), 239 (M^+, 6), 183 (19), 149 (30), 133 (100), 104 (14), 77 (19), 41 (26). Anal. Calcd for $C_{10}H_{10}NOBr$: C, 50.02; H, 4.20; N, 5.83%. Found: C, 50.14; H, 4.38; N, 5.73%.

4.5.21. 2-(3-Chloropropyl)benzooxazole (5a). This compound was obtained as a pale oil, yield: 46 mg, 79%. IR (CH_2Cl_2): ν 1003, 1104, 1143, 1169, 1242, 1277, 1298, 1456, 1573, 1615, 2926, 2961 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 2.37 (tt, $J=7.2$, 6.6 Hz, 2H, CH_2), 3.13 (t, $J=7.2$ Hz, 2H, CH_2), 3.71 (t, $J=6.6$ Hz, 2H, CH_2), 7.27–7.33 (m, 2H, Ar), 7.46–7.50 (m, 1H, Ar), 7.66–7.69 (m, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 25.6, 29.2, 43.7, 110.26, 119.5, 124.1, 124.6, 141.1, 150.7, 165.6; MS (EI) *m/z*: 197 (5), 195 (M^+, 11), 183 (16), 160 (6), 133 (100), 109 (28), 97 (13), 57 (17); HRMS (EI) Calcd for $(C_{10}H_{10}NOCl)^+$: 195.0451, found: 195.0447.

4.5.22. 2-(3-Chloropropyl)-5-methylbenzooxazole (5b). This compound was obtained as a pale oil, yield: 40 mg, 64%. IR (CH_2Cl_2): ν 1119, 1146, 1177, 1261, 1297, 1430, 1444, 1482, 1574, 2924, 2960 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 2.36 (tt, $J=7.2$, 6.6 Hz, 2H, CH_2), 2.45 (s, 3H, CH_3), 3.10 (t, $J=7.2$ Hz, 2H, CH_2), 3.69 (t, $J=6.6$ Hz, 2H, CH_2), 7.11 (dd, $J=8.4$, 0.9 Hz, 1H, Ar), 7.35 (d, $J=8.4$ Hz, 1H, Ar), 7.45 (d, $J=0.9$ Hz, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 21.4, 25.7, 29.2, 43.7, 109.6, 119.5, 125.6, 133.9, 141.3, 148.9, 165.7; MS (EI) *m/z*: 211 (5), 209 (M^+, 11), 183 (2), 174 (6), 160 (12), 147 (100), 106 (14), 78 (26); HRMS (EI) Calcd for $(C_{11}H_{12}NOCl)^+$: 209.0607, found: 209.0621.

4.5.23. 2-(3-Chloropropyl)-5-methoxybenzooxazole (5c). This compound was obtained as a colorless oil, yield: 56 mg, 89%. IR (CH_2Cl_2): ν 1027, 1152, 1196, 1284, 1341, 1441, 1483, 1574, 1615, 2835, 2959, 2999 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 2.35 (tt, $J=7.2$, 6.0 Hz, 2H, CH_2), 3.09 (t, $J=7.2$ Hz, 2H, CH_2), 3.70 (t, $J=6.0$ Hz, 2H, CH_2), 3.84 (s, 3H, OCH_3), 6.89 (dd, $J=8.7$, 2.7 Hz, 1H, Ar), 7.16 (d, $J=2.7$ Hz, 1H, Ar), 7.35 (d, $J=8.7$ Hz, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 25.7, 29.2, 43.7, 55.8, 102.7, 110.3, 112.9, 141.9, 145.3, 157.0, 166.4; MS (EI) *m/z*: 227 (11), 225 (M^+, 40), 189 (7), 176 (31), 163 (100), 148 (14), 107 (19), 79 (25); HRMS (EI) Calcd for $(C_{11}H_{12}NO_2Cl)^+$: 225.0557, found: 225.0545.

4.5.24. 5-Chloro-2-(3-chloropropyl)benzooxazole (5d). This compound was obtained as a white solid, yield: 58 mg, 84%, mp 47–49 °C. IR (CH_2Cl_2): ν 1055, 1145, 1161, 1257, 1428, 1452, 1568, 1609, 2962 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 2.37 (tt, $J=7.2$, 6.0 Hz, 2H, CH_2), 3.14 (t, $J=7.2$ Hz, 2H, CH_2), 3.71 (t, $J=6.0$ Hz, 2H, CH_2), 7.29 (dd, $J=8.7$, 2.4 Hz, 1H, Ar), 7.41 (d, $J=8.7$ Hz, 1H, Ar), 7.65 (d, $J=2.4$ Hz, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 25.7, 29.1, 43.7, 111.1, 119.7, 125.0, 129.7, 142.3, 149.4, 167.2; MS (EI) *m/z*: 233 (1), 231 (7), 229 (11, M^+), 194 (7), 180 (9), 167 (100), 138 (6), 127 (5), 102 (10), 63 (26); HRMS (EI) Calcd for $(C_{10}H_9NOCl_2)^+$: 229.0061, found: 229.0077.

4.5.25. 2-(3-Chloropropyl)-5-fluorobenzooxazole (5e). This compound was obtained as a pale oil, yield: 44 mg, 69%. IR (CH_2Cl_2): ν 1131, 1167, 1249, 1276, 1299, 1440, 1478, 1572, 2926, 2961 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 2.37 (tt, $J=7.2$, 6.0 Hz, 2H, CH_2), 3.13 (t, $J=7.2$ Hz, 2H, CH_2), 3.71 (t, $J=6.0$ Hz, 2H, CH_2), 7.01–7.08 (m, 1H, Ar), 7.34–7.44 (m, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 25.8, 29.1, 43.7, 106.1 (d, $J_{C-F}=25.7$ Hz), 110.6 (d, $J_{C-F}=9.7$ Hz), 112.2 (d, $J_{C-F}=25.7$ Hz), 142.1, 147.1, 159.9 (d, $J_{C-F}=238.7$ Hz), 167.6; MS (EI) *m/z*: 215 (4), 213 (9, M^+), 178 (5), 164 (8), 151 (100), 122 (7), 111 (5), 95 (5), 82 (9); HRMS (EI) Calcd for $(C_{10}H_9ClFNO)^+$: 213.0357, found: 213.0343.

4.5.26. 2-(3-Chloropropyl)naphtho[2,3-*d*]oxazole (5f). This compound was obtained as a pale oil, yield: 54 mg, 73%. IR (CH_2Cl_2): ν 1005, 1226, 1274, 1300, 1373, 1445, 1567, 1589, 2924, 2959 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 2.42 (tt, $J=7.2$, 6.6 Hz, 2H, CH_2), 3.22 (t, $J=7.2$ Hz, 2H, CH_2), 3.74 (t, $J=6.6$ Hz, 2H, CH_2), 7.49–7.55 (m, 1H, Ar), 7.62–7.67 (m, 2H, Ar), 7.76 (d, $J=9.0$ Hz, 1H, Ar), 7.95 (d, $J=8.1$ Hz, 1H, Ar), 8.46 (d, $J=8.1$ Hz, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 26.0, 29.7, 43.9, 110.7, 121.9, 125.2, 125.5, 126.3, 126.9, 128.5, 131.0, 136.4, 147.9, 164.7; MS (EI) *m/z*: 247 (11), 245 (M^+, 32), 209 (47), 196 (6), 183 (100), 154 (8), 140 (4), 127 (11), 114 (20); HRMS (EI) Calcd for $(C_{14}H_{12}ClNO)^+$: 245.0607, found: 245.0596.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.11.077. The X-ray crystal data of **5d** is included in Supporting information. This material is available free of charge via the Internet.

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10. The crystal data of **5d** has been deposited in CCDC with number 283183. Empirical formula: $C_{10}H_9NOCl_2$; formula weight: 230.08; crystal size: $0.508\times0.472\times0.080$; crystal color, habit: colorless, prismatic; crystal system: monoclinic; lattice type: primitive; lattice parameters: $a=5.4568(8)$ Å, $b=25.949(4)$ Å, $c=7.5903(11)$ Å, $\alpha=90°$, $\beta=25.949(4)°$, $\gamma=90°$, $V=1048.2(3)$ Å^3; space group: $P2(1)/c$; $Z=4$; $D_{calcd}=1.458$ g/cm^3; $F_{000}=472$; $R1=0.0511$, $wR2=0.1176$. Diffractometer: Rigaku AFC7R.
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