ELSEVIER

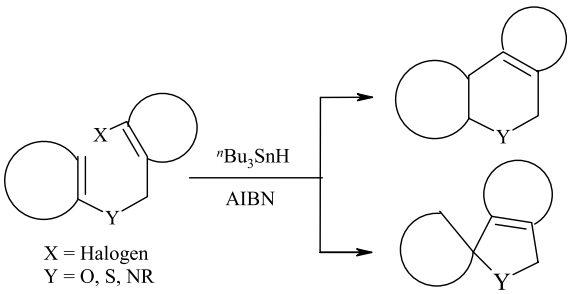
Tetrahedron

Tetrahedron Vol. 61, No. 45, 2005

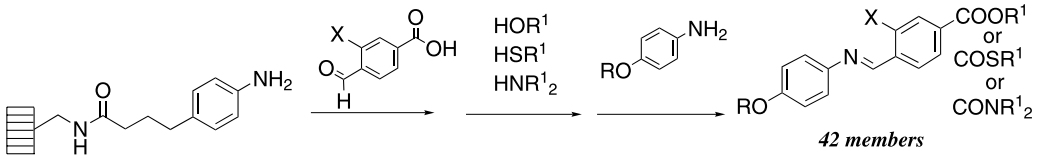
Contents

REPORT

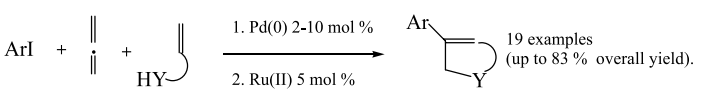
This review describes the formation of five- and six-membered heterocyclic rings in various compounds by radical cyclisation and covers mostly the recent literature published in 2004.

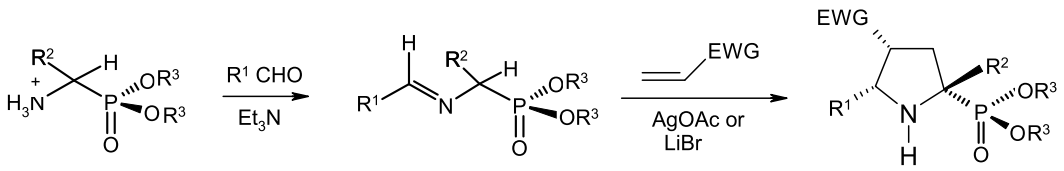


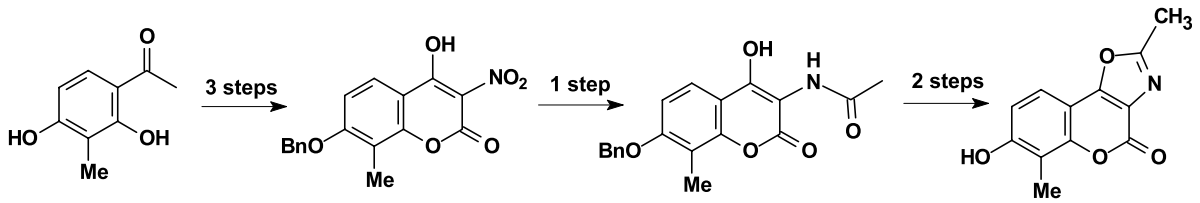
ARTICLES

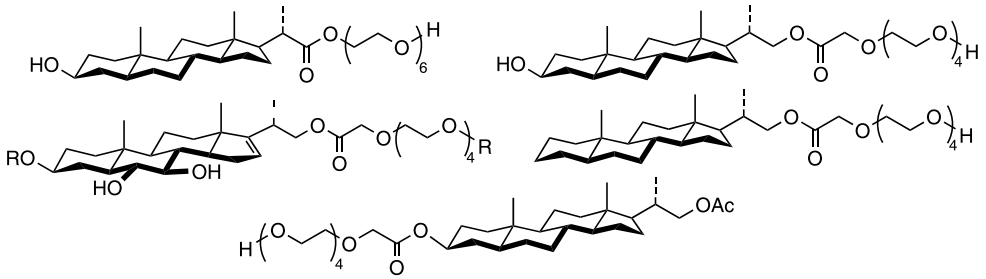


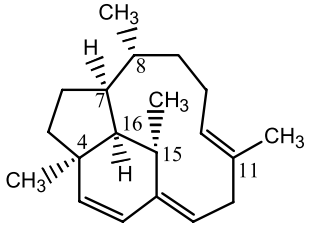
A novel traceless linker



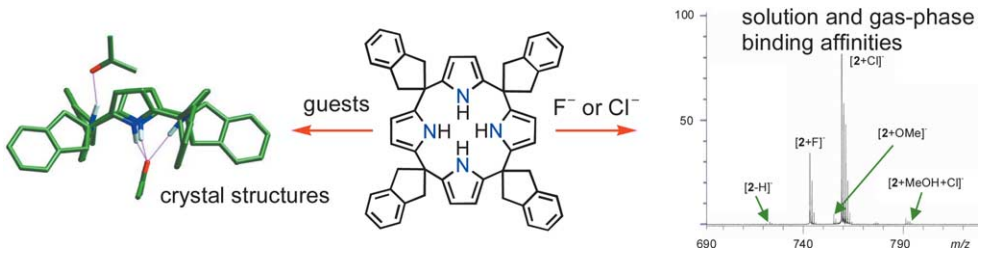


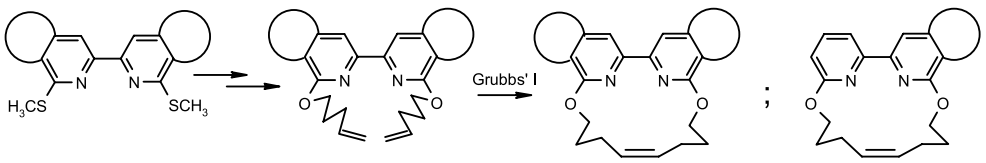


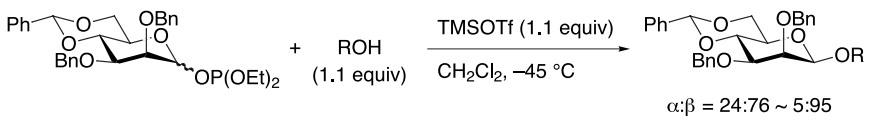


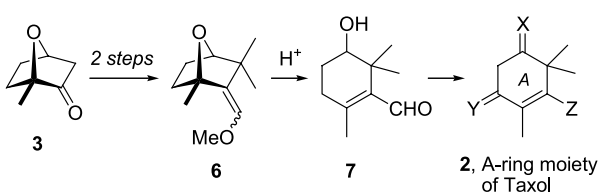


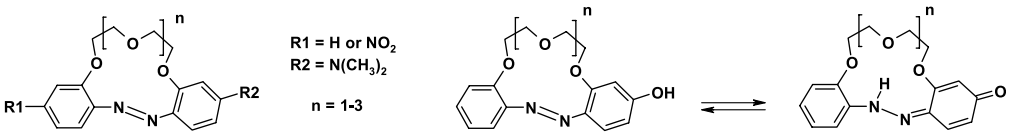
(4*R*,7*S*,8*R*,11*E*,15*S*,16*S*)-trinervita-1(14),2,11-triene



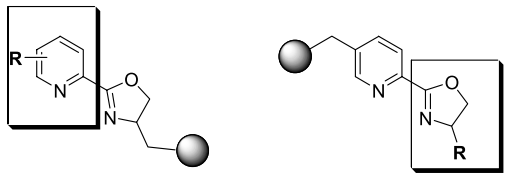


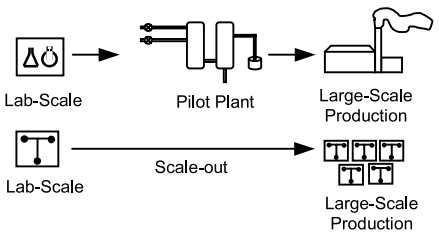




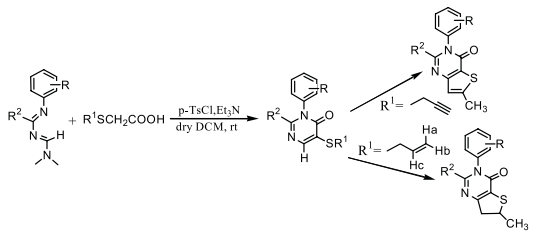


Functionalized azobenzocrown ethers—synthetic approach, metal cation complexation





Using the preparation and reaction of enolates, we demonstrate numerous advantages associated with the use of micro reaction technology including rapid reaction optimisation, reduced reaction times, enhanced conversion, reduced by-product formation, in situ generation of reactive intermediates and the ability to synthesise reaction products that require no further purification.



OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

A new traceless linker was developed to synthesize the compounds possessing an azomethine linkage on a solid-phase support. 42 liquid crystal candidates were prepared by three-step parallel syntheses utilizing the linker. The background pictures show the textures of the library members. *Tetrahedron* **2005**, *61*, 10643–10651.

Indexed/Abstracted in: AGRICOLA, Beilstein, BIOSIS Previews, CAB Abstracts, Chemical Abstracts, Chemical Engineering and Biotechnology Abstracts, Current Biotechnology Abstracts, Current Contents: Life Sciences, Current Contents: Physical, Chemical and Earth Sciences, Current Contents Search, Derwent Drug File, Ei Compendex, EMBASE/Excerpta Medica, Medline, PASCAL, Research Alert, Science Citation Index, SciSearch

ELSEVIER

ISSN 0040-4020

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 61 (2005) 10603–10642

Tetrahedron report number 739

Formation of five- and six-membered heterocyclic rings under radical cyclisation conditions

Krishna C. Majumdar,* Pradipta K. Basu† and Partha P. Mukhopadhyay

Department of Chemistry, University of Kalyani, Kalyani 741 235, WB, India

Received 15 July 2005

Available online 16 August 2005

Contents

Keywords: Radical cyclisation; Five- and six-membered heterocycles; Tributyltin hydride; Cascade cyclisation; Sulphur heterocycles.
Abbreviations: ACN, 1,1′-azobis(cyclohexanecarbonitrile); AIBN, azobis(isobutyronitrile); AMBN, azobis(methylisobutyronitrile); ATRA, atom transfer radical addition; ATRC, atom transfer radical cyclisation; CAN, ceric ammonium nitrate; CTAB, cetyltrimethylammonium bromide; CTAN, cerictetra-*n*-butylammonium nitrate; DBU, 1,8-diazabicyclo[5.4.0]undecene-7; DCE, 1,2-dichloroethane; DEPO, diethylphosphineoxide; DFT, density functional theorem; DLP, dilauroyl peroxide; DME, dimethoxyethane; DMF, dimethylformamide; EPHP, *N*-ethylpiperidine hypophosphite; FMO, frontier molecular orbital; HOMO, highest occupied molecular orbital; HMPA, hexamethylphosphoramide; LUMO, lowest unoccupied molecular orbital; MW, microwave; OTBS, *tert*-butyldimethylsilyloxy; PMB, *para*-methoxybenzyl; PMDTA, *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylene triamine; PRC, polarity reversal catalysis; SET, single-electron transfer; SH^i, intramolecular homolytic substitution; SOMO, singly occupied molecular orbital; TBHP, tetra-butyl hydroperoxide; TBTH, tributyltin hydride; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TMEDA, *N*,*N*,*N*,*N*-tetramethyl-1,2-ethylenediamine; TMS, trimethylsilyl; TOCO, thiol-olefin co-oxygenation; $TTMSH/(TMS)_3SiH$, tris(trimethylsilyl)silane; VA-061, 2,2′-azobis[2-(2-imidazoline-2-yl)propane]; VOL(OEt), 2,4-di-*tert*-butyl-6({[(1*S*)-1-(hydroxymethyl)-3-(methylthio)propyl]imino}methyl)phenol.

* Corresponding author. Tel.: +91 33 2582 7521; fax: +91 33 2582 8282; e-mail addresses: kcm_ku@yahoo.co.in; kcm@klyuniv.ernet.in
† Present address: Department of Chemistry, Hooghly Mohsin College, Chinsurah, Hooghly, WB, India.

doi:10.1016/j.tet.2005.07.079

1. Introduction

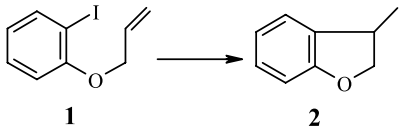
The chemistry of radical cyclisation has been at the forefront of research in a significant number of disciplines.[1] These results underscore the importance of developing new methods for the synthesis of various heterocycles and this may be done by constructing five- and six-membered rings, either in separate or in multistep processes. Rapid progress in free-radical reactions and their applications in organic synthesis have been achieved during the last three decades[2] and, due to this extraordinary development, carbon–carbon bond formation[1,3] is nowadays routinely considered in retrosynthetic analysis. Acyl radicals[4] take part in a large range of inter- and intramolecular reactions and, hence, they are useful synthetic intermediates.[5] Ryu and co-workers have shown that acyl radicals can also be generated by the reaction of alkyl radicals with carbon monoxide.[4,6,7] Primary, secondary, and tertiary radicals can be effectively carbonylated to transform them into carbonyl derivatives such as aldehydes,[8] ketones,[9] esters,[10] lactones,[11] thiolactones,[12] amides,[13] lactams,[14] and acyl selenides.[15] Some of these transformations are associated with atom or group transfer, inter- or intramolecular radical addition, cascade reactions, radical translocation, one-electron oxidation, or ionic chemistry. Intramolecular radical *ipso*-substitution has not received much attention in organic synthesis.[16] Alkyl radicals obtained by the treatment of thiocarbamates of conformationally favourable 3-alkyl-3-arylpropan-1-ols with tris(trimethylsilyl)silane and AIBN were found to undergo intramolecular *ipso*-substitution of the methoxy group, producing the corresponding cyclised products. On the other hand, either conformationally favourable or flexible 1-arylalkan-3- or 4-ones easily cyclised into five- or six-membered condensed rings by treatment with SmI_2 via ketyl radical intermediates.[17] Spirocycles can be effectively synthesised by a radical cyclisation procedure employing an intramolecular radical attack onto a cyclic olefin,[18] intramolecular addition of tertiary cyclic radicals to an alkene[19] or alkyne,[20] or cyclisation of a radical species containing a preoccupied quaternary carbon centre.[21]

Radical reaction is emerging as one of the leading methods in many industrial processes especially for producing a whole class of useful plastics or polymers such as polyethylene, teflon, polystyrene etc. Radical reactions are of vital importance in biology and medicine. The search for various heterocycles and many new methodologies has been a central goal for free-radical chemists in recent years. This review has the same goal as its predecessors to provide the most effective literatures in the particular area. The main aim of this review is to reflect upon, and to summarise, the main developments that have taken place in the application of free-radical chemistry to synthesise five- and six-membered heterocycles and to stimulate further studies in this continually evolving field. In order to keep the review to a reasonable length, coverage has been focused[22] only on five- and six-membered heterocyclic ring constructions and has largely excluded heterocyclic syntheses in which the heterocyclic ring(s) are not part of a radical cyclisation.

2. Reagents, solvents and radical initiators used in radical cyclisation

Tributyltin hydride has proved to be an excellent radical-generating reagent for the development of modern synthetic radical chemistry, but, due to its high toxicity[‡], it is not useful in pharmaceutical synthesis. Additionally, it is very difficult to remove the tributyltin residues from the reaction mixtures and this reagent is very unstable and decomposes steadily, even if carefully stored. Tributylgermanium hydride (Bu_3GeH)[23] is a superior alternative to Bu_3SnH, devoid of all these problems. The use of tris(trimethylsilyl)silane [$(TMS)_3SiH$ or TTMSH][23] and polymethylhydrosiloxanes[24] has been extensively developed. Triphenylgermanium hydride-mediated radical carbonylation/cyclisation reactions[25] are also very useful.

Bowman et al. reported[26] the cyclisation of 2-iodo-1-(prop-2-enyloxy)benzene **1** to give a similar yield of 3-methyl-2,3-dihydrobenzofuran **2** using Bu_3GeH and Bu_3SnH, respectively, but the reaction is slightly slower with Bu_3GeH (Scheme 1).



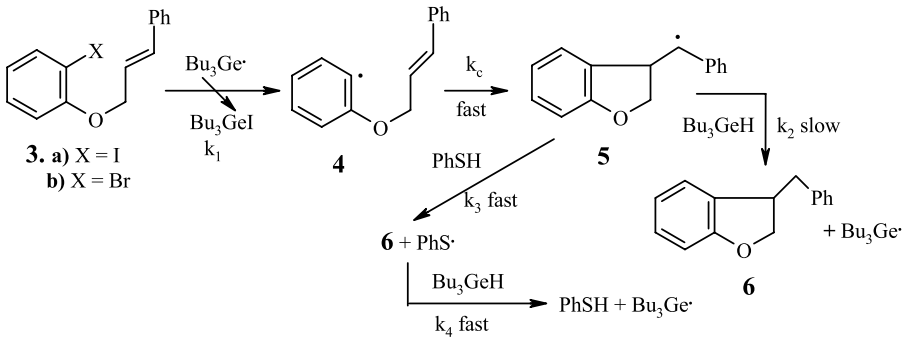
1 **2**

Reaction conditions	Yield of **2**
Bu_3SnH (1.2 equiv), ACN, PhMe, reflux, 2 h	86%
Bu_3GeH (1.2 equiv), ACN, PhMe, reflux, 3 h	91%

Scheme 1.

The radical cyclisation reactions of 1-iodo-**3a** and 1-bromo-2-[(3-phenylprop-2-enyl)oxy]benzene **3b** were also studied using Bu_3SnH and Bu_3GeH. The rate of bromine abstraction from bromobenzene by $Bu_3Ge^{\cdot}$ radicals at ambient temperature is relatively slow, but will be faster at higher temperature and the rate of abstraction of iodine (k_1) will be faster. Bowman et al. observed[26] that Bu_3SnH-mediated radical cyclisation of the radical precursors **3a** and **3b** gave the cyclised product **6** in good yield, whereas the yields with Bu_3GeH were extremely low. Various reaction conditions and initiators failed to improve the yield of the cyclised product **6**. The poor reactions with Bu_3GeH were due to the slow rate of H-abstraction (k_2) by the intermediate benzyl radical **5** (via **4**) from Bu_3GeH; the rate of H-abstraction from Bu_3GeH is too slow (20–30-fold slower than that with Bu_3SnH) to facilitate propagation and, hence, the chain reaction was inhibited. This is a drawback of Bu_3GeH, compared to Bu_3SnH. The yield of the cyclisation product **6** was increased to 75% by using the polarity reversal catalysis (PRC) technique developed by Roberts,[27] in which the nucleophilic benzylic radical intermediate **5** reacts relatively rapidly (k_3) with the electrophilic source of hydrogen (PhSH). This was the first example of the use of PRC with a triorganogermanium hydride (Scheme 2).

[‡] Tributyltin compounds can be handled safely on a small scale in the lab, provided that good lab practice is observed (see: Thomas, E. J., Science of Synthesis; Georg Thieme: Stuttgart, 2003; Vol. 5, pp 200–201).



Reaction condition	Radical precursor	Yield of **6**
Bu_3SnCl (0.1 equiv), $NaBH_4$, AIBN, *t*BuOH, reflux, 4 h	**3a**	59%
	3b	77%
Bu_3SnH (2 equiv), AMBN, cyclohexane, reflux, 3 h	**3a**	92%
	3b	52%
Bu_3GeH (1.3 equiv), AMBN, cyclohexane, reflux, 3 h	**3a**	0%
Bu_3GeH (1.0 equiv), PhSH (0.1 equiv), ACN, cyclohexane, reflux, 9 h	**3a**	75%
Bu_3SnH (2.2 equiv), syringe pump addition AMBN, MeCN, PhMe, reflux, 3 h	**3a**	52%
Bu_3SnH (2.0 equiv), Et_3B, THF, 25 ^{0}C, 21 h	**3a**	64%

Scheme 2.

The use of water as a solvent is an excellent achievement from both an economical and an environmental standpoint.[28] The indium-mediated carbon–carbon bond-forming reactions in aqueous media are very useful in organic synthesis.[29] Nambu et al.[30] synthesised 1-methoxy-4-(4-methyl-2-oxolanyl)benzene from 2-iodo-1-(4-methoxyphenyl)-1-prop-2-enyloxyethane by using VA-061 as the water-soluble initiator and EPHP as the chain carrier and an overall increase in the product yield was obtained by employing 1–10 equiv of NaCl as a 'salting out' salt. The reaction was best carried out by using various surfactants, for example, cetyltrimethylammonium bromide (CTAB), in the presence of 2,2′-azobis[2-(2-imidazolin-2-yl)propane] (VA-061) and *N*-ethylpiperidine hypophosphite (EPHP). Recently, Barton et al. have reported a radical reaction using hypophosphorous acid.[31] The radical cyclisation of hydrophobic substrates using a combination of the water-soluble radical initiator, VA-061,[32] the water soluble-chain carrier, EPHP and the surfactant, CTAB, in water[33] has been used. Kita et al. have reported[34] a radical reduction in aqueous isopropyl alcohol using a combination of VA-061, hypophosphorous acid and triethylamine.

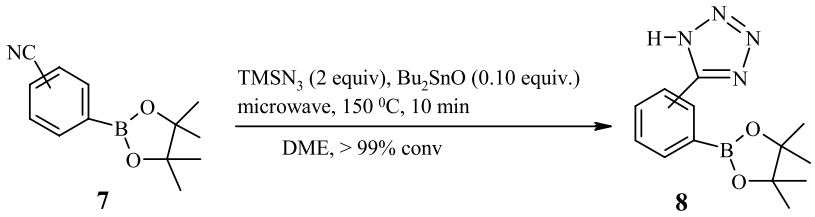
Murphy and co-workers synthesised[35] indolones in excellent yields from the reaction of iodoarenes with diethylphosphine oxide (DEPO) in water at 80 °C via aryl-radical formation, hydrogen-atom abstraction, cyclisation and re-aromatisation. The reaction featured V-501 as a water-soluble initiator and no other additives were needed. This reagent afforded an extremely easy work up, high yield of products and was free from phosphorous- or initiator-derived byproducts. The process proceeded at a much lower temperature than was required for efficient reaction with tributyltin hydride in benzene and the yield was even higher than that from the corresponding reaction annulated by EPHP.

Triethylborane (Et_3B) is a powerful reagent for radical cyclisation and the novel tandem radical addition cyclisation of oxime ethers and hydrazones intramolecularly concerted with an α,β-unsaturated carbonyl group was demonstrated.[36] Diethyl phosphite, $(EtO)_2P(O)H$, has proved to be a useful alternative and more versatile reagent for radical cyclisation.[37] Many indium-mediated reactions have been initiated by single-electron transfer (SET) in tandem carbon–carbon bond-forming processes in aqueous media.[38]

Studer et al. studied[39] intermolecular addition followed by cyclisation reactions by reacting various dienes (3 equiv) with alkoxyamines in $ClCH_2CH_2Cl$ to afford the 1,4-functionalised malonates in moderate to good yield as a cis/trans mixture of isomers. In this connection, it is important to note that the diastereomers could not be separated, but their relative configuration was assigned on the basis of literature reports[40] on similar cyclisations.

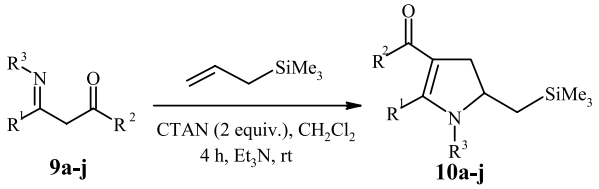
The rapid and homogeneous heating in the case of microwave-assisted organic synthesis is advantageous over the conventional thermal heating techniques. The addition of azidotrimethylsilane (2 equiv) to arylnitrileboronate esters **7** was found to proceed rapidly in dimethoxyethane (0.10 equiv) to give the aryltetrazoleboronates **8** in moderate to good yield, with dibutyltin oxide as catalyst.[41] It is important to note that the same reaction required >22 h for complete conversion under refluxing conditions (Scheme 3).

During the last few years, there has been flurry of applications of Ce(IV) reagents for producing radicals and radical cations that can further react with other substrates to form C–C bonds.[42] Ce(IV)-mediated oxidative additions of enolisable carbonyl compounds to activated olefins is of particular importance.[43] Ceric ammonium nitrate (CAN) is the most commonly used reagent for this purpose, but the poor solubility of CAN may be avoided by preparing



Scheme 3.

ceric-tetra-*n*-butylammonium nitrate (CTAN), having a more lipophilic ammonium counterion.[44] The use of CTAN has been exemplified in the oxidative additions of 1,3-dicarbonyl substrates to allyltrimethylsilane.[45] The oxidative coupling of β-carbonyl imines **9a–j** and allyltrimethylsilane with CTAN were investigated in MeCN and CH_2Cl_2.[46] In MeCN, allylation products were generated predominantly, whereas, in CH_2Cl_2, the dihydropyrrole products **10a–j** were obtained exclusively. Here, solvent-assisted nucleophilic cleavage of the intermediate β-silyl cation is found to play an important role in the solvent-dependent chemoselectivity (Scheme 4).



9 **a)** (R^1, R^2 = Me, R^3 = CH_2Ph)
b) (R^1, R^2 = Me, R^3 = Pr)
c) (R^1, R^2 = Me, R^3 = CH(Ph)(CO_2Me)
d) (R^1, R^2 = Ph, R^3 = CH_2Ph)
e) (R^1 = Me, R^2 = OMe, R^3 = -CH_2Ph)
f) (R^1 = Me, R^2 = OMe, R^3 = Pr)
g) (R^1 = Me, R^2 = OMe, R^3 = CH(Ph)(CO_2Me))
h) (R^1 = Me, R^2 = OCH_2CH_3, R^3 = CH_2Ph)
i) (R^1 = Me, R^2 = O-*t*Bu, R^3 = CH_2Ph)
j) (R^1 + R^2 = -$CH_2CH_2CH_2$-, R^3 = CH_2Ph)

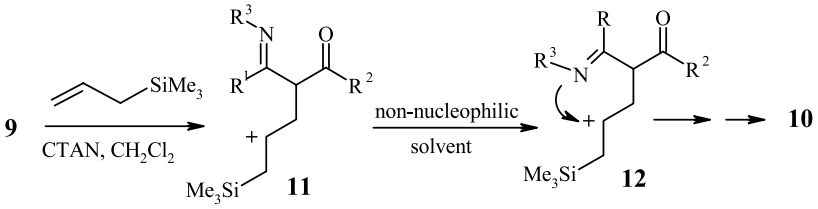
10. **a)** 78%
b) 71%
c) 54%
d) 65%
e) 82%
f) 72%
g) 48%
h) 76%
i) 80%
j) 74%

Scheme 4.

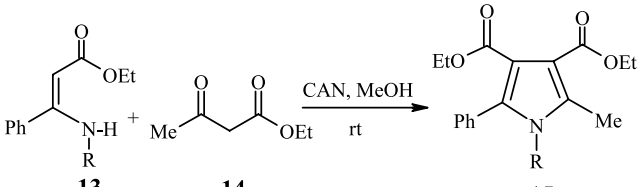
The conversion of **9** to **10** in the presence of a non-nucleophilic solvent proceeded via (**11**→**12**→**10**). The intermediate β-silyl cation was quenched by the presence of a proximal nucleophilic imine (Scheme 5).

The CAN-mediated reaction between β-aminocinnamates **13** and ethyl acetoacetate (β-dicarbonyl compound) **14** in methanol at rt can lead to the formation of highly substituted pyrroles **15** (Scheme 6).[47]

A plausible mechanism for the above conversion suggests that initiation occurs with CAN oxidation of **14** to produce



Scheme 5.



13 **a)** R = *p*-ClC_6H_4
b) R= *p*-BrC_6H_4
c) R = *p*-$EtO_2CC_6H_4$
d) R = Ph
e) R = CH_2CN

15 **a)** 54%
b) 54%
c) 54%
d) 45%
e) 53%

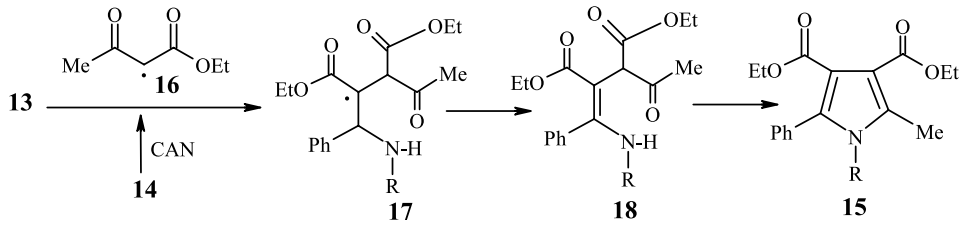
Scheme 6.

radical **16**. This radical intermediate **16** undergoes intermolecular addition followed by oxidation to give **18** (via **17**), which undergoes a condensation reaction to afford **15** (Scheme 7).

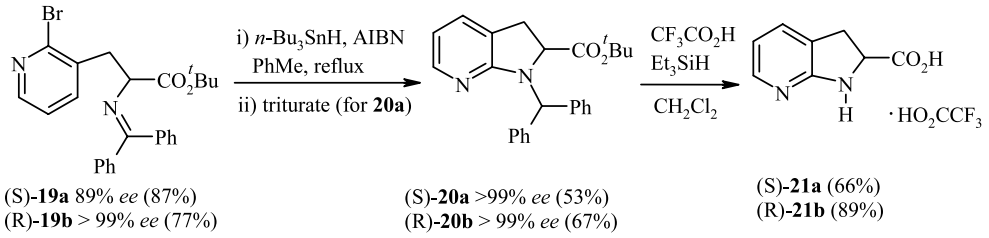
3. Synthesis of nitrogen heterocycles

3.1. Imine and enamine substrates and related systems

Naito et al. exemplified[48] the radical cyclisation of various oxime ethers and the sulphanyl radical addition–cyclisation of different hydrazones. Radical additions to C-2, C-3 and C-4 of a quinoline were found to proceed under neutral conditions.[49] Johnston et al. have developed[50,51] the free radical-annulated vinyl amination by non-conventional vinyl radical addition to the azomethine nitrogen, following 5-*exo-trig* cyclisation. This new vinyl amination protocol is very effective for synthetic access to non-stabilised *N*,*N*-dialkyl enamines and tandem bond-forming processes.[50] Recently, the tributyltin hydride-mediated radical cyclisation of various ketimines was carried out to analyse the aryl radical additions to the nitrogen of azomethines.[52] Aryl, trifluoromethyl, alkyl and α,β-unsaturated ketimines were engaged in regioselective aryl nitrogen bond formation via 5-*exo* cyclisations of an aryl radical to the azomethine nitrogen. C–N bond formation is more selective than C–C



Scheme 7.



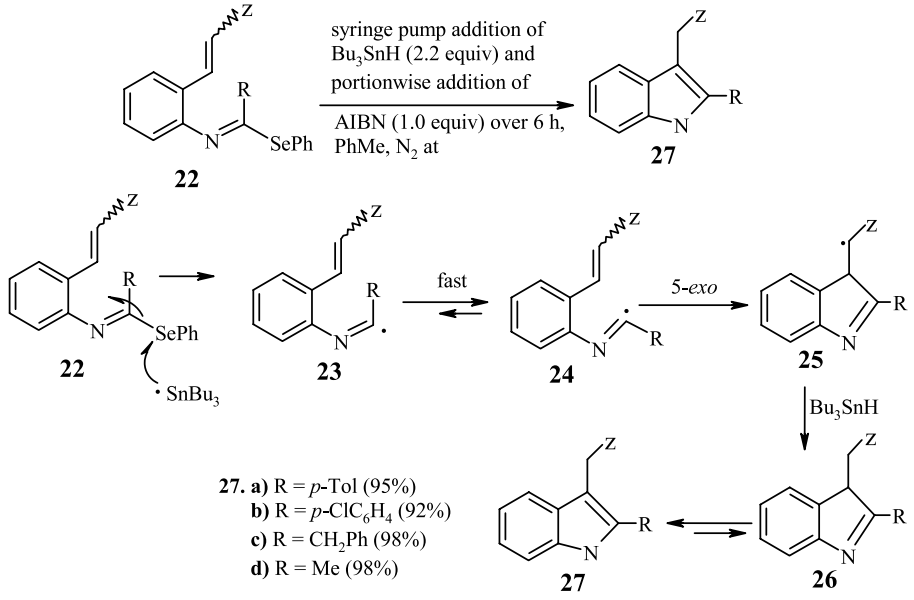
Scheme 8.

bond formation and competes only with direct aryl radical reduction by the stannane.

Johnston et al. have recently prepared[53] two non-natural proline derivatives (**21a**,**b**), (*S*)- and (*R*)-7-azaindoline-α-aminoacetate, as their trifluoroacetate salts on a gram scale, in which the key step was the tri-*n*-butyltinhydride-mediated radical cyclisation of (*S*)- and (*R*)-2-(benzhydryl-idene-amino)-3-(2-bromopyridin-3-yl)-propionic acid *tert*-butyl ester **19a** and **19b** to produce 1-benzhydryl-2,3-dihydro-1*H*-indole-2-carboxylic acid *tert*-butyl ester **20a** and **20b**, respectively. This large-scale free radical cyclisation protocol replaces benzene solvent with toluene without any complication and the crystalline nature of the intermediates and the final product enables straightforward purification at each stage, including enantiomeric enrichment (89–99% ee for **19b**). Deprotection to the free amino acid **21a**,**b** from **20a**,**b** was readily achieved by trifluoroacetic acid in CH_2Cl_2 and its isolation as the trifluoroacetate salt is most convenient for both characterisation and storage (Scheme 8).

Recently, Bowman et al. have synthesised[54] 2,3-disubstituted indoles **27** from imidoyl phenylselanide precursors **22** under Bu_3SnH-mediated standard radical cyclisation conditions. The unpaired electron of the imidoyl radicals is placed in an sp^2 orbital. From a study of the NOESY NMR spectrum, it was found that the phenylselanide group is *anti* to the *N*-substituent in the imidoyl selanides **22** and the imidoyl radicals will therefore, initially have the two substituents in the *syn* position **23**, which is unfavourable for cyclisation.

Although the literature reveals[55] that the barrier to inversion between the *syn*- and *anti*-imidoyl radicals is higher than that for vinyl radicals, the rate of inversion and cyclisation



Scheme 9.

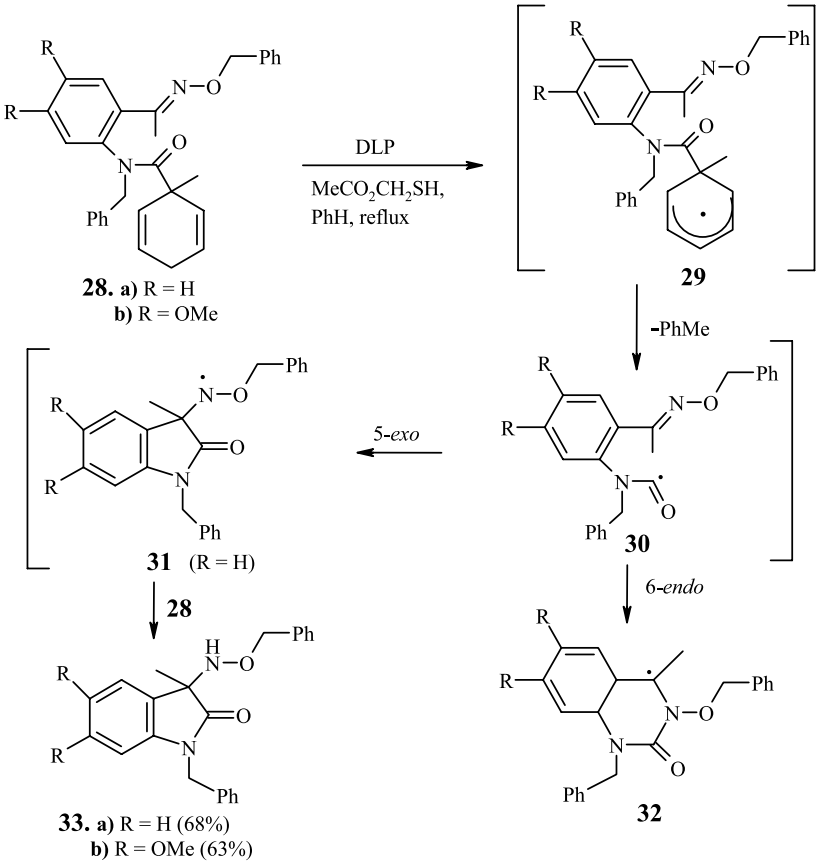
must be rapid, compared to the bimolecular reaction with Bu_3SnH, even at high concentrations of Bu_3SnH. Compound **25** was therefore, formed by 5-*exo* cyclisation of **24** (obtained from the rapid conversion of **23**) and the 3*H*-indole intermediates **26** (not isolated) were subsequently produced from **25** and were rapidly tautomerised to the indoles **27** (Scheme 9).

Studer et al. have introduced[56] silylated 1,4-cyclohexadienes having the capacity to release silyl radicals for use in conjunction with an organic halide precursor. 1-Carbamoyl-2,5-cyclohexadienes released carbamoyl radicals (aminoacyl radicals), which underwent ring closure to give the β- or γ-lactams in moderate yields.[57] The high regioselectivity of oxime ethers was demonstrated by Warkentin et al. who showed[58] that even the normally disfavoured 6-*endo*-attack was preferred at the carbon centre over 5-*exo*-cyclisation at the nitrogen. Radical addition on to oxime ether derivatives is rapidly developing and is very effective in synthesising various complex natural products,[59] for example, 1-deoxynorjirimycin,[60] (+)-7-deoxypancratistatin,[61] morphine alkaloids,[62] (−)-balanol fragments[63] and pyrrolidine nucleoside analogues.[64]

N-Benzyl-*N*-[2{*N*-(benzyloxy)ethanimidoyl}phenyl]-1-methyl-2,5-cyclohexadiene-1-carboxamide **28a** was allowed to react[65] with dilauroyl peroxide as initiator and a catalytic amount of methyl thioglycolate in refluxing benzene. After a 30 h reflux of a benzene solution of **28a**, 1-benzyl-3-[(benzyloxy)amino]-3-methyl-1,3-dihydro-2*H*-indol-2-one **31** (R=H) was isolated in 68% yield. The electrophilic sulfanyl radical RS˙, obtained from methyl thioglycolate, will preferentially abstract hydrogen from the bisallylic site of **28**, due to a favourable polar effect, to generate a cyclohexadienyl radical **29** and regenerate RSH. In refluxing benzene, radical **29** will undergo rapid β-scission to produce a carbamoyl radical **30**, together with toluene as a benign and easily removable byproduct. The indolinyl aminyl radical **31** should be produced by the 5-*exo*-ring closure of **30** and the radical **31** will readily abstract a hydrogen atom from additional **28** and, hence, propagate a chain reaction with the 3-substituted indoline derivative **33a** as the end product. The cyclisation steps were very rapid and took place regioselectively at the C-atoms of the C=N bonds, by 5-*exo* ring closure. Competition from 6-*endo* cyclisation of the carbamoyl radical **30** will generate the dihydroquinazolin-2-one intermediate **32**. Compound **28b** under a very similar kind of reaction sequence furnished 1-benzyl-3[(benzyloxy)-amino]-5,6-dimethoxy-3-methyl-1,3-dihydro-2*H*-indol-2-one **33b** in 63% yield (Scheme 10).

3.2. Substrates with ketenimine functions

1-(2-Bromoethyl)-2-isocyanatobenzene was reacted with tributyltin hydride using thermal initiation with AIBN, photochemical initiation and conditions of slow organotin addition[66] and 3,4-dihydro-1*H*-quinolin-2-one was obtained as the major product via 6-*endo* cyclisation. Alternatively, the cyclisation might be treated as 6-*exo*. The inter- and



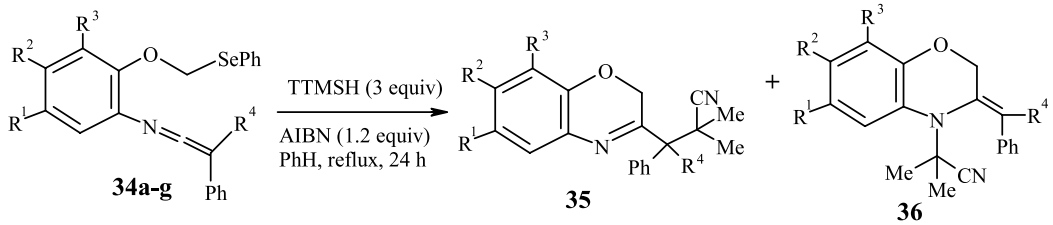
Scheme 10.

intramolecular addition of free radicals onto ketenimines was explored[67] very recently by Vidal et al. They found that the intramolecular addition of benzylic radicals generated from xanthates, onto the central carbon of a ketenimine function with its *N*-atom joined to the *ortho*-position of the aromatic ring occurred under a variety of reaction conditions and provided a novel radical-annulated synthesis of 2-alkylindoles.

Recently, Vidal et al. demonstrated[68] the radical cyclisation of the C,C-disubstituted ketenimines **34a–g** by a three-portion addition of a stoichiometric excess of tris(trimethylsilyl)silane (3 equiv) and AIBN (1.2 equiv) to a 0.015 M solution of the ketenimines in boiling benzene. Under these reaction conditions, the ketenimines **34** were totally consumed to produce the 2*H*-1,4-benzoxazines **35a–g** and **36a–g** in moderate to good combined yields (36–82%). These radical cyclisations are controlled by a persistent radical effect[69] (Scheme 11).

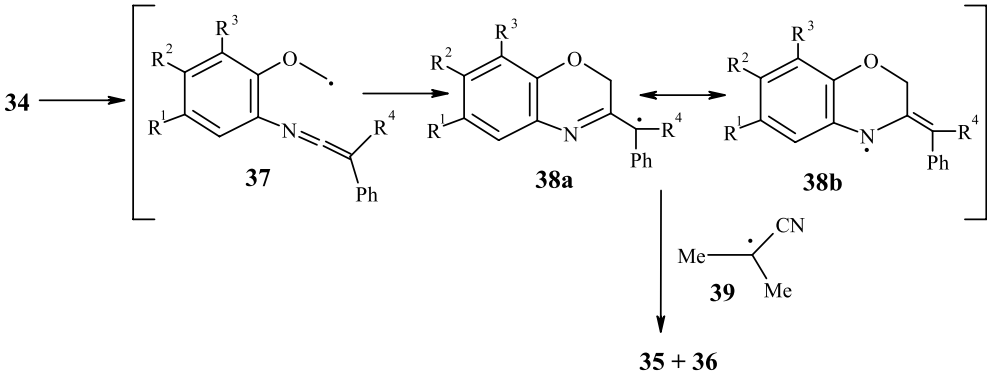
The mechanism for the formation of **35** and **36** from **34** may be explained as follows. The in situ-formed $[(CH_3)_3Si]_3Si$ radical should attack the selenium atom of the ketenimines **34** to give $PhSeSi[Si(Me)_3]_3$ and the expected aryloxymethyl radicals **37**. These, in turn, undergo cyclisation to the *tertiary* radicals **38a** by intramolecular addition of the radical moiety onto the central carbon atom of the ketenimine function. The (2*H*-1,4-benzoxazin-3-yl)methyl radicals **38a** subsequently underwent radical–radical cross coupling with the 1-cyano-1-methylethyl radical **39** obtained from the thermal decomposition of AIBN to give the compounds **35**. Another possibility is that the unpaired electron of the radicals **38a** can also reside on the nitrogen atom of the 1,4-benzoxazine substituent, as directed by the canonical form **38b**. The formation of the compounds **36** may be explained by the radical–radical coupling of **38b** with the 1-cyano-1-methylethyl radical **39** present in the reaction medium (Scheme 12).

Wang et al. observed[70] that the thermolysis of benzannulated enyne–isocyanates such as **40** initiated a cycloaromatisation reaction to generate in situ *O*,4-didehydro-2-hydroxyquinolines **41a**,**b** as reactive intermediates. This cycloaromatised intermediate could be captured either as biradicals **41a** and/or as zwitterions **41b**, depending on the nature of the substituent at the alkynyl terminus. Compound **40** was refluxed in 1,2-dichlorobenzene in the presence of an excess of γ-terpinene in a sealed glass tube at 230 °C for 24 h to produce 3-phenyl-2(1*H*)-quinolinone **42** in 47% yield, along with a small amount of the chlorinated adduct **43** in 6% yield. The intermediate obtained from cycloaromatisation of **40** bearing a phenyl substituent could be regarded as biradical **41a**, which then abstracted hydrogen atoms from γ-terpinene, leading to 2(1*H*)-quinolinone **42**. Alternatively, the same intermediate could also be regarded as zwitterion **41b**, which then underwent an initial hydride

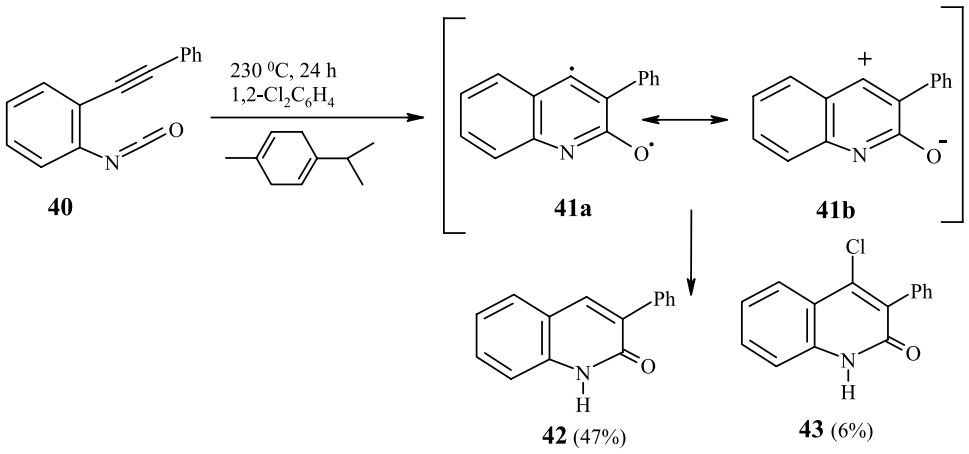


35a, 36a) $R^1 = R^2 = R^3 = H$, $R^4 = Ph$ (**35:36** = 0.7:1) (79%)
35b,36b) $R^1 = Me$, $R^2 = R^3 = H$, $R^4 = Ph$ (**35:36** = 1:1) (74%)
35c, 36c) $R^1 = OMe$, $R^2 = R^3 = H$, $R^4 = Ph$ (**35:36** = 1:1) (36%)
35d, 36d) $R^1 = H$, $R^2, R^3 = C_6H_4$, $R^4 = Ph$ (**35:36** = 0.7:1) (73%)
35, 36e) $R^1 = R^3 = H$, $R^2 = Me$, $R^4 = Ph$ (**35:36** = 0.7:1) (66%)
35f, 36f) $R^1 = Cl$, $R^2 = R^3 = H$, $R^4 = Ph$ (**35:36** = 0.5:1) (82%)
35g, 36g) $R^1 = Cl$, $R^2 = R^3 = H$, $R^4 = Me$ (**35:36** = 1.8:1) (78%)

Scheme 11.



Scheme 12.



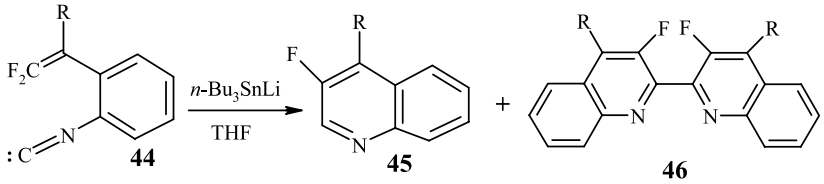
Scheme 13.

abstraction from γ-terpinene, followed by protonation to produce **42**. The chloro-substituent in **43** was presumably obtained from 1,2-dichlorobenzene. The presence of a 2-phenylethyl substituent in place of a phenyl substituent in **40** also allowed the resulting intermediates to be captured intramolecularly, either as biradicals or as zwitterions, producing 2(1*H*)-quinolinone in 81% yield. On the other hand, with a 2-methoxyphenyl, a 2-(dimethylamino)phenyl, or a 3-methoxypropyl substituent, the chemical behaviour of the cycloaromatised adduct could be best explained in terms of a zwitterionic intermediate, leading to benzofuro[3,2-*c*]-quinolin-6(5*H*)-one (53–68%); 5,11-dihydro-11-methyl-6*H*-indolo[3,2-*c*]quinolin-6-one (59–82%); benzofuro[3,2-*c*]-pyridin-1(2*H*)-one (90%) and 2,5-dihydro-2,5-dimethyl-1*H*-pyrido[4,3-*b*]indol-1-one (38%) and related compounds. The efficiency and selectivity of the cycloaromatisation reaction could also be enhanced by the introduction of 1.1–10 equiv of dimethylphenylsilyl chloride to the reaction mixture to capture the resulting zwitterions (Scheme 13).

Fluorine-containing quinolines have received considerable attention, because the presence of fluorine atoms into organic molecules modifies their biological and physical properties.[71,72] 3-Fluorinated quinolines have been found to exhibit notable biological activities, giving rise to their medicinal and agricultural use.[73]

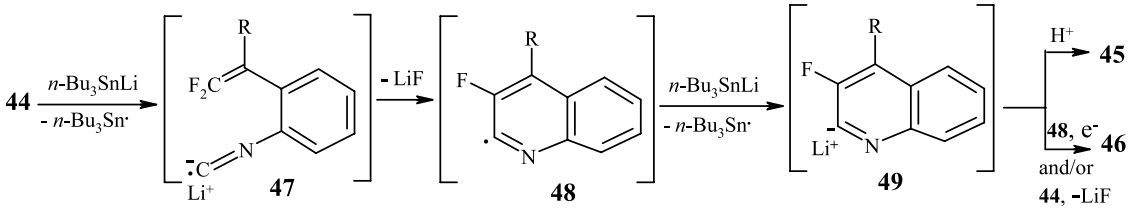
When *o*-isocyano-substituted-β,β-difluorostyrenes **44a–c** were added to *n*-Bu_3SnLi (Scheme 14, method-A), 2,4-disubstituted 3-fluoroquinolines **45a–c** were exclusively obtained in high yield.[74] On the other hand, the addition in a reverse manner (Scheme 14, method-B) afforded 4,4′-disubstituted 3,3′-difluoro-2,2′-biquinolines **46** as major products.[75,76] Thus, by just changing the order of addition of the substrates and tin reagent, both fluoroquinolines **45** and difluorobiquinolines **46** were selectively synthesized (Scheme 14).

The mechanism for the formation of **45** and **46** from **44** may



Substrate	R	*n*-Bu_3SnLi (equiv)	Method	Conditions	Yield of **45**	Yield of **46**
44a	*n*-Bu	3.0	**A**	-78°C, 1 h	80%	-
44b	Et	3.0	**A**	-78°C, 0.25 h	77%	-
44c	*s*-Bu	4.1	**A**	-78°C, 2 h	65%	-
44a	*n*-Bu	2.5	**B**	0°C, 1 h to rt, 1 h	4%	59%
44b	Et	2.1	**B**	0°C, 1 h to rt, 1h	12%	42%
44c	*s*-Bu	2.5	**B**	0°C, 1 h to rt, 1 h	-	42%

Scheme 14.



Scheme 15.

be explained as follows. Isocyanides **44** underwent a one-electron reduction with *n*-Bu_3SnLi to produce the radical anions **47**, which, in turn, cyclised to give the quinolyl radicals **48**. These radicals were readily reduced further to generate the 2-quinolyllithiums **49**. In method-A, an excess amount of *n*-Bu_3SnLi smoothly reduced **46** to afford the anions **49**, which exclusively produced the quinolines **45**. On the other hand, the reverse addition, that is by adding *n*-Bu_3SnLi to **44**, method-B, allowed the generated quinolyl anions **49** to react with the quinolyl radicals **48** and/or with the remaining substrates **44** to produce the biquinolines **46** (Scheme 15).

3.3. *N*-Vinylic substrates and related systems

Tamura et al. observed[77] the effect of a halogen atom in the 5-*endo* radical cyclisation of α-haloamides on *N*-benzyl amides. The cyclisation ability decreased from the chloro- to bromo- to iodo-amide and the same reaction course was also followed in $(TMS)_3SiH$-mediated reactions.

Jones et al. have reported[78] that the regiochemistry of the cyclisation of aryl radicals onto pyrroles attached through an amide at the C-3 position is influenced by the *N*-substituent on the pyrrole. Pyrroles substituted with an electron-donating group (methyl) on nitrogen, produced exclusively 8-methoxy-1-methyl-5-(2-trimethylsilylethoxymethyl)-4,5-dihydro-1*H*-pyrrolo[3,2-*c*]quinolin-4-one in 43% yield, arising from 6-*endo* cyclisation. No 5-*exo* or 6-*exo* cyclisation product was isolated from the reaction. On the other hand, pyrroles substituted on nitrogen with an electron-withdrawing group (carbamate) gave the cyclisation product (32%), along with a small amount of the aromatised product in 15% yield. From a consideration of the above results, it has been concluded that the formation of either the spiropyrrolidinyloxindole or pyrrolo[3,2-*c*]-qinoline nucleus from a common intermediate can be controlled by changing the substituent on the pyrrole, and the regiochemistry is not influenced by the substituents on the benzene ring.

Recently, it was observed[79] that the tributyltin hydride-mediated radical cyclisation of the 2-styrylindole took place at C-3 of the indole via a 6-*endo-trig* pathway to produce the benzo[*c*]carbazole in 58% yield as the major product.

Parsons et al. have shown[80] that the 5,5,6-ring system present in mitomycins can be prepared via tandem radical cyclisation sequences involving either a tandem 5-*endo*/5-*exo* radical cyclisation or, alternatively, a [1,6]-hydrogen-atom transfer, followed by a 5-*exo* cyclisation sequence.

Recently, Zhang et al. have described[81] a general method for constructing a variety of nitrogen heterocycles. They treated the *N*-acylated cyclic nitrogen compounds with $(TMS)_3SiH$ and AIBN to generate the tricyclic isoindolinones as the major product, along with some reduction product.

The oxidative radical cyclisation of enamides by using *n*-Bu_3SnH and dilauroyl peroxide has recently been reported by Miranda et al.[82] and an efficient 5-*endo* and 6-*endo* oxidative radical cyclisation was observed. *n*-Bu_3SnH and dilauroyl peroxide were used both as radical initiators and as oxidants in cyclisations onto enamide systems. Dibenzoyl peroxide and dicumyl peroxide were tested in the same reaction and the product yields were very similar to those obtained with dilauroyl peroxide.

Recently, we have reported[83] the regioselective synthesis of a number of pyrimidino[3,2-*c*]tetrahydroisoquinolin-2,4-diones from the 1,3-dialkyl-5-(*N*-2′-bromobenzyl,*N*-methyl)amino-pyrimidine-2,4-diones by the intramolecular addition of an aryl radical to the uracil ring bearing the amino nitrogen atom. The beauty of this reaction sequence is that the usual aerial oxidation in this type of cyclisation with *n*-Bu_3SnH is not observed and the dihydro compounds are isolated in excellent yield.

N-(*o*-Bromobenzyl)-*N*-[2,2-bis(phenylthio)ethenyl]propanamide underwent a Bu_3SnH-mediated radical cyclisation in a 5-*exo* manner to produce 1-[bis(phenylthio)methyl] dihydroisoindoles, which were partially desulphurised with Bu_3SnH-AIBN to give the 1-mono(phenylthio)methyl congeners.[84]

Harrowven et al. reported[85] the intramolecular 6-*exo*/*endo-trig* and 5-*exo-trig* cyclisations of aryl radical intermediates to the α-, β- and γ-carbons of pyridine at neutral pH. The tether conjoining the radical donor to the pyridine plays an important role in determining the fate of the reaction. When a *Z*-alkene was used as a tether, for example, (*Z*)-3[2-(6-iodo-1,3-benzodioxol-5-yl)-1-ethenyl]pyridine, the *n*-Bu_3SnH-mediated radical cyclisation afforded a 5:4 mixture of benzo[*h*]quinoline (54%) and benzo[*f*]isoquinoline (43%). The reaction was more complex when a saturated two-carbon tether, for example, 2-[2-(6-iodo-1,3-benzodioxol-5-yl)-ethyl]pyridine, was employed. In this case, a mixture of products, 2-[2-(1,3-benzodioxol-5-yl)ethyl]-pyridine (35%), 5,6-dihydro-[1,3]dioxolo[4′5′:4,5]-benzo[*f*]quinoline (33%) and 5,6-dihydro-[1,3]dioxolo-[4′5′:4,5] benzo[*h*]quinoline (27%), was obtained from the hydrogen-atom abstraction, *ipso*-cyclisation and *ortho*-cyclisation pathways.

A few years ago, Mitchell and Rees reported[86] a photochemical conversion of 9-(benzotriazol-1-yl)acridine **50** in to 8*H*-quino[4,3,2-*kl*]acridine **54** in acetonitrile and suggested that an intermediate carbene (obtained initially from a triplet diradical) in the guise of its dipolar form cyclised to the pentacycle **54**. Previously, they had explored[87] the parallel thermal transformation (**50**→**54**) by differential scanning calorimetry. The same quino-acridine **54** was also prepared[87,88] from 9-(2-bromoanilino)-acridine with tributyltin hydride and AIBN in boiling toluene under standard radical-cyclisation conditions.

Recently, Stevens et al. have reported[89] the cyclisation of 9-(benzotriazol-1-yl)acridine **50** to the pentacycle, 8*H*-quino[4,3,2-*kl*]acridine **54**, in a range of low-boiling solvents, which is mechanistically distinct from the previously published photochemical (carbene) and thermolytic (radical) cyclisations. The degradation of **50** in 98% yield in boiling triglyme (216 °C), and yields of 98% in ethanol (78 °C) and 95% in methanol (65 °C), (Table 1) cannot be accommodated reasonably within the diradical

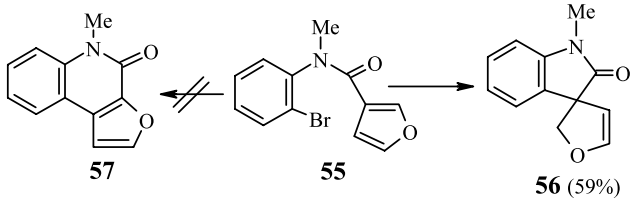
Table 1. Yields of 8*H*-quino[4,3,2-*kl*]acridine **54** from the thermolysis of 9-(benzotriazole-1-yl)acridine **50** in boiling solvents

Solvent	Temperature (°C)	Reaction time (h)	Yield (%)
Methanol	65	36	95
Ethanol	78	24	98
Trifluoroethanol	88	72	0
Propan-1-ol	97	24	Trace
Propan-2-ol	82	29	50
Butan-1-ol	117	24	90
Butan-2-ol	98	24	Trace
Diglyme	162	24	0
Triglyme	216	2	98
Diphenyl ether	259	1	97
Benzene	80	48	0
Toluene	110	48	0
Triethyl amine	89	24	80
Pyridine	115	24	6
Dimethyl formamide	156	24	80

hypothesis. The formation of **50** to **54** may be explained by the formation of a diazonium species **51**, which can cyclise to quinoacridine **54** via zwitterion **52** and the carbonium ion reactive species **53**, in a process showing affinities to the intramolecular arylation by diazonium compounds (Pschorr cyclisation),[90] but without requiring any copper catalysis. Several factors, for example, the propensity of benzotriazole to undergo N–N bond cleavage, resonance stabilisation and solvation of cationic reactive species, are responsible for the initiation of heterolytic fission of the benzotriazole (Scheme 16).

Ganguly and co-workers observed[91] that furan-3-carboxy-amide **55** on reaction with TBTH furnished the spiro compound **56** (59%) and no rearrangement product **57** was detected (Scheme 17).

Ganguly et al. also explored[91] the TBTH reaction with compound **58** to obtain compound **61** (20%), **62** (16%), **63** (47.2%) and **64** (8%). Here, compound **64** was obtained as a minor product from the spiro radical intermediate **59**. The major products were obtained by rearrangement of the spiro radical **59** to the radical **60**, which accepts a hydrogen radical



Scheme 17.

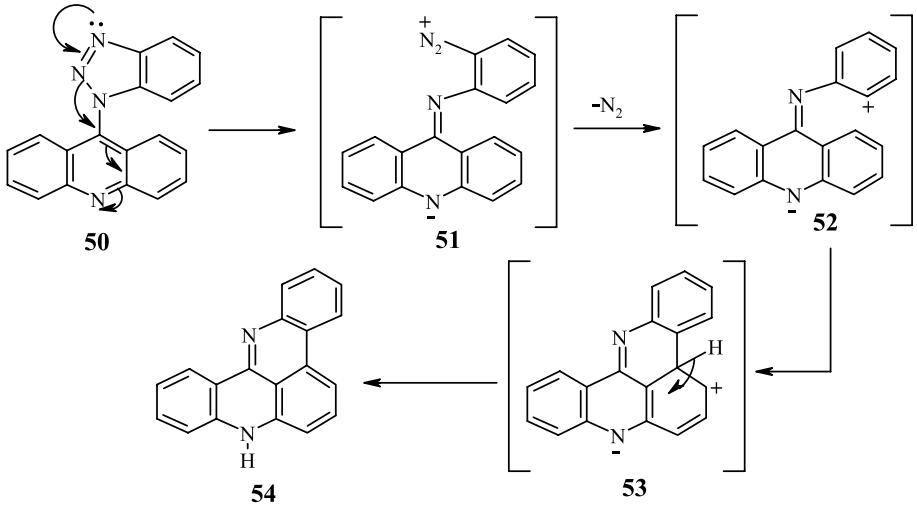
to give cis-**62** and trans-**61** and, in addition, the radical **60** undergoes oxidation to yield the compound **63** (Scheme 18).

A tributyltin hydride-mediated radical reaction[92] of compound **65** afforded **66** (11%) and **67** (16.9%) along with the starting material (45%). The formation of **66** and **67** from **65** may be explained as follows. The initial radical **68** underwent spiro cyclisation to give the intermediate **69**, which after further rearrangement, bond cleavage and subsequent oxidative cyclisation (path-A) produced benz-imidazole **67**, via **70**. The intermediate **69** may also undergo bond migration, followed by loss of a hydrogen radical, to give **66** via **71** (path-B, Scheme 19).

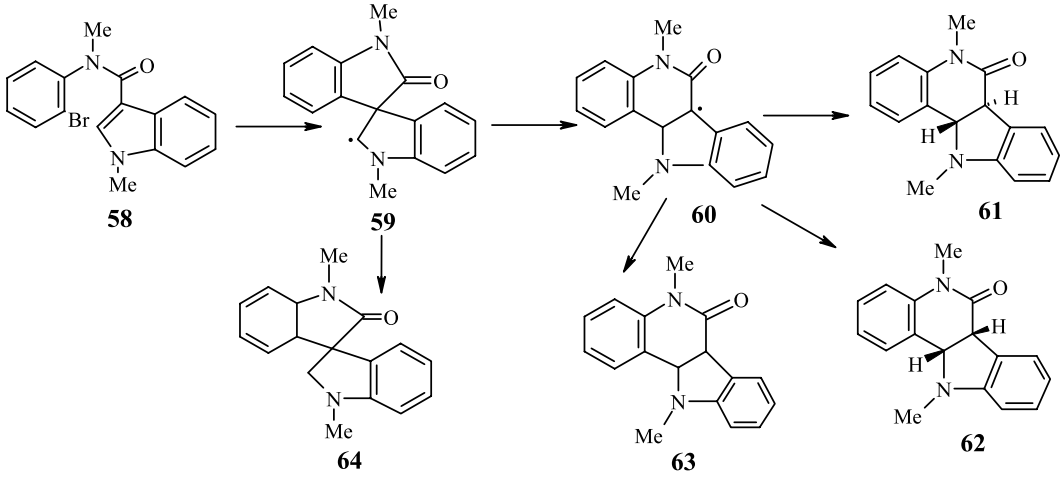
Cordes et al. reported[93] a relatively rare 7-*endo* cyclisation process to generate octahydrocyclopenta[*b*]azepines in reasonable yield and excellent stereoselectivity. The vinylogous amide **72** underwent 6-*exo* ring closure to the azaspirocycles **73** and **74** in a moderate yield and in a 1:1 ratio of diastereomers (Scheme 20).

Recently, Kamimura et al. carried out Bu_3SnH-mediated radical cyclisation[94] reactions of α-chloro-acrylamide **75** or acrylamide **76**. α-Unsubstituted **76** underwent exclusive 5-*exo* cyclisation to give **77** in 78% yield, while the existence of an α-chloro substituent again controlled the regioselectivity to 6-*endo* cyclisation, to afford the 3,4-dihydro-1*H*-quinolin-2-one **78** in 71% yield (Scheme 21).

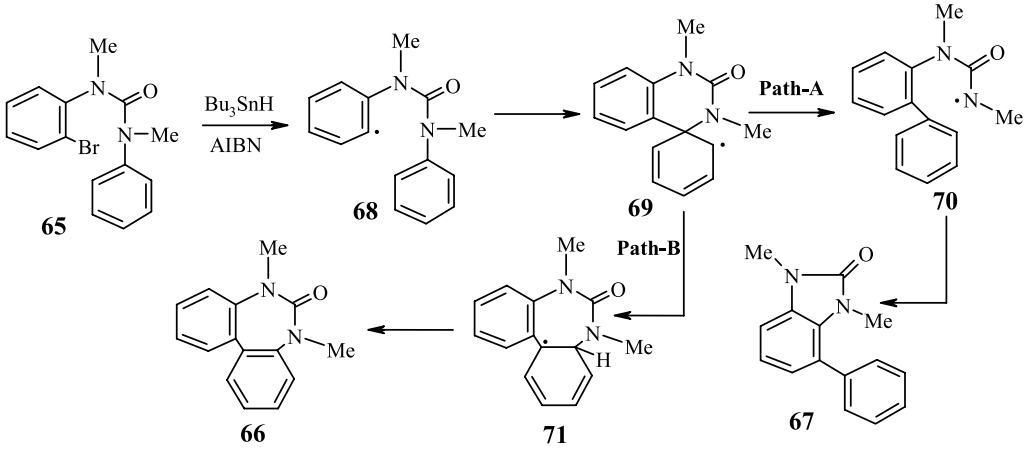
A spirocyclic fragment containing two fused five-membered saturated heterocycles is found in many naturally occurring compounds, for example, marine amathaspiramides[95] and pseudoindoxyl alkaloids.[96] Radical *ipso*-type substitution



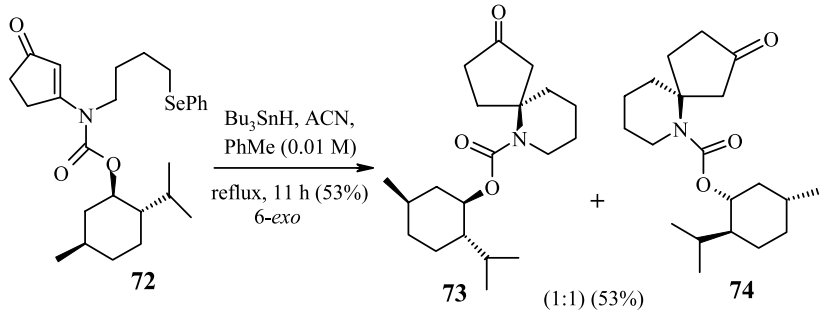
Scheme 16.



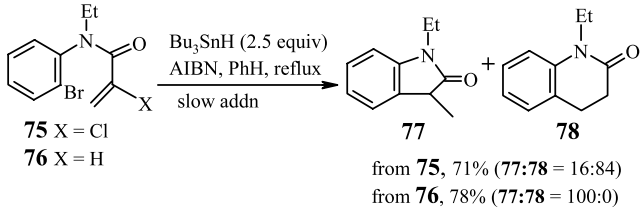
Scheme 18.



Scheme 19.



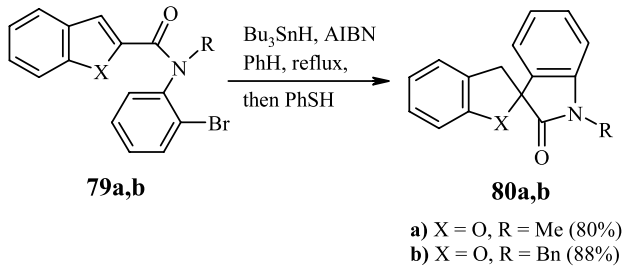
Scheme 20.



Scheme 21.

on to aryl rings mainly proceeds with rearomatisation.[97] Zard and co-workers reported[98] radical spirocyclisation to generate the dearomatised spirocycle. Parsons et al. have described[99] vinyl radical *ipso*-type substitution on furan. Jones et al. have applied aryl radical spirocyclisations on to pyrroles[78] and the C-3 position of indoles,[100] which afforded the spirocycles in moderate to good yield.

Recently, Baldwin and co-workers have subjected[101] the radical cyclisation precursors **79a**,**b** to the standard radical

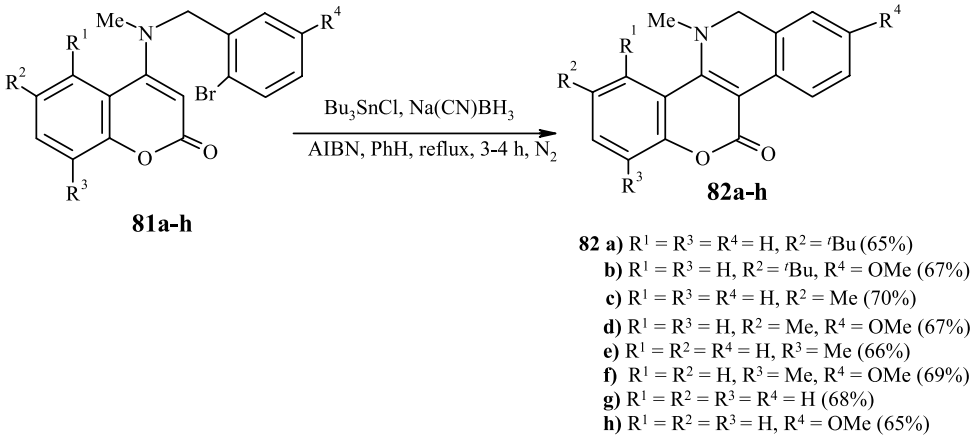


Scheme 22.

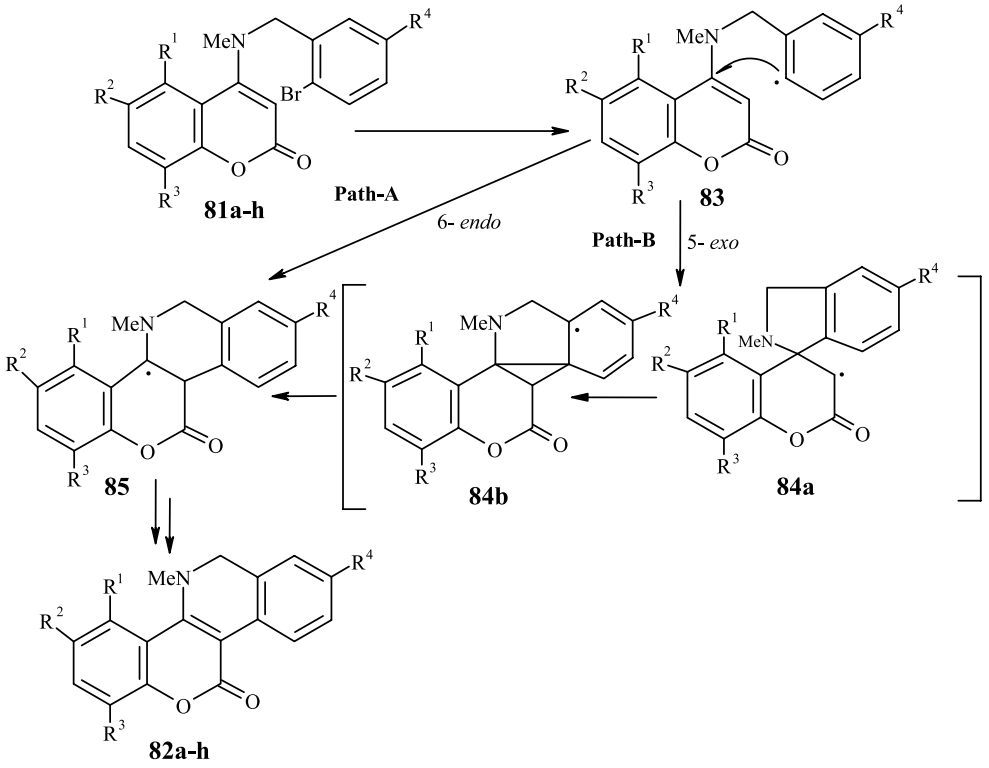
cyclisation conditions to obtain the spirocycles **80a**,**b** (Scheme 22).

A number of 4-tosyloxycoumarins were treated with *N*-methyl,*N*-(2-bromobenzyl)amine and *N*-methyl,*N*-(2-bromo-5-methoxybenzyl)amine in refluxing ethanol to give different 4-[*N*-(2′-bromobenzyl),*N*-methyl] amino coumarins **81a–h** in 70–75% yield. These tertiary amine substrates were then refluxed in dry benzene under nitrogen with tri-*n*-butyltin chloride and sodium cyanoborohydride in the presence of 0.5–0.6 mol equiv of AIBN for 4–5 h to give the title compounds **82a–h** in 65–68% yield (Scheme 23).[102]

The formation of the products **82a–h** from the substrates **81a–h** may easily be explained by the generation of an aryl radical **83** in the tri-*n*-butyltin hydride- and AIBN-mediated reaction.The aryl radical **83** may undergo cyclisation by two different modes, a 6-*endo* trig cyclisation[103] to afford the heterocyclic radical **85** (path-A) or a 5-*exo-trig* cyclisation to give the spiroheterocyclic radical[104] **84b** via **84a** (not isolated; path-B). The relatively more stable heterocyclic radical **85**



Scheme 23.



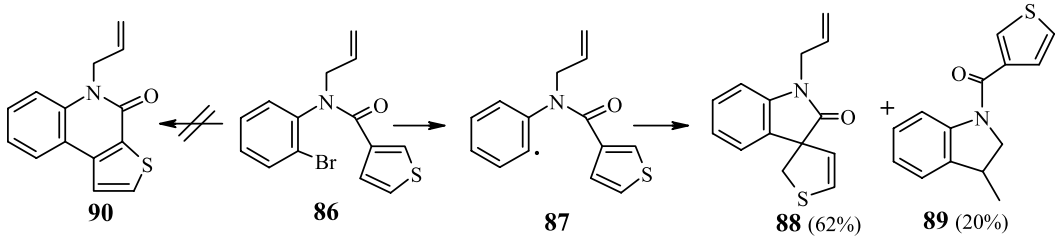
Scheme 24.

(benzyl radical) may form a conjugated double bond to yield the products **82a–h** by an unknown mechanism, which is usual for this type of synthetic sequence, that is an oxidation step in a Bu_3SnH-mediated cyclisation.[105,106] The possibility of the formation of the heterocyclic radical **85** via the spirocyclic radicals **84a** and **84b** by a neophyl rearrangement[107] cannot be ruled out (Scheme 24).

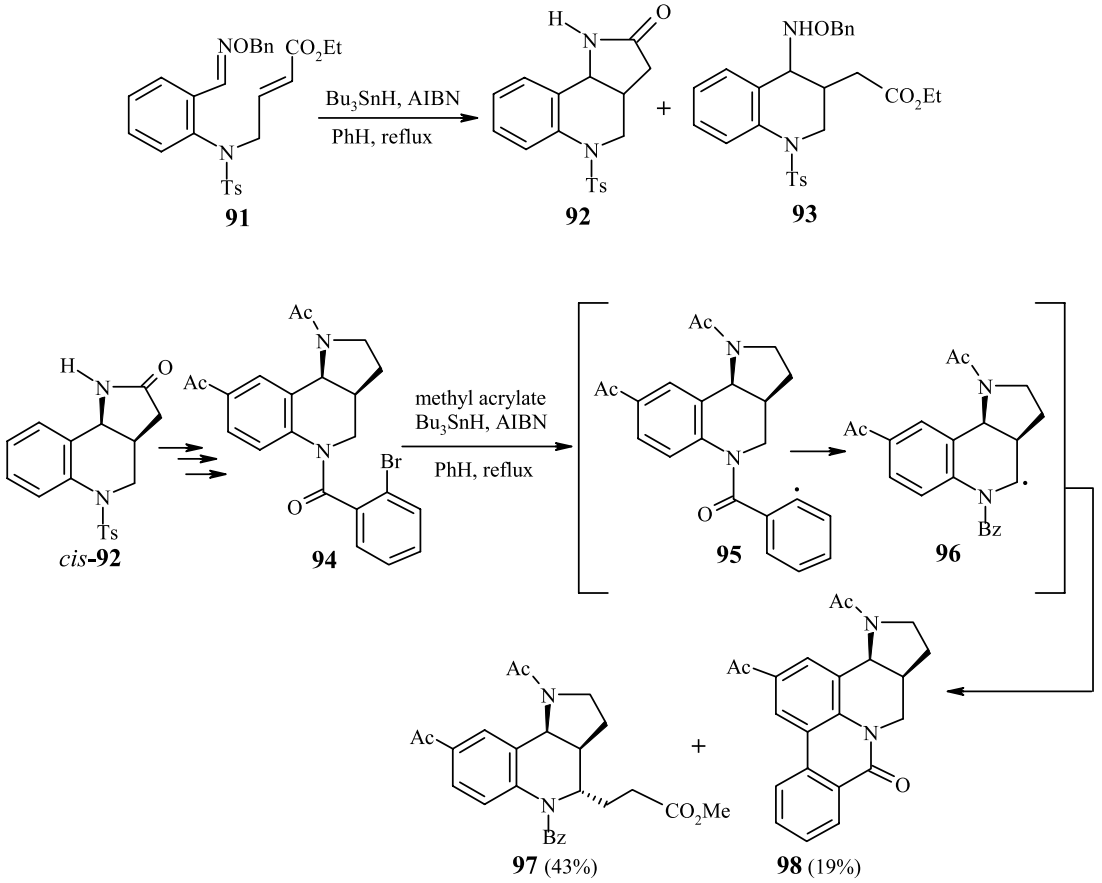
3.4. *N*-Allylic substrates and related systems

Ganguly et al. observed[91] that the the thiophenecarboxamide **86** on treatment with TBTH yielded the spiroindole **88** in 62% yield as a major product and compound **89** in 20% yield. This result indicates that the radical **87** combined with the thiophene double bond or the allyl substituent instead of undergoing rearrangement to the fused aromatic compound **90** (Scheme 25).

According to the published procedure developed[108] for the radical addition–cyclisation of oxime ethers, treatment of an oxime ether carrying an unsaturated ester **91** with TBTH and AIBN in refluxing benzene gave two types of products **92** and **93**. The major product of the reaction was an unexpected tricyclic pyrroloquinoline **92**, having no benzyloxy group (52%, cis:trans = 1:1) in the molecule, whereas the expected bicyclic tetrahydroquinoline **93** (22%, cis:trans = 1:1.5) was obtained as the minor product. Naito et al. examined[109] the introduction of a carbonyl group into the C(8) position and a C_3 unit into the C(4) position of cis-**92** possessing the requisite stereostructure for the synthesis of martinelline. The radical precursor **94** was produced from compound cis-**92** in several steps. When a solution of Bu_3SnH and AIBN in benzene was slowly added to a solution of **94** and methyl acrylate in refluxing benzene using a syringe pump, the expected compound **97** was produced (via the radical intermediates **95** and **96**) as a single diastereomer in 43% yield, along with the pentacyclic product **98** (19%). Compound **98** might have been produced by the radical



Scheme 25.

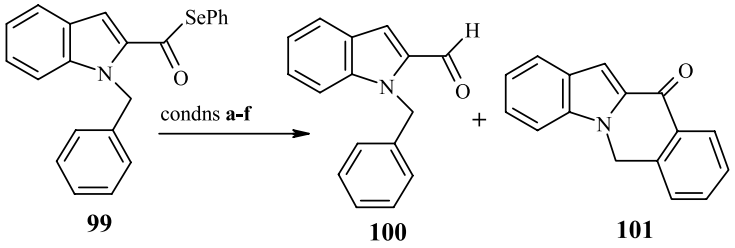


Scheme 26.

cyclisation of the transiently formed aryl radical **95** into the aromatic ring, followed by oxidation (Scheme 26).

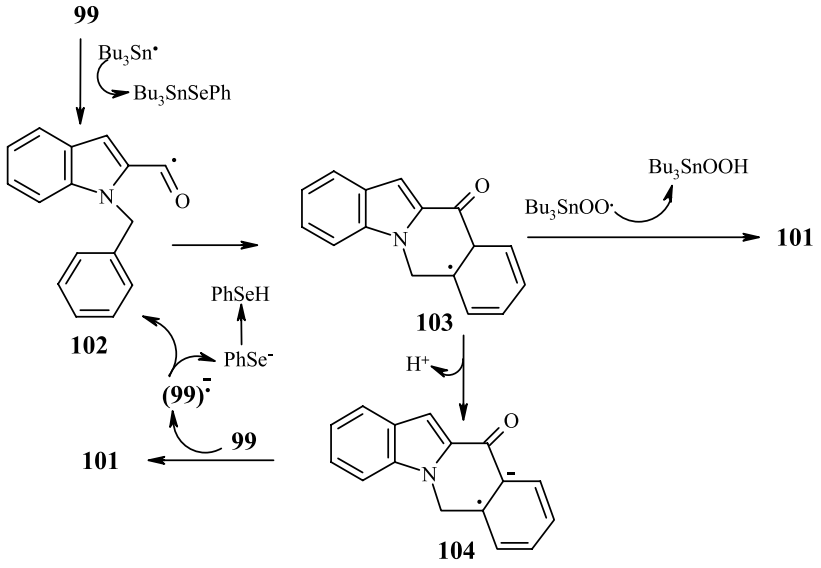
Intramolecular reactions of nucleophilic carbon-centered radicals with aromatic systems have received considerable synthetic attention in the last few years, in order to construct complex polycyclic molecules incorporating aromatic rings.[110] TBTH-mediated radical cyclisations of aryl and, to a lesser extent, alkyl radicals upon arenes[110,111] and heteroarenes,[110] including pyridines,[112] quinolines,[49] azoles[113] or indoles,[114,115] have already been reported, but, similar processes involving acyl radicals have rarely been studied.[79,116] The generation of 2- and 3-indolylacyl radicals from the corresponding phenyl selenoesters and their reactions with alkene acceptors under reductive conditions were reported earlier.[117] Recently, Bennasar et al. explored[118] the TBTH-annulated radical cyclisation of selenoester **99** separated by one methylene group under several experimental conditions. They also reported the cyclisation of **99** under non-reductive conditions (n-Bu_6Sn_2, 300 W sunlamp). This reaction was successful because of the comparatively longer effective lifetime of the indolylacyl radical, and, when substrate **99** was treated with 2.2 mol of n-Bu_6Sn_2, the tetracycle **101** was obtained in 65% isolated yield, with no trace of the reduction product **100** (Scheme 27).

The mechanism of this reaction is depicted as follows. After cleavage of n-Bu_6Sn_2 under the influence of heat and/or light, the resulting tributyltin radical generates the 2-indolylacyl radical **102**, which, in the absence of competitive reactions, can react intramolecularly upon the benzene ring to give the cyclohexadienyl radical **103**. By using substoichiometric amounts of the radical mediator, conversion of **103** into **101** must be explained via a chain-propagation

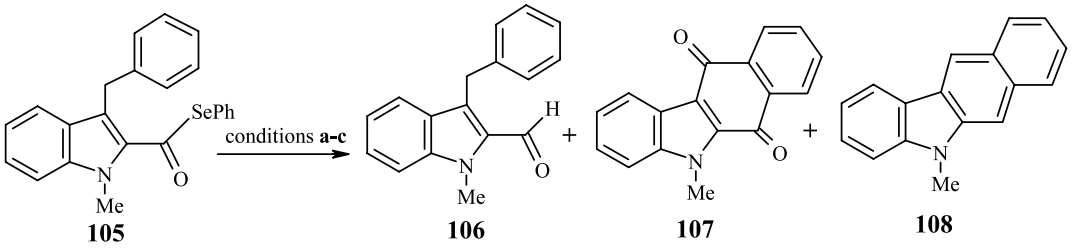


Reaction conditions	Product (yield, %)
a) n-Bu_3SnH (1.5 mol), AIBN (0.1 mol), PhH, 0.03 M, reflux, syringe pump, 2 h	**100** (90%)
b) n-Bu_3SnH (1.8 mol), AIBN (1.8 mol), MeCN- hexane, 0.03 M, reflux, syringe pump, 4 h	**100** (90%)
c) n-Bu_3SnH (1.2 mol), AIBN (0.1 mol), $PhSe_2$ (cat), PhH, 0.01 M, reflux, syringe pump, 20 h	**100:99** (1:1)
d) TTMSS (1.2 mol), AIBN (2.0 mol), PhH, 0.03 M, reflux syringe pump, 4 h	**100:101** (4:1)
e) n-Bu_6Sn_2 (0.2 mol), 300 W, PhH, 0.01 M, reflux, 24 h	**100** (10%), **99** (25%), **101** (40%)
f) n-Bu_6Sn_2 (2.2 mol), 300 W, PhH, 0.01 M, reflux, 24 h	**101** (65%)

Scheme 27.



Scheme 28.



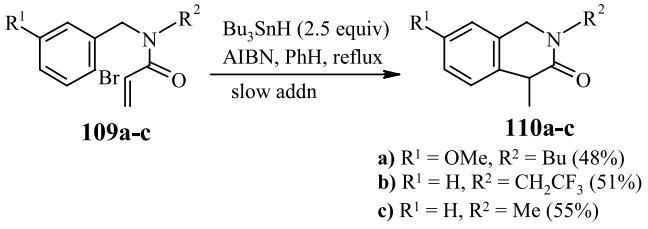
Reaction conditions	Product (yield, %)
a) *n*-Bu_3SnH (1.8 mol), AIBN (1.8 mol), MeCN-hexane, 0.06 M, reflux, syringe pump, 4 h	**106** (50%), **107** (40%)
b) *n*-Bu_6Sn_2 (0.2 mol), 300 W, PhH, 0.01 M, reflux, 24 h	**105** (25%), **106** (14%), **107** (30%), **108** (5%)
c) *n*-Bu_6Sn_2 (2.2 mol), 300 W, PhH, 0.01 M, reflux, 24 h	**101** (65%)

Scheme 29.

mechanism involving an S^1_{RN}-type reaction. Deprotonation of the radical **103**, followed by an SET reaction from the resulting radical anion **104** to the selenoester **99** would generate the tetracycle **101** and a new radical anion, which would lose a phenylselenolate anion to give the radical **102** to propagate the chain. The phenylselenol thus obtained could reduce the radical **102** and thereby explain the formation of the aldehyde **100** (Scheme 28).

The selenoester **105** having a benzyl group at the 3-position of the indole ring underwent cyclisations leading to 2,3-fused-ring indole derivatives **106–108** in both reductive and non-reductive conditions[118] (Scheme 29).

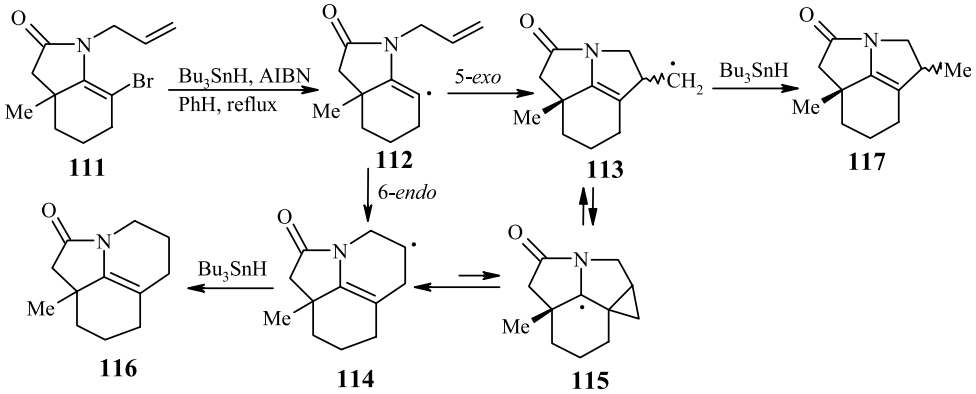
Kamimura et al. also observed[94] that α-unsubstituted acrylamides **109a–c** always furnished **110a–c** via 6-*exo* adducts, whereas the corresponding α-chloro substituent effectively switched the mode of cyclisation from 6-*exo* to 7-*endo* (Scheme 30).



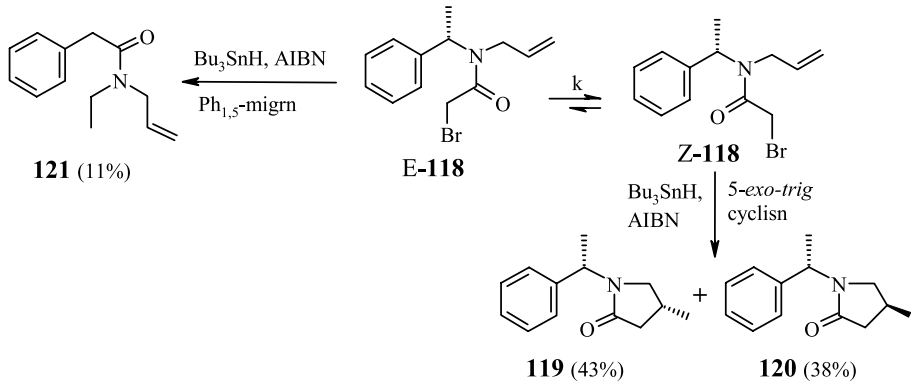
Scheme 30.

Tributyltin hydride-mediated radical cyclisation[119] of *N*-allyl-7-bromo-3*a*-methyl-hexahydroindol-2-one **111** was found to afford a six-membered-ring product **116** that prevails over the isomeric five-membered compound. The reaction was initiated by the generation of a cyclohexenyl radical **112** from compound **111**. When the hydride concentration was kept low, rearrangement of the kinetically formed radical **113** obtained from the cyclohexenyl radical **112** to the thermodynamically more stable radical **114** would occur (via **115**), leading to a six-membered product **116**. When the substrate **111** (0.01 M) was allowed to react with TBTH and a catalytic amount of AIBN, the six-membered ring product **116** was the major product (89%), but, when the bromide **111** was treated with Bu_3SnH at a concentration of 0.1 M, a significant quantity (20%) of the 5-*exo* cyclisation product **117** (3:1 mixture of diastereomers) was produced, along with the 6-*endo* cyclisation product **116** in a 1:3 ratio, together with the simple reduction product (19%) (Scheme 31).

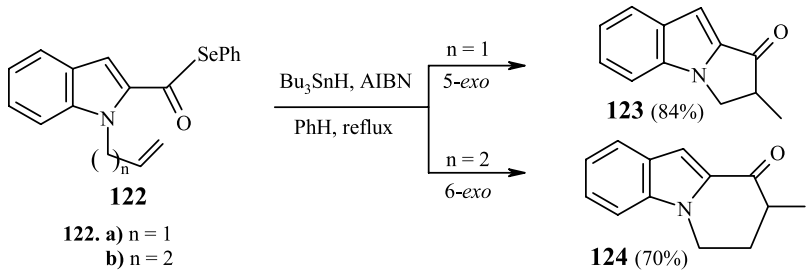
Bu_3SnH-annulated standard radical cyclisation conditions afforded pyrrolo[3,2,1-*de*]phenanthridinone (68%) as the major product from *N*-benzyl-substituted hexahydroindolinones. (*S*)-*N*-Allyl-2-bromo-*N*-(phenylethyl)acetamide **118** exists as a mixture of *E*/*Z* isomers in a ratio of 3:1, favouring to (*Z*)-rotamer.[120,121] This mixture was treated with tributyltin hydride and catalytic amounts of AIBN in benzene at reflux. The formation of the pyrrolidinones **119** and **120** was achieved when the *Z*-**118** rotamer was present, while the $Ph_{1,5}$-migration product **121**



Scheme 31.



Scheme 32.

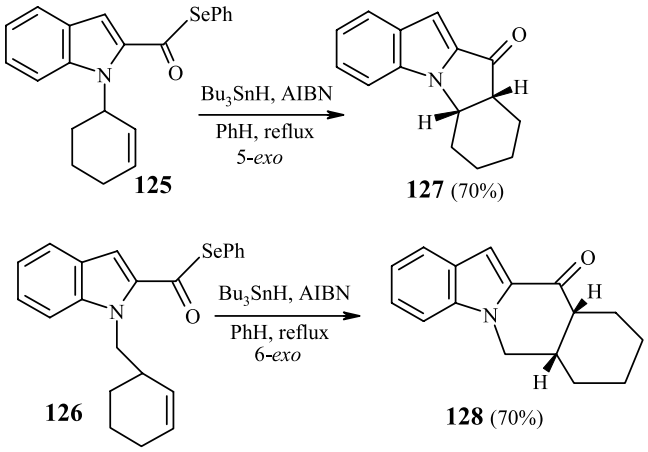


Scheme 33.

was obtained when the *E*-**118** rotamer was highly populated or the rotation of the amide bond was quite slow (Scheme 32).[122]

Indole selenoesters, carrying different alkenyl, cyclohexenyl or tetrahydropyridyl moieties at the nitrogen atom, were chosen as radical precursors[123] and these were treated with *n*-Bu_3SnH and AIBN in refluxing benzene. Compound **122a** preferred to form the five-membered ring through the 5-*exo* mode to give the compound **123** having a pyrrolo-[1,2-*a*]indole skeleton in 84% yield. Again, compound **122b** was found to cyclise in a 6-*exo* manner to give the pyrido[1,2-*a*]indole **124** in 70% yield (Scheme 33).

The selenoesters **125** and **126**, containing a 2-cyclohexenyl moiety, furnished stereoselectively the cis-fused tetracycles



Scheme 34.

127 (via a 5-*exo* route) and **128** (via a 6-*exo* route), respectively (Scheme 34).

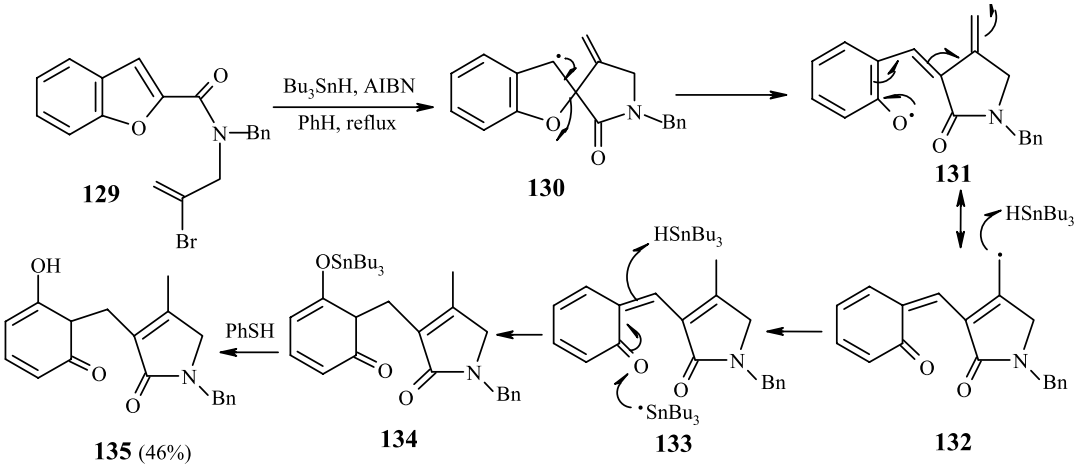
Baldwin et al. utilised[101] the benzofuran derivative **129**, which underwent spirocyclisation, followed by a reductive fragmentation, to give **135**. The mechanistic aspect of the above reaction sequence is outlined as follows. The spirocyclic radical **130** obtained from **129** underwent fragmentation with the formation of a more stable phenoxy radical **131**. Reduction of the quinone resonance form **132** by tributyltin hydride resulted in the oxystannane **134** (via **133**), which was hydrolysed to the phenol **135** after work up (Scheme 35).

3.5. Cascade/tandem cyclisation

Curran et al. found[124] that phenylcarbamic acid pent-3-ynyl esters in the presence of AIBN (1 equiv) and tris(trimethylsilyl)silane (TTMSH) (4 equiv) in benzene under standard conditions involving UV irradiation generated the furoquinolines. They also examined the standard radical cyclisation of various thioamides and thioureas to furnish 2,3-dihydro-1*H*-cyclopenta[*b*]quinoline and indoloquinoline derivatives, respectively.

The planned cascade [4+1] radical annulation involving *o*,*o*′-dialkyl-substituted aryl isonitriles and *N*-propargyl-6-iodopyridones furnished a mixture of the 7,9- and 7,12-isomers of 11*H*-indolizino[1,2-*b*]quinolin-9-ones, with significant regioselectivity in favour of the more-crowded product.[125] This was illustrated with a regioselective synthesis of (20*S*)-7-trimethylsilyl-9-isopropyl camptothecin.

Cascade radical reactions via α-(arylsulphanyl)imidoyl radicals were successfully used[126] for the competitive



Scheme 35.

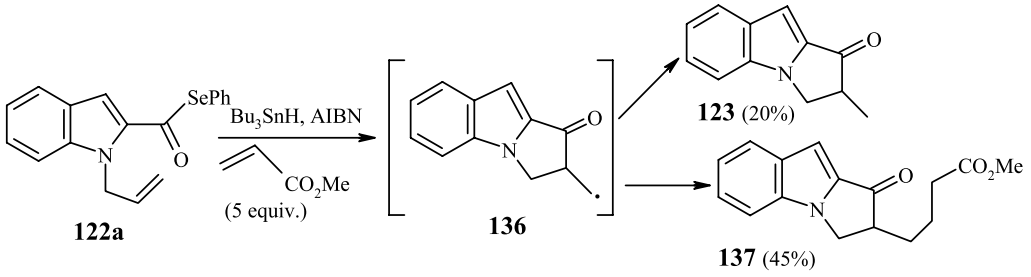
[4+2] and [4+1] radical annulations of alkynyl isothiocyanates with aryl radicals, leading to a new class of compounds, the thiochromeno[2,3-*b*]indoles.

Tandem cyclisation of *N*-propargylaminyl radicals produced by *N*-chlorination of (*E*)-alk-4-enylamines, followed by treatment with tributyltin radicals, using *n*-Bu_3SnH and a catalytic amount of AIBN, afforded 2-methylenepyrrolizidines[127] and the reaction is highly stereoselective.

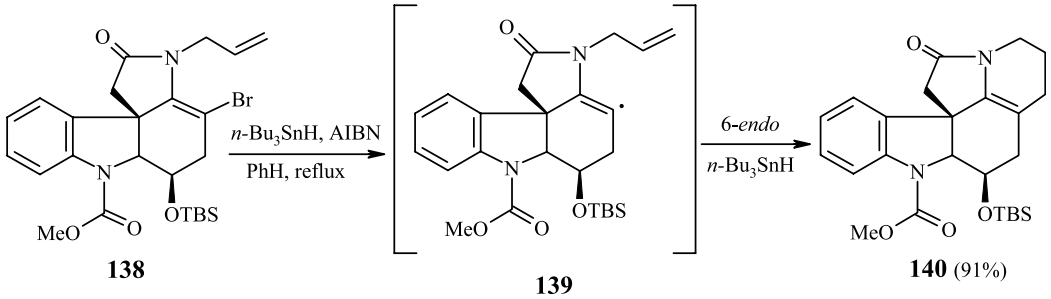
The synthesis of the spiropyrrolidinyloxindoles, horsfiline and coerulescine, has been described,[128] in which the key step is the tandem radical cyclisation of iodoaryl alkenyl azides. The radical cyclisation of 2-(2-azidoethyl)-*N*-benzyl-*N*-(2-iodo-4-methoxyphenyl)acrylamide by using $(TMS)_3SiH$ and AIBN in refluxing benzene furnished 1-benzyl-5-methoxy-1*H*-spiro[indole-3,3′-pyrrolidin]-2-one. This was subjected to in situ methylation to produce 1-benzyl-5-methoxy-1′-methyl-1*H*-spiro[indole-3,3′-pyrrolidin]-2-one in 60% yield.

Thermolysis of the enyne–carbodiimides having the central C–C double bond incorporated as part of the cyclopentene ring favours the formation of the corresponding *N*,4-didehydro-2-(phenylamino)pyridine intermediates, either as the σ–π biradicals or as the zwitterions.[129] Many intramolecular decay routes were obtained for the initially formed σ–π biradicals or zwitterions, leading to 5,6-dihydrobenzo[*c*][1,8]naphthyridine, 1,2,3,4-tetrahydro-[1,8]naphthyridine, 5,6-dihydrobenz[*f*]isoquinoline and the benzofuro[3,2-*c*]pyridine.

Recently, Bennasar et al. observed[123] the feasibility of promoting a cascade reaction from the selenoester **122a**, involving a cyclisation process followed by an intermolecular addition of the intermediate cyclopentylmethyl



Scheme 36.



Scheme 37.

radical **136** to an external electron-deficient alkene.[5a,130] In this case, compound **122a** was treated with *n*-Bu_3SnH and AIBN in the presence of 5 equiv of methyl acrylate to furnish the 2-substituted pyrrolo[1,2-*a*]indole **137** (45%), via a cyclopentylmethyl radical **136**. Direct reduction of the radical **136** also gave a very small amount (20%) of **123** (Scheme 36).

Exposure of 7-acetyl-3-allyl-4-bromo-6-(*tert*-dimethyl-silanyloxy)-5,6,6*a*,7-tetrahydro-3*H*-pyrrolo[2,3-*d*]carbazol-2-one **138** in the presence of *n*-Bu_3SnH and AIBN in refluxing benzene under slow addition conditions afforded 6-acetyl-5-(*tert*-dimethyl-silanyloxy)-2,3,4,5,5a,6-hexa-hydro-1*H*-6,12a-diaza-indeno[7,1-*cd*]fluoren-12-one[131] **140** (91%), via an initially generated cyclohexenyl radical **139**, either by a direct 6-*endo-trig* cyclisation or, alternatively, by a vinyl radical rearrangement pathway[132] (Scheme 37).

3.6. Diastereoselective radical cyclisation

TBTH and AIBN slowly added to a solution of the substrates **141a–f** in refluxing benzene gave excellent yields of the diastereomeric piperidines **142a–f** and **143a–f**, while the same products were obtained with diastereomeric ratios up to 99:1 by using tris(trimethylsilyl)silane (TTMSH) instead of TBTH[133] (Scheme 38).

The formation of the trans-piperidines **142a–f** as the major diastereomers may be explained by the preference of the 2-substituent to adopt an axial position in the chair-like transition state **A**, thus, avoiding the pseudo $A^{1,3}$ strain with the sulfonamide,[134] the radical finally cyclising onto an equatorial olefin **B** (Fig. 1).

3.7. Synthesis of nitrogen heterocycles with non-conventional reagents

The radical cyclisation[135] of halo-amides has been designed to obtain the functionalised pyrrolidinones via 5-*endo-trig* and 5-*exo-trig* radical cyclisation routes. The trichloro-

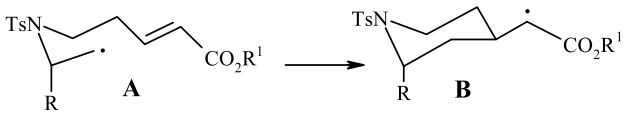


Figure 1. Proposed pathway to major isomers **142a–f**.

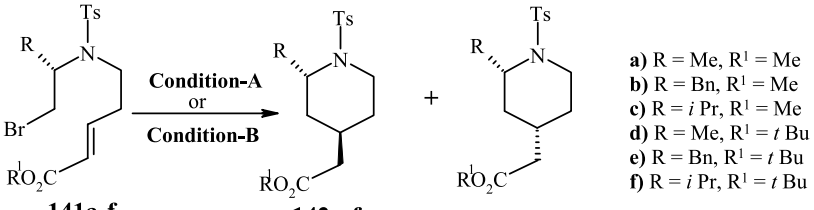
enamide was heated with copper(I) chloride/bipyridine to obtain the desired trichlorinated spirocycle, following 5-*endo-trig* cyclisation, and the resulting spirocycle was then allowed to react with tributyltin hydride (3.3 equiv) to remove all three chlorine atoms. Parsons et al. succeeded in obtaining the unsaturated pyrrolidinone, pulchellalactam, by using 5-*endo* cyclisation.[135]

Ishibashi et al. decided[136] to react *N*-[2-(3,4-dimethoxy-phenyl)ethyl]-α-(methylthio)acetamide with $Mn(OAc)_3$ in the presence of $Cu(OAc)_2$ and obtained the tetrahydroindol-2-one, which was then cyclised with $Mn(OAc)_3$ to give 4-acetoxyerythrinane.

Microwave-assisted free radical cyclisation[137] of alkenyl and alkynyl isocyanides with thiols gave the five-membered nitrogen heterocycles. In a typical reaction, a thiyl radical ($RS^{\cdot}$) was found to add to an alkenyl isocyanide, generating a thioimidoyl radical, which underwent 5-*exo* cyclisation and subsequent hydrogen-atom abstraction to produce the cis- and trans-pyrrolines.[137]

Suitably substituted heteroaromatic compounds such as indole and pyrrole derivatives were found to serve as excellent acceptor units for intramolecular couplings of samarium ketyls, and produced highly functionalised indole derivatives with very good diastereoselectivities. The intermediate samarium enolates were trapped by electro-philes, permitting efficient tandem reactions.[138]

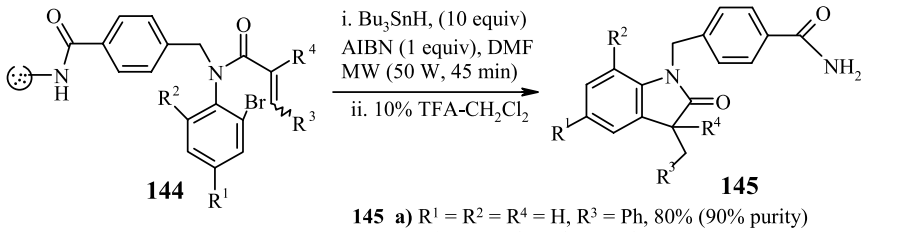
The formation of various indolines was exemplified by the reaction of different unsymmetrically substituted anilines with the Tordo-type alkoxyamines.[139]



Condition-A: Bu_3SnH, AIBN, PhH, 80 °C
Condition-B: TTMSH, AIBN, PhMe, 90 °C

Bromide	Condition-A 142:143	Yield (%)	Condition-B 142:143	Yield (%)
141 a)	70:30	98	72:28	97
b)	80:20	89	77:23	86
c)	86:14	95	92:8	76
d)	75:25	99	96:4	63
e)	83:17	85	97:3	73
f)	86:14	84	99:1	75

Scheme 38.



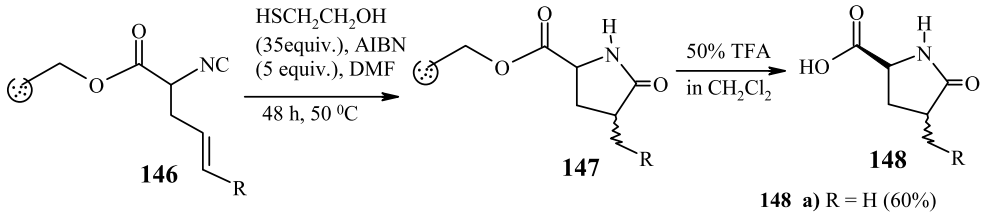
145 **a)** $R^1 = R^2 = R^4 = H$, $R^3 = Ph$, 80% (90% purity)
b) $R^1 = Me$, $R^2 = R^4 = H$, $R^3 = Ph$, 93% (100% purity)
c) $R^1 = F$, $R^2 = R^4 = H$, $R^3 = Ph$, 91% (86% purity)
d) $R^1 = R^2 = Me$, $R^3 = Ph$, $R^4 = H$, 100% (78% purity)
e) $R^1 = OCF_3$, $R^2 = R^4 = H$, $R^3 = Ph$, 55% (78% purity)
f) $R^1 = R^2 = R^4 = H$, $R^3 = 3\text{-}MeOC_6H_4$, 90% (100% purity)

Scheme 39.

Solid-phase synthesis of various indol-2-ones **145a–f** by means of aryl radical cyclisation of resin-bound *N*-(2-bromophenyl)acrylamides **144a–f** using Bu_3SnH in DMF was demonstrated very recently.[140] The reaction proceeded smoothly under microwave irradiation to give the desired indol-2-ones within a very short reaction time, in comparison to conventional thermal heating (Scheme 39).

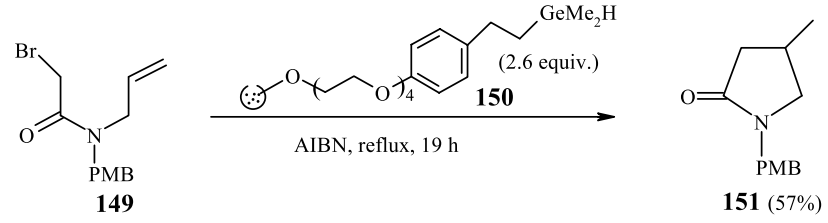
Polymer-supported isocyanides **146a**,**b** were reacted[141] with 2-mercaptoethanol and AIBN in DMF at 50 °C to obtain the cyclised products **147a**,**b**, which were cleaved from the solid support using TFA in CH_2Cl_2, to produce the pyroglutamic acid derivatives **148a**,**b** (Scheme 40).

New solid-phase triorganogermanium hydrides have been synthesised[142] by the addition of a simple triorganogermanium hydride unit into Quadragel™ and Merrifield resins. These solid-phase germanium hydrides have been used to

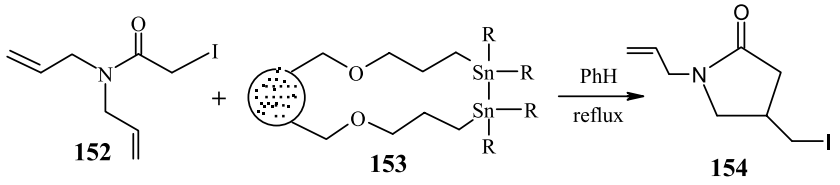


148 **a)** R = H (60%)
b) R = Me (41%)

Scheme 40.



Scheme 41.



153 **a)** R = *n* Bu
b) R = Me

Ditin reagent (0.1 equiv)	Time (h)	yield of **154** (%)
153a	4	98 (90)[a]
153b	1	99 (93)[a]

[a] Isolated yields are in parenthesis.

Scheme 42.

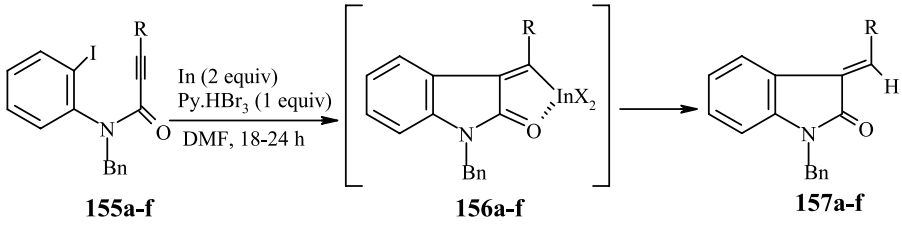
explore a range of synthetic radical reactions. The radical cyclisation of the α-bromoamide **149** was best carried out by using 2.6 equiv of Quadragel™-germanium hydride **150** to produce compound **151** via a 5-*exo* route. In general, the Quadragel™-germanium hydride furnished better results than the Merrifield-germanium hydride (Scheme 41).

Cyclisation of the diallyl amide **152** has been employed[143] with 10 mol% of the ditin reagents **153a** or **153b** and very high yields of the cyclised product **154** were obtained, with no reduced byproducts being detected. The reaction took 1 h to complete when the methyl-substituted ditin resin **153b** was used, but the same reaction was somewhat slower using the sterically more encumbered butyl-substituted ditin resin **153a** (Scheme 42).

3-Alkylidenehexahydrofuro[2,3-*b*]pyrans [a mixture of (*E*)- and (*Z*)-isomers] were prepared[38,144] in good yields with moderate stereoselectivity by using a reductive cyclisation procedure with indium and iodine. Takemoto and co-workers have synthesised[145] various (*E*)-3-alkylideneoxindoles **157a–f** from the substrates **155a–f** via the vinylindium intermediates **156a–f** in the presence of In and $Py\cdot HBr_3$ in DMF. The In-mediated cyclisations of **155a–d** furnished the desired products **157a–d** as single *E*-isomers in good yields. Treatment of **155e** and **155f**, containing an electron-donating group on the aromatic ring in the R group, with In and $Py\cdot HBr_3$, however, afforded the corresponding (*E*)-isomers **157e**,**f**, along with very small amounts of the (*Z*)-isomers. The ratio of *Z*/*E* was dependent on the substituents on the aromatic ring in the R group (Scheme 43).

The two isomers (*Z*/*E*, with the (*Z*)-isomers preferred) of 4-iodo-3-octenoamide **158a**, without separation, were allowed to react[146] with *t*BuOCl and I_2 in CH_2Cl_2 in the dark at rt. The reaction took 10 h and the cyclic iminoketone **159a** was isolated in 72% yield. The other *N*-unsubstituted substrates **158b–d** afforded the cyclic iminoketones **159b–d** in the same fashion in good yield. The reactions of the *N*-phenyl-substrates **158e**,**f**, however, led to the formation of the dienes **159e**,**f** with excellent stereoselectivity (Scheme 44).

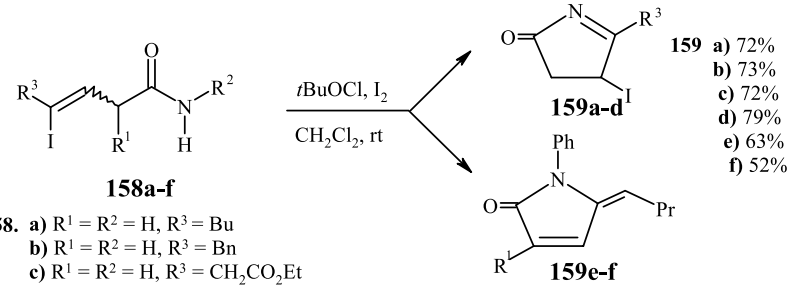
A plausible mechanism for the conversion of **158a–f** in to **159a–f** may be depicted as follows. The iodine atom in **158** plays a vital role in the cyclisation reactions by providing the driving force for the 5-*endo* cyclisation via β-elimination of the iodine radical (**161**→**162**). The products **158** obtained under atom transfer radical addition (ATRA) reaction, on treatment with *t*BuOI generated the corresponding amidyl radicals **160**, which might add to the C=C bond in a 5-*endo* manner to produce the cyclised radicals **161**. The radicals **161** then underwent β-elimination to give the lactams **162**. In presence of an excess amount of I_2 or ICl (formed by the reaction of *t*BuOCl and I_2),[147] the lactams **162** underwent iodination to give **163**. The intermediates **163** then rearranged to produce **164**. When R^2=H, the corresponding iminoketones **159a–d** were formed as the products, but, when R^2 is an aryl group, dehydroiodination



155a-f **156a-f** **157a-f**

	Product and yield	Reaction time
157	**a)** R = Et, 75% (E)	24 h
	b) R = CH_2OBn, 70% (E)	24 h
	c) *p*-CF_3-Ph, 75% (E)	18 h
	d) Ph, 80% (E)	24 h
	e) *p*-Me-Ph, 84% (E:Z = 19:1)	18 h
	f) *p*-MeO-Ph, 80% (E:Z = 10:1)	18 h

Scheme 43.



158a-f

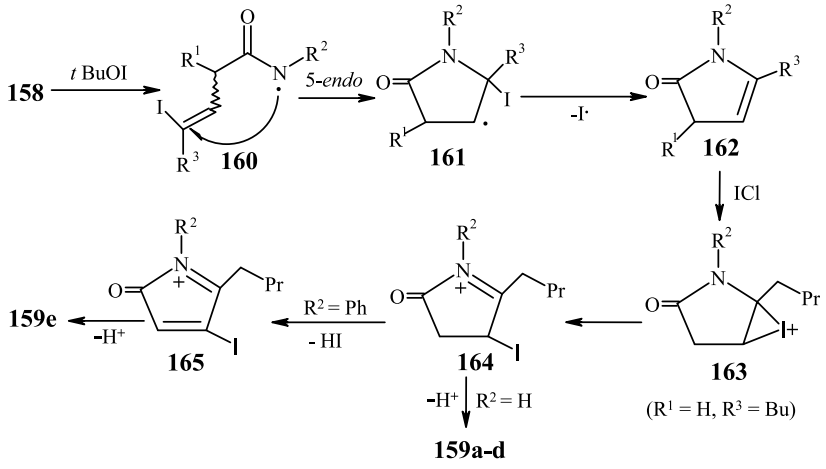
158. **a)** $R^1=R^2=H$, $R^3=Bu$
b) $R^1=R^2=H$, $R^3=Bn$
c) $R^1=R^2=H$, $R^3=CH_2CO_2Et$
d) $R^1=Me$, $R^2=H$, $R^3=Bu$
e) $R^1=H$, $R^2=Ph$, $R^3=Bu$
f) $R^1=Me$, $R^2=Ph$, $R^3=Bu$

159a-d

159 **a)** 72%
b) 73%
c) 72%
d) 79%
e) 63%
f) 52%

159e-f

Scheme 44.



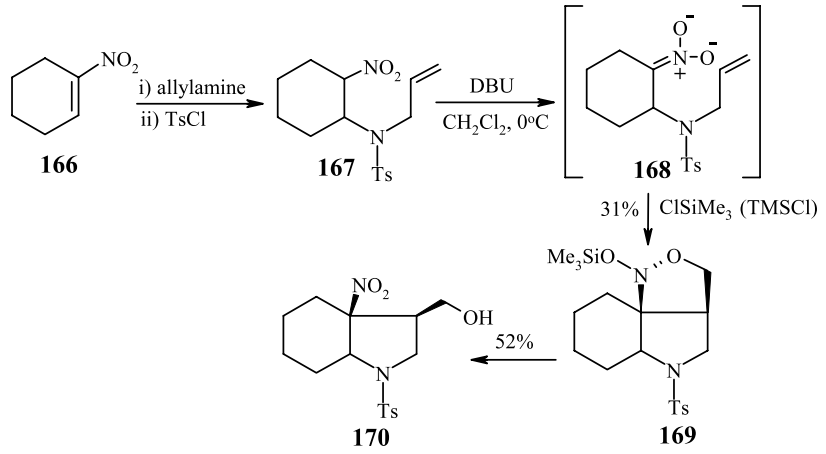
Scheme 45.

took place, to give the intermediates **165**, which generated the unsaturated lactams **159e**,**f** via the loss of a proton (Scheme 45).

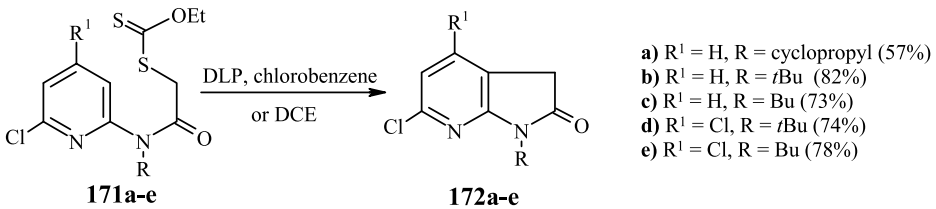
aci-Nitro anions were found to be very useful and versatile intermediates and have many important synthetic applications.[148] CAN-promoted one-electron oxidation of unsaturated *aci*-nitronates was reported earlier.[149] Silylation of nitronate **168**, obtained by an aza Michael addition of tosylallylamine **167** to nitroalkene **166**, furnished *N*-(silyloxy)-isoxazolidine **169** in 31% yield, which was then diastereoselectively transformed into 3-nitro-4-hydroxymethylpyrrolidine **170** after desilylation[150] (52% yield) (Scheme 46).

Compounds bearing a pyridine nucleus fused to a saturated nitrogen-containing ring, including 7-azaoxindoles, 7-azaindolines, tetrahydro[1,8]naphthyridines and tetrahydro-5*H*-pyrido[2,3-*b*]azepin-8-ones, were synthesised[151] in good yields starting from various 2,6-dichloropyridines. The addition of lauroyl peroxide to a refluxing solution of xanthates **171a–e** in DCE or chlorobenzene furnished the 7-azaoxindoles **172a–e** in good yields (Scheme 47).

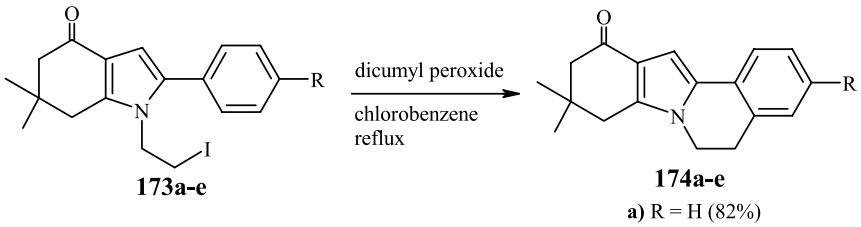
During the last few years, the addition of radicals to aromatic nuclei, followed by oxidation to restore the aromatic system, has received considerable attention and is of preparative value.[110,152–156] Dicumyl peroxide-annulated radical cyclisations of alkyl iodides to various aromatic systems including pyrrole, indole, isoquinolone, pyridone and benzene have very recently been



Scheme 46.



Scheme 47.



173a-e **174a-e**

a) R = H (82%)
b) R = F (91%)
c) R = Cl (85%)
d) R = Br (53%)
e) R = NO_2 (75%)

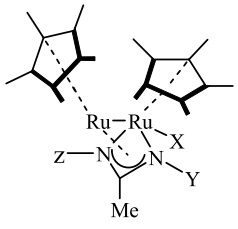
Scheme 48.

exemplified.[157] It is very important to note that such cyclisations have been reported to fail under Bu_3SnH/AIBN-annulated reaction conditions.[158]

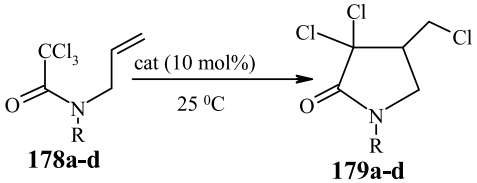
To a degassed solution of 1-(2-iodoethyl)tetrahydroindolones **173a–e** in refluxing chlorobenzene was added dicumyl peroxide (1.5 equiv) portionwise, and the cyclised products **174a–e** were obtained in good yields (Scheme 48).

The most important transition-metal complex catalyst system is a 1:1 mixture of CuCl and bipyridine for cyclisation of *N*-protected-*N*-allyltrichloroacetamides into the corresponding α,α,γ-trichlorinated γ-lactams.[159–161] Mono-nuclear ruthenium amidinates, (η^5-C_5Me_5)Ru(amidinate) **175** and (η^5-C_5Me_5)Ru(amidinate)Cl **176**, were reported to be novel catalysts for the cyclisation of *N*-allyltrichloroacetamides[160] and were found to have comparable reactivity to the CuCl/bipyridine system. A cationic diruthenium amidinate, (η^5-C_5Me_5)Ru(μ_2-*i*-PrN=C(Me)Ni–Pr)Ru(η^5-C_5Me_5)]$^+$, is generated by treatment of (η^5-C_5Me_5)Ru(μ_2-*i*-PrN=C(Me)Ni–Pr)Ru(Cl)(η^5-C_5Me_5) **177** with $NaPF_6$ or other metal salts of weakly coordinating anions, and this complex is active towards catalytic ATRC of *N*-allyltrichloroacetamides **178a–d** to produce **179a–d**[162] (Scheme 49).

Halogen-substituted tin hydride systems such as Bu_2SnIH and Bu_2SnClH-HMPA were found to promote the effective



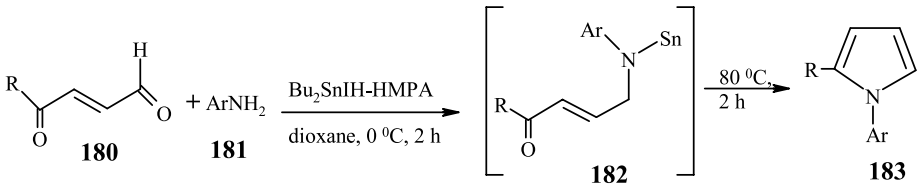
175 X = Y = Z = H
176 X = Cl, Y = Z = H
177 X = Cl, Y = Z = *i*-Pr



178a-d **179a-d**

Entry	Substrate	Catalyst	Solvent	Time (h)	Yield (%)
1	**178a** (R = Bn)	**177**	CH_2Cl_2	4	30
2	**178a**	**177** + $NaPF_6$	CH_2Cl_2	0.5	>99
3	**178a**	**177** + $NaBPh_4$	CH_2Cl_2	0.5	>99
4	**178a**	**175**	PhMe	4	85
5	**178a**	**176**	PhMe	4	88
6	**178b** (R = Ts)	**177**	CH_2Cl_2	4	97
7	**178b**	**177** + $NaPF_6$	CH_2Cl_2	0.5	>99
8	**178b**	**177** + $NaBPh_4$	CH_2Cl_2	0.5	>99
9	**178b**	**175**	PhH	4	31
10	**178b**	**176**	PhH	4	0
11	**178c** (R = Ph)	**177** + $NaPF_6$	CH_2Cl_2	1	52
12	**178d** (R = allyl)	**177** + $NaPF_6$	CH_2Cl_2	1	>99

Scheme 49.



183 **a)** R = *n*-C_8H_{17}, Ar = *p*-ClC_6H_4 (81%)
b) R = *n*-C_8H_{17}, Ar = Ph (54%)
c) R = *n*-C_8H_{17}, Ar = *p*-Tol (60%)
d) R = *n*-C_8H_{17}, Ar = *p*-$MeOC_6H_4$ (66%)

Scheme 50.

reduction of imines[163] and, especially, Bu_2SnClH–HMPA afforded effective reductive amination to give a wide range of secondary and tertiary amines in one-pot procedures.[164] Although pyrroles are found in naturally occurring and biologically active molecules,[165] very few methods have been developed for the construction of a 2-monosubstituted pyrrole ring.[166]

Enals having aromatic ketones **180** were allowed to react[167] with various aromatic amines **181** in one-pot procedures by the reductive amination of **180** using the Bu_2SnIH-HMPA system followed by heating at 80 °C; the result was the formation of various 2-monosubstituted pyrroles **183a–d** (through **182a–d**) in good yield (Scheme 50).

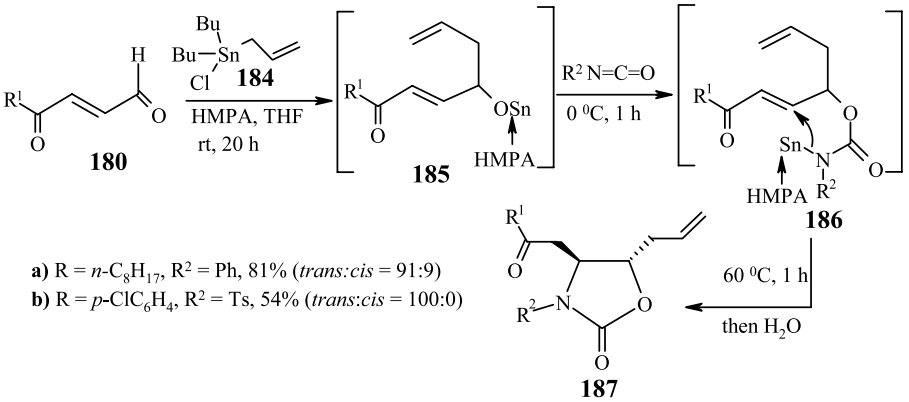
It has been found that the allylic chlorodi-*n*-butyltin **184** system effectively reacted with the formyl group of substrates **180** without any strong Lewis acid. The allylation was highly chemoselective to the formyl group where the enone moiety of **180** was unreactive. After the allylation, successive reaction with an isocyanate, followed by heating, afforded the 4,5-trans-disubstituted-2-oxazolidinones **187a** and **187b** selectively.[168] The chloro substituents on the tin centre were essential because allyltri-*n*-butyltin was not reactive. HMPA is useful to cause the cyclisation to give **187**, avoiding the linear adduct. The reaction sequence of **180** to **187** may be explained as follows. After the chemoselective allylation of the formyl group, the generated tin–oxygen bond of **185** reacted with an isocyanate spontaneously,[169] to form the adduct **186**. The resulting tin–nitrogen bond in **186** successively added to the enone moieties of **180** in a conjugate addition to give the 2-oxazolidinones **187** in a one-pot procedure (Scheme 51).

4. Synthesis of oxygen heterocycles

Tri-*n*-butyltin hydride-mediated radical cyclisation[170] of the *Z*-hydroxy vinyl bromide was achieved via a 5-*exo*-*trig* cyclisation of an alkoxy radical, possibly involving a rare [1,5]-hydrogen shift from the hydroxyl group to the vinyl radical, to generate an unusual furan in 55% yield as the major product.

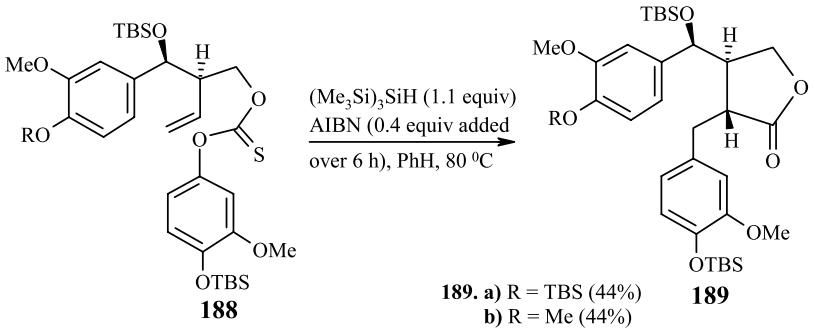
Bu_3SnH-mediated radical cyclisation reaction of a simple carbohydrate-derived imidazole thioate afforded[171] the thiolactone (cis:trans = 2.1:1.0) in 58% yield. When a dilute solution of the same substrate in benzene was added to an excess of Ph_3SnH at 80 °C (reverse addition), an imidazole glycoside was obtained in 88% yield. Diphenyl phosphate[172] was subjected to reflux with tributyltin hydride in a 3:1 mixture of benzene and allyl alcohol to synthesise a (1:10) trans:cis mixture of 2,2,4-trimethyl-3-phenyltetrahydrofuran.

Zhang et al. reported a novel double ipso substitution process for the synthesis of azabenzoisocoumarins.[81] The same group also reported[173] a straightforward two-step parallel synthesis for structurally diverse spiro compounds, where 2-bromobenzoic acids were used as the common building blocks to couple with a series of conjugated enols or enamines. Sequential intramolecular free-radical Michael



a) R = *n*-C_8H_{17}, R^2 = Ph, 81% (*trans*:*cis* = 91:9)
b) R = *p*-ClC_6H_4, R^2 = Ts, 54% (*trans*:*cis* = 100:0)

Scheme 51.



Scheme 52.

addition led to the formation of spirobenzolactones, spirobenzolactams, spirobenzolactone–lactams, spirobenzolactone–thiolactones, spirodilactones and bridged-spirolactones.

Recently, we have reported[103] the regioselective synthesis of 1*H*,3*H*,6*H*-[2]benzopyrano[4,3-*d*]pyrimidine-2,4-diones (75–85%) and 12*H*-benzopyrano[3,2-*c*][1]benzopyran-5-ones (70–85%), respectively, by radical cyclisation reactions. Earlier, we have synthesised[174] 2*H*-benzopyrano[3,2-*c*]quinolin-7(8*H*)-ones by a Bu_3SnH-mediated radical cyclisation of 4-(2′-bromobenzyloxy)quinolin-2(1*H*)-one derivatives. We have also reported[175] the synthesis of various spiroheterocycles by the tri-*n*-butyltin hydride-induced radical cyclisation of 5-(*o*-bromoaryloxymethylene)-6,7,8-trihydropyrido[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-diones. These heterocycles can additionally be obtained under acid-catalysed enol–ether cleavage conditions.

(*E*)-3-(1-Benzyl-2-phenylselenenyl-ethoxy)-acrylic acid ethyl ester underwent carbonylation or reductive cyclisation in the presence of TTMSH-AIBN and carbon monoxide (80 atm) to produce (5-benzyl-3-oxo-tetrahydrofuran-2-yl)-acetic acid ethyl ester in 86% yield as a 9:1 mixture of cis- and trans-isomers. Again, radical carbonylation or reductive cyclisation of various *N*-vinyl-β-amino-alkyl phenyl selenides were found to give 2,5-disubstituted pyrrolidin-3-ones, predominantly as the cis-isomers (cis: trans = 3:1–12:1).[176]

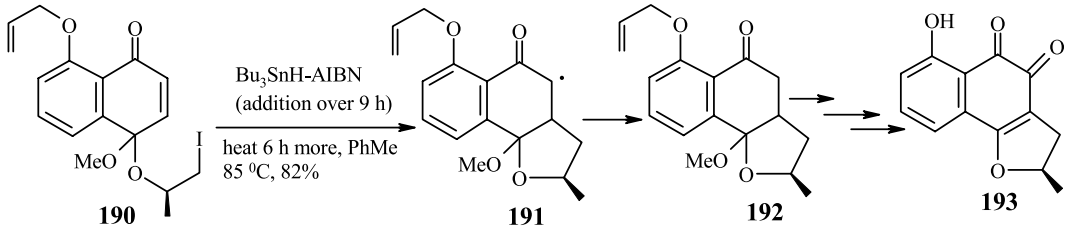
Enantiomerically pure 5-acetyl-3-amino-3,4-dihydro-2*H*-1-benzopyran and methyl-3-amino-3,4-dihydro-2*H*-1-benzopyran-5-carboxylate were synthesised starting from D- or L-serine, in which the key step was the formation of the benzopyran ring involving Bu_3SnH–AIBN-annulated radical cyclisation conditions.[177]

Sherburn and co-workers proposed[178] the total syntheses of 7(*S*)-hydroxymatairesinol and 7(*S*)-hydroxyarctigenin, in which the key step was the radical cyclisation of thionocarbonates **188** to produce the compounds **189** in very high (>95%) trans-diastereoselectivity with the $(Me_3Si)_3SiH$ reagent (Scheme 52).

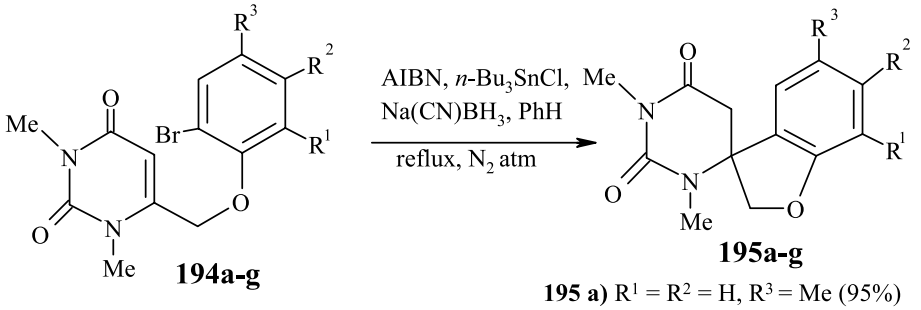
Recently, Clive et al. have synthesised[179] *ent*-nocardione A **193**, in which the key step was the Bu_3SnH-mediated radical cyclisation of 8-allyloxy-4[(1*R*)-2-iodo-1-methylethoxy]-4-methoxy-4*H*-naphthalen-1-one **190**. Radical cyclisation of **190** under standard conditions (slow addition of a dilute solution of stannane and initiator to a dilute solution of the substrate at 85 °C) furnished the desired product **192** in 82% yield; evidently, the intermediate radical **191** is quenched by the stannane, rather than undergoing closure through oxygen onto the double bond of the allyl group (Scheme 53).

Recently, we found that aryl radical cyclisation of a range of 6-(2′-bromophenoxymethyl)-1,3-dimethyluracils **194a–g** with tributyltin chloride and sodium cyanoborohydride in the presence of AIBN for 4 h furnished exclusively the 5-*exo* cyclisation products, 1,3-dimethylspiro[pyrimidine-6,3′-2′,3′-tetrahydrobenzofuran]-2,4-diones[180] **195a–g** in 92–95% yield (Scheme 54).

The regioselective formation of a five-membered heterocyclic ring can be explained by the application of the FMO theory. Aryl radicals are high-energy species and, hence, are nucleophilic in character. The presence of a highly electron-withdrawing carbonyl group confers considerable electrophilic character to the C-6 position of the uracil moiety. Thus, in the case of the nucleophilic radicals **196**, FMO theory suggests that the mode of ring closure is largely determined by the interaction between the radical SOMO (≡HOMO) and the alkene LUMO of the acceptor (electron-deficient centre) and, accordingly, more favourable bond formation occurs between the radical centre (nucleophilic)



Scheme 53.



195 a) $R^1 = R^2 = H$, $R^3 = Me$ (95%)
b) $R^1 = R^3 = H$, $R^2 = Me$ (92%)
c) $R^1 = Me$, $R^2 = R^3 = H$ (92%)
d) $R^1 = R^2 = H$, $R^3 = OMe$ (94%)
e) $R^1 = R^3 = Me$, $R^2 = H$ (92%)
f) $R^1 = R^2 = R^3 = H$ (94%)
g) R^1, R^2 = -5,6-phenylene, $R^3 = H$ (95%)

Scheme 54.

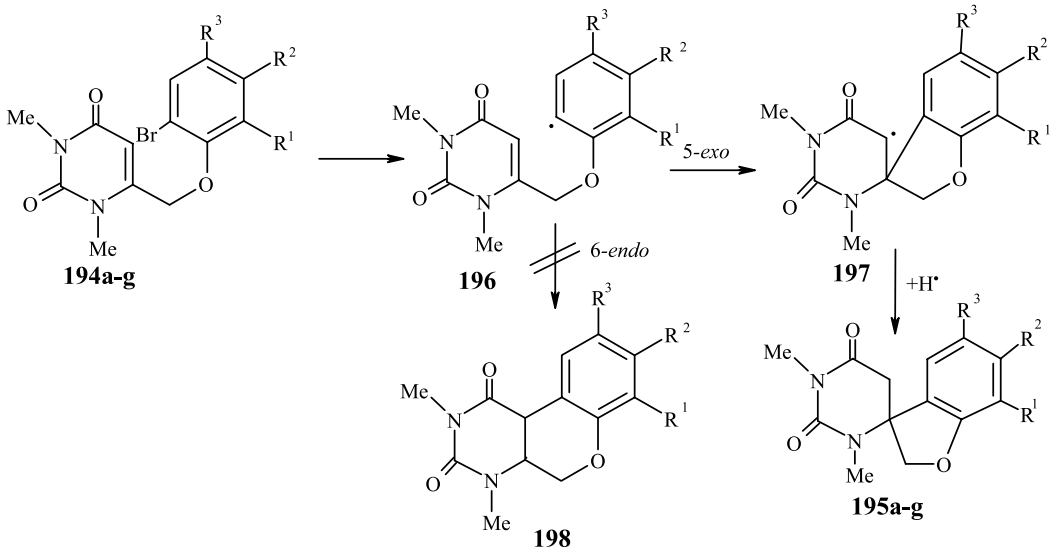
and C_6 of the uracil ring for the 5-*exo* products **195a–g** via **197** (Scheme 55).

Majumdar and co-workers recently synthesised[181] spiro-[chroman-3,3′ (2′*H*)-benzofurans] **200a–f** in 60–75% yields from a number of 3-(2-bromophenoxymethyl)coumarins **199a–f** with tributyltin chloride and sodium cyanoborohydride in refluxing benzene for 7–10 h under nitrogen, in the presence of a catalytic amount of AIBN. The aryl radical **196** did not afford compound **198** in an alternative 6-*endo-trig* mode (Scheme 56).

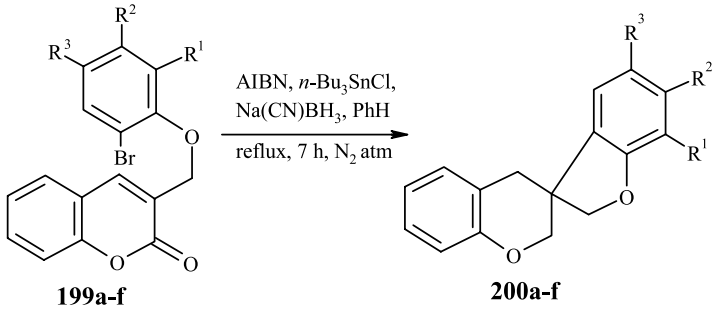
The formation of the spiro furan ring in compounds **200a–f** from **199a–f** can be explained by 5-*exo-trig* radical cyclisation of the initially generated aryl radical onto the double bond of the coumarin moiety. Although both 5-*exo* and 6-*endo* cyclisations are possible, in spite of our best efforts, by varying the reaction conditions, we could not generate the 6-*endo-trig* cyclised product or the corresponding lactone of compound **200**. The reason for the exclusive formation of the 5-*exo* cyclisation product is not clear. The stability of the intermediate benzylic radical may facilitate the formation of the spiro benzofuran ring.

Deoxygenation of a carbonyl group, giving the corresponding saturated hydrocarbon, is a frequently encountered process in organic syntheses.[182,183] The conversion of a lactone carbonyl into a cyclic ether by employing certain Lewis acid hydride complexes is well established in the literature.[184] In such reactions, the in situ-generated diborane in the presence of the Lewis acid presumably facilitates the deoxygenation reaction through the formation of an oxonium ion intermediate.[185] Although $Na(CN)BH_3$ in the presence of a Lewis acid can deoxygenate carbonyl groups,[182] the reaction fails with lactones.

Compound **199a** on treatment with Bu_3SnH in the presence of a catalytic amount of AIBN in refluxing benzene under nitrogen furnished only the debrominated product. No deoxygenated compound **200a** or the corresponding lactone was obtained. This excludes the possibility of a radical pathway for the deoxygenation with simultaneous



Scheme 55.



199a-f

200a-f

200. a) $R^1 = R^2 = H$, $R^3 = Me$ (72%)
b) $R^1 = R^2 = R^3 = H$ (75%)
c) $R^1 = R^3 = H$, $R^2 = Me$ (65%)
d) $R^1 = R^2 = H$, $R^3 = OMe$ (68%)
e) $R^1 = Me$, $R^2 = R^3 = H$ (64%)
f) $R^1 = R^3 = Me$ $R^2 = H$ (60%)

Scheme 56.

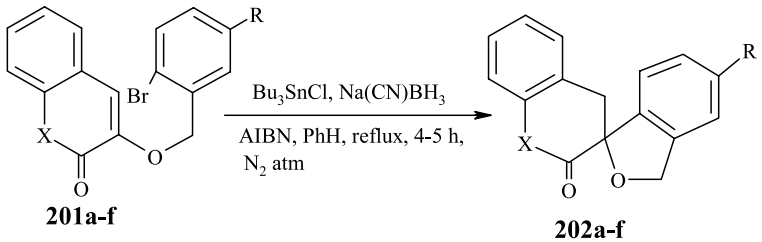
cyclisation and signifies that $Na(CN)BH_3$ plays an important role in the deoxygenation reaction. The compounds **199a–f** were treated with Bu_3SnCl and $Na(CN)BH_3$ in the absence of AIBN in refluxing benzene under nitrogen, but, no reaction was observed. Coumarin and 3-phenoxymethylcoumarin were also treated with Bu_3SnCl and $Na(CN)BH_3$ in the presence of, and in the absence of, AIBN in refluxing benzene, but, here, too, no deoxygenation of the lactone carbonyl was observed. These observations clearly indicate that the deoxygenation process does not proceed via the oxonium ion intermediate pathway. In addition tri-*n*-butyltin chloride and $Na(CN)BH_3$ could not have effected deoxygenation without the involvement of a radical intermediate.

Recently, we have extended our efforts towards the radical cyclisation[186] of 3-(2′-bromobenzyloxy)quinolin-2-ones **201a–d** and 3-(2′-bromobenzyloxy)benzopyran-7-ones **201e,f** in the presence of *n*-Bu_3SnCl–$Na(CN)BH_3$–AIBN and obtained the spiro-quinolone and coumarin derivatives **202a–f** in 80–85% yield (Scheme 57).

The regioselectively exclusive formation of a spiroheterocyclic ring in the products **202a–f** from the starting material **201a–f** may be explained by the generation of aryl radicals **203**. Subsequent 5-*exo* cyclisation may give the spiroheterocyclic radicals **204**, which then readily abstract the hydrogen atom from the in situ formed *n*-Bu_3SnH to produce the spiroheterocycles **202a–f**. At this point in time, the exclusive formation of five-membered heterocyclic compounds **202a–f** from the substrates **201a–f** suggests that the benzylic radicals **204a–f**, generated by 5-*exo-trig* ring closure of radicals **203**, might be more stable than the radical **205**, generated from 6-*endo-trig* ring closure. Inspection of the molecular models indicates that the radical intermediates **204** should be much more stabilised, due to excellent overlapping of the p-orbital of the radical centre with the neighbouring aromatic π-system (Scheme 58).

4.1. Diastereoselective radical cyclisation

N-(1-Phenyl-6-methyl-5-hepten-1-oxy)thiazolethiones **206** were allowed to react[187] with $BrCCl_3$ in the presence of AIBN in refluxing benzene at 80 °C to generate 2-(1-bromo-1-methylethyl)-6-phenyltetrahydropyran **207** (34%, cis:-trans=65:35) and 2-phenyl-5-(dimethylvinyl)tetrahydrofuran **208** (46%, cis:trans=50:50). The relative configurations of the 2,6-disubstituted tetrahydropyrans, cis-**207** and trans-**207**, were obtained from the 6-*exo-trig* cyclisation of 5-hexen-1-oxyl radical **209** (trichloromethylsulfanyl-substituted thiazoles **212** were also obtained and were determined by NMR spectroscopy) and subsequent bromine-atom trapping of the intermediate **210**, via an energetically favoured transition state. In the synthesis of the 2,5-disubstituted tetrahydrofuran **208**, a δ-H atom

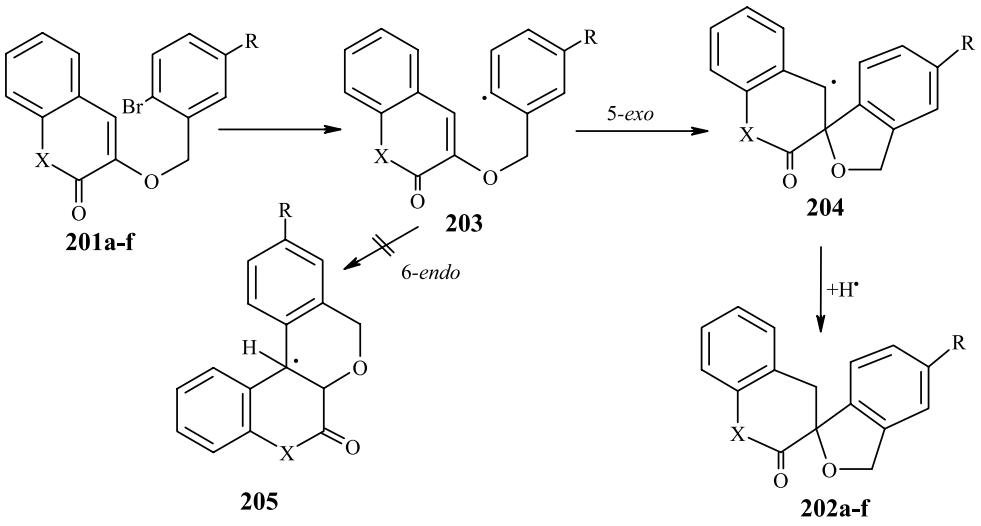


201a-f

202a-f

202 a) X = NEt, R = H (80%)
b) X = NEt, R = OMe (82%)
c) X = NMe, R = H (84%)
d) X = NMe, R = OMe (80%)
e) X = -O-, R = H (85%)
f) X = -O-, R = OMe (84%)

Scheme 57.

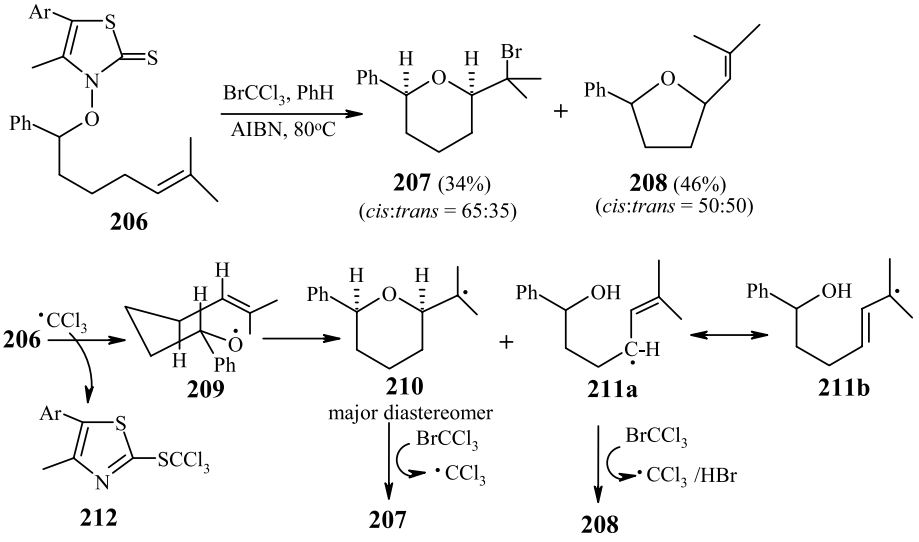


Scheme 58.

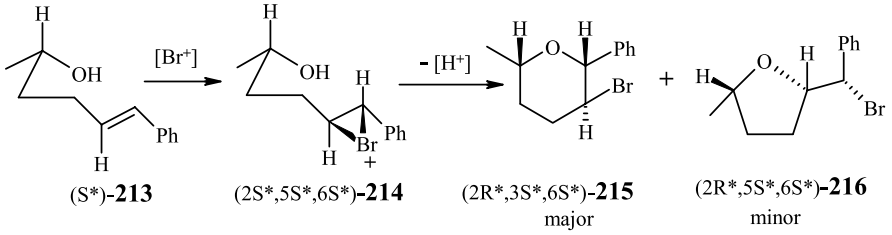
transfer takes place in the initial step (**209**→**211**) and this is followed by bromine-atom trapping of the intermediate **211**-starting either from the resonance formula **211a** or from **211b** and subsequent HBr elimination (Scheme 59).

Recently, Hartung et al. treated[188] (*E*)-6-phenyl-5-hexen-2-ol **213** with TBHP, Py·HBr and VOL(OEt) and obtained brominated tetrahydropyran **215** as the major product (58%, 2,6-cis:2,6-trans=86:14) and 2-(phenylbromomethyl)-5-methyl tetrahydrofuran **216** as a minor product (5%, cis:trans=42:58), via the diastereoselective generation of 2,5-like-2,6-like-configured bromiranium ion **214** as the major intermediate. Polar effects favour rearrangement of **214** into tetrahydropyran 2,3-trans-2,6-cis **215** via *O*,C-6 bond formation. 2,6-Unlike-configured tetrahydrofuran trans-**216** was originated from the disfavoured 5-*exo*-selective rearrangement of intermediate **214** (Scheme 60).

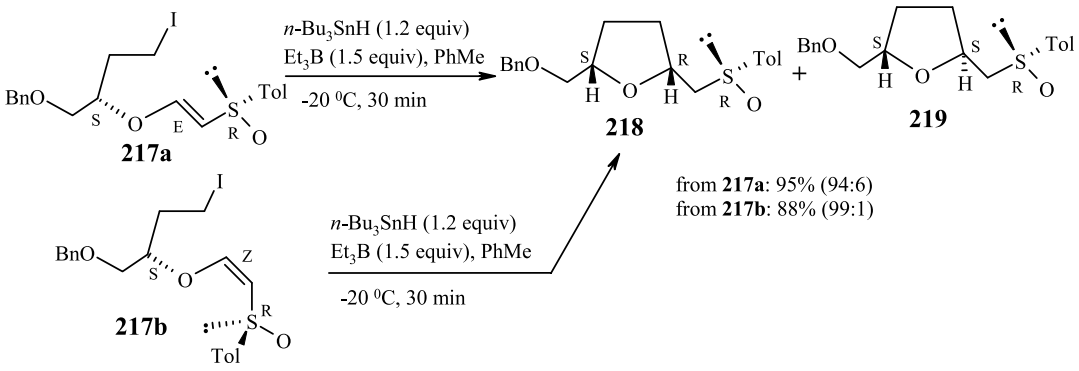
Reaction of (*E*)-vinyl sulfoxide **217a** with tributylstannane in the presence of triethylborane at −20 °C in toluene furnished a 94:6 mixture of the tetrahydrofuranyl products



Scheme 59.



Scheme 60.



Scheme 61.

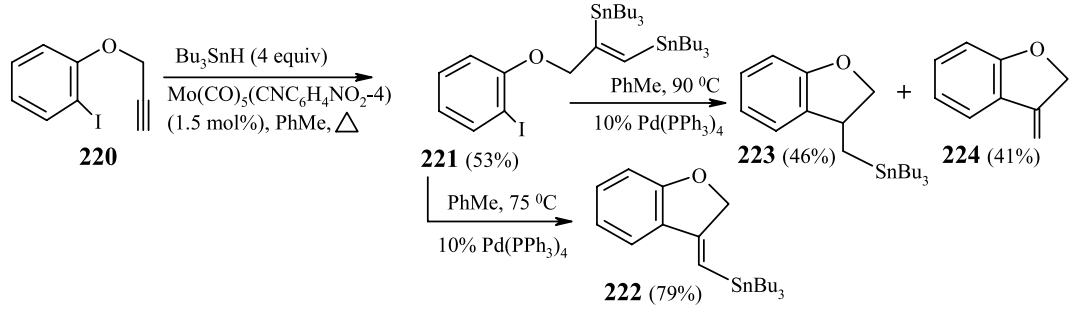
218 and **219**. The (*Z*)-vinyl sulfoxide **217b** under similar reaction conditions was converted almost exclusively into **218** (**218**:**219**=99:1)[189] (Scheme 61).

4.2. Synthesis of oxygen heterocycles with non-conventional reagents

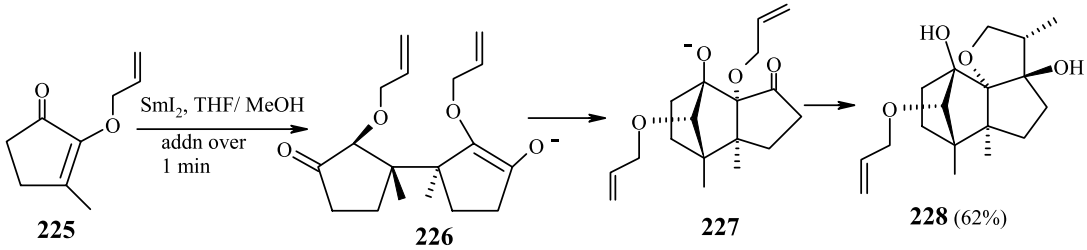
Molybdenum-catalysed stannylation reactions can be used for constructing heterocyclic ring systems[190] via subsequent intramolecular Stille couplings, because aromatic halides are not affected by the metalation step. Distannation of the phenyl ester **220** can lead to the distannylated product **221** (in addition to 7% of the hydrostannylated α-product) and subsequent Stille coupling at 70 °C afforded (*E*)-3-tributylstannylmethyliden-2*H*-benzo[*b*]furan **222** in good yield (79%). It is expected that the *exo*-double bond should show a high tendency to isomerise to the heteroaromatic ring system. The same reaction was also carried out at 90 °C and it was found that, in place of the expected product **222**, a mixture of the reduced product **223** and the photodestannylated product **224** was obtained (Scheme 62).

There has been a tremendous development of SmI_2-mediated reactions over the last 20 years.[191] It has been discovered that a mixture of SmI_2 in THF, water and an amine (e.g., Et_3N, TMEDA or PMDTA) resulted in unexpected rates in the reduction of ketones, imines, α, β-unsaturated esters and alkyl halides.[192] 1-Allyloxy-2-iodobenzene on treatment with SmI_2 and Et_3N, followed by water, gave an almost instantaneous reaction to produce the coupled product, 3-methyl-2,3-dihydrobenzofuran, in 99% yield. Again, the coupling of 1-iodo-2-(2-propynyloxy)benzene initially furnished the corresponding five-membered styrene derivative ring, which, within 5 min, was reduced to 3-methyl-2,3-dihydrobenzofuran in the presence of excess SmI_2–H_2O–amine.[193] Diastereoselective coupling of 1-(cyclohex-2-enyloxy)-2-iodobenzene analogues with SmI_2–H_2O–amine yielded hexahydrodibenzofuran derivatives in good to high yields.[193]

Kilburn et al. reported[194] samarium diiodide-annulated 6-*exo*-cyclisation of various methylenecyclopropyl ketones to synthesise cycloheptane derivatives, provided that the



Scheme 62.



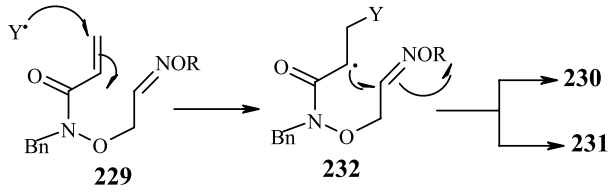
Scheme 63.

stereochemistry of the starting material favours suitable conformations for the cyclisation.

Recently, the same workers also treated[195] cyclic allyloxy enones **225** with a solution of 2.5 equiv of SmI_2 in the presence of a mixed THF/MeOH (4:1) solvent at −78 °C, and obtained a new compound **228** in 45% yield as a single diastereomer, via **226** and **227** (Scheme 63).

Sulphanyl radical addition–cyclisation of hydroxamates **229a** having an *O*-benzyloxime ether in the presence of thiophenol (1 equiv) and AIBN (0.5 equiv) proceeded smoothly at 80 °C to give a ca. 3:1 separable mixture of the amino-1,2-oxazinones **230a** and **231a** in good yield.[196] Similarly, the hydroxamate **229b** with an *O*-methyloxime ether was found to give cis-**230b** and trans-**231b** in 76% combined yield. The ethyl radical addition–cyclisation of **229a**,**b** was also described by using triethylborane as an ethyl radical source. The hydroxamate **229a**, on treatment with Et_3B (5 equiv) at rt, gave a 3.5:1 mixture of cis-**230c** and trans-**231c** in 71% combined yield. The ethyl radical addition–cyclisation of **229a** at −78 °C gave cis-**230c** with high stereoselectivity, whereas the hydroxamate **229b** furnished the cyclic hydroxamates cis-**230d** and trans-**231d** in 72% combined yield (Scheme 64).

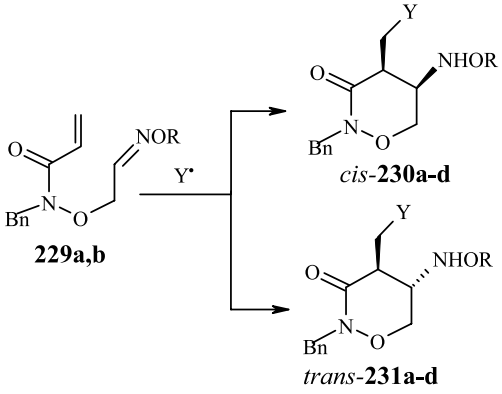
Addition of sulphanyl and alkyl radicals to the alkene and subsequent cyclisation onto the oxime ether in **229** took place regioselectively to produce the substituted 1,2-oxazinones with an alkoxyamino group in the intermediate **232**, which underwent cyclisation in a 6-*exo-trig* route to produce the cis-1,2-oxazinones **230a–d** and the trans-isomers **231a–d** (Scheme 65).



Scheme 65.

The high preference for the cis-isomer in the alkyl radical addition at −78 °C may be explained according to Beckwith's hypothesis.[197] The radical **X** leads to the formation of cis-**230** and is more stable than the radical **Y** (the intermediate of trans-**231**), due to the effects of orbital symmetry in **X** (Fig. 2).

Thiol-olefin co-oxygenation (TOCO) of substituted allylic alcohols **233** generates α-hydroxyperoxides that can be



	R	Y
230a, 231a	Bn	PhS
230b, 231b	Me	PhS
230c, 231c	Bn	Et
230d, 231d	Me	Et

Sulphanyl radical addition (Y = PhS):

Substrates	R	Conditions	Solvent	T (°C)	Yield (%)	*cis*-**230**:*trans*-**231**
229a	Bn	PhSH (1 equiv) + AIBN (0.5 equiv)	PhH	80	80	*cis*-**230a**:*trans*-**231a** = 71:29
229b	Me	PhSH (1 equiv) + AIBN (0.5 equiv)	PhH	80	76	*cis*-**230a**:*trans*-**231a** = 71:29

Ethyl radical addition (Y = Et):

Substrates	R	Conditions	Solvent	T (°C)	Yield (%)	*cis*-**230**:*trans*-**231**
229a	Bn	Et_3B (5 equiv)	PhMe	rt	71	*cis*-**230c**:*trans*-**231c** = 78:22
229a	Bn	Et_3B (5 equiv)	PhMe	0	84	*cis*-**230c**:*trans*-**231c** =80:20
229a	Bn	Et_3B (5 equiv)	PhMe	-78	79	*cis*-**230c**:*trans*-**231c** =91:9
229b	Me	Et_3B (5 equiv)	PhMe	rt	71	*cis*-**230d**:*trans*-**231d** = 68:32
229b	Me	Et_3B (5 equiv)	PhMe	0	81	*cis*-**230d**:*trans*-**231d**=79:21
229b	Me	Et_3B (5 equiv)	PhMe	-78	72	*cis*-**230d**:*trans*-**231d** =89:11

Scheme 64.

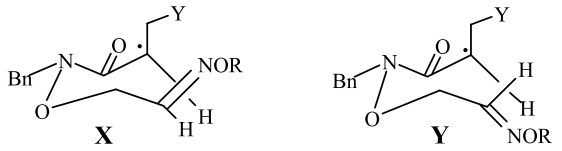


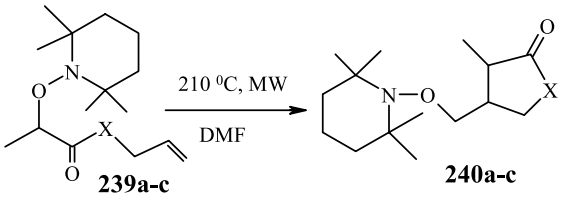
Figure 2.

condensed in situ with various ketones to afford a series of functionalised 1,2,4-trioxanes **238** in good yield[198] (Schemes 66 and 67 and Table 2).

A phenylthiyl radical, generated from thiophenol through initiation with AIBN/hν, attacks the double bond of the allyl alcohol **233** in a Markovnikov fashion to produce a tertiary carbon radical **234**. This radical then traps oxygen to form a peroxy radical **235**. Radical hydrogen abstraction from thiophenol affords the α-hydroxyperoxide **236** and regenerates a phenylthiyl radical to propagate the reaction. The α-hydroxyperoxide **236** subsequently undergoes a smooth condensation with cyclohexanone **237** in the presence of a catalytic amount of tosic acid to yield 1,2,4-trioxane **238** (Scheme 67).

This methodology has been applied to various combinations of ketones **237** and allylic alcohols **233**, to generate a series of spiro-trioxanes **238**, as shown in Table 2.

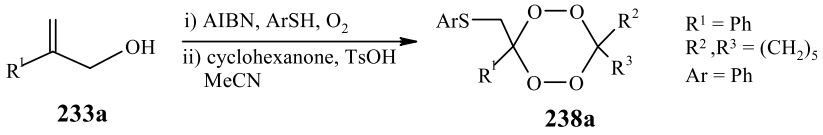
Various alkoxyamines **239a–c** were isomerised using microwave irradiation at high temperatures (210 °C) and short reaction times (2.5 min).[199] Under these conditions, allyltosylamide **239a** was isomerised efficiently to give **240a** (70%, trans:cis=3.3:1). A lower yield was observed for the cyclisation of the ester (**239b** to **240b**, 36%, trans:cis=2.5:1). In order to carry out the isomerisation of the amide **239c**, addition of camphor-10-sulfonic acid was required. The reaction took 12 min to complete to afford the amide **240c** in a 40% yield (trans:cis=1.9:1) (Scheme 68).



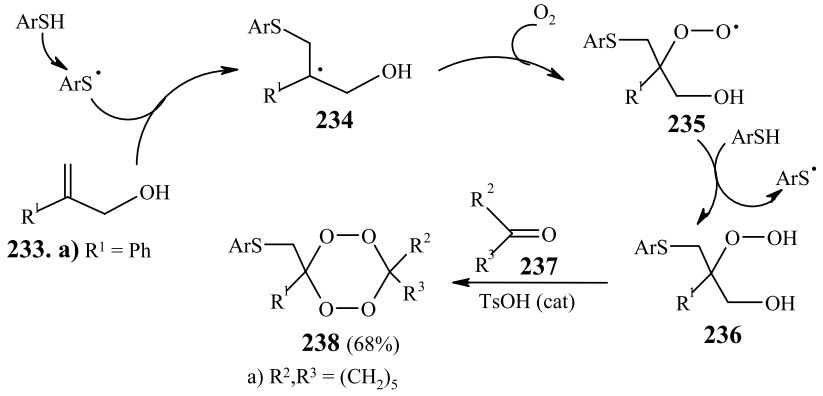
240. a) X = NTs (70%)
b) X = O (36%)
c) X = NH (40%)

Scheme 68.

Iodoalkene **241a** on reaction with indium (2 equiv) and iodine (1 equiv) in MeOH gave a highly polar compound **242a**, which, in the presence of 1 N HCl, proceeded to give the alkyl iodide **243a** as a mixture of stereoisomers (α:β=8:1).[200] The reaction was found to be more effective with 1 N NaOH–H_2O_2 or with H_2O_2. The same radical cyclisation procedure was applied to other di- and tri-substituted olefins (**241b** and **241c**) to give **243b** and **243c** via **242b** and **242c**, respectively. Alkenes containing leaving groups at the allylic positions were transformed only into



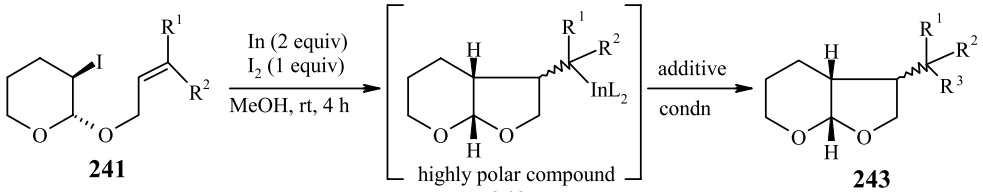
Scheme 66.



Scheme 67.

Table 2

Allylic alcohol (**233**)	Ketone (**237**)	Trioxane (**238**)	Yield (%)
(**233a**) R^1=Ph	Cyclohexanone	**238a**: R^1=Ph, R^2, R^3=$(CH_2)_5$, Ar=Ph	68
(**233a**) R^1=Ph	Cyclopentanone	**238b**: R^1=Ph, R^2, R^3=$(CH_2)_4$, Ar=Ph	54
(**233b**) R^1=Me	Cyclohexanone	**238c**: R^1=Me, R^2, R^3=$(CH_2)_5$, Ar=Ph	53
(**233b**) R^1=Me	Cyclopentanone	**238d**: R^1=Me, R^2, R^3=$(CH_2)_4$, Ar=*p*-Cl-Ph	46
(**233b**) R^1=Me	Cyclobutanone	**238e**: R^1=Me, R^2, R^3=$(CH_2)_3$, Ar=Ph	61



241

241. a) $R^1 = R^2 = H$
b) $R^1 = Ph$, $R^2 = H$
c) $R^1 = R^2 = Me$

242

243

243 a) $R^1 = R^2 = H$, $R^3 = I$
b) $R^1 = Ph$, $R^2 = H$, $R^3 = OH$
c) $R^1 = R^2 = Me$, $R^3 = OH$

Substrate	Temp (^{0}C)	Time	Additives (2 equiv)	Product (**243**)	Yield (%)
241a	80	18 h	1 N HCl	**243a**	63
241a	80	18 h	1 N NaOH	**243a**	50
241a	rt	20 min	1 N NaOH, H_2O_2	**243a**	73
241a	rt	20 min	H_2O_2	**243a**	75
241b	0	20 min	H_2O_2	**243b**	68
241c	0	20 min	H_2O_2	**243c**	71

Scheme 69.

the corresponding vinyl-substituted cyclic compounds. Alkynes bearing good leaving groups at the propargylic position, however, gave allenic products selectively (Scheme 69).

A novel indium-mediated atom transfer radical cyclisation reaction has been studied[201] using a catalytic amount of In and I_2 and a reductive radical cyclisation reaction using an excess amount of In and I_2 without the use of a radical initiator such as AIBN or Et_3B/O_2. Treatment of iodoalkyne **244** with a catalytic amount of In (0.1 equiv) and I_2 (0.05 equiv) promotes atom-transfer 5-*exo* cyclisation to give the five-membered alkenyl iodide **245** as the major product (69%). On the other hand, on reaction with In (2 equiv) and I_2 (1 equiv), the iodoalkyne **244** furnished the reductive 5-*exo* cyclisation product **246** (85%). Both these processes were initiated by low-valent indium species. To prove the versatility of these reactions, optically active HIV protease inhibitors were synthesized by this reductive cyclisation method (Scheme 70).

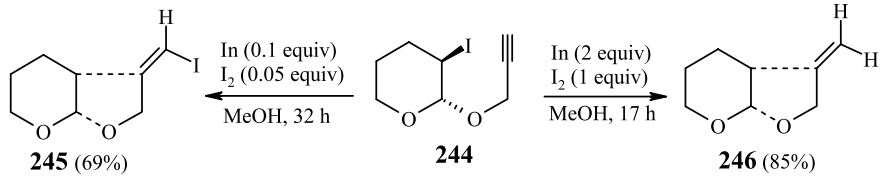
5. Synthesis of sulphur heterocycles

The radical reactions of some thiol esters were carried out[202] by adding a benzene solution of PhSH and AIBN under refluxing conditions. The cyclised indanone and tetralone in a ca. 96:4 ratio (overall 73% yield), along with comparable amounts of the (*E*)- and (*Z*)-dihydrothiophene, were obtained. Small amounts of the (*E*)- and (*Z*)-vinyl sulphide adduct were also isolated. Recently, we have described[203] a simple convergent synthesis of the cis-benzothiopyrano-[3,2-*c*]benzopyran-7(2*H*)-ones (70–75%) through the implementation of a regioselective 6-*endo-trig* aryl radical cyclisation of the respective 4-(2′-bromobenzyl)thiobenzopyran-7-ones with tributyltin hydride in presence of AIBN.

Various *para*-substituted benzenesulphonyloxyethyl bromides were treated[204] with tributyltin hydride in refluxing benzene under a nitrogen atmosphere and Smiles-type rearrangement products were obtained, as well as *ortho*-substitution products and reduction products, in varying yields. *para*-Substituted 2-phenylethanols were formed by *ipso*-substitution followed by loss of sulphur dioxide and hydrogen abstraction from the tin hydride and free radical substitution at the *ortho*-position resulted in the cyclisation products.

The radical reactions[205] of pentynylthiol esters **247a–e** with PhSH were carried out by adding a benzene solution of the thiol (1.1 equiv) and AIBN (0.2 equiv) with a syringe pump over ca. 3 h to a refluxing solution of the appropriate substrate (2 mmol) in benzene under an N_2 atmosphere. The reaction mixture was refluxed for an additional period of 1–2 h for a greater conversion of the starting material to the desired product(s). The benzocarbothiate **247a** under the above reaction conditions afforded benzaldehyde **250a** in excellent yield, along with equal amounts of the (*E*)- and (*Z*)-dihydrothiophene **248**. Additionally, small amounts of the (*E*)- and (*Z*)-vinyl sulphide adducts **249a** were isolated. Similarly, some comparable results were obtained with other substrates **247b–e** and the yield of the products **249b–e** and **250b–e** were also recorded (Scheme 71).

The unique mode of ring closure of α-sulphenyl-, α-sulphinyl-, α-sulphonyl- and 5-methyl-5-hexenyl radicals

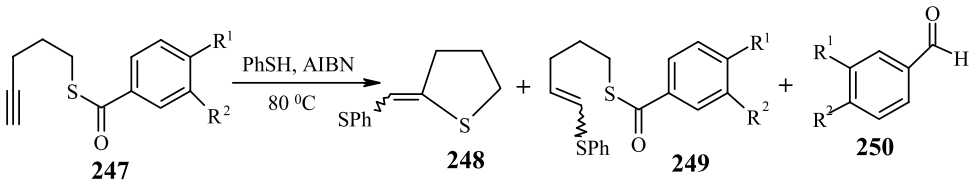


245 (69%)

244

246 (85%)

Scheme 70.



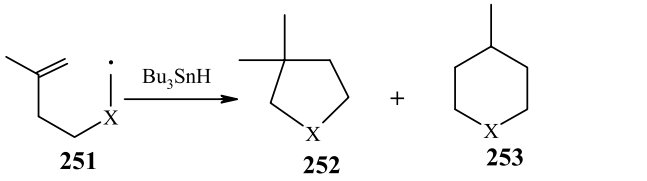
247 **a)** $R^1 = R^2 = H$
b) $R^1 = Cl$, $R^2 = H$
c) $R^1 = NO_2$, $R^2 = H$
d) $R^1 = N_3$, $R^2 = H$
e) $R^1 = H$, $R^2 = N_3$

Products and yields (%)

248 (92%), **249a** (5%), **250a** (93%)
248 (87%), **249b** (1%), **250b** (88%)
248 (78%), **249c** (6%), **250c** (65%)
248 (81%), **249d** (3%), **250d** (70%)
248 (81%), **249e** (1%), **250e** (80%)

Scheme 71.

has been exposed by Della and co-workers.[206] In the case of 5-hexenyl radicals, the sulphinyl-substituted species shows an unexpected regioselectivity relative to its analogues. Therefore, the α-S– and α-SO_2–5-hexenyl radicals gave measurable and increasing quantities of the 6-*endo* product, whereas the α-sulphinyl species cyclised with high selectivity (95.5:4.5) via the 5-*exo* mode. Della et al. then studied the regiochemistry of cyclisation of the 5-hexenyl systems bearing a substituent at C-5. The combined effects of the steric factors associated with the presence of the methyl group at C-5 and the longer C–S bonds are responsible for the sulphenyl **251a** and sulphonyl **251b** radicals generating the enhanced quantities of the 6-*endo* products **253a** and **253b**, respectively, in comparison to the corresponding 5-*exo* products **252a** and **252b**, respectively. The high regioselectivity associated with ring closure of **251b** afforded the cyclohexyl sulphone **253b**. Although the 6-*endo* mode of cyclisation of the sulphinyl radical **251c** is highly preferable, more of the 5-*exo* product **252c** was obtained from **251c** with respect to the 6-*endo* product **253c** (Scheme 72).



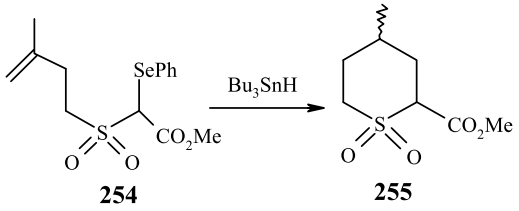
251. a) X = S
b) X = SO_2
c) X = SO

252. a) X = S
b) X = SO_2
c) X = SO (major)

253. a) X = S (major)
b) X = SO_2 (major)
c) X = SO

Scheme 72.

Again, the selenide **254** was converted into the sulphone **255** with a high degree of selectivity under Bu_3SnH-mediated radical cyclisation conditions. In this case, the electrophilic nature of the radical centre is greatly influenced by the ester function, which promotes the 6-*endo* cyclisation[206] (Scheme 73).

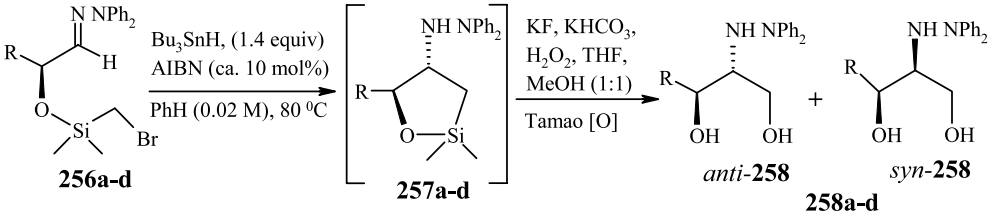


Scheme 73.

6. Synthesis of silicon-containing heterocycles

Tributyltin hydride-annulated (1.4 equiv of Bu_3SnH, 10 mol% AIBN, PhH, 0.02 M) radical cyclisation of bromomethyldimethylsilyl ethers **256a–d** led to the formation of heterocyclic, oxasilacyclopentane products **257a–d**,[207] but these cyclic silanes were not stable under normal silica gel chromatography.

They could, however, be preserved in benzene at −5 °C without any significant decomposition. Tamao oxidation[208] for the oxidative removal of the tether[209] (KF, $KHCO_3$,



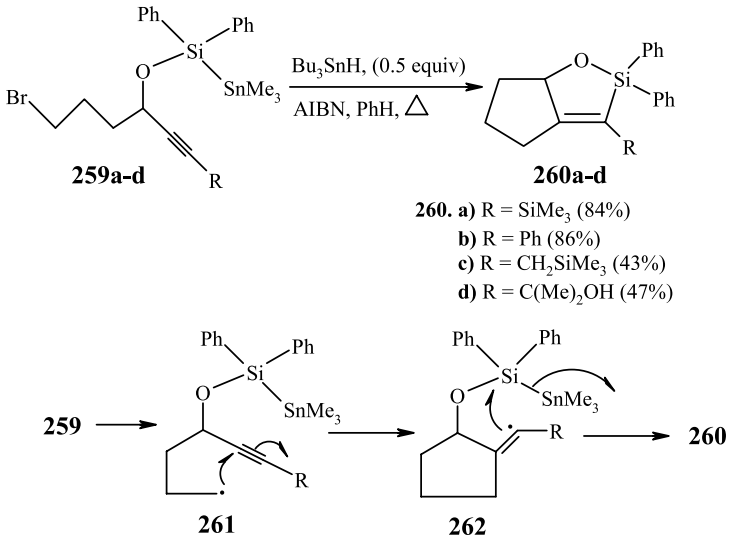
oxasilacyclopentane product ratio (*trans:cis*)

256a) R = Me — **257a)** 80:20
256b) R = *i* Bu — **257b)** 88:12
256c) R = *i* Pr — **257c)** 95:5
256d) R = Ph — **257d)** > 98.2

2-hydrazino 1,3-diol product ratio (*anti:syn*)

258a) 79:21
258b) 85:15
258c) 96:4
258d) > 98.2

Scheme 74.



Scheme 75.

H_2O_2) resulted in the *anti*-2-hydrazino-1,3-diols **258a–d** in good yield (Scheme 74).

A few years ago, it was reported that acyl radicals were capable of undergoing SH^i reactions at silicon to furnish the cyclic acylsilanes.[210] 1-(3-Bromopropyl)-3-(trimethylsilyl)-2-propynyldiphenyl(trimethylstannyl) silyl ether **259a** was allowed to react with TBTH (0.5 equiv) and AIBN in refluxing benzene to produce 2,2-diphenyl-3-(trimethylsilyl)4,5,6,6a-tetrahydro-2*H*-cyclopenta[*d*][1,2]oxasilole **260a** in 84% yield.[211] The phenyl-substituted acetylene **259b** was transformed into the vinylsilane **260b** (86%) under the same reaction conditions. In the same way, the other silanes **260c** and **260d** were obtained from **259c** and **259d**, respectively. The radicals **261** obtained from the stannylated silyl ethers **259** underwent 5-*exo*-*dig*-cyclisation to generate the vinyl radicals **262**. SH^i reaction at silicon afforded the cyclic alkoxysilanes **260** (Scheme 75).

7. Conclusions

It is evident from the foregoing discussions that the literature on the syntheses of heterocycles by radical cyclisation is vast and it is beyond the scope of this review to include all related aspects of radical cyclisations. Only the introduction, mechanism and recent representative examples of radical cyclisation in general have been included. We have limited ourselves to the application of radical cyclisation for the formation of fused furan and pyran rings. A detailed discussion has been confined to the literature published during 2004. Mechanistic aspects of various radical cyclisation reactions have also been discussed in detail. In recent years, there has been a considerable study of the cyclisation of radicals on heterocyclic compounds, a reaction that had previously been ignored. Radical cyclisation reactions, however, still offer enormous challenges to synthetic organic chemists.

Acknowledgements

We thank the CSIR (New Delhi) for financial assistance. P. P. M. is grateful to the CSIR (New Delhi) for a Senior Research Fellowship.

References and notes

1. (a) Renaud, P., Sibi, M. P., Eds.; Radicals in Organic Synthesis; Wiley-VCH: Weinheim, 2001; Vol. 1. (b) Renaud, P., Sibi, M. P., Eds.; Radicals in Organic Synthesis; Wiley-VCH: Weinheim, 2001; Vol. 2. (c) Giese, B. Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds; Pergamon: Oxford, 1988. (d) Curran, D. P. In Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Comprehensive Organic Synthesis; Pergamon: Oxford, 1991; Vol. 4, p 715; See also p 779. (e) Motherwell, W. B.; Crich, D. Free Radical Chain Reactions in Organic Synthesis; Academic: London, 1992. (f) Fossey, J.; Lefort, D.; Sorba, J. Free Radicals in Organic Chemistry; Wiley: New York, 1995. (g) Chatgilialoglu, C.; Renaud, P. In *General Aspects of the Chemistry of Radicals*; Alfassi, Z. B., Ed.; Wiley: Chichester, 1999; p 501.
2. (a) Curran, D. P. *Synthesis* **1988**, 417. (b) Curran, D. P. *Synthesis* **1988**, 489. (c) Jasperse, C. P.; Curran, D. P.; Felvig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (d) Melikyan, G. G. *Synthesis* **1993**, 833. (e) Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1996**, *96*, 339. (f) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1995. (g) Gansauer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771.
3. Giese, B.; Kopping, B.; Gobel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301.
4. Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991.
5. (a) Boger, D. L.; Mathvink, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 4003. (b) Boger, D. L.; Mathvink, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 4008. (c) Boger, D. L.; Mathvink, R. J.

J. Org. Chem. **1992**, *57*, 1429. (d) Crich, D.; Chen, C.; Hwang, J.-T.; Yuan, H.; Papadatos, A.; Walter, R. I. *J. Am. Chem. Soc.* **1994**, *116*, 8937. (e) Crich, D.; Yao, Q. *J. Org. Chem.* **1996**, *61*, 3566. (f) Crich, D.; Hao, X. *J. Org. Chem.* **1997**, *62*, 5982. (g) Chen, L.; Gill, G. B.; Pattenden, G.; Simonian, H. *J. Chem. Soc., Perkin Trans. 1* **1996**, 31. (h) Batsanov, A.; Chen, L.; Gill, G. B.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1996**, 45. (i) Pattenden, G.; Roberts, L.; Blake, A. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 863.

6. (a) Ryu, I.; Sonoda, N. *Angew. Chem., Int. Ed.* **1996**, *35*, 1050. (b) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177.
7. Ryu, I. *Chem. Soc. Rev.* **2001**, *30*, 16.
8. Ryu, I.; Kusano, K.; Ogawa, A.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1990**, *112*, 1295.
9. (a) Ryu, I.; Kusano, K.; Yamazaki, H.; Sonoda, N. *J. Org. Chem.* **1991**, *56*, 5003. (b) Ryu, I.; Yamazaki, H.; Kusano, K.; Ogawa, A.; Sonoda, N. *J. Am. Chem. Soc.* **1991**, *113*, 8558. (c) Ryu, I.; Yamazaki, H.; Ogawa, A.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1993**, *115*, 1187. (d) Brinza, I. M.; Fallis, A. G. *J. Org. Chem.* **1996**, *61*, 3580. (e) Nagahara, K.; Ryu, I.; Yamazaki, H.; Kambe, N.; Komatsu, M.; Sonoda, N.; Baba, A. *Tetrahedron* **1997**, *53*, 14615.
10. Nagahara, K.; Ryu, I.; Komatsu, M.; Sonoda, N.; Baba, A. *J. Am. Chem. Soc.* **1997**, *119*, 5465.
11. (a) Tsunoi, S.; Ryu, I.; Okuda, T.; Tanaka, M.; Komatsu, M.; Sonoda, N. *J. Am. Chem. Soc.* **1998**, *120*, 8692. (b) Kreimerman, S.; Ryu, I.; Minakata, S.; Komatsu, M. *Org. Lett.* **2000**, *2*, 389.
12. Ryu, I.; Okuda, T.; Nagahara, K.; Kambe, N.; Komatsu, M.; Sonoda, N. *J. Org. Chem.* **1997**, *62*, 7550.
13. Ryu, I.; Nagahara, K.; Kambe, N.; Sonoda, N.; Kreimerman, S.; Komatsu, M. *Chem. Commun.* **1998**, 1953.
14. Ryu, I.; Matsu, K.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **1998**, *120*, 5838.
15. Ryu, I.; Muraoka, H.; Kambe, N.; Komatsu, M.; Sonoda, N. *J. Org. Chem.* **1996**, *61*, 6396.
16. (a) Testaferri, L.; Tiecco, M.; Tingoli, M. *J. Chem. Soc., Chem. Commun.* **1978**, 93. (b) Henriquez, R.; Nonhebel, D. C. *Tetrahedron* **1993**, *49*, 6497. (c) Aihara, K.; Urano, Y.; Higuchi, T.; Hirobe, M. *J. Chem. Soc., Perkin Trans. 2* **1993**, 2165. (d) Aboutayab, K.; Caddick, S.; Jenkins, K.; Khan, J. S. *Tetrahedron* **1996**, *52*, 11329. (e) Giraud, L.; Lacote, E.; Renaud, P. *Helv. Chim. Acta* **1997**, *80*, 2148.
17. Ohno, H.; Wakayama, R.; Maeda, S.; Iwasaki, H.; Okumura, M.; Iwata, C.; Mikamiyama, H.; Tanaka, T. *J. Org. Chem.* **2003**, *68*, 5909.
18. (a) Middleton, D. S.; Simpkins, J. S. *Tetrahedron Lett.* **1988**, *29*, 1315. (b) Ishizaki, M.; Ozaki, K.; Kanematsu, A.; Isoda, T.; Hoshino, O. *J. Org. Chem.* **1993**, *58*, 3877. (c) Zhang, W.; Pugh, G. *Tetrahedron Lett.* **1999**, *40*, 7595. (d) Koreeda, M.; Wang, Y.; Zhang, L. *Org. Lett.* **2002**, *4*, 3329.
19. (a) Rao, A. V. R.; Rao, B. V.; Reddy, D. R.; Singh, A. K. *J. Chem. Soc., Chem. Commun.* **1989**, 400. (b) Rao, A. V. R.; Singh, A. K.; Reddy, K. M.; Ravikumar, K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3171. (c) Back, T. G.; Gladstone, P. L. *Synlett* **1993**, 699. (d) Kittaka, A.; Asakura, T.; Kuze, T.; Tanaka, H.; Yamada, N.; Nakamura, K. T.; Miyasaka, T. *J. Org. Chem.* **1999**, *64*, 7081.
20. (a) Clive, D. L. J.; Angoh, A. G.; Bennett, S. M. *J. Org. Chem.* **1987**, *52*, 1339. (b) Srikrishna, A.; Nagaraju, S.; Sharma, G. V. R. *J. Chem. Soc., Chem. Commun.* **1993**, 285. (c) Sha, C.-K.; Ho, W.-Y. *Chem. Commun.* **1998**, 2709. (d) Srikrishna, A.; Nagaraju, S.; Venkateswarlu, S.; Hiremath, U. S.; Reddy, T. J.; Venugopalan, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2069.
21. (a) Harling, J. D.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1988**, 1380. (b) Cossy, J.; Poitevin, C.; Pardo, D. G. *Synlett* **1998**, 251. (c) Sulsky, R.; Gougoutas, J. Z.; DiMarco, J.; Biller, S. A. *J. Org. Chem.* **1999**, *64*, 5504. (d) Robertson, J.; Lam, H. W.; Abazi, S.; Roseblade, S.; Lush, R. K. *Tetrahedron* **2000**, *56*, 8959.
22. (a) Majumdar, K. C.; Basu, P. K. *Heterocycles* **2002**, *57*, 2413. (b) Majumdar, K. C.; Basu, P. K.; Mukhopadhyay, P. P. *Tetrahedron* **2004**, *60*, 6239. (c) Majumdar, K. C.; Mukhopadhyay, P. P.; Basu, P. K. *Heterocycles* **2004**, *63*, 1903.
23. Chatgilialoglu, C. In Renaud, P., Sibi, M. P., Eds.; Radicals in Organic Synthesis; Wiley-VCH: Weinheim, 2001; Vol. 1, Chapter 1.3, p 28.
24. Lawrence, N. J.; Drew, M. D.; Bushell, S. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3381.
25. (a) Tsunoi, S.; Ryu, I.; Yamasaki, S.; Fukushima, H.; Tanaka, M.; Komatsu, M.; Sonoda, N. *J. Am. Chem. Soc.* **1996**, *118*, 10670. (b) Nagahara, K.; Ryu, I.; Komatsu, M.; Sonoda, N. *J. Am. Chem. Soc.* **1997**, *119*, 5465. (c) Ryu, I. *Chem. Soc. Rev.* **2001**, *30*, 16.
26. Bowman, W. R.; Krintel, S. L.; Schilling, M. B. *Org. Biomol. Chem.* **2004**, *2*, 585.
27. (a) Roberts, B. P. *Chem. Soc. Rev.* **1999**, *28*, 25. (b) Dang, H. S.; Roberts, B. P.; Tocher, D. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2452.
28. Garner, P. P.; Parker, D. T.; Gajewski, J. J.; Lubineau, A.; Ange, J.; Queneau, Y.; Beletskaya, I. P.; Cheprakov, A. V.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Kobayashi, S. In *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic and Professional: London, 1998.
29. (a) Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 11149. (b) Yang, Y.; Chan, T. H. *J. Am. Chem. Soc.* **2000**, *122*, 402. (c) Chan, T. H.; Yang, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3228. (d) Paquette, L. A.; Rothhaar, R. R. *J. Org. Chem.* **1999**, *64*, 217.
30. Nambu, H.; Anilkumar, G.; Matsugi, M.; Kita, Y. *Tetrahedron* **2003**, *59*, 77.
31. (a) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1992**, *33*, 5709. (b) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *J. Org. Chem.* **1993**, *58*, 6838. (c) Jang, D. O. *Tetrahedron Lett.* **1996**, *37*, 5367. (d) Jang, D. O.; Cho, D. H.; Barton, D. H. R. *Synlett* **1998**, 39. (e) Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Chem. Lett.* **2000**, 104. (f) Jang, D. O.; Cho, D. H. *Synlett* **2002**, 631. (g) Jang, D. O.; Cho, D. H. *Synlett* **2002**, 1523. (h) Jang, D. O.; Cho, D. H. *Tetrahedron Lett.* **2002**, *43*, 5921. (i) Sugiura, M.; Hagio, H.; Kobayashi, S. *Chem. Lett.* **2003**, 898.
32. Kita, Y.; Matsugi, M. In Renaud, P., Sibi, M. P., Eds. Radicals in Organic Synthesis; Wiley-VCH: Weinheim, 2001; Vol. 1, pp 1–10.
33. Kita, Y.; Nambu, H.; Ramesh, N. G.; Anilkumar, G.; Matsugi, M. *Org. Lett.* **2001**, *3*, 1157.
34. Nambu, H.; Alinejad, A. H.; Hata, K.; Fujioka, H.; Kita, Y. *Tetrahedron Lett.* **2004**, *45*, 8927.
35. Khan, T. A.; Tripoli, R.; Crawford, J. J.; Martin, C. G.; Murphy, J. A. *Org. Lett.* **2003**, *5*, 2971.

36. Miyabe, H.; Ueda, M.; Fujii, K.; Nishimura, A.; Naito, T. *J. Org. Chem.* **2003**, *68*, 5618.
37. Jessop, C. M.; Parsons, A. F.; Routledge, A.; Irvine, D. *Tetrahedron Lett.* **2003**, *44*, 479.
38. Ueda, M.; Miyabe, H.; Nishimura, A.; Miyata, O.; Takemoto, Y.; Naito, T. *Org. Lett.* **2003**, *5*, 3835.
39. Wetter, C.; Jantos, K.; Woithe, K.; Studer, A. *Org. Lett.* **2003**, *5*, 2899.
40. Amrein, S.; Studer, A. *Helv. Chim. Acta* **2002**, *85*, 3559.
41. Schulz, M. J.; Coats, S. J.; Hlasta, D. J. *Org. Lett.* **2004**, *6*, 3265.
42. (a) Nair, V.; Balagopal, L.; Rajan, R.; Mathew, J. *Acc. Chem. Res.* **2004**, *37*, 21. (b) Nair, V.; Mathew, J.; Prahakaran, J. *Chem. Soc. Rev.* **1997**, 127. (c) Molander, A. G. *Chem. Rev.* **1992**, *92*, 29.
43. (a) Paolobelli, A. B.; Ceccherelli, P.; Pizzo, F.; Ruzziconi, R. *J. Org. Chem.* **1995**, *60*, 4954. (b) Hwu, J. R.; Chen, C. N.; Shiao, S. S. *J. Org. Chem.* **1995**, *60*, 856. (c) Nair, V.; Mathew, J.; Alexander, S. *Synth. Commun.* **1995**, *25*, 3981. (d) Nair, V.; Mathew, J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 187. (e) Paolobelli, A. B.; Gioacchini, R.; Ruzziconi, R. *Tetrahedron Lett.* **1993**, *34*, 721. (f) Baciocchi, E.; Ruzziconi, R. *Synth. Commun.* **1988**, *18*, 1841.
44. (a) Muathen, H. A. *Indian J. Chem.* **1991**, 522. (b) Chen, C.; Mariano, P. S. *J. Org. Chem.* **2000**, *65*, 3252.
45. Zhang, Y.; Raines, A. J.; Flowers, R. A., II *Org. Lett.* **2003**, *5*, 2363.
46. Zhang, Y.; Raines, A. J.; Flowers, R. A., II *J. Org. Chem.* **2004**, *69*, 6267.
47. Chuang, C.-P.; Wu, Y.-L. *Tetrahedron* **2004**, *60*, 1841.
48. Miyata, O.; Muroya, K.; Kobayashi, T.; Yamanaka, R.; Kajisa, S.; Koide, J.; Naito, T. *Tetrahedron* **2002**, *58*, 4459.
49. Harrowven, D. C.; Sutton, B. J.; Coulton, S. *Tetrahedron* **2002**, *58*, 3387.
50. Prabhakaran, E. N.; Nugent, B. M.; Williams, A. L.; Nailor, K. E.; Johnston, J. N. *Org. Lett.* **2002**, *4*, 4197.
51. Nugent, B. M.; Williams, A. L.; Prabhakaran, E. N.; Johnston, J. N. *Tetrahedron* **2003**, *59*, 8877.
52. Viswanathan, R.; Prabhakaran, E. N.; Plotkin, M. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2003**, *125*, 163.
53. Srinivasan, J. M.; Burks, H. E.; Smith, C. R.; Viswanathan, R.; Johnston, J. N. *Synthesis (Practical Synthetic Procedures)* **2005**, 330.
54. Bowman, W. R.; Fletcher, A. J.; Lovell, P. J.; Pedersen, J. M. *Synlett* **2004**, 1905.
55. Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* **1991**, *113*, 2127.
56. (a) Studer, A.; Amrein, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3080. (b) Studer, A.; Amrein, S.; Schleth, F.; Schulte, T.; Walton, J. C. *J. Am. Chem. Soc.* **2003**, *125*, 5726.
57. (a) Jackson, L. V.; Walton, J. C. *Chem. Commun.* **2000**, 2327. (b) Bella, A. F.; Jackson, L. V.; Walton, J. C. *Org. Biomol. Chem.* **2004**, *2*, 421.
58. Tomaszewski, M. J.; Warkentin, J.; Werstiuk, N. H. *Aust. J. Chem.* **1995**, *48*, 291.
59. (a) Naito, T.; Honda, Y.; Miyata, O.; Ninomya, I. *J. Chem. Soc., Perkin Trans. 1* **1995**, 19. (b) Miyata, O.; Nishiguchi, A.; Ninomya, I.; Aoe, K.; Okamura, K.; Naito, T. *J. Org. Chem.* **2000**, *65*, 6922. (c) Miyata, O.; Muroya, K.; Koide, J.; Naito, T. *Synlett* **1998**, 271.
60. Naito, T.; Kiguchi, T.; Tajiri, K.; Ninomya, I.; Hiramatsu, H. *Tetrahedron Lett.* **1995**, *36*, 253.
61. Keck, G. E.; McHardy, S. F.; Murry, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 7289.
62. Parker, K. A.; Spero, D. M.; VanEpp, J. *J. Org. Chem.* **1988**, *53*, 4628.
63. Naito, T.; Miyabe, H.; Torieda, M.; Tajiri, K. I. K.; Kiguchi, T. *J. Org. Chem.* **1998**, *63*, 4397.
64. Miyabe, H.; Kanehira, S.; Kume, K.; Kandori, H.; Naito, T. *Tetrahedron* **1998**, *54*, 5883.
65. Bella, A. F.; Slawin, A. M. Z.; Walton, J. C. *J. Org. Chem.* **2004**, *69*, 5926.
66. Minin, P. L.; Walton, J. C. *J. Org. Chem.* **2003**, *68*, 2960.
67. (a) Alajarin, M.; Vidal, A.; Ortin, M.-M. *Tetrahedron Lett.* **2003**, *44*, 3027. (b) Alajarin, M.; Vidal, A.; Ortin, M.-M. *Org. Biomol. Chem.* **2003**, *1*, 4282.
68. Alajarin, M.; Vidal, A.; Ortin, M.-M.; Bautista, D. *Synlett* **2004**, 991.
69. (a) Nakatsuji, M.; Miura, Y.; Teki, Y. *J. Chem. Soc., Perkin Trans. 2* **2001**, 738. (b) Miura, Y.; Momoki, M.; Fuchikami, T.; Teki, Y.; Itoh, K.; Mizutani, H. *J. Org. Chem.* **1996**, *61*, 4300.
70. Li, H.; Yang, H.; Petersen, J. L.; Wang, K. K. *J. Org. Chem.* **2004**, *69*, 4500.
71. (a) Silvester, M. J. *Adv. Heterocycl. Chem.* **1994**, *1*, 59. (b) Silvester, M. J. *Aldrichim. Acta* **1991**, *24*, 31. (c) *Organofluorine Chemistry, Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum: New York, 1994.
72. Hirano, Y.; Uehara, M.; Saeki, K.; Kato, T.; Takahashi, K.; Mizutani, T. *J. Health Sci.* **2002**, *48*, 118.
73. Kato, T.; Saeki, K.; Kawazoe, Y.; Hakura, A. *Mutat. Res.* **1999**, *439*, 149.
74. Ichikawa, J.; Mori, T.; Miyazaki, H.; Wada, Y. *Synlett* **2004**, 1219.
75. (a) Uchida, Y.; Echikawa, N.; Oae, S. *Heteroat. Chem.* **1994**, *5*, 409. (b) Fort, Y.; Becker, S.; Caubere, P. *Tetrahedron* **1994**, *50*, 11893.
76. (a) Bhattacharyya, R.; Drago, R. S.; Abboud, K. A. *Inorg. Chem.* **1997**, *36*, 2913. (b) Gogoll, A.; Gomes, J.; Bergkvist, M.; Grennberg, H. *Organometallics* **1995**, *14*, 1354. (c) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. *J. Am. Chem. Soc.* **1998**, *120*, 6419.
77. Tamura, O.; Matsukida, H.; Toyao, A.; Takeda, Y.; Ishibashi, H. *J. Org. Chem.* **2002**, *67*, 5537.
78. (a) Escolano, C.; Jones, K. *Tetrahedron Lett.* **2000**, *41*, 8951. (b) Escolano, C.; Jones, K. *Tetrahedron* **2002**, *58*, 1453.
79. Flanagan, S. R.; Harrowven, D. C.; Bradley, M. *Tetrahedron Lett.* **2003**, *44*, 1795.
80. Allan, G. M.; Parsons, A. F.; Pons, J.-F. *Synlett* **2002**, 1431.
81. Zhang, W.; Pugh, G. *Tetrahedron* **2003**, *59*, 3009.
82. Guerrero, M. A.; Cruz-Almanza, R.; Miranda, L. D. *Tetrahedron* **2003**, *59*, 4953.
83. Majumdar, K. C.; Mukhopadhyay, P. P. *Synthesis* **2003**, 920.
84. Kato, I.; Higashimoto, M.; Tamura, O.; Ishibashi, H. *J. Org. Chem.* **2003**, *68*, 7983.
85. Harrowven, D. C.; Sutton, B. J.; Coulton, S. *Org. Biomol. Chem.* **2003**, *1*, 4047.
86. Mitchell, G.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1987**, 403.
87. Hagan, D. J.; Gimenez-Arnau, E.; Schwalbe, C. H.; Stevens, M. F. G. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2739.
88. Ellis, M. J.; Stevens, M. F. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3180.
89. Hutchinson, I.; McCarroll, A. J.; Heald, R. A.; Stevens, M. F. G. *Org. Biomol. Chem.* **2004**, *2*, 220.
90. Hassner, A.; Stumer, C. *Organic Reactions Based on Name*

Reactions and Unnamed Reactions; Elsevier Science: Oxford, 1994; p 307.
91. Ganguly, A. K.; Wang, C. H.; Chan, T. M.; Ing, Y. H.; Buevich, A. V. *Tetrahedron Lett.* **2004**, *45*, 883.
92. Ganguly, A. K.; Wang, C. H.; Misiaszek, T. M.; Chan, T. M.; Pramanik, B. N.; McPhail, A. T. *Tetrahedron Lett.* **2004**, *45*, 8909.
93. Cordes, M.; Franke, D. *Synlett* **2004**, 1917.
94. Kamimura, A.; Taguchi, Y. *Tetrahedron Lett.* **2004**, *45*, 2335.
95. Morris, B. D.; Prinsep, M. R. *J. Nat. Prod.* **1999**, *62*, 688.
96. (a) Takayama, H.; Kurihira, M.; Subhadhirasakul, S.; Kitajima, M.; Aimi, N.; Sakai, S.-I. *Heterocycles* **1996**, *42*, 87. (b) Takayama, H.; Ishikawa, H.; Kurihira, M.; Kitajima, M.; Aimi, N.; Ponglux, D.; Koyama, F.; Matsumoto, K.; Moriyama, T.; Yamamoto, L. T.; Watanabe, K. *J. Med. Chem.* **2002**, *45*, 1949.
97. (a) Narasimhan, N. S.; Aidhen, I. S. *Tetrahedron Lett.* **1988**, *29*, 2987. (b) Ohno, H.; Wakayama, R.; Maedo, S.-I.; Iwasaki, H.; Okumura, M.; Iwata, C.; Mikamiyama, H.; Tanaka, T. *J. Org. Chem.* **2003**, *68*, 5909. (c) Harrowven, D. C.; L'Helias, N.; Moseley, J. D.; Blumire, N. J.; Flanagan, S. R. *Chem. Commun.* **2003**, *21*, 2658.
98. Boivin, J.; Yousfi, M.; Zard, S. Z. *Tetrahedron Lett.* **1997**, *38*, 5985.
99. (a) Parsons, P. J.; Penverne, M.; Pinto, I. L. *Synlett* **1994**, 721. (b) Demircan, A.; Parsons, P. J. *Synlett* **1998**, 1215.
100. (a) Hilton, S. T.; Ho, T. C. T.; Pljevaljcic, G.; Schulte, M.; Jones, K. *Org. Lett.* **2000**, *2*, 2639. (b) Hilton, S. T.; Ho, T. C. T.; Pljevaljcic, G.; Schulte, M.; Jones, K. *Chem. Commun.* **2001**, 209.
101. Kyei, A. S.; Tchabanenko, K.; Baldwin, J. E.; Adlington, R. M. *Tetrahedron Lett.* **2004**, *45*, 8931.
102. Majumdar, K. C.; Sarkar, S. *Synth. Commun.* **2004**, *34*, 2873.
103. Majumdar, K. C.; Basu, P. K.; Mukhopadhyay, P. P.; Sarkar, S.; Ghosh, S. K.; Biswas, P. *Tetrahedron* **2003**, *59*, 2151.
104. Ishibashi, H.; Kawanami, H.; Nakagawa, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2291.
105. Rosa, A. M.; Lobo, A. M.; Branco, P. S.; Prabhakar, S.; Pereira, A. M. D. L. *Tetrahedron* **1997**, *55*, 269.
106. Rosa, A. M.; Lobo, A. M.; Branco, P. S.; Prabhakar, S.; Sa-da-Costa, M. *Tetrahedron* **1997**, *53*, 299.
107. Abeywickrema, A. N.; Beckwith, A. L. J.; Gerba, S. *J. Org. Chem.* **1987**, *52*, 4072.
108. Naito, T.; Fukumoto, D.; Takabayashi, K.; Kiguchi, T. *Heterocycles* **1999**, *51*, 489.
109. Takeda, Y.; Nakabayashi, T.; Shirai, A.; Fukumoto, D.; Kiguchi, T.; Naito, T. *Tetrahedron Lett.* **2004**, *45*, 3481.
110. Studer, A.; Bossart, M. In Renaud, P., Sibi, M. P., Eds.; Radicals in Organic Synthesis; Wiley-VCH: Weinheim, 2001; Vol. 2, pp 62–82.
111. (a) Fiumana, A.; Jones, K. *Tetrahedron Lett.* **2000**, *41*, 4209. (b) Kaoudi, T.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem., Int. Ed.* **2000**, *39*, 731.
112. (a) Minisci, F.; Vismara, E.; Fontana, F. *Heterocycles* **1989**, *28*, 489. (b) Murphy, J. A.; Sherburn, M. S. *Tetrahedron* **1991**, *47*, 4077. (c) Harrowven, D. C.; Nunn, M. I. T.; Blumire, N. J.; Fenwick, D. R. *Tetrahedron* **2001**, *57*, 4447. (d) Harrowven, D. C.; Sutton, B. J.; Coulton, S. *Tetrahedron Lett.* **2001**, *42*, 9061.
113. (a) Aldabbagh, F.; Bowman, W. R.; Mann, E.; Slawin, A. M. Z. *Tetrahedron* **1999**, *55*, 8111. (b) Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett.* **2002**, *43*, 4191.
114. (a) Kraus, G. A.; Kim, H. *Synth. Commun.* **1993**, *23*, 55. (b) Artis, D. R.; Cho, I.-S.; Jaime-Figueroa, S.; Muchowski, J. M. *J. Org. Chem.* **1994**, *59*, 2456. (c) Wang, S.-F.; Chuang, C.-P. *Tetrahedron Lett.* **1997**, *38*, 7597. (d) Moody, C. J.; Norton, C. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2639. (e) Caddick, S.; Shering, C. L.; Wadman, S. N. *Tetrahedron* **2000**, *56*, 465.
115. (a) Ziegler, F. E.; Jeroncic, L. O. *J. Org. Chem.* **1991**, *56*, 3479. (b) Gribble, G. W.; Fraser, H. L.; Badenock, J. C. *Chem. Commun.* **2001**, 805.
116. (a) Motherwell, W. B.; Vazquez, S. *Tetrahedron Lett.* **2000**, *41*, 9667. (b) Fontana, F.; Minisci, F.; Barbosa, M. C. N.; Vismara, E. *J. Org. Chem.* **1991**, *56*, 2866. (c) Miranda, L. D.; Cruz-Almanza, R.; Pavon, M.; Alva, E.; Muchowski, J. M. *Tetrahedron Lett.* **1999**, *40*, 7153. (d) Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett.* **2001**, *42*, 7887. (e) Doll, M. K.-H. *J. Org. Chem.* **1999**, *64*, 1372.
117. (a) Bennasar, M.-L.; Roca, T.; Griera, R.; Bosch, J. *Org. Lett.* **2001**, *3*, 1697. (b) Bennasar, M.-L.; Roca, T.; Griera, R.; Bassa, M.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 6268. (c) Bennasar, M.-L.; Roca, T.; Ferrando, F. *Org. Lett.* **2004**, *6*, 759.
118. Bennasar, M.-L.; Roca, T.; Ferrando, F. *Tetrahedron Lett.* **2004**, *45*, 5605.
119. Rashatasakhon, P.; Ozdemir, A. D.; Willis, J.; Padwa, A. *Org. Lett.* **2004**, *6*, 917.
120. (a) Clark, J. T.; Chandrasekhar, G. W.; Spitznagel, G. W.; Schleyer, P. V. R. *J. Comput. Chem.* **1983**, *4*, 294. (b) Frisch, M. J.; Pople, J. A.; Binkley, J. S. *J. Chem. Phys.* **1984**, *80*, 3265.
121. (a) Becke, A. D. *J. Am. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C. W.; Yang, R. G. P. *Phys. Rev. B* **1988**, *37*, 785.
122. Rodriguez, V.; Sanchez, M.; Quintero, L.; Sartillo-Piscil, F. *Tetrahedron* **2004**, *60*, 10809.
123. Bennasar, M.-L.; Roca, T.; Ferrando, F. *Org. Lett.* **2004**, *6*, 759.
124. Du, W.; Curran, D. P. *Org. Lett.* **2003**, *5*, 1765.
125. Du, W.; Curran, D. P. *Synlett* **2003**, 1299.
126. Benati, L.; Calestani, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Strazzari, S.; Zanardi, G. *J. Org. Chem.* **2003**, *68*, 3454.
127. Hasegawa, H.; Senboku, H.; Kajizuka, Y.; Orito, K.; Tokuda, M. *Tetrahedron* **2003**, *59*, 827.
128. Lizos, D. E.; Murphy, J. A. *Org. Biomol. Chem.* **2003**, *1*, 117.
129. Li, H.; Peterson, J. L.; Wang, K. K. *J. Org. Chem.* **2003**, *68*, 5512.
130. Tsunoi, S.; Ryu, I.; Fukushima, H.; Tanaka, M.; Komatsu, M.; Sonoda, N. *Synlett* **1995**, 1249.
131. Padwa, A.; Brodney, M. A.; Lynch, S. M.; Rashatasakhon, P.; Wang, Q.; Zhang, H. *J. Org. Chem.* **2004**, *69*, 3735.
132. Stork, G.; Baine, N. H. *J. Am. Chem. Soc.* **1982**, *104*, 2321.
133. Gandon, L. A.; Russell, A. G.; Snaith, J. S. *Org. Biomol. Chem.* **2004**, *2*, 2270.
134. Johnson, F. *Chem. Rev.* **1968**, *68*, 375.
135. Bryans, J. S.; Chessum, N. E. A.; Huther, N.; Parsons, A. F.; Ghelfi, F. *Tetrahedron* **2003**, *59*, 6221.
136. Chikaoka, S.; Toyao, A.; Ogasawara, M.; Tamura, O.; Ishibashi, H. *J. Org. Chem.* **2003**, *68*, 312.
137. Lamberto, M.; Corbett, D. F.; Kilburn, J. D. *Tetrahedron Lett.* **2003**, *44*, 1347.
138. Gross, S.; Reissig, H.-U. *Org. Lett.* **2003**, *5*, 4305.
139. Leroi, C.; Bertin, D.; Dufils, P.-E.; Gigmes, D.; Marque, S.;

Tordo, P.; Couturier, J.-L.; Guerret, O.; Ciufolini, M. A. *Org. Lett.* **2003**, *5*, 4943.
140. Akamatsu, H.; Fukase, K.; Kusumoto, S. *Synlett* **2004**, 1049.
141. Lamberto, M.; Corbett, D. F.; Kilburn, J. D. *Tetrahedron Lett.* **2004**, *45*, 8541.
142. Bowman, W. R.; Krintel, S. L.; Schilling, M. B. *Synlett* **2004**, 1215.
143. Hernan, A. G.; Kilburn, J. D. *Tetrahedron Lett.* **2004**, *45*, 831.
144. (a) Yanada, R.; Nishimori, N.; Matsumura, A.; Fujii, N.; Takemoto, Y. *Tetrahedron Lett.* **2002**, *43*, 4585. (b) Yanada, R.; Koh, Y.; Nishimori, N.; Matsumura, A.; Obika, S.; Mitsuya, H.; Fujii, N.; Takemoto, Y. *J. Org. Chem.* **2004**, *69*, 2417. (c) Yanada, R.; Obika, S.; Nishimori, N.; Yamauchi, M.; Takemoto, Y. *Tetrahedron Lett.* **2004**, *45*, 2331.
145. Yanada, R.; Obika, S.; Oyama, M.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 2825.
146. Tang, Y.; Li, C. *Org. Lett.* **2004**, *6*, 3229.
147. Barton, D. H. R.; Beckwith, A. L. J.; Goosen, A. *J. Chem. Soc.* **1965**, 181.
148. (a) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001. (b) Torssell, K. B. G. *Nitrones and Nitronates in Organic Synthesis*; VCH: New York, 1988.
149. Durand, A.-C.; Dumez, E.; Rodriguez, J.; Dulcere, J.-P. *Chem. Commun.* **1999**, 2437.
150. Roger, P.-Y.; Durand, A.-C.; Rodriguez, J.; Dulcere, J.-P. *Org. Lett.* **2004**, *6*, 2027.
151. Bacque, E.; Qacemi, M. E.; Zard, S. Z. *Org. Lett.* **2004**, *6*, 3671.
152. (a) Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Storey, J. M. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 95. (b) Suzuki, F.; Kuroda, K. *J. Heterocycl. Chem.* **1993**, *30*, 811. (c) Antonio, Y.; de la Cruz, E.; Galeazzi, E.; Guzman, A.; Bray, B. L.; Greenhouse, R.; Kruz, L. J.; Lustig, D. A.; Maddox, M. L.; Muchowski, J. M. *Can. J. Chem.* **1994**, *72*, 15. (d) Tim, C. T.; Jones, K.; Wilkinson, J. *Tetrahedron Lett.* **1995**, *36*, 6743. (e) Osaki, S.; Mitoh, H.; Ohmori, H. *Chem. Pharm. Bull.* **1996**, *44*, 2020. (f) Dobbs, P. A.; Jones, K.; Veal, K. T. *Tetrahedron* **1997**, *53*, 8287. (g) Aldabbagh, F.; Bowman, W. R.; Mann, E. *Tetrahedron Lett.* **1997**, *38*, 7937. (h) Marco-Contelles, J.; Rodriguez-Fernandez, M. *Tetrahedron Lett.* **2000**, *41*, 381. (i) Bowman, W. R.; Mann, E. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2991.
153. (a) Mohan, R.; Kates, S. A.; Dombroski, M. A.; Snider, B. B. *Tetrahedron Lett.* **1987**, *28*, 845. (b) Snider, B. B.; Buckman, B. O. *Tetrahedron* **1989**, *45*, 6969. (c) Aidhen, I. S.; Narasimhan, N. S. *Tetrahedron Lett.* **1989**, *30*, 5323. (d) Artis, D. R.; Cho, I.-S.; Muchowski, J. M. *Can. J. Chem.* **1992**, *70*, 1838.
154. (a) Citterio, A.; Sebaetiano, R.; Marion, A. *J. Org. Chem.* **1991**, *56*, 5328. (b) Citterio, A.; Sebastiano, R.; Caceres, C. M. *J. Org. Chem.* **1991**, *56*, 5335.
155. Snider, B. B.; Kown, T. *J. Org. Chem.* **1990**, *55*, 4786.
156. (a) Gagosz, F.; Zard, S. Z. *Org. Lett.* **2002**, *4*, 4345. (b) Axon, J.; Boiteau, L.; Boivin, J.; Forbes, J. E.; Zard, S. Z. *Tetrahedron Lett.* **1994**, *35*, 1719. (c) Ly, T.-M.; Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2533.
157. Menes-Arzate, M.; Martinez, R.; Cruz-Almanza, R.; Muchowski, J. M.; Osornio, Y. M.; Miranda, L. D. *J. Org. Chem.* **2004**, *69*, 4001.
158. Nadin, A.; Harrison, T. *Tetrahedron Lett.* **1999**, *40*, 4073.
159. Nagashima, H.; Wakamatsu, H.; Ito, K.; Tomo, Y.; Tsuji, J. *Tetrahedron Lett.* **1983**, *23*, 2395.
160. Nagashima, H.; Ozaki, N.; Ishii, M.; Seki, K.; Washiyama, M.; Itoh, K. *J. Org. Chem.* **1993**, *58*, 464.
161. (a) Yamaguchi, Y.; Nagashima, H. *Organometallics* **2000**, *19*, 725. (b) Kondo, H.; Kageyama, A.; Yamaguchi, Y.; Haga, M.; Kirchner, K.; Nagashima, H. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1927. (c) Nagashima, H.; Gondo, M.; Masuda, S.; Kondo, H.; Yamaguchi, Y.; Matsubara, K. *Chem. Commun.* **2003**, 442. (d) Nagashima, H.; Kondo, H.; Hayashida, T.; Yamaguchi, Y.; Gondo, M.; Masuda, S.; Miyazaki, K.; Matsubara, K.; Kirchner, K. *Coord. Chem. Rev.* **2003**, *245*, 177.
162. Motoyama, Y.; Gondo, M.; Masuda, S.; Iwashita, Y.; Nagashima, H. *Chem. Lett.* **2004**, *33*, 442.
163. Shibata, I.; Moriuchi-Kawakami, T.; Tanizawa, D.; Suwa, T.; Sugiyama, E.; Matsuda, H.; Baba, A. *J. Org. Chem.* **1998**, *63*, 383.
164. Suwa, T.; Sugiyama, E.; Shibata, I.; Baba, A. *Synlett* **2000**, 556.
165. (a) Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54. (b) Sayah, B.; Pelloux-Leon, N.; Vallee, Y. *J. Org. Chem.* **2000**, *65*, 2824. (c) Liu, J.-H.; Yang, Q.-C.; Mak, T. C. W.; Wong, H. N. C. *J. Org. Chem.* **2000**, *65*, 3587.
166. (a) Gadzhily, R. A.; Fedoseev, V. M.; Dzhafarov, V. G. *Chem. Heterocycl. Compd.* **1990**, *26*, 874. (b) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074.
167. Shibata, I.; Kato, H.; Kanazawa, N.; Yasuda, M.; Baba, A. *Synlett* **2004**, 137.
168. Shibata, I.; Kato, H.; Kanazawa, N.; Yasuda, M.; Baba, A. *J. Am. Chem. Soc.* **2004**, *126*, 466.
169. (a) Bloodworth, A. J.; Davies, A. G. *J. Chem. Soc.* **1965**, 5238. (b) Bloodworth, A. J.; Davies, A. G.; Vasishtha, S. C. *J. Chem. Soc.* **1967**, 1309. (c) Sakai, S.; Miura, M.; Wada, N.; Fujinami, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1873. (d) Yasuda, H.; Choi, J.-C.; Lee, S.-C.; Sakakura, T. *J. Organomet. Chem.* **2002**, *659*, 133.
170. Yokota, M.; Toyota, M.; Ihara, M. *Chem. Commun.* **2003**, 422.
171. Rhee, J. U.; Bliss, B. I.; Rajanbabu, T. V. *J. Am. Chem. Soc.* **2003**, *125*, 1492.
172. Crich, D.; Ranganathan, K.; Neelamkavil, S.; Huang, X. *J. Am. Chem. Soc.* **2003**, *125*, 7942.
173. Zhang, W.; Pugh, G. *Tetrahedron* **2003**, *59*, 4237.
174. Majumdar, K. C.; Mukhopadhyay, P. P. *Synthesis* **2003**, 97.
175. Majumdar, K. C.; Sarkar, S.; Bhattacharrya, T. *Tetrahedron* **2003**, *59*, 4309.
176. Berlin, S.; Ericsson, C.; Engman, L. *J. Org. Chem.* **2003**, *68*, 8386.
177. Pave, G.; Usse-Versluys, S.; Viaud-Massuard, M.-C.; Guillaumet, G. *Org. Lett.* **2003**, *5*, 4253.
178. Fischer, J.; Reynolds, A. J.; Sharp, L. A.; Sherburn, M. S. *Org. Lett.* **2004**, *6*, 1345.
179. Clive, D. L. J.; Fletcher, S. P.; Liu, D. *J. Org. Chem.* **2004**, *69*, 3282.
180. Majumdar, K. C.; Mukhopadhyay, P. P. *Synthesis* **2004**, 1864.
181. Majumdar, K. C.; Chattopadhyay, S. K. *Tetrahedron Lett.* **2004**, *45*, 6871.
182. Srikrishna, A.; Viswajanani, R.; Sattigeri, J. A.; Yeldmaggad, C. V. *Tetrahedron Lett.* **1995**, *36*, 2347.
183. (a) Srikrishna, A.; Sattigeri, J. A.; Viswajanani, R.; Yeldmaggad, C. V. *Synlett* **1995**, 93. (b) Eisch, J. J.; Liu,

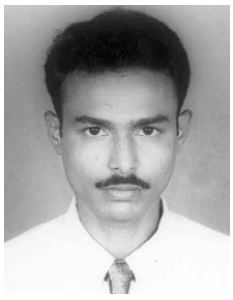
Z. R.; Boleslawski, M. P. *J. Org. Chem.* **1992**, *57*, 2143. (c) Baldwin, S. W.; Haunt, S. A. *J. Org. Chem.* **1975**, *40*, 3885. (d) Pettit, G. R.; Piatak, D. M. *J. Org. Chem.* **1962**, *27*, 2127. (e) Pettit, G. R.; Kasturi, T. R. *J. Org. Chem.* **1961**, *26*, 4553.

184. (a) Kraus, G. A.; Frazier, K. A.; Roth, B. D.; Taschner, M. J.; Neuenschwander, K. *J. Org. Chem.* **1981**, *46*, 2417. (b) Pettit, G. R.; Green, B.; Kasturi, T. R.; Ghatak, U. R. *Tetrahedron* **1962**, *18*, 953.
185. Pettit, G. R.; Dias, J. R. *J. Org. Chem.* **1971**, *36*, 3485.
186. Majumdar, K. C.; Mukhopadhyay, P. P.; Basu, P.K. *Synth. Commun.* **2005**, *35*, 1291.
187. Hartung, J.; Gottwald, T. *Tetrahedron Lett.* **2004**, *45*, 5619.
188. Gottwald, T.; Greb, M.; Hartung, J. *Synlett* **2004**, 65.
189. Keum, G.; Kang, S. B.; Kim, Y.; Lee, E. *Org. Lett.* **2004**, *6*, 1895.
190. Braune, S.; Pohlman, M.; Kazmaier, U. *J. Org. Chem.* **2004**, *69*, 468.
191. Namy, J. L.; Girard, P.; Kagan, H. *Nouv. J. Chim.* **1977**, *1*, 5.
192. (a) Dahlen, A.; Hilmersson, G. *Tetrahedron Lett.* **2002**, *43*, 7197. (b) Dahlen, A.; Hilmersson, G. *Chem. Eur. J.* **2003**, *9*, 1123. (c) Dahlen, A.; Hilmersson, G.; Knettle, B. W.; Flowers, R. A., II *J. Org. Chem.* **2003**, *68*, 4870.
193. Dahlen, A.; Petersson, A.; Hilmersson, G. *Org. Biomol. Chem.* **2003**, *1*, 2423.
194. Underwood, J. J.; Hollingworth, G. J.; Horton, P. N.; Hursthouse, M. B.; Kilburn, J. D. *Tetrahedron Lett.* **2004**, *45*, 2223.
195. Howells, D. M.; Barker, S. M.; Watson, F. C.; Light, M. E.; Hursthouse, M. B.; Kilburn, J. D. *Org. Lett.* **2004**, *6*, 1943.
196. Miyata, O.; Namba, M.; Ueda, M.; Naito, T. *Org. Biomol. Chem.* **2004**, *2*, 1274.
197. Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073.
198. O'Neill, P. M.; Mukhtar, A.; Ward, S. A.; Bickley, J. F.; Davies, J.; Bachi, M. D.; Stocks, P. A. *Org. Lett.* **2004**, *6*, 3035.
199. Wetter, C.; Studer, A. *Chem. Commun.* **2004**, 174.
200. Yanada, R.; Obika, S.; Nishimori, N.; Yamauchi, M.; Takemoto, Y. *Tetrahedron Lett.* **2004**, *45*, 2331.
201. Yanada, R.; Koh, Y.; Nishimori, N.; Matsumura, A.; Obika, S.; Mitsuya, H.; Fujii, N.; Takemoto, Y. *J. Org. Chem.* **2004**, *69*, 2417.
202. Benati, L.; Calestani, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Strazzari, S. *Org. Lett.* **2003**, *5*, 1313.
203. Majumdar, K. C.; Biswas, A.; Mukhopadhyay, P. P. *Synthesis* **2003**, 2385.
204. Tada, M.; Shijima, H.; Nakamura, M. *Org. Biomol. Chem.* **2003**, *1*, 2499.
205. Benati, L.; Leardini, R.; Minozzi, M.; Nanni, D.; Scialpi, R.; Spagnolo, P.; Zanardi, G. *Synlett* **2004**, 987.
206. Della, E. W.; Graney, S. D. *J. Org. Chem.* **2004**, *69*, 3824.
207. Friestad, G. K.; Massari, S. E. *J. Org. Chem.* **2004**, *69*, 863.
208. Tamao, K.; Ishida, N.; Ito, Y.; Kumada, M. *Organic Syntheses*; Wiley: New York, 1984; p 275.
209. Fleming, I. *Chemtracts-Org. Chem.* **1996**, *9*, 1.
210. (a) Studer, A.; Amrein, S.; Matsubara, H.; Schiesser, C. H.; Doi, T.; Kawamura, T.; Fukuyama, T.; Ryu, I. *Chem. Commun.* **2003**, 1190. (b) Matsubara, H.; Schiesser, C. H. *Org. Biomol. Chem.* **2003**, *1*, 4335.
211. Blum, A.; Hess, W.; Studer, A. *Synthesis* **2004**, 2226.

Biographical sketch

Krishna C. Majumdar received his BSc (1966) and MSc (1968) degrees from the University of Calcutta and PhD from the university of Idaho, completing his doctoral thesis in 1972 as a teaching fellow under the direction of Professor B. S. Thyagarajan. He was then awarded a research associateship with Professor Thyagarajan at the same university and in 1974 he moved to the University of Alberta as a postdoctoral fellow with Professor R. K. Brown. Next year he joined the group of Professor J. William Lown at the same university to study the mode of action of cancer antibiotics. After returning to India (1977) he was with the Birla Institute of Technology and Science as reader for a brief stint. He then moved to the University of Kalyani first as Lecturer (1977) and then as Reader (1984), Professor (1995) and Professor and Head (2003). He also served the Indian Institute of Technology (Kharagpur) for a short period as an Associate Professor (1990–91) and also North Eastern Hill University as a visiting Professor (1996). His research interests centered around synthetic organic chemistry with more than 160 publications mainly based on [1,3], [1,5], [2,3], [3,3] and [3,4]-sigmatropic rearrangements of which Claisen rearrangement is specially notable. His recent research interests also include radical reactions and design and synthesis of liquid crystals. He has also published a good number of research papers on these areas. Under his guidance 29 students have already received their PhD degrees. He is associated with the discovery of sulphoxide and amine oxide rearrangements for the synthesis of fused thiophenes and pyrroles. He has affiliation with a number of professional bodies. He has also authored a number of review articles and a book chapter. He is recipient of the Chemical Research Society of India medal (2004). He is a fellow of the West Bengal Academy of Science and Technology.

Pradipta K. Basu was placed first in first class in both his BSc and MSc in Chemistry from the University of Kalyani and received National Merit Scholarship (Govt. of India). He completed his PhD in 2003 with a UGC research fellowship from the University of Kalyani under the guidance of Prof. K. C. Majumdar. Presently he is a Lecturer in Chemistry (W. B. E. S) at Hooghly Mohsin College, Govt. of West Bengal. His research interests mainly embrace the synthesis of heterocyclic compounds by radical cyclisation and reagents leading to heterocycles. He is associated in writing a number of review articles. He is also a life member of the Indian Association for the Cultivation of Science, Kolkata, West Bengal, India.



Partha P. Mukhopadhyay was born at Barakuri, Purulia and received his BSc (1998) from the Burdwan University with a National Merit Scholarship (Govt. of India) and MSc (2000) from the University of Kalyani. He then joined the research group of Professor K. C. Majumdar as a Research Fellow (C.S.I.R.) in the same University. He worked mainly on the synthesis of heterocycles by radical cyclisation. He had also worked on sigmatropic rearrangements and synthetic methodology. He received his PhD in 2004 and is at present doing his postdoctoral research at Universite de Bourgogne, Dizon, France with Dr. Jean-Claude Chambron.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 10643–10651

Development of a new traceless aniline linker for solid-phase synthesis of azomethines. Application to parallel synthesis of a rod-shaped liquid crystalline library

Hideaki Hioki,[a,*] Mizuki Fukutaka,[a] Hideki Takahashi,[a] Miwa Kubo,[a] Kimihito Matsushita,[a] Mitsuaki Kodama,[a] Kanji Kubo,[b] Keiko Ideta[b] and Akira Mori[b,*]

[a]*Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770-8514, Japan*
[b]*Institute for Materials Chemistry and Engineering, Kyushu University, Kasuga-koen, Kasuga, Fukuoka 816-8580, Japan*

Received 20 July 2005; revised 20 August 2005; accepted 22 August 2005

Available online 19 September 2005

Abstract—A new traceless linker was developed to synthesize a library of 42 compounds possessing an azomethine linkage using combinatorial solid-phase parallel synthesis. The loading of the substrates on a solid support and cleavage from the solid support were performed by an imine synthesis and by imine-exchanged process under mild conditions, respectively. Thioesters with a hydroxy group on the central core exhibited liquid crystalline properties with the widest transition temperatures in the library.

1. Introduction

Solid-phase organic synthesis has been commonly used for combinatorial synthesis to rapidly discover new drugs and materials. Many types of linkers were recently developed in combinatorial solid-phase syntheses because the selection of an adequate linker is important to efficiently build the desired libraries.[1] Linkers should be easy to load starting materials onto the solid support, must be stable during the reactions and must be cleavable without damage to the product at the final stage. Especially, traceless linkers have advantages because the point of attachment on the solid support is not apparent in the target molecules.[2]

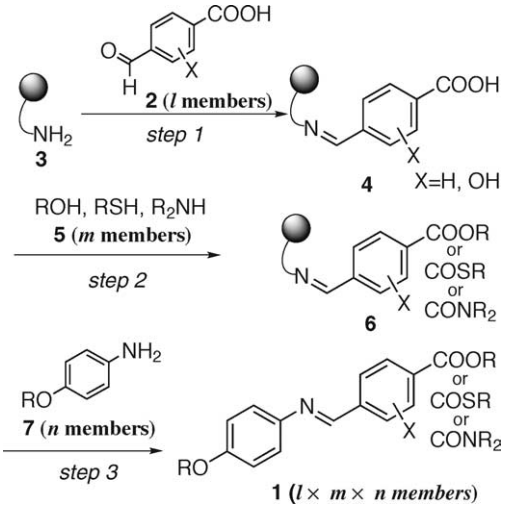
Liquid crystals are widely used in optoelectric devices and electron-transporting materials. Considerable synthetic effort and time are required to develop new liquid crystals. We previously demonstrated an efficient combinatorial synthesis to search for new liquid crystals and to systematically investigate the substitution effect on mesomorphism by preparing liquid crystalline libraries on a solid support.[3–6]

In this paper, we focus on the development of a new traceless linker to synthesize rod-shaped azomethine derivatives,[7] which are typical liquid crystals.[8]

2. Results and discussion

2.1. Development of a new aniline linker and synthesis of a liquid crystalline library

The structure of the target molecules **1** synthesized on the



Scheme 1. Synthetic plan of an azomethine-type liquid crystalline library.

Keywords: Liquid crystals; Combinatorial synthesis; Traceless linker; Azomethines.
* Corresponding authors. Tel.: +81 88 622 9611; fax: +81 88 655 3051 (H.H.); tel.: +81 92 583 7806; fax: +81 92 583 7810 (A.M.); e-mail addresses: hioki@ph.bunri-u.ac.jp; mori-a@cm.kyushu-u.ac.jp

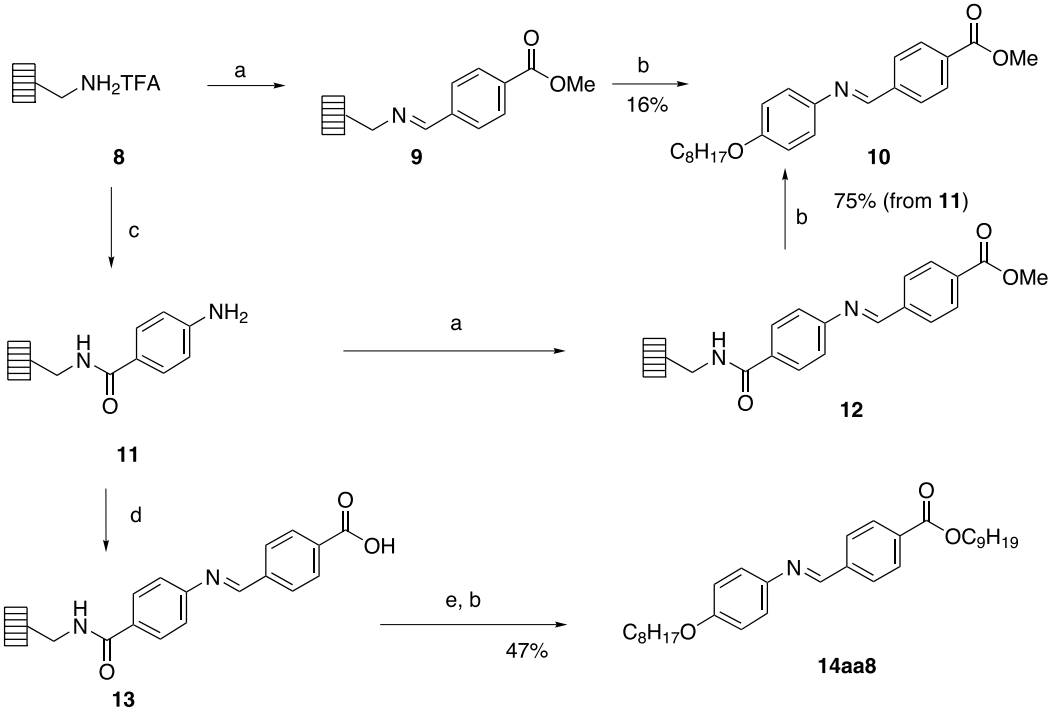
0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.08.086

solid phase is shown in Scheme 1. They are composed of a rigid aromatic core with an azomethine linkage, an alkoxy side chain, and an ester or amide group. We planned to construct a liquid crystalline library through solid-phase synthesis by employing imine-exchange reactions[9] because the target molecules **1** have no extra functional groups to attach to the solid support. In addition, because the azomethine linkage is labile to acids and bases, we designed a new linker suitable for synthesizing the liquid crystals with an azomethine linkage on a solid support under mild conditions. In the first step, *l* members of 4-formylbenzoic acids **2** are condensed with an amine **3** on the solid support to afford resin-bound azomethine **4** (step 1). In the second step, *m* members of alcohols, thiols, and amines **5** are reacted with **4** to give azomethine **6** (step 2). Finally, the azomethines on the solid support are cleaved by *n* members of 4-alkoxyanilines **7** through an imine-exchange process to give **1** (step 3). In the consecutive procedure, $l \times m \times n$ members of compounds are synthesized in these three steps.

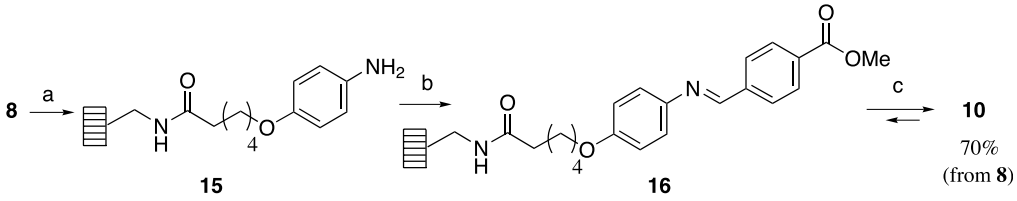
Methyl 4-formylbenzoate was linked to aminomethylated SynPhase Lantern **8**, a multipin solid support, through imine formation to give resin-bound methyl benzoate **9**. 4-Octyloxyaniline was added to proceed to the imine-exchange reaction, which gave the desired product **10** in only 16% yield due to the instability of resin-bound azomethine **9**. To stabilize the resin-bound azomethine, we synthesized a linker **11** from **8** and a 4-aminobenzoic acid derivative. The loading of methyl 4-formylbenzoate and cleavage with 4-octyloxyaniline on the resin **12** gave the azomethine **10** in 75% yield. A three-step procedure involving 4-formylbenzoic acid loading followed by condensation with 1-nonanol and cleavage with 4-octyloxyaniline afforded **14aa8** in 47% yield. This reduced yield might result from partial alcoholysis of a resin-bound azomethine **13** during the condensation step. (Scheme 2)

4-Alkoxyaniline linker **15** was synthesized to stabilize a resin-bound azomethine intermediate. Simple loading and cleavage using **15** gave the desired product **10** in 70% yield. The equilibrium between **10** and **16** was not shifted effectively in favor of **10** due to their comparable stability even addition of 4 equiv of 4-octyloxyaniline. (Scheme 3)

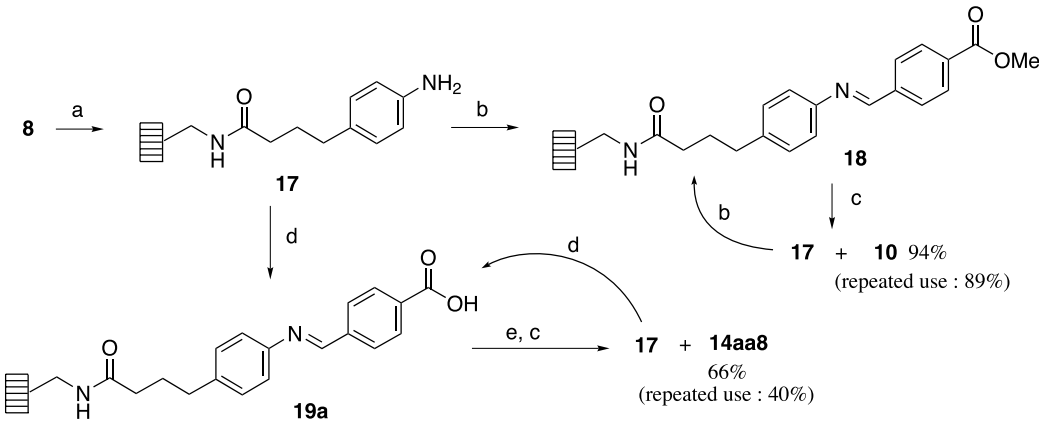
The product yields were dependent on the delicate stability balance of the resin-bound azomethine. The ideal linker should resist alcoholysis during condensation and cause an equilibrium shift favorable to the product in the final step.



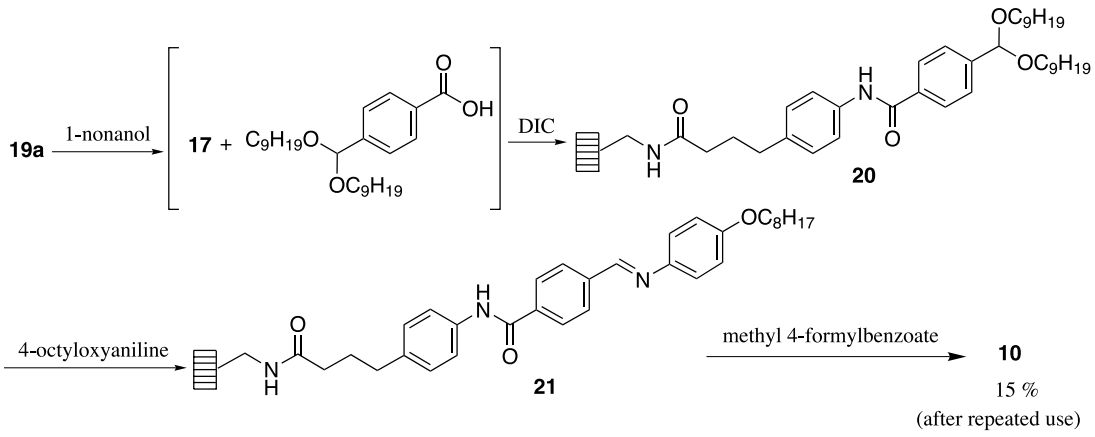
Scheme 2. Model synthesis of azomethines on a solid support from **8** or **11**. Reaction conditions: (a) methyl 4-formylbenzoate, DMF, rt, 24 h; (b) 4-octyloxyaniline, 50 °C, 3 h; (c) 4-*tert*-butoxycarbonylaminobenzoic acid, DIC, HOBt, DCM, then TFA, DCM; (d) 4-formylbenzoic acid, DMF, rt, 24 h; (e) 1-nonanol, DIC, DMAP, DCM, rt, 3 h.



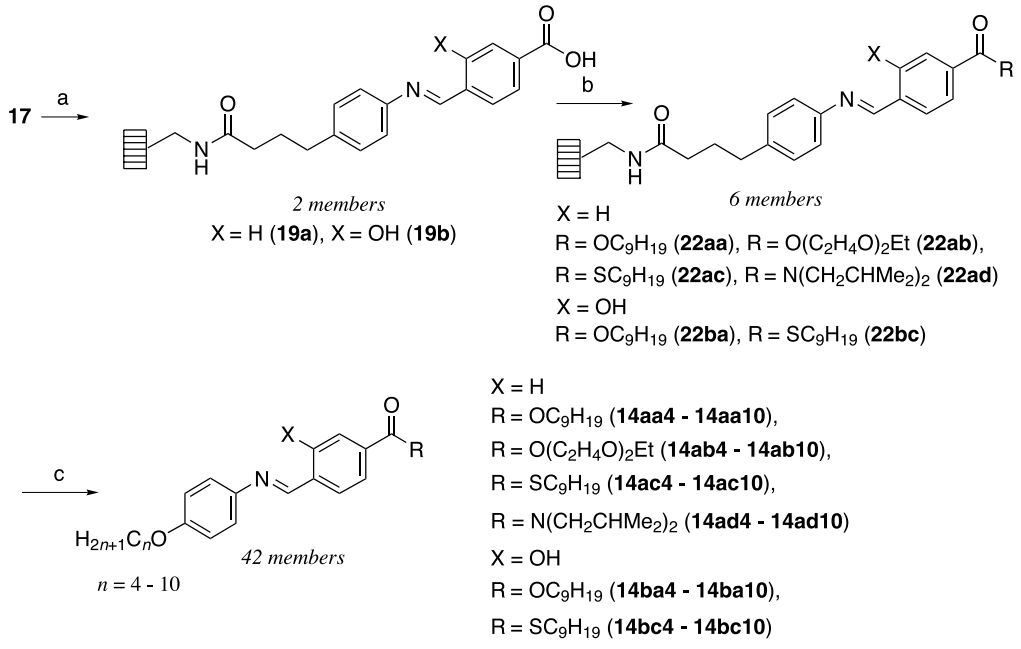
Scheme 3. Model synthesis of azomethine **10** on a solid support using an aniline linker **15**. Reaction conditions: (a) 6-(4-*tert*-butoxycarbonylaminophenoxyl)-hexanoic acid, DIC, HOBt, DCM, then TFA, DCM; (b) methyl 4-formylbenzoate, DMF, rt, 24 h; (c) 4-octyloxyaniline, 50 °C, 3 h.



Scheme 4. Model synthesis of azomethines on a solid support using an aniline linker **17**. Reaction conditions: (a) 4-(4-*tert*-butoxycarbonylaminophenyl)-butyric acid, DIC, HOBt, DCM, then TFA, DCM; (b) methyl 4-formylbenzoate, DMF, rt, 24 h; (c) 4-octyloxyaniline, 50 °C, 3 h; (d) 4-formylbenzoic acid, DMF, rt, 24 h; (e) 1-nonanol, DIC, DMAP, DCM, rt, 3 h.



Scheme 5. Partial alcoholysis and subsequent condensation in the second step.



Scheme 6. Parallel synthesis of an azomethine library on a solid support. Reaction conditions: (a) 2 kinds of 4-formylbenzoic acid (4-formylbenzoic acid, 4-formyl-3-hydroxybenzoic acid), DMF, rt, 24 h; (b) 4 kinds of alcohols, thiol, and amine (n-$C_9H_{19}OH$, $Et(OC_2H_4)_2OH$, n-$C_9H_{19}SH$, $(Me_2CHCH_2)_2NH$), DIC, DMAP, DCM, rt, 3 h; (c) 7 kinds of 4-alkoxyanilines (n=4–10), DMF, 50 °C, 24 h.

Finally, 4-alkylaniline linker **17** was investigated. (Scheme 4) The resin-bound intermediate **18** was expected to have moderate stability between **12** and **16**. The product **10** was obtained in 94% yield by simple loading and cleavage. The three-step procedure involving condensation with 1-nonanol gave **14aa8** in 66% yield.

Because the original linker **17** must be recovered after cleavage of the resin-bound azomethines, we investigated the possibility of recycling of the linker **17**. In the case of simple loading and cleavage, the yield of the repeated using was comparable to the first one. However, the yield decreased considerably from 66 to 40% for the recycling in the three-step procedure. (Scheme 4) To elucidate the details of the reaction occurred on the resin, the recycled resin was treated with methyl 4-formylbenzoate. The methylester **10** was obtained in 15% yield. This result indicates that azomethine **21** was partially formed on the solid support via alcoholysis of **19a** and consecutive condensation in the second step. (Scheme 5).

2.2. Library synthesis of rod-shaped liquid crystals

The linker **17** was most suitable for the synthesis of azomethines on the solid support in our experiment. We applied the linker **17** to parallel synthesis of a rod-shaped liquid crystalline library shown in Scheme 6. 4-Formylbenzoic acid and 4-formyl-3-hydroxybenzoic acid were linked to **17** to afford two members of resin-supported azomethines **19a** and **19b**. The reaction of **19a** with two alcohols, a thiol, and an amine gave the corresponding esters **22aa**, **22ab**, a thioester **22ac** and an amide **22ad**. On the other hand, **19b** was reacted with an alcohol and a thiol to form an ester **22ba** and a thioester **22bc**. Finally, all six members of azomethines are reacted with 7 kinds of 4-alkoxyanilines to afford the 42 final products through imine-exchange reactions. Esters **14aa4–14aa10** (n=4–10) and **14ab4–14ab10** (n=4–10) and thioesters **14ac4–14ac10** (n=4–10) were obtained in moderate yield after chromatographic purification (Table 1). On the other hand, amides **14ad4–14ad10** (n=4–10) were obtained in low yield,

Table 1. Isolated yields and transition temperatures of all library members

Compounds	X	R	n	Yield (%)	Transition temperatures (°C) and enthalpy changes (kJ mol^{-1})[a]
14aa4	H	OC_9H_{19}	4	55	Cr 58.7 (25.2) SmA 81.3 (3.3) Iso
14aa5			5	58	Cr 58.1 (27.0) SmA 76.0 (3.0) Iso
14aa6			6	59	Cr 57.8 (27.6) SmA 84.3 (3.8) Iso
14aa7			7	57	Cr 65.1 (30.4) SmA 84.4 (3.8) Iso
14aa8			8	66	Cr 63.7 (28.1) SmA 88.3 (3.9) Iso
14aa9			9	58	Cr_1 67.8 (12.4) Cr_2 70.4 (15.8) SmC 85.7 SmA 87.6 (4.2) Iso
14aa10			10	55	Cr 75.1 (17.3) SmC 80.7 SmA 89.6 (4.4) Iso
14ab4	H	$O(C_2H_4O)_2Et$	4	71	Cr 74.2 (32.2) [SmA 42.8 (3.1)] Iso[b]
14ab5			5	53	Cr 57.0 (27.5) [SmA 27.5 (2.4)] Iso
14ab6			6	57	Cr 62.2 (31.1) [SmA 40.3 (3.2)] Iso
14ab7			7	58	Cr 43.5 (23.0) [SmA 38.8 (3.0)] Iso
14ab8			8	52	Cr_1 40.0 (5.3) Cr_2 43.5 (15.3) SmA 46.7 (3.9) Iso
14ab9			9	51	Cr 58.4 (28.6) Iso
14ab10			10	60	Cr 56.9 (28.0) Iso
14ac4	H	SC_9H_{19}	4	53	Cr 78.3 (16.7) SmF 82.9 (0.8) SmA 150.8 (3.5) Iso
14ac5			5	58	Cr 72.8 (21.8) SmF 83.4 (1.1) SmC 100.5 SmA 148.5 (3.5) Iso
14ac6			6	82	Cr 70.2 (14.7) SmF 92.7 (1.6) SmC 111.2 SmA 149.8 (4.3) Iso
14ac7			7	52	Cr 75.1 (23.2) SmF 95.2 (1.8) SmC 131.0 SmA 147.8 (4.4) Iso
14ac8			8	53	Cr 76.9 (19.1) SmF 102.4 (2.3) SmC 133.7 SmA 148.7 (4.3) Iso
14ac9			9	33	Cr 87.1 (24.4) SmF 102.6 (2.9) SmC 137.4 SmA 143.5 (4.3) Iso
14ac10			10	33	Cr 90.0 (22.7) SmF 106.6 (3.4) SmC 142.6 SmA 146.1 (5.8) Iso
14ad4	H	$N(CH_2CHMe_2)_2$	4	25	Cr 98.7 Iso
14ad5			5	12	Cr 72.7 Iso
14ad6			6	18	Cr 83.3 Iso
14ad7			7	16	Cr 85.2 Iso
14ad8			8	20	Cr 105.5 Iso
14ad9			9	22	Cr 93.4 Iso
14ad10			10	24	Cr 78.5 Iso
14ba4	OH	OC_9H_{19}	4	47	Cr 70.6 (19.8) SmA 128.7 (4.2) Iso
14ba5			5	46	Cr 73.2 (21.3) SmA 123.8 (4.2) Iso
14ba6			6	52	Cr 77.0 (18.3) SmA 126.7 (4.7) Iso
14ba7			7	50	Cr 76.0 (23.3) SmC 81.0 SmA 124.0 (4.8) Iso
14ba8			8	47	Cr 85.7 (25.4) SmC 99.0 SmA 125.0 (5.0) Iso
14ba9			9	43	Cr 92.0 (27.1) SmC 113.0 (0.2) SmA 123.7 (4.6) Iso
14ba10			10	30	Cr 85.1 (31.6) SmC 118.2 (0.1) SmA 124.3 (5.4) Iso
14bc4	OH	SC_9H_{19}	4	17 (38)[c]	Cr_1 47.8 (1.3) Cr_2 62.7 (8.2) SmA 188.1 (4.4) Iso
14bc5			5	20 (38)	Cr 68.6 (13.6) SmA 185.2 (5.3) Iso
14bc6			6	18 (40)	Cr_1 55.9 (3.3) Cr_2 58.7 (8.8) SmA 185.7 (5.2) Iso
14bc7			7	21 (39)	Cr 60.1 (11.2) SmC 149.0 SmA 182.5 (5.5) Iso
14bc8			8	19 (40)	Cr 64.7 (12.5) SmC 161.0 SmA 182.1 (5.6) Iso
14bc9			9	20 (32)	Cr 71.2 (14.3) SmC 171.0 (0.2) SmA 178.6 (6.1) Iso
14bc10			10	17 (34)	Cr 70.7 (16.1) SmC 173.5 (0.2) SmA 177.6 (6.4) Iso

[a] The transition temperatures and the enthalpy changes shown in parentheses were determined by the second heating of DSC except for **14ad** series. The transition temperatures of **14ad** series were determined by the second heating of optical microscopy.
[b] Mesomorphic phases, transition temperatures and enthalpy changes in brackets were observed in the first cooling process.
[c] Values in parentheses refer to yields for 16 equiv of 1-nonanethiol in step 2.

possibly because the imine-exchange reaction between **19a** and diisobutylamine partially occurs at the second step. The yields of **14b** series (X=OH) were lower than corresponding **14a** series (X=H) probably due to partial self-condensation between a phenolic hydroxy and carboxylic group in **19b** on the resin. Addition of large excess (16 equiv) of thiol at the second step improved the yield in **14bc** series.

2.3. Mesomorphic behavior

The transition temperature and the thermal behavior of the library members were determined using a polarizing microscope equipped with a hot stage and differential scanning calorimetry (DSC) measurement. The results are summarized in Table 1. Esters **14aa4–14aa10** (n=4–10) exhibited smectic A (SmA) and C (SmC) phases, in which the SmA phase was demonstrated by observation of fan and homeotropic textures while the SmC phase was assigned by observation of fan and schlieren textures. The X-ray diffraction study of **14aa10** (n=10) indicated that the layer spacings of the SmA and SmC phases were 34.3 Å at 87 °C and 33.8 Å at 78 °C, respectively. Because the calculated molecular length of **14aa10** (n=10) is 37.1 Å, molecules should partially intercalate in the SmA phase and the molecules are tilted 24 ° in the SmC phase when they form a monolayer arrangement. On the other hand, **14ac10** (n=10) had SmA, SmC, and smectic F (SmF) phases. The SmF phase was assigned by the observation of the mosaic texture. The X-ray diffraction study of **14ac10** (n=10) indicated that the layer spacings of the SmA, SmC, and SmF phases were 33.1 Å at 145 °C, 32.2 Å at 130 °C, and 34.5 Å at 98 °C, respectively. The calculated molecular length of **14ac10** (n=10) is 37.5 Å. The molecular packing models are similar to those of **14aa10** (n=10). The layer spacing of the tilted SmF phase is slightly larger than that of the SmA phase. It might be due to that the SmA phase has more molten side chains than the SmF phase appeared at the lower temperature. Monoethyl diethylene glycol esters **14ab4–14ab10** had a less stable SmA phase monotropically. The reduction of the thermal stability of **14ab4–14ab10** might be due to the flexibility of the diethylene glycol chain. The secondary amides **14ad4–14ad10** were not mesomorphic because of the increase in molecular width of their branching.

Thioesters **14ac4–14ac10** exhibited liquid crystalline properties with the higher thermal stability compared to corresponding esters **14aa4–14aa10**, and **14ab4–14ab10**. The thermal stability of the SmA phase of **14ac4–14ac10** was enhanced by approximately 60 °C when compared with **14aa4–14aa10** because the thioester linkage is superior in linearity and longitudinal length to corresponding ester linkage.[10] The clearing temperature for **14b** series (X=OH) was 40–60 °C higher than that for **14a** series (X=H) as a result of hydrogen bond formation between azomethine nitrogen and phenolic hydrogen, which enhanced the planarity of the molecule.[11] The thioesters possessing a hydroxy group on the aromatic nuclei (**14bc** series, R=SC_9H_{19}, X=OH) showed smectic phase in the widest temperature range.

3. Conclusion

We developed a new traceless linker, which made it possible to synthesize a library of liquid crystals with an azomethine linkage using imine-exchange reactions through combinatorial solid-phase parallel syntheses. This linker has the advantage of being able to release the final product under mild conditions. Thioesters at the terminal position with hydroxy group on the central core exhibited smectic phases with the widest transition temperatures in the library consisting of 42 members. Thermal stability of the library members was explained by consideration of the linearity and planarity of the molecules and flexibility and bulkiness of the substituents of the ester and the amide groups.

4. Experimental

4.1. General

All commercially available chemicals were used without further purification except 4-alkoxyanilines. The 4-alkoxyanilines were further purified by recrystallization. The SynPhase Lantern **8** was purchased from Mimotopes Pty Ltd (Victoria, Australia). Melting points were determined using a Büchi B-545 apparatus and are uncorrected. IR spectra were recorded with a JASCO FT/IR410 spectrophotometer equipped with SensIR Technologies Durascope™ for ATR (attenuated total reflectance) and only characteristic peaks are reported. ^{1}H NMR spectra were recorded at 200 or 300 MHz with Varian Gemini-200 or Mercury-300 spectrometers, using tetramethylsilane as the internal standard. Mass spectra were taken on JEOL AX-500. Elemental analyses were performed using PerkinElmer 2400. The transition temperatures and the mesomorphic phase were observed by a polarizing microscope (Olympus BHSP BH-2) equipped with a hot stage (Linkam TH-600RMS). Enthalpy changes were measured using a differential scanning calorimeter (Seiko DSC 200). The X-ray diffraction measurements were carried out with a Rigaku Rint 2100 system using Ni-filtered Cu Kα radiation at various temperatures. The measuring temperatures were controlled with a Linkam HFS-91 hot stage.

4.2. Preparation of aniline linkers 11, 15, and 17

4.2.1. Ethyl 6-(4-*tert*-butoxycarbonylaminophenoxy)hexanoate. To a mixture of ethyl 6-[(4-methylbenzenesulfonyl)-oxy]hexanoate[12] (1.09 g, 3.47 mmol) and potassium carbonate (1.67 g, 12.1 mmol) in acetonitrile (5 mL) was added *N*-Boc-4-hydroxyaniline (0.722 g, 3.45 mmol) in acetonitrile (5 mL). The reaction mixture was heated at reflux for 17 h. After being cooled to room temperature, the reaction was quenched by addition of saturated aqueous NH_4Cl (10 mL). The mixture was extracted with ethyl acetate (3×15 mL). The combined organic layers were dried over sodium sulfate and concentrated to furnish the crude product, which was purified by flash chromatography (silica gel 45 g, ethyl acetate/hexane 1:5) followed by recrystallization (ethyl acetate/hexane) to give the product (776 mg, 2.21 mmol, 64%) as a colorless needles: mp 73.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (3H, t, J=

7.1 Hz), 1.44–1.57 (2H, m), 1.51 (9H, s), 1.69 (2H, quint, J=7.4 Hz), 1.78 (2H, quint, J=6.3 Hz), 2.33 (2H, t, J=7.4 Hz), 3.92 (2H, t, J=6.3 Hz), 4.13 (2H, q, J=7.1 Hz), 6.34 (1H, br s), 6.82 (2H, d, J=8.8 Hz), 7.24 (2H, d, J=8.8 Hz); IR (ATR) 3364, 1733, 1690 cm^{-1}; MS (CI): *m/z* 296 (100%), 351 ($[M]^+$, 59%); HRMS (CI): calcd for $C_{19}H_{29}NO_5$ ($[M]^+$), 351.2046, found 351.2057. Anal. Calcd for $C_{19}H_{29}NO_5$: C, 64.93; H, 8.32; N, 3.37. Found: C, 65.21; H, 8.55; N, 4.14.

4.2.2. 6-(4-*tert*-Butoxycarbonylaminophenoxy)hexanoic acid. To a solution of ethyl 6-(4-*tert*-butoxycarbonylaminophenoxy)hexanoate (776 mg, 2.21 mmol) in ethanol (12 mL) was added 1 M NaOH solution (4 mL). The reaction mixture was stirred at room temperature for 10 h and quenched by addition of saturated aqueous NaH_2PO_4 (10 mL). The mixture was extracted with ethyl acetate (3× 15 mL). The combined organic layers were dried over sodium sulfate and concentrated to give the crude product, which was purified by flash chromatography (silica gel 30 g, ethyl acetate) and followed by recrystallization (ethyl acetate/hexane). The product (575 mg, 1.78 mmol, 81%) was isolated as a colorless needles: mp 115 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45–1.57 (2H, m), 1.51 (9H, s), 1.71 (2H, quint, J=7.6 Hz), 1.79 (2H, quint, J=6.3 Hz), 2.39 (2H, t, J=7.6 Hz), 3.92 (2H, t, J=6.3 Hz), 6.45 (1H, br s), 6.81 (2H, d, J=8.9 Hz), 7.23 (2H, d, J=8.9 Hz); IR (ATR) 3362, 1697, 1672 cm^{-1}; MS (CI): *m/z* 268 (100%), 323 ($[M]^+$, 62%); HRMS (CI): calcd for $C_{17}H_{25}NO_5$ ($[M]^+$), 323.1733, found 323.1727. Anal. Calcd for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 63.35; H, 8.01; N, 4.51.

4.2.3. 6-(4-*tert*-Butoxycarbonylaminophenyl)butyric acid. To a mixture of 4-(4-aminophenyl)butyric acid (3.00 g, 16.7 mmol) in dioxane (25 mL) and water (25 mL) were added triethylamine (3.6 mL, 25.8 mmol) followed by di-*tert*-butyl dicarbonate (5.61 g, 25.7 mmol) in dioxane (25 mL). The reaction mixture was stirred at room temperature for 24 h and quenched slowly by addition of 3 M HCl solution (100 mL) to the reaction mixture. The mixture was extracted with ethyl acetate (3×100 mL). The combined organic layers were washed with brine (2× 60 mL), dried over sodium sulfate and concentrated to furnish the crude product, which was further purified by flash chromatography (silica gel 40 g, ethyl acetate/hexane 1:1). The product (4.36 g, 15.6 mmol, 94%) was isolated as a colorless solid: mp 119.4 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.47 (9H, s), 1.74 (2H, tt, J= 8.2, 7.4 Hz), 2.16 (2H, t, J=7.4 Hz), 2.50 (2H, t, J=8.2 Hz), 7.05 (2H, d, J=8.5 Hz), 7.36 (2H, d, J=8.5 Hz), 9.23 (1H, s); IR (ATR) 1700, 1522 cm^{-1}; MS (CI): *m/z* 223 (100%), 279 ($[M]^+$, 39%); HRMS (CI): calcd for $C_{15}H_{21}NO_4$ ($[M]^+$), 279.1471, found 279.1461. Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.64; H, 7.77; N, 5.18.

4.2.4. Acylation and Boc-deprotection on the Synphase Lantern. Four hundred and five pieces of the aminomethylated Lantern **8** (D-series, loading: 38 μmol×405, 15.4 mmol) were shaken twice for 10 min in a 1:1 solution (500 mL) of DMF and DCM containing 5% TEA. The solution was removed by decantation and the Lanterns were shaken with a 1:1 solution of DMF and DCM (3×3 min) and DCM (2×10 min). The neutralized Lanterns were reacted with 4-(4-*tert*-butoxycarbonylaminophenyl)butyric acid (8.32 g, 61.6 mmol, 4 equiv), $HOBt\cdot H_2O$ (8.32 g, 61.6 mmol, 4 equiv), and DIC (19.3 mL, 123 mmol, 8 equiv) in a 4:1 solution (220 mL) of DCM and DMF at room temperature for 15 h. The solution was removed by decantation and the Lanterns were washed with DMF (3× 3 min) and DCM (3×3 min). The *N*-protected Lanterns were shaken in DCM (500 mL, 2×3 h) containing 15% TFA. The Lanterns were washed with DMF (3×3 min) and treated with a 1:1 solution (500 mL) of DMF and DCM containing 5% TEA (2×10 min). The solution was removed by decantation and the Lanterns were washed with a 1:1 solution of DMF and DCM (2×10 min) and DCM (2×10 min) to give aniline linker **17**.

Linkers **11**, and **15** were prepared by the same procedure above from **8** and 4-*tert*-butoxycarbonylaminobenzoic acid or 6-(4-*tert*-butoxycarbonylaminophenoxy)hexanoic acid.

4.2.5. Loading of methyl 4-formylbenzoate and cleavage with 4-octyloxyaniline using the resin 8, 11, 15 and 17. Two pieces of the Lantern of the solid supported aniline **17** (A-series, loading 75 μmol×2, 150 μmol) were reacted with methyl 4-formylbenzoate (130.5 mg, 790 μmol, 5.3 equiv) in DMF solution at room temperature for 24 h. The solution was removed by decantation and the Lanterns were washed with DMF (3×0.5 min) and DCM (3× 0.5 min) to give the solid supported ester **18**. The solid supported ester **18** was reacted with 4-octyloxyaniline (132.8 mg, 4 equiv) in DMF (5 mL) at 50 °C for 3 h. The Lanterns were washed with DMF (3×3 min). The combined DMF solution was evaporated and purified by HPLC (hexane/EtOAc 9:1) to give **10** in 94% yield (51.9 mg, 141 μmol) as colorless solid. When the same procedure was applied to the recovered resin, the product **10** was obtained in 89% yield.

The same procedures were also tested to the resin **8**, **11**, and **15**. Their yields were described in the text.

Mp 135.5–136 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89 (3H, t, J=7.0 Hz), 1.21–1.54 (12H, m), 1.80 (2 H, m), 3.95 (3H, s), 3.98 (2H, d, J=6.6 Hz), 6.94 (2H, d, J=8.8 Hz), 7.27 (2H, d, J=8.8 Hz), 7.96 (2H, d, J=8.4 Hz), 8.13 (2H, d, J=8.4 Hz), 8.54 (1H, s); IR (ATR) 1721, 1621 cm^{-1}; MS (CI): *m/z* 368 ($[M+H]^+$, 100%); HRMS (CI): calcd for $C_{23}H_{30}NO_3$ ($[M+H]^+$), 368.2226, found 368.2235. Anal. Calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 75.14; H, 7.95; N, 3.78.

4.2.6. Loading of 4-formylbenzic acid, condensation with 1-nonanol and cleavage with 4-octyloxyaniline on the resin 15 and 17. Three pieces of the solid supported aniline **17** (A-series, loading 75 μmol×3, 225 μmol) were reacted with 4-carboxybenzaldehyde (179.4 mg, 1.19 mmol, 5.3 equiv) in DMF solution (4 mL) at room temperature for 24 h. The solution was removed by decantation and the Lanterns were washed with DMF (3×0.5 min), and DCM (3×0.5 min) to give the solid supported azomethine **19a**. The azomethine **19a** were reacted with 4-*N*,*N*-dimethylaminopyridine (6.9 mg, 56 μmol, 0.25 equiv), 1-nonanol (157 μL, 900 μmol, 4 equiv) and 1,3-diisopropylcarbodiimide (273 μL, 1.76 mmol, 8 equiv) in DCM (4 mL) at

room temperature for 3 h. The solution was removed by decantation and the Lanterns were washed with DMF (3×0.5 min), and DCM (3×0.5 min) to give the solid supported nonyl ester **22aa**. The solid supported ester **22aa** were reacted with 4-*n*-octyloxyaniline (202 mg, 0.91 mmol, 4 equiv) in DMF (5 mL) at 50 °C for 3 h. The Lanterns were washed with DMF (3×3 min). The combined DMF solution was evaporated and purified by HPLC (hexane/EtOAc 19:1) to give **14aa8** ($n=8$) in 66% yield (71.2 mg, 148 μmol) as pale yellow solid. When the same procedure was applied to the recovered resin, the product **14aa8** was obtained in 40% yield (43.5 mg, 90.7 μmol). The resulting lantern was treated with methyl 4-formylbenzoate (147.7 mg, 900 μmol, 4 equiv) in DMF at 50 °C for 3 h. The Lanterns were washed with DMF (3×3 min). The combined DMF solution was evaporated and purified by HPLC (hexane/EtOAc 4:1) to give **10** in 15% yield (12.4 mg, 33.7 μmol) as pale yellow solid.

The same procedures were also tested to the resin **11**. The product **14aa8** ($n=8$) was obtained in 47% yield (50.8 mg, 106 μmol) as pale yellow solid.

4.3. Parallel synthesis of liquid crystalline library on the solid support 17

4.3.1. Loading of 4-formylbenzic acid (synthesis of 19a). Eighty four pieces of the solid supported aniline **17** (D-series, loading: 38 μmol×84, 3.19 mmol) were reacted with 4-carboxybenzaldehyde (2.54 g, 16.9 mmol, 5.3 equiv) in DMF solution (80 mL) at room temperature for 24 h. The solution was removed by decantation and the Lanterns were washed with DMF (3×0.5 min), and DCM (3×0.5 min).

Compound **19b** was also synthesized by the same procedure as described above.

4.3.2. Condensation with 1-nonanol (synthesis of 22aa). Twenty eight pieces of the solid supported azomethine **19aa** (D-series, loading: 38 μmol×28, 1.06 mmol) were reacted with 4-*N*,*N*-dimethylaminopyridine (32.5 mg, 0.266 mmol, 0.25 equiv), 1-nonanol (0.74 mL, 4.2 mmol, 4 equiv) and 1,3-diisopropylcarbodiimide (1.3 mL, 8.5 mmol, 8 equiv) in DCM at room temperature for 3 h. The solution was removed by decantation and the Lanterns were washed with DMF (3×0.5 min), and DCM (3×0.5 min).

Compounds **22ab**, **22ac**, **22ad**, **22ba** and **22bc** were also synthesized by the same procedure as described above.

4.3.3. Cleavage from the solid support (synthesis of 14aa4). Two pieces of the solid supported ester **22aa** (D-series, loading: 38 μmol×2, 76 μmol) were reacted with 4-*n*-butyloxyaniline (63 mg, 0.38 mmol, 5 equiv) in DMF (5 mL) at 50 °C for 3 h. The Lanterns were washed with DMF (3×3 min). The combined DMF solution was evaporated and purified by HPLC (hexane/EtOAc 19:1) to give **14aa4** ($n=4$) in 55% yield (17.8 mg, 42.0 μmol) as pale yellow solid.

All library members were also synthesized by the same procedure as described above.

All new compounds described gave satisfied spectral and elemental analytic data. One example of spectral data for one homologue of each compound type and only elemental analytic data of new compounds are given.

4.3.3.1. Nonyl 4-[(4-butoxyphenylimino)methyl]benzoate (14aa4, $n=4$). Pale yellow needles; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (3H, t, $J=6.8$ Hz), 0.99 (3H, t, $J=7.1$ Hz), 1.28–1.60 (14H, m), 1.72–1.82 (4H, m), 3.99 (2H, t, $J=6.6$ Hz), 4.34 (2H, t, $J=6.6$ Hz), 6.93 (2H, d, $J=8.8$ Hz), 7.27 (2H, d, $J=8.8$ Hz), 7.95 (2H, d, $J=8.3$ Hz), 8.12 (2H, d, $J=8.3$ Hz), 8.54 (1H, s); IR (ATR) 1710, 1620 cm^{-1}; MS (CI): *m*/*z* 423 ([M]$^+$, 100%); HRMS (CI): calcd for $C_{27}H_{37}NO_3$ ([M]$^+$), 423.2773, found 423.2774. Anal. Calcd for $C_{27}H_{37}NO_3$: C, 76.56; H, 8.80; N, 3.31. Found: C, 76.85; H, 9.09; N, 3.37.

4.3.3.2. Nonyl 4-[(4-pentyloxyphenylimino)methyl]-benzoate (14aa5, $n=5$). Pale yellow needles. Anal. Calcd for $C_{28}H_{39}NO_3$: C, 76.85; H, 8.98; N, 3.20. Found: C, 77.03; H, 9.15; N, 3.28.

4.3.3.3. Nonyl 4-[(4-hexyloxyphenylimino)methyl]-benzoate (14aa6, $n=6$). Pale yellow needles. Anal. Calcd for $C_{29}H_{41}NO_3$: C, 77.12; H, 9.15; N, 3.10. Found: C, 77.30; H, 9.41; N, 3.23.

4.3.3.4. Nonyl 4-[(4-heptyloxyphenylimino)methyl]-benzoate (14aa7, $n=7$). Pale yellow needles. Anal. Calcd for $C_{30}H_{43}NO_3$: C, 77.38; H, 9.31; N, 3.01. Found: C, 77.64; H, 9.50; N, 3.12.

4.3.3.5. Nonyl 4-[(4-octyloxyphenylimino)methyl]benzoate (14aa8, $n=8$). Pale yellow needles. Anal. Calcd for $C_{31}H_{45}NO_3$: C, 77.62; H, 9.46; N, 2.92. Found: C, 77.76; H, 9.74; N, 3.03.

4.3.3.6. Nonyl 4-[(4-nonyloxyphenylimino)methyl]-benzoate (14aa9, $n=9$). Pale yellow needles. Anal. Calcd for $C_{32}H_{47}NO_3$: C, 77.85; H, 9.60; N, 2.84. Found: C, 78.04; H, 9.79; N, 2.99.

4.3.3.7. Nonyl 4-[(4-decyloxyphenylimino)methyl]-benzoate (14aa10, $n=10$). Pale yellow needles. Anal. Calcd for $C_{33}H_{49}NO_3$: C, 78.06; H, 9.73; N, 2.76. Found: C, 78.02; H, 9.50; N, 2.90.

4.3.3.8. 2-(2-Ethoxyethoxy)ethyl 4-[(4-butoxyphenylimino)methyl]benzoate (14ab4, $n=4$). Pale yellow needles; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (3H, t, $J=7.3$ Hz), 1.21 (3H, t, $J=7.0$ Hz), 1.51 (2H, qt, $J=7.0$, 6.6 Hz), 1.78 (2H, quint, $J=6.6$ Hz), 3.54 (2H, q, $J=7.3$ Hz), 3.63 (2H, m), 3.71 (2H, m), 3.87 (2H, t, $J=4.8$ Hz), 3.99 (2H, t, $J=6.6$ Hz), 4.52 (2H, t, $J=4.8$ Hz), 6.94 (2H, d, $J=8.8$ Hz), 7.27 (2H, d, $J=8.8$ Hz), 7.95 (2H, d, $J=8.4$ Hz), 8.15 (2H, d, $J=8.4$ Hz), 8.54 (1H, s); IR (ATR) 1705, 1621 cm^{-1}; MS (CI): *m*/*z* 413 ([M]$^+$, 100%); HRMS (CI): calcd for $C_{24}H_{31}NO_5$ ([M]$^+$), 413.2202, found 413.2188. Anal. Calcd for $C_{24}H_{31}NO_5$: C, 69.71; H,7.56; N, 3.39. Found: C, 69.86; H, 7.39; N, 3.44.

4.3.3.9. 2-(2-Ethoxyethoxy)ethyl 4-[(4-pentyloxyphenylimino)methyl]benzoate (14ab5, $n=5$). Pale yellow needles.

Anal. Calcd for $C_{25}H_{33}NO_5$: C, 70.23; H,7.78; N, 3.28. Found: C, 70.27; H, 7.90; N, 3.28.

4.3.3.10. 2-(2-Ethoxyethoxy)ethyl 4-[(4-hexyloxyphenylimino)methyl]benzoate (14ab6, $n=6$). Pale yellow needles. Anal. Calcd for $C_{26}H_{35}NO_5$: C, 70.72; H, 7.99; N, 3.17. Found: C, 70.87; H, 8.10; N, 3.16.

4.3.3.11. 2-(2-Ethoxyethoxy)ethyl 4-[(4-heptyloxyphenylimino)methyl]benzoate (14ab7, $n=7$). pale yellow needles. Anal. Calcd for $C_{27}H_{37}NO_5$: C, 71.18; H, 8.19; N, 3.07. Found: C, 71.43; H, 8.38; N, 2.95.

4.3.3.12. 2-(2-Ethoxyethoxy)ethyl 4-[(4-octyloxyphenylimino)methyl]benzoate (14ab8, $n=8$). Pale yellow needles. Anal. Calcd for $C_{28}H_{39}NO_5$: C, 71.61; H, 8.37; N, 2.98. Found: C, 71.86; H, 8.56; N, 2.97.

4.3.3.13. 2-(2-Ethoxyethoxy)ethyl 4-[(4-nonyloxyphenylimino)methyl]benzoate (14ab9, $n=9$). Pale yellow needles. Anal. Calcd for $C_{29}H_{41}NO_5$: C, 72.02; H, 8.54; N, 2.90. Found: C, 72.29; H, 8.82; N, 3.07.

4.3.3.14. 2-(2-Ethoxyethoxy)ethyl 4-[(4-decyloxyphenylimino)methyl]benzoate (14ab10, $n=10$). Pale yellow needles. Anal. Calcd for $C_{30}H_{43}NO_5$: C, 72.40; H, 8.71; N, 2.81. Found: C, 72.42; H, 8.78; N, 2.85.

4.3.3.15. *S*-Nonyl 4-[(4-butoxyphenylimino)methyl]thiobenzoate (14ac4, $n=4$). Pale yellow needles; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (3H, t, $J=6.6$ Hz), 0.98 (3H, t, $J=7.3$ Hz), 1.20–1.88 (18H, m), 3.09 (2H, t, $J=7.3$ Hz), 3.99 (2H, t, $J=6.2$ Hz), 6.94 (2H, d, $J=9.2$ Hz), 7.27 (2H, d, $J=9.2$ Hz), 7.95 (2H, d, $J=8.1$ Hz), 8.05 (2H, d, $J=8.1$ Hz), 8.53 (1H, s); IR (ATR) 1650, 1620 cm^{-1}; MS (CI): *m/z* 439 ($[M]^+$, 100%); HRMS (CI): calcd for $C_{27}H_{37}NO_2S$ ($[M]^+$), 439.2545, found 439.2569. Anal. Calcd for $C_{27}H_{37}NO_2S$: C, 73.76; H, 8.48; N, 3.19. Found: C, 73.65; H, 8.51; N, 3.24.

4.3.3.16. *S*-Nonyl 4-[(4-pentyloxyphenylimino)methyl]thiobenzoate (14ac5, $n=5$). Pale yellow needles. Anal. Calcd for $C_{28}H_{39}NO_2S$: C, 74.13; H, 8.66; N, 3.09. Found: C, 74.17; H, 8.37; N, 3.25.

4.3.3.17. *S*-Nonyl 4-[(4-hexyloxyphenylimino)methyl]thiobenzoate (14ac6, $n=6$). Pale yellow needles. Anal. Calcd for $C_{29}H_{41}NO_2S$: C, 74.47; H, 8.84; N, 2.99. Found: C, 74.68; H, 9.12; N, 3.08.

4.3.3.18. *S*-Nonyl 4-[(4-heptyloxyphenylimino)methyl]thiobenzoate (14ac7, $n=7$). Pale yellow needles. Anal. Calcd for $C_{30}H_{43}NO_2S$: C, 74.80; H, 9.00; N, 2.91. Found: C, 74.83; H, 9.21; N, 3.00.

4.3.3.19. *S*-Nonyl 4-[(4-octyloxyphenylimino)methyl]thiobenzoate (14ac8, $n=8$). Pale yellow needles. Anal. Calcd for $C_{31}H_{45}NO_2S$: C, 75.10; H, 9.15; N, 2.83. Found: C, 74.87; H, 9.39; N, 2.97

4.3.3.20. *S*-Nonyl 4-[(4-nonyloxyphenylimino)methyl]thiobenzoate (14ac9, $n=9$). Pale yellow needles. Anal. Calcd for $C_{32}H_{47}NO_2S$: C, 75.39; H, 9.29; N, 2.75. Found: C, 75.30; H, 9.53; N, 3.03.

4.3.3.21. *S*-Nonyl 4-[(4-decyloxyphenylimino)methyl]thiobenzoate (14ac10, $n=10$). Pale yellow needles. Anal. Calcd for $C_{33}H_{49}NO_2S$: C, 75.67; H, 9.43; N, 2.67. Found: C, 75.97; H, 9.75; N, 2.84.

4.3.3.22. *N*,*N*-Diisobutyl-4-[(4-butoxyphenylimino)methyl]benzamide (14ad4, $n=4$). Pale yellow needles; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.74 (6H, d, $J=6.6$ Hz), 0.99 (3H, t, $J=7.3$ Hz), 1.01 (6H, d, $J=7.0$ Hz), 1.53 (2H, m), 1.80 (3H, m), 2.14 (1H, m), 3.10 (2H, d, $J=7.3$ Hz), 3.38 (2H, d, $J=7.7$ Hz), 3.99 (2H, t, $J=6.6$ Hz), 6.94 (2H, d, $J=8.8$ Hz), 7.24 (2H, d, $J=8.8$ Hz), 7.45 (2H, d, $J=8.1$ Hz), 7.91 (2H, d, $J=8.1$ Hz), 8.52 (1H, s); IR (ATR) 1622 cm^{-1}; MS (CI): *m/z* 409 ($[M+1]^+$, 100%); HRMS (CI): calcd for $C_{26}H_{37}N_2O_2$ ($[M+H]^+$), 409.2855, found 409.2872. Anal. Calcd for $C_{26}H_{36}N_2O_2$: C, 76.43; H, 8.88; N, 6.86. Found: C, 76.62; H, 9.07; N, 6.89.

4.3.3.23. *N*,*N*-Diisobutyl-4-[(4-pentyloxyphenylimino)methyl]benzamide (14ad5, $n=5$). Pale yellow needles. Anal. Calcd for $C_{27}H_{38}N_2O_2$: C, 76.74; H, 9.06; N, 6.63. Found: C, 76.65; H, 9.37; N, 6.60.

4.3.3.24. *N*,*N*-Diisobutyl-4-[(4-hexyloxyphenylimino)methyl]benzamide (14ad6, $n=6$). Pale yellow needles. Anal. Calcd for $C_{28}H_{40}N_2O_2$: C, 77.02; H, 9.23; N, 6.42. Found: C, 77.19; H, 9.55; N, 6.43.

4.3.3.25. *N*,*N*-Diisobutyl-4-[(4-heptyloxyphenylimino)methyl]benzamide (14ad7, $n=7$). Pale yellow needles. Anal. Calcd for $C_{29}H_{42}N_2O_2$: C, 77.29; H, 9.39; N, 6.22. Found: C, 77.26; H, 9.69; N, 6.22.

4.3.3.26. *N*,*N*-Diisobutyl-4-[(4-octyloxyphenylimino)methyl]benzamide (14ad8, $n=8$). Pale yellow needles. Anal. Calcd for $C_{30}H_{44}N_2O_2$: C, 77.54; H, 9.54; N, 6.03. Found: C, 77.76; H, 9.55; N, 6.06.

4.3.3.27. *N*,*N*-Diisobutyl-4-[(4-nonyloxyphenylimino)methyl]benzamide (14ad9, $n=9$). Pale yellow needles. Anal. Calcd for $C_{31}H_{46}N_2O_2$: C, 77.78; H, 9.69; N, 5.85. Found: C, 77.79; H, 9.97; N, 5.84.

4.3.3.28. *N*,*N*-Diisobutyl-4-[(4-decyloxyphenylimino)methyl]benzamide (14ad10, $n=10$). Pale yellow needles. Anal. Calcd for $C_{32}H_{48}N_2O_2$: C, 78.00; H, 9.82; N, 5.69. Found: C, 78.12; H, 10.04; N, 5.66.

4.3.3.29. Nonyl 4-[(4-butoxyphenylimino)methyl]-3-hydroxybenzoate (14ba4, $n=4$). Yellow needles; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89 (3H, t, $J=6.8$ Hz), 0.99 (3H, t, $J=6.6$ Hz), 1.25–1.60 (14H, m), 1.70–1.86 (4H, m), 4.00 (2H, t, $J=6.6$ Hz), 4.32 (2H, t, $J=6.6$ Hz), 6.95 (2H, d, $J=9.0$ Hz), 7.30 (2H, d, $J=9.0$ Hz), 7.43 (1H, d, $J=8.1$ Hz), 7.60 (1H, dd, $J=8.1$, 1.1 Hz), 7.67 (1H, d, $J=1.5$ Hz), 8.66 (1H, s); 13.48 (1H, s); 13.50 (1H, s); IR (ATR) 1713, 1616 cm^{-1}; MS (CI): *m/z* 440 ($[M+H]^+$, 100%); HRMS (CI): calcd for $C_{27}H_{38}NO_4$ ($[M+H]^+$), 440.2801, found 440.2799. Anal. Calcd for $C_{27}H_{37}NO_4$: C, 73.77; H, 8.48; N, 3.19. Found: C, 73.79; H, 8.65; N, 3.17.

4.3.3.30. Nonyl 4-[(4-pentyloxyphenylimino)methyl]-3-hydroxybenzoate (14ba5, $n=5$). Yellow needles. Anal. Calcd for $C_{28}H_{39}NO_4$: C, 74.14; H, 8.67; N, 3.09. Found: C, 73.93; H, 8.85; N, 3.09.

4.3.3.31. Nonyl 4-[(4-hexyloxyphenylimino)methyl]-3-hydroxybenzoate (14ba6, $n=6$). Yellow needles. Anal. Calcd for $C_{29}H_{41}NO_4$: C, 74.48; H, 8.84; N, 3.00. Found: C, 74.58; H, 8.51; N, 3.11.

4.3.3.32. Nonyl 4-[(4-heptyloxyphenylimino)methyl]-3-hydroxybenzoate (14ba7, $n=7$). Yellow needles. Anal. Calcd for $C_{30}H_{43}NO_4$: C, 74.81; H, 9.00; N, 2.91. Found: C, 74.60; H, 9.20; N, 2.97.

4.3.3.33. Nonyl 4-[(4-octyloxyphenylimino)methyl]-3-hydroxybenzoate (14ba8, $n=8$). Yellow needles. Anal. Calcd for $C_{31}H_{45}NO_4$: C, 74.96; H, 9.33; N, 2.82. Found: C, 75.14; H, 9.27; N, 2.88.

4.3.3.34. Nonyl 4-[(4-nonyloxyoxyphenylimino)-methyl]-3-hydroxybenzoate (14ba9, $n=9$). Yellow needles. Anal. Calcd for $C_{32}H_{47}NO_4$: C, 75.40; H, 9.29; N, 2.75. Found: C, 75.43; H, 9.52; N, 2.79.

4.3.3.35. Nonyl 4-[(4-decyloxyphenylimino)methyl]-3-hydroxybenzoate (14ba10, $n=10$). Yellow needles. Anal. Calcd for $C_{33}H_{49}NO_4$: C, 75.68; H, 9.43; N, 2.67. Found: C, 75.48; H, 9.03; N, 2.59.

4.3.3.36. *S*-Nonyl 4-[(4-butoxyphenylimino)methyl]-3-hydroxybenzoate (14bc4, $n=4$). Light orange needles; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, $J=6.9$ Hz), 0.99 (3H, t, $J=7.1$ Hz), 1.21–1.36 (10H, m), 1.38–1.58 (4H, m), 1.68 (2H, m), 1.79 (2H, m), 3.07 (2H, t, $J=7.1$ Hz), 4.00 (2H, t, $J=6.3$ Hz), 6.95 (2H, d, $J=9.1$ Hz), 7.30 (2H, d, $J=9.1$ Hz), 7.43 (1H, d, $J=8.0$ Hz), 7.50 (1H, dd, $J=8.0$, 1.6 Hz), 7.59 (1H, d, $J=1.6$ Hz), 8.65 (1H, s), 13.55 (1H, s); IR (ATR) 1651, 1626 cm^{-1}; MS (CI): *m/z* 456 ($[M+H]^+$, 100%); HRMS (CI): calcd for $C_{27}H_{38}NO_3S$ ($[M+H]^+$), 456.2572, found 456.2589. Anal. Calcd for $C_{27}H_{37}NO_3S$: C, 71.17; H, 8.18; N, 3.07. Found: C, 71.21; H, 8.29; N, 3.45.

4.3.3.37. *S*-Nonyl 4-[(4-pentyloxyphenylimino)-methyl]-3-hydroxybenzoate (14bc5, $n=5$). Light orange needles. Anal. Calcd for $C_{28}H_{39}NO_3S$: C, 71.60; H, 8.37; N, 2.98. Found: C, 71.80; H, 8.52; N, 3.07.

4.3.3.38. Nonyl 4-[(4-hexyloxyphenylimino)methyl]-3-hydroxybenzoate (14bc6, $n=6$). Light orange needles. Anal. Calcd for $C_{29}H_{41}NO_3S$: C, 72.01; H, 8.54; N, 2.90. Found: C, 72.27; H, 8.80; N, 2.96.

4.3.3.39. *S*-Nonyl 4-[(4-heptyloxyphenylimino)-methyl]-3-hydroxybenzoate (14bc7, $n=7$). Light orange needles. Anal. Calcd for $C_{30}H_{43}NO_3S$: C, 72.39; H, 8.71; N, 2.81. Found: C, 72.38; H, 8.96; N, 2.92.

4.3.3.40. *S*-Nonyl 4-[(4-octyloxyphenylimino)methyl]-3-hydroxybenzoate (14bc8, $n=8$). Light orange needles. Anal. Calcd for $C_{31}H_{45}NO_3S$: C, 72.76; H, 8.86; N, 2.74. Found: C, 73.02; H, 9.13; N, 2.81.

4.3.3.41. *S*-Nonyl 4-[(4-nonyloxyphenylimino)-methyl]-3-hydroxybenzoate (14bc9, $n=9$). Light orange needles. Anal. Calcd for $C_{32}H_{47}NO_3S$: C, 73.10; H, 9.01; N, 2.66. Found: C, 73.08; H, 9.27; N, 2.73.

4.3.3.42. *S*-Nonyl 4-[(4-decyloxyphenylimino)methyl]-3-hydroxybenzoate (14bc10, $n=10$). Light orange needles. Anal. Calcd for $C_{33}H_{49}NO_3S$: C, 73.42; H, 9.15; N, 2.59. Found: C, 73.70; H, 9.44; N, 2.68.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.08.086

References and notes

1. Guillier, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091–2157.
2. Blaney, P.; Grigg, R.; Sridharan, V. *Chem. Rev.* **2002**, *102*, 2607–2624. Takahashi, T.; Inoue, H.; Yamamura, Y.; Doi, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 3230–3233.
3. Mori, A.; Akahoshi, I.; Hashimoto, M.; Doi, T.; Takahashi, T. *Tetrahedron Lett.* **2004**, *45*, 813–815.
4. Hashimoto, M.; Mori, A.; Inoue, H.; Nagamiya, H.; Doi, T.; Takahashi, T. *Tetrahedron Lett.* **2003**, *44*, 1251–1254.
5. Haino, T.; Tanaka, M.; Ideta, K.; Kubo, K.; Mori, A.; Fukazawa, Y. *Tetrahedron Lett.* **2004**, *45*, 2277–2279.
6. Kang, S.; Thisayukta, J.; Takezoe, H.; Watanabe, J.; Ogino, K.; Doi, T.; Takahashi, T. *Liq. Cryst.* **2004**, *31*, 1323–1336.
7. The preliminary account has been published. Hioki, H.; Fukutaka, M.; Takahashi, H.; Kodama, M.; Kubo, K.; Ideta, K.; Mori, A. *Tetrahedron Lett.* **2004**, *45*, 7591–7594.
8. Demus, D.; Goodby, J.; Gray, G. W.; Spiess, H.-W.; Vill, V. *Handbook of Liquid Crystals*; VCH: Weinheim, 1998.
9. Condensation of resin-bound aniline and aromatic aldehydes was reported, see: Patteux, C.; Levacher, V.; Dupas, G. *Org. Lett.* **2003**, *5*, 3061–3063.
10. Kelker, H.; Hatz, R. *Handbook of Liquid Crystals*; Chemie GmbH: Weinheim, 1998; p 55.
11. Sakagami, S.; Takase, A. *Chem. Lett.* **1995**, 521–522.
12. Burns, D. H.; Miller, J. D.; Chan, H.-K.; Delaney, M. O. *J. Am. Chem. Soc.* **1997**, *119*, 2125–2133.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 10652–10666

Δ^3-Aryl/heteroaryl substituted heterocycles via sequential Pd-catalysed termolecular cascade/ring closing metathesis (RCM)

H. Ali Dondas,[a,b] Blandine Clique,[a] Bekir Cetinkaya,[c] Ronald Grigg,[a,*] Colin Kilner,[a] James Morris[a] and Visuvanathar Sridharan[a]

[a]*Molecular Innovation, Diversity and Automated Synthesis (MIDAS) Centre, School of Chemistry, Leeds University, Leeds LS2 9JT, UK*
[b]*Department of Chemistry, Faculty of Pharmacy, Mersin University, Yenisehir, 33342 Mersin, Turkey*
[c]*Chemistry Department, Science Faculty, Ege University, Bornova, İzmir, Turkey*

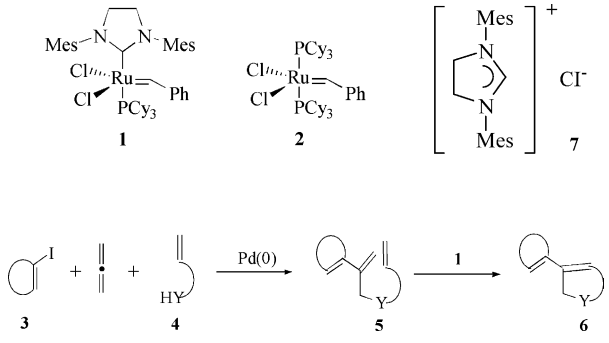
Received 24 June 2005; revised 5 August 2005; accepted 19 August 2005

Available online 15 September 2005

Abstract—A novel sequential Pd-catalysed termolecular allenylation cascade/Ru catalysed RCM process affords a diverse range of Δ^3-aryl/heteroaryl substituted five–seven membered nitrogen and oxygen heterocycles. Further elaboration, via 1,3-dipolar cycloaddition, in selected cases, afforded fused heterocyclic ring systems.

1. Introduction

Multicomponent cascade reactions are highly attractive from a drug discovery point of view.[1,2] Products of high complexity and diversity, which are often difficult to synthesize in a stepwise linear fashion, can be quickly accessed in a single reaction vessel. Our own efforts in this area have recently focused on employing allenes as 3-carbon building blocks in Pd-catalysed molecular queuing processes, which, combined with core organic reactions, afford products, which are of high synthetic value. Recent examples include termolecular Pd-catalysed allenylation/1,3-dipolar cycloadditions,[3,4] Pd/In Barbier type allylation,[5] and Petasis/Pd termolecular queuing processes.[6] Ring closing metathesis continues to be a highly popular reaction for the formation of carbo- and heterocyclic ring systems.[7,8] This is largely to the discovery of air-stable, second generation Ru catalysts, such as **1**, which exhibit higher thermal stability and wider functional group tolerance than parent complex **2**.[9–11] The formation of previously unattainable tri-and tetrasubstituted double bonds by **1** has also extended the scope of this excellent reaction.[12,13] Our previous work in this area has involved combination of RCM with a subsequent Heck reaction affording fused, spiro and bridged ring heterocycles.[14] Examples of strategies involving a fluorous biphasic solvent system and polymer support palladium catalyst were developed, which afforded good yields of bridged tricyclic heterocycles.[15] In other studies, we combined our palladium-catalysed cyclisation-anion capture methodology with subsequent RCM as an additional strategy for the synthesis of fused, spiro and bridged ring heterocycles.[16] Further studies showed *N*-allyl-anilines,[17] and isoquinoline and β-carboline enamines[18] were viable RCM substrates with the first generation catalyst **2**. We now report in full a 3-component Pd-catalysed cascade process employing an aryl/heteroaryl/vinyl iodide **3**, allene gas and an alkene tethered nucleophile **4**, which when coupled with RCM affords a novel and diverse strategy for the synthesis of heterocycles **6** (Scheme 1).[19–21]



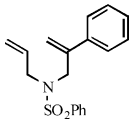
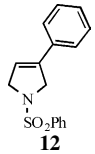
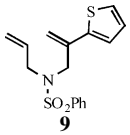
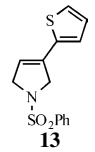
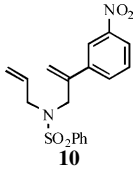
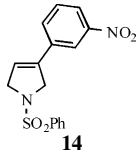
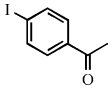
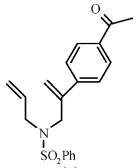
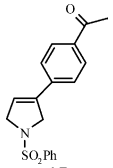
Scheme 1.

Our initial studies employed *N*-allylbenzene sulphonamide as the nucleophile in the 3-component cascade and $Pd(OAc)_2$ (10 mol%) and PPh_3 (20 mol%) as the catalyst system. 1,6-Dienes **8–11** were obtained in 79–88% yield

Keywords: Ruthenium; Allene; Dipolar cycloaddition; Azomethine ylides.
* Corresponding author. Tel.: +44 113 343 6501; fax: +44 113 233 6501; e-mail: r.grigg@chem.leeds.ac.uk

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.08.078

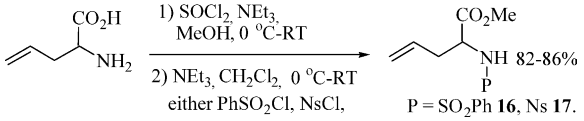
Table 1. 3-Pyrrolines via sequential pd catalysed cascade synthesis of *N*,*N*-diallylsulphonamides/RCM

Entry	Aryl/heteroaryl/vinyl iodide	Pd-cascade product[a]	Yield (%)	RCM product[b]	Yield (%)[c]
1		 **8**	86[a]/(86)[d]	 **12**	74
2		 **9**	79[a]/(72)[d]	 **13**	73
3		 **10**	85[a]/(68)[d]	 **14**	85
4		 **11**	88[a]/(70)[d]	 **15**	75

[a] Reactions carried out in toluene at 80 °C for 18 h and employed 1 mmol aryl/heteroaryl/vinyl iodide, 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, 2 mol equiv K_2CO_3, allene (1 bar) and 1 mol equiv of *N*-allylbenzene sulphonamide.
[b] Reactions carried out in toluene at 80 °C for 2–4 h and employed 5 mol% of catalyst **1**.
[c] Isolated yield.
[d] Reactions carried out in toluene at 80 °C for 16 h and employed 1 mmol aryl/heteroaryl/vinyl iodide, 2 mol% $Pd(OAc)_2$, 4 mol% of salt **7**, 3 mol equiv Cs_2CO_3, allene (0.5 bar) and 1 mol equiv of *N*-allylbenzene sulphonamide.

(Table 1).[22] We have also utilized a low loading (2 mol%) palladium/dihydroimidazol-2-ylidine catalyst system for the synthesis of the 1,6-dienes.[5,15] In this latter case, aryl/heteroaryl/vinyl iodides (1 mmol) reacted with allene (0.5 atm), $Pd(OAc)_2$ (2 mol%), salt **7** (4 mol%), Cs_2CO_3 (3 mol equiv) and *N*-allylbenzene sulphonamide in toluene at 70–80 °C over 16 h to give **8–11** (Table 1, entries 1–4) in 68–86% yield

Subjecting dienes **8–11** to **1** in toluene at 80 °C afforded Δ^3-pyrrolidines **12–15** in 73–94% yield (Table 1). With the process successfully established variation of the nucleophile tether was investigated. Nucleophile **16** was readily prepared in 86% yield from commercially available racemic allyl glycinate (Scheme 2). Employing the above conditions in the multi-component Pd-cascade afforded the α,ω-dienes **18–26** in yields of 41–81% (Table 2). The addition of tetraalkylammonium salt NEt_4Cl was found to be beneficial in this case.[23] Subjecting **18–26** to **1** in toluene at 80 °C afforded Δ^3- tetrahydropyridines **27–35** in 75–96% yield. Electron rich, deficient or sterically encumbered aryl groups

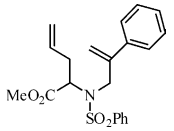
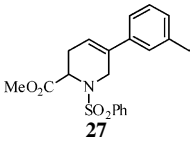
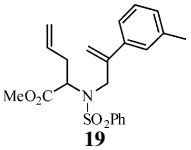
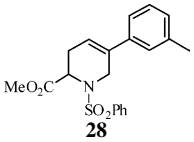
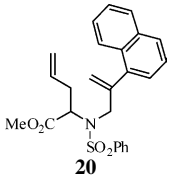
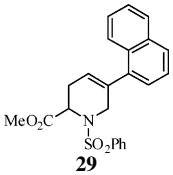
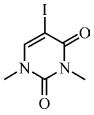
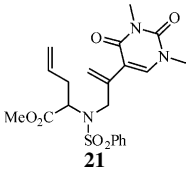
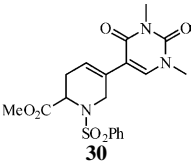
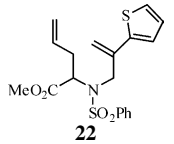
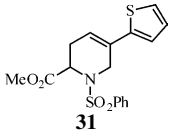
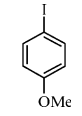
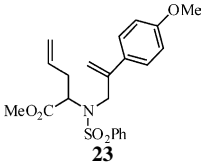
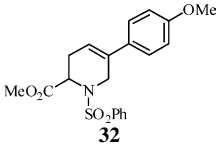
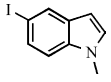
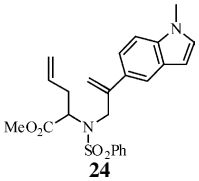
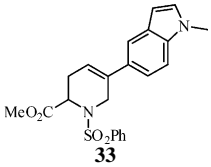
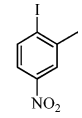
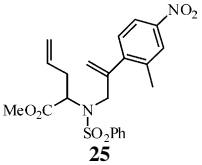
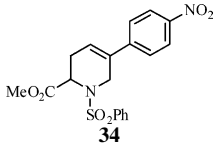
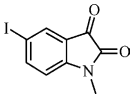
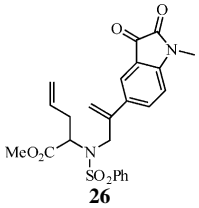
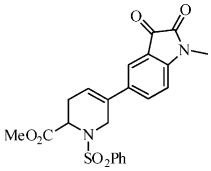


Scheme 2.

can thus be incorporated into this process with equal success. The poor yield in the Pd-cascade for entry 9 may be the result of nucleophilic attack of **16** on the activated carbonyl of the isatin. A limited investigation into nitrogen protecting groups for methyl allylglycinate (Scheme 2) showed the 2,4-dinitrobenzenesulfonyl (DNs) and Boc groups to be incompatible with the Pd-cascade conditions. However, the 4-nitrobenzenesulfonyl (Ns)[24] group proved to be suitable and nucleophile **17** was employed in the 3-component Pd-cascade process to afford **36–38** in 43–71% yield (Table 3). On subjecting **36–38** to **1** tetrahydropyridines **39–41** were formed in 76–98% yield (Table 3). Facile removal of the Ns group afforded the pipecolinic acid derivatives **42** and **43** in 83 and 70% yield, respectively, (Scheme 3).

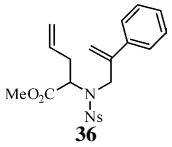
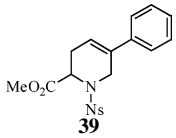
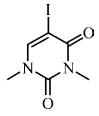
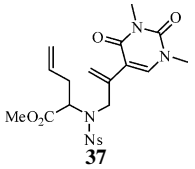
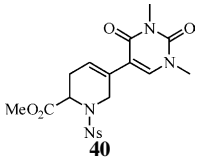
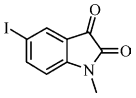
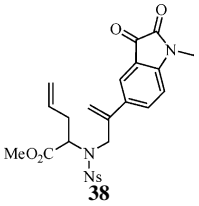
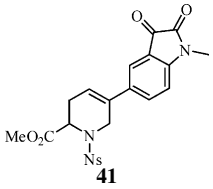
The free amino esters allowed further structural elaboration through cycloaddition chemistry. Refluxing **42**, benzaldehyde and *N*-methyl maleimide (NMM) in toluene afforded a 3.5:1 mixture of *endo* and *exo* cycloadducts **44** and **45** (Scheme 4) arising from the *syn*-dipole formed from the iminium ion generated in situ from **42** and benzaldehyde.[25] The structure of the major isomer **44** was established by X-ray crystallography (Fig. 1) and that of the minor isomer **45** by NOE studies and coupling constants. These structures are in agreement with previous related work.[26] Refluxing **42** and **43** with salicylaldehyde **46** afforded cycloadducts **47** and **48** in 56 and 54% yield, respectively.[27] The relative stereochemistry of **47** and **48** was assigned from chemical

Table 2. 3-Piperideines via sequential cascade synthesis of *N*-allyl-*N*-homoallylsulphonamides/RCM

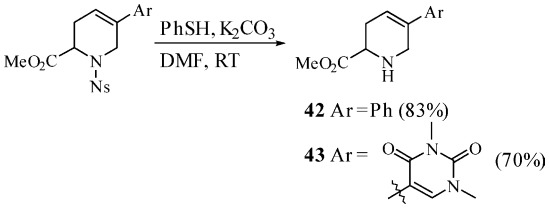
Entry	Aryl/heteroaryl/vinyl iodide	Pd-cascade product[a]	Yield (%)	RCM product[b]	Yield (%)[c]
1		 **18**	81	 **27**	77
2		 **19**	80	 **28**	75
3		 **20**	70	 **29**	75
4		 **21**	70	 **30**	84
5		 **22**	71	 **31**	71
6		 **23**	68	 **32**	96
7		 **24**	80	 **33**	83
8		 **25**	72	 **34**	74
9		 **26**	41	 **35**	83

[a] Reactions were carried out in toluene at 80 °C for 18 h and employed 1 mmol aryl/heteroaryl/vinyl iodide, 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, 2 mol equiv K_2CO_3, allene (1 bar), 1 mol equiv NEt_4Cl and 1 mol equiv **7**.
[b] Reactions were carried out in toluene at 80 °C for 2–4 h and employed 5 mol% of catalyst **1**.
[c] Isolated yield.

Table 3. Sequential Pd/Ru processes employing 4-nitrobenzenesulphonyl protection

Entry	Aryl/heteroaryl/vinyl iodide	Pd-cascade product[a]	Yield (%)	RCM product[b]	Yield (%)[c]
1		 **36**	71	 **39**	98
2		 **37**	67	 **40**	93
3		 **38**	43	 **41**	76

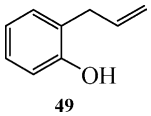
[a] Reactions carried out in toluene at 80 °C for 18 h and employed 1 mmol aryl/heteroaryl/vinyl iodide, 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, 2 mol equiv K_2CO_3, allene (1 bar), 1 mol equiv NEt_4Cl and 1 mol equiv **7**.
[b] Reactions carried out in toluene at 80 °C for 2–4 h and employed 5 mol% of catalyst **1**.
[c] Isolated yield.



Scheme 3.

shift values, coupling constants and NOE studies and is in agreement with related work previously reported by our group (Scheme 5).[28]

There has been comparatively little exploration of RCM routes to benzoxepines although there are examples involving both α,ω-diene and ene-yne precursors.[14,29] This lack of examples encouraged us to explore the alkene tethered oxygen nucleophile **49** in our Pd cascade/RCM process with three representative aryl iodides. The Pd-cascade afforded dienes **53–55** in 78–80% yield (Table 4). The RCM reaction of these dienes, utilizing **1**, proved to be more sluggish than for the formation of the five- and six-membered *N*-heterocycles and reaction times of 18 h were required to afford moderate yields of **56–58** (Table 4, 56–62%).


49

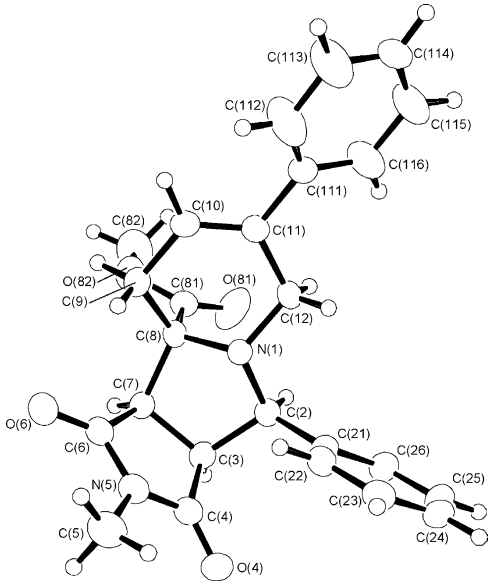
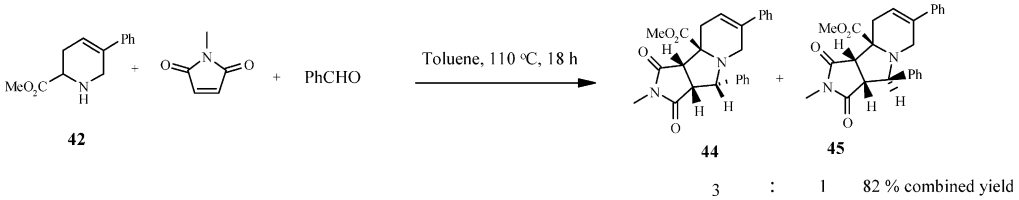
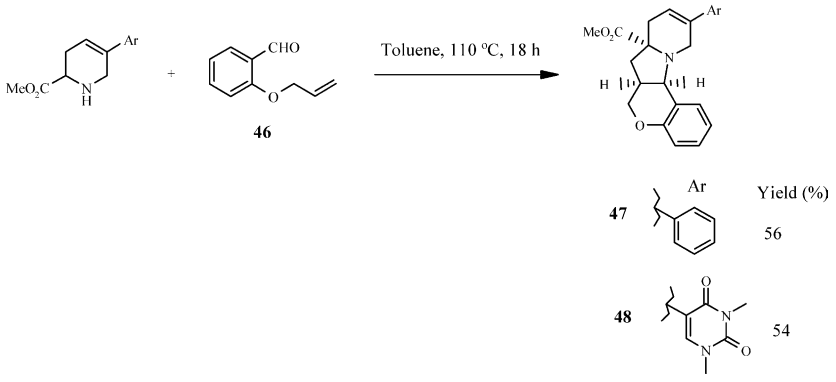


Figure 1. X-ray structure of **44**.

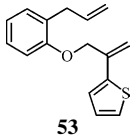
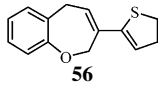
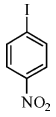
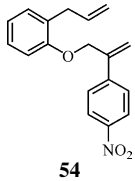
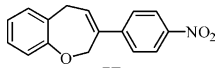
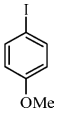
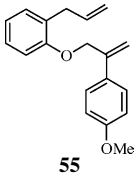
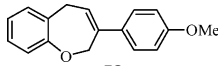


Scheme 4.



Scheme 5.

Table 4. Benzoxapines via sequential pd catalysed cascade synthesis/RCM

Entry	Aryl/heteroaryl/vinyl iodide	Pd-cascade product[a]	Yield (%)	RCM product[b]	Yield (%)[c]
1		 **53**	78	 **56**	69
2		 **54**	78	 **57**	62
3		 **55**	80	 **58**	56

[a] Reactions were carried out in toluene at 80 °C for 18 h and employed 1 mmol aryl/heteroaryl iodide, 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, 2 mol equiv K_2CO_3, allene (1 bar), and 1 mol equiv **7**.
[b] Reactions were carried out in toluene at 80 °C for 18 h and employed 5 mol% of catalyst **1**.
[c] Isolated yield.

In summary, a novel and diverse route accessing 3-aryl/heteroaryl/vinyl substituted heterocycles has been developed via the sequential employment of a chemoselective 3-component Pd-cascade/RCM sequence. An investigation into the compatibility of other alkene-tethered nucleophiles in this process is currently underway.

2. Experimental

Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. Mass spectral data were obtained from a VG Autospec instrument operating at 70 eV (EI and FAB) or ZD 2000 electrospray instrument (ES). Accurate molecular masses were obtained from the EPSRC Swansea Mass Spectroscopy service using perfluorotributylamine or polyethylenimine as an internal standard. Microanalyses were obtained using a Carbo Erba MOD11016 instrument. IR spectra were determined on a Nicolet Magna FT-IR 560 spectrometer. The IR samples were prepared as thin films by evaporation of a solution of the compound in DCM onto a germanium plate. X-ray structural data were collected on a Stadi 4-circle diffractometer. Column chromatography was performed using silica gel 60 (Merck, 230–400 mesh). Nuclear magnetic resonance spectra were recorded on Bruker DPX250, DPX300 and DPX500 instruments operating at 250, 300 and 500 MHz, respectively. Solvents were dried according to established methods,[30] unless purchased dry from Aldrich in sure-seal bottles. Palladium acetate was supplied by Johnson Matthey and ruthenium alkylidene catalysts were purchased from Strem and Aldrich and used as received. The term ether refers to diethyl ether and the term petrol refers to the 40–60 °C boiling point fraction of petroleum ether. All the compounds are named according to the IUPAC system and names were obtained using the ACD/*i*-Lab software.

2.1. General termolecular cascade procedure

With PPh_3 ligands. Palladium acetate (23 mg, 0.1 mmol), triphenylphosphine (53 mg, 0.2 mmol), potassium carbonate (276 mg, 2 mmol), tetraethylammonium chloride

(166 mg, 1 mmol) for **18–26** and toluene (8 ml) were added to a Schlenk tube, containing a magnetic stirrer bar. A solution of the nucleophile (1 mmol), and aryl iodide (1–1.2 mmol) in toluene (2 ml) was then added. The tube was then sealed and the mixture frozen in liquid nitrogen, and degassed by vacuum pump. The solid mixture was then allowed to reach room temperature, resulting in a liquid mixture, followed by re-freezing and degassing for a second time. Allene (1 bar) was then added to the Schlenk tube, and the mixture heated in an oil bath at 80 °C for 40 h. On completion of the reaction the excess gas was released and the mixture filtered. Concentration of the filtrate in vacuo afforded the crude product, which was purified by flash chromatography.

With in situ generated carbene ligands. *N*-Sulfonylpropargylamine (1 mol equiv), aryl iodide (1.1 mol equiv), palladium acetate (2 mol%), 1,3-dimesityl-4,5-dihydroimidazol-2-ylidine (4 mol%) and cesium carbonate (3 mol equiv) were dissolved in toluene (10 ml) in a Schlenk tube. The mixture was subjected to two freeze, pump, thaw cycles, charged with allene (0.5 atm), stirred for 16–18 h at 70–80 °C, cooled, excess allene vented and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography.

2.1.1. *N*-Allyl-*N*-(2-phenyl-allyl)-benzenesulfonamide (8). The product was isolated as a pale yellow oil (86%); (Found: C, 69.20; H, 5.90; N, 4.30; S, 10.20; $C_{18}H_{19}NO_2S$ requires C, 69.00; H, 6.11; N, 4.50; S, 10.20%); ν_{max}/cm^{-1} (CH_2Cl_2 solution) 1635 (C=C), 1344 (S=O_{as}), 1161 (S=O_s), 991 (CH), 911; δ_H (250 MHz; $CDCl_3$) 7.75 (2H, dd, $J=8.5$, 1.2 Hz, $PhSO_2$), 7.25–7.47 (8H, m, Ph and $PhSO_2$), 5.52–5.38 (1H, m, CH=), 5.43 (1H, s, CH_2=), 5.21 (1H, s, CH_2=), 5.06 (1H, d, $J=10.1$ Hz, CH_{cis}H=CH), 5.04 (1H, d, $J=16.2$ Hz, CHH_{trans}=CH), 4.24 (2H, s, CH_2–C=), 3.73 (2H, d, $J=6.5$ Hz, CH_2–CH=); δ_C (50 MHz; $CDCl_3$) 142.9, 140.4, 138.9, 133.1 132.6, 129.6, 128.9, 128.5, 127.7, 126.9, 119.9, 116.9, 50.9, 49.9; *m/z* (%) 313 (10, M^+), 210 (70, M−$PhCCH_2$), 172 (41, M−$PhSO_2$), 141 (74, $PhSO_2$), 118 (79, PhC=CH_2CH_3), 77 (100, Ph).

2.1.2. *N*-Allyl-*N*-(2-thiophen-2-yl-allyl)benzenesulfonamide (9). The product was isolated as a pale yellow oil (79%); (Found: C, 59.90; H, 5.20; N, 4.10; S, 20.00; $C_{16}H_{17}NO_2S_2$ requires C, 60.20; H, 5.36; N, 4.40; S, 20.10%); ν_{max}/cm^{-1} (CH_2Cl_2 solution) 1653 (C=C), 1341 (S=O_{as}), 1163 (S=O_s), 998 (CH), 900 (CH); δ_H (250 MHz; $CDCl_3$) 7.83 (2H, dd, $J=8.4$, 1.5 Hz, $PhSO_2$), 7.46–7.55 (3H, m, $PhSO_2$), 6.94 (1H, dd, $J=5.1$, 3.7 Hz, thienyl-H), 7.14 (1H, d, $J=5.1$ Hz, thienyl-H), 7.22 (1H, d, $J=3.5$ Hz, thienyl-H), 5.52 (1H, s, CH_2=), 5.47–5.38 (1H, m, CH=), 5.09 (1H, s, CH_2=), 5.07 (1H, d, $J=10.0$ Hz, CHH_{cis}=CH), 5.03 (1H, dd, $J=16.2$, 1.1 Hz, CH_{trans}H=CH), 4.19 (2H, s, CH_2–C=), 3.82 (2H, d, $J=6.5$ Hz, CH_2–CH=); δ_C (50 MHz; $CDCl_3$) 142.2, 140.4, 136.2, 133.1, 132.3, 129.6, 128.1, 127.7, 125.2, 120.0, 115.1, 50.8, 50.1; *m/z* (%) 319 (6, M^+), 210 (50, M−$PhCCH_2$), 178 (52, M−$PhSO_2$), 141 (66, $PhSO_2$), 124 (100, thiophen-C=CH_2CH_3), 109 (56, thiophen-C=CH_2), 77 (95, Ph).

2.1.3. *N*-Allyl-*N*-[2-(3nitrophenyl)allyl]benzenesulfonamide (10). The product was isolated as a pale yellow solid (85%); mp 75–77 °C; (Found: C, 60.10; H, 5.15; N, 7.80; S, 8.80; $C_{18}H_{18}N_2O_4S$ requires C, 60.30; H, 5.10; N, 7.80; S, 8.90%); ν_{max}/cm^{-1} (CH_2Cl_2 solution) 1653 (C=C), 1636 (C=C), 1528 (NO_2), 1347 (S=O_{as}), 1161 (S=O_s), 998; δ_H (250 MHz; $CDCl_3$) 8.23 (1H, d, $J=1.9$ Hz, $PhNO_2$), 8.15 (1H, d, $J=8.4$ Hz, $PhNO_2$), 7.78–7.81 (3H, m, $PhNO_2$ and $PhSO_2$), 7.47–7.60 (4H, m, $PhNO_2$ and $PhSO_2$), 5.60 (1H, s, CH_2=), 5.36–5.50 (1H, m, CH=), 5.38 (1H, s, CH_2=), 5.12 (1H, dd, $J=10.1$, 0.8 Hz, CH_{cis}H=CH), 5.07 (1H, dd, $J=16.1$, 1.1 Hz, CH_{trans}H=CH), 4.27 (2H, s, CH_2–C=), 3.76 (2H, d, $J=6.5$ Hz, CH_2–CH=); δ_C (50 MHz; $CDCl_3$) 148.7, 141.3, 140.4, 140.1, 133.2, 133.1, 132.2, 129.9, 129.6, 127.6, 123.2, 121.9, 120.3, 119.4, 50.8, 50.2; *m/z* (%) 358 (1, M^+), 210 (21, M−$PhCCH_2$), 141 (29, $PhSO_2$), 77 (100, Ph).

2.1.4. *N*-[2-(4-Acetyl-phenyl)-allyl]-*N*-allyl-benzenesulfonamide (11). The product was isolated as a pale orange solid. (88%); mp 100–102 °C; ν_{max}/cm^{-1} (CH_2Cl_2 solution) 1682 (C=O), 1345 (S=O_{as}), 1162 (S=O_s), 998 (CH), 925 (CH), 847 (PhCOMe); δ_H (250 MHz; $CDCl_3$) 7.92 (2H, d, $J=8.5$ Hz, PhCOMe), 7.79 (2H, dd, $J=8.5$, 1.3 Hz, $PhSO_2$), 7.44–7.53 (5H, m, PhCOMe and $PhSO_2$), 5.57 (1H, s, CH_2=), 5.30–5.50 (1H, m, CH=), 5.34–5.04 (2H, m, C$H_{cis}H_{trans}$=C), 5.09 (1H, s, CH_2=), 4.27 (2H, s, CH_2–C=), 3.74 (2H, d, $J=6.5$ Hz, CH_2–CH=), 2.62 (3H, s, CH_3); δ_C (50 MHz; $CDCl_3$) 198.2 (C=O), 143.4, 142.2, 140.2, 136.9, 133.1, 132.3, 129.6, 128.9, 127.6, 127.1, 120.0, 118.8, 50.8, 49.9, 27.1; *m/z* (%) 355 (9, M^+), 210 (77, M−$PhCCH_2$), 141 (72, M−$PhSO_2$), 77 (100, Ph), 43 (58, allyl); HRMS Found: 355.1242, $C_{20}H_{21}NO_3S$ requires 355.1245.

2.2. General ring closing metathesis procedure

Grubbs' second generation catalyst (5 mol%) was added to a magnetically stirred solution of the diene (0.13 mmol), in anhydrous toluene (40 ml) and the mixture stirred under an argon atmosphere at 80 °C for 2–4 h. Concentration in vacuo afforded the crude product as a brown oil, which was purified by flash chromatography.

2.2.1. 1-Benzenesulfonyl-3-phenyl-2,5-dihydro-1*H*-pyrrole (12). The product was isolated as a pale yellow solid (34 mg, 74%); mp 120–122 °C; ν_{max}/cm^{-1} (CH_2Cl_2 solution) 1446 (Ph C=C), 1339 (S=O_{as}), 1167 (S=O_s), 830 (CH); δ_H (250 MHz; $CDCl_3$) 7.89 (2H, dd, $J=8.2$, 1.5 Hz, $PhSO_2$), 7.53–7.58 (3H, m, $PhSO_2$), 7.29–7.33 (5H, m, Ph), 6.01 (1H, qi, $J=2.1$ Hz, CH=), 4.29–4.34 and 4.48–4.53 (4H, m, CH_2–C= and CH_2–CH=); δ_C (50 MHz; $CDCl_3$) 137.7, 137.4, 133.3, 132.8, 129.7, 129.1, 128.9, 127.8, 125.8, 119.3, 56.1, 55.3; *m/z* (%) 285 (8, M^+), 144 (54, M−$PhSO_2$), 77 (93, Ph), 41 (100, allyl).

2.2.2. 1-Benzenesulfonyl-3-thiophen-2-yl-2,5-dihydro-1*H*-pyrrole (13). The product was isolated as a colourless solid (38 mg, 82%); mp 105–107 °C; Found: C, 57.50; H, 4.35; N, 4.60; S, 21.90; $C_{16}H_{15}NO_2S$ requires C, 57.70; H, 4.50; N, 4.80; S, 22.00%; ν_{max}/cm^{-1} (CH_2Cl_2 solution) 1339 (S=O_{as}), 1166 (S=O_s), 830 (CH); δ_H (250 MHz; $CDCl_3$) 7.88 (2H, dd, $J=7.8$, 1.4 Hz, $PhSO_2$), 7.54–7.59

(3H, m, $PhSO_2$), 7.22 (1H, d, $J=5.3$ Hz, thienyl-H), 6.96 (1H, dd, $J=5.3$, 3.5 Hz, thienyl-H), 6.88 (1H, m, thienyl-H), 6.01 (1H, qi, $J=2.0$ Hz, CH=), 4.25–4.34 and 4.43–4.45 (4H, m, CH_2–C= and CH_2–CH=); δ_C (50 MHz; $CDCl_3$) 137.3, 136.4, 133.3, 132.2, 129.7, 128.0, 127.8, 125.9, 125.2, 118.6, 55.8, 55.7; *m/z* (%) 291 (9, M^+), 150 (100, $M-PhSO_2$), 77 (56, Ph).

2.2.3. 1-Benzenesulfonyl-3-(3-nitro-phenyl)-2,5-dihydro-1*H*-pyrrole (14). The product was isolated as a colourless solid (49 mg, 93%); mp 130–132 °C; Found: C, 58.50; H, 4.50; N, 8.20; S, 9.90; $C_{16}H_{15}NO_2S$ requires C, 58.20; H, 4.27; N, 8.50; S, 9.70; ν_{max}/cm^{-1} (CH_2Cl_2 solution) 3088, 2918, 1530 (NO_2), 1348 (S=O_{as}), 1166 (S=O_s), 830 (CH); δ_H (250 MHz; $CDCl_3$) 8.12–8.22 (2H, m, $PhNO_2$), 7.91 (2H, dd, $J=8.2$, 1.5 Hz, $PhSO_2$), 7.55–7.64 (5H, m, $PhSO_2$ and $PhNO_2$), 6.01 (1H, t, $J=2.1$ Hz, CH=), 4.37–4.40 and 4.51–4.55 (4H, m, CH_2–C= and CH_2–CH=); δ_C (50 MHz; $CDCl_3$) 148.9, 137.2, 135.9, 134.4, 133.5, 131.6, 130.2, 129.8, 127.8, 123.4, 122.8, 120.6, 56.1, 55.1; *m/z* (%) 330 (34, M^+), 189 (100, $M-PhSO_2$), 143 (54, $M-PhSO_2$ and NO_2), 115 (68, $M-PhNO_2$ and OPh), 77 (86, Ph).

2.2.4. 1-[4-(1-Benzenesulfonyl-2,5-dihydro-1*H*-pyrrol-3-yl)-phenyl]-ethanone (15). The product was isolated as a colourless solid (32 mg, 75%); mp 145–147 °C; Found: C, 66.20; H, 5.30; N, 4.10; S, 9.60; $C_{18}H_{17}NO_3S$ requires C, 66.00; H, 5.23; N, 4.30; S, 9.80; ν_{max}/cm^{-1} (CH_2Cl_2 solution) 2919, 1680 (C=O), 1339 (S=O_{as}), 1166 (S=O_s), 828 (CH); δ_H (250 MHz; $CDCl_3$) 7.94 (4H, m, $PhSO_2$ and PhCOMe), 7.55–7.60 (3H, m, $PhSO_2$), 7.37 (2H, d, $J=$ 8.5 Hz, PhCOMe), 6.18 (1H, t, $J=2.1$ Hz, CH=), 4.33–4.37 and 4.50–4.55 (4H, m, CH_2–C= and CH_2–CH=), 2.60 (3H, s, CH_3); δ_C (50 MHz; $CDCl_3$) 197.3 (C=O), 137.1, 137.0, 136.9, 133.4, 129.8, 129.2, 127.7, 125.9, 122.3, 56.1, 55.1, 27.0; *m/z* (%) 327 (23, M^+), 186 (100, $M-PhSO_2$), 170 (57, $M-PhSO_2$ and O), 144 (42, $M-PhSO_2N(CH_2)_2$), 115 (43, M−PhCOMe and OPh), 77 (57, Ph), 43 (63, COMe).

2.3. General allyl glycinate ester formation and *N*-sulfonyl protection

2.3.1. Methyl 2-[(phenylsulfonyl)amino]-4-pentenoate (16). Thionyl chloride (1.35 ml, 0.0181 mol) was added dropwise to a stirred solution of allyl glycinate (2.09 g, 0.0181 mol) in methanol (150 ml) at 0 °C and the solution was allowed to warm to ambient temperature. After 1 h the methanol was removed and the residue dissolved in DCM (100 ml). Benzenesulfonyl chloride (2.35 ml, 0.0181 mol) dissolved in DCM (20 ml) was added to the reaction mixture followed by triethylamine (5.7 ml, 0.056 mol). After 16 h the mixture was washed with water (2×20 ml), dried ($MgSO_4$), filtered and the filtrate concentrated. Purification of the residue by flash chromatography eluting with DCM afforded the product (3.8 g, 78%), which crystallised from DCM/petrol as colourless needles, mp 75–76 °C; R_f 0.13; (Found: C, 53.40; H, 5.45; N, 4.95. $C_{12}H_{15}NO_4S$ requires C, 53.50; H, 5.60; N, 5.20%); ν_{max}/cm^{-1} (Nujol) 3291 (NH), 1741 (C=O), 1331 (S=O_{as}), 1163 (S=O_s), 1092; δ_H (250 MHz, $CDCl_3$) 7.88–7.83 (2H, m, ArH), 7.62–7.47 (3H, m, ArH), 5.62 (1H, ddt, $J=18.0$, 14.3, 6.8 Hz, C*H*=CH_2), 5.27 (1H, d, $J=9.0$ Hz, NH), 5.13–5.04 (2H, m, CH=CH_2), 4.10–4.02 (1H, dt, $J=9.0$, 6.8 Hz NCH), 3.5 (3H, s, CH_3), 2.47 (2H, t, $J=6.8$ Hz, CH_2); δ_C (63 MHz, $CDCl_3$) 171.6 (C=O), 140.1, 133.3, 131.6, 129.5, 127.6, 120.3, 55.6, 52.9, 37.9; *m/z* (ES) 292 (M^+ + Na).

2.3.2. Methyl 2-{[(4-nitrophenyl)sulfonyl]amino}pent-4-enoate (17).[31] Prepared by the above *N*-sulfonyl protection procedure on a 0.05 mol scale. Purification by flash chromatograpy eluting with DCM afforded the product (8.65 g, 55%) as a pale yellow solid. Crystallisation from DCM/petrol afforded colourless needles, mp 134–136 °C; R_f 0.15; (Found: C, 45.80; H, 4.40; N, 8.75. $C_{12}H_{14}N_2O_6S$ requires C, 45.85; H, 4.50; N, 8.90%); ν_{max}/cm^{-1} (film) 1741 (C=O), 1539 (NO_2), 1350 (S=O_{as}), 1171 (S=O_s); δ_H (250 MHz, $CDCl_3$) 8.35 (2H, d, $J=9.0$ Hz, ArH), 8.04 (2H, d, $J=9.0$ Hz, ArH), 5.61 (1H, ddt, $J=16.9$, 10.4, 7.2 Hz, C*H*=CH_2), 5.32 (1H, d, $J=8.6$ Hz, NH), 5.18–5.08 (2H, m, CH=CH_2), 4.13 (1H, dt, $J=8.6$, 5.9 Hz, NCH), 2.55–2.49 (2H, m, CH_2); *m/z* (ES) 337 (M^+ + Na).

2.3.3. Methyl 2-[(2-phenyl-2-propenyl)(phenylsulfonyl) amino]-4-pentenoate (18). Prepared by the general termolecular cascade procedure on a 1 mmol scale, using 1.2 mmol of the aryl iodide and a reaction time of 40 h. Purification by flash chromatograpy eluting with DCM afforded the product (312 mg, 81%) as a colourless oil; R_f 0.34; (Found: C, 65.15; H, 6.15; N, 3.90. $C_{21}H_{23}NO_4S$ requires C, 65.45; H, 6.00; N, 3.65%); ν_{max}/cm^{-1} (film) 1741 (C=O), 1447, 1345 (S=O_{as}), 1158 (S=O_s) 1091, 916; δ_H (250 MHz, $CDCl_3$) 7.85–7.81 (2H, m, SO_2PhH), 7.61–7.46 (3H, m, SO_2PhH), 7.38–7.28 (5H, m, PhH), 5.78 (1H, ddt, $J=16.7$, 9.8, 6.8 Hz, C*H*=CHH), 5.85 (1H, d, $J=$ 0.9 Hz, =CH*H*), 5.41 (1H, d, $J=0.9$ Hz, =C*H*H), 5.00 (1H, d, $J=16.7$ Hz, CH=CH_{trans}), 4.98 (1H, d, $J=$ 9.8 Hz, CH=CH_{cis}H), 4.48 (1H, dd, $J=8.0$, 6.9 Hz, NCH), 4.42 (1H, d, $J=16.0$ Hz, NC*H*H), 4.36 (1H, d, $J=16.0$ Hz, NCH*H*), 3.89 (s, 3H, CH_3), 2.64–2.58 (1H, m, =CHC*H*H), 2.43–2.35 (m, 1H, =CH*H*); δ_C (63 MHz, $CDCl_3$) 170.8 (C=O), 144.0, 139.9, 139.2, 133.7, 133.2, 129.3, 128.8, 128.4, 128.1, 126.8, 118.7, 116.5, 59.8 (NCH), 52.2 (OCH_3), 50.2 (NCH_2), 35.2 (=CH*C*H_2); *m/z* (%) (EI) 385 (4, M^+), 326, (43, $M-CO_2Me$), 284 (78), 244 (34, $M-SO_2Ph$), 144 (45), 117 (95), 77 (100, Ph).

2.3.4. Methyl 2-{[2-(3-methylphenyl)-2-propenyl]-(phenylsulfonyl)amino}-4-pentenoate (19). Prepared by the general termolecular cascade procedure on a 1 mmol scale, using 1.2 mmol of the aryl iodide and a reaction time of 34 h. Purification by flash chromatograpy eluting with DCM afforded the product (318 mg, 80%) as a colourless oil; R_f 0.24; (Found: C, 66.25; H, 6.40; N, 3.50. $C_{22}H_{25}NO_4S$ requires C, 66.15; H, 6.30; N, 3.50%); ν_{max}/cm^{-1} (film) 1742 (C=O), 1447, 1437, 1345 (S=O_{as}), 1159 (S=O_s), 1091, 919; δ_H (250 MHz, $CDCl_3$) 7.85–7.81 (2H, m, SO_2PhH), 7.59–7.49 (3H, m, SO_2PhH), 7.26–7.12 (4H, m, ArH), 5.63 (1H, ddt, $J=16.8$, 9.7, 6.9 Hz, C*H*=CHH), 5.46 (1H, d, $J=0.8$ Hz, =CH*H*), 5.39 (1H, d, $J=0.8$ Hz, =C*H*H), 5.01 (1H, d, $J=16.8$ Hz, CH=CH_{trans}), 5.00 (1H, d, $J=9.7$ Hz, CH=CH_{cis}H), 4.48 (1H, dd, $J=8.0$, 6.8 Hz, NCH), 4.48 (1H, d, $J=17.5$ Hz, NC*H*H), 4.38 (1H, d, $J=17.5$ Hz, NCH*H*), 3.40 (3H, s, OCH_3), 2.64–2.60 (1H, m, =CHC*H*H), 2.43–2.34 (1H, m, =CHCH*H*), 2.34 (3H, s, $ArCH_3$); δ_C (63 MHz, $CDCl_3$) 170.9 (C=O), 144.1, 138.3,

133.7, 133.1, 129.3, 129.1, 128.7, 127.5, 123.8, 118.7, 116.2, 59.9 (NCH), 52.2 (OCH_3), 50.2 (NCH_2), 35.2 (=CHCH_2), 21.9 (ArCH_3); *m/z* (%) (FAB) 400 (69, M^++H), 399 (19, M^+), 340 (27, M−CO_2Me), 259 (100), 258 (34, M−SO_2Ph), 158 (20), 131 (47), 77 (13, C_6H_5).

2.3.5. Methyl 2-{[2-(2-naphthyl)-2-propenyl](phenylsulfonyl)amino}-4-pentenoate (20). Prepared by the general termolecular cascade procedure on a 1 mmol scale, using 1.1 mmol of aryl iodide, $Pd_2(dba)_3$ (0.05 mmol) and a reaction time of 44 h. Purification by flash column chromatography eluting with 4:1 v/v petrol/ethyl acetate afforded the product (295 mg, 69%) as a viscous, pale yellow oil; R_f 0.22; (Found: C, 68.75; H, 5.95; N, 3.20. $C_{23}H_{25}NO_4S$ requires C, 68.95; H, 5.80; N, 3.20%); ν_{max}/cm^{-1} (film) 1742 (C=O), 1447, 1347 (S=O_{as}), 1158 (S=O_s), 1091, 921; δ_H (250 MHz, $CDCl_3$) 8.11–8.08 (1H, m, ArH), 7.83–7.79 (4H, m, ArH), 7.54–7.43 (6H, m, ArH), 7.28 (1H, dd, *J*=7.5, 1.2 Hz, ArH), 5.82 (1H, d, *J*=1.4 Hz, =CH_CH_D), 5.72 (1H, ddt, *J*=16.9, 10.2, 6.8 Hz, C*H*=CHH), 5.32, (1H, d, *J*=1.4 Hz, =C*H*H), 5.12 (1H, d, *J*=10.2 Hz, CH=CH_{cis}H), 5.09 (1H, d, *J*=16.9 Hz, CH=CHH_{trans}), 4.59 (1H, dd, *J*=8.2, 5.5 Hz, NCH), 4.32 (1H, d, *J*=18.5 Hz, NC*H*H), 4.19 (1H, d, *J*=18.5 Hz, NCH*H*), 3.39 (3H, s, CH_3), 2.67–2.58 (1H, m, =CHC*H*H), 2.49–2.38 (1H, m, =CHCH*H*); δ_C (63 MHz, $CDCl_3$) 170.9 (C=O), 144.6, 139.7, 138.8, 134.0, 133.3, 133.2, 131.8, 129.3, 128.7, 128.3, 128.0, 126.8, 126.3, 126.1, 125.8, 125.6, 119.0, 117.5, 60.2 (NCH), 52.3 (OCH_3), 52.0 (NCH_2), 35.4 (=CHCH_2); *m/z* (ES) 458 (M^++Na).

2.3.6. Methyl 2-{[2-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinyl)-2-propenyl](phenylsulfonyl)amino}-4-pentenoate (21). Prepared by the general termolecular cascade procedure on a 1 mmol scale, using 1.2 mmol of aryl iodide and a reaction time of 40 h. Purification by flash chromatography eluting with 9:1 v/v ether/ethyl acetate afforded the product (314 mg, 70%) as a colourless oil; R_f 0.27; (Found: C, 56.30; H, 5.75; N, 9.45. $C_{21}H_{26}N_2O_6S$ requires C, 56.35; H, 5.65; N, 9.40%), ν_{max}/cm^{-1} (film) 1741 (MeOC=O), 1702 (N–C=O), 1655 (N(N)C=O), 1448, 1340 (S=O_{as}), 1266, 1159 (S=O_s), 1091; δ_H (250 MHz, $CDCl_3$) 7.82 (2H, m, SO_2PhH), 7.60–7.48 (3H, m, SO_2PhH), 7.27 (1H, d, *J*=0.8 Hz, =CH), 5.73 (1H, ddt, *J*=16.9, 10.1, 6.8 Hz, C*H*=CHH), 5.49 (1H, d, *J*=0.8 Hz, =CH*H*), 5.39 (1H, s, =C*H*H), 5.05 (1H, ddd, *J*=16.9, 2.9, 1.4 Hz, CH=CHH_{trans}), 5.01 (1H, dd, *J*=10.1, 1.4 Hz, CH=CH_{cis}H), 4.50 (1H, dd, *J*=8.3, 6.8 Hz, NCH), 4.28 (1H, d, *J*=16.3 Hz, NC*H*H), 4.19 (1H, d, *J*=16.3 Hz, NCH*H*), 3.46 (3H, s, CH_3), 3.44 (3H, s, CH_3), 3.42 (3H, s, CH_3), 2.75–2.66 (1H, m, =CHC*H*H), 2.57–2.45 (1H, m, =CHCH*H*); δ_C (63 MHz, $CDCl_3$), 170.8 (C=O), 162.7 (C=O), 151.8 (C=O), 142.0, 139.6, 138.5, 134.1, 133.2, 129.2, 128.2, 120.0, 118.4, 112.5, 60.4 (NCH), 52.4 (OCH_3), 50.6 (NCH_2), 37.5 (NCH_3), 34.8 (NCH_3), 28.4 (=CHCH_2); *m/z* (ES) 470 (M^++Na).

2.3.7. Methyl 2-{(phenylsulfonyl)[2-(2-thienyl)-2-propenyl]amino}-4-pentenoate (22). Prepared by the general termolecular cascade procedure on a 1 mmol scale, using 1.2 mmol of aryl iodide and a reaction time of 38 h. Purification by flash chromatography afforded the product (278 mg, 71%), as a viscous, pale yellow oil, R_f 0.15; (Found: C, 58.30; H, 5.35; N, 3.80. $C_{19}H_{21}NO_4S$ requires C, 58.30; H, 5.40; N, 3.60%); ν_{max}/cm^{-1} (film) 1740 (C=O), 1447, 1437, 1343 (S=O_{as}), 1160 (S=O_s), 1191, 1091, 923; δ_H (250 MHz, $CDCl_3$) 7.87–7.83 (2H, m, SO_2PhH), 7.64–7.49 (3H, m, SO_2PhH), 7.20 (1H, dd, *J*=5.1, 1.0 Hz, ArH), 7.13 (1H, dd, *J*=3.7, 1.0 Hz, ArH), 6.98 (1H, dd, *J*=5.1, 3.7 Hz, ArH), 5.65 (1H, ddt, *J*=16.9, 9.9, 6.9 Hz, C*H*=CHH), 5.58 (1H, s, =CH*H*), 5.30 (1H, s, =C*H*H), 4.99–5.04 (2H, m, CH=C$H_{cis}H_{trans}$), 4.53 (1H, t, *J*=7.4 Hz, NCH), 4.42 (1H, d, *J*=17 Hz, NC*H*H), 4.35 (1H, d, *J*=17 Hz, NCH*H*), 3.40 (3H, s, CH_3), 2.64–2.56 (1H, m, =CHC*H*H), 2.49–2.40 (1H, m, =CHCH*H*); δ_C (63 MHz, $CDCl_3$), 170.8 (C=O), 142.5, 139.8, 137.5, 133.6, 133.3, 129.4, 128.0, 127.9, 125.1, 124.5, 118.8, 114.7, 59.9 (NCH), 52.3 (OCH_3), 49.7 (NCH_2), 35.3 (=CHCH_2); *m/z* (ES) 414 (M^+ + Na).

2.3.8. Methyl 2-{[2-(-methoxyphenyl)-2-propenyl]-(phenylsulfonyl)amino}-4-pentenoate (23). Prepared by the general termolecular cascade procedure on a 1 mmol scale, using 1.2 mmol of aryl iodide and a reaction time of 42 h. Purification by flash chromatography eluting with DCM afforded the product (259 mg, 63%), as a colourless oil, R_f 0.11; (Found: C, 63.50; H, 6.20; N, 3.40. $C_{22}H_{25}NO_5S$ requires C, 63.60; H, 6.05; N, 3.35%); ν_{max}/cm^{-1} (film) 1741 (C=O), 1514, 1342 (S=O_{as}), 1249 (O–Me), 1159 (S=O_s), 1090, 1030, 836; δ_H (500 MHz, $CDCl_3$) 7.84–7.82 (2H, m, SO_2PhH), 7.58–7.56 (1H, m, SO_2PhH), 7.51–7.48 (2H, m, SO_2PhH), 7.31 (2H, d, *J*=8.9 Hz, ArH), 6.84 (2H, d, *J*=8.9 Hz, ArH), 5.61 (1H, ddt, *J*=16.5, 9.7, 6.9 Hz, C*H*=CHH), 5.39 (1H, d, *J*=0.8 Hz, =CH*H*), 5.29 (1H, d, *J*=0.8 Hz, =C*H*H), 4.99 (1H, d, *J*=9.7 Hz, CH=CH_{cis}H), 4.98 (1H, d, *J*=16.5 Hz, CH=CHH_{trans}), 4.45 (1H, dd, *J*=8.1, 6.7 Hz, NCH), 4.38 (1H, d, *J*=16.6 Hz, NC*H*H), 4.34 (1H, d, *J*=16.6 Hz, NCH*H*), 3.81 (3H, s, CH_3), 3.39 (3H, s, CH_3), 2.66–2.61 (1H, m, =CHC*H*H), 2.40–2.35 (1H, m, =CHCH*H*); δ_C (125 MHz, $CDCl_3$), 170.4 (C=O), 159.5, 142.9, 139.7, 133.5, 132.7, 131.2, 128.9, 127.7, 127.6, 118.2, 114.8, 113.8, 59.5 (CH_3), 55.3 (NCH), 51.8 (CH_3), 50.0 (NCH_2), 34.8 (=CHCH_2); *m/z* (%) (EI) 415 (17, M^+), 356 (20, M−CO_2Me), 274 (100, M−SO_2Ph), 174 (88), 147 (86), 133 (78).

2.3.9. Methyl 2-{[2-(1-methyl-1*H*-indol-5-yl)-2-propenyl](phenylsulfonyl)amino}-4-pentanoate (24). Prepared by the general termolecular cascade procedure on a 1 mmol scale, using 1.2 mmol of aryl iodide and a reaction time of 40 h. Purification by flash chromatography, eluting with DCM yielded the product (353 mg, 80%) as a viscous colourless oil, R_f 0.1; (Found: C, 66.00; H, 5.95; N, 6.25. $C_{24}H_{26}N_2O_4S$ requires C, 65.75; H, 5.95; N, 6.25%); ν_{max}/cm^{-1} (film) 1741 (C=O), 1446, 1336 (S=O_{as}), 1159 (S=O_s), 1091; δ_H (250 MHz, $CDCl_3$) 7.87–7.82 (2H, m, SO_2PhH), 7.58–7.45 (4H, m, ArH), 7.26 (2H, br s, ArH), 7.05 (1H, d, *J*=3.1 Hz, ArH), 6.44 (1H, d, *J*=3.1 Hz, ArH), 5.63 (1H, ddt, *J*=17.0, 10.3, 6.9 Hz, C*H*=CHH), 5.46 (1H, d, *J*=1.0 Hz, =CH*H*), 5.35 (1H, d, *J*=1.0 Hz, =C*H*H), 5.03–4.95 (2H, m, CH=C$H_{cis}H_{trans}$), 4.49 (1H, dd, *J*=8.2, 6.6 Hz, NCH), 4.46 (2H, br s, NCH_2), 3.79 (3H, s, CH_3), 3.39 (3H, s, CH_3), 2.70–2.64 (1H, m, =CHC*H*H), 2.45–2.38 (1H, m, =CHCH*H*); δ_C (63 MHz, $CDCl_3$), 171.0

(C=O), 144.7, 140.1, 136.9, 133.9, 133.0, 130.6, 129.8, 129.2, 128.7, 128.1, 120.9, 119.1, 118.6 (=CH_2), 114.8 (=CH_2), 109.4, 101.8, 59.3 (NCH), 52.2 (OCH_3), 50.8 (NCH_2), 35.3 (=CHCH_2), 33.3 (NCH_3); *m/z* (ES) 461 (M^+ + Na).

2.3.10. Methyl 2-{[2-(2-methyl-4-nitrophenyl)-2-propenyl](phenylsulfonyl)amino}-4-pentenoate (25). Prepared by the general termolecular cascade procedure on a 1 mmol scale, using 1.1 mmol aryl iodide and $Pd_2(dba)_3$ (0.05 mmol, 92 mg) in place of $Pd(OAc)_2$ and a reaction time of 40 h. Purification by flash column chromatography eluting with 4:1 v/v petrol/ethyl acetate afforded the product (322 mg, 72%) as a viscous pale yellow oil, which solidified on standing. Crystallisation from DCM/petrol afforded colourless needles, mp 67–69 °C; R_f 0.18; (Found: C, 59.35; H, 5.60; N, 6.20; $C_{22}H_{24}N_2O_6S$ requires C, 59.45; H, 5.45; N, 6.30%); ν_{max}/cm^{-1} (film) 1742 (C=O), 1519 (C–NO_2), 1447, 1346 (S=O_{as}), 1311, 1158 (S=O_s), 1091, 926; δ_H (500 MHz; $CDCl_3$) 8.04 (1H, d, J=2.4 Hz, ArH_E), 7.98 (1H, dd, J=8.4, 2.4 Hz, ArH), 7.81–7.79 (2H, m, SO_2Ph), 7.58–7.58 (1H, m, SO_2PhH), 7.50–7.47 (2H, m, SO_2PhH), 7.24 (1H, d, J=8.4 Hz, ArH), 5.69 (1H, ddt, J=17.0, 10.2, 6.8 Hz, C*H*=CHH), 5.66 (1H, d, J=0.8 Hz, =CH*H*), 5.14 (1H, d, J=0.8 Hz, =C*H*H), 5.11 (1H, ddd, J=10.2, 2.9, 1.4 Hz, CH=CH_{cis}H), 5.08 (1H, d, J=17.0 Hz, CH=CHH_{trans}), 4.53 (1H, dd, J=8.4, 6.5 Hz, NCH), 4.14 (1H, dt, J=18.3, 1.6 Hz, NC*H*H), 4.09 (1H, dt, J=18.3, 6 Hz, NCH*H*), 3.43 (1H, s, OCH_3), 2.65–2.59 (1H, m, =CHC*H*H), 2.42 (1H, s, $ArCH_3$), 2.42–2.38 (1H, m, =CHCH*H*); δ_C (125 MHz, $CDCl_3$) 170.4 (C=O), 147.2, 146.9, 143.9, 139.3, 137.5, 133.0, 132.7, 129.9, 129.0, 127.6, 125.0, 120.8, 118.8, 117.4, 59.6 (NCH), 51.9 (OCH_3), 50.32 (NCH_2), 35.0 (=CHCH_2), 19.8 ($ArCH_3$); *m/z* (ES) 467 (M^+ + Na).

2.3.11. Methyl 2-{[2-(1-methyl-2,3-dioxo)-2,3-dihydro-1*H*-indole-5-yl]prop-2-enyl(phenylsulfonyl)amino}pent-4-enoate (26). Prepared by the general termolecular cascade procedure on a 1 mmol scale, using 1.2 mmol of aryl iodide and a reaction time of 48 h. Purification by flash chromatography eluting with 2:3 v/v ethyl acetate/petrol affords the product (193 mg, 41%), as red solid, which crystallised from DCM/petrol as red needles, mp 116–118 °C; R_f 0.2; (Found: C, 61.35; H, 5.25; N, 5.85. $C_{24}H_{24}N_2O_6S$ requires C, 61.55; H, 5.15; N, 6.0%); ν_{max}/cm^{-1} (film) 1740 (MeOC=O), 1619, 1593, 1331 (S=O_{as}), 1267, 1160 (S=O_s), 1091; δ_H (250 MHz, $CDCl_3$) 7.84–7.81 (2H, m, SO_2PhH), 7.72 (1H, dd, J=8.3, 2.0 Hz, ArH), 7.65–7.49 (4H, m, SO_2PhH and ArH), 6.89 (1H, d, J=8.3 Hz, ArH), 5.60 (1H, ddt, J=16.9, 9.8, 6.9 Hz, C*H*=CHH), 5.49 (1H, s, =CH*H*), 5.45 (1H, s, =C*H*H), 5.02 (1H, d, J=16.9 Hz CH=CHH_{trans}), 5.02 (1H, d, J=9.8 Hz CH=CH_{cis}H), 4.48 (1H, t, J=7.4 Hz, NCH), 4.41 (1H, d, J=16.9 Hz, NC*H*H), 4.30 (1H, d, J=16.9 Hz, NCH*H*), 3.41 (3H, s, CH_3), 3.27 (3H, s, CH_3), 2.67–2.55 (1H, m, =CHC*H*H), 2.42–2.30 (m, 1H, =CHCH*H*); δ_C (63 MHz, $CDCl_3$) 183.7 (C=O), 170.6 (C=O), 158.7 (C=O), 151.2, 142.4, 139.6, 136.9, 135.2, 133.4, 129.4, 128.0, 123.5, 118.9, 117.7, 117.3, 110.3, 59.7 (NCH), 52.4 (OCH_3), 50.0 (NCH_2), 35.2 (=CHCH_2), 26.8 (N–CH_3); *m/z* (%) (EI); 468 (57, M^+), 409 (72, M−CO_2Me), 327 (82, M−SO_2Ph), 200 (55), 144 (70), 77 (100).

2.3.12. Methyl 5-phenyl-1-(phenylsulfonyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (27). Prepared by the general ring closing metathesis procedure on a 0.13 mmol scale and a reaction time of 3 h. Purification by flash column chromatography eluting with 1:1 v/v petrol/ether to afforded the product (36 mg, 77%) as a viscous, colourless oil. R_f 0.25; (Found: C, 63.65; H, 5.40; N, 4.00; $C_{19}H_{19}NO_4S$ requires C, 63.85; H, 5.35; N, 3.90%); ν_{max}/cm^{-1} (film) 1744 (C=O), 1447, 1342 (S=O_{as}), 1202, 1164 (S=O_s), 1097; δ_H (500 MHz, $CDCl_3$) 7.78–7.76 (2H, m, SO_2PhH), 7.51–7.49 (1H, m, SO_2PhH), 7.45–7.41 (2H, m, SO_2PhH), 7.25–7.18 (5H, m, PhH), 5.94–5.96 (1H, br m, =CH), 4.86 (1H, dd, J=5.5, 3.0 Hz, NCH), 4.50 (1H, ddd, J=16.4, 3.9, 1.9 Hz, NC*H*H), 4.09 (1H, ddd, J=16.4, 5.3, 3.0 Hz, NCH*H*), 3.40 (3H, s, CH_3), 2.66–2.64 (2H, br m, =CHCH_2); δ_C (75 MHz, $CDCl_3$) 171.2 (C=O), 139.5, 138.6, 134.1, 133.1, 129.3, 128.9, 128.3, 127.6, 125.6, 119.7, 52.7 (NCH), 52.6 (OCH_3), 43.9 (NCH_2), 28.5 (=CHCH_2); *m/z* (%) (EI) 357 (11, M^+), 298 (40, M−CO_2Me), 216 (48, M−SO_2Ph), 156 (100), 129 (44), 77 (70, Ph).

2.3.13. Methyl 5-(3-methylphenyl)-1-(phenylsulfonyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (28). Prepared by the general ring closing metathesis procedure on a 0.14 mmol scale and reaction time of 2 h. Purification by flash chromatography eluting with 4:1 v/v petrol/ethyl acetate afforded the product (38 mg, 75%) as a colourless oil, which crystallised on standing to afford colourless needles, mp 59–61 °C; R_f 0.23; (Found: C, 64.80; H, 5.95; N, 3.85. $C_{20}H_{21}NO_4S$ requires C, 64.65; H, 5.70; N, 3.75%); ν_{max}/cm^{-1} (film) 1744 (C=O), 1447, 1340 (S=O_{as}), 1202, 1163 (S=O_s), 1098, 1032, 971; δ_H (250 MHz, $CDCl_3$), 7.86–7.82 (2H, m, SO_2PhH), 7.62–7.48 (3H, m, SO_2PhH), 7.25–7.22 (4H, m, ArH), 6.03–6.00 (1H, br m, =CH), 4.93 (1H, t, J=4.3 Hz, NCH), 4.51 (1H, dd, J=16.4, 2.0 Hz, NC*H*H), 4.14 (1H, ddd, J=16.4, 5.0, 2.8 Hz, NCHC*H*), 3.46 (3H, s, OCH_3), 2.73–2.72 (2H, br m, =CHCH_2), 2.35 (3H, s, $ArCH_3$); δ_c (63 MHz, $CDCl_3$) 171.2 (C=O), 139.5, 138.6, 134.2, 133.1, 129.4, 129.1, 128.8, 128.5 127.6, 126.3, 122.7, 119.5, 52.7 (NCH), 52.6 (OCH_3), 44.0 (NCH_2), 28.6 (=CHCH_2), 21.9 ($PhCH_3$); *m/z* (%) (EI) 371 (27, M^+), 312 (54, M−CO_2Me), 230 (86, M−SO_2Ph), 170 (10), 77 (60, Ph).

2.3.14. Methyl 5-(2-naphthyl)-1-(phenylsulfonyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (29). Prepared by the general ring closing metathesis procedure on a 0.14 mmol scale and a reaction time of 5 h. Purification by flash chromatography eluting with 4:1 v/v petrol/ethyl acetate afforded the product (43 mg, 75%), which crystallised from petrol/DCM as colourless needles, mp 144–146 °C; R_f 0.21; (Found: C, 67.65; H, 5.20; N, 3.70. $C_{23}H_{21}NO_4S$ requires C, 67.80; H, 5.20; N, 3.45%); ν_{max}/cm^{-1} (film) 1742 (C=O), 1447, 1341 (S=O_{as}), 1201, 1164 (S=O_s), 1095; δ_H (250 MHz, $CDCl_3$) 7.86–7.76 (5H, m, ArH), 7.62–7.41 (6H, m, ArH), 7.23 (1H, dd, J=7.0, 1.6 Hz, ArH), 5.78 (1H, bdd, J=5.5, 2.3 Hz, =CH), 5.06 (1H, dd, J=6.3, 2.0 Hz, NCH), 4.39 (1H, br d, J=16.5 Hz, NC*H*H), 4.08 (1H, dd, J=16.5, 2.2 Hz, NCH*H*), 3.56 (3H, s, CH_3), 2.93–2.73 (2H, br m, =CHCH_2); δ_C (63 MHz, $CDCl_3$), 171.4 (C=O), 139.2, 137.9, 134.8, 134.0, 133.1, 131.8, 129.3, 128.8, 128.5, 127.7, 126.7, 126.3, 125.6, 125.4, 122.8, 122.4, 52.7

(NCH), 52.6, (OCH_3), 46.4 (NCH_2), 28.7 (=CH*C*H_2); *m*/*z* (%) (EI) 407 (44, M^+), 348 (25, $M-CO_2Me$), 266 (100, $M-SO_2Ph$), 206 (73), 179 (76), 165 (50), 141 (42), 77 (80).

2.3.15. Methyl 5-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinyl)-1-(phenylsulfonyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (30). Prepared by the general ring closing metathesis procedure on a 0.12 mmol scale and a reaction time of 3 h. Purification by flash column chromatography eluting with 3:2 v/v petrol/ethyl acetate afforded the product (48 mg, 84%), which crystallised from DCM/petrol as colourless needles, mp 196–198 °C; R_f 0.1; (Found: C, 54.40; H, 5.05; N, 9.85. $C_{19}H_{21}N_3O_6S$ requires C, 54.40; H, 5.05; N, 10.0%); ν_{max}/cm^{-1} (film) 1742 (MeOC=O), 1702 (NC=O), 1652 (N(N)C=O), 1448, 1339 (S=O_{as}), 1164 (S=O_s), 1095; δ_H (250 MHz, $CDCl_3$) 7.88–7.83 (2H, m, SO_2PhH), 7.62–7.47 (3H, m, SO_2PhH), 7.06 (1H, s, ArH), 6.10–6.07 (1H, br m, =CH_B), 4.88 (1H, dd, $J=5.6$, 2.9 Hz, NCH), 4.43 (1H, d, $J=16.3$ Hz, NC*H*H), 4.05 (1H, ddd, $J=16.3$, 4.9, 3.2 Hz, NCH*H*), 3.51 (3H, s, CH_3), 3.41 (3H, s, CH_3), 3.34 (3H, s, CH_3), 2.65–2.63 (2H, br m, =CHCH_2); δ_C (63 MHz, $CDCl_3$) 171.1 (C=O), 162.3 (C=O), 151.6 (C=O), 140.0, 139.6, 133.1, 129.4, 128.6, 127.6, 122.7, 112.8, 52.7 (NCH), 52.5 (OCH_3), 43.7 (NCH_2), 37.5 (CH_3), 28.5 (CH_3), 28.1 (=CH*C*H_2) *m*/*z* (%) (EI) 419 (9, M^+), 278 (68, $M-SO_2Ph$), 218 (100), 77 (25, Ph).

2.3.16. Methyl 1-(phenylsulfonyl)-5-(2-thienyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (31). Prepared by the general ring closing metathesis procedure on a 0.13 mmol scale and a reaction time of 3 h. Purification by flash column chromatography eluting with DCM affords the product (33 mg, 71%) as a viscous colourless oil; R_f 0.15; (Found: C, 55.90; H, 4.90; N, 3.60; $C_{17}H_{17}NO_4S_2$ requires C, 56.20; H, 4.7; N, 3.85%); ν_{max}/cm^{-1} (film) 1743 (C=O), 1447, 1339 (S=O_{as}), 1202, 1164 (S=O_s), 1098. δ_H (250 MHz, $CDCl_3$), 7.86–7.82 (2H, m, SO_2PhH), 7.63–7.49 (3H, m, SO_2PhH), 7.16 (1H, dd, $J=5.0$, 0.8 Hz, ArH), 7.05–6.93 (2H, m, ArH and ArH), 6.09–6.06 (1H, br m, =CH), 4.25 (1H, t, $J=$ 4.5 Hz, NCH), 4.71 (1H, dd, $J=16.1$, 1.9 Hz, NC*H*H), 4.17 (dd, 1H, $J=16.1$, 1.9 Hz, NCH*H*), 3.40 (3H, s, CH_3), 2.71–7.76 (2H, br m, =CHCH_2). δ_C (63 MHz, $CDCl_3$) 171.0 (C=O), 142.1, 139.5, 133.2, 129.4, 128.5, 127.8, 127.5, 124.4, 122.6, 118.8, 52.8 (NCH), 52.7 (OCH_3), 43.6 (NCH_2), 28.2 (=CH*C*H_2); *m*/*z* (%) (EI) 363 (6, M^+), 304 (18, $M-CO_2Me$,), 222 (72, $M-SO_2$ Ph,), 162 (100), 77 (59, Ph).

2.3.17. Methyl 5-(4 methoxyphenyl)-1-(phenylsulfonyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (32). Prepared by the general ring closing metathesis procedure on a 0.12 mmol scale and a reaction time of 2 h. Purification by flash column chromatography eluting with 4:1 v/v ether/ petrol afforded the product (43 mg, 96%) as a viscous, colourless oil; R_f 0.35; (Found: C, 61.85; H, 5.75, N, 3.55. $C_{20}H_{21}NO_5S$ requires C, 62.00; H, 5.46; N, 3.62%); ν_{max}/cm^{-1} (film) 1744 (C=O), 1514, 1341 (S=O_{as}), 1248 (OCH_3), 1163 (S=O_s), 1097, 1024; δ_H (250 MHz, $CDCl_3$), 7.86–7.82 (2H, m, SO_2PhH), 7.58–7.51 (3H, m, SO_2PhH), 7.23 (2H, d, $J=8.9$ Hz, ArH), 6.85 (2H, d, $J=8.9$ Hz, ArH), 5.96–5.93 (1H, br m, =CH), 4.92 (1H, t, $J=4.2$ Hz, NCH), 4.48 (1H, dd, $J=16.3$, 1.9 Hz, NC*H*H), 4.11 (1H, dd, $J=$ 16.3, 1.9 Hz, NCH*H*), 3.80 (3H, s, CH_3), 3.46 (3H, s, CH_3), 2.74–2.71 (2H, br m, =CHCH_2); δ_C (63 MHz, $CDCl_3$) 171.2 (C=O), 159.8, 139.5, 133.4, 133.1, 131.1, 129.3, 127.6, 126.6, 118.1, 114.3, 55.7 (OCH_3), 52.8 (NCH), 52.6 (OCH_3), 44.0 (NCH_2), 28.5 (=CH*C*H_2); *m*/*z* (ES) 410 ($M^+ + Na$).

2.3.18. Methyl 5-(1-methyl-1*H*-indole-5-yl)-1-(phenylsulfonyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (33). Prepared by the general ring closing metathesis procedure on a 0.12 mmol scale and a reaction time of 5 h. Purification by flash column chromatography eluting with 4:1 v/v ether/ petrol affords the product (41 mg, 85%) as a colourless oil, which solidified on standing, mp 138–140 °C; R_f 0.35; (Found: C, 64.25; H, 5.55; N, 6.90; $C_{22}H_{22}N_2O_4S$ requires C, 64.35; H, 5.40; N, 6.80%); ν_{max}/cm^{-1} (film) 1743 (C=O), 1446, 1339 (S=O_{as}), 1201, 1161 (S=O_s), 1097; δ_H (250 MHz, $CDCl_3$) 7.87–7.83 (2H, m, SO_2PhH), 7.57–7.46 (4H, m, 3×SO_2PhH and ArH), 7.26 (1H, d, $J=8.6$ Hz, ArH_E) 7.19 (1H, dd, $J=8.6$, 1.7 Hz, ArH), 7.05 (1H, d, $J=3.1$ Hz, ArH), 6.46 (1H, d, $J=3.1$ Hz, ArH), 6.00–5.97 (1H, m, =CH), 4.95 (1H, t, $J=4.2$ Hz, NCH), 4.60 (1H, dd, $J=16.3$, 1.9 Hz, NC*H*H), 4.21 (1H, ddd, $J=$ 16.3, 5.0, 2.8 Hz, NCH*H*), 4.17 (3H, s, CH_3), 3.45 (3H, s, CH_3), 2.76–2.73 (2H, br m, =CHCH_2); *m*/*z* (ES) 433 ($M^+ + Na$).

2.3.19. Methyl 5-(2-methyl-4-nitrophenyl)-1-(phenylsulfonyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (34). Prepared by the general ring closing metathesis procedure on a 0.12 mmol scale and a reaction time of 5 h. Purification by flash chromatography eluting with 1:4 v/v ethyl acetate/ petrol afforded the product (35 mg, 74%), which crystallised from petrol/DCM as colourless needles, mp 154–156 °C; R_f 0.1; (Found: C, 57.90; H, 4.90; N, 6.50. $C_{22}H_{24}N_2O_6S$ requires C, 57.70; H, 4.85; N, 6.75%); ν_{max}/cm^{-1} (film) 1743 (C=O), 1518 (NO_2), 1447, 1344 (S=O_{as}), 1289, 1021, 1166 (S=O_s), 1095; δ_H (500 MHz, $CDCl_3$) 8.04 (1H, d, $J=2.4$ Hz, ArH), 7.99 (1H, dd, $J=8.4$, 2.4 Hz, ArH), 7.81–7.79 (2H, m, SO_2PhH), 7.60–7.58 (1H, m, SO_2PhH) 7.53–7.50 (2H, m, SO_2PhH), 7.17 (1H, d, $J=8.4$ Hz, ArH), 5.65–5.62 (1H, m, =CH), 4.97 (1H, dd, $J=6.7$, 1.8 Hz, NCH), 4.22–4.18 (1H, m, NC*H*H), 3.96–3.92 (1H, m, NCH*H*), 3.52 (3H, s, OCH_3), 2.78–2.72 (2H, m, =CHCH_2), 2.28 (3H, s, $ArCH_3$); δ_C (125 MHz, $CDCl_3$) 170.6 (C=O), 147.4, 145.9, 138.7, 137.8, 134.1, 132.9, 129.8, 129.0, 127.2, 125.1, 122.5, 120.9, 52.3 (NCH), 52.0 (OCH_3), 44.8 (NCH_2), 28.0 (=CH*C*H_2), 19.6 ($ArCH_3$); *m*/*z* (%) (EI) 416 (2, M^+), 357 (75, $M-CO_2Me$), 275 (93, $M-SO_2Ph$), 215 (61), 141 (53, SO_2Ph), 77 (100, C_6H_5).

2.3.20. Methyl 5-(1-methyl-2,3,dioxo-2,3-dihydro-1*H*-indol-5-yl)-1-(phenylsulfonyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (35). Prepared by the general ring closing metathesis procedure on a 0.12 mmol scale and a reaction time of 3 h. Purification by flash column chromatography eluting with 3:2 v/v ethyl acetate/petrol afforded the product (39 mg, 83%) as red needles, mp 175–177 °C; R_f 0.2; (Found: C, 57.85; H, 5.05; N, 5.75. $C_{22}H_{20}N_2O_6S$ with 1 equiv of H_2O requires C, 57.65; H, 4.85; N, 6.36%); ν_{max}/cm^{-1} (film) 1739 (MeO–C=O), 1620, 1338 (S=O_{as}), 1164 (S=O_s), 1098; δ_H (250 MHz, $CDCl_3$) 7.86–7.83 (2H, m, SO_2PhH), 7.65–7.50 (5H, m, 3×

SO_2PhH and ArH), 6.87 (1H, d, $J=8.4$ Hz, ArH), 6.09–6.01 (1H, br m, =CH), 4.94 (1H, t, $J=4.2$ Hz, NCH), 4.44 (1H, dd, $J=16.3$, 1.9 Hz, NC*H*H), 4.11 (1H, dd, $J=16.3$, 1.9 Hz, NCH*H*), 3.47 (3H, s, CH_3), 3.26 (3H, s, CH_3), 2.76 (2H, br s, =CHCH_2). δ_C (63 MHz, $CDCl_3$) 183.1 (C=O), 170.2 (C=O), 157.9 (C=O), 150.5, 138.5, 134.6, 134.0, 132.6, 131.6, 128.8, 126.9, 121.6, 119.9, 117.2, 109.8, 52.0 (NCH), 52.8 (OCH_3), 43.0 (NCH_2), 27.5 (=CCH_2), 26.1 (CH_3); *m/z* (ES) 463 ($M^+ + Na$); HRMS found 463.0940, [$C_{22}H_{20}N_2O_6S + Na$] requires 463.0961.

2.3.21. Methyl 2-{[(4-nitrophenyl)sulfonyl](2-phenylprop-2-enyl)amino}pent-4-enoate (36). Prepared by the general termolecular cascade procedure on a 1 mmol scale, using 1.2 mmol of aryl iodide and a reaction time of 42 h. Purification by flash chromatography eluting with 4:1 v/v petrol/ether afforded the product (611 mg, 71%), which crystallised from DCM/petrol as colourless needles, mp 81–83 °C. R_f 0.2; (Found: C, 58.70; H, 5.15; N, 6.40; $C_{21}H_{22}N_2O_6S$ requires C, 58.60; H, 5.15; N, 6.50%); ν_{max}/cm^{-1} (film) 1742 (C=O), 1530 (NO_2), 1350 ($S=O_{as}$), 1163 ($S=O_{as}$), 1090; δ_H (500 MHz, $CDCl_3$) 8.27 (2H, d, $J=8.9$ Hz, ArH), 7.97 (2H, d, $J=8.9$ Hz, ArH_E), 7.30–7.26 (5H, m, ArH), 5.69–5.61 (1H, ddt, $J=16.8$, 9.8, 6.8 Hz, C*H*=CHH), 5.44 (1H, s, =C*H*H), 5.34 (1H, s, =CH*H*), 5.07–5.03 (2H, m, CH=C$H_{cis}H_{trans}$), 4.54 (1H, t, $J=$ 7.4 Hz, NCH), 4.43 (1H, d, $J=16.6$ Hz, NC*H*H), 4.35 (1H, d, $J=16.6$ Hz, NCH*H*), 3.50 (3H, s, CH_3), 2.74–2.68 (1H, m, =CH–C*H*H), 2.52–2.46 (1H, m,=CH*H*); δ_C (125 MHz, $CDCl_3$) 170.1 (C=O), 150.0, 145.5, 143.1, 138.6, 133.0, 129.0, 128.5, 128.2, 126.4, 124.0, 118.7, 117.0, 60.1 (NCH), 52.1 (OCH_3), 50.3 (N–CH_2), 34.8 (=CHCH_2); *m/z* (ES) 453 ($M^+ + Na$).

2.3.22. Methyl 2-{[2-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)prop-2-enyl][(4-nitrophenyl sufonyl)]amino}pent-4-enoate (37). Prepared by the general termolecular cascade procedure on a 2.9 mmol scale, using 3.3 mmol of aryl iodide and a reaction time of 46 h. Purification by flash chromatography eluting with 1:1 v/v ethyl acetate/ether afforded the product (960 mg, 67%), which crystallised from DCM/petrol as colourless needles, mp 140–142 °C. R_f 0.17; (Found: C, 51.25; H, 5.00; N, 11.45. $C_{21}H_{24}N_4O_8S$ requires C, 51.20; H, 4.90; N, 11.40%); ν_{max}/cm^{-1} (film) 1742 (MeO–C=O), 1702 (N–C=O), 1653 (N(N)C=O), 1531 (NO_2), 1350 ($S=O_2$), 1161 ($S=O_3$); δ_H ($CDCl_3$ 250 MHz) 8.35 (2H, d, $J=9.0$ Hz, ArH), 8.02 (2H, d, $J=9.0$ Hz, ArH), 7.27 (1H, s, ArH), 5.71 (1H, ddt, $J=16.9$, 10.2, 6.6 Hz, C*H*=CHH), 5.43 (1H, d, $J=1.0$ Hz, =C*H*H), 5.38 (1H, d, $J=1.0$ Hz, =CH*H*), 5.11 (1H, ddd, $J=16.9$, 3.1, 1.5 Hz, CH=CHH_{trans}), 5.05 (1H, ddd, $J=10.2$, 2.6, 1.7 Hz, CH=CH_{cis}) 4.58 (1H, dd, $J=8.7$, 6.4 Hz, NCH), 4.24 (2H, s, NCH_2), 3.51 (3H, s, CH_3), 3.43 (3H, s, CH_3), 3.33 (3H, s, CH_3), 2.81–2.69 (1H, m, =CHC*H*H); 2.64–2.52 (1H, m, =CHCH*H*); δ_C (63 MHz, $CDCl_3$) 170.5 (C=O), 162.7 (C=O), 152.5 (C=O), 150.2, 145.1, 141.8, 138.7, 133.7, 129.5, 124.3, 119.8 (=CH_2), 118.8 (=CH_2), 112.7, 61.0 (NCH), 52.6 (OCH_3), 50.4 (NCH_2), 37.5 (NCH_3), 34.8 (=CHCH_2), 28.4 NCH_3; *m/z* (EI) 492 (4, M^+), 433 (21, $M-CO_2Me$), 387 (100), 369 (47), 306 (100, $M-SO_2PhNO_2$).

2.3.23. Methyl 2-{[(4-nitrophenyl)sulfonyl][2-(1-methyl-2,3,-dioxo-2,3,-dihydro-1*H*-indol-5-yl)prop-2-enyl]amino}-pent-4-enoate (38). Prepared by the general termolecular cascade procedure on a 2.0 mmol scale, using 2.0 mmol of aryl iodide and a reaction time of 48 h. $Pd_2(dba)_3$ (0.05 mmol) was used in place of $Pd(OAc)_2$. Purification by flash column chromatography eluting with 7:3 v/v petrol/ethyl acetate afforded the product (380 mg, 43%) as red needles, mp 141–143 °C; R_f 0.21; (Found: C, 55.90; H, 4.45; N, 8.05. $C_{24}H_{23}N_3O_8S$ requires C, 56.15; H, 4.50; N, 8.20%); ν_{max}/cm^{-1} (film) 1741 (MeO–C=O), 1620, 1529 (NO_2), 1349 ($S=O_{as}$), 1165 ($S=O_s$) 1092; δ_H (250 MHz, $CDCl_3$) 8.35 (2H, d, $J=8.9$ Hz, ArH), 8.01 (2H, d, $J=8.9$ Hz, ArH), 7.68 (1H, dd, $J=8.2$, 1.9 Hz, ArH_I), 7.58 (1H, d, $J=1.9$ Hz, ArH), 6.88 (1H, d, $J=8.2$ Hz, ArH), 5.63 (1H, ddt, $J=16.7$, 9.8, 6.9 Hz, C*H*=CHH), 5.5 (1H, s, =C*H*H), 5.4 (1H, s, =CH*H*), 5.02–5.09 (2H, m, CH=C$H_{cis}H_{trans}$), 4.54 (1H, t, $J=7.4$ Hz, NCH), 4.44 (1H, d, $J=16.8$ Hz, NC*H*H), 4.26 (1H, d, $J=16.8$ Hz, NCH*H*), 3.49 (3H, s, CH_3), 3.28 (3H, s, CH_3), 2.61–2.73 (1H, m, =CHC*H*H), 2.36–2.50 (1H, m, =CHCH*H*); δ_C (75 MHz, $CDCl_3$) 183.6 (C=O), 170.3 (C=O), 158.6 (C=O), 151.4, 150.6, 145.3, 141.8, 136.7, 134.8, 133.1, 129.3, 124.5, 123.4, 119.4, 117.8, 110.4, 60.4 (NCH), 52.7 (OCH_3), 50.4 (NCH_2), 35.3 (=CHCH_2), 23.0 (NCH_3); *m/z* (ES) 536 ($M^+ + Na$).

2.3.24. Methyl 1-[(4-nitrophenyl)sulfonyl]-5-phenyl-1,2,3,6-tetrahydropyridine-2-yl(propan-1-one) (39). Prepared by the general ring closing metathesis procedure on a 0.05 mmol scale and a reaction time of 1 h. Purification by flash column chromatography eluting with 3:2 v/v petrol/ether afforded the product (206 mg, 98%) as colourless needles, mp 112–114 °C. R_f 0.19; (Found: C, 56.65; H, 4.75; N, 6.95. $C_{19}H_{18}N_2O_6S$ requires C, 56.71; H, 4.50; N, 6.95%); ν_{max}/cm^{-1} (film) 1743 (C=O), 1530 (NO_2), 1349 ($S=O_{as}$), 1167 ($S=O_{as}$), 1097; δ_H (250 MHz, $CDCl_3$), 8.37 (2H, d, $J=8.6$ Hz, ArH), 8.03 (2H, d, $J=8.6$ Hz, ArH), 7.38–7.26 (5H, m, ArH), 6.10–6.06 (1H, br m, =CH), 4.98 (1H, dd, $J=5.5$, 2.8 Hz, NCH), 4.57 (1H, dd, $J=16.1$, 1.7 Hz, NC*H*H), 4.13 (1H, ddd, $J=16.1$, 5.3, 3.2 Hz, NCH*H*) 3.54 (3H, s, CH_3), 2.81–2.77 (2H, br m, =CHCH_2); δ_C (63 MHz, $CDCl_3$) 170.6 (C=O), 150.4, 145.1, 138.2, 133.8, 129.1, 128.9, 128.6, 125.5, 124.6, 119.9, 53.1, 52.9, 44.0, 28.6; *m/z* (%) (EI) 402 (3, M^+), 343 (6, $M-CO_2Me$), 216 (40), 156 (100, SO_2PhNO_2), 129 (32).

2.3.25. Methyl 5-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-1-[(4-nitorphenyl)sulfonyl]-1,2,3,6-tetrahydropyridine-2-carboxylate (40). Prepared by the general ring closing metathesis procedure on a 0.16 mmol scale and a reaction time of 1 h. Purification by flash chromatography eluting with 3:2 v/v ethyl acetate/petrol afforded the product (702 mg, 93%) as colourless needles, mp 221–223 °C; R_f 0.14; (Found: C, 49.05; H, 4.40; N, 12.20. $C_{19}H_{20}N_4O_8S$ requires C, 49.15; H, 4.35; N, 12.05%); ν_{max}/cm^{-1} (film) 1742 (MeO–C=O), 1702 (N–C=O), 1653 (N(N)C=O), 1530 (NO_2), 1350 ($S=O_{as}$), 1167 ($S=O_s$); δ_H ($CDCl_3$, 250 MHz) 8.36 (2H, d, $J=$ 8.9 Hz, ArH), 8.06 (2H, d, $J=8.9$ Hz, ArH), 7.08 (1H, s, ArH), 5.98–5.94 (1H, br m, =CH), 4.91 (1H, dd, $J=6.6$, 1.65 Hz, NCH), 4.61 (1H, d, $J=16.6$ Hz, NC*H*H), 4.06–3.99 (1H, m, NCH*H*), 3.58 (3H, s, CH_3), 3.41 (3H, s, CH_3), 3.34 (3H, s, CH_3), 2.70–2.61 (2H, br m, =CHCH_2); δ_C (63 MHz, $CDCl_3$) 170.6 (C=O), 162.4 (C=O), 151.6

(C=O), 150.4, 145.4, 140.4, 128.9, 124.6, 122.6, 112.6, 53.0 (NCH), 52.9 (OMe), 43.8 (NCH_2), 37.5 (NCH_3), 28.5 (=CHCH_2), 27.9 (NCH_3); *m/z* (%) (FAB) 465 (100, M+ H^+), 279 (31, M−SO_2PhNO_2), 218 (24).

2.3.26. Methyl 5-(1,3-dimethyl-2,4,-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-1-[(4-nitrophenyl)sulfonyl]-1,2,3,6-tetrahydropyridine-2-carboxylate (41). Prepared by the general ring closing metathesis procedure on a 0.058 mmol scale and a reaction time of 1 h. Purification by flash column chromatography eluting with 1:1 v/v ethyl acetate/petrol afforded the product (216 mg, 76%) as red needles, mp 224–226 °C; R_f 0.16; (Found: C, 54.40; H, 3.90; N, 8.45. $C_{22}H_{19}N_3O_8S$ requires C, 54.45; H, 3.95; 8.65%); ν_{max}/cm^{-1} (film) 1740 (MeO–C=O), 1621, 1530 (NO_2), 1349 ($S{=}O_{as}$) 1168 ($S{=}O_s$); δ_H (250 MHz, $CDCl_3$), 8.39 (2H, d, J=9.0 Hz, ArH), 8.03 (2H, d, J=9.0 Hz, ArH), 7.56 (2H, dd, J=7.3, 1.8 Hz, ArH), 7.54 (1H, s, ArH), 6.88 (1H, dd, J=7.3, 1.8 Hz, ArH), 6.11–6.09 (1H, br m, =CH), 4.98 (1H, t, J=4.2 Hz, NCH), 4.48 (1H, dd, J=16.2, 1.9 Hz, NC*H*H), 4.08 (m, 1H, NCH*H*), 3.54 (3H, s, CH_3), 3.27 (3H, s, CH_3), 2.83 (2H, br s, =CHCH_2); *m/z* (ES) 508 (M^+ + Na).

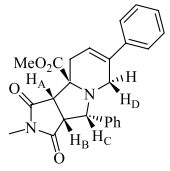
2.3.27. Methyl 5-phenyl-1,2,3,6-tetrahydropyridine-2-carboxylate (42). A solution of 39 (215 mg, 0.5 mmol) and benzene thiol (62 μl, 0.6 mmol) in DMF (4 ml) was added to a suspension of K_2CO_2 (0.208 g, 1.5 mmol) in DMF (3 ml) and the mixture stirred for 3 h at room temperature, quenched with 10% $NaHCO_3$ solution (6 ml) and extracted with ether (3×5 ml). The combined organic extracts were washed with water (5 ml), dried ($MgSO_4$), filtered and the filtrate concentrated in vacuo. Purification of the residue by flash chromatography eluting with ether afforded the product (88 mg, 83%) as pale yellow needles, mp 46–48 °C; R_f 0.1; (Found: C, 71.60; H, 7.20; N, 6.35. $C_{13}H_{15}NO_2$ requires C, 71.85; H, 6.95; N, 6.45%); ν_{max}/cm^{-1} (film) 3342 (NH), 1738 (C=O), 1435, 1202, 1174; δ_H (300 MHz, $CDCl_3$) 7.33–7.23 (5H, m, ArH), 6.16–6.13 (1H, br m, =CH), 3.90–3.80 (2H, m, NCH_2), 3.77 (3H, s, CH_3), 3.65 (1H, dd, J=9.1, 5.0 Hz, NCH), 2.55–2.45 (2H, m, =CHCH_2); δ_C (75 MHz, $CDCl_3$) 174.2 (C=O), 139.9, 136.8, 128.8, 127.7, 125.3, 121.5, 55.0 (OCH_3), 52.6 (NCH), 46.5 (NCH_2), 29.0 (=CHCH_2); *m/z* (EI) 217 (21, M^+), 158 (100, M−CO_2Me), 91 (38).

2.3.28. Methyl 5-(1,3,-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-1,2,3,6-tetrahydropyridine-2-carboxylate (43). Prepared by the above method, on a 1.4 mmol scale and a reaction time of 18 h. Purification by flash chromatography eluting with 9:1 v/v DCM/MeOH afforded the product (266 mg, 70%) as a pale yellow solid, mp 76–78 °C; R_f 0.28; (Found: C, 55.75; H, 5.80; N, 15.20. $C_{13}H_{15}NO_2$ requires C, 55.25; H, 6.10; N, 15.05%); ν_{max}/cm^{-1} (film) 1701 (C=O), 1653, 1437, 1293; δ_H (250 MHz, $CDCl_3$), 7.08 (1H, s, ArH), 6.15–6.14 (1H, br m, =CH), 3.76 (3H, s, CH_3), 3.69 (2H, br s, NCH_2), 3.64 (1H, dd, J= 9.2, 5.2 Hz, NCH), 3.42 (3H, s, CH_3), 3.35 (3H, s, CH_3), 2.50–2.32 (2H, m, =CHCH_2); *m/z* (%) (FAB) 280 (100, M^+), 220 (10, M−CO_2Me,), 193 (6).

2.4. Intermolecular cycloaddition

Benzaldehyde (22 μl, 0.2 mmol), and *N*-methyl maleimide (25 mg, 0.23 mmol) were added to a stirred solution of **42** (45 mg, 0.2 mmol) in toluene (6 ml). The reaction mixture was immersed in a pre-heated oil bath at 110 °C and stirred under a nitrogen atmosphere for 54 h. Concentration in vacuo gave the crude product, which comprised 3.5:1 mixture of **44** and **45**. Preparative HPLC (Luna C18/7:3 v/v MeCN/H_2O, 0.6 ml/min, detection at 254 nm) afforded pure **44** and **45** in 80% combined yield.

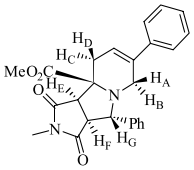
2.4.1. *endo*-Methyl 2-methyl-1,3-dioxo-4,7-diphenyl 1,2,3,3a,4,6,9,9b-octahydro-9a*H*-pyrrolo[3,4-*a*]indolizine-9a-carboxylate (44). Crystallisation from DCM/petrol afforded colourless needles, mp 105–107 °C; R_f 0.17; (Found: C, 72.15; H, 5.65; N, 6.50. $C_{25}H_{24}N_2O_4$ requires C, 72.10; H, 5.80; N, 6.75%); ν_{max}/cm^{-1} (film) 1750 (MeOC=O), 1702 (N–C=O), 1435, 1286; δ_H (500 MHz, C_6D_6), 7.16–7.03 (7H, m, ArH), 6.97–6.96 (3H, m, ArH), 6.02 (1H, m, =CH), 4.80 (1H, d, J=9.7 Hz, NCH_C), 3.82–3.80 (1H, m, NC*H*H|), 3.79–3.77 (1H, m, NCH*H*) 3.38 (1H, ddd, J=17.5, 6.5, 2.9 Hz, =CHC*H*H), 3.25 (3H, s, Me), 3.22 (1H, ddd, J=17.5, 6.4, 1.7 Hz, =CHCH*H*), 3.07 (1H, dd, J=9.7, 7.9 Hz, PhCHCH_B), 2.84 (1H, d, J=7.9 Hz, $NCCH_A$), 2.56 (3H, s, Me); δ_C (63 MHz, $CDCl_3$) 175.5 (C=O), 175.4 (C=O), 173.7 (C=O), 139.2, 137.4, 135.1, 131.0, 129.0, 128.7, 128.3, 127.8, 125.3, 120.6, 68.5, 68.3, 52.6, 51.1, 49.7, 48.7 (NCH_2), 31.8 (=CHCH_2), 25.3; *m/z* (%) (EI) 416 (1, M^+), 357 (100, M−CO_2Me);



NOE data:

Signal irradiated	Enhancement (%)			
	H_A	H_B	H_C	H_D
H_A		8.5		
H_B	12.1		9.5	
H_C		17.7		5.6

2.4.2. *exo*-Methyl 2-methyl-1,3-dioxo-4,7-diphenyl 1,2,3,3a,4,6,9,9b-octahydro-9a*H*-pyrrolo[3,4-*a*]indolizine-9a-carboxylate (45). Crystallisation from CH_3CN/H_2O afforded colourless needles, mp 212–214 °C, R_f 0.27; (Found: C, 71.90; H, 5.55; N, 6.50. $C_{25}H_{24}N_2O_4$ requires C, 72.10; H, 5.80; N, 6.75%); ν_{max}/cm^{-1} (film) 1769 (MeOC=O), 1693 (N–C=O), 1496, 1443, 1380, 1076; δ_H (500 MHz, C_6D_6), 7.58–7.57 (2H, m, ArH), 7.23–7.20 (2H, m, ArH), 7.14–7.12 (1H, m, ArH), 7.03–6.97 (5H, m, ArH), 6.10–6.09 (1H, m, =CH), 4.88 (1H, d, J=5.2 Hz, NCH_G), 3.63–3.60 (1H, m, NCH_AH_B), 3.43–3.34 (2H, m, NCH_AH_B and =CHCH_CH_D), 3.20 (3H, s, CO_2Me), 2.80 (1H, d, J= 9.8 Hz, CH_E), 2.77 (1H, dd, J=9.8, 5.2 Hz, CH_F), 2.73 (3H, s, NMe), 2.45–2.40 (1H, m, $CHCH_CH_D$); δ_C (75 MHz, $CDCl_3$) 175 (C=O), 174.4 (C=O), 171.3 (C=O), 139.7, 137.7, 133.4, 128.0, 127.3, 127.1, 126.4, 126.3, 123.8, 120.5, 68.4 (*C*CO_2Me), 66.5 (NCH), 53.2, 52.4, 50.9, 46.1 (NCH_2), 35.2 (=CHCH_2), 23.9 (NCH_3); *m/z* (ES) 416 (M);



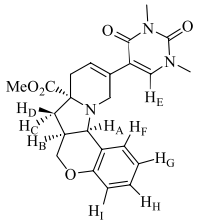
NOE data:

Signal irradiated	Enhancement (%)					
	H_A	H_B	H_C	H_D	H_E	H_G
H_A		25.0				6.9
H_C				31.7	15.2	
H_E			3.3			
H_G	5.7					

2.5. Intramolecular cycloaddition

2.5.1. Methyl-10-phenyl-6a,8,11,12a,tetrahydro-6*H*-chromeno[3,4-β]indolizine-7a(7*H*)-carboxylate (47). Salicylic aldehyde **46** (92 mg, 0.57 mmol) in toluene (2 ml) was added to a solution of **42** (112 mg, 0.52 mmol) in toluene (8 ml). The reaction mixture was immersed in a pre-heated oil bath at 110 °C and stirred under a nitrogen atmosphere for 26 h. Concentration in vacuo afforded a yellow gum, which was purified by flash column chromatography eluting with DCM to afford **47** (101 mg, 56%), which crystallised from DCM/petrol as colourless plates, mp 157–159 °C; R_f 0.34; ν_{max}/cm^{-1} (film) 1727 (C=O), 1488, 1224, 1192, 1172; δ_H (500 MHz, C_6D_6), 7.31–7.29 (2H, m, ArH), 7.26 (1H, dd, J=7.5, 1.6 Hz, ArH), 7.18–7.04 (m, 5H, ArH), 6.81 (1H, td, J=7.5, 1.5 Hz, ArH), 5.98 (1H, ddd, J=6.4, 4.0, 1.8 Hz =CH), 4.45 (1H, d, J=6.7 Hz, NCH), 4.28 (1H, br d, J=15.7 Hz, NC*H*H), 4.06 (1H, br d, J=15.7 Hz, NCH*H*), 3.77 (1H, dd, J=10.7, 8.5 Hz, OC*H*H) 3.67 (1H, dd, J=10.7, 4.4 Hz, OCH*H*), 3.33 (3H, s, CH_3), 2.98 (1H, ddd, J=16.4, 6.4, 1.8 Hz, =CC*H*H), 2.28–2.23 (1H, m, CH_2CH), 2.14–2.07 (2H, m, =CCH*H* and CHC*H*H), 1.43 (1H, dd, J=13.3, 5.0 Hz, CHCH*H*); δ_C (75 MHz, $CDCl_3$) 176.0 (C=O), 156.3, 140.1, 136.8, 131.6, 129.0, 128.7, 127.6, 125.6, 123.1, 121.7, 120.9, 117.8, 68.6 (OCH_2), 65.3 (NC), 58.3 (NCH), 51.9, 47.8 (CH_2), 38.3 (CH_2), 37.2 (CH_2), 34.9; *m/z* (%) (EI) 361 (1, M^+), 302 (100, $M-CO_2Me$). HRMS found 362.1747. $C_{23}H_{24}NO_3$ requires 362.1756.

2.5.2. Methyl 10-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-6a,8,11,12a-tetrahydro-6*H*-chromeno[3,4-β]indolizine-7a (7*H*)-carboxylate (48). Salicylic aldehyde **46** (70 mg, 0.43 mmol) in toluene (2 ml) was added to a solution of **43** (100 mg, 0.36 mmol) in toluene (8 ml). The reaction mixture was immersed in a pre-heated oil bath at 110 °C and stirred under a nitrogen atmosphere for 34 h. Work up (as above) followed by flash column chromatography eluting with 3:2 v/v ethyl acetate/petrol afforded **48** (82 mg, 54%), which crystallised from DCM/petrol as colourless plates, mp 238–240 °C; R_f 0.25; (Found: C, 65.40; H, 6.00; N, 9.70. $C_{23}H_{25}N_3O_5$ requires C, 65.25; H, 5.95; N, 9.90%) ν_{max}/cm^{-1} (film) 1725 (MeO–C=O), 1701 (N–C=O), 1652 (N(N)C=O), 1488, 1453, 1224, 1174, 1196; δ_H (500 MHz, $CDCl_3$) 7.22 (1H, dd, J=7.5, 1.7 Hz, ArH_F) 7.18 (1H, td, J=7.5, 1.7 Hz, ArH_G), 6.98 (1H, s, ArH_E), 6.94–6.90 (2H, m, ArH_H and ArH_I), 6.12–6.11 (1H, m, =CH), 4.25 (1H, d, J=7.1 Hz, NCH), 3.96 (1H, dd, J=10.6, 4.7 Hz, OC*H*H), 3.93 (1H, d, J=15.4 Hz, NC*H*H), 3.90 (1H, dd, J=10.6, 8.1 Hz, OCH*H*), 3.74 (3H, s, CH_3), 3.57 (d, 1H, J=15.4 Hz, NCH*H*) 3.38 (3H, s, CH_3), 3.33 (3H, s, CH_3), 2.97 (1H, ddd, J=16.6, 6.3, 2.0 Hz, =CHC*H*H), 2.60–2.56 (1H, m, OCH_2CH), 2.41 (1H, dd, J=13.3, 8.5 Hz, NCC*H*H), 2.21 (1H, d, J=16.6 Hz, =CHCH*H*), 1.71 (1H, dd, J=13.3, 5.3 Hz, NCCH*H*); *m/z* (%) (FAB) 424 (49, M^++H), 464 (55, $M-CO_2Me$);



NOE data:

Signal irradiated	Enhancement (%)		
	H_A	H_B	H_C
H_A		9.6	
H_B	6.8		3.4

2.5.3. 2-Allylphenyl-2-(thienyl)prop-2-en-1yl ether (53). Prepared by the general termolecular cascade procedure employing 2-allyphenol as the nucleophile on a 2 mmol scale, using 2.5 mmol of aryl iodide and a reaction time of 16 h. Purification by flash chromatograpy eluting with 19:1 v/v petrol/ether afforded the product (398 mg, 78%) as a colourless liquid; R_f 0.05; (Found: C, 74.90; H, 6.15; $C_{16}H_{16}OS$. requires C, 74.95; H, 6.30%); ν_{max}/cm^{-1} (film) 1638, 1600, 1586, 1488, 1231, 1090; δ_H (250 MHz, $CDCl_3$) 7.25 (1H, d, J=4.0 Hz, ArH), 7.18 (2H, d, J=7.7 Hz, ArH and ArH), 7.13 (1H, d, J=3.7 Hz, ArH) 7.02 (1H, dd, J=4.0, 3.7 Hz, ArH) 6.93 (2H, t, J=7.7 Hz, ArH and ArH), 5.98 (1H, ddt, J=16.9, 10.2, 6.7 Hz, C*H*=CHH), 5.62 (1H, s, =CH*H*), 5.38 (1H, s, =C*H*H), 5.03 (1H, d, J=16.9 Hz, CH=CHH_{trans}), 5.02 (1H, d, J=10.2 Hz, CH=CH_{cis}H), 4.87 (2H, s, OCH_2), 3.42 (2H, d, J=6.7 Hz, CH_2); δ_C (63 MHz, $CDCl_3$) 156.5, 142.4, 137.5, 137.4, 130.4, 129.5, 127.8, 127.7, 125.0, 124.3, 121.4, 115.9, 113.3, 112.1, 70.0 (OCH_2), 34.8 (CH_2); *m/z* (%) (EI) 256 (14, M^+), 215 (39), 123 (100), 79 (50).

2.5.4. 2-Allylphenyl-2-(4-nitrophenyl)prop-2-en-1-yl ether (54). Prepared by the general termolecular cascade procedure employing 2-allyphenol as the nucleophile on a 2 mmol scale, using 2.5 mmol of aryl iodide and a reaction time of 21 h. Purification by flash chromatography eluting with 9:1 v/v petrol/ether afforded the product (460 mg, 78%), which crystallised from DCM/petrol as colourless needles, mp 51–53 °C; R_f 0.16; (Found: C, 73.05; H, 6.00; N, 4.50. $C_{18}H_{17}NO_3$ requires C, 73.20; H, 5.80; N, 4.75%); ν_{max}/cm^{-1} (film) 1597, 1505 (NO_2), 1492, 1343 (NO_2), 1243; δ_H (250 MHz, $CDCl_3$) 8.20 (2H, d, J=8.9 Hz, ArH), 8.14 (2H, d, J=8.9 Hz, ArH), 7.22 (1H, d, J=8.0 Hz, ArH), 7.16 (1H, d, J=8.0 Hz, ArH), 6.94 (2H, t, J=8.0 Hz, ArH), 5.87 (1H, ddt, J=17.2, 10.7, 6.6 Hz, C*H*=CHH), 5.76 (1H, s, =CH*H*), 5.68 (1H, s, =C*H*H), 4.95 (1H, d, J=10.7 Hz, CH=CH_{cis}H), 4.94 (1H, d, J=17.2 Hz, CH=CHH_{trans})

4.92 (2H, s, OCH_3), 3.29 (2H, d, $J=6.6$ Hz, CH_2); δ_C (63 MHz, $CDCl_3$) 156.2, 147.8, 145.3, 142.3, 137.1, 130.6, 129.4, 127.8, 127.4, 124.1, 121.7, 118.9, 115.9, 111.9, 69.9 (OCH_2), 34.7 (CH_2); *m/z* (%) (EI) 295 (18, M^+), 131 (42), 115 (100), 77 (35).

2.5.5. 1-Allyl-2{[2-(4-methoxyphenyl)prop-2-en-1-yl] oxy}benzene (55). Prepared by the general termolecular cascade procedure employing 2-allyphenol as the nucleophile on a 3 mmol scale, using 3.5 mmol of aryl iodide and a reaction time of 30 h. Purification by flash chromatograpy eluting with 19:1 v/v petrol/ether afforded the product (680 mg, 80%) as a colourless liquid; R_f 0.4; (Found: C, 81.10; H, 7.10; $C_{19}H_{20}O_2$ requires C, 81.40; H, 7.19%); ν_{max}/cm^{-1} (film) 1635, 1607, 1513, 1491, 1243, 1031; δ_H (250 MHz, $CDCl_3$) 7.42 (2H, d, $J=8.7$ Hz, ArH), 7.23–7.14 (2H, m, ArH), 6.95–6.83 (2H, m, ArH), 6.86 (2H, d, $J=$ 8.7 Hz, ArH), 5.98 (1H, ddt, $J=17.0$, 10.3, 6.7 Hz, C*H*=CHH), 5.51 (1H, s, =CH*H*), 5.39 (1H, s, =C*H*H), 5.04–4.97 (2H, m, C_X=$H_{cis}H_{trans}$), 4.87 (2H, s, OCH_2), 3.36 (2H, d, $J=6.7$ Hz, CH_2); δ_C (63 MHz, $CDCl_3$) 159.8, 156.6, 143.0, 137.4, 131.4, 130.3, 129.5, 127.7, 127.6, 121.2, 115.8, 114.2, 113.2, 112.1, 70.3 (OCH_2), 55.7 (OCH_3), 34.8 (CH_2); *m/z* (ES) 281 ($M^+ + H$).

2.6. Modified ring closing metathesis procedure

2.6.1. 3-(2-Thienyl)-2,5-dihydro-1-benzoxepine (56). Catalyst **1** (22 mg, 2.5 μm) was added to a magnetically stirred solution of 53 (130 mg, 0.5 mmol), in anhydrous toluene (120 ml). The mixture then stirred under an argon atmosphere at 80 °C for 16 h. Concentration in vacuo afforded a brown oil, which was purified by flash chromatography eluting with 7:3 v/v petrol/DCM to afford the product (68 mg, 59%), which crystallised from DCM/hexane as colourless needles, mp 84–86 °C; R_f 0.35; (Found: C, 73.35; H, 5.40. $C_{14}H_{12}OS$ requires C, 73.65; H, 5.30%); ν_{max}/cm^{-1} (film) 1614, 1440, 1254, 1234; δ_H (250 MHz, $CDCl_3$) 7.26–7.02 (5H, m, ArH), 6.94 (1H, dd, $J=5.1$, 3.5 Hz, ArH), 6.84 (1H, d, $J=3.5$ Hz, ArH), 6.34 (1H, br t, $J=5.7$ Hz, =CH), 4.93 (2H, d, $J=1.8$ Hz, OCH_2), 3.62 (2H, d, $J=5.7$ Hz, CH_2); δ_C (63 MHz, $CDCl_3$) 129.1, 128.5, 127.7, 124.7, 124.0, 123.9, 122.2, 121.5, 72.6 (OCH_2), 31.6 (CH_2); *m/z* (%) (EI) 228 (100, M^+), 165 (27), 131 (47), 97 (44).

2.6.2. 3-(4-Nitrophenyl)-2,5-dihydro-1-benzoxepine (57). Prepared by the modified general RCM procedure on a 0.46 mmol scale and a reaction time of 23 h. Purification by flash chromatography eluting with 1:1 v/v DCM/petrol afforded the product (76 mg, 62%), which crystallized from petrol/DCM as pale yellow needles, mp 94–96 °C; R_f 0.3; (Found: C, 71.65; H, 5.05. N, 5.10; $C_{16}H_{13}NO_3$ requires C, 71.90; H, 4.90; N, 5.25%); ν_{max}/cm^{-1} (film) 1652, 1516 (NO_2), 1343 (NO_2), 1229; δ_H (250 MHz, $CDCl_3$) 8.17 (2H, d, $J=8.8$ Hz, ArH), 7.37 (2H, d, $J=8.8$ Hz, ArH), 7.27–7.05 (4H, m, ArH), 6.31 (1H, br t, $J=5.7$ Hz, =CH), 4.95 (2H, d, $J=1.7$ Hz, OCH_2), 3.70 (2H, d, $J=5.7$ Hz, CH_2), δ_C (63 MHz, $CDCl_3$) 158.8, 147.3, 147.0, 137.3, 134.2, 129.4, 128.9, 128.8, 127.0, 124.7, 124.2, 121.5, 72.3 (OCH_2), 32.1 (CH_2); *m/z* (%) (EI) 267 (100, M^+), 252 (47), 220 (36), 131 (71), 91 (49).

2.6.3. 3-(4-Methoxyphenyl)-2,5-dihydro-1-benzoxepine (58). Prepared by the modified general RCM procedure on a 0.46 mmol scale and a reaction time of 22 h. Purification by flash chromatography eluting with 1:1 v/v DCM/petrol afforded the product (68 mg, 56%), which crystallised from hexane as colourless needles, mp 72–74 °C; R_f 0.35; ν_{max}/cm^{-1} (film) 1603, 1491, 1254, 1229, 1030; δ_H (300 MHz, $CDCl_3$) 7.24–7.02 (4H, m, ArH), 7.18 (2H, d, $J=8.7$ Hz, ArH), 6.83 (2H, d, $J=8.7$ Hz, ArH), 6.05 (1H, br t, $J=$ 5.5 Hz, =CH), 4.90 (2H, d, $J=2.1$ Hz, OCH_2), 3.62 (2H, d, $J=5.5$ Hz, CH_2); δ_C (75 MHz, $CDCl_3$) 159.5, 158.9, 138.3, 135.4, 133.1, 129.2, 128.4, 127.6, 124.4, 123.8, 121.5, 114.2, 73.2 (OCH_2), 55.7 (OCH_3), 31.9 (CH_2); *m/z* (%) (EI) 252 (100, M^+), 237 (82, $M-CH_3$) 131 (45); HRMS found 252.1143, $C_{17}H_{16}O_2$ requires 252.1145.

2.7. Single-crystal X-ray analysis for 44

Crystallographic data for **44** was measured on a Nonius Kappa CCD area-detector diffractometer using ϕ and ω-scans and graphite monochromated Mo Kα radiation ($\lambda=0.71073$ Å). The structure was solved by direct methods using SHELXS-86[32] and were refined by full-matrix least-squares (based on F^2) using SHELXL-97.[33] The weighting scheme used was $w=[\sigma^2(F_o^2)+(0.1235P)^2+0.0127P]^{-1}$ where $P=(F_o^2+2F_c^2)/3$. All non-hydrogen atoms were refined with anisotropic displacement parameters whilst hydrogen atoms were constrained to predicted positions using a riding model. The residuals wR_2 and R_1, given below, are defined as $wR_2=(\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[wF_o^2]^2)^{1/2}$ and $R_1=\Sigma||F_o|-|F_c||/\Sigma|F_o|$.

Crystal data for **44**. $C_{25}H_{24}N_2O_4$, $0.33\times0.20\times0.10$ mm, $M=416.46$, monoclinic, space group $P2_1/n$, $a=6.4754(1)$, $b=12.1259(2)$, $c=30.0988(6)$ Å, $\beta=93.3630(10)°$, $U=$ 2359.29(7) Å^3, $Z=2$, $D_c=1.172$ Mg m^{-3}, $\mu=0.08$ mm^{-1}, $F(000)=880$, $T=150(2)$ K.

Data collection. $1.36 \leq\theta\leq 26°$; 4602 independent reflections were collected [$R_{int}=0.082$]; 3209 reflections with $I>2\sigma(I)$.

Structure refinement. Number of parameters=283, goodness of fit, $s=1.084$; $wR_2=0.1980$, $R_1=0.0611$.

Full supplementary crystallographic data, which include hydrogen co-ordinates, thermal parameters and complete bond lengths and angles, have been deposited at the Cambridge Crystallographic Data Centre (CCDC 275316) and are available on request.

Acknowledgements

We thank GlaxoSmithKline and the EPSRC for their support.

References and notes

1. Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321–3329.

2. Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133–1144.
3. Aftab, T.; Grigg, R.; Sridharan, V.; Ladlow, M.; Thornton-Pett, M. *Chem. Commun.* **2000**, 1754–1755.
4. Gardiner, M.; Grigg, R.; Kordes, M.; Sridharan, V.; Vicker, N. *Tetrahedron* **2001**, *57*, 7729–7735.
5. Anwar, U.; Grigg, R.; Rasparini, M.; Savic, V.; Sridharan, V. *Chem. Commun.* **2000**, 933–934.
6. Grigg, R.; Sridharan, V.; Thayaparan, A. *Tetrahedron Lett.* **2003**, *44*, 9017–9019.
7. Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238.
8. McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239–2258.
9. Briot, A.; Bujard, M.; Gouverneur, V.; Nolan, S. P.; Mioskowski, C. *Org Lett.* **2000**, *2*, 1517–1519.
10. Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29.
11. Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117–7140.
12. Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247–2250.
13. For a classic paper evaluating, categorising and examplifying the application of **1** and **2** to alkene cross-metathesis see: Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem Soc.* **2003**, *125*, 11360–11370.
14. Grigg, R.; Sridharan, V.; York, M. *Tetrahedron Lett.* **1998**, *39*, 4139–4142.
15. Grigg, R.; York, M. *Tetrahedron Lett.* **2000**, *41*, 7255–7258.
16. Evans, P.; Grigg, R.; Ramzan, M. I.; Sridharan, V.; York, M. *Tetrahedron Lett.* **1999**, *40*, 3021–3024.
17. Evans, P.; Grigg, R.; Manteilt, M. *Tetrahedron Lett.* **1999**, *40*, 5247–5250.
18. Evans, P.; Grigg, R.; York, M. *Tetrahedron Lett.* **2000**, *41*, 3967–3970.
19. Preliminary communications: Dondas, H. A.; Balme, G.; Clique, B.; Grigg, R.; Hodgeson, A.; Morris, J.; Sridharan, V. *Tetrahedron Lett.* **2001**, *42*, 8673–8675.
20. For a closely related Pd catalysed 4-component cascade/RCM processes involving both carbon monoxide and allene insertion see: Grigg, R.; Martin, W.; Morris, J.; Sridharan, V. *Tetrahedron*, **2005**, Symposium in print, in press.
21. For related work see: Kinderman, S. S.; van Maarseven, J. H.; Schoemaker, H. E.; Heimstra, H.; Rutjes, F. P. J. T. *Org. Lett.* **2001**, *3*, 2045–2048. Kinderman, S. S.; De Gelder, R.; Van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F P.J. T. *J. Am. Chem. Soc.* **2004**, *126*, 4100–4101. De Matteis, V.; van Delft, F. L.; de Gelder, R.; Tiebes, J.; Rutjes, F.P.J. T. *Tetrahedron Lett.* **2004**, *45*, 959–963. Hekking, K. F. W.; Van Delft, F. L.; Rutjes, F.P.J. T. *Tetrahedron* **2003**, *59*, 6751–6758. Yang, Y.-K.; Tae, J. *Synlett* **2003**, 1043–1045. Gille, S.; Ferry, A.; Billard, T.; Langlois, B. R. *J. Org. Chem.* **2003**, *68*, 8932–8935. Hunt, J. C. A.; Laurent, P.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2378–2389. Agami, C.; Couty, F.; Rabasso, N. *Tetrahedron* **2001**, *57*, 5393–5401. Ahn, J.-B.; Yun, C.-S.; Kim, K. H.; Ha, D.-C. *J. Org. Chem.* **2000**, *65*, 9249–9251. Reviews: Basra, S.; Blechert, S. *Strategies Tactics Org. Synth.* **2004**, *4*, 315–346. Philips, A. J.; Abell, A. D. *Aldrichim. Acta* **1999**, *32*, 75–89.
22. (a) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089–4092. (b) For a review, see: Hermann, W. A.; Bohm, V. P. W.; Reisinger, C. P. *J. Organomet. Chem.* **1999**, *576*, 23.
23. Jeffrey, T. *Tetrahedron Lett.* **1985**, *26*, 2667–2670.
24. Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373–6374.
25. In some cases trace amounts of an additional minor isomer were detected.
26. Joucla, M.; Mortier, J.; Hamelin, J. *Tetrahedron Lett.* **1985**, *26*, 2775–2778.
27. ^{1}H NMR spectra of the crude reaction suggests the formation of trace amounts of other isomers.
28. Grigg, R.; Duffy, L. M.; Dorrity, M. J.; Malone, J. F.; Rajviroongit, S.; Thornton-Pett, M. *Tetrahedron* **1990**, *46*, 2213–2230.
29. Gruijters, B. W. T.; Van Veldhuizen, A.; Weijers, C. A. G. M.; Wijnberg, J. B. P. A. *J. Nat. Prod.* **2002**, *65*, 558–561. Furstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H. J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204–2207. Wang, E.-C.; Hsu, M.-K.; Lin, Y.-L.; Huang, K.-S. *Heterocycles* **2002**, *57*, 1997–2010. Roger, F.; Vilain, C.; Elkaim, L.; Grimaud, L. *Org Lett.* **2003**, *5*, 2007–2009. van Otterlo, W. A. L.; Ngidi, E. L.; de Koning, C. B.; Fernandes, M. A. *Tetrahedron Lett.* **2004**, *45*, 659–662.
30. Armarego, W. L. F.; Perrin, D. D. *The Purification of Laboratory Chemicals*, 4th ed.; Butterworth-Heinemann: Oxford, 1996.
31. Vogel, A. I.; Furniss, B. S. *Textbook of Practical Organic Chemistry*, 5th ed.; Longman: Harlow, UK, 1989.
32. Sheldrick, G. M. *Acta Crystallogr., Sect. A* **1990**, *46*, 467–473.
33. Sheldrick, G. M. *SHELXl-97*: *Program for Refinement of Crystal Structures*; University of Göttingen: Germany, 1997.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 10667–10682

X=Y=ZH systems as potential 1,3-dipoles. Part 62:[1] 1,3-Dipolar cycloaddition reactions of metallo-azomethine ylides derived from α-iminophosphonates

H. Ali Dondas,[a,b] Yasar Durust,[a,c] Ronald Grigg,[a,*] Martin J. Slater[a] and Mohammed Abul Basher Sarker[a]

[a]*Molecular Innovation, Diversity and Automated Synthesis (MIDAS) Centre, School of Chemistry, Leeds University, Leeds LS2 9JT, UK*
[b]*Department of Chemistry, Faculty of Pharmacy, Mersin University, Yenisehir, 33342, Mersin, Turkey*
[c]*Department of Chemistry, Faculty of Science and Arts, Abant İzzet Baysal University, Bolu, Turkey*

Received 23 March 2005; revised 5 August 2005; accepted 19 August 2005

Available online 19 September 2005

Abstract—Metallo-azomethine ylides, generated from iminophosphonates in combination with LiBr or AgOAc and bases Et_3N, DBU, *t*-butyl tetramethylguanidine(BTMG) undergo cycloaddition to give dialkyl pyrrolidine-2-phosphonates along with the corresponding Michael adduct in some cases. Cycloadditions with the chiral dipolarophile 5*R*-(1′*R*,2′*S*,5′*R*-menthyloxy)-2-(5*H*)-furanone (MOF) afforded enantiopure cycloadducts.

1. Introduction

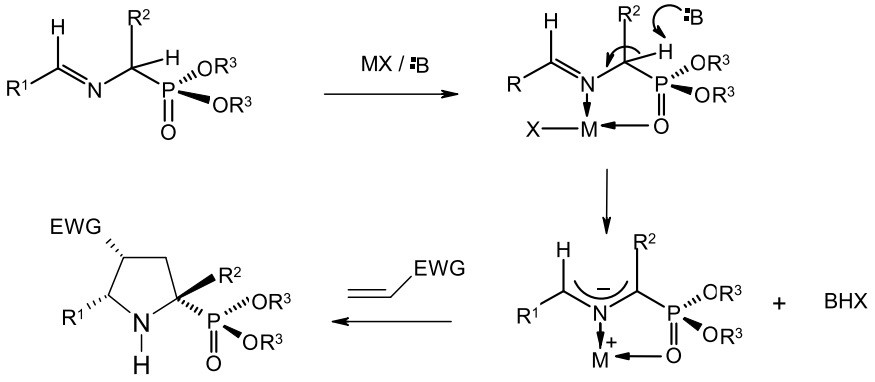
α-Amino phosphonates are an important class of compounds in that they serve as bioisoesters of α-amino acids.[2] Moreover when they are incorporated into peptides they mimick the tetrahedral transition state of peptide hydrolysis and can thus, be designed to be transition state inhibitors of specific peptidases or esterases.[3]

The metal ion catalysed cycloaddition of ester (lactone, lactam) stabilised azomethine ylides with appropriate dipolarophiles has been widely developed to access proline analogues, α-amino acids[4] and peptidomimetics.[5] This reaction has been utilised as the key step in the synthesis of many complex heterocycles.[6–8] The metallo-azomethine ylide cycloaddition has also been exploited in conjunction with other high yielding core reactions in sequential and cascade processes, thus, producing more complex heterocycles[9–15] with maximum synthetic efficiency. Chiral versions of these processes have been developed, which employ chiral dipolarophiles,[16] chiral azomethine ylides[17] or chiral catalysts.[18,19] These processes are dependent on the presence of an electron withdrawing carbanion stabilising group, which becomes conjugated to the putative azomethine ylide in the reaction.[20] We have shown that a wide range of such groups are effective in both the 1,2-prototropy and the metal catalysed protocols for in situ generation of azomethine ylides.[21] A wide range of metal and bases have been employed to promote the metal catalysed cycloaddition, including [Ag(I), Li(I), Zn(II), Mg(II), Mn(II), Co(II), Sn(IV)],[21] Ti(IV),[22] Ni(II),[1] Cu(I),[1] Cu(II)[19] and samarium[23] and a range of rare earth[24] triflates. However, LiBr and AgOAc are the most commonly used metal salts, while DBU and Et_3N are the most frequently used bases.[19,25]

In this paper, we report the metal catalysed cycloaddition reactions of α-imino phosphonates with various dipolarophiles including chiral menthyloxy furanone with (AgOAc or LiBr) and a suitable bases [DBU, Et_3N, BTMG (*t*-butyl tetramethylguanidine)] as outlined in Scheme 1. Scheme 1 affords access to a wide variety of proline analogues and conformationally constrained α-amino phosphonates. Moreover, this application of our metal catalysed imine→metalloazomethine ylide→cycloaddition cascade appeared ideally suited to the phosphonate, which is a relatively weak EWG.[20] The rate of reaction can be further increased by employing a stronger base, such as 2-*t*-butyl 1,1,3,3-tetramethyl guanidine (BTMG). There is also scope for the introduction of chirality in the dipole, since phosphorus can be easily asymmetrically substituted.

Keywords: Cycloaddition; Iminophosphonate metallo-dipole; Azomethine ylide.
* Corresponding author. Tel.: +44 113 343 6501; fax: +44 113 343 6530; e-mail: r.grigg@chemistry.leeds.ac.uk

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.08.079



Scheme 1.

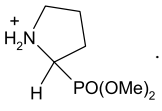
2. Synthesis of α-amino phosphonates

The synthesis of α-amino phosphonates can be achieved in several ways, for example, addition of phosphites, phosphonites and hypophosphorus acids to imines,[2,26] reaction of appropriate phosphorus compounds with *N*,*O*-acetals[27,28] and alkyl bromides,[29] or by alkylation of amino methanephosphonate derivatives.[30] Such analogues of all the natural amino acids are known. The simplest α-amino phosphonate, the glycine analogue, can be obtained in almost quantitative yield from *N*-phthalimidomethyl bromide via an Arbuzov reaction with an appropriate phosphite.[29] *N*-Deprotection via hydrazinolysis[3] gives the α-aminophosphonate in moderate to excellent yield depending on the phosphite.

One of the most efficient syntheses of α-amino phosphonates is due to Corcoran and Green.[31] The primary advantage of this method is the use of readily available natural amino acids as precursors. The four-step procedure is relatively simple with the final step involving hydrogenolysis of **1** to **2**. The products are obtained in good yield (Table 1). The first step involves *N*-protection of the amino acids with the *N*-benzyloxycarbonyl group (Cbz) under standard Shotten–Baumann conditions. The *N*-Cbz amino acids then undergo oxidative decarboxylation upon treatment with lead tetraacetate. The serine analogue was *O*-protected prior to this stage with a TBDMS group.

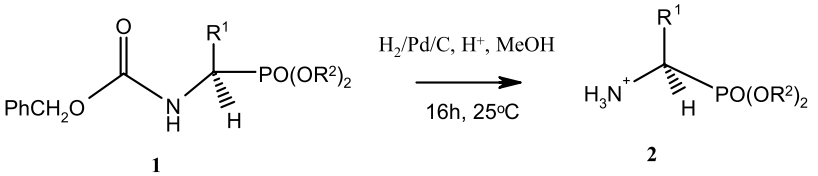
Table 1. Synthesis of α-aminophosphonates **2a–h**

Entry	R^1	R^2	Product	Yield[a]
1	H	Me	**2a**[b]	Quant
2	H	Ethyl	**2b**[b]	Quant
3	Me	Me	**2c**	Quant
4	Ph	Me	**2d**	Quant
5	$PhCH_2$	Me	**2e**	Quant
6	—[c]	Me	**2f**	Quant
7	CH_2OH	Me	**2g**	Quant
8	$CH_2Osi(Me)_2$–*t*-Bu	Me	**2h**	Quant

[a] Isolated yield.
[b] Compound **2a** and **2b** were synthesised according to literature procedures.[3,29]
[c] Product **2f** is  .

Quantitative yields for the hydrogenolysis (Scheme 2) were obtained in methanol, using 5% Pd on charcoal as the catalyst. At least 1 equiv of glacial acetic acid, which remains as an impurity in the amine, is required for this procedure. The literature method (treatment with $NaHCO_3$ in dry DCM) does not remove the acid completely.

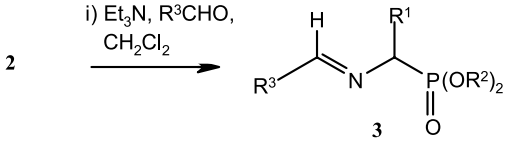
A technical improvement in the *N*-deprotection (Scheme 2) was achieved by using *p*-toluenesulfonic acid as the proton source. The sodium sulfonate salt can be easily removed by filtration, after stirring with moist $NaHCO_3$ in DCM, leaving the pure amine. This method was found to be unsuitable for the serine derivative **2h**, since *O*-desilylation occurs during this procedure. Compounds **2a** and **2b** were prepared according to the literature procedures.[3,29]



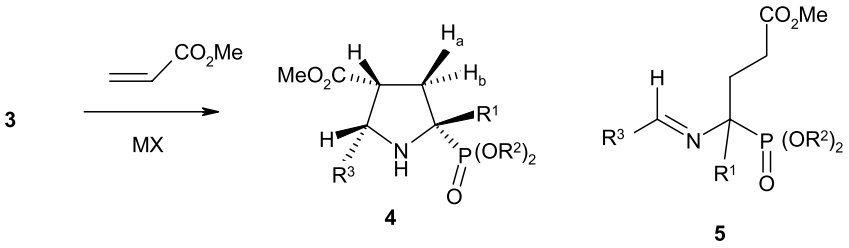
Scheme 2.

3. Synthesis of α-iminophosphonates

Imines **3a–t** were synthesised in excellent yield in most cases by reacting a range of aldehydes with α-aminophosphonates **2a–h** (Scheme 3). Prior treatment of the α-aminophosphonate salts with 1 equiv of triethylamine generated the free amines. Unfortunately, the isolated yield



Scheme 3.



Scheme 4.

of pure crystalline arylidene imines was adversely affected by the presence of the triethylammonium acetate contaminant. This became more of a problem with the aliphatic imines **3i–k**, since these products were thick oils and adequate microanalyses could not be obtained. The aliphatic imines were also less stable than their arylidene analogues, and gradually decomposed at rt.

3.1. Cycloadditions with methyl acrylate

Cycloadditions were carried out with a range of imines **3** using methyl acrylate as the dipolarophile (Scheme 4). The conditions employed, time and yield for the reactions are collected in Table 3. The reaction times are very much longer than those required for cycloadditions of the imines of α-amino esters. This is ascribed to the relatively high pK_a of the α-CH proton in the imino phosphonates.[20]

To increase the rate of the reaction, 2-*t*-butyl 1,1,3,3-tetramethylguanidine (BTMG), a stronger base, was used in the cycloaddition of the alanine analogue **3c**. Contrary to expectations, a longer reaction time was required and a lower overall yield was obtained (Table 2). The possible reaction of the phosphonate and the base was ruled out by monitoring a mixture of the two compounds over 16 h by ^{1}H NMR. The most likely explanation is that the imine's bulky dimethylphosphonate group impedes efficient deprotonation by the similarly sterically hindered base. We have recently published a related similar case of kinetic acidity impacting an azomethine ylide cycloadditions.[32]

The mechanism for the cycloaddition reaction (Scheme 5) is directly analogous to that proposed by us for imines of α-amino esters.[33] The stereo-specific formation of the *syn* or *E*,*E*-metallo-dipole (A and/or B), via deprotonation of the complexed imine, precedes regio- and *endo*-specific cycloaddition giving cycloadduct **4**.

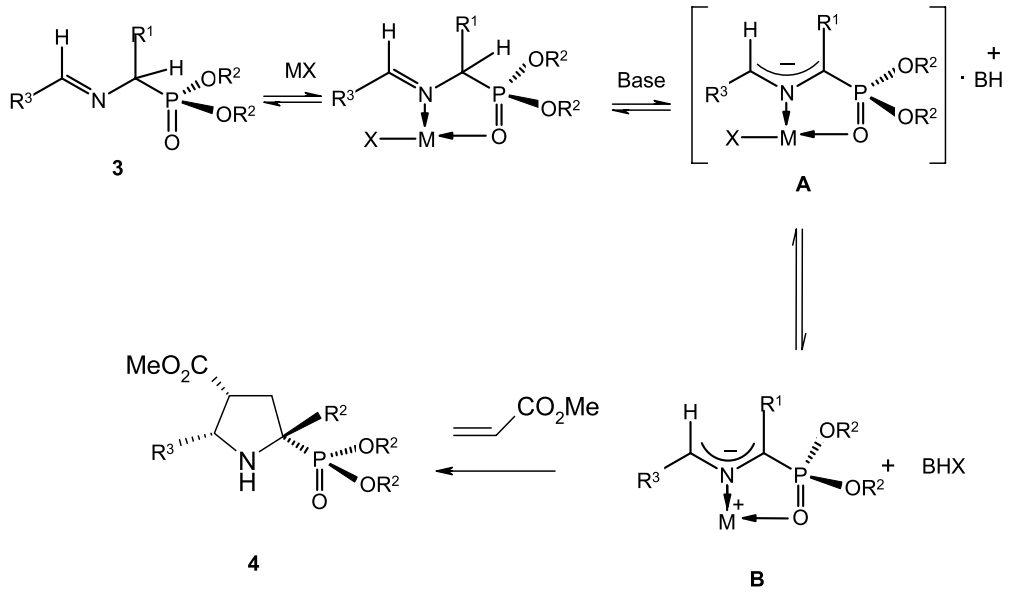
Reaction of phosphonate imine **3a** with methyl acrylate in acetonitrile with AgOAc/DBU afforded cycloadduct **4a** in 61% yield together with a trace Michael adduct **5a** (Scheme 4) (Table 3, entry 1). In contrast, the diethyl phosphonate **3b** with LiBr or AgOAc gave cycloadduct **4b** together with lactam **6**. Lactam **6** arises from **5b** via cycloaddition to methyl acrylate to afford **7** followed by cyclisation to the lactam **6**.

The ratio of the bicyclic lactam **6** to the cycloadduct **4b** was found to be 1:1 and 1:2.5 in the lithium and silver salt catalysed reactions, respectively. These results indicate that the Michael addition and cycloaddition have comparable rates in this case. Lactam **6** was isolated and fully characterised (see Section 6). The tendency of LiBr to favour Michael addition is well known but it is rare for silver salts to exhibit this trait.[21] In this case it is clearly related to the comparatively high pK_a of the crucial hydrogen α to the phosphonate (Scheme 6).

Table 2. Synthesis of iminophosphonates **3a–s**[a]

Entry	R^1	R^2	R^3	Product	Yield[b]
1	H	Me	2-Naphthyl	**3a**	Quant
2	H	Ethyl	2-Naphthyl	**3b**	95
3	Me	Me	2-Naphthyl	**3c**	57
4	Ph	Me	2-Naphthyl	**3d**	59
5	CH_2Ph	Me	2-Naphthyl	**3e**	44
6	**2f**		2-Thienyl	**3f**	—[c]
7	CH_2OH	Me	2-Naphthyl	**3g**	74
8	$CH_2OSi(CH_3)_2t$-Bu	Me	2-Naphthyl	**3h**	80
9	Me	Me	Cyclohexyl	**3i**	94
10	Ph	Me	Cyclohexyl	**3j**	75
11	CH_2Ph	Me	Cyclohexyl	**3k**	86
12	Me	Me	4-Nitrophenyl	**3l**	94
13	Me	Me	2-Iodophenyl	**3m**	90
14	Me	Me	2-Pyridyl	**3n**	88
15	Ph	Me	2-Pyridyl	**3o**	91
16	CH_2Ph	Me	2-Pyridyl	**3p**	Quant
17	Me	Me	2-Thienyl	**3q**	79
18	Ph	Me	2-Thienyl	**3r**	Quant
19	CH_2Ph	Me	2-Thienyl	**3s**	Quant

[a] Reaction employed amine (1 mmol), aldehyde (1 mmol) and NEt_3 (2 mmol) in dichloromethane at rt for 16 h.
[b] Isolated yield.
[c] Iminium ion generated in situ.

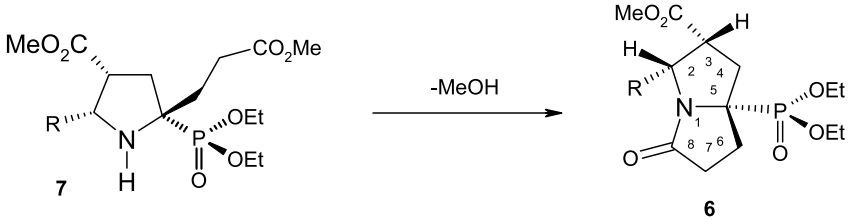


Scheme 5.

Table 3. Cycloaddition reactions of imines **3** with methyl acrylate (MA) to give **4**[a]

Entry	Imine	Metal salt	Solvent	Time (days)[b]	Product	Yield (%)
1	**3a**	AgOAc	MeCN	4	**4a**	61[c]
2	**3b**	AgOAc	MeCN	2	**4b**	47[c]
3	**3b**	LiBr	THF	3	**4b**	44[c]
4	**3c**	AgOAc	MeCN	3	**4c**	73
5	**3c**	AgOAc[d]	MeCN	6	**4c**	30[d,e]
6	**3d**	AgOAc	MeCN	7	**4d**	22[e]
7	**3d**	LiBr	THF	4	**4d**	73
8	**3e**	AgOAc	MeCN	4	**4e**	20
9	**3e**	LiBr	THF	3	**4e**	69
10	**3g**	AgOAc	MeCN	4	**4g**	8
11	**3h**	AgOAc	MeCN	5.8	**4h**	12
12	**3h**	LiBr	THF	6.8	**4h**	47
13	**3l**	AgOAc	MeCN	5.0	**4l**	37[f]
14	**3m**	AgOAc	MeCN	2.8	**4m**	80[c]
15	**3n**	AgOAc	MeCN	5.0	**4n**	90
16	**3o**	LiBr	THF	1.8	**4o**	32
17	**3p**	LiBr	THF	1.8	**4p**	75
18	**3r**	AgOAc	MeCN	5.0	**4r**	98
19	**3s**	LiBr	THF	0.9	**4s**	64[c]
20	**3t**	LiBr	THF	1.8	**4t**	79[c]

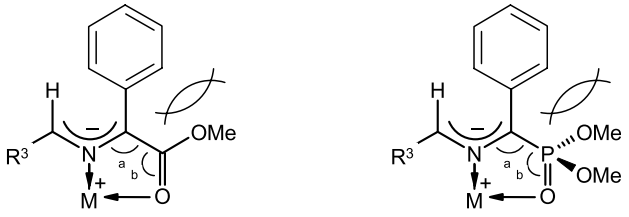
[a] The metal salt (1.5 mol equiv), DBU(1.0 mol equiv), imine (1 mol equiv) and methyl acrylate (1 mol equiv) were reacted at rt using a foil protected flask in the case of AgOAc.
[b] The reaction times relate to the disappearance of starting material, which was monitored by TLC.
[c] Small amount of Michael adduct (<10%) also formed.
[d] 2-*t*-Butyl 1,1,3,3-tetramethyl guanidine was used as the base.
[e] Obtained as a mixture of the imine and cycloadduct (% yield calculated by NMR).
[f] Michael adduct **5l** (29%) also formed.



Scheme 6.

The cycloadditions of methyl acrylate with the *N*-(2-naphthylidene) dimethyl phosphonate imines **3c–e** were relatively straightforward, and gave only the expected cycloadducts **4c–e** whose stereochemistry was established by 2-D COSY and NOE data (see Section 6).

The efficiencies of the two metal salts (AgOAc and LiBr) in the cycloaddition of phosphonate imines follows the same trend as that observed for imines of α-amino esters. Thus, imines of phenylglycine have been shown to work better with Li(I) rather than Ag(I) salts. We have argued that this preference is a result of steric compression between the phenyl substituent and the ester moiety caused by the increase in the angles *a* and *b* (Scheme 7) necessary for chelation of the larger silver ion (the respective ionic radii of Ag(I) and Li(I) are 1.26 and 0.68 Å). This compression is relieved by the phenyl ring twisting out of plane, which disrupts resonance stabilisation (higher pK_a for the crucial proton α to the ester) and hinders the cycloaddition.



Scheme 7.

In the case of the phosphonate imines the effect extends to the phenylalanine analogues (Table 3, entries 8, 9, 17 and 20) and the TBDMS protected serine imine (Table 3, entries 11 and 12).

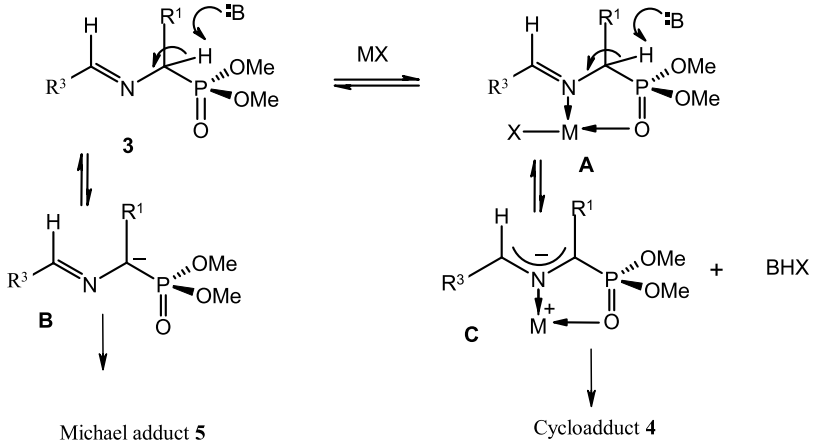
The geometries of the phosphonate and carboxylate metallo-dipoles (Scheme 7) are slightly different. In the tetrahedral phosphonate the angle *b* will be closer to 109° rather than the 120° angle of the carboxylate dipole. The tightening of the angles will be compensated for, to some extent, by the increase in bond lengths to phosphorus, (which are ~20% longer than the corresponding bond lengths to carbon). However, the results clearly suggest that the steric compression necessary to accommodate the larger silver ion and to achieve more appropriate bond angles, is more pronounced in the phosphonate case compared to the carboxylate. A further feature of Table 3 is the large amount of Michael adduct formed from imine **3l** (entry 13) but not from imines **3h**, **3o** and **3p** (Table 3, entries 15–17).

The effect of increasing the electron-withdrawing properties of the substituents at R^1 and R^3 (Scheme 8) would be two fold. Firstly, the basicity of the imine *N*-atom would decrease, which would lower the stability of the metal complexes **A** and **C**. Thus, the proportion of species **3** and **B** would increase relative to **A** and **C**. Secondly, the pK_a of the α-CH proton would decrease; resulting in the species **B** and **C** being favoured relative to **3** and **A**. Assuming the anion **B** reacts to give the Michael adduct, and that the metallo-dipole **C** reacts to give cycloadduct only, combining the two factors could result in an increase in the proportion of Michael adduct. However, this would be moderated by the increased stability of the anion. Thus, in considering the relative rates of the two processes, our results indicate Michael addition becomes somewhat more competative and in the case of **3l** the rates are approximately the same. If this were true, it would require only a slight disturbance of the equilibrium for Michael addition to become the more prevalent reaction pathway.

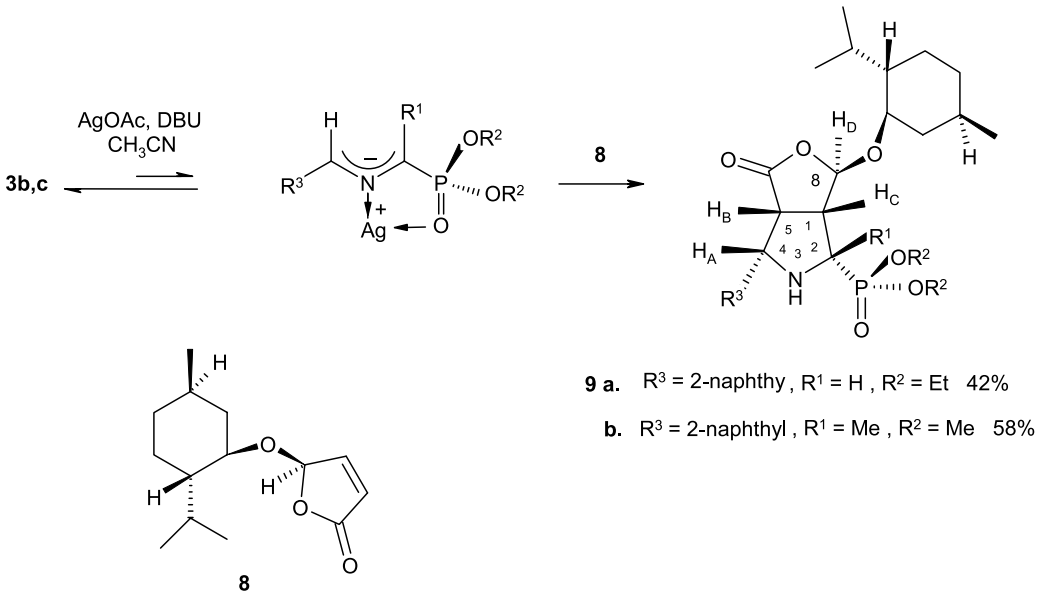
Generally, the use of electron-withdrawing substituents to activate the imino phosphonates is very effective in improving the efficiency of the cycloaddition reaction. Only when the structure is intrinsically activated are additional electron-withdrawing substituents either unnecessary or even detrimental. The trends observed in this series of reactions should prove useful in the fine tuning of future cycloadditions.

3.2. Cycloadditions with (*R*)-5(1*R*)-menthyloxy-2-(5*H*)-furanone 8

A second series of cycloadducts was prepared from imines **3b**,**c** and the chiral dipolarophile **8** (Scheme 9). Reaction of **3a**,**b** with **8** occurred over 10–18 h at rt in acetonitrile using silver acetate-DBU as the catalyst. Enantiopure cyclo-adducts **9a**,**b** were obtained as single stereoisomers in good yield (Table 4). The stereochemistry of **9a**,**b** is based on NOE data (see Section 6) and an X-ray crystal structure[5] from our previous related work. Once again the process



Scheme 8.



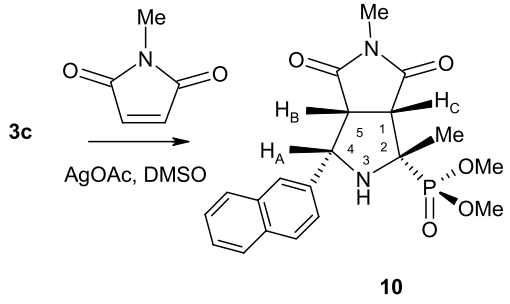
Scheme 9.

proceeds via an *endo* transition state and as expected the silver azomethine ylide adds to the face of the dipolarophile **8** *trans* to the *O*-menthyl group.[5] Hence the newly created stereocentres are 1*S*, 2*R*, 4*S* and 5*R* (Scheme 9).

4. Variation of the dipolarophile

4.1. *N*-Methyl maleimide

The AgOAc catalysed reactions of imine **3c** with *N*-methylmaleimide (NMM) in MeCN (BTMG as base) or DMSO (Et_3N as base) gave cycloadduct **10** (Scheme 10). Low yields resulted in both cases (Table 4, entries 3 and 4). The low yield when BTMG was used is due to Michael addition



Scheme 10.

of the base to NMM and polymerisation of the resultant zwitterion. This unwanted side reaction is accompanied by the appearance of a characteristic deep red colour.[34] Use of DBU in MeCN results in a similar outcome.

The reaction of **3c** and NMM, using triethylamine as base in MeCN or DMSO were also very disapponting. No cycloadduct was isolated from the reaction carried out in MeCN after stirring for two weeks, whilst a low yield of **10** was obtained in DMSO after 9 days. This suggest that in DMSO the Michael addition of the weaker nucleophile (Et_3N) to NMM is accelerated and competes and effectively suppresses cycloaddition.

4.2. Methyl vinyl ketone (MVK)

The reaction of **3c** with (MVK) gave **11** (Scheme 11, Table 4, entry 5) in poor yield. The mechanism of formation **11** involves stereospecific formation of the *syn* or *E*,*E*-metallo-dipole followed by regio- and *endo*- specific cycloaddition to the dipolarophile. Michael addition of the cycloadduct to a second molecule of dipolarophile (Scheme 11) gives **11**.

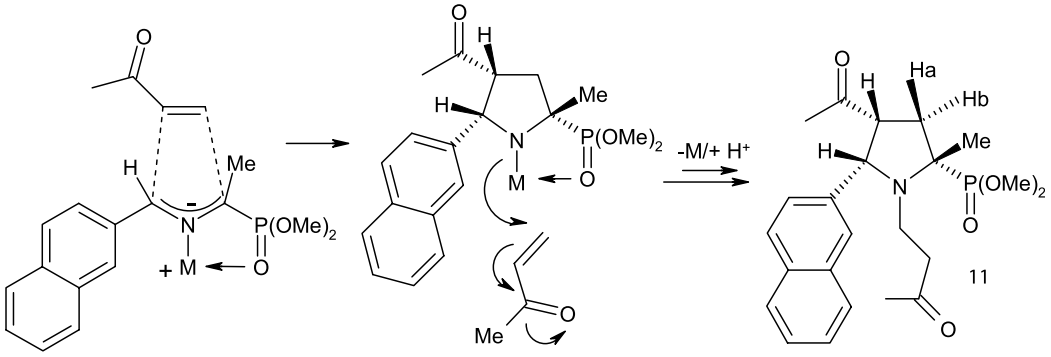
4.3. Thermal iminium ion cycloaddition

The dimethyl phosphonate analogue of proline **2f** was

Table 4. Cycloaddition of Imines **3b**,**c** with various dipolarophiles[a]

Entry	Imine	Dipolarophile	Time (h)	Product	Yield (%)
1	**3b**	8	18	**9a**	42
2	**3c**	8	10	**9b**	58
3[b]	**3c**	NMM	9	**10**	21
4[c]	**3c**	NMM	3	**10**	15
5	**3c**	MVK[d]	240	**11**	25

[a] Reaction conditions: MeCN, AgOAc (1.5 equiv), DBU (1.0 equiv), 25 °C.
[b] NEt_3 and DMSO used.
[c] 2-*t*-Butyl 1,1,3,3-tetramethyl guanidine used as base.
[d] Methylvinyl ketone.



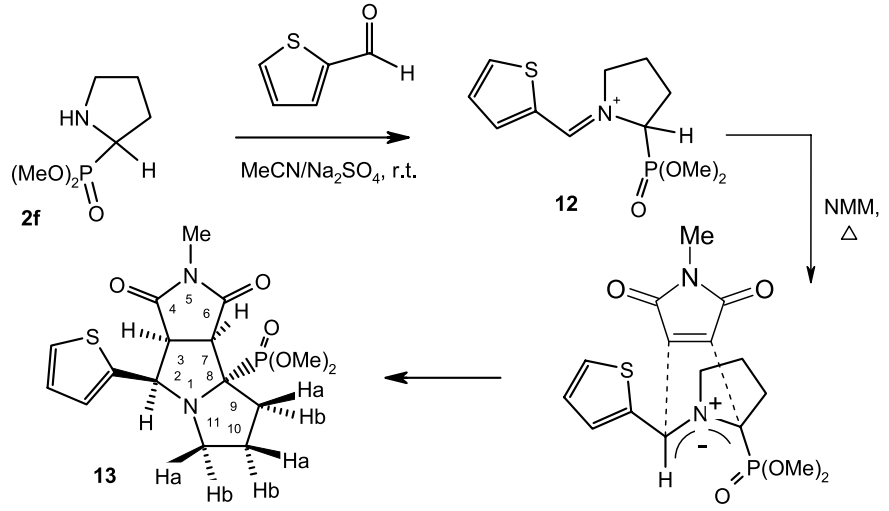
Scheme 11.

reacted in boiling acetonitrile with thiophene-2-carboxaldehyde and NMM. Deprotonation of the intermediate iminium ion **12** afforded the azomethine ylide (Scheme 12), which furnished a single cycloadduct **13**. The stereochemistry of **13** was assigned on the basis of ^{1}H NMR and NOE data (see Section 6). The magnitude of the J_{CH-CP} coupling constant (16 Hz) is characteristic of a *cis*-relationship between 7-H and phosphorus. The 15% enhancement of the signal for 3-H (observed on irradiating the signal for 2-H) is consistent with a *cis* relationship between these two protons.

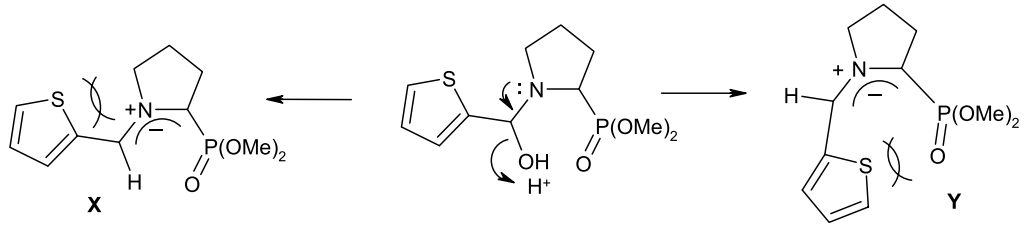
The cycloaddition is *endo*-specific and proceeds via the stereoselective formation of the *syn*-dipole, where *syn* and *anti* refer to the relative configurations of the 1,3-H/$PO(OMe)_2$ dipole substituents.

By analogy with the cycloaddition of iminium ion derived from secondary α-amino esters.[35] The observed stereoselective dipole formation is due to the interaction between the 1- and 3-substituents of the two dipoles (Scheme 13).[35] There is significant out of plane twisting of the thienyl group, as a consequence of the unfavourable steric interaction, which disrupts conjugation. This effect is far greater in **Y**, due to the size of the dimethyl phosphonate ester group, and this dipole is effectively totally suppressed. It is likely that the *endo*-transition state of the cycloaddition to **X** would also experience the least steric hindrance.

An alternative azaallyl anion cycloaddition approach has been reported,[36] which leads to mixtures of phosphonate



Scheme 12.



Scheme 13.

analogues of proline and 1-pyrrolidines. The latter are formed by elimination of the phosphonate moiety.

5. Summary

The metallo-azomethine ylide cycloaddition route has been implemented for α-iminophophonates following a previous single thermal example, which gave a 1:1 mixture of *endo* and *exo*-isomers. The rt metallo-azomethine ylide process is catalysed by AgOAc/DBU or LiBr/DBU. When methyl acrylate is employed as dipolarophile the cycloaddition is slow 0.9–6.8 days and yields range from 8–98%. The cycloadducts are derived from the corresponding *E*,*E*-metallo-azomethine ylides via *endo* transition states. The steric compression necessary to accommodate the larger Ag(I) ion, and achieve appropriate bond angles, is more pronounced in the case of the sterically more demanding phosphonate imines compared to the imines of α-amino esters. As a result of these factors, in the former cases, Michael addition competes with cycloaddition in some cases. The significantly slower rate of cycloaddition, compared to that of imines of α-amino esters, reflects the higher pK_a of α-proton(s) in the iminophosphonates. Cycloadditions with *R*-5(1*R*)-menthyloxy-2-(5*H*)-furanone, NMM and MVK were likewise slow (10 h–10 days) and yields, in these cases, ranged from 15–58%. The cycloadducts from the chiral dipolarophile were enantiopure.

6. Experimental

Melting points were determined on a Koffler hot-stage apparatus and are uncorrected. Mass spectral data were obtained from VG 7070 and Autospec instruments operating at 70 eV. Nuclear magnetic resonance spectra were recorded on Bruker WM250, QE300 and Bruker AM400 instruments operating at 250, 300 and 400 MHz, respectively. Unless otherwise specified deuteriochloroform was used as solvent. The following abbreviations are used; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; br s, broad singlet; and app, apparent. Microanalyses were obtained using a Carlo Erba MOD 11016 instrument. Preparative TLC plates were prepared using silica gel 60 PF (Merck 7748). Column chromatography was performed with silica gel 60 (Merck 9385). Chiral HPLC. was performed on a Chiralcel OD or OG columns (Daicel) using specified eluants. Petroleum ether refers to the fraction with bp 40–60 °C. (*R*)-5(1*R*)-menthyloxy-2-(5*H*)-furanone was purchased from Aldrich and used as received. Dimethyl *N*-(phthalimido)methylphosphonate, diethyl *N*-(phthalimido)-methylphosphonate, dimethyl aminomethylphosphonate **2a** and diethyl aminomethylphosphonate **2b** were synthesised according to literature procedures.[3,29]

6.1. General procedure for the preparation of α-amino phosphonates (2c–h)

N-Deprotection of the *N*-Cbz α-amino phosphonates **1c–h** was achieved by catalytic hydrogenation, using a modification of the method of Campbell et al.[27]

Compound **2c**. Dimethyl *N*-(benzyloxycarbonyl)-1-amido ethylphosphonate **1c** (1 g, 3.49 mmol) and glacial acetic acid (0.43 g, 7.16 mmol) were dissolved in methanol (89 mL) in a 250 mL flask. After the addition of 5% palladium on charcoal (0.95 g), the flask was evacuated and the air replaced with hydrogen. The contents of the flask were then vigorously stirred 16 h at rt. The resulting suspension was filtered and evaporated under reduced pressure (<25 °C), to give the crude acetate salt of the amine **2c** in quantitative yield.

An alternatively procedure was used, in which glacial acetic acid was replaced by *p*-toluenesulfonic acid (0.7 g, 3.7 mmol), to give the *p*-toluenesulfonate salt of the amine **2c**. Stirring this salt for 30 min, with damp $NaHCO_3$ (1.2 g) in dichloromethane (100 mL), resulted in the formation of crystalline sodium *p*-toluenesulfonate. The sodium salt was removed easily by filtration through Celite and the filtrate was evaporated to give the pure amine **2c** (410 mg, 77%). This method also provided the serine phosphonate analogue **2g** via the quantitative removal of both *N*- and *O*-protecting groups of compound **1h**.

6.2. General procedure for the preparation of imines 3a–t

The crude acetate salts of α-amino phosphonates **2a–h** (1 equiv) in dry dichloromethane were stirred with triethylamine (2 equiv) and anhydrous Na_2SO_4 (excess) for 1 h, prior to the addition of the aldehyde (0.9 equiv). After stirring 16 h, the suspension was filtered and the filtrate was evaporated under reduced pressure (<25 °C). In the case of the aryl aldimines, the resulting gum was suspended in diethyl ether—from which the imine crystallised on prolonged storage at 0–4 °C. The aliphatic aldimines were obtained, after heating (~50 °C) under vacuum (1–5 mmHg) for ~5 h, as thick oils contaminated with trace amounts of acetic acid.

Where the free base was available the aldehyde (0.95 equiv) was used in the absence of triethylamine, and the imines were obtained relatively pure after evaporation of the solvent.

6.2.1. Dimethyl *N*-(2-naphthylidene)iminomethyl-phosphonate 3a. Dimethyl aminomethylphosphonate **2a**[3,29] (300 mg, 2.17 mmol) and 2-naphthaldehyde (32 mg, 2.06 mmol) were reacted for 16 h to yield the crude imine **3a** (600 mg, quant) as a pale yellow solid, mp 85–86 °C; *m*/*z* (%) 277 (M^+, 3), 168 (17), 167 (17), 141 (52), 124 (100) and 94 (59); δ 8.45 (d, 1H, J=4.7 Hz, CH=N), 8.15–7.25 (m, 7H, naphthyl-H), 4.19 (d, 2H, $J_{P–CH}$=17.6 Hz,CH_2P), and 3.84 (d, 6H, $J_{P–OCH}$=10.9 Hz, 2×MeOP).

6.2.2. Diethyl *N*-(2-naphthylidene) imino methylphosphonate 3b. Diethyl aminomethyl phosphonate **2b**[3,29] (1.68 g, 10 mmol) and 2-naphthaldehyde (1.32 g, 8.5 mmol) were reacted for 16 h to yield the product **3b** (95%) as a thick yellow oil, which was purified by distillation using a mole still, 100–200 °C/1–3 mmHg (found: C, 59.6; H, 6.95; N, 4.08. $C_{16}H_{20}NO_3P·H_2O$ requires: C, 59.50; H, 6.85; N, 4.35%); *m*/*z* (%) 306 (MH^+, 6), 168 (56), 152 (100), 141 (88) and 125 (97); δ

8.46 (d, 1H, J=4.8 Hz, CH=N), 8.05–8.00 (m, 2H, naphthyl-H), 7.94–7.84 (m, 3H, naphthyl-H), 7.56–7.50 (m, 2H, naphthyl-H), 4.27–4.12 (m, 6H, 2×CH_2OP and CH_2P) and 1.35 (t, 6H, J=7.1 Hz, $MeCH_2OP$).

6.2.3. Dimethyl *N*-(2-naphthylidene)imino ethylphosphonate 3c. The crude amine salt **2c** (0.88 g, 3.5 mmol), triethylamine (1.1 mL, 7.89 mmol) and 2-naphthaldehyde (496 mg, 3.18 mmol) were reacted for 16 h to give the product **3c** (580 mg, 57%), which crystallised from diethyl ether/petroleum ether as colourless needles, mp 124–125 °C (found: C, 61.55; H, 6.10; N, 4.65. $C_{15}H_{18}NO_3P$ requires: C, 61.79; H, 6.31; N, 4.80%); *m/z* (%) 291 (M^+, 2), 182 (66), 155 (31), 138 (100) and 110 (42); δ 8.49 (d, 1H, J=4.7 Hz, CH=N), 8.00–7.49 (m, 7H, naphthyl-H), 3.99 (d of quart, 1H, J=6.8, 13.5 Hz, CHP), 3.83 (d, 6H, J_{P-OCH}=10.5 Hz, 2×MeOP) and 1.61 (dd, 3H, J=7.0 Hz, J_{P-C-CH}=18.2 Hz, Me).

6.2.4. Dimethyl *N*-(2-naphthylidene)-1-imino-1-phenyl methylphosphonate 3d. The crude amine salt **2d** (963 mg, 2.9 mmol), triethylamine (640 mg, 6.32 mmol) and 2-naphthaldehyde (399 mg, 2.55 mmol) were reacted for 16 h to give the product **3d** (530 mg, 59%), which was crystallised from diethyl ether/petroleum ether as colourless needles, mp 113–116 °C (found: C, 67.70; H, 5.55; N, 3.85. $C_{20}H_{20}NO_3P$ requires: C, 67.98; H, 5.70; N, 3.96%); *m/z* (%) 353 (M^+, 0.2), 244 (100) and 200 (41); δ 8.56 (d, 1H, J=4.6 Hz, CH=N), 8.16–7.27 (m, 12H, naphthyl and Ar-H), 5.05 (d, 1H, J_{P-CH}=18.4 Hz, CHP), 3.74 (d, 3H, J_{P-OCH}=9.8 Hz, MeOP) and 3.71 (d, 3H, J_{P-OCH}=10.0 Hz, MeOP).

6.2.5. Dimethyl *N*-(2-naphthylidene)-1-imino-2-phenyl-ethylphosphonate 3e. The crude amine salt **2e** (800 mg, 2.76 mmol), triethylamine (680 mg, 2.77 mmol) and 2-naphthaldehyde (431 mg, 2.76 mmol) were reacted for 16 h to give the product **3e** (440 mg, 44%), which was crystallised from diethyl ether/petroleum ether as colourless needles, mp 72–75 °C (found: C, 65.65; H, 5.65; N, 3.45. $C_{21}H_{22}NO_3P\cdot H_2O$ requires: C, 65.45; H, 5.75; N, 3.65%); *m/z* (%) 367 (M^+, 9), 276 (64), 258 (72), 214 (98) and 167 (100); δ 8.05–7.09 (m, 12H, naphthyl and Ar-H), 7.94 (d, 1H, J=4.6 Hz, CH=N), 3.95 (dt, 1H, J=2.2 Hz, J_{P-CH}=11.3 Hz, CHP), 3.96 (d, 3H, J_{P-OCH}=10.5 Hz, MeOP), 3.85 (d, 3H, J_{P-OCH}=10.1 Hz, MeOP), 3.42–3.38 (m, 1H, CH_2Ph) and 3.32–3.24 (m, 1H, CH_2Ph).

6.2.6. Dimethyl *N*-(2-naphthylidene)-1-imino-2-hydroxy-ethylphosphonate 3g. The crude amine **2g** (260 mg, 1.54 mmol) and 2-naphthaldehyde (228 mg, 1.46 mmol) were reacted for 16 h to give the product **3g** (330 mg, 74%), which was crystallised from diethyl ether/petroleum ether as colourless prisms, mp 113–114 °C (found: C, 58.60; H, 6.10; N, 4.45. $C_{15}H_{18}NO_4P$ requires: C, 58.65; H, 5.90; N, 4.60%); *m/z* (%) 307 (M^+, 32), 305 (82), 289 (51), 276 (60), 196 (76), 180 (97) and 154 (100); δ 8.47 (d, 1H, J=4.6 Hz, CH=N), 8.05–7.50 (m, 7H, naphthyl-H), 4.20–4.13 (m, 2H, CH_2O), 4.05 (dt, 1H, J=8.1 Hz, J_{P-CH}=12.7 Hz, CHP), 3.82 (d, 3H, J_{P-OCH}=10.9 Hz, MeOP) and 3.81 (d, 3H, J_{P-OCH}=10.4 Hz, MeOP).

6.2.7. Dimethyl *N*-(cyclohexylidene)imino ethylphosphonate 3h. The crude amine **2c** (410 mg, 2.68 mmol) and cyclohexane carboxaldehyde (284 mg, 2.53 mmol) were reacted for 16 h to give the product **3h** (668 mg, 94%) as a pale yellow oil. *m/z* (%) 245 (M^+-2, 17), 138 (100), 110 (43) and 95 (24); δ 7.59 (t, 1H, J=4.9 Hz, CH=N), 3.80 (d, 3H, J_{P-OCH}=10.3 Hz, MeOP), 3.77 (d, 3H, J_{P-OCH}=10.4 Hz, MeOP), 3.63 (dt, 1H, J=6.3 Hz, J_{P-CH}=12.7 Hz, CHP), 2.25 (br m, 1H, CHC=N), 1.82–1.60 (m, 5H, cyclohexyl-H), 1.45 (dd, 3H, J=6.9 Hz, J_{P-C-CH}=8.3 Hz, Me) and 1.38–1.13 (m, 5H, cyclohexyl-H).

6.2.8. Dimethyl *N*-(cyclohexylidene)-1-imino-1-phenyl methylphosphonate 3i. The crude amine salt **2d** (960 mg, 2.87 mmol), triethylamine (609 mg, 6.0 mmol) and cyclohexane carboxaldehyde (290 mg, 2.58 mmol) were reacted for 16 h to give the product **3i** (75%) a thick brown oil purified by heating under vacuum (60 °C/1–5 mmHg). *m/z* (%) 310 (MH^+, 7), 241 (14), 200 (100) and 106 (37); δ 7.68 (t, 1H, J=2.4 Hz, CH=N), 7.57–7.26 (m, 5H, Ar-H), 4.69 (d, 1H, J_{P-CH}=18.0 Hz, CHP), 3.69 (d, 3H, J_{P-OCH}=15.8 Hz, MeOP), 3.66 (d, 3H, J_{P-OCH}=15.9 Hz, MeOP), 2.36–2.30 (br m, 1H, CHC=N), 1.94–1.62 (m, 5H, cyclohexyl-H) and 1.45–1.18 (m, 5H, cyclohexyl-H).

6.2.9. Dimethyl *N*-(cyclohexylidene)-1-imino-2-phenyl ethylphosphonate 3j. The crude amine salt **2e** (900 mg, 2.76 mmol), triethylamine (447 mg, 4.4 mmol) and cyclohexane carboxaldehyde (279 mg, 2.49 mmol) were reacted for 16 h to give the product **3j** (86%) as a thick brown oil purified by heating under vacuum (60 °C/1–5 mmHg). *m/z* (%) 323 (MH^+, 3), 255 (34), 232 (31), 214 (100) and 110 (44); δ 7.33–7.07 (m, 5H, Ar-H), 7.00 (t, 1H, J=4.7 Hz, CH=N), 3.84 (d, 3H, J_{P-OCH}=12.7 Hz, MeOP), 3.80 (d, 3H, J_{P-OCH}=12.6 Hz, MeOP), 3.58 (dt, 1H, J=2.2 Hz, J_{P-CH}=11.1 Hz, CHP), 3.32–3.24 (m, 1H, CHPh), 3.11–3.00 (m, 1H, CHPh), 2.41–2.03 (br m, 1H, CHC=N), 1.66–1.52 (m, 5H, cyclohexyl-H) and 1.31–0.97 (m, 5H, cyclohexyl-H).

6.2.10. Dimethyl *N*-(2′-naphthylidene)-1-imino-2-{[(*t*-butyl)dimethylsilyl]oxy} ethylphosphonate 3k. The crude acetate salt of the α-aminophosphonate **2h** (720 mg, 2.1 mmol), triethylamine (246 mg, 2.4 mmol) and 2-naphthaldehyde (311 mg, 2.0 mmol) were reacted for 16 h. The reaction mixture was filtered, washed with brine and evaporated under reduced pressure (<25 °C). The resulting gum was crystallised from petroleum ether to give the product **3k** (737 mg, 80%) as colourless needles, mp 88–90 °C (found: C, 59.85; H, 7.60; N, 3.30. $C_{21}H_{32}NO_4PSi$ requires: C, 59.85; H, 7.65; N, 3.30%); *m/z* (%) 406 (M−Me, 4), 391 (M−Me_2, 1), 364 (100), 276 (9), 254 (35) and 167 (57); δ 8.41 (d, 1H, J=3.7 Hz, CH=N), 8.07–8.04 (m, 2H, naphthyl-H), 7.95–7.84 (m, 3H, naphthyl-H), 7.54–7.52 (m, 2H, naphthyl-H), 4.23–4.20 (m, 1H, CHOSi), 4.06 (dt, 1H, J=4.2 Hz, J_{CH-P}=10.1 Hz, CHP), 4.03–3.93 (m, 1H, CHOSi), 3.84 (d, 3H, J_{CH-OP}=10.3 Hz, MeOP), 3.83 (d, 3H, J_{CH-OP}=10.4 Hz, MeOP), 0.81 (s, 9H, *t*-Bu), 0.04 (s, 3H, SiMe) and −0.06 (s, 3H, SiMe).

6.2.11. Dimethyl *N*-(4′-nitrobenzylidene)-1-imino ethylphosphonate 3l. The amine **2c** (577 mg, 3.77 mmol) and *p*-nitrobenzaldehyde (5.22 mg, 3.65 mmol) were reacted for 16 h to give the product **3l** as a thick dark brown oil (1.04 g, 94% yield) purified by distillation using a mole still, 220 °C/

0.9 mmHg (found: C, 46.85; H, 5.45; N, 9.60. $C_{11}H_{15}N_2O_5P$ requires: C, 46.15; H, 5.30; N, 9.80%); *m/z* (%) 287 (MH^+, 4), 177 (96), 138 (100), 131 (67) and 110 (80); δ 8.46 (d, 1H, J=4.8 Hz, CH=N), 8.28 (d, 2H, J=8.4 Hz, *p*-nitrophenyl 3,5-H), 7.96 (d, 2H, J=8.4 Hz, *p*-nitrophenyl 2,6-H), 4.03 (d quart, 1H, J=6.8 Hz, J_{CH-P}=13.8 Hz, CHP), 3.83 (d, 6H, J_{CH-OP}=10.3 Hz, 2×MeOP) and 1.61 (dd, 3H, J=6.9 Hz, J_{CH-CP}=18.1 Hz, *Me*CHP).

6.2.12. Dimethyl *N*-(2′-iodobenzylidene)-1-imino ethylphosphonate 3m. The amine **2c** (1.15 g, 7.5 mmol) and *o*-iodobenzaldeyde (1.6 g, 6.9 mmol) were reacted for 16 h to yield a thick colourless oil **3m** (1.14 g, 90%), (found: C, 35.95; H, 4.05; N, 4.0. $C_{11}H_{15}INO_3P$ requires: C, 36.0; H, 4.10; N, 3.80%); *m/z* (%) 368 (MH^+, 4), 258 (66), 232 (29), 203 (7), 138 (100), 130 (65) and 110 (77); δ 8.51 (d, 1H, J=4.8 Hz, CH=N), 8.01 (d, 1H, J=7.6 Hz, *o*-iodophenyl 3-H), 7.86 (d, 1H, J=7.8 Hz, *o*-iodophenyl 6-H), 7.37 (t, 1H, J=7.4 Hz, *o*-iodophenyl 4-H), 7.13 (t, 1H, J=7.5 Hz, *o*-iodophenyl 5-H), 4.03 (d quart, 1H, J=6.8 Hz, J_{CH-P}=13.5 Hz, CHP), 3.83 (d, 3H, J_{CH-OP}=10.3 Hz, MeOP), 3.82 (d, 3H, J_{CH-OP}=10.4 Hz, MeOP) and 1.60 (dd, 3H, J=6.8 Hz, J_{CH-CP}=18.1 Hz, *Me*CHP).

6.2.13. Dimethyl *N*-(2′-pyridylidene)-1-imino ethylphosphonate 3n. The amine **2c** (577 mg, 3.77 mmol) and pyridine-2-carboxaldehyde (399 mg, 3.73 mmol) were reacted for 16 h to give the product **3n** as a thick dark brown oil (830 mg, 88%), (found: C, 49.45; H, 6.10; N, 11.45. $C_{10}H_{15}N_2O_3P$ requires: C, 49.60; H, 6.25; N, 11.55%); *m/z* (%) 243 (MH^+, 2), 227 (3), 195 (4), 139 (7), 133 (100), 110 (57) and 92 (89); δ 8.67 (d, 1H, J=4.3 Hz, CH=N), 8.45 (d, 1H, J=4.7 Hz, pyridyl 3-H), 8.08 (d, 1H, J=7.7 Hz, pyridyl 6-H), 7.77 (t, 1H, J=7.5 Hz, pyridyl 4-H), 7.36 (*t*-1H, J=6.0 Hz, pyridyl 5-H), 4.05 (d quart, 1H, J=6.8 Hz, J_{CH-P}=13.5 Hz, CHP), 3.83 (d, 6H, J_{CH-OP}=10.5 Hz, 2×MeOP) and 1.61 (dd, 3H, J=6.9 Hz, J_{CH-CP}=18.1 Hz, *Me*CHP).

6.2.14. Dimethyl *N*-(2′-pyridylidene)-1-imino-1-phenyl methylphosphonate 3o. The amine **2d** (634 mg, 2.95 mmol) and pyridine-2-carboxaldehyde (577 mg, 5.39 mmol) were reacted for 16 h to yield (1.15 g, 91%) the product **3o**, which was crystallised from dichloromethane/diethylether as colourless prisms, mp 106–108 °C (found: C, 59.20; H, 5.35; N, 9.15. $C_{15}H_{17}N_2O_3P$ requires: C, 59.20; H, 5.65; N, 9.20%); *m/z* (%) 305 (MH^+, 1), 227 (2), 200 (45), 195 (100), 167 (13), 105 (8) and 92 (50); δ 8.56 (d, 1H, J=4.5 Hz, CH=N), 8.41 (d, 1H, J=4.8 Hz, pyridyl 3-H), 8.13 (d, 1H, J=7.9 Hz, pyridyl 6-H), 7.69 (t, 1H, J=7.2 Hz, pyridyl 4-H), 7.56 (d, 2H, J=7.4 Hz, Ar 2,6-H), 7.33–7.21 (m, 4H, Ar-H and pyridyl 5-H), 4.97 (d, 1H, J_{CH-P}=18.6 Hz, CHP), 3.62 (d, 3H, J_{CH-OP}=10.7 Hz, MeOP) and 3.60 (d, 3H, J_{CH-OP}=10.6 Hz, MeOP).

6.2.15. Dimethyl *N*-(2′-pyridylidene)-1-imino-2-phenyl ethylphosphonate 3p. The amine **2e** (654 mg, 2.85 mmol) and pyridine-2-carboxaldehyde (554 mg, 5.17 mmol) were reacted for 16 h to yield the product **3p** in quantitative yield, which was crystallised from diethyl ether/ethyl acetate as colourless prisms, mp 78–81 °C (found: C, 60.25; H, 5.70; N, 8.65. $C_{16}H_{19}N_2O_3P$ requires: C, 60.35; H, 6.0; N, 8.80%); *m/z* (%) 318 (M^+, 1), 287 (1), 240 (1), 227 (100), 214 (51), 209 (95), 195 (40), 182 (31), 118 (33), 110 (37) and 91 (72); δ 8.50 (d, 1H, J=4.6 Hz, CH=N), 7.99 (d, 1H, J=7.8 Hz, pyridyl 3-H), 7.88 (d, 1H, J=4.7 Hz, pyridyl 6-H), 7.66 (td, 1H, J=1.4, 7.8 Hz, pyridyl 4-H), 7.23 (apparent t, 1H, J=6.9 Hz, pyridyl 5-H), 7.15–7.03 (m, 5H, Ar-H), 3.91 (dt, 1H, J=2.5, 11.3 Hz, CHP), 3.75 (d, 6H, J_{CH-OP}=10.3 Hz, 2×MeOP), 3.34 (ABXY, 1H, J=2.8, 8.2, 13.8 Hz, CHCP).

6.2.16. Dimethyl *N*-(2′-thienylidene)-1-imino ethylphosphonate 3r. The amine **2c** (577 mg, 3.77 mmol) and thiophene-2-carboxaldehyde (429 mg, 3.83 mmol) were reacted for 16 h to give the product **3r** (780 mg, 79% yield) as a yellow oil by distillation using a mole still (60–100 °C/0.3–0.4 mmHg) (found: C, 43.55; H, 5.75; N, 5.60. $C_9H_{14}NO_3PS$ requires: C, 43.75; H, 5.70; N, 5.65%); *m/z* (%) 248 (MH^+, 1), 138 (100), 111 (87), 110 (62), 109 (22) and 96 (19); δ 8.42 (d, 1H, J=4.3 Hz, CH=N), 7.41 (d, 1H, J=5.0 Hz, thienyl 5-H), 7.34 (d, 1H, J=3.4 Hz, thienyl 3-H), 7.06 (apparent t, 1H, J=4.3 Hz, thienyl 4-H), 3.90 (d quart, 1H, J=7.0 Hz, J_{CH-P}=14.1 Hz, CHP), 3.79 (d, 6H, J_{CH-OP}=10.3 Hz, 2×MeOP) and 1.53 (dd, 3H, J=7.0 Hz, J_{CH-CP}=18.0 Hz, *Me*CHP).

6.2.17. Dimethyl *N*-(2′-thienylidene)-1-imino-1-phenyl methylphosphonate 3s. The amine **2d** (664 mg, 3.09 mmol) and thiophene-2-carboxaldehyde (604 mg, 5.39 mmol) were reacted for 16 h to yield the product **3s** in quantitative yield by distillation using a Kugelrohr apparatus (40–84 °C/0.3 mmHg) (found: C, 50.95; H, 5.10; N, 4.25. $C_{15}H_{18}NO_3PS\cdot H_2O$ requires: C, 51.35; H, 5.55; N, 4.30%); *m/z* (%) 310 (MH^+, 1), 231 (1), 218 (3), 200 (100), 173 (9), 153 (16), 148 (18) and 111 (18); δ 8.39 (d, 1H, J=4.6 Hz, CH=N), 7.50 (d, 2H, J=7.4 Hz, Ar 2,6-H), 7.36–7.18 (m, 5H, Ar-H and thienyl 3,5-H), 6.99 (t, 1H, J=4.3 Hz, thienyl 4-H), 4.87 (d, 1H, J_{CH-P}=18.9 Hz, CHP), 3.66 (d, 3H, J_{CH-OP}=10.4 Hz, MeOP) and 3.60 (d, 3H, J_{CH-OP}=10.6 Hz, MeOP).

6.2.18. Dimethyl *N*-(2′thienylidene)-1-imino-2-phenyl ethylphosphonate 3t. The amine **2e** (705 mg, 3.08 mmol) and thiophene-2-carboxaldehyde (580 mg, 5.17 mmol) were reacted for 16 h to yield the product **3t** in quantitative yield by distillation using a Kugelrohr apparatus (20–70 °C/0.09 mmHg) followed by crystallisation from diethyl ether to afford colourless prisms, mp 68–70 °C, (found: C, 55.95; H, 5.45; N, 4.45. $C_{15}H_{18}NO_3PS$ requires: C, 55.71; H, 5.61; N, 4.35%); *m/z* (%) 323 (M^+, 5), 232 (56), 214 (100), 200 (20), 123 (20), 110 (47) and 93 (32); δ 7.90 (d, 1H, J=4.5 Hz, CH=N), 7.39 (d, 1H, J=5.1 Hz, thienyl 5-H), 7.24–7.12 (m, 6H, Ar-H and thienyl 3-H), 7.0 (dd, 1H, J=3.8, 4.9 Hz, thienyl 4-H), 3.84 (d, 4H, J_{CH-OP}=10.4 Hz, MeOP and CHP), 3.81 (d, 3H, J_{CH-OP}=10.6 Hz, MeOP), 3.34 (ABXY, 1H, J=2.6, 7.9, 13.6 Hz, CHCP) and 3.19 (ABXY, 1H, J=7.5, 10.8, 13.6 Hz, CHCP).

6.3. General procedure for the metal catalysed cycloaddition reactions

A mixture of the imine **3** (1 mol equiv), base (DBU or BTMG) (1 mol equiv), dipolarophile (1 mol equiv) and metal salt (AgOAc or LiBr) (1.5 mol equiv) in an appropriate solvent (MeCN, THF or toluene) was stirred

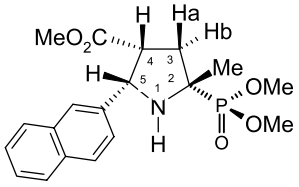
for the time shown in Tables 2 and 3. To compensate for loss by evaporation, 2–3 equiv of the lower boiling dipolarophiles (e.g., methyl-acrylate, -propiolate and -vinyl ketone) were used. The reaction mixture was filtered, and quenched by the addition of saturated ammonium chloride. The organic layer was separated and the aqueous layer extracted twice with diethyl ether. The combined organic layers were then washed with brine, dried (anhyd. Na_2SO_4) and the solvent removed under reduced pressure. The residue was purified by flash column chromatography. Yields are collected in Tables 2 and 3.

6.3.1. Dimethyl c-4-methoxycarbonyl-c-5-(2′-naphthyl) pyrrolidine-r-phosphonate 4a. Work-up followed by flash chromatography eluting with 10:1 v/v ethyl acetate/ethanol afforded the product **4a** as a pale brown gum (contaminated with a trace amount of Michael adduct **5a**); δ 7.92–7.68 (m, 4H, naphthyl-H), 7.49–7.39 (m, 3H, naphthyl-H), 4.63 (d, 1H, $J=10.2$ Hz, 5-H), 3.96 (d, 3H, $J_{P-OCH}=17.1$ Hz, MeOP), 3.92 (d, 3H, $J_{P-OCH}=17.0$ Hz, MeOP), 3.66 (br s, 1H, NH), 3.56 (m, 1H, 2-H), 3.39 (q, 1H, $J=9.2$ Hz, 4-H), 3.00 (s, 3H, MeOC), 2.63 (m, 1H, 3-H_b) and 2.31 (m, 1H, 3-H_a).

6.3.2. Diethyl c-4-methoxycarbonyl-c-5-(2′-naphthyl) pyrrolidine-r-phosphonate 4b. Work-up followed by flash chromatography eluting with 10:1 v/v ethyl acetate/ethanol afforded several fractions containing different amounts of cycloadduct **4b** and Michael adduct **5b** (Scheme 4). The best sample of cycloadduct (contaminated with only a small amount of Michael adduct **5b**) was analysed by ^{1}H NMR and mass spectroscopy; *m/z* (%) 390 (M^+, 36), 330 (28), 254 (100), 194 (67), 167 (78) and 127 (62); δ 7.87–7.75 (m, 4H, naphthyl-H), 7.52–7.41 (m, 3H, naphthyl-H), 4.68 (d, 1H, $J=9.1$ Hz, 5-H), 4.42–4.23 (m, 4H, CH_2OP), 3.55 (ABX, 1H, $J=4.8$, 6.7, 11.1 Hz, 2-H), 3.43 (q, 1H, $J=8.5$ Hz, 4-H), 3.05 (s, 3H, MeOC), 2.70–2.63 (m, 4H, CH_2 and NH_2) and 1.5–1.28 (m, 6H, *Me*CH_2OP). The lithium bromide-catalysed reaction afforded fractions containing different amounts of lactam **6** and cycloadduct **4b**. A sample consisting of a 2:1 mixture of lactam **6** and cycloadduct **4b** was analysed by ^{1}H NMR and mass spectroscopy; *m/z* 445 (M^+, 33), 389 (34), 308 (100) and 254 (45); δ 5.25 (d,1H, $J=10.0$ Hz, 2-H).

6.3.3. Diethyl 1-aza-c-2-(2′-naphthyl)-c-3-methoxycarbonyl-8-oxobicyclo[3.3.0]octane-r-5-phosphonate 6. Work-up followed by flash chromatography eluting with 10:1 v/v ethyl acetate/methanol afforded three fractions containing different mixtures of the lactam **6** and the cycloadduct **4b**. The fraction containing the most lactam (3.5:1 by ^{1}H NMR) was subjected to a further column chromatography purification step. Elution with 5:1 v/v ethyl acetate/methanol afforded a thick yellow oil (4:1 by ^{1}H NMR), which crystallised from diethyl ether as colourless prisms, mp 103–104 °C; *m/z* (%) 445 (M^+, 7), 384 (42), 308 (100), 276 (35), 248 (64), 206 (31), 180 (32), 116 (18), 55 (45); HRMS of ($M-PO(OEt)_2$): found 308.128, calcd 308.129; δ 7.82–7.70 (m, 4H, naphthyl-H), 7.47–7.41 (m, 3H, naphthyl-H), 5.41 (d, 1H, $J=8.6$ Hz, 2-H), 4.14–3.95 (m, 5H, 2×CH_2OP and 3-H), 3.74 (s, 3H, MeOC), 3.08 (ABXY, 1H, $J=8.8$, 12.7, 16.8 Hz, 7-H_b), 2.85 (ABXY,1H, $J=7.5$, 10.2, 13.2 Hz, 4-H_b), 2.79 (dt, 1H, $J=8.7$, 12.7 Hz, 6-H_b), 2.52 (dd, 1H, $J=9.2$, 16.7 Hz, 7-H_a), 2.20 (dt, $J=8.9$, 12.9 Hz, 4-H_a), 2.10 (dt, 1H, $J=4.5$, 12.5 Hz, 6-H_a) and 1.19–1.13 (m, 6H, 2×*Me*CH_2OP).

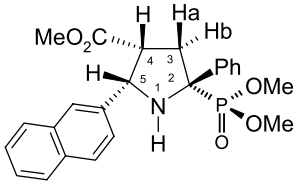
6.3.4. Dimethyl c-4-methoxycarbonyl-2-methyl-c-5-(2′-naphthyl)pyrrolidine-r-2-phosphonate 4c. Work-up followed by flash chromatography eluting with a diethyl ether/ethyl acetate afforded the product **4c**, which was crystallised from ether/hexane as colourless prisms, mp 113–114 °C (found: C, 60.30; H, 6.65; N, 3.75. $C_{19}H_{24}NO_5P$ requires: C, 60.47; H, 6.40; N, 3.71%); *m/z* (%) 377 (M^+, 2), 291 (39), 267 (46), 208 (100), 181 (90) and 140 (63); δ 7.83–7.74 (m, 4H, naphthyl-H), 7.51–7.40 (m, 3H, naphthyl-H), 4.97 (d, 1H, $J=9.4$ Hz, 5-H), 3.99 (d, 3H, $J_{P-OCH}=10.1$ Hz, MeOP), 3.88 (d, 3H, $J_{P-OCH}=10.4$ Hz, MeOP), 3.59 (apparent dt, 1H, $J=8.7$, 9.4 Hz, 4-H), 3.02 (s, 3H, MeOC), 2.92 (ABXY and br s, 2H, $J=9.3$, 13.0, 15.6 Hz, 3-H_b and NH), 1.92 (ABXY, 1H, $J=2.0$, 8.1, 13.0 Hz, 3-H_a) and 1.51 (d, 3H, $J_{P-C-CH}=15.7$ Hz, 2-Me).



NOE data:

Signal irradiated	Enhancement (%)			
	3-Ha	3-Hb	4-H	5-H
3-Ha	—	25	8	—
3-Hb	19	—	—	4
4-H	4	—	—	9
5-H	—	—	11	—

6.3.5. Dimethyl c-4-methoxycarbonyl-2-phenyl-c-5-(2′-naphthyl)pyrrolidine-r-2-phosphonate 4d. Work-up followed by flash chromatography eluting with 10:1 v/v ethyl acetate/ethanol afforded the product **4d**, which was crystallised from diethyl ether/petroleum ether as colourless plates, mp 120–121 °C (found: C, 65.60; H, 5.70; N, 3.10. $C_{24}H_{26}NO_5P$ requires: C, 65.59; H, 5.96; N, 3.18%); *m/z* (%) 439 (M^+, 0.1), 408 (0.5), 330 (57), 270 (100) and 243 (85); δ 7.84–7.32 (m, 12H, naphthyl and Ar-H), 4.68 (t, 1H, $J=8.1$ Hz, 5-H), 3.79 (d, 3H, $J_{P-OCH}=10.5$ Hz, MeOP), 3.72 (d, 3H, $J_{P-OCH}=10.4$ Hz, MeOP), 3.27 (m, 3H, 3-H_b, 4-H and NH), 3.02 (s, 3H, MeOC) and 2.76 (ABXY, 1H, $J=13$, 7.3, 12.7 Hz, 3-H_a).



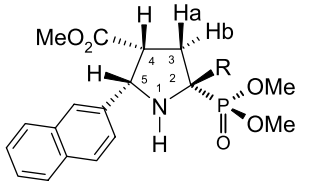
NOE data:

Signal irradiated	Enhancement (%)			
	3-Ha	3-Hb	4-H	5-H
3-Ha	—	26	8	—
3-Hb	16	—	—	
4-H	4	—	—	9
5-H	—	—	10	—

6.3.6. Dimethyl c-4-methoxycarbonyl-2-benzyl-c-5-(2′-naphthyl)pyrrolidine-r-2-phosphonate 4e. Work-up followed by flash chromatography eluting with 10:1 v/v ethyl acetate/ethanol afforded the product **4e**, which crystallised from hexane as colourless prisms, mp 122–123 °C (found: C, 66.40; H, 6.05; N, 3.15. $C_{25}H_{28}NO_5P$ requires: C, 66.20; H, 6.20; N, 3.10%); *m/z* (%) 453 (M^+, 0.2), 422 (0.8), 362 (51), 343 (61), 284 (86), 257 (49) and 91 (100); δ 7.77–7.70 (m, 4H, naphthyl), 7.46–7.28 (m, 8H, naphthyl and Ar-H), 4.64 (d, 1H, $J=9.2$ Hz, 5-H), 3.87 (d, 3H, $J_{P-OCH}=10.2$ Hz, MeOP), 3.86 (d, 3H, $J_{P-OCH}=10.3$ Hz, MeOP), 3.22 (ABX, 1H, $J=10.1$, 13.7 Hz, CHPh), 3.13–2.91 (m, 3H, CHPh, 4-H and 3-H_a), 3.26–2.97 (m, 4H, CH_2Ph, 4-H and 3-H_b), 2.94 (s, 3H, MeOC), 2.34 (br s, 1H, NH) and 2.23–2.12 (m, 1H, 3-H_a).

6.3.7. Dimethyl 2-hydroxymethyl-c-4-methoxycarbonyl-c-5-(2′-naphthyl)pyrrolidine-r-2-phosphonate 4g. Work-up followed by flash chromatography eluting with 5:1 v/v ethyl acetate/ethanol afforded the product **4g** as a colourless oil. *m/z* (%) 362 (MH^+, 47), 310 (43), 265 (27), 167 (38) and 83 (100); δ 7.97–7.68 (m, 4H, naphthyl), 7.58–7.37 (m, 3H, naphthyl and Ar-H), 4.62 (d, 1H, $J=10.2$ Hz, 5-H), 4.05 (d, 3H, $J_{P-OCH}=10.2$ Hz, MeOP), 3.86 (d, 4H, $J_{P-OCH}=10.2$ Hz, MeOP and C*H*OH), 3.71–3.66 (m, 1H, C*H*OH), 3.59–3.42 (m, 1H, 4-H) 3.05 (s, 3H, MeOC), 2.97–2.76 (m, 1H, 3-H_b) and 2.00–1.85 (m, 1H, 3-H_a).

6.3.8. Dimethyl 2-{[(*t*-buty1)dimethylsilyl]oxy} methyl-c-4-methoxycarbonyl-c-5-(2′-naphthyl)pyrrolidine-r-2 phosphonate 4h. Work-up followed by flash chromatography (the column was pre-washed with chloroform/triethylamine to prevent cleavage of the OTBDMS group) eluting with diethyl ether afforded the product **4h** as a brown gum (found: C, 57.65; H, 7.20; N, 2.85. $C_{25}H_{38}NO_6PSi$ requires: C, 59.15; H, 7.20; N, 2.75%); HRMS found 507.223, calcd 507.221; *m/z* (%) 507 (M^+, 2), 476 (5), 448 (20), 389 (35), 362 (95), 340 (95), 216 (13), 170 (100), 156 (94) and 127 (5); δ 7.84 (s, 1H, naphthyl-H), 7.80–7.77 (m, 2H, naphthyl-H), 7.75 (d, 1H, $J=8.7$ Hz, naphthyl-H), 7.52 (dd, 1H, $J=1.7$, 8.5 Hz, naphthyl-H), 7.45–7.40 (m, 2H, naphthyl H), 5.06 (d, 1H, $J=9.8$ Hz, 5-H), 3.94 (d, 3H, $J_{CH-OP}=10.3$ Hz, MeOP), 3.90 (ABX, 1H, $J=10.4$ Hz, $J_{CH-CP}=21.5$ Hz, CHOSi), 3.89 (d, 3H, $J_{CH-OP}=10.4$ Hz, MeOP), 3.80 (ABX, 1H, $J_{CH-CP}=9.2$, 10.5 Hz, CHOSi), 3.63 (dt, 1H, $J=8.8$, 9.5 Hz, 4-H), 2.99 (s, 3H, MeOC), 2.94 (ABXY, 1H, $J=8.9$, 13.4 Hz, $J_{CH-OP}=17.2$ Hz, 3-Hb), 2.08 (ABXY, 1H, $J_{CH-OP}=2.8$ Hz, $J=8.6$, 13.3 Hz, 3-H_a), 0.94 (s, 9H, *t*-BuSi) and 0.12 (s, 6H, 2× MeSi).



R = - $CH_2OSi(CH_3)_2C(CH_3)_3$

NOE data:

Signal irradiated	Enhancement (%)				
	2-$H_{(downfield)}$	3-H_a	3-H_b	4-H	5-H
2-$H_{(upfield)}$	16	—	—	—	1
3-H_a	11	—	22	9	—
3-H_b	—	11	—	—	—
4-H	—	3	—	—	10
5-H	—	—	—	10	—

6.3.9. Dimethyl 2-methy1-c-4-methoxycarbony1-c-4′-nitrophenyl) pyrrolidine-r-2-phosphonate 4l. Work-up followed by flash chromatography, eluting with a gradient from diethyl ether to 1:1 v/v ethyl acetate/methanol, afforded four fractions containing different mixtures of the cycloadduct **4l** and the Michael adduct **5l**. The two fractions containing the most cycloadduct were subjected to a further column chromatography purification step. Elution with 10:1 v/v ethyl acetate/methanol afforded the pure cycloadduct, which was crystallised from ethyl acetate/diethyl ether as yellow prisms, mp 156–158 °C (found: C, 48.30; H, 5.65; N, 7.45. $C_{15}H_{21}N_2O_7P$ requires: C, 48.40; H, 5.70; N, 7.55%); *m/z* (%) 357 (M−Me, 2), 341 (2), 286 (1), 263 (100), 203 (38) and 176 (33); δ 8.14 (d, 2H, $J=8.7$ Hz, *p*-nitrophenyl 3′, 5′-H), 7.59 (d, 2H, $J=8.7$ Hz, *p*-nitrophenyl 2′, 6′-H), 4.93 (d, 1H, $J=9.7$ Hz, 5-H), 3.92 (d, 3H, $J_{CH-OP}=10.3$ Hz, MeOP), 3.85 (d, 3H, $J_{CH-OP}=10.5$ Hz, MeOP), 3.60 (dt, 1H, $J=8.2$, 9.7 Hz, 4-H), 3.19 (s, 3H, MeOC), 2.83 (ABXY, 1H, $J=10.2$, 13.1 Hz, $J_{CH-OP}=15.4$ Hz, 3-H_b), 2.09 (br s, 1H, NH), 1.95 (ABXY, 1H, $J_{CH-OP}=1.6$ Hz, $J=7.9$, 13.0 Hz, 3-H_a) and 1.48 (d, 3H, $J_{CH-OP}=15.5$ Hz, 2-Me).

6.3.10. Dimethyl *N*-(4′-nitrobenzylidene)-1-imino-1-methyl-3methoxycarbonylpropylphosphonate 5l. The two fractions, which contained the most Michael adduct (described in Section 6) were combined and subjected to a further column chromatography purification step. Elution with an ethyl acetate/methanol gradient afforded the product **5l** as a thick brown oil, (found: C, 46.10; H, 5.45; N, 7.10. $C_{15}H_{21}N_2O_7P\cdot H_2O$ requires: C, 46.15; H, 5.95; N, 7.20%); *m/z* (%) 373 (M^+, 2), 359 (2), 341 (10), 263 (100), 224 (27), 203 (54), 176 (18) and 151 (82); δ 8.46 (d, 1H, $J=5.2$ Hz, CH═N), 8.28 (d, 2H, $J=8.7$ Hz, *p*-nitrophenyl 3′, 5′-H), 7.95 (d, 2H, $J=8.6$ Hz, *p*-nitrophenyl 2′, 6′-H), 3.79 (d, 3H, $J_{CH-OP}=10.4$ Hz, MeOP), 3.78 (d, 3H, $J_{CH-OP}=10.4$ Hz, MeOP), 3.64 (s, 3H, MeOC), 2.58–2.16 (m, 4H, 2×CH_2 and 1.56 (d, 3H, $J_{CH-OP}=15.5$ Hz, MeCP).

6.3.11. Dimethyl 2-methyl-c-4-methoxycarbonyl-c-5-(2′-iodophenyl)pyrrolidine-r-2-phosphonate 4m. Work up followed by flash chromatography eluting with 5:1 v/v ethyl acetate/methanol afforded the product **4m**, which crystallised from dichloromethane as colourless prisms, mp 121–123 °C (found: C, 39.55; H, 4.40; N, 3.0. $C_{15}H_{21}INO_5P$ requires: C, 39.75; H, 4.65; N, 3.10%); *m/z* (%) 452 (M−1, 0.2), 344 (100), 284 (27), 257 (40) and 216 (53); δ 7.78 (d, 1H, $J=7.8$ Hz, *o*-iodophenyl 3′-H), 7.58 (d, 1H, $J=7.8$ Hz, *o*-iodophenyl 6′-H), 7.30 (t, 1H, $J=6.4$ Hz, *o*-iodophenyl 4′-H), 6.94 (t, 1H, $J=7.6$ Hz, *o*-iodophenyl 5′-H), 4.98 (d, 1H, $J=9.2$ Hz, 5-H), 4.00 (d, 3H, $J_{CH-OP}=10.0$ Hz, MeOP), 3.86 (d, 3H, $J_{CH-OP}=10.4$ Hz, MeOP), 3.68 (dt, 1H, $J=8.1$, 8.5 Hz, 4-H), 3.10 (s, 3H, MeOC), 2.86 (ABXY,

1H, J=7.5, 13.2 Hz, J_{CH-OP}=16.1 Hz, 3-H_b), 2.01–1.93 (br s, 1H, NH), 1.94 (ABXY, 1H, J=3.1, 8.8, 13.3 Hz, 3-H_a) and 1.52 (d, 3H, J_{CH-OP}=15.6 Hz, 2-Me).

6.3.12. Dimethyl *N*-(2′-iodobenzylidene)-1-imino-1-methyl-3-methoxycarbonyl propylphosphonate 5m. The Michael adduct **5m** was observed in the crude reaction mixture and as a minor component (~8% by ^{1}H NMR) in fractions of the cycloadduct **4m**; δ 8.52 (d, 1H, J=4.6 Hz, CH=N), 7.95 (d, 1H, J=8.1 Hz, *o*-iodophenyl 3′-H), 7.85 (d, 1H, J=8.6 Hz, *o*-iodophenyl 6′-H), 7.36 (t, 1H, J=8.1 Hz, *o*-iodophenyl 4′-H), 7.11 (t, 1H, J=8.6 Hz, *o*-iodophenyl 5′-H), 3.81 (d, 3H, J_{CH-OP}=10.2 Hz, MeOP), 3.79 (d, 3H, J_{CH-OP}=10.1 Hz, MeOP), 3.63 (s, 3H, MeOC), 2.61–2.12 (m, 4H, 2×CH_2) and 1.57 (d, 3H, J_{CH-OP}= 14.7 Hz, MeCP).

6.3.13. Dimethyl 2-methy1-c-4-methoxycarbonyl-c-5-(2′-pyridyl)pyrrolidine-r-2-phosphonate 4n. Work-up followed by flash chromatography eluting with a gradient from ethyl acetate to 3:2 v/v ethyl acetate/methanol afforded the product **4n** as a dark brown gum; HRMS of M−PO(OMe)$_2$; found 219.113, calcd 219.113; *m*/*z* (%) 326 (M−2, 10), 311 (3), 297 (2), 283 (3), 267 (5), 253 (2), 233 (53), 219 (100), 187 (32), 159 (43), 132 (53) and 79 (42); δ 8.49 (d, 1H, J=5.1 Hz, pyridyl 6′-H), 7.66 (dt, 1H, J=1.7, 7.6 Hz, pyridyl 4′-H), 7.57 (d, 1H, J=7.6 Hz, pyridyl 3′-H), 7.15 (ABX, 1H, J=1.2, 5.5, 7.1 Hz, pyridyl 5′-H), 4.91 (d, 1H, J=9.4 Hz, 5-H), 3.88 (d, 3H, J_{CH-OP}=10.3 Hz, MeOP), 3.87 (d, 3H, J_{CH-OP}=10.4 Hz, MeOP), 3.61 (dt, 1H, J=8.4, 9.1 Hz, 4-H), 3.25 (s, 3H, MeOC), 2.79 (ABXY, 1H, J=9.3, 13.0 Hz, J_{CH-OP}=15.5 Hz, 3-H_b), 2.58 (br s, 1H, NH), 2.01 (ABXY, 1H, J_{CH-OP}=2.3 Hz, J=8.0, 12.9 Hz, 3-H_a) and 1.48 (d, 3H, J_{CH-OP}=15.7 Hz, 2-Me).

6.3.14. Dimethyl 2-phenyl-c-4-methoxycarbonyl-c-5-(2′-pyridyl)pyrrolidine-r-2-phosphonate 4o. Work-up followed by flash chromatography (the column was pre-washed with with 2% v/v concd ammonia in ether (4 mL of 33% w/w aqueous ammonia in 250 mL of ether) to aid the separation) eluting with a gradient from 1:1 v/v ether/ethyl acetate to 5:1 v/v ethyl acetate/methanol afforded a dark brown gum. Crystallisation from diethyl ether/ethyl acetate gave **4o** as colourless prisms, mp 129–130 °C, (found: C, 58.20; H, 5.90; N, 7.0. $C_{19}H_{23}N_2O_5P$ requires: C, 58.45; H, 5.95; N, 7.20%); *m*/*z* (%) 391 (MH^+, 1), 359 (1), 329 (1), 313 (2), 281 (100), 249 (16), 221 (37) and 195 (28); δ 8.55 (d, 1H, J=4.6 Hz, pyridyl 6′-H), 7.74 (dd, 2H, J=1.8, 7.4 Hz, phenyl 2′, 6′-H), 7.65 (dt, 1H, J=1.6, 7.7 Hz, pyridyl 4′-H), 7.42–7.29 (m, 4H, phenyl-H and pyridyl 3′-H), 7.17 (dd, 1H, J=5.3, 7.1 Hz, pyridyl 5′-H), 4.58 (d, 1H, J=9.7 Hz, 5-H), 3.82 (d, 3H, J_{CH-OP}=10.3 Hz, MeOP), 3.55 (d, 3H, J_{CH-OP}=10.0 Hz, MeOP), 3.18 (s, 3H, MeOC), 3.16 (dt, 1H, J=7.3, 9.7 Hz, 4-H), 2.97 (dt, 1H, J= 9.8, 13.0 Hz, J_{CH-OP}=12.9 Hz, 3-H_b) and 2.76 (ABXY, 1H, J=1.1, 7.4, 12.5 Hz, 3-H_a).

6.3.15. Dimethyl 2-benzyl-c-4-methoxycarbonyl-c-5-(2′-pyridyl)pyrrolidine-r-2-phosphonate 4p. Work-up followed by flash chromatography (the column was pre-washed with with 2% v/v concd ammonia in ether (4 mL of 33% w/w aqueous ammonia in 250 mL of ether) to aid the separation) eluting with a gradient from ethyl acetate to 1:1 v/v ethyl acetate/methanol afforded the product **4p** as a pale brown gum; HRMS of M−PO(OMe)$_2$, found, 313.095, calcd 313.095; *m*/*z* (%) 402 (M−2, 2), 373 (2), 343 (2), 313 (100), 295 (27), 281 (22), 263 (14), 235 (48), 227 (4 1), 208 (66) and 91 (60); δ 8.41 (d, 1H, J=5.2 Hz, pyridyl 6′-H), 7.66–7.58 (m, 2H, pyridyl 3′, 4′-H), 7.36–7.28 (m, 5H, phenyl-H), 7.12–7.07 (m, 1H, pyridyl 5′-H), 4.64 (d, 1H, J=9.1 Hz, 5-H), 3.81 (d, 3H, J_{CH-OP}=10.0 Hz, MeOP), 3.76 (d, 3H, J_{CH-OP}=10.6 Hz, MeOP), 3.18 (5, 3H, MeOC), 3.17 (ABX, 1H, J=9.8, 13.7 Hz, CHPh), 3.07–2.88 (m, 3H, CHPh, 3-H_b and 4-H), 2.58 (br s, 1H, NH) and 2.76 (m, 1H, 3-H_a).

6.3.16. Dimethyl 2-methyl-c-4-methoxycarbonyl-c-5-(2′-thienyl)pyrrolidine-r-2-phosphonate 4r. Work-up followed by flash chromatography eluting with 10:1 v/v ethyl acetate/methanol afforded the product **4r**, which crystallised from ethyl acetate–ether as colourless prisms, mp 86–88 °C (found: C, 46.70; H, 5.85; N, 3.90. $C_{13}H_{20}NO_5P$ requires: C, 46.85; H, 6.05; N, 4.20%); *m*/*z* (%) 331 (M−2, 3), 302 (7), 286 (4), 272 (2), 224 (100), 192 (34), 164 (44), 137 (44) and 96 (38); δ 7.17 (dd, 1H, J=1.0, 5.0 Hz, thienyl 5′-H), 6.95–6.92 (m, 2H, thienyl 3′, 4′-H), 5.13 (d, 1H, J=9.6 Hz, 5-H), 3.99 (d, 3H, J_{CH-OP}=10.1 Hz, MeOP), 3.84 (d, 3H, J_{CH-OP}=10.4 Hz, MeOP), 3.51 (dt, 1H, J=8.2, 9.5 Hz, 4-H), 3.33 (s, 3H, MeOC), 2.85 (ABXY, 1H, J=10.0, 13.1 Hz, J_{CH-OP}=15.6 Hz, 3-H_b), 2.31, (br s, 1H, NH), 1.92 (ABXY, 1H, J=1.2, 7.8, 12.8 Hz, 3-H_a) and 1.46 (d, 3H, J_{CH-OP}=15.6 Hz, 2-Me).

6.3.17. Dimethyl 2-phenyl-c-4-methoxycarbonyl-c-5-(2′-thienyl)pyrrolidine-r-2-phosphonate 4s. Work-up followed by flash chromatography eluting with diethyl ether/ethyl acetate afforded the product **4s**, which crystallised from dichloromethane/diethyl ether as colourless prisms, mp 114–115 °C (found: C, 54.55; H, 5.55; N, 3.30. $C_{18}H_{22}NO_5PS$ requires: C, 54.65; H, 5.60; N, 3.55%); *m*/*z* (%) 395 (M^+, 0.1), 364 (2), 309 (3), 286 (100), 254 (13), 226 (34), 199 (30), 96 (44) and 77 (59); δ 7.62 (dd, 2H, J= 1.9, 7.5 Hz, phenyl 2′, 6′-H), 7.40 (t, 2H, J=7.6 Hz, phenyl 3′, 5′-H), 7.31 (t, 1H, J=6.9 Hz, phenyl 4′-H), 7.20 (dd, 1H, J=1.9, 4.4 Hz, thienyl 5′-H), 6.96–6.93 (m, 2H, thienyl 3′, 4′-H), 4.82 (d, 1H, J=9.0 Hz, 5-H), 3.74 (d, 3H, J_{CH-OP}= 10.4 Hz, MeOP), 3.74 (d, 3H, J_{CH-OP}=10.3 Hz, MeOP), 3.30 (s, 3H, MeOC), 3.15–2.98 (m, 3H, NH, 3-H_b and 4-H) and 2.72–2.62 (m, 1H, 3-H_a).

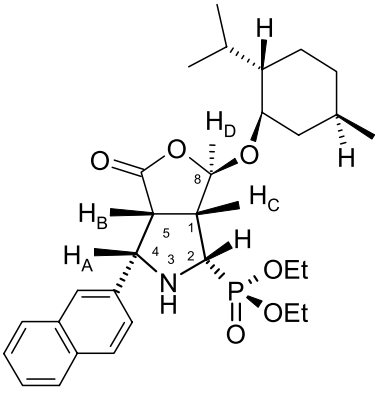
6.3.18. Dimethyl *N*-(2′-thienylidene)-1-imino-1-phenyl-3-methoxycarbonyl propylphosphonate 5s. The Michael adduct **5s** was observed in the crude reaction mixture and as a minor component (a 3:1:1 ratio of cycloadduct **4s**, imine and **5s** by ^{1}H NMR, respectively), in a fraction obtained via chromatography. Due to the very small proportions involved, a pure sample of the Michael adduct could not be obtained, but a couple of the characteristic ^{1}H NMR resonances could be assigned as follows: 8.70 (d, 1H, J=4.1 Hz, CHN), 3.60 (s, 3H, MeOC).

6.3.19. Dimethyl 2-benzyl-c-4-methoxycarbonyl-c-5-(2′-thienyl)pyrrolidine-r-2-phosphonate 4t. Work-up followed by flash chromatography eluting with a diethyl ether/ethyl acetate afforded the product **4t**, which crystallised from dichloromethane/diethyl ether as colourless

prisms, mp 105–107 °C (found: C, 55.80; H, 5.75; N, 3.20. $C_{19}H_{24}NO_5PS$ requires: C, 55.75; H, 5.90; N, 3.40%); *m/z* (%) 407 (M−2, 0.3), 378 (3), 318 (100), 299 (49), 286 (49), 286 (59), 258 (17), 240 (38), 213 (34) and 91 (87); δ 7.34–7.25 (m, 5H, phenyl-H), 7.11 (d, 1H, J=4.8 Hz, thienyl 5′-H), 6.88–6.83 (m, 2H, thienyl 3′, 4′-H), 4.72 (d, 1H, J=9.1 Hz, 5-H), 3.85 (d, 3H, J_{CH-OP}=10.4 Hz, MeOP), 3.81 (d, 3H, J_{CH-OP}=10.9 Hz, MeOP), 3.24 (s, 3H, MeOC), 3.18 (ABX, 1H, J=10.3, 13.8 Hz, CHPh), 3.02–2.89 (m, 3H, CHPh, 3-H_b and 4-H), 2.52–2.49 (br s, 1H, NH) and 2.16–2.06 (m, 1H, 3-H_a).

6.3.20. Dimethyl *N*-(2′-thienylidene)-1-imino-1-benzyl-3-methoxycarbonyl propylphosphonate 5t. The Michael adduct **5t** was observed in the crude reaction mixture and as a major component (a 1.2:1 ratio of Michael adduct to cycloadduct by ^{1}H NMR, respectively), in a fraction obtained via chromatography. Due to the very small proportions involved, a pure sample of the Michael adduct could not be obtained, but a couple of the characteristic ^{1}H NMR resonances could be assigned as follows; δ 8.25 (d, 1H, J=4.6 Hz, CH=N), 3.64 (s, 3H, MeOC).

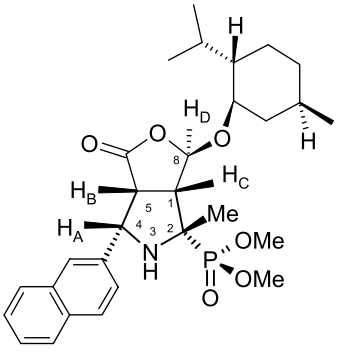
6.3.21. Diethyl 1*S*,2*S*,4*S*,5*R*,8*R*-4-(2′naphthyl)-3-aza-6-oxo-7-oxa-8-(1′*R*,2′*S*,5′*R*-menthyloxy)-bicyclo[3.3.0]-octane-2-phosphonate 9a. Work-up followed by flash chromatography eluting with a gradient from ethyl acetate to 5:1 v/v ethyl acetate/methanol afforded the product, which crystallised from diethyl ether as colourless needles, mp 206–207 °C (found: C, 66.10; H, 7.60; N, 2.60. $C_{30}H_{42}NO_6P$ requires: C, 66.30; H, 7.80; N, 2.60%); *m/z* (%) 543 (M^+, 6), 405 (25), 305 (16), 238 (10), 221 (15), 194 (100), 167 (42) and 139 (16); δ 7.82–7.79 (m, 4H, naphthyl-H)., 7.45–7.43 (m, 3H, naphthyl-H), 6.24 (d, 1H, J=1.5 Hz, 8-H), 4.56 (d, 1H, J=8.1 Hz, 4-H), 4.34 (m, 2H, CH_2OP), 4.26 (quin., 2H, J=7.1 Hz, CH_2OP), 3.60 (dd, 1H, J=7.4, 9.7 Hz, 2_H), 3.53 (dt, 1H, J=4.1, 10.6 Hz, menthyl-OCH), 3.48 (t, 1H, J=8.3 Hz, 5-H), 3.13 (m, 1H, 1-H), 2.39 (br s, 1H, NH), 2.29 (d, 1H, J=12.4 Hz, menthyl 6′-H), 2.05 (d quart, 1H, J=2.3, 6.8 Hz, menthyl 2′-H), 1.68–1.60 (m, 2H, menthyl 2′-H), 1.44 (t, 3H, J=7.1 Hz, *Me*CH_2OP), 1.40 (t, 5H, J=7.1 Hz, *Me*CH_2OP and menthyl 2′-H), 1.19 (m, 1H, menthyl-H), 0.96 (d, 5H, J=6.5 Hz, menthyl-Me and 2× menthyl-H), 0.84 (d, 3H, J=7.1 Hz, menthyl-Me) and 0.70 (d, 3H, J=6.9 Hz, menthyl-Me).



NOE data:

Signal irradiated	Enhancement (%)					
	1-H	2-H	4-H	5-H	8-H	$Menth_{OCH}$
1-H	—	10	—	9	4	—
2-H	11	—	6	—	—	—
4-H	—	5	—	12	—	—
5-H	7	—	8	—	—	—
8-H	3	—	—	—	—	6

6.3.22. Dimethyl 1*S*,2*S*,4*S*,5*R*,8*R*-2-methyl-4-(2′-naphthyl)-3-aza-6-oxo-7-oxa-8-(1′*R*,2′*S*,5′*R*-menthyl-oxy)-bicyclo[3.3.0]octane-2-phosphonate 9b. Work-up followed by flash chromatography eluting with a diethyl ether/ethylacetate gradient afforded the product (97% de) (diastereomeric excess was determined by chiral HPLC using a Chiralcel OG column (Daicel) eluting with 9.5:0.5 v/v hexane/isopropanol, detecting at a wavelength of 254 nm. The retention times of the two diasteroisomers were 11.55 (1.48%) and 15.29 (98.52%) min), which crystallised from diethyl ether/petroleum ether as colourless needles, mp 154–157 °C (found: C, 65.95; H, 7.9; N, 2.45. $C_{29}H_{40}NO_6P$ requires C, 65.75; H, 7.6; N, 2.65%); *m/z* (%) 529 (M^+, 0.6), 419 (100), 252 (24), 207 (39) and 181 (33); δ 7.86–7.79 (m, 4H, naphthyl-H), 7.46–7.42 (m, 3H, naphthyl-H), 6.21 (s, 1H, 8-H), 4.96 (d, 1H, J=8.0 Hz, 4-H), 4.02 (d, 3H, J_{P-OCH}=10.2 Hz, MeOP), 3.89 (d, 3H, J_{P-OCH}=10.6 Hz, MeOP), 3.57 (t, 1H, J=8.2 Hz, 5-H), 3.53 (dt, 1H, J=4.1, 10.6 Hz, menthyl-OCH), 2.89–2.86 (m, 1H, 1-H), 2.23 (br d, 1H, J=12.5 Hz, menthyl-H), 2.13 (br s, 1H, NH), 2.02 (m, 1H, menthyl-H), 1.69–1.63 (m, 3H, menthyl-H), 1.58 (d, 3H, J_{P-C-CH}=14.7 Hz, 2-Me), 1.52–1.39 (m, 2H, menthyl-H), 1.26–1.16 (m, 2H, menthyl-H), 1.00–0.86 (m, 1H, menthyl-H), 0.96 (d, 3H, J=6.4 Hz, Me), 0.83 and 0.69 (2×d, 2×3H, J=6.9 Hz, CH*Me*$_2$).



NOE data:

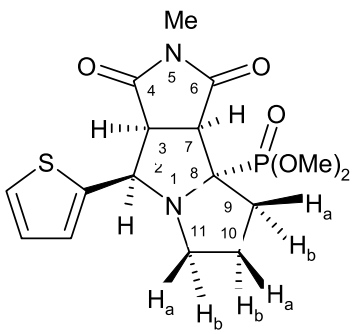
Signal irradiated	Enhancement (%)			
	1-H	5-H	4-H	8-H
1-H	—	5	—	—
5-H	2	—	3	3
4-H	—	11	—	—
8-H	4	—	—	—

6.3.23. Dimethyl c-4-(2′naphthyl)-*t*-2,7-dimethyl-c-6,8-dioxo-3,7-diazabicyclo[3.3.0]octane-r-2-phosphonate 10. Work-up followed by flash chromatography eluting with 10:1 v/v ethyl acetate/methanol afforded the product **13**,

which crystallised from ethyl acetate as colourless prisms, mp 179–180 °C (found: C, 57.55; H, 5.45; N, 6.7. $C_{20}H_{23}N_2O_5P\cdot H_2O$ requires C, 57.15; H, 6.0; N, 6.7%); *m/z* (%) 402 (M^+, 2), 387 (2), 293 (8), 234 (8), 207 (20), 181 (66), 165 (25) and 140 (45); 7.84–7.74 (m, 4H, naphthyl-H), 7.49–7.45 (m, 3H, naphthyl-H), 4.96 (d, 1H, J=7.5 Hz, 4-H), 3.97 (d, 3H, J_{CH-OP}=10.3 Hz, MeOP), 3.89 (d, 3H, J_{CH-OP}=10.9 Hz, MeOP), 3.59 (t, 1H, J=7.7 Hz, 5-H), 3.20 (dd, 1H, J_{CH-CP}=4.0, 7.8 Hz, 1-H), 2.91 (s, 3H, N-Me), 2.25–2.10 (br s, 1H, NH) and 1.69 (d, 3H, J_{CH-OP}= 14.7 Hz, 2-Me).

6.3.24. Dimethyl *N*-(4′-but-2-onyl)-2-methyl-c-4-acetyl-c-5-(2′-napthyl)pyrrolidine-r-2-phosphonate 11. Work-up followed by flash chromatography eluting with a diethyl ether/ethyl acetate afforded the product **11** as a thick brown oil; *m/z* (%) 389 (M−MeC=O, 2), 375 (14), 347 (1), 331 (86), 299 (18), 284 (22), 223 (43), 208 (26), 194 (19), 172 (97), 155 (100) and 127 (94); 7.86–7.69 (m, 5H, naphthyl-H), 7.46–7.38 (m, 2H, naphthyl-H), 4.58 (d, 1H, J=9.7 Hz, 5-H), 3.86 (d, 6H, J_{CH-OP}=10.3 Hz, 2×MeOP), 3.51 (dt, 1H, J= 7.7, 9.2 Hz, 4-H), 2.68–2.56 (m, 1H, 3-H_b), 2.2–1.66 (m, 5H, 2×CH_2 and 3-H_a), 1.83 (s, 3H, MeC=O), 1.81 (s, 3H, MeC=O) and 1.50 (d, 3H, J_{CH-OP}=15.3 Hz, 2-Me).

6.3.25. Dimethyl *t*-1,5-diaza-*t*-4,6-dioxo-5-methyl-*t*-2(2′-thienyl)-tricyclo[3.3.3.0.0]undecane-r-8-phosphonate 13. The amine **2f** (172 mg, 0.96 mmol), thiophene-2-carboxaldehyde (102 mg, 0.91 mmol) and anhydrous sodium sulphate (excess) were stirred 16 h in acetonitrile at rt. The dipolarophile, *N*-methyl maleimide (101 mg, 0.91 mmol), was added to the mixture and the flask was then flushed with nitrogen and left to reflux 16 h. The reaction mixture was filtered, washed with dichloromethane and evaporated under reduced pressure. Flash chromatography eluting with from ethyl acetate to 5:1 v/v ethyl acetate/methanol afforded the product **13**, which crystallised from ethyl acetate/diethyl ether as yellow prisms, mp 176–178 °C (found: C, 50.25; H, 5.5; N, 7.2. $C_{16}H_{21}N_2O_5PS$ requires C, 50.0; H, 5.5; N, 7.3%); *m/z* (%) 384 (M^+, 1), 275 (100), 216 (6), 190 (21), 162 (12), 109 (12) and 79 (15); δ 7.39–7.38 (m, 1H, thienyl 5′-H), 7.28–7.27 (m, 1H, thienyl 3′-H), 7.00–6.98 (m, 1H, thienyl 4′-H), 5.37 (d, 1H, J= 7.6 Hz, 2-H), 3.92 (d, 3H, J_{CH-OP}=10.0 Hz, MeOP), 3.83 (d, 4H, J_{CH-OP}=10.5 Hz, MeOP and 3-H), 3.64 (dt, 1H, J= 8.0 Hz, J_{CH-CP}=16.0 Hz, 7-H), 3.05 (ABXY, 1H, J=4.6, 8.0, 9.7 Hz, 11-H_b), 2.92 (s, 3H, NMe), 2.58 (dt, 1H, J=7.7, 9.8 Hz, 11-H_a) 2.39 (t, 1H, J=7.3 Hz, 9-H_b), 2.34 (t, 1H J= 7.3 Hz, 9-H_a), 1.95–1.88 (m, 1H, 10-H_b) and 1.70–1.66 (m, 1H, 10-H_a).



NOE data:

Signal irradiated	Enhancement (%)							
	2-H	3-H	7-H	10-H_a	10-H_b	11-H_a	11-H_b	Thienyl-3′-H
2-H	—	—	—	—	—	—	—	—
7-H	2	1	—	—	—	—	—	—
9-H	—	—	2	—	—	—	—	—
10-H_a	—	—	—	—	21	5	—	—
10-H_b	—	—	—	20	—	—	5	—
11-H_a	—	—	—	3	—	—	22	2
11-H_b	1	—	—	—	4	22	—	—

Acknowledgements

We thank Leeds University, Mersin University, TÜBİTAK (Turkish Scientific and Research Council), the Royal Society, the Commonwealth Commision UK and the British Council for providing financial support.

References and notes

1. Part 61. Grigg, R.; Cooper, D. M.; Holloway, S.; McDonald, S.; Millington, E.; Sarker, M. A. B. *Tetrahedron*, **2005**, *61*, 8677–8685.
2. Baylis, E. K.; Campbell, C. D.; Dingwall, J. G. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2845–2853.
3. Bartlette, P. A.; Jacobsen, N. E. *J. Am. Chem. Soc.* **1981**, *103*, 654–657.
4. Gothelf, K. V.; Jorgenson, K. A. *Chem. Rev.* **1998**, *98*, 863–909. Sebahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666–5667. Williams, R. M.; Zhai, W.; Aldous, D. J.; Aldous, S. C. *J. Org. Chem.* **1992**, *57*, 6527–6532. Sebahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666–5667. Barr, D. A.; Dorrity, M. J.; Grigg, R.; Malone, J. F.; Montgomery, J.; Rajviroongit, S.; Stevenson, P. *Tetrahedron Lett.* **1990**, *31*, 6569–6572.
5. Dondas, H. A.; Grigg, R.; Killner, C. *Tetrahedron* **2003**, *59*, 8481–8487.
6. Fejes, I.; Nyerges, M.; Szollosy, S.; Blasko, G.; Toke, L. *Tetrahedron* **2001**, *57*, 1129–1137. Ruano, J. L. G.; Tito, A.; Peromingo, M. T. *J. Org. Chem.* **2002**, *67*, 981–987.
7. Grigg, R.; Hargreaves, S.; Redpath, J.; Turchi, S.; Yoganathan, G. *Synthesis* **1999**, 441–446.
8. Grigg, R.; Thornton-Pett, M.; Yoganathan, G. *Tetrahedron* **1999**, *55*, 1763–1780.
9. Grigg, R.; Thornton-Pett, M.; Xu, L. H. *Tetrahedron* **1999**, *55*, 13841–13866.
10. Grigg, R.; Sridharan, V.; Suganathan, S.; Bridge, A. W. *Tetrahedron* **1995**, *51*, 295–306.
11. Grigg, R.; Thornton-Pett, M.; Yoganathan, G. *Tetrahedron* **1999**, *55*, 8129–8140.
12. Dondas, H. A.; Durisingham, J.; Grigg, R.; Maclachlan, W. S.; MacPherson, D. T.; Thornton-Pett, M.; Sridharan, V.; Suganathan, S. *Tetrahedron* **2000**, *56*, 4063–4070.
13. Grigg, R.; Lansdell, M. I.; Thornton-Pett, M. *Tetrahedron* **1999**, *55*, 2025–2044.
14. Dondas, H. A.; Grigg, R.; Thornton-Pett, M. *Tetrahedron* **1996**, *52*, 13455–13466.

15. Blaney, P.; Grigg, R.; Rankovic, Z.; Thornton-Pett, M.; Xu, J. *Tetrahedron* **2002**, *58*, 1719–1737.
16. Nyerges, M.; Gajdics, L.; Szollosy, A.; Toke, L. *Synlett* **1999**, 111–113. Cooper, D. M.; Grigg, R.; Hargreaves, S.; Kennewell, P.; Redpath, J. *Tetrahedron* **1995**, *51*, 7791–7808.
17. Anslow, A. S.; Harwood, L. M.; Phillips, H.; Watkin, D. J. *Tetrahedron: Asymmetry* **1991**, *2*, 169–172. Anslow, A. S.; Harwood, L. M.; Phillips, H.; Watkin, D. J. *Tetrahedron: Asymmetry* **1991**, *2*, 997–1000. Anslow, A. S.; Harwood, L. M.; Phillips, H.; Watkin, D. J.; Wong, L. F. *Tetrahedron: Asymmetry* **1991**, *2*, 1343–1358. Harwood, L. M.; Manage, A. C.; Robin, S.; Hopes, S. F. G.; Watkin, D. J.; Williams, C. E. *Synlett* **1993**, 777–780. Anslow, A. S.; Harwood, L. M.; Lilley, I. A. *Tetrahedron: Asymmetry* **1995**, *6*, 2465–2480.
18. Allway, P.; Grigg, R. *Tetrahedron Lett.* **1991**, *32*, 5817–5820. Grigg, R. *Tetrahedron: Asymmetry* **1995**, *6*, 2475–2486. Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400–13401.
19. Gothelf, K. V.; Hazell, R. G.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4236–4238. Oderaotoshi, Y.; Cheng, W.; Fujitomi, S.; Kasano, Y.; Minakata, S.; Komatsu, M. *Org. Lett.* **2003**, *5*, 5043–5046.
20. Donegan, G.; Grigg, R.; Gunaratne, H. Q. N.; Kennedy, D. A.; Malone, J. F.; Sridrahan, V.; Thianpatanagul, S. *Tetrahedron* **1989**, *45*, 1723–1746.
21. Grigg, R.; Sridharan, V. *Adv. Cycloaddition* **1993**, *3*, 161–204.
22. Barr, D. A.; Grigg, R.; Sridharan, V. *Tetrahedron Lett.* **1989**, *30*, 4727–4730.
23. Katritzky, A. R.; Fang, D.; Fang, Y. *Synlett* **1999**, 590.
24. Lansdell, M.I. Ph.D. Thesis, University of Leeds, 1998.
25. Grigg, R.; Najera, C.; Sansano, J. M. *Eur. J. Org. Chem.* **2001**, 1971–1982. Dogan, O.; Koyuncu, H. *J. Organomet. Chem.* **2001**, *631*, 135–138. Alvares-Ibarra, C.; Csaky, A. G.; Martinez, M.; Qiroga, M. L. *Tetrahedron Lett.* **1996**, *37*, 6573–6574.
26. Afarinkia, K.; Rees, W. *Tetrahedron* **1990**, *46*, 7175–7196.
27. Campbell, M. M.; Carruthers, N. I.; Mickel, S. J. *Tetrahedron* **1982**, *38*, 2513–2524.
28. Seebach, D.; Charczuk, R.; Gerber, C.; Renaud, P.; Bener, H.; Schnieder, H. *Helv. Chim. Acta* **1989**, *72*, 401–425.
29. Hubert, P.; Marmot, R. S.; Seyferth, D. *J. Org. Chem.* **1971**, *36*, 1379–1386.
30. Bennani, Y. L.; Hanessian, S. *Tetrahedron Lett.* **1990**, *31*, 6465–6468.
31. Corcoran, R. C.; Green, J. M. *Tetrahedron Lett.* **1990**, *31*, 6827–6830.
32. Grigg, R.; Sridharan, V.; Thornton-Pett, M.; Xu, J.; Zhang, J. *Tetrahedron* **2002**, *58*, 2627–2640.
33. Barr, D. A.; Dorrity, M. J.; Grigg, R.; Hargreaves, S.; Malone, J. F.; Montgomery, J.; Redpath, J.; Stevenson, P.; Thortnton-Pett, M. *Tetrahedron* **1995**, *51*, 273–294.
34. Ma, L.; Dolphin, D. *J. Chem. Soc., Chem. Commun.* **1995**, 2251–2252.
35. Aly, M. F.; Ardill, H. E.; Grigg, R.; Leong-Ling, S.; Surendrakumar, S.; Rajviroongit, S. *Tetrahedron Lett.* **1987**, *28*, 6077–6080. Ardill, H. E.; Fontaine, X. L. R.; Grigg, R.; Henderson, D.; Montgomery, J.; Sridharan, V.; Surendrakumar, S. *Tetrahedron* **1990**, *6449*, 6466. Grigg, R.; Rankovic, Z.; Thornton-Pett, M.; Somasunderam, A. *Tetrahedron* **1993**, *49*, 8679–8690.
36. Dehnel, A.; Lavielle, G. *Tetrahedron Lett.* **1980**, *21*, 1315–1318. Dehnel, A.; Kanabus-Kaminska, J. M.; Lavielle, G. *Can. J. Chem.* **1988**, *66*, 310–318.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 10683–10688

An efficient synthesis of 7-hydroxy-2,6-dimethylchromeno[3,4-*d*] oxazol-4-one—a protected fragment of novenamine

David W. Gammon, Roger Hunter* and Seanette A. Wilson

Department of Chemistry, University of Cape Town, Private Bag, Rondebosch, Cape Town 7701, South Africa

Received 24 June 2005; revised 4 August 2005; accepted 19 August 2005

Available online 19 September 2005

Abstract—The high-yielding six-step synthesis of 7-hydroxy-2,6-dimethylchromeno[3,4-*d*]oxazol-4-one **17** from commercially available 2,4-dihydroxy-3-methylacetophenone is described. Coumarin **17** constitutes a useful synthon for coumarin antibiotic synthesis. A new methodology for oxazole formation applicable to 3-aminocoumarins has been developed, and a mechanistic rationalization is proposed.

1. Introduction

Novenamine **1** is the glycosylated 3-aminocoumarinyl subunit of novobiocin **2**, a naturally occurring antimicrobial agent that was first isolated in 1956 from several Streptomyces species including *S. spheroides* and *S. niveus* (Fig. 1).[1]

Novobiocin, together with the structurally related coumarin antibiotics, clorobiocin **3**, and coumermycin A_1 **4**, show potent activity against Gram-positive bacteria, including methicillin-resistant strains of staphylococcus species (Fig. 1).[2]

The coumarin-containing antibiotics are powerful inhibitors of DNA-gyrase, which is a type II topoisomerase and an essential prokaryotic enzyme.[3] Since DNA-gyrase has no counterpart in eukaryotes, it is a very attractive drug-target for antibiotics. Recently, novobiocin has also been identified as an antitumour agent in that it is an inhibitor of the 90 kDa heat shock protein, Hsp90.[4,5]

There are only two published total syntheses of the coumarin moiety of novenamine, neither of which were used in the coupling to noviose.[6,7]

The first of these (Scheme 1), published in 1958, started

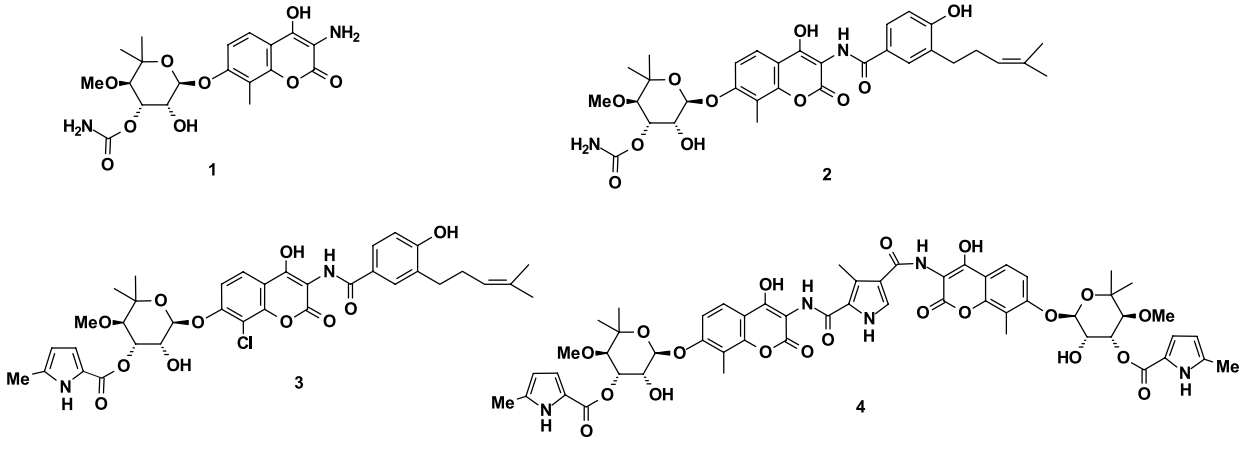
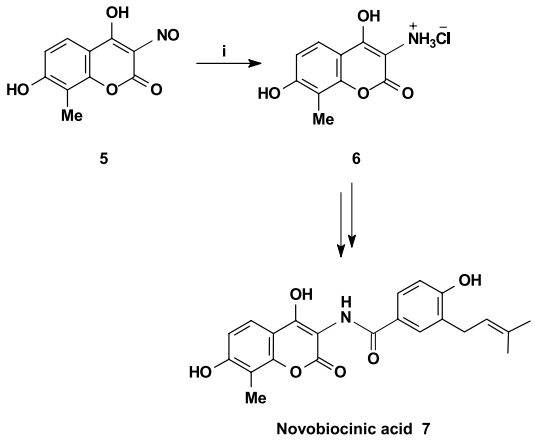


Figure 1. Structure of novenamine **1**, novobiocin **2**, clorobiocin **3** and coumermycin A_1 **4**.

Keywords: Novobiocin; Coumarin antibiotics; Oxazoles; Robinson–Gabriel mechanism; $POCl_3$/pyridine.
* Corresponding author. Tel.: +27 21 650 2544; fax: +27 21 689 7499; e-mail: roger@science.uct.ac.za

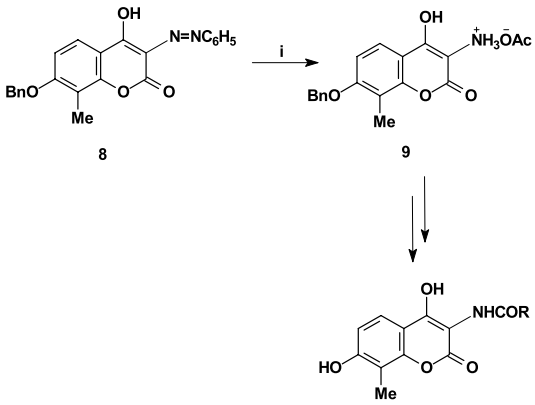
0040–4020/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tet.2005.08.083



Scheme 1. Reagents and conditions: (i) 10% Pd/C, 2.5 N HCl, H_2, ethanol, no yield given.

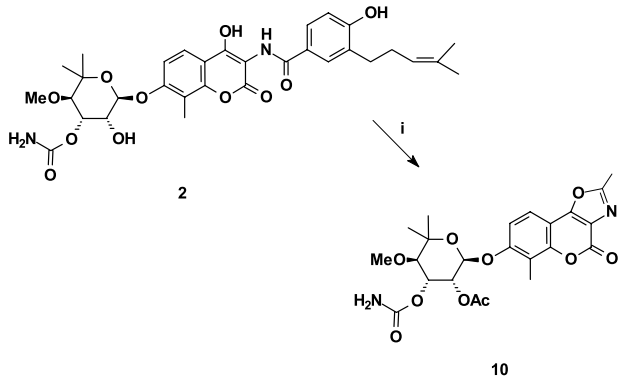
from 2-methylresorcinol and concerned the synthesis of novobiocinic acid **7**, with the aim of elucidating the structure of the coumarin moiety.[6] The synthesis was very low-yielding (<7%), with the 3-amino functionality being introduced via reduction of the unstable nitroso intermediate **5** to form the ammonium salt **6**.

The second report, published in 1984, described a synthesis from 2,4-dihydroxy-3-methylacetophenone, of two 3-acylamino-4,7-dihydroxy-8-methylcoumarin derivatives (Scheme 2) and their subsequent biological testing.[7] In this instance, the introduction of the 3-amido functionality involved preparation and reduction of the 3-phenylazo derivative **8**, followed by *N*-acylation of the resulting ammonium salt **9**.



Scheme 2. Reagents and conditions: (i) Sodium dithionite, sodium acetate, ethanol, water, reflux, 90%.

Traditionally, the total syntheses of novenamine and its derivatives have involved coupling the sugar moiety to 4-*O*-protected-4,7-dihydroxy-8-methylcoumarin prior to the introduction of the C-3 amino functionality thereby necessitating further post-glycosylation steps.[8,9] In contemplating a synthetic strategy towards novenamine, which would minimize such post-glycosylation steps, it was noted that a derivative of novenamine with the vicinal hydroxyamine protected as an oxazole **10** was formed and isolated by Hinman et al. via cleavage of the amide bond in novobiocin **2** with acetic anhydride and pyridine (Scheme 3).[10]



Scheme 3. Reagents and conditions: (i) Acetic anhydride, pyridine, 110 °C, 24 h, 65%.

Furthermore, Ueda et al. reported successful cleavage of the oxazole of **10** using mildly acidic conditions, without destruction of the glycosidic bond.[11] This therefore prompted us to develop a novel synthesis of 3-amino-4,7-dihydroxy-8-methyl coumarin with the 3-amino and 4-hydroxyl groups protected as an oxazole as in **17** (Fig. 2).

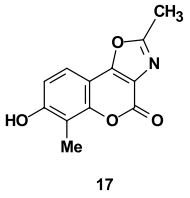


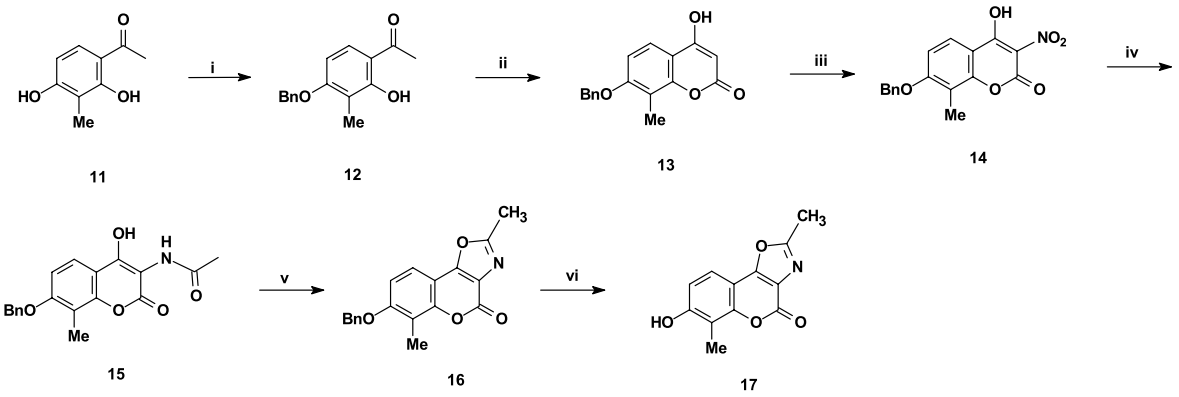
Figure 2. Structure of target molecule, 2,6-dimethyl-7-hydroxychromeno[3,4-*d*]oxazol-4-one **17**.

It was considered that this derivative would be a promising coupling partner to the carbohydrate unit of novenamine, noviose, which has been synthesized in our laboratories recently.[12]

2. Results and discussion

A retrosynthetic analysis of **17** revealed commercially available 2,4-dihydroxy-3-methylacetophenone **11** to be an appropriate starting material. The envisaged strategy involved formation of the 4-hydroxycoumarin unit, introduction of the 3-amino functionality via reduction of a nitro group regioselectively installed at C-3, and finally oxazole formation.

To this end, chemoselective benzylation of 2,4-dihydroxy-3-methylacetophenone gave the 4-benzyloxy derivative **12** in 88% yield,[13] presumably as a result of the 4-hydroxyl group being less sterically hindered than the 2-hydroxyl group, as well as not being involved in hydrogen-bonding to the acetyl oxygen (Scheme 4). The *o*-hydroxyacetophenone derivative **12** was then converted directly into the 4-hydroxycoumarin **13** in 76% yield using diethyl carbonate and sodium hydride, methodology first described by Barker et al.[14] Nitration at the C-3 position with fuming nitric acid in chloroform at room temperature,[15] furnished **14** in nearly quantitative yield. The insolubility of **14** in a range of standard solvents contributed to numerous failed attempts to reduce the nitro functionality via the following reagents:



Scheme 4. Reagents and conditions: (i) BnCl, K_2CO_3, KI, acetone, 56 °C, 88%; (ii) NaH, $CO(OEt)_2$, toluene, 110 °C, 76%; (iii) HNO_3, H_2SO_4, $CHCl_3$, room temperature, 93%; (iv) Zn, AcOH, 110 °C, 86%; (v) $POCl_3$, pyridine, THF, 66 °C, 87%; (vi) 10% Pd/C, H_2, THF/CH_2Cl_2, room temperature, 74%.

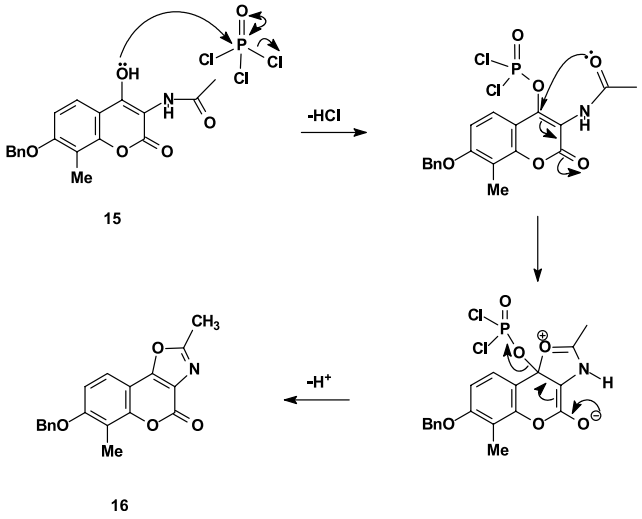
(i) sodium dithionite in pyridine;[7] (ii) Pd/C, H_2; (iii) Fe, 1 M HCl, MeOH; (iv) Fe, 1 M HCl, THF; (v) Zn dust, 1 M NaOH, EtOH. Ultimately, however, conversion of the nitro group to acetamide **15** could be achieved in a gratifyingly high yield (86%) using zinc in refluxing acetic acid, involving a slight modification of the method developed by Okumura to reduce 4,7-dihydroxy-3-phenylazocoumarin to the corresponding 3-acetamido-4,7-dihydroxycoumarin.[16] The work-up and product isolation of the nitration and reduction steps simply involved filtration of the solid from the cooled reaction medium and recrystallization, making this strategy an attractive choice for the introduction of an amino group at C-3.

Numerous methods are available for conversion of 3-amino-4-hydroxycoumarin derivatives into the corresponding oxazole including (i) heating 3-amino-4-hydroxycoumarin as its hydrochloride with the appropriate carboxylic acid in polyphosphoric acid for 3.5 h at 160–200 °C;[17] (ii) condensing 3-amino-4-hydroxycoumarin derivatives with aromatic aldehydes to yield the corresponding Schiff bases which, by heating in nitrobenzene, undergo cyclization and H_2 elimination to afford the corresponding oxazole derivatives[18] and (iii) heating 3-amino-4-hydroxycoumarin derivatives with the appropriate anhydride in pyridine.[19] An examination of these methods revealed that they invariably require high temperatures, long reaction times and often give unsatisfactory yields.

An alternative method was therefore investigated using phosphorus oxychloride ($POCl_3$) and pyridine in refluxing tetrahydrofuran, which pleasingly converted acetamide **15** into its corresponding oxazole **16** in a Robinson–Gabriel-type cyclodehydration reaction.[20] The reaction times were typically between 5 and 10 min, with yields of greater than 85% following recrystallization. Evidence for the formation of the oxazole was provided by the ^{1}H NMR spectrum of **16**, which revealed a downfield shift in one of the methyl singlets from δ_H 2.11 in **15** to 2.56 as well as the disappearance of the amide proton. In the ^{13}C NMR of **16**, the oxazole carbon C-2 resonated at δ_C 162.6 whereas the carbonyl carbon of the acetamide **15** resonated at δ_C 171.2, revealing an upfield shift for this carbon in the oxazole structure. The IR spectrum of **16** revealed the absence of a signal in the NH region as well as the amide carbonyl bands, a further indication that oxazole formation had taken place.

In a recent and independent study, Nicolaou et al. found that pyridine-buffered $POCl_3$ was effective in converting hindered ketoamides into oxazoles,[21] although their study did not extend to the coumarin series or related structures. The mechanism for the PCl_5-promoted Robinson–Gabriel cyclodehydration of ketoamides was determined by Wassermann and Vinick in 1973 with the use of oxygen-18 labelling. Their experiments established that the amide oxygen is the one incorporated into the oxazole ring and that the ketone carbonyl oxygen is expelled.[20] In keeping with the Robinson–Gabriel mechanism, and in view of the 3-amido-4-hydroxycoumarin structure of **15** having its 'ketone' carbonyl already fixed as an enol in conjugation with the coumarin carbonyl group, it seemed reasonable to postulate a nucleophilic substitution mechanism via a Michael addition/elimination sequence to account for cyclization. It was also considered reasonable to postulate prior activation of the enolic hydroxyl group as a superior chlorophosphate leaving group, since this was in keeping with the rapid reaction observed (5–10 min).

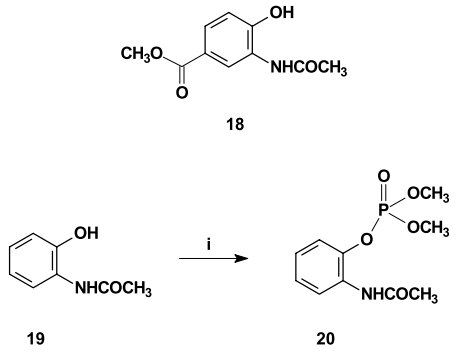
This activation step has been postulated by Meyers et al. in the condensation of carboxylic acids with amino alcohols to form oxazolines using Ph_3P–CCl_4–Et_3N, whereby the intermediate hydroxy amide reacts with $Ph_3PCl^+CCl_3^-$ at



Scheme 5. Proposed mechanism for oxazole formation via nucleophilic substitution.

the hydroxyl group, with subsequent displacement by the amide carbonyl oxygen.[22] Our postulated mechanism is depicted in Scheme 5.

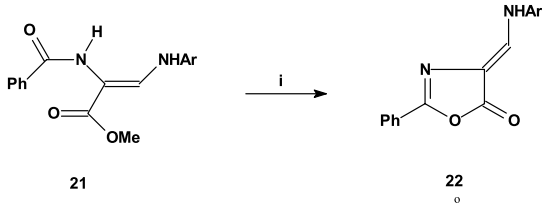
Mechanistic studies were carried out by investigating the cyclization of two model compounds **18** and **19** (Scheme 6).



Scheme 6. Reagents and conditions: (i) (a) $POCl_3$, pyridine, THF, reflux; (b) MeOH, reflux, 18% over two steps.

The two substrates were chosen as having varying degrees of electron-deficiency in their aromatic rings, so as to probe the importance of this parameter, and the cyclization conditions were kept the same as for **15**. Neither structure afforded an oxazole, highlighting the importance of a strongly electron-withdrawing group to promote the Michael-addition step. However, **19** did furnish a phosphate derivative **20**, derived by substitution of the dichlorophosphate intermediate with methanol. Dimethoxyphosphate ester **19** could be isolated and characterized by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy, lending support for formation of a similar transient chlorophosphate in the mechanism postulated in Scheme 5 for cyclization of **15**.

Apart from Nicolaou's work, only one other literature analogy for the use of this reagent was found. This involved conversion of methyl 2-benzoylamino-3-arylaminopropenoate **21** with phosphorus oxychloride and pyridine into 4-arylaminomethylene-2-phenyl-2-oxazolin-5-one **22** (Scheme 7).[23] The relatively few number of literature analogies was confirmed by a recent review detailing the synthesis of oxazole-containing natural products by Yeh in 2004.[24]



Scheme 7. Reagents and conditions: (i) $POCl_3$, pyridine, 70 °C, 83%.

In the final step, debenzylation of oxazole **16** furnished the desired 7-hydroxycoumarin **17** in 74% yield (Scheme 4). Compound **17** has been prepared previously by refluxing 3-acetamido-7-acetoxy-4-hydroxy-8-methylcoumarin, isolated from novobiocin, in acetic anhydride followed by acetate saponification but no NMR data was reported.[25] Accordingly, a full characterization of **17** was carried out, which gave the anticipated NMR spectroscopic and microanalytical information as reported in Section 4.

3. Conclusion

A protected coumarin fragment of novenamine has been synthesized in only six steps from commercially available 2, 4-dihydroxy-3-methylacetophenone **11** and in 40% overall yield. Only one of the six steps required an aqueous work-up, and the purification of each product was achieved in high yield by recrystallization, with no chromatography being necessary. New methodology has been developed for oxazole formation applicable to 3-aminocoumarins, providing a useful alternative protecting-group strategy in the synthesis of coumarin antibiotics. Work is currently underway to couple **17** to 3-*O*-carbamoyl-*C*-4-epi-noviose, the C-4-epimer of 3-*O*-carbamoyl noviose.

4. Experimental

4.1. General

All moisture-sensitive reactions were performed in flame-dried glassware equipped with a rubber septun under a positive pressure of nitrogen. THF was distilled from sodium benzophenone under nitrogen and CH_2Cl_2 over P_2O_5. Silica-gel 60 and DC-Alufolien 60 F_{254} were used for column chromatography and analytical TLC, respectively. Melting points were determined on a Reichert Jung hot-stage microscope and are uncorrected. Microanalyses were performed with a Fisons EA 110 CHN analyzer and high-resolution mass spectrometry were obtained using a VG70-SEQ micromass spectrometer. NMR were recorded on either a Varian VXR-300 or Varian Unity 400 spectrometer. Chemical shifts (δ) are reported in ppm and J values are given in hertz. The IR spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer and the frequencies are given in cm^{-1}.

4.1.1. 7-Benzyloxy-4-hydroxy-8-methylchromen-2-one (13). Acetophenone **12**[13] (0.50 g, 1.9 mmol) was dissolved in toluene (10 ml) and added to sodium hydride (60% in oil, 0.17 g, 4.3 mmol) suspended in toluene (10 ml). Diethyl carbonate (0.31 ml, 2.5 mmol) was added and the mixture refluxed for 2 h before being cooled to 0 °C, quenched with water and extracted with ethyl acetate (×1). The aqueous phase was acidified with 1 M HCl and extracted with ethyl acetate (×3). The combined organic extracts from the acidic extractions were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The residue was crystallized from methanol to give **13** (0.42 g, 76%) as colourless crystals: mp 233–234 °C (lit.[7] mp 233–236 °C); IR $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1514, 1587 (aromatic C=C), 1723, 1667 (C=O stretch); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.19 (s, 3H, $ArCH_3$), 5.22 (s, 2H, $-CH_2C_6H_5$), 5.44 (s, 1H, H-3), 7.07 (d, 1H, H-6, J=8.7 Hz), 7.31–7.47 (m, 5H, $-CH_2C_6H_5$), 7.62 (d, 1H, H-5, J=8.7 Hz), 12.20 (br, 1H, –OH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 8.2 ($ArCH_3$), 69.9 ($-CH_2C_6H_5$), 88.5 (C-3), 108.3 (C-6), 109.3 (C-4a), 112.6 (C-8), 121.3 (C-5), 127.3, 127.8, 128.4, 136.7 ($-CH_2C_6H_5$), 152.5 (C-8a), 159.3 (C-4),

162.2 (C-7), 166.1 (C-2); HRMS *m/z* 282.0883 (M^+), $C_{17}H_{14}O_4$ requires 282.0892. Anal. Calcd for $C_{17}H_{14}O_4$: C, 72.33%; H, 5.00%. Found: C, 72.16%; H, 4.82%.

4.1.2. 7-Benzyloxy-4-hydroxy-8-methyl-3-nitrochromen-2-one (14). Concentrated sulphuric acid (1.61 ml, 22.1 mmol) and concentrated nitric acid (1.00 ml, 18.4 mmol) were mixed slowly at 0 °C and then added, over a period of 15 min, to **13** (2.08 g, 7.4 mmol) suspended in $CHCl_3$. After an additional 1 h, the solvent was evaporated under reduced pressure and 1 M HCl (30 ml) was added. The yellow solid was filtered, rinsed well with methanol, and crystallized from glacial acetic acid to give **14** (2.23 g, 93%) as yellow plates: mp 205–208 °C; IR ν_{max}(KBr pellet)/cm^{-1} 1325 and 1530 (NO stretch), 1754 (C=O stretch), 3540 (OH stretch); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.18 (s, 3H, $ArCH_3$), 5.07 (br, 1H, –OH), 5.22 (s, 2H, $-CH_2C_6H_5$), 7.06 (d, 1H, H-6, J=9.0 Hz), 7.30–7.48 (m, 5H, $-CH_2C_6H_5$), 7.77 (d, 1H, H-5, J=9.0 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 8.2 ($ArCH_3$), 69.9 ($-CH_2C_6H_5$), 108.1 (C-6), 112.2 (C-3), 113.9 (C-4a), 119.5 (C-8), 123.9 (C-5), 127.3, 127.8, 128.5, 136.8 ($-CH_2C_6H_5$), 151.3 (C-8a), 157.0 (C-4), 159.7 (C-7), 166.4 (C-2). Anal. Calcd for $C_{17}H_{13}NO_6$: C, 62.39%; H, 4.00%; N, 4.28%. Found: C, 62.14%; H, 3.88%; N, 4.31%.

4.1.3. *N*-(7-Benzyloxy-4-hydroxy-8-methyl-2-oxo-(2*H*)-chromen-3-yl)-acetamide (15). Compound **14** (1.00 g, 3.1 mmol) and Zn (1.00 g, 15.5 mmol) were refluxed in acetic acid (10 ml) for 1 h, in which time the solution turned deep purple and then colourless. The Zn salts were filtered and rinsed well with hot acetic acid. The filtrate was cooled to room temperature, allowing the amide to precipitate. The product was filtered and crystallized with ethyl acetate to yield **15** (0.87 g, 86%) as colourless crystals: mp 240–243 °C; IR ν_{max}(CH_2Cl_2)/cm^{-1} 1500 (aromatic C=C), 1572 (amide I), 1598 (aromatic C=C), 1632 (amide II), 1686 (C=O stretch), 3288 (NH stretch), 3500 (OH stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.11 (s, 3H, $-NHCOCH_3$), 2.23 (s, 3H, $ArCH_3$), 5.24 (s, 2H, $-CH_2C_6H_5$), 7.16 (d, 1H, H-6, J=9.0 Hz), 7.38–7.48 (m, 5H, $-CH_2C_6H_5$), 7.68 (d, 1H, H-5, J=9.0 Hz), 9.42 (s, 1H, –NH), 12.2 (br, 1H, –OH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 8.1 ($ArCH_3$), 22.6 ($-NHCOCH_3$), 69.9 ($-CH_2C_6H_5$), 101.4 (C-3), 108.9 (C-6), 109.7 (C-4a), 112.5 (C-8), 121.7 (C-5), 127.3, 127.9, 128.4, 136.7 ($-CH_2C_6H_5$), 150.1 (C-8a), 157.4 (C-4), 158.9 (C-7), 160.3 (C-2), 171.2 ($-COCH_3$). Anal. Calcd for $C_{19}H_{17}NO_5$: C, 67.25%; H, 5.05%; N, 4.13%. Found: C, 67.27%; H, 4.94%; N, 4.07%.

4.1.4. 7-Benzyloxy-2,6-dimethylchromeno[3,4-*d*]oxazol-4-one (16). Amide **15** (2.06 g, 6.1 mmol), pyridine (1.72 ml, 18.3 mmol) and $POCl_3$ (2.96 ml, 30.4 mmol) were suspended in tetrahydrofuran (50 ml) and refluxed for 10 min. After cooling to room temperature, the mixture was filtered, the excess solvent evaporated under vacuum and the remaining slurry azeotroped with toluene (×3) to remove traces of pyridine. The product was crystallized with ethyl acetate to yield **16** (1.70 g, 87%) as colourless crystals: mp 206–207 °C; IR ν_{max}(CH_2Cl_2)/cm^{-1} 1503, 1605 (aromatic C=C), 1647 (coumarin C=C), 1748 (C=O stretch); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H, $ArCH_3$), 2.56 (s, 3H, $-CH_3$), 5.10 (s, 2H, $-CH_2C_6H_5$), 6.88 (d, 1H, H-8, J=8.8 Hz), 7.29–7.34 (m, 5H, $-CH_2C_6H_5$), 7.48 (d, 1H, H-9, J=8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.8 ($ArCH_3$), 14.1 ($-CH_3$), 70.79 ($-CH_2C_6H_5$), 105.1 (C-9a), 108.9 (C-8), 115.8 (C-6), 118.9 (C-9), 122.4 (C-3a), 127.1, 128.2, 128.7, 136.3 ($-CH_2C_6H_5$), 152.1 (C-5a), 156.2 (C-1a), 156.3 (C-7), 159.3 (C-4), 162.6 (C-2). Anal. Calcd for $C_{19}H_{15}NO_4$: C, 71.02%; H, 4.71%; N, 4.36%. Found: C, 70.96%; H, 4.56%; N, 4.34%.

4.1.5. 2,6-Dimethyl-7-hydroxychromeno[3,4-*d*]oxazol-4-one (17). 10% Pd/C (0.50 g, 0.05 mmol) was added to compound **16** (0.15 g, 0.5 mmol) in a mixture of THF (10 ml) and CH_2Cl_2 (5 ml) and the solution stirred for 3 h at room temperature in an atmosphere of H_2 using a balloon. The excess solvent was evaporated after removing the Pd/C by filtration (rinsing with hot methanol). The product was recrystallized with methanol to yield **17** (0.08 g, 74%) as colourless crystals: mp 330–332 °C (decomp.) (lit.[25] mp 295–303 °C (decomp.) from water/dimethylformamide); IR ν_{max}(CH_2Cl_2)/cm^{-1} 1503, 1584, 1604 (aromatic C=C), 1647 (coumarin C=C), 1749 (C=O stretch), 3150 (OH stretch); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 3H, $ArCH_3$), 2.59 (s, 3H, $-CH_3$), 6.91 (d, 1H, H-8, J=8.4 Hz), 7.48 (d, 1H, H-9, J=8.4 Hz), 10.55 (s, 1H, –OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.0 ($ArCH_3$), 14.4 (CH_3), 103.5 (C-9a), 112.5 (C-6), 113.3 (C-8), 119.8 (C-9), 120.8 (C-3a), 152.8 (C-5a), 156.2 (C-1a), 157.0 (C-7), 159.5 (C-4), 163.0 (C-2). Anal. Calcd for $C_{12}H_9NO_4$: C, 62.34%; H, 3.92%; N, 6.06%. Found: C, 62.13%; H, 3.99%; N, 5.98%.

4.1.6. Dimethyl (2-acetamido)phenyl phosphate (20). 2-Acetamidophenol (0.20 g, 1.32 mmol) was suspended in THF (10 ml). Pyridine (0.43 ml, 5.29 mmol) and $POCl_3$ (0.25 ml, 2.65 mmol) were added and the mixture refluxed for 1 h. Methanol was added and the reaction mixture was refluxed for a further 20 min before being diluted with water and the aqueous phase extracted with ethyl acetate (×1). The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The crude product (0.44 g) was purified by column chromatography (10 g silica, 50% ethyl acetate/hexane) to afford **20** (0.06 g, 18%) as colourless crystals: mp 65–67 °C; IR ν_{max}(CH_2Cl_2)/cm^{-1} 1637 (C=O); ^{1}H NMR (400 MHz; DMSO-d_6) δ 2.05 (3H, s, $-NHCOCH_3$), 3.79 (6H, d, J_{HP}=11.2 Hz, $-OCH_3$), 7.16 (2H, m, Ar-H), 7.27 (1H, m, Ar-H), 7.69 (1H, d, J=6.4 Hz, Ar-H), 9.40 (1H, s, $-NHCOCH_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.1 ($-NHCOCH_3$), 55.7 (d, J_{CP}=6 Hz, 2×$-OCH_3$), 120.6, 125.7, 126.0, 126.2 (aromatics), 130.1 (C-2), 143.1 (C-1), 169.1 (C=O); ^{31}P NMR (300 MHz, DMSO-d_6) δ 0.87 ($PO(OCH_3)_2OR$).

Acknowledgements

This work was supported by the National Research Foundation (NRF) as well the Equity Development Programme of the Department of Chemistry, University of Cape Town.

References and notes

1. (a) Wallik, H.; Harris, D. A.; Reagan, M. A.; Ruger, M.; Woodruff, H. B. *Antibiot. Annu.* **1955–1956**, *3*, 909–917. (b) Lin, F. K.; Coriell, L. L. *Antibiot. Med.* **1956**, *2*, 268–276.
2. Musicki, B.; Periers, A. M.; Laurin, P.; Ferroud, D.; Benedetti, Y.; Lachaud, S.; Chatreaux, F.; Haesslein, J.; Iltis, A.; Pierre, C.; Khider, J.; Tessot, N.; Airault, M.; Demassey, J.; Vicat, P.; Klich, M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1695–1699.
3. (a) Holdgate, G. A.; Tunnicliffe, A.; Ward, W. H. J.; Weston, S. A.; Barth, P. T.; Taylor, I. W. F.; Paupit, R. A.; Timms, D. *Biochemistry* **1997**, *36*, 9663–9673. (b) Lewis, R. J.; Singh, O. M.; Smith, C. V.; Skarzynski, T.; Maxwell, A.; Wonacott, A. J.; Wigley, D. B. *EMBO J.* **1996**, *15*, 1412–1420. (c) Freel Meyers, C. L.; Oberthur, M.; Xu, H.; Heide, L.; Kahne, D.; Walsh, C. T. *Angew. Chem., Int. Ed.* **2004**, *43*, 67–70. (d) Albermann, C.; Soriano, A.; Jiang, J.; Vollmer, H.; Biggins, J. B.; Barton, W. A.; Lesniak, J.; Nikolov, D. B.; Thorson, J. S. *Org. Lett.* **2003**, *5*, 933–936.
4. Blagosklonny, M. V. *Leukaemia* **2002**, *16*, 455–462.
5. Adams, J.; Elliot, P. J. *Oncogene* **2000**, *19*, 6687–6692.
6. Spencer, C. F.; Stammer, C. H.; Rodin, J. O.; Walton, E.; Holly, F. W.; Folkers, K. *J. Am. Chem. Soc.* **1958**, *80*, 140–143.
7. Patonay, T.; Litkei, G.; Bognar, R.; Erdei, J.; Miszti, C. *Pharmazie* **1984**, *39*, 86–91.
8. (a) Vaterlaus, B. P.; Kiss, J.; Spiegelberg, H. *Helv. Chim. Acta* **1964**, *47*, 381–390. (b) Vaterlaus, B. P.; Doebel, K.; Kiss, J.; Rachlin, A. I.; Spiegelberg, H. *Helv. Chim. Acta* **1964**, *49*, 390–398. (c) Vaterlaus, B. P.; Spiegelberg, H. *Helv. Chim. Acta* **1964**, *47*, 508–514.
9. Periers, A. M.; Laurin, P.; Ferroud, D.; Haesslein, J.; Klich, M.; Dupuis-Hamelin, C.; Mauvais, P.; Lassaigne, P.; Bonnefoy, A.; Musicki, B. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 161–165.
10. Hinman, J. W.; Caron, E. L.; Hoeksema, H. J. *J. Am. Chem. Soc.* **1957**, *79*, 3789–3800.
11. Ueda, Y.; Chuang, J. M.; Crast, L. B.; Partyka, R. A. *J. Org. Chem.* **1988**, *53*, 5107–5113.
12. Gammon, D. W.; Hunter, R.; Wilson, S. *Tetrahedron Lett.* **2002**, *43*, 3141–3144.
13. Raphael, R. A.; Ravenscroft, P. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1823–1828.
14. Barker, W. M.; Hermodson, M. A.; Link, K. P. *J. Med. Chem.* **1971**, *14*, 167–169.
15. Klosa, J. *Pharmazie* **1953**, *8*, 221–223.
16. Okumura, K., Tanabe Seiyaku Co. JP 37004874.
17. (a) Merchant, J. R.; Venkatesh, M. S. *Chem. Ind. (London)* **1979**, 478–479. (b) Colotta, V.; Catarzi, D.; Varano, F.; Cecchi, L.; Filacchioni, G.; Martini, C.; Giusti, L.; Lucacchini, A. *II Farmaco* **1998**, *53*, 375–381.
18. Merchant, J. R.; Desai, H. K. *Indian J. Chem.* **1973**, *11*, 433–436.
19. Merchant, J. R.; Venkatesh, M. S.; Martyres, G. *Indian J. Chem., Sect. B* **1981**, *20*, 711–712.
20. Wasserman, H. H.; Vinick, F. J. *J. Org. Chem.* **1973**, *38*, 2407–2408.
21. Nicolaou, K. C.; Hao, J.; Reddy, M. V.; Bheema Rao, P.; Rassias, G.; Snyder, S. A.; Huang, X.; Chen, D. Y.-K.; Brenzovich, W. E.; Giuseppone, N.; Giannakakou, P.; O'Brate, A. *J. Am. Chem. Soc.* **2004**, *126*, 12897–12906.
22. Meyers, A. I.; Hoyer, D. *Tetrahedron Lett.* **1985**, *26*, 4687–4690.
23. Singh, M. K.; Singh, R. S.; Singh, R. M. *Indian J. Chem., Sect. B* **1999**, *38*, 920–924.
24. Yeh, V. S. C. *Tetrahedron* **2004**, *60*, 11995–12042.
25. Stammer, C. H. *J. Org. Chem.* **1960**, *25*, 460–461.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 10689–10698

Steroid-based head-to-tail amphiphiles as effective iono- and protonophores

Elvira Avallone,[a] Elena Cressina,[b] Massimo Fregonese,[b] Paolo Tecilla,[b,*] Irene Izzo[a,*] and Francesco De Riccardis[a,*]

[a]*Department of Chemistry, University of Salerno, via S. Allende, Baronissi I-84081, Salerno, Italy*
[b]*Department of Chemical Sciences, University of Trieste, via L. Giorgieri, I-34127 Trieste, Italy*

Received 14 June 2005; revised 5 August 2005; accepted 19 August 2005

Available online 16 September 2005

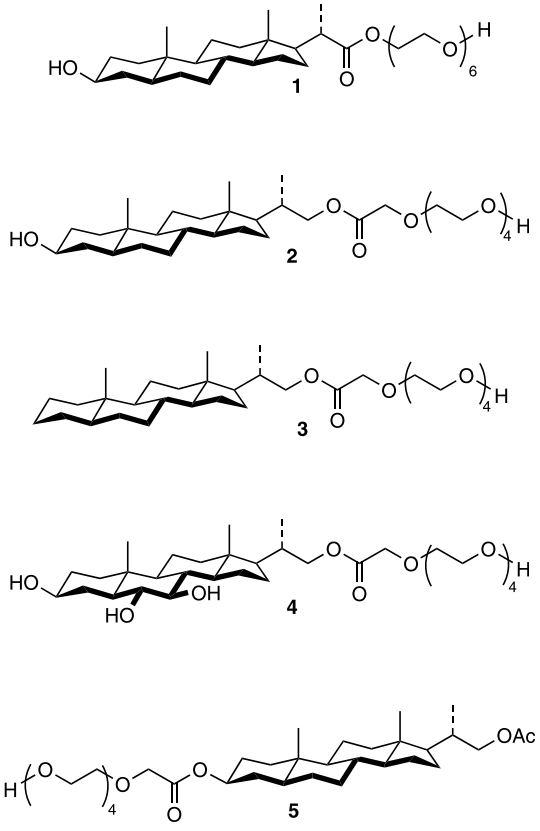
Abstract—The synthesis of five steroid-oligo(ethyleneglycol) conjugates (**1**–**5**) has been accomplished starting from commercially available *epi*-androsterone (**8**) and known 3β-[(*tert*-butyldiphenylsilyl)oxy]-5α-23,24-bisnorchol-16-en-6α,7β,22-triol (**27**). The synthetic strategy was based on a convergent approach including stereoselective C-17 side chains construction and standard coupling reactions. The activities of the head-to-tail amphiphiles, once incorporated in 95:5 egg PC/PG vesicular membranes, have been assessed by direct determination of transported species by NMR techniques ($^{23}Na^+$) and fluorescence spectroscopy (H^+). The sodium and proton transmembrane transport was compared to those evaluated for the polyene macrolide antibiotic amphotericin B and those shown by the known related C_2-symmetric sterol-polyether conjugates **6** and **7**.

1. Introduction

A large number of organisms control microbial growth through the biosynthesis of membrane-lytic compounds. Steroidal alkaloids, such as squalamine,[1] polyketides, such as amphotericin B,[2] and helical peptides, such as gramicidin,[3] are examples of secondary metabolites whose bactericidal and fungicidal activity is based on their transmembrane ion channel/pore formation.

Despite intense multidisciplinary efforts, the structural requirements for membrane permeabilization are still uncertain.[4] Evidence in the literature shows that the separation between the polar and non-polar domains along the major axis of the molecule (facially amphiphilic morphology)[5] is crucial for ion transport.[6]

In this paper, we wish to report the design, synthesis and the iono- and protonophoric properties of the structurally simple head-to-tail steroid-oligo(ethyleneglycol) conjugate amphiphiles **1**–**5** and the comparison of their activities with those exerted by the antibiotic amphotericin B and the related, known, C_2-symmetric **6** and **7**.[5d]



Keywords: Ionophore; Protonophore; Amphiphile; Steroids.
* Corresponding authors. Tel.: +39 89965230; fax: +39 89965296 (F.D.R.); e-mail: dericca@unisa.it

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.08.085

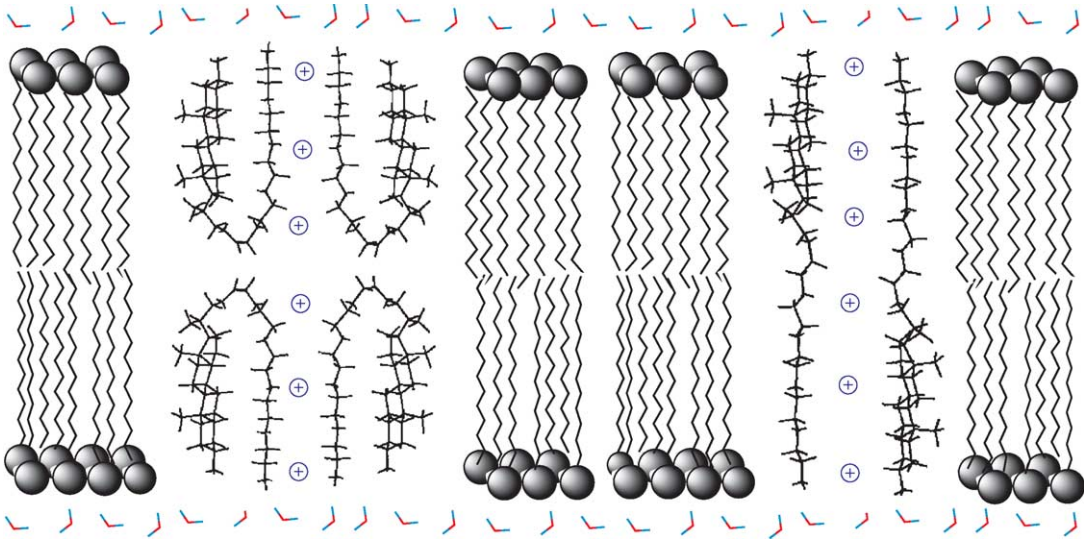
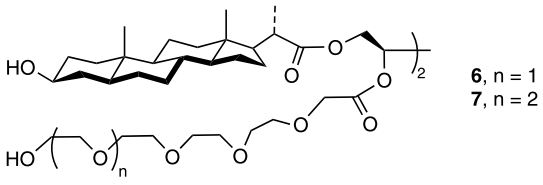


Figure 1. On the left, **2**, in the 'folded' conformation, constitutes a barrel-rosette[6] self-assembly and two half-channels aggregate in order to produce a contiguous pore across the bilayer.[9] On the right, a structurally simpler supramolecular alternate barrel-stave[6] assembly architecture is formed when **2** is in the 'extended' conformation.[10]



Conjugates **1**–**5** were designed considering that special cases of head-to-tail amphiphilicity[7] could induce the formation of membrane-active clusters similar to those shown by facially amphiphilic molecules, as shown in Figure 1.[8]

2. Results and discussion

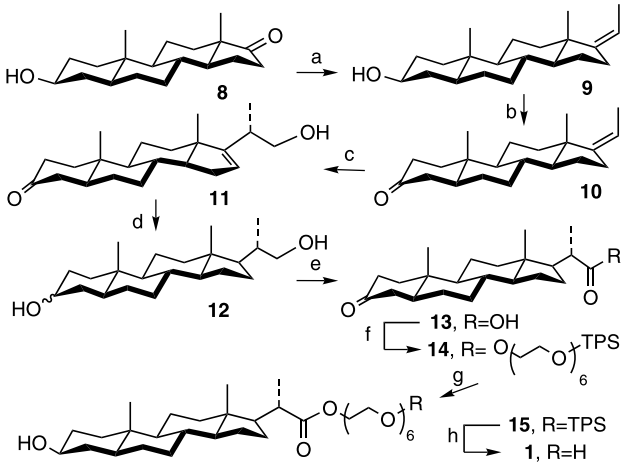
2.1. Synthesis and Na^+-transporting activities of 1 and 2

The synthesis of **1**, **2**, and that of the penta- and hexa(ethyleneglycol) side chains, is depicted in Schemes 1–3 and, in part, follows the procedure previously communicated for the construction of the C_2-symmetric sterol-polyether conjugates **6** and **7**.[5d]

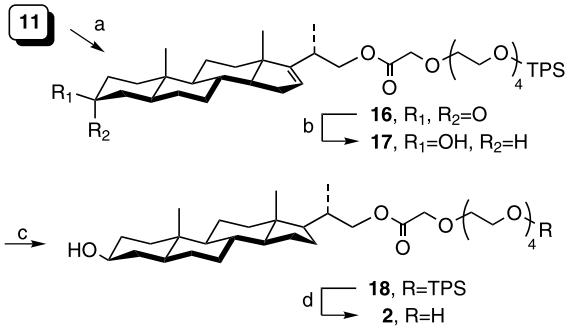
Amphiphile **1** was assembled using, as a key intermediate, the 3-oxo-5α-23,24-bisnorcholanic acid (**13**). This was obtained, in five steps and 43% overall yield, from commercially available *epi*-androsterone (**8**) and coupled with the mono-protected hexa(ethyleneglycol) **21** (see Scheme 3), in order to yield adduct **14**. Stereoselective $BH_3 \cdot SMe_2$-mediated C-3 carbonyl reduction and final deprotection with HF/pyridine, afforded target **1** in 7% overall yield (eight steps) from **8**.

The construction of the C-22 alcohol conjugate **2**, prototype of the latter reported amphiphiles **3**–**5**, proceeded through a shorter and higher yielding synthetic route.

Scheme 2 reports its elaboration, starting from 5α-23,24-

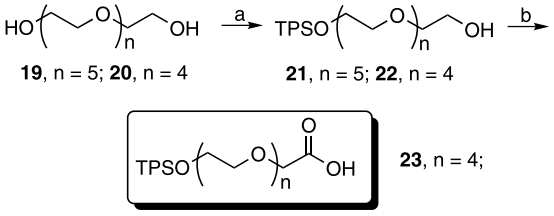


Scheme 1. Reagents and conditions: (a) $CH_3CH_2PPh_3Br$, *t*BuOK, THF, reflux, 78%; (b) PDC, CH_2Cl_2, 86%; (c) paraformaldehyde, $BF_3 \cdot OEt_2$, 0 °C, 98%; (d) H_2, PtO_2, EtOH, AcOEt; (e) Jones reagent, acetone/CH_2Cl_2, 65% for two steps; (f) **21**, EDC, DMAP, CH_2Cl_2, 35%; (g) $BH_3 \cdot SMe_2$, THF, 0 °C, 65%; (h) HF, Py, 0 °C, 73%.



Scheme 2. Reagents and conditions: (a) **23**, EDC, DMAP, CH_2Cl_2, 58%; (b) $BH_3 \cdot SMe_2$, THF, 0 °C, 97%; (c) H_2, Pt/C, EtOH; (d) HF, Py, 0 °C, 62% for two steps.

bisnorchol-16-en-22-ol-3-one (**11**), including the coupling with the acid **23** (see Scheme 3) and the final HF-induced desilylation. The desired amphiphile **2** was thus synthesized in 23% overall yield (seven steps), starting from *epi*-androsterone (**8**).



Scheme 3. Reagents and conditions: (a) TPSCl, DBU, CH_2Cl_2, 37% (for $n=5$), 39% (for $n=4$); (b) Jones reagent, acetone, 43%.

The synthesis of the two polar oligo(ethyleneglycol) heads, the previously cited **21** and **23**, started from hexa- and penta(ethyleneglycols) (**19** and **20**, respectively) and proceeded according to Scheme 3.

The ionophoric properties of **1** and **2** were investigated using a $^{23}Na^+$ NMR based assay.[11] The experimental kinetic profiles, compared with those previously reported for **6**, are shown in Figure 2.

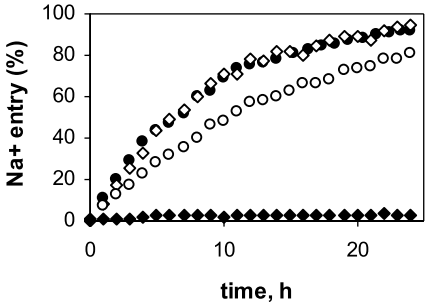


Figure 2. Kinetic profiles for the entry of Na^+ into 95:5 egg PC/PG vesicles contaning **1** (1.0%, ●), **2** (1.0%, ○), **6** (1.0%, ◇), and without additives (♦) at 25 °C. The concentration of steroid derivative is given in percent with respect to the total concentration of lipid. The total concentration of lipids was 10 mM.

Inspection of Figure 2 shows that compounds **1** and **2** behave as powerful ionophores. Surprisingly, they have a very similar activity to that found for the related, C_2-symmetric, **6**. Fitting of the data to a first order rate equation gives the apparent rate constants (k_{obsd}, h^{-1}) for the Na^+ entry process, which are 0.099 and 0.073 h^{-1} for **1** and **2**, and 0.096 h^{-1} for **6**, respectively. This means that, the preorganization in a dimeric structure (via covalent bond, as in **6**) seems unnecessary for the Na^+-transporting activity. In any case, the activities of the steroid derivatives compare well with that of the naturally occurring ionophore amphotericin B ($k_{obsd}=0.16\ h^{-1}$)[5b] underling the efficacy of these artificial ionophores.

2.2. Synthesis of 3–5 and H^+-transporting activities of 1–5

In recent years there has been intense research aimed at discovering new proton conductors.[12] The conversion of acquired energy (due to electron transfer or light harvesting) into a proton gradient, provides the energy for ATP synthesis and it is of fundamental importance for organisms from bacteria to man.[13] Most of the proton channels conduct H^+ ions by a hydrogen-bonded chain mechanism in which the proton hops from one molecule of water to the next (Grotthuss' mechanism or 'prototropic' transfer).[14] The whole process explains why proton permeability is much higher than that of other cations[15] and provides a tool to better understand the structural features of the membrane pores.

On the basis of these considerations, we decided to study the proton conductivities of **1** and **2** and compare them with those from **6** and **7** as shown in Figure 3.[16]

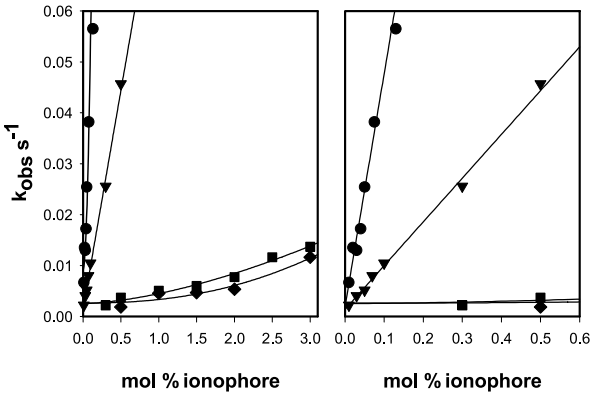


Figure 3. Plot of k_{obsd} as a function of mol% of **1** (■), **2** (♦), **6** (▼) and **7** (●) for the H^+-transport. The two panels are the same graph with different *X*-axis.

This time the variation of the H^+-transport, in relation to the structure of the conjugate, is striking. Amphiphiles **1** and **2** show a similar activity, comparable with that of amphotericin B.[17] On the other hand, the C_2-symmetric sterol-polyether conjugates **6** and **7** show much higher activities. Interestingly, the shape of the kinetic profiles is different, being linear in the case of dimeric compounds **6** and **7** and showing an upward curvature in the case of the shorter analogs **1** and **2**, suggesting a different mechanism of action. Taking into account the length of the two molecular systems it seems likely that **6** and **7** act as a single molecule in stabilizing the continuous transmembrane row of molecules of water thus limiting its fluctuation and favoring the H^+-transport. On the contrary, in the case of **1** and **2** it seems that a less stable supramolecular assembly is formed, having a negative impact on the proton transport. These types of non-linear kinetic profiles are usually fitted with the Hill equation in order to determine the Hill coefficient *n*, indicative for the number of monomers needed to form an active supramolecular pore.[18] In the case of **1** and **2** we obtained *n* values close to 2, indicating that two monomers assemble in the membrane to form the active transmembrane species probably following a barrel-rosette or a barrel-stave model[6] (Fig. 4A and B). In any case, it is evident that this supramolecular pore is less stable with respect to the unimolecular one formed by the dimeric steroid derivatives and, as a consequence, the activity is remarkably lower.

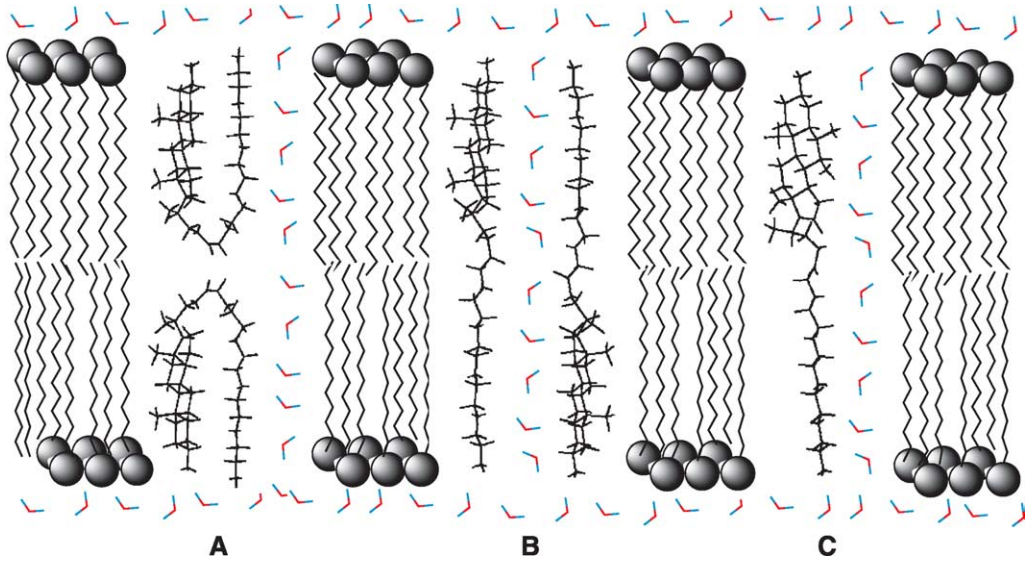
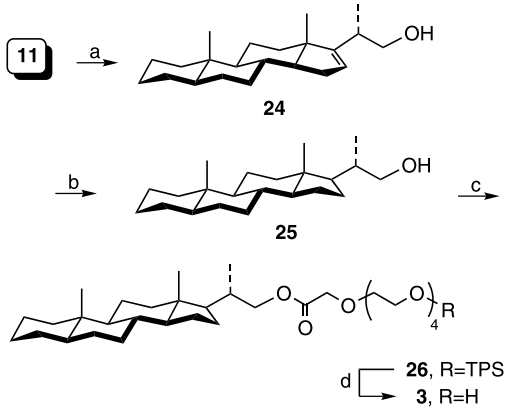


Figure 4. Proposed structure for the proton conducting pore formed by the different steroid derivatives.

In this context, we decided to vary the structure of our head-to-tail amphiphiles in order to stabilize the pore aggregate and, consequently, we designed the new derivatives **3**–**5**. In particular, compounds **3** and **4**, showing a different number of the hydroxyl groups on the tetracyclic nucleus, were conceived on the basis of theoretical studies correlating the polarity of the channel with the efficiency of proton transport.[19]

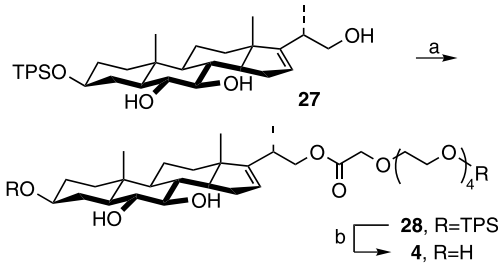
Compound **5**, in which the polar side chain was switched from C-22 to C-3, was designed in order to evaluate the effect of the oligo(ethyleneglycol) attachment (from the D to the A ring) on the proton transport.[20]

The synthesis of **3**, reported in Scheme 4, started with a C-3 Wolff-Kishner deoxygenation of the 5α-23,24-bisnorchol-16-en-22-ol-3-one (**11**). Its stereoselective hydrogenation, a coupling with acid **23** and desilylation, gave the expected target in 9% yield.



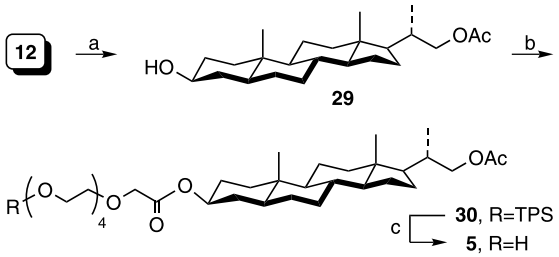
Scheme 4. Reagents and conditions: (a) $NH_2NH_2 \cdot H_2O$, KOH, $HOCH_2CH_2OH$, EtOH, 62%; (b) H_2, Pt/C, EtOH, 97%; (c) **23**, EDC, DMAP, CH_2Cl_2, 34%; (d) HF, Py, 0 °C, 44%.

The synthesis of **4** started from the known[5c] 3β-[(*tert*-butyldiphenylsilyl)oxy]-5α-23,24-bisnorchol-16-en-6α,7β,22-triol (**27**, Scheme 5). This was regioselectively acylated at C-22 with 1.1 equiv of **23**, to give conjugate **28**. Its desilylation, with HF/pyridine, afforded **4** in 16% overall yield (from **27**).



Scheme 5. Reagents and conditions: (a) **23**, EDC, DMAP, CH_2Cl_2, 31%; (b) HF, Py, 0 °C, 51%.

Compound **5** was synthesized in three steps and 34% overall yield, starting from the C-3 epimeric mixture **12**, according to Scheme 6. Regioselective acetylation on primary C-22 and subsequent silica gel purification, afforded 22-acetoxy-5α-23,24-bisnorcholan-6β-ol (**29**). The free hydroxyl at C-3 was coupled with the protected penta(ethyleneglycol) derivative **23** to yield conjugate **30**. Standard deprotection from the *tert*-butyldiphenylsilyl group afforded **5**.



Scheme 6. Reagents and conditions: (a) Ac_2O, Py, CH_2Cl_2, 50%; (b) **23**, EDC, DMAP, CH_2Cl_2, 82%; (c) HF, Py, 0 °C, 82%.

The protonophoric properties of the head-to-tail amphiphiles **3**–**5** and, for comparison, of steroid **1** are reported in Figure 5.

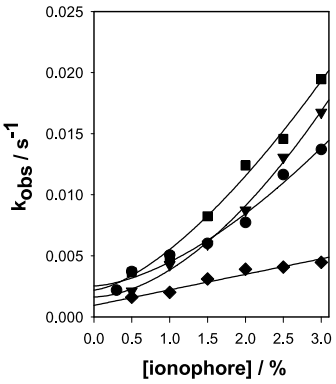


Figure 5. Plot of k_{obsd} as a function of mol% of **1** (●), **3** (▼), **4** (♦), and **5** (■) for the H^+-transport.

Steroids **3** and **5** behave very similarly to **1**. Again we observe an upward curvature of the kinetic profiles and the fitting of the curves with the Hill equation gives *n* values close to 2. Therefore, these two amphiphiles seem to act in a way similar to **1** forming small supramolecular assemblies, which perturb the membrane permeability and the system is little sensitive to the structural variations. On the other side, compound **4** is less active, probably because of the higher hydrophilicity, but shows a linear dependence of the transport rate from the ionophore concentration suggesting the formation of a unimolecular pore. Due to the presence of the hydroxyl groups on the steroid nucleus, in the extended conformation, steroid **4** is able to span the membrane forming a continuous polar surface, which may interact with the transmembrane row of water molecules promoting the proton transport (Fig. 4C). As a consequence, it acts as a single molecule in a way similar to ionophores **6** and **7**. If this hypothesis is correct then we may speculate that a similar mode of insertion in the membrane should be valid also for the other monomeric steroid derivatives and, therefore, that reported in Figure 4B should be preferred to that of Figure 4A. However, further studies are necessary to confirm such a hypothesis.

3. Conclusions

The synthesis of five new head-to-tail steroid-oligo(ethyleneglycol) conjugates **1**–**5** has been accomplished from readily available starting materials. These amphiphiles, once incorporated in a 95:5 egg PC/PG vesicular membranes, showed ionophoric activities (Na^+ and H^+ transfer) comparable with those reported for the channel-forming antibiotic amphotericin B. Head-to-tail amphiphiles **1**–**5** represent the simplest steroid-based cation-conductors and establish a new class of prototypes for membrane permeabilization. Moreover, these studies have shown the importance of the molecular structure on the proton-transport ability of the steroid derivatives with the dimeric ionophores **6** and **7** being much more active than the monomeric analogs.

4. Experimental

4.1. General methods

All reactions were carried out under a dry argon atmosphere using freshly distilled and dried solvents, unless otherwise noted. Tetrahydrofuran (THF) was distilled from $LiAlH_4$. Toluene, methylene chloride, and diethyl ether were distilled from calcium hydride. Glassware was flame-dried (0.05 Torr) prior to use. When necessary, compounds were dried in vacuo over P_2O_5 or by azeotropic removal of water with toluene under reduced pressure. Starting materials and reagents purchased from commercial suppliers were generally used without purification. Reaction temperatures were measured externally; reactions were monitored by TLC on Merck silica gel plates (0.25 mm) and visualized by UV light and spraying with H_2SO_4–$Ce(SO_4)_2$, *p*-anisaldeyde-EtOH–H_2SO_4–AcOH solutions and drying. Flash cromatography was performed on Merck silica gel (60, particle size: 0.040–0.063 mm). Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) pure materials. The NMR spectra were recorded at rt on a Bruker DRX 400 spectrometer (^1H at 400 MHz, ^{13}C at 100 MHz) or on Bruker DRX 300 spectrometer (^1H at 300 MHz, ^{13}C at 75 MHz). Chemical shifts are reported relative to the residual solvent peak ($CHCl_3$: $\delta=7.26$, $^{13}CDCl_3$: $\delta=77.0$). HR ESMS were performed on a Q-Star Applied Biosystem mass spectrometer. Optical rotations were measured with a JASCO DIP-1000 polarimeter.

4.2. Procedures for the synthesis of compounds described in Scheme 1

4.2.1. Compound 9. To a solution of ethyltriphenylphosphonium bromide (19.1 g, 51.6 mmol) in dry THF (50 ml), *t*BuOK (5.21 g, 46.5 mmol) was added. The resulting mixture was stirred at rt for 10 min, then a solution of *epi*-androsterone (5.00 g, 17.2 mmol) in dry THF (10 ml) was added. The reaction mixture was refluxed for 3 h, cooled to rt, quenched with water, concentrated under reduced pressure to remove the excess of THF and the aqueous layer was extracted with diethyl ether (3×20 ml). The combined organic phases were dried over Na_2SO_4, filtered and concentrated in vacuo to give a crude product, which was purified by flash chromatography (40–70% diethyl ether in petroleum ether) to afford **9** (4.1 g, 78%) as a white amorphous solid.

Compound **9**. $R_f=0.07$ (10% diethyl ether in petroleum ether). $[\alpha]_D$ +17.6 (*c* 2.0, $CHCl_3$).^1H NMR ($CDCl_3$, 400 MHz) δ: 0.80 (3H, s, C*H*$_3$-18), 0.85 (3H, s, C*H*$_3$-19), 1.66 (3H, d, $J=7.1$ Hz, C*H*$_3$-21), 3.58 (1H, m, H-3), 5.09 (1H, q, $J=7.0$ Hz, H-20). ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 12.2, 13.0, 16.8, 21.34, 24.3, 28.6, 31.4, 31.8 (×2), 55.0, 35.4, 36.9 (×2), 37.1, 38.1, 44.7, 54.3, 56.1, 71.1, 113.1, 150.3. HRES-MS, *m*/*z*: 303.2643 (calcd 303.2688 for $C_{21}H_{35}O$) [MH^+].

4.2.2. Compound 10. To a solution of **9** (4.05 g, 1.34 mmol) in dry CH_2Cl_2 (200 ml) at rt, molecular sieves (powered, 4 Å, 7.5 g) and pyridinium dichromate (PDC, 7.66 g, 20.2 mmol) were added. The resulting suspension was stirred for 3 h, quenched with diethyl ether, filtered through

a pad of silica gel–$CaSO_4$ (w/w: 90/10) and concentrated in vacuo to give the crude product, which was purified by flash chromatography (0–30% ethyl acetate in petroleum ether) to afford **10** (3.45 g, 86%) as a white amorphous solid.

Compound **10**. R_f=0.8 (20% ethyl acetate in petroleum ether). $[\alpha]_D$ +45.8 (*c* 2.5, $CHCl_3$).^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.84 (3H, s, C*H*$_3$-18), 0.97 (3H, s, C*H*$_3$-19), 1.59 (3H, d, *J*=7.2 Hz, C*H*$_3$-21), 5.06 (1H, q, *J*=7.0 Hz, H-20). ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 11.2, 13.0, 16.7, 21.5, 24.2, 28.8, 31.2, 31.4, 34.8, 35.5, 36.9, 38.0, 38.3 (× 2), 44.5, 46.4, 53.7, 55.8, 113.3, 149.8, 211.4. HRES-MS, *m/z*: 301.2571 (calcd 301.2531 for $C_{21}H_{33}O$) [MH^+].

4.2.3. Compound 11. To a solution of **10** (1.69 g, 5.63 mmol) in dry CH_2Cl_2 (170 ml) at 0 °C, paraformaldehyde (0.93 g, 60.5 mmol) and $BF_3\cdot OEt_2$ (0.80 g, 0.56 mmol), were added. The resulting mixture was stirred at rt for 10 min, then quenched with water (30 ml), extracted with CH_2Cl_2 (3×30 ml), dried on Na_2SO_4 and concentrated in vacuo to give the crude product, which was purified by flash chromatography (40–70% diethyl ether in petroleum ether) to afford **11** (1.82 g, 98%) as a white amorphous solid.

Compound **11**. R_f=0.40 (30% ethyl acetate in petroleum ether). $[\alpha]_D$ +21.4 (*c* 1.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.77 (3H, s, C*H*$_3$-18), 0.99 (3H, d, *J*=7.1 Hz, C*H*$_3$-21), 1.00 (3H, s, C*H*$_3$-19), 3.49 (1H, dd, *J*=10.4, 6.3 Hz, H-22), 3.60 (1H, dd, *J*=10.4, 7.7 Hz, H-22′), 5.37 (1H, br s, H-16). ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 12.0, 16.2, 18.8, 21.9, 24.5, 31.7, 32.2, 34.7, 35.4, 35.9, 36.7, 37.9, 38.7, 39.0, 44.6, 47.5, 55.0, 57.6, 67.1, 123.4, 157.5, 201.3. HRES-MS, *m/z*: 331.2682 (calcd 331.2637 for $C_{22}H_{35}O_2$) [MH^+].

4.2.4. Compound 13. To a solution of **11** (0.450 g, 1.36 mmol) in absolute ethanol (20 ml) and ethyl acetate (1 ml), palladium(II) oxide (0.025 g) was added. The flask was evacuated (20 Torr) and flushed with hydrogen three times. The reaction mixture was vigorously stirred under an atmosphere of hydrogen for 14 h, filtered and concentrated under reduced pressure to give the C-3 epimeric mixture **12** (0.340 g) as a white amorphous solid, which was used in the next step without further purification.

To a solution of crude **12** (0.340 g, 1.02 mmol) in acetone (22 ml) and CH_2Cl_2 (2 ml) at rt, Jones reagent (1.0 ml) was added dropwise. The reaction mixture was stirred at rt for 2 h, then quenched with water (5 ml), concentrated under reduced pressure to remove the excess of acetone and CH_2Cl_2, and the aqueous layer extracted with ethyl acetate (3×10 ml). The organic layer was dried over Na_2SO_4/$NaHCO_3$ and concentrated in vacuo to give **13** (0.305 g, 65%, two steps from **11**) as a white amorphous solid, which was used in the next step without further purification.

Compound **13**. R_f=0.45 (5% methanol in CH_2Cl_2). $[\alpha]_D$ +14.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.69 (3H, s, C*H*$_3$-18), 1.00 (3H, s, C*H*$_3$-19), 1.23 (3H, d, *J*=7.0 Hz, C*H*$_3$-21), 10.0 (1H, br s, COO*H*). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 11.4, 12.2, 16.9, 21.3, 24.2, 27.2, 28.8, 31.5, 35.3, 35.6, 38.0, 38.4, 39.5, 42,3, 42.6, 44.6, 46.5, 52.4, 53.6, 55.8, 181.1, 212.2. HRES-MS, *m/z*: 347.2601 (calcd 347.2586 for $C_{22}H_{35}O_3$) [MH^+].

4.2.5. Compound 14. To a solution of crude **13** (0.29 g, 0.84 mmol) in CH_2Cl_2 (1 ml) at rt, DMAP (0.31 g, 2.54 mmol), a solution of **21** (0.49 g, 0.94 mmol) in CH_2Cl_2 (2 ml) and EDC (0.81 g, 4.26 mmol) were sequentially added. The reaction mixture was stirred for 16 h, quenched with water (5 ml) and extracted with ethyl acetate (10 ml). The organic layer was washed with a saturated solution of $NaHCO_3$, with water, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude (0.86 g) was purified by flash chromatography (0–1% methanol in chloroform), to furnish **14** (0.25 g, 35%) as a white amorphous solid.

Compound **14**. R_f=0.81 (10% methanol in $CHCl_3$). $[\alpha]_D$ +8.6 (*c* 2.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.64 (3H, s, C*H*$_3$-18), 0.97 (3H, s, C*H*$_3$-19), 1.03 (9H, s, C(C*H*$_3$)$_3$), 1.17 (3H, d, *J*=7.0 Hz, C*H*$_3$-21), 3.62 (20H, m, O–(C*H*$_2$C*H*$_2$O)$_5$), 3.79 (2H, t, *J*=5.3 Hz, C*H*$_2$OTPS), 4.18 (2H, br t, *J*=4.8 Hz, C*H*$_2$OCOR), 7.40 (6H, m, Ar-*H*), 7.66 (4H, m, Ar-*H*).^{13}C NMR (400 MHz, $CDCl_3$) δ: 11.4, 12.2, 17.0, 18.8, 21.3, 24.1, 26.7 (×3), 27.0, 28.8, 31.5, 35.3, 35.6, 38.0, 38.4, 39.5, 42.4, 42.6, 44.6, 46.4, 52.8, 53.6, 55.7, 62.9, 63.3, 69.1, 70.5 (×8), 72.3, 127.5 (×4), 129.5 (×2), 133.6 (×2), 135.6 (×4), 176.7, 211.8. HRES-MS, *m/z*: 849.5311 (calcd 849.5337 for $C_{50}H_{77}O_9Si$) [MH^+].

4.2.6. Compound 15. To a solution of **14** (0.25 g, 0.29 mmol) in THF (5 ml) at 0 °C, $BH_3\cdot SMe_2$ (300 µl, 0.56 mmol) was added. The reaction mixture was stirred for 1.5 h at 0 °C, quenched with water (5 ml), concentrated in vacuo to remove the excess of THF and extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give **15** (0.16 g, 65%) as a white amorphous solid, which was used without further purification.

Compound **15**. R_f=0.47 (10% methanol in CH_2Cl_2). $[\alpha]_D$ +2.3 (*c* 2.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.65 (3H, s, C*H*$_3$-18), 0.79 (3H, s, C*H*$_3$-19), 1.03 (9H, s, C(C*H*$_3$)$_3$), 1.17 (3H, d, *J*=7.0 Hz, C*H*$_3$-21), 2.42 (1H, m, *H*-20), 3.63 (21H, m, O–(C*H*$_2$C*H*$_2$O)$_5$– and *H*-3), 3.79 (2H, t, *J*=5.3 Hz, C*H*$_2$OTPS), 4.19 (2H, br t, *J*=4.7 Hz, C*H*$_2$OCOR), 7.38 (6H, m, Ar-*H*), 7.67 (4H, m, Ar-*H*). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 12.2 (×2), 17.0, 19.1, 21.1, 24.2, 26.8 (×3), 27.1, 28.6, 31.4, 32.0, 35.4 (×2), 36.9, 38.1, 39.7, 42.5, 42.6, 44.7, 52.8, 54.2, 55.9, 63.0, 63.4, 69.2, 70.5 (×8), 71.2, 72.4, 127.6 (×4), 129.6 (×2), 133.6 (×2), 135.6 (×4), 176.9. HRES-MS, *m/z*: 851.5560 (calcd 851.5493 for $C_{50}H_{79}O_9Si$) [MH^+].

4.2.7. Compound 1. To a solution of **15** (0.16 g, 0.18 mmol) in pyridine (0.5 ml) at 0 °C, a solution of 70% hydrofluoric acid in pyridine (70 µl, 2.44 mmol) was added. The reaction mixture was stirred for 1.5 h and concentrated under a stream of N_2. The residue was purified by flash chromatography (silica gel, 3% methanol in $CHCl_3$) to afford **1** (0.080 g, 73%) as a white amorphous solid.

Compound **1**: R_f=0.4 (10% methanol in CH_2Cl_2). $[\alpha]_D$ +3.3 (*c* 2.7, $CHCl_3$). ^{1}H NMR.(400 MHz, $CDCl_3$) δ: 0.63

(3H, s, CH_3-18), 0.77 (3H, s, CH_3-19), 1.14 (3H, d, J= 6.7 Hz, CH_3-21), 2.40 (1H, m, *H*-20), 3.62 (23H, m, O–(CH_2CH_2O)$_5$–, CH_2OH and *H*-3), 4.17 (2H, t, J= 4.7 Hz, CH_2OCOR). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 12.3 (×2), 17.0, 21.0, 24.2, 27.0, 28.6, 31.4, 31.9, 35.4 (×2), 36.9, 38.0, 39.7, 42.4, 42.6, 44.7, 52.8, 54.2, 56.0, 61.6, 62.9, 69.1, 70.2, 70.5 (×7), 71.1, 72.4, 176.8. HRES-MS, *m/z*: 613.4321 (calcd 613.4316 for $C_{34}H_{61}O_9$) [MH^+].

4.3. Procedures for the synthesis of compounds described in Scheme 2

4.3.1. Compound 16. To a solution of **11** (0.10 g, 0.30 mmol) in CH_2Cl_2 (1 ml) at rt, DMAP (0.11 g, 0.91 mmol), a solution of **23** (0.22 g, 0.45 mmol) in CH_2Cl_2 (2 ml) and EDC (0.29 g, 1.51 mmol) were sequentially added. The mixture was stirred for 16 h, quenched with water (5 ml) and extracted with ethyl acetate (5 ml). The organic layer was washed with a saturated solution of $NaHCO_3$, then water, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude (0.30 g) was purified by flash chromatography (20–90% diethyl ether in petroleum ether) to furnish **16** (0.14 g, 58%) as a white amorphous solid.

Compound **16**. R_f=0.2 (20% diethyl ether in petroleum ether). $[\alpha]_D$ +19.5 (*c* 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.73 (3H, s, CH_3-18), 1.05 (15H, br s, CH_3-19, CH_3-21, (CH_3)$_3$Si–, overlapped), 3.57–3.69 (14H, m, (OCH_2CH_2O)$_3$CH_2, overlapped), 3.79 (2H, J=5.3 Hz, CH_2OTPS), 4.01 (1H, m, H-22), 4.11 (2H, br s, OCOCH_2O), 4.19 (1H, m, H′-22), 5.38 (1H, br s, H-16), 7.34–7.40 (6H, m, Ar-*H*), 7.66–7.68 (4H, m, Ar-*H*). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 11.4, 16.2, 18.6, 19.1, 21.2, 26.8 (×3), 28.8, 29.6, 31.4, 31.5, 34.0, 34.7, 35.8, 38.1, 38.3, 44.7, 46.8, 47.2, 54.4, 56.7, 63.4, 68.6, 68.7, 70.5 (×4), 70.7, 70.9, 72.4, 122.8, 127.6 (×4), 129.5 (×2), 133.6 (×2), 135.6 (×4), 156.5, 170.5, 212.0. HRES-MS, *m/z*: 803.4992 (calcd 803.4918 for $C_{48}H_{71}O_8Si$) [MH^+].

4.3.2. Compound 17. To a solution of **16** (0.134 g, 0.167 mmol) in THF (3 ml) at 0 °C, $BH_3 \cdot SMe_2$ (230 µl, 0.56 mmol) was added. The reaction mixture was stirred for 1 h at 0 °C, the reaction was quenched with water (3 ml), concentrated in vacuo to remove the excess of THF and extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give **17** (0.131 g, 97%) as a white amorphous solid, which was used without further purification.

Compound **17**. R_f=0.2 (20% petroleum ether in diethyl ether). $[\alpha]_D$ +0.2 (*c* 2.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.74 (3H, s, CH_3-18), 0.83 (3H, s, CH_3-19), 1.03–1.04 (12H, br s, (CH_3)$_3$Si– and CH_3-21, overlapped), 2.44 (1H, m, *H*-20), 3.57–3.69 (15H, m, (OCH_2CH_2O)$_3$CH_2 and H-3 overlapped), 3.79 (2H, J=5.3 Hz,, CH_2OTPS), 4.01 (1H, m, H-22), 4.12 (2H, br s, OCOCH_2O), 4.19 (1H, m, H′-22), 5.38 (1H, s, H-16), 7.34–7.40 (6H, m, Ar-*H*), 7.66–7.68 (4H, m, Ar-*H*). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 12.3, 16.3, 18.6, 19.2, 21.1, 26.8 (×3), 28.6, 29.7, 31.2, 31.5, 31.9, 34.1, 34.9, 35.7, 36.8, 38.2, 45.1, 47.3, 55.0, 56.9, 63.4, 68.6, 68.7, 70.6 (×4), 70.7, 70.9, 71.3, 72.4, 122.8, 127.6 (×4), 129.6 (×2), 133.7 (×2), 135.6 (×4), 156.7, 170.5. HRES-MS, *m/z*: 805.5012 (calcd 805.5075 for $C_{48}H_{73}O_8Si$) [MH^+].

4.3.3. Compounds 18 and 2. To a solution of crude **17** (0.135 g, 0.168 mmol) in absolute ethanol (2 ml), Pt/C (5% w/w, 0.016 g) was added. The flask was evacuated (20 Torr) and flushed with hydrogen three times. The reaction mixture was stirred vigorously under hydrogen for 24 h, filtered through a pad of Celite, the Celite was washed with chloroform and the solvent concentrated in vacuo to afford **18** (0.128 g) as a white amorphous solid, which was used in the next step without further purification.

To a solution of crude **18** (0.128 g, 0.159 mmol) in pyridine (0.5 ml) at 0 °C, a solution of 70% hydrofluoric acid in pyridine (60 µl, 2.09 mmol) was added. The reaction mixture was stirred for 1.5 h and concentrated under a stream of N_2. The residue was purified by flash chromatography (silica gel, 3% methanol in $CHCl_3$) to afford **2** (0.056 g, 62% for two steps) as a white amorphous solid.

Compound **2**. R_f=0.1 (diethyl ether). $[\alpha]_D$ +10.4 (*c* 0.7 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.66 (3H, s, CH_3-18), 0.79 (3H, s, CH_3-19), 0.98 (3H, d, J=6.6 Hz, CH_3-21), 3.60 (3H, m, CH_2OH and H-3, overlapped), 3.64–3.74 (14H, m, (OCH_2CH_2O)$_3$CH_2–), 3.83 (1H, m, H-22), 4.12 (2H, s, COCH_2O), 4.13 (1H, m, H′-22). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 12.1, 12.3, 17.1, 21.2, 24.2, 27.6, 28.6, 31.5, 32.0, 35.5 (×2), 35.8, 36.9, 38.1, 39.8, 42.7, 44.8, 52.7, 54.3, 56.1, 61.7, 68.6, 69.8, 70.3, 70.5 (×4), 70.8, 71.3, 72.5, 170.7. HRES-MS, *m/z*: 569.4031 (calcd 569.4053 for $C_{32}H_{57}O_8$) [MH^+].

4.4. Procedures for the synthesis of compounds described in Scheme 3

4.4.1. Compound 21. To a solution of **19** (1.00 g, 3.54 mmol) in CH_2Cl_2 (10 ml) at rt, 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU, 0.82 ml, 5.30 mmol) and *tert*-butyldiphenylsilylchloride (TPS-Cl, 0.92 ml, 3.54 mmol) were sequentially added. The solution was stirred for 3 h, quenched with a solution of HCl (2 M, 6 ml) and extracted with CH_2Cl_2. The organic layer was washed with a saturated solution of $NaHCO_3$ (4 ml), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude was purified by flash chromatography (1–2% methanol in CH_2Cl_2) to furnish **21** (0.69 g, 37%) as a colorless oil.

Compound **21**. R_f=0.6 (4% methanol in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.04 (9H, s, (CH_3)$_3$Si–), 3.56–3.63 (20H, m, –CH_2(OCH_2CH_2O)$_4$CH_2), 3.68 (2H, m, CH_2OH), 3.79 (2H, d, J=5.3 Hz, CH_2OTPS), 7.34–7.40 (6H, m, Ar-*H*), 7.66–7.68 (4H, m, Ar-*H*). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 19.4, 27.0 (×3), 62.0, 63.7, 70.5, 70.9 (×7), 72.7, 72.8, 127.9 (×4), 129.8 (×2), 133.5 (×2), 135.9 (×4). HRES-MS, *m/z*: 521.2890 (calcd 521.2935 for $C_{28}H_{45}O_7Si$) [MH^+].

4.4.2. Compound 22. To a solution of **20** (5.00 g, 20.9 mmol) in CH_2Cl_2 (50 ml) at rt, DBU (4.69 ml, 31.3 mmol) and TPS-Cl (5.30 ml, 20.9 mmol) were sequentially added. The solution was stirred for 3 h, quenched with a solution of HCl (2 M, 30 ml) and extracted with CH_2Cl_2.

The organic layer was washed with a saturated solution of $NaHCO_3$ (20 ml), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude was purified by flash chromatography (1–2% methanol in CH_2Cl_2) to furnish **22** (3.88 g, 39%) as a colorless oil.

Compound **22**. R_f=0.6 (4% methanol in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.04 (3H, s, $(CH_3)_3Si$–), 3.56–3.63 (16H, m, $-CH_2(OCH_2CH_2O)_3CH_2$), 3.68 (2H, m, CH_2OH), 3.79 (2H, d, J=5.3 Hz, CH_2OTPS), 7.34–7.40 (6H, m, Ar-*H*), 7.66–7.68 (4H, m, Ar-*H*). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 19.1, 26.7 (×3), 61.9, 63.6, 70.5, 70.8 (×4), 70.9, 72.6, 72.8, 127.9 (×4), 129.8 (×2), 133.5 (×2), 135.9 (×4). HRES-MS, *m*/*z*: 477.2703 (calcd 477.2672 for $C_{26}H_{41}O_6Si$) [MH^+].

4.4.3. Compound 23. To a solution of **22** (1.40 g, 2.94 mmol) in acetone (30 ml) at rt, Jones reagent (2.2 ml) was added dropwise. The reaction mixture was stirred at rt for 0.5 h, then quenched with water (10 ml), concentrated under reduced pressure to remove the excess of acetone, extracted with ethyl acetate (3×15 ml). The organic layer was finally dried over Na_2SO_4/$NaHCO_3$ and concentrated in vacuo. The crude was purified by flash chromatography (2–3% methanol in CH_2Cl_2) to give **23** (0.63 g, 43%) as a colorless oil.

Compound **23**. R_f=0.4 (6% methanol in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.05 (3H, s, $(CH_3)_3Si$–), 3.56–3.63 (14H, m, $-(OCH_2CH_2O)_3CH_2$), 3.79 (2H, d, J=5.3 Hz, CH_2OTPS), 4.13 (2H, m, CH_2COOH), 7.34–7.40 (6H, m, Ar-*H*), 7.66–7.68 (4H, m, Ar-*H*). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 19.1, 26.9 (×3), 63.7, 70.5, 70.6, 70.9 (×4), 71.3, 72.6, 127.9 (×4), 129.8 (×2), 133.5 (×2), 135.9 (×4), 172.0. HRES-MS, *m*/*z*: 491.2460 (calcd 491.2465 for $C_{26}H_{39}O_7Si$) [MH^+].

4.5. Procedures for the synthesis of compounds described in Scheme 4

4.5.1. Compound 24. To a suspension of **11** (0.243 g, 0.736 mmol) in dry di(ethylene)glycol (4 ml) and absolute ethanol (1 ml) at rt, potassium hydroxide (KOH, 0.177 g, 3.17 mmol) and hydrazine monohydrate ($NH_2NH_2\cdot H_2O$, 0.43 ml, 8.82 mmol) were added. The reaction mixture was stirred for 30 min at 110 °C, the temperature was then raised up to 200 °C, for 3 h. The reaction was quenched with water (4 ml) and the resulting mixture was extracted four times with dichloromethane. The organic layer was dried over Na_2SO_4, filtered and evaporated in vacuo, affording a crude that was purified by flash chromatography (silica gel, 20–30% diethyl ether in petroleum ether) to furnish **24** (0.144 g, 62%) as a white amorphous solid.

Compound **24**. R_f=0.6 (40% petroleum ether in diethyl ether). $[\alpha]_D$ +4.1 (*c* 1.0 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.76 (3H, s, CH_3-18), 0.79 (3H, s, CH_3-19), 1.00 (3H, d, J=6.9 Hz, CH_3-21), 2.35 (1H, m, H-20), 3.54 (2H, m, H-22), 5.39 (1H, s, H-16). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 12.2, 16.4, 18.1, 20.6, 22.1, 26.8, 28.9, 29.0, 31.1, 32.0, 34.2, 34.9, 35.3, 36.5, 38.5, 47.2, 47.3, 55.3, 57.4, 66.5, 122.9, 157.7. HRES-MS, *m*/*z*: 317.2822 (calcd 317.2844 for $C_{22}H_{37}O$) [MH^+].

4.5.2. Compound 25. To a solution of **24** (0.167 g, 0.528 mmol) in absolute ethanol (3 ml), Pt/C (5% w/w, 0.011 g) was added. The flask was evacuated (20 Torr) and flushed with hydrogen three times. The reaction mixture was vigorously stirred under hydrogen overnight, then filtered through a pad of Celite, the Celite washed with chloroform and the solvent concentrated in vacuo to afford **25** (0.141 g, 97%) as a white amorphous solid.

Compound **25**. R_f=0.6 (40% petroleum ether in diethyl ether). $[\alpha]_D$ +13.9 (*c* 0.7 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.67 (3H, s, CH_3-18), 0.77 (3H, s, CH_3-19), 1.03 (3H, d, J=6.8 Hz, CH_3-21), 3.35 (1H, dd, J=10.5, 7.0 Hz, H-22), 3.62 (1H, dd, J=10.5, 3.1 Hz, H′-22). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 12.1, 12.2, 16.7, 20.8, 22.1, 24.3, 26.8, 27.7, 29.0 (×2), 32.1, 35.5, 36.2, 38.6, 38.8, 39.9, 42.7, 47.0, 52.5, 54.7, 56.3, 68.0. HRES-MS, *m*/*z*: 319.2976 (calcd 319.3001 for $C_{22}H_{39}O$) [MH^+].

4.5.3. Compound 26. To a solution of **25** (0.033 g, 0.104 mmol) in CH_2Cl_2 (1 ml) at rt, DMAP (0.039 g, 0.032 mmol), a solution of **23** (0.104 g, 0.19 mmol) in CH_2Cl_2 (1 ml) and EDC (0.102 g, 0.53 mmol) were sequentially added. The reaction mixture was stirred for 16 h, quenched with water (5 ml) and extracted with ethyl acetate (10 ml). The organic layer was washed with a saturated solution of $NaHCO_3$, with water, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude was purified by flash chromatography (silica gel, 50% diethyl ether in petroleum ether) to furnish **26** (0.028 g, 34%) as a white amorphous solid.

Compound **26**. R_f=0.3 (40% petroleum ether in diethyl ether). $[\alpha]_D$ +8.6 (*c* 1.4 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.66 (3H, s, CH_3-18), 0.77 (3H, s, CH_3-19), 0.99 (3H, d, J=6.5 Hz, CH_3-21), 1.04 (9H, s, $(CH_3)_3Si$–), 3.58–3.70 (14H, m, $O(CH_2CH_2)_3OCH_2$–), 3.81 (2H, m, $-CH_2$-OTPS), 3.85 (1H, m, H-22), 4.13 (2H, br s, $OCOCH_2O$) 4.14 (1H, m, H′-22) 7.34–7.40 (6H, m, Ar-*H*), 7.66–7.68 (4H, m, Ar-*H*). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 12.1 (×2), 17.1, 19.2, 20.8, 20.8, 22.2, 24.3, 26.8 (×4), 27.7, 29.0 (×2), 32.1, 35.6, 35.9, 38.7, 39.9, 42.8, 47.0, 52.8, 54.7, 56.3, 63.4, 68.6, 69.9, 70.6 (×5), 70.9, 72.4, 127.6 (×4), 129.6 (×2), 133.6 (×2), 135.6 (×4), 170.1. HRES-MS, *m*/*z*: 791.5302 (calcd 791.5282 for $C_{48}H_{75}O_7Si$) [MH^+].

4.5.4. Compound 3. To a solution of **26** (0.027 g, 0.034 mmol) in pyridine (200 µl) at 0 °C, a solution of 70% hydrofluoridric acid in pyridine (40 µl, 1.39 mmol) was added. The reaction mixture was stirred for 1.5 h and concentrated under a stream of N_2. The residue was purified by flash chromatography (silica gel, 0–5% methanol in CH_2Cl_2) to afford **3** (0.0082 g, 44%) as a white amorphous solid.

Compound **3**. R_f=0.1 (100% diethyl ether). $[\alpha]_D$ +24.7 (*c* 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.66 (3H, s, CH_3-18), 0.76 (3H, s, CH_3-19), 0.98 (3H, d, J=6.5 Hz, CH_3-21), 3.60 (2H, m, OCH_2CH_2OH), 3.66–3.77 (14H, m, $O(CH_2CH_2)_3OCH_2$–, overlapped), 3.84 (1H, m, H-22), 4.15 (2H, m, $OCOCH_2O$) 4.16 (1H, m, H′-22). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 12.4, 12.5, 17.4, 21.1, 22.5, 24.5, 27.1, 27.9, 29.3 (×2), 32.4, 35.8, 36.1, 36.5, 39.0, 40.2,

43.0, 47.3, 53.0, 55.0, 56.6, 62.0, 68.9, 70.2, 70.5, 70.8 (× 4), 71.2, 72.9, 171.0. HRES-MS, *m/z*: 553.4110 (calcd 553.4104 for $C_{32}H_{57}O_7$) [MH^+].

4.6. Procedures for the synthesis of compounds described in Scheme 5

4.6.1. Compound 28. To a solution of **27** (0.088 g, 0.146 mmol) in CH_2Cl_2 (0.5 ml) at rt, DMAP (0.055 g, 0.45 mmol), a solution of **23** (0.080 g, 0.163 mmol) in CH_2Cl_2 (1 ml) and EDC (0.140 g, 0.73 mmol) were sequentially added. The reaction mixture was stirred for 16 h, quenched with water (2 ml) and extracted with ethyl acetate (4 ml). The organic layer was washed with a saturated solution of $NaHCO_3$, with water, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude was purified by flash chromatography (silica gel, 0–1% methanol in $CHCl_3$) to afford **28** (0.049 g, 31%) as a white amorphous solid.

Compound **28**. R_f=0.3 (5% methanol in $CHCl_3$). $[\alpha]_D$ +14.0 (*c* 1.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.74 (3H, s, C*H*$_3$-18), 0.87 (3H, s, C*H*$_3$-19), 1.02 (3H, d, *J*= 6.9 Hz, C*H*$_3$-21), 1.05 (9H, s, (C*H*$_3$)$_3$Si–), 2.48 (1H, m, H-20), 3.08 (1H, m, H-6 or H-7), 3.27 (1H, m, H-7 or H-6), 3.59–3.70 (15H, m, –(OC*H*$_2$C*H*$_2$O)$_3$C*H*$_2$– and H-3, overlapped), 3.81, (2H, m, –C*H*$_2$OTPS), 4.04 (1H, m, H-22), 4.13 (2H, br s, OCOC*H*$_2$O), 4.25 (1H, m, H′-22), 5.41 (1H, s, *H*-16), 7.34–7.40 (6H, m, Ar-*H*), 7.66–7.68 (4H, m, Ar-*H*). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 13.6, 16.1, 18.7, 19.2, 20.9, 26.8 (×3), 26.9 (×3), 31.3 (×2),, 32.2, 33.9, 34.5, 35.9, 37.1, 39.8, 47.6, 48.0, 52.2, 55.8, 63.4, 68.6, 68.7, 70.6 (×4), 70.7 (×2), 70.9, 72.4, 72.5, 74.8, 80.3, 123.5, 127.4 (×4), 127.6 (×4), 129.5 (×2), 129.6 (×2), 133.7 (×2), 134.6, 134.8, 135.6 (×4), 135.8 (×4), 155.4, 170.4; HRES-MS, *m/z*: 1077.6326 (calcd 1077.6307 for $C_{64}H_{93}O_{10}Si_2$) [MH^+].

4.6.2. Compound 4. To a solution of **28** (0.060 g, 0.056 mmol) in pyridine (0.3 ml) at 0 °C, a solution of 70% hydrofluoric acid in pyridine (200 µl, 7.00 mmol) was added. The reaction mixture was stirred for 1.5 h and concentrated under a stream of N_2. The residue was purified by flash chromatography (silica gel, 30–70% ethyl acetate in petroleum ether) to afford **4** (0.017 g, 51%) as a white amorphous solid.

Compound **4**. R_f=0.1 (8% methanol in $CHCl_3$). $[\alpha]_D$ +41.3 (*c* 0.8 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.75 (3H, s, C*H*$_3$-18), 0.87 (3H, s, C*H*$_3$-19), 1.04 (3H, d, *J*=6.8 Hz, C*H*$_3$-21), 2.46 (1H, m, H-20), 3.09 (1H, m, H-6 or H-7), 3.24 (1H, m, H-7 or H-6), 3.54 (1H, m, H-3), 3.58 (2H, m, C*H*$_2$OH), 3.67–3.71 (14H, m, –(OC*H*$_2$C*H*$_2$O)$_3$C*H*$_2$–), 3.99 (1H, dd, *J*=10.5, 7.9 Hz, H-22), 4.12 (2H, s, COC*H*$_2$O), 4.21 (1H, dd, *J*=10.5, 6.4 Hz, H′-22), 5.42 (1H, s, H-16). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 13.6, 16.1, 18.7, 21.0, 30.7, 31.4, 32.3, 33.9, 34.6, 35.9, 37.1, 39.8, 47.7, 48.1, 52.3, 55.9, 61.6, 68.6, 68.7, 70.2, 70.4 (×4), 70.8, 72.1, 72.6, 74.6, 80.1, 123.7, 155.3, 170.5. HRES-MS, *m/z*: 601.3948 (calcd 601.3952 for $C_{32}H_{57}O_{10}$) [MH^+].

4.7. Procedures for the synthesis of compounds described in Scheme 6

4.7.1. Compound 29. To a solution of **12** (0.600 g, 1.80 mmol) in dichloromethane (10 ml) at 0 °C, pyridine (5 ml) and acetic anhydride (0.5 ml) were sequentially added. The reaction mixture was allowed to warm to rt, stirred overnight and quenched with a solution of HCl (2 M, 3 ml). The aqueous layer was extracted three times with dichloromethane, the organic layer was dried over Na_2SO_4, filtered, evaporated in vacuo and purified by flash chromatography (silica gel, 10–15% ethyl acetate in petroleum ether) to furnish **29** (0.338 g, 50%) as a white amorphous solid.

Compound **29**. R_f=0.45 (30% ethyl acetate in petroleum ether). $[\alpha]_D$ +12.3 (*c* 2.5 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.65 (3H, s, C*H*$_3$-18), 0.78 (3H, s, C*H*$_3$-19), 0.97 (3H, d, *J*=6.6 Hz, C*H*$_3$-21), 2.03 (3H, s, C*H*$_3$CO–), 3.55 (1H, m, H-3), 3.75 (1H, dd, *J*=10.6, 7.6 Hz, H-22), 4.05 (1H, dd, *J*=10.6, 3.4 Hz, H′-22). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 12.0, 12.2, 17.0, 20.9, 21.2, 24.2, 27.6, 28.6, 31.4, 32.0, 35.4, 35.5, 35.7, 37.0, 38.1, 39.8, 42.7, 44.8, 52.8, 54.3, 56.1, 69.5, 71.2, 171.3. HRES-MS, *m/z*: 377.3019 (calcd 377.3056 for $C_{24}H_{41}O_3$) [MH^+].

4.7.2. Compound 30. To a solution of **29** (0.116 g, 0.308 mmol) in CH_2Cl_2 (1 ml) at rt, DMAP (0.123 g, 1.00 mmol), a solution of **23** (0.200 g, 0.407 mmol) in CH_2Cl_2 (1 ml) and EDC (0.321 g, 1.67 mmol) were sequentially added. The reaction mixture was stirred for 24 h, quenched with water (2 ml) and extracted with ethyl acetate (4 ml). The organic layer was washed with a saturated solution of $NaHCO_3$, with water, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude was purified by flash chromatography (silica gel, 10–40% ethyl acetate in petroleum ether) to afford **30** (0.214 g, 82%) as a white amorphous solid.

Compound **30**. R_f=0.3 (30% ethyl acetate in petroleum ether). $[\alpha]_D$ +4.4 (*c*=1.1 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.67 (3H, s, C*H*$_3$-18), 0.81 (3H, C*H*$_3$-19), 1.00 (3H, d, *J*=6.7 Hz, C*H*$_3$-21), 1.04 (9H, s, (C*H*$_3$)$_3$Si–), 2.04 (3H, s, C*H*$_3$CO), 3.63–3.74 (14H, m, (OC*H*$_2$C*H*$_2$O)$_3$C*H*$_2$–), 3.76, (1H, m, H-22), 3.80 (2H, m, –C*H*$_2$OTPS), 4.07 (1H, m, H′-22), 4.09 (2H, br s, COC*H*$_2$O), 4.76 (1H, m, H-3), 7.34–7.41 (6H, m, Ar-*H*), 7.66–7.68 (4H, m, Ar-*H*). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 12.0, 12.2, 17.0, 19.1, 20.9, 21.1, 24.2, 26.8 (×3), 27.4, 27.6, 28.5, 31.8, 33.9, 35.4 (×2), 35.7, 36.6, 39.7, 42.7, 44.5, 52.8, 54.1, 56.0, 63.4, 68.8, 69.4, 70.5(×4), 70.7, 70.8, 72.4, 74.2, 127.5 (×4), 129.5 (×2), 133.7 (×2), 135.5(×4), 169.9, 171.2. HRES-MS, *m/z*: 849.5341 (calcd 849.5337 for $C_{50}H_{77}O_9Si$) [MH^+].

4.7.3. Compound 5. To a solution of **30** (0.214 g, 0.252 mmol) in pyridine (0.4 ml) at 0 °C a solution of 70% hydrofluoric acid in pyridine (200 µl, 7.00 mmol) was added. The reaction mixture was stirred for 1.5 h and concentrated under a stream of N_2. The residue was purified by flash chromatography (silica gel, 30–70% ethyl acetate in petroleum ether) to afford **5** (0.126 g, 82%) as a white amorphous solid.

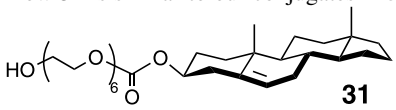
Compound **5**. R_f=0.1 (30% ethyl acetate in petroleum ether). $[\alpha]_D$ +5.2 (*c* 1.1 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.67 (3H, s, C*H*$_3$-18), 0.77 (3H, s, C*H*$_3$-19), 1.00 (3H, d, *J*=6.6 Hz, C*H*$_3$-21), 3.60 (2H, m, –C*H*$_2$OH), 3.63–3.74 (14H, m, (OC*H*$_2$C*H*$_2$O)$_3$C*H*$_2$–), 3.76, (1H, m, H-22), 4.07 (1H, m, H′-22), 4.09 (2H, br s, COC*H*$_2$O), 4.76 (1H, m, H-3). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 12.0, 12.1, 17.0, 20.8, 21.1, 24.1, 27.3, 27.5, 28.4, 31.8, 33.8, 35.3 (×2), 35.6, 36.6, 39.6, 42.6, 44.5, 52.7, 54.0, 56.0, 61.6, 68.7, 69.4, 70.2, 70.4 (×4), 70.7, 72.4, 74.3, 169.9, 171.2. HRES-MS, *m*/*z*: 611.4148 (calcd 611.4159 for $C_{34}H_{59}O_9$) [MH^+].

Acknowledgements

This work has been supported by the MIUR (‘Sostanze naturali ed analoghi sintetici con attività antitumorale’) and by the University of Salerno.

References and notes

1. Moore, K. S.; Wehrli, S.; Roder, H.; Rogers, M.; Forrest, J. N., Jr.,; McCrimmon, D.; Zasloff, M. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 1354–1358.
2. Bolard, J. *Biochim. Biophys. Acta* **1986**, *864*, 257–304.
3. (a) Urry, D. W.; Goodall, M. C.; Glickson, J. D.; Meyers, D. F. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1907–1911. (b) Urry, D. W. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 672–676.
4. Shai, Y. *Biochim. Biophys. Acta* **1999**, *1462*, 55–70.
5. (a) Chen, Y.; Ho, D. M.; Gottlieb, C. R.; Kahne, D. *J. Am. Chem. Soc.* **1992**, *114*, 7319–7320. (b) De Riccardis, F.; Di Filippo, M.; Garrisi, D.; Izzo, I.; Mancin, F.; Pasquato, L.; Scrimin, P.; Tecilla, P. *Chem. Commun.* **2002**, 3066–3067. (c) Di Filippo, M.; Izzo, I.; Savignano, L.; Tecilla, P.; De Riccardis, F. *Tetrahedron* **2003**, *59*, 1711–1717. (d) Avallone, E.; Izzo, I.; Vuolo, G.; Costabile, M.; Garrisi, D.; Pasquato, L.; Scrimin, P.; Tecilla, P.; De Riccardis, F. *Tetrahedron Lett.* **2003**, *44*, 6121–6124. (e) Maulucci, N.; De Riccardis, F.; Botta, C. B.; Casapullo, A.; Cressina, E.; Fregonese, M.; Tecilla, P.; Izzo, I. *Chem. Commun.* **2005**, 1354–1356.
6. Matile, S.; Som, A.; Sordé, N. *Tetrahedron* **2004**, *60*, 6405–6435.
7. A case in which the polar head (the oligo(ethyleneglycol) moiety), matches the length of the lipophilic part (the sterol nucleus).
8. Molecular mechanic calculations (MM3) were performed in order to optimize the geometries of the ‘folded’ and the ‘extended’ conformations of **2**.
9. This is generally believed to be the active conformation of the poly(ethyleneglycol) derivative (see: Stadler, E.; Dedek, P.; Yamashita, K.; Regen, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 8975–8976.). It is worth noting that on note 23 of the paper from Stadler et al., no ionophoric activity was found for 5-androsten-3β-(oxycarbonyl)-hexa(ethylenglycol) (**31**, 2% mol in egg PC vesicles) over a 20 h period. It is easy to recognize how **31** is similar to our conjugates **1**–**5**.



31

10. It must be noted that for ‘complex minimalist systems’ (see Ref. 6), such as those represented by monomeric steroids, this kind of structurally simple self-assembly motif (never proposed before), can be equally probable.
11. As previously described (see Ref. 5b), a solution of NaCl (75.0 mM) plus a membrane-impermeable paramagnetic shift reagent ($DyCl_3$–tripolyphosphate complex, 4.0 mM) were added to a 95:5 egg phosphatidylcholine (PC) and egg phosphatidylglycerol (PG) dispersion (100 nm diameter, large unilamellar vesicles) prepared in aqueous LiCl (100.0 mM). Compounds **1** and **2** were incorporated in the lipid mixture before the formation of vesicles, which were then prepared by extrusion through polycarbonate filters with a 100 nm pore diameter. Because the shift reagent is confined in the external bulk aqueous phase, the Na^+ entering the vesicular compartment appears as a separate (unshifted) resonance and integration of internal Na^+ signal, as a function of time, yields the kinetic profiles.
12. Decoursey, T. E. *Physiol. Rev.* **2003**, *83*, 475–579.
13. Weber, J.; Senior, A. E. *FEBS Lett.* **2003**, *545*, 61–70.
14. (a) Marx, D.; Tuckerman, M. E.; Hutter, J.; Parrinello, M. *Nature* **1999**, *397*, 601–604. (b) Tuckerman, M. E.; Marx, D.; Parrinello, M. *Nature* **2002**, *417*, 925–929.
15. Myers, V. B.; Haydon, D. A. *Biochim. Biophys. Acta* **1972**, *274*, 313–322.
16. The protonophoric activities were measured using an assay based on the response of the intravesicular pH-sensitive pyranine fluorophore. See: Clement, N. R.; Gould, J. M. *Biochemistry* **1981**, *20*, 1534–1538.
17. In our experimental conditions the observed rate constant in the presence of 1.5% of ionophore were: **1**, $k_{obsd}=5.0\times10^{-3}$ s^{-1}; **2**, $k_{obsd}=4.7\times10^{-3}$ s^{-1}, amphotericin B, $k_{obsd}=2.3\times10^{-3}$ s^{-1}.
18. Litvinchuk, S.; Bollot, G.; Nared, J.; Som, A.; Ronan, D.; Shah, M. R.; Perrottet, P.; Sakai, N.; Matile, S. *J. Am. Chem. Soc.* **2004**, *126*, 10067–10075.
19. Theoretical studies showed that the size and polarity of the inner channel influences proton transport acting on the degree of proton solvatation. See: Wu, Y.; Voth, G. *Biophys. J.* **2003**, *85*, 864–875.
20. It is well known that in most of the membrane-active saponins and steroidal oligoglycosides the polar sugars are linked at C-3 and/or C-6. See: D’Auria, M. V.; Minale, L.; Riccio, R. *Chem. Rev.* **1993**, *93*, 1839–1895.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 61 (2005) 10699–10704

NMR structure determination of (11*E*)-trinervita-1(14),2,11-triene, a new diterpene from sexual glands of termites

Miloš Buděšínský,[a] Irena Valterová,[a,*] Etienne Sémon,[b] Eliana Cancello[c] and Christian Bordereau[d]

[a]*Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo 2, 166 10 Prague, Czech Republic*
[b]*INRA, Unité mixte INRA/ENESAD de recherches FLAVIC, 17 rue Sully, 21000 Dijon, France*
[c]*Museu de Zoologia da Universidade de São Paulo, CP 42594, CEP 04299-970 São Paulo, Brazil*
[d]*Université de Bourgogne, UMR CNRS 5548, 6 Bd Gabriel, F-21000 Dijon, France*

Received 10 June 2005; revised 4 August 2005; accepted 19 August 2005

Available online 16 September 2005

Abstract—Female alates of *Nasutitermes ephratae* termites from Guadeloupe and *Nasutitermes* sp. from Brazil produce a diterpene hydrocarbon of the molecular formula $C_{20}H_{30}$ as the main component of their tergal gland secretion. Analysis of NMR, IR, and mass spectra of the diterpene led to a structure of (11*E*)-trinervita-1(14),2,11-triene. Based on a comparison with the published oxygenated trinervitane skeleton from termites we prefer the enantiomer with absolute configurations (4*R*,7*S*,8*R*,15*S*,16*S*). The suggested structure is supported by ab initio quantum chemical calculation of ^{1}H and ^{13}C chemical shifts for the optimized geometry of the molecule.

1. Introduction

Diterpenoid compounds often play a role in chemical communication of termites of the subfamily *Nasutitermitinae*. They function as trail pheromones or sex pheromones,[1–5] but most of the diterpenoid compounds were reported as defensive substances of termite soldiers (Refs. 6,7 and references therein). Over 60 different structures have been isolated from the soldiers' frontal gland secretions since the description of first diterpenoid defence substance, a tricyclic trinervitane derivative, from *Trinervitermes gratiosus*.[8] Defence substances usually possess a bicyclic (secotrinervitane), tricyclic (trinervitane), or tetracyclic (kempane, rippertane or longipane) skeleton. A trinervitane skeleton is the most common; the other skeleta show considerably less structural diversity. These skeleta (Scheme 1) are unique to termites and they are likely to be formed via cyclisation of cembrane precursors.[9] Except for neocembrene, all other skeleta shown in Scheme 1 only occur with oxygen substituents.

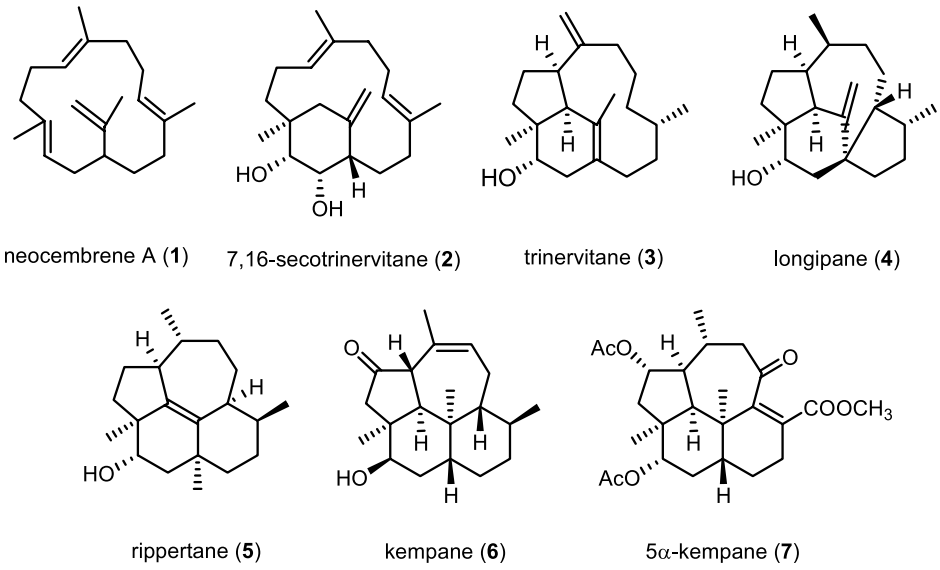
Diterpenic hydrocarbons are relatively rare in termites. Most of them were described in the family *Termitidae*. Cubitene (**8**), bifloratriene (**9**), cubugene (**10**), and two cembrene isomers neocembrene A (**1**) and (3*Z*)-cembrene A (**11**) occur in the genus *Cubitermes* (Scheme 2).[10,11] These compounds have a molecular formula $C_{20}H_{32}$ and their structures differ substantially from our compound. Thus, the diterpene reported here, and isolated from two species of *Nasutitermes* is the first example of a naturally occurring trinervitane hydrocarbon.

2. Results and discussion

Trinervita-1(14),2,11-triene (**12**) was the main component of solid phase microextraction (SPME) samples from the surface of tergal glands of female alates of both *Nasutitermes ephratae* (92%) and *Nasutitermes* sp. (52% of all compounds adsorbed on the SPME fibre; figures taken from GC integration areas). To obtain larger amounts of the compound for the structure elucidation, whole females were extracted and the diterpene **12** was purified from the crude extract. Its EI mass spectrum was consistent with that of a hydrocarbon of the molecular formula $C_{20}H_{30}$ ($M^{+\cdot}$ *m/z* 270). The molecular mass was confirmed by chemical

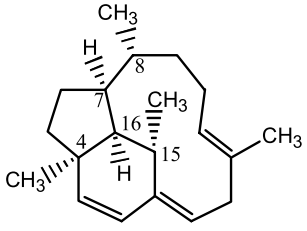
Keywords: Diterpene hydrocarbon; Trinervitane; Termite; Pheromone; Female tergal gland; ^{1}H and ^{13}C NMR.
* Corresponding author. Tel.: +420 220 183 298; fax: +420 220 183 582; e-mail: irena@uochb.cas.cz

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.08.084



Scheme 1. Examples of diterpenes with different skeletons found in termites.

ionization (methane); pseudomolecular ions *m/z* 271 ($MH^{+\cdot}$), *m/z* 229 [$(M+C_2H_5)^{+\cdot}$], and *m/z* 311 [$(M+C_3H_5)^{+\cdot}$] were observed. By analogy of the fragment ions *m/z* 159 ($C_{12}H_{15}$) and *m/z* 119 (C_9H_{11}) with those of the previously described trinervitane alcohol **3**,[12] *m/z* 175 ($C_{12}H_{15}O$) and *m/z* 135 ($C_9H_{11}O$) it was indicated that the isolated diterpene may be a trinervitatriene. The infrared spectrum showed a presence of a trisubstituted double bond (850 cm^{-1}) and excluded an exomethylene group (absence of a band at 890 cm^{-1}).

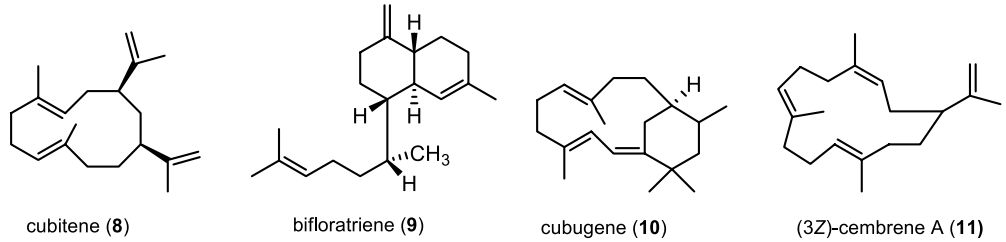


12
(4*R*,7*S*,8*R*,11*E*,15*S*,16*S*)-trinervita-1(14),2,11-triene

The proton 1D-NMR spectrum displayed four methyl signals—two secondary methyl groups (doublets at δ 0.77 and 1.11), one tertiary methyl (singlet at δ 1.22) and one methyl on the double bond (broad singlet at δ 1.62). The low-field region of its ^{1}H NMR spectrum contained multiplets of four olefinic protons (δ 5.89dt, 5.49ddt, 5.36bdd and 5.23dq). The additional four protons gave well separated multiplets at 3.58bq, 2.88bdd, 2.64bdd and 2.17m (their chemical shifts indicated allylic type of protons) while 10 remaining protons appeared in the upfield region δ 0.95–1.95.

The 'attached proton test' ^{13}C NMR spectrum confirmed the presence of 20 carbon atoms in the molecule, consisting of four CH_3, five CH_2, eight CH and three quaternary carbon atoms (see Table 1). Six low-field signals between 145 to 123 ppm clearly indicated the presence of three double bonds that could be (in agreement with ^{1}H NMR data) identified as one disubstituted (–CH=CH–) and two trisubstituted (>C=CH–) double bonds. Three double bonds together with the inferred molecular formula $C_{20}H_{30}$ led to the conclusion that there are three rings in the molecule.

Directly bonded carbon and hydrogen atoms were assigned from the 2D-^{1}H,^{13}C-HSQC spectrum as is indicated in Table 1. The *J*-couplings between protons in the identified CH_3, CH_2 and CH groups were detected in 2D-^{1}H,^{1}H-PFG-COSY and allowed us to determine structural fragments (spin systems) shown in Figure 1A. They had to be connected via three quaternary carbon atoms and such interconnection could be accomplished from the detailed analysis of its 2D-^{1}H,^{13}C-HMBC spectrum using the correlation of carbon and hydrogen via *J*(C,H) over two and three bonds. The topology of the molecule containing the anellated five-, six- and eleven-membered rings was thus established (Fig. 1B).



Scheme 2. Diterpene hydrocarbons previously isolated from termites.[10,11]

Table 1. ^{13}C and ^{1}H NMR data of compound **12**

$\delta(^{13}C)$	Carbon type	Position	$\delta(^{1}H)$	J(H,H)
144.28	>C=	**1**	—	—
135.98	–CH=	**3**	5.23dq	$J(3,2)=10.0$; $J(3,14)\sim J(3,16)\sim J(3,13)\sim 0.9$
135.53	>C=	**12**	—	—
129.04	–CH=	**11**	5.36bdd	$J(11,10\beta)=11.5$; $J(11,10\alpha)=4.5$; $J(11,20)<1$
127.99	–CH=	**2**	5.89dt	$J(2,3)=10.0$; $J(2,14)\sim J(2,13)<1$
123.27	–CH=	**14**	5.49ddm	$J(14,13\beta)=8.8$; $J(14,13\alpha)=6.6$; $J(14,2)\sim J(14,3)\sim J(14,15)\sim J(14,11)\sim 0.8$
50.18	>CH–	**7**	1.71m	$J(7,6\beta)=13.0$; $J(7,6\alpha)=6.0$; $J(7,8)\sim J(7,16)=11.0$
49.69	>CH–	**16**	1.94dm	$J(16,7)=11.0$; $J(16,15)=1.9$; $J(16,3)\sim 0.9$
43.05	>C<	**4**	—	—
42.64	$-CH_2-$	**5**	β: 1.29ddd	$J(5\beta,5\alpha)=13.4$; $J(5\beta,6\alpha)=12.0$; $J(5\beta,6\beta)=5.0$
			α: 1.37m	$J(5\alpha,5\beta)=13.4$; $J(5\alpha,6\beta)=11.3$
39.21	$-CH_2-$	**9**	α: 1.45btd	$J(9\alpha,9\beta)\sim J(9\alpha,8)=13.4$; $J(9\alpha,10\beta)=12.9$; $J(9\alpha,10\alpha)=2.5$; $J(9\alpha,19)=0.8$ (3×)
			β: 1.16m	$J(9\beta,9\alpha)=13.4$; $J(9\beta,10\beta)=2.3$
38.80	$-CH_2-$	**13**	α: 2.88bdd	$J(13\alpha,13\beta)=12.9$; $J(13\alpha,14)=6.6$
			β: 2.64ddm	$J(13\beta,13\alpha)=12.9$; $J(13\beta,14)=8.8$
30.17	$-CH_2-$	**6**	α: 1.39m	$J(6\alpha,6\beta)=13.3$; $J(6\alpha,5\beta)=12.0$; $J(6\alpha,7)=6.0$
			β: 0.95m	$J(6\beta,6\alpha)=13.3$; $J(6\beta,7)=13.0$; $J(6\beta,5\alpha)=11.3$; $J(6\beta,5\beta)=5.0$
29.24	>CH–	**8**	1.26um	$J(8,7)=11.0$; $J(8,9\alpha)=13.4$; $J(8,9\beta)=$[a]; $J(8,19)=6.6$ (3×)
28.81	$-CH_3$	**18**	1.22s	—
27.35	>CH–	**15**	3.58bq	$J(15,17)=7.3$ (3×); $J(15,16)=1.9$
24.95	$-CH_2-$	**10**	β: 2.17m	$J(10\beta,10\alpha)\sim J(10\beta,9\alpha)=12.9$; $J(10\beta,11)=11.5$; $J(10\beta,9\beta)=2.3$
			α: 1.91um	$J(10\alpha,10\beta)=12.9$; $J(10\alpha,9\alpha)=2.5$; $J(10\alpha,9\beta)=$[a]; $J(10\alpha,11)=4.5$;
22.93	$-CH_3$	**17**	1.11d	$J(17,15)=7.3$
19.28	$-CH_3$	**19**	0.77dd	$J(19,8)=6.6$; $J(19,9\alpha)=0.8$
16.31	$-CH_3$	**20**	1.62br s	$J(20,11)<1$

[a] Value of J(H,H) could not be determined.

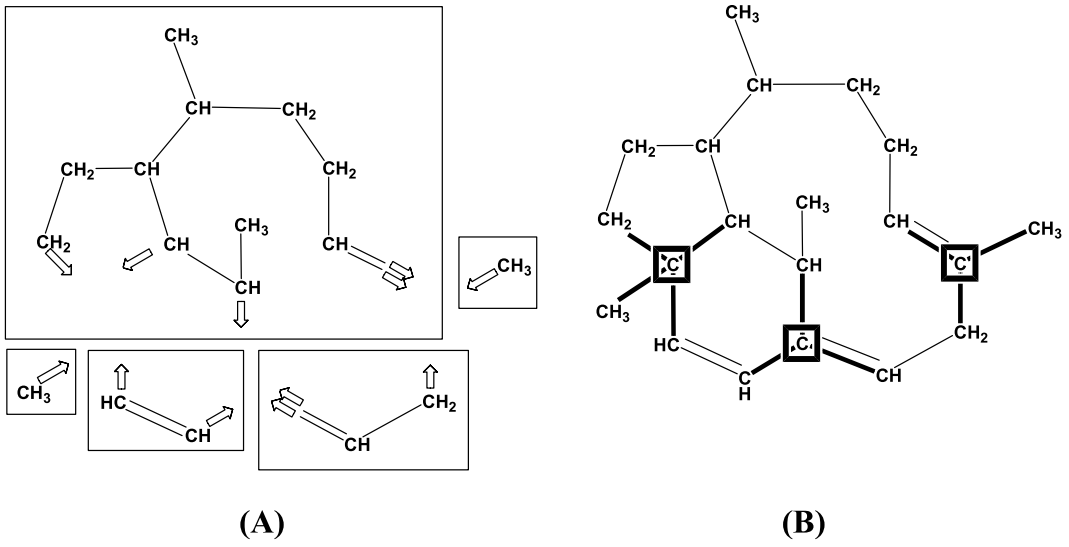


Figure 1. (A) Structural fragments of diterpene derived from 2D-$^{1}H,^{13}C$-HSQC and 2D-$^{1}H,^{1}H$-PFG-COSY spectra (the arrows indicate connections of fragments to three quaternary carbons); (B) The topology of the molecule completed by connecting of fragments (thick bonds) with quaternary carbons (in squares) according to their contacts observed in its 2D-$^{1}H,^{13}C$-HMBC spectrum.

Since the structure contains five chiral centres and three double bonds (Fig. 2A), the subsequent task was to determine a stereochemistry of the molecule. The (*Z*)-configuration at double bonds C(3)=C(2) and C(1)=C(14) is unequivocally given by their positions and ring closures, while the configuration at double bond C(11)=C(12) followed from the 2D-$^{1}H,^{1}H$-ROESY spectrum. The absence of NOE contact between C(12)–CH_3 methyl protons and olefinic proton H-11 on one hand and the observed contact of methyl protons to one of H-10 methylene protons prove the (*E*)-configuration. The five chiral centres lead to 32 theoretically possible stereoisomers.

Fortunately, they all appear at neighbouring carbon atoms. Therefore it was possible from the observed NOE contacts to derive a relative *cis*-configuration of hydrogen H-16 (at 1.94 ppm) to methyl groups C(4)–CH_3 (at 1.22 ppm) and C(15)–CH_3 (at 1.11 ppm) as well as to hydrogen H-7 (at 1.71 ppm). Finally hydrogen H-7 showed NOE contact to methyl group C(8)–CH_3 (at 0.77 ppm), which together with further NOEs (H-6 (at 1.39 ppm) to H7 and the same H-6 to C(8)–CH_3), indicate a mutual cis-orientation of H-7 and C(8)–CH_3. The established relative configurations at neighbouring chiral centres reduce the number of stereoisomers to just two enantiomers. On the basis of a comparison with previously described oxygenated

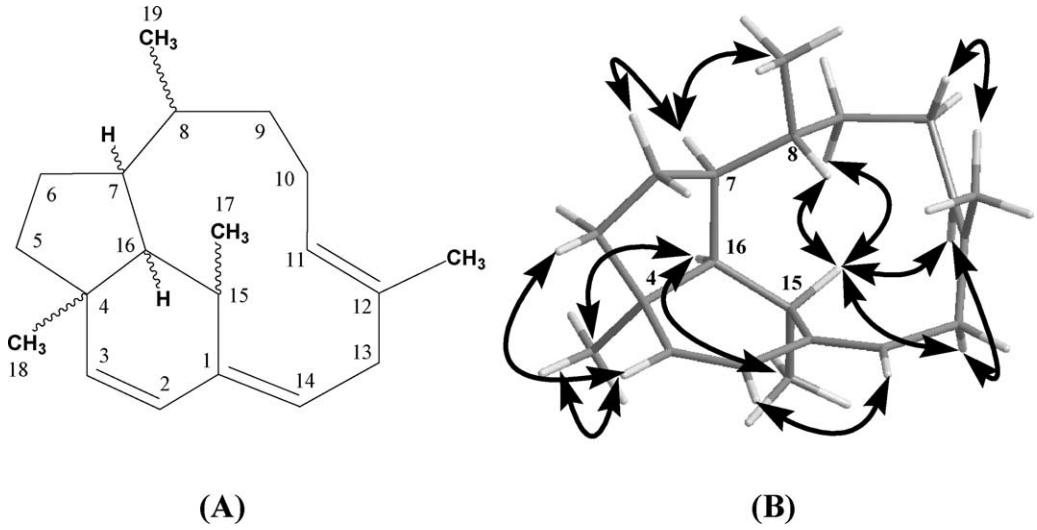


Figure 2. (A) Structure with five chiral centers at positions 4,7,8,15,16; (B) Selected non-trivial observed NOEs leading to the stereostructure **12** (rel-4*R*,7*S*,8*R*,15*S*,16*S*). Conformation of the molecule was obtained by geometry optimization using an ab initio quantum chemical calculation with DFT method (see text below).

trinervitane skeleton from termites we prefer the enantiomer with absolute configuration (4*R*,7*S*,8*R*,15*S*,16*S*). The selected non-trivial observed NOEs are shown in Figure 2B.

The values of *J*(H,H) couplings were extracted from the 1D-^{1}H NMR spectrum, series of selective homonuclear decoupled spectra and 2D-*J*-resolved spectrum (which allowed resolution of the fine structural pattern of some overlapped multiplets). Some of the couplings were still not accessible due to a strong coupling. The obtained *J*(H,H) couplings are summarized in Table 1.

To support the suggested structure **12** we applied an ab initio quantum chemical calculation to find an optimized geometry of the molecule and calculate the NMR parameters. The Gaussian 03 program package[13] and DFT b3lyp method with a basis set at 6-311(d,p) level of theory was used. The optimized geometry is shown in Figure 2B. Calculated proton and carbon chemical shifts showed a very good linear correlation with the experimental data (see Figs. 3 and 4) with rms values 0.998 and 0.999, respectively.

Also the calculated coupling constants *J*(H,H) showed a good linear correlation with the observed values (see Fig. 5) with rms = 0.962.

We were unable to determine the absolute configuration of the isolated compound from the spectral methods used. However, based on the previous determination of the absolute configuration of the trinervitane skeleton[8,14] we assume the structure of (4*R*,7*S*,8*R*,11*E*,15*S*,16*S*)-trinervita-1(14),2,11-triene (**12**). The biological significance of this new compound is probably related to sex behaviour. However, this has yet to be proven by bioassays and will be published elsewhere later.

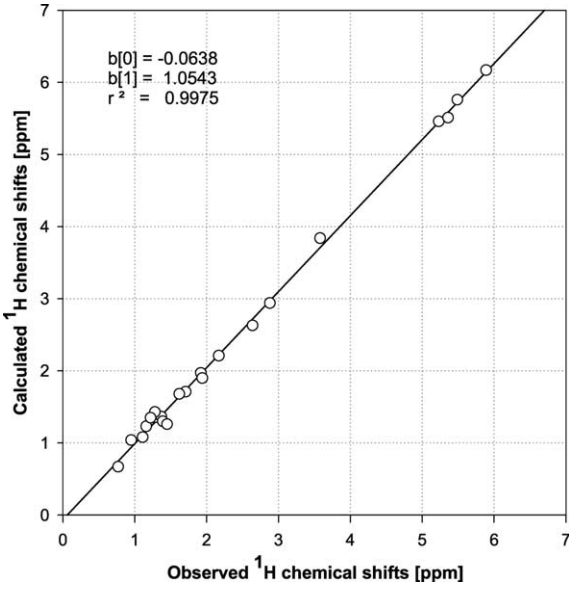


Figure 3. Comparison between the observed and calculated chemical shifts of hydrogen atoms.

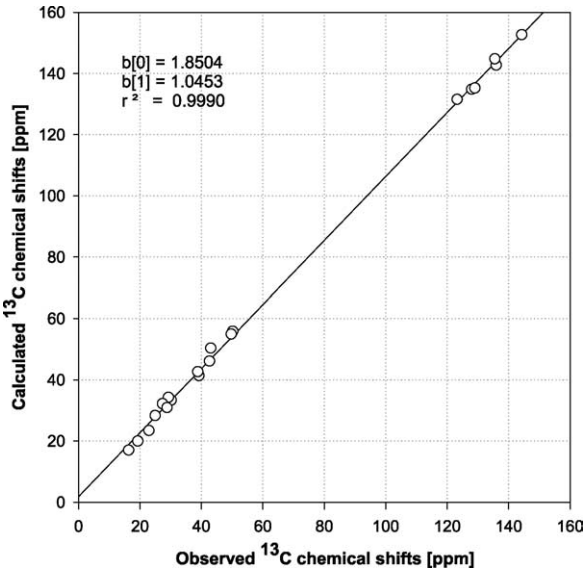


Figure 4. Comparison between the observed and calculated chemical shifts of carbon atoms.

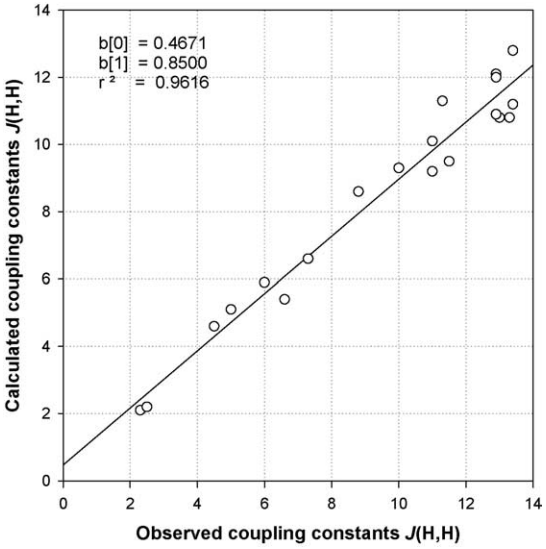


Figure 5. Comparison between the observed and calculated geminal and vicinal coupling constants *J*(H,H).

3. Experimental

3.1. General

The diterpene was obtained from two species of *Nasutitermes* (Isoptera, Termitidae, Nasutitermitinae), *Nasutitermes ephratae* from Guadeloupe (sample number MZUSP 11297) and *Nasutitermes* sp. (sample number MZUSP 11296) from Goiânia, Goiás, Brazil, certainly a different species from *N. ephratae* and probably an undescribed species. For *N. ephratae*, 1,280 female alates were collected in June 2004 in a nest at the presumed time of the dispersal flights. They were dealated and extracted with 100 ml redistilled hexane. After TLC, 0.4 mg of the diterpene was obtained. For *Nasutitermes* sp. 11,600 female alates were collected in October 2004 from two nests just before swarming. They were extracted with 600 ml hexane. Part of this sample gave 0.4 mg of very pure diterpene after several steps of preparative TLC.

For preparative TLC, the extract was concentrated under argon flow to the volume of approximately 200 µl. A TLC plate (10×20 cm, layer thickness 0.25 mm, Adsorbosil-Plus, Applied Science Laboratories) was pre-eluted with a mixture of redistilled chloroform/methanol (1:1) and activated at 100 °C for 20 min. The concentrated extract was chromatographed on the pre-cleaned TLC plate in hexane, detection with an ethanolic solution of Rhodamin 6G (0.05%), UV visualisation at 254 nm. The diterpene fraction (R_f 0.95) was scraped off the plate and the compound was eluted with redistilled pentane (1.5 ml) in a Pasteur pipette.

The purity of the obtained diterpene fraction was checked on analytical TLC (elution with hexane, detection with sulphuric acid) and on a Fisons MD 800 GC–MS instrument equipped with a DB-5 capillary column (30 m×0.25 mm, film thickness 0.25 µm). Temperature programme: 50 °C (1 min), increase to 320 °C at a rate of 10 °C/min; helium constant flow 1 ml/min.

GC-FTIR spectrum was recorded on the spectrometer Bruker Equinox 55 coupled with GC Agilent Technologies 6850. The GC temperature programme was the same as described above.

NMR spectra were measured on Varian UNITY-500 and/or Bruker AVANCE-500 apparatus (^{1}H at 500 MHz, ^{13}C at 125.7 MHz) equipped with cryogenic-probe in $CDCl_3$. Chemical shifts (in ppm, δ-scale) were referenced to tetramethylsilane (in ^{1}H NMR spectra) and/or to signal of solvent ($\delta(CDCl_3)=77.0$ in ^{13}C NMR spectra); coupling constants (*J*) are given in Hz. Series of two-dimensional homonuclear (^{1}H,^{1}H-PFG-COSY, ^{1}H,^{1}H-PFG-ROESY, ^{1}H-*J*-resolved) and heteronuclear (^{1}H,^{13}C-PFG-HSQC, ^{1}H,^{13}C-PFG-HMBC) NMR spectra were measured using standard pulse sequences from Bruker and/or Varian software package.

Mass spectrum (EI, 70 eV) of compound **12**, *m/z* (%): 270 ($M^{+\cdot}$, 73), 255 (53), 241 (9), 227 (9), 213 (16), 199 (28), 185 (22), 173 (13), 171 (38), 159 (100), 157 (50), 145 (43), 132 (35), 119 (69), 105 (39), 91 (48), 79 (32), 67 (25), 55 (54), 41 (53).

IR spectrum of compound **12**, (gas phase), ν_{max} 3016, 2960 (CH_3), 2933 (CH_2), 2868, 1363 (δ CH_3), 850 (trisubstituted C=C), 780 cm^{-1}.

Retention indices of compound **12**: Isolation from *N. ephratae* females—1948 (Equity 5 column), 2291 (DB-wax column); Isolation from *N.* sp. females—1942 (RTX-5-sil column), 2290 (DB-wax column).

Acknowledgements

This work was done in the framework of the research project Z4 055 0506 (Academy of Sciences of the Czech Republic). The authors thank Dr. Soňa Vašíčková for measurement of the GC-FTIR spectrum and Dr. Michael Lacey (CSIRO Entomology, Canberra, Australia) for his valuable comments on this manuscript. C.B. thanks Professors Divino Brandão (Laboratory of Termite Ecology) and Pedro Henrique Ferri (Laboratory of Chemistry) for their hospitality and their help during his stay at the Federal University of Goias, Goiás state, Brazil.

References and notes

1. Moore, B. P. *Nature* **1966**, *211*, 746–747.
2. Birch, A. J.; Brown, W. V.; Corrie, J. E. T.; Moore, B. P. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2653–2658.
3. McDowell, P. G.; Oloo, G. W. *J. Chem. Ecol.* **1984**, *10*, 835–851.
4. Sillam-Dussès, D.; Sémon, E.; Moreau, C.; Valterová, I.; Šobotník, J.; Robert, A.; Bordereau, C. *Chemoecology* **2005**, *15*, 1–6.
5. Pasteels, J. M.; Bordereau, C. In *Pheromone Communication in Social Insects*; Vander Meer, R. K., Breed, M. D., Espelie,

K. E., Winston, M. L., Eds.; CO-Boulder Westview: USA, 1998; pp 193–215.
6. Wahlberg, I.; Eklund, A.-M. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Kirby, G. W., Moore, R. E., Steglich, W., Tamm, Ch., Eds.; Cyclized Cembranoids of Natural Occurrence; Springer: Wien, 1992; Vol. 60, pp 9–17.
7. Raldugin, V. A.; Shevtsov, S. A. *Khim. Prir. Soedin.* **1987**, 327–342.
8. Prestwich, G. D.; Tanis, S. P.; Springer, J. P.; Clardy, J. *J. Am. Chem. Soc.* **1976**, *98*, 6061–6062.
9. Prestwich, G. D.; Jones, R. W.; Collins, M. S. *Insect Biochem.* **1981**, *11*, 331–336.
10. Prestwich, G. D. *J. Chem. Ecol.* **1984**, *10*, 1219–1231.
11. Tempesta, M. S.; Pawlak, J. K.; Iwasita, T.; Naya, Y.; Nakanishi, K.; Prestwich, G. D. *J. Org. Chem.* **1984**, *49*, 2077–2079.
12. Vrkoč, J.; Buděšínský, M.; Sedmera, P. *Collect. Czech. Chem. Commun.* **1978**, *43*, 1125–1133.
13. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P.M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C. and Pople, J.A. *Gaussian 03* (Revision B.02, Gaussian, Inc., Pittsburgh PA, 2003).
14. Valterová, I.; Vašíčková, S.; Buděšínský, M.; Vrkoč, J. *Collect. Czech. Chem. Commun.* **1986**, *51*, 2884–2895.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 10705–10712

meso-Indanyl calix[4]pyrrole receptors

Xue Kui Ji, David StC. Black,* Stephen B. Colbran,* Donald C. Craig, Khaled M. Edbey, Jason B. Harper and Gary D. Willett

School of Chemistry, The University of New South Wales, Sydney 2052, Australia

Received 6 June 2005; revised 8 August 2005; accepted 19 August 2005

Available online 16 September 2005

Abstract—Two new *meso*-indanyl-substituted calix[4]pyrrole receptors, **2** and **3**, have been synthesized. A range of calix[4]pyrrole host-neutral molecule complexes crystallise from solutions of **2** in a variety of solvents and the structures of four have been elucidated by X-ray crystallography. The F^- and Cl^- anion affinities of **2** have been measured in acetonitrile, and are significantly different from the corresponding affinities of the prototypical calix[4]pyrrole, the octamethyl-derivative, **1**. ESI-FTICR-MS has been used to determine the relative F^- and Cl^- anion affinities of receptors **1** and **2** in methanol–acetonitrile solution. Deprotonation of **1** and **2** by fluoride is observed (under the conditions of the MS experiment).

1. Introduction

The recent renaissance in the study of calix[4]pyrroles, such as prototypal **1** discovered well over a century ago,[1] has been spurred on by the discovery that these are remarkably versatile molecules: they exhibit rich and unique redox, metal complexation, and anion and molecular recognition behaviour.[2–21]

Calix[4]pyrroles (i.e., porphyrinogen derivatives without *meso*-hydrogens) adapt their core conformation (Scheme 1) in order to bind strongly with a variety of hydrogen bond acceptor substrates, ranging from neutral aprotic molecules to halide ions and oxyanions. For instance, **1** adopts 1,3-alternate and 1,2-alternate core conformations in complexes with methanol and DMF molecules, respectively, but a cone conformation in binding to halide ions in solution and in the solid-state.[2,7] The relative halide ion affinities of calix[4]-pyrroles in general, and of **1** in particular, is a contentious issue hotly debated in the literature.[2,10–21] A recent (theoretical) study predicts the ordering of the halide ion affinities to depend strongly on anion solvation and, consequently, on the hydrogen-bond donor capacity of the solvent.[20,21] In most of the studies of halide ion affinities,[10–21] acetonitrile has been employed as the solvent and so impurities (e.g., water) may be the source of the observed variation in relative anion affinities.

This report describes the syntheses of two novel indanyl-substituted calix[4]pyrroles, **2** and **3**. The structural modifications in **2** and **3**, compared to **1**, perturb their molecular and ion recognition behaviours, as revealed by X-ray crystal structures of four receptor-neutral guest complexes and parallel surveys of the receptor-halide ion behaviour of **2** and, for comparison, **1**, in acetonitrile solution by NMR spectroscopy and in 1:1 v/v methanol–acetonitrile solution by ESI-FTICR-MS spectroscopy.

2. Results and discussion

2.1. Synthesis

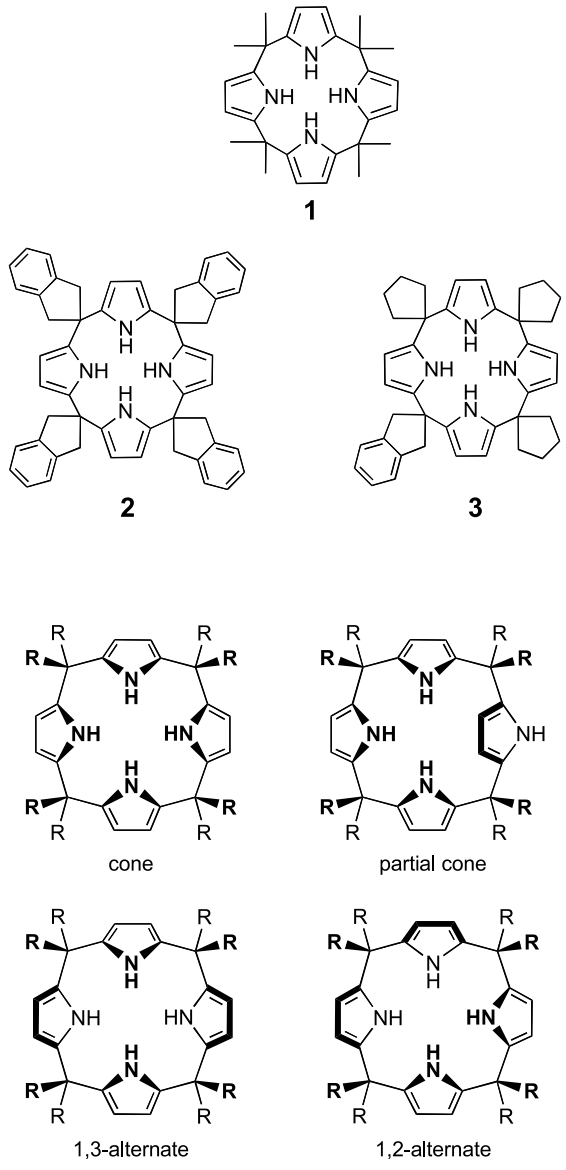
Calix[4]pyrrole **2** was obtained from the one-step condensation of pyrrole and 2-indanone catalysed by methanesulfonic acid in methanol. Analogous reactions of pyrrole with various proportions of 2-indanone and cyclopentanone always afforded the 1:3 indanyl/cyclopentyl-derivative **3** as the only mixed-substituent calix[4]pyrrole product, along with **1** and/or **2**. The optimum yield of **3** (52%) was obtained from 2:1:1 pyrrole, 2-indanone and cyclopentanone. Reduced strain upon closing the macrocyclic ring might play a role in making **3** the favoured mixed-substituent derivative.

2.2. Host–guest complexes of neutral substrates

Microanalytical results were obtained for samples of **2** and **3** from recrystallisations employing a range of solvents, such as DMF, acetone, acetonitrile and ethanol, Table 1. Clearly

Keywords: Anion receptor; Calix-pyrrole.
* Corresponding authors. Tel.: +61 9385 5473; fax: +61 9385 6141; (D.StC.B.); (S.B.C.); e-mail addresses: d.black@unsw.edu.au; s.colbran@unsw.edu.au

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.08.082



Scheme 1. Conformational isomers of calix[4]pyrroles.

2 and **3** tenaciously retain these solvents and solvent-free **2** and **3** could not be obtained. Notably, the solvents in which **2** and **3** are soluble are potential hydrogen bond acceptors implicating the formation of calix[4]pyrrole donor-solvent acceptor complexes. This was confirmed by X-ray crystallography.

Colourless crystals of **2**·3$(CH_3)_2CO$, **2**·2H_2O, **2**·2DMF and **3**·DMF suitable for X-ray structural analyses were obtained from recrystallisations of the calix[4]pyrrole using the indicated solvent, except for **2**·2H_2O, which was obtained from ethanol–ether. Remarkably, the X-ray crystal structures, Figures 1 and 2 and Table 1, reveal that **2** adopts a different core conformation in each of the three complexes crystallised.

The complex **2**·2H_2O, Figure 1a, has a C_2-symmetric structure. The host **2** assumes a 1,3-alternate core conformation and the pairs of opposite pyrrolic NH groups form hydrogen bonds with a guest water molecule, one above and one below the plane of the macrocycle. The four $N_{pyrrole}\cdots O_{H_2O}$ distances, 3.312(4) Å, are symmetry-equivalent and significantly longer than the comparable $N_{pyrrole}\cdots O_{MeOH}$ distances 3.155(4) Å in **1**·2MeOH,[7] even though both complexes display a similar (1,3-alternate) structural motif. The longer hydrogen bond distances for **2** compared to **1** could arise from the more rigid *meso*-indanyl substitution in the former. The $N_{pyrrole}\cdots O_{H_2O}\cdots N_{pyrrole}$ angle, between the two hydrogen bonds to each water molecule, in **2**·2H_2O is 89.91(6)°.

In **2**·2DMF, Figure 1b, the two DMF guest molecules are hydrogen bonded, one above and one below, with the adjacent pyrrole-NH groups of the calix[4]pyrrole donor in the 1,2-alternate conformation. The complex is centrosymmetric and the two unique $N_{pyrrole}\cdots O_{DMF}$ distances to each DMF molecule are 2.952(5) Å and 3.013(5) Å. The associated angle between the two hydrogen bonds to each DMF molecule, $N_{pyrrole}\cdots O_{DMF}\cdots N_{pyrrole}$, is acute at 70.11(6)°. Each of the DMF molecules lies π-stacked ~3.4 Å over the plane of the opposite, parallel pyrrole ring. The analogue **1**·2DMF[7] shows a similar π–π stacking arrangement, which may help to stabilise the 1,2-alternate conformation in these calix[4]pyrrole–DMF complexes.

The crystal structure of **2**·3$(CH_3)_2CO$, Figure 1c, reveals **2** adopts an asymmetrical partial cone core conformation in this complex. Two of the acetone molecules hydrogen bond with **2**, one by three pyrrole-NH to acetone-O hydrogen bonds [$N_{pyrrole}\cdots O_{acetone}$ distances: 3.174(6), 3.030(6) and 3.251(6) Å] and the other, on the opposite side of the macrocycle, by a single pyrrole NH to acetone-O hydrogen bond [$N_{pyrrole}\cdots O^*_{acetone}$ distance: 2.928(6) Å]. The third acetone molecule occupies voids in the crystal lattice. This structure represents a rare example[11] of a calix[4]pyrrole presenting as the partial cone conformer.

The arrangement of the *meso*-indanyl substituents with respect to the macrocyclic plane varies in the three complexes of **2**. In **2**·2H_2O the indanyl groups alternate above and below the macrocyclic plane, Figure 2a, whereas in **2**·2DMF they lie in the macrocyclic plane, Figure 2b, and in **2**·3$(CH_3)_2CO$ they lie to the same side of the macrocyclic plane as does the triply hydrogen bonded acetone guest, Figure 2c. Presumably the differing *meso*-indanyl arrangements facilitate the three different core conformations, thereby maximising the host–guest interaction in each case. Crystal packing might also play a role in the observed molecular conformations, although no significant intermolecular interactions, outside those within each host–guest complex, are noted in the three crystal structures.

For **3**, colourless crystals of **3**·2DMF were obtained from the DMF solution. In the crystal structure, **3** is 1:1 disordered over two sites related by a crystallographic center of symmetry at the center of the calix[4]pyrrole core (for a labelled figure, see the Supplementary Material). As a result, the indanyl and the 'opposite' cyclopentyl substituents are 1:1 disordered, whereas the two other cyclopentyl substituents and the macrocyclic core of **3** are fully ordered. The DMF guest molecules are stabilised by hydrogen bonds with two adjacent pyrroles of the 1,2-alternate core analogously to in **2**·2DMF; the

Table 1. Numerical and refinement data for the X-ray crystal structures of the complexes of **2** and **3** with neutral substrates

	2·2H_2O	**2**·2DMF	**2**·3$(CH_3)_2CO$	**3**·2DMF
Formula	$C_{52}H_{48}N_4O_2$	$C_{58}H_{58}N_6O_2$	$C_{61}H_{62}N_4O_3$	$C_{46}H_{58}N_6O_2$
Model M_W	761.0	871.1	899.2	727.0
Crystal System	Tetragonal	Triclinic	Triclinic	Monoclinic
Space group	$P\bar{4}$	$P\bar{1}$	$P\bar{1}$	$P2_1/n$
a/Å	11.740 (3)	11.371 (6)	11.982 (6)	8.657 (3)
b/Å	11.740 (3)	11.404 (7)	14.239 (8)	15.236 (3)
c/Å	7.517 (2)	11.633 (7)	16.077 (8)	15.526 (5)
α/°	90	115.73 (3)	96.54 (3)	90
β/°	90	105.41 (3)	108.69 (3)	90.01 (1)
γ/°	90	104.78 (3)	102.80 (3)	90
V/Å^3	1036.1 (4)	1185 (1)	2482 (2)	2048 (1)
D_c/g cm^{-3}	1.22	1.22	1.20	1.06
Z	1	1	2	2
Crystal color	Colorless	Colorless	Colorless	Colorless
Crystal type	Block	Plate	Block	Irregular
Crystal size/mm	0.26×0.15×0.14	0.2×0.2×0.03	0.2×0.2×0.1	—
μ/mm^{-1} (Mo Kα)	0.069	0.070	0.069	0.060
$2\theta_{max}$/°	50	46	46	46
No. of Reflns.	1089	3488	7189	3060
R_{merge}	0.039	0.019	0.035	0.022
R_{obs} [$I/\sigma(I)>2$]	835	2249	4162	2006
No. of parameters	132	280	310	140
Final R, R_w [$I/\sigma(I)>2$]	0.059, 0.074	0.054, 0.062	0.056, 0.065	0.077, 0.124
GoF	1.79	1.83	1.76	1.93

$N_{pyrrole}\cdots O_{DMF}$ distances [2.903(5) and 2.983(5) Å] and the associated $N_{pyrrole}\cdots O_{DMF}\cdots N_{pyrrole}$ angle [70.79(7)°] differ only slightly from those in **2**·2DMF. In **3**·2DMF, the amido group of each DMF guest also lies π-stacked ~3.4 Å over the plane of the opposite pyrrole ring (as in the other calix[4]pyrrole–DMF complexes described above).

2.3. Anion binding studies

2.3.1. In CD_3CN by ^1H NMR titrations. The fluoride and chloride ion affinities of **2**, compared to those of **1**, were assayed by ^1H NMR titrations in CD_3CN (Aldrich: highest available quality). A Karl-Fischer titration established the solvent contained 0.04% w/w water, which at the concentrations employed in the titrations corresponds to approximately five molecules of water for every molecule of calix[4]pyrrole receptor. Figure 2 reproduces spectra from a representative titration of **2** with fluoride ion. Importantly, Job plots reveal 1:1 stoichiometries for the receptor–halide complex ions for **2** (as they do for **1**). The $^{19}F\{^1H\}$ NMR spectrum at a 1:1 ratio of **2**:fluoride ion shows only a sharp septet at δ −92.94 (J_{F-H}=180 Hz)—the scalar coupling is

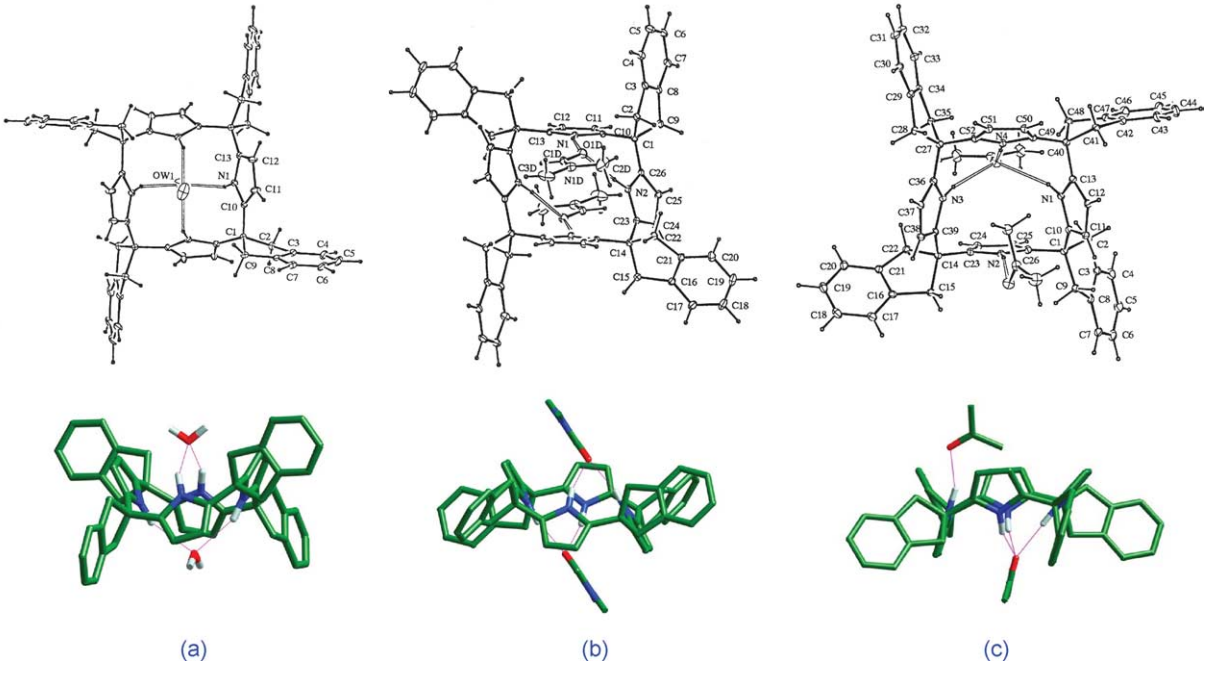


Figure 1. ORTEP plots[22] showing the atom labelling scheme (perspective: 'above' the macrocyclic plane) and stick plots[23] (perspective: 'side-on' to the macrocyclic plane; hydrogen atoms attached to carbon omitted for clarity) of the X-ray crystal structures of (a) **2**·2H_2O, (b) **2**·2DMF and (c) **2**·3$(CH_3)_2CO$ (with one lattice acetone omitted).

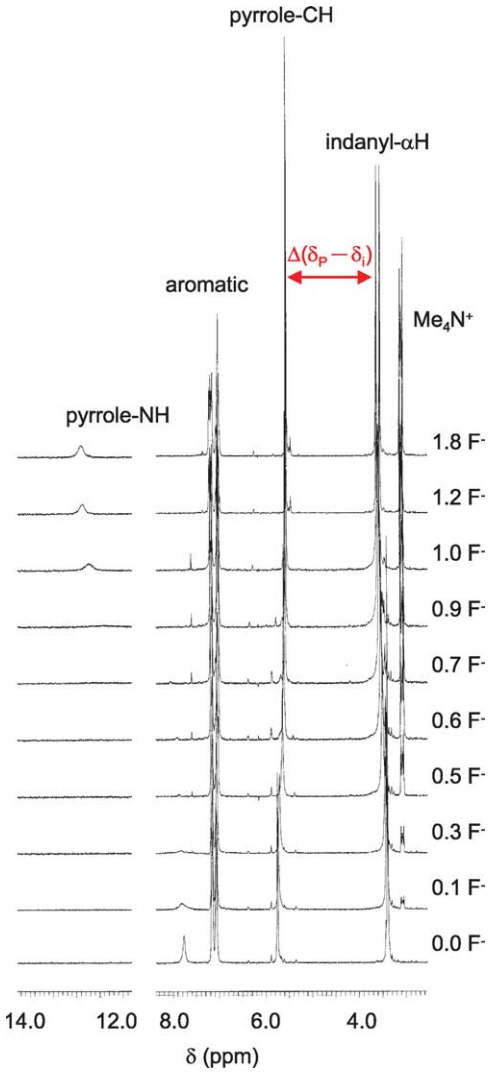


Figure 2. ^{1}H NMR (300 MHz) spectra for titration of receptor **2** (4.0 mM) with tetrabutylammonium fluoride in CD_3CN at 298 K.

to the four pyrrolic N–H protons—fully consistent with 1:1 complex formation. The halide ion affinity constants were obtained from non-linear regression fits to the titration curves. Typical plots are given in the Supplementary materials and the halide ion affinity constants obtained are summarised in Table 2.

As the halide ion affinity constants are large, small errors in the observed chemical shifts of the receptors translate into significant errors in the affinity constants. Particularly notable in the titrations of **1** and **2** is the case where there is little or no halide ion present; here the chemical shift values predicted by the analyses deviate from the experimental data. A possible reason is that water is bound and must be displaced from the receptors, **1** and **2**, by the entering halide ion; thus the chemical shift predicted by the non-linear regression analysis is for the uncomplexed calix[4]pyrrole whereas the observed value is for the water adduct. However, attempts to model such behaviour failed. The effect of this error on the affinity constants can be seen from the outcome of ignoring the first point in the titrations, for example, Table 2. Constants calculated by ignoring the first data point have reduced error (and slightly lower affinity constants). In the ensuing discussion, the affinity constants determined from all data are used.

The calculated halide ion affinities for **1** are very similar to those previously obtained from calorimetric and NMR titrations using as rigorously anhydrous conditions as was experimentally possible,[13–15] and confirm that **1** is able to recognise fluoride ions selectively over chloride ions in acetonitrile at 298 K. A startling finding is that **2** has a five-fold higher chloride ion affinity, but a 10-fold lower fluoride ion affinity, than does **1**, that is, $K_{2(F)} < K_{1(F)}$ and $K_{2(Cl)} > K_{1(Cl)}$. As a result, **2** does not selectively bind fluoride ions over chloride ions. The bulkier, less flexible *meso*-2-indanyl substituents in **2**, compared with the methyl substituents in **1**, could not only increase the rigidity of the calix[4]pyrrole core but cause the pyrroles in the optimum cone conformer to be more splayed out and, consequently, better adapted to hydrogen bonding with the larger chloride anion.

As mentioned in the Introduction, recent theoretical predictions suggest that the relative fluoride ion to chloride ion affinities of calix[4]pyrrole **1** should reverse [i.e., $K_{(Cl)} > K_{(F)}$] in hydrogen bond donor solvents, such as water and methanol, because strong hydrogen bonding to the solvent should lower the available fluoride ion.[21] Unfortunately, the calix[4]pyrroles **1** and **2**, at concentrations sufficient for accurate NMR titrations with halide ion, precipitated as MeOH was added to MeCN solutions. This thwarted investigations of the effect of methanol by NMR titrations.

2.3.2. In MeOH–MeCN by ESI-FTICR mass spectrometry. Electrospray ionisation mass spectrometry provided a way forward. The technique allows pre-existing ionic species in solution to be aspirated and studied as gas-phase ions,[24,25] and has been used to evaluate the relative affinities of various cations in the positive ion mode for organic receptors based on the observation and intensities of complex (metal-receptor adduct) cations in the mass spectra.[24–30] One very recent study also reports receptor-anion adducts studied by ESI-MS.[31] Methanol and acetonitrile are ideal solvents for ESI-MS and only very low (μM) concentrations of the receptor are needed. Thus, negative-ion 'electrospray ionisation Fourier transform ion cyclotron resonance mass spectrometry' (ESI-FTICR-MS) has been employed to investigate the relative fluoride and chloride anion affinities of **1** and **2** in 1:1 v/v methanol–acetonitrile solution. This study is a rare example of gas-phase observation of receptor-anion complexation[29–31] and the first of gas-phase calix[4]pyrrole-anion complexation.

Table 2. Affinity constants (K^a) for calix[4]pyrroles, **1** and **2**, with fluoride and chloride ions in CD_3CN (0.04% w/w H_2O) at 298 K; The affinity constants estimated by ignoring the first data point in the titrations, corresponding to the 'free' receptor, are given in brackets

	Calix[4]pyrrole **1**	Calix[4]pyrrole **2**
F^-	$2.1\ (\pm 1.2)\times 10^6$	$2.5\ (\pm 0.9)\times 10^5$, $[1.3\ (\pm 0.2)\times 10^5]$
Cl^-	$5.2\ (\pm 0.8)\times 10^4$	$2.6\ (\pm 1.4)\times 10^5$, $[1.6\ (\pm 0.7)\times 10^5]$

ESI-FTICR-MS spectra of **1** and **2** with various mole ratios of fluoride and chloride ions were recorded, including at several capillary-skimmer potential differences (ξ/V) in order to further probe adduct ion stabilities (see below). Above ~20 mol equiv of halide ion to **1** or **2**, invariant spectra were obtained. Hence, only data from solutions containing 50 mol equiv of halide ion to receptor are given and discussed.

The receptor-halide ion species formed in solution and observed in the gas-phase were determined from negative-ion ESI-FTICR-MS spectra of **1** and **2** with 50 mol equiv of fluoride ion and chloride ion [acquired at a small ξ setting (< -5 V) to minimise any receptor-ion adduct decomposition], Figures 3 and 4. The major peaks in each spectrum are the 1:1 receptor (R)–halide ion complexes, $[R+F]^-$ and $[R+Cl]^-$. There is no evidence for the calix[4]pyrroles binding with two halide anions. Minor peaks are seen for the methanol-containing species, $[R+Cl+MeOH]^-$ and $[R+MeO]^-$ (presumably the methoxide adduct, akin to the receptor–fluoride complexes) and for the mono-deprotonated receptor, $[R-H]^-$.

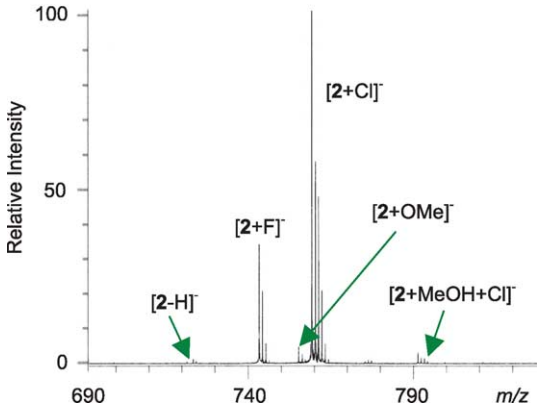


Figure 3. Negative-ion ESI-FTICR mass spectrum of 1:50:50 mole ratio of **2**: F^-:Cl^- in 1:1 v/v MeOH–CH_3CN solution at ξ of -2 V.

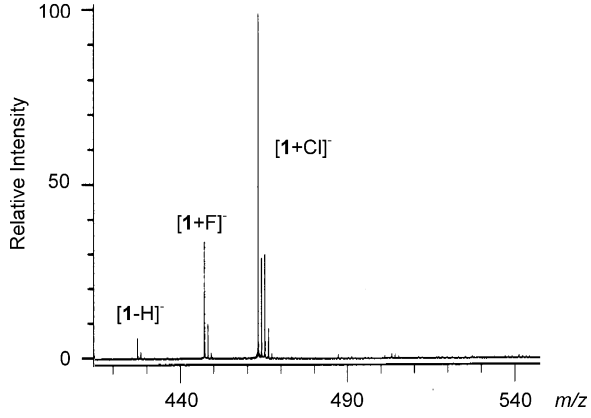


Figure 4. Negative-ion ESI-FTICR mass spectrum of 1:50:50 mole ratio of **1**: F^-:Cl^- in 1:1 v/v MeOH–CH_3CN solution at ξ of -3 V.

To obtain relative fluoride and chloride anion affinities from such ESI-FTICR-MS spectra, the relative abundances of the receptor–halide complex ions must be corrected for the overall efficiency, at which each appears in the spectrum in the absence of competition from the other halide ion. This was done by obtaining the absolute peak intensities for the complex ion in the ESI-FTICR-MS spectrum of each of the receptors **1** and **2**, and 50 mol equiv of the each halide ion (for spectra, see Supplementary Materials). The peak intensities for the $[R+F]^-$ and $[R+Cl]^-$ complex ions in the spectra of the receptor with excess fluoride and chloride ions, Figures 3 and 4, were then corrected for this 'ESI efficiency'.[27,28] After correction for ESI efficiency, **1** shows a 2.4-fold and **2** a 3.1-fold preference for chloride ion over fluoride ion when sprayed from 1:1 v/v methanol–acetonitrile. These results accord with the expectation that fluoride ion should be more strongly solvated, thus less available for complex formation in the presence of the hydrogen-bond donor solvent, methanol [i.e., in each case, $K_{(Cl)} > K_{(F)}$ as anticipated]. The larger selectivity of **2** for chloride over fluoride ion, compared to **1**, concurs with the relative affinities found in acetonitrile alone (see above), and further highlights the effect of *meso*-substitution on the halide ion selectivities.

The decomposition of the $[\mathbf{2}+\text{halide}]^-$complex ions was further investigated by employing larger ξ settings to provide higher collisional energies prior to detection of the product ions and indicate some interesting fragmentation pathways. Notably, peaks for the mono-deprotonated receptors, $[\mathbf{2}-H]^-$only appear when fluoride ion is present in the aspirated solution and grow markedly in intensity with collisional energy (higher ξ magnitudes) at the expense of the $[\mathbf{2}+F]^-$complex ions. Typical absolute intensity data is graphically presented and compared in Figure 5. Clearly the basic fluoride ion deprotonates receptor **2**, especially when higher collisional energies are available during product ion formation. Although this is the first evidence for deprotonation of calix[4]pyrroles by fluoride ion, Gale has previously demonstrated this phenomenon for 2,5-diamidopyrrole anion receptors.[32] What is most intriguing about the present results is the inhibitory effect of chloride ion on the formation of $[\mathbf{2}-H]^-$when both fluoride and chloride ion are present in the originally aspirated solution—in this case, the relative amount of $[\mathbf{2}+F]^-$:$[\mathbf{2}-H]^-$ at a particular ξ setting distinctly increases, Figure 5. For instance, at $\xi = -50$ V, the ratio

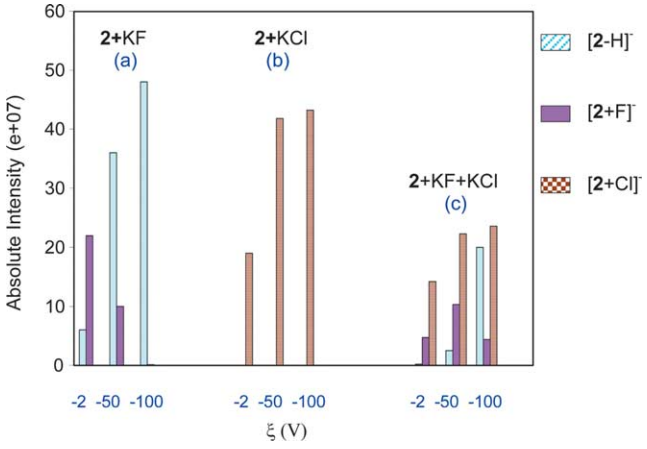


Figure 5. The intensities of $[\mathbf{2}-H]^-$(lightly stripped bars), $[\mathbf{2}+F]^-$(filled bars) and $[\mathbf{2}+Cl]^-$(cross-hashed bars) versus ξ from ESI-FTICR-MS experiments of **2** with F^- (a), **2** with Cl^- (b) and **2** with F^- and Cl^- (c) at 1:50 mole ratio of **2**: anion in 1:1 v/v MeOH–CH_3CN.

$[\mathbf{2}-\mathrm{H}]^-/[\mathbf{2}+\mathrm{F}]^- \gg 1$ when chloride ion is absent (Fig. 5a), but $\ll 1$ with chloride ion present (Fig. 5c). This inhibitory effect of chloride ion could reflect the higher affinity of receptor **2** for chloride ion and the fact that chloride ion for fluoride ion exchange can favourably compete with deprotonation of $[\mathbf{2}+\mathrm{F}]^-$, which is equivalent to the loss of HF, especially at higher collisional energies.

3. Conclusion

Two new *meso*-indanyl-substituted calix[4]pyrroles, **2** and **3**, have been prepared and shown to form 1:1 adducts with water, MeOH, acetone, DMSO and DMF. Crystal structures suggest that **2** can adapt its core conformation in order to maximise the binding with these hydrogen bond acceptor molecules. The relative fluoride and chloride ion affinities of **2** have been ascertained in acetonitrile by quantitive NMR titration methods and in methanol–acetonitrile by qualitative ESI-FTICR-MS methods. The results have been compared with those for the prototypical *meso*-octamethyl-derivative, **1**, measured under identical experimental conditions. In all cases, 1:1 receptor–halide complex ions form. With methanol present, fluoride ion is highly solvated and, consequently, the 'apparent' affinity of the receptors for this ion is lowered, which accords with theoretical predictions. Finally, this study clearly reveals the subtle but pivotal effect that *meso*-substitution exerts on calix-pyrrole receptor-(halide) anion adduct formation: **2** shows a higher affinity for chloride ion than does **1**.

4. Experimental

4.1. Physical methods

^{1}H and ^{13}C NMR spectra were recorded using a Bruker AC-300 (300 MHz). Routine mass spectroscopic data were obtained on a VG Quattro mass spectrometer. Melting points were measured in unsealed capillary tubes and are uncorrected. Microanalyses for C, H and N were determined at the Research School of Chemistry, Australian National University.

4.2. ^{1}H NMR titrations

The ^{1}H NMR titration experiments were carried out at room temperature (25 °C) in acetonitrile-d_3 (99.9 atom % D). All procedures were performed under a dry nitrogen atmosphere. The water content of the 'as-purchased' acetonitrile-d_3 was determined to be 0.04% w/w H_2O by Karl-Fischer titration using a Coulometric GR Scientific 2000 Titrator. A solution of calix[4]pyrrole receptor ($\sim$4 mM) in CD_3CN (1.0 mL) was first prepared in an NMR tube. Aliquots of a tetrabutylammonium fluoride or chloride salt solution (20 mM) in CD_3CN were added to produce solutions containing 0, 0.1, 0.2, 0.3… 1, 1.5, 2, 3, 5 equiv of the halide and the ^{1}H NMR spectrum obtained. Halide affinity constants were obtained from non-linear regression fits of the changes in chemical shift differences (for **2**, $\Delta(\delta_p-\delta_i)$ between the pyrrole CH and indanyl CH_2 peaks; for **1**, $\Delta(\delta_p-\delta_m)$ between the pyrrole CH and methyl peaks) against the concentration of added halide ion ($[X^-_{added}]$) to Eqs. 1 and 2.

$$K = \frac{[\text{complex}]}{[\text{calix[4]pyrrole}][X^-]} \quad (1)$$

$$\Delta\delta = \frac{[\text{calix[4]pyrrole}]\Delta\delta_{free} + [\text{complex}]\Delta\delta_{complex}}{[\text{calix[4]pyrrole}] + [\text{complex}]} \quad (2)$$

where $\Delta\delta=\Delta(\delta_p-\delta_i)$ or $\Delta(\delta_p-\delta_m)$ at $[X^-_{added}]$; $\Delta\delta_{free}=\Delta(\delta_p-\delta_i)$ or $\Delta(\delta_p-\delta_m)$ when $[X^-_{added}]=0$; $\Delta\delta_{complex}=\Delta(\delta_p-\delta_i)$ or $\Delta(\delta_p-\delta_m)$ when $[X^-_{added}] \gg [\mathbf{2}]$ or $[\mathbf{1}]$.

4.3. ESI-FTICR mass spectrometry

The negative-ion ESI-FTICR-MS experiments used a Bruker BioApex-II 7 Tesla FT/ICR mass spectrometer equipped with off-axis Analytica ESI source. The relative 'ESI efficiency' for each receptor-halide ion complex was estimated from comparison of peak intensities in the spectra of each receptor (5×10^{-6} M) combined with each halide ion (KF or KCl, 2.5×10^{-4} M) in 1:1 v/v methanol–acetonitrile. To establish the relative halide affinities of each receptor, spectra were obtained from solutions of each receptor (5×10^{-6} M) and both KF and KCl (2.5×10^{-4} M for each anion) in 1:1 v/v methanol–acetonitrile. The sample solutions were injected into the electrospray source by a Cole-Parmer 74900 Series syringe pump at a flow rate of 115 μL/h. All experimental parameters were kept constant for each series of experiments, such as drying gas (nitrogen gas with a flow rate of 2 L min^{-1} and heated to 280 °C), skimmer voltage (−5 V for negative ions), hexapole delay (ions pass through the skimmer and trapped in a hexapole ion trap of 2 s to accumulate prior to injection into the ICR cell), and ultra high vacuum in the ICR cell ($\sim10^{-9}$ Torr). To investigate the decomposition of the F^- adducts at higher collisional energies, the capillary voltages were adjusted from −7 to −150 V (thus increasing the capillary-skimmer potential difference (ξ)). All reported spectra are an average of 120 independent scans and are based on at least three parallel experiments. Data acquisition and processing, together with fittings of the experimental and theoretical isotope patterns and mass values for all product ions, were performed using Bruker XMass 6.02 software.[33] In all cases, there was excellent agreement (to within 5 ppm) between the experimental and calculated isotopic mass distributions.

4.4. Syntheses

4.4.1. Tetra(2-indanyl)calix[4]pyrrole 2. Methanesulfonic acid (1 g, 10 mmol) in methanol (2 mL) was slowly added to a solution of 2-indanone (2.64 g, 20 mmol) and pyrrole (1.34 g 20 mmol) in methanol (30 mL). The resultant blue mixture was stirred for 3 h. A green precipitate formed, which was collected by filtration, washed with cold methanol until colourless, and dried to afford a white microcrystalline solid, **2** (2.7 g, 75%); mp 245–246 °C (dec); [Found MS *m/z*: 724.4; $C_{52}H_{44}N_4$ requires 724.4; Found: C, 82.91; H, 6.47; N, 6.97. $C_{52}H_{44}N_4\cdot1.5H_2O$ requires C, 83.05; H, 6.30; N, 7.45%]; ^{1}H NMR spectrum (acetone-d_6): δ 3.40 (s, 16H, indanyl-αH), 5.71 (d, $J=2$ Hz,

8H, pyrrole-*H*), 7.02 (t, $J=2$ Hz, 8H, indanyl-Ar*H*), 7.10 (d, $J=3$ Hz, 8H, indanyl-Ar*H*), 8.40 (s, 4H, N*H*); $^{13}C\{^1H\}$ NMR spectrum (acetone-d_6): δ 45.3, 47.5, 103.4, 123.9, 126.0, 136.9, 142.1.

4.4.2. *meso*-(2-Indanyl)tri(cyclopentanyl)calix[4]-pyrrole 3. Over 0.5 h, a solution of methanesulfonic acid (0.3 g, 3 mmol) in methanol (10 mL) was added dropwise to a mixture of 2-indanone (0.66 g, 5 mmol), cyclopentanone (0.42 g, 5 mmol) and pyrrole (0.7 g 10 mmol) in methanol (50 mL). The resultant mixture was stirred for 16 h during, which time a pale green precipitate formed that was collected by filtration and washed with cold methanol until colourless. The residue was recrystallised from DMF to give colourless crystals of **3** (0.5 g, 52%); mp 140–142 °C; [Found MS *m/z*: 580.4; $C_{40}H_{44}N_4$ requires 580.4; Found: C, 75.18; H, 8.46; N, 11.32. $C_{40}H_{44}N_4\cdot 2\text{-DMF}\cdot 0.5H_2O$ requires C, 75.06; H, 8.08; N, 11.42%]; ^1H NMR spectrum (acetone-d_6): δ 1.61 (m, 12H, cyclopentanyl-*H*), 2.02 (m, 12H, cyclopentanyl-*H*), 3.40 (d, $J=4$ Hz, 4H, indanyl-αH), 5.74 (m, 8H, pyrrole-*H*), 7.06 (t, $J=2$ Hz, 2H, indanyl-Ar*H*), 7.14 (d, $J=3$ Hz, 2H, indanyl-Ar*H*), 8.10 (s, br, 2H, N*H*); 8.24 (s, 2H, N*H*); $^{13}C\{^1H\}$ NMR spectrum ($CDCl_3$): δ 23.7, 38.8, 38.9, 39.0, 45.9, 46.0, 46.8, 47.3, 102.9, 103.0, 103.1, 103.2, 103.7, 124.2, 126.3, 136.5, 136.6, 137.0, 137.1, 137.2, 137.5, 137.6, 141.7, 141.8.

4.4.3. Compound 2·2DMF. Colourless crystals, suitable for X-ray analysis, formed directly from a solution of **2** (72 mg, 0.1 mmol) in DMF (3 mL). They were collected and dried in the air (44 mg, 50%); [Found C, 79.75; H, 7.05; N, 9.81. $C_{52}H_{44}N_4\cdot 2HCON(CH_3)_2$ requires C, 79.97; H, 6.71; N, 9.65%].

4.4.4. Compound $2\cdot 3(CH_3)_2CO$. Colourless crystals, suitable for X-ray diffraction, were grown from **2** in acetone (50 mg, 56%); [Found C, 81.51; H, 7.08; N, 6.34. $C_{52}H_{44}N_4\cdot 3(CH_3)_2CO$ requires C, 81.48; H, 6.95; N, 6.23%].

4.4.5. Compound $2\cdot CH_3CN\cdot 2.5H_2O$. The title compound formed upon slow cooling of a warm solution **2** (72 mg, 0.1 mmol) in acetonitrile (10 mL) (30 mg, 37%); [Found C, 80.25; H, 6.60; N, 8.42. $C_{52}H_{44}N_4\cdot CH_3CN\cdot 2.5H_2O$ requires C, 79.97; H, 6.46; N, 8.64%].

4.4.6. Compound $2\cdot 2H_2O$. Colourless crystals, suitable for X-ray diffraction, crystallised upon diffusion of ether vapour into a solution of **2** (72 mg, 0.1 mmol) in ethanol (10 mL) (25 mg, 33%). Upon removal from the mother liquor and drying the following analytical data was obtained: Found C, 82.01; H, 6.47; N, 6.97. $C_{52}H_{44}N_4\cdot 2H_2O$ requires C, 82.07; H, 6.36; N, 7.36%.

5. X-ray crystallography

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 265161 - 265164. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: 144 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.08.082

References and notes

1. Baeyer, A. *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 2184–2185.
2. Gale, P. A.; Sessler, J. L.; Král, V.; Lynch, V. *J. Am. Chem. Soc.* **1996**, *118*, 5140–5141.
3. (a) Gale, P. A.; Sessler, J. L.; Král, V. *J. Chem. Soc., Chem. Commun.* **1998**, 1–8. (b) Sessler, J. L.; Gale, P. A. In Kadish, K. M., Smith, L. M., Guilard, R., Eds.; Calixpyrroles: Novel Anion and Neutral Substrate Receptors in the Porphyrin Handbook; Academi: San Diego, CA, 1999; Vol. 6, pp 257–278. (c) Sessler, J. L.; Anzenbacher, P., Jr.; Jursíková, K.; Miyaji, H.; Genge, J. W.; Tvermoes, N. A.; Allen, W. E.; Schriver, J.; Gale, P. A.; Král, V. *Pure Appl. Chem.* **1998**, *70*, 2401–2408.
4. Floriani, C. *Chem. Commun.* **1996**, 1257–1263.
5. Guillemot, G.; Solari, E.; Rizzoli, C.; Floriani, C. *Chem. Eur. J.* **2002**, 2072–2080.
6. Bachmann, J.; Nocera, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 2829–2837.
7. Allen, W. E.; Gale, P. A.; Brown, C. T.; Lynch, V. M.; Sessler, J. L. *J. Am. Chem. Soc.* **1996**, *118*, 12471–12472.
8. Gale, P. A.; Twyman, L. J.; Handlin, C. I.; Sessler, J. L. *Chem. Commun.* **1999**, 1851–1852.
9. Anzenbacher, P.; Try, A. C.; Miyaji, H.; Jursíková, K.; Marquez, M.; Sessler, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 10268–10272.
10. Gale, P. A.; Sessler, J. L.; Genge, J. *Chem. Eur. J.* **1998**, *4*, 1095–1099.
11. Anzenbacher, P., Jr.; Jursíková, K.; Lynch, V. M.; Gale, P. A.; Sessler, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 11020–11021.
12. Sessler, J. L.; Anzenbacher, P., Jr.; Miyaji, H.; Jursíková, K.; Bleasdale, E. R.; Gale, P. A. *Ind. Eng. Chem. Res.* **2000**, *39*, 3471–3478.
13. Turner, B.; Shterenberg, A.; Kapon, M.; Surwinska, K.; Eichen, Y. *Chem. Commun.* **2001**, 13–14.
14. Schmidtchen, F. P. *Org. Letts.* **2002**, *4*, 431–434.
15. Namor, A. F. D.; Shehab, M. *J. Phys. Chem. B* **2003**, *107*, 6462–6468.
16. Camiolo, S.; Gale, P. A. *Chem. Commun.* **2000**, 1129–1130.
17. Lee, C.-H.; Na, H.-K.; Yoon, D.-W.; Won, D.-H.; Cho, W. S.; Lynch, V. M.; Shevchuk, S. V.; Sessler, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 7301–7306.
18. Hoorn, W. P.; Jorgensen, W. L. J. *Org. Chem.* **1999**, *64*, 7439.
19. (a) Miyaji, H.; Sato, W.; Sessler, J. L. *Angew. Chem., Int. Ed.* **2000**, *39*, 1777–1780. (b) Wu, Y. D.; Wang, D. F.; Sessler, J. L. *J. Org. Chem.* **2001**, *66*, 3739–3746.
20. Woods, C. J.; Camiolo, S.; Light, M. E.; Coles, S. J.;

Hursthouse, M. B.; King, M. A.; Gale, P. A.; Essex, J. W. *J. Am. Chem. Soc.* **2002**, *124*, 8644–8652.
21. Blas, J. R.; Márquez, M.; Sessler, J. L.; Luque, F. J.; Orozco, M. *J. Am. Chem. Soc.* **2002**, *124*, 12796–12805.
22. Johnson, C. K. *ORTEP-II*; Oak Ridge National Laboratory: Tennessee, USA, 1976.
23. Palmer, D.C. *CrystalMaker*, version 6.3; CrystalMaker Software Ltd, Oxford, UK, 2004.
24. Fisher, K. J.; Dance, I. G.; Willett, G. D.; Zhang, R.; Alyea, E. C. *Eur. J. Mass Spectrom.* **2000**, *6*, 23–30.
25. (a) Fisher, K. J.; Henderson, W.; Dance, I. G.; Willett, G. D. *J. Chem. Soc., Dalton Trans.* **1996**, 4109–4113. (b) Lover, T.; Henderson, W.; Bowmaker, G. A.; Seakins, J. M.; Cooney, R. P. *Inorg. Chem.* **1997**, *36*, 3711–3723. (c) Chin, C. C. H.; Yeo, J. S. L.; Loh, Z. H.; Vittal, J. J.; Henderson, W.; Hor, T. S. A. *J. Chem. Soc., Dalton Trans.* **1998**, 3777–3784. (d) Neo, K. E.; Neo, Y. C.; Chien, S. W.; Tan, G. K.; Wilkins, A. L.; Henderson, W.; Hor, T. S. A. *J. Chem. Soc., Dalton Trans.* **2004**, 2281–2287.
26. (a) Nicoll, J. B.; Dearden, D. V. *Int. J. Mass Spectrom.* **2001**, *204*, 171–183. (b) Cole, R. B.; Harrata, A. K. *J. Am. Soc. Mass. Spectrom.* **1993**, *4*, 546–556. (c) Wampler, F. M.; Blades, A. T.; Kebarle, P. *J. Am. Soc. Mass Spectrom.* **1993**, *4*, 289–295. (d) Straub, R. F.; Voyksner, R. D. *J. Am. Soc. Mass Spectrom.* **1993**, *4*, 578–587.
27. Williams, S. M.; Brodbelt, J. S.; Marchand, A. P.; Cal, D.; Majerski, K. M. *Anal. Chem.* **2002**, *74*, 4423–4433.
28. (a) Williams, S.; Blair, S. M.; Brodbelt, J. S.; Huang, X. W.; Bartsch, R. A. *Int. J. Mass Spectrom.* **2001**, *212*, 389–401. (b) Blair, S. M.; Kempen, E. C.; Brodbelt, J. S. *J. Am. Soc. Mass. Spectrom.* **1998**, *9*, 1049–1059. (c) Blair, S. M.; Brodbelt, J. S.; Reddy, G. M.; Marchand, A. P. *J. Mass. Spectrom.* **1998**, *33*, 721–728. (d) Goolsby, B. J.; Brodbelt, J. S.; Adou, E.; Blanda, M. *Int. J. Mass Spectrom.* **1999**, *193*, 197–204. (e) Kempen, E. C.; Brodbelt, J.; Bartsch, R. A.; Jang, Y.; Kim, J. S. *Anal. Chem.* **1999**, *71*, 5493–5500.
29. Zhu, J. H.; Cole, R. B. *J. Am. Soc. Mass Spectrom.* **2000**, *11*, 932–941.
30. Liou, C. C.; Brodbelt, J. S. *J. Am. Soc. Mass Spectrom.* **1993**, *4*, 242–248.
31. Oshovsky, G. V.; Verboom, W.; Fokkens, R. H.; Reinhoudt, D. N. *Chem. Eur. J.* **2004**, *10*, 2739–2748.
32. (a) Camiolo, S.; Gale, P. A.; Hursthouse, M. B.; Light, M. E.; Shi, A. J. *Chem. Commun.* **2002**, 758–759. (b) Gale, P. A.; Navakhun, K.; Camiolo, S.; Light, M. E.; Hursthouse, M. E. *J. Am. Chem. Soc.* **2002**, *124*, 11228–11229. (c) Camiolo, S.; Gale, P. A.; Hursthouse, M. B.; Light, M. E. *Org. Biomol. Chem.* **2003**, *1*, 741–744.
33. Bruker Xmass version 6.0.2. 1993-2001. Usage'C:\Bruker\Xmass\prog\CurInst\bin-\Xmass.exe'.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 10713–10718

Ring-closing metathesis approach to symmetrical and unsymmetrical cycloakeno[*c*]fused 2,2′-bipyridine-based cyclophanes☆

D. Branowska* and A. Rykowski

Department of Chemistry, Faculty of Sciences, University of Podlasie, ul.3 Maja 54, 08-110 Siedlce, Poland

Received 6 May 2005; revised 5 August 2005; accepted 19 August 2005

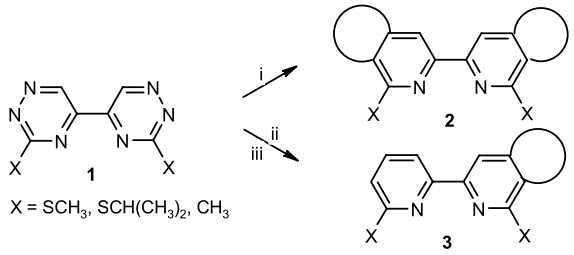
Available online 16 September 2005

Abstract—Ring-closing metathesis reactions of symmetrical and unsymmetrical cycloalkeno[*c*]fused 2,2′-bipyridines, substituted at the α and α′ positions of the pyridine rings with sufficiently long alkenyl ethers, afforded 16-membered cyclophanes, possessing variously annulated 2,2′-bipyridine subunits.

1. Introduction

Ring-closing metathesis (RCM) is widely used for the formation of different ring systems[2] and has recently been recognized as one of the most appropriate methods for the synthesis of macrocycles.[3] A number of macrocyclization metatheses with substrates having suitable double bond arrangement, including *N*-heterocycles, have been well recognized and applied to the synthesis of complex molecules.[4] Among these examples, the synthesis of 1,10-phenanthroline-based macrocycles, from the corresponding tetraalkene precursors,[5] can serve as an elegant means for the preparation of cyclophanes possessing a masked 2,2′-bipyridine subunit. Such chelating ligands encapsulate specific metal ions or neutral organic molecules,[6] and have been the focus of much recent work.[7] Incorporation of electron-donating substituents or attachment of a cycloalkene ring into 2,2′-bipyridine based cyclophanes can result in a higher efficiency of metal–ligand interactions, since the basicity of the bipyridine nitrogens is enhanced.[8] However, the study of these interesting and useful compounds is hampered by inefficient chemical synthesis. Direct nucleophilic displacement by the glycolates on 6,6′-bis(halomethyl)-2,2′-bipyridine afforded complicated mixtures of products, that is, bipyrido crown ethers, and poor yields.[6] The typical Kröhnke synthesis[9] of functionalized cycloalkeno-fused 2,2′-bipyridines is limited by inaccessible starting compounds.

During the course of our recent work on Diels–Alder reactions of dimeric 1,2,4-triazines with electron-rich dienophiles, we have reported the use of easily available 5,5′-bi-1,2,4-triazines **1**,[10] as electron-deficient dienes, for the preparation of a range of symmetrical (**2**), and unsymmetrical (**3**), annulated 2,2′-bipyridine derivatives with attached cycloalkene rings (Scheme 1).[11]



Scheme 1. (i) *N*-pyrrolidine 1-cycloalkene, 140 °C ; (ii) vinylimidazole, bromobenzene, 165 °C ; (iii) *N*-pyrrolidine 1-cycloalkene, 140 °C.

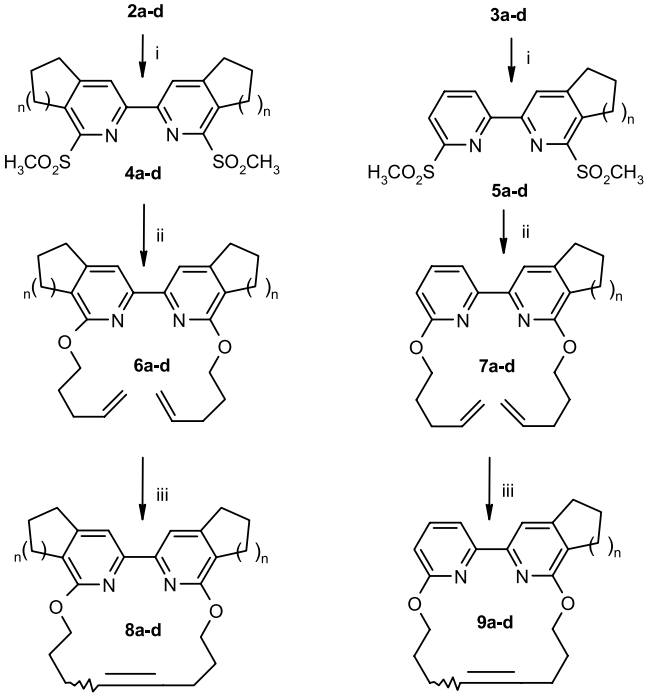
The presence of an alkylsulfanyl substituent in compounds **2** and **3** makes these derivatives attractive starting materials for the synthesis of macrocycles, because this group can be readily oxidized into an alkylsulfonyl group, being more reactive toward nucleophilic displacements.[12] We present herein a synthesis of variously annulated, symmetrical and unsymmetrical cycloalkeno[*c*]fused 2,2′-bipyridine- based cyclophanes **8a–d** and **9a–d**, starting from **2** and **3** (X= SCH_3), and using as the key steps: (1) nucleophilic

☆ See Ref. 1.

Keywords: Ring-closing metathesis; 2,2-Bipyridine; Cyclophanes.
* Corresponding author. Tel.: +48 25 6441116; fax: +48 25 6442045; e-mail: dankab@ap.siedlce.pl

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.08.081

substitution of methylsulfonyl group in **4a–d** and **5a–d**, and (2) ring-closing metathesis of the corresponding alkenyl ethers **6a–d** and **7a–d**. The essential features of the strategy are summarized in Scheme 2.



Scheme 2. (i) $KMnO_4$, AcOH, H_2O/C_6H_6, Bu_4NBr ; (ii) NaH, DMF, pent-4-en-1-ol, rt ; (iii) Grubbs' catalyst $I[Cl_2(PCy_3)_2Ru{=}CHPh]$, CH_2Cl_2, reflux $n=1$–4.

Table 1. Yields of 2,2′-bipyridine derivatives **4a–d**, **5a–d** and precyclophanes **6a–d**, **7a–d**

Compound	*n*	Yield (%)
4a	1	88
4b	2	90
4c	3	93
4d	4	87
5a	1	86
5b	2	92
5c	3	95
5d	4	99
6a	1	98
6b	2	97
6c	3	80
6d	4	97
7a	1	87
7b	2	95
7c	3	90
7d	4	73

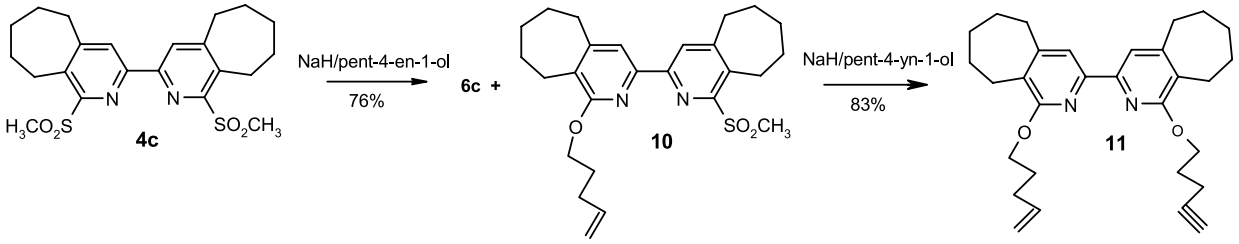
2. Results and discussion

The sulfides **2a–d**, **3a–d** were efficiently oxidized to the sulfones **4a–d** and **5a–d**. The highest yields of the latter, isolated as precipitated solids from the reaction mixtures, were obtained when the oxidation reaction was carried out with potassium permanganate under phase transfer catalytic conditions (Table 1).

Generally, an alkyl sulfonyl group directly bound to the 2-position of a pyridine ring is readily displaced by several nucleophiles such as RO^-, RS^- and CN^- to afford the corresponding *ipso*-substitution products.[12] However, the reactivity of analogous 2,2′-bipyridine derivatives toward nucleophilic substitution has not yet been investigated. To establish optimal conditions for nucleophilic displacement of methylsulfinate from the compounds **4a–d** and **5a–d**, the reaction of symmetrical derivative **4c** with sodium pent-4-en-1-oxide has been preliminary investigated (Scheme 3). During these studies we have found that *ipso*-substitution of methylsulfinate group in **4c** takes place under very mild reaction conditions (room temperature, 2 h) and the yield of the resulting alkenyl ether **6c** strongly depends on an amount of nucleophile used. When **4c** is treated with at least 6 equiv of sodium pent-4-en-1-oxide in DMF for 2 h, the reaction affords **6c** exclusively, in good yield. Generality of this reaction was further demonstrated by the one step synthesis of a range of symmetrical or unsymmetrical alkenyl ethers **6a–d** and **7a–d**, respectively. All these derivatives were formed in excellent yields (see Table 1).

When an equivalent amount of sodium pent-4-en-1-oxide is used, and the same reaction conditions were applied as mentioned above, the reaction stops at the mono-substitution stage affording the mixture of **6c** (minor) and **10** (major), respectively. The latter compound, after separation by chromatography, appeared to be a valuable intermediate for the preparation of the unsymmetrical derivative **11**, by condensation of **10** with sodium salt of pent-5-yn-1-ol (see Scheme 3). Compound **11** is a potential substrate for ene-yne metathesis.

The synthesis of cycloalkeno[*c*]fused 2,2′-bipyridine based cyclophanes **8a–d** and **9a–d** in which the bridging oxygens are directly attached to both pyridine rings is carried out via RCM as shown in Scheme 2. Treatment of the alkenyl ether **6c** with ruthenium benzylidene complex $Cl_2(PCy_3)_2$-Ru=CHPh (Grubbs' catalyst I) (10 mol%) as a 0.01 M solution in methylene chloride under reflux for 6 h resulted in the formation of the corresponding olefin cyclophane **8c** in reasonable yield. The ratio of the *E*/*Z* isomers in **8c** is determined by GC/MS (Table 2).

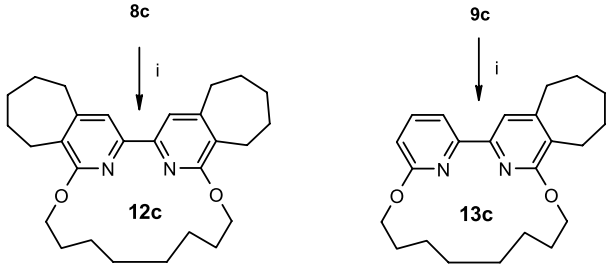


Scheme 3.

Table 2. Yield and ratios *E*/*Z* of **8a–d** and **9a–d**

Compound	*n*	Ratio *E*/*Z*	Yield (%)
8a	1	4:1	68
8b	2	13:1	35
8c	3	4:1	44
8d	4	10:1	71
9a	1	5:1	98
9b	2	3:1	48
9c	3	4:1	88
9d	4	3:1	73

The assignment of configuration at the double bond in the predominant isomer was made analysing ^{13}C satellites in ^{1}H NMR spectrum.[13] The vinyl protons are part of an ABX spin system where X is olefinic ^{13}C atom. Decoupling of the protons in the allylic position and long acquisition enabled observation of the vicinal coupling constant in the satellite spectrum of **8c**. This coupling constant (14 Hz) indicated a trans arrangement of the vinyl protons. Finally, both cis- and trans- isomers **8c** and **9c** prepared in a similar manner are readily hydrogenated to compounds **12c** and **13c** containing the same alkane chain using a Pd/C catalyst (Scheme 4).



Scheme 4. (i) H_2 (balloon), Pd/C, CH_2Cl_2, rt.

RCM of alkenyl ethers **6a**,**b**,**d** and **7a–d** were performed under the same reaction conditions giving directly symmetrical and unsymmetrical cycloalkeno[*c*]fused 2,2′-bipyridine based cyclophanes **8a**,**b**,**d** and **9a–d** (Table 2). The major products in all these RCM reactions were the *E* isomers.

3. Conclusions

In conclusion, the present work demonstrates the efficient application of the RCM approach for the synthesis of symmetrical and unsymmetrical cycloalkeno[*c*]fused 2,2′-bipyridinophanes with potential diverse applications in supramolecular chemistry. We anticipate that this method will find considerable use in the preparation of other macrocycles containing biheteroaromatic unit.

4. Experimental

4.1. General

Melting points are uncorrected. IR spectra were measured with a Magna IR-760 spectrophotometer. The ^{1}H NMR spectra were recorded in deuterated chloroform on a Varian-Gemini 200 MHz spectrometer. Mass spectra were measured with an AMD 604 (AMD Intectra GmbH, Germany) and GC/MS QP 5050 Shimadzu (30 m× 0.25 mm ID-BPX 5 0.25). Column chromatography was performed on silica gel (230–400 mesh, 60 Merck). All solvents used were dried and distilled according to standard procedures. Merck $60F_{254}$ plates were used for analytical (TLC) chromatography.

4.2. General procedure for the synthesis of sulfones 4a–d, 5a–d

A solution of $KMnO_4$ (12 mmol) in water (32 ml) was added to a solution of **2a–d**, **3a–d** (1 mmol) and catalytic amounts of Bu_4NBr (0.005 g) in a mixture of AcOH (3 ml) and benzene (37 ml). The reaction mixture was stirred at room temperature for 3 h. A saturated solution of $Na_2S_2O_5$ in water was added to the mixture until the purple color disappeared. The precipitate was filtered. The organic layer was separated and water phase was extracted with benzene (3×50 ml). The organic layers were then combined and dried over $MgSO_4$. After removal of solvent the crude product was combined with the precipitate and recrystallized from chloroform.

4.2.1. 1,1′-Dimethylsulfanyl-6,7,6′,7′-tetrahydro-5*H*,5*H*′-3,3′-bicyclopenta[*c*]pyridine 4a. Mp 338–339 °C. IR (KBr) cm^{-1}: 1130 and 1310 (SO_2). ^{1}H NMR (CF_3COOD) δ: 2.49–2.53 (m, 2×2H), 2.58–2.68 (m, 2×2H), 3.61–3.77 (m, 2×2H), 3.68 (s, 2×3H), 8.78 (s, 2×1H). HR-EI: calcd for $C_{18}H_{20}N_2O_4S_2$ 392.0865. Found 392.0890. Anal. Calcd for $C_{18}H_{20}N_2O_4S_2\cdot H_2O$: C, 52.66; H, 5.36; N, 6.83. Found: C, 52.33; H, 5.09; N, 6.53.

4.2.2. 1,1′-Dimethylsulfanyl-5,6,7,8,5′,6′,7′,8′,-octahydro-3,3′-biisoquinoline 4b. Mp 343–344 °C. IR (KBr) cm^{-1}: 1130 and 1301 (SO_2). ^{1}H NMR ($CDCl_3$) δ: 1.78–1.91 (m, 4×2H), 2.78–2.98 (m, 2×2H), 3.01–3.47 (m, 2×2H), 3.68 (s, 2×3H), 7.80 (s, 2×1H). HR-EI: calcd for $C_{20}H_{24}N_2O_4S_2$ 420.1177. Found 420.1216. Anal. Calcd for $C_{20}H_{24}N_2O_4S_2$: C, 57.12; H, 5.75; N, 6.66. Found: C, 56.97; H, 5.89; N, 6.47.

4.2.3. 1,1′-Dimethylsulfanyl-6,7,8,9,6′,7′,8′,9′-octahydro-5*H*,5*H*′-3,3′-bicyclohepta[*c*]pyridine 4c. Mp 354–355 °C. IR (KBr) cm^{-1}: 1130 and 1301 (SO_2). ^{1}H NMR ($CDCl_3$) δ: 1.71–1.78 (m, 4×2H), 1.80–1.98 (m 2×2H), 2.98 (t, 2×2H, J=5.4 Hz), 3.35 (t, 2×2H, J=5.5 Hz), 3.51 (s, 2×3H), 8.12 (s, 2×1H). HR-EI: calcd for $C_{22}H_{28}N_2O_4S_2$ 448.1490. Found 448.1468. Anal. Calcd for $C_{22}H_{28}N_2O_4S_2$: C, 58.90; H, 6.29; N, 6.24. Found: C, 58.83; H, 6.50; N, 6.11.

4.2.4. 1,1′-Dimethylsulfanyl-5,6,7,8,9,10,5′6′,7′,8′,9′,10′-dodecahydro-3,3′-bicycloocta[*c*]pyridine 4d. Mp 350–351 °C. IR (KBr) cm^{-1}: 1130 and 1305 (SO_2). ^{1}H NMR ($CDCl_3$) δ: 1.20–1.40 (m, 4×2H), 1.75–1.82 (m, 2×2H), 1.98–2.06 (m, 2×2H), 2.98 (t, 2×2H, J=5.8 Hz), 3.27 (t, 2×2H, J=5.7 Hz), 3.58 (s, 2×3H),8.12 (s, 2×1H). Anal. Calcd for $C_{24}H_{32}N_2O_4S_2$: C, 60.47; H, 6.76; N, 5.87. Found: C, 60.18; H, 6.89; N, 5.64.

4.2.5. 1-Methylsulfanyl-3-(6-methylsulfanyl-pyridin-2-yl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine 5a. Mp

263–264 °C. IR (KBr) cm^{-1}: 1122 and 1298 (SO_2). ^1H NMR ($CDCl_3$) δ: 1.78–1.88 (m, 2H), 2.98 (t, 2H, $J=6.2$ Hz, 5-CH_2), 3.35 (t, 2H, $J=6.1$ Hz, 7-CH_2), 3.38 (s, 3H), 3.45 (s, 3H), 8.15 (dd, 1H, $J=2.4$, 6.8 Hz), 8.18 (t, 1H, $J=$ 6.8 Hz), 8.40 (s, 1H), 8.45 (dd, 1H, $J=2.5$, 6.8 Hz). Anal. Calcd for $C_{15}H_{16}N_2O_4S_2$: C, 51.12; H, 4.57; N, 7.95. Found: C, 51.22; H, 4.60; N, 7.90.

4.2.6. 1-Methylsulfanyl-3-(6-methylsulfanyl-pyridin-2-yl)-5,6,7,8-tetrahydro-isoquinoline 5b. Mp 267–268 °C. IR (KBr) cm^{-1}: 1122 and 1298 (SO_2). ^1H NMR ($CDCl_3$) δ: 1.88–1.98 (m, 2×2H), 2.88–3.02 (m, 2H), 3.12 (t, 2H, $J=$ 6.2 Hz), 3.38 (s, 3H), 3.45 (s, 3H), 8.15 (dd, 1H, $J=2.4$, 6.8 Hz), 8.18 (t, 1H, $J=6.8$ Hz), 8.40 (s, 1H), 8.45 (dd, 1H, $J=2.5$, 6.8 Hz). Anal. Calcd for $C_{16}H_{18}N_2O_4S_2$: C, 52.44; H, 4.95; N, 7.64. Found: C, 52.37; H, 5.05; N, 7.56.

4.2.7. 1-Methylsulfanyl-3-(6-methylsulfanyl-pyridin-2-yl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*c*]pyridine 5c. Mp 286–287 °C. IR (KBr) cm^{-1}: 1130 and 1300 (SO_2). ^1H NMR ($CDCl_3$) δ: 1.70–1.86 (m, 2×2H), 1.89–1.98 (m, 2H), 2.98 (t, 2H, $J=5.4$ Hz), 3.39 (t, 2H, $J=5.1$ Hz), 3.34 (s, 3H), 3.40 (s, 3H), 8.15 (dd, 1H, $J=2.1$, 7.7 Hz), 8.14 (t, 1H, $J=7.4$ Hz), 8.39 (s, 1H), 8.50 (dd, 1H, $J=2.5$, 6.6 Hz). HR-EI: Calcd for $C_{17}H_{20}N_2O_4S_2$: 380.0864. Found 380.0851. Anal. Calcd for $C_{17}H_{20}N_2O_4S_2$: C, 53.66; H, 5.30; N, 7.36. Found: C, 53.57; H, 5.40; N 7.31.

4.2.8. 1-Methylsulfanyl-3-(6-methylsulfanyl-pyridin-2-yl)-5,6,7,8,9,10-hexahydro-cycloocta[*c*]pyridine 5d. Mp 246–247 °C. IR (KBr) cm^{-1}: 1122 and 1298 (SO_2). ^1H NMR ($CDCl_3$) δ: 1.38–1.41 (m, 2×2H), 1.78–1.88 (m, 2×2H), 2.98 (t, 2H, $J=6.2$ Hz), 3.35 (t, 2H, $J=6.1$ Hz), 3.38 (s, 3H), 3.45 (s, 3H), 8.15 (dd, 1H, $J=2.4$, 6.8 Hz), 8.18 (t, 1H, $J=6.8$ Hz), 8.40 (s, 1H), 8.45 (dd, 1H, $J=2.5$, 6.8 Hz). Anal. Calcd for $C_{18}H_{22}N_2O_4S_2$: C, 54.80; H, 5.62; N, 7.10. Found: C, 54.71; H, 5.75; N, 7.16.

4.3. General procedure for the nucleophilic substitution of 4a–d and 5a–d with pent-4-en-1-ol into 6a–d, 7a–d

To a mixture of pent-4-en-1-ol (6 mmol) and 60% NaH in mineral oil (6.6 mmol) in dry DMF (15 ml), the substrate **4a–d** or **5a–d** (1 mmol) in 25 ml DMF was added. The mixture was stirred at room temperature for 5–6 h. The reaction mixture was poured into ice/H_2O and acidified with AcOH. The precipitate was filtered off and recrystallized from ethanol.

4.3.1. 1,1′-Bis-pent-4-enyloxy-6,7,6′,7′-tetrahydro-5*H*,5′*H*-3,3′-bicyclopenta[*c*]pyridine 6a. Mp 89–90 °C. IR (KBr) cm^{-1}: 920, 1090, 1355, 1440, 1590, 2890, 2950. ^1H NMR ($CDCl_3$) δ: 1.94 (qui, 2×2H, $J=6.5$ Hz), 1.90–2.10 (m, 2×2H), 2.20–2.35 (m, 2×2H), 2.87 (t, 2×2H, $J=$ 7.4 Hz), 2.96 (t, 2×2H, $J=7.5$ Hz), 4.50 (t, 2×2H, $J=$ 6.5 Hz), 4.90–5.13 (m, 2×2H), 5.80–6.00 (m, 2×1H), 7.96 (s, 2×1H). ^{13}C NMR ($CDCl_3$) δ: 159.57, 156.77, 52.42, 139.36, 125.35, 114.76, 110.58, 64.66, 33.19, 30.42, 29.62, 28.40, 24.46. Anal. Calcd for $C_{26}H_{32}N_2O_2\cdot0.5H_2O$: C, 75.54; H, 7.99; N, 6.78. Found: C, 75.23; H, 7.58; N, 6.87.

4.3.2. 1,1′-Bis-pent-4-enyloxy-5,6,7,8,5′,6′,7′,8′-octahydro-3,3′-biisoquinoline 6b. Mp 108–109 °C. IR (KBr) cm^{-1}: 920, 1105, 1350, 1435, 1595, 2895, 2945. ^1H NMR ($CDCl_3$) δ: 1.60–1.78 (m, 4×2H), 1.80–2.00 (m, 2×2H), 2.20–2.34 (m, 2×2H), 2.63–2.50 (m, 2×2H), 2.80–3.00 (m, 2×2H), 4.40 (t, 2×2H, $J=6.4$ Hz), 4.90–5.15 (m, 2×2H), 5.90–6.00 (m, 2×1H), 7.60 (s, 2×1H). ^{13}C NMR ($CDCl_3$) δ: 160.99, 149.91, 148.11, 138.40, 119.68, 114.72, 113.98, 64.73, 30.48, 29.39, 28.48, 22.85, 22.63, 22.41. Anal. Calcd for $C_{28}H_{36}N_2O_2$: C, 77.74; H, 8.39; N, 6.47. Found: C, 77.60; H, 8.64; N, 6.62.

4.3.3. 1,1′-Bis-pent-4-enyloxy-6,7,8,9,6′,7′,8′,9′-octahydro-5*H*,5′*H*-3,3′-bicyclohepta[*c*]pyridine 6c. Mp 119–120 °C. IR (KBr) cm^{-1}: 920, 1120, 1335, 1440, 1585, 2870, 2930. ^1H NMR ($CDCl_3$) δ: 1.60–1.78 (m, 4×2H), 1.80–2.00 (m, 4×2H), 2.20–2.35 (m, 2×2H), 2.80–3.00 (m, 4×2H), 4.40 (t, 2×2H, $J=6.4$ Hz), 4.90–5.15 (m, 2×2H), 5.80–6.05 (m, 2×1H), 7.70 (s, 2×1H). ^{13}C NMR ($CDCl_3$) δ: 160.40, 154.86, 150.50, 138.42, 124.95, 114.71, 114.71, 65.09, 36.25, 32.77, 30.52, 28.48, 27.37, 27.20, 25.75. HR-EI: Calcd for $C_{30}H_{40}N_2O_2$: 460.3090. Found 460.3092. Anal. Calcd for $C_{30}H_{40}N_2O_2\cdot0.25H_2O$: C, 77.39; H, 8.71; N, 6.03. Found: C, 77.46; H, 8.45; N, 6.30.

4.3.4. 1,1′-Bis-pent-4-enyloxy-5,6,7,8,9,10,5′,6′,7′,8′,9′,10′-tetrahydro-3,3′-bicycloocta[*c*]pyridine 6d. Mp 90–91 °C. IR (KBr) cm^{-1}: 925, 1100, 1355, 1435, 1595, 2870, 2960. ^1H NMR ($CDCl_3$) δ: 1.50–1.36 (m, 2×4H), 1.63–1.75 (m, 4×2H), 1.86–2.00 (m, 2×2H), 2.20–2.35 (m, 2×2H), 2.86–3.00 (m, 4×2H), 4.45 (t, 2×2H, $J=6.4$ Hz), 4.90–5.12 (m, 2×2H), 5.80–6.00 (m, 2×1H), 7.70 (s, 2×1H). ^{13}C NMR ($CDCl_3$) δ: 160.72, 152.39, 150.63, 138.46, 122.74, 114.73, 114.24, 64.82, 32.54, 31.63, 30.57, 29.31, 28.56, 26.16, 26.13, 23.71. Anal. Calcd for $C_{32}H_{44}N_2O_2$: C, 78.64; H, 9.07; N, 5.73. Found: C, 78.73; H, 8.83; N, 5.74.

4.3.5. 1-Pent-4-enyloxy-3-(6-pent-4-enyloxy-pyridin-2-yl)-6,7-dihydro-cyclopenta[*c*]pyridine 7a. Oil. IR (KBr) cm^{-1}: 925, 1095, 1325, 1445, 1585, 2880, 2970. ^1H NMR ($CDCl_3$) δ: 1.98 (qui, 4H, $J=6.6$ Hz), 2.08–2.20 (m, 2H), 2.22–2.34 (m, 2×2H), 2.88 (t, 2H, $J=7.5$ Hz), 2.98 (t, 2H, $J=7.5$ Hz), 4.46 (t, 2H, $J=6.9$ Hz), 4.50 (t, 2H, $J=6.9$ Hz), 4.99–5.15 (m, 2×2H), 5.82–6.03 (m, 2H), 6.70 (d, 1H, $J=$ 8.2 Hz), 7.65 (t, 1H, $J=7.8$ Hz), 7.80 (s,1H), 7.95 (d, 1H, $J=7.3$ Hz). ^{13}C NMR ($CDCl_3$) δ: 163.14, 159.63, 156.01, 154.13, 151.75, 139.07, 138.26, 138.15, 126.04, 114.98, 114.79, 113.45, 110.64, 110.21, 64.99, 64.71, 33.16, 30.37, 30.32, 28.63, 28.43, 28.36, 24.41. HR-EI: Calcd for $C_{23}H_{28}N_2O_2$: 364.2151. Found 364.2157.

4.3.6. 1-Pent-4-enyloxy-3-(6-pent-4-enyloxy-pyridin-2-yl)-5,6,7,8-tetrahydro-isoquinoline 7b. Oil. IR (KBr) cm^{-1}: 920, 1100, 1340, 1440, 1590, 2895, 2950. ^1H NMR ($CDCl_3$) δ: 1.88–2.08 (m, 4×2H), 2.20–2.38 (m, 2×2H), 2.58–2.89 (m, 2×2H), 4.43 (t, 2×2H, $J=6.4$ Hz), 4.99–5.18 (m, 2×2H), 5.80–6.01 (m, 2H), 6.70 (d, 1H, $J=$ 8.1 Hz), 7.60 (s, 1H), 7.64 (t, 1H, $J=7.7$ Hz), 7.93 (d, 1H, $J=7.5$ Hz). ^{13}C NMR ($CDCl_3$) δ: 163.14, 160.99, 154.14, 149.13, 148.14, 139.06, 138.26, 138.12, 120.44, 114.86, 114.75, 114.37, 113.11, 110.02, 65.00, 64.74, 30.44, 30.32, 29.34, 28.42, 28.32, 22.83, 22.66, 22.33. HR-EI: Calcd for $C_{24}H_{30}N_2O_2$: 378.2307. Found 378.2300.

4.3.7. 1-Pent-4-enyloxy-3-(6-pent-4-enyloxy-pyridin-2-yl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*c*]pyridine 7c. Oil. IR (KBr) cm^{-1}: 925, 1085, 1335, 1445, 1585, 2870, 2955. ^1H NMR ($CDCl_3$) δ: 1.55–1.75 (m, 2×2H), 1.80–2.05 (m, 3×2H), 2.20–2.38 (m, 2×2H), 2.70–2.95 (m, 2×2H), 4.40 (t, 2×2H, $J=6.0$ Hz), 4.80–5.15 (m, 4H), 5.55–5.85 (m, 2H), 6.60 (d, 1H, $J=8.0$ Hz), 7.60 (t, 1H, $J=7.8$ Hz), 7.80 (s, 1H), 7.95 (d, 1H, $J=7.4$ Hz). ^{13}C NMR ($CDCl_3$) δ: 163.13, 160.38, 154.89, 153.99, 149.92, 139.00, 138.24, 138.08, 125.58, 114.86, 114.73, 113.19, 110.12, 65.06, 64.97, 36.17, 32.71, 30.44, 30.30, 28.24, 28.39, 28.31, 27.29, 27.07, 25.72. HR-EI: Calcd for $C_{25}H_{32}N_2O_2$: 392.2464. Found 392.2474.

4.3.8. 1-Pent-4-enyloxy-3-(6-pent-4-enyloxy-pyridin-2-yl)-5,6,7,8,9,10-hexahydro-cycloocta[*c*]pyridine 7d. Oil. IR (KBr) cm^{-1}: 920, 1115, 1355, 1445, 1585, 2880, 2970. ^1H NMR ($CDCl_3$) δ: 1.56–1.41 (m, 2×2H), 1.80–1.60 (m, 2×2H), 1.90–2.03 (m, 2×2H), 2.20–2.33 (m, 2×2H), 2.80–3.00 (m, 2×2H), 4.50 (t, 2×2H, $J=6.5$ Hz), 4.99–5.15 (m, 2×2H), 5.82–6.03 (m, 2H), 6.70 (d, 1H, $J=8.2$ Hz), 7.65 (t, 1H, $J=7.9$ Hz), 7.70 (s, 1H), 7.96 (d, 1H, $J=7.4$ Hz). ^{13}C NMR ($CDCl_3$) δ: 163.21, 160.70, 154.12, 152.66, 150.07, 139.36, 139.12, 139.10, 123.17, 114.90, 114.88, 114.66, 113.16, 110.09, 65.09, 64.85, 32.52, 31.60, 30.52, 30.35, 29.69, 29.53, 29.26, 28.36, 26.14, 23.73. HR-EI: Calcd for $C_{26}H_{34}N_2O_2$: 406.2620. Found 406.2628.

4.4. General procedure: ring closing metathesis of 6a–d and 7a–d into 8a–d and 9a–d

A solution of each of the substrates **6a–d**, **7a–d** in CH_2Cl_2 ($c=0.01$ M) and Grubbs' catalyst I (10 mol%) was heated under reflux for 4–6 h under argon. The solvent was removed and the crude products were separated by column chromatography, using CH_2Cl_2/hexane (10:1).

4.4.1. Cyclophane 8a. Mp 149–150 °C. IR (KBr) cm^{-1}: 980, 1080, 1370, 1445, 1595, 2870, 2960. ^1H NMR ($CDCl_3$) δ: 1.94–2.00 (m, 2×2H), 2.08–2.19 (m, 4×2H), 2.80–2.96 (m, 4×2H), 4.73 (t, 2×2H, $J=8.0$ Hz), 5.60–5.65 (m, 2×1H), 7.34 (s, 2×1H). ^{13}C NMR ($CDCl_3$) δ: 159.96, 156.71, 156.61, 152.33, 130.38, 110.83, 64.37, 33.03, 28.56, 28.40, 28.03, 24.43. Anal. Calcd for $C_{24}H_{28}N_2O_2$: C, 76.56; H, 7.49; N, 7.44. Found: C, 76.77; H, 7.64; N, 7.36.

4.4.2. Cyclophane 8b. Mp 164–165 °C. IR (KBr) cm^{-1}: 980, 1100, 1355, 1420, 1595, 2880, 2975. ^1H NMR ($CDCl_3$) δ: 1.60–1.87 (m, 4×2H), 1.90–2.05 (m, 2×2H), 2.17–2.04 (m, 2×2H), 2.58–2.62 (m, 2×2H), 2.68–2.73 (m, 2×2H), 4.68 (t, 2×2H, $J=8.0$ Hz), 5.60–5.63 (m, 2×1H), 7.12 (s, 2×1H). ^{13}C NMR ($CDCl_3$) δ: 161.47, 149.86, 147.80, 130.38, 119.19, 114.55, 64.44, 29.33, 28.54, 28.09, 22.69, 22.59, 22.39. Anal. Calcd for $C_{26}H_{32}N_2O_2\cdot 0.25H_2O$: C, 77.19; H, 7.97; N, 6.92. Found: C, 77.16; H, 8.28; N, 6.54.

4.4.3. Cyclophane 8c. Mp 158–159 °C. IR (KBr) cm^{-1}: 975, 1120, 1365, 1450, 1585, 2875, 2945. ^1H NMR ($CDCl_3$) δ: 1.54–1.66 (m, 4×2H), 1.80–1.96 (m, 4×2H), 2.12–2.17 (m, 2×2H), 2.79 (t, 2×2H, $J=5.5$ Hz), 2.88 (t, 2×2H, $J=5.6$ Hz), 4.62 (t, 2×2H, $J=8.1$ Hz), 5.58–5.62 (m, 2×1H), 7.27 (s, 2×1H). ^{13}C NMR ($CDCl_3$) δ: 161.19, 152.40, 150.28, 130.44, 122.30, 114.64, 64.79, 32.39, 31.72, 29.25, 28.75, 27.96, 26.14, 26.00. HR-EI: Calcd for $C_{28}H_{36}N_2O_2$: 432.2777. Found 432.2784. Anal. Calcd for $C_{28}H_{36}N_2O_2\cdot 0.5H_2O$: C, 76.19; H, 8.39; N, 6.35. Found: C, 76.30; H, 8.30; N, 6.46.

4.4.4. Cyclophane 8d. Mp 169–170 °C. IR (KBr) cm^{-1}: 980, 1100, 1355, 1440, 1595, 2875, 2945. ^1H NMR ($CDCl_3$) δ: 1.25–1.50 (m, 4×2H), 1.52–1.95 (m, 4×2H), 1.84–1.98 (m, 2×2H), 2.12–2.17 (m, 2×2H), 2.74–2.84 (m, 4×2H), 4.71 (t, 2×2H, $J=8.1$ Hz), 5.58–5.64 (m, 2×1H), 7.27 (s, 2×1H). ^{13}C NMR ($CDCl_3$) δ: 161.19, 152.40, 150.28, 130.44, 122.30, 114.64, 64.79, 32.39, 31.72, 29.25, 28.75, 27.96, 26.14, 26.00, 23.57. Anal. Calcd for $C_{30}H_{40}N_2O_2$: C, 78.22; H, 8.75; N, 6.08. Found: C, 78.30; H, 8.40; N, 6.26.

4.4.5. Cyclophane 9a. Mp 114–115 °C. IR (KBr) cm^{-1}: 920, 1090, 1355, 1440, 1590, 2890, 2950. ^1H NMR ($CDCl_3$) δ: 1.80–2.19 (m, 3×2H), 2.20–2.40 (m, 2×2H), 2.60–2.95 (m, 2×2H), 4.20–4.60 (m, 2×2H), 5.48–5.65 (m, 2H), 6.70 (d, 1H, $J=8.2$ Hz), 7.27 (s, 1H), 7.37 (d, 1H, $J=7.2$ Hz), 7.57 (t, 1H, $J=7.9$ Hz). ^{13}C NMR ($CDCl_3$) δ: 163.51, 162.25, 156.87, 155.99, 139.00, 137.93, 130.63, 130.35, 125.04, 124.76, 113.46, 112.76, 65.12, 64.93, 32.81, 29.87, 29.10, 28.90, 28.04, 24.44, 24.19. Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 75.00; H, 7.19; N, 8.33. Found: C, 75.09; H, 7.20; N, 8.28.

4.4.6. Cyclophane 9b. Mp 124–125 °C. IR (KBr) cm^{-1}: 985, 1095, 1325, 1445, 1575, 2857, 2930. ^1H NMR ($CDCl_3$) δ: 1.61–1.78 (m, 2×2H), 1.80–2.05 (m, 4H), 2.15–2.35 (m, 2×2H), 2.42–2.65 (m, 2×2H), 4.25–4.40 (m, 2×2H), 5.42–5.61 (m, 2H), 6.45 (d, 1H, $J=7.9$ Hz), 7.18 (s, 1H), 7.32 (d, 1H, $J=7.2$ Hz), 7.50 (t, 1H, $J=7.8$ Hz). ^{13}C NMR ($CDCl_3$) δ: 162.41, 162.21, 153.69, 153.42, 148.47, 147.47, 138.24, 130.64, 130.52, 129.77, 119.68, 119.48, 65.04, 64.91, 29.11, 28.99, 28.86, 28.08, 27.96, 22.81, 22.67, 22.31. Anal. Calcd for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48.; N, 7.99. Found: C, 75.31; H, 7.40; N, 8.01.

4.4.7. Cyclophane 9c. Mp 91–92 °C. IR (KBr) cm^{-1}: 970, 1085, 1335, 1450, 1570, 2850, 2930. ^1H NMR (CDCl3) δ: 1.57–1.65 (m, 2×2H), 1.82–1.98 (m, 3×2H), 2.15–2.17 (m, 2×2H), 2.80 (t, 2H, $J=5.4$ Hz), 83 (t, 2H, $J=5.5$ Hz), 4.61–4.92 (m, 2×2H), 5.56–5.58 (m, 2H), 6.68 (d, 1H, $J=7.9$ Hz), 7.18 (s, 1H), 7.36 (d, 1H, $J=7.3$ Hz), 7.57 (t, 1H, $J=7.8$ Hz). 13C NMR (CDCl3) δ: 163.57, 161.02, 154.93, 153.57, 149.77, 138.99, 130.66, 130.31, 125.17, 124.74, 115.56, 113.33, 110.03, 65.19, 64.72, 36.21, 32.72, 28.79, 28.70, 27.79, 27.36, 27.05, 25.61. HR-EI: Calcd for $C_{23}H_{28}N_2O_2$: 364.2151. Found 364.2156. Anal. Calcd for $C_{23}H_{28}N_2O_2$: C, 75.80; H, 7.74.; N, 7.69. Found: C, 75.72; H, 7.81; N, 7.56.

4.4.8. Cyclophane 9d. Mp 95–96 °C. IR (KBr) cm^{-1}: 980, 1110, 1325, 1445, 1585, 2880, 2980. ^1H NMR ($CDCl_3$) δ: 1.20–1.41 (m, 2×2H), 1.52–1.74 (m, 2×2H), 1.83–2.00 (m, 2×2H), 2.18–2.34 (m, 2×2H), 2.58–2.78 (m, 2×2H), 4.19–4.40 (m, 2×2H), 5.50 (t, 2H, $J=6.7$ Hz), 6.37 (d, 1H, $J=6.7$ Hz), 7.15 (s, 1H), 7.24 (d, 1H, $J=7.3$ Hz), 7.56 (t, 1H, $J=7.3$ Hz). ^{13}C NMR ($CDCl_3$) δ: 163.46, 161.18, 153.55, 152.47, 149.85, 132.36, 130.50, 130.17, 128.69, 122.89, 113.24, 109.90, 64.73, 64.55, 38.63, 32.30, 31.61, 30.27, 29.12, 28.64, 27.86, 26.04, 25.98, 23.51. Anal. Calcd

for $C_{24}H_{30}N_2O_2$: C, 75.75; H, 8.48; N, 7.36. Found: C, 75.98; H, 8.28; N, 7.35.

4.4.9. 1′-Methylsulfanyl-1-pent-4-enyloxy-6,7,8,9,6′,7′,8′,9′-octahydro-5*H*,5*H*′-3,3′-bicyclohepta[*c*]pyridine 10. To a mixture of pent-4-en-1-ol 0.19 g (2.2 mmol) and NaH (0.09 g, 2.2 mmol, 60% in mineral oil) in anhydrous DMF (6 ml), the compound **4c** 0.89 g (2.0 mmol) in DMF (20 ml) was added. After 2 h the reaction mixture was poured into ice/H_2O and acidified with AcOH. The precipitate was filtered off and recrystallized from ethanol to give 0.68 g (76%) of **10** as white solid. Mp 168–169 °C. IR (KBr) cm^{-1}: 1590, 1298 1089 (C–O–C). ^1H NMR ($CDCl_3$) δ: 1.62–1.93 (m, 7×2H), 2.18–2.33 (m, 2H), 2.88–3.05 (m, 3×2H), 3.25–3.33 (m, 2H), 3.51 (s, 3H), 4.43 (t, 2H, $J=6.3$ Hz), 5.00–5.12 (m, 2H), 5.82–5.98 (m, 1H), 7.57 (s, 1H), 8.21 (s, 1H). HR-EI: Calcd for $C_{26}H_{34}N_2O_3S$: 454.2290. Found 454.2288.

4.4.10. 1-Pent-4-enyloxy-1′-pent-4-ynyloxy-6,7,8,9,6′,7′,8′,9′-octahydro-5*H*,5*H*′-3,3′-bicyclohepta[*c*]pyridine 11. To a mixture of pent-4-yn-1-ol 0.17 g (2.0 mmol) and NaH (0.08 g, 2.0 mmol, 60% in mineral oil) in anhydrous DMF (3 ml), the compound **10a** 0.31 g (0.677 mmol) in DMF (20 ml) was added. After 3 h the reaction mixture was poured into ice/H_2O and acidified with AcOH. The precipitate was filtered off and recrystallized from ethanol to give 0.26 g (83%) of **11** as white solid. Mp 126 °C. IR (KBr) cm^{-1}: 3300 (C≡C) 1590, 1089 (C–O–C). ^1H NMR ($CDCl_3$) δ: 1.62–1.83 (m, 4×2H), 1.81–1.92 (m, 3×2H), 1.98 (t, 1H, $J=2.6$ Hz), 2.08 (q, 2H, $J=6.1$ Hz), 2.21–2.35 (m, 2H), 2.42 (dt, 2H, $J=2.5$ Hz), 2.80–2.91 (m, 4×2H), 4.43 (t, 2H, $J=6.3$ Hz), 4.51 (t, 2H, $J=6.2$ Hz), 5.00–5.12 (m, 2H), 5.82–5.98 (m, 1H), 7.62 (s, 2H). HR-EI: Calcd for $C_{30}H_{38}N_2O_2$: 458.2933. Found 458.2912.

4.5. General procedure for hydrogenolysis of the double bonds of the RCM products 8c and 9c

Cyclophanes **8c** and **9c** (0.5 mmol) were dissolved in dichloromethane (10 ml). After the addition of 25 mg of palladium (10%) on activated carbon the suspension was stirred for 18 h under a hydrogen atmosphere at room temperature. After filtration and evaporation of the solvent, the crude products **12c** and **13c** were recrystallized from ethanol.

4.5.1. Compound 12c. Yield 80%. Mp 95–96 °C. IR (KBr) cm^{-1}: 1592, 1290, 1082 (C–O–C). ^1H NMR ($CDCl_3$) δ: 1.45–1.67 (m, 8×2H), 1.80–1.87 (m, 4×2H), 2.77 (t, 2×2H, $J=5.3$ Hz), 2.87 (t, 2×2H, $J=5.3$ Hz), 4.66 (t, 2×2H, $J=8.3$ Hz), 7.08 (s, 2×1H). ^{13}C NMR ($CDCl_3$) δ: 161.23, 152.32, 151.25, 122.41, 115.25, 63.78, 32.44, 31.67, 29.22, 27.36, 26.12, 26.07, 24.32, 23.65. Anal. Calcd for $C_{28}H_{38}N_2O_2$: C, 77.31; H, 8.74; N, 6.44. Found: C, 77.34; H, 8.35; N, 6.17.

4.5.2. Compound 13c. Yield 65%. Mp 72–73 °C. IR (KBr) cm^{-1}: 1590, 1294, 1086 (C–O–C). ^1H NMR ($CDCl_3$) δ: 1.19–1.25 (m, 5×2H), 1.87–1.94 (m, 3×2H), 2.70–2.90 (m, 3×2H), 4.65 (t, 2H, $J=5.4$ Hz), 4.68 (t, 2H, $J=5.5$ Hz), 7.10 (s, 1H), 7.30 (d, 1H), 7.57 (d, 1H, $J=7.8$ Hz), 7.59 (t, 1H, $J=7.3$ Hz). Anal. Calcd for $C_{23}H_{30}N_2O_2$: C, 75.31; H, 8.18; N, 7.64. Found: C, 75.11; H, 8.10; N, 7.45.

Acknowledgements

The authors are grateful to Professor L. Kozerski and Dr. R. Kawecki for the special ^1H NMR measurement of compound **8c** and the interpretation of the resulting data.

References and notes

1. Part 30 in '1,2,4-triazines in organic synthesis'. For part 29, see Branowska, D. *Molecules* **2005**, *10*, 274.
2. For representative reviews see: Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013. Hoveyda, A.; Schrock, R. R. *Chem. Eur. J.* **2001**, *7*, 945.
3. Han, S.-Y.; Chang, S. In Grubbs, R. H., Ed.; Handbook of metathesis; Wiley-VCH: Weinheim, 2003; Vol. 2; Chapter 2.2.
4. Rowan, S. J.; Cantrill, S. J.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 898.
5. Lüning, U.; Fahrenkrug, F.; Hagen, M. *Eur. J. Org. Chem.* **2001**, 2161.
6. Newkome, G. R.; Kiefer, G. E.; Kohli, D. K.; Xia, Y.-I.; Fronczek, F. R.; Baker, G. R. *J. Org. Chem.* **1989**, *54*, 5105.
7. Collin, J. P.; Laemmel, A. C.; Sauvage, J.-P. *New J. Chem.* **2001**, *25*, 22.
8. Summers, L. *Adv. Heterocycl. Chem.* **1984**, *35*, 282–372.
9. Kröhnke, F. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 386 and references therein.
10. Branowska, D. *Molecules* **2005**, *10*, 265–273.
11. (a) Rykowski, A.; Branowska, D.; Kielak, J. *Tetrahedron Lett.* **2000**, *41*, 3657. (b) Branowska, D.; Rykowski, A. *Synlett* **2002**, 1892. (c) Branowska, D. *Synthesis* **2003**, 2096. (d) Branowska, D.; Kielak, J. *Pol. J. Chem.* **2003**, *77*, 1149. (e) Branowska, D. *Tetrahedron* **2004**, *60*, 6021.
12. (a) Shepard, R. G.; Fedrick, J. L. *Adv. Heterocycl. Chem.* **1965**, *4*, 145. (b) Furakawa, N.; Ogawa, S.; Kawai, T.; Oae, S. *Tetrahedron Lett.* **1983**, *24*, 3243.
13. Lambert, J. B.; Shurvell, H. F.; Verbit, L.; Cooks, R. G.; Stout, G. H. *Organic structural analysis*; Macmillan: New York, 1976; pp 91–93.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 10719–10733

Direct and stereoselective synthesis of β-D-mannosides using 4,6-*O*-benzylidene-protected mannosyl diethyl phosphite as a donor

Toshifumi Tsuda, Ryoichi Arihara, Shinya Sato, Miyuki Koshiba, Seiichi Nakamura and Shunichi Hashimoto*

Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan

Received 22 July 2005; revised 17 August 2005; accepted 18 August 2005

Available online 19 September 2005

Abstract—A direct and practical method for the construction of β-mannosidic linkages is described. While β-selectivities in the TMSOTf-promoted glycosidation of 2,3,4,6-tetra-*O*-benzyl-D-mannosyl diethyl phosphite are found to be highly dependent on the reactivity of acceptor alcohols, 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-mannosyl diethyl phosphite reacts with a wide range of acceptor alcohols in the presence of TMSOTf in CH_2Cl_2 at −45 °C to give β-mannosides in high yields with good to high β-selectivities.

1. Introduction

The rapidly growing significance of glycosides and oligosaccharides as constituents of biologically important compounds such as antitumor antibiotics and glycoconjugates has created an interest in the rational design and development of stereocontrolled glycosidation reactions.[1] Since the β-D-mannosidic linkage is present in virtually all eukaryotic *N*-linked glycoproteins as part of the core pentasaccharide, an enormous amount of creative endeavor has been devoted to the construction of this linkage.[2] Despite these efforts, the stereoselective synthesis of β-mannosides is recognized as one of the most challenging problems in carbohydrate chemistry, because both the anomeric effect and the steric repulsion between a non-participating group disposed axially at C-2 and an incoming alcohol uniformly favor the formation of α-mannosidic linkages. Departing from the seminal work of Paulsen and Lockhoff on the direct construction of this linkage via an S_N2-type displacement in the presence of insoluble silver silicate,[3] a number of indirect methods involving the epimerization of accessible β-glucosides at C-2,[4] the hexo-2-ulosyl bromide approach,[5] the reductive cleavage of mannosyl anomeric orthoesters,[6] intramolecular aglycon delivery (IAD)[7] using a temporary mixed acetal[8–10] or silyl ether connectors,[11] and intramolecular mannosylation via prearranged glycosides,[12] have been reported.

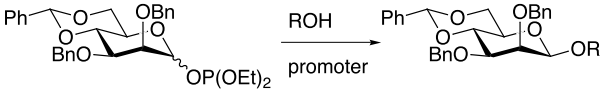
Although these indirect methods provide reliable access to pure β-mannosides, additional synthetic steps are required for the substrate preparation. Therefore, it is clear that a direct β-mannosylation method would constitute an ideal procedure in terms of efficiency and practicality. In this context, good to high β-selectivities have been achieved using some per-*O*-benzylated mannosyl donors.[13] The use of sulfonates as non-participating protecting groups at O-2 enhances β-selectivity due to a strong dipole effect.[14,15] The locked anomeric configuration method, wherein 1,2-*O*-dibutylstannylene derivatives of mannose are used as glycosyl donors and the roles of the donor and acceptor are reversed, results in complete β-selectivity; however, a significantly long reaction time is required to reach completion.[16] Among the direct methods reported to date, the protocol recently developed by Crich and Sun is a notable landmark in this field, in which the activation of 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-protected mannosyl sulfoxide or thioglycoside at −78 °C in dichloromethane with trifluoromethanesulfonic (triflic) anhydride or benzenesulfenyl triflate, respectively, is followed by the addition of acceptor alcohols to provide β-mannosides in high yields and with excellent levels of selectivity.[17] They claimed that the success of the two methods hinges critically on the presence of the 4,6-*O*-benzylidene group, where the α-mannosyl triflate as a common intermediate generated in situ from the donors reacts predominantly via an S_N2-like

Keywords: 4,6-*O*-Benzylidene acetal; Mannosyl diethyl phosphite; β-Selective glycosidation.
* Corresponding author. Tel.: +81 11 706 3236; fax: +81 11 706 4981; e-mail: hsmt@pharm.hokudai.ac.jp

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.08.090

displacement.[18] Very recently, Crich and Chandrasekera, based on kinetic isotope effects (KIEs) measurements, proposed that the displacement of the α-mannosyl triflate by an acceptor alcohol proceeded with the development of a substantial oxocarbenium ion character.[19] The effectiveness of the intermediate was also recognized by Weingart and Schmidt[20] with the corresponding trichloroacetimidate and by Kim and co-workers[21] with the 2-(hydroxycarbonyl)-benzyl 4,6-*O*-benzylidenemannoside.[22]

We have developed glycosyl donors that incorporate various phosphorus-containing leaving groups. The glycosidations constitute mild and efficient methods for the highly stereocontrolled construction of 1,2-*trans*-β- and 1,2-*cis*-α-glycosidic linkages with or without a participating group at C-2.[23] The exceptionally high levels of β-selectivity observed with 2,3,4,6-tetra-*O*-benzyl-protected glycosyl diphenyl phosphates,[23a] *N*,*N*,*N*′,*N*′-tetramethylphosphorodiamidates,[23d] and diethyl phosphites[23e] suggest that these leaving groups would also be promising candidates for the construction of β-mannosidic linkages. In the following discussion, the details of our investigations in this area are presented (Eq. 1).[24,25]

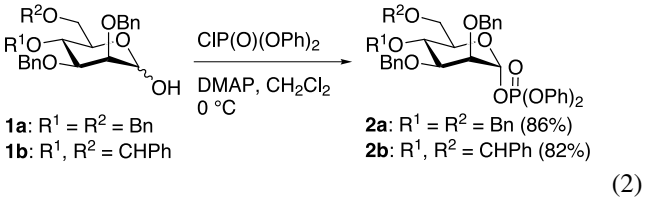


(1)

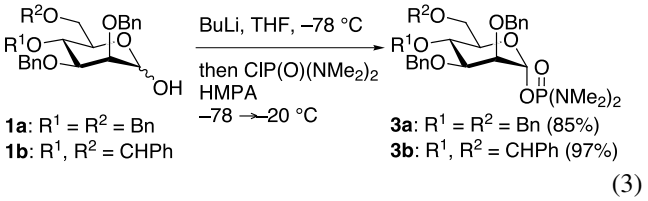
2. Results and discussion

2.1. Preparation of D-mannosyl donors

2,3,4,6-Tetra-*O*-benzyl-D-mannosyl and 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-mannosyl donors were prepared from the corresponding mannoses **1a**[26] and **1b**[27] according to standard procedures. Phosphorylation with diphenyl chlorophosphate under the Sabesan conditions[28] (DMAP, CH_2Cl_2, 0 °C) provided diphenyl phosphates **2a** and **2b** in good yields (Eq. 2). Tetramethylphosphorodiamidates **3a** and **3b** were obtained by the condensation of lithium alkoxides derived from **1a** and **1b**, respectively, with bis(dimethylamino)phosphorochloridate in THF–HMPA (Eq. 3).[23d]

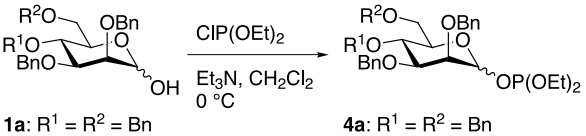


(2)



(3)

Diethyl phosphites **4a** and **4b** were prepared by the reaction of mannose derivatives with diethyl chlorophosphite and triethylamine at 0 °C (Eq. 4). Donors with an α-configuration were predominantly formed in all cases except for the diethyl phosphites **4a** and **4b**. The obtained mannosyl donors were purified by silica gel column chromatography, and could be stored without decomposition in a freezer (at −30 °C) for several months.

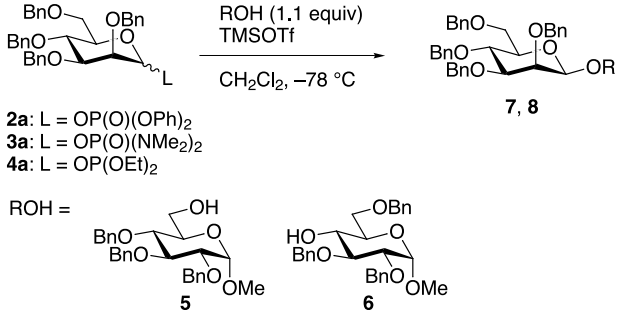


(4)

2.2. Glycosidation of 2,3,4,6-tetra-*O*-benzyl-D-mannosyl donors

At the outset of this study, the glycosidation of 2,3,4,6-tetra-*O*-benzyl-D-mannosyl donors was explored using *O*-6- or *O*-4-unprotected glycosides **5** or **6** (1.1 equiv each) as highly reactive and less reactive acceptor alcohols, respectively (Table 1).[29,30] The addition of a 1.0 M solution of TMSOTf (1.1 equiv) in CH_2Cl_2 to a cooled solution of the donor and acceptor in CH_2Cl_2 afforded a disaccharide and the α:β ratio was assayed by HPLC (Zorbax® Sil column). The TMSOTf-promoted glycosidation of diphenyl phosphate **2a** with **5** in CH_2Cl_2 proceeded at −78 °C within 1 h to give disaccharide **7** in 86% yield with good β-selectivity (α:β = 21:79) (Fig. 1). Almost the same results were obtained when phosphorodiamidate **3a** and diethyl phosphite **4a** were used (entries 2 and 3). However, a limitation of the TMSOTf-promoted glycosidations of 2,3,4,6-tetra-*O*-benzyl-D-mannosyl donors **2a**, **3a**, and **4a** was encountered with the unreactive *O*-4-unprotected glycoside **6**, the mannosylation

Table 1. TMSOTf-promoted glycosidation of 2,3,4,6-tetra-*O*-benzyl-D-mannosyl donors **2a**, **3a**, and **4a**[a]



Entry	Donor[b]	Acceptor	Time, h	Disaccharide		
					Yield, %	α:β[c]
1	**2a**	**5**	1	**7**	86	21:79
2[d]	**3a**	**5**	1	**7**	91	22:78
3	**4a**	**5**	1	**7**	86	25:75
4	**2a**	**6**	1.5	**8**	75	77:23
5[d]	**3a**	**6**	1.5	**8**	89	80:20
6	**4a**	**6**	1.5	**8**	74	76:24

[a] Donor/acceptor/TMSOTf molar ratio = 1.0/1.1/1.1 unless otherwise noted.
[b] The anomeric ratio of the donors: **2a**, 100:0; **3a**, 100:0; **4a**, 87:13.
[c] The ratio was determined by HPLC (column, Zorbax® Sil, 4.6×250 mm; eluent, 13% THF in hexane or 20% ethyl acetate in hexane; flow rate 1.5 or 1.0 mL/min).
[d] The reaction was performed using 2.0 equiv of TMSOTf.

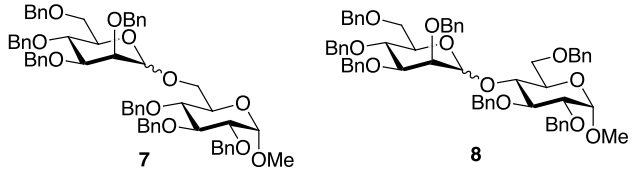


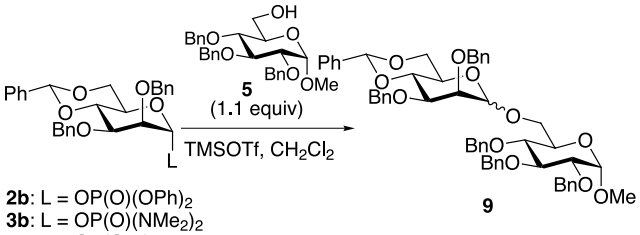
Figure 1. Products of the mannosylation of alcohols **5** and **6** with 2,3,4,6-tetra-*O*-benzyl-D-mannosyl donors.

of which produced disaccharide **8** favoring the α-mannoside in high yields (entries 4–6).

2.3. Glycosidation of 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-mannosyl donors

2.3.1. Reaction optimization. Since the glycosidation of the fully benzylated mannosyl donors **2a–4a** proved to be an unreliable method for the construction of β-mannosidic linkages, we were prompted to investigate the glycosidation of 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-mannosyl donors. Consistent with a general trend that 4,6-*O*-benzylidene-protected glycosyl donors exhibit reduced reactivities,[31] mannosyl donors **2b–4b** were activated with TMSOTf in CH_2Cl_2 at a higher temperature than that required for the corresponding per-*O*-benzylated donors **2a–4a**, but the reaction with **5** gave disaccharide **9** with an enhanced β-selectivity (Table 2). Although Seeberger and co-workers reported that the use of 4,6-*O*-benzylidene-protected mannosyl phosphate met with failure due to the partial hydrolysis of the cyclic acetal functionality under acidic conditions,[32] mannosylation with diphenyl phosphate **2b** provided disaccharide **9** in 54% yield with an α:β ratio of 10:90 (entry 1). The use of phosphorodiamidate **3b** as a donor gave virtually the same results as those found with **2b** (entries 1 vs 2), although a protracted reaction time was required. On the other hand, the TMSOTf-promoted mannosylation of **5** with diethyl phosphite **4b** in CH_2Cl_2 proceeded to completion at −45 °C within 30 min, affording disaccharide **9** in 83% yield with a similar high level of β-selectivity (entry 3). As a result of these observations, we selected the phosphite method for the β-selective mannosylation in terms of reactivity and product yield.[33]

Table 2. TMSOTf-promoted glycosidation of 4,6-*O*-benzylidene-D-mannosyl donors **2b**, **3b**, and **4b** with **5**



2b: L = $OP(O)(OPh)_2$
3b: L = $OP(O)(NMe_2)_2$
4b: L = $OP(OEt)_2$

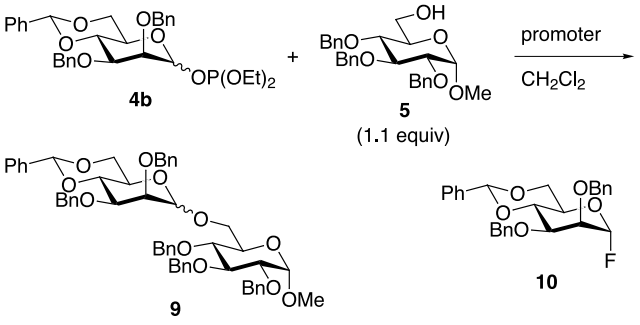
Entry	Donor[a]	TMSOTf (equiv)	Temperature (°C)[b]	Time (h)	Yield (%)	α:β[c]
1	**2b**	1.5	−30	1	54	10:90
2	**3b**	2.0	−30	2	55	12:88
3	**4b**	1.1	−45	0.5	83	10:90

[a] The anomeric ratio of the donors: **2b**, 100:0; **3b**, 100:0; **4b**, 93:7.
[b] Temperature limit for a smooth reaction.
[c] The ratio was determined by HPLC (column, Zorbax® Sil, 4.6×250 mm; eluent, 20% ethyl acetate in hexane; flow rate, 1.0 mL/min; t_R α-mannoside, 21.1 min; t_R β-mannoside, 24.4 min).

Promoters other than TMSOTf were screened for their ability to activate the mannosyl diethyl phosphite **4b** (Table 3). Although a previous study from this laboratory demonstrated that the $BF_3{\cdot}OEt_2$-promoted glycosidations of per-*O*-benzyl-protected glycosyl diethyl phosphites exhibited the highest levels of β-selectivities known to date,[23e] the coupling of **4b** with **5** in the presence of $BF_3{\cdot}OEt_2$ gave disaccharide **9** in only 54% yield with an α:β ratio of 40:60 and considerable amounts of mannosyl fluoride **10** (entry 2). It has been well documented in the literature that some Brønsted acids such as TfOH are effective activators of glycosyl phosphites.[23g,23j,25,34] While mannosyl diethyl phosphate **4b** could also be activated by TfOH at −65 °C in CH_2Cl_2, the reaction with **5** afforded no discernible benefits (entry 3). Reactions of glycosyl phosphites have been shown to be promoted by catalytic amounts of TMSOTf;[23f,34a,35] however, the use of 0.2 equiv of TMSOTf resulted in a diminished β-selectivity (α:β = 19:81, entry 4). The reason for the attenuated selectivity in the catalytic reaction is unclear at present.

We next explored the optimal solvent for this reaction (Table 4). Solvents such as toluene and Et_2O were found to be less effective in terms of stereoselectivity (entries 2 and 3). The use of propionitrile gave a complex mixture of products, most likely due to the low anomeric reactivity of the nitrilium ion intermediates that causes a nucleophilic attack by alcohol **5** on a nitrilium carbon (entry 4).[23i] The temperature profile of the reaction of **4b** with **5** in CH_2Cl_2 demonstrated that this reaction performed extremely well over a wide temperature range; only minor erosion (2%) in β-selectivity was observed (entries 1 vs 5 and 6).

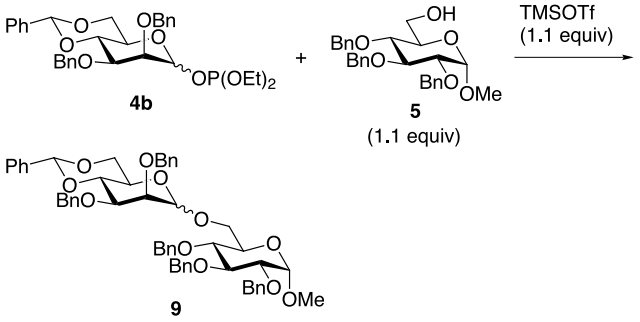
Table 3. Effect of promoter in the glycosidation of 4,6-*O*-benzylidene-D-mannosyl diethyl phosphite **4b** with **5**



Entry	Promoter	equiv	Temperature, °C	Time, h	Yield, %	α:β[a]
1	TMSOTf	1.1	−45	0.5	83	10:90
2	$BF_3{\cdot}OEt_2$	1.1	−45	6	54[b]	40:60
3[c]	TfOH	1.1	−65	6	79	9:91
4	TMSOTf	0.2	−45	1	81	19:81

[a] The ratio was determined by HPLC (column, Zorbax® Sil, 4.6×250 mm; eluent, 20% ethyl acetate in hexane; flow rate, 1.0 mL/min; t_R α-mannoside, 21.1 min; t_R β-mannoside, 24.4 min).
[b] Mannosyl fluoride **10** was obtained in 31% yield.
[c] In the presence of 4 Å molecular sieves (4 Å MS).

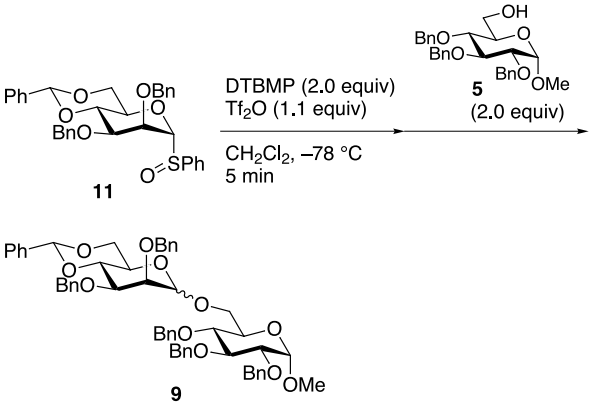
Table 4. Effect of solvent and temperature in the TMSOTf-promoted glycosidation of 4,6-*O*-benzylidene-D-mannosyl diethyl phosphite **4b** with **5**



Entry	Solvent	Temperature, °C	Time, min	Yield, %	α:β[a]
1	CH_2Cl_2	−45	30	83	10:90
2	Toluene	−45	30	86	20:80
3	Et_2O	−45	30	77	22:78
4	EtCN	−45	15	Complex mixture	
5	CH_2Cl_2	−23	15	74	11:89
6	CH_2Cl_2	0	15	75	12:88

[a] The ratio was determined by HPLC (column, Zorbax® Sil, 4.6×250 mm; eluent, 20% ethyl acetate in hexane; flow rate, 1.0 mL/min; t_R α-mannoside, 21.1 min; t_R β-mannoside, 24.4 min).

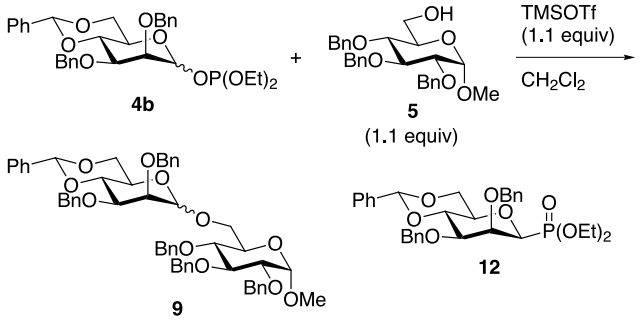
Although it appeared likely that the conditions employed in the coupling of **4b** with **5** could be optimized, the observed β-selectivity (α:β=10:90) did not match the selectivity (α:β ratio with **5** was 4:96 at −78 °C and 6:94 at −45 °C) obtained by us using the corresponding sulfoxide **11** (Eq. 5).[17] It is clear that the difference in selectivity between the two methods cannot be attributed to the reaction temperature used. In this context, it is likely that another factor accounts for the difference in stereoselectivity. Our procedure involves the dropwise addition of TMSOTf to a mixture of **4b** and **5** in CH_2Cl_2. On the other hand, in Crich and Sun's study, the order of addition of reactants was critical for the success of the reaction, since the intermediate triflate should be prepared before the addition of the alcohol.



(5)

Thus, we focused on the possibility of improving the β-selectivity by changing the mixing sequence (Table 5). Pretreatment of donor **4b** with TMSOTf in CH_2Cl_2 at

Table 5. Effect of mixing sequence of the reactants in the TMSOTf-promoted glycosidation of 4,6-*O*-benzylidene-D-mannosyl diethyl phosphite **4b** with **5**



Entry	Method[a]	Temperature, °C	Time, min	Yield, %	α:β[b]
1	A	−45	30	83	10:90
2	B	−45	30	65[c]	8:92
3	B	−78	120	55[c]	5:95
4	C	−45	30	79	10:90

[a] *Method A*. A 1 M solution of TMSOTf in CH_2Cl_2 was added to a mixture of donor **4b** and alcohol **5** in CH_2Cl_2 at −45 °C. *Method B*. After stirring a solution of donor **4b** and TMSOTf in CH_2Cl_2 at −45 °C for 30 min, a solution of alcohol **5** in CH_2Cl_2 was added at the indicated temperature. *Method C* (inverse conditions). A solution of donor **4b** in CH_2Cl_2 was added to a solution of alcohol **5** and TMSOTf in CH_2Cl_2 at −45 °C.

[b] The ratio was determined by HPLC (column, Zorbax® Sil, 4.6×250 mm; eluent, 20% ethyl acetate in hexane; flow rate, 1.0 mL/min; t_R α-mannoside, 21.1 min; t_R β-mannoside, 24.4 min).

[c] Phosphonate **12** was obtained as a by-product in ca. 15–20% yield.

−45 °C for 30 min followed by the addition of alcohol **5** was found to increase the α:β ratio to 8:92 (method B, entry 2). This protocol enabled the β-selectivity to be enhanced further by lowering the temperature to −78 °C during the addition (entry 3). It is noteworthy that the observed selectivity (α:β=5:95) is comparable to that obtained by the sulfoxide method. However, the permuted order of addition provided much lower yields of mannoside **9** due to the inevitable formation (ca. 15–20%) of phosphonate **12**.[36,37] Although Schmidt and Weingart employed the 'inverse conditions'[38] for the formation of β-mannosides using 4,6-*O*-benzylidene-protected mannosyl trichloroacetimidate,[20] no difference in stereoselectivity was observed under inverse conditions, in which **4b** was added to a mixture of **5** and TMSOTf at −45 °C (method C, entry 4). These results strongly suggest that the problem associated with the phosphite method is that the mannosyl donor **4b** cannot be cleanly converted into the α-mannosyl triflate by treatment with TMSOTf before the addition of an acceptor alcohol. This also means that Crich's optimal protocol is crucial not only for the preferential formation of β-mannosides using Kahne's sulfoxide glycosidation method[39] but also for general use whenever the efficient in situ generation of the α-mannosyl triflate from 4,6-*O*-benzylidene-protected mannosyl donors is possible.

2.3.2. Scope of the TMSOTf-promoted glycosidations of 4,6-*O*-benzylidene-D-mannosyl diethyl phosphite 4b. With the reaction conditions optimized, the scope of the glycosidation reaction of **4b** with a range of acceptor alcohols was then investigated (Fig. 2). The results are compiled in Table 6.

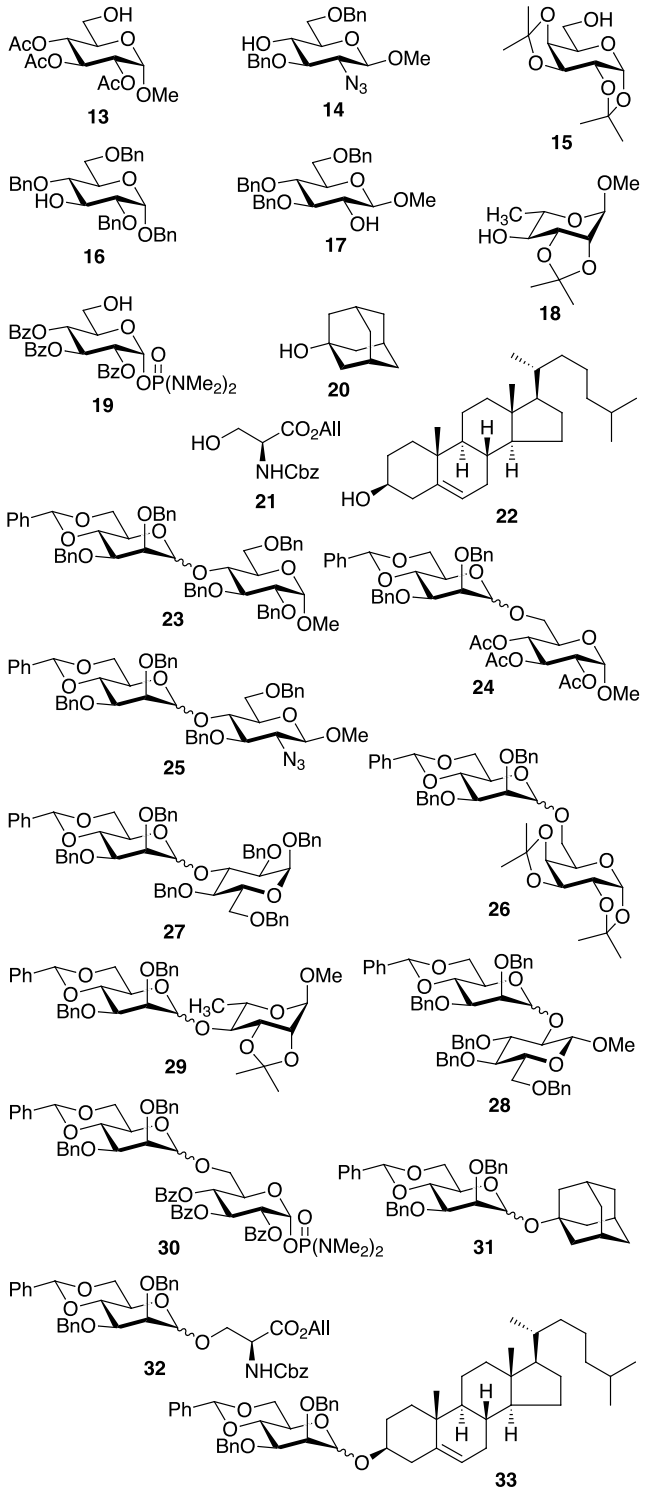
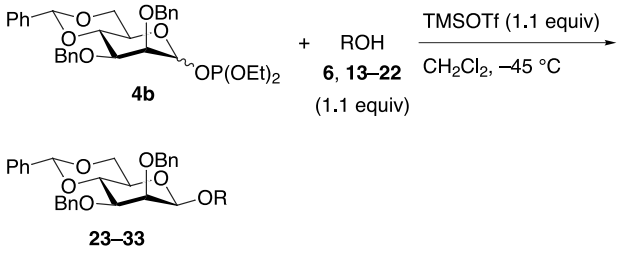


Figure 2. Acceptor alcohols and products in Table 6.

As anticipated from the preceding experiments, the β-selectivities obtained in the reaction of **4b** did not surpass the selectivities observed with the corresponding sulfoxide **11** (entries 2, 4, and 7);[17] however, the TMSOTf-promoted glycosidation in CH_2Cl_2 at −45 °C offered a facile and high-yielding route to β-mannosides in all cases, wherein the α:β ratios ranged from 24:76 to 5:95. The mannosylation of less reactive *O*-4-unprotected glycosides **6** and **14**[40] proceeded to completion within 1 h under these conditions

Table 6. TMSOTf-promoted glycosidation of 4,6-*O*-benzylidene-D-mannosyl diethyl phosphite **4b** with acceptor alcohols[a,b]



Entry	ROH	Time, min	Product		
				Yield, %	α:β[c]
1	**6**	60	**23**	84	11:89
2	**13**	30	**24**	85	11:89
3	**14**	60	**25**	72	17:83
4	**15**	30	**26**	89	24:76
5	**16**	30	**27**	77	15:85[d]
6	**17**	30	**28**	96	5:95
7	**18**	30	**29**	89	11:89
8[e]	**19**	30	**30**	85	14:86[f]
9	**20**	30	**31**	89	16:84
10	**21**	15	**32**	87	15:85
11	**22**	30	**33**	86	17:83

[a] The reaction was carried out on a 0.1 mmol scale.
[b] Donor **4b**/ROH/TMSOTf molar ratio=1.0/1.1/1.1 unless otherwise noted.
[c] The ratio was determined by HPLC (column, Zorbax® Sil, 4.6×250 mm; eluent, 5–17% ethyl acetate in hexane or 5–20% THF in hexane; flow rate, 1.0 mL/min), unless otherwise stated.
[d] Determined by 500 MHz ^{1}H NMR.
[e] The reaction was performed with 2.0 equiv of TMSOTf.
[f] Determined by 126 MHz ^{13}C NMR.

(entries 1 and 3), and the glycosidation of **14** led to the preferential formation of β-mannoside **25**β, which corresponds to a constituent of *N*-linked glycoproteins (entry 3). As previously mentioned by Crich, the coupling with 1,2:3,4-di-*O*-isopropylidenegalactose (**15**) exhibited a much lower selectivity (α:β=24:76, entry 4). Considering that the reaction reached completion within 30 min, this stereochemical outcome might be attributed to a sterically mismatched interaction in the transition state leading to the β-linked disaccharide **26**β.[41] The best β-selectivity (α:β=5:95) was achieved by the mannosylation of the *O*-2-unprotected glucoside **17** (entry 6). It is also noteworthy that chemoselective glycosidation was realized when *O*-6-unprotected glucosyl phosphorodiamidate **19** was used as a disarmed acceptor because **19** was unaffected by such conditions when kept at temperatures below −5 °C (entry 8).[34b,42] Crich and co-workers demonstrated that some *tert*-alcohols such as 1-adamantanol (**20**) could be mannosylated upon activation of phenyl thiomannoside with a variety of thiophilic reagents.[17d,f,g] In our system, glycoside **31** with an α:β ratio of 16:84 was obtained from **20** in 89% yield (entry 9). The serine derivative **21** and cholesterol (**22**) could be safely glycosylated under these conditions with good β-selectivities (entries 10 and 11).

2.4. Mechanistic considerations

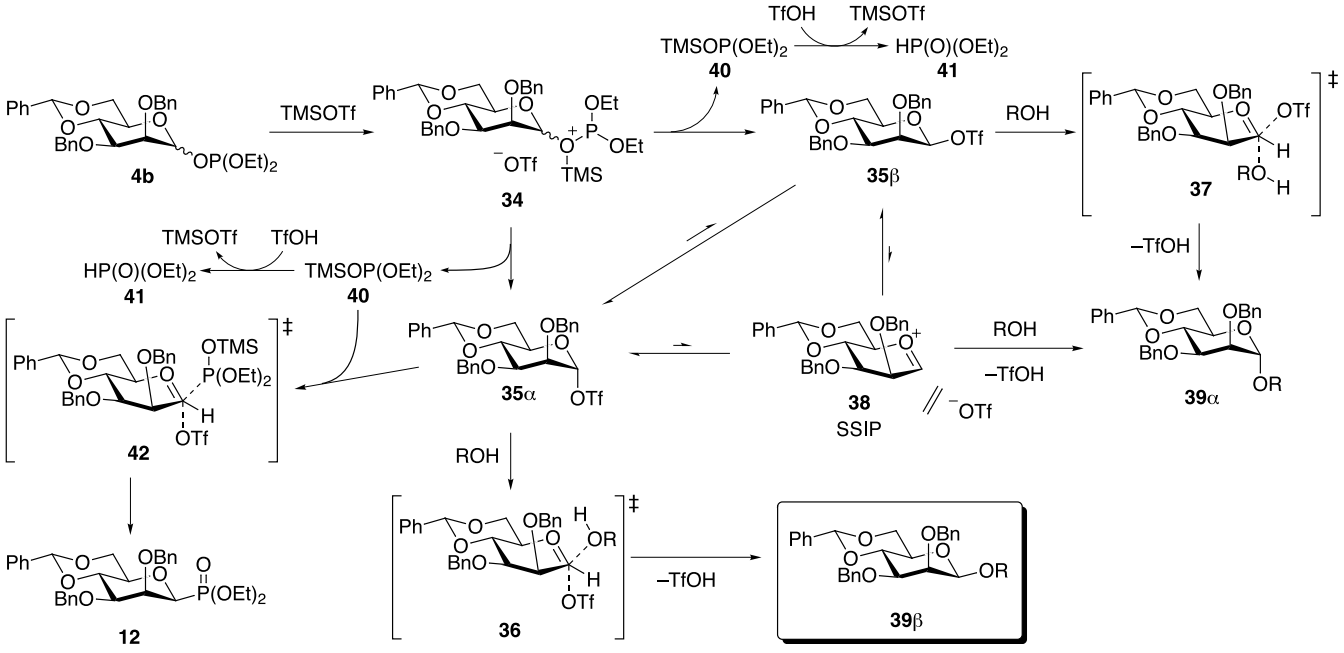
Crich and Sun proposed, based on NMR experiments, that mannosyl triflate was cleanly generated from 4,6-*O*-benzylidene-D-mannosyl sulfoxide upon treatment with

Tf_2O in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) in CD_2Cl_2 at −78 °C within 5 min.[18] As alluded to above, Crich and Chandrasekera, based on the KIEs, proposed that the displacement of the α-mannosyl triflate by an acceptor alcohol proceeded with the development of a substantial oxocarbenium ion character, although the complete set of equilibria between mannosyl triflates, the transient contact ion pair (CIP) and the solvent-separated ion pair (SSIP) lie very heavily toward the α-mannosyl triflate.[19] The possibility that the 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-mannosyl triflate is also an intermediate in the phosphite method is suggested by the following: (1) the effectiveness of the triflate as a counterion of the promoter and (2) almost the same β-selectivity as that obtained with the sulfoxide method when premixing the phosphite with TMSOTf prior to addition of the acceptor alcohol. Based on these results, the similar reaction mechanism would be applicable to the phosphite method. While CIP, in which the triflate anion is necessarily closely associated with the face of the oxocarbenium ion, would be a possible intermediate in this reaction, a mechanism involving an 'exploded' transition state[19] is outlined in Scheme 1.

Diethyl phosphite **4b** is activated by silylation of the oxygen atom[34a] and the phosphite group is cleaved, to produce an equilibrium mixture of α- and β-mannosyl triflates **35**α and **35**β. The displacement by acceptor alcohols at the anomeric carbon of **35**α and **35**β affords glycosides **39**β and **39**α via triplets **36** and **37**, respectively, along with generation of TfOH. Since the equilibrium between the mannosyl triflates would heavily lie to **35**α on kinetic and thermodynamic grounds, high β-selectivities are observed in the present method. The generation of SSIP (**38**) from **35**α and **35**β results in the formation of α-mannoside **39**α. Trimethylsilyl phosphite **40** is converted to diethyl phosphite (**41**) during the course of the reaction. Since phosphite **40** is less nucleophilic than the acceptor alcohols, high yields can be obtained when the promoter is added to a mixture of donor **4b** and the acceptor alcohol. However, α-mannosyl triflate **35**α reacts with phosphite **40** in the absence of the acceptor alcohol, providing β-mannosyl phosphonate **12** as a by-product.

3. Conclusion

The effectiveness of the diethyl phosphite group as a leaving group of mannosyl donors has been demonstrated. β-Selectivities in the TMSOTf-promoted glycosidation of 2,3,4,6-tetra-*O*-benzyl-D-mannosyl donors were found to be highly dependent on the reactivity of the acceptor alcohols used. On the other hand, the TMSOTf-promoted glycosidation of 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-mannosyl diethyl phosphite with a broad variety of acceptor alcohols in CH_2Cl_2 at −45 °C offered a facile and high-yielding route to β-mannosides, wherein the α:β ratios ranged from 24:76 to 5:95. Although the β-selectivities did not surpass those reported by Crich with the sulfoxide or thioglycoside method, the present method has the following advantages in terms of practicality: (1) high product yield can be achieved with approximately equimolar proportions of glycosyl donors and acceptors; (2) the reaction is very clean, allowing very easy isolation of the product, in contrast to the sulfoxide method in which several by-products derived from the sulfinate moiety are produced; and (3) TMSOTf is a stable and inexpensive reagent compared to those used for the activation of thioglycosides. The effectiveness of the triflate as a counterion of the promoter and almost the same β-selectivity as that obtained with the sulfoxide method when the phosphite is premixed with TMSOTf prior to the addition of the acceptor alcohol suggest that the corresponding mannosyl triflate is an intermediate in the present mannosidation method.



Scheme 1. Potential pathways for the TMSOTf-promoted glycosidation of 4,6-*O*-benzylidene-protected mannosyl diethyl phosphite **4b**.

4. Experimental

4.1. General

Melting points were determined on a Büchi 535 digital melting point apparatus and were uncorrected. Optical rotations were recorded on a JASCO P-1030 digital polarimeter. Infrared (IR) spectra were recorded on a JASCO FT/IR-5300 spectrophotometer and absorbance bands are reported in wavenumber (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Bruker ARX500 (500 MHz) spectrometer with tetramethylsilane (δ_H 0.00) as an internal standard. Coupling constants (J) are reported in hertz (Hz). Abbreviations of multiplicity are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Data are presented as follows: chemical shift, multiplicity, coupling constants, integration and assignment. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on JEOL AL400 (100 MHz) or Bruker ARX500 (126 MHz) spectrometers with $CDCl_3$ (δ_C 77.0) as an internal standard. Phosphorus nuclear magnetic resonance (^{31}P NMR) spectra were recorded on JEOL EX270 (109 MHz) or Bruker ARX500 (202 MHz) spectrometers with H_3PO_4 (δ_P 0.00) as an external standard. Fast atom bombardment (FAB) mass spectra were obtained on a JEOL JMS HX110 spectrometer in the Center for Instrumental Analysis, Hokkaido University.

Column chromatography was carried out on Kanto silica gel 60 N (40–50 μm or 63–210 μm) or Wakogel C-200 (75–150 μm). Analytical thin-layer chromatography (TLC) was carried out on Merck Kieselgel 60 F_{254} plates. Visualization was accomplished with ultraviolet light and anisaldehyde or phosphomolybdic acid stain, followed by heating. HPLC analyses were performed on a JASCO PU-980 and UV-970 (detector, $\lambda=254$ nm). Retention times (t_R) and peak ratios were determined with a Shimadzu Chromatopac C-R6A. Hexane was HPLC grade, and filtered and degassed prior to use.

Reagents and solvents were purified by standard means or used as received unless otherwise noted. Dehydrated stabilizer free THF was purchased from Kanto Chemical Co. Inc. Dichloromethane and propionitrile were distilled from P_2O_5, and redistilled from calcium hydride prior to use. 4 Å molecular sieves was finely ground in mortar and heated in vacuo at 220 °C for 12 h.

All reactions were conducted under an argon atmosphere. Lactols **1a**[26] and **1b**[27] were prepared according to literature procedures.

4.2. Preparation of D-mannosyl donors

4.2.1. 2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl diphenyl phosphate (2a). Diphenylphosphoryl chloride (0.57 mL, 2.74 mmol) was added to a stirred solution of lactol **1a** (1.14 g, 2.11 mmol) and DMAP (645 mg, 5.28 mmol) in CH_2Cl_2 (15 mL) at 0 °C. After 30 min, the reaction was quenched with crushed ice, followed by stirring at room temperature for 15 min. The mixture was poured into a two-layer mixture of Et_2O (10 mL) and saturated aqueous $NaHCO_3$ (15 mL), and the whole was extracted with AcOEt (25 mL). The organic extract was washed with brine (2×15 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the pale yellow oil (1.74 g), which was purified by column chromatography (silica gel 40 g, 8:1 hexane/AcOEt with 2% Et_3N) to give diphenyl phosphate **2a** (1.41 g, 86%) as a colorless oil: $[\alpha]_D^{23}$ +29.6 (*c* 1.01, $CHCl_3$); IR (film) 3063, 3030, 2905, 2868, 1952, 1877, 1811, 1726, 1591, 1491, 1454, 1364, 1292, 1188, 1103, 1026, 949, 876, 739, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.53 (dd, J= 1.5, 11.2 Hz, 1H, H-6a), 3.74 (dd, J=4.1, 11.2 Hz, 1H, H-6b), 3.76 (dd, J=1.9, 3.1 Hz, 1H, H-2), 3.82 (dd, J=3.1, 9.6 Hz, 1H, H-3), 3.85 (ddd, J=1.5, 4.1, 9.8 Hz, 1H, H-5), 4.10 (dd, J=9.6, 9.8 Hz, 1H, H-4), 4.43 (d, J=11.8 Hz, 1H, OC*H*Ph), 4.46 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.48 (d, J= 11.8 Hz, 1H, OC*H*Ph), 4.52 (d, J=10.7 Hz, 1H, OC*H*Ph), 4.63 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.69 (s, 2H, OCH_2Ph), 4.85 (d, J=10.7 Hz, 1H, OC*H*Ph), 5.99 (dd, J=1.9, 4.3 (J_{H-P}) Hz, 1H, H-1), 7.13–7.19 (m, 8H, Ar-H), 7.24–7.35 (m, 22H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 68.4, 72.2, 72.7, 73.3, 74.1 (d, J_{C-P}=9.0 Hz), 74.2, 75.1, 78.8, 97.6 (d, J_{C-P}=7.0 Hz), 120.0 (d, J_{C-P}=5.0 Hz), 125.4 (d, J_{C-P}= 6.0 Hz), 127.4, 127.5, 127.60, 127.61, 127.72, 127.75, 127.88, 127.90, 128.21, 128.25, 128.32, 128.34, 129.71, 129.74, 137.5, 138.1, 138.15, 138.20, 150.2, 150.29, 150.34; ^{31}P NMR (202 MHz, $CDCl_3$) δ −13.4; FAB-HRMS *m/z* calcd for $C_{46}H_{46}O_9P$ $(M+H)^+$ 773.2879, found 773.2870. Anal. Calcd for $C_{46}H_{45}O_9P$: C, 71.49; H, 5.87, found: C, 71.27; H, 5.88.

4.2.2. 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranosyl diphenyl phosphate (2b). Diphenylphosphoryl chloride (0.37 mL, 1.8 mmol) was added to a stirred solution of lactol **1b** (673 mg, 1.5 mmol) and DMAP (367 mg, 3.0 mmol) in CH_2Cl_2 (7 mL) at 0 °C. After 30 min, the reaction was quenched with crushed ice, followed by stirring at room temperature for 15 min. The mixture was poured into a two-layer mixture of Et_2O (7 mL) and saturated aqueous $NaHCO_3$ (10 mL), and the whole was extracted with AcOEt (20 mL). The organic extract was washed with brine (2×10 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the pale yellow oil (1.50 g), which was purified by column chromatography (silica gel 40 g, 4:1 hexane/AcOEt with 2% Et_3N) to give diphenyl phosphate **2b** (838 mg, 82%) as a colorless oil: $[\alpha]_D^{25}$ +30.1 (*c* 2.00, $CHCl_3$); IR (film) 3065, 2868, 1589, 1489, 1454, 1373, 1288, 1188 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.75 (dd, J=10.0, 10.2 Hz, 1H, H-6ax), 3.80 (dd, J=1.5, 3.2 Hz, 1H, H-2), 3.85 (ddd, J= 4.7, 9.4, 10.2 Hz, 1H, H-5), 3.90 (dd, J=3.2, 10.1 Hz, 1H, H-3), 4.00 (dd, J=4.7, 10.0 Hz, 1H, H-6eq), 4.25 (dd, J= 9.4, 10.1 Hz, 1H, H-4), 4.55 (d, J=12.2 Hz, 1H, OC*H*Ph), 4.67 (d, J=12.0 Hz, 1H, OC*H*Ph), 4.73 (d, J=12.2 Hz, 1H, OC*H*Ph), 4.74 (d, J=12.0 Hz, 1H, OC*H*Ph), 5.57 (s, 1H, C*H*Ph), 5.88 (dd, J=1.5, 6.4 (J_{H-P}) Hz, 1H, H-1), 7.11–7.20 (m, 6H, Ar-H), 7.25–7.37 (m, 17H, Ar-H), 7.46–7.48 (m, 2H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 66.0, 68.0, 73.0, 73.7, 75.0, 75.7 (d, J_{C-P}=9.8 Hz), 78.0, 98.0 (d, J_{C-P}= 6.3 Hz), 101.4, 119.85 (d, J_{C-P}=5.0 Hz), 119.91 (d, J_{C-P}= 5.0 Hz), 125.50, 125.53, 125.9, 127.4, 127.5, 127.9, 128.0, 128.1, 128.2, 128.4, 128.8, 129.8, 137.2, 138.1, 150.1 (d, J_{C-P}=7.5 Hz), 150.2 (d, J_{C-P}=7.5 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ −13.4; FAB-HRMS *m/z* calcd for

$C_{39}H_{38}O_9P$ $(M+H)^+$681.2254, found 681.2252. Anal. Calcd for $C_{39}H_{37}O_9P$: C, 68.82; H, 5.48, found: C, 68.71; H, 5.71.

4.2.3. 2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl *N*,*N*,*N*′,*N*′-tetramethylphosphorodiamidate (3a). Butyllithium in hexane (1.58 M, 1.0 mL, 1.58 mmol) was added to a stirred solution of lactol **1a** (800 mg, 1.48 mmol) in THF (15 mL) at −78 °C. After 15 min, a solution of bis(dimethylamino)phosphorochloridate (0.22 mL, 1.48 mmol) in HMPA (2.0 mL) was added, and the mixture was allowed to warm to −20 °C over 30 min. After stirring at this temperature for 2 h, the reaction was quenched with crushed ice, followed by stirring at 0 °C for 30 min. The mixture was poured into a two-layer mixture of Et_2O (10 mL) and saturated aqueous $NaHCO_3$ (15 mL), and the whole was extracted with AcOEt (50 mL). The organic extract was washed with brine (2×15 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the yellow residue (1.55 g), which was purified by flash column chromatography (silica gel 40 g, 1:3→1:4 hexane/AcOEt) to give diamidate **3a** (850 mg, 85%) as a colorless oil: $[\alpha]_D^{24}$ +24.2 (*c* 1.00, $CHCl_3$); IR (film) 3030, 2895, 1954, 1454, 1306, 1225, 990 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.46 (d, J_{H-P}=10.1 Hz, 6H, N(C*H*$_3$)$_2$), 2.60 (d, J_{H-P}=10.1 Hz, 6H, N(C*H*$_3$)$_2$), 3.72 (dd, *J*=1.5, 10.9 Hz, 1H, H-6a), 3.80 (dd, *J*=4.7, 10.9 Hz, 1H, H-6b), 3.81 (dd, *J*=1.8, 3.1 Hz, 1H, H-2), 3.88 (dd, *J*=3.1, 9.5 Hz, 1H, H-3), 3.86 (ddd, *J*=1.5, 4.7, 9.7 Hz, 1H, H-5), 4.05 (dd, *J*=9.5, 9.7 Hz, 1H, H-4), 4.52 (d, *J*=12.0 Hz, 1H, OC*H*Ph), 4.55 (d, *J*=10.6 Hz, 1H, OC*H*Ph), 4.60 (s, 2H, OCH_2Ph), 4.66 (d, *J*=12.0 Hz, 1H, OC*H*Ph), 4.74 (d, *J*=12.1 Hz, 1H, OC*H*Ph), 4.78 (d, *J*=12.1 Hz, 1H, OC*H*Ph), 4.92 (d, *J*=10.6 Hz, 1H, OC*H*Ph), 5.75 (dd, *J*=1.8, 8.2 (J_{H-P}) Hz, 1H, H-1), 7.21 (m, 2H, Ar-H), 7.24–7.34 (m, 16H, Ar-H), 7.42 (m, 2H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 36.2 (d, J_{C-P}=3.9 Hz), 36.4 (d, J_{C-P}=4.3 Hz), 69.0, 71.8, 72.4, 73.3, 73.6, 74.4, 75.0 (d, J_{C-P}=6.5 Hz), 75.3, 78.5, 93.3 (d, J_{C-P}=3.8 Hz), 127.3, 127.51, 127.54, 127.6, 127.7, 127.9, 128.0, 128.08, 128.14, 128.19, 128.25, 137.9, 138.1, 138.21, 138.22; ^{31}P NMR (202 MHz, $CDCl_3$) δ 19.1; FAB-HRMS *m*/*z* calcd for $C_{38}H_{48}N_2O_7P$ $(M+H)^+$675.3199, found 675.3189. Anal. Calcd for $C_{38}H_{47}N_2O_7P$: C, 67.54; H, 7.16; N, 4.15, found: C, 67.71; H, 7.15; N, 4.29.

4.2.4. 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranosyl *N*,*N*,*N*′,*N*′-tetramethylphosphorodiamidate (3b). Butyllithium in hexane (1.59 M, 0.89 mL, 1.42 mmol) was added to a stirred solution of lactol **1b** (606 mg, 1.35 mmol) in THF (10 mL) at −78 °C. After 15 min, a solution of bis(dimethylamino)phosphorochloridate (0.20 mL, 1.35 mmol) in HMPA (1.5 mL) was added, and the mixture was allowed to warm to −20 °C over 30 min. After stirring at this temperature for 2 h, the reaction was quenched with crushed ice, followed by stirring at 0 °C for 30 min. The mixture was poured into a two-layer mixture of Et_2O (5 mL) and saturated aqueous $NaHCO_3$ (10 mL), and the whole was extracted with AcOEt (25 mL). The organic extract was washed with brine (2× 10 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the yellow residue (1.12 g), which was purified by column chromatography (silica gel 40 g, 1:3→1:4 hexane/AcOEt) to give diamidate **3b** (731 mg, 97%) as a colorless oil: $[\alpha]_D^{22}$ +31.9 (*c* 1.00, $CHCl_3$); IR (film) 3063, 3032, 1454, 1308, 1218, 993 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.45 (d, J_{H-P}=10.1 Hz, 6H, N(C*H*$_3$)$_2$), 2.62 (d, J_{H-P}=10.0 Hz, 6H, N(C*H*$_3$)$_2$), 3.82 (dd, *J*=1.5, 3.2 Hz, 1H, H-2), 3.85–3.91 (m, 2H, H-6ax, H-6eq), 3.93 (dd, *J*=3.2, 9.9 Hz, 1H, H-3), 4.23 (m, 1H, H-5), 4.29 (dd, *J*=9.5, 9.9 Hz, 1H, H-4), 4.66 (d, *J*=12.5 Hz, 1H, OC*H*Ph), 4.77 (d, *J*=12.0 Hz, 1H, OC*H*Ph), 4.81 (d, *J*=12.0 Hz, 1H, OC*H*Ph), 4.81 (d, *J*=12.5 Hz, 1H, OC*H*Ph), 5.65 (dd, *J*=1.5, 5.7 (J_{H-P}) Hz, 1H, H-1), 5.66 (s, 1H, C*H*Ph), 7.24–7.43 (m, 13H, Ar-H), 7.52 (m, 2H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 36.1 (d, J_{C-P}=4.2 Hz), 36.3 (d, J_{C-P}=4.2 Hz), 65.7, 68.5, 72.8, 73.3, 74.6, 76.7 (d, J_{C-P}=6.8 Hz), 77.3, 78.5, 94.3 (d, J_{C-P}=3.9 Hz), 101.3, 125.9, 127.5, 127.6, 127.7, 128.06, 128.13, 128.2, 128.3, 128.7, 137.4, 137.6, 138.2; ^{31}P NMR (202 MHz, $CDCl_3$) δ 18.8; FAB-HRMS *m*/*z* calcd for $C_{31}H_{40}N_2O_7P$ $(M+H)^+$583.2573, found 583.2568. Anal. Calcd for $C_{31}H_{39}N_2O_7P$: C, 63.91; H, 6.75; N, 4.81, found: C, 63.75; H, 6.81; N, 4.82.

4.2.5. 2,3,4,6-Tetra-*O*-benzyl-D-mannopyranosyl diethyl phosphite (4a). Diethyl chlorophosphite (0.26 mL, 1.81 mmol) was added to a stirred solution of lactol **1a** (0.85 g, 1.57 mmol) and Et_3N (0.44 mL, 3.14 mmol) in CH_2Cl_2 (15 mL) at 0 °C. After 30 min, the reaction was quenched with crushed ice, followed by stirring at room temperature for 15 min. The mixture was poured into a two-layer mixture of Et_2O (10 mL) and saturated aqueous $NaHCO_3$ (15 mL), and the whole was extracted with AcOEt (30 mL). The organic extract was washed with brine (2× 15 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the pale yellow oil (1.18 g), which was purified by column chromatography (silica gel 25 g, 8:1 hexane/AcOEt with 2% Et_3N) to give diethyl phosphite **4a** (755 mg, 73%, α:β=87:13) as a colorless oil. The anomeric α:β ratio of the product was determined by ^{31}P NMR: $[\alpha]_D^{24}$ +36.5 (*c* 1.00, $CHCl_3$); IR (film) 3063, 3030, 1454, 1310, 1207, 1101, 1028, 988 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (data for α-anomer) δ 1.16–1.19 (m, 6H, 2×OCH$_2$C*H*$_3$), 3.69–3.82 (m, 7H, H-2, H-6a, H-6b, 2× OCH_2CH$_3$), 3.94–3.96 (m, 2H, H-3, H-5), 4.05 (t, *J*=9.6 Hz, 1H, H-4), 4.51 (d, *J*=12.0 Hz, 1H, OC*H*Ph), 4.55 (d, *J*=10.8 Hz, 1H, OC*H*Ph), 4.61 (d, *J*=11.8 Hz, 1H, OC*H*Ph), 4.65 (d, *J*=11.8 Hz, 1H, OC*H*Ph), 4.66 (d, *J*=12.0 Hz, 1H, OC*H*Ph), 4.73 (d, *J*=12.5 Hz, 1H, OC*H*Ph), 4.76 (d, *J*=12.5 Hz, 1H, OC*H*Ph), 4.90 (d, *J*=10.8 Hz, 1H, OC*H*Ph), 5.56 (dd, *J*=1.5, 8.2 (J_{H-P}) Hz, 1H, H-1), 7.17 (m, 2H, Ar-H), 7.23–7.39 (m, 18H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 16.67, 16.71, 58.2 (d, J_{C-P}=9.8 Hz), 58.4 (d, J_{C-P}=11.9 Hz), 69.0, 72.1, 72.4, 72.8, 73.2, 74.7, 75.4 (d, J_{C-P}=3.2 Hz), 79.2, 91.9 (d, J_{C-P}=13.3 Hz, C-1α), 94.6 (d, J_{C-P}=12.9 Hz, C-1β), 127.3, 127.4, 127.5, 127.57, 127.63, 127.7, 127.8, 128.1, 128.15, 128.18, 138.1, 138.27, 138.30, 138.4; ^{31}P NMR (202 MHz, $CDCl_3$) δ 139.7 (β), 139.8 (α); FAB-HRMS *m*/*z* calcd for $C_{38}H_{46}O_8P$ $(M+H)^+$661.2931, found 661.2921. Anal. Calcd for $C_{38}H_{45}O_8P$: C, 69.08; H, 6.86, found: C, 68.92; H, 6.83.

4.2.6. 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-D-mannopyranosyl diethyl phosphite (4b). Diethyl chlorophosphite (0.21 mL, 1.47 mmol) was added to a stirred solution of lactol **1b** (576 mg, 1.28 mmol) and Et_3N (0.36 mL, 2.56 mmol) in CH_2Cl_2 (6 mL) at 0 °C. After 20 min, the

reaction was quenched with crushed ice, followed by stirring at room temperature for 15 min. The mixture was poured into a two-layer mixture of Et_2O (7 mL) and saturated aqueous $NaHCO_3$ (10 mL), and the whole was extracted with AcOEt (25 mL). The organic extract was washed with brine (2×10 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the pale yellow oil (741 mg), which was purified by column chromatography (silica gel 15 g, 8:1 hexane/AcOEt with 2% Et_3N) to give diethyl phosphite **4b** (644 mg, 88%, α:β=93:7) as a colorless oil. The anomeric α:β ratio of the product was determined by ^{31}P NMR: $[\alpha]_D^{23}$ +45.7 (*c* 1.01, $CHCl_3$); IR (film) 3065, 3032, 1454, 1242, 1215, 1026, 916 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (data for α-anomer) δ 1.18–1.27 (m, 6H, 2×OCH_2CH_3), 3.72–3.89 (m, 6H, H-2, H-6ax, 2×OCH_2CH_3), 3.97 (ddd, 1H, *J*=4.6, 9.6, 10.1 Hz, H-5), 4.01 (dd, *J*=3.1, 10.0 Hz, 1H, H-3), 4.13 (dd, *J*=4.6, 10.1 Hz, 1H, H-6eq), 4.27 (dd, *J*=9.6, 10.0 Hz, 1H, H-4), 4.66 (d, *J*=12.2 Hz, 1H, OC*H*Ph), 4.75 (d, *J*=12.2 Hz, 1H, OC*H*Ph), 4.83 (d, *J*=12.2 Hz, 1H, OC*H*Ph), 4.85 (d, *J*=12.2 Hz, 1H, OC*H*Ph), 5.45 (dd, *J*=1.4, 8.2 (J_{H-P}) Hz, 1H, H-1), 5.65 (s, 1H, C*H*Ph), 7.26–7.40 (m, 13H, Ar-H), 7.51 (m, 2H, Ar-H). The β-anomer had an additional signal at 5.62 (s, 1H, PhC*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 16.70, 16.74, 16.8, 58.2 (d, J_{C-P}=10.0 Hz), 58.5 (d, J_{C-P}=12.1 Hz), 65.0, 68.6, 73.1, 73.4, 75.5, 77.1 (d, J_{C-P}=3.3 Hz), 79.0, 93.2 (d, J_{C-P}=13.4 Hz, C-1α), 94.9 (d, J_{C-P}=13.1 Hz, C-1β), 101.4, 126.0, 127.4, 127.5, 127.7, 128.0, 128.1, 128.2, 128.3, 128.7, 137.6, 137.9, 138.5; ^{31}P NMR (202 MHz, $CDCl_3$) δ 139.0 (β), 139.5 (α); FAB-HRMS *m/z* calcd for $C_{31}H_{38}O_8P$ $(M+H)^+$569.2304, found 569.2295.

4.3. Glycosidations of 2,3,4,6-tetra-*O*-benzyl-D-mannosyl donors 2a–4a

4.3.1. Typical procedure for glycosidation of 2,3,4,6-tetra-*O*-benzyl-D-mannosyl donors: methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-mannopyranosyl)-α-D-glucopyranoside (7). TMSOTf in CH_2Cl_2 (1.0 M, 0.11 mL, 0.11 mmol) was added to a stirred solution of diphenyl phosphate **2a** (73.6 mg, 0.10 mmol) and alcohol **5** (51.1 mg, 0.11 mmol) in CH_2Cl_2 (1 mL) at −78 °C. After stirring at this temperature for 1 h, the reaction was quenched with Et_3N (0.15 mL). The reaction mixture was poured into a two-layer mixture of AcOEt (3 mL) and $NaHCO_3$ (6 mL), and the whole was extracted with AcOEt (15 mL). The organic extract was successively washed with saturated aqueous $NaHCO_3$ (6 mL) and brine (2×6 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (100.2 mg), from which an anomeric mixture of the known disaccharide **7**[13i] (84.4 mg, 86%, α:β=21:79) was obtained as a colorless oil after column chromatography (silica gel 7 g, 5:1 hexane/AcOEt). The anomeric ratio of the disaccharide was determined by HPLC analysis [column, Zorbax® Sil, 4.6×250 mm; eluent, 7:1 hexane/THF; flow rate, 1.5 mL/min; detection, 254 nm; t_R (α-mannoside)=29.4 min, t_R (β-mannoside)=31.7 min]. The α- and β-mannosides were separated by flash column chromatography with 5:1 hexane/AcOEt.

4.3.2. Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-D-mannopyranosyl)-α-D-glucopyranoside (8). The glycosidation was performed according to the typical procedure (1 mL, CH_2Cl_2, −78 °C, 1.5 h) employing diphenyl phosphate **2a** (73.6 mg, 0.10 mmol), alcohol **6** (51.1 mg, 0.11 mmol) and TMSOTf (1.0 M in CH_2Cl_2, 0.11 mL, 0.11 mmol). An anomeric mixture of the known disaccharide **8**[13i] (74.2 mg, 75%, α:β=77:23) was obtained as a colorless oil from the crude product (107 mg) after column chromatography (silica gel 12 g, 20:1→17:1 toluene/AcOEt). The anomeric ratio of the product was determined by HPLC analysis [eluent, 4:1 hexane/AcOEt; flow rate, 1.0 mL/min; t_R (α-mannoside)=14.3 min, t_R (β-mannoside)=26.2 min].

4.4. Glycosidations of 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-mannosyl donors 2b–4b

4.4.1. Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-mannopyranosyl)-α-D-glucopyranoside (9). The glycosidation was performed according to the typical procedure (1 mL CH_2Cl_2, −45 °C, 30 min) employing diethyl phosphite **4b** (56.9 mg, 0.10 mmol), alcohol **5** (51.1 mg, 0.11 mmol) and TMSOTf (1.0 M in CH_2Cl_2, 0.11 mL, 0.11 mmol). An anomeric mixture of disaccharide **9**[25b] (73.9 mg, 83%, α:β=10:90) was obtained as a white solid from the crude product (102 mg) after column chromatography (silica gel 5 g, 4:1 hexane/AcOEt). The anomeric ratio of **9** was determined by HPLC analysis [eluent, 4:1 hexane/AcOEt; flow rate, 1.0 mL/min; t_R (α-mannoside)=21.1 min, t_R (β-mannoside)=24.4 min].

Data for 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranosyl fluoride (**10**): $[\alpha]_D^{23}$ +13.0 (*c* 1.06, $CHCl_3$); IR ($CHCl_3$) 3624, 3026, 3016, 2401, 1226, 1205, 792, 719 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.85 (t, *J*=10.0 Hz, 1H, H-6ax), 3.91–3.98 (m, 3H, H-2, H-3, H-5), 4.26–4.31 (m, 2H, H-4, H-6eq), 4.69 (d, *J*=12.0 Hz, 1H, OC*H*Ph), 4.71 (d, *J*=12.0 Hz, 1H, OC*H*Ph), 4.87 (d, *J*=12.0 Hz, 2H, 2×OC*H*Ph), 5.49 (dd, *J*=1.4, 49.8 (J_{H-F}) Hz, 1H, H-1), 5.64 (s, 1H, C*H*Ph), 7.29–7.40 (13H, m, Ar-H), 7.50 (2H, m, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 66.0 (d, J_{C-F}=1.8 Hz), 68.1, 73.2, 74.0, 74.9 (d, J_{C-F}=36.0 Hz), 75.5, 78.1, 101.4, 106.8 (d, J_{C-F}=222.6 Hz), 125.9, 127.4, 127.5, 127.8, 127.9, 128.0, 128.2, 128.3, 128.7, 137.3, 137.5, 138.2; FAB-HRMS *m/z* calcd for $C_{27}H_{28}O_5F$ $(M+H)^+$451.1921, found 451.1950.

Data for diethyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranosylphosphonate (**12**): $[\alpha]_D^{25}$ −73.0 (*c* 1.33, $CHCl_3$); IR ($CHCl_3$) 3013, 1454, 1369, 1249, 1227, 1097, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.16 (t, *J*=7.1 Hz, 3H, OCH_2CH_3), 1.31 (t, *J*=7.0 Hz, 3H, OCH_2CH_3), 3.41 (ddd, *J*=5.0, 9.8, 10.5 Hz, 1H, H-5), 3.72 (dd, *J*=3.0, 9.8 Hz, 1H, H-3), 3.85 (t, *J*=10.5 Hz, 1H, H-6ax), 3.89 (dd, *J*=1.1, 15.3 (J_{H-P}) Hz, 1H, H-1), 3.98–4.16 (m, 4H, OCH_2CH_3), 4.27–4.34 (m, 3H, H-2, H-4, H-6eq), 4.75 (d, *J*=12.5 Hz, 1H, OC*H*Ph), 4.81 (d, *J*=10.4 Hz, 1H, OC*H*Ph), 4.85 (d, *J*=12.5 Hz, 1H, OC*H*Ph), 5.11 (d, *J*=10.4 Hz, 1H, OC*H*Ph), 5.65 (s, 1H, C*H*Ph), 7.25–7.38 (m, 11H, Ar-H), 7.47–7.51 (m, 4H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 16.2 (d, J_{C-P}=5.9 Hz), 16.4 (d, J_{C-P}=5.8 Hz), 62.3 (d, J_{C-P}=6.5 Hz), 63.3 (d, J_{C-P}=6.4 Hz), 68.3, 72.8, 73.8, 73.9, 75.4, 75.5 (d, J_{C-P}=2.2 Hz), 77.1 (d, J_{C-P}=173 Hz), 78.85, 79.5 (d, J_{C-P}=15.8 Hz), 101.5, 126.05,

127.48, 127.51, 127.6, 128.0, 128.2, 128.4, 128.5, 128.9, 137.5, 138.3, 138.4; ^{31}P NMR (109 MHz, $CDCl_3$) δ 17.6; FAB-HRMS *m/z* calcd for $C_{31}H_{38}O_8P$ $(M+H)^+$569.2304, found 569.2257.

4.4.2. Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-mannopyranosyl)-α-D-glucopyranoside (23). The glycosidation was performed according to the typical procedure (1 mL CH_2Cl_2, −45 °C, 60 min) employing diethyl phosphite **4b** (56.9 mg, 0.10 mmol), alcohol **6** (51.1 mg, 0.11 mmol) and TMSOTf (1.0 M in CH_2Cl_2, 0.11 mL, 0.11 mmol). An anomeric mixture of the known disaccharide **23**[25b] (75.0 mg, 84%, α:β=11:89) was obtained as a colorless oil from the crude product (106.8 mg) after column chromatography (silica gel 10 g, 4:1 hexane/AcOEt). The anomeric ratio of **23** was determined by HPLC analysis [eluent, 5:1 hexane/AcOEt; flow rate, 1.0 mL/min; t_R (α-mannoside)=16.2 min, t_R (β-mannoside)=30.6 min].

4.4.3. Methyl 2,3,4-tri-*O*-acetyl-6-*O*-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-mannopyranosyl)-α-D-glucopyranoside (24). The glycosidation was performed according to the typical procedure (1 mL CH_2Cl_2, −45 °C, 30 min) employing diethyl phosphite **4b** (56.9 mg, 0.10 mmol), alcohol **13** (35.2 mg, 0.11 mmol) and TMSOTf (1.0 M in CH_2Cl_2, 0.11 mL, 0.11 mmol). An anomeric mixture of the known disaccharide **24**[17d] (63.7 mg, 85%, α:β=11:89) was obtained from the crude product (88.7 mg) after column chromatography (silica gel 5 g, 2:1 hexane/AcOEt). The anomeric ratio of **24** was determined by HPLC analysis [eluent, 4:1 hexane/THF; flow rate, 1.0 mL/min; t_R (α-mannoside)=21.1 min, t_R (β-mannoside)=26.1 min].

4.4.4. Methyl 2-azido-3,4-di-*O*-benzyl-2-deoxy-4-*O*-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-mannopyranosyl)-β-D-glucopyranoside (25). The glycosidation was performed according to the typical procedure (1 mL CH_2Cl_2, −45 °C, 60 min) employing diethyl phosphite **4b** (56.9 mg, 0.10 mmol), alcohol **14** (43.9 mg, 0.11 mmol) and TMSOTf (1.0 M in CH_2Cl_2, 0.11 mL, 0.11 mmol). An anomeric mixture of disaccharide **25** (59.8 mg, 72%, α:β=17:83) was obtained as a colorless oil from the crude product (100.5 mg) after flash column chromatography (silica gel 7 g, 30:1 toluene/AcOEt). The anomeric ratio of **25** was determined by HPLC analysis [eluent, 5:1 hexane/AcOEt; flow rate, 1.0 mL/min; t_R (α-mannoside)=10.3 min, t_R (β-mannoside)=18.9 min]. The α- and β-mannosides were separated by flash column chromatography with 30:1 toluene/AcOEt. Data for β-anomer (**25**β): $[\alpha]_D^{24}$ −58.2 (*c* 1.00, $CHCl_3$); IR (film) 3030, 2922, 2857, 2110, 1497, 1454, 1366, 1279, 1213, 1092, 1055 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.07 (ddd, *J*=4.8, 9.6, 10.4 Hz, 1H, H-5′), 3.29 (ddd, *J*=2.0, 3.4, 9.4 Hz, 1H, H-5), 3.34–3.41 (m, 3H, H-2, H-3, H-3′), 3.49 (t, *J*=10.4 Hz, 1H, H-6′ax), 3.54 (dd, *J*=3.4, 11.1 Hz, 1H, H-6a), 3.56 (s, 3H, OC*H*$_3$), 3.64 (dd, *J*=2.0, 11.1 Hz, 1H, H-6b), 3.72 (d, *J*=3.0 Hz, 1H, H-2′), 3.96 (dd, *J*=9.0, 9.4 Hz, 1H, H-4), 4.05 (dd, *J*=4.8, 10.4 Hz, 1H, H-6′eq), 4.09 (t, *J*=9.6 Hz, 1H, H-4′), 4.13 (d, *J*=7.5 Hz, 1H, H-1), 4.38 (d, *J*=12.1 Hz, 1H, OC*H*Ph), 4.48 (s, 1H, H-1′), 4.58 (d, *J*=12.4 Hz, 1H, OC*H*Ph), 4.63 (d, *J*=12.1 Hz, 1H, OC*H*Ph), 4.64 (d, *J*=10.4 Hz, 1H, OC*H*Ph), 4.74 (d, *J*=12.4 Hz, 1H, OC*H*Ph), 4.79 (d, *J*=11.9 Hz, 1H, OC*H*Ph), 4.87 (d, *J*=11.9 Hz, 1H, OC*H*Ph), 5.09 (d, *J*=10.4 Hz, 1H, OC*H*Ph), 5.51 (s, 1H, C*H*Ph), 7.20–7.41 (m, 23H, Ar-H), 7.47 (m, 2H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 57.1, 65.7, 67.3, 68.3, 68.5, 72.6, 73.6, 74.8, 75.11, 75.13, 77.1, 78.4, 78.7, 81.6, 101.3 (C-1′), 101.4, 102.8 (C-1), 126.1, 127.4, 127.49, 127.54, 127.8, 127.96, 128.01, 128.10, 128.14, 128.30, 128.31, 128.5, 128.8, 137.6, 138.48, 138.53, 138.6; FAB-HRMS *m/z* calcd for $C_{48}H_{52}N_3O_{10}$ $(M+H)^+$830.3653, found 830.3660. Data for α-anomer (**25**α): $[\alpha]_D^{24}$ −16.0 (*c* 0.30, $CHCl_3$); IR (film) 3032, 2922, 2858, 2110, 1496, 1454, 1363, 1275, 1116, 1064 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.32 (dd, *J*=9.4, 9.8 Hz, 1H, H-3), 3.38–3.42 (m, 2H, H-2, H-5), 3.57 (s, 3H, OC*H*$_3$), 3.72 (dd, *J*=4.5, 11.0 Hz, 1H, H-6a), 3.76–3.81 (m, 4H, H-4, H-6b, H-2′, H-6′ax), 3.83 (dt, *J*=3.9, 10.3 Hz, 1H, H-5′), 3.90 (dd, *J*=3.1, 10.3 Hz, 1H, H-3′), 4.12 (m, 1H, H-6′eq), 4.19 (d, *J*=7.9 Hz, 1H, H-1), 4.24 (t, *J*=10.3 Hz, 1H, H-4′), 4.25 (d, *J*=11.8 Hz, 1H, OC*H*Ph), 4.47 (d, *J*=11.8 Hz, 1H, OC*H*Ph), 4.54 (d, *J*=11.4 Hz, 1H, OC*H*Ph), 4.56 (d, *J*=12.1 Hz, 1H, OC*H*Ph), 4.59 (d, *J*=12.2 Hz, 1H, OC*H*Ph), 4.63 (d, *J*=12.1 Hz, 1H, OC*H*Ph), 4.82 (d, *J*=12.2 Hz, 1H, OC*H*Ph), 4.94 (d, *J*=11.4 Hz, 1H, OC*H*Ph), 5.26 (d, *J*=1.2 Hz, 1H, H-1′), 5.61 (s, 1H, C*H*Ph), 7.15 (m, 2H, Ar-H), 7.21–7.37 (m, 21H, Ar-H), 7.50 (m, 2H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 57.1, 65.3, 66.2, 68.6, 69.0, 73.1, 73.4, 73.6, 74.6, 74.7, 76.2, 76.3, 77.7, 79.0, 83.0, 101.2 (C-1′), 101.4, 103.0 (C-1), 126.1, 127.0, 127.46, 127.48, 127.6, 127.7, 127.8, 128.2, 128.3, 128.4, 128.6, 128.8, 137.7, 138.1, 138.2, 138.7; FAB-HRMS *m/z* calcd for $C_{48}H_{52}N_3O_{10}$ $(M+H)^+$830.3653, found 830.3669.

4.4.5. 6-*O*-(2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-D-mannopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (26). The glycosidation was performed according to the typical procedure (1 mL CH_2Cl_2, −45 °C, 30 min) employing diethyl phosphite **4b** (56.9 mg, 0.10 mmol), alcohol **15** (28.6 mg, 0.11 mmol) and TMSOTf (1.0 M in CH_2Cl_2, 0.11 mL, 0.11 mmol). An anomeric mixture of the known disaccharide **26**[17d] (61.5 mg, 89%, α:β=24:76) was obtained as a colorless oil from the crude product (83.0 mg) after column chromatography (silica gel 6 g, 5:1 hexane/AcOEt). The anomeric ratio of **26** was determined by HPLC analysis [eluent, 7:2 hexane/AcOEt; flow rate, 1.0 mL/min; t_R (α-mannoside)=8.2 min, t_R (β-mannoside)=11.4 min].

4.4.6. Benzyl 2,4,6-tri-*O*-benzyl-3-*O*-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-mannopyranosyl)-α-D-glucopyranoside (27). The glycosidation was performed according to the typical procedure (1 mL CH_2Cl_2, −45 °C, 30 min) employing diethyl phosphite **4b** (56.9 mg, 0.10 mmol), alcohol **16** (60.0 mg, 0.11 mmol) and TMSOTf (1.0 M in CH_2Cl_2, 0.11 mL, 0.11 mmol). An anomeric mixture of disaccharide **27** (75.4 mg, 77%, α:β=15:85) was obtained as a colorless syrup from the crude product (105.9 mg) after column chromatography (silica gel 6 g, 5:1 hexane/AcOEt). The anomeric ratio of the product was determined by ^{1}H NMR [integration of benzylidene proton, β-anomer (5.57 ppm), α-anomer (5.60 ppm)]. The α- and β-mannosides were separated by flash column chromatography with 5:1 hexane/AcOEt. Data for β-anomer (**27**β): $[\alpha]_D^{23}$ +32.5 (*c* 1.01, $CHCl_3$); IR ($CHCl_3$) 3067, 3025, 3015, 2872, 1497, 1454, 1366, 1209, 1090, 791, 671 cm^{-1}; ^{1}H NMR (500 MHz,

$CDCl_3$) δ 3.27 (ddd, J=4.9, 9.5, 10.4 Hz, 1H, H-5′), 3.41 (dd, J=3.6, 9.7 Hz, 1H, H-2), 3.45 (dd, J=3.0, 9.9 Hz, 1H, H-3′), 3.56–3.59 (m, 2H, H-4, H-6a), 3.68–3.75 (m, 2H, H-6b, H-6′ax), 3.77 (m, 1H, H-5), 3.81 (d, J=3.0 Hz, 1H, H-2′), 4.14 (dd, J=9.5, 9.9 Hz, 1H, H-4′), 4.17 (dd, J=9.2, 9.7 Hz, 1H, H-3), 4.21 (dd, J=4.9, 10.4 Hz, 1H, H-6′eq), 4.26 (d, J=11.6 Hz, 1H, OC*H*Ph), 4.33 (d, J=10.1 Hz, 1H, OC*H*Ph), 4.37 (d, J=11.6 Hz, 1H, OC*H*Ph), 4.48–4.52 (m, 3H, 3×OC*H*Ph), 4.62–4.67 (m, 3H, 3×OC*H*Ph), 4.84–4.90 (m, 4H, H-1, H-1′, 2×OC*H*Ph), 5.13 (d, J=10.1 Hz, 1H, OC*H*Ph), 5.57 (s, 1H, C*H*Ph), 7.15 (m, 2H, Ar-H), 7.21–7.36 (m, 29H, Ar-H), 7.45–7.49 (m, 4H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 67.3, 68.4, 68.7, 69.2, 70.1, 72.5, 72.6, 73.6, 74.7, 74.9, 75.9, 78.6, 78.8, 80.3, 81.1, 94.9 (C-1′), 101.3, 102.8 (C-1), 126.1, 127.4, 127.47, 127.51, 127.7, 127.9, 127.97, 128.02, 128.05, 128.06, 128.11, 128.25, 128.31, 128.37, 128.39, 128.5, 128.7, 136.9, 137.7, 137.8, 138.0, 138.6, 138.9; FAB-HRMS m/z calcd for $C_{61}H_{62}O_{11}Na$ $(M+Na)^+$993.4190, found 993.4234. Anal. Calcd for $C_{61}H_{62}O_{11}$: C, 75.44; H, 6.43, found C, 75.13; H, 6.55. Data for α-anomer (**27**α): $[\alpha]_D^{24}$ +38.2 (c 0.33, $CHCl_3$); IR ($CHCl_3$) 3029, 3007, 2928, 1497, 1454, 1366, 1229, 1071, 1026, 756, 737, 716, 669 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.38 (dd, J=3.7, 9.7 Hz, 1H, H-2), 3.50 (dd, J=1.8, 10.8 Hz, 1H, H-6a), 3.58–3.63 (m, 2H, H-4, H-6b), 3.74–3.81 (m, 3H, H-5, H-2′, H-6′ax), 3.96 (dd, J=3.1, 9.6 Hz, 1H, H-3′), 4.14–4.19 (m, 2H, H-3, H-6′eq), 4.22 (t, J=9.6 Hz, 1H, H-4′), 4.29 (ddd, J=4.7, 9.6, 9.9 Hz, 1H, H-5′), 4.36 (d, J=12.0 Hz, 1H, OC*H*Ph), 4.41–4.49 (m, 5H, 5×OC*H*Ph), 4.53–4.61 (m, 4H, 4×OC*H*Ph), 4.63 (d, J=12.2 Hz, 1H, OC*H*Ph), 4.80 (d, J=12.5 Hz, 1H, OC*H*Ph), 4.82 (d, J=3.7 Hz, 1H, H-1), 5.34 (d, J=1.0 Hz, 1H, H-1′), 5.60 (s, 1H, C*H*Ph), 7.14–7.36 (m, 33H, Ar-H), 7.47 (m, 2H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 64.2, 68.3, 68.8, 69.3, 70.0, 72.6, 73.0, 73.2, 73.6, 74.0, 76.5, 77.5, 77.8, 78.8, 79.2, 95.6 (C-1′), 99.9 (C-1), 101.4, 126.2, 126.8, 127.4, 127.5, 127.6, 127.7, 127.77, 127.83, 127.96, 128.04, 128.1, 128.2, 128.3, 128.36, 128.39, 128.44, 128.5, 128.6, 137.2, 137.7, 137.8, 138.0, 138.1, 138.2, 138.9; FAB-HRMS m/z calcd for $C_{61}H_{63}O_{11}$ $(M+H)^+$971.4371, found 971.4413.

4.4.7. Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-mannopyranosyl)-β-D-glucopyranoside (28). The glycosidation was performed according to the typical procedure (1 mL CH_2Cl_2, −45 °C, 30 min) employing diethyl phosphite **4b** (56.9 mg, 0.10 mmol), alcohol **17** (51.2 mg, 0.11 mmol) and TMSOTf (1.0 M in CH_2Cl_2, 0.11 mL, 0.11 mmol). An anomeric mixture of disaccharide **28** (85.6 mg, 96%, α:β=5:95) was obtained as a colorless syrup from the crude product (105.4 mg) after column chromatography (silica gel 15 g, 20:1→15:1 toluene/AcOEt). The anomeric ratio of **28** was determined by HPLC analysis [eluent, 4:1 hexane/AcOEt; flow rate, 1.0 mL/min; t_R (α-mannoside)=4.9 min, t_R (β-mannoside)=26.7 min]. The α- and β-mannosides were separated by column chromatography with 5:1 hexane/AcOEt. Data for β-anomer (**28**β): $[\alpha]_D^{24}$ −27.5 (c 1.02, $CHCl_3$); IR (film) 3021, 2976, 2895, 1522, 1424, 1215, 1047, 928, 775, 673 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.25 (ddd, J=4.8, 9.6, 10.3 Hz, 1H, H-5′), 3.37 (dd, J=2.9, 9.6 Hz, 1H, H-3′), 3.48 (m, 1H, H-5), 3.54 (s, 3H, OCH_3), 3.56–3.67 (m, 3H, H-2, H-3, H-4), 3.70–3.77 (m, 3H, H-6a, H-6b, H-2′), 3.92 (t, J=10.3 Hz, 1H, H-6′ax), 4.18 (t, J=9.6 Hz, 1H, H-4′), 4.30 (dd, J=4.8, 10.3 Hz, 1H, H-6′eq), 4.36 (d, J=7.1 Hz, 1H, H-1), 4.45 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.51 (d, J=11.7 Hz, 1H, OC*H*Ph), 4.55–4.60 (m, 3H, 3×OC*H*Ph), 4.64 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.72–4.74 (m, 2H, H-1′, OC*H*Ph), 4.78 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.84 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.85 (d, J=11.7 Hz, 1H, OC*H*Ph), 5.59 (s, 1H, C*H*Ph), 7.14–7.38 (m, 28H, Ar-H), 7.48 (m, 2H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 56.7, 67.4, 68.6, 68.7, 72.5, 73.5, 74.5, 74.78, 74.81, 75.1, 76.4, 78.2, 78.6, 78.7, 80.9, 85.0, 101.3, 102.0 (C-1′), 102.6 (C-1), 126.0, 126.9, 127.3, 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 128.1, 128.2, 128.3, 128.37, 128.42, 128.7, 137.6, 137.8, 138.1, 138.4, 138.5; FAB-HRMS m/z calcd for $C_{55}H_{59}O_{11}$ $(M+H)^+$895.4057, found 895.4059. Anal. Calcd for $C_{55}H_{58}O_{11}$: C, 73.81; H, 6.53, found: C, 73.62; H, 6.54. Data for α-anomer (**28**α): $[\alpha]_D^{24}$ +51.1 (c 1.00, $CHCl_3$); IR (film) 3030, 2926, 2865, 1497, 1454, 1368, 1215, 1092, 914, 750, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.40 (s, 3H, OCH_3), 3.42 (ddd, J=1.5, 4.5, 9.4 Hz, 1H, H-5), 3.48 (dd, J=9.1, 9.2 Hz, 1H, H-3), 3.59 (dd, J=7.8, 9.1 Hz, 1H, H-2), 3.60 (dd, J=9.2, 9.4 Hz, 1H, H-4), 3.67 (dd, J=4.5, 9.8 Hz, 1H, H-6a), 3.72 (dd, J=1.5, 9.8 Hz, 1H, H-6b), 3.77 (t, J=10.0 Hz, 1H, H-6′ax), 3.84 (dd, J=1.0, 3.1 Hz, 1H, H-2′), 3.92 (dd, J=3.1, 10.0 Hz, 1H, H-3′), 4.03 (ddd, J=4.8, 9.6, 10.0 Hz, 1H, H-5′), 4.09 (dd, J=4.8, 10.0 Hz, 1H, H-6′eq), 4.13 (d, J=7.8 Hz, 1H, H-1), 4.24 (dd, J=9.6, 10.0 Hz, 1H, H-4′), 4.50 (d, J=10.8 Hz, 1H, OC*H*Ph), 4.53 (d, J=12.3 Hz, 1H, OC*H*Ph), 4.60 (d, J=12.3 Hz, 1H, OC*H*Ph), 4.64 (d, J=12.3 Hz, 1H, OC*H*Ph), 4.70 (d, J=10.7 Hz, 1H, OC*H*Ph), 4.74–4.81 (m, 5H, 5×OC*H*Ph), 5.38 (d, J=1.0 Hz, 1H, H-1′), 5.60 (s, 1H, C*H*Ph), 7.11–7.16 (m, 5H, Ar-H), 7.22–7.43 (m, 25H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 56.7, 64.4, 68.66, 68.70, 72.9, 73.0, 73.5, 74.9, 75.1, 75.7, 75.9, 76.1, 76.9, 78.2, 79.1, 83.2, 98.7 (C-1′), 101.3, 104.3 (C-1), 126.2, 127.4, 127.56, 127.60, 127.62, 127.7, 127.8, 127.9, 128.0, 128.2, 128.3, 128.35, 128.38, 128.6, 137.7, 137.90, 137.94, 138.0, 138.2, 138.6; FAB-HRMS m/z calcd for $C_{55}H_{59}O_{11}$ $(M+H)^+$895.4057, found 895.4064. Anal. Calcd for $C_{55}H_{58}O_{11}$: C, 73.81; H, 6.53, found: C, 73.48; H, 6.60.

4.4.8. Methyl 4-*O*-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-mannopyranosyl)-2,3-*O*-isopropylidene-α-L-rhamnopyranoside (29). The glycosidation was performed according to the typical procedure (1 mL CH_2Cl_2, −45 °C, 30 min) employing diethyl phosphite **4b** (56.9 mg, 0.10 mmol), alcohol **18** (25.6 mg, 0.11 mmol) and TMSOTf (1.0 M in CH_2Cl_2, 0.11 mL, 0.11 mmol). An anomeric mixture of the known disaccharide **29**[17d] (59.1 mg, 89%, α:β=11:89) was obtained as a colorless oil from the crude product (79 mg) after column chromatography (silica gel 7 g, 10:1 hexane/AcOEt). The anomeric ratio of **29** was determined by HPLC analysis [eluent, 13:1 hexane/AcOEt; flow rate, 1.0 mL/min; t_R (β-mannoside)=47.7 min, t_R (α-mannoside)=51.9 min].

4.4.9. 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-D-mannopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranosyl *N*,*N*,*N*′,*N*′-tetramethylphosphorodiamidate (30). The glycosidation was performed according to the typical procedure (1 mL CH_2Cl_2, −45 °C, 30 min) employing diethyl phosphite **4b** (56.9 mg, 0.10 mmol), alcohol **19** (68.9 mg,

0.11 mmol) and TMSOTf (1.0 M in CH_2Cl_2, 0.20 mL, 0.20 mmol). An anomeric mixture of disaccharide **30** (90.0 mg, 85%, α:β=14:86) was obtained as a colorless syrup from the crude product (101 mg) after column chromatography (silica gel 4 g, 3:4 hexane/AcOEt). The anomeric ratio of the product was determined by ^{13}C NMR [peak height of C-1′, β-anomer (102.7 ppm), α-anomer (99.9 ppm)]. The α- and β-mannosides were separated by flash column chromatography with 10:1 CH_2Cl_2/acetone. Data for β-anomer (**30**β): $[\alpha]_D^{23}$ −5.20 (*c* 1.07, $CHCl_3$); IR ($CHCl_3$) 3016, 1730, 1452, 1278, 1093 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.59 (d, J_{H-P}=10.1 Hz, 6H, N(C*H*$_3$)$_2$), 2.65 (d, J_{H-P}=10.0 Hz, 6H, N(C*H*$_3$)$_2$), 3.27 (ddd, J=4.8, 9.6, 10.2 Hz, 1H, H-5′), 3.60 (dd, J=3.0, 9.9 Hz, 1H, H-3′), 3.68 (dd, J=5.0, 11.6 Hz, 1H, H-6a), 3.86 (dd, J=10.2, 10.4 Hz, 1H, H-6′ax), 4.10 (d, J=3.0 Hz, 1H, H-2′), 4.17 (dd, J=0.9, 11.6 Hz, 1H, H-6b), 4.18 (dd, J=9.6, 9.9 Hz, 1H, H-4′), 4.23 (dd, J=4.8, 10.4 Hz, 1H, H-6′eq), 4.448 (s, 1H, H-1′), 4.453 (ddd, J=0.9, 5.0, 10.0 Hz, 1H, H-5), 4.62 (d, J=12.5 Hz, 1H, OC*H*Ph), 4.71 (d, J=12.5 Hz, 1H, OC*H*Ph), 4.93 (d, J=12.0 Hz, 1H, OC*H*Ph), 4.99 (d, J=12.0 Hz, 1H, OC*H*Ph), 5.35 (ddd, J=3.2, 10.0, 1.6 (J_{H-P}) Hz, 1H, H-2), 5.58 (s, 1H, C*H*Ph), 5.63 (t, J=10.0 Hz, 1H, H-4), 6.13 (dd, J=3.2, 8.1 (J_{H-P}) Hz, 1H, H-1), 6.17 (t, J=10.0 Hz, 1H, H-3), 7.26–7.55 (m, 24H, Ar-H), 7.87 (m, 2H, Ar-H), 7.92–7.96 (m, 4H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 36.4 (d, J_{C-P}=3.9 Hz), 36.5 (d, J_{C-P}=3.9 Hz), 67.6, 68.1, 68.3, 68.4, 68.6, 70.0, 70.8, 71.5 (d, J_{C-P}=6.3 Hz), 72.2, 75.1, 76.2, 77.2, 77.9, 78.4, 92.0 (d, J_{C-P}=3.3 Hz, C-1), 101.3, 102.7 (C-1′), 126.0, 127.4, 127.5, 128.07, 128.13, 128.2, 128.27, 128.33, 128.34, 128.4, 128.68, 128.74, 128.9, 129.6, 129.7, 129.8, 133.2, 133.3, 133.5, 137.5, 138.3, 138.5, 165.2, 165.4, 165.9; ^{31}P NMR (109 MHz, $CDCl_3$) δ 19.9; FAB-HRMS *m*/*z* calcd for $C_{58}H_{62}N_2O_{15}P$ $(M+H)^+$1057.3888, found 1057.3900. Anal. Calcd for $C_{58}H_{61}N_2O_{15}P$: C, 65.90; H, 5.82; N, 2.65, found: C, 65.66; H, 5.88; N, 2.72. Data for α-anomer (**30**α): $[\alpha]_D^{24}$ +43.3 (*c* 0.86, $CHCl_3$); IR ($CHCl_3$) 3016, 1730, 1452, 1278, 1093 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.59 (d, J_{H-P}=10.5 Hz, 6H, N(C*H*$_3$)$_2$), 2.66 (d, J_{H-P}=10.0 Hz, 6H, N(C*H*$_3$)$_2$), 3.62 (dd, J=3.5, 11.4 Hz, 1H, H-6a), 3.65 (ddd, J=4.8, 9.5, 10.2 Hz, 1H, H-5′), 3.73–3.78 (m, 2H, H-2′, H-6′ax), 3.88 (dd, J=3.8, 11.4 Hz, 1H, H-6b), 3.96 (dd, J=3.3, 9.9 Hz, 1H, H-3′), 4.00 (dd, J=4.8, 10.1 Hz, 1H, H-6′eq), 4.18 (dd, J=9.5, 9.9 Hz, 1H, H-4′), 4.37 (ddd, J=3.5, 3.8, 9.8 Hz, 1H, H-5), 4.56 (d, J=11.9 Hz, 1H, OC*H*Ph), 4.69 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.76 (d, J=11.9 Hz, 1H, OC*H*Ph), 4.78 (d, J=12.1 Hz, 1H, OC*H*Ph), 4.82 (d, J=1.0 Hz, 1H, H-1′), 5.38 (ddd, J=3.2, 10.0, 1.6 (J_{H-P}) Hz, 1H, H-2), 5.58 (s, 1H, C*H*Ph), 5.67 (dd, J=9.8, 10.0 Hz, 1H, H-4), 6.08 (dd, J=3.2, 7.8 (J_{H-P}) Hz, 1H, H-1), 6.14 (t, J=10.0 Hz, 1H, H-3), 7.26–7.53 (m, 24H, Ar-H), 7.88 (m, 2H, Ar-H), 7.92–7.96 (m, 4H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 36.4 (d, J_{C-P}=4.0 Hz), 36.5 (d, J_{C-P}=4.0 Hz), 64.4, 66.1, 68.6, 68.9, 70.0, 70.1, 71.5 (d, J_{C-P}=6.3 Hz), 73.2, 73.6, 76.3, 76.4, 78.9, 92.1 (d, J_{C-P}=3.5 Hz, C-1), 99.9 (C-1′), 101.3, 126.2, 127.6, 127.7, 128.00, 128.03, 128.3, 128.35, 128.38, 128.5, 128.7, 129.0, 129.7, 129.8, 129.9, 133.3, 133.36, 133.42, 137.8, 138.1, 138.8; ^{31}P NMR (109 MHz, $CDCl_3$) δ 19.9; FAB-HRMS *m*/*z* calcd for $C_{58}H_{61}N_2O_{15}PNa$ $(M+Na)^+$1079.3703, found 1079.3750.

4.4.10. 1-Adamantyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-mannopyranoside (31). The glycosidation was performed according to the typical procedure (1 mL CH_2Cl_2, −45 °C, 30 min) employing diethyl phosphite **4b** (56.9 mg, 0.10 mmol), 1-adamantanol (**20**, 16.7 mg, 0.11 mmol) and TMSOTf (1.0 M in CH_2Cl_2, 0.11 mL, 0.11 mmol). An anomeric mixture of the known mannoside **31**[17d] (52.0 mg, 89%, α:β=16:84) was obtained as a colorless oil from the crude product (69.8 mg) after column chromatography (silica gel 10 g, 9:1 hexane/AcOEt). The anomeric ratio of **31** was determined by HPLC analysis [eluent, 20:1 hexane/AcOEt; flow rate, 1.0 mL/min; t_R (α-mannoside)=27.4 min, t_R (β-mannoside)=40.1 min].

4.4.11. Allyl *N*-(benzyloxycarbonyl)-*O*-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-mannopyranosyl)-L-serinate (32). The glycosidation was performed according to the typical procedure (1 mL CH_2Cl_2, −45 °C, 15 min) employing diethyl phosphite **4b** (56.9 mg, 0.10 mmol), alcohol **21** (30.7 mg, 0.11 mmol) and TMSOTf (1.0 M in CH_2Cl_2, 0.11 mL, 0.11 mmol). An anomeric mixture of mannoside **32** (61.7 mg, 87%, α:β=15:85) was obtained from the crude product (95.9 mg) after column chromatography (silica gel 7 g, 3:1 hexane/AcOEt). The anomeric ratio of **32** was determined by HPLC analysis [eluent, 5:1 hexane/AcOEt; flow rate, 1.0 mL/min; t_R (α-mannoside)=24.9 min, t_R (β-mannoside)=30.0 min]. The α- and β-mannosides were separated by flash column chromatography with 5:1 hexane/AcOEt. Data for β-anomer (**32**β): $[\alpha]_D^{24}$ −35.4 (*c* 1.74, $CHCl_3$); IR ($CHCl_3$) 3020, 2878, 1720, 1508, 1217, 1093 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.28 (ddd, J=4.7, 9.5, 10.3 Hz, 1H, H-5), 3.55 (dd, J=2.9, 9.8 Hz, 1H, H-3), 3.78 (dd, J=2.9, 10.1 Hz, 1H, Ser-β-C*H*), 3.87–3.91 (m, 2H, H-2, H-6ax), 4.18 (dd, J=9.5, 9.8 Hz, 1H, H-4), 4.28 (dd, J=4.7, 10.4 Hz, 1H, H-6eq), 4.34 (dd, J=3.0, 10.1 Hz, 1H, Ser-β-C*H*), 4.40 (s, 1H, H-1), 4.57 (m, 1H, Ser-α-C*H*), 4.60 (d, J=12.4 Hz, 1H, OC*H*Ph), 4.62–4.73 (m, 2H, CH_2CH=CH$_2$), 4.70 (d, J=12.4 Hz, 1H, OC*H*Ph), 4.75 (d, J=12.3 Hz, 1H, OC*H*Ph), 4.87 (d, J=12.3 Hz, 1H, OC*H*Ph), 5.11 (d, J=12.4 Hz, 1H, CO$_2$-C*H*Ph), 5.14 (d, J=12.4 Hz, 1H, CO$_2$C*H*Ph), 5.23 (d, J=10.4 Hz, 1H, CH$_2$CH=C*H*), 5.33 (d, J=17.2 Hz, 1H, CH$_2$CH=C*H*), 5.57 (d, J=8.2 Hz, 1H, N*H*), 5.60 (s, 1H, C*H*Ph), 5.88 (m, 1H, CH$_2$C*H*=CH$_2$), 7.22–7.42 (m, 18H, Ar-H), 7.49 (m, 2H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 54.2, 66.4, 67.2, 67.7, 68.4, 69.8, 72.5, 74.5, 75.2, 77.8, 78.5, 101.4, 102.4 (C-1), 118.9, 126.0, 127.5, 127.59, 127.63, 128.16, 128.20, 128.29, 128.32, 128.5, 128.6, 128.9, 131.4, 136.1, 137.5, 138.2, 155.9, 169.5; FAB-HRMS *m*/*z* calcd for $C_{41}H_{44}NO_{10}$ $(M+H)^+$710.2965, found 710.2920. Data for α-anomer (**32**α): $[\alpha]_D^{23}$ +36.0 (*c* 0.61, $CHCl_3$); IR ($CHCl_3$) 3020, 2935, 1722, 1504, 1454, 1238, 1199, 1062 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.70–3.75 (m, 2H, H-2, H-5), 3.84 (t, J=10.1 Hz, 1H, H-6ax), 3.87 (dd, J=3.2, 9.9 Hz, 1H, H-3), 3.88 (dd, J=3.2, 10.2 Hz, 1H, Ser-β-C*H*), 3.93 (dd, J=2.8, 10.2 Hz, 1H, Ser-β-C*H*), 4.21–4.25 (m, 2H, H-4, H-6eq), 4.54 (m, 1H, Ser-α-C*H*), 4.59 (br d, J=4.7 Hz, 2H, CH_2CH=CH$_2$), 4.63 (d, J=12.0 Hz, 1H, OC*H*Ph), 4.68 (d, J=12.3 Hz, 1H, OC*H*Ph), 4.74 (s, 1H, H-1), 4.79 (d, J=12.3 Hz, 1H, OC*H*Ph), 4.84 (d, J=12.0 Hz, 1H, OC*H*Ph), 5.10 (d, J=12.1 Hz, 1H, CO$_2$C*H*Ph), 5.15 (d, J=12.1 Hz, 1H, CO$_2$C*H*Ph), 5.19 (d, J=10.6 Hz, 1H, CH$_2$CH=C*H*), 5.28 (d, J=17.2 Hz, 1H, CH$_2$CH=C*H*),

5.59 (d, J=8.1 Hz, 1H, N*H*), 5.63 (s, 1H, C*H*Ph), 5.83 (m, 1H, CH_2CH=CH_2), 7.25–7.39 (m, 18H, Ar-H), 7.49 (m, 2H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 54.3, 64.7, 66.3, 67.3, 68.3, 68.6, 73.4, 73.7, 76.3, 78.9, 100.1 (C-1), 101.5, 119.1, 126.1, 127.5, 127.6, 127.8, 128.0, 128.1, 128.2, 128.3, 128.4, 128.6, 128.8, 131.3, 136.0, 137.6, 138.0, 138.6, 155.8, 169.5; FAB-HRMS m/z calcd for $C_{41}H_{44}NO_{10}$ $(M+H)^+$710.2965, found 710.2974.

4.4.12. Cholesteryl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-mannopyranoside (33). The glycosidation was performed according to the typical procedure (1 mL CH_2Cl_2, −45 °C, 30 min) employing diethyl phosphite **4b** (56.9 mg, 0.10 mmol), cholesterol (**22**, 42.6 mg, 0.11 mmol) and TMSOTf (1.0 M in CH_2Cl_2, 0.11 mL, 0.11 mmol). An anomeric mixture of mannoside **33** (70.5 mg, 86%, α:β=17:83) was obtained from the crude product (110.6 mg) after column chromatography (silica gel 8 g, 10:1 hexane/AcOEt). The anomeric ratio of **33** was determined by HPLC analysis [eluent, 20:1 hexane/THF; flow rate, 1.0 mL/min; t_R (α-mannoside)=8.1 min, t_R (β-mannoside)=9.1 min]. The α- and β-mannosides were separated by flash column chromatography with 15:1 hexane/AcOEt. Data for β-anomer (**33**β): mp 108.0–109.0 °C (colorless fine needles from MeOH): $[\alpha]_D^{25}$ +49.6 (c 1.62, $CHCl_3$); IR ($CHCl_3$) 3018, 2943, 1454, 1381, 1217, 1095 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.68 (s, 3H, H-18), 0.86–1.67 (m, 33H), 1.81–1.87 (m, 2H), 1.96–2.03 (m, 3H), 2.21 (m, 1H, H-4a), 2.29 (m, 1H, H-4b), 3.31 (ddd, J=4.8, 9.4, 10.2 Hz, 1H, H-5′), 3.56 (m, 1H, H-3), 3.58 (dd, J=3.0, 9.7 Hz, 1H, H-3′), 3.87 (d, J=3.0 Hz, 1H, H-2′), 3.92 (dd, J=10.2, 10.4 Hz, 1H, H-6′ax), 4.21 (dd, J=9.4, 9.7 Hz, 1H, H-4′), 4.28 (dd, J=4.8, 10.4 Hz, 1H, H-6′eq), 4.58 (s, 1H, H-1′), 4.59 (d, J=12.5 Hz, 1H, OC*H*Ph), 4.68 (d, J=12.5 Hz, 1H, OC*H*Ph), 4.90 (d, J=12.4 Hz, 1H, OC*H*Ph), 4.99 (d, J=12.4 Hz, 1H, OC*H*Ph), 5.35 (m, 1H, H-6), 5.61 (s, 1H, C*H*Ph), 7.25–7.37 (m, 11H, Ar-H), 7.48–7.50 (m, 4H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 11.8, 18.7, 19.4, 21.0, 22.5, 22.8, 23.8, 24.3, 28.0, 28.2, 29.6, 31.88, 31.94, 35.8, 36.2, 36.8, 37.2, 38.8, 39.5, 39.8, 42.3, 50.2, 56.1, 56.7, 67.5, 68.7, 72.3, 74.7, 76.3, 77.2, 78.1, 78.6, 100.0 (C-1′), 101.4, 122.0, 126.0, 127.4, 127.48, 127.49, 128.0, 128.1, 128.3, 128.7, 128.8, 137.7, 138.4, 138.5, 140.5; FAB-HRMS m/z calcd for $C_{54}H_{72}O_6Na$ $(M+Na)^+$839.5226, found 839.5244. Anal. Calcd for $C_{54}H_{72}O_6$: C, 79.37; H, 8.88, found: C, 79.12; H, 8.86. Data for α-anomer (**33**α): $[\alpha]_D^{23}$ +37.5 (c 0.99, $CHCl_3$); IR ($CHCl_3$) 3009, 2939, 1454, 1375, 1099 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.67 (3H, s, H-18), 0.86–1.58 (m, 33H), 1.74–1.84 (m, 3H), 1.95–2.02 (m, 2H), 2.28 (br d, J=7.5 Hz, 2H, H-4a, H-4b), 3.43 (m, 1H, H-3), 3.80 (dd, J=1.3, 3.1 Hz, 1H, H-2′), 3.84–3.91 (m, 2H, H-5′, H-6′ax), 4.00 (dd, J=3.1, 9.9 Hz, 1H, H-3′), 4.22–4.28 (m, 2H, H-4′, H-6′eq), 4.67 (d, J=12.2 Hz, 1H, OC*H*Ph), 4.72 (d, J=12.2 Hz, 1H, OC*H*Ph), 4.84 (d, J=12.2 Hz, 1H, OC*H*Ph), 4.85 (d, J=12.2 Hz, 1H, OC*H*Ph), 4.93 (d, J=1.3 Hz, 1H, H-1′), 5.33 (br d, J=4.1 Hz, 1H, H-6), 5.65 (s, 1H, C*H*Ph), 7.26–7.39 (m, 13H, Ar-H), 7.52 (m, 2H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 11.9, 18.7, 19.3, 21.1, 22.6, 22.8, 23.8, 24.3, 27.5, 28.0, 28.2, 31.87, 31.91, 35.8, 36.2, 36.7, 37.0, 39.5, 39.8, 39.9, 42.3, 50.1, 56.2, 56.8, 64.3, 68.9, 73.2, 73.6, 79.4, 97.3 (C-1′), 101.4, 122.0, 126.0, 127.40, 127.43, 127.7, 128.1, 128.2, 128.3, 128.4, 128.8, 137.8, 138.3, 138.9, 140.5; FAB-HRMS m/z calcd for $C_{54}H_{71}O_6$ $(M-H)^+$815.5250, found 815.5275.

Acknowledgements

This research was supported in part by a Grant-in-Aid for Scientific Research on Priority Areas (A) 'Exploitation of Multi-Element Cyclic Molecules' from the Ministry of Education, Culture, Sports, Science and Technology, Japan. T. T. is grateful to JSPS for a graduate fellowship. We thank Ms. H. Matsumoto, A. Maeda, S. Oka, and M. Kiuchi of the Center for Instrumental Analysis, Hokkaido University, for technical assistance in MS and elemental analysis.

References and notes

1. For recent reviews, see: (a) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503–1531. (b) Boons, G.-J. *Tetrahedron* **1996**, *52*, 1095–1121. (c) *Modern methods in carbohydrate synthesis*; Khan, S. H., O'Neil, R. A., Eds.; Harwood Academic: Amsterdam, 1996. (d) *Carbohydrates in chemistry and biology*; Ernst, B., Hart, G. W., Sinaÿ, P., Eds.; Wiley-VCH: Weinheim, 2000; Part I. (e) Davis, B. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2137–2160. (f) Demchenko, A. V. *Synlett* **2003**, 1225–1240.
2. For recent reviews, see: (a) Gridley, J. J.; Osborn, H. M. I. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1471–1491. (b) Pozsgay, V. In *Carbohydrates in chemistry and biology*; Ernst, B., Hart, G. W., Sinaÿ, P., Eds.; Wiley-VCH: Weinheim, 2000; pp 319–343. (c) El Ashry, E. S. H.; Rashed, N.; Ibrahim, E. S. I. *Curr. Org. Synth.* **2005**, *2*, 175–213.
3. Paulsen, H.; Lockhoff, O. *Chem. Ber.* **1981**, *114*, 3102–3114.
4. (a) Shaban, M. A. E.; Jeanloz, R. W. *Carbohydr. Res.* **1976**, *52*, 115–127. (b) Kunz, H.; Günther, W. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1086–1087. (c) Günther, W.; Kunz, H. *Carbohydr. Res.* **1992**, *228*, 217–241. (d) Fürstner, A.; Konetzki, I. *Tetrahedron Lett.* **1998**, *39*, 5721–5724.
5. (a) Lichtenthaler, F. W.; Cuny, E.; Weprek, S. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 891–892. (b) Lichtenthaler, F. W.; Schneider-Adams, T. *J. Org. Chem.* **1994**, *59*, 6728–6734.
6. (a) Iimori, T.; Ohtake, H.; Ikegami, S. *Tetrahedron Lett.* **1997**, *38*, 3415–3418. (b) Ohtake, H.; Ichiba, N.; Ikegami, S. *J. Org. Chem.* **2000**, *65*, 8171–8179.
7. For reviews, see: (a) Jung, K.-H.; Müller, M.; Schmidt, R. R. *Chem. Rev.* **2000**, *100*, 4423–4442. (b) Madsen, J.; Bols, M. In *Carbohydrates in chemistry and biology*; Ernst, B., Hart, G. W., Sinaÿ, P., Eds.; Wiley-VCH: Weinheim, 2000; pp 449–466. (c) Fairbanks, A. J. *Synlett* **2003**, 1945–1958.
8. (a) Barresi, F.; Hindsgaul, O. *J. Am. Chem. Soc.* **1991**, *113*, 9376–9377. (b) Barresi, F.; Hindsgaul, O. *Synlett* **1992**, 759–761. (c) Barresi, F.; Hindsgaul, O. *Can. J. Chem.* **1994**, *72*, 1447–1465.
9. (a) Ito, Y.; Ogawa, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1765–1767. (b) Ito, Y.; Ohnishi, Y.; Ogawa, T.; Nakahara, Y. *Synlett* **1998**, 1102–1104. (c) Lergenmüller, M.; Nukada, T.; Kuramochi, K.; Dan, A.; Ogawa, T.; Ito, Y. *Eur. J. Org. Chem.* **1999**, 1367–1376. (d) Ito, Y.; Ando, H.; Wada, M.; Kawai, T.; Ohnish, Y.; Nakahara, Y. *Tetrahedron* **2001**, *57*, 4123–4132.
10. (a) Ennis, S. C.; Fairbanks, A. J.; Tennant-Eyles, R. J.; Yeates,

H. S. *Synlett* **1999**, 1387–1390. (b) Seward, C. M. P.; Cumpstey, I.; Aloui, M.; Ennis, S. C.; Redgrave, A. J.; Fairbanks, A. J. *Chem. Commun.* **2000**, 1409–1410. (c) Ennis, S. C.; Fairbanks, A. J.; Slinn, C. A.; Tennant-Eyles, R. J.; Yeates, H. S. *Tetrahedron* **2001**, *57*, 4221–4230.

11. (a) Stork, G.; Kim, G. *J. Am. Chem. Soc.* **1992**, *114*, 1087–1088. (b) Stork, G.; La Clair, J. J. *J. Am. Chem. Soc.* **1996**, *118*, 247–248.
12. (a) Ziegler, T.; Lemanski, G. *Angew. Chem., Int. Ed.* **1998**, *37*, 3129–3132. (b) Lemanski, G.; Ziegler, T. *Helv. Chim. Acta* **2000**, *83*, 2655–2675. (c) Lemanski, G.; Ziegler, T. *Helv. Chim. Acta* **2000**, *83*, 2676–2697. (d) Abdel-Rahman, A. A.-H.; El Ashry, E. S. H.; Schmidt, R. R. *Carbohydr. Res.* **2002**, *337*, 195–206.
13. (a) Yamanoi, T.; Nakamura, K.; Takeyama, H.; Yanagihara, K.; Inazu, T. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1359–1366. (b) Tatsuta, K.; Yasuda, S. *Tetrahedron Lett.* **1996**, *37*, 2453–2456. (c) Kim, W.-S.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett.* **1996**, *37*, 7797–7800. (d) Toshima, K.; Kasumi, K.; Matsumura, S. *Synlett* **1998**, 643–645. (e) Nagai, H.; Kawahara, K.; Matsumura, S.; Toshima, K. *Tetrahedron Lett.* **2001**, *42*, 4159–4162. (f) Chung, S.-K.; Park, K.-H. *Tetrahedron Lett.* **2001**, *42*, 4005–4007. (g) Hashihayata, T.; Mandai, H.; Mukaiyama, T. *Chem. Lett.* **2003**, *32*, 442–443. (h) Hashihayata, T.; Mandai, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 169–178. (i) Toshima, K.; Nagai, H.; Kasumi, K.; Kawahara, K.; Matsumura, S. *Tetrahedron* **2004**, *60*, 5331–5339.
14. (a) Srivastava, V. K.; Schuerch, C. *Carbohydr. Res.* **1980**, *79*, C13–C16. (b) Srivastava, V. K.; Schuerch, C. *J. Org. Chem.* **1981**, *46*, 1121–1126.
15. (a) Abdel-Rahman, A. A.-H.; Jonke, S.; El Ashry, E. S. H.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2972–2974. (b) Crich, D.; Hutton, T. K.; Banerjee, A.; Jayalath, P.; Picione, J. *Tetrahedron: Asymmetry* **2005**, *16*, 105–119.
16. (a) Srivastava, V. K.; Schuerch, C. *Tetrahedron Lett.* **1979**, 3269–3272. (b) Hodosi, G.; Kováč, P. *J. Am. Chem. Soc.* **1997**, *119*, 2335–2336. (c) Nicolaou, K. C.; van Delft, F. L.; Conley, S. R.; Mitchell, H. J.; Jin, Z.; Rodríguez, R. M. *J. Am. Chem. Soc.* **1997**, *119*, 9057–9058. (d) Hodosi, G.; Kováč, P. *Carbohydr. Res.* **1998**, *308*, 63–75. (e) Nicolaou, K. C.; Fylaktakidou, K. C.; Mitchell, H. J.; van Delft, F. L.; Rodríguez, R. M.; Conley, S. R.; Jin, Z. *Chem. Eur. J.* **2000**, *6*, 3166–3185.
17. (a) Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 4506–4507. (b) Crich, D.; Sun, S. *J. Org. Chem.* **1997**, *62*, 1198–1199. (c) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1998**, *120*, 435–436. (d) Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321–8348. (e) Crich, D.; Dudkin, V. *Tetrahedron Lett.* **2000**, *41*, 5643–5646. (f) Crich, D.; Smith, M. *Org. Lett.* **2000**, *2*, 4067–4069. (g) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015–9020. (h) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2002**, *124*, 8867–8869. (i) Crich, D.; Jayalath, P. *Org. Lett.* **2005**, *7*, 2277–2280.
18. Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217–11223.
19. Crich, D.; Chandrasekera, N. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5386–5389.
20. Weingart, R.; Schmidt, R. R. *Tetrahedron Lett.* **2000**, *41*, 8753–8758.
21. Kim, K. S.; Kim, J. H.; Lee, Y. J.; Lee, Y. J.; Park, J. *J. Am. Chem. Soc.* **2001**, *123*, 8477–8481.
22. Glycosidation of 4,6-*O*-benzylidene-protected ethylthio α-mannosides in the presence of *N*-iodosuccinimide (NIS)/TfOH was reported to exhibit good β-selectivities, but the intermediacy of α-mannosyl triflate was not mentioned: Yun, M.; Shin, Y.; Chun, K. H.; Shin, J. E. N. *Bull. Korean Chem. Soc.* **2000**, *21*, 562–566.
23. (a) Hashimoto, S.; Honda, T.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1989**, 685–687. (b) Hashimoto, S.; Honda, T.; Ikegami, S. *Heterocycles* **1990**, *30*, 775–778. (c) Hashimoto, S.; Honda, T.; Ikegami, S. *Tetrahedron Lett.* **1990**, *31*, 4769–4772. (d) Hashimoto, S.; Yanagiya, Y.; Honda, T.; Harada, H.; Ikegami, S. *Tetrahedron Lett.* **1992**, *33*, 3523–3526. (e) Hashimoto, S.; Umeo, K.; Sano, A.; Watanabe, N.; Nakajima, M.; Ikegami, S. *Tetrahedron Lett.* **1995**, *36*, 2251–2254. (f) Hashimoto, S.; Sano, A.; Sakamoto, H.; Nakajima, M.; Yanagiya, Y.; Ikegami, S. *Synlett* **1995**, 1271–1273. (g) Tanaka, H.; Sakamoto, H.; Sano, A.; Nakamura, S.; Nakajima, M.; Hashimoto, S. *Chem. Commun.* **1999**, 1259–1260. (h) Tsuda, T.; Nakamura, S.; Hashimoto, S. *Tetrahedron Lett.* **2003**, *44*, 6453–6457. (i) Tsuda, T.; Nakamura, S.; Hashimoto, S. *Tetrahedron* **2004**, *60*, 10711–10737. (j) Arihara, R.; Nakamura, S.; Hashimoto, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 2245–2249. See also: http://www.glycoforum.gr.jp/science/word/glycotechnology/GT-A01E.html.
24. For a preliminary communication, see: Tsuda, T.; Sato, S.; Nakamura, S.; Hashimoto, S. *Heterocycles* **2003**, *59*, 509–515.
25. Independent of our studies, Toshima and co-workers reported the β-selective glycosidation of 4,6-*O*-benzylidene-protected mannosyl diethyl phosphite using a heterogeneous solid acid, montmorillonite K-10: (a) Nagai, H.; Matsumura, S.; Toshima, K. *Carbohydr. Res.* **2003**, *338*, 1531–1534. (b) Nagai, H.; Sasaki, K.; Matsumura, S.; Toshima, K. *Carbohydr. Res.* **2005**, *340*, 337–353.
26. Rathore, H.; From, A. H. L.; Ahmed, K.; Fullerton, D. S. *J. Med. Chem.* **1986**, *29*, 1945–1952.
27. RajanBabu, T. V.; Fukunaga, T.; Reddy, G. S. *J. Am. Chem. Soc.* **1989**, *111*, 1759–1769.
28. Sabesan, S.; Neira, S. *Carbohydr. Res.* **1992**, *223*, 169–185.
29. TMSOTf-promoted glycosidation of 2,3,4,6-tetra-*O*-benzyl-D-mannosyl diphenyl phosphate with 2-*O*-unprotected glucoside in CH_2Cl_2 was reported to display modest β-selectivity ($\alpha:\beta=1:3$): (a) Plante, O. J.; Palmacci, E. R.; Seeberger, P. H. *Org. Lett.* **2000**, *2*, 3841–3843. (b) Plante, O. J.; Palmacci, E. R.; Andrade, R. B.; Seeberger, P. H. *J. Am. Chem. Soc.* **2001**, *123*, 9545–9554.
30. Watanabe and co-workers reported that the $ZnCl_2$-promoted glycosidation of 2,3,4,6-tetra-*O*-benzyl-D-mannosyl dimethyl phosphite gave almost 1:1 mixtures of glycosides: (a) Watanabe, Y.; Nakamoto, C.; Ozaki, S. *Synlett* **1993**, 115–116. (b) Watanabe, Y.; Nakamoto, C.; Yamamoto, T.; Ozaki, S. *Tetrahedron* **1994**, *50*, 6523–6536.
31. (a) Fraser-Reid, B.; Wu, Z.; Andrews, C. W.; Skowronski, E.; Bowen, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 1434–1435. (b) Fraser-Reid, B.; Udodong, U. E.; Wu, Z.; Ottosson, H.; Merritt, J. R.; Rao, C. S.; Roberts, C.; Madsen, R. *Synlett* **1992**, 927–942. (c) Douglas, N. L.; Ley, S. V.; Lücking, U.; Warriner, S. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 51–65. (d) Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734–753.
32. Palmacci, E. R.; Plante, O. J.; Seeberger, P. H. *Eur. J. Org. Chem.* **2002**, 595–606.
33. Since the anomeric mixture of 4,6-*O*-benzylidene-protected mannosyl diethyl phosphite could not be separated, the influence of the anomeric configuration of the donor on stereoselectivity is not clear at this time.
34. (a) Kondo, H.; Aoki, S.; Ichikawa, Y.; Halcomb, R. L.; Ritzen,

H.; Wong, C.-H. *J. Org. Chem.* **1994**, *59*, 864–877. (b) Sakamoto, H.; Nakamura, S.; Tsuda, T.; Hashimoto, S. *Tetrahedron Lett.* **2000**, *41*, 7691–7695.

35. (a) Kondo, H.; Ichikawa, Y.; Wong, C.-H. *J. Am. Chem. Soc.* **1992**, *114*, 8748–8750. (b) Martin, T. J.; Schmidt, R. R. *Tetrahedron Lett.* **1992**, *33*, 6123–6126. (c) Sim, M. M.; Kondo, H.; Wong, C.-H. *J. Am. Chem. Soc.* **1993**, *115*, 2260–2267. (d) Martin, T. J.; Brescello, R.; Toepfer, A.; Schmidt, R. R. *Glycoconjugate J.* **1993**, *10*, 16–25.
36. We indicated in our preliminary communication (Ref. 24) that an α-phosphonate was formed as a by-product. The incorrect assignment was based on a preliminary ^{1}H NMR analysis at the time that our preliminary account was published. The ^{1}H NOE (6%) between H-3 and H-1 unambiguously established the β-configuration of phosphonate **12**.
37. We previously reported that 3,5-di-*O*-benzoyl-2-deoxy-D-ribofuranosyl diethyl phosphite was readily converted into the corresponding phosphonate by treatment with TMSOTf: Hashimoto, S.; Inagaki, J.; Sakamoto, H.; Sano, A.; Nakajima, M. *Heterocycles* **1997**, *46*, 215–220.
38. Schmidt, R. R.; Toepfer, A. *Tetrahedron Lett.* **1991**, *32*, 3353–3356.
39. Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881–6882.
40. Crich and Dudkin demonstrated that the hydroxyl group of **14** is more reactive than those of the corresponding 2-phthalimido- and 2-acetamido-2-deoxyglucose derivatives: Crich, D.; Dudkin, V. *J. Am. Chem. Soc.* **2001**, *123*, 6819–6825.
41. Spijker, N. M.; van Boeckel, C. A. A. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 180–183.
42. (a) Hashimoto, S.; Sakamoto, H.; Honda, T.; Ikegami, S. *Tetrahedron Lett.* **1997**, *38*, 5181–5184. (b) Hashimoto, S.; Sakamoto, H.; Honda, T.; Abe, H.; Nakamura, S.; Ikegami, S. *Tetrahedron Lett.* **1997**, *38*, 8969–8972.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 10734–10737

A novel approach to the Taxol A-ring synthetic equivalents

Zhang-Hua Gao,[a] Bing Liu[a] and Wei-Dong Z. Li[a,b,*]

[a]*State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China*
[b]*State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China*

Received 14 June 2005; revised 17 August 2005; accepted 18 August 2005

Available online 16 September 2005

Abstract—A novel short approach to the A-ring synthetic equivalents of Taxol was described. Oxabicyclic ketone **3** served as a versatile template for selective functionalization leading to oxabicyclic vinylic ether **6** in two steps, which was hydrolyzed under mild acidic conditions to afford the hydroxy aldehyde derivative **7**. Synthetic equivalents **2** of Taxol A-ring were thus, accessible from hydroxy aldehyde **7**.

1. Introduction

Substituted cyclohexene derivatives **2** (Fig. 1) have been devised as common A-ring synthetic equivalents (synthons) in various total synthetic studies of paclitaxel (**1**, Taxol),[1] a clinically proven effective antitumor chemotherapeutics bearing a unique 6-8-6 carbocyclic ring system (ABC). A number of synthetic entries[2–9] have been developed for these densely functionalized intermediates **2** en route to Taxol, including various cationic cyclization protocols (pathways a[2], b[3] or c[4]) from geraniol-derived precursors, Diels–Alder cycloaddition approach (pathways d[5] and d′),[6] intramolecular nitrone [3+2] cycloaddition (pathway e),[7] and conventional multi-step transformation of a cyclohexdione derivative (pathway f),[8] as depicted in Figure 1, respectively.[9] In connection with our ongoing program on the development of novel synthetic strategies based on the use of oxabicyclic ketone **3** as a stereocontroling template, herein we report an alternative novel approach for the facile and general synthesis of this type of multi-functionalized cyclohexene derivatives.

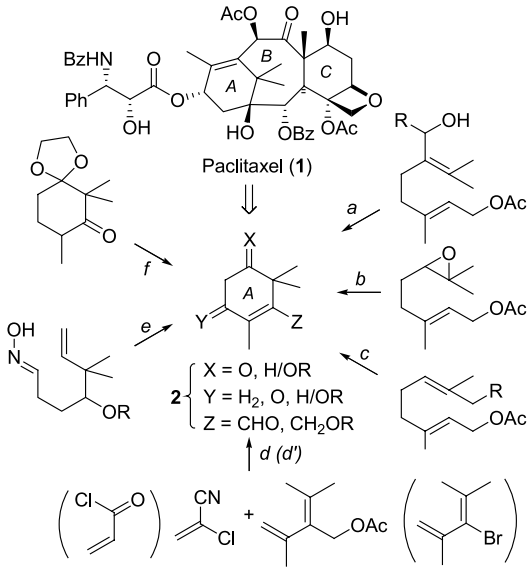


Figure 1. Syntheses of Taxol A-ring equivalents **2**.

We have recently developed[10a,b] a general quasi-biomimetic strategy for the stereocontrolled synthesis of naturally occurring eudesmane sesquiterpenoids from functionalized oxabicyclic templates **4**, derived from readily available oxabicyclic ketone **3**, as illustrated in a concise stereocontrolled total synthesis of balanitol and the first total synthesis of gallicadiol (Fig. 2).

As shown in Scheme 1, oxabicyclic ketone **3** was bismethylated with excess methyl iodide in a mixture of DMSO–THF (1/1) by using potassium *tert*-butoxide as a base to give *gem*-dimethyl oxabicyclic ketone **5** in 92% yield.[11] (Methoxy)vinylation of ketone **5** was performed smoothly by employing Magnus protocol[12] as described previously[10b] to afford a mixture of geometric isomers of methoxy vinylic ethers (*E*/*Z* 3:4, determined by analysis of ^{1}H NMR spectrum of the product mixture), which without further purification, was subjected to acidic hydrolysis by exposing to 90% (aqueous) acetic acid to furnish the hydroxy α,β-unsaturated aldehyde **7** in 68% overall yield

Keywords: Taxol; Diels–Alder cycloaddition; Oxabicyclic template.
* Corresponding author. Tel./fax: +86 22 23494613;
e-mail: wdli@nankai.edu.cn

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.08.061

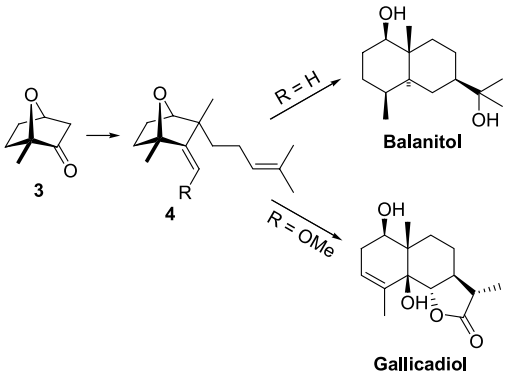
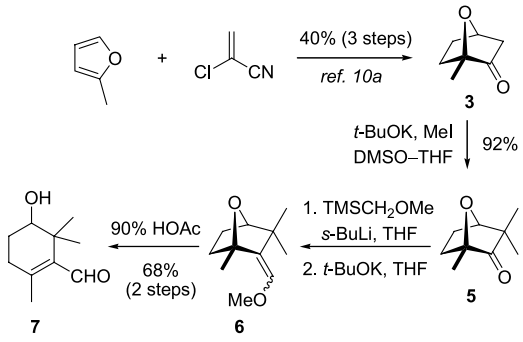
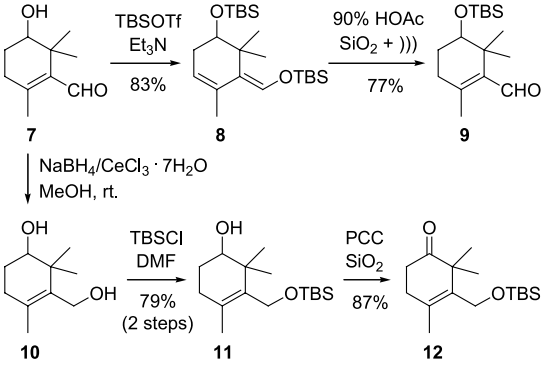


Figure 2. General synthesis of eudesmanoids from oxabicyclic ketone **3** (Ref. 10).



Scheme 1. A short synthesis of Taxol A-ring equivalent **7**.

(two steps from ketone **5**). The structure of **7** was confirmed spectroscopically and unambiguously ensured by subsequent conversion to known Taxol A-ring equivalents, that is, functionalized cyclohexene derivatives **9** and **12** (Scheme 2), respectively.[13]



Scheme 2. Facile synthesis of Taxol A-ring equivalents.

Thus, silylation of hydroxy aldehyde **7** with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) in the presence of triethylamine ($-65\rightarrow -10$ °C, 1 h) in methylenechloride (DCM) produced a bis-*O*-silylated conjugated silyl dienol ether **8** in good yield,[14] which was then selectively protonated by treatment with a slurry mixture of 90% aqueous acetic acid and normal chromatographic silica gel (200–300 mesh) under ultrasonic irradiation conditions (water bath, 20 kHz, 250 W, 25–30 °C, 12 min),[15] to give the known[7] siloxy aldehyde **9** in good yield. Alternatively, Luche reduction[16] of **7** followed by selective *O*-silylation with *tert*-butyldimethylsilyl chloride (TBSCl) in the presence of imidazole in DMF furnished the allylic silyl ether **11**[3] in 79% overall yield from **7**, which was subsequently oxidized with PCC (suspended on silica gel) to afford the known[5] siloxy ketone **12** in 87% yield.

In view of the ready accessibility of the chiral oxabicyclic ketone **3** via optical resolution,[17] the enantioselective synthesis of the general Taxol A-ring equivalents **2** would be achievable via the above described approach. Furthermore, this approach would also be applicable in principle to the synthesis of unsymmetrically substituted (instead of *gem*-dimethyl) analogs of **2** as the building blocks in natural product synthesis (cf. **4** in Fig. 2), that is, coincidentally Taxol C-ring equivalents (Fig. 3) as devised by Takahashi et al. [3] and Monti et al.[9c]

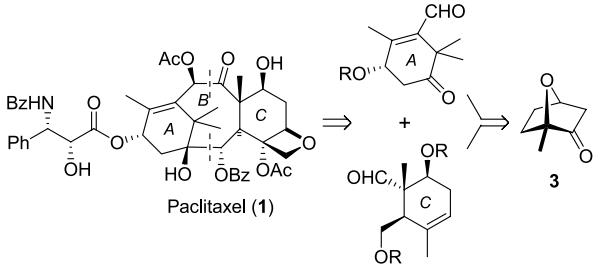


Figure 3.

In short summary, a general and alternative synthesis of the functionalized cyclohexene derivatives **2**, the classical A-ring moiety of Taxol synthesis, was realized from readily available oxabicyclic template **3** in a short and convenient synthetic sequence. This application further demonstrated[18] the versatility of the oxabicyclic templates **3** (and **4**) in organic synthesis, and they (and their variants) would find other useful applications in the stereocontrolled synthesis of various types of natural products.[19]

2. Experimental

2.1. General

For product purification by flash column chromatography, silica gel (200–300 mesh) and light petroleum ether (bp 30–60 °C) were used. All solvents were purified and dried by standard techniques, and distilled prior to use. All organic extracts were dried over Na_2SO_4, unless otherwise noted. IR spectra were recorded on a Nicolet FT-170SX spectrometer as liquid film. ^1H and ^{13}C NMR spectra were taken on a Varian mercury 300 MHz spectrometer with TMS as an internal standard and $CDCl_3$ as solvent unless otherwise noted. EI-MS spectra were obtained on HP-5988A GC/MS instrument. HRMS were determined on a Bruker Daltonics APEXII 47e FT-ICR spectrometer. All air and moisture-sensitive reactions were performed in a flame-dried glassware under a stream of nitrogen. Other commercially available chemical reagents and solvents

were used as received without further purification unless indicated otherwise.

2.1.1. 1,3,3-Trimethyl-7-oxabicyclo[2.2.1]heptan-2-one (5). To a mixture of ketone **3** (1.26 g, 10 mmol) and methyl iodide (1.50 mL, 24.0 mmol) in 5 mL of anhydrous DMSO and 30 mL of THF was added a solution of potassium *tert*-butoxide (2.69 g, 24.0 mmol) in 25 mL of DMSO at room temperature. The mixture was stirred for 20 min at ambient temperature and extracted with petroleum ether (bp 30–60 °C, 3×100 mL), successively washed with water (5× 50 mL), brine, dried, filtered, and concentrated. The resulting trimethyl bicyclic ketone **5** (1.43 g, 92%)[11] was dried azeotropically with benzene and used in the next step without further purification. IR (film) ν_{max} 2975, 1757, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, 3H), 1.20 (s, 3H), 1.44 (s, 3H), 1.50–1.70 (m, 2H), 1.90–2.05 (m, 2H), 4.26 (br s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.7, 20.0, 22.8, 25.5, 31.1, 48.9, 83.6, 86.0, 217.9 ppm; EIMS (*m/z*, %) 154 (M^+, 1.3), 139 (0.3), 126 (48), 43 (100).

2.1.2. 2-Methoxymethylene-1,3,3-trimethyl-7-oxabicyclo[2.2.1]-heptane (6). To a solution of (methoxylmethyl)trimethylsilane (93%, 1.14 mL, 7.5 mmol) in 13 mL of THF was added *sec*-butyllithium (1.3 M, 5.7 mL, 7.5 mmol) at −60 °C. The resulting reaction mixture was warmed gradually to −23 °C over 40 min, then cooled to −78 °C, to which ketone **5** (924 mg, 6.0 mmol) in 3.2 mL of THF was added dropwise. The reaction mixture was stirred at −60 °C for another 1 h and powdered potassium *tert*-butoxide (1.32 g, 12 mmol) was introduced in one portion. The reaction mixture was allowed to warm to ambient temperature over 1 h and stirred for additional 2.5 h, and then quenched with 1 mL of water. The reaction mixture was diluted with petroleum ether (bp 30–60 °C), successively washed with water, dried, and concentrated. The residue was purified by flash silica gel chromatography eluting with petroleum ether–ether (v/v 20/1) to give 926 mg (85%) of the enol ether **6** (*E*/*Z* 3:4) as a colorless oil. IR (film) ν_{max} 2972, 2933, 1696, 1460, 1381, 1216, 1119, 991, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) Characteristic data for *Z*-isomer: δ 1.03 (s, 3H), 1.11 (s, 3H), 1.65 (s, 3H), 3.49 (s, 3H), 5.55 (s, 1H) ppm; *E*-isomer: δ 1.18 (s, 6H), 1.53 (s, 3H), 3.50 (s, 3H), 5.72 (s, 1H); EIMS (*m/z*, %) 182 (M^+, 29), 113 (100); HRMS (ESI) *m/z* obsd 183.1376 ($[M+H]^+$, calcd for $C_{11}H_{19}O_2$ 183.1380).

2.1.3. 5-Hydroxy-2,6,6-trimethylcyclohex-1-enecarbaldehyde (7). A mixture of the above enol ether **6** (925 mg, 5.10 mmol) in 7.2 mL of acetic acid and 0.8 mL of water was stirred at room temperature for 15 h. It was diluted with 10 mL of water, neutralized with sodium bicarbonate and then extracted with ether (4×30 mL). The combined organic phases were washed with saturated aqueous sodium bicarbonate, brine, dried, and concentrated. The residue was purified by flash silica gel column chromatography to give hydroxy aldehyde **7** (680 mg, 68% from **5**). IR (film) ν_{max} 3420, 2968, 2942, 2877, 2756, 1667, 1379, 1286, 1066 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, 3H), 1.25 (s, 3H), 1.70–1.90 (m, 2H), 2.12 (s, 3H), 2.25 (dt, 1H, J=19.8, 6.3 Hz), 2.43 (dt, 1H, J=19.8, 6.4 Hz), 3.51 (dd, 1H, J= 8.1, 3.0 Hz), 10.12 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.0, 21.0, 25.3, 25.7, 32.1, 37.6, 75.6, 138.5, 155.1, 192.3 ppm; EIMS (*m/z*, %) 168 (M^+, 26), 150 (16), 125 (100), 109 (93), 81 (82); HRMS (ESI) *m/z* obsd 169.1221 ($[M+H]^+$, calcd for $C_{10}H_{17}O_2$ 169.1223).

2.1.4. Preparation of dienol silyl ether 8. To a mixture of aldehyde **7** (41 mg, 0.24 mmol) and triethylamine (0.13 mL, 0.93 mmol) in 1 mL of dry dichloromethane was added TBSOTf (0.12 mL, 0.52 mmol) at −65 °C. The reaction vessel was warmed gradually to −10 °C over 1 h. The reaction mixture was quenched with 0.2 mL of water, and diluted with petroleum ether (bp 30–60 °C). The organic phase was successively washed with water, dried, and concentrated. The resulting residue was filtered through a short pad of chromatographic silica gel to give the bis-silyl ether **8** (80 mg, 0.20 mmol, 83%) as a colorless oil. IR (film) ν_{max} 2956, 2931, 2890, 2858, 1612, 1468, 1254, 1159, 1092, 1048, 882, 837, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.035 (s, 6H), 0.156 (s, 6H), 0.89 (s, 9H), 0.95 (s, 9H), 1.03 (s, 3H), 1.37 (s, 3H), 1.71 (s, 3H), 2.12 (br s, 2H), 3.49 (t, 1H, J=7.4 Hz), 5.23 (br s, 1H), 6.36 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.5, −5.4, −4.9, −3.9, −3.0, 18.1, 18.9, 20.4, 24.8, 25.7, 25.9, 32.0, 38.8, 75.4, 119.9, 126.1, 131.2, 138.0 ppm; EIMS (*m/z*, %) 396 (M^+, 0.9), 339 (10), 147 (23), 133 (19), 73 (100); HRMS (ESI) *m/z* obsd 397.2946 ($[M+H]^+$, calcd for $C_{22}H_{45}Si_2O_2$ 397.2953).

2.1.5. Preparation of siloxy α,β-unsaturated aldehyde 9. A mixture of **8** (33 mg, 0.083 mmol), silica gel (200–300 mesh, 230 mg) in 3 mL of acetic acid and 0.3 mL of water was immerged in a water bath (25–30 °C) and sonicated for 12 min (20 kHz, 250 W). TLC monitoring of the reaction showed a complete disappearance of starting bis-silyl ether **8**. The reaction mixture was diluted with ether, washed with aqueous saturated $NaHCO_3$, brine, dried, and concentrated. The residue was purified by silica gel column chromatography eluting with petroleum ether–ether (v/v 30/1) to give siloxy aldehyde **9** (18 mg, 0.064 mmol, 77%).[7] IR (film) ν_{max} 2954, 2931, 2888, 2858, 1675, 1466, 1254, 1088, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.059 (s, 3H), 0.064 (s, 3H), 0.89 (s, 9H), 1.16 (s, 3H), 1.19 (s, 3H), 1.60–1.78 (m, 2H), 2.09 (s, 3H), 2.10–2.25 (m, 1H), 2.36 (dt, 1H, J=19.5, 6.3 Hz), 3.45 (dd, 1H, J=7.8, 3.5 Hz), 10.10 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.9, −4.2, 18.1, 19.0, 21.7, 25.8, 26.2, 32.6, 38.3, 76.1, 139.1, 154.5, 192.5 ppm; EIMS (*m/z*, %) 267 (M^+−15, 1.3), 241 (1.7), 225 (100), 75 (98).

2.1.6. 3-(*tert*-Butyldimethylsilyloxymethyl)-2,2,4-trimethyl-2-cyclohexen-3-ol (11). To a mixture of the hydroxy aldehyde **7** (69 mg, 0.41 mmol) and cerium trichloride heptahydrate (153 mg, 0.41 mmol) in 2 mL of methanol at 0 °C was added sodium borohydride (16 mg, 0.38 mmol). The reaction mixture was stirred at 0 °C for 10 min, quenched with 3 M HCl (0.5 mL), and diluted with 3 mL of ether. The organic layer was separated and the aqueous layer was saturated with sodium sulfate, and then extracted with ether (3×5 mL). The combined organic extracts were dried and concentrated in vacuo. The residue (75 mg) was azeotropically dried with benzene and taken up in DMF (0.5 mL) and cooled to 0 °C, to which imidazole (63 mg, 0.93 mmol) and TBSCl (70 mg, 0.46 mmol) were added successively at 0 °C. The resulting mixture was stirred at 0 °C for 15 min, diluted with ether, washed with

water, brine, dried, and concentrated. The residue was purified by silica gel column chromatography to give **11** (92 mg, 79%);[3] ^{1}H NMR (300 MHz, $CDCl_3$) 0.08 (s, 6H), 0.90 (s, 9H), 1.03 (s, 3H), 1.10 (s, 3H), 1.68 (s, 3H), 1.65–1.80 (m, 2H), 2.09 (t, 2H, J=6.4 Hz), 3.50 (br s, 1H), 4.10 and 4.15 (ABq, 2H, J=10.5 Hz) ppm.

2.1.7. 3-(*tert*-Butyldimethylsilyloxymethyl)-2,2,4-trimethyl-cyclohexen-3-one (12). A mixture of alcohol **11** (8.0 mg), PCC (32.0 mg) and silica gel (ca. 60 mg) in 1 mL of dichloromethane was stirred at room temperature for 2 h, filtered through a pad of silica gel, concentrated and purified by silica gel column chromatography to give ketone **12**[5] (7 mg, 87%); ^{1}H NMR (300 MHz, $CDCl_3$) 0.092 (s, 6H), 0.90 (s, 9H), 1.21 (s, 6H), 1.79 (s, 3H), 2.39 (t, 2H, J=6.8 Hz), 2.54 (t, 2H, J=6.8 Hz), 4.15 (s, 2H) ppm.

Acknowledgements

We thank the National Natural Science Foundation (Distinguished Youth Fund 29925204 and QT 20021001) for financial support. The Cheung Kong Scholars program and the Outstanding Scholars program of Nankai University are gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.08.061

References and notes

1. Goodman, J.; Walsh, V. *The Story of Taxol. Nature and Politics in the Pursuit of an Anti-Cancer Drug*; Cambridge University Press: Cambridge, UK, 2001.
2. Doi, T.; Robertson, J.; Stork, G.; Yamashita, A. *Tetrahedron Lett.* **1994**, *35*, 1481–1484.
3. Nakai, K.; Kamoshita, M.; Doi, T.; Yamada, H.; Takahashi, T. *Tetrahedron Lett.* **2001**, *42*, 7855–7857.
4. Nishiyama, S.; Ikeda, Y.; Yamamura, S. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 875–878. Although Yamamura's earlier cationic cyclization approach mediated by $Hg(O_2CCF_3)_2$ led to the C-ring synthetic equivalent of Taxol® as shown (R=OH or OBz) instead of A-ring equivalents, it represents an alternative pathway to **2** in principle.
5. (a) Nicolaou, K. C.; Hwang, C.-K.; Sorensen, E. J.; Clairborne, C. F. *J. Chem. Soc., Chem. Commun.* **1992**, 1117–1118. (b) Nicolaou, K. C.; Liu, J.-J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C.-K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634–644.
6. Magnus, P.; Westwood, N.; Spyvee, M.; Frost, C.; Linnane, P.; Tavares, F.; Lynch, V. *Tetrahedron* **1999**, *55*, 6435–6452.
7. Ishikawa, T.; Ikeda, S.; Ibe, M.; Saito, S. *Tetrahedron* **1998**, *54*, 5869–5882.
8. (a) Roy, O.; Pattenden, G.; Pryde, D. C.; Wilson, C. *Tetrahedron* **2003**, *59*, 5115–5121. (b) Di Grandi, M. J.; Jung, D. K.; Krol, W. J.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 4989–4992. (c) Queneau, Y.; Krol, W. J.; Bornmann, W. D.; Danishefsky, S. J. *J. Org. Chem.* **1992**, *57*, 4043–4047.
9. For some other methods, see: (a) Ding, Y.; Jiang, X.-R. *J. Chem. Soc., Chem. Commun.* **1995**, 1693–1694. (b) Audran, G.; Uttaro, J.-P.; Monti, H. *Synlett* **2002**, 1261–1264. (c) Uttaro, J.-P.; Audran, G.; Monti, H. *J. Org. Chem.* **2005**, *70*, 3484–3489.
10. (a) Zhang, Z.; Li, W.-D.Z.; Li, Y.-L. *Org. Lett.* **2001**, *3*, 2555–2557. (b) Li, W.-D.Z.; Gao, Z.-H. *Org. Lett.* **2005**, *7*, 2917–2920.
11. DiFazio, M. P.; Wallace, W. A.; Sneden, A. T. *Heterocycles* **1989**, *29*, 2391–2397. The methylation procedure described in this work is suitable for scalable preparation.
12. Magnus, P.; Roy, G. *Organometallics* **1982**, *1*, 553–559.
13. Further oxygenative or alkylative derivatization of compounds **7**, **9** or **12** to other more densely functionalized variants of **2** would be achievable according to Refs. 5 and 8.
14. Mild *O*-silylation conditions (TBSCl, imidazole, DMF) led to a sluggish (low yield) silyl ether formation.
15. This interesting chemoselective effect by the action of ultrasonication implies again the selective activation of more delocalized conjuated electronic structure by ultrasonic irradiation, which would deserve further investigations on the exact mode of action (activation mechanism) of the sonochemical process. See: Wei, K.; Gao, H.-T.; Li, W.-D.Z. *J. Org. Chem.* **2004**, *69*, 5763–5765.
16. Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.
17. Guan, Y.-K.; Li, Y.-L. *Chirality* **2005**, *17*, 113–118.
18. Cf.Li, W.-D.Z.; Wei, K. *Org. Lett.* **2004**, *6*, 1333–1335.
19. Further studies along these lines are on going in this laboratory.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 61 (2005) 10738–10747

Synthesis and properties of azobenzocrown ethers with π-electron donor, or π-electron donor and π-electron acceptor group(s) on benzene ring(s)

Elżbieta Luboch,[a,*] Ewa Wagner-Wysiecka,[a] Zuzanna Poleska-Muchlado[a] and Victor Ch. Kravtsov[b]

[a]*Department of Chemical Technology, Chemical Faculty, Gdansk University of Technology, Narutowicza 11/12, 80-952 Gdańsk, Poland*
[b]*Institute of Applied Physics, Academy of Science of Moldova, Kishinev, Academy 5, MD 2028, Moldova*

Received 19 May 2005; revised 29 July 2005; accepted 18 August 2005

Available online 21 September 2005

Abstract—New azobenzocrown ethers of differentiated size and with substituted benzene residues have been synthesized. These crown ethers possess π-electron donor, or π-electron donor–π-electron acceptor pair of functional group(s) in benzene ring(s) in the *para* position to azo-grouping. Their metal ion complexation abilities in solution were studied using UV–vis spectrophotometry. The X-ray structure of a 19-membered crown ether with 4-dimethylamino-4′-nitroazobenzene fragment has been solved.

1. Introduction

Crown ethers possessing an azo group as a part of the macrocycle are interesting metal complexing reagents preserving properties typical for azo metallochromic reagents.[1] The arrangement of lone electron pairs and the diameter of the macrocyclic cavity additionally discriminates between complexed species according to their size. Moreover, the presence of benzene rings allows almost unlimited modifications of these compounds to obtain new chromo- or fluoroionophores. Azobenzocrown ethers bearing 2,2′-linked azobenzene were prepared by Williamson ether synthesis using 2,2′-dihydroxyazobenzene.[2,3] Another route leading to the discussed crown ethers consists in using 2,2′-difluoroazobenzene; this method also enables the preparation of aza and thia analogs.[4] Alternatively, azobenzocrown ethers were obtained by stannite reduction followed by macrocyclization of the respective bis(2-nitrophenoxy)-oxaalkanes.[5] The last procedure was used in the synthesis of numerous azobenzocrown ethers, and derivatives substituted mainly with alkyl groups in aromatic rings.[6,7]

The behaviour of lipophilic azobenzocrown ethers as ionophores in ion selective membrane electrodes (ISME's)[6,7] and chemically sensitive field effect transistors (ChemFET's)[8] was studied. As found for non-cyclic azobenzene derivatives, amphiphilic azobenzocrown ethers form stable Langmuir monolayers[6,9] capable of $E \rightleftarrows Z$ isomerization.

The complexation properties of azobenzocrown ethers with alkali and alkaline earth metal salts were investigated spectrophotometrically in acetonitrile solution.[3,10,11] 13- and 16-membered chromoionophoric azobenzocrown ethers with a hydroxyl or dimethylamino group in aromatic ring, in the *para* position to the azo group, were investigated among others.[11]

For *para* or *ortho* hydroxyazobenzenes the tautomerization to quinone–hydrazone form is known to occur.[12] The physical properties of azo dyes (e.g., colour) are closely related to this tautomerism. The phenylazophenol ⇄ quinone–phenylhydrazone tautomerization also proceeds in the case of macrocyclic azophenol chromoionophores, cf.[13]

It was stated that compound **1** (Fig. 1) dissolved in, for example, chloroform, acetonitrile or methanol exists in the quinone–hydrazone form; in dimethyl sulfoxide this form predominates.[11] The structure of the quinone–hydrazone form of crown ether **1** (**1-QH**) was solved by X-ray crystallographic analysis.[14] Compound **2** (Fig. 1) in chloroform and in acetonitrile exists, like **1**, in the quinone–hydrazone form but in dimethyl sulfoxide only the

Keywords: Azo compounds; Chromoionophores; Macrocyclic ligands; Synthetic methods; UV–vis spectroscopy.
* Corresponding author. Tel.: +48 58 3471759; fax: +48 58 3471949; e-mail: elub@chem.pg.gda.pl

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.08.071

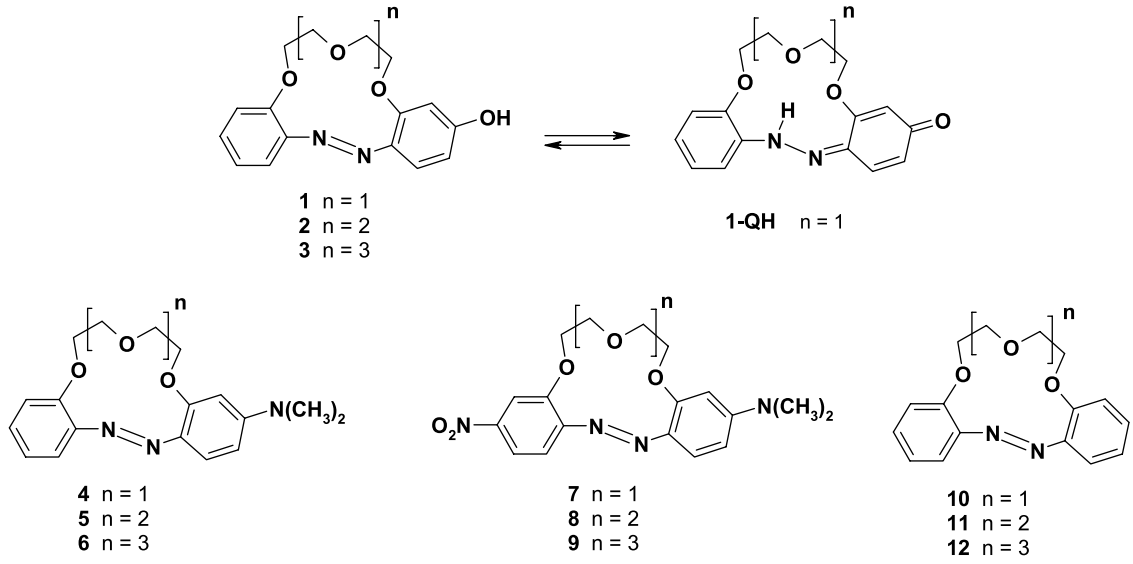


Figure 1. Structures of investigated azobenzocrown ethers.

azophenol form was observed. Cation complexation by compounds **1** and **2** affects the tautomeric equilibrium.[11]

The presence of the dimethylamino substituent (*para* to the azo group) in azobenzocrowns **4** and **5** (Fig. 1) made the absorption maxima well pronounced compared to the spectra of parent compounds **10** and **11**.[11] In the case of compounds **4** and **5** complexation of lithium ions in acetonitrile is clearly evident from spectrophotometric studies due to adequate spectral band separation (60 nm) of crown ether and its complex.

This paper describes the synthesis and properties of new 19-membered azobenzocrown ethers containing hydroxyl or dimethylamino group in *para* position to azo group.

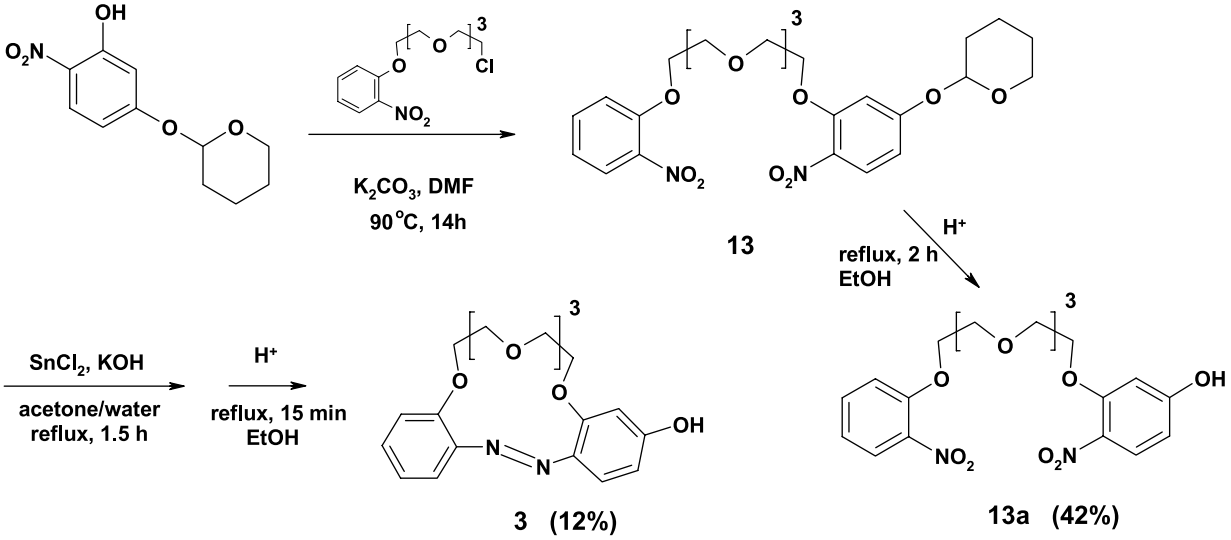
The synthesis of new 13-, 16- and 19-membered crowns bearing two different electron donating/accepting groups (dimethylamino and nitro) in the azobenzene fragment was also elaborated. For the synthesized compounds, spectral properties and metal ion complexation studies were carried out. Their complexation properties were compared to properties of unsubstituted azobenzocrown ethers **10**–**12**.[3,10]

2. Results and discussion

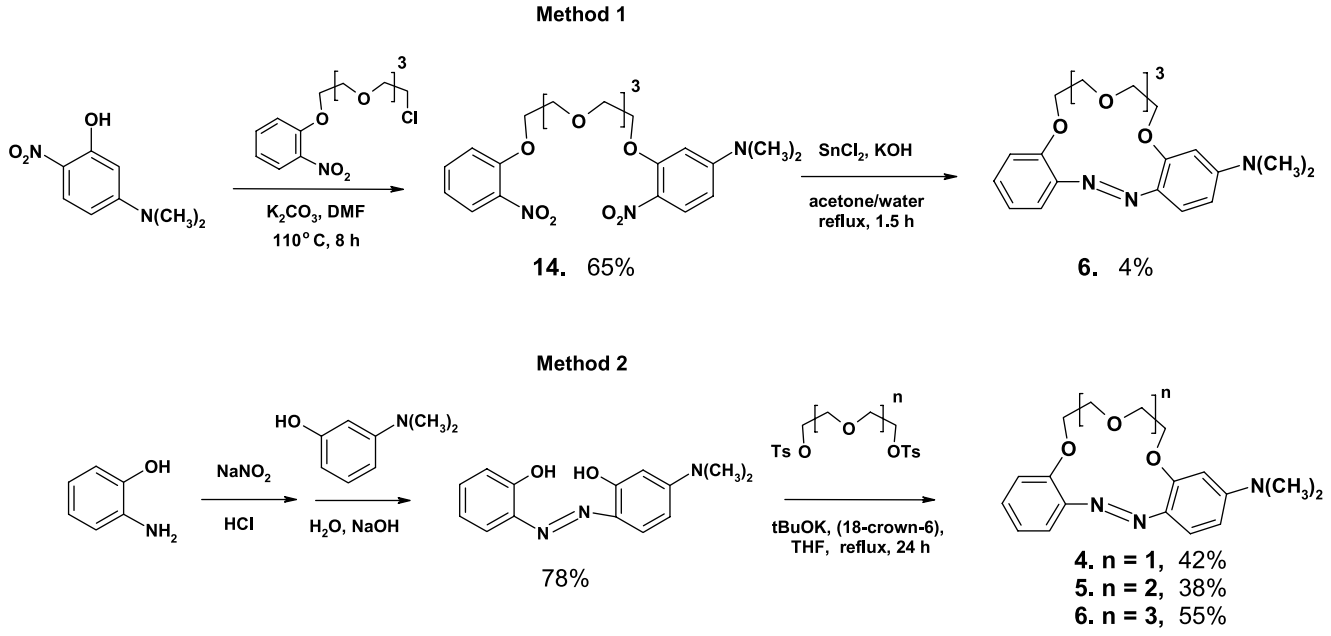
2.1. Synthesis

The synthesis of compounds **3**, **4**–**6** and **7**–**9** is presented in Schemes 1–3. The 19-membered hydroxyazobenzocrown ether **3** was obtained by stannite reduction of dinitropodand **13** (Scheme 1) in a way similar to the method described earlier for azobenzocrown ethers of smaller size.[11] It is worth noting that Williamson synthesis of this compound starting from 4-protected 2,2′,4 -trihydroxyazobenzene resulted in lower yield (around 1%) of **3**.

Tautomeric equilibria for 19-membered azobenzocrown ether with a hydroxyl group were successfully investigated



Scheme 1. Synthesis of 19-membered azobenzocrown ether **3**.



Scheme 2. Synthesis of azobenzocrown ethers **4**–**6**.

using ^{1}H NMR spectroscopy and compared with data for smaller analogs. It was found that the equilibrium depends on the size of the macrocycle. 13-Membered compound **1** exists in quinone–hydrazone form, which is stabilized by a strong intramolecular hydrogen bond.[14] 19-Membered compound **3** exclusively exists in the azophenol form in DMSO and chloroform, whereas in acetonitrile this form is present in no less than 75%.

Compound **6** was obtained by two routes. The first synthesis was performed analogously to the previously described method,[11] which consists of reductive macrocyclization of the appropriate dinitropodand **14** (yield 4%, Scheme 2, method 1). The second synthetic procedure involved diazocoupling of 2-hydroxybenzenediazonium salt with 3-dimethylaminophenol. The obtained 4-dimethylamino-2,2′-dihydroxyazobenzene, upon reaction with 1,13-ditosyl-1,4,7,10,13-pentaoxatridecane produced macrocyclic azo compound **6** (Scheme 2, method 2) with much better yield (55%). This method was also used for the efficient synthesis of compounds **4** and **5** with yields of 42 and 38%, respectively.

Azobenzocrowns **7**–**9** were obtained by reacting 4-dimethylamino-4′-nitro-2,2′-dihydroxyazobenzene with the appropriate ditosylates (Scheme 3, $n=1$–3).

It was found that compounds **7**–**9**, contrary to the parent azobenzocrown ethers, in solution and in the solid state, only exist in *E* form. Single crystal X-ray diffraction study of **9**·2H$_2$O confirmed the *E* geometry of the azo unit with aromatic moieties in the *trans*-positions and proved the existence of a molecular diaqua-complex (Fig. 2).

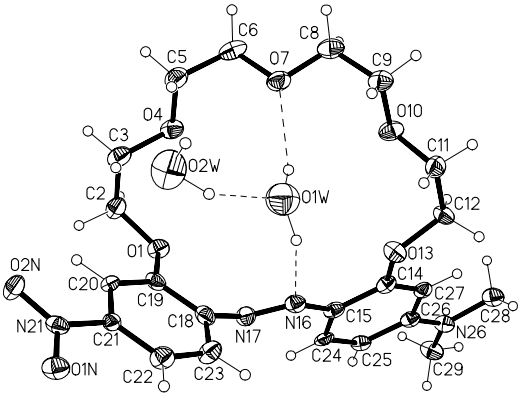
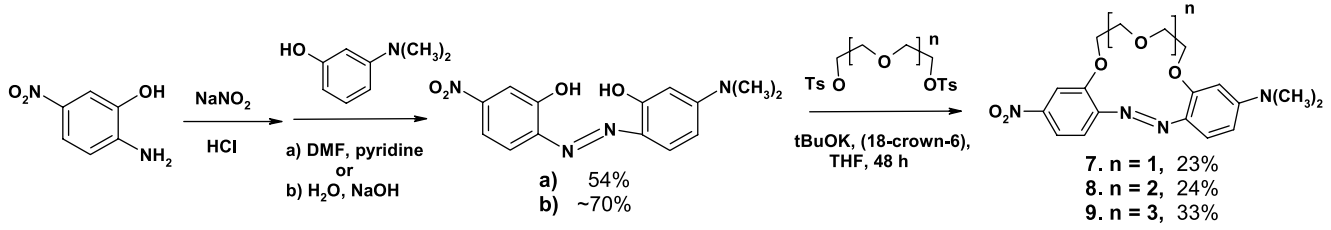


Figure 2. Molecular structure of **9**·2H$_2$O with the atom labeling scheme; ellipsoids are drawn at 50% probability level.

The heteroatoms of macrocyclic unit deviate from their mean plane in the range of −0.255(2)–0.217(2) Å. The flat nitrobenzene and dimethylaminobenzene moieties are located at opposite sides of the plane. The dihedral angle between these two aromatic systems equals 79.4(2)°. The torsion angles around C15–N16 and N17–C18 bonds equal



Scheme 3. Synthesis of azobenzocrown ethers **7**–**9**.

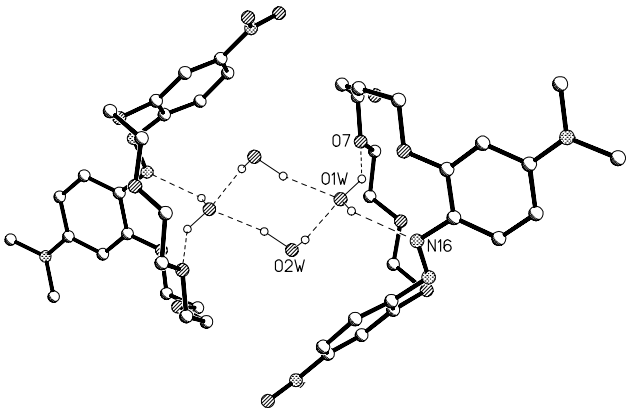


Figure 3. Hydrogen bonded centrosymmetric dimer in the structure of **9**·2H_2O. Hydrogen atoms of crown ethers are omitted for clarity.

164.0(4) and 125.7(4)°, respectively. These differences indicate various degree of π-conjugation of the azo-group with the adjacent aromatic rings and agree well with the corresponding bond lengths of C15–N16 [1.417(6) Å] and N17–C18 [1.431(6) Å]. In the polyether chain the torsion angles around C–C bonds are *gauche* and equal 62.4(5), −73.7(5), 67.8(5) and −72.1° clockwise starting from the C2–C3 bond. The majority of C–O bonds adopt an *anti* conformation and their deviations from 180° are less than 20° except for the torsion angle C19–O1–C2–C3, which is *gauche* and equals 71.4°. The sequence of two *gauche* torsion angles at C2 atom forms the corner fragment.[15]

To the best of our knowledge, this is the first structurally characterized example of water molecule coordination by crown ethers with azobenzene subunit in the macrocycle, although water complexation by Pedersen type macrocycles[16] is an ordinary and well established phenomenon.[17] One water molecule is located 1.723(5) Å above the macrocycle mean plane, and donates protons to form O1w–H···O7 and O1w–H···N16 hydrogen bonds. Two other water molecules bridge neighbouring aqua complexes via O2w–H···O1w hydrogen bonds and result in formation of a centrosymmetric H-bonded dimer. In this dimer, two crown ether molecules encapsulate a tetrameric water cluster (Fig. 3, Table 1).

Table 1. Hydrogen bonds in the structure of **9**·2H_2O (Å and °)[a]

D–H···A	*d* (D–H)	*d* (H···A)	*d* (D···A)	Angle (D–H···A)
O1w–H1w1···O7	1.01(2)	2.10(6)	2.923(6)	137(7)
O1w–H2w1···N16	1.00(2)	2.31(7)	3.157(6)	142(8)
O2w–H1w2···O1w#1	1.05(2)	1.87(3)	2.904(7)	166(6)
O2w–H2w2···O1w	1.08(2)	1.97(4)	2.967(7)	153(6)

[a] Symmetry transformations used to generate equivalent atoms: #1 $-x, -y+2, -z+1$.

In turn, the dimers associate to form chains along the [0 −1 1] direction of crystal due to π-stacked assembly of centrosymmetrically related dimethylaminobenzene moieties. The centroid–centroid distance and the interplanar separations between the corresponding aromatic rings in the stack are 3.908 and 3.530 Å, respectively. No distinct π–π stacking interactions were found for the nitrobenzene aromatic moiety (Fig. 4).

2.2. Spectroscopy and complexation behaviour

The UV–vis spectroscopic properties of investigated and parent compounds (Fig. 1) are collected in Table 2.

The general solvatochromic effect for the above dimethylaminocrown ethers was studied for 19-membered crown ether **6** as an example. UV–vis spectra of **6** in methylene chloride, acetonitrile, acetone, methanol and DMSO were recorded. Characteristic absorption bands and molar absorptivity coefficients in different solvents are collected in Table 3. In all cases noticeable bathochromic shifts of absorption bands at about 390 nm were observed comparing to spectra in acetonitrile. The most significant intensity changes were found for methylene chloride and DMSO; hyper- or hypochromic effects were observed for these solvents, respectively, (Fig. 5).

As expected, the presence of π-electron donor, or π-electron donor and π-electron acceptor groups attached to benzene ring(s) of azobenzocrown ether causes a red shift of the absorption maximum.

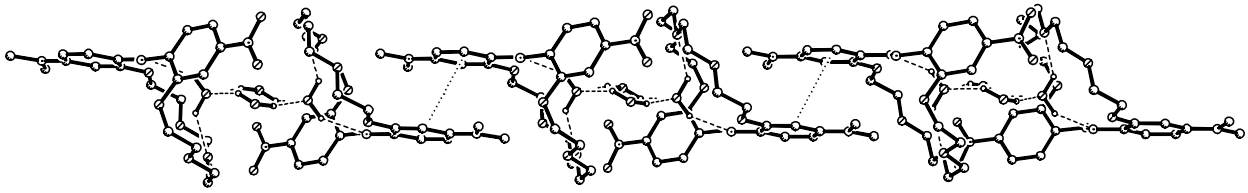


Figure. 4. Hydrogen bonds and π–π stacking interactions linking crown ether and water molecules into chain laying in the [0 −1 1] direction of crystal. Only hydrogen atoms involved in H-bonds are shown.

Table 2. Characteristic absorption bands and molar absorptivity coefficients for azobenzocrown ethers in acetonitrile

Crown ether	λ_{max} (nm)	ε_{max}	Crown ether	λ_{max} (nm)	ε_{max}
1[11]	434	2.31×10^4	**7**	459	1.90×10^4
2[11]	431	2.05×10^4	**8**	463	1.90×10^4
3	342, 434	1.70×10^4, 1.60×10^4	**9**	287, 485	8.30×10^3, 1.70×10^4
4[11]	403	7.70×10^3	**10**(*trans*)	347, 456	1.10×10^4, 5.04×10^2
5[11]	400	1.78×10^4	**11**(*trans*)[10]	351, 461	9.40×10^3, 9.80×10^2
6	380, 455	1.30×10^4, 8.10×10^3	**12**(*trans*)[10]	337, 439	7.88×10^3, 2.83×10^3

Table 3. Characteristic absorption bands and molar absorptivity coefficients for azobenzocrown ether **6** in different solvents

Solvent	λ_{max} (nm)	ε_{max}	Solvent	λ_{max} (nm)	ε_{max}
Methylene chloride	394, ~460	2.40×10^4, 1.20×10^4	Acetone	393, ~460	1.40×10^4, 6.50×10^3
Methanol	389, ~460	1.70×10^4, 1.20×10^4	Dimethyl sulfoxide	392, ~460	7.00×10^3, 4.60×10^3

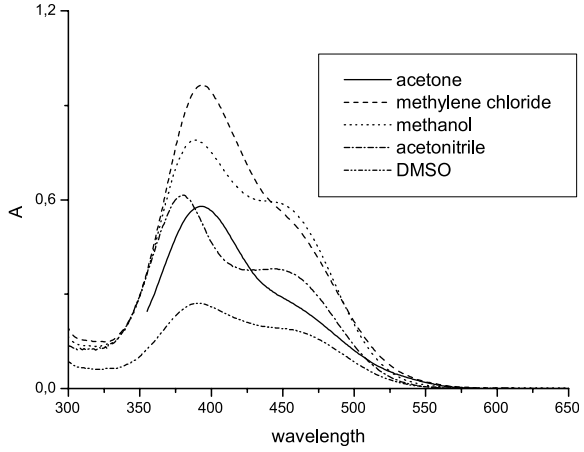


Figure 5. Absorption spectra of compound **6** ($c=4.1\times10^{-5}$ mol dm^{-3}) in different solvents.

Furthermore, the absorption maxima for substituted crown ethers are well pronounced compared with the spectra of the parent unsubstituted crown ethers. A significant effect of the presence of dimethylamino-, or dimethylamino- and nitro-group(s) in benzene rings for compounds **4**–**6** and **7**–**9** is that the $E\rightarrow Z$ isomerization in different solvents under usual conditions is not observed. Absorption spectra of 13-membered crown ethers **10**, **4** and **7** in acetonitrile are presented in Figure 6.

Complexation of alkali and alkaline earth metal ions by macrocycles was investigated by UV–vis spectroscopy in organic solvents. Studies of metal cation complexation performed for 19-membered hydroxyazobenzocrown ether **3** were combined with studies of azophenol⇄quinone–hydrazone equilibration. It was found that the azophenol form is stabilized by complexation of metal cations. In ^{1}H NMR spectra recorded in acetonitrile well pronounced signals for only the azophenol form are observed in the presence of barium, strontium and calcium salts. UV–vis absorption spectra registered in acetonitrile show a decrease of band intensity at 430 nm followed by an increase of the band at 350 nm (typical for the azo form) upon titration with the above metal perchlorates. The respective changes for interaction with strontium perchlorate are exemplified in Figure 7.

The results of spectrophotometric titration did not allow full characterization of the equilibria that occur in the system with compound **3**. It was only stated that beside complex formation tautomeric equilibrium takes place.

For 19-membered azobenzocrown ether with dimethylamino group (compound **6**) selective complex formation was found with the magnesium cation among alkali and alkaline earth metal cations in acetonitrile solution. The complexation was manifested by characteristic colour change from orange to pink. The spectral changes accompanying complex formation are presented in Figure 8.

Other studied cations do not cause such distinct colour changes. Comparison of spectral changes of compound **6** in the presence of potassium, strontium and magnesium perchlorate with evident selectivity for magnesium is shown in Figure 9.

Complexation studies for compound **6** were also carried out in methanol. In this case, no significant spectral changes enabling determination of binding constants were found in the presence of lithium, sodium, potassium and magnesium salts. As could be expected the values of stability constants in methanol are smaller than in acetonitrile. However, in both solvents the largest value of stability constant was found for barium complex (Table 4).

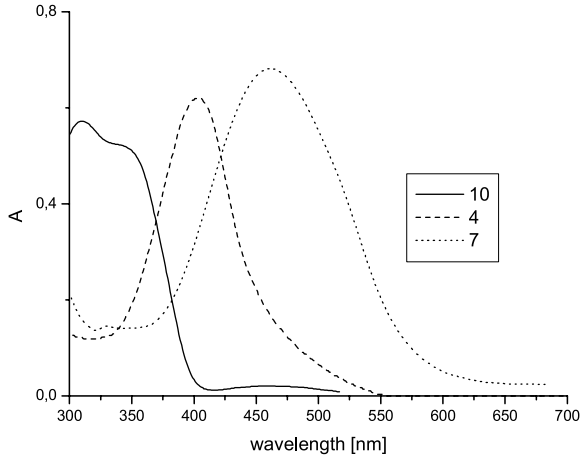


Figure 6. Absorption spectra of azobenzocrown ethers: **10**, **4** and **7** ($c=7.0\times10^{-5}$ mol dm^{-3}) in acetonitrile.

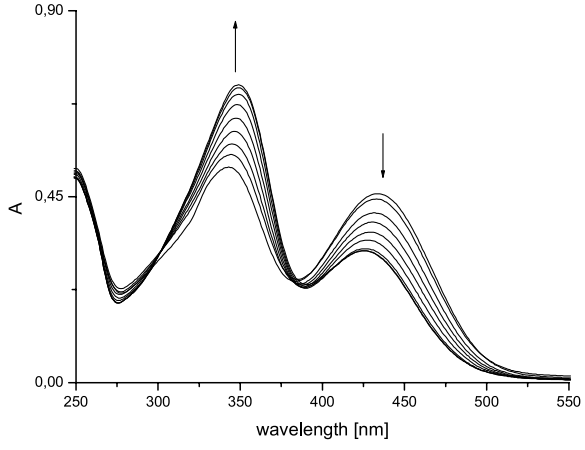


Figure 7. Changes of absorption spectra upon titration of compound **3** ($c=3.0\times10^{-5}$ mol dm^{-3}) with strontium perchlorate (0–4.4×10^{-5} mol dm^{-3}) in acetonitrile.

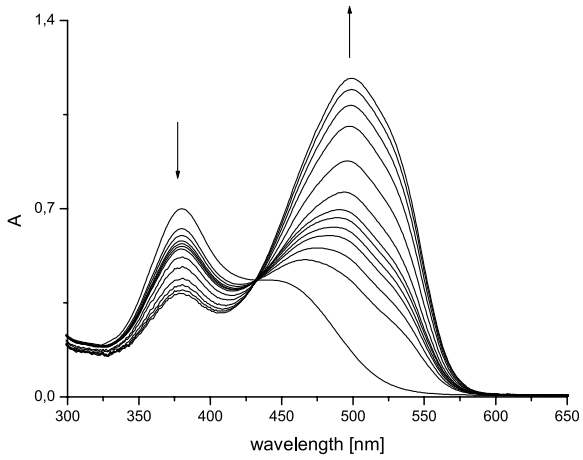


Figure 8. Spectral changes of compound **6** ($c=5.7\times10^{-5}$ mol dm^{-3}) upon titration with magnesium perchlorate (0–1.9×10^{-3} mol dm^{-3}) in acetonitrile.

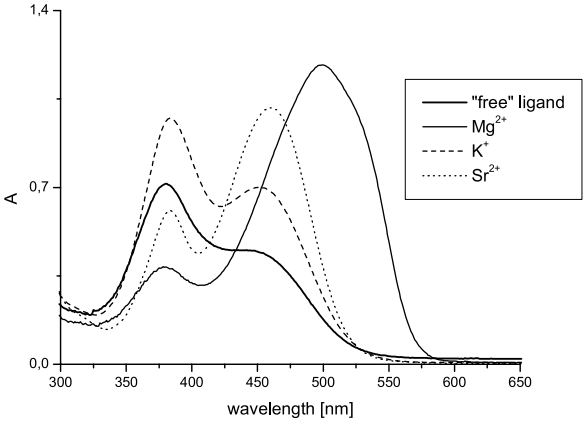


Figure 9. Absorption spectra of compound **6** and its complexes. 'Free' ligand ($c=5.7\times10^{-5}$ mol dm^{-3}) and limiting spectra in the presence of: potassium ($c=2.6\times10^{-3}$ mol dm^{-3}); strontium ($c=4.4\times10^{-5}$ mol dm^{-3}); and magnesium ($c=1.9\times10^{-3}$ mol dm^{-3}) perchlorates in acetonitrile.

Investigations of metal ion complexation were performed also for new type of synthesized compounds containing two different functional groups on the benzene rings (compounds **7–9**). It was found that the crown ethers complex alkali and alkaline earth metal cations and that the selectivity depends on the cavity size. 13-Membered azobenzocrown **7** forms complexes with most of the investigated metal cations. Only the presence of potassium salt causes small changes in the absorption spectra preclude determination of stability constant, similarly to other 13-membered azobenzocrowns. For the sodium complex of compound **7** the calculated stability constant is a little smaller than for sodium complex of compound **4**, whereas for unsubstituted compound **10**, changes in the absorption spectra made determination of stability constant impossible. Generally, the values of the stability constants are higher for alkaline earth metal cation complexes than for lithium and sodium. Changes in the absorption spectra of compound **7** in the presence of alkaline earth metal cations perchlorates are presented in Figure 10. Changes upon titration of above crown ether with lithium perchlorate are shown in Figure 11. The respective values of stability constants for compounds **7–9** and shifts of absorption bands are collected in Table 5.

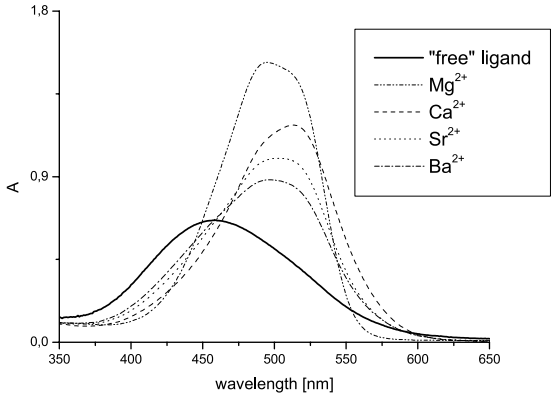


Figure 10. Absorption spectra of compound **7** and its complexes. 'Free' ligand ($c=3.5\times10^{-5}$ mol dm^{-3}); and limiting spectra in the presence of: magnesium ($c=2.2\times10^{-4}$ mol dm^{-3}); calcium ($c=4.5\times10^{-4}$ mol dm^{-3}); strontium ($c=4.1\times10^{-4}$ mol dm^{-3}); and barium ($c=3.9\times10^{-4}$ mol dm^{-3}) perchlorates in acetonitrile.

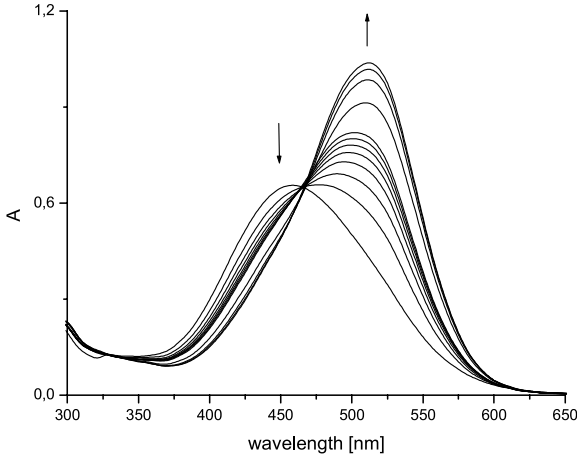


Figure 11. Changes of absorption spectra upon titration of compound **7** ($c=3.5\times10^{-5}$ mol dm^{-3}) with lithium perchlorate (0–4.1×10^{-3} mol dm^{-3}) in acetonitrile.

Table 4. Stability constants of 1:1 complexes of compound **6** with metal perchlorates in acetonitrile and methanol

Solvent	Log K_{Me} ($\Delta\lambda$ (nm))						
	Li	Na	K	Mg	Ca	Sr	Ba
Acetonitrile	2.7[a]	3.4[a]	4.3[b]	4.2 (46)	5.1[a]	5.4[a]	6.7[a]
Methanol	—	—	—	—	2.7[a]	3.5[a]	4.3[a]

[a] Increase of intensity for band at 442 nm.
[b] Increase of intensity for bands at 380 and 442 nm.

Table 5. Stability constants of 1:1 complexes of compounds **7–9** with metal perchlorates in acetonitrile

Compound	Log K_{Me} ($\Delta\lambda$ (nm))						
	Li	Na	K	Mg	Ca	Sr	Ba
7	3.1 (51)	1.8 (28)	—	4.3 (37)	4.5 (56)	3.6 (45)	3.8 (39)
8	4.3 (37)	3.7 (37)	3.2 (27)	5.0 (35)	5.3 (55)	5.4 (55)	5.1 (37)
9	2.1[a]	2.9[a]	2.8[a]	2.5[a]	6.2[a]	5.7[a]	5.6[a]

[a] Increase of intensity for band at ~480 nm.

3. Conclusions

New approaches to the synthesis of functionalized azobenzocrown ethers were presented. In most cases these unsymmetrical compounds were obtained with more than satisfactory yield (even over 55%). For the synthesized compounds, in particular for compounds **7–9**, no detectable $E \rightleftarrows Z$ isomerization under ordinary conditions was found. This presents an advantage of the synthesized macrocycles because it simplifies UV–vis and NMR spectra and limits the number of species during complexation. Selective magnesium cation complexation was found for 19-membered dimethylaminoazobenzocrown ether **6**. Compared with the parent, non-functionalized azobenzocrown ethers, for the studied compounds beneficial influence of the presence of functional groups on changes in absorption spectra upon metal cation complexation was observed.

4. Experimental

4.1. General

All solvents were of analytical reagent grade. Tetrahydrofuran was distilled from $LiAlH_4$ and stored over molecular sieves. For spectrophotometric measurements HPLC grade solvents were used. The reagents from Aldrich were used without further purification. Silica gel 60 (63–200 μm) was used for column chromatography (Merck). ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian instrument at 500 and 125 MHz, respectively. Chemical shifts are reported as δ values in ppm in relation to TMS. IR spectra were recorded on Mattson Genesis II instrument. UV–vis spectra were recorded on a UNICAM UV 300 apparatus. Mass spectrometry was conducted on an AMD-604 apparatus (70 eV, EI method). Melting points (mp) are uncorrected.

4.2. Synthesis

4.2.1. Synthesis of azobenzocrown ether with peripheral hydroxyl group (compound 3).

4.2.1.1. 1-Chloro-11-(2-nitrophenoxy)-3,6,9-trioxaundecane. A mixture of 2-nitro-phenol (3.8 g, 25 mmol), anhydrous potassium carbonate (5 g), 1,11-dichloro-3,6,9-trioxaundecane (17.33 g, 75 mmol) and dimethylformamide (10 mL) was heated for 20 h at 95 °C. The cooled reaction mixture was diluted with water and extracted with chloroform. The desired product was isolated by column chromatography using hexane/methylene chloride 5:1 mixture as an eluent. Yield 3.2 g (38%) of oily product. ^{1}H NMR ($CDCl_3$): δ 3.63 (t, J=6.1 Hz, 2H), 3.65–3.69 (m, 6H), 3.73–3.77 (m, 4H), 3.91 (t, J=4.9 Hz, 2H), 4.27 (t, J=4.9 Hz, 2H), 7.04 (dt, J_1=7.6 Hz, J_2=1.5 Hz, 1H), 7.11 (d, J=8.8 Hz, 1H), 7.50–7.54 (m, 1H), 7.83 (dd, J_1=8.3 Hz, J_2=1.6 Hz, 1H).

4.2.1.2. Podand 13. A mixture of 2-nitro-5-tetrahydropyranyloxyphenol[11] (3 g, 12.5 mmol), anhydrous potassium carbonate (4 g), 1-chloro-11-(2-nitrophenoxy)-3,6,9-trioxaundecane (3.9 g, 11.7 mmol) and dimethylformamide (12 mL) was heated for 14 h at 90 °C. The cooled reaction mixture was diluted with water and extracted with chloroform. The desired product was isolated by column chromatography using methylene chloride as an eluent. A crude product **13** was obtained of insufficient purity. Therefore, the product was fully characterized after removing tetrahydropyranyl protecting group. To the crude product in ethanol (20 mL), catalytic amount of *p*-toluenesulfonic acid was added and the mixture was refluxed for 2 h. After solvent evaporation, the residue was chromatographed using methylene chloride at the beginning and methylene chloride/acetone 10:1 v/v mixture at the end. Yield 2.63 g (42%) of product **13a** as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 3.66–3.72 (m, 4H), 3.72–3.76 (m, 2H), 3.81–3.85 (m, 4H), 3.93 (t, J=4.4 Hz, 2H), 4.19–4.24 (m, 4H), 6.40 (dd, J_1=8.8 Hz, J_2=2.4 Hz, 1H), 6.68 (d, J=2.4 Hz, 1H), 7.01–7.05 (m, 2H), 7.50 (dt, J_1=7.8 Hz, J_2=1.7 Hz, 1H), 7.80–7.84 (m, 2H). IR (film): ν_{max} 3167, 3113, 2925, 2878, 1607, 1584, 1518, 1487, 1453, 1352, 1304, 1275, 1197, 1126, 1093, 1046, 949, 851, 747 cm^{-1}. HRMS *m*/*z*: calcd for $C_{20}H_{24}O_{10}N_2$: 452.1431; found: 452.1436.

4.2.1.3. Azobenzocrown ether 3. To a vigorously stirred suspension of podand **13** (0.72 g, 1.3 mmol) stannous chloride dihydrate (1.47 g, 6.43 mmol), potassium hydroxide (2.5 g), and acetone (9 mL) water (8 mL) was added dropwise. When the exothermic reaction ceased, the mixture was heated to 55 °C for 1.5 h. After this time chloroform was added, the organic layer was separated, washed with water and evaporated to dryness. The residue was chromatographed on a column. The orange fraction containing azocrown was hydrolyzed in ethanol in the presence of catalytic amount of *p*-toluenesulfonic acid for 15 min. The solvent was removed and the residue was rechromatographed. Azobenzocrown ether **3** was eluted with methylene chloride/acetone 4:1 mixture. An oily orange-red crown ether (0.062 g, 12%) was obtained. ^{1}H NMR (*d*-acetonitrile), signals characteristic for azo form, selected from spectrum of mixture of tautomeric forms: δ 3.42–3.54 (m, 8H), 3.70–3.77 (m, 4H), 4.23–4.34 (m, 4H), 6.50 (d, J=8.3 Hz, 1H), 6.64 (s, 1H), 6.93–7.15 (m, 4H), 7.35–7.42 (m, 1H). Some selected signals of quinone–hydrazone form: 5.91 (s); 6.22 (d, J=7.8 Hz); 11.78 (s); ratio 3:1 azophenol:quinone–hydrazone. ^{1}H NMR (*d*-acetonitrile + strontium perchlorate): δ 3.78–3.81 (m, 4H), 3.85–3.90 (m, 4H), 3.97 (d, J=4 Hz, 2H), 4.03 (d, J=4.4 Hz, 2H), 4.42–4.47 (m, 4H), 6.77 (dd, J_1=8.8 Hz, J_2=2.4 Hz, 1H), 6.82

(d, $J=2$ Hz, 1H), 7.24 (t, $J=7.6$ Hz, 1H), 7.32 (d, $J=8.3$ Hz, 1H), 7.50–7.55 (2H, m), 7.70 (d, $J=8.8$ Hz, 1H), 8.34 (br s, 1H). ^{13}C NMR (*d*-acetonitrile + strontium perchlorate): δ 69.43, 69.56, 69.74, 70.22, 70.47, 70.49, 70.89, 70.92, 103.01, 111.33, 114.94, 124.02, 124.79, 131.56, 133.00, 137.61, 163.92, 151.08, 151.49, 162.73. IR (film): ν_{max} 3303, 2924, 1622, 1601, 1518, 1488, 1447, 1308, 1263, 1240, 1182, 1108, 1047, 946, 854, 753 cm^{-1}. HRMS *m/z*: calcd for $C_{20}H_{24}O_6N_2$: 388.1634; found: 388.1639.

4.2.2. Synthesis of azobenzocrown ethers with peripheral dimethylamino group (compounds 4–6). *Method A*. According to this method, compound **6** was obtained, as described above for compounds **4** and **5**,[11] using 1-chloro-11-(2-nitrophenoxy)-3,6,9-trioxaundecane.

4.2.2.1. Podand 14. A mixture of 5-dimethylamino-2-nitro-phenol[11] (1.46 g, 8 mmol), 1-chloro-11-(2-nitrophenoxy)-3,6,9-trioxaundecane (2.7 g, 8.2 mmol), potassium carbonate (2.2 g) and dimethylformamide (10 mL) was stirred and heated at 110 °C for 8 h. Then water was added and the product was extracted with methylene chloride. The evaporated extract was chromatographed using methylene chloride as an eluent. Compound **14** (2.5 g, 65%) was obtained as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 3.1 (s, 6H), 3.67–3.72 (m, 4H), 3.74–3.83 (m, 4H), 3.90–3.98 (m, 4H), 4.24–4.29 (m, 4H), 6.21 (s, 1H), 6.29 (dd, $J_1=9.3$ Hz, $J_2=2.4$ Hz, 1H), 7.03 (t, $J=7.8$ Hz, 1H), 7.12 (d, $J=8.3$ Hz, 1H), 7.52 (t, $J=7.8$ Hz, 1H), 7.83 (dd, $J_1=8.3$ Hz, $J_2=1.5$ Hz, 1H), 8.01 (d, $J=9.3$ Hz, 1H). IR (film): ν_{max} 2875, 1607, 1572, 1524, 1491, 1349, 1300, 1252, 1130, 1096, 1046, 947, 928, 852, 810, 747 cm^{-1}. HRMS *m/z*: calcd for $C_{22}H_{29}O_9N_3$: 479.1904; found: 479.1913.

4.2.2.2. Azobenzocrown ether 6. To vigorously stirred mixture of podand **14** (1.29 g, 2.7 mmol) in acetone (10 mL), stannous chloride dihydrate (2.5 g, 11 mmol) and potassium hydroxide (4.76 g) water (9 mL) was added and the mixture was gently boiled for 1.5 h. Isolation was carried out as described.[11] The desired product was eluted from chromatographic column as the last using methanol as an eluent. Compound **6**, crystallized from acetone/hexane mixture, was obtained (44 mg, 4%) as a fire-brick solid. Mp 105–107 °C. ^{1}H NMR (*d*-acetone): δ 3.10 (s, 6H), 3.38–3.44 (m, 4H), 3.48–3.52 (t, $J=4.6$ Hz, 2H), 3.54–3.58 (t, $J=4.40$ Hz, 2H), 3.78–3.82 (t, $J=4.6$ Hz, 2H), 3.83–3.86 (t, $J=4.6$ Hz, 2H), 4.28–4.32 (t, $J=4.8$ Hz, 2H), 4.34–4.38 (m, 2H), 6.41–6.46 (m, 2H), 7.02 (t, $J=7.6$ Hz, 1H), 7.15 (d, $J=7.8$ Hz, 1H), 7.30 (t, $J=7.8$ Hz, 2H), 7.55 (d, $J=8.3$ Hz, 1H). ^{13}C NMR (*d*-acetone): δ 39.76, 69.55, 69.58, 69.87, 70.12, 70.69, 70.71, 70.74, 70.78, 98.29, 105.06, 116.03, 119.97, 121.24, 129.31, 135.63, 146.08, 153.86, 154.00, 157.52. IR (film): ν_{max} 2923, 2874, 1608, 1516, 1485, 1446, 1363, 1279, 1243, 1107, 1048, 950, 810, 753 cm^{-1}. HRMS *m/z*: calcd for $C_{22}H_{29}O_5N_3$: 415.2107; found: 415.2091.

Method B

4.2.2.3. 4-Dimethylamino-2,2′-dihydroxyazobenzene. A suspension of 2-amino-phenol (0.44 g, 4 mmol) in water (10 mL) was cooled and acidified with concd hydrochloric acid (1 mL). The solution was diazotized with sodium nitrite (0.28 g in 2 mL cold water). Then the reaction mixture was kept at 5 °C for 15 min.

The obtained diazonium salt was added dropwise to an ice-cold solution of 3-dimethylamino-phenol (0.55 g, 4 mmol) and NaOH (0.4 g) in water (10 mL). The reaction mixture was stirred at 10 °C for 1 h. The mixture was then cooled and made slightly acidic with 0.1 M hydrochloric acid. The precipitated solid was separated and washed with water. The solid was in turn suspended in a small amount of acetone, cooled and filtered. The crude, solid 4-dimethylamino-2,2′-dihydroxyazobenzene (0.8 g, 78%) was used for macrocycle synthesis. Analytical sample was obtained by purifying crude product on column chromatography using methylene chloride/acetone 30:1 mixture as an eluent. Crystallization from propan-2-ol gave the title compound as a red-brown solid. Mp 235–237 °C. ^{1}H NMR (*d*-DMSO): δ 3.06 (s, 6H), 6.05 (d, $J=2.9$ Hz, 1H); 6.50 (dd, $J_1=9.2$ Hz, $J_2=2.4$ Hz, 1H); 6.92 (dt, $J_1=7.6$ Hz, $J_2=1$ Hz, 1H); 6.98 (dd, $J_1=8.3$ Hz, $J_2=1.2$ Hz, 1H); 7.19 (dt, $J_1=7.6$ Hz, $J_2=1.5$ Hz, 1H); 7.52 (d, $J=9.2$ Hz, 1H); 7.67 (dd, $J=8.3$, 1.5 Hz, 1H); 10.95 (s, 1H); 13.88 (s, 1H). The NOESY spectrum confirms the position of the dimethylamino group in benzene ring. IR (nujol): ν_{max} 1631, 1535, 1328, 1255, 1238, 1213, 1147, 795, 750 cm^{-1}. UV–vis (acetonitrile): $\lambda_1=264$ nm, $\varepsilon_1=2.56\times10^3$; $\lambda_2=287$ nm, $\varepsilon_2=2.161\times10^3$; $\lambda_3=470$ nm, $\varepsilon_3=1.50\times10^4$. MS *m/z*: calcd for $C_{14}H_{15}O_2N_3$: 257; found: 257. HRMS *m/z*: calcd for $C_{14}H_{15}O_2N_3$: 257.1164; found: 257.1169.

4.2.2.4. Azobenzocrown ethers 4–6. To 4-dimethylamino-2,2′-dihydroxyazobenzene (0.52 g, 2 mmol) potassium *tert*-butoxide (0.78 g, 7 mmol) in dry THF (50 mL) was added. The mixture was stirred for 0.5 h at room temperature and then (in case of compounds **4** and **5**) 18-crown-6 (10 mg) was added. After that, the appropriate ditosyl derivative[18] (2.2 mmol) in THF (50 mL) was added dropwise over 1 h. The reaction mixture was heated at 70 °C for 24 h. The solid was removed by filtration and washed with THF until colorless filtrate was obtained. The filtrate was evaporated under reduced pressure, the residue was dissolved in methylene chloride and chromatographed on column using methylene chloride, acetone/methanol mixtures and finally pure methanol as eluents. The fractions containing the azobenzocrown ether were evaporated, the red residue was dissolved in methylene chloride, filtered and the filtrate was evaporated to dryness. Crystallization from acetone/hexane mixture or propan-2-ol gave desired compounds identical with those obtained by method A or described earlier.[11]

By this method were obtained: compound **4** as a dark red solid, yield 42%, mp 121–123 °C; compound **5** as a fire-brick solid, yield 38%, mp 113–116 °C; compound **6** as a dark red solid, yield 55%, mp 105–107 °C.

4.2.3. Synthesis of azobenzocrown ethers 7–9.

4.2.3.1. 4-Dimethylamino-4′-nitro-2,2′-dihydroxyazobenzene. *Method A*. To a suspension of 2-amino-5-nitrophenol (1.23 g, 8 mmol) in water (10 mL) concd HCl (2 mL) was added. The mixture was diazotized with $NaNO_2$ (0.56 g) dissolved in water (4 mL). The precipitated, wet solid was collected (caution!), suspended in a mixture of

DMF (10 mL) and pyridine (4 mL), stirred and cooled in an ice-water bath. To this mixture solution of 3-dimethylamino-phenol (1.1 g, 8 mmol) in DMF (10 mL) was added. The reaction mixture was stirred for 3 h at 5 °C, 3 h at room temperature and diluted with cold water (30 mL). The solid was collected and dried (2 g). Afterwards the solid was triturated with acetone (10 mL), filtered and the solid washed with cold acetone. The crude solid product (1.32 g, 54%) was used in the synthesis of azobenzocrown ethers. An analytical sample was obtained by column chromatography using THF as an eluent. The eluate was evaporated and the product was precipitated with propan-2-ol.

The residual acetone filtrate contains mainly isomeric compound—2-dimetylamino-4′-nitro-2′,4-dihydroxyazobenzene (about 30% in the main reaction product), which was also isolated (purification: column chromatography with a methylene chloride/acetone 30:1 mixture) and characterized by spectroscopic methods.

4-Dimethylamino-4′-nitro-2,2′-dihydroxyazobenzene. Black solid, mp 275 °C (dec). ^{1}H NMR (*d*-DMSO): δ 3.14 (s, 6H), 5.82 (d, $J=2.4$ Hz, 1H), 6.71 (dd, $J_1=9.6$ Hz, $J_2=2.5$ Hz, 1H), 7.30 (d, $J=9.6$ Hz, 1H), 7.75 (s, 1H), 7.80 (s, 2H), 11.28 (s, 1H), 14.6 (br s, 1H). IR (nujol): ν_{max} 1633, 1602, 1535, 1504, 1320, 1259, 1240, 1271, 1150, 1074, 929, 870, 816, 791, 745 cm^{-1}. (UV–vis (acetonitrile): $\lambda_1=292$ nm, $\varepsilon_1=2.89\times10^2$; $\lambda_2=518$ nm, $\varepsilon_2=2.21\times10^3$. HRMS *m/z*: calcd for $C_{14}H_{14}O_4N_4$: 302.1015; found: 302.1013.

2-Dimethylamino-4′-nitro-2′,4-dihydroxyazobenzene. Black solid, mp 164–165 °C. ^{1}H NMR (*d*-DMSO): δ 3.08 (s, 6H), 6.34 (dd, $J_1=9.2$ Hz, $J_2=2.1$ Hz, 1H), 6.39 (d, $J=2.1$ Hz, 1H), 7.67 (d, $J=8.6$ Hz, 1H), 7.75–7.80 (m, 2H), 7.87 (d, $J=8.8$ Hz, 1H), 10.36 (s, 1H), 11.18 (s, 1H). The NOE spectrum confirms position of dimethylamino group in benzene ring. IR (nujol): ν_{max} 3301, 1607, 1566, 1511, 1339, 1304, 1257, 1178, 1123, 1074, 985, 856, 740 cm^{-1}. UV–vis (acetonitrile): $\lambda_1\sim280$ nm, $\varepsilon_1=9.88\times10^2$; $\lambda_2=385$ nm, $\varepsilon_2=1.20\times10^3$; $\lambda_3=499$ nm, $\varepsilon_3=1.43\times10^3$. MS *m/z*: calcd for $C_{14}H_{14}O_4N_4$: 302; found: 302.

Method B. Solution A: to a suspension of 5-nitro-2-amino-phenol (1.23 g, 8 mmol) in water (20 mL) concd HCl (2 mL) was added. The mixture was diazotized with $NaNO_2$ (0.56 g) dissolved in water (4 mL) for 15 min at $\sim$3 °C.

Solution B: 3-dimethylamino-phenol (1.1 g, 8 mmol) and NaOH (0.8 g) were dissolved in cold water (20 mL).

Both solutions were added dropwise to ice-cold water (60 mL) over 15 min with the same molar rate. The mixture was kept at 5 °C at the beginning and at 15 °C at the end for 3 h. The reaction mixture was cooled and 0.1 M HCl (50 mL) was added. The precipitate (2.2 g, 91%), containing 4-dimethylamino-4′-nitro-2,2′-dihydroxyazobenzene and 2-dimethylamino-4′-nitro-2′,4-dihydroxyazobenzene in 4:1 ratio, was separated, washed with water and dried at room temperature. The mixture of isomers was separated as described above in method A.

4.2.3.2. Azobenzocrown ethers 7–9. To 4-dimethylamino-4′-nitro-2,2′-dihydroxyazobenzene 0.3 g (1 mmol) potassium *tert*-butoxide (0.39 g, 3.5 mmol) in dry THF (30 mL) was added. The mixture was stirred at room temperature for 0.5 h, then heated to 40 °C. 5 mg 18-crown-6 was added and next the appropriate ditosyl derivative (1 mmol) in THF (30 mL) was added dropwise over 3 h. The synthesis was continued at gentle boiling for 48 h. The solid was separated and washed with THF until a colorless filtrate was obtained. The filtrate was evaporated and the residue was extracted with methylene chloride. The concentrated extract was chromatographed on a column. Mixtures of methylene chloride with acetone and finally acetone were used as eluents. The crude product was rechromatographed using the same eluents. Azobenzocrown ethers were crystallized from propan-2-ol. By this method were obtained compounds **7**, **8**, **9** as black-brown solids with 23, 24 and 33% yield, respectively.

Compound 7. Mp 165–168 °C. ^{1}H NMR (*d*-acetone): δ 3.16 (s, 6H), 3.89 (t, $J=4.5$ Hz, 2H), 3.93 (t, $J=4.3$ Hz, 2H), 4.33 (t, $J=4.5$ Hz, 2H), 4.42 (t, $J=4.3$ Hz, 2H), 6.45 (d, $J=2.6$ Hz, 1H), 6.60 (dd, $J_1=9.2$ Hz, $J_2=2.7$ Hz, 1H), 7.78 (d, $J=9.3$ Hz, 1H), 7.81 (d, $J=8.8$ Hz, 1H), 7.97 (d, $J=2.3$ Hz, 1H), 8.02 (dd, $J_1=8.8$ Hz, $J_2=2.3$ Hz, 1H). ^{13}C NMR ($CDCl_3$ and one drop of CD_3OD): δ 40.49, 69.57, 70.02, 70.99, 71.36, 100.34, 106.89, 113.22, 117.97, 123.86, 125.54, 135.92, 147.10, 149.50, 152.38, 154.59, 157.44. IR (nujol): ν_{max} 1610, 1542, 1509, 1327, 1256, 1211, 1172, 1136, 1108, 1080, 1046, 955, 922, 892, 828, 807, 723 cm^{-1}. HRMS *m/z*: calcd for $C_{18}H_{20}N_4O_5$: 372.1434; found: 372.1431.

Compound 8. Mp 168–170 °C. ^{1}H NMR (*d*-acetone): δ 3.17 (s, 6H), 3.69–3.73 (m, 4H), 3.93–3.67 (m, 4H), 4.29 (t, $J=4.5$ Hz, 2H), 4.38 (t, $J=4.5$ Hz, 2H), 6.40 (d, $J=2.4$ Hz, 1H), 6.54 (dd, $J_1=9.2$ Hz, $J_2=2.5$ Hz, 1H), 7.64 (d, $J=8.6$ Hz, 1H), 7.79 (d, $J=9.3$ Hz, 1H), 7.94 (dd, $J_1=8.6$ Hz, $J_2=2.5$ Hz, 1H), 7.96 (d, $J=2$ Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 40.56, 68.98, 69.17, 69.46, 70.22, 70.48, 96.39, 105.28, 108.90, 116.75, 121.22, 131.07, 147.37, 148.60, 153.12, 154.28, 155.15. IR (nujol): ν_{max} 1614, 1511, 1321, 1254, 1218, 1162, 1136, 1084, 964, 861, 809, 730 cm^{-1}. HRMS *m/z*: calcd for $C_{20}H_{24}N_4O_6$: 416.1696; found: 416.1688.

Compound 9. Mp 133–135 °C. ^{1}H NMR (*d*-acetone): δ 3.15 (s, 6H), 3.37–3.43 (m, 4H), 3.49 (t, $J=4.6$ Hz, 2H), 3.58 (t, $J=4.6$ Hz, 2H), 3.82–3.87 (m, 4H), 4.37 (t, $J=4.6$ Hz, 2H), 4.45 (t, $J=4.6$ Hz, 2H), 6.42 (d, $J=2.4$ Hz, 1H), 6.49 (dd, $J_1=8.7$ Hz, $J_2=2.4$ Hz, 1H), 7.40 (d, $J=8.3$ Hz, 1H), 7.64 (d, $J=9.3$ Hz, 1H), 7.92 (dd, $J_1=8.7$ Hz, $J_2=2.4$ Hz, 1H), 7.96 (d, $J=2$ Hz, 1H). NOE spectrum confirmed the position of substitution of the benzene rings. ^{13}C NMR (*d*-acetone): δ 39.75, 69.44, 69.48, 69.81, 70.60, 70.61, 70.67, 70.74, 70.85, 97.43, 105.28, 110.93, 116.82, 119.84, 122.21, 135.61, 147.51, 150.62, 153.88, 155.05, 158.44. IR (nujol): ν_{max} 1609, 1544, 1512, 1328, 1245, 1226, 1138, 1083, 1028, 979, 876, 866, 807, 728 cm^{-1}. HRMS *m/z*: calcd for $C_{22}H_{28}N_4O_7$ 460.1958; found: 460.1950.

4.3. X-ray structure determination

Crystallographic data for $\mathbf{9}\cdot2H_2O$ were collected at 100 K on a Bruker SMART-APEX diffractometer using Mo K_α radiation ($\lambda=0.7107$ Å) equipped with CCD-type area

detector and an Oxford Cryosystems open flow Nitrogen gas cooling device. The data were corrected for Lorentz and polarization effects and for absorption using the SADABS program. The structure was solved using direct methods and refined by full-matrix least squares on F^2.[19] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms of water molecules were located on a difference Fourier map and refined isotropically. Other hydrogen atoms were placed in geometrically calculated positions and refined with temperature factors 1.2 and 1.5 times of those of their bonded atoms for CH_2 and CH_3 groups, respectively. Crystal data for $\mathbf{9}\cdot 2H_2O$: triclinic, space group P-1, $a=8.647(3)$, $b=12.109(4)$, $c=12.505(5)$ Å, $\alpha=85.538(7)$, $\beta=75.995(6)$, $\gamma=76.519(6)°$, $V=1235.1(8)$ Å^3, $Z=2$, $D_c=1.335$ g/m^3, $\mu=1.04$ cm^{-1}, $F(000)=528$, $\theta_{max}=25.25°$ ($-10\leq h\leq 10$, $-14\leq k\leq 8$, $-14\leq l\leq 14$), reflections collected 5167, independent reflections 4068 ($R_{int}=0.0405$), GOF on F^2 1.016. Final residuals (for 334 parameters) $R1=0.0822$, $wR2=0.1930$ for 2270 reflections with $I>2\sigma(I)$, and $R1=0.1424$, $wR2=0.2139$ for all data. Residual electron density: 0.767 and -0.493 e Å^{-3}.

Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 287144. 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. Determination of stability constants

Stability constants for complexes were determined by spectrophotometric titration of ligand solution with the appropriate metal perchlorate solution. The stability constants were calculated with a program DynaFit.[20]

Acknowledgements

Financial support of this work from the Gdansk University of Technology (DS Grant no. 014668/003) and Grant 3 T09A 151 27 from Polish State Committee for Scientific Research are kindly acknowledged. The authors are indebted to Professor J. F. Biernat for his assistance in preparation of this manuscript. The authors thank Jolanta Żochowska for remarkable experimental help.

References and notes

1. For example see review: Luboch, E.; Bilewicz, R.; Kowalczyk, M.; Wagner-Wysiecka, E.; Biernat, J. F. Azo Macrocyclic Compounds. In Gokel, G. W., Ed.; Advances in Supramolecular Chemistry; Cerberus: South Miami, USA, 2003; Vol. 9, p 71.
2. Shiga, M.; Takagi, M.; Ueno, K. *Chem. Lett.* **1980**, 1021.
3. Shiga, M.; Nakamura, H.; Tagaki, M.; Ueno, K. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 412.
4. Luboch, E.; Biedrzycka, A. *Pol. J. Chem.* **2003**, *77*, 47.
5. Biernat, J. F.; Luboch, E.; Cygan, A.; Simonov, Yu. A.; Dvorkin, A. A.; Muszalska, E.; Bilewicz, R. *Tetrahedron* **1992**, *48*, 4399.
6. Luboch, E.; Biernat, J. F.; Muszalska, E.; Bilewicz, R. *Supramol. Chem.* **1995**, *5*, 201.
7. Luboch, E.; Biernat, J. F.; Simonov, Yu. A.; Dvorkin, A. A. *Tetrahedron* **1998**, *54*, 4977.
8. Pijanowska, D. G.; Luboch, E.; Biernat, J. F.; Dawgul, M.; Torbicz, W. *Sens. Actuators, B* **1999**, *58*, 384.
9. For example see: (a) Huesmann, H.; Maack, J.; Möbius, D.; Biernat, J. B. *Sens. Actuators, B* **1995**, *29*, 148. (b) Muszalska, E.; Bilewicz, R. *Analyst* **1994**, *119*, 1235. (c) Muszalska, E.; Bilewicz, R.; Luboch, E.; Skwierawska, A.; Biernat, J. F. *J. Inclusion Phenom.* **1996**, *26*, 47. (d) Zawisza, I.; Bilewicz, R.; Luboch, E.; Biernat, J. F. *J. Chem. Soc., Dalton Trans.* **2000**, 499.
10. Tahara, R.; Morozumi, T.; Nakamura, H.; Shimomura, M. *J. Phys. Chem. B* **1997**, *101*, 7736.
11. Luboch, E.; Wagner-Wysiecka, E.; Biernat, J. F. *J. Supramol. Chem.* **2002**, *2*, 279.
12. Hofer, E.; Uffman, H. *Tetrahedron Lett.* **1971**, 3241.
13. Chapoteau, E.; Czech, B. P.; Gebauer, C. R.; Kumar, A.; Leong, K.; Mytych, D.; Zazulak, W.; Desai, D. H.; Luboch, E.; Krzykawski, J.; Bartsch, R. A. *J. Org. Chem.* **1991**, *56*, 2575.
14. Luboch, E.; Kravtsov, V. Ch. *J. Mol. Struct.* **2004**, *699*, 9.
15. Dale, J. *Acta Chem. Scand.* **1973**, *27*, 1115.
16. Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 2945.
17. (a) Mootz, D.; Albert, A.; Schaefgen, S.; Stäben, D. *J. Am. Chem. Soc.* **1994**, *116*, 12045. (b) Krongsuk, S.; Kerdcharoen, T.; Hannongbua, S. *J. Phys. Chem. B* **2003**, *107*, 4175.
18. Ouchi, M.; Inoue, Y.; Liu, Y.; Nagamune, S.; Nakamura, S.; Wada, K.; Hakushi, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1260.
19. Sheldrik, G. M. *SHELX-97: Programs for the solution and refinement of crystal structures*; University of Gottingen: Gottingen, Germany, 1997.
20. Kuzmič, P. *Anal. Biochem.* **1996**, *237*, 260; http://wwwbiokin.com.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 61 (2005) 10748–10756

Ligand creation via linking—a rapid and convenient method for construction of novel supported PyOX-ligands

Markku J. Oila, Jan E. Tois and Ari M. P. Koskinen*

Laboratory of Organic Chemistry, Helsinki University of Technology, PO Box 6100, FIN-02015 HUT Espoo, Finland

Received 22 April 2005; revised 1 August 2005; accepted 18 August 2005

Available online 12 September 2005

Abstract—A novel supported amino alcohol linker was synthesized and utilized for attachment of picolinic acid derivatives onto different supports. When the resin bound molecule was further activated, the PyOX-moiety could be constructed reliably in enantiopure form. Furthermore, an efficient Pd-catalyzed modification of a picolinic acid derivative is presented.

1. Introduction

For economic and environmental reasons, the trend towards the application of enantiopure compounds is undoubtedly increasing. Asymmetric induction with chiral ligands and their transition metal complexes constitutes one of the most versatile methods for the preparation of chiral compounds in enantiopure form.[1] Covalent immobilization of catalysts on insoluble polymer or other supports has received considerable attention in recent years.[2] Heterogeneous catalysis has two major advantages over homogenous catalysis: (1) separation of the catalyst from reagents and products is technically easier and facilitates recycling and recovery of the valuable catalyst material; (2) optimization of either the diversity of the ligand or the reaction conditions is facilitated. In particular, polymer supported ligands have been studied extensively.[3] Whereas the PyOX-core (Fig. 1) has been widely reported in several applications as soluble ligands, solid-supported PyOX-ligands are still very rarely published,[4] despite their obvious usefulness in various catalytic asymmetric reactions.[5–7] More intensively, the C_2-symmetric PyBOX-core has been attached to a solid support using various methods.[8]

In modification processes of the PyOX-core, the modification has traditionally been carried out by altering the amino alcohols, which are used to form the oxazoline part of the PyOX-core (Fig. 1). Much less attention has been focused on the pyridine part.[7c,d] In this paper, we will introduce a new method to simultaneously link picolinic acid derivatives to a solid support and form the PyOX-core via cyclization on the solid support. For this purpose, a novel tyrosine-based aminoalcohol linker **1** was synthesized. This methodology allows the possibility of systematically optimizing the substituents of the pyridine ring in the PyOX. When the pyridine is adorned with a functional tail, the Py-part can be attached to a support and optimization of the oxazoline part can take place.

2. Results and discussion

The main plan for the formation of a novel linker was to utilize the amino alcohol functionality for both linking carboxylic acids and oxazoline formation via varying the substituents of the pyridine ring. Natural tyrosine provides the necessary orthogonal functionalities for linking and oxazoline formation, and was therefore used as the starting material for the linker. As the support we chose the robust Merrifield resin with no additional linkers. Attachment to the resin can be achieved via an ether bond between the resin and the phenolic group of tyrosine. This linking strategy gives us the possibility to prepare additional linkers in the future, if flexibility is needed.

In solution phase model experiments for linker preparation the solid support was replaced with a benzyl group as a soluble analogue of the Merrifield resin. The model reactions were performed in order to optimize the reaction conditions with respect to reaction rate, conversion and retention of stereochemistry. The protected tyrosine **3** was prepared according to published methods (Scheme 1).[9] Benzylation of the protected tyrosine posed some critical technical issues: the use of cesium carbonate in benzylation

Keywords: Supported PyOX-ligand; Amino alcohol linker; Tyrosine; Picolinic acid derivative.
* Corresponding author. Tel.: +358 9451 2526; fax: +358 9451 2538; e-mail: ari.koskinen@hut.fi

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.08.073

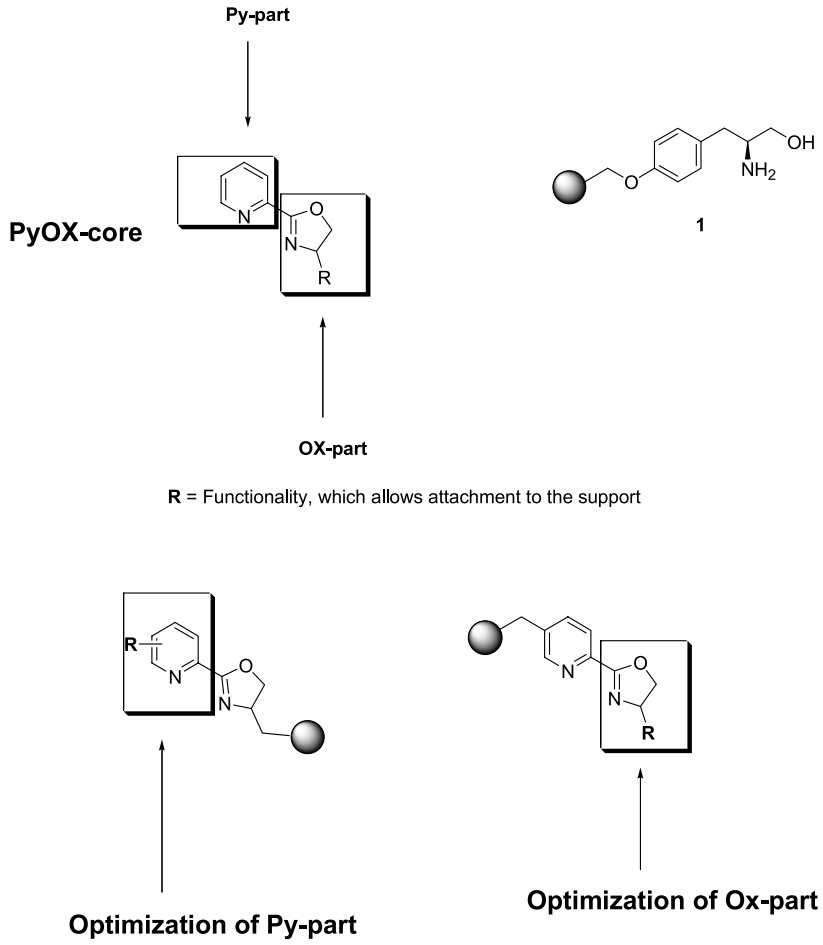
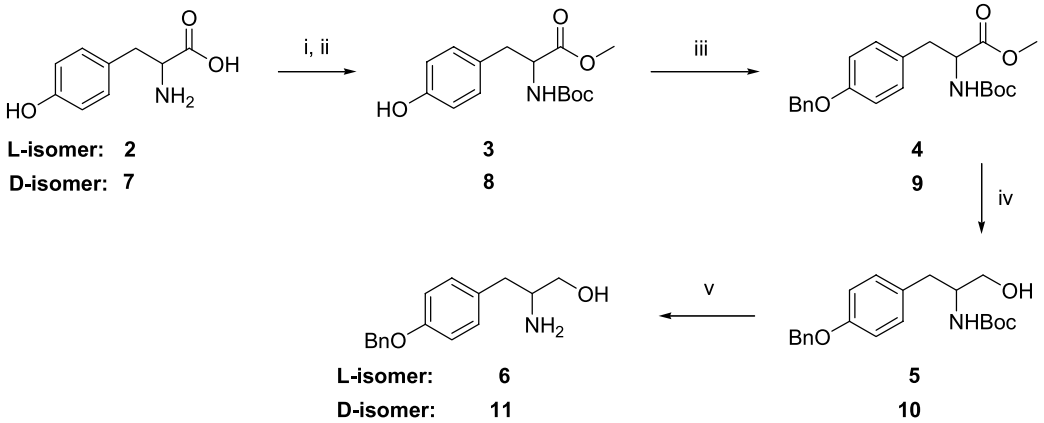


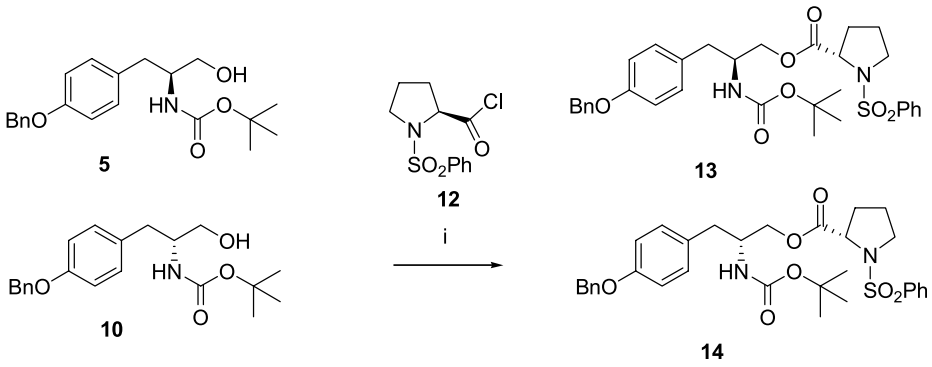
Figure 1. The PyOX-core and its possibilities for optimization.



Scheme 1. Model experiments with soluble analogues, starting from (L)-tyrosine (**2**–**6**) and (D)-tyrosine (**7**–**11**). (i) $SOCl_2$, MeOH, −72 °C to reflux, 20 h; (ii) NEt_3, Boc_2O, MeOH, rt, 17 h, 89% (two steps); (iii) BnBr, K_2CO_3, KI, acetone, reflux, 4 h, 100%; (iv) $NaBH_4$, LiI, THF, reflux, 3 h, 87%; (v) *p*-TsOH, CH_2Cl_2, THF, rt, 20 h, 68% (1 crop).

is reported to lead to racemization.[10] On the other hand, it has been reported that the use of K_2CO_3 in acetone evades the racemization in liquid-phase experiments.[6a] However, acetone cannot be used with the Merrifield resin due to poor swelling. We soon discovered that the optical rotation of **4** remained identical, when the solvent was changed from acetone to DMF.[11]

Reduction of **4** could be carried out using the standard $LiAlH_4$-procedure, but we chose $NaBH_4$/LiI-reduction[12] for milder conditions and more convenient work-up with resins. The procedure used for Boc removal was designed for solid phase use.[13] Standard Boc cleavage (50% TFA/CH_2Cl_2) caused some cleavage of the phenolic ether in **5**, whereas *p*-TsOH proved mild enough to avoid this side reaction. The



Scheme 2. (i) **12**, DIPEA, CH_2Cl_2, rt, **5**→**13**: 18 h; **10**→**14**: 20 min.

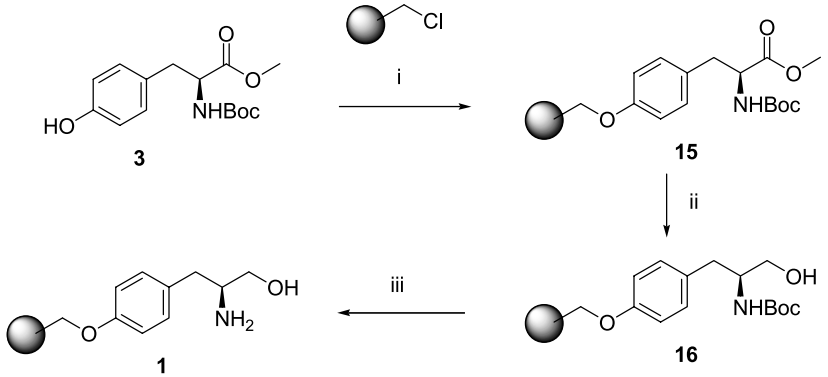
synthesis was repeated with D-tyrosine to ascertain that no racemization had occurred during the steps (compounds **7**–**11**). Compounds **4**–**6** were analyzed by IR and the characteristic signals mapped for comparison with the solid phase analogues.

Enantiomers **5** and **10** were derivatized with the chiral proline derivative **12** to form diastereomers **13** and **14** (Scheme 2).[14] These were shown to be pure by achiral HPLC and NMR.

The optimized reaction conditions from liquid phase experiments (Scheme 1) were applied with the supported **4**. Phenol **3** was attached to the Merrifield resin using the benzylation protocol developed above. Reaction monitoring on solid support could easily be performed by FTIR, as the characteristic signals were found by model experiments in solution. The easiest region to follow is the carbonyl region ($\nu = 1750$–$1600\ cm^{-1}$) due to the strong signals and characteristic changes.[15] Scheme 3 illustrates the formation of linker **1**.

Picolinic acid derivatives were attached to **1** to form the amido alcohol functionality. We focused our attention on acids substituted also at the 5-position, because the corresponding picolinic acids (e.g., **18** and **19**, Fig. 2) can be prepared utilizing the differing reactivities of the 2- and 5-positions. The picolinic acid derivatives **18** and **19** were selected so that they have electronically different substituents. Furthermore, these functionalities could be utilized as attachment sites (Fig. 1). Picolinic acid (**17**) was selected as 'standard' with neither electron withdrawing nor donating groups. 5-(Methoxycarbonyl)picolinic acid **18** was prepared using a known procedure through exhaustive esterification and selective hydrolysis (Scheme 6).[16]

Methyl 5-bromopicolinate **22** was prepared according to known procedures by selective lithiation (Scheme 4).[17,18] We attempted to prepare the acetylenic adduct **19** using standard Sonogashira-conditions[19] in various solvents, but a reproducible protocol was not achieved. Excluding the copper, however, gave excellent results, in contrast to previous literature studies regarding pyridine ring coupling at the 5-position.[20] In that paper, a strict Cu/Pd-ratio was required to achieve acetylenic coupling at the 5-position.



Scheme 3. (i) Merrifield resin, loading 1.59 mmol/g, K_2CO_3, KI, DMF, 70 °C, 19 h; (ii) $NaBH_4$, LiI, THF, reflux, 7 h; (iii) *p*-TsOH, CH_2Cl_2, THF, rt, 1.5 h.

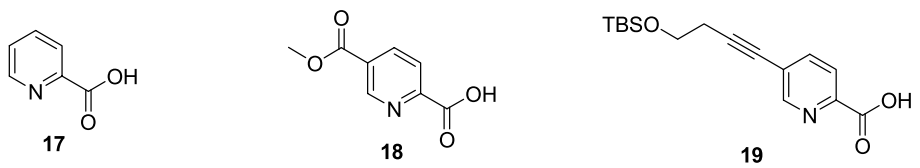
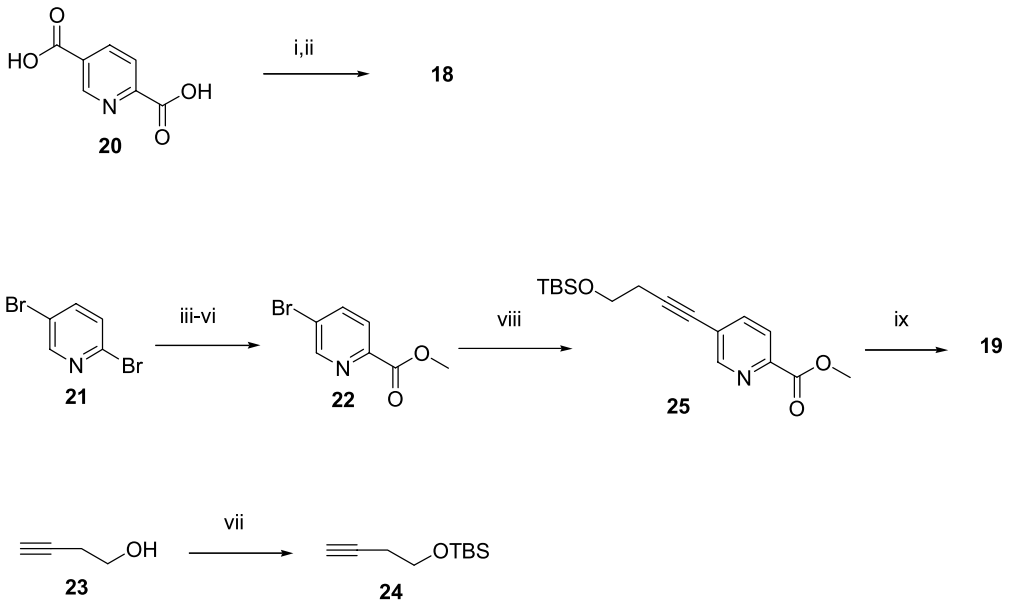
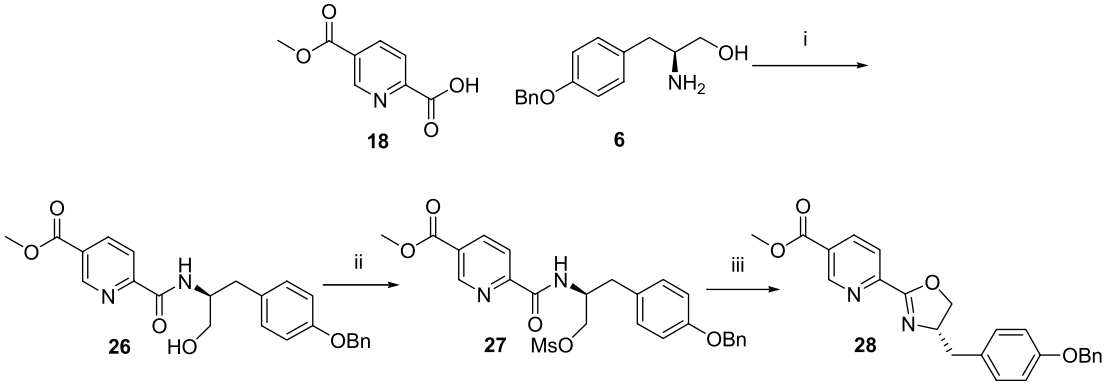


Figure 2. The picolinic acid derivatives used in linking and PyOX formation.



Scheme 4. (i) MeOH, H_2SO_4, reflux, 22 h; (ii) NaOH, MeOH, reflux, 2 h, 62% (from **20**); (iii) *n*-BuLi, PhMe, −77 °C, 3 h; (iv) CO_2; (v) $SOCl_2$, reflux, 4 h; (vi) MeOH, NEt_3, rt, 46% (over four steps); (vii) TBSCl, NEt_3, DMAP, CH_2Cl_2, rt, 20 h, 85%; (viii) **24**, $Pd(PPh_3)_2Cl_2$, NEt_3, THF, reflux, 24 h, 92%; (ix) NaOH, aqueous MeOH, reflux, 6 h, 64%.



Scheme 5. Model compounds for FTIR analysis. (i) (a) **18**, $SOCl_2$, reflux, 2.5 h, (b) **6**, NEt_3, CH_2Cl_2, rt, 15 min, 62% (from **18**); (ii) MsCl, NEt_3, DMAP, CH_2Cl_2, rt, 1 min, 81%; (iii) DBU, THF, 40 °C, 24 h, 43%.

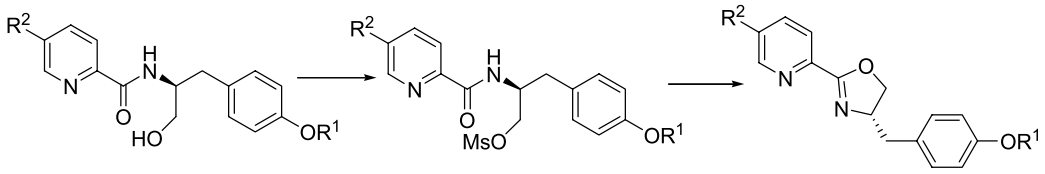
An explanation for this controversial result is probably the methyl ester group at the 2-position in our case (compound **22**, Scheme 4). In our hands, coupling of **22** and **23** proceeded, but did not reach complete conversion. Instead, coupling of **22** and **24**[21] gave a total conversion and excellent yield. The ester **25** was then hydrolyzed[16] to give **19** (Scheme 4).

The PyOX core on solid support was constructed by first coupling the picolinic acid and the amine followed by cyclization of the formed amido alcohol using suitable reagents.[22] We optimized the cyclization to suit all PyOX-precursors tested thus far using mesylate activation and DBU assisted cyclization.[23]

Model experiments were performed to examine the signals on FTIR and define characteristic signals for a facile monitoring of the reaction progress on solid support. The most informative signal turned out to be the amide signal: the signal of amido alcohol **26** was present, as the coupling of **6** and **18** was made. Mesylation of **26** shifted the amide signal to a higher wave number, as expected. The mesyl signal was in the fingerprint region and thus very hard to detect and define, especially in the case of the resins. The slowest reaction step, that is, cyclization to **28** (Scheme 5), could also be monitored using FTIR, because of the apparent signal shift towards a lower wavenumber. A summary of changes in the IR shift is shown in Table 1.

To our knowledge, this is the first time a solid-supported PyOX-ligand has been prepared by simultaneous linking and cyclization. In the rare reported cases, the solid-supported PyOX-ligands have been prepared by forming the PyOX-core and then attaching the compound to a solid support.[4a,8] We reasoned that formation of the PyOX on the solid support allows to use efficient reactions and monitor the reactions reliably. The picolinic acid derivatives **18–19** were all attached using a peptide coupling protocol, viz.

Table 1. The IR signals of either the amide or the C=N-group of oxazoline



R^1	R^2	Amido alcohol	Mesylate	PyOX
Bn	CO_2Me	1651	1666	1637
	H	1662	1669	1641
	CO_2Me	1664	1668	1635
		1656	1671	1636

HOBt/DIC-activation.[24] Acid chloride formation turned out to be too vigorous, since the use of acid chlorides also gave rise to double coupling, that is, also the corresponding amido ester was formed. In the case of picolinic acid **17** attachment, however, this was not the case and the acid chloride protocol could be used. Activation of the amido alcohols **29–31** was achieved with the usual mesylation protocol and cyclization was efficiently performed with DBU to form the PyOX-ligands **35–37** (Scheme 6).[22] In none of the cases could the cyclization be brought to completion using the one-step cyclization by Meyers,[25] involving either the tosylate or the mesylate activation. The general reaction path is shown in Scheme 6.

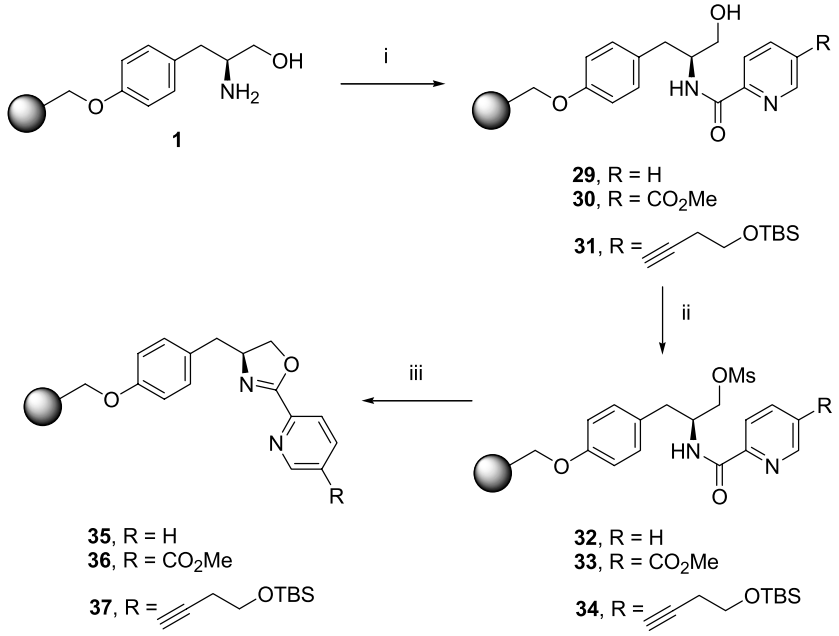
3. Conclusions

A new and general method to form PyOX-ligands on solid support is presented. It involves a simple path to link picolinic acids and functionalize them as the PyOX-core in three steps. Functionalization at the 5-position of the pyridine ring has also been carried out. The aim of functionalizing the 5-position was to build further functional groups for various needs. It is also surprisingly easy to differentiate between the 2-position and the 5-position of the pyridine ring due to the reactivity gap between these positions. This gives nearly unlimited resources, when variation around the PyOX-core is needed. Our strategy gives also the opportunity to link the PyOX-core from either the oxazoline or the pyridine ring. New support materials will also be used in the formation of supported PyOX-ligands. We are currently exploring one application, the use of the mercapto ester derived PyOX in nanotechnology,[23] which will be reported in due course.

4. Experimental

4.1. General methods

All reactions were carried out under an argon atmosphere in flame-dried glassware, unless otherwise noted. Non-aqueous reagents were transferred under argon via syringe and dried prior to use. Toluene was distilled from Na, THF was distilled from Na/benzophenone. CH_2Cl_2 was distilled from CaH_2. Other solvents and reagents were used as



Scheme 6. Formation of the PyOX-ligands. (i) 5-R-picolinic acid, HOBt, DIC, CH_2Cl_2, DMF, rt; (ii) MsCl, NEt_3, DMAP, CH_2Cl_2, rt; (iii) DBU, THF, 50 °C.

obtained from supplier, unless otherwise noted. Analytical TLC was performed using Merck silica gel F254 (230–400 mesh) plates and analyzed by UV light or by staining upon heating with $KMnO_4$-solution (1.0 g $KMnO_4$, 6.7 g K_2CO_3, 1.7 ml 5% aqueous NaOH-solution, 100 ml H_2O) or ninhydrin solution (1.0 g ninhydrin, 0.2 ml glacial AcOH, 100 ml EtOH). For silica gel chromatography, the flash chromatography technique was used, with Merck silica gel 60 (230–400 mesh) and p.a. grade solvents unless otherwise noted. The ^{1}H and ^{13}C NMR spectra were recorded in either $CDCl_3$ or d_6-DMSO on a Bruker Avance 400 (^{1}H 399.98 MHz; ^{13}C 100.59 MHz) spectrometer. The chemical shifts are reported in ppm relative to $CDCl_3$ (δ 7.26) or d_6-DMSO (δ 2.50)[26] for ^{1}H NMR. For the ^{13}C NMR spectra, the residual $CDCl_3$ (δ 77.0) or d_6-DMSO (δ 39.5) were used as the internal standard. The optical purity of products **13** and **14** were determined by HPLC in comparison to the corresponding racemic samples using Waters 501 pump and Waters 486 detector, ThermoHypersil column and *i*-PrOH/hexane as eluent. IR spectra were recorded on a Perkin-Elmer Spectrum One spectrometer using KBr-disc. Optical rotations were obtained with a Perkin-Elmer 343 polarimeter. High-resolution mass spectrometric data were obtained at the University of Oulu on Micromass LCT spectrometer. The elemental analyses were performed at the Analytical Services of the Department of Chemical Technology, Laboratory of Organic Chemistry.

4.1.1. Phenylsulfonylproline *O*-benzyl-*tert*-butyloxycarbonyltyrosinyl esters 13 and 14. Compound **12** was prepared according to a literature procedure[14] by dissolving (*S*)-phenylsulfonyl proline (1.27 g, 5.0 mmol) in 10 ml CH_2Cl_2. Oxalyl chloride (1.0 ml, 11.5 mmol, 230 mol%) was added, followed by two drops of DMF. This caused a violent heat evolution, which settled after 5 min. The volatiles were evaporated after 1.5 h and the slurry product was dissolved in benzene and washed with saturated aqueous $NaHCO_3$ and brine. After drying over $MgSO_4$, **12** solidified at vacuum pump overnight.

Compounds **5** and **10** were treated with the identical procedure. Tyrosinol derivative **5** or **10** (16 mg, 0.045 mmol, 100 mol%) was dissolved in 2 ml CH_2Cl_2. To this solution was added phenylsulfonylproline **12** (25 mg, 0.091 mmol, 200 mol%) dissolved in 1 ml CH_2Cl_2 and 0.035 ml DIPEA. According to TLC, the starting material was totally consumed after 18 h. The reaction was quenched with 10% aqueous citric acid and extracted twice with CH_2Cl_2. The combined organic phases were washed with brine and dried over Na_2SO_4. Baseline impurities were removed by filtration through a short pad of silica (EtOAc/hexane 1:2) to yield the compounds **13** and **14** for analysis of enantiopurity.

Compound **13**. White solid. R_f=0.50 (EtOAc/hexane 1:1, UV); $[\alpha]_D^{22}$ −60.0 (*c* 0.2; CH_2Cl_2); mp=121–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ($CDCl_3$) 7.89 (m, 2H, Ar-*H*), 7.61–7.51 (m, 3H, Ar-*H*), 7.44–7.31 (m, 5H, Ar-*H*), 7.13 (d, *J*=8.5 Hz, 2H, Ar-*H*), 6.91 (d, *J*=8.6 Hz, 2H, Ar-*H*), 5.04 (s, 2H, PhCH_2OAr), 4.84 (d, *J*=7.3 Hz, 1H, –N*H*Boc), 4.34 (dd, *J*=5.1, 7.1 Hz, 1H, –CH_2C*H*(NHBoc)(CH_2OCOR)), 4.12 (m, 3H, –CHCH_2OCOR, 2-Pro-C*H*), 3.51 (m, 1H, Ar-CH_2CHR$_2$-A), 3.31 (m, 1H, Ar-CH_2CHR$_2$-B), 2.81 (m, 2H, 5-Pro-CH_2), 2.03 (m, 3H, 3-Pro-CH_2, 4-Pro-CH_2-A), 1.78 (m, 1H, 4-Pro-CH_2-B), 1.40 (s, 9H, –C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ ($CDCl_3$) 172.0 (2-Pro-C(*O*)OR), 157.7 (RNHC(*O*)OC(CH$_3$)$_3$), 138.3 (Ar), 137.1 (Ar), 132.8 (Ar), 130.4 (Ar), 129.5 (Ar), 129.1 (Ar), 128.6 (Ar), 127.9 (Ar), 127.4 (Ar), 115.0 (Ar), 79.4 (–NHCO$_2$*C*(CH$_3$)$_3$), 70.1 (Ph*C*H$_2$OAr), 65.4 (–CH*C*H$_2$OCOR), 60.5 (2-Pro-*C*H), 51.1 (–CH$_2$*C*H(NHBoc)(CH$_2$OCOR)), 48.4 (Ar-*C*H$_2$CHR$_2$), 30.9 (5-Pro-*C*H$_2$), 29.7 (3-Pro-*C*H$_2$), 28.3 (–C(*C*H$_3$)$_3$), 24.7 (4-Pro-*C*H$_2$); HRMS (ESI) calcd for $C_{32}H_{38}N_2O_7SNa$ 617.2297, found 617.2281 (M+Na); Enantiomeric purity was determined by HPLC (ThermoHypersil column, 1% *i*-PrOH/hexanes, flow rate 1.5 ml/min): τ=25.59 min.

Compound **14**. Colourless oil. R_f=0.50 (EtOAc/hexane 1:1, UV); $[\alpha]_D^{22}$ −102 (*c* 0.15; CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (m, 2H, Ar-*H*), 7.61–7.51 (m, 3H, Ar-*H*), 7.44–7.31 (m, 5H, Ar-*H*), 7.14 (d, *J*=8.5 Hz, 2H, Ar-*H*), 6.91 (d, *J*=8.6 Hz, 2H, Ar-*H*), 5.04 (s, 2H, PhCH_2OAr), 4.94 (d, *J*=8.1 Hz, 1H, –N*H*Boc), 4.30 (dd, *J*=5.9, 6.2 Hz, 1H, –CH_2C*H*(NHBoc)(CH_2OCOR)), 4.20 (m, 1H, 2-Pro-C*H*), 4.04 (m, 2H, –CHCH_2OCOR), 3.57 (m, 1H, Ar-CH_2-CHR$_2$-A), 3.30 (m, 1H, Ar-CH_2CHR$_2$-B), 2.83 (m, 2H, 5-Pro-CH_2), 2.02 (m, 3H, 3-Pro-CH_2, 4-Pro-CH_2-A), 1.77 (m, 1H, 4-Pro-CH_2-B), 1.41 (s, 9H, –C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8 (2-Pro-C(*O*)OR), 157.6 (RNHC(*O*)OC(CH$_3$)$_3$), 138.1 (Ar), 137.1 (Ar), 132.8 (Ar), 130.3 (Ar), 129.6 (Ar), 129.1 (Ar), 128.5 (Ar), 127.9 (Ar), 127.4 (Ar), 127.3 (Ar), 114.9 (Ar), 77.2 (–NHCO$_2$*C*(CH$_3$)$_3$), 70.0 (Ph*C*H$_2$OAr), 65.5 (–CH*C*H$_2$OCOR), 60.6 (2-Pro-*C*H), 51.1 (–CH$_2$*C*H(NHBoc)(CH$_2$OCOR)), 48.4 (Ar-*C*H$_2$CHR$_2$), 30.9 (5-Pro-*C*H$_2$), 29.6 (3-Pro-*C*H$_2$), 28.3 (–C(*C*H$_3$)$_3$), 24.6 (4-Pro-*C*H$_2$); HRMS (ESI) calcd for $C_{32}H_{38}N_2O_7SNa$ 617.2297, found 617.2297 (M+Na); Enantiomeric purity was determined by HPLC (ThermoHypersil column, 1% *i*-PrOH/hexanes, flow rate 1.5 ml/min): τ=27.61 min.

4.1.2. *N-tert*-butoxycarbonyl tyrosine methyl ester resin 15. Merrifield resin (4.61 g, 7.33 mmol based on reported loading, 100 mol%) and KI (430 mg, 2.59 mmol, 40 mol%) were suspended in 20 ml DMF. In another flask, **3** (4.10 g, 13.9 mmol, 190 mol%) was dissolved in 40 ml DMF and K_2CO_3 (3.55 g, 25.7 mmol, 350 mol%) was added. After 15 min, the suspension of **3**/K_2CO_3 was added to the resin and the mixture was heated on a 70 °C oil bath for 19 h. The resin was filtered and washed subsequently with DMF, DMF/H_2O 1:1, DMF, methanol and CH_2Cl_2. The resin was dried at the aspirator pressures and finally under high vacuum. IR (KBr, cm^{-1}) 1717.

4.1.3. *N-tert*-butoxycarbonyl tyrosinol resin 16. Functionalised resin **15** (2.10 g, 3.34 mmol, 100 mol%) was suspended in 50 ml THF. LiI (4.47 g, 33.4 mmol, 1000 mol%) was added, followed by $NaBH_4$ (1.26 g, 33.3 mmol, 1000 mol%).The mixture was set for reflux for 7 h and filtered. It was washed subsequently with THF/H_2O 1:1, THF, methanol and CH_2Cl_2. The resin was dried at the aspirator pressures and finally under high vacuum. IR (KBr, cm^{-1}) 1685.

4.1.4. Tyrosinol resin 1. To **16** (2.00 g, 3.18 mmol, 100 mol%) was added a stock solution[13] of *p*-TsOH

(10.57 g, 55.6 mmol, 1700 mol%), 11 ml CH_2Cl_2 and 21 ml THF. The resin was filtered after 1.5 h, followed by subsequent wash with NEt_3/DMF 1:2, DMF, DMF/H_2O 2:1, DMF, methanol and CH_2Cl_2. The resin was dried at the aspirator pressures and finally under high vacuum. IR (KBr, cm^{-1}) 3385.

4.1.5. 5-(1′-*tert*-Butyldimethylsilyloxy-3-butynyl)methyl picolinate 25. Bromopyridine **22** (590 mg, 2.73 mmol, 100 mol%), 18 ml dry THF, NEt_3 (0.58 ml, 4.16 mmol, 150 mol%) and **24** (1003 mg, 5.44 mmol, 200 mol%) were loaded into a Schlenk apparatus. Retaining the oxygen-free atmosphere, $Pd(PPh_3)_2Cl_2$ (100 mg, 0.14 mmol, 5 mol%) was added to the solution. The mixture was heated to reflux for 24 h and diluted with CH_2Cl_2. It was quenched with saturated aqueous $NaHCO_3$ and extracted three times with CH_2Cl_2. The organics were washed with brine and dried over Na_2SO_4 to give 1.56 g of a dark brown oil. It was purified by FC (EtOAc/hexane 1:4) to give **25** (800 mg, 2.50 mmol, 92%) as an almost colourless oil. R_f=0.29 (EtOAc/hexane 1:1, UV); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (dd, J=0.8, 2.0 Hz, 1H, 6-Py-C*H*), 8.04 (dd, J=0.8, 8.0 Hz, 1H, 4-Py-C*H*), 7.77 (dd, J=2.0, 8.0 Hz, 1H, 3-Py-C*H*), 3.98 (s, 3H, –CO_2Me), 3.81 (t, J=6.8 Hz, 2H, –$CH_2CH_2OSiR_3$), 2.65 (t, J=6.8 Hz, 2H, –$CH_2CH_2OSiR_3$), 0.89 (s, 9H, –C(CH_3)$_3$), 0.07 (s, 6H, –Si(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2 (–CO_2CH_3), 152.2 (6-Py-*C*), 145.7 (2-Py-*C*–CO_2Me), 139.2 (4-Py-*C*), 124.4 (3-Py-*C*), 124.3 (5-Py-*C*-R), 94.6 (Ar-C≡*C*–CH_2R), 77.9 (Ar-*C*≡C–CH_2R), 61.4 (–$CH_2CH_2OSiR_3$), 52.8 (–CO_2CH_3), 25.8 (–$SiR_2C(CH_3)_3$), 24.0 (–C≡C–CH_2CH_2–), 18.3 (–$SiR_2C(CH_3)_3$), −5.3 (–Si(CH_3)$_2$C(CH_3)$_3$); HRMS (ESI) calcd for $C_{17}H_{25}NO_3Si$ 320.1682, found 320.1690 (M+1).

4.1.6. 5-(1′-*tert*-Butyldimethylsilyloxy-3-butynyl)picolinic acid 19. Ester **25** (620 mg, 1.94 mmol, 100 mol%) was dissolved in 30 ml of 90% aqueous methanol. Finely ground NaOH (82 mg, 2.05 mmol, 110 mol%) was added and the mixture was set for reflux for 6 h. The solution was concentrated to a small volume and acidified carefully with 1 M aqueous HCl at 0 °C. The formed solid was filtered and dried at pump to yield **19** (380 mg, 1.24 mmol, 64%) as a white solid; mp 104–105 °C (dec); IR (KBr, cm^{-1}) 2229, 1703; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.62 (s, 1H, 6-Py-C*H*), 7.97 (d, J=7.9 Hz, 1H, 4-Py-C*H*), 7.90 (d, J=8.0 Hz, 1H, 3-Py-C*H*), 3.80 (t, J=6.4 Hz, 2H, –CH_2CH_2-$OSiR_3$), 2.68 (t, J=6.4 Hz, 2H, –$CH_2CH_2OSiR_3$), 2.08 (s, 1H, –CO_2H), 0.89 (s, 9H, –C(CH_3)$_3$), 0.08 (s, 6H, –Si(CH_3)$_2$); ^{13}C NMR (100 MHz, d_6-DMSO) δ 165.8 (–CO_2H), 151.1 (6-Py-*C*), 147.9 (2-Py-*C*–CO_2H), 139.3 (4-Py-*C*), 124.1 (3-Py-*C*), 122.7 (5-Py-*C*-R), 94.5 (Ar-C≡*C*–CH_2R), 77.9 (Ar-*C*≡C–CH_2R), 61.0 (–CH_2-CH_2OSiR_3), 25.7 (–$SiR_2C(CH_3)_3$), 23.3 (–C≡C–CH_2CH_2–), 17.9 (–$SiR_2C(CH_3)_3$), −5.3 (–Si(CH_3)$_2$C(CH_3)$_3$); HRMS (ESI) calcd for $C_{16}H_{23}NO_3SiNa$ 328.1345, found 328.1342 (M+Na).

4.1.7. 5-Methoxycarbonylpicolinyl-(1′-(*S*)-(*p*-benzyloxyphenyl)-2′-hydroxy)ethylamide 26. Acid **18** (70 mg, 0.39 mmol, 100 mol%) was refluxed in 3 ml $SOCl_2$ for 2.5 h. The mixture was evaporated to dryness. Aminoalcohol **6** (100 mg, 0.39 mmol, 100 mol%) was dissolved in 4 ml CH_2Cl_2 and 0.30 ml NEt_3. The residue of **18** was dissolved in 2 ml CH_2Cl_2 and this solution was added to the solution of **6**. After 15 min, ice water was added to the mixture and it was extracted three times with CH_2Cl_2. The combined organics were washed with brine and dried over Na_2SO_4. The solvents were evaporated and the crude product recrystallized from EtOAc/hexane to yield 100 mg (0.24 mmol, 62%) of **26** as a white solid. R_f=0.15 (EtOAc/hexane 1:1, $KMnO_4$); $[\alpha]_D^{22}$ −25.5 (*c* 0.07; $CHCl_3$); mp 165–165.5 °C; IR (KBr, cm^{-1}) 1717, 1651; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (dd, J=0.9, 2.0 Hz, 1H, 6-Py-C*H*), 8.44 (dd, J=2.0, 8.0 Hz, 1H, 4-Py-C*H*), 8.30 (d, J=8.2 Hz, 1H, –N*H*COAr), 8.25 (dd, J=0.8, 8.0 Hz, 1H, 3-Py-C*H*), 7.43–7.30 (m, 5H, Ar-*H*), 7.19 (d, J=8.6 Hz, 2H, Ar-*H*), 6.92 (d, J=8.6 Hz, 2H, Ar-*H*), 5.04 (s, 2H, PhCH_2OAr), 4.32 (m, 1H, –CH_2CH(NHCOAr)(CH_2OH)), 3.99 (s, 3H, –CO_2CH_3), 3.81 (m, 1H, –R_2CHCH_2OH-A), 3.73 (m, 1H, –R_2CHCH_2OH-B) 2.96 (m, 2H, Ar-CH_2-CHR_2), 2.47 (t, J=5.4 Hz, 1H, –CH_2O*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0 (Ar-CO_2CH_3), 163.7 (–NH*C*OAr), 157.6 (C_{Ar}-OR), 152.6 (2-Py*C*-CONHR), 149.4 (6-Py-*C*), 138.5 (C_{Ar}–CH2OAr), 137.0 (4-Py-*C*), 130.2 (Ar), 129.7 (Ar), 128.5 (Ar), 128.1 (Ar), 127.9 (Ar), 127.4 (Ar), 121.8 (Ar), 115.0 (Ar), 70.0 (PhCH_2OAr), 64.3 (–R_2CHCH_2OH), 53.5 (–R_2CHCH_2OH), 52.6 (–CO_2CH_3), 36.3 (ArCH_2CHR_2); HRMS (ESI) calcd for $C_{24}H_{24}N_2O_5Na$ 443.1583, found 443.1576 (M+Na).

4.1.8. 5-Methoxycarbonylpicolinyl-(1′-(*S*)-(*p*-benzyloxyphenyl)-2′-mesyloxy)ethylamide 27. Amide **26** (50 mg, 0.12 mmol, 100 mol%) was dissolved in 3 ml CH_2Cl_2. NEt_3 (0.10 ml, 0.72 mmol, 600 mol%) and DMAP (3 mg, 0.03 mmol, 20 mol%) were added, followed by MsCl (30 μl, 0.39 mmol, 320 mol%). This caused a spontaneous heating of the mixture. TLC monitoring showed total conversion after 3 min. The reaction was quenched with water 10 min later. The mixture was extracted three times with CH_2Cl_2. The combined organics were washed with brine and dried over Na_2SO_4. The solvents were evaporated and the crude mixture filtered through a short pad of silica and recrystallized from EtOAc/hexane to yield 48 mg (0.10 mmol, 81%) of **27** as a white solid. R_f=0.15 (EtOAc/hexane 1:1, $KMnO_4$); $[\alpha]_D^{22}$ +21.0 (*c* 0.07; CH_2Cl_2); mp 115–117.5 °C; IR (KBr, cm^{-1}) 1725, 1666; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (dd, J=0.8, 2.0 Hz, 1H, 6-Py-C*H*), 8.44 (dd, J=2.0, 8.0 Hz, 1H, 4-Py-C*H*), 8.25 (d, J=8.2 Hz, 1H, –N*H*COAr), 8.23 (dd, J=0.8, 8.2 Hz, 1H, 3-Py-C*H*), 7.43–7.29 (m, 5H, Ar-*H*), 7.19 (d, J=8.6 Hz, 2H, Ar-*H*), 6.93 (d, J=8.6 Hz, 2H, Ar-*H*), 5.03 (s, 2H, PhCH_2OAr), 4.59 (m, 1H, R_2CH(CH_2OSO_2Me)-(NHCOAr)), 4.36 (m, 1H, $R_2CHCH_2OSO_2$Me-A), 4.26 (m, 1H, $R_2CHCH_2OSO_2$Me-B), 3.99 (s, 3H, 5-Py-CO_2CH_3), 3.00 (m, 2H, Ar-CH_2CHR_2), 3.00 (s, 3H, –$CH_2OSO_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0 (Ar-CO_2CH_3), 163.2 (–NH*C*OAr), 157.9 (C_{Ar}-OR), 152.2 (2-Py*C*-CONHR), 149.5 (6-Py-*C*), 138.6 (4-Py-*C*), 136.9 (Ar), 130.3 (Ar), 128.6 (Ar), 128.5 (Ar), 128.3 (Ar), 127.9 (Ar), 127.4 (Ar), 121.9 (Ar), 115.2 (Ar), 70.0 (R_2CHCH_2-OSO_2Me), 69.4 (PhCH_2OAr), 52.7 (–CO_2CH_3), 50.0 (–R_2CHCH_2OH), 37.3 (–$CH_2OSO_2CH_3$), 36.1 (ArCH_2-CHR_2); HRMS (ESI) calcd for $C_{25}H_{27}N_2O_7S$ 499.1539, found 499.1521 (M+1).

4.1.9. 5-Methoxycarbonyl-2-(4′-(*S*)-*p*-benzyloxybenzyl-2′-oxazolinyl)-pyridine 28. Mesylate **27** (26 mg, 52 μmol, 100 mol%) was dissolved in 4 ml THF. DBU (35 μl, 230 μmol, 450 mol%) was added and the mixture was heated on a 40 °C oil bath for 24 h. The reaction was quenched with water and extracted three times with EtOAc. The combined organics were washed with water and brine and dried over Na_2SO_4. The crude product was purified by FC (EtOAc/hexane 2:1) to yield 9 mg (22 μmol, 43%) of **28** as a white solid. R_f=0.45 (EtOAc/hexane 2:1, UV); $[\alpha]_D^{22}$ +18.0 (*c* 0.07; CH_2Cl_2); mp 165–170 °C (dec); IR (KBr, cm^{-1}) 1716, 1637; ^1H NMR (400 MHz, $CDCl_3$) δ 9.28 (dd, *J*=0.5, 2.0 Hz, 1H, 6-Py-C*H*), 8.38 (dd, *J*=2.1, 8.2 Hz, 1H, 4-Py-C*H*), 8.13 (dd, *J*=0.5, 8.2 Hz, 1H, 3-Py-C*H*), 7.44–7.30 (m, 5H, Ar-*H*), 7.17 (d, *J*=8.6 Hz, 2H, Ar-*H*), 6.92 (d, *J*=8.6 Hz, 2H, Ar-*H*), 5.05 (s, 2H, PhCH_2OAr), 4.65 (app dq, *J*=5.3, 8.7 Hz, 1H, 4-oxazoline-C*H*), 4.48 (app t, *J*=8.7 Hz, 1H, 5-oxazoline-CH_2-A), 4.25 (app t, *J*=8.7 Hz, 1H, 5-oxazoline-CH_2-B), 3.98 (s, 3H, –CO_2CH_3), 3.22 (dd, *J*=5.3, 13.9 Hz, 1H, Ar-CH_2-oxazoline-A), 2.74 (dd, *J*=8.7, 13.9 Hz, 1H, Ar-CH_2-oxazoline-B); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2 (–*C*O_2CH_3), 162.5 (RN=*C*-OR), 157.7 (C_{Ar}-OR), 150.8 (2-Py-*C*-oxazoline), 150.0 (6-Py-*C*), 137.8 (Ar), 137.1 (Ar), 130.2 (Ar), 129.9 (Ar), 128.6 (Ar), 127.9 (Ar), 127.4 (Ar), 127.4 (Ar), 123.5 (Ar), 115.0 (Ar), 72.7 (5-oxazoline-*C*), 70.1 (Ph*C*H_2OAr), 68.4 (4-oxazoline-*C*), 52.6 (–CO_2CH_3), 40.6 (Ar-*C*H_2-oxazoline); HRMS (ESI) calcd for $C_{24}H_{22}N_2O_4$ 403.1658, found 403.1653 (M+1).

4.1.10. Picolinyl amido alcohol resin 29. Resin **1** (203 mg, 0.32 mmol based on the reported Merrifield resin loading 1.59 mmol/g, 100 mol%) was suspended in 3 ml CH_2Cl_2 and 0.2 ml NEt_3. To the solution was added 46 mg (0.32 mmol, 100 mol%) of picolinyl chloride (prepared from **17**). The solution turned dark blue in a matter of minutes. The resin was filtered 3 h later and washed subsequently with DMF/H_2O 3:1, DMF, methanol and CH_2Cl_2. Resin **29** was dried, first at the aspirator pressures and finally under high vacuum. IR (KBr, cm^{-1}) 1662.

4.1.11. (5-Methoxycarbonyl)picolinyl amido alcohol resin 30. Acid **18** (46 mg, 0.25 mmol, 110 mol%) was dissolved in 3 ml CH_2Cl_2 and 1 ml DMF. HOBt (35 mg, 0.26 mmol, 110 mol%) was added and allowed to stir for 60 min. The mixture was added to the suspension of resin **1** (150 mg, 0.24 mmol, 100 mol%) in 5 ml CH_2Cl_2, followed by DIC (40 μl, 0.26 mmol, 110 mol%). The solution turned orange after 30 min. After 24 h stirring, the resin was filtered and washed subsequently with CH_2Cl_2, DMF/H_2O 3:1, DMF, methanol and CH_2Cl_2. The resin was dried at aspirator pressures and finally under high vacuum. IR (KBr, cm^{-1}) 1733, 1664.

4.1.12. (5-(1′-*t*-Butyldimethylsilyloxy)-4′-butynyl)picolinyl amido alcohol resin 31. Acid **19** (97 mg, 0.32 mmol, 100 mol%) was dissolved in 4 ml CH_2Cl_2 and 1 ml DMF. HOBt (43 mg, 0.32 mmol, 100 mol%) was added and allowed to stir for 60 min. The mixture was added to the suspension of resin **1** (200 mg, 0.32 mmol, 100 mol%) in 6 ml CH_2Cl_2, followed by DIC (50 μl, 0.32 mmol, 100 mol%). The solution turned orange after a few hours. After 23 h stirring, the resin was filtered and washed subsequently with DMF, DMF/H_2O 2:1, DMF, methanol and CH_2Cl_2. The resin was dried at aspirator pressures and finally under high vacuum. IR (KBr, cm^{-1}) 2238, 1656.

4.1.13. Picolinyl amido mesylate resin 32. Amide resin **29** (50 mg, 80 μmol, 100 mol%) was suspended in 6 ml CH_2Cl_2 and 0.2 ml NEt_3. DMAP (3 mg, 25 μmol, 30 mol%) was added, followed by MsCl (30 μl, 0.39 mmol, 490 mol%). The reaction mixture turned bright yellow with slight heating. After 17.5 h, the resin was filtered and washed subsequently with CH_2Cl_2, DMF and CH_2Cl_2 and dried at aspirator pressures and finally under high vacuum. IR (KBr, cm^{-1}) 1669.

4.1.14. (5-Methoxycarbonyl)picolinyl amido mesylate resin 33. Resin **30** (70 mg, 110 μmol, 100 mol%) was suspended in 6 ml CH_2Cl_2 and 0.2 ml NEt_3. DMAP (5 mg, 40 μmol, 40 mol%) was added, followed by MsCl (50 μl, 0.64 mmol, 580 mol%). The reaction mixture turned orange with slight heating. After 17.5 h, the resin was filtered and washed subsequently with CH_2Cl_2, DMF and CH_2Cl_2 and dried at aspirator pressures and finally under high vacuum. IR (KBr, cm^{-1}) 1727, 1668.

4.1.15. (5-(1′-*t*-Butyldimethylsilyloxy)-4′-butynyl)picolinyl amido mesylate resin 34. Resin **31** (190 mg, 0.30 mmol, 100 mol%) was suspended in 5 ml CH_2Cl_2 and 0.3 ml NEt_3. DMAP (10 mg, 82 μmol, 30 mol%) was added, followed by MsCl (70 μl, 0.90 mmol, 300 mol%). The reaction mixture turned orange with slight reflux. After 25 min, the resin was filtered and washed subsequently with CH_2Cl_2, DMF and CH_2Cl_2 and dried at aspirator pressures and finally under high vacuum. IR (KBr, cm^{-1}) 2238, 1671.

4.1.16. Pyridine 2-(2′-oxazolinyl)resin 35. Resin **32** (40 mg, 60 μmol, 100 mol%) was suspended in 3 ml THF. DBU (0.24 ml, 1.60 mmol, 2500 mol%) was added and the mixture was heated in a 50 °C oil bath for 48 h and filtered. The resin was washed subsequently with THF, DMF/10% aqueous citric acid 2:1, THF, methanol and CH_2Cl_2. The resin was dried at aspirator pressures and finally under high vacuum. IR (KBr, cm^{-1}) 1641.

4.1.17. (5-Methoxycarbonyl)pyridine 2-(2′-oxazolinyl) resin 36. Resin **33** (65 mg, 100 μmol, 100 mol%) was suspended in 4 ml THF. DBU (0.12 ml, 0.80 mmol, 800 mol%) was added and the mixture was heated on a 45 °C oil bath for 20 h and filtered. The resin was washed subsequently with THF, DMF/10% aqueous citric acid 2:1, DMF, methanol and CH_2Cl_2. The resin was dried at aspirator pressures and finally under high vacuum. IR (KBr, cm^{-1}) 1728, 1635.

4.1.18. (5-(1′-*t*-Butyldimethylsilyloxy)-4′-butynyl)pyridine 2-(2′-oxazolinyl)resin 37. Resin **34** (175 mg, 280 μmol, 100 mol%) was suspended in 5 ml THF. DBU (0.23 ml, 1.54 mmol, 550 mol%) was added and the mixture was heated in a 50 °C oil bath for 22 h and filtered. The resin was washed successively with THF, THF/H_2O 2:1, THF, methanol and CH_2Cl_2. The resin was dried at aspirator pressures and finally under high vacuum. IR (KBr, cm^{-1}) 2237, 1636.

Acknowledgements

This work was financially supported by a grant from the Finnish National Technology Agency.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.08.073

References and notes

1. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; p 400.
2. Gladysz, J. A. (Ed.) *Chem. Rev.* **2002**, *102*, 3215–3892 (whole issue).
3. Review on polymer-supported ligands: Leadbeater, N. E.; Marco, M. *Chem. Rev.* **2002**, *102*, 3217–3274.
4. (a) Hallman, K.; Macedo, E.; Nordström, K.; Moberg, C. *Tetrahedron: Asymmetry* **1999**, *10*, 4037–4046. (b) Brunner, H.; Brandl, P. *Z. Naturforsch.* **1992**, 609–613.
5. (a) Brunner, H.; Obermann, U. *Chem. Ber.* **1989**, *122*, 499–507. (b) Brunner, H.; Brandl, P. *J. Organomet. Chem.* **1990**, *390*, C81–C83. (c) Balavoine, G.; Clinet, J. C.; Lellouche, I. *Tetrahedron Lett.* **1989**, *30*, 5141–5144.
6. Christoffers, J.; Mann, A.; Pickardt, J. *Tetrahedron* **1999**, *55*, 5377–5388.
7. (a) Nordström, K.; Macedo, E.; Moberg, C. *J. Org. Chem.* **1997**, *62*, 1604–1609. (b) Bremberg, U.; Larhed, M.; Moberg, C.; Hallberg, A. *J. Org. Chem.* **1999**, *64*, 1082–1084. (c) Chelucci, G.; Medici, S.; Saba, A. *Tetrahedron: Asymmetry* **1999**, *10*, 543–550. (d) Chelucci, G.; Deriu, S.; Saba, A.; Valenti, R. *Tetrahedron: Asymmetry* **1999**, *10*, 1457–1464.
8. (a) Lundgren, S.; Lutsenko, S.; Jönsson, C.; Moberg, C. *Org. Lett.* **2003**, *5*, 3663–3666. (b) Cornejo, A.; Fraile, J. M.; Garcia, J. I.; Garcia-Verdugo, E.; Gil, M. J.; Legarreta, G.; Luis, S. V.; Martinez-Merino, V.; Mayoral, J. A. *Org. Lett.* **2002**, *4*, 3927–3930.
9. (a) Wolf, C.; Francis, C. J.; Hawes, P. A.; Shah, M. *Tetrahedron: Asymmetry* **2002**, *13*, 1733–1741. (b) Schroeder, E. *Justus Liebigs Ann. Chem.* **1963**, *670*, 127–136. (c) Gennari, C.; Longari, C.; Ressel, S.; Salom, B.; Mielgo, A. *Eur. J. Org. Chem.* **1998**, *6*, 945–960. (d) Chen, P.; Cheng, P. T. W.; Alam, M.; Beyer, B. D.; Bisacchi, G. S.; Dejneka, T.; Evans, A. J.; Greytok, J. A.; Hermsmeier, M. A.; Humphreys, W. G.; Jacobs, G. A.; Kocy, O.; Lin, P.; Lis, K. A.; Marella, M. A.; Ryono, D. E.; Sheaffer, A. K.; Spergel, S. H.; Sun, C.; Tino, J. A.; Vite, G.; Colonno, R. J.; Zahler, R.; Barrish, J. C. *J. Med. Chem.* **1996**, *39*, 1991–2007.
10. Richter, L. S.; Gadek, T. R. *Tetrahedron Lett.* **1994**, *35*, 4705–4706.
11. Mizutani, H.; Takayama, J.; Soeda, Y.; Honda, T. *Tetrahedron Lett.* **2002**, *43*, 2411–2414.
12. Hwang, D. R.; Helquist, P.; Shekhani, M. S. *J. Org. Chem.* **1985**, *50*, 1264–1271.
13. Brinkman, H. R.; Landi, J. J.; Paterson, J. B.; Stone, P. J. *Synth. Commun.* **1991**, 459–465.
14. Maurer, P. J.; Takahata, H.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 1095–1098.
15. Copies of all spectra of new compounds can be found in the Supporting information of this article.
16. Paul, M. M.; Ratz, A. M.; Sullivan, K. A.; Trankle, W. G.; Winneroski, L. L. *J. Org. Chem.* **2001**, *66*, 5772–5782.
17. Wang, X.; Rabbat, P.; O′Shea, P.; Tillyer, R.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **2000**, *41*, 4335–4338.
18. Cottet, F.; Marull, M.; Lefebvre, O.; Schlosser, M. *Eur. J. Org. Chem.* **2003**, 1559–1568.
19. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470.
20. Hartner, F. W.; Hsiao, Y.; Eng, K. K.; Rivera, N. R.; Palucki, M.; Tan, L.; Yasuda, N.; Hughes, D. L.; Weissman, S.; Zewge, D.; King, T.; Tschaen, D.; Volante, R. P. *J. Org. Chem.* **2004**, *69*, 8723–8730.
21. Protection of 3-butyn-1-ol: Krafft, M. E.; Cheung, Y. Y.; Abboud, K. A. *J. Org. Chem.* **2001**, *66*, 7443–7448.
22. Wuts, P. G. M.; Northuis, J. M.; Kwan, T. A. *J. Org. Chem.* **2000**, *65*, 9223–9225.
23. Oila, M. J.; Tois, J. E.; Koskinen, A. M. P. *Tetrahedron Lett.* **2005**, *46*, 967–969.
24. Application on solid support: Rahman, S. S.; Busby, D. J.; Lee, D. C. *J. Org. Chem.* **1998**, *63*, 6196–6199.
25. Meyers, A. I.; Robichaud, A. J.; McKennon, M. J. *Tetrahedron Lett.* **1992**, *33*, 1181–1184.
26. NMR solvent shifts: Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512–7515.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 10757–10773

The preparation and reaction of enolates within micro reactors

Charlotte Wiles,[a] Paul Watts,[a,*] Stephen J. Haswell[a] and Esteban Pombo-Villar[b]

[a]*Department of Chemistry, The University of Hull, Cottingham Road, Hull HU6 7RX, UK*
[b]*Novartis Institute for BioMedical Research, WSJ-386.07.15, CH4002 Basel, Switzerland*

Received 4 April 2005; revised 26 July 2005; accepted 18 August 2005

Available online 13 September 2005

Abstract—Over the past 5 years, interest in the miniaturisation of chemical synthesis has grown rapidly, however in order to facilitate transfer of the technology from its current position as a research tool to industrial applications, a core understanding of the challenges associated with transferring reactions from the macro to the micro domain is required. This paper therefore aims to broach this problem by investigating the application of micro reactors to a range of commonly employed synthetic reactions including acylation, aldol, alkylation, 1,4-conjugate addition (Michael addition) and the Knoevenagel condensation. Comparison of the results obtained with traditional batch techniques enable us to highlight some of the advantages associated with micro reaction technology.

1. Introduction

Although less common than their analytical counterparts,[1] miniaturised devices capable of performing chemical synthesis, termed micro reactors, have recently received widespread interest from both industry and academia. The desire to miniaturise synthetic reactions has been driven by a need for greater process control, not only as a means of increasing product purity and plant productivity, but also reactor safety.[2,3] With these factors in mind, the micro reactor group at Hull have successfully demonstrated the application of miniaturised systems to a range of solution phase chemistries, contributing greatly to the initial evaluation of micro reactors for synthetic applications.[4,5] This paper follows a series of communications and aims to illustrate, in detail, the challenges associated with the transfer of reactions from the macro to the micro domain, laying the foundations necessary for the ultimate goal of performing novel synthetic procedures in micro fabricated devices.[6–11]

In this context, we define a micro reactor as a device that contains a series of interconnecting channels with cross-sectional dimensions in the range of 10–500 μm. Depending on the end use of the device, a range of substrates have been employed, these include; silicon, glass, quartz, ceramics, polymers and metals.[12] However, due to its compatibility with organic solvents, high mechanical strength, temperature resistance and optical transparency, borosilicate glass is the chosen substrate for the work described herein. As Figure 1 illustrates, the devices consist of a borosilicate glass base plate, containing an etched channel network, and a top block through which reagents are delivered. Thermal bonding of the two layers affords a sealed micro reactor, with typical dimensions of 2.5 cm × 2.5 cm × 2.0 cm for electroosmotic devices[13] and 2.5 cm × 2.5 cm × 0.6 cm for pressure driven applications. Using a suitable pumping mechanism, reagents are brought together within the micro channels, where they are reacted for a specified period of time, prior to collection and analysis. In order to manipulate reagents and products within micro fabricated devices accurate pumping mechanisms are

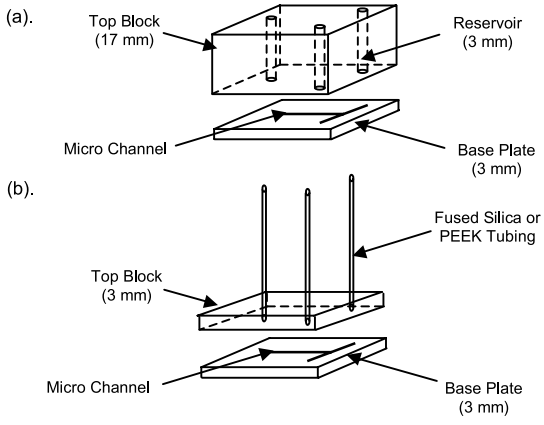


Figure 1. Exploded view of borosilicate glass micro reactors for (a) electroosmotic and (b) pressure-driven applications.

Keywords: Micro reactor; Enolate synthesis.
* Corresponding author. Tel.: +44 1482 465471; fax +44 1482 466416; e-mail: p.watts@hull.ac.uk

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.08.076

required, these are loosely categorised as either mechanical or non-mechanical.[14]

1.1. Non-mechanical pumping

In the early 1990's, Manz and co-workers[15] described the use of electrokinetic flow in a miniaturised flow injection system, a concept further investigated by Dasgupta et al.[16] Harrison and co-workers[17] later applied the principle to the mobilisation of fluorescein labelled amino acids in a glass reactor manifold, whereby valve-less control of fluid at a T-shaped intersection was observed. In comparison to the use of mechanical micro pumps, field induced flow is advantageous as the electric field acts as a pump and a valve, enabling both the direction and magnitude of flow to be controlled.[18]

1.1.1. Scope and limitations of electrokinetic flow. Electrokinetic flow comprises of two physical effects; electroosmotic flow (EOF), which is responsible for the velocity of the solvent system as a whole, and electrophoretic flow (EPF), which is an additional velocity effect experienced by charged species within the solvent system. As Figure 2 illustrates, when an ionisable surface such as glass, quartz or Teflon comes into contact with a suitable solvent system, the surface is neutralised with a diffuse layer of positive ions from the bulk liquid.[12] A proportion of the counterions are adsorbed onto the surface, resulting in the formation of an immobile layer, and the remaining positive ions form a transient double layer. Application of an electric field causes the double layer to move towards the most negative electrode, inducing bulk flow within the micro channel.

Although the use of EOF has been well documented within the literature, the manipulation of fluid within open channel networks is inherently irreproducible due to hydrodynamic pressure effects.[19] Consequently, in order to obtain reproducible controlled flow, it is important to ensure that non-uniformities in velocity profile (that arise as a result of different reservoir heights) are excluded or minimised. One such approach is the fabrication of micro porous silica frits (MPS frits) within the micro channels.[20] The porous silica structure acts to reduce the cross sectional area of the micro channel in a specific region, therefore minimising pressure effects while maintaining EOF.[21] Alternatively, Fletcher et al.[22] recently reported the fabrication of a series of narrow channels (restrictions) at strategic points within the main channel network, thus providing the necessary regions of resistance. Clearly, compared to the use of micro porous silica frits, the fabrication of restrictions is more amenable to the large-scale manufacture of micro fluidic devices.

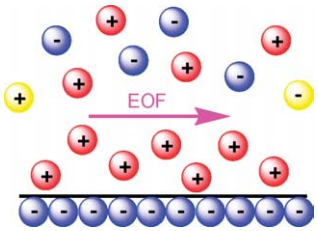


Figure 2. Schematic illustrating the principle of electroosmotic flow.

Table 1. Summary of the flow rates obtained for a series of commonly employed organic solvents

Applied field ($V\ cm^{-1}$)	Average flow rate ($\mu l\ min^{-1}$)[a]			
	MeCN	THF	DMF	EtOH
417	5.30	1.00	1.67	0.90
311	4.08	0.73	1.50	0.70
208	3.00	0.45	1.33	0.50
104	1.90	0.17	1.17	0.30

[a] ≥ 10 measurements were made at each applied field.

$$\nu_{eof} = -\frac{E_{\varepsilon\varepsilon_0}\zeta}{\eta} \quad (1)$$

ν_{eof}=electroosmotic flow velocity, E=applied field, ε=relative dielectric constant of the fluid, ε_0=the permittivity of free space, ζ=zeta potential and η=viscosity.

Equation 1. Determination of the electroosmotic flow velocity.[23]

While EOF has generally been associated with the manipulation of aqueous systems for analytical applications,[23] we have more recently demonstrated the mobilisation of polar solvent systems such as MeOH and DMF.[24] With this in mind, the flow rates of a series of common organic solvents were investigated over a range of applied fields ($V\ cm^{-1}$) (Table 1 and Fig. 3). As Table 2 illustrates, the electroosmotic flow rate is largely determined by the dielectric constant, polarity and viscosity of the solvent system (Eq. 1).[25] Consequently, the technique is restricted to the use of solvents such as alcohols, tetrahydrofuran, dimethylformamide, acetonitrile and aqueous systems.

1.2. Mechanical pumping

Most mechanical or reciprocating pumps are based on the movement of a piston or membrane, resulting in the delivery of fluids or gases in discrete aliquots. Due to the wide array of primary sources actuation of a membrane can be achieved using a variety of techniques including piezoelectric[26] and shape memory alloys.[27] As the pumping mechanism is independent of the device material any fluid can be mobilised, the flow is however, often pulsed (exceptions have been demonstrated[28]). Alternatively, external displacement pumps such as syringe pumps have found widespread use, at a research level, due to their ability to deliver stable, bi-directional flow. The main challenge

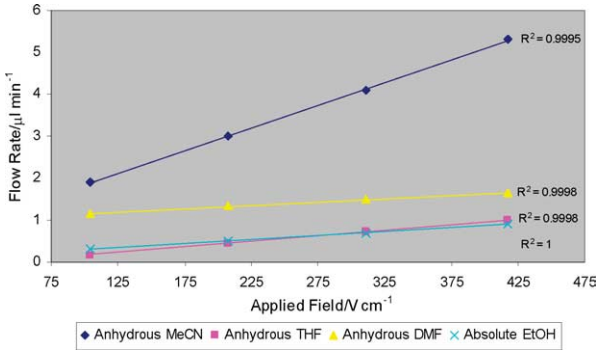


Figure 3. Graph illustrating the relationship between flow rate and applied field for a range of organic solvents.

Table 2. Relationship between the magnitude of EOF and the physical properties of a range of common organic solvents

Solvent	Dielectric constant	Viscosity (cP)	Polarity index (*P*)	Flow rate ($\mu l\ min^{-1}$)
MeCN	37.50 (20 °C)	0.38	5.8	5.30
DMF	36.71 (25 °C)	0.92	6.4	1.67
EtOH	24.55 (25 °C)	1.10	5.2	0.90
THF	7.58 (25 °C)	0.55	4.0	1.00

associated with the use of displacement pumps is obtaining low dead volume, leak free connections between the pump and device.[29] The mechanism is currently very cumbersome resulting in a system whereby the pumps dwarf the device. The low tolerance to particulates also results in the generation of high back-pressure within the system. In addition, the control of multiple inputs represents a challenge, as careful balancing of the flow rates and internal pressures is required.[30] Consequently, we believe that electrokinetic pumping is advantageous as it enables us to obtain reproducible, pulse-free, low flow rates without the generation of high back-pressures. As the pumping mechanism requires no moving parts, the technique is simple to use and free from component wear and tear making it ideal for the continuous manipulation of fluid within miniaturised systems. Therefore, unless otherwise stated, electroosmotic flow is employed for the manipulation of reagents and reaction products within the micro fabricated devices described herein.

1.3. Advantages of miniaturisation

Current production technology is based on the scale-up of successful bench-scale processes to a pilot plant, followed by a final increase in scale to achieve mass production. This approach is however fundamentally flawed as at each stage of scale-up, reactor modifications result in changes to the surface to volume ratio, which in turn have a profound effect on the thermal and mass transportation properties of the reaction. As a result of these variations, it is often necessary to re-optimise the process at each stage of scale-up; consequently the route from bench to production is both costly and time-consuming. It is therefore proposed that through the application of micro reaction technology, the transfer of reactions from the laboratory to production will be both rapid and cost effective as processes would initially be optimised on a single device and in order to increase production capacity, more devices would be employed.[3] Therefore instead of the traditional approach of scaling-up the reactor vessel, the approach of scale-out or numbering-up would be employed (Fig. 4).

From a production perspective, the scale-out approach is advantageous as it enables changes in production volume to be met by simply increasing or decreasing the number of devices employed, therefore meeting customer demand. Additionally, the use of generic reactor designs, such as those described herein, would enable custom syntheses to be performed with relative ease. Compared to a production plant where reactors are generally configured/optimised for a single function, this flexibility is both advantageous and cost effective. In addition, the predictable thermal and mass transportation properties observed within a laminar flow

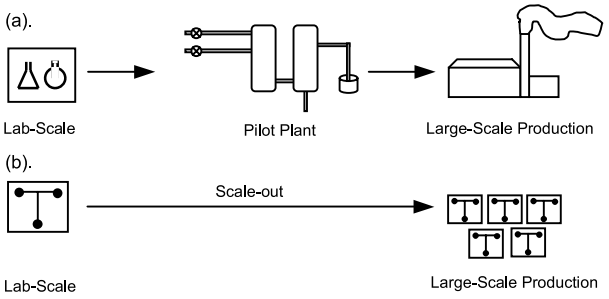
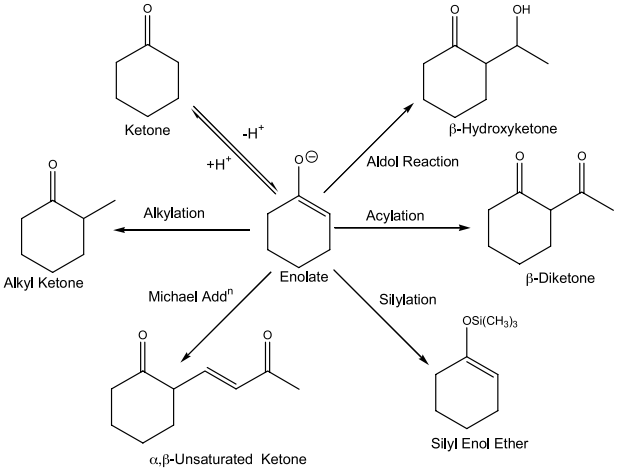


Figure 4. Schematic illustrating the (a) traditional, versus (b) miniaturised approaches to mass production.

environment result in increased reactor control.[2] In traditional large-scale reactor vessels, fluctuations in temperature and concentration are difficult to rapidly address as any alterations made take time to have an effect on the system as a whole. Along with increasing the rate of mixing, decreasing the reactor dimensions results in an inherently high surface to volume ratio. Consequently, heat generated by exothermic reactions can be dissipated rapidly, reducing the likelihood of thermal runaway or hot spot formation. As a result of the uniform reactor conditions obtained, extended reaction times are no longer required in order to obtain high conversions, resulting in fewer, but more often, no side reactions.[2,6]

2. Results and discussion

As a result of the importance of enolate chemistry in the pharmaceutical industry, the synthesis of 1,3-diketones, β-hydroxyketones, α,β-unsaturated ketones and 1,4-addition products (Scheme 1), has been used to demonstrate the key advantages associated with micro reaction technology, these include; rapid reaction optimisation, reduced reaction time, enhanced conversions, reduced by-product formation, in-situ generation of reactive intermediates and the ability to synthesise compounds that require no further purification.



Scheme 1. Illustration of the reaction diversity exhibited by an enolate.

2.1. The regioselective acylation of silyl enol ethers[7,8]

The preparation and subsequent acylation of enolates is a fundamental transformation used in organic synthesis; their ambident nature however, allows the formation of bonds at either the carbon or the oxygen. This often results in the undesirable formation of a mixture of both *O*- and *C*-acylated products, which can prove difficult to separate, resulting in low yields.[31] Consequently, a large amount of work has been undertaken in order to explore and understand those reaction conditions that promote the regioselective acylation of enolates; that is, the nature of the counterion, reaction temperature, solvent; stoichiometry of reagents, order of reagent addition and type of acylating reagent employed.[32]

Although careful selection of the aforementioned conditions has been shown to influence reaction regioselectivity, many of the 1,3-diketones prepared remain contaminated with small amounts of *O*-acylated product.[33] With this in mind, we recently demonstrated a simple technique for the regioselective synthesis of 1,3-diketones, free from any competing *O*-acylation or diacylation products. The procedure involved regeneration of enolates from silyl enol ethers[34] using a catalytic quantity of 'anhydrous' tetra-*n*-butylammonium fluoride (TBAF) **1**, followed by acylation using acyl halides (1 h) or acyl cyanides (24 h).[8] Using this approach, α-substituted ketones were found to give *C*-acylated products when treated with either acyl halides or cyanides, whereas non α-substituted ketones reacted to give *O*-acylation with acyl halides and *C*-acylation with acyl cyanides. Based on these findings, the catalytic desilylation approach was further investigated within an EOF-based micro reactor.[7]

Prior to performing an EOF-based micro reaction it is important to consider what reagent concentration, flow rate (a function of applied field) and length of experiment to use. As one of the aims of micro reaction technology is to synthesise compounds more efficiently, the use of higher reagent concentrations is desirable as this enables a greater quantity of product to be synthesised in a shorter time; consequently the limiting factor is reagent solubility (Section 2.5.2). When employing EOF, the flow rate is dependant on both the applied field and the physical properties of the reagents; as a result applied fields vary to ensure that equal flow of reagents is obtained from all reservoirs. Finally, the length of experiment is chosen in order to obtain a sufficient quantity of product for off-line analysis by GC–MS and does not reflect the residence time of reagents within the micro reactor channel; unless otherwise stated reactions are performed for 20 min.

In order to perform the acylation reaction, solutions of 'anhydrous' TBAF **1** (40 μl, 0.1 M), benzoyl fluoride **2** (40 μl, 1.0 M) and trimethyl(1-phenylvinyloxy)silane **3** (40 μl, 1.0 M) in anhydrous THF were placed in reservoirs A, B and C, respectively, (Fig. 5). The reagents were then manipulated within the device, using the following applied fields 333, 455, 333 and 0 V cm^{-1} (to reservoirs A, B, C and D, respectively), and the reaction products collected in reservoir D. Analysis of the reaction mixture by off-line GC–MS showed that 100.0% conversion of silyl enol ether

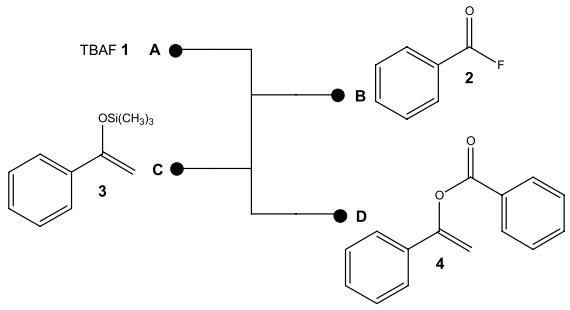


Figure 5. Schematic of the reactor manifold used for the synthesis of benzoic acid 1-phenylvinyl ester **4**.

3 to benzoic acid 1-phenylvinyl ester **4** had occurred and crucially, no *C*-acylated **5** or diacylated products were detected. Having successfully demonstrated the micro-scale synthesis of benzoic acid 1-phenylvinyl ester **4**, the kinetically slower *C*-acylation reaction (24 h in batch) was investigated.

Substitution of benzoyl fluoride **2** with benzoyl cyanide **6** (40 μl, 1.0 M) enabled the synthesis of 1,3-diphenylpropane-1,3-dione **5** to be investigated using the same micro reactor manifold. Manipulation of the reagents using 417, 318, 476 and 0 V cm^{-1}, resulted in 100.0% conversion of the enol ether **3** to 1,3-diphenylpropane-1,3-dione **5**, again no competing *O*-acylated **4** or diacylated products were observed. The generality of the technique was subsequently demonstrated using trimethyl(1-phenyl-propenyloxy)silane **7** and cyclohex-1-enyloxy(trimethylsilane) **8** to afford 2-methyl-1,3-diphenylpropane-1,3-dione **9** and 2-benzoylcyclohexanone **10**, respectively. Again, all standard solutions were prepared in anhydrous THF and the reagents introduced into the reactor as follows; 'anhydrous' TBAF **1** (40 μl, 0.1 M) in reservoir A, acylating reagent (40 μl, 1.0 M) in reservoir B, the enol ether (40 μl, 1.0 M) in reservoir C and the reaction products collected in reservoir D. Manipulation of the reagents using the applied fields reported in Table 3 resulted in 100.0% conversion to the respective 1,3-diketone. In summary, we have demonstrated a simple, regioselective technique for the acylation of an array of tetra-*n*-butylammonium enolates in an EOF-based micro reactor (Table 3); demonstrating an approach, which is clearly suited to the generation of combinatorial libraries.

2.2. The synthesis of β-hydroxyketones using silyl enol ethers[9]

Having successfully demonstrated the use of silyl enol ethers as enolate precursors with respect to regioselective acylation, the investigation was extended to incorporate the synthesis of β-hydroxyketones. In the mid 1970's, Noyori

Table 3. Comparison of the conversions obtained for the acylation of silyl enol ethers in batch and in a micro reactor

Product no.	Conversion (%)		Applied field (V cm^{-1})
	Batch	Micro reaction	
4	100.0	100.0	333, 455, 333 and 0
5	95.0	100.0	417, 318, 476 and 0
9	100.0	100.0	375, 455, 405 and 0
10	100.0	100.0	208, 409, 357 and 0

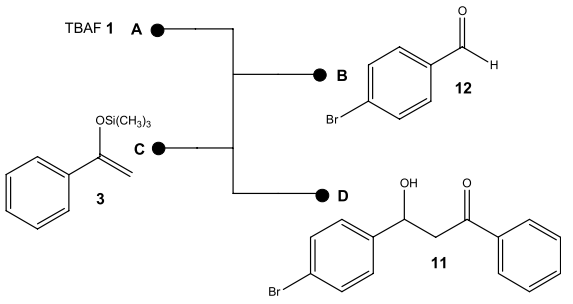


Figure 6. Schematic of the micro reactor manifold used for the synthesis of 3-(4-bromophenyl)-3-hydroxy-1-phenylpropan-1-one **11**.

et al.[35] demonstrated the aldol reaction of silyl enol ethers as a means of circumventing the dehydration step frequently associated with the aldol condensation. As the resulting β-hydroxyketone is a versatile synthon finding application for example in the synthesis of natural products derived from polyketide biosynthetic pathways, we investigated their synthesis in an EOF-based micro reactor.

The synthesis of 3-(4-bromophenyl)-3-hydroxy-1-phenylpropan-1-one **11** was investigated using anhydrous THF as the solvent system. As Figure 6 illustrates, 'anhydrous' TBAF **1** (40 μl, 0.1 M) was placed in reservoir A, 4-bromobenzaldehyde **12** (40 μl, 1.0 M) was placed in reservoir B and trimethyl(1-phenylvinyloxy)silane **3** (40 μl, 1.0 M) in reservoir C. Manipulation of the reagents using 375, 409, 381 and 0 V cm^{-1} resulted in 100.0% conversion of the silyl enol ether **3** to 3-(4-bromophenyl)-3-hydroxy-1-phenylpropan-1-one **11**. Using the aforementioned procedure, the reaction was subsequently repeated using cyclohex-1-enyloxy(trimethylsilane) **8** (40 μl, 1.0 M), whereby application of 417, 455, 476 and 0 V cm^{-1} resulted in only 1.0% conversion of the enol ether **8** to 2-[(4-bromophenyl)-hydroxymethyl]cyclohexanone **13**. Upon altering the applied fields to 417, 341, 333 and 0 V cm^{-1}, and hence increasing reagent residence time within the device, the conversion to product **13** was increased to 100.0% wrt residual enol ether **8**. As Table 4 illustrates, compared to traditional batch techniques, enhancements in conversion were obtained as a result of performing the reactions within a micro reactor; in the case of 3-(4-bromophenyl)-3-hydroxy-1-phenylpropan-1-one **11**, an increase of 20.0% was observed. Along with a reduction in reaction times, the technique is highly desirable as no dehydration products were detected.

2.2.1. Alternative silylation technique. The use of preformed enolates, in the form of silyl enol ethers,[36,37] has allowed us to successfully demonstrate the regeneration and subsequent reaction of a series of enolates within a micro reactor (Sections 2.1 and 2.2). This approach can however be disadvantageous when base sensitive molecules are employed as poor conversions result in products often contaminated with inorganic salts.[38] In order to circumvent these problems, many groups have investigated mild and efficient alternatives.[39,40] Nakamura and co-workers[41] demonstrated the use of ethyltrimethylsilylacetate (ETSA) **14** and 'anhydrous' TBAF **1** for the *O*-silylation of ketones and alcohols under nearly neutral conditions. As Scheme 2 illustrates, TBAF **1** acts catalytically with the only by-product of the reaction being ethyl acetate. Consequently, this approach was of particular interest as the reaction conditions are mild and no inorganic residues are formed during the reaction.

Table 4. Summary of the conversions obtained for the synthesis of β-hydroxyketones **11** and **13** in batch and a micro reactor

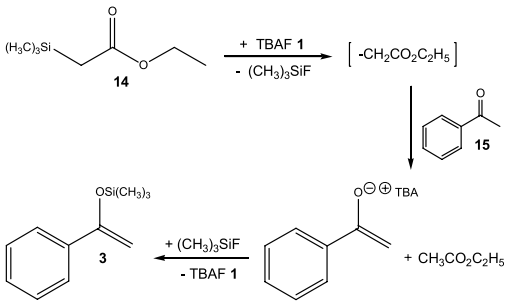
Product no.	Conversion (%)		Applied field (V cm^{-1})
	Batch	Micro reaction	
11	80.0	100.0	375, 409, 381 and 0
13	93.0	1.0	417, 341, 333 and 0
13	93.0	100.0	333, 455, 333 and 0

Prior to transferring the technique to a micro reactor, the synthesis of trimethyl(1-phenylvinyloxy)silane **3** was investigated in batch. Reaction of ETSA **14** and acetophenone **15** in the presence of 'anhydrous' TBAF **1** (0.1 equiv) afforded 56.2% conversion to enol ether **3** after only 20 min. Surprisingly however, after 2 h only 6.0% trimethyl(1-phenylvinyloxy)silane **3** remained; an observation that is attributed to competing desilylation and protonation of the tetra-*n*-butylammonium enolate. Obviously when performing the reaction in batch, the limited lifetime of the enol ether is disadvantageous, however by transferring the reaction to a micro reactor we believed that the spatial control obtained would enable us to synthesise the enol ether, generate the tetra-*n*-butyl ammonium enolate and react it to afford the desired product in high conversion.

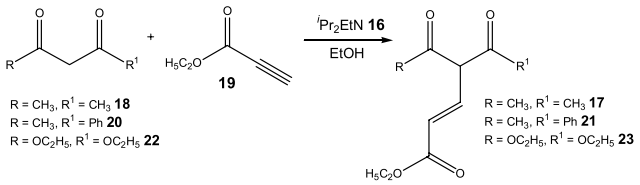
In order to demonstrate the technique, the synthesis of trimethyl(1-phenylvinyloxy)silane **3** and its subsequent reaction to afford benzoic acid 1-phenylvinyl ester **4**, was selected as a model reaction. A premixed solution of acetophenone **15** and ETSA **14** (40 μl, 1.0 M) in anhydrous THF was placed in reservoir A, a solution of 'anhydrous' TBAF **1** (40 μl, 0.1 M) in THF in reservoir B and a solution of benzoyl fluoride **2** (40 μl, 1.0 M) in THF in reservoir C. Manipulation of the reagents using 417, 417 and 0 V cm^{-1}, resulted in 100.0% conversion of acetophenone **15** to product **3**, demonstrating the potential of this technique for the in-situ synthesis of silyl enol ethers and their subsequent reaction within the micro fluidic device.

2.3. Michael addition[6]

Following the successful synthesis of a series of β-hydroxyketones, 1,3-diketones and *O*-acylated ketones within an EOF-based micro reactor, we were interested in extending



Scheme 2. Preparation of trimethyl(1-phenylvinyloxy)silane **3** using ETSA **14**/TBAF **1**.

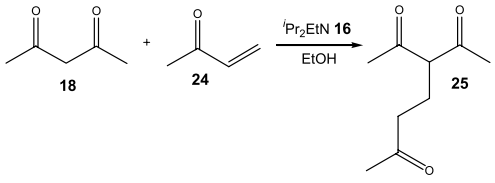


Scheme 3. Synthesis of Michael adducts **17**, **21** and **23** using diisopropylethylamine **16**.

the investigation to include the preparation of 1,3-diketone enolates. In order to demonstrate their synthetic utility, a series of 1,4-conjugate additions were investigated (Scheme 3). With the extensive range of donor and acceptor compounds featured within the literature serving to demonstrate the synthetic scope associated with the Michael reaction,[42,43] the investigation concentrated on the reaction of 1,3-diketones (donor) and α,β-unsaturated carbonyl compounds (acceptor). As the protons of 1,3-dicarbonyl compounds are relatively acidic ($^{MeCN}pK_{BH^+}$ 9–13), deprotonation was achieved using the organic base diisopropylethylamine **16**.

Prior to investigating the reactions within a micro reactor, synthetic standards of the target products were synthesised. (*E*)-4-Acetyl-5-oxohex-2-enoic acid ethyl ester **17** was prepared in 89.0% yield via the dropwise addition of 2,4-pentanedione **18** to a stirred solution of ethyl propiolate **19** and diisopropylethylamine **16** in absolute EtOH. Analysis of the product by ^{1}H NMR, indicated that the Michael adduct **17** formed was predominantly the trans isomer (>99.0% selectivity). With this in mind, the reaction was subsequently repeated using 1-phenylbutane-1,3-dione **20** to afford (*E*)-4-benzoyl-5-oxohex-2-enoic acid ethyl ester **21** in 77.0% yield and diethyl malonate **22** to give (*E*)-4-ethoxycarbonylpent-2-enedioic acid ethyl ester **23** in 82.5% yield. The generality of the technique was examined using the alkenic acceptor methyl vinyl ketone **24**, whereby 3-acetylheptane-2,6-dione **25** was obtained in 91.0% yield (Scheme 4).

Using absolute EtOH as the solvent system, the synthesis of (*E*)-4-acetyl-5-oxohex-2-enoic acid ethyl ester **17** was investigated in a micro reactor (Fig. 7). Diisopropylethylamine **16** (40 μl, 5.0 M), 2,4-pentanedione **18** (40 μl, 5.0 M) and ethyl propiolate **19** (40 μl, 5.0 M) were manipulated within the device using 417, 318, 333 and 0 V cm^{-1}. Off-line analysis of the reaction mixture showed 56.0% conversion of 2,4-pentanedione **18** to (*E*)-4-acetyl-5-oxohex-2-enoic acid ethyl ester **17**, with the remaining 44.0% being unreacted starting material **18**. This was subsequently increased to 95.0% by employing stopped flow (Flow Regime B) (for a detailed discussion of flow regimes see Section 4.2.2). The increase in conversion was



Scheme 4. Synthesis of 3-acetylheptane-2,6-dione **25** using diisopropylethylamine **16**.

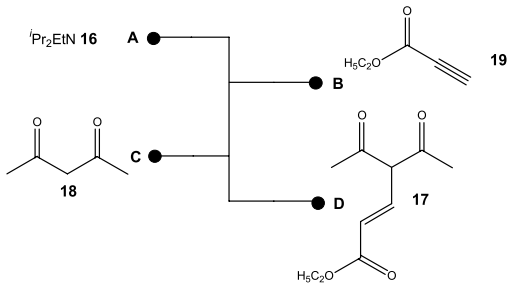


Figure 7. Schematic of the micro reactor manifold used for the synthesis of (*E*)-4-acetyl-5-oxohex-2-enoic acid ethyl ester **17**.

originally attributed to an increase in diffusive mixing between the reagent streams,[6] this is however, unlikely as micro-scale reactions are often regarded as being rate limited, not diffusion limited.[2] As both reactions were performed over the same period of time, the observed increase in conversion is attributed to an increase in residence time within the micro reactor.

Based on these initial observations, the synthesis of (*E*)-4-benzoyl-5-oxohex-2-enoic acid ethyl ester **21** was subsequently investigated using absolute EtOH as the solvent system. Standard solutions of diisopropylethylamine **16** (40 μl, 5.0 M), ethyl propiolate **19** (40 μl, 5.0 M) and 1-phenylbutane-1,3-dione **20** (40 μl, 5.0 M) were manipulated within the device using the following applied fields, 417, 318, 333 and 0 V cm^{-1}. Employing Flow Regime A resulted in 15.0% conversion of 1-phenylbutane-1,3-dione **20** to (*E*)-4-benzoyl-5-oxohex-2-enoic acid ethyl ester **21**, with the remaining 85.0% being unreacted diketone **20**. Again, application of a stopped flow regime (Flow Regime B) resulted in an increase in conversion to 34.0%, which was further increased to 100.0% by employing a longer period of stopped flow (Flow Regime C). The technique was further exemplified using the synthesis of (*E*)-4-ethoxycarbonylpent-2-enoic acid ethyl ester **23**, whereby Flow Regime A (417, 386, 381 and 0 V cm^{-1}) resulted in 40.0% conversion to product **23** compared to 100.0% as a result of employing Flow Regime B.

Having successfully demonstrated a number of conjugate additions using the alkynic acceptor ethyl propiolate **19**, the synthesis of 3-acetylheptane-2,6-dione **25** was subsequently investigated using methyl vinyl ketone **24** (Scheme 4). Using absolute EtOH as the solvent system, diisopropylethylamine **16** (40 μl, 5.0 M), 2,4-pentanedione **18** (40 μl, 5.0 M) and MVK **24** (40 μl, 5.0 M) were manipulated within the device (417, 455, 476 and 0 V cm^{-1}) and the reaction products collected in reservoir D. As a result of employing Flow Regime A, 13.0% conversion to product **25** was obtained, this was further increased to 96.0% conversion as a result of employing Flow Regime B (Table 5).

To summarise, using the Michael addition as a model reaction, we have demonstrated the ability to rapidly optimise reactions by employing a range of flow regimes in an EOF-based micro reactor. In addition, it must also be noted that as a result of the increased reaction control obtained within the micro fluidic device, no by-products were detected; compared to batch, where a competing

Table 5. Comparison of the effect of flow regime on conversion to Michael adduct in an EOF-based micro reactor

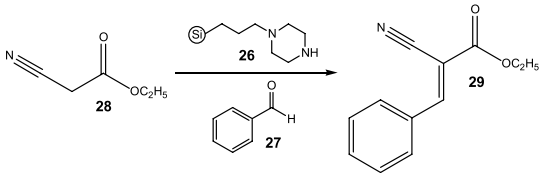
Product no.	Conversion (%)		
	Flow regime A	Flow regime B	Flow regime C
17	56.0	95.0	—
21	15.0	34.0	100.0
23	40.0	100.0	—
25	13.0	96.0	—

reaction between the base **16** and the Michael acceptor **19** was frequently observed.[44]

2.4. The use of solid-supported bases for the synthesis of analytically pure condensation products[10]

Due to the widespread pharmaceutical interest in the Knoevenagel condensation (Scheme 5), we investigated the synthesis of α,β-unsaturated compounds in an EOF-based micro reactor. As the reactions are base catalysed, one of the main disadvantages is that the reaction products require purification in order to remove the organic base and its salt. With this in mind, we proposed that by incorporating a series of supported bases (Fig. 8) into a micro fabricated device, product purity could be increased while simultaneously maintaining the advantages associated with reaction miniaturisation. In order to evaluate the use of supported reagents within an EOF-based system, a miniaturised flow reactor was designed (Fig. 9). This approach not only enabled reagents to be packed with ease but also provided a relatively inexpensive, versatile system. Using the set-up illustrated in Figure 9, 5 mg of 3-(1-piperazino)propyl-functionalised silica gel **26** (4.75×10^{-3} mmol) was packed into a borosilicate glass capillary (500 μm×3.0 cm) and micro porous silica frits placed at both ends, the capillary was then placed between two glass reservoirs. A 1:1 mixture of benzaldehyde **27** and ethyl cyanoacetate **28** (40 μl, 1.0 M) in MeCN was placed in reservoir A and MeCN in reservoir B (40 μl).

Application of 333 and 0 V cm^{-1} resulted in the mobilisation of the reaction mixture through the packed bed at a flow rate of 0.5 μl min^{-1}. Operating the device continually for 4.75 h (14×20 min runs) resulted in the synthesis of 0.025 g (0.124 mmol, 98.9%) of 2-cyano-3-phenyl acrylic acid ethyl ester **29**. The 'crude' reaction products were then analysed by NMR spectroscopy to confirm product purity.[10] The generality of the technique was subsequently investigated using 4-bromobenzaldehyde **12**, 3,5-dimethoxybenzaldehyde **30** and 4-benzyloxybenzaldehyde **31**. As Table 6 illustrates, the respective condensation products **32**, **33**, and **34** were obtained in >95.0% conversion. In addition, we investigated the condensation of malononitrile **35** with the aforementioned aldehydes to afford condensation products



Scheme 5. General scheme illustrating the use of a functionalized silica gel **26**, in the Knoevenagel condensation.

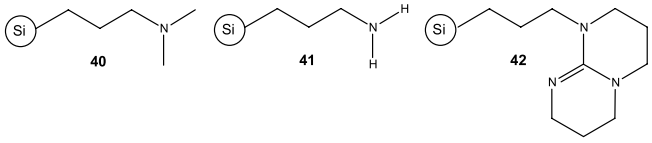


Figure 8. Schematic illustrating the silica-supported bases investigated.

36 (96.9%), **37** (96.3%), **38** (97.8%) and **39** (99.7%), respectively.

Using the synthesis of unsaturated ketone **29** as a model reaction, we also investigated the use of other supported bases, namely; 3-(dimethylamino)propyl-functionalised silica gel **40**, 3-aminopropyl-functionalised silica gel **41** and 3-(1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-*a*]-pyrimidino)propyl-functionalised silica gel **42** (Fig. 8) whereby 99.4, 100.0 and 99.3% conversion to the desired product 2-cyano-3-phenyl acrylic acid ethyl ester **29** was observed. Compared to standard batch techniques, the approach described is advantageous as the supported reagents can be recycled with ease, enabling more consistent results to be obtained. In addition, the generation of localised concentration gradients enables reactions to be driven to completion without the need to employ large quantities of catalyst. In summary, we have demonstrated the successful incorporation of a series of silica-supported bases within an EOF-based device, enabling the synthesis and characterisation of eight condensation products whereby no additional product purification was required.

2.5. Enolate alkylation

Following the successful preparation of a range of 1,3-diketone enolates using both solution phase and solid-supported organic bases, the next step was to evaluate the preparation of enolates directly from ketones such as acetophenone **15**. This was firstly demonstrated using organic peralkylated polyaminophosphazene bases (Section 2.5.1) and secondly using inorganic bases (Section 2.5.2–2.5.3).

2.5.1. Phosphazene bases. Over the past 30 years, research has been undertaken in order to increase the inherent strength (pK_{BH^+}) of organic bases[45] and although a few examples are commercially available, such as heptamethylisobiguanide,[46] however they were not well received by synthetic chemists.[47] The field was however transformed in the early 1990's by Schwesinger and co-workers[48,49] with

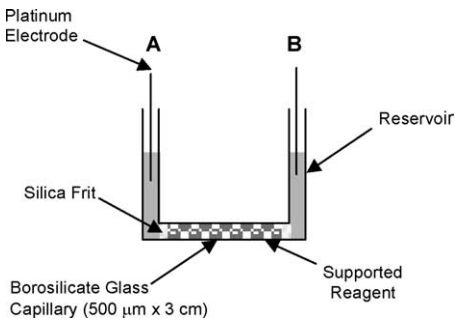


Figure 9. Schematic of the reaction set-up used for the evaluation of solid-supported reagents, in a miniaturized system.

Table 6. Summary of the conversions obtained in a micro fabricated device using 3-(1-piperazino)propyl-functionalised silica gel **26**

Product no.	Applied field ($V\ cm^{-1}$)	Flow rate ($\mu l\ min^{-1}$)	Conversion[a] (%)
29	333	0.5	99.1
32	333	0.3	99.5
33	333	0.3	94.7
34	333	0.5	95.1
36	167	1.0	96.9
37	167	0.5	96.3
38	167	0.7	97.8
39	167	1.0	99.7

[a] ≥ 10 replicates were performed for each compound.

the synthesis of a series of strong, uncharged bases, termed peralkylated polyaminophosphazenes or simply phosphazenes (Fig. 10).[50] Compared to traditional organic bases such as diisopropylethylamine **16** and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) **43**, the peralkylated phosphazene bases demonstrate a dramatic increase in basicity, of between 14.9 and 30.6 pK_{BH^+} units, representing base strengths more commonly associated with inorganic bases such as *n*-butyllithium **44** (Table 7).[51]

In order to demonstrate enolate formation within a micro reactor, the synthesis of 2-benzylcyclohexanone **47** was selected as a model reaction (Scheme 6). As a means of identifying any advantages associated with the miniaturisation of this technique, the reaction was initially performed in batch. As Table 8 illustrates, despite the fact that 2-benzylcyclohexanone **47** was successfully synthesised

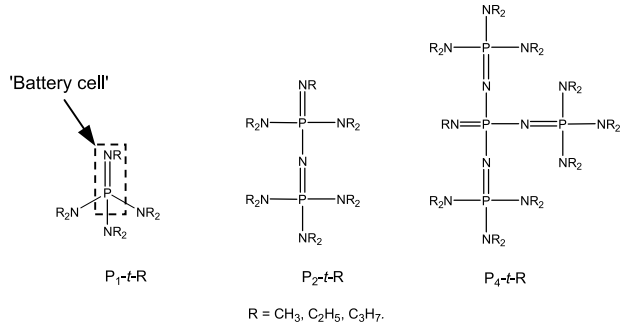
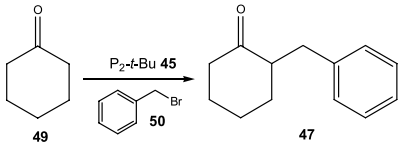


Figure 10. General structure of a series of peralkylated polyaminophosphazenes bases.

Table 7. Comparison of base strength as a function of charge delocalization for a range of organic bases

Base	$^{MeCN}pK_{BH^+}$	Charge declocalisation
DBU **43**	24.3	2
P_1-*t*-Bu	26.9	5
P_2-*t*-Bu **45**	33.5	9
P_3-*t*-Bu	38.6	13
P_4-*t*-Bu **46**	42.6	17



Scheme 6. Preparation of 2-benzylcyclohexanone **47** using P_2-*t*-Bu **45**.

Table 8. Comparison of the proportion of by-product formed in batch and a micro reactor for the alkylation of cyclohexanone **49**

Base	Conversion ratio **47**:**48**[a]	
	Batch	Micro reaction
P_2-*t*-Bu **45**	40.0:7.0	84.0:0.0
P_4-*t*-Bu **46**	15.0:40.0	N/A

[a] Remainder is unreacted starting material.

using both P_2-*t*-Bu **45** and P_4-*t*-Bu **46**, the reaction mixtures were found to contain appreciable amounts of the dialkylated product 2,2-dibenzylcyclohexanone **48**. With this in mind, we investigated the synthesis of 2-benzylcyclohexanone **47** in an EOF-based micro reactor.

Using anhydrous THF as the solvent system, cyclohexanone **49** (40 µl, 0.25 M) was placed in reservoir A, P_2-*t*-Bu **45** (40 µl, 0.25 M) in reservoir B and benzyl bromide **50** (40 µl, 0.25 M) in reservoir C (Fig. 11). The reagents were mobilised within the device using the following applied fields, 417, 455, 476 and $0\ V\ cm^{-1}$ and the reaction products collected in anhydrous THF (40 µl) at reservoir D. Analysis of the reaction products by GC–MS illustrated 84.0% conversion to product **47** (with respect to residual cyclohexanone **49**) demonstrating a significant increase in conversion compared to that obtained in batch (44.0%). The technique also proved advantageous as no dialkylation products **48** were detected when the reaction was performed in a micro reactor. This observation is attributed to the reduced reaction times employed in a micro reactor, i.e. the reaction mixture is removed from the reactor and quenched prior to the 2nd alkylation. The spatial control obtained within such a device therefore enabled by-product formation to be eliminated, enabling the synthesis of uncontaminated products.[52]

In spite of the array of examples featured within the literature, chemists remain hesitant to employ phosphazene bases, in preparative scale reactions, due to their cost (typically £21 g^{-1}). To some extent, this has been addressed by the availability of polymer-supported derivatives, which enable their efficient separation and recovery from a reaction mixture.[53] Incorporation of these supported bases into a micro fabricated device (Section 2.4) would enable the continuous synthesis of base free reaction products coupled with enhanced reaction control.

In summary, using the synthesis of 2-benzylcyclohexanone **47** as a model reaction, we have demonstrated significant

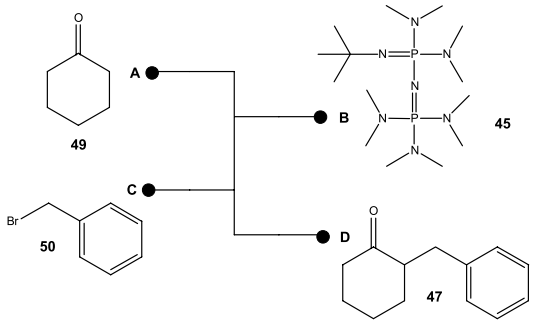


Figure 11. Schematic of the reactor manifold used for the synthesis of 2-benzylcyclohexanone **47**.

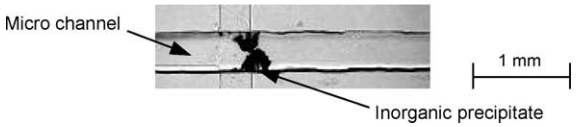


Figure 12. Optical microscope image of a blocked micro channel, caused by the precipitation of an inorganic base.

enhancements in conversion compared to batch, i.e. 84.0% cf. 40.0%, along with significantly enhancing product selectivity. In addition, the use of phosphazene bases enabled us to demonstrate the synthesis of previously inaccessible carbanions within an EOF-based micro reactor.

2.5.2. Inorganic bases. Although we have described numerous techniques for the preparation of enolates within a micro reaction environment, we are yet to discuss their preparation using inorganic bases. Again, the synthesis of 2-benzylcyclohexanone **47** was used as a model reaction for the investigation of the following bases; lithium bis(trimethylsilyl)amide **51**, sodium bis(trimethylsilyl) amide **52**, potassium bis(trimethylsilyl)amide **53**, sodium *tert*-butoxide **54**, potassium *tert*-butoxide **55**, lithium *tert*-butoxide **56**, lithium 2,2,6,6-tetramethylpiperidine **57**, lithium diisopropylamide **58**, lithium phenoxide **59**, sodium methoxide **60** and sodium ethoxide **61**.

Due to their inherent ionic nature, many reagents used in organic synthesis are largely insoluble in non-polar organic solvents. In this case, the relative insolubility of inorganic bases within solvents such as THF, DMF and MeCN (0.05–1.0 M) proved problematic, as blockage formation within the micro channels resulted in retardation of EOF (Fig. 12). These observations were initially surprising as Skelton et al.[54] had previously demonstrated the use of NaOMe **60** in MeOH, within an EOF-based device, for the synthesis of a range of stilbenes. The mobilisation of NaOMe **60** was inferred via the generation of a purple coloured intermediate (ylide) within the micro channel and the subsequent off-line detection of the respective stilbene ester. We however postulate that the base was successfully mobilised as a result of its enhanced solubility within the polar solvent system employed. Consequently, in order to further investigate the mobilisation of inorganic bases by EOF, a means of ensuring greater solubility was required.

2.5.3. Enhanced base solubility using crown ethers. In 1967, Pedersen et al.[55] demonstrated the complete dissolution of potassium permanganate in benzene by employing a stoichiometric quantity of the cyclic ether, 18-crown-6 **62**. A phenomenon that was later attributed to the separation of the metal ion from its associated ions, rendering the salt soluble in the non-polar media. With this in mind, we postulated that by solvating inorganic bases with their respective crown ether, increased solubility could be achieved; enabling their electro osmotic mobilisation in solvents such as THF. In order to evaluate this approach, we again used the preparation of 2-benzylcyclohexanone **47** in THF as a model reaction. As Figure 13 illustrates, a solution of cyclohexanone **49** and benzyl bromide **50** (40 μl, 1:1) was placed in reservoir A and a solution of base and crown ether (40 μl, 1:1) was placed in reservoir B. The reagents were manipulated within the device using 417, 455 and

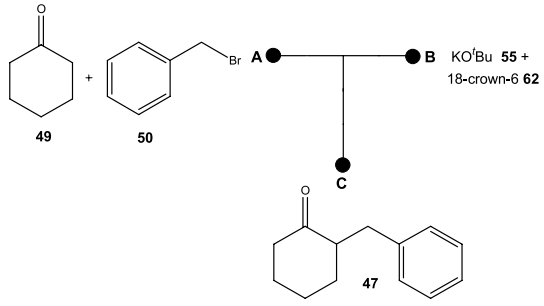


Figure 13. Typical reactor manifold used for the determination of inorganic base flow by EOF.

0 V cm^{-1} and the reaction products collected in reservoir C. As the aim of the investigation was to rationalise the problems associated with the mobilisation of inorganic bases by EOF, at this stage, the detection of 2-benzylcyclohexanone **47** (and the respective crown ether) by GC–MS was considered indicative of base mobilisation. Consequently, conversions and optimised reaction conditions are not provided. In accordance with the literature, 18-crown-6 **62** was investigated for potassiated bases, 15-crown-6 **63** for sodiated bases and 12-crown-4 **64** for lithiated bases.[55]

Using the aforementioned methodology, 0.5–1.0 M solutions of KHMDS **53**, NaO^{t}Bu **54** and KO^{t}Bu **55** were successfully mobilised by EOF. Extension of the technique to NaHMDS **52**, LiO^{t}Bu **56** and LiHMDS **51** however, proved problematic as over the course of the micro reaction, the contents of reservoir B became turbid, resulting in the partial blockage of the micro channel; an observation attributed to decomposition of the base. In order to prevent base decomposition, the reagent reservoirs were covered with a series of PTFE bungs, as illustrated in Figure 14. Using this approach, reagent turbidity was prevented, enabling the successful mobilisation of NaHMDS **52** and LiO^{t}Bu **56** by EOF.[56] In contrast, no electrokinetic flow was observed for LiHMDS **51**; with all solutions forming a gelatinous precipitate within the reagent reservoir and micro channel.

Due to the widespread application of the base sodium hydride **65**, its mobilisation by EOF was also investigated, however as NaH **65** is not strong enough to provide complete deprotonation of cyclohexanone **49**, the benzylation of phenol **66** was employed as a model reaction (Scheme 7). Using either anhydrous THF or MeCN as the solvent system, NaH **65** and 15-crown-5 **63** (40 μl, 0.5 M) were placed in reservoir A, phenol **66** (40 μl, 0.5 M) in reservoir B and benzyl bromide **50** (40 μl, 0.5 M) in reservoir C (Fig. 15). The reagents were manipulated within the micro reactor using applied fields, 417, 455, 476 and

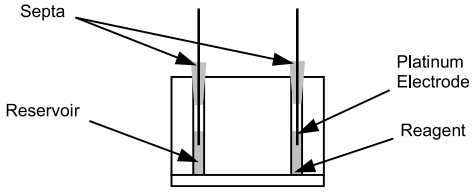
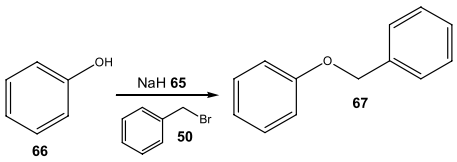


Figure 14. Schematic illustrating the reaction set-up used for moisture/air sensitive micro reactions.



Scheme 7. Synthesis of benzyloxybenzene **67** using NaH **65**.

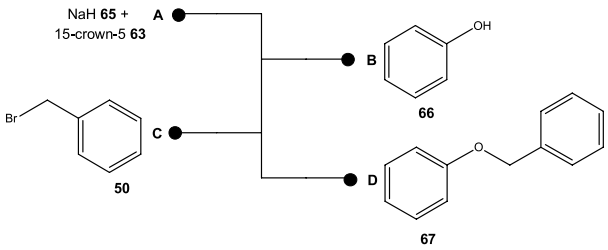


Figure 15. Schematic illustrating the reaction manifold used for the synthesis of benzyloxybenzene **67**.

0 V cm^{-1} (500, 588, 769 and 0 V cm^{-1} when employing MeCN) and the reaction products collected in reservoir D. The detection of benzyloxybenzene **67** and 15-crown-5 **63** was indicative of base mobilisation. In summary, as a result of increasing inorganic base solubility, by the addition of a stoichiometric quantity of crown ether, we have successfully demonstrated the electrokinetic mobilisation of six inorganic bases and their subsequent use for the synthesis of 2-benzylcyclohexanone **47** (Table 9).

2.6. Diastereoselective alkylation[11]

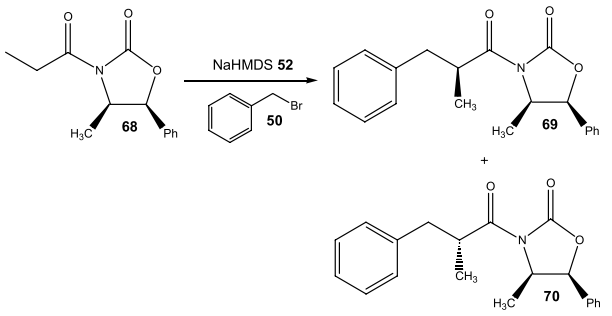
The preparation of compounds with specific stereochemistry is of great interest to pharmaceutical companies as often one enantiomer exhibits biological activity whereas the other may be inactive or even harmful. With this in mind, one such approach for the synthesis of enantiomerically pure compounds is the use of chiral auxiliaries.[57]

Based on initial observations by Skelton et al.,[54] where product stereoselectivity was found to be influenced as a result of synthesising a series of stilbene esters in a micro reactor, the effect on reaction diastereoselectivity was of interest. In order to investigate the factors that affect product diastereoselectivity, the reactions were initially performed in batch, enabling the preparation and characterisation of synthetic standards (Scheme 8). Using methodology established by Evans et al.[58] the enolate of 4-methyl-5-phenyl-3-propionyloxazolidinone **68** was alkylated, using

Table 9. Mobilisation of inorganic base/crown ether complexes by EOF

Base	Crown ether	Applied field (V cm^{-1})	EOF
KO^{t}Bu **55**	18-Crown-6 **62**	417, 455 and 0	✓
KHMDS **53**	18-Crown-6 **62**	417, 455 and 0	✓
NaO^{t}Bu **54**	15-Crown-5 **63**	417, 455 and 0	✓
NaHMDS **52**	15-Crown-5 **63**	417, 455 and 0	✓
NaH **65**	15-Crown-5 **63**	417, 455, 476 and 0	✓
NaH **65**[a]	15-Crown-5 **63**	500, 588, 769 and 0	✓
LiO^{t}Bu **56**	12-Crown-4 **64**	417, 455 and 0	✓
LiHMDS **51**	12-Crown-4 **64**	417, 455 and 0	×

[a] Performed in anhydrous MeCN.



Scheme 8. Diastereoselective alkylation of 4-methyl-5-phenyl-3-propionyl oxazolidinone **68**.

benzyl bromide **50**, to afford diastereomers **69** and **70** in an overall yield of 68.0% and a ratio of 85:15 (**69**:**70**) (at −100 °C). Although Evans et al.[69] report greater diastereoselectivities, in practise they are difficult to reproduce. With this in mind, it was postulated that due to the excellent thermal and mass transportation properties observed within micro fluidic devices, product diastereoselectivity, and reaction reproducibility, could be improved as a result of conducting the reaction in a micro reactor.

Although many reactions have been demonstrated within micro reactors at temperatures ranging from 4 to 300 °C,[59] few authors with the exception of Yoshida[60] and Schwalbe,[2] report reactions performed at reduced temperatures. Using the following experimental procedure, the synthesis of diastereomers **69** and **70** was investigated within a pressure-driven system; a standard solution of NaHMDS **52** (0.5 M) in anhydrous THF was added from syringe A (50 µl min^{-1}), a solution of 4-methyl-5-phenyl-3-propionyloxazolidinone **68** (0.5 M) in anhydrous THF was added from syringe B (50 µl min^{-1}) and a solution of benzyl bromide **50** (0.5 M) from syringe C (50 µl min^{-1}). In order to maintain the reactor temperature, the device was submerged within a CO_2–ether bath and the reaction products collected at room temperature (Fig. 16). To ensure results obtained were representative of reactions occurring within the micro fabricated device, the reaction products were quenched upon collection. Using this approach, the chiral enolate was formed within the central micro channel and reacted with benzyl bromide in the microtee, to afford diastereomers **69** and **70** in 31.0% conversion and a ratio of 94:6 (**69**:**70**). In order to increase the conversion obtained, the flow rate was firstly reduced to 20 µl min^{-1} and finally to 10 µl min^{-1}, resulting in an increase in conversion to 38.0% and 41.0% respectively. Most importantly however, the observed diastereoselectivity increased to from 94:6 to 99:1

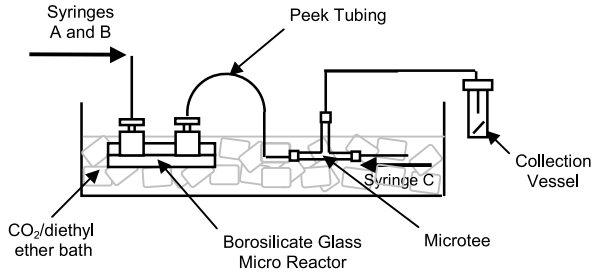


Figure 16. Schematic of the reaction set-up used for the evaluation of reduced temperature micro reactions.

Table 10. Effect of flow rate on product diastereoselectivity and conversion in a pressure-driven micro reactor

Flow Rate ($\mu l\ min^{-1}$)	Conversion (%)	Ratio (**69**:**70**)	Decomposition **71** (%)
50	31	94:6	0
20	38	99:1	0
10	41	99:1	0

(Table 10). Although these results represent initial observations and currently remain unoptimised, compared to traditional batch techniques the approach described is advantageous as no decomposition products, 3-benzyl-4-methyl-5-phenyloxazolidin-2-one **71** and 4-methyl-5-phenyloxazolidin-2-one **72**, were detected. We attribute this observation to the ability to accurately control both residence time and temperature of the reaction mixture within the micro fluidic device.

Consequently we propose that by either increasing the residence time within the device or reducing the reagent concentrations, that product conversion could be further increased. In summary, we have demonstrated a simple technique for the diastereoselective alkylation of a metal stabilised enolate, using a pressure-driven micro reactor at $-100\ ^{\circ}C$, whereby increased diastereoselectivity was observed compared to batch.

3. Conclusions

In order to demonstrate the application of micro reaction technology to chemical synthesis, the preparation and reaction of enolates was selected as it enabled a range of reactions to be investigated while maintaining a common element, i.e. deprotonation followed by nucleophilic substitution. Due to initial problems encountered with the mobilisation of inorganic bases by EOF, the use of preformed enolates, in the form of silyl enol ethers, was investigated. Using this approach, a series of tetra-*n*-butylammonium enolates were prepared using anhydrous TBAF **1** and subsequently reacted to afford 1,3-diketones, phenyl vinyl esters and β-hydroxyketones. The technique was subsequently extended to the use of organic bases whereby the Michael addition and alkylations were employed as model reactions. In addition, we demonstrated the synthesis of two carbanions using solid-supported organic bases and their subsequent reaction in the Knoevenagel condensation. Based on these observations, the use of inorganic bases was reinvestigated, this time enhancing base solubility by the addition of a stoichiometric quantity of crown ether, resulting in their successful electrokinetic mobilization. Inorganic bases were also successfully employed in a pressure-driven system demonstrating the diastereoselective alkylation of an Evans auxiliary derivative.

In conclusion, using the preparation and reaction of carbanions and enolates, we have demonstrated numerous advantages associated with micro reaction technology including; rapid reaction optimization, reduced reaction times, enhanced conversions, reduced by-product formation and the ability to generate reagents in-situ, whilst demonstrating some of the challenges associated with performing organic synthesis within micro fabricated devices.

4. Experimental procedures

4.1. Materials and methods

All materials (analytical reagent grade) were obtained from commercial suppliers and unless otherwise stated were used without further purification. Sodium hydride **65** (60% dispersion in mineral oil) was washed free of any mineral oil using *n*-hexane, to afford the purified reagent as a pale grey solid. Column chromatography was performed using Kieselgel silica gel 60 (Fluka) as the solid support and compounds eluted using mixtures of ethyl acetate and *n*-hexane of varying polarity. Thin-layer chromatography was carried out using Kieselgel 60, HF_{254} aluminium backed TLC plates (Merck), with mixtures of ethyl acetate and hexane as eluent. Visualisation was achieved using one of the following methods: exposure to short wave ultra violet light (λ 254 nm), or; development in an aqueous potassium permanganate (0.5%) and sodium carbonate (2.5%) solution, followed by heating with a hot air gun.

All NMR spectra were recorded as solutions in deuteriochloroform ($CDCl_3$) using tetramethylsilane (TMS) as an internal standard. The spectra were recorded on a Jeol GX400 spectrometer and the chemical shifts given in parts per million (ppm) with coupling constants in Hertz (Hz). The following abbreviations are used to report NMR data: s=singlet, d=doublet, t=triplet, q=quartet, dt=doublet of triplets, m=multiplet and C_0=quaternary carbon. Elemental analyses were performed using a Fisons Carlo Erba EA1108 CHN analyser. Infra-red spectra were recorded (4000–600 cm^{-1}) using a Perkin Elmer Paragon 1000 FT-IR spectrometer and peaks (ν_{max}) reported in wavenumbers (cm^{-1}). Gas-Chromatography–Mass Spectrometry (GC–MS) was performed using a Varian GC (CP-3800) coupled to a Varian MS (2000) with a CP-Sil 8 (30 m) column (Phenomenex) and ultra high purity helium (99.999%, Energas) carrier gas. Samples were analysed using one of the following methods. *Method A*. Injector temperature 200 °C, helium flow rate 1 ml min^{-1}, oven temperature 50 °C for 4 min then ramped to 250 °C at 30 °C min^{-1}, with a 3 min filament delay. *Method B*. Injector temperature 200 °C, helium flow rate 1 ml min^{-1}, oven temperature 50 °C for 1 min then ramped to 250 °C at 30 °C min^{-1}, with a 3 min filament delay. *Method C*. Injector temperature 250 °C, helium flow rate 1 ml min^{-1}, oven temperature 60 °C for 1 min then ramped to 270 °C at 35 °C min^{-1}, with a 3 min filament delay and. *Method D*. Injector temperature 250 °C, helium flow rate 1 ml min^{-1}, oven temperature 60 °C for 1 min then ramped to 270 °C at 20 °C min^{-1}, with a 3 min filament delay. All known compounds prepared had spectroscopic data consistent with the literature.

The electroosmotic micro reactions described herein were carried out using in-house fabricated borosilicate glass micro reactors with channel dimensions of 350 μm (wide)× 53 μm (deep). In order to minimise the effect of pressure gradients within the micro channels, micro porous silica frits were placed within the channels.[29] To mobilise

reagents by EOF, platinum electrodes (0.5 mm o.d.× 2.5 cm) were placed within the reagent reservoirs and voltages applied using a Paragon 3B high voltage power supply (capable of applying 0–1000 V to four outputs) (Kingfield electronics, Sheffield, UK). Automation of the HVPS using an in-house LabVIEW™ program enabled complex sequences of voltages to be investigated. To enable the results obtained to be applied to devices of different dimensions, voltages are reported as applied fields (V cm^{-1}), i.e. voltage/channel length. Prior to commencing an electroosmotic micro reaction, the micro channels were filled with anhydrous solvent in order to remove air from the micro porous silica frits and to ensure a complete circuit is formed.

The pressure driven micro reactions were performed using a device purchased from Micro Chemical Systems Ltd (Hull, UK), which consisted of a two layer borosilicate glass device with ceramic fittings (Macor) located over each of the etched micro channels (152 μm (wide)×51 μm (deep)). PTFE tubing (178 μm o.d.×2.5 cm (Supelco)) was attached to the micro reactor using PEEK microtight fittings (Upchurch Scientific); subsequent attachment to a gas-tight syringe (Hamilton) resulted in a pressure tight connection. In order to employ three input solutions and a single output, a PEEK microtee (Upchurch scientific) was incorporated into the system. The magnitude of flow was controlled using two displacement pumps (MD-1001, Bioanalytical Systems Inc.) capable of delivering fluid at flow rates of 1–100 μl min^{-1}. To monitor the progress of both EOF and pressure-driven micro reactions, experiments were conducted over a period of 20 min, after which the product reservoir was analysed by GC–MS, whereby comparison of the amount of residual starting material enabled the progression of the reaction to be determined.

4.2. Micro-scale methodology

4.2.1. Typical procedure for an electroosmotic micro reaction. After priming with THF, a standard solution of 'anhydrous' TBAF **1** (40 μl, 0.1 M) in anhydrous THF was placed in reservoir A, a solution of benzoyl cyanide **6** (40 μl, 1.0 M) in anhydrous THF was placed in reservoir B and a solution of trimethyl(1-phenylvinyloxy)silane **3** (40 μl, 1.0 M) in anhydrous THF was placed in reservoir C. The reaction products were manipulated within the device by applying an electric field to the platinum electrodes placed in each reservoir. In this case, the following applied fields were employed, 417, 318, 476 and 0 V cm^{-1}. The reaction products were collected in reservoir D, in anhydrous THF (40 μl), over a period of 20 min and analysed off-line by GC–MS. The progress of the reaction was subsequently determined by calculating the proportion of starting material converted to product (% conversion); 100% conversion to 1,3-diphenylpropane-1,3-dione **5** was observed in this case.

4.2.2. Electroosmotic flow regimes. *Flow Regime A*: Application of a constant applied field is referred to as continuous flow (unless otherwise stated this flow regime was employed); *Flow Regime B*: In this case, the field is applied for 2.5 s and no field for 5 s, the steps are subsequently cycled over a period of 20 min; *Flow Regime C*: As for Flow Regime B, with an applied field for 5 s and no field for 10 s.

4.3. Batch reactions

4.3.1. 'Anhydrous' tetra-*n*-butylammonium fluoride 1. Tetra-*n*-butylammonium fluoride trihydrate (TBAF·$3H_2O$) **73** was dried over phosphorus pentoxide under vacuum (10 mmHg) for 48 h to afford 'anhydrous' TBAF **1** as a gelatinous, colourless solid.

4.3.2. General procedure 1: synthesis of silyl enol ethers. The ketone in THF (2 ml per mmol) was added dropwise to a stirred solution of LiHMDS **51** (1.1 equiv) in THF (10 ml per mmol) over a period of 30 min at room temperature. The resulting solution was stirred for a further 15 min prior to the addition of chlorotrimethylsilane **74** (1.0 equiv) in THF (1 ml per mmol). In order to remove any residual inorganic material, the reaction mixture was concentrated in vacuo and the residue dissolved in DCM (5 ml per mmol). The reaction mixture was then filtered and the filtrate concentrated in vacuo to afford the silyl enol ether, which was stored at −10 °C and used without further purification.

4.3.3. General procedure 2: acylation using acyl halides. The silyl enol ether in anhydrous THF (2 ml per mmol) was added dropwise to a stirred solution of 'anhydrous' TBAF **1** (0.1 equiv) and acyl halide (1.0 equiv) in anhydrous THF (10 ml per mmol) under N_2, over a period of 30 min. After stirring for a further 30 min, the reaction mixture was concentrated in vacuo prior to the addition of dilute NaOH (50 ml, 0.1 M). The reaction products were extracted into ethyl acetate (3×50 ml) and the combined organic extracts were dried ($MgSO_4$), prior to concentrating in vacuo. The product was subsequently purified by silica gel chromatography.

4.3.4. General procedure 3: acylation of using acyl cyanides. The silyl enol ether in anhydrous THF (2 ml per mmol) was added dropwise to a stirred solution of 'anhydrous' TBAF **1** (0.1 equiv) and acyl cyanide (1.0 equiv) in anhydrous THF (10 ml per mmol) under N_2, over a period of 30 min. After stirring overnight, the reaction mixture was concentrated in vacuo prior to the addition of dilute NaOH (50 ml, 0.1 M). The reaction products were extracted into ethyl acetate (3×50 ml) and the combined organic extracts were dried ($MgSO_4$), prior to concentrating in vacuo. The product was subsequently purified by silica gel chromatography.

4.3.5. General procedure 4: aldol reaction of silyl enol ethers. The silyl enol ether in anhydrous THF (2 ml per mmol) was added dropwise to a stirred solution of 'anhydrous' TBAF **1** (0.1 equiv) and 4-bromobenzaldehyde **12** (1.0 equiv) in anhydrous THF (10 ml per mmol) under N_2, over a period of 30 min. After stirring overnight, the reaction mixture was concentrated in vacuo prior to the addition of distilled water (50 ml). The reaction products were extracted into ethyl acetate (3×50 ml) and the combined organic extracts were dried ($MgSO_4$), prior to concentrating in vacuo. The product was subsequently purified by silica gel chromatography.

4.3.6. General procedure 5: Michael addition. The 1,3-diketone in absolute EtOH (4 ml per mmol) was added to a stirred solution of Michael acceptor (1.0 equiv) and diisopropylethylamine **16** (2 equiv) in absolute EtOH (5 ml per mmol) and the reaction mixture stirred overnight. The reaction mixture was concentrated in vacuo and subsequently purified by silica gel chromatography to afford the respective product.

4.3.7. General procedure 6: Knoevenagel condensation. 3-(1-Piperazino)propyl-functionalised silica gel **26** (1.9 mmol N g^{-1}, 200–400 mesh) (0.10 g, 0.1 mmol) was added to a stirred solution of activated methylene (1.0 mmol) and aldehyde (1.0 mmol) in anhydrous MeCN (10 ml per mmol). After stirring overnight, the reaction mixture was filtered and the filtrate concentrated in vacuo to afford the respective condensation product.

4.3.8. Trimethyl(1-phenylvinyloxy)silane 3.[8] The reaction was carried out in accordance with general procedure 1 using acetophenone **15** (0.50 g, 4.13 mmol), LiHMDS **51** (0.77 g, 4.58 mmol) and chlorotrimethylsilane **74** (0.39 ml, 4.13 mmol) to give trimethyl(1-phenylvinyloxy)silane **3** (0.79 g, 98.0%) as a pale yellow oil; GC–MS retention time (Method A) R_T=8.55 min.

4.3.9. Benzoic acid 1-phenylvinyl ester 4.[8] The reaction was carried out in accordance with general procedure 2 using trimethyl(1-phenylvinyloxy)silane **3** (0.10 g, 0.52 mmol), TBAF **1** (0.014 g, 0.05 mmol) and benzoyl fluoride **2** (0.06 ml, 0.52 mmol) to afford benzoic acid 1-phenylvinyl ester **4** (0.12 g, 99.0%) as a pale yellow oil; GC–MS retention time (Method A) R_T=11.36 min.

4.3.10. 1,3-Diphenylpropane-1,3-dione 5.[8,61] The reaction was carried out in accordance with general procedure 3 using trimethyl(1-phenylvinyloxy)silane **3** (0.10 g, 0.52 mmol), TBAF **1** (0.02 g, 0.05 mmol) and benzoyl cyanide **6** (0.07 g, 0.59 mmol) to afford 1,3-diphenylpropane-1,3-dione **5** (0.11 g, 98.0%) as a white solid; GC–MS retention time (Method A) R_T=12.67 min.

4.3.11. Trimethyl(1-phenylpropenyloxy)silane 7.[8,62] The reaction was carried out in accordance with general procedure 1 using propiophenone **75** (1.00 g, 7.48 mmol), LiHMDS **51** (1.37 g, 8.21 mmol) and chlorotrimethylsilane **74** (1.04 ml, 7.48 mmol) to give trimethyl(1-phenylpropenyloxy)silane **7** (1.47 g, 96.0%) as a pale yellow oil; GC–MS retention time (Method A) R_T=8.92 min.

4.3.12. Cyclohex-1-enyloxy(trimethylsilane) 8.[8,37] The reaction was carried out in accordance with general procedure 1 using cyclohexanone **49** (1.00 g, 10.20 mmol), LiHMDS **51** (1.88 g, 11.22 mmol) and chlorotrimethylsilane **74** (0.95 ml, 10.20 mmol) to afford cyclohex-1-enyloxy(trimethylsilane) **8** (1.60 g, 93.0%) as a pale yellow oil; GC–MS retention time (Method A) R_T=7.40 min.

4.3.13. 2-Methyl-1,3-diphenylpropane-1,3-dione 9.[8,61] The reaction was carried out in accordance with general procedure 2 using trimethyl(1-phenylpropenyloxy)silane **7** (0.10 g, 0.48 mmol), TBAF **1** (0.013 g, 0.05 mmol) and benzoyl fluoride **2** (0.07 ml, 0.48 mmol) to afford 2-methyl-1,3-diphenylpropane-1,3-dione **9** (0.11 g, 96.0%) as a pale yellow oil; GC–MS retention time (Method A) R_T=11.67 min.

4.3.14. 2-Benzoylcyclohexanone 10.[8,63] The reaction was carried out in accordance with general procedure 2 using cyclohex-1-enyloxy(trimethylsilane) **6** (0.10 g, 0.59 mmol), TBAF **1** (0.0015 g, 0.06 mmol) and benzoyl fluoride **2** (0.06 ml, 0.59 mmol) to give 2-benzyloxycyclohexanone **10** (0.12 g, 99.0%) as a white solid; GC–MS retention time (Method A) R_T=11.20 min.

4.3.15. 2-Benzoylcyclohexanone 10.[8,63] The reaction was carried out in accordance with general procedure 3 using cyclohex-1-enyloxy(trimethylsilane) **8** (0.10 g, 0.59 mmol), TBAF **1** (0.0015 g, 0.06 mmol) and benzoyl cyanide **6** (0.08 g, 0.59 mmol) to give 2-benzyloxycyclohexanone **10** (0.11 g, 94.0%) as a white solid; GC–MS retention time (Method A) R_T=11.20 min.

4.3.16. 3-(4-Bromophenyl)-3-hydroxy-1-phenylpropan-1-one 11.[64] The reaction was carried out in accordance with general procedure 4 using trimethyl(1-phenylvinyloxy) silane **3** (0.09 g, 0.48 mmol), TBAF **1** (0.013 g, 0.048 mmol) and 4-bromobenzaldehyde **12** (0.09 g, 0.48 mmol) to afford 3-(4-bromophenyl)-3-hydroxy-1-phenylpropan-1-one **11** (0.13 g, 87.0%) as a white crystalline solid; GC–MS retention time (Method A) R_T=14.71 min.

4.3.17. 2-[(4-Bromophenyl)hydroxymethyl]cyclohexanone 13.[65] The reaction was carried out in accordance with general procedure 4 using cyclohex-1-enyloxy(trimethylsilane) **7** (0.11 g, 0.65 mmol) and 4-bromobenzaldehyde **12** (0.12 g, 0.65 mmol) to afford 2-[(bromophenyl)hydroxymethyl]cyclohexanone **13** (0.16 g, 94.0%) as a cream solid; δ_H 1.31 (1H, m, CH), 2.33 (1H, m, CH), 1.51 (1H, m, CH), 1.71 (1H, m, CH), 1.86 (3H, m, 3×CH), 2.08 (1H, m, CH), 2.33 (1H, m, CHOH), 7.69 (2H, d, J=6.8 Hz, Ar) and 7.74 (2H, d, J=6.8 Hz, Ar); δ_C 24.8 (CH_2), 27.0 (CH_2), 27.7 (CH_2), 30.7 (CH_2), 42.6 (CH), 67.9 (CHOH), 127.5 (2× CH), 128.6 (2×CH), 131.4 (C_0), 140.4 (C_0Br) and 191.1 (CO); 267 (M^++1, 15%), 266 (60), 264 (55) and 185 (100); GC–MS retention time (Method A) R_T=12.45 min.

4.3.18. (*E*)-4-Acetyl-5-oxohex-2-enoic acid ethyl ester 17. The reaction was carried out in accordance with general procedure 5 using 2,4-pentanedione **18** (0.50 g, 5.00 mmol), diisopropylethylamine **16** (1.29 g, 10.00 mmol) and ethyl propiolate (0.49 g, 5.00 mmol). The reaction mixture was concentrated in vacuo and subsequently purified by silica gel chromatography. Elution with 7% ethyl acetate in hexane afforded (*E*)-4-acetyl-5-oxohex-2-enoic acid ethyl ester **17** (0.88 g, 89.0%) as a colourless oil. (Found C, 60.78; H, 7.25, $C_{10}H_{14}O_4$ requires C, 60.60; H, 7.12%); υ_{max}/cm^{-1} 1667, 1703, 1740 and 2970; δ_H 1.34 (3H, t, J=7.0 Hz, CH_2CH_3), 2.13 (6H, s, CH_3), 4.24 (2H, q, J=7.0 Hz, CH_2CH_3), 4.24 (1H, J=7.0 Hz, COCHCO), 5.74 (1H, d, J=16.9 Hz, CH) and 7.39 (1H, d, J=16.9 Hz, CH); δ_C 14.3 (2×CH_3), 18.5 (CH_2CH_3), 61.6 (CH_2CH_3), 61.8 (COCHCO), 125.4 (CH), 141.8 (CH), 165.4 (2×CO) and 203.5 (CO_2); 199 (M^++1, 15%), 198 (27), 181 (20), 153

(30), 124 (100) and 109 (20); GC–MS retention time (Method B) $R_T = 10.21$ min (trans).

4.3.19. (*E*)-4-Benzoyl-5-oxohex-2-enoic acid ethyl ester 21. The reaction was carried out in accordance with general procedure 5 using 1-phenylbutane-1,3-dione **20** (0.25 g, 1.54 mmol), ethyl propiolate **19** (0.15 g, 1.54 mmol) and diisopropylethylamine **16** (0.40 g, 3.00 mmol). The reaction mixture was concentrated in vacuo and subsequently purified by silica gel chromatography. Elution with 5% ethyl acetate in hexane afforded (*E*)-4-benzoyl-5-oxohex-2-enoic acid ethyl ester **21** (0.31 g, 77.0%) as a pale yellow oil. (Found C, 69.48; H, 6.42, $C_{15}H_{16}O_4$ requires C, 69.22; H, 6.20%); υ_{max}/cm^{-1} 1183, 1676, 1721 and 2929; δ_H 1.34 (3H, t, $J=7.3$ Hz, CH_2CH_3), 1.96 (3H, s, CH_3), 4.23 (3H, m, CH_2CH_3 and COCHCO), 5.47 (1H, d, $J=16.8$ Hz, CH), 7.69 (1H, d, $J=16.8$ Hz, CH), 7.70 (1H, m, Ar), 7.80 (2H, m, Ar) and 7.93 (2H, m, Ar); δ_C 14.2 (CH_3), 19.1 (CH_2CH_3), 60.7 (CH_2CH_3), 96.7 (COCCO), 125.2 (CH), 128.6 (2×CH), 128.7 (2×CH), 129.7 (CH), 135.2 (C_0), 142.9 (CH), 165.5 (CO), 195.8 (CO) and 204.2 (CO_2); 261 ($M^+ + 1$, 10%), 260 (15), 181 (40) and 105 (100); GC–MS retention time (Method C) $R_T = 12.45$ min.

4.3.20. (*E*)-4-Ethoxycarbonylpent-2-enedioic acid ethyl ester 23. The reaction was carried out in accordance with general procedure 5 using diethyl malonate **22** (0.50 g, 3.10 mmol), ethyl propiolate **19** (0.30 g, 3.10 mmol) and diisiopropylethylamine **16** (0.80 g, 6.20 mmol). The reaction mixture was concentrated in vacuo and subsequently purified by silica gel chromatography. Elution with 5% ethyl acetate in hexane afforded (*E*)-4-ethoxycarbonylpent-2-enedioic acid ethyl ester **23** (0.60 g, 82.5%) as a colourless oil; δ_H 1.29 (9H, t, $J=7.4$ Hz, 3×CH_2CH_3), 4.19–4.27 (7H, m, 3×CH_2CH_3 and COCHCO), 5.88 (1H, d, $J=16.4$ Hz, CH) and 7.28 (1H, d, $J=16.4$ Hz, CH); δ_C 18.6 (3×CH_2CH_3), 61.5 (3×CH_2CH_3), 64.0 (COCHCO), 123.5 (CH), 143.0 (CH), 169.1 (2×CO) and 203.5 (CO_2); 259 ($M^+ + 1$, 5%), 258 (15), 257 (50), 255 (95), 227 (100), 212 (80), 182 (23), 167 (50), 109 (40) and 81 (15);GC–MS retention time (Method B) $R_T = 10.85$ min.

4.3.21. 3-Acetylheptane-2,6-dione 25. The reaction was carried out in accordance with general procedure 5 using 2,4-pentanedione **18** (0.50 g, 5.00 mmol), methyl vinyl ketone **24** (0.35 g, 5.00 mmol) and diisopropylethylamine **16** (1.29 g, 10.00 mmol). The reaction mixture was concentrated in vacuo and subsequently purified by silica gel chromatography. Elution with 10% ethyl acetate in hexane afforded 3-acetylheptane-2,6-dione **25** (0.77 g, 91.0%) as a colourless oil; δ_H 2.08 (2H, dt, $J=7.0$, 7.0 Hz, CH_2), 2.10 (3H, s, CH_3), 2.20 (6H, s, CH_3), 2.46 (2H, t, $J=7.0$ Hz, CH_2CO) and 3.39 (1H, t, $J=7.0$ Hz, COCHCO); δ_C 29.3 (2×CH_3), 30.0 (CH_3), 37.9 (CH_2), 40.5 (CH_2CO), 66.9 (COCHCO), 204.2 (2×CO) and 207.1 (CO); 171 ($M^+ + 1$, 5%), 170 (1), 153 (15), 128 (25), 110 (20), 95 (40) and 43 (100); GC–MS retention time (Method B) $R_T = 8.79$ min.

4.3.22. 2-Cyano-3-phenyl-acrylic acid ethyl ester 29.[66] The reaction was carried out in accordance with general procedure 6 using benzaldehyde **27** (0.106 g, 1.00 mmol), ethyl cyanoacetate **28** (0.113 g, 1.00 mmol) and 3-(1-piperazino)propyl functionalised silica gel (0.100 g, 0.10 mmol) to afford the product **29** (0.195 g, 97.0%) as a white crystalline solid; GC–MS retention time (Method C) $R_T = 6.63$ min.

4.3.23. 2-Benzylcyclohexanone 47.[67] Cyclohexanone **49** (0.50 g, 5.10 mmol) in THF was added dropwise to a stirred solution of KO^{t}Bu **55** (0.63 g, 5.61 mmol) in THF (100 ml) over a period of 30 min to afford a yellow enolate solution. The reaction mixture was stirred for a further 15 min prior to the addition of benzyl bromide **50** (0.61 ml, 5.10 mmol). After stirring overnight, the reaction mixture was concentrated in vacuo and the residual oil dissolved in ethyl acetate (50 ml) and washed with distilled water (50 ml). The aqueous layer was further extracted using ethyl acetate (2×50 ml) and the combined organic extracts dried ($MgSO_4$) and concentrated in vacuo. Purification was achieved by silica gel chromatography, whereby elution with 2.5% ethyl acetate in hexane afforded 2-benzylcyclohexanone **47** (0.85 g, 89.0%) as a pale yellow oil; GC–MS retention time (Method C) $R_T = 10.36$ min.

4.3.24. 2,2-Dibenzylcyclohexanone 48.[68] Cyclohexanone **49** (0.25 g, 2.60 mmol) in THF (10 ml) was added dropwise to a stirred solution of KO^{t}Bu **55** (0.63 g, 5.61 mmol) in THF (100 ml) over a period of 30 min to afford a yellow enolate solution. The reaction was stirred for a further 15 min prior to the addition to the addition of benzyl bromide **50** (0.61 ml, 5.10 mmol). After stirring overnight, the reaction mixture was concentrated in vacuo and the residual oil dissolved in ethyl acetate (50 ml) and washed with water (50 ml). The aqueous layer was further extracted using ethyl acetate (2×50 ml) and the combined organic extracts and the combined organic extracts dried ($MgSO_4$). Purification was achieved by silica gel chromatography, whereby elution with 20% ethyl acetate in hexane afforded 2,2-dibenzylcyclohexanone **48** (0.71 g, 85.0%) as a yellow oil; GC–MS retention time (Method A) $R_T = 14.50$ min.

4.3.25. Benzyloxybenzene 67.[69] NaH **65** (0.13 g, 5.33 mmol) in THF (10 ml) was added dropwise to a stirred solution of phenol **66** (0.50 g, 5.32 mmol) in THF (50 ml) and stirred for 5 min prior to the addition of benzyl bromide **50** (0.63 ml, 5.32 mmol). After stirring overnight, the reaction mixture was concentrated in vacuo and the residue diluted with DCM (50 ml) prior to washing with dilute sodium hydroxide (50 ml, 0.1 M). The aqueous layer was further extracted using DCM (2×50 ml) and the combined organic extracts dried ($MgSO_4$) and concentrated in vacuo. Purification was achieved by silica gel chromatography, whereby elution with 11% ethyl acetate in hexane afforded benzyloxybenzene **67** (0.70 g, 71.0%) as a pale yellow oil; GC–MS retention time (Method A) $R_T = 10.14$ min.

4.3.26. 4-Methyl-5-phenyloxazolidin-2-one 71.[70] Diphenyl carbonate **76** (10.60 g, 49.49 mmol), (1*S*, 2*R*) (+) norephedrine hydrochloride **77** (8.44 g, 44.97 mmol) and anhydrous potassium carbonate **78** (6.84 g, 49.49 mmol) were stirred at 100 °C for 6 h. The reaction mixture was subsequently cooled to 70 °C, methanol (100 ml) was added and the mixture heated to reflux for a further 30 min. The reaction mixture was concentrated in vacuo and subjected to an aqueous work up. The product was dissolved into DCM

(1×150 ml) and the organic layer washed with sodium hydroxide (2×150 ml, 1.0 M) and hydrochloric acid (2×150 ml, 1.0 M). The organic extract was subsequently dried ($MgSO_4$) and concentrated in vacuo to afford 4-methyl-5-phenyloxazolidin-2-one **71** (5.96 g, 75.0%) as an analytically pure light brown solid, which was used without further purification; GC–MS retention time (Method B) R_T=8.54 min.

4.3.27. 4-Methyl-5-phenyl-3-propionyloxazolidin-2-one 68.[71] *n*-Butyllithium **44** in hexane (4.97 ml, 2.5 M, 12.43 mmol) was added dropwise to a stirred solution of 4-methyl-5-phenyloxazolidin-2-one **71** (2.00 g, 11.30 mmol) in THF (50 ml) under N_2. The solution was maintained at −78 °C for 30 min prior to the addition of propionyl chloride **79** (1.96 ml, 22.47 mmol) and the reaction mixture warmed to room temperature and stirred overnight. The reaction mixture was concentrated in vacuo and subjected to an aqueous work up. The organic layer was neutralised using sodium hydrogen carbonate and the product extracted into DCM (3×50 ml), the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by silica gel chromatography (9% ethyl acetate in hexane) afforded the title compound **68** (2.58 g, 98.0%) as a pale yellow gum; GC–MS retention time (Method B) R_T=8.82 min.

4.3.28. (2′*S*,4*R*,5*S*)-2-(2′-methyl-3′-phenylpropionyl-4-methyl)-5-phenyloxazolidin-2-one 69.[58] NaHMDS **52** (2.63 ml, 1.0 M, 2.63 mmol) was added dropwise to a stirred solution of 4-methyl-5-phenyl-3-propionyloxazolidin-2-one **68** (0.50 g, 2.15 mmol) in THF (50 ml) under N_2 at −78 °C, the enolate was formed over a period of 20 min prior to the addition of benzyl bromide **50** (0.31 ml, 2.60 mmol). The reaction mixture was maintained at −78 °C for 40 min prior to quenching with distilled water (10 ml). The reaction mixture was concentrated in vacuo and subjected to an aqueous work up. The reaction products were extracted into DCM (4×50 ml), dried ($MgSO_4$) and concentrated in vacuo to afford a pale yellow oil. Purification was achieved by silica gel chromatography (10% ethyl acetate in hexane) to afford the diastereomer **69** (0.48 g, 59.0%) as a pale yellow oil; GC–MS retention time (Method B) R_T=12.16 min.

4.4. Micro-scale reactions[10]

4.4.1. 2-Cyano-3-phenyl acrylic acid ester 29.[66] White solid (0.025 g, 98.9%); GC–MS retention time (Method C) R_T=6.63 min.

4.4.2. 3-(4-Bromophenyl)-2-cyano acrylic acid ethyl ester 32.[72] White solid (0.012 g, 99.5%); GC–MS retention time (Method D) R_T=10.84 min.

4.4.3. 3-(3,5-Dimethoxyphenyl)-2-cyano acrylic acid ethyl ester 33.[73] White solid (0.011 g, 99.5%); δ_H 1.40 (3H, t J=7.0 Hz, CH_2CH_3), 3.85 (6H, s, 2×OCH_3), 4.39 (2H, q, J=7.0 Hz, CH_2CH_3), 6.65 (1H, m, Ar), 7.15 (2H, m, Ar) and 8.17 (1H, s, CH); δ_C 14.2 (CH_3), 55.7 (2×OCH_3), 62.8 (CH_2), 103.4 (C_0CN), 106.2 (CH), 108.6 (2×CH), 115.6 (CN), 133.1 (C_0), 155.2 (CH), 161.1 (2×C_0) and 162.5 (CO); 262 (M^++1, 20%), 261 (100), 189 (55), 161 (25) and 77 (10); GC–MS retention time (Method C) R_T=8.06 min.

4.4.4. 3-(4-Benzyloxyphenyl)-2-cyano acrylic acid ethyl ester 34. (0.021 g, 99.1%) as a cream solid (Found C, 74.51; H, 5.77; N 4.62, $C_{19}H_{17}O_3N$ requires C, 74.25; H, 5.58; N, 4.56%); δ_H 1.39 (3H, t, J=7.3 Hz, CH_2CH_3), 4.37 (2H, q, J=7.3 Hz, CH_2CH_3), 5.15, (2H, s, CH_2), 7.00 (2H, d, J=8.7 Hz, Ar), 7.40 (5H, m, Ar), 7.99 (2H, d, J=8.7 Hz, Ar) and 8.17 (1H, s, CH); δ_C 14.2 (CH_3), 62.5 (CH_2), 70.4 (C_0CN), 77.8 (CH_2O), 99.5 (C_0), 115.6 (2×CH), 124.6 (CN), 127.5 (2×CH), 128.4 (CH), 128.8 (2×CH), 133.7 (2×CH), 135.8 (C_0), 154.4, (CH), 162.9 (OC_0) and 163.1 (CO); 308 (M^++1, 5%), 307 (20), 91 (100) and 65 (20); GC–MS retention time (Method D) R_T=12.35 min.

4.4.5. 2-Benzylidene-malononitrile 36[66] Pale yellow solid (0.015 g, 100%); GC–MS retention time (Method C) R_T=5.84 min.

4.4.6. 2-(4-Bromobenzylidene)-malononitrile 37.[74] Pale yellow solid (0.035 g, 99.9%); GC–MS retention time (Method D) R_T=9.65 min.

4.4.7. 2-(3,5-Dimethoxybenzylidene)-malononitrile 38.[66] Yellow solid (0.024 g, 99.2%); GC–MS retention time (Method C) R_T=7.50 min.

4.4.8. 2-(4-Benzyloxybenzylidene)-malononitrile 39.[75] Pale yellow solid (0.024 g, 99.6%); GC–MS retention time (Method D) R_T=11.97 min.

Acknowledgements

We wish to thank Novartis Pharmaceuticals (P.W. and C.W.) and the EPSRC (C.W.) (Grant No. GR/S34106/01) for financial support. We are grateful to Dr. Tom McCreedy and Mr. Mike Bailey (The University of Hull) for help in fabricating the micro reactor devices.

References and notes

1. Gisin, M.; Thommen, C. *Anal. Chim. Acta* **1986**, *190*, 165–176.
2. Schwalbe, T.; Volker, A.; Wille, G. *Chimia* **2002**, *56*, 636–646.
3. Jahnisch, K.; Hessel, V.; Löwe, H.; Baerns, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 406–446.
4. Fletcher, P. D. I.; Haswell, S. J.; Pombo-Villar, E.; Warrington, B. H.; Watts, P.; Wong, S. Y. F.; Zhang, X. *Tetrahedron* **2002**, *58*, 4735–4757.
5. Watts, P.; Haswell, S. J. *Chem. Soc. Rev.* **2005**, *34*, 235–246.
6. Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *Lab Chip* **2002**, *2*, 62–64.
7. Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *Chem. Commun.* **2002**, 1034–1035.
8. Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *Tetrahedron Lett.* **2002**, *43*, 2945–2948.

9. Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *Lab Chip* **2001**, *1*, 100–101.
10. Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *Tetrahedron* **2004**, *60*, 8421–8427.
11. Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *Lab Chip* **2004**, *4*, 171–173.
12. Ehrfeld, W.; Hessel, V.; Löwe, H. *Microreactors: New Technology for Modern Chemistry*; Wiley-VCH: New York, 2000.
13. McCreedy, T. *Anal. Chim. Acta* **2001**, *427*, 39–43.
14. (a) Reyes, D. R.; Iossifidis, D.; Auroux, P. A.; Manz, A. *Anal. Chem.* **2002**, *74*, 2626–2636. (b) Reyes, D. R.; Iossifidis, D.; Auroux, P. A.; Manz, A. *Anal. Chem.* **2002**, *74*, 2637–2652. (c) Woias, P. In *Microfluidics and BioMEMS*, Mastrangelo, C. H.; Becker, H., Eds. SPIE Conference Proceedings 2001, **2001**, 4560, 39.
15. Manz, A.; Fettinger, J. C.; Ludi, H.; Widmer, H. M.; Harrison, J. D. *Trends Anal. Chem.* **1991**, *10*, 144–149.
16. Dasgupta, P. K.; Lui, S. *Anal. Chem.* **1994**, *66*, 1792–1798.
17. Seller, K.; Fan, Z. H.; Fluri, K.; Harrison, D. J. *Anal. Chem.* **1994**, *66*, 3485–3491.
18. Manz, A.; Effenhauser, C. S.; Buggraf, N.; Harrison, J. D.; Seiler, K.; Fluri, K. *J. Micromech. Microeng.* **1994**, *4*, 257.
19. Boer, G.; Dodge, A.; Fluri, K.; van der Schoot, H.; Verpoorte, E.; de Rooji, N. F. In *Micro Total Analysis Systems*; Ramsey, J. M., van den Berg, A., Eds.; Kluwer: Dordecht, 1998; pp 53–56.
20. Christensen, P. D.; Johnson, S. W. P.; McCreedy, T.; Skelton, V.; Wilson, N. G. *Anal. Commun.* **1998**, *35*, 341–342.
21. Zeng, S.; Chen, C.; Mikkelsen, J. C., Jr.; Santiago, J. G. *Sens. Actuators, B* **2001**, *79*, 107–114.
22. Fletcher, P. D. I.; Haswell, S. J.; Zhang, X. *Lab Chip* **2002**, *2*, 102–112.
23. Rice, C. L.; Whitehead, R. *J. Phys. Chem.* **1965**, *69*, 4017–4024.
24. Haswell, S. J.; Middleton, R. J.; O'Sullivan, B.; Skelton, V.; Watts, P.; Styring, P. *J. Chem. Soc., Chem. Commun.* **2001**, 391–398.
25. Snyder, L. R. *J. Chromatogr. A* **1974**, *92*, 223–230.
26. Smits, J. G. *Sens. Actuators, A* **1990**, *21*, 203–206.
27. Makino, E.; Mitsuya, T.; Shibata, T. *Sens. Actuators, A* **2001**, *88*, 256–262.
28. Shoji, S.; Nakagakawa, S.; Esashi, M. *Sens. Actuators, B* **1990**, *21*, 189–192.
29. (a) Bings, N. H.; Wang, C.; Skinner, C. D.; Colyer, C. L.; Thibault, P.; Harrison, D. J. *Anal. Chem.* **1999**, *71*, 3292–3926. (b) Nittis, V.; Fortt, R.; Legge, C. H.; de Mello, A. J. *Lab Chip* **2001**, *1*, 148–152.(c) Gray, B. L.; Collins, S. D.; Smith, R. L. In *Micro total analysis systems*, Ramsey, J. M., van den Berg, A., Eds. Kluwer: Enschede, 2001; Vol. 1, pp 153–158.
30. Kikuntani, Y.; Hibara, A.; Uchiyama, K.; Hisamoto, H.; Tokeshi, M.; Kitamori, T. *Lab Chip* **2002**, *2*, 193–196.
31. House, H.; Auerbach, R. A.; Gall, M.; Peet, P. *J. Org. Chem.* **1972**, *38*, 514–522.
32. Deitch, J.; Rathke, M. W. *Tetrahedron Lett.* **1971**, *12*, 2953–2956.
33. Rathke, M. W.; Tirpak, R. E. *J. Org. Chem.* **1982**, *47*, 5099–5102.
34. (a) Kuwajima, I.; Nakamura, E. *Acc. Chem. Res.* **1985**, *18*, 181–187. (b) Kuwajima, I.; Nakamura, E.; Hashimoto, K. *Org. Synth.* **1982**, *61*, 122–128.
35. Noyori, R.; Yokoyma, K.; Sakata, J.; Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **1977**, *97*, 1265–1266.
36. Howard, A. S.; Meerholz, C. A.; Michael, J. P. *Tetrahedron Lett.* **1979**, *15*, 1339–1340.
37. House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324–2336.
38. Veysoglu, T.; Mitscher, L. A. *Tetrahedron Lett.* **1981**, *22*, 1299–1302.
39. Morita, T.; Okamoto, Y.; Sakurai, H. *Tetrahedron Lett.* **1980**, *21*, 835–838.
40. Kita, Y.; Haruta, J.; Segawa, J.; Tamura, Y. *Tetrahedron Lett.* **1979**, *20*, 4311–4314.
41. Nakamra, E.; Murofushi, T.; Shimizu, M.; Kuwajima, I. *J. Am. Chem. Soc.* **1976**, *98*, 2346–2348.
42. LeBel, N. A.; Cherluck, R. M.; Curtius, E. A. *Synthesis* **1973**, 678–679.
43. Cooke, M. P., Jr.; Pollock, C. M. *J. Org. Chem.* **1993**, *58*, 7474–7481.
44. Picquet, M.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron* **1999**, *55*, 3937–3948.
45. Oediger, H.; Moller, F.; Eiter, K. *Synthesis* **1972**, 591–598.
46. Flynn, K. G.; Nenortas, D. R. *J. Org. Chem.* **1963**, *28*, 3527–3530.
47. Barton, D. H. R.; Elliot, J. D.; Gero, S. D. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2085–2090.
48. Schwesinger, R.; Willaredt, J.; Schlemper, H.; Keller, M.; Schmidt, D.; Fritz, H. *Chem. Ber.* **1994**, *127*, 2435–2454.
49. Schwesinger, R.; Schlemper, H.; Hasenfratz, C.; Willaredt, J.; Dambacher, T.; Breuer, T.; Ottaway, C.; Fletschinger, M.; Boele, J.; Fritz, H.; Putzas, D.; Roter, H. W.; Bordwell, F. G.; Satish, A. V.; Ji, J.; Peters, E.; Peters, K.; von Schnering, H. G.; Walz, L. *Liebigs Ann. Chem.* **1996**, 1055–1081.
50. Schwesinger, R.; Hasenfratz, C.; Schlemper, H.; Walz, E.; Peters, E.; Peters, K.; von Schnering, H. G. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1361–1363.
51. Schwesinger, R. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1164–1167.
52. In addition, we investigated the manipulation of a stronger phosphazene derivative, P_4-*t*-Bu **46** (0.25 M in anhydrous THF), by EOF. Application of 417 V cm^{-1}, resulted in the successful mobilisation of the reagent at a flow rate of 0.15 μl min^{-1}. Analysis of the product reservoir by TLC confirmed the successful transfer of P_4-*t*-Bu **46** from reservoir B–D.
53. O'Donnell, M. J.; Zhou, C.; Scott, W. L. *J. Am. Chem. Soc.* **1996**, *118*, 6070–6071.
54. (a) Skelton, V. *An Investigation of Synthetic and Combinatorial Reactions in Miniaturised Devices*. PhD Thesis, The University of Hull, **2000**, 114. (b) Skelton, V.; Greenway, G. M.; Haswell, S. J.; Styring, P.; Morgan, D. O.; Warrington, B. H.; Wong, S. Y. F. *Analyst* **2001**, *126*, 7–10. (c) Skelton, V.; Greenway, G. M.; Haswell, S. J.; Styring, P.; Morgan, D. O.; Warrington, B. H.; Wong, S. Y. F. *Analyst* **2001**, *126*, 11–13.
55. Pederson, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017–7036.
56. Alternatively micro-scale reactions could be performed in an inert atmosphere, i.e. glove-box purged with N_2.
57. Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.
58. Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737–1739.
59. Ehrfeld, W.; Hessel, V.; Löwe, H. *Microreactors: New Technology for Modern Chemistry*; Wiley-VCH: New York, 2000.
60. Suga, S.; Okajima, M.; Fujiwara, K.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 7941–7942.

61. Barluenga, J.; Jardon, J.; Gotor, V. *J. Org. Chem.* **1985**, *50*, 802–804.
62. Heathcock, C. H.; Buse, C. T.; Kieschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066–1081.
63. Hermanson, J. R.; Gunther, M. L.; Michael, I.; Belletine, J. L.; Pinhas, A. R. *J. Org. Chem.* **1995**, *60*, 1900–1903.
64. Marx, A.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 178–182.
65. Huitric, A. C.; Kumler, W. D. *J. Am. Chem. Soc.* **1956**, *78*, 1147–1151.
66. Choudray, B. M.; Lakshmi-Kantam, M.; Kavita, B.; Venkat Reddy, C.; Figueras, F. *Tetrahedron* **2000**, *56*, 9357–9364.
67. House, H. O.; Gall, M.; Holmstead, H. D. *J. Org. Chem.* **1971**, *36*, 2361–2371.
68. Bates, R. B.; Taylor, S. R. *J. Org. Chem.* **1993**, *58*, 4469–4470.
69. Forrestor, J.; Ray, R. V. H.; Newton, L.; Preston, N. P. *Tetrahedron* **2001**, *57*, 2871–2884.
70. Evans, D. A.; Matre, D. J. *J. Org. Chem.* **1985**, *50*, 1830–1835.
71. Pettit, G. R.; Burkett, D. D.; Barkoczy, J.; Breneman, G. L.; Pettit, W. E. *Synthesis* **1996**, 719–725.
72. Shen, Y.; Yang, B. *Synth. Commun.* **1989**, 3069–3072.
73. Arya, V. P.; Ghate, S. P. *Indian J. Chem.* **1971**, *9*, 1209–1212.
74. Obrador, E.; Castro, M.; Tamariz, J.; Zepeda, G.; Miranda, R. *Synth. Commun.* **1998**, 4649–4664.
75. Cornelis, A.; Lambert, S.; Laszlo, P. *J. Org. Chem.* **1977**, *42*, 381–382.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 61 (2005) 10774–10780

Facile synthesis and regioselective thio-Claisen rearrangements of 5-prop-2-ynyl/enyl-sulfanyl pyrimidinones: transformation to thienopyrimidinones

Chander Mohan, Parvesh Singh and M. P. Mahajan*

Department of Applied Chemistry, Guru Nanak Dev University, Amritsar 143005, Punjab, India

Received 11 March 2005; revised 29 July 2005; accepted 18 August 2005

Available online 19 September 2005

Abstract—A successful generation and utilization of prop-2-ynyl/enyl-sulfanyl ketene in the synthesis of previously unknown pyrimidinones and their thio-Claisen rearrangements leading to thienopyrimidinones is described.

1. Introduction

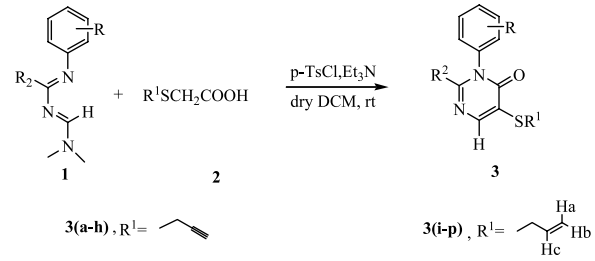
Many pyrimidine derivatives have been reported to possess useful medicinal and biological activities.[1,2] In the last few years, various pyrimidinone and pyrimidindione derivatives substituted either at C-5 or C-6 position have emerged in the field of chemotherapy. In this context, C-5 or C-6 substituted pyrimidinone and pyrimidindione derivatives showed selective antitumor, antiviral, antitubercular, and antifungal activities, which suggests the importance of this family of compounds as broad spectrum-drugs.[3] Recently, the pyrimidinone derivatives 2-methylthio-6-[(2-alkylamino)ethyl]-4(3*H*)-pyrimidinones have been shown to posses activity against positive strand (vesicular stomatitis virus) RNA virus.[4] A series of 1-(biphenylmethylamidoalkyl)pyrimidinones have also been designed as nanomolar inhibitors of recombinant lipoprotein-associated phospholipase A_2 with high potency in whole human plasma.[5] Also, thienopyrimidine derivatives have been reported to possess useful molluscidal, larvacidal activities against *Biomphalaria alexendra* and *Schistosoma mansoni,* snails.[6] Thus, it is well documented that the functionalization of pyrimidinones at C-5 and C-6 position leads to biological interesting molecules. Although the Claisen rearrangement is an excellent method for C–C bond formation and has been successfully employed for the synthesis of a number of furo[3,2-*d*]pyrimidines, pyrano[3,2-*d*]pyrimidines and dihydrofuro[2,3-*d*]pyrimidines derivatives,[7,8] there are hardly any reports in the pyrimidinone series. In continuation with our ongoing interest in developing new synthetic strategies for the construction of novel fused pyrimidinones,[9] in a recent communication,[10] we have reported a facile methodology for the synthesis and transformation of pyrimidinones to pyrimidinones fused at C-5 and C-6 position by the application of thio-Claisen rearrangement. Herein, we report a detailed account of our focussed attention towards construction of the pyrimidinones, having latent functionalities at C-5 position, which could form useful building blocks for the synthesis of various C-5, C-6 heterocyclic ring fused pyrimidinones via thio-Claisen rearrangement.

2. Results and discussion

The desired pyrimidinones **3a–p** were easily obtained in excellent yields (75–88%) by the [4+2] cycloaddition reaction of 4-dimethylamino-1-aryl-2-phenyl-1,3-diazabuta-1,3-dienes with prop-2-ynylsulfanyl ketene/allylsulfanyl ketene, generated in situ from the corresponding acids and *p*-toulenesulfonylchloride in the presence of triethylamine in dry methylene chloride at room temperature (Scheme 1). The detailed spectral features are given in the Section 2, however, only the salient features are presented here. The pyrimidinone **3a**, for example, analysed for $C_{20}H_{16}N_2O_2S$ exhibited the molecular ion peak at *m/z* 348 in its mass spectrum. Its IR spectrum (KBr) showed a strong peak at 1690 cm^{-1} due to the α,β unsaturated carbonyl group. Its ^1H NMR spectrum exhibited a triplet at δ 2.35 ($J=2.6$ Hz) for the acetylenic proton, one doublet of doublets at δ 3.65 ($J=16.9$, 2.6 Hz) and another doublet of doublets at δ 3.79 ($J=16.9$, 2.6 Hz) for two CH_2 protons

Keywords: 1,3-Diazabuta-1,3-diene; Thio-Claisen; Thienopyrimidinones; Sulfanylketene; Thiazolopyrimidinone.
* Corresponding author. Tel.: +91 183 2258802 09x3320; fax: 91 183 2258819 20; e-mail: mahajanmohinderp@yahoo.co.in

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.08.074

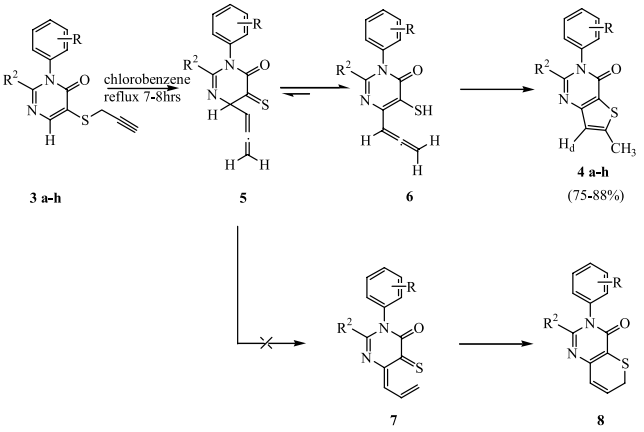


	R	R^2	Yield(%age)		R	R^2	Yield(%age)
3 a.	*p*-OCH_3	Ph	75%	**3 i.**	*p*-OCH_3	SCH_3	77%
3 b.	H	Ph	78%	**3 j.**	H	SCH_3	82%
3 c.	*p*-CH_3	Ph,	78%	**3 k.**	*p*-CH_3	SCH_3	76%
3 d.	*p*-Cl	Ph	80%	**3 l.**	*p*-Cl	SCH_3	80%
3 e.	*o*-CH_3	Ph	77%	**3 m.**	*o*-CH_3	Ph	78%
3 f.	*p*-CH_3	SCH_3	86%	**3 n.**	*p*-CH_3	Ph	81%
3 g.	H	SCH_3	81%	**3 o.**	H	Ph	85%
3 h.	*p*-OCH_3	SCH_3	79%	**3 p.**	*p*-OCH_3	Ph	76%

Scheme 1.

and a characteristic singlet at δ 8.29 for the olefinic proton. In few cases for pyrimidinones **3b–h**, these protons appeared as doublets while in other cases as broad peak. The assigned structure was further supported by the ^{13}C NMR chemical shifts. The resonance at δ 55.0 attests to the presence of the OCH_3 group. The resonance at δ 24.3 due to CH_2 also supports the assigned structure. Similarly the pyrimidinone (**3m**) in its mass spectrum showed a molecular ion peak at *m/z* 334 and its IR spectrum (KBr) showed a strong peak at 1680 cm^{-1} due to the α,β unsaturated carbonyl group. Its ^1H NMR spectrum exhibited the appearance of a doublet at δ 3.63 ($J=7.2$ Hz) due to the SCH_2 protons, a doublet at δ 5.15 ($J=9.4$ Hz) due to H_b, another doublet at δ 5.21 ($J=15.6$ Hz) due to H_a, a multiplet due to H_c at δ 5.76–5.94 and a characteristic singlet at δ 8.01 due to the olefinic proton. ^{13}C NMR signals were also in agreement with the assigned structure.

Pyrimidinones (**3a–h**) containing a propargyl moiety at C-5 appeared to be a potent auxiliary, which upon heating can undergo sigmatropic rearrangement leading to the synthesis of various 5,6-fused pyrimidinones. Accordingly, the thermolysis of pyrimidinones (**3a–h**) in refluxing chlorobenzene resulted in good yields of previously unknown thieno[3,2-*d*]pyrimidinones (Scheme 2). The characteristic

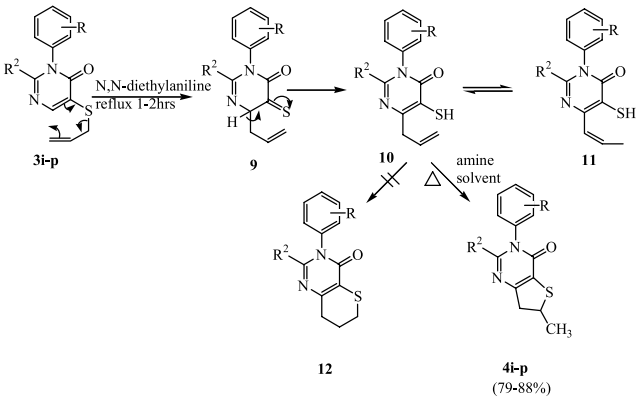


Scheme 2.

spectral features for the compound **4e**, for example, include a molecular ion peak at *m/z* 332 (M^+) in its mass spectrum. Its ^1H NMR spectrum showed a three-proton singlet at δ 2.34 due to the *o*-substituted $-CH_3$, a three-proton singlet at δ 2.69 due to CH_3 and a 10-proton multiplet at δ 7.23–7.52 due to the nine aromatic and one olefinic proton. The presence of the three-proton singlet at δ 2.69 indicated the formation of a five-membered thiophene ring. Moreover, its IR absorption spectrum showed the absence of the terminal acetylenic moiety. Its ^{13}C NMR spectrum exhibited apart from other carbon signals, the signal for thiophene ring substituted $-CH_3$ at δ 16.2 thus confirming the predicted structure and excluding the formation of **8**.

The plausible mechanism for the formation of 3-aryl-6-methyl-2-phenyl-3*H*-thieno[3,2-*d*]pyrimidinone is outlined in (Scheme 2) and involves an initial [3,3] thio-Claisen rearrangement to form an intermediate allene **5** followed by its enolisation to ene-thiol **6**. The thiol **6** can then yield either the usually obtained product **8** or thieno[3,2-*d*]-pyrimidinone **4**, via reported rearrangements. However, none of the substrates (**3a–h**) gave products of the type **8**,[11,12] instead these sulfides interestingly underwent regioselective ring closure leading to thieno[3,2-*d*]pyrimidinone derivatives (**4a–h**) in excellent yields. The radical difference in the regiochemistry observed in the present case from that described for benzopyran[11,12] may be ascribed to the preferential nucleophilic attack of the thiol at the highly electrophilic central allenic carbon, especially being in conjugation with an enone group.

In continuation of these studies, we have examined the thermal transformation of the previously unknown 3-aryl-2-phenyl-5-allylsulfanyl-3*H*-pyrimidin-4-ones (**3i–p**). The thermolysis of substrate **3i** in chlorobenzene as well as in higher boiling solvents 1,2-dichlorobenzene (179 °C) for several hours did not show any transformation and the starting material was recovered unchanged. However, refluxing in still high boiling solvent, *N*,*N*-diethylaniline (216 °C), showed the complete disappearance of **3i** in 1–2 h as monitored by TLC, Removal of solvent under reduced pressure and chromatography of crude product resulted in the isolation of a yellow crystalline compound in 79% yield (Scheme 3). This was characterized as 3-(4-methoxyphenyl)-6-methyl-2-methylsulfanyl-6,7-dihydro-3*H*-thieno[3,2-*d*]pyrimidin-4-one(**4i**). Its ^1H NMR spectrum showed the appearance of a doublet at δ 1.50 due to CH_3

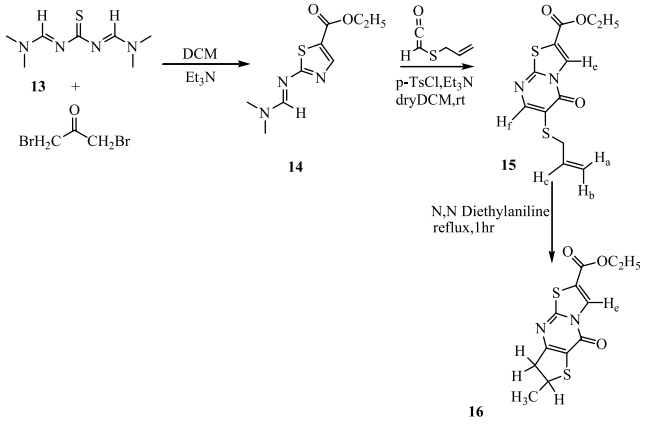


Scheme 3.

with a coupling constant of 6.8 Hz, two doublet of doublets at δ 2.95 and 3.44 ($J=17.0$, 6.0, 17.0, 8.4 Hz) due to CH_2 and a multiplet at δ 3.91–3.95 due to the methine proton. The signals in ^{13}C NMR also attest to the assigned structure. The mass spectrum showed the appearance of a molecular ion peak at *m/z* 320 (M^+). The reaction was successfully generalised by carrying out the thermolysis of seven other 5-allylsulfanyl-3*H*-pyrimidin-4-ones **3j–p**, which afforded dihydro-3*H*-thieno[3,2-*d*]pyrimidin-4-ones **4j–p** in excellent yields (79–88%).

The plausible mechanistic pathway, explaining the preferential formation of dihydro-3*H*-thieno[3,2-*d*]pyrimidin-4-one (**4i–p**), is outlined in (Scheme 3). In this scheme, it is assumed that an initial [3,3] sigmatropic rearrangement of **3i–p** gives an intermediate **9**, which upon rapid enolisation may result in the formation of allyl-ene-thiols **10**. The subsequent base catalysed cyclization of **10** may either result in the formation of five-membered (**4i–p**) or six-membered (**12**) ring fused pyrimidinones. It is also possible that the consequence of thermally induced prototropic isomerisation may lead to the formation of **11**. However, as is expected in high boiling amine medium, the usual base catalysed cyclisation of **10** then leads to the observed dihydro-3*H*-thieno[3,2-*d*]pyrimidin-4-ones(**4i–p**).

The observed thio-Claisen rearrangement route has been further extended to the synthesis of a novel tricyclic fused pyrimidinone. The thermolysis of 6-allylsulfanyl-thiazolo [3,2-*a*]pyrimidin-5-one **15**, (formed by the cycloaddition reaction of thiazole ring fused 1,3-diazabuta-1,3 dienes **14** with allylsulfanyl ketene) in *N*,*N*-diethylaniline resulted in the formation of dihydro-thiazolo[3,2-*a*]thieno[3,2-*d*]pyrimidin-9-one **16** (Scheme 4). The structures of pyrimidinone **15** and the tricyclic fused pyrimidinone **16** were unambiguously assigned with the help of spectral and analytical data.



Scheme 4.

In conclusion, the reactions of dimethylamino-1-aryl-2-phenyl-1,3-diazabuta-1,3-dienes with prop-2-ynylsulfanyl ketene/allylsulfanyl ketene and their thermolysis in appropriate solvents offer an easy access to various C-5 and C-6 ring fused pyrimidinones. Careful manipulation of the functionalities present in these pyrimidinones may lead to the development of biologically and medicinally important heterocyclic-fused pyrimidnones.

3. Experimental

Melting points were determined by open capillary using Veego Precision Digital Melting Point apparatus (MP-D) and are uncorrected. IR spectra were recorded on a Shimadzu D-8001 spectrophotometer. ^1H NMR spectra were recorded in deuterochloroform with Bruker AC-E 200 (200 MHz) spectrometers using TMS as internal standard. Chemical shift values are expressed as ppm downfield from TMS and *J* values are in Hz. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; m, multiplet; q, quartet; br, broad peak; and br s, broad singlet. ^{13}C NMR spectra were also recorded on a Bruker AC-200E (50.4 MHz) spectrometers in deuterochloroform using TMS as internal standard. Mass spectra were recorded on Shimadzu GCMS-QP-2000 mass spectrometer. Elemental analyses were performed on Heraus CHN-O-Rapid Elemental Analyzer. Column chromatography was performed on a silica gel (60–120) mesh or Harrison Research Chromatotron using 2 mm plates (Silica gel 60 PF254).

3.1. Starting materials

1,3-Diazabuta-1,3-dienes,[13] DMF–DMA,[14] *N*′-bis [(dimethylamino)methylene]thiourea, *N*′-[5-ethoxycarbonyl)thiazol-2-yl]-*N*,*N*-dimethylformamide[15] (**14**) were prepared according to the reported procedures.

3.2. Reactions of 1,3-diaza-1,3-butadienes with prop-2-ynylsulfanyl/allylsulfanyl ketenes and reaction of *N*′-[5-ethoxycarbonyl)thiazol-2-yl]-*N*,*N*-di-methylformamide with allylsulfanyl ketene. General procedure

To a well stirred solution of prop-2-ynylsulfanylaceticacid/allylsulfanylaceticacid (6 mmol), 1,3-diazabuta-1,3-diene/*N*′-[5-(ethoxycarbonyl)thiazol-2-yl]-*N*,*N*-di-methylformamide (4 mmol) and triethylamine (10 mmol) in dry methylene chloride (40 mL) was added dropwise a solution of *p*-toluenesulfonylchloride (8 mmol) in dry methylene chloride (30 mL) over a period of 20–30 min at room temperature. Reaction was allowed to stir for 2–3 h. After the completion of the reaction (TLC), the reaction mixture was first washed with saturated sodium bicarbonate solution (2×40 mL) followed by washing with water and the organic layer was dried over anhydrous sodium sulphate. Removal of solvent under reduced pressure yielded crude product, which was purified by silica gel column chromatography using (1/10) ethylacetate–hexane mixture.

3.2.1. 3-(4-Methoxyphenyl)-2-phenyl-5-prop-2-ynyl-sulfanyl-3*H*-pyrimidin-4-one (3a). Pale yellow solid, yield 75%; mp 160–161 °C. Anal. Calcd for $C_{20}H_{16}N_2O_2S$: C, 68.94; H, 4.63; N, 8.04. Found: C, 68.72; H, 4.70; N, 8.20%; ν_{max} (KBr); 2120, 1690 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 2.35 (t, 1H, $J=2.6$ Hz, acetylenic); 3.65 (dd, $J=16.9$, 2.6 Hz, 1H for SCH_2); 3.79 (dd, $J=16.9$, 2.6 Hz, 1H for SCH_2); 3.86 (s, 3H, OCH_3); 6.89 (d, 2H, $J=$ 8.6 Hz, ArH); 7.11 (d, 2H, $J=8.6$ Hz, ArH); 7.20–7.34 (m, 5H, ArH); 8.29 (s, 1H, olefinic); δ_C (50.4 MHz, $CDCl_3$): 24.3 (CH_2); 55.0 (OCH_3); 115.2, 120.7, 123.5, 124.7, 127.5, 128.9, 129.0, 129.5, 130.3, 133.4, 150.3, 155.7, 157.8, 159.1; *m/z* 348 (M^+).

3.2.2. 2,3-Diphenyl-5-prop-2-ynylsulfanyl-3*H*-pyrimidin-4-one (3b). White solid, yield 78%; mp 154–156 °C. Anal. Calcd for $C_{19}H_{14}N_2OS$: C, 71.67; H, 4.43; N, 8.80. Found: C, 71.42; H, 4.52; N, 8.96%; ν_{max} (KBr): 2110, 1680 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 2.29 (s, 1H, acetylenic); 3.76 (br s, 2H, SCH_2); 7.17–7.33 (m, 10H, ArH); 8.25 (s, 1H, olefinic); δ_C (50.4 MHz, $CDCl_3$): 24.0 (CH_2), 115.8, 119.1, 123.0, 124.2, 126.9, 128.2, 128.8, 129.5, 130.1, 132.5, 150.7, 156.0, 157.5, and 159.0; *m/z* 318 (M^+).

3.2.3. 2-Phenyl-3-*p*-tolyl-5-prop-2-ynylsulfanyl-3*H*-pyrimidin-4-one (3c). Creamish solid, yield 78%; mp 163–164 °C. Anal. Calcd for $C_{20}H_{16}N_2OS$: C, 72.26; H, 4.85; N, 8.43. Found: C, 72.42; H, 4.71; N, 8.41%; ν_{max} (KBr): 2115, 1684 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 2.29 (t, 1H, $J=2.4$ Hz, acetylenic); 2.31 (s, 3H, $-CH_3$); 3.79 (d, $J=2.5$ Hz, 2H, SCH_2); 6.82 (d, 2H, $J=8.5$ Hz, ArH); 7.03 (d, 2H, $J=8.5$ Hz); 7.20–7.34 (m, 5H, ArH); 8.25 (s, 1H, olefinic); δ_C (50.4 MHz, $CDCl_3$): 19.0 (CH_3), 24.7 (CH_2), 115.7, 118.9, 122.8, 124.7, 127.8, 128.3, 128.9, 129.5, 130.7, 133.0, 150.8, 155.7, 157.9, and 159.0; *m/z* 332 (M^+).

3.2.4. 3-(4-Chlorophenyl)-2-phenyl-5-prop-2-ynylsulfanyl-3*H*-pyrimidin-4-one (3d). White solid, yield 80%; mp 148–149 °C. Anal. Calcd for $C_{19}H_{13}ClN_2OS$: C, 64.68; H, 3.71; N, 7.94. Found: C, 64.52; H, 3.83; N, 7.98%; ν_{max} (KBr): 2122, 1678 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 2.25 (t, 1H, $J=2.8$ Hz, acetylenic); 3.72 (d, $J=2.6$ Hz, 2H, SCH_2); 7.18–7.35 (m, 9H, ArH); 8.28 (s, 1H, olefinic); δ_C (50.4 MHz, $CDCl_3$): 24.6 (CH_2), 115.0, 119.2, 123.4, 124.5, 127.8, 128.8, 129.1, 129.6, 130.2, 133.5, 150.0, 156.1, 157.5, and 159.2; *m/z* 352 (M^+).

3.2.5. 2-Phenyl-3-*o*-tolyl-5-prop-2-ynylsulfanyl-3*H*-pyrimidin-4-one (3e). Yellow solid, yield 77%; mp 168–170 °C. Anal. Calcd for $C_{20}H_{16}N_2OS$: C, 72.26; H, 4.85; N, 8.43. Found: C, 72.40; H, 4.81; N, 8.33%; ν_{max} (KBr): 2120, 1682 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 2.08 (s, 3H, CH_3); 2.23 (s, 1H, acetylenic); 3.77 (br s, 2H, SCH_2); 6.99–7.29 (m, 9H, ArH); 8.26 (s, 1H, olefinic); δ_C (50.4 MHz, $CDCl_3$): 19.3 (CH_3), 24.6 (CH_2), 113.7, 119.2, 122.8, 123.9, 125.8, 127.9, 128.8, 129.3, 129.7, 130.5, 131.7, 132.8, 149.1, 154.2, 156.0, and 158.8; *m/z* 332 (M^+).

3.2.6. 2-Methylsulfanyl-3-*p*-tolyl-5-prop-2-ynylsulfanyl-3*H*-pyrimidin-4-one (3f). Creamish solid, yield 86%; mp 158–159 °C. Anal. Calcd for $C_{15}H_{14}N_2OS_2$: C, 59.57; H, 4.67; N, 9.26. Found: C, 59.40; H, 4.81; N, 9.29%; ν_{max} (KBr): 2120, 1660 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 2.23 (s, 1H, acetylenic); 2.40 (s, 3H, CH_3); 2.90 (s, 3H, SCH_3); 3.89 (br s, 2H, SCH_2); 7.13 (d, 2H, $J=8.2$ Hz, ArH); 7.33 (d, 2H, $J=8.2$ Hz, ArH); 8.11 (s, 1H, olefinic); δ_C (50.4 MHz, $CDCl_3$): 16.5 (SCH_3), 19.2 (CH_3), 24.3 (CH_2), 120.8, 123.7, 124.5, 127.3, 128.8, 129.5, 148.7, 155.0, 157.6, and 159.1; *m/z* 302 (M^+).

3.2.7. 2-Methylsulfanyl-3-phenyl-5-prop-2-ynylsulfanyl-3*H*-pyrimidin-4-one (3g). White solid, yield 81%; mp 151–153 °C. Anal. Calcd for $C_{14}H_{12}N_2OS_2$: C, 58.31; H, 4.19; N, 9.71. Found: C, 58.48; H, 4.07; N, 9.66%; ν_{max} (KBr): 2105, 1670 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 2.24 (t, 1H, $J=2.4$ Hz, acetylenic); 2.82 (s, 3H, SCH_3); 3.75 (d, $J=2.5$ Hz, 2H, SCH_2); 7.15–7.46 (m, 5H, ArH); 8.15 (s, 1H, olefinic); δ_C (50.4 MHz, $CDCl_3$): 16.8 (SCH_3), 24.8 (CH_2), 120.4, 123.2, 125.6, 127.0, 128.5, 129.5, 149.9, 154.8, 158.6, and 159.4; *m/z* 288 (M^+).

3.2.8. 3-(4-Methoxyphenyl)-2-methylsulfanyl-5-prop-2-ynylsulfanyl-3*H*-pyrimidin-4-one (3h). Pale yellow solid; yield 79%; mp 155–157 °C. Anal. Calcd for $C_{15}H_{14}N_2O_2S_2$: C, 56.58; H, 4.43; N, 8.80. Found: C, 56.42; H, 4.47; N, 8.92%; ν_{max} (KBr): 2115, 1675 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 2.24 (t, 1H, $J=2.5$ Hz, acetylenic); 2.90 (s, 3H, SCH_3), 3.79 (d, $J=2.6$ Hz, 2H, SCH_2); 3.84 (s, 3H, OCH_3); 6.89 (d, 2H, $J=8.6$ Hz) 7.11 (d, 2H, $J=8.5$ Hz); 8.13 (s, 1H, olefinic); δ_C (50.4 MHz, $CDCl_3$): 17.0 (SCH_3), 24.4 (CH_2), 56.2 (OCH_3), 120.1, 122.8, 124.1, 127.7, 128.5, 130.1, 149.0, 154.7, 158.0, and 159.2; *m/z* 318 (M^+).

3.2.9. 5-Allylsulfanyl-3-(4-methoxyphenyl)-2-methylsulfanyl-3*H*-pyrimidin-4-one (3i). Yellow solid, yield 77%; mp 145–147 °C. Anal. Calcd for $C_{15}H_{16}N_2O_2S_2$: C, 56.22; H, 5.03; N, 8.74. Found: C, 56.37; H, 5.11; N, 8.52%; ν_{max} (KBr): 1680 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 2.85 (s, 3H, SCH_3); 3.64 (d, 2H, $J=7.2$ Hz, CH_2); 3.83 (s, 3H, OCH_3); 5.12 (d, $J=9.6$ Hz, 1H, H_b); 5.22 (d, $J=16.0$ Hz, 1H, H_a); 5.76–5.93 (m, 1H, H_c); 6.90 (d, 2H, $J=8.2$ Hz, ArH), 7.04 (d, 2H, $J=8.4$ Hz, ArH); 8.05 (s, 1H, olefinic); δ_C (50.4 MHz, $CDCl_3$): 17.2 (SCH_3), 38.6 (CH_2), 56.4 (OCH_3), 114.2, 120.0, 122.2, 126.4, 127.2, 132.0, 149.0, 153.9, 155.8, and 159.2: *m/z* 320 (M^+).

3.2.10. 5-Allylsulfanyl-2-methylsulfanyl-3-phenyl-3*H*-pyrimidin-4-one (3j). Pale yellow solid, yield 82%; mp 138–139 °C. Anal. Calcd for $C_{14}H_{14}N_2OS_2$: C, 57.90; H, 4.86; N, 9.65. Found: C, 57.83; H, 4.72; N, 9.86%; ν_{max} (KBr): 1680 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 2.91 (s, 3H, SCH_3); 3.62 (d, 2H, $J=7.1$ Hz, CH_2); 5.15 (d, $J=9.4$ Hz, 1H, H_b); 5.25 (d, $J=15.8$ Hz, 1H, H_a); 5.70–5.91 (m, 1H, H_c); 7.10–7.18 (m, 5H, ArH); 8.01 (s, 1H, olefinic); δ_C (50.4 MHz, $CDCl_3$): 17.4 (SCH_3), 37.8 (CH_2), 115.1, 119.8, 122.1, 126.0, 127.2, 131.8, 150.1, 153.8, 155.6, and 159.0: *m/z* 290 (M^+).

3.2.11. 5-Allylsulfanyl-2-methylsulfanyl-3-*p*-tolyl-3*H*-pyrimidin-4-one (3k). Yellow solid, yield 76%; mp 132–133 °C. Anal. Calcd for $C_{15}H_{16}N_2OS_2$: C, 59.81; H, 5.18; N, 9.08. Found: C, 59.41; H, 5.18; N, 9.08%; ν_{max} (KBr): 1678 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 2.36 (s, 3H, CH_3); 2.93 (s, 3H, SCH_3); 3.64 (d, 2H, $J=7.4$ Hz, CH_2); 5.16 (d, $J=9.2$ Hz, 1H, H_b); 5.21 (d, $J=15.6$ Hz, 1H, H_a); 5.71–5.90 (m, 1H, H_c); 6.84 (d, 2H, $J=8.2$ Hz, ArH), 7.03 (d, 2H, $J=8.6$ Hz, ArH); 8.05 (s, 1H, olefinic); δ_C (50.4 MHz, $CDCl_3$): 17.4 (SCH_3), 19.2 (CH_3), 37.3 (CH_2), 115.2, 120.4, 123.2, 126.5, 128.0, 131.3, 150.0, 153.2, 155.2, and 159.2; *m/z* 304 (M^+).

3.2.12. 5-Allylsulfanyl-3-(4-chlorophenyl)-2-methylsulfanyl-3*H*-pyrimidin-4-one (3l). Light yellow solid, yield 80%; mp 140–141 °C. Anal. Calcd for $C_{14}H_{13}ClN_2OS_2$: C, 51.76; H, 4.03; N, 8.62. Found: C, 51.82; H, 4.21; N, 8.39%; ν_{max} (KBr): 1660 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 2.92 (s, 3H, SCH_3); 3.63 (d, 2H, $J=7.2$ Hz, CH_2); 5.13 (d, $J=9.2$ Hz, 1H, H_b); 5.21 (d, $J=16.0$ Hz, 1H, H_a); 5.69–5.88 (m, 1H, H_c); 6.83 (d, 2H, $J=8.2$ Hz, ArH), 7.06 (d, 2H,

J=8.4 Hz, ArH); 8.02 (s, 1H, olefinic); δ_C (50.4 MHz, $CDCl_3$): 17.4 (SCH_3), 37.8 (CH_2), 115.8, 121.0, 123.4, 126.5, 127.6, 131.2, 150.2, 153.6, 155.3, and 159.1; *m/z* 324 (M^+).

3.2.13. 5-Allylsulfanyl-2-phenyl-3-*o*-tolyl-3*H*-pyrimidin-4-one (3m). Yellow solid, yield 78%; mp 129–130 °C. Anal. Calcd for $C_{20}H_{18}N_2OS$: C, 71.83; H, 5.42; N, 8.38. Found: C, 71.93; H, 5.21; N, 8.49%; ν_{max} (KBr): 1680 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 2.07 (s, 3H, CH_3); 3.63 (d, 2H, J= 7.2 Hz, CH_2); 5.15 (d, J=9.4 Hz, 1H, H_b); 5.21 (d, J= 15.6 Hz, 1H, H_a); 5.76–5.94 (m, 1H, H_c); 6.98–7.30 (m, 9H, ArH); 8.01 (s, 1H, olefinic); δ_C (50.4 MHz, $CDCl_3$): 19.6 (CH_3), 38.6 (CH_2), 115.2, 119.3, 120.6, 122.2, 123.5, 126.2, 127.2, 128.5, 129.9, 130.5, 132.5, 149.2, 154.3, 156.9, and 158.9; *m/z* 334 (M^+).

3.2.14. 5-Allylsulfanyl-2-phenyl-3-*p*-tolyl-3*H*-pyrimidin-4-one (3n). Light yellow solid, yield 81%; mp 143–144 °C. Anal. Calcd for $C_{20}H_{18}N_2OS$: C, 71.83; H, 5.42; N, 8.38. Found: C, 71.62; H, 5.61; N, 8.40%; ν_{max} (KBr): 1675 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 2.36 (s, 3H, CH_3); 3.62 (d, 2H, J= 7.0 Hz, CH_2); 5.15 (d, J=9.4 Hz, 1H, H_b); 5.23 (d, J= 15.8 Hz, 1H, H_a); 5.78–5.95 (m, 1H, H_c); 6.97 (d, 2H, J= 8.2 Hz, ArH), 7.10 (d, 2H, J=8.4 Hz, ArH); 7.14–7.29 (m, 5H, ArH); 8.03 (s, 1H, olefinic); δ_C (50.4 MHz, $CDCl_3$): 19.8 (CH_3), 38.4 (CH_2), 115.8, 119.2, 120.7, 122.5, 123.0, 125.9, 127.0, 128.9, 129.5, 132.5, 149.7, 154.5, 156.9, and 158.8.0; *m/z* 334 (M^+).

3.2.15. 5-Allylsulfanyl-2,3-diphenyl-3*H*-pyrimidin-4-one (3o). Yellow solid, yield 85%; mp 148–149 °C. Anal. Calcd for $C_{19}H_{16}N_2OS$: C, 71.22; H, 5.03; N, 8.74. Found: C, 71.12; H, 5.29; N, 8.59%; ν_{max} (KBr): 1665 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 3.64 (d, 2H, J=7.2 Hz, CH_2); 5.14 (d, J=9.6 Hz, 1H, H_b); 5.19 (d, J=16.0 Hz, 1H, H_a); 5.78–5.93 (m, 1H, H_c); 7.15–7.33 (m, 10H, ArH); 8.01 (s, 1H, olefinic); δ_C (50.4 MHz, $CDCl_3$): 38.5 (CH_2), 115.4, 119.1, 120.7, 122.0, 123.5, 126.3, 127.7, 128.2, 129.4, 132.5, 149.9, 154.5, 156.2, and 158.9; *m/z* 320 (M^+).

3.2.16. 5-Allylsulfanyl-3-(4-methoxyphenyl)-2-phenyl-3*H*-pyrimidin-4-one (3p). Pale yellow solid, yield 76%; mp 158–159 °C. Anal. Calcd for $C_{20}H_{18}N_2O_2S$: C, 68.55; H, 5.18; N, 7.99. Found: C, 68.67; H, 5.01; N, 8.04%; ν_{max} (KBr): 1680 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 3.62 (d, 2H, J= 7.6 Hz, CH_2); 3.83 (s, 3H, OCH_3); 5.15 (d, J=9.6 Hz, 1H, H_b); 5.23 (d, J=15.8 Hz, 1H, H_a); 5.76–5.93 (m, 1H, H_c); 6.90 (d, 2H, J=8.6 Hz, ArH), 7.09 (d, 2H, J=8.6 Hz, ArH); 7.14–7.29 (m, 5H, ArH); 8.01 (s, 1H, olefinic); δ_C (50.4 MHz, $CDCl_3$): 38.6 (CH_2), 55.0 (OCH_3), 115.3, 119.2, 120.5, 122.4, 123.2, 126.2, 127.6, 128.3, 129.5, 132.2, 150.0, 153.9, 156.3, and 158.8.0; *m/z* 350 (M^+).

3.2.17. 6-Allylsulfanyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one-2-carboxylicacid ethylester 15. Pale yellow solid, yield 82%; mp 84–85 °C. Anal. Calcd for $C_{12}H_{12}N_2O_3S_2$: C, 48.63; H, 4.08; N, 9.45. Found: C, 48.72; H, 3.95; N, 9.49%; ν_{max} (KBr): 1620, 1680 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 1.31 (t, 3H, J=7.4 Hz, CH_3); 3.60 (d, 2H, J=7.5 Hz, CH_2); 4.42 (q, J=7.4 Hz, 2H, OCH_2); 5.13 (d, J=9.4 Hz, 1H, H_b); 5.22 (d, J=16.0 Hz, 1H, H_a); 5.74–5.91 (m, 1H, H_c); 8.12 (s, 1H, H_e); 8.52 (s, 1H, H_f); δ_C (50.4 MHz, $CDCl_3$): 14.2, 38.6 (CH_2); 62.9 (OCH_2); 113.6, 118.1, 121.2, 127.0, 133.3, 156.4, 157.2, 159.6, and 162.4. *m/z* 296 (M^+).

3.3. General procedure for the synthesis of compounds 4a–h

Pyrimidinones **3a**–**h** (0.2 g) were refluxed in chlorobenzene (5 mL) for 7–8 h. The reaction mixture was then cooled and directly subjected to column chromatography over silica gel. Chlorobenzene was eluted out with petroleum ether. All the products **4a**–**h** were obtained by silica gel column chromatography using (1/25) ethylacetate–hexane mixture.

3.3.1. 3-(4-Methoxyphenyl)-6-methyl-2-phenyl-3*H*-thieno[3,2-*d*]pyrimidin-4-one (4a). White solid, yield 75%; mp 220–221 °C. Anal. Calcd for $C_{20}H_{16}N_2O_2S$: C, 68.94; H, 4.63; N, 8.04. Found: C, 68.73; H, 4.73; N, 8.19%; ν_{max} (KBr); 1680 cm^{-1}; δ_H(200 MHz): 2.64 (s, 3H, CH_3); 3.74 (s, 3H, OCH_3); 6.76 (d, 2H, J=8.8 Hz, ArH); 6.99 (d, 2H, J=8.8 Hz, ArH); 7.05–7.33 (m, 6H, ArH and H_d); δ_C (50.4 MHz, $CDCl_3$): 16.7 (CH_3); 55.2 (OCH_3); 114.1, 120.8, 123.5, 127.9, 128.9, 129.0, 129.9, 130.1, 135.5, 150.2, 156.6, 157.0, 157.8, 159.1: *m/z* 348 (M^+).

3.3.2. 2,3-Diphenyl-6-methyl-3*H*-thieno[3,2-*d*]pyrimidin-4-one (4b). Creamish solid, yield 78%; mp 223–224 °C. Anal. Calcd for $C_{19}H_{14}N_2OS$: C, 71.67; H, 4.43; N, 8.80. Found: C, 71.81; H, 4.27; N, 8.82%; ν_{max} (KBr): 1665 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 2.70 (s, 3H, CH_3); 7.15–7.31 (m, 11H, ArH and H_d); δ_C (50.4 MHz, $CDCl_3$): 17.2 (CH_3), 116.2, 118.9, 122.3, 126.0, 128.8, 129.2, 129.9, 134.7, 149.6, 155.2, 156.8, 157.5, and 158.8; *m/z* 318 (M^+).

3.3.3. 6-Methyl-2-phenyl-3-*p*-tolyl-3*H*-thieno[3,2-*d*]pyrimidin-4-one (4c). Light yellow solid, yield 78%; mp 231–233 °C. Anal. Calcd for $C_{20}H_{16}N_2OS$: C, 72.26; H, 4.85; N, 8.43. Found: C, 72.18; H, 4.99; N, 8.41%; ν_{max} (KBr): 1670 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 2.28 (s, 3H, CH_3); 2.63 (s, 3H, CH_3); 7.00 (d, 2H, J=8.4 Hz, ArH); 7.08 (d, 2H, J=8.4 Hz, ArH); 7.18–7.30 (m, 6H, ArH and H_d); δ_C (50.4 MHz, $CDCl_3$): 16.7 (CH_3), 19.6 (CH_3), 114.0, 120.2, 122.8, 127.5, 128.5, 129.0, 129.7, 130.3, 136.0, 150.1, 155.7, 157.1, 157.7, and 159.0; *m/z* 332 (M^+).

3.3.4. 3-(4-Chlorophenyl)-6-methyl-2-phenyl-3*H*-thieno[3,2-*d*]pyrimidin-4-one (4d). Creamish solid, yield 80%; mp 239–240 °C. Anal. Calcd for $C_{19}H_{13}ClN_2OS$: C, 64.68; H, 3.71; N, 7.94. Found: C, 64.97; H, 3.58; N, 7.78%; ν_{max} (KBr): 1680 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 2.65 (s, 3H, CH_3); 6.96 (d, 2H, J=8.4 Hz, ArH); 7.04 (d, 2H, J=8.4 Hz, ArH); 7.18–7.30 (m, 6H, ArH and H_d); δ_C (50.4 MHz, $CDCl_3$): 16.7 (CH_3), 115.1, 121.0, 123.7, 127.9, 128.6, 129.2, 129.8, 130.3, 135.7, 150.0, 156.8, 157.2, 158.1, and 159.5; *m/z* 352 (M^+).

3.3.5. 6-Methyl-2-phenyl-3-*o*-tolyl-3*H*-thieno[3,2-*d*]pyrimidin-4-one (4e). Creamish solid, yield 77%; mp 237–238 °C. Anal. Calcd for $C_{20}H_{16}N_2OS$: C, 72.26; H, 4.85; N, 8.43. Found: C, 72.35; H, 4.91; N, 8.28%; ν_{max} (KBr): 1685 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 2.34 (s, 3H, CH_3); 2.69 (s, 3H, CH_3); 7.23–7.52 (m, 10H, ArH and H_d); δ_C (50.4 MHz, $CDCl_3$): 16.2 (CH_3), 19.2 (CH_3), 114.0, 120.7,

122.8, 123.8, 127.9, 129.2, 129.9, 130.3, 134.7, 149.8, 155.7, 156.8, 157.9, and 159.5; *m/z* 332 (M^+).

3.3.6. 6-Methyl-2-methylsulfanyl-3-*p*-tolyl-3*H*-thieno-[3,2-*d*]pyrimidin-4-one (4f). White solid, yield 75%; mp 212–213 °C. Anal. Calcd for $C_{15}H_{14}N_2OS_2$: C, 59.57; H, 4.67; N, 9.26. Found: C, 59.82; H, 4.58; N, 9.10%; ν_{max} (KBr): 1670 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 2.34 (s, 3H, CH_3); 2.67 (s, 3H, CH_3); 2.90 (s, 3H, SCH_3); 6.98–7.12 (m, 5H, ArH and H_d); δ_C (50.4 MHz, $CDCl_3$): 16.5 (SCH_3), 16.7 (CH_3), 19.0 (CH_3), 115.3, 119.7, 123.5, 127.9, 128.9, 148.5, 154.5, 157.2, 158.1, and 159.3; *m/z* 302 (M^+).

3.3.7. 6-Methyl-2-methylsulfanyl-3-phenyl-3*H*-thieno-[3,2-*d*]pyrimidin-4-one (4g). Creamish solid, yield 82%; mp 218–219 °C. Anal. Calcd for $C_{14}H_{12}N_2OS_2$: C, 58.31; H, 4.19; N, 9.71. Found: C, 58.47; H, 4.11; N, 9.63%; ν_{max} (KBr): 1676 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 2.70 (s, 3H, CH_3); 2.89 (s, 3H, SCH_3); 7.23–7.42 (m, 6H, ArH and H_d); δ_C (50.4 MHz, $CDCl_3$): 16.4 (SCH_3), 16.8 (CH_3), 116.2, 129.5, 123.8, 127.5, 128.8, 149.3, 155.1, 157.7, 158.2, and 159.0; *m/z* 288 (M^+).

3.3.8. 3-(4-Methoxyphenyl)-6-methyl-2-methylsulfanyl-3*H*-thieno[3,2-*d*]pyrimidin-4-one (4h). White solid, yield 88%; mp 215–216 °C. Anal. Calcd for $C_{15}H_{14}N_2O_2S_2$: C, 56.58; H, 4.43; N, 8.80. Found: C, 56.49; H, 4.68; N, 8.64%; ν_{max} (KBr): 1668 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 2.68 (s, 3H, CH_3); 2.90 (s, 3H, SCH_3); 3.75 (s, 3H, OCH_3); 7.05–7.27 (m, 5H, ArH and H_d); δ_C (50.4 MHz, $CDCl_3$): 16.4 (SCH_3), 16.7 (–CH_3), 55.7 (OCH_3), 114.7, 120.5, 123.5, 127.9, 130.1, 150.2, 156.4, 157.1, 157.9, and 159.0; *m/z* 318 (M^+).

3.4. General procedure for the synthesis of compounds 4i–p and 16

Pyrimidinones **3i–p** and bicyclic pyrimidinone **15** (0.2 g) were refluxed in 5 mL of *N*,*N*-diethylaniline for 1–2 h. The reaction mixture was then cooled and poured into 50 mL of ice-cold 6 N HCl and extracted with chloroform to give a viscous liquid, which was purified by silica gel column chromatography using (1/20) ethylacetate–hexane mixture to obtained the product.

3.4.1. 3-(4-Methoxyphenyl)-6-methyl-2-methylsulfanyl-6,7-dihydro-3*H*-thieno[3,2-*d*]pyrimidin-4-one (4i). Yellow solid, yield: 79%; mp 197–198 °C. Anal. Calcd for $C_{15}H_{16}N_2O_2S_2$: C, 56.22; H, 5.03; N, 8.74. Found: C, 56.35; H, 4.89; N, 8.76%; ν_{max} (KBr): 1660 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 1.50 (d, 3H, J=6.8 Hz, CH_3); 2.69 (s, 3H, SCH_3); 2.95 (dd, J=17.0, 6.0 Hz, 1H of CH_2); 3.44 (dd, J=17.0, 8.4 Hz, 1H of CH_2); 3.75 (s, 3H, OCH_3); 3.91–3.95 (m, 1H, CH); 7.13 (d, 2H, J=8.3 Hz, ArH); 7.28 (d, 2H, J=8.3 Hz, ArH); δ_C (50.4 MHz, $CDCl_3$): 16.2 (SCH_3), 23.7 (CH_3), 25.2 (CH), 43.7 (CH_2), 55.6 (OCH_3), 117.2, 122.3, 124.7, 128.2, 150.1, 156.4, 157.2, and 159.1. *m/z* 320 (M^+).

3.4.2. 6-Methyl-2-methylsulfanyl-3-phenyl-6,7-dihydro-3*H*-thieno[3,2-*d*]pyrimidin-4-one (4j). Yellow solid, yield 80%; mp 182–183 °C. Anal. Calcd for $C_{14}H_{14}N_2OS_2$: C, 57.90; H, 4.86; N, 9.65. Found: C, 58.08; H, 4.81; N, 9.52%; ν_{max} (KBr): 1667 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 1.52 (d, 3H, J=6.6 Hz, CH_3); 2.72 (s, 3H, CH_3); 2.90 (dd, J=17.1, 5.8 Hz, 1H of CH_2); 3.46 (dd, J=17.2, 8.2 Hz, 1H of CH_2); 3.89–3.94 (m, 1H, CH); 7.20–7.38 (m, 5H, ArH); δ_C (50.4 MHz, $CDCl_3$): 16.2 (SCH_3), 24.1 (CH_3), 25.2 (CH), 43.3 (CH_2), 117.3, 123.4, 124.8, 127.9, 150.3, 156.5, 157.4, and 159.2. *m/z* 258 (M^+).

3.4.3. 6-Methyl-2-methylsulfanyl-3-*p*-tolyl-6,7-dihydro-3*H*-thieno[3,2-*d*]pyrimidin-4-one (4k). Pale yellow solid, yield 84%; mp 189–190 °C. Anal. Calcd for $C_{15}H_{16}N_2OS_2$: C, 59.18; H, 5.30; N, 9.20. Found: C, 59.08; H, 5.47; N, 9.12%; ν_{max} (KBr): 1672 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 1.51 (d, 3H, J=6.6 Hz, CH_3); 2.34 (s, 3H, CH_3); 2.72 (s, 3H, SCH_3); 2.95 (dd, J=17.0, 5.8 Hz, 1H of CH_2); 3.39 (dd, J=17.2, 8.4 Hz, 1H of CH_2); 3.93–3.97 (m, 1H, CH); 7.12 (d, 2H, J=8.3 Hz, ArH); 7.28 (d, 2H, J=8.4 Hz, ArH); δ_C (50.4 MHz, $CDCl_3$): 16.1 (SCH_3), 19.4 (CH_3), 23.8 (CH_3), 25.2 (CH), 44.0 (CH_2), 117.7, 122.0, 124.8, 128.1, 150.5, 156.0, 157.1, and 159.0. *m/z* 272 (M^+).

3.4.4. 3-(4-Chlorophenyl)-6-methyl-2-methylsulfanyl-6,7-dihydro-3*H*-thieno[3,2-*d*]pyrimidin-4-one (4l). Pale yellow solid, yield: 80%; mp 193–194 °C. Anal. Calcd for $C_{14}H_{13}ClN_2OS_2$: C, 51.70; H, 4.03; N, 8.62. Found: C, 51.89; H, 3.95; N, 8.58%; ν_{max} (KBr): 1665 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 1.53 (d, 3H, J=6.4 Hz, CH_3); 2.76 (s, 3H, SCH_3); 2.98 (dd, J=17.2, 6.0 Hz, 1H of CH_2); 3.40 (dd, J=17.4, 8.6 Hz, 1H of CH_2); 3.90–3.94 (m, 1H, CH); 7.16 (d, 2H, J=8.2 Hz, ArH); 7.22 (d, 2H, J=8.3 Hz, ArH); δ_C (50.4 MHz, $CDCl_3$): 16.4 (SCH_3), 22.4 (CH_3), 25.3 (CH), 43.8 (CH_2), 117.6, 123.2, 124.5, 128.3, 150.8, 156.2, 157.7, and 159.3. *m/z* 292 (M^+).

3.4.5. 6-Methyl-2-phenyl-3-*o*-tolyl-6,7-dihydro-3*H*-thieno[3,2-*d*]pyrimidin-4-one (4m). Pale yellow solid, yield: 87%; mp 209–210 °C. Anal. Calcd for $C_{20}H_{18}N_2OS$: C, 71.83; H, 5.42; N, 8.38. Found: C, 71.97; H, 5.25; N, 8.41%; ν_{max} (KBr): 1670 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 1.50 (d, 3H, J=6.2 Hz, CH_3); 2.23 (s, 3H, CH_3); 2.96 (dd, J=17.1, 6.2 Hz, 1H of CH_2); 3.43 (dd, J=17.2, 8.6 Hz, 1H of CH_2); 3.89–3.93 (m, 1H, CH); 7.25–7.57 (m, 9H, ArH); δ_C (50.4 MHz, $CDCl_3$): 19.4 (CH_3), 23.8 (CH_3), 25.6 (CH), 44.0 (CH_2), 114.2, 118.7, 122.5, 123.8, 125.6, 127.7, 128.3, 129.7, 129.9, 130.2, 149.7, 153.8, 155.9, and 158.7. *m/z* 334 (M^+).

3.4.6. 6-Methyl-2-phenyl-3-*p*-tolyl-6,7-dihydro-3*H*-thieno[3,2-*d*]pyrimidin-4-one (4n). Yellow solid, yield: 80%; mp 215–216 °C. Anal. Calcd for $C_{20}H_{18}N_2OS$: C, 71.83; H, 5.42; N, 8.38. Found: C, 71.62; H, 5.47; N, 8.54%; ν_{max} (KBr): 1671 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 1.51 (d, 3H, J=6.4 Hz, CH_3); 2.32 (s, 3H, CH_3); 2.96 (dd, J=17.0, 6.4 Hz, 1H of CH_2); 3.48 (dd, J=17.1, 8.6 Hz, 1H of CH_2); 3.93–3.97 (m, 1H, CH); 6.93 (d, 2H, J=8.2 Hz, ArH); 7.02 (d, 2H, J=8.2 Hz, ArH); 7.07–7.19 (m, 5H, ArH); δ_C (50.4 MHz, $CDCl_3$): 19.5 (CH_3), 24.0 (CH_3), 25.1 (CH), 44.2 (CH_2), 114.2, 120.7, 122.7, 127.6, 128.5, 129.2, 129.9, 131.0, 149.3, 154.7, 157.6, and 158.4. *m/z* 334 (M^+).

3.4.7. 2,3-Diphenyl-6-methyl-6,7-dihydro-3*H*-thieno[3,2-*d*]pyrimidin-4-one (4o). Yellow solid, yield 82%; mp 199–200 °C. Anal. Calcd for $C_{19}H_{16}N_2OS$: C, 71.22; H, 5.03; N, 8.74. Found: C, 71.47; H, 4.91; N, 8.62%; ν_{max} (KBr): 1667 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 1.44 (d, 3H, J=6.2 Hz,

CH_3); 2.96 (dd, $J=17.2$, 6.2 Hz, 1H of CH_2); 3.46 (dd, $J=17.2$, 8.5 Hz, 1H of CH_2); 3.90–3.94 (m, 1H, CH); 7.07–7.51 (m, 10H, ArH); δ_C (50.4 MHz, $CDCl_3$): 24.2 (CH_3), 25.2 (CH), 44.0 (CH_2), 114.7, 120.2, 122.8, 127.4, 128.7, 129.0, 130.3, 149.7, 153.8, 157.8, and 158.6. *m/z* 320 (M^+).

3.4.8. 2-Phenyl-3-(4-methoxyphenyl)-6-methyl-6,7-dihydro-3*H*-thieno[3,2-*d*]pyrimidin-4-one (4p). White solid, yield 88%; mp 216–217 °C. Anal. Calcd for $C_{20}H_{18}N_2O_2S$: C, 68.55; H, 5.18; N, 7.99. Found: C, 68.67; H, 5.00; N, 8.05%; ν_{max} (KBr): 1668 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 1.49 (d, 3H, $J=6.8$ Hz, CH_3); 2.95 (dd, $J=17.0$, 6.2 Hz, 1H of CH_2); 3.41 (dd, $J=17.2$, 8.4 Hz, 1H of CH_2); 3.71 (s, 3H, OCH_3); 3.91–3.95 (m, 1H, CH); 6.97 (d, 2H, $J=8.2$ Hz, ArH); 7.04 (d, 2H, $J=8.0$ Hz, ArH); 7.10–7.22 (m, 5H, ArH); δ_C (50.4 MHz, $CDCl_3$): 24.1 (CH_3), 25.2 (CH), 44.2 (CH_2), 55.8 (OCH_3), 114.2, 120.7, 122.5, 127.6, 128.7, 129.3, 129.9, 131.3, 149.1, 153.9, 157.9, and 158.5. *m/z* 350 (M^+).

3.4.9. 2-Methyl-3,9-dihydro-2*H*-thiazolo[3,2-*a*]thieno-[3,2-*d*]pyrimidin-9-one-6-carboxylic acid ethylester (16). White solid, yield: 78%; mp 116–117 °C. Anal. Calcd for $C_{12}H_{12}N_2O_3S_2$: C, 48.63; H, 4.08; N, 9.45. Found: C, 48.76; H, 4.01; N, 9.39%; ν_{max} (KBr): 1618, 1668 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 1.29 (t, $J=7.2$ Hz, 3H, CH_3); 1.49 (d, 3H, $J=6.8$ Hz, CH_3); 2.98 (dd, $J=17.0$, 6.1 Hz, 1H of CH_2); 3.46 (dd, $J=17.2$, 8.4 Hz, 1H of CH_2); 3.92–3.99 (m, 1H, CH); 4.40 (q, $J=7.2$ Hz, 2H, OCH_2); 8.52 (s, 1H, H_e); δ_C (50.4 MHz, $CDCl_3$): 14.3, 24.2, 25.4 (CH); 43.8 (CH2); 63.0 (OCH_2); 121.2, 127.2, 128.8, 155.2, 156.8, 159.3, 162.7. *m/z* 296 (M^+).

References and notes

1. (a) Barton, D. H. R.; Ollis, W. D. Comprehensive Organic Synthesis; Pergamon: Oxford, 1974; p 493. (b) Brown, J. D. In Katritzky, A. R., Rees, C. W., Eds.; Comprehensive Heterocyclic Chemistry; Pergamon: Oxford, 1984; Vol. 3, p 57. (c) Sasaki, T.; Minamoto, K.; Suzuki, T.; Yamashita, S. *Tetrahedron* **1980**, *36*, 865. (d) Bradshow, T. K.; Hutchison, D. W. *Chem. Soc. Rev.* **1977**, *6*, 43.
2. (a) Maumato, R.; Farukawa, Y. *Chem. Pharm. Bull.* **1977**, *25*, 2974. (b) Cheng, C. C.; Roth, B. *Prog. Med. Chem.* **1971**, *8*, 61. (c) Jones, A. S.; Swgers, J. R.; Walker, R. T.; Clercq, E. D. *J. Med. Chem.* **1988**, *31*, 268. (d) Griengl, H. H.; Wanck, E.; Schwarz, W.; Streicher, W.; Rosenwirth, B.; Clercq, E. D. *J. Med. Chem.* **1987**, *30*, 1199. (e) Clercq, E. D.; Benaerts, R. *J. Biol. Chem.* **1987**, *262*, 14905.
3. Botta, M.; Parlato, M. C.; Mugnaini, C.; Renzulli, M. L.; Corelli, F. *Arkivoc* **2004** (v), 349.
4. Botta, M.; Occhionero, F.; Nicoletti, R.; Mastromarino, P.; Conti, C.; Margini, M.; Saladino, J. *Bioorg. Med. Chem.* **1999**, *9*, 1925.
5. Boyd, H. F.; Fell, S. C. M.; Hickey, D. M. B.; Ife, R. J.; Leach, C. A.; Macphee, C. H.; Milliner, K. J.; Pinto, I. L.; Rawlings, A.; Smith, S. A.; Stansfield, I. G.; Stanway, S. J.; Theobald, C. J.; Whittakerr, C. M. J. *Bioorg. Med. Chem.* **2002**, *12*, 51.
6. Hosni, H. M.; Basyouni, W. M.; El-Nahas, H. A. *J. Chem. Res. (S).* **1999**, 646.
7. Kawahara, N.; Nakajima, T.; Itoh, T.; Ogura, H. *Chem. Pharm. Bull.* **1985**, *33*, 4740.
8. (a) Majumdar, K. C.; Das, U. *J. Chem. Res., Synop.* **1997**, 309. (b) Majumdar, K. C.; Das, U. *Synth. Commun.* **1997**, *27*, 4013.
9. (a) Jayakumar, S.; Ishar, M. P. S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379–471. Report no. 595. (b) Sharma, A. K.; Jayakumar, S.; Hundal, M. S.; Mahajan, M. P. *J. Chem. Soc., Perkin. Trans. 1* **2002**, 774–784 and references cited there in.
10. Mohan, C.; Kumar, V.; Mahajan, M. P. *Tetrahedron Lett.* **2004**, *45*, 6075.
11. Majumdar, K. C.; Ghosh, M.; Jana, M.; Saha, D. *Tetrahedron Lett.* **2002**, *43*, 2111.
12. Majumdar, K. C.; Ghosh, S. K. *Tetrahedron Lett.* **2002**, *43*, 2115.
13. Dey, P. D.; Sharma, A. K.; Rai, S. N.; Mahajan, M. P. *Tetrahedron* **1995**, *51*, 7459.
14. Brinkmeyer, R. S.; Abdullah, R. F. *Tetrahedron* **1979**, *Report Vol. 35*, 1675–1735.
15. Landreau, C.; Meslin, J. C.; Deniaud, D. *J. Org. Chem.* **2003**, *68*, 4912–4917.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 10781–10792

Synthesis and utilisation of 2,7′-diindolylmethanes and a 2-(2-indolyl)pyrrolylmethane as macrocyclic precursors

Paul K. Bowyer,[a,*] David StC. Black[b,*] and Donald C. Craig[b]

[a]*School of Agriculture and Wine, The University of Adelaide, Waite Campus, Glen Osmond SA 5064, Australia*
[b]*School of Chemistry, The University of New South Wales, UNSW Sydney NSW 2052, Australia*

Received 9 February 2005; revised 1 August 2005; accepted 18 August 2005

Available online 19 September 2005

Abstract—Treatment of 3-(4-chlorophenyl)-7-hydroxymethyl-4,6-dimethoxyindole with 3-(4-chlorophenyl)-4,6-dimethoxyindole results in the generation of two geometrically isomeric diindolylmethanes in addition to a novel triindolyl oligomer, which has been structurally characterised. The 2,7′-diindolylmethanes were found to be unstable under Vilsmeier formylation conditions, thus hampering macrocyle precursor construction. In an alternate approach, the 3-(4-chlorophenyl)-4,6-dimethoxyindole-7-carbaldehyde was converted into the indolyl-pyrrolyl macrocycle precursor 5-(3-(4-chlorophenyl)-4,6-dimethoxyindole-2-ylmethyl)-4-ethyl-3-methylpyrrole-2,7-dicarbaldehyde, which was used to generate an unsymmetrical pentaaza macrocycle.

1. Introduction

We have been interested in the non-template synthesis of indole-containing ligands for some time,[1–4] and have recently reported our latest results.[5] We now report some results relating to the generation of precursors of macrocyclic imines based on the 2,7′-diindolylmethane and 2-(2-indolyl)pyrrole structures. Such diarylmethanes are usually constructed by the reaction of electron-rich arenes with formaldehyde, or by the acid-catalysed addition of an arene to a benzylic alcohol, the latter being the initial intermediate in the addition of an arene to formaldehyde. The most effective route to the indolylmethanols proceeds via the reduction of indole-carbaldehydes.

2. Results and discussion

2.1. Diindolylmethane ligand systems

The first strategy has already been used to generate the symmetrical 2,2′-diiindolylmethane system.[6] The construction of an unsymmetrical diindolylmethane would permit the development of a series of macrocycles that would no longer have a symmetrical coordination field. This would further allow the investigation of the chemical and physical properties of metal complexes incorporating the indole unit.

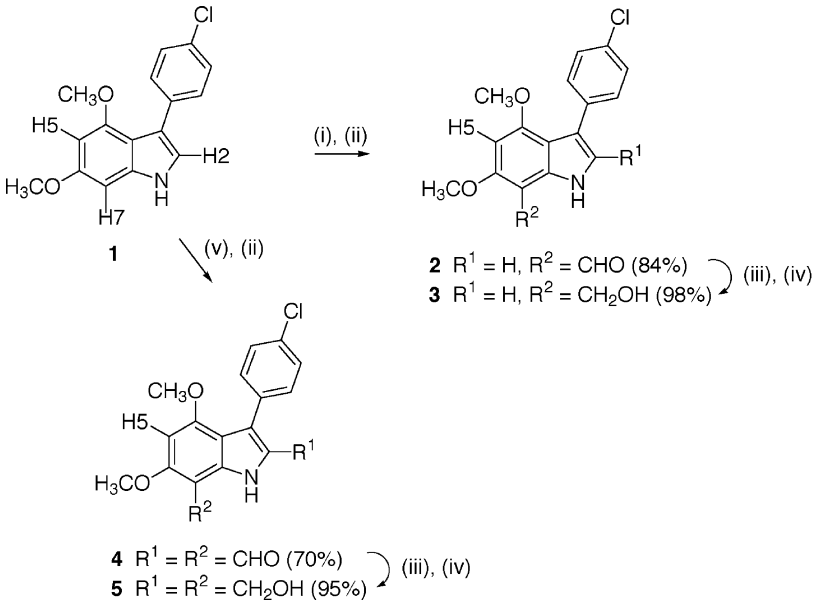
It has been shown previously[7] that reduction of the 7-carbaldehyde functionality to the corresponding methyl alcohol, followed by treatment with acid, promotes the nucleophilic attack of existing unsubstituted indole sites on the carbocation so generated. Such a procedure may also give rise to trimeric cyclic and tetrameric oligomeric species if self-condensation occurs.[7]

It has been observed that the nucleophilic attack of a 3-(4-halophenyl)-4,6-dimethoxyindole on an indolyl-7-methanol occurs primarily via position 2-to produce a 2,7′-linked diindolylmethane.[7] A second isomer, the 7,7′-linked diindolylmethane, was also observed, although in much lower yield. The latter would generate an eight-membered bisanionic coordination sphere on coordination and was thus, eliminated from this study.

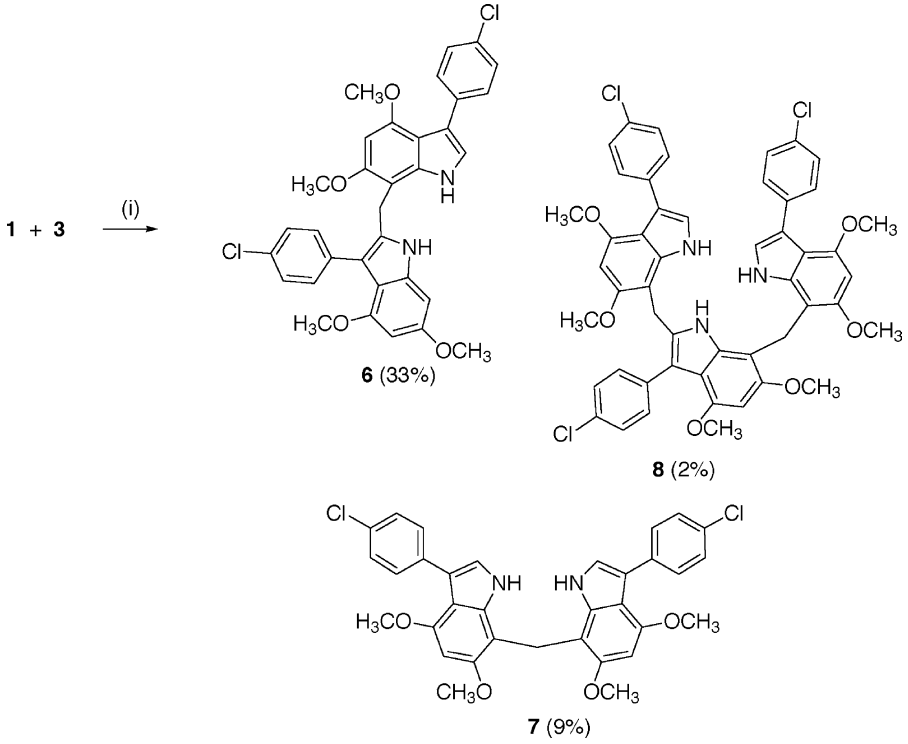
Treatment of the aldehyde **2**, derived from highly substituted indole **1**,[5] with an excess of sodium borohydride in tetrahydrofuran affords the corresponding 7-methanol **3** (Scheme 1). This alcohol was found to be particularly sensitive to acidic environments, presumably due to the promotion of self-condensation reactions. Similarly, the reaction of indole **1** with an excess of Vilsmeier reagent at elevated temperature followed by basic work-up afforded a good yield of the diformyl species **4**, which can be converted to **5** in the same manner (Scheme 1).

Keywords: Indole; Diindolylmethane; Vilsmeier; Macrocycle.
* Corresponding authors. Tel.: +61 8 83037239; fax: +61 8 83037116 (P.K.B.); tel.: +61 2 9385 4657; fax: + 61 2 9385 6141 (D.Stc.B); e-mail addresses: paul.bowyer@adelaide.edu.au; d.black@unsw.edu.au

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.08.075



Scheme 1. Reagents and conditions: (i) $POCl_3$, DMF, 0 °C; (ii) NaOH, H_2O; (iii) $NaBH_4$, THF, Δ; (iv) H_2O; (v) $POCl_3$, DMF, 50 °C.



Scheme 2. Reagents and conditions: (i) HOAc, Δ.

Reaction of **1** with **3** (Scheme 2) in boiling glacial acetic acid gave three products: unsymmetrical 2,7′-diindolylmethane **6** (separated from co-incident **1** after extensive chromatography) and the 7,7′-diindolylmethane **7**. The third product gave a mass spectral base peak that indicated the presence of three chlorine atoms at *m/z* 885–891 and ^{1}H NMR data indicated a trimeric oligomer with two inequivalent methylene groups, containing both 2,7- and 7,7-indolyl linkages. X-ray quality crystals of oligomer **8** were obtained such that an unambiguous structural assignment could be made.

The trimer (Fig. 1) crystallises in the monoclinic space group $P2_1/c$ and is a 2,7-disubstituted indole, where the substituent indoles are pendant from the central indole via the two methylene linkages. There are two distinct trimers (A and B) within the unit cell with slightly differing structural parameters, as indicated in Table 1. The tetrahedral nature of the linkages enables the molecule to adopt a partial box configuration (Fig. 2). An edge-to-face arene–arene interaction[8] is apparent within the lattice between the edge of a chlorophenyl moiety of the central indole of one molecule and the face of a terminal 7,7-linked indole of the adjacent molecule (median distance

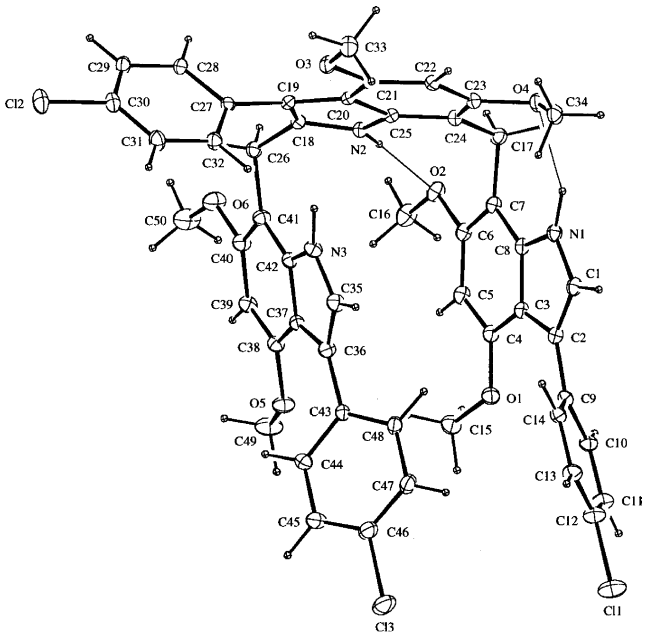


Figure 1. ORTEP view of trimer **8**, showing atom-labelling scheme for non-hydrogen atoms and the adopted partial box conformation. Thermal ellipsoids enclose 10% probability levels.

Table 1. Selected bond lengths (Å) and angles (°) for **8**

	Trimer A	Trimer B
Pendant indole interplanar angle	11.08	27.99
2,7- Linkage angle	116.04	115.03
7,7-Linkage angle	110.56	112.84
O2-HN2	1.982	1.904
O4-HN1	2.075	2.180

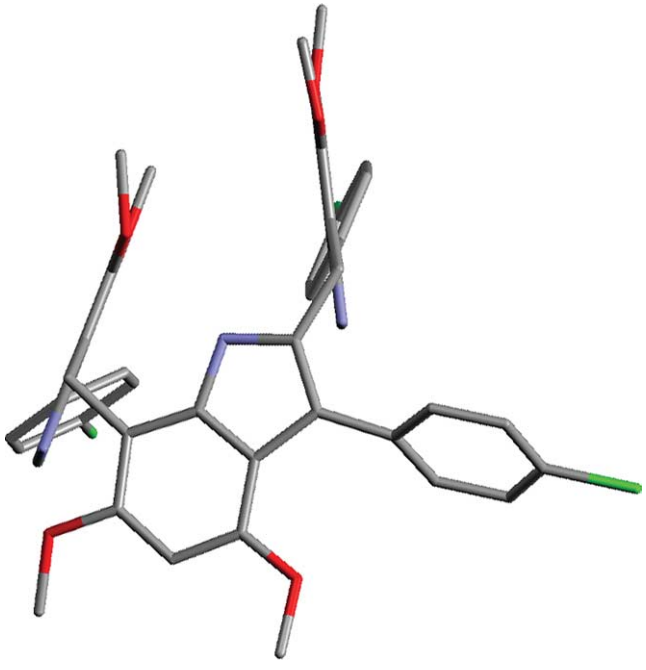


Figure 2. Partial molecular structure of **8**, showing the orientation of pendant indole substituents in substructure B. Hydrogen atoms have been removed for clarity.

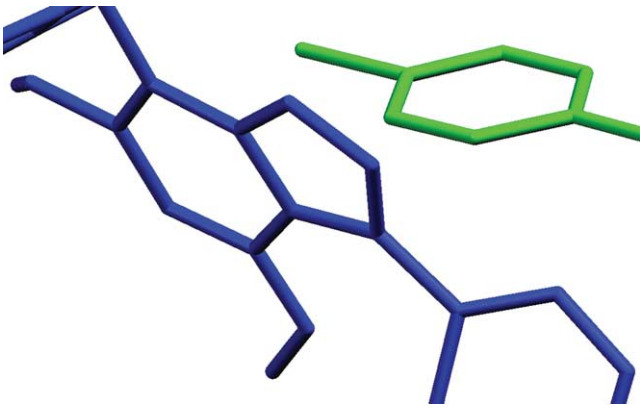


Figure 3. Partial unit cell diagram of **8**, showing a tilted T-shaped edge-to-face arene interaction. Hydrogen atoms have been removed and the illustrated portions of different molecules have been shaded for clarity.

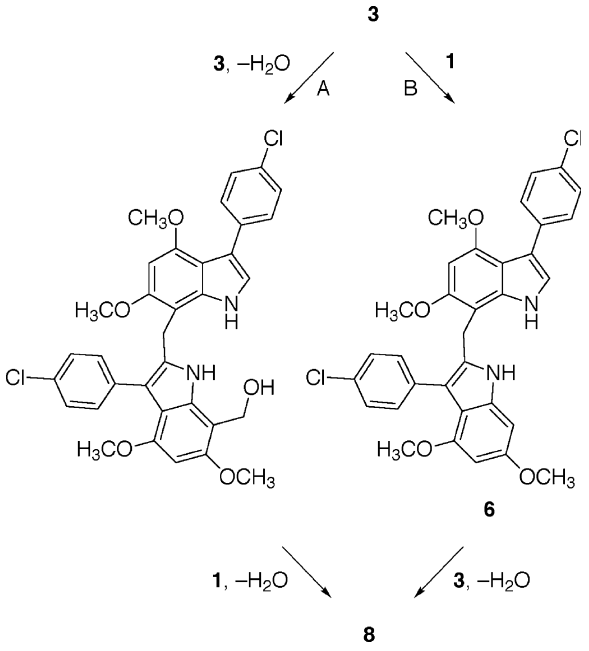
HC29A−C4B/C5B=2.800 Å, Fig. 3). The centroid-to-centroid distance of 5.267 Å is consistent with theoretical calculations for such tilted T-shaped interactions.[8] Selected bond lengths and angles for **8** are given in Table 1; crystallographic data are given in Table 2.

Table 2. Crystallographic data for **8**

Formula	$C_{50}H_{42}Cl_3N_3O_6$
M	887.3
Crystal system	Monoclinic
Space group	$P2_1/c$
a/Å	21.259(6)
b/Å	19.554(3)
c/Å	23.289(6)
α/°	90
β/°	116.75(1)
γ/°	90
u/Å^3	8645(4)
Z	8
*μ*Cu K_α/cm^{-1}	23.85
T/K	294
No. of reflections	
(total)	8865
(unique)	5021
R_{int}	0.014
R, R_w	0.064, 0.092

Two possible mechanisms exist for the formation of such an oligomer, outlined in Scheme 3. Mechanism A is possible but unlikely, as unsubstituted dimethoxyindoles have been observed in previous studies to attack benzylic alcohols preferentially via the C2 position.[7] Mechanism B involves the synthesis of the initial target 2,7-diindolylmethane precursor **6**, which then attacks another 7-hydroxymethylindole to form **8**. The slow addition of an excess of the 7-hydroxymethylindole **3** to the reaction mixture affords initially the 2,7-diindolylmethane **6**, but continued addition results in its total consumption and almost total isolation of the oligomer **8**, suggesting that mechanism B is favoured. Interestingly, the amount of 7,7-diindolylmethane **7** is also observed to increase under these conditions, indicating that it is the product of self-condensation of 7-hydroxymethylindole **3**.

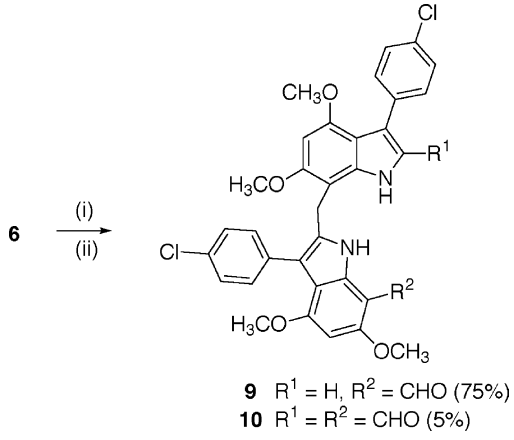
It was envisaged that reaction of the trimeric oligomer **8** with 1 equiv of a 2,7-dihydroxymethylindole **5** could lead to



Scheme 3. Reagents and conditions: (i) as in Scheme 2.

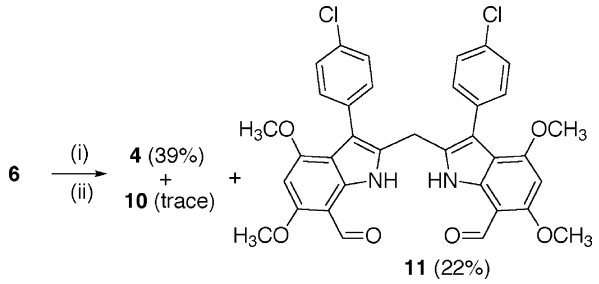
the synthesis of a tetrameric box-type structure, however, only polymeric material was obtained.

Vilsmeier formylation of **6** at −15 °C afforded mono- and diformyl products: **9** was isolated in a yield of 75% whilst the desired diformyl product **10** was obtained in a yield of only 5% (Scheme 4).



Scheme 4. Reagents and conditions: (i) $POCl_3$, DMF, −15 °C; (ii) NaOH, H_2O.

Clearly the relative nucleophilicities of the 2′- and 7-positions of **6** are very different, with 7-formylation preceding 2′-formylation as noted previously.[5] The reaction was investigated further, as **10** was not obtained quantitatively. When **6** was reacted with a slight excess of the Vilsmeier reagent at room temperature, work-up afforded only a trace of **10** and a large amounts of dialdehyde **4** and 2,2′-diindolylmethane-7,7′-dicarbaldehyde[6] **11** (Scheme 5) as identified by structural elucidation and comparison with authentic samples. It is believed that **10** is produced initially but rapidly decomposes into **4** and **11** via splitting of the diindolyl bridge and subsequent reaction with breakdown



Scheme 5. Reagents and conditions: (i) 1.5 equiv $POCl_3$, DMF, 20 °C; (ii) NaOH, H_2O.

products from **6**. Procedural variations failed to yield further **10**, as did alternative formylation reactions (data not shown). Since a reliable method of securing macrocyclic precursor **10** could not be found, a different approach to the synthesis of unsymmetrical macrocycles was warranted.

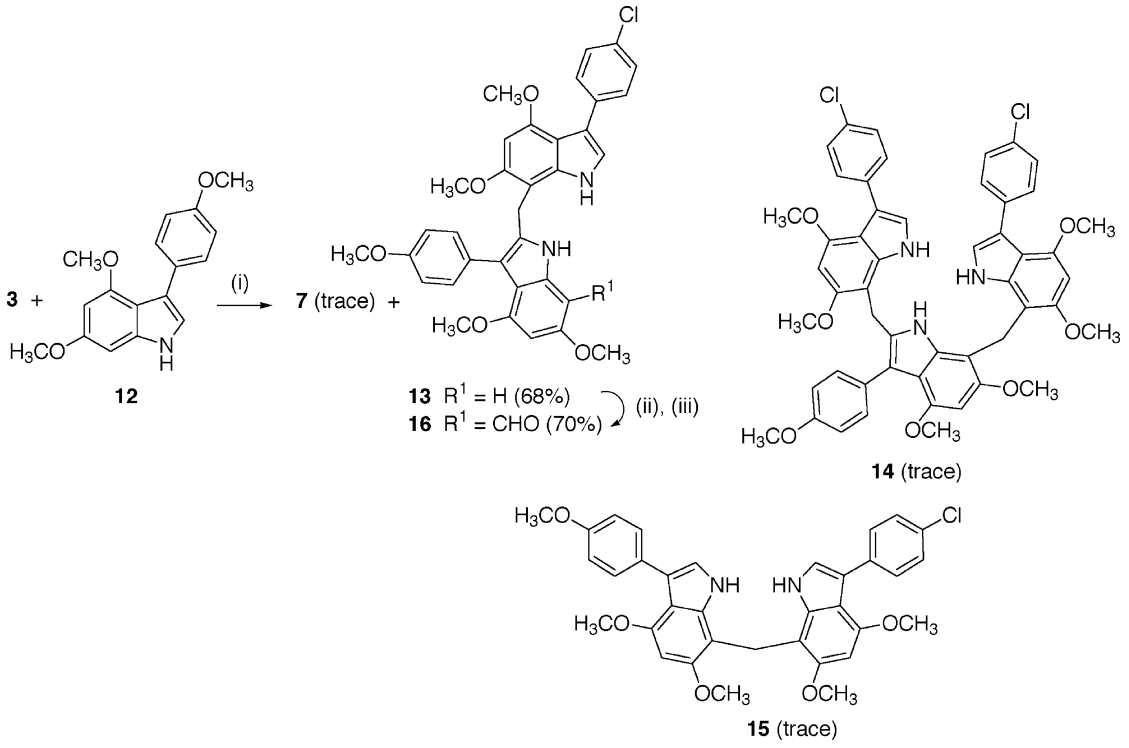
A higher yield of an analogue of the unsymmetrical macrocyclic precursor **6** was obtained by using the highly activated indole **12**[9] to produce **13** in addition to the two other products **14** and **15** (Scheme 6) in addition to **7**. The observation of **7**, **14** and **15** (trace amounts only; data not shown) supports the hypotheses that 7,7′-diindolylmethanes form through self-condensation of hydroxymethyl species, and that mechanism B (Scheme 3) is favoured for the formation of indolyl trimers of this type. Formylation of **13** gave the monoformyl derivative **16** in good yield, but consistently failed to produce the target diformyl species, which parallels the synthetic difficulties associated with the synthesis of **10**. The methylene resonance in the ^{1}H NMR spectrum of **16** (δ 4.21) shows moderate deshielding compared with the equivalent resonance in **9** (δ 4.16), indicating a difference in electron density about the respective sp^3 centres.

Clearly, electronic activity between the indole moieties of **6** and **13** prohibits diformylation under a range of conditions, requiring an alternative method of generating unsymmetrical ligand systems.

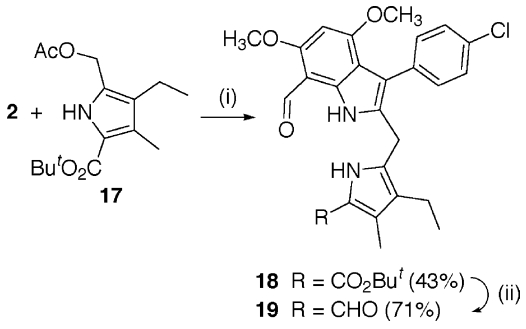
2.2. Indolylpyrrolylmethane ligand systems

It was initially envisaged that the employment of established methods of annular linkage would permit the synthesis of the desired 2- and 7-indolyl-pyrrole systems. However, the product of condensation between **3** and pyrrole was known to be highly unstable.[10] Clearly, the system required electronic deactivation and a simple way of effecting this was to introduce an electron-withdrawing formyl group to the already deactivated 3-halophenylindole molecule. The poor availability of the 2-formyl analogue of **2**[6] reduced the possibility of synthesising the 7-(2-pyrrolyl)indole structure in good yield. Further electronic stability was obtained by using pyrrole carboxylic ester **17**.

Thus, **2** and **17**[11] were combined to afford the indolyl-pyrrole ester intermediate **18**, which was treated with trifluoroacetic acid followed by an excess of triethylorthoformate[12] to give **19** (Scheme 7).



Scheme 6. Reagents and conditions: (i) as in Scheme 2; (ii) $POCl_3$, DMF, 0 °C; (iii) NaOH, H_2O.

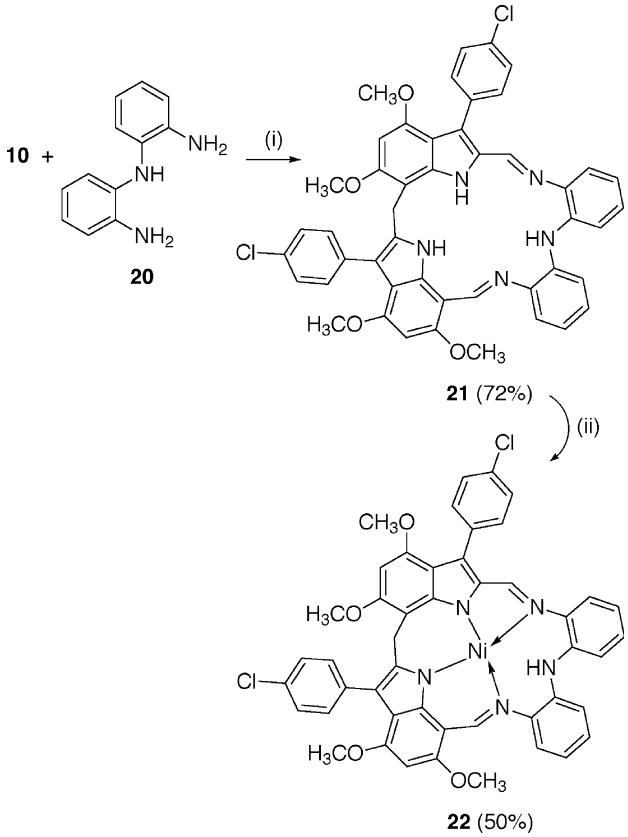


Scheme 7. Reagents and conditions: (i) K_{10} clay, N_2, CH_2Cl_2; (ii) N_2, TFA, TEOF.

2.3. Formation of macrocycles and metal complexes

Dialdehyde **10** and 1,2-diaminobenzene could not be condensed into a macrocycle using a standardised procedure,[5] presumably due to spatial incompatibility, however, **10** reacted with 2,2′-diaminodiphenylamine **20**[13] to yield the unsymmetrical macrocycle **21** (Scheme 8). The bridging NH resonance at δ 7.94 (Fig. 4) is markedly deshielded with respect to the field position of the bridging NH proton in the corresponding symmetrical 2,2′-linked system[6] (δ 6.85), reflecting the vastly different electronic environments in the geometric isomers. It is also an indication that the 2,7-methylene linkage is likely to behave significantly differently from the symmetrical 2,2′-diindolyl linkage during chemical manipulation, and supports the synthetic difficulties experienced during formylation reactions.

Ligand **21** was reacted with nickel(II) acetate tetrahydrate to yield the highly insoluble orange-brown complex **22** (Scheme 8), which gave a molecular ion corresponding to the NiL mass unit.



Scheme 8. Reagents and conditions: (i) C_6H_6, Δ, N_2; (ii) $Ni(OAc)_2 \cdot 4H_2O$, CH_3CN, Et_3N, Δ.

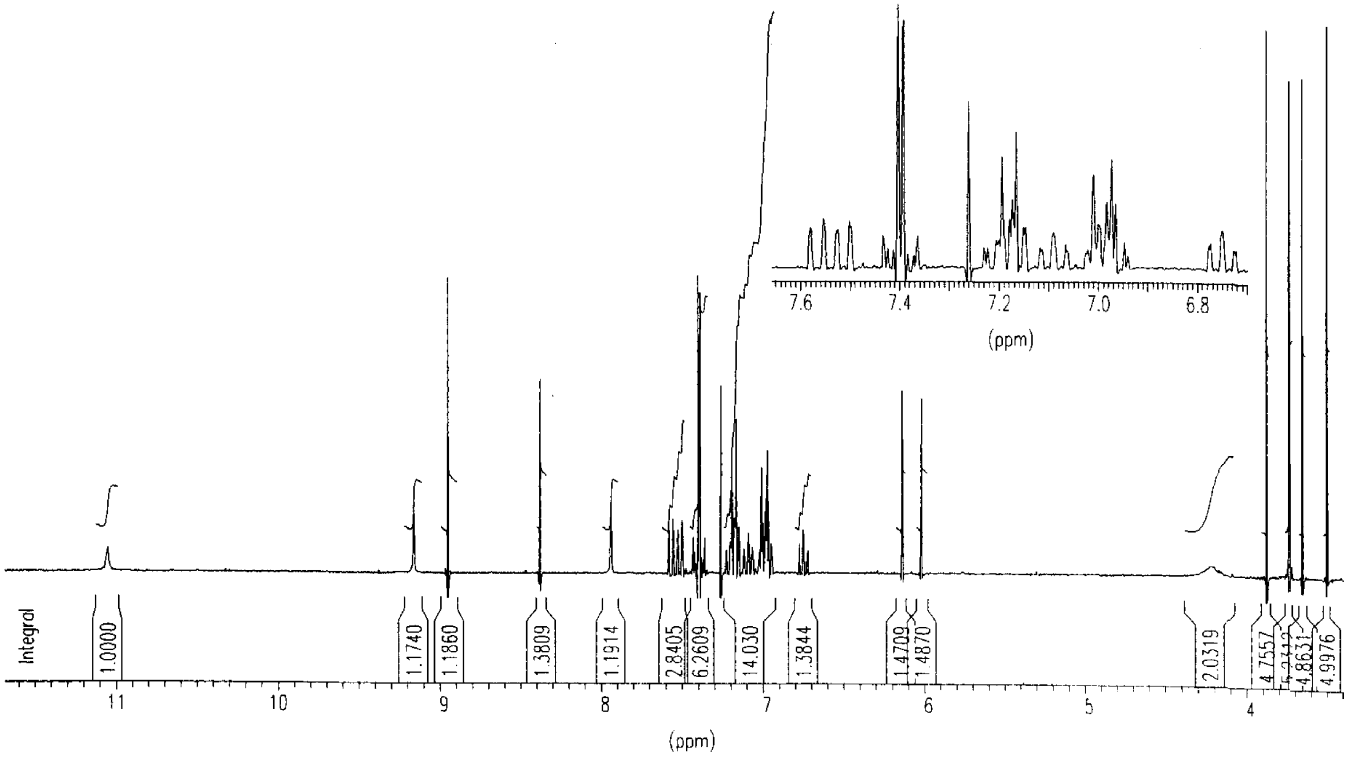
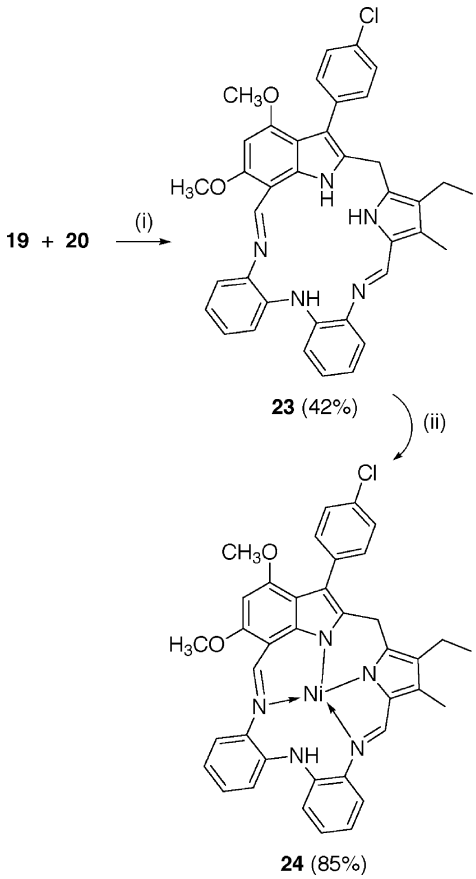


Figure 4. ^{1}H NMR spectrum (300 MHz; $CDCl_3$) of **21**, illustrating the unsymmetrical nature of the ligand.



Scheme 9. Reagents and conditions: (i) and (ii) as in Scheme 8.

Bisaldehyde **19** also failed to react with 1,2-diaminobenzene yet reacted with **20** to produce macrocycle **23** (Scheme 9). It is believed that the relatively low yield (42%) is a consequence of some strain in this rather unusual ligand, given that imine formation is an equilibrium process. Ligand **23** was treated with nickel(II) acetate tetrahydrate to afford red crystals of complex **24** (Scheme 9).

The presence of the nickel atom was confirmed by the mass spectral molecular ion corresponding to the ^{35}Cl M−1 isotopomer. The bridging amino group appears not to be involved in metal chelation due to the presence of a strong IR absorption at 3468 cm^{-1}, as noted in previous studies.[5] Both the colours of the complexes (for example, from previous studies[5] λ_{max}(square-planar)=517 nm with moderately intense red-brown colouration; λ_{max}(tetrahedral)=398 nm with highly intense dark brown colouration) and the ^{1}H NMR spectrum of complex **24** (only in the specific case of a square-planar Ni(II) complex is a diamagnetic spectrum obtained; other geometries generate paramagnetic spectra) indicate the presence of square-planar nickel.[5]

The reaction of **10** and **19** with larger diamino spacers resulted in the formation of polymeric materials only, indicating that these diformyl species are subject to very strict spatial compatibility limitations.

3. Conclusion

The acid-catalysed reaction of nucleophilic indoles with

hydroxymethylindoles leads to diindolylmethanes in a rather unselective manner. Unfavourable electronic interactions between indole groups in these unsymmetrical species made formylation exceedingly difficult, resulting in molecular decomposition. A viable alternative synthetic route to an asymmetric pentaazamacrocycle was developed via an indolylpyrrolylmethane. The macrocycles formed from these precursors were found to coordinate nickel(II) to yield square-planar neutral complexes.

4. Experimental

4.1. General information

Melting points are uncorrected. Microanalyses were performed by Dr. Pham of The University of New South Wales or the Microanalysis Unit of the Australian National University, Canberra. ^{1}H and ^{13}C NMR spectra were obtained in the designated solvents on a Bruker AC300F (300 MHz) spectrometer. Chemical shifts are quoted as δ values in $CDCl_3$ relative to internal Me_4Si unless otherwise stated; chemical shift measured in parts per million (ppm), proton count, multiplicity, observed coupling constant (J) in Hertz (Hz). Multiplicities are reported as singlet (s), broad singlet (s(br)), doublet (d), triplet (t), quartet (q) and multiplet (m). ^{13}C NMR chemical shifts are reported in ppm downfield from TMS (δ) and identifiable carbons are given. Infrared spectra were recorded as KBr discs on a Mattson Sirius 100 FTIR spectrometer. Ultraviolet–visible spectra were recorded in acetonitrile on a Hitachi UV-3200 spectrophotometer. EI mass spectra were recorded on an AEI MS 12 mass spectrometer at 70 eV ionising potential and 8000 V accelerating voltage with an ion source temperature of 210 °C. MALDI-TOF mass spectra were recorded on a Finnigan MAT Lasermat 2000. The principal ion peaks m/z are reported together with their percentage intensities relative to the base peak. Flash chromatography was carried out using Merck silica gel 7730 $60GF_{254}$.

Anhydrous tetrahydrofuran (THF) was distilled from potassium and benzophenone; *N*,*N*-dimethylformamide (DMF) was dried over calcium hydride then distilled under reduced pressure onto activated 4Å molecular sieves; chloroform ($CHCl_3$) was distilled from phosphorus pentoxide; diethyl ether was distilled from sodium and benzophenone. 3-(4-Chlorophenyl)-4,6-dimethoxyindole **1**,[9] 3-(4-chlorophenyl)-4,6-dimethoxyindole-7-carbaldehyde **2**,[5] 2,2′-diaminodiphenylamine **20**,[13] and pyrrolylester **17**[11] were prepared according to the literature procedures, or obtained from previous studies (**11**[6]). 1,2-Diaminobenzene was obtained commercially and purified before use. **14** and **15** were structurally confirmed by NMR and MS but not otherwise characterised.

4.2. Crystallography

The data were collected on a Nonius CAD-4 instrument. Crystallographic data are summarised in Table 2. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 181655. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +144 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.3. Preparation of diindolylmethanes

4.3.1. 3-(4-Chlorophenyl)-7-hydroxymethyl-4,6-dimethoxyindole (3). The 7-formylindole **2**[5] (1.00 g, 3.17 mmol) was dissolved in anhydrous THF with stirring, sodium borohydride (excess) was added and the mixture heated at reflux under a nitrogen atmosphere for 12 h. The colourless mixture was cooled to room temperature and the excess borohydride quenched by the slow addition of water (10 mL). THF was then removed under reduced pressure and the resulting solid filtered and washed with water (100 mL) to afford title compound **3** (0.099 g, 98%) as white microcrystals, mp 186–188 °C. (Found: C 64.6, H 5.4, N 4.1. $C_{17}H_{16}ClNO_3$ requires C 64.3, H 5.1, N 4.4) ν_{max} (KBr)/cm^{-1} 3437, 2994, 2951, 2836, 1622, 1599, 1566, 1553, 1518, 1498, 1464, 1451, 1429, 1397, 1346, 1331, 1310, 1275, 1252, 1206, 1173, 1144, 1109, 1092, 1017, 999, 936, 839, 816, 787, 749. λ_{max}/nm (ε/M^{-1} cm^{-1}) 230 (28,600), 285 (13,500), 301 (12,000). δ_H(299.95 MHz; $(CD_3)_2CO$; Me_4Si) 3.85 and 3.90 (6H, s, OCH_3), 5.04 (2H, d, J=5.6 Hz, CH_2), 6.31 (1H, s, indole H5), 7.06 (1H, d, J=2.6 Hz, indole H2), 7.31 and 7.51 (4H, dt, J=8.2, 2.6 Hz, chlorophenyl), 8.91 (1H, s(br), NH); sample too insoluble for δ_C; m/z (EI) 320 (M+1, ^{37}Cl, 3%), 319 (M, ^{37}Cl, 25), 318 (M+1, ^{35}Cl, 10), 317 (M, ^{35}Cl, 75), 299 (100).

4.3.2. 3-(4-Chlorophenyl)-4,6-dimethoxyindole-2,7-dicarbaldehyde (4). To a stirred solution of **1** (3.00 g, 10.5 mmol) in anhydrous DMF at 0 °C was added dropwise an ice-cold solution of phosphoryl chloride (excess) in DMF (3 mL). The mixture was stirred at this temperature for 1 h, then heated to 50 °C for 1 h. When no starting material remained (TLC) water followed by 2 M NaOH was added until a basic solution resulted. The solution was extracted with chloroform (3×150 mL) and the combined extracts washed with water until neutral rinsings were obtained. The organic layer was collected, dried ($MgSO_4$) and concentrated to afford title compound **4** (2.53 g, 70%) as yellow needles, mp 250–252 °C. (Found: C 63.1, H 4.4, N 3.9. $C_{18}H_{14}ClNO_4$ requires C 62.9, H 4.1, N 4.1) ν_{max} (KBr)/cm^{-1} 3420, 2971, 2851, 1645, 1591, 1566, 1534, 1515, 1478, 1452, 1431, 1400, 1377, 1353, 1335, 1235, 1219, 1161, 1121, 1092, 990, 862, 797, 735, 637, 610, 557. λ_{max}/nm (ε/M^{-1} cm^{-1}) 226 (19,500), 254 (24,200), 306 (16,700), 349 (22,100), 366 (18,600). δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 3.87 and 4.02 (6H, s, OCH_3), 6.17 (1H, s, indole H5), 7.39 and 7.44 (4H, d, J=8.7 Hz, chlorophenyl), 9.54 (1H, s, indole 2-CHO), 10.36 (1H, s, indole 7-CHO), 10.92 (1H, s(br), NH); δ_C(75.42 MHz; $CDCl_3$) 55.68 and 56.47 (2C, OCH_3), 87.57, 127.80 and 132.49 (5C, aryl CH), 104.03, 111.70, 128.31, 130.41, 132.15, 134.10, 138.09, 163.17 and 166.15 (9C, aryl C), 180.96 (1C, indole 2-CHO), 187.77 (1C, indole 7-CHO); m/z (EI) 346 (M+1, $^{35/37}$Cl, 5%), 345 (M, $^{35/37}$Cl, 35), 344 (M+1, $^{35/35}$Cl, 25), 343 (M, $^{35/35}$Cl, 100), 342 (M−1, $^{35/35}$Cl, 20).

4.3.3. 3-(4-Chlorophenyl)-2,7-dihydroxymethyl-4,6-dimethoxyindole (5). The 2,7-diformylindole **4** (0.500 g,

1.45 mmol) was dissolved in anhydrous THF and reacted with sodium borohydride according to the method of preparation of compound **3** to afford title compound **5** (0.479 g, 95%) as white microcrystals, mp 208–210 °C. (Found: C 60.9, H 5.1, N 3.6. $C_{18}H_{18}ClNO_4$ requires C 60.6, H 5.4, N 3.9) ν_{max} (KBr)/cm^{-1} 3362, 3229, 3003, 2959, 2938, 2907, 2841, 1624, 1601, 1568, 1551, 1524, 1495, 1466, 1451, 1433, 1397, 1368, 1346, 1289, 1263, 1215, 1181, 1157, 1123, 1105, 1092, 1057, 1024, 1009, 986, 909, 845, 822, 791, 766, 745, 716. λ_{max}/nm (ε/M^{-1} cm^{-1}) 214 (26,700), 230 (36,200), 284 (14,200), 300 (12,100). δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 3.74 and 3.90, (6H, s, OCH_3), 4.72 and 5.02 (4H, s(br), CH_2), 6.26 (1H, s, indole H5), 7.34 (4H, s, chlorophenyl), 9.08 (1H, s(br), NH); sample too insoluble for δ_C; *m/z* (EI) 350 (M+1, ^{37}Cl, 8%), 349 (M, ^{37}Cl, 35), 348 (M+1, ^{35}Cl, 20), 347 (M, ^{35}Cl, 100), 328 (50), 300 (45).

4.3.4. 3-(4-Chlorophenyl)-4,6-dimethoxy-2-(3-(4-chlorophenyl)-4,6-dimethoxyindol-7-ylmethyl)indole (6), 7,7′-di(3-(4′-chlorophenyl)-4,6-dimethoxyindolyl)methane (7) and 3-(4-chlorophenyl)-4,6-dimethoxy-2,7-di[3-(4-chlorophenyl)-4,6-dimethoxyindol-7-ylmethyl]indole (8). 3-(4-Chlorophenyl)-4,6-dimethoxyindole **1** (0.090 g, 0.32 mmol) was dissolved in the minimum amount of hot glacial acetic acid and added rapidly to solid **3** (0.100 g, 0.315 mmol) under a nitrogen atmosphere and the reaction monitored by TLC. After 10 min no further reaction was observed and water (10 mL) was added. The mixture was extracted with dichloromethane (3×50 mL), the organic layer washed with water to neutrality, collected, dried ($MgSO_4$) and the solvent removed. Three products were obtained using preparative TLC.

(i) The third uppermost band (R_f 0.6 in 70:30 dichloromethane/*n*-hexane), colouring green on exposure to iodine vapour, gave title compound **6** (0.061 g, 33%) as colourless plates, mp 279–280 °C. (Found: C 67.6, H 5.1, N 4.6. $C_{33}H_{28}Cl_2N_2O_4$ requires C 67.5, H 4.8, N 4.8) ν_{max} (KBr)/cm^{-1} 3428, 3349, 3003, 2932, 2839, 1624, 1595, 1564, 1549, 1514, 1489, 1464, 1451, 1337, 1308. 1211, 1163, 1144, 1128, 1117, 1090, 1051, 1013, 993, 966, 837, 824, 808, 789. λ_{max}/nm (ε/M^{-1} cm^{-1}) 232 (59,600), 378 (27,500), 301 (24,800). δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 3.73, 3.78, 3.84 and 4.05 (12H, s, OCH_3), 4.21 (2H, s, CH_2), 6.20 (1H, d, J=2.0 Hz, indole H5), 6.37 (1H, d, J=1.6 Hz, indole H7), 6.39 (1H, s, indole H5), 6.72 (1H, d, J=2.6 Hz, indole H2), 7.19 (1H, br d, J=2.0 Hz, NH), 7.29 and 7.44 (4H, dt, J=8.7, 2.6 Hz, chlorophenyl), 7.48 and 7.50 (4H, dt, J=8.7, 2.0 Hz, chlorophenyl), 8.33 (1H, s(br), NH); δ_C(75.42 MHz; $CDCl_3$) 20.87 (1C, CH_2), 55.03, 55.31, 55.57 and 57.36 (4C, OCH_3), 86.70 and 89.30 (2C, indole C5), 92.00 (1C, indole C7), 102.50, 110.69, 111.13, 112.32, 117.66, 131.46, 131.98, 132.54, 136.89 and 137.43 (12C, aryl C), 121.56 (1C, indole C2), 127.59, 127.85, 130.57 and 132.39 (8C, chlorophenyl CH), 153.19, 153.39, 154.19 and 157.25 (4C, *C*-OCH_3); *m/z* 591 (M, $^{37/37}$Cl, 2%), 590 (M+1, $^{35/37}$Cl, 3), 589 (M, $^{35/37}$Cl, 4), 588 (M+1, $^{35/35}$Cl, 16), 587 (M, $^{35/35}$Cl, 8), 586 (M−1, $^{35/35}$Cl, 20), 585 (M-2, $^{35/35}$Cl, 2), 303 (6), 302 (33), 300 (100), 287 (50).

(ii) The highest-R_f band (R_f 0.8 in 70:30 dichloromethane/*n*-hexane), colouring red on exposure to iodine vapour, gave title compound **7** (0.017 g, 9%) as white plates, mp 219–220 °C. (Found: C 67.3, H 5.0, N 4.6. $C_{33}H_{28}Cl_2N_2O_4$ requires C 67.5, H 4.8, N 4.8) ν_{max} (KBr)/cm^{-1} 3345, 2996, 2957, 2938, 2837, 1622, 1595, 1564, 1537, 1520, 1487, 1462, 1451, 1431, 1408, 1396, 1364, 1333, 1295, 1217, 1202, 1157, 1123, 1111, 1090, 1040, 1012, 990, 947, 862, 835, 793, 729. λ_{max}/nm (ε/M^{-1} cm^{-1}) 230 (67,300), 270 (25,200), 296 (33,000). δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 3.79 and 4.18 (12H, s, OCH_3), 4.30 (2H, s, CH_2), 6.39 (2H, d, J=2.0 Hz, indole H2), 7.29 and 7.45 (8H, dt, J=8.7, 2.6 Hz, chlorophenyl), 9.93 (2H, s(br), NH); δ_C(75.42 MHz; $CDCl_3$) 18.76 (1C, CH_2), 55.39 and 59.02 (4C, OCH_3), 90.30 (2C, indole C5), 105.10, 111.37, 117.58, 131.33, 134.79 and 138.12 (12C, aryl C), 122.01 (2C, indole C2), 127.63 and 130.65 (8C, chlorophenyl CH), 151.61 and 153.33 (4C, *C*-OCH_3); *m/z* (EI) 591 (M, $^{37/37}$Cl, 1%), 590 (M+1, $^{35/37}$Cl, 2), 589 (M, $^{35/37}$Cl, 3), 588 (M+1, $^{35/35}$Cl, 15), 587 (M, $^{35/35}$Cl, 8), 586 (M−1, $^{35/35}$Cl, 18), 300 (75), 287 (100), 237 (65).

(iii) The second uppermost band (R_f 0.7 in 70:30 dichloromethane/*n*-hexane), colouring olive green on exposure to iodine vapour, gave title compound **8** (0.003 g, 2%) as colourless needles, mp 159–161 °C. (Found: C 66.2, H 5.1, N 4.5. $C_{50}H_{42}Cl_3N_3O_6$ requires C 66.3, H 4.9, N 4.6) ν_{max} (KBr)/cm^{-1} 3434, 3372, 3308, 2996, 2938, 2837, 1622, 1597, 1562, 1514, 1522, 1489, 1464, 1427, 1398, 1335, 1273, 1215, 1155, 1109, 1013, 995, 945, 839, 791, 735. λ_{max}/nm (ε/M^{-1} cm^{-1}) 233 (98300), 286 (46000), 302 (44300). δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 3.55, 3.63, 3.71, 3.87 and 3.99 (15H, s, OCH_3), 4.14 (5H, s, OCH_3 +2,7-CH_2), 4.31 (2H, s, 7,7-CH_2), 6.00, 6.35 and 6.44 (3H, s, indole H5), 6.61 and 7.03 (2H, d, J=2.6, 2.1 Hz, indole H2), 7.36 (13H, m, chlorophenyl + NH), 9.74 and 9.87 (2H, s(br), NH); δ_C(75.42 MHz; $CDCl_3$) 18.61 (1C, 7,7-CH_2), 21.63 (1C, 2,2-CH_2), 55.12, 57.61, 57.83 and 59.09 (4C, OCH_3), 55.41 (2C, OCH_3), 89.75 (2C, indole C5), 90.45 (1C, indole C5), 101.89, 104.63, 105.19, 110.92, 112.70, 113.27, 117.07, 117.50, 131.29, 131.40, 131.80, 132.97, 134.39, 134.53, 134.82, 136.69 and 138.03 (19C, aryl C), 121.79 and 121.89 (2C, indole C2), 127.62 (6C, chlorophenyl CH), 130.55, 130.60 and 132.34 (6C, chlorophenyl CH), 151.31, 151.51, 152.69, 153.05, 153.50 and 154.05 (6C, *C*-OCH_3); *m/z* (EI) 891 (M+1, $^{35/37/37}$Cl, 1%), 890 (M, $^{35/37/37}$Cl, 2), 889 (M+1, $^{35/35/37}$Cl, 3), 888 (M, $^{35/35/37}$Cl, 4), 887 (M+1, $^{35/35/35}$Cl, 5), 886 (M, $^{35/35/35}$Cl, 4), 885 (M−1, $^{35/35/35}$Cl, 5), 300 (100), 84 (65), 44 (85).

4.3.5. 3-(4-Chlorophenyl)-4,6-dimethoxy-2-(3-(4-chlorophenyl)-4,6-dimethoxy-indol-7-ylmethyl)indole-7-carbaldehyde (9) and 3-(4-chlorophenyl)-4,6-dimethoxy-2-(3-(4-chlorophenyl)-4,6-dimethoxy-indol-7-ylmethyl)-indole-2,7-dicarbaldehyde (10). To a stirred solution of **6** (0.030 g, 0.051 mmol) in anhydrous DMF at −15 °C was added dropwise an ice cold solution of phosphoryl chloride (1 mL) in DMF (3 mL) and the mixture stirred for 30 min, then allowed to come to room temperature. Water (5 mL) was added and the mixture stirred for 1 h, made alkaline (pH 8) with 10% sodium hydroxide solution and stirred overnight. The mixture was extracted with dichloromethane (3×50 mL) and the organic layer washed to neutrality with water. The organic layer was collected, dried ($MgSO_4$), the

solvent removed and the crude product purified by preparative TLC (3 exposures in 50:50 dichloromethane/*n*-hexane eluent) to afford two bands.

(i) The higher R_f band gave title compound **9** (0.024 g, 75%) as yellow plates, mp 228–230 °C. (Found: C 66.6, H 4.8, N 4.3. $C_{34}H_{28}Cl_2N_2O_5$ requires C 66.4, H 4.6, N 4.6) ν_{max} (KBr)/cm^{-1} 3414, 3351, 2994, 2959, 2932, 2839, 1632, 1593, 1564, 1547, 1537, 1520, 1489, 1464, 1451, 1433, 1397, 1368, 1352, 1339, 1325, 1309, 1252, 1211, 1190, 1157, 1121, 1092, 1013, 993, 937, 831, 822, 797, 735. λ_{max}/nm (ε/M^{-1} cm^{-1}) 208 (39,600), 224 (36,400), 244 (30,700), 286 (15,200), 306 (15,600), 358 (6450). δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 3.79, 3.80, 3.93 and 4.17 (12H, s, OCH_3), 4.16 (2H, s, CH_2), 6.08 and 6.37 (2H, s, 2× indole H5), 6.69 (1H, d, J=2.6 Hz, indole H2), 6.94 (1H, s(br), NH), 7.26 and 7.41 (4H, dt, J=8.7, 2.6 Hz, chlorophenyl), 7.42 and 7.48 (4H, d, J=8.7 Hz, chlorophenyl), 10.34 (1H, s, CHO), 10.78 (1H, s(br), NH); δ_C(75.42 MHz; $CDCl_3$) 20.80 (1C, CH_2), 55.34 (2C, OCH_3), 56.35 and 56.66 (2C, OCH_3), 86.55 and 88.70 (2C, indole C5), 101.92, 104.34, 110.32, 111.04, 111.73, 117.86, 131.44, 134.40, 134.67, 136.30 and 137.29 (14C, aryl C), 153.29 (1C, *C*-C=O), 121.22 (1C, indole C2), 127.59, 128.05, 130.56 and 132.40 (8C, chlorophenyl CH), 160.41 and 162.46 (2C, *C*-OCH_3), 188.17 (1C, CHO); *m*/*z* 619 (M, $^{37/37}$Cl, 3%), 618 (M+1, $^{35/37}$Cl, 6), 617 (M, $^{35/37}$Cl, 10), 616 (M+1, $^{35/35}$Cl, 30), 615 (M, $^{35/35}$Cl, 20), 614 (M−1, $^{35/35}$Cl, 37), 300 (70), 299 (100).

(ii) The lower band colouring turquoise on exposure to iodine vapour gave title compound **10** (0.002 g, 5%) as yellow plates, mp 280–282 °C (dec). (Found: C 65.4, H 4.6, N 4.2. $C_{35}H_{28}Cl_2N_2O_6$ requires C 65.3, H 4.4, N 4.4) ν_{max} (KBr)/cm^{-1} 3408, 3262, 2969, 2939, 2876, 2845, 1678, 1655, 1647, 1636, 1618, 1593, 1561, 1551, 1539, 1525, 1514, 1503, 1489, 1464, 1451, 1435, 1398, 1368, 1354, 1331, 1279, 1254, 1223, 1192, 1179, 1157, 1117, 1092, 1059, 999, 841, 822, 801. λ_{max}/nm (ε/M^{-1} cm^{-1}) 262 (33,200), 325 (17,700), 361 (13,900). δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 3.74, 3.80, 3.94 and 4.17 (12H, s, OCH_3), 4.14 (2H, s, CH_2), 6.09 and 6.32 (2H, s, 2×indole H5), 7.35 and 7.36 (4H, s, chlorophenyl), 7.42 and 7.49 (4H, dt, J=8.7, 2.1 Hz, chlorophenyl), 8.03 (1H, s(br), NH), 9.38 (1H, s, indole 2-CHO), 10.32 (1H, s, indole 7-CHO), 10.64 (1H, s(br), NH); δ_C(75.42 MHz; $CDCl_3$) 20.71 (1C, CH_2), 55.23, 55.39, 56.38 and 56.61 (4C, OCH_3), 86.61 and 88.99 (2C, indole C5), 101.35, 104.28, 111.22, 112.30, 112.70, 128.75, 130.88, 131.50, 132.89, 133.54, 133.65, 133.68, 136.31 and 138.07 (14C, aryl C), 127.55, 127.82, 132.16 and 132.50 (8C, chlorophenyl CH), 155.91, 157.29, 160.72 and 162.62 (4C, *C*-OCH_3), 180.72 (1C, 2-CHO), 188.24 (1C, 7-CHO); *m*/*z* 645 (M, $^{35/37}$Cl, 1%), 644 (M+1, $^{35/37}$Cl, 4), 643 (M, $^{35/35}$Cl, 2), 642 (M−1, $^{35/35}$Cl, 5), 279 (100).

4.3.6. 2,2′-Di-3-(4′-chlorophenyl)-4,6-dimethoxyindolylmethane-7,7′-dicarbaldehyde (11). To a stirred solution of **6** (0.030 g, 0.051 mmol) in anhydrous DMF at −15 °C was added dropwise an ice cold solution of phosphoryl chloride (0.012 g, 0.077 mmol) in DMF (1 mL) and the mixture stirred for 30 min, then allowed to come to room temperature. Water (5 mL) was added and the mixture stirred for 1 h, made alkaline (pH 8) with 10% sodium hydroxide solution and stirred overnight. The mixture was extracted with dichloromethane (3×50 mL) and the organic layer washed to neutrality with water. The organic layer was collected, dried ($MgSO_4$), the solvent removed and the crude mixture purified by preparative TLC (3 exposures in 50:50 dichloromethane/*n*-hexane eluent) to afford two bands. The uppermost band (R_f 0.5 in dichloromethane) was identified as **10**, whilst the lower band (R_f 0.3) colouring blue on exposure to iodine vapour was identified as a mixture of coincident **4** (0.007 g, 39%) and the title compound **11** (0.007 g, 22%), mp 299–301 °C. (Found: C 65.1, H 4.5, N 4.1. $C_{35}H_{28}Cl_2N_2O_6$ requires C 65.3, H 4.4, N 4.4) ν_{max} (KBr)/cm^{-1} 3399, 3333, 2938, 2847, 1704, 1645, 1598, 1564, 1510, 1489, 1464, 1435, 1394, 1368, 1355, 1325, 1294, 1246, 1219, 1162, 1119, 1089, 1060, 1017, 988, 934, 850, 821, 795, 745, 720, 600, 566, 544. λ_{max}/nm (ε/M^{-1} cm^{-1}) 225 (41,100), 255 (54,000), 320 (24,500), 356 (19,000). δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 3.77 and 3.90 (12H, s, OCH_3), 4.06 (2H, s, CH_2), 6.07 (2H, s, indole H5), 7.29 (8H, s, chlorophenyl), 10.06 (2H, s(br), NH), 10.23 (2H, s, CHO); δ_C(75.42 MHz; $CDCl_3$) 23.39 (1C, CH_2), 55.38 and 56.41 (4C, OCH_3), 86.88, (2C, indole C5), 127.73 and 132.13 (8C, aryl CH), 104.28, 111.53, 114.05, 130.54, 132.26, 133.29 and 136.44 (18C, aryl C), 160.80 and 162.73 (4C, *C*-OCH_3), 188.21 (2C, CHO); *m*/*z* 585 (M+1, ^{37}Cl, 2%), 584 (M, ^{37}Cl, 4), 583 (M+1, ^{35}Cl, 4), 582 (M, ^{35}Cl, 10), 283 (100).

4.3.7. 3-(4-Methoxyphenyl)-4,6-dimethoxy-2-(3-(4-chlorophenyl)-4,6-dimethoxyindol-7-ylmethyl)indole (13). The reaction of 4,6-dimethoxy-3-(4-methoxyphenyl)indole **12** (0.256 g, 0.944 mmol) and 3-(4-chlorophenyl)-4,6-dimethoxy-7-hydroxymethylindole **3** (0.200 g, 0.629 mmol), as described for the reaction of compounds **1** and **3**, gave after thin-layer chromatography (R_f 0.4 in 70:30 dichloromethane/*n*-hexane), colouring dark green on exposure to iodine vapour, a white solid, which was washed with glacial acetic acid (5 mL), water (10 mL) then dried to afford title compound **13** (0.250 g, 68%) as colourless microcrystals, mp 199–200 °C. (Found: C 68.0, H 5.7, N 4.4. $C_{34}H_{31}ClN_2O_5 \cdot H_2O$ requires C 67.9, H 5.5, N 4.7) ν_{max} (KBr)/cm^{-1} 3403, 2996, 2957, 2934, 2837, 1624, 1595, 1559, 1518, 1505, 1489, 1464, 1435, 1420, 1335, 1295, 1287, 1242, 1215, 1200, 1179, 1149, 1120, 1098, 1047, 1032, 1015, 995, 949, 924, 835, 797. λ_{max}/nm (ε/M^{-1} cm^{-1}) 216 (56,300), 231 (66,200), 250 (27,000), 259 (23,000), 275 (27,600), 296 (25,000). δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 3.71, 3.79, 3.83, 3.93, and 4.05 (15H, s, OCH_3), 4.22 (2H, s, CH_2), 6.19 (1H, d, J=2.0 Hz, indole H5), 6.37 (1H, s, indole H5), 6.38 (1H, d, J=2.1 Hz, indole H7), 6.89 (1H, d, J=2.6 Hz, indole H2), 7.09 and 7.53 (4H, d, J=8.7 Hz, methoxyphenyl), 7.20 (1H, s(br), NH), 7.29 and 7.44 (4H, d, J=8.7 Hz, chlorophenyl), 8.29 (1H, s(br), NH); δ_C(75.42 MHz; $CDCl_3$) 20.76 (1C, CH_2), 55.17 (2C, OCH_3), 55.35, 55.60 and 57.40 (3C, OCH_3), 86.70 and 89.29, 2 (2C, indole C5), 91.87 (1C, indole C7), 103.09, 110.65, 112.91, 117.47, 128.39, 131.39, 132.35, 134.47, 136.89 and 137.50 (11C, aryl C), 113.30 and 132.19 (4C, methoxyphenyl CH), 121.62 (1C, indole C2), 127.58 and 130.56 (4C, chlorophenyl CH), 152.93, 153.24, 154.35, 157.07 and 158.14 (5C, *C*-OCH_3); *m*/*z* 585 (M+1, ^{37}Cl, 2%), 584 (M, ^{37}Cl, 4), 583 (M+1, ^{35}Cl, 4), 582 (M, ^{35}Cl, 10), 283 (100).

4.3.8. 3-(4-Methoxyphenyl)-4,6-dimethoxy-2-(3-(4-chlorophenyl)-4,6-dimethoxy-indol-7-ylmethyl)indole-7-carbaldehyde (16). To a stirred solution of the diindolylmethane **13** (0.200 g, 0.343 mmol) in anhydrous DMF at −15 °C was added dropwise an ice-cold solution of phosphoryl chloride (0.105 g, 0.686 mmol) in DMF (1 mL) until no starting material remained (TLC). Water (5 mL) was added and the mixture stirred for 1 h, then made alkaline (pH 8) with 10% sodium hydroxide solution. The mixture was extracted with dichloromethane (3×50 mL) and the organic layer washed to neutrality with water. The organic layer was collected, dried ($MgSO_4$), the solvent removed and the crude product purified by preparative TLC (dichloromethane eluent). The yellow band (R_f 0.4) gave title compound **16** (0.147 g, 70%) as yellow plates, mp 229–230 °C. (Found: C 68.5, H 5.4, N 4.3. $C_{35}H_{31}ClN_2O_6$ requires C 68.8, H 5.1, N 4.6) ν_{max} (KBr)/cm^{-1} 3414, 2999, 2935, 2843, 1636, 1595, 1573, 1561, 1510, 1487, 1464, 1439, 1404, 1370, 1354, 1331, 1296, 1285, 1245, 1215, 1196, 1181, 1138, 1119, 1092, 1034, 1015, 995, 831, 797. λ_{max}/nm (ε/M^{-1} cm^{-1}) 226 (48,400), 254 (38,900), 306 (18,800), 362 (9400). δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 3.71, 3.81, 3.82 and 3.97 (12H, s, OCH_3), 4.21 (5H, s, OCH_3+CH_2), 5.96 and 6.41 (2H, s, 2×indole H5), 6.73 (1H, s, indole H2), 7.13, 7.32 and 7.49 (9H, m, aryl H+NH), 10.40 (1H, s, CHO), 10.79 (1H, s(br), NH); δ_C(75.42 MHz; $CDCl_3$) 20.50 (1C, CH_2), 53.36, 55.06, 55.21, 55.85 and 56.47 (5C, OCH_3), 86.07 and 88.46 (2C, indole C5), 102.26, 104.00, 110.06, 111.03, 112.22, 117.45, 127.83, 131.10, 134.09, 134.41, 136.05 and 137.30 (12C, aryl C), 113.24 and 132.02 (4C, methoxyphenyl CH), 121.22 (1C, indole C2), 127.39 and 130.37 (4C, chlorophenyl CH), 153.01 (2C, *C*-OCH_3), 158.19, 160.39 and 162.11 (3C, *C*-OCH_3), 187.81 (1C, CHO); *m/z* 614 (M+1, ^{37}Cl, 3%), 613 (M, ^{37}Cl, 5), 612 (M+1, ^{35}Cl, 20), 611, (M, ^{35}Cl, 20), 610 (M−1, ^{35}Cl, 50), 324 (65), 311 (95), 299 (100).

4.4. Preparation of indolyl-pyrrolyl systems

4.4.1. 7-Formyl-*t*-butyl-5-(3-(4-chlorophenyl)-4,6-dimethoxyindol-2-ylmethyl)-4-ethyl-3-methylpyrrole-2-carboxylate (18). Under a nitrogen atmosphere **2** (0.500 g, 1.58 mmol) and **17** were stirred rapidly together with K_{10} clay (1.5 g) in dichloromethane (100 mL). After approximately 5 min the product spot was observed (R_f 0.3, CH_2Cl_2, colouring red in iodine vapour). The reaction was left stirring overnight then the mixture was filtered, the solvent removed and the residue purified chromatographically (80:20 dichloromethane/*n*-hexane). The band with R_f 0.2 gave title compound **18** (0.364 g, 43%) as yellow crystals, mp 110–111 °C. (Found: C 66.9, H 6.4, N 5.1. $C_{30}H_{33}ClN_2O_5$ requires C 67.1, H 6.2, N 5.2) ν_{max} (KBr)/cm^{-1} 3451, 3410, 3368, 2967, 2928, 2868, 1678, 1643, 1595, 1566, 1555, 1510, 1491, 1464, 1452, 1435, 1395, 1368, 1356, 1326, 1276, 1254, 1215, 1198, 1161, 1121, 1095, 1061, 1018, 993, 822, 797, 774, 748. λ_{max}/nm (ε/M^{-1} cm^{-1}) 211 (34,600), 252 (41,200), 276 (36,800), 322 (15,400), 354 (12,300). δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 1.01 (3H, t, J=7.5 Hz, CH_3), 1.51 (9H, s, Bu^t), 2.23 (3H, s, CH_3), 2.36 (2H, q, J=7.5 Hz, ethyl CH_2), 3.83 and 3.97 (6H, s, OCH_3), 3.96 (2H, s, CH_2), 6.15 (1H, s, indole H5), 7.29 and 7.33 (4H, d, J=8.7 Hz, chlorophenyl), 8.32 (1H, s(br), pyrrole NH), 10.25 (1H, s(br), indole NH), 10.33 (1H, s, CHO); δ_C(75.42 MHz; $CDCl_3$) 10.50 (1C, ethyl CH_3), 15.50 (1C, CH_3), 17.23 (1C, ethyl CH_2), 23.19 (1C, CH_2), 28.52 (3C, C(*C*H_3)), 55.41 and 56.42 (2C, OCH_3), 80.28 (1C, *C*CH_3), 86.92 (1C, indole C5), 127.75 and 132.00 (4C, chlorophenyl CH), 104.37, 111.43, 114.16, 119.24, 124.02, 125.92, 128.03, 130.56, 132.26, 133.37, 136.57, 160.80, 161.27 and 162.79 (14C, aryl C), 188.32 (1C, CHO); *m/z* 539 (M+1, ^{37}Cl, 5%), 538 (M, ^{37}Cl, 20), 537 (M+1, ^{35}Cl, 15), 536 (M, ^{35}Cl, 45), 165 (60), 57 (100).

4.4.2. 5-(3-(4-Chlorophenyl)-4,6-dimethoxyindole-2-ylmethyl)-4-ethyl-3-methylpyrrole-2,7-dicarbaldehyde (19). Under a nitrogen atmosphere **18** (0.300 g, 0.559 mmol) and TFA (5 mL) were stirred together at room temperature for 30 min, then triethylorthoformate (2 mL) was added dropwise. The solution was stirred for a further 45 min, water (20 mL) was added and the aqueous solution extracted with dichloromethane (3×100 mL). The organic layer was collected, dried ($MgSO_4$) and the solvent removed. The resulting solid was purified by preparative thin-layer chromatography to afford title compound **19** (0.185 g, 71%) as colourless microcrystals, mp 217–218 °C. (Found: C 65.6, H 5.5, N 5.8. $C_{26}H_{25}ClN_2O_4 \cdot 5\ H_2O$ requires C 65.9, H 5.5, N 5.9) ν_{max} (KBr)/cm^{-1} 3351, 3248, 2967, 2920, 2851, 1628, 1607, 1597, 1566, 1510, 1491, 1464, 1449, 1395, 1366, 1329, 1300, 1275, 1250, 1213, 1200, 1165, 1119, 1090, 993, 874, 820, 795, 669. λ_{max}/nm (ε/M^{-1} cm^{-1}) 210 (34,000), 253 (37,700), 309 (36,000), 354 (13,300). δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 1.00 (3H, t, J=7.7 Hz, CH_3), 2.20 (3H, s, CH_3), 2.29 (2H, q, J=7.7 Hz, CH_2), 3.82 and 3.92 (6H, s, OCH_3), 3.98 (2H, s, CH_2), 6.07 (1H, s, H5), 7.31 (4H, s, chlorophenyl), 9.28 (1H, s, pyrrole CHO), 9.79 (1H, s(br), pyrrole NH), 10.06 (1H, s, indole CHO), 10.81 (1H, s(br), indole NH); δ_C(75.42 MHz; $CDCl_3$) 8.70 (1C, ethyl CH_3), 14.96 (1C, CH_3), 16.81, (1C, ethyl CH_2), 23.34 (1C, CH_2), 55.32 and 56.26 (2C, OCH_3), 86.61 (1C, indole C5), 127.66 and 132.08 (2C, chlorophenyl CH), 104.29, 111.49, 114.86, 124.51, 128.23, 129.62, 132.19, 133.52, 135.50, 136.40, 160.66 and 162.60 (12C, aryl C), 175.86 (1C, pyrrole CHO), 187.67 (1C, indole CHO); *m/z* 467 (M+1, ^{37}Cl, 5%), 466 (M, ^{37}Cl, 30), 465 (M+1, ^{35}Cl, 20), 464 (M, ^{35}Cl, 85), 315 (55), 149 (100).

4.5. Preparation of macrocycles and metal complexes

4.5.1. 4,28-Di-(4-chlorophenyl)-6,8,30,32-tetramethoxy-11,18,25,34,35-pentaazaheptacyclo[25,5,2,2,^{3,9}0,^{5,36}0,^{12,17}0,^{19,24}0^{29,33}]hexatria-contane-1(32),3,5(36),6,8,10,12,14,16,19,21,23,25,27,29(33),30-hexadecaene (21). The bisaldehyde **10** (0.010 g, 0.016 mmol) and 2,2′-diaminodiphenylamine **20** (0.004 g, 0.02 mmol) were reacted according to the general Schiff base procedure.[5] The solution was heated at reflux for 14 h, after which all solvent was removed and the crude orange solid was purified by preparative thin-layer chromatography (80:20 dichloromethane/*n*-hexane eluent) to afford title compound **21** (0.009 g, 72%) as orange crystals, mp>280 °C (dec). (Found: C 69.7, H 4.6, N 8.6. $C_{47}H_{37}Cl_2N_5O_4$ requires C 70.0, H 4.6, N 8.7) ν_{max} (KBr)/cm^{-1} 3435, 3370, 2955, 2929, 2843, 1620, 1591, 1568, 1555, 1512, 1495, 1464, 1452, 1433, 1414, 1381, 1360, 1346, 1325, 1271, 1254, 1211, 1171, 1144, 1099, 1011, 993, 831, 818, 795, 743. λ_{max}/nm (ε/M^{-1} cm^{-1}) 222 (40,200), 264 (38,700), 316

(20,700), 364 (18,600), 444 (11,800). δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 3.50, 3.66, 3.75 and 3.88 (12H, s, OCH_3), 4.17 (2H, s(br), CH_2), 6.01 and 6.14 (2H, s, 2×indole H5), 6.75 (1H, t, $J=6.7$ Hz, aryl H), 6.98 and 7.19 (8H, m, aryl H+chlorophenyl), 7.09 (1H, t, $J=8.2$ Hz, aryl H), 7.37 and 7.41 (4H, d, $J=8.7$ Hz, chlorophenyl), 7.51 (1H, d, $J=7.2$ Hz, aryl H), 7.56 (1H, d, $J=7.7$ Hz, aryl H), 7.94 (1H, s, bridging NH), 8.38 and 8.95 (2H, s, CH=N), 9.16 and 11.05 (2H, s(br), indole NH); δ_C(75.42 MHz; $CDCl_3$) 21.56 (1C, CH_2), 55.16, 55.27, 55.58 and 56.63 (4C, OCH_3), 86.82 and 87.66 (2C, indole C5), 110.51, 115.72, 119.04, 119.33, 122.39, 122.81, 123.30, 126.79, 127.57, 131.58, 132.26 and 132.5 (12C, aryl CH), 112.47, 112.90, 114.44, 116.98, 120.05, 121.21, 123.31, 125.20, 127.42, 131.37, 131.50, 132.31, 132.88, 135.08, 135.68, 138.49, 139.39, and 144.02 (18C, aryl C), 154.41, 154.91, 158.12 and 159.11 (4C, *C*-OCH_3), 159.00 and 159.48 (2C, CH=N); *m/z* (MALDI) 805 (M−1, $^{35/35}$Cl, 100%).

4.5.2. {4,28-Di-(4-chlorophenyl)-6,8,30,32-tetramethoxy-11,18,25,34,35-pentaazaheptacyclo[25,5,2,2,^{3,9}0,^{5,36}0,^{12,17}0,^{19,24}0^{29,33}]hexatria-contane-1(32),3,5(36),6,8,10,12,14,16,19,21,23,25,27,29(33),30-hexadecaenato(2-)}nickel (II) (22). The macrocycle **21** (0.005 g, 6.2×10^{-3} mmol) was dissolved in the minimum amount of acetonitrile at 60 °C and triethylamine (2 drops) was added, followed by nickel(II) acetate tetrahydrate (0.002 g, 6.8×10^{-3} mmol). The orange solution was observed to darken on addition of the salt, and was heated at 60 °C for a further 3 h. The solution was filtered hot and the solvent removed to afford title compound **22** (0.003 g, 50%) as orange-brown microcrystals, mp >250 °C (dec). ν_{max} (KBr)/cm^{-1} 3444, 2955, 2929, 2843, 1590, 1575, 1554, 1509, 1492, 1453, 1449, 1432, 1413, 1376, 1362, 1346, 1324, 1269, 1254, 1210, 1172, 1146, 1097, 1010, 998, 836, 817, 794, 744. λ_{max}/nm ($\varepsilon/M^{-1}\,cm^{-1}$) 210 (sample too insoluble for the calculation of extinction coefficients), 220, 261, 232, 359. 446. *m/z* (MALDI) 864 (M+1, $^{35/35}$Cl, 20%), 805 (M-Ni, $^{35/35}$Cl, 70%).

4.5.3. 29-(4-Chlorophenyl)-2-ethyl-25,27-dimethoxy-3-methyl-8,15,22,30,32-pentaazacyclo[25,2,1,2,^{22,28}0,^{7,12}0^{14,19}]-dotriacontane-1,3,5,7,9,11,14,16,18,20,22,24,26(32),27-tetradecaene (23). The bisaldehyde **19** (0.030 g, 0.065 mmol) and **20** (0.012 g, 0.065 mmol) were reacted in anhydrous benzene according to the general Schiff base procedure.[5] After 48 h no further reaction was observed, the solution was allowed to cool to room temperature and all solvent was removed. The residue was purified by preparative thin-layer chromatography (70:30 CH_2Cl_2/*n*-hexane eluent) and the uppermost band collected to afford title compound **23** (0.017 g, 42%) as bright yellow crystals, mp 280–282 °C. (Found: C 70.7, H 5.8, N 10.5. $C_{38}H_{34}ClN_5O_2\cdot H_2O$ requires C 70.6, H 5.6, N 10.8) ν_{max} (KBr)/cm^{-1} 3457, 3366, 1605, 1580, 1562, 1507, 1479, 1464, 1412, 1383, 1362, 1327, 1294, 1271, 1213, 1171, 1121, 1094, 997, 895, 829, 795. λ_{max}/nm ($\varepsilon/M^{-1}\,cm^{-1}$) 210 (sample too insoluble for the calculation of extinction coefficients), 266, 324, 351, 397. δ_H(75.42 MHz; $CDCl_3$; Me_4Si) 0.99 (3H, t, $J=7.4$ Hz, ethyl CH_3), 2.18 (3H, s, CH_3), 2.30 (2H, q, $J=7.4$ Hz, ethyl CH_2), 3.81 and 3.92 (6H, s, OCH_3), 4.00 (2H, s, bridging CH_2), 6.25 (1H, s, indole H5), 6.88 (4H, m, aryl H+bridging NH), 7.11 (2H, m, aryl H), 7.21 (1H, dd, $J=7.7$, 1.3 Hz, aryl H), 7.32 and 7.37 (4H, d, $J=8.7$ Hz, chlorophenyl), 7.53 (2H, t, $J=9.0$ Hz, aryl H), 7.88 (1H, s(br), pyrrole NH), 8.32 (1H, s, pyrrole CH=N), 9.04 (1H, s, indole CH=N), 10.73 (1H, s(br), indole NH); δ_C(299.95 MHz; $CDCl_3$) 8.86 (1C, ethyl CH_3), 15.29 (1C, pyrrole CH_3), 17.13 (1C, ethyl CH_2), 22.79 (1C, bridging CH_2), 55.33 and 56.77 (2C, OCH_3), 87.97 (1C, indole C5), 102.48, 111.56, 114.53, 123.21, 125.02, 127.28, 129.95, 132.13, 133.74, 136.35, 136.57, 137.51, 138.44 and 143.97 (14C, aryl C), 111.61, 115.71, 116.49, 119.41, 120.11, 120.23, 125.72 and 125.81 (8C, aryl CH), 127.53 and 132.30 (4C, chlorophenyl CH), 142.96 (1C, pyrrole CH=N), 158.23 and 159.67 (2C, *C*-OCH_3), 158.78 (1C, indole CH=N); *m/z* (MALDI) 628 (M, ^{35}Cl, 100%).

4.5.4. {29-(4-Chlorophenyl)-2-ethyl-25,27-dimethoxy-3-methyl-8,15,22,30,32-pentaazacyclo[25,2,1,2,^{22,28}0,^{7,12}0^{14,19}]-dotriacontane-1,3,5,7,9,11,14,16,18,20,22,24,26(32),27-tetradecaenato(2-)}nickel(II) (24). Macrocycle **23** (0.070 g, 0.11 mmol) was suspended in acetonitrile, the mixture heated to 70 °C and triethylamine (3 drops) added. Nickel(II) acetate tetrahydrate (0.0305 g, 0.123 mmol) was added, resulting in an immediate colour change from yellow to blood red. The mixture was heated for a further 1 h then cooled to room temperature. The solution was filtered to remove impurities, and the filtrate concentrated under reduced pressure to afford title compound **24** (0.065 g, 85%) as red crystals, mp 300 °C (dec). (Found: C 66.6, H 4.8, N 10.0. $C_{38}H_{32}ClN_5NiO_2$ requires C 66.7, H 4.7, N 10.2) ν_{max} (KBr)/cm^{-1} 3468, 2967, 2932, 2843, 1572, 1528, 1503, 1470, 1400, 1383, 1364, 1344, 1263, 1235, 1179, 1135, 1088, 1011, 1003, 897, 847, 801, 750. λ_{max}/nm ($\varepsilon/M^{-1}\,cm^{-1}$) 228 (42,900), 276 (20,300), 296 (18,600), 316 (19,500), 461 (15,000), 562 (17,600). δ_H(299.95 MHz; $CDCl_3$; Me_4Si) 1.05 (3H, t, $J=7.4$ Hz, ethyl CH_3), 2.23 (3H, s, CH_3), 2.45 (2H, q, $J=7.4$ Hz, ethyl CH_2), 3.93 and 4.12 (6H, s, OCH_3), 4.77 (2H, s, bridging CH_2), 6.12 (1H, s, indole H5), 6.86 and 7.13 (8H, m, aryl H), 7.28 and 7.47 (5H, m, chlorophenyl+bridging NH), 8.18 (1H, s(br), pyrrole CH=N), 8.96 (1H, s, indole CH=N); Sample too insoluble for δ_C; *m/z* (MALDI) 683 (M−1, ^{35}Cl, 90%).

Acknowledgements

We are grateful to the Australian Research Council for financial support including an Australian Postgraduate Award to P. K. B.

References and notes

1. Black, D. Stc. ; Hartshorn, A. J.; Horner, M.; Hünig, S. *Aust. J. Chem.* **1977**, *30*, 2553.
2. Black, D. Stc. ; Hartshorn, A. J.; Horner, M.; Hünig, S. *Aust. J. Chem.* **1977**, *30*, 2493.
3. Black, D. Stc. ; Craig, D. C.; Kumar, N; Wong, L. C. H. *Chem. Commun.* **1985**, 1172.
4. Black, D. Stc. ; Brockway, D. J.; Moss, G. I. *Aust. J. Chem.* **1986**, *39*, 1231.

5. Black, D. Stc. ; Bowyer, P. K.; Craig, D. C.; Rae, A. D.; Willis, A. C. *J. Chem. Soc., Dalton Trans.* **2001**, 1948–1958.
6. Bowyer, P. K. Honours Thesis, UNSW, 1991.
7. Black, D. Stc. ; Bowyer, M. C.; Kumar, N.; Mitchell, P. S. R. *Chem. Commun.* **1993**, 819.
8. Jorgensen, W. L.; Severance, D. L. *J. Am. Chem. Soc.* **1990**, *112*, 4768–4774.
9. Black, D. Stc. ; Bowyer, M. C.; Bowyer, P. K.; Ivory, A.; Kim, M.; Kumar, N.; McConnell, D. B.; Popiolek, M. *Aust. J. Chem.* **1994**, *47*, 1741.
10. Bowyer, M. C. Ph.D. Thesis, UNSW, 1991.
11. Clezy, P. S.; Crowly, R. J.; Hai, T. T. *Aust. J. Chem.* **1982**, *35*, 411.
12. Clezy, P. S.; Fookes, J. R.; Liepa, A. J. *Aust. J. Chem.* **1972**, *25*, 1979.
13. Black, D. Stc. ; Rothnie, N. E. *Aust. J. Chem.* **1983**, *36*, 1141.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 61 (2005) 10793–10800

Pyridine mediated supramolecular assemblies of 3,5-dinitro substituted benzoic acid, benzamide and benzonitrile

Kapildev K. Arora, Jayarama PrakashaReddy and Venkateswara Rao Pedireddi*

Division of Organic Chemistry, Solid State and Supramolecular Structural Chemistry Lab, National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411 008, India

Received 16 May 2005; revised 11 August 2005; accepted 19 August 2005

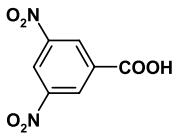
Available online 16 September 2005

Abstract—Synthesis and characterization of molecular assemblies of pyridine adducts, **1a**, **2a** and **3a**, of 3,5-dinitrobenzoic acid, **1**, 3,5-dinitrobenzamide, **2** and 3,5-dinitrobenzonitrile, **3**, respectively, have been reported. All these adducts were obtained by crystallization of **1**, **2** and **3** from pyridine. However, crystallization of **1** from pyridine in the presence of benzene resulted in the formation of a pyridinium adduct, **1b**, along with a water molecule. All the adducts crystallize in a 1:1 molecular ratio except **1a**, which forms a 1:2 adduct, as characterized by single crystal X-ray diffraction method. The adducts crystallize in different space groups—**1a**, orthorhombic, $Pna2_1$; **1b**, monoclinic, $P2_1$; **2a**, monoclinc, C2/c; **3a**, triclinic, $P\bar{1}$. In two-dimensional arrangement, **1a**, **1b** and **3a** form sheet structures. In **1a**, within the two-dimensional sheets, large cavities are formed, which are occupied by pyridine molecules. In **1b**, the sheets are catenated to form a chicken-wire network. However, **2a** formed a crossed ribbon packing pattern with empty channels in the three-dimensional structure.

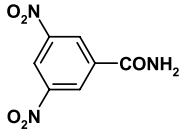
1. Introduction

Organic solvents, which are often used to create a conducive environment to carry out chemical reactions at accelerated rates,[1] because of the increased mobility of molecules and/or ions in solution medium, also play an important role towards the purification of compounds in the solid form through crystallization or recrystallization.[2] Thus, it is expected that solvent of crystallization would not affect the molecular composition, physical properties etc. of the compounds after crystallization. However, there are some examples in the literature, which are in fact exponentially increasing (especially in recent years), wherein the influence of the solvents is remarkably seen with the formation of different type of three-dimensional structures depending upon the solvent of crystallization. This phenomenon is well recognized as polymorphism and it has emerged as one of the frontier areas of research especially in solid state organic chemistry.[3–6] Another facet of crystallization process is the occlusion of solvents into the crystal lattice along with the substrate(s) leading to the formation of a variety of supramolecular architectures. In fact, some compounds are known to crystallize only along with the solvent of crystallization in the crystal lattice. For instance, trithiocyanuric acid,[7] 1,2,4,5-benzenetetracarboxylic acid etc. have not been reported to date without solvent molecules in their solid state structures.[8]

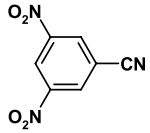
One of the plausible explanations for the incorporation of the solvents into the crystal lattice is the availability of void space in the crystal lattice. However, it is not so clear whether solvents influence the creation of the void space or whether the solute molecules arrange themselves forming the voids. This dilemma is due to the fact that some compounds form solvated assemblies with and without cavities depending upon the solvent of crystallization. The ability of functional groups on the solvent molecules to interact with functional groups on solute molecule also often plays a crucial role for the incorporation of the solvents in the crystal lattices.[9] In this connection, the formation of molecular adducts of cyanuric acid with solvents like dimethylsulfoxide, dimethylamine, dimethylformamide,[10] reported by us recently, is one of the best known examples to demonstrate solute-solvent interaction.



1



2



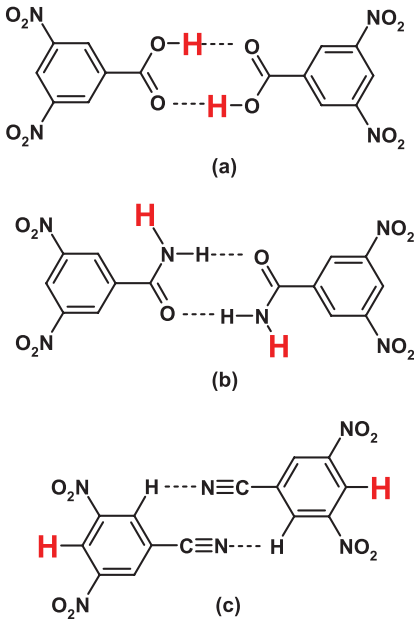
3

Keywords: 3,5-Dinitrobenzoic acid; 3,5-Dinitrobenzamide; 3,5-Dinitrobenzonitrile; Pyridine; Host–guest complexes; Molecular recognition; Channel structures; Layered structures.
* Corresponding author. Tel.: +91 20 25902097; fax: +91 20 2589 3153; e-mail: vr.pedireddi@ncl.res.in

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.08.080

However, studies pertaining to the influence of a solvent on the formation of different type of structures on analogous compounds, which differ from each other by a particular functional group are not well known. In this report, we present such a study by crystallizing 3,5-dinitrobenzoic acid, **1**, 3,5-dinitrobenzamide, **2** and 3,5-dinitrobenzonitrile, **3**, from pyridine.

We have chosen compounds **1**, **2** and **3**, based on our prior experience of utilizing them for the creation of novel supramolecular assemblies.[11–13] All three compounds, in their parent crystal structures, exist as dimers due to the formation of hydrogen bonds as shown in Scheme 1.[13a,14] It is evident from these structural patterns that pyridine can interact in different modes with **1**, **2** and **3** by establishing recognition with the acidic hydrogen atoms, highlighted in red in Scheme 1, through the formation of different type of hydrogen bonds, O–H···N, N–H···N and C–H···N. For this purpose, we crystallized **1**, **2** and **3** along with pyridine. The choice of pyridine is obviously due to its basic nature, which facilitates interaction with acidic hydrogen atoms to form hydrogen bonds or abstraction of hydrogen atoms to yield ionic hydrogen bonds through the formation of pyridinium species.



Scheme 1. Similarity in the hydrogen bond motifs formed in 3,5-dinitrobenzoic acid, **1**, amide, **2** and nitrile, **3**.

2. Results and discussion

All three compounds **1**, **2** and **3** yield pyridine adducts upon crystallization from pyridine. We labeled the resultant adducts as **1a**, **2a** and **3a**, respectively. However, crystallization of **1** from pyridine in the presence of benzene gave an entirely different adduct and we labeled it as **1b**. Analysis of the packing arrangement of the constituents reveals that in all the adducts, **1a**, **1b**, **2a** and **3a**, the recognition pattern between pyridine and the corresponding substrate, as anticipated, occurred through the formation of O–H···N, N–H···N and C–H···N hydrogen bonds except in **1b**. The salient features of these structures will be discussed in detail independently followed by a comparison of the structures.

2.1. Adduct of 3,5-dinitrobenzoic acid and pyridine, 1a

3,5-Dinitrobenzoic acid crystallizes from pyridine in a 2:1 molecular ratio as determined by single crystal X-ray diffraction methods. An ORTEP drawing of the contents of the asymmetric unit is shown in Figure 1.

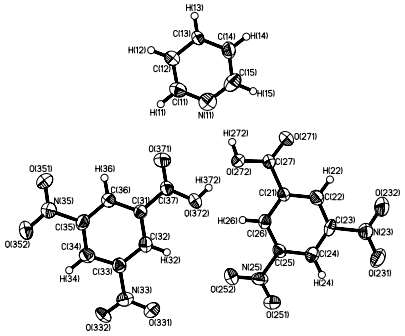


Figure 1. ORTEP (50% probability level) drawing of the molecular adduct of 3,5-dinitrobenzoic acid and pyridine, **1a**.

Crystal structure analysis reveals that recognition between acid, **1** and pyridine molecules is established through the formation of pair-wise hydrogen bonds O–H···N and C–H···O (H···N, 1.98 and H···O, 2.45 Å, Table 1), which are well-known to form between carboxyl group and aza donor compounds. The recognition pattern and assembly of the molecules into a two-dimensional arrangement is shown in Figure 2.

Further analysis discloses that both the symmetry independent acid molecules interact with each other in such a manner that a cluster of six molecules (three from each one) form a hexagonal ensemble by connecting together exclusively by C–H···O hydrogen bonds (Fig. 2a) through different types of cyclic networks. One of the networks is formed due to the interaction between a $-NO_2$ group and a phenyl hydrogen with H···O distances of 2.49 and 2.91 Å. The other two networks are formed between phenyl hydrogen atoms and the oxygen atoms of the carboxyl group as well as $-NO_2$ group. The H···O distances in these patterns are 2.29, 2.94; 2.61, 2.87 Å (Table 1).

Finally, this ensemble created a cavity of ~8 Å in dimension, which is being occupied by pyridine molecules. Thus, this assembly demonstrates, further, the influence of weak hydrogen bonds such as C–H···O bonds towards the formation of specific architecture even in the presence of potential strong hydrogen bonds. In the crystal lattice, the assembly constitutes two-dimensional corrugated sheets, which are further stacked in a three-dimensional arrangement as shown in Figure 2b.

In three-dimensional stacking, however, the sheets are not aligned; hence, the cavities which appeared in two-dimensional arrangement could not constitute channels. Such a situation was encountered earlier in some other complexes of 3,5-dinitrobenzoic acid.[11c,e] For example, a

Table 1. Details of characteristics of hydrogen bonds (distances, Å and angles, °) in the adducts, **1a**, **1b**, **2a** and **3a**[a]

Hydrogen bonds	**1a**			**1b**			**2a**			**3a**		
O–H···O	1.69	2.50	163.6									
O–H···N	1.98	2.80	166.5									
N^+-H···O^-				1.66	2.59	172.5						
N–H···O							1.97	2.90	173.1			
N–H···N							2.08	2.94	167.0			
C–H···O	2.29	3.13	148.3	2.59	3.40	160.3	2.49	3.43	168.1	2.49	3.25	137.0
	2.45	3.28	146.8	2.63	3.35	132.4	2.57	3.47	155.4	2.53	3.35	143.6
	2.46	3.21	137.0	2.65	3.29	128.2	2.58	3.25	127.7	2.67	3.54	159.2
	2.49	3.32	146.9	2.70	3.35	131.3				2.80	3.52	132.5
	2.61	3.43	146.0	2.72	3.60	161.0						
	2.73	3.57	150.4	2.77	3.67	153.6						
	2.87	3.81	177.6	2.78	3.40	127.1						
	2.91	3.85	178.0									
C–H···N							2.54	3.37	151.9	2.34	3.27	166.8
										2.64	3.50	149.6
										2.73	3.55	143.6

[a] In each column, the numbers correspond to distances H···donor, acceptor···donor and angles of donor -H···acceptor.

molecular complex of 3,5-dinitrobenzoic acid and anthracene in the presence of benzene is one of the representative examples.[11e]

A close look at Figure 2a led us to question ourselves whether a molecule similar to pyridine in dimension would perturb the host–guest arrangement noted in the adduct **1a**. For this purpose, we attempted crystallization of adduct **1a** in the presence of benzene, as pyridine and benzene are very much alike in their dimensions. Characterization of the crystals, thus, obtained revealed that, indeed, a different type of molecular adduct, **1b**, was obtained.

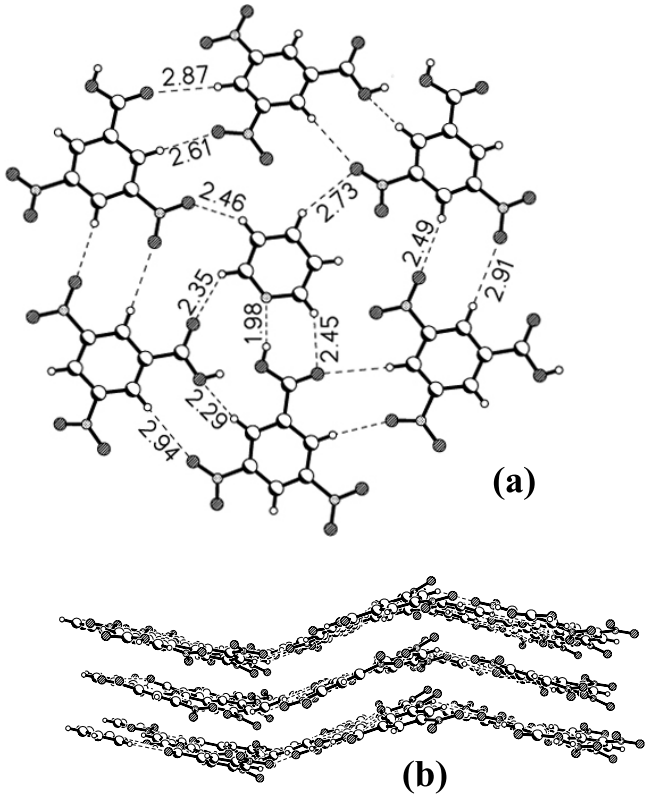


Figure 2. (a) Arrangement of cluster of molecules of 3,5-dinitrobenzoic acid, **1** forming a cyclic network with a cavity, which is being occupied by pyridine molecule. Notice the stabilization of the cluster by C–H···O hydrogen bond cylic networks. Hydrogen bond distances are in Å. (b) Stacking of corrugated sheets in three-dimensional arrangement.

2.2. Adduct of 3,5-dinitrobenzoic acid and pyridine from benzene, 1b

Crystal structure determination by X-ray diffraction methods reveals that **1b** is an adduct of 3,5-dinitrobenzoate and pyridinium along with a water molecule in a 1:1:1 ratio as shown in Figure 3. This is indeed a surprising adduct at least for three reasons—(i) incorporation of water molecule and absence of benzene in the crystal lattice, (ii) deprotonation of acid molecule and (iii) crystallization into chiral space group.[15] With this noted differences between **1a** and **1b** due to the presence of benzene during the crystallization process, we carried out crystallization of **1a** from some other solvents as well, like methanol, to study the effect of the solvent on the formation of adduct between **1** and pyridine. The resultant crystals, however, are similar to **1a** suggesting that benzene played a crucial role for the formation of adduct of **1b**.

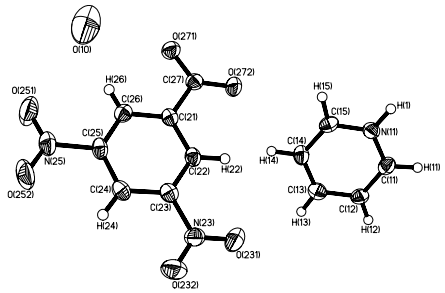


Figure 3. An ORTEP (50% probability level) drawing of molecular adduct, **1b**.

Analysis of the arrangement of molecular components in the adduct **1b**, reveals that **1** and pyridinium interact with each other through the formation of pair-wise N^+–H···O^- and C–H···O hydrogen bonds rather than O–H···N and C–H···O hydrogen bonds, due to the process of deprotonation. The H···O^- and H···O distance are 1.66 and 2.63 Å (Table 1), respectively. The recognition pattern and two-dimensional

arrangement of molecules in the crystal lattice is shown in Figure 4. The adjacent ensembles connect to each other through C–H···O hydrogen bonds forming hexagonal assemblies, with cavities of dimension ~10 Å. Such assemblies are further held together by C–H···O hydrogen bonds with H···O distances of 2.65 and 2.72 Å (Table 1), as depicted in Figure 4a.

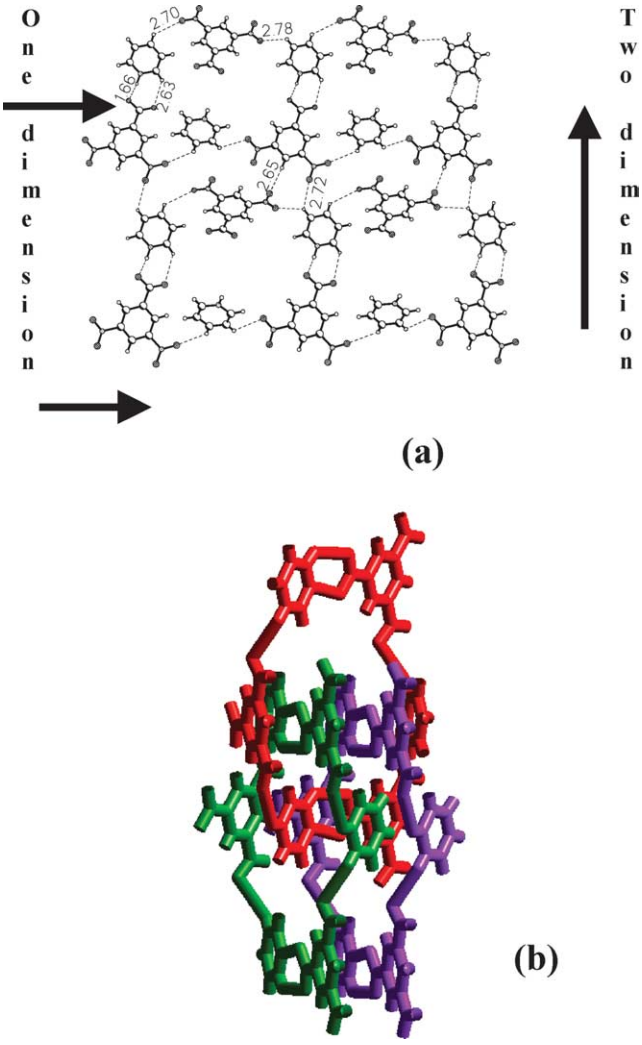


Figure 4. (a) Two-dimensional arrangement of molecular components in the adduct **1b**. Notice the formation of cavities due to the self-assembly of neighbouring molecules. Hydrogen bond distances are in Å. (b) Catenation of three adjacent cyclic networks.

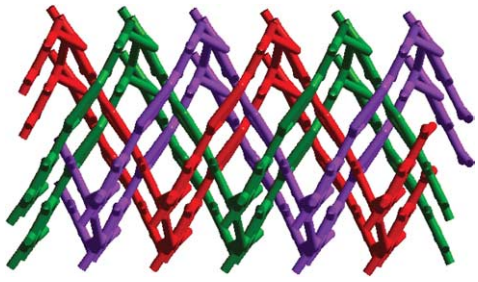


Figure 5. Catenation of each of the three adjacent sheets forming a chicken-wire frame-work. The three sheets are shown in different colours.

The cavities seen in these two-dimensional sheets are, however, not completely available to fill with guest molecules as the adjacent sheets catenate yielding a chicken-wire frame-work. The catenation of sheets is shown in Figures. 4b and 5. Because of this unusual catenation, the real void space is minimized to ~6 Å, but this space constitutes channels in the three-dimensional arrangement, which are being occupied by water molecules. The channel structure with water molecules is shown in Figure 6. An interesting feature is that analysis of channels reveals that channels are formed due to the overlay of helices as shown in Figure 6b.

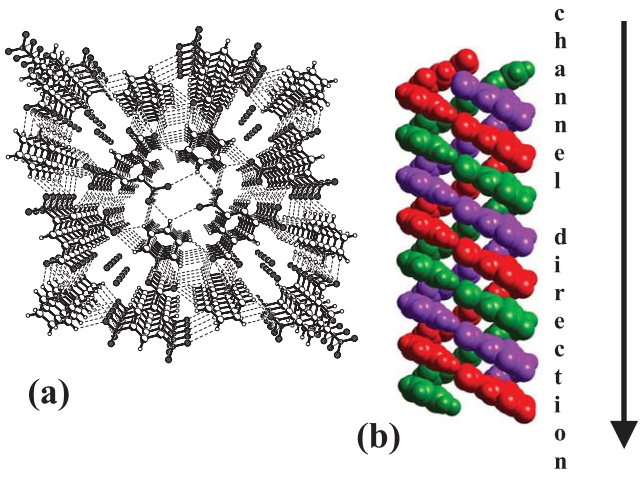


Figure 6. (a) Representation of three-dimensional packing of sheets observed in the adduct **1b**. Notice the channels being occupied by water molecules. (b) Dissection of channels to reveal the overlay of helices.

A comparison of **1a** and **1b** reveals that the structures of both the adducts are closely related in the two-dimensional arrangement with the formation of sheet structures but drastically differ in three-dimensional arrangement. Such a distinct difference appears to be the result of formation of pyridinium in **1b**. This led us to perform a statistical analysis of pyridine and pyridinium adducts using CSD[16] to find precedent examples of the present findings in the literature. It has been noted that a very few systems like formic acid have structures with pyridine as well as pyridinium. However, the adducts are mostly alike in terms of molecular packing, unlike, as we noted in **1a** and **1b**. Nevertheless the CSD analysis revealed further interesting information about the nature of the adducts of pyridine and pyridinium.

CSD Analysis:

A search was performed on CSD version 5.26, consisting of 325709 crystal structures of organic and organometallic compounds,[17] to obtain the total number of pyridine and pyridinium adducts. It retrieved 298 entries, of which 162 correspond to pyridine adducts and 124 are pyridinium structures (see Supplementary information). In addition, six compounds (refcodes: LAQYEH, PIRLUX, PYDMPS, SITTAQ, XICBAM, XIMXIA)[18] possess both pyridine and pyridinium within an asymmetric unit. Also, it is interesting to note that only two compounds (formic acid and hydrogen fluoride) reported by Mootz and co-workers[19] form neutral and ionic adducts like in the present study.

Further analysis reveals that, the aromatic carboxyl derivatives form adducts through pyridinium only rather than pyridine and neither of the structures form channel type assemblies. Thus, adducts **1a** and **1b** are novel pyridine adducts, without deprotonation of either of the two acid molecules in **1a** and forming a channel structure in **1b**. With these encouraging observations, we carried out crystallization of **2** and **3** from pyridine to evaluate the solvent effect on the homologous compounds.

2.3. Adduct of 3,5-dinitrobenzamide and pyridine, 2a

3,5-Dinitrobenzamide forms single crystals in a 1:1 molar ratio (see Fig. 7) upon crystallization from pyridine by occluding solvent of crystallization. Both the components recognize each other through the formation of N–H···N hydrogen bonds, as anticipated, between the *anti*-hydrogen atom of the amide functionality and the pyridyl nitrogen. The H···N distance and N–H···N angle are 2.08 Å and 167° (Table 1) respectively. Such a recognition pattern generated an infinite molecular tape in such a manner that pyridine molecules exist as pendant groups to a chain of amide molecules which are connected together by cyclic centrosymmetric N–H···O hydrogen bonds (H···O, 1.97 Å) as well as C–H···O (H···O, 2.49 Å) hydrogen bonds. This arrangement is shown in Figure 8.

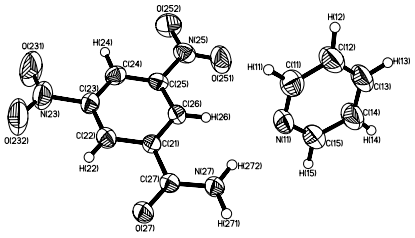


Figure 7. ORTEP (50% probability level) drawing of a molecular complex of 3,5-dinitrobenzamide and pyridine, **2a**.

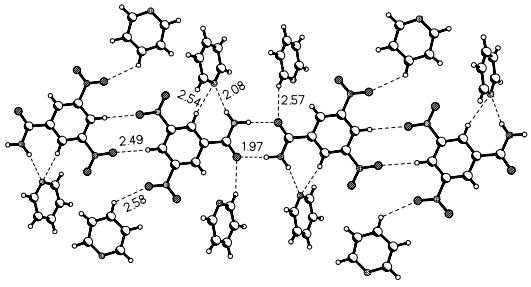


Figure 8. Recognition pattern between pyridine and amide, **2** in the crystal structure of adduct, **2a**. Also, notice the chain of amide molecules. Hydrogen bond distances are in Å.

The molecular tapes are arranged in three dimensions in a crossed manner (Fig. 9) and the tapes make an angle of 95° with each other. Such tapes are linked together by C–H···O hydrogen bonds with a H···O distance of 2.58 Å.

2.4. Adduct of 3,5-dinitrobenzonitrile and pyridine, 3a

3,5-Dinitrobenzonitrile, **3**, crystallizes from pyridine incorporating the solvent into the crystal lattice to yield a 1:1 molecular adduct as shown in Figure 10. The structure

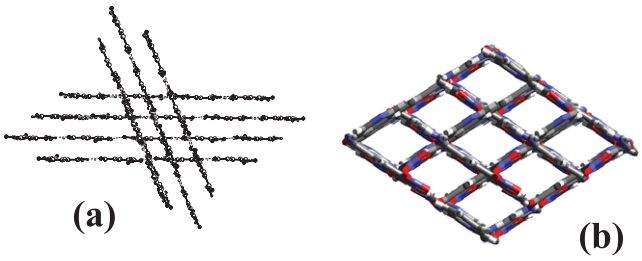


Figure 9. (a) Crossed tapes arrangement in the adduct, **2a**. (b) representation of three-dimensional arrangement in cylinders mode.

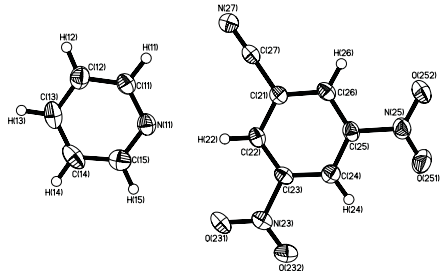


Figure 10. ORTEP (50% probability level) drawing of the adduct of 3,5-dinitrobenzonitrile and pyridine, **3a**.

analysis shows that pyridine and nitrile, **3** molecules established recognition through the formation of a trimeric hydrogen bonding pattern comprising of two C–H···N and one C–H···O hydrogen bonds. Recognition pattern and arrangement of molecules in two-dimensions is shown in Figure 11.

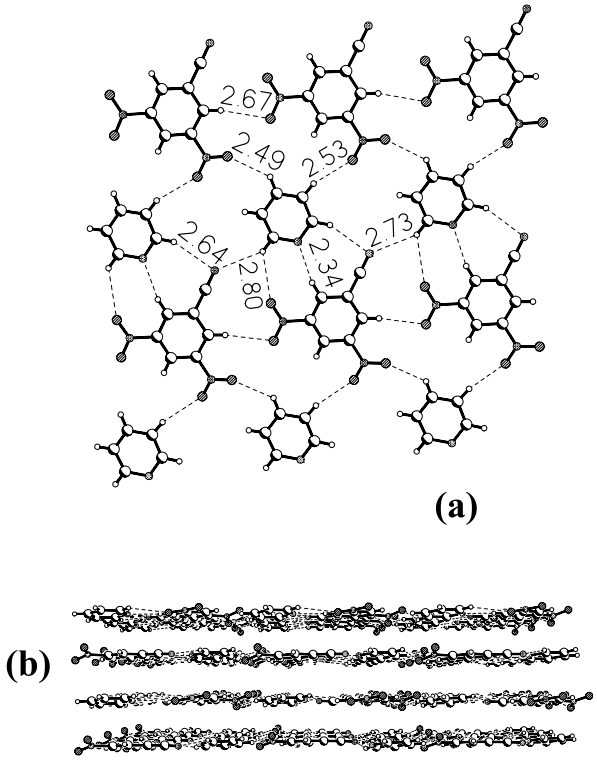


Figure 11. (a) Arrangement of molecules of pyridine and 3,5-dinitrobenzonitrile in the adduct, **3a**. Hydrogen bond distances are in Å. (b) Stacking of two-dimensional planar sheets in the adduct, **3a**.

While one of the C–H···N hydrogen bonds is formed between the pyridyl nitrogen atom and phenyl hydrogen atom of nitrile with a H···N distance of 2.34 Å, the second C–H···N hydrogen bond is formed between pyridyl hydrogen atom and nitrogen atom of nitrile group with a H···N distance of 2.64 Å. The H···O distance in the C H···O hydrogen bond was found to be 2.80 Å. CSD analysis, further, unveils that this kind of trimeric hydrogen bonding pattern is unique as out of 162 pyridine adducts, none of the adducts have this pattern in their crystal structures. Exploration of this type of new patterns will have a profound impact in the development of novel assemblies as the present concepts in crystal engineering and supramolecular chemistry are associated with the robustness of noncovalent bonds in the formation of clusters. Though the pyridine interacts with aromatic hydrogen bond forming a C–H···N hydrogen bond, it is worth mentioning that the most acidic hydrogen atom situated in the *para* position to the –CN group, as shown in Scheme 1, is not the one participating in the recognition pattern. This supermolecule interacts with the adjacent units through a C–H···O hydrogen bond (H···O, 2.67 Å) as well as a C–H···N hydrogen bond (H···N, 2.73 Å) constituting molecular tapes. In the two dimensional arrangement, these molecular tapes form planar sheet structures, as depicted in Figure 11. Within each sheet, the molecular tapes are held together by C–H···O hydrogen bonds (H···O, 2.49 and 2.53 Å). These planar sheets stack in a three-dimensional arrangement by π–π interactions, 3.75 Å, as shown in Figure 11b.

Since we noted structural variations by crystallizing **1a** from benzene, we carried out similar experiments for **2a** and **3a** also. However, **2a** and **3a** did not yield any structures other than **2a** and **3a** upon crystallization from other solvents including benzene. In further comparison of all the adducts, **1a** and **1b** are found to be quite stable but **2a** and **3a** are not. This suggests that the interaction between pyridine and the other substrate is certainly weaker in **2a** and **3a** than in **1a** and **1b**, which is in agreement with the actual interaction found in these adducts. In **1a** and **1b** the interaction is through a pair-wise cyclic hydrogen bonds involving strong hydrogen bonds either O–H···N or N^+–H···O^-, whereas in **3a**, the interaction is through a weak C–H···N hydrogen bond. Although, pyridine and amide recognize each other through a strong N–H···O hydrogen bond in **2a**, since pyridine molecules are situated as pendant moieties and also formation of empty channels in three-dimensional packing, might have lead to the instability of **2a** compared to **1a** and **1b**. In fact, the instability also reflects in the calculated density of the adducts (**1a**, 1.642; **1b**, 1.545; **2a**, 1.492; **3a**, 1.421 g cm^{-3}). As a result, the adducts can be arranged in the following decreasing order of stability **1a** > **1b** > **2a** > **3a**.

3. Conclusions

We have reported different types of sheet structures formed by analogous compounds, which are different from each other by a particular functional group, by crystallizing from pyridine solvent. Although, these structures basically form sheet structures in two-dimensional arrangement, the assembly of the sheets in three-dimensions is quite different ranging from—a simple stacking (**3a**) to a complex catenated networks (**1b**). In addition, the cavity and channel structures noted in the adducts, **1a** and **1b** are unique among pyridine adducts.

4. Experimental

4.1. Synthesis of molecular adducts

All the chemicals (3,5-dinitrobenzoic acid, 3,5-dinitrobenzamide, 3,5-dinitrobenzonitrile) used in this study were obtained from the commercial suppliers and used as such without any further purification. HPLC grade solvents were used for the crystallization experiments. The synthesis of the adducts **1a**–**3a** was carried out by dissolving the reactants in pyridine at room temperature followed by slow-evaporation of the solvent. However, **1b** was obtained by the crystallization of **1** from pyridine in the presence of benzene (carcinogen!).[20] Colorless needle shaped single crystals were obtained over a period of 3 days and were used for X-ray diffraction studies.

4.2. Crystal structure determination by X-ray diffraction methods

Well grown and good quality single crystals of adducts **1a**, **1b**, **2a** and **3a** have been carefully chosen by looking under Leica microscope equipped with CCD camera. The crystals were glued to a glass fibre using an adhesive (cyano acrylate) and mounted on the goniometer of Bruker X-ray diffractometer. While, the intensity data for **1a** were collected using SMART detector, the data for **1b**, **2a** and **3a** were collected using APEX detector. The adducts **1a** and **1b** are stable at ambient conditions but adducts **2a** and **3a** are not. Hence, additional precautionary measurements have been taken during the data collection of **2a** and **3a** by smearing the crystals in paraffin oil. The intensity data were processed using Bruker suite of programmes (SAINT)[21] and the absorption corrections were made using SADABS[22] package, except for **1b**. The structures were determined and refined using SHELXTL-PLUS[23] package and the refinements progressed quite routinely without any ambiguity. The non-hydrogen atoms were refined anisotropically and the hydrogen atoms were refined isotropically using the electron density derived from Fourier maps. However, in the structure, **1b**, the hydrogen atoms correspond to water molecules could not obtained from Fourier maps, hence were not considered in the refinement. All the structures refined to good R-factors as given in Table 2 along with complete details of data collection procedures, structure determination and refinement parameters. All the intermolecular parameters, listed in Table 1, were calculated using PLATON.[24] Full details of crystallographic information are deposited at Cambridge Crystallographic Data Centre as supplementary publication (**1a**, 272149; **1b**, 272150; **2a**, 272151; **3a**, 272152). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB12 1EZ, UK [fax: +44 1223 336033 or email: deposit@ccdc.cam.ac.uk].

Table 2. Crystallographic information of adducts **1a**, **1b**, **2a** and **3a**

	1a	**1b**	**2a**	**3a**
Formula	$2(C_7H_4N_2O_6):(C_5H_5N_1)$	$(C_7H_4N_2O_6):(C_5H_5N_1):(H_2O)$	$(C_7H_5N_3O_5):(C_5H_5N_1)$	$(C_7H_3N_3O_4):(C_5H_5N_1)$
Fw	503.34	307.22	290.24	272.22
Crystal morphology	Rectangular plate	Rectangular plate	Rectangular block	Long-plate
Crystal color	Colorless	Colorless	Colorless	Colorless
Crystal system	Orthorhombic	Monoclinic	Monoclinic	Triclinic
Space group	$Pna2_1$	$P2_1$	$C2/c$	$P\bar{1}$
a (Å)	6.695(2)	12.788(4)	19.950(6)	7.032(2)
b (Å)	13.420(4)	3.836(1)	5.789(2)	8.053(3)
c (Å)	22.665(7)	13.528(5)	24.245(8)	11.889(4)
α (deg)	90	90	90	87.72(1)
β (deg)	90	95.55(1)	104.29(1)	80.86(1)
γ (deg)	90	90	90	65.76(1)
V (Å^3)	2036.5(11)	660.5(4)	2713.4(15)	605.9(4)
Z	4	2	8	2
D_{calc} (g cm^{-3})	1.642	1.545	1.421	1.492
T (K)	203(2)	298(2)	153(2)	133(2)
Mo kα	0.71073	0.71073	0.71073	0.71073
μ (mm^{-1})	0.140	0.130	0.114	0.116
2θ range (deg)	57.26	46.64	46.78	46.60
limiting indices	$-9\le h\le 9$, $-16\le k\le 18$, $-30\le l\le 25$	$-13\le h\le 14$, $-4\le k\le 4$, $-13\le l\le 15$	$-16\le h\le 22$, $-6\le k\le 6$, $-27\le l\le 21$	$-7\le h\le 7$, $-8\le k\le 8$, $-7\le l\le 13$
$F(000)$	1032	316	1200	280
No. reflns measured	15946	2849	5632	2573
No. unique reflns	4495	1823	1985	1720
No. reflns used	1586	1681	1295	1599
No. parameters	326	235	230	214
Reflection\parameter	13.79	7.75	8.63	8.04
GOF on F^2	0.901	1.067	0.906	1.092
R_1 ($I>2\sigma(I)$)	0.0578	0.0448	0.0393	0.0388
wR_2	0.1592	0.1200	0.0868	0.1065
Final diff. Four map (e^-. Å^{-3}) max, min	0.31, −0.28	0.38, −0.28	0.12, −0.14	0.18, −0.25

Acknowledgements

We thank Dr. Sivaram (Director, National Chemical Laboratory) and Dr. K. N. Ganesh (Head, Organic Chemistry Division) for their encouragement. We also thank Professor Roland Boese, University of Essen, Germany, for his interest in this work and the help he extended for the structure determination of **1a**. Additionally, J.P. and K.K.A. thank CSIR for the award of Research Fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.08.080. X-ray data with details of refinement procedures (cif files), ORTEP plots, lists of bond parameters (bond lengths and angles) of molecular complexes **1a**, **1b**, **2a** and **3a**. Also, refcodes of CSD analysis were given.

References and notes

1. (a) Reichardt, C. *Solvent effects in organic chemistry*; Verlag Chemie: Weinheim, New York, 1979. (b) Whitesides, G. M.; Simanek, E. E.; Mathias, J. P.; Seto, C. T.; Chin, D. N.; Mammen, M.; Gorden, D. M. *Acc. Chem. Res.* **1995**, *28*, 37–44. (c) Ramamurthy, V.; Venkatesan, K. *Chem. Rev.* **1987**, *87*, 433–481.
2. (a) Mullin, J. W. *Crystallization*, 3rd ed.; Butterworth-Heinemann: London, 1993. (b) Rodriguez-Hornedo, N.; Murphy, D. *J. Pharm. Sci.* **1999**, *88*, 651–660. (c) Morrissette, S. L.; lmarsson, O.; Peterson, M. L.; Remenar, J. F.; Read, M. J.; Lemmo, A. V.; Ellis, S.; Cima, M. J.; Gardner, C. R. *Adv. Drug Deliv. Rev.* **2004**, *56*, 275–300.
3. (a) Bernstein, J. *Polymorphism in molecular crystals*; Oxford University Press: New York, 2002. (b) Dunitz, J. D.; Bernstein, J. *Acc. Chem. Res.* **1995**, *28*, 193–200. (c) Davey, R. J. *Chem. Commun.* **2003**, 1463–1467. (d) McMahon, J. A.; Zaworotko, M. J.; Remenar, J. F. *Chem. Commun.* **2004**, 278–279. (e) Aakeroy, C. B.; Nieuwenhuyzen, M.; Price, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 8986–8993. (f) Pedireddi, V. R. *CrystEngComm* **2001**, *15*, 1–3.
4. (a) Beyer, T.; Day, G. M.; Price, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 5086–5094. (b) Dale, S. H.; Elsegood, M. R. J.; Redshaw, C. *CrystEngComm* **2003**, *5*, 368–373. (c) Hosokawa, T.; Datta, S.; Sheth, A. R.; Brooks, N. R.; Young, V. G., Jr.; Grant, D. J. W. *Cryst. Growth Des.* **2004**, *4*, 1195–1201. (d) Ischenko, V.; Englert, U.; Jansen, M. *Chem. Eur. J.* **2005**, *11*, 1375–1383. (e) Mirza, S.; Miroshnyk, I.; Heinamaki, J.; Christiansen, L.; Karjalainen, M.; Yliruusi, J. *Pharm. Sci.* **2003**, *5*, 1–9.
5. (a) Gu, C.-H.; Young, V., Jr.; Grant, D. J. W. *J. Pharma. Sci.* **2001**, *90*, 1878–1890. (b) Teychene, S.; Autret, J. M.; Biscans, B. *Cryst. Growth Des.* **2004**, *4*, 971–977. (c) Veesler, S.; Ferte, N.; Costes, M.-S.; Czjzek, M.; Astier, J.-P. *Cryst. Growth Des.* **2004**, *4*, 1137–1141. (d) Khoshkhoo, S.; Anwar, J. *J. Phys. D: Appl. Phys.* **1993**, *26*, B90–B93.

6. (a) Cardew, P. T.; Davey, R. J. *Proc. Roy. Soc. London. A* **1982**, *398*, 415–428. (b) Blagden, N.; Davey, R. J.; Lieberman, H. F.; Williams, L.; Payne, R.; Roberts, R.; Rowe, R.; Docherty, R. *J. Chem. Soc. Faraday Trans.* **1998**. (c) Caira, M. R.; Alkhamis, K. A.; Obaidat, R. M. *J. Pharma. Sci.* **2004**, *93*, 601–611.
7. Pedireddi, V. R.; Chatterjee, S.; Ranganathan, A.; Rao, C. N. R. *J. Am. Chem. Soc.* **1997**, *119*, 10867–10868.
8. (a) Dale, S. H.; Elsegood, M. R. J. *Acta Crystallogr., Sect. E* **2003**, *59*, o1205–o1207. (b) Dale, S. H.; Elsegood, M. R. J. *Acta Crystallogr., Sect. E* **2003**, *59*, o1087–o1088. (c) Dale, S. H.; Elsegood, M. R. J. *Acta Crystallogr., Sect. C* **2004**, *60*, o444–o448. (d) Jin, Z. M.; Pan, Y. J.; Shen, L.; Li, M. C.; Hu, M. L. *Acta Crystallogr., Sect. C* **2003**, *59*, o205–o206. (e) Takusagawa, F.; Hirotsu, K.; Shimada, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1274.
9. Nangia, A.; Desiraju, G. R. *Chem. Commun.* **1999**, 605–606.
10. Pedireddi, V. R.; Belhekar, D. *Tetrahedron* **2002**, *58*, 2937–2941.
11. (a) Pedireddi, V. R.; PrakashaReddy, J. *Tetrahedron Lett.* **2002**, *43*, 4927–4930. (b) Pedireddi, V. R.; Ranganathan, A.; Chatterjee, S. *Tetrahedron Lett.* **1998**, *39*, 9831–9834. (c) Pedireddi, V. R.; Jones, W.; Chorlton, A. P.; Docherty, R. *Tetrahedron Lett.* **1998**, *39*, 5409–5412. (d) Ranganathan, A.; Pedireddi, V. R. *Tetrahedron Lett.* **1998**, *39*, 1803–1806. (e) Pedireddi, V. R.; Jones, W.; Chorlton, A. P.; Docherty, R. *Chem. Commun.* **1996**, 987–988. (f) Pedireddi, V. R.; Jones, W.; Chorlton, A. P.; Docherty, R. *Chem. Commun.* **1996**, 997–998.
12. (a) PrakashaReddy, J.; Pedireddi, V. R. *Tetrahedron* **2004**, *60*, 8817–8827. (b) PrakashaReddy, J.; Pedireddi, V. R. *Tetrahedron Lett.* **2004**, *60*, 6679–6681.
13. (a) Pedireddi, V. R.; PrakashaReddy, J.; Arora, K. K. *Tetrahedron Lett.* **2003**, *44*, 4857–4860. (b) Arora, K. K.; Pedireddi, V. R. *Tetrahedron* **2004**, *60*, 919–925.
14. Prince, P.; Fronczek, F. R.; Gandour, R. D. *Acta Crystallogr., Sect. C* **1991**, *47*, 895–898.
15. (a) Sakai, K.; Sakurai, R.; Hirayama, N. *Tetrahedron: Asymmetry* **2004**, *15*, 1073–1076. (b) Sakai, K.; Sakurai, R.; Nohira, H.; Tanaka, R.; Hirayama, N. *Tetrahedron: Asymmetry* **2005**, *15*, 3495–3500. (c) Sakai, K.; Sakurai, R.; Yuzawa, A.; Hirayama, N. *Tetrahedron: Asymmetry* **2003**, *14*, 3713–3718.
16. Allen, F. H.; Davies, J. E.; Galloy, J. J.; Johnson, O.; Kennard, O.; Macrae, C. F.; Watson, D. G. *J. Chem. Inf. Comput. Sci.* **1991**, *31*, 204.
17. We excluded organometallic compounds as pyridine take part as a ligand rather than as a solvate in the majority of their crystal structures.
18. (a) Kilian, P.; Slawin, A. M. Z.; Woollins, J. D. *Eur. J. Inorg. Chem.* **1999**, 2327. (b) Freeman, D.; Frolow, F.; Kapinus, E.; Lavie, D.; Lavie, G.; Meruelo, D.; Mazur, Y. *Chem. Commun.* **1994**, 891. (c) Minshall, P. C.; Sheldrick, G. M. *Acta Crystallogr., Sect. B* **1978**, *34*, 1378. (d) Olejnik, Z.; Lis, T.; Grech, E.; Nowicka-Scheibe, J. *Pol. J. Chem.* **1998**, *72*, 1255. (e) Krepps, M. K.; Parkin, S.; Atwood, D. A. *Cryst. Growth Des.* **2001**, *1*, 291. (f) Agbaria, K.; Biali, S. E.; Bohmer, V.; Brenn, J.; Cohen, S.; Frings, M.; Grynszpan, F.; Harrowfield, J. M. B.; Sobolev, A. N.; Thondorf, I. *J. Org. Chem.* **2001**, *66*, 2900.
19. (a) Wiechert, D.; Mootz, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 1974–1976. (b) Boenigk, D.; Mootz, D. *J. Am. Chem. Soc.* **1988**, *110*, 2135–2139. (c) Wiechert, D.; Mootz, D.; Franz, R.; Siegemund, G. *Chem. Eur. J.* **1998**, *4*, 1043–1047. (d) Boenigk, D.; Mootz, D. *Z. Kristallogr.* **1985**, *170*, 16.
20. Although the solvents of HPLC grade were used, since the crystallization was carried out at ambient conditions, the water in the crystal lattice of **1b** could be attributed to the moisture in the atmosphere.
21. Siemens, *SMART System*; Siemens Analytical X-ray Instruments Inc: Madison, WI, USA, 1995.
22. Sheldrick, G. M. *SADABS: Software for empirical absorption corrections;* University of Gottingen: Gottingen, Germany, 2000.
23. Sheldrick, G. M. *SHELXTL-PLUS: Program for crystal structure solution and refinements;* University of Gottingen: Gottingen, Germany, 1997.
24. Spek, A. L. *PLATON: Molecular geometry program;* University of Utrecht, The Netherlands, 1995.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 61 (2005) 10801–10810
Tetrahedron

Pyrazolyl–benzoxazole derivatives as protein kinase inhibitors. Design and validation of a combinatorial library

Daniela Berta, Marzia Villa,† Anna Vulpetti and Eduard R. Felder*

Department of Chemistry, Nerviano Medical Science, Viale Pasteur 10, I-20014 Nerviano (MI), Italy

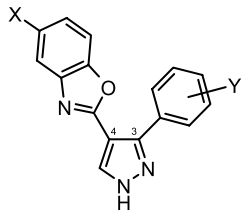
Received 29 November 2004; revised 3 August 2005; accepted 18 August 2005

Available online 19 September 2005

Abstract—The malfunctioning of protein kinases is a hallmark of numerous diseases, for which a satisfactory therapy is missing. We describe the design and synthesis of a kinase targeted library based on a novel 2-(3-phenyl-1*H*-pyrazol-4-yl)-1,3-benzoxazole scaffold. Ethyl 3-(3-nitrophenyl)pyrazole-4-carboxylate and its 4-nitro regioisomer were bound to trityl chloride resin, saponified with NaOH in MeOH, and amidated with a choice of two *o*-aminophenols. The resulting *N*-(2-hydroxyphenyl)amides were cyclized by Mitsunobu reaction to form four variants of the pyrazolyl–benzoxazole core template. Straightforward stannous chloride reduction of the nitro group on solid phase allowed subsequent scaffold derivatization via acylation or sulfonylation of the obtained amino function. Cleavage with TFA gave rise to the final compounds (36 examples).

1. Introduction

Protein kinases (PKs) play a crucial role in the cellular control of many different processes, including metabolic pathways, cell growth and differentiation, membrane transport, and apoptosis. A large share of the oncogenes and proto-oncogenes involved in human cancers codes for PKs. The anomalous activities of PKs are also implicated in many non-malignant diseases, in inflammatory conditions and in the multiplication of viruses and parasites. PKs may also play a major role in the pathogenesis and development of neurodegenerative disorders. Inhibitors of these enzymes may arrest cell proliferation and trigger apoptosis. Their use is being extensively evaluated for cancer chemotherapy and other therapeutic areas. Flat heterocyclic hydrophobic compounds, such as pyrazoles, have been reported to bind to the hinge region of various kinase ATP pockets, mimicking the adenine (purine) pharmacophore and effectively competing with ATP.[1] Searching for potent and selective inhibitors of protein kinases has intensified over the past few years[1–4] culminating in the approval of Imatinib[5] (Gleevec) and Gefitinib[6] (Iressa) for the oncology drug market. In our internal high-throughput screening for new potent kinase inhibitors compound **1** (Fig. 1, X, Y = H) emerged as a binder of Cyclin dependent kinase 2 (CDK2).



1

Figure 1. The pyrazolyl–benzoxazole scaffold (X = variable from aminophenol building blocks; Y = variable from derivatization of amino group in either *meta* or *para* position.

In order to understand how **1** may interact in the ATP pocket of the CDK2/Cyclin A complex an in silico docking simulation was performed. The computational docking experiment suggested that the pyrazole moiety could interact with the hinge region in three different ways.

Figure 2a–c shows the three binding modes, which involve two distinct tautomeric forms, differing by the presence of a proton on either N1 or N2 of the pyrazole ring of the inhibitor. The two binding modes A and C (reported, respectively, in Fig. 2a and c) resemble the dual binding modes observed by X-ray analysis on a 3-aryl-1*H* pyrazole scaffold.[7] In binding modes A and B the pyrazole ring is making two hydrogen bond interactions with the carbonyl

Keywords: Solid-phase synthesis; Scaffold; Mitsunobu; Parallel synthesis; Building blocks.
* Corresponding author. Tel.: +39 331 581474; fax: +39 331 581347; e-mail: eduard.felder@nervianoms.com
† Present address: Roche Palo Alto LLC MS R6 E3, 3431 Hillview Ave. Palo Alto, CA 94304, USA.

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.08.070

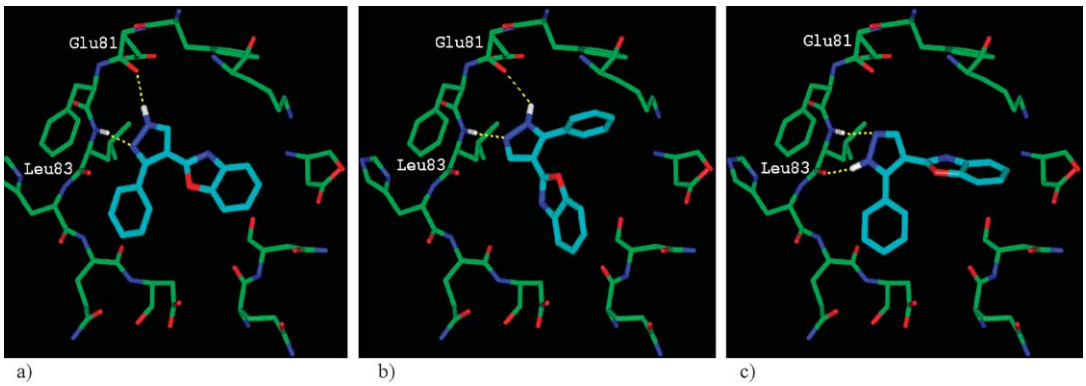


Figure 2. Three binding modes of **1**.

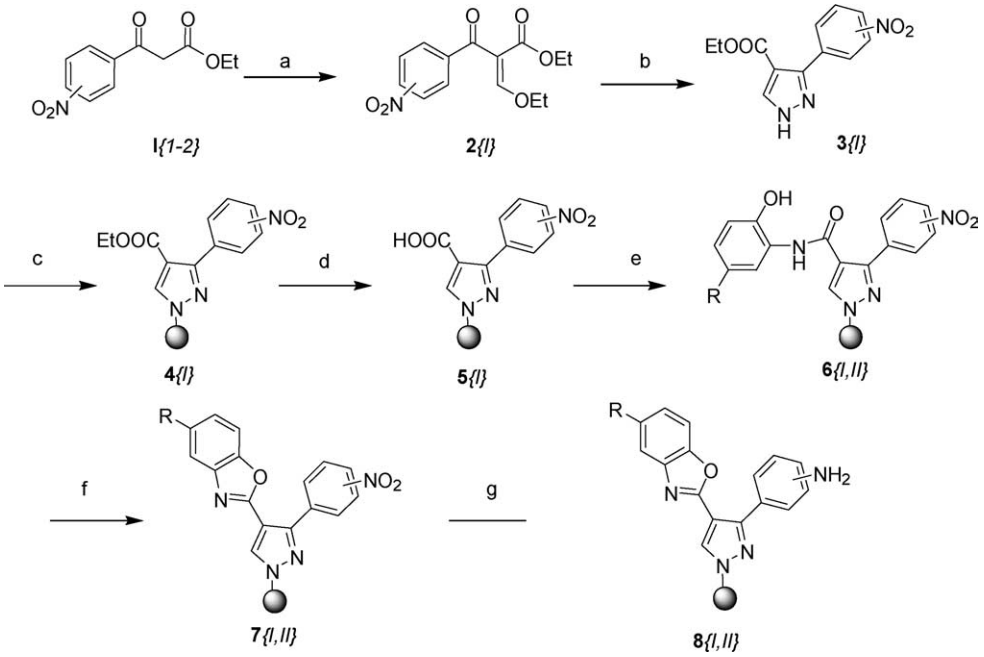
oxygen of Glu81 and the amide nitrogen of Leu83. In binding mode C, both pyrazole nitrogens, N1 and N2–H, interact, respectively, with the amide nitrogen and the carbonyl oxygen of Leu83. Depending on the binding mode, the phenyl ring at position 3 and the benzoxazole at position 4 can be oriented toward different regions of the ATP pocket.

Combining structural considerations and chemical feasibility we therefore, planned a scaffold expansion based on three diversity points given by the substituents and their position on the benzoxazole ring, as well as the substituents on the phenyl ring (Fig. 1). In this article, we describe a solid phase synthetic route, which builds up the 2-(3-phenyl-1*H*-pyrazol-4-yl)-1,3-benzoxazole scaffold from variably interchangeable building blocks. The synthesis of 36 examples reported here allowed us to validate the method for the subsequent production of a much larger kinase targeted library.[8]

2. Results and discussion

The synthetic strategy is outlined in Scheme 1. The pyrazole core **3** was synthesized starting from commercial *para* or *meta* nitrobenzoylacetate, which was refluxed with triethylorthoformate to give enolether **2**[9] (Scheme 1). Cyclization of **2** with hydrazine afforded **3** that was then linked to trityl resin through one of the pyrazole nitrogens. The hydrolysis of ethyl ester **4** to acid **5** required four treatments for a complete conversion. The synthesis of amide **6** was performed in the first instance according to Wang et al.[10] by means of benzotriazol-1-yl-*N*-oxy tris (pyrrolidino)-phosphonium hexafluorophosphate (PyBoP) as coupling agent. This approach led to the desired product along with a high percentage of a side product at *m*/*z* 564, to which we assigned the hypothetical structure **A** (Fig. 3).

Upon replacing PyBOP with *N*-[1*H*-benzotriazol-1-yl) (dimethylamino) methylene]-*N*-methyl methanaminium



Scheme 1. Reagents and conditions: (a) $(EtO)_3CH$, Ac_2O reflux, 3 h; (b) NH_2NH_2, EtOH 22 °C, 3 h; (c) Trityl-Cl resin, DIEA, DCM/DMF 22 °C, 16 h; (d) NaOH, DMF/H_2O, 70 °C, 64 h, four times; (e) **II**{1-2}, HOBt, TBTU, DMF, 22 °C, 16 h; (f) TBP, DEAD, THF, 22 °C, 16 h; (g) $SnCl_2 \cdot 2H_2O$, DMF, 22 °C, 16 h.

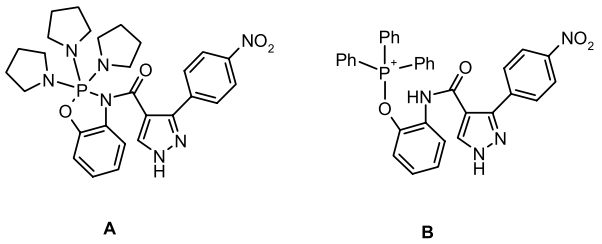


Figure 3. Assumed structures of principal side products eliminated during method development. Structure **A** is linked to PyBOP promoted aminophenol coupling. Structure **B** is linked to TPP use in the cyclization reaction.

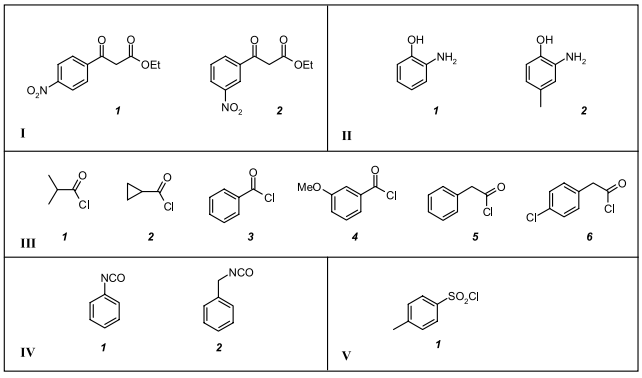
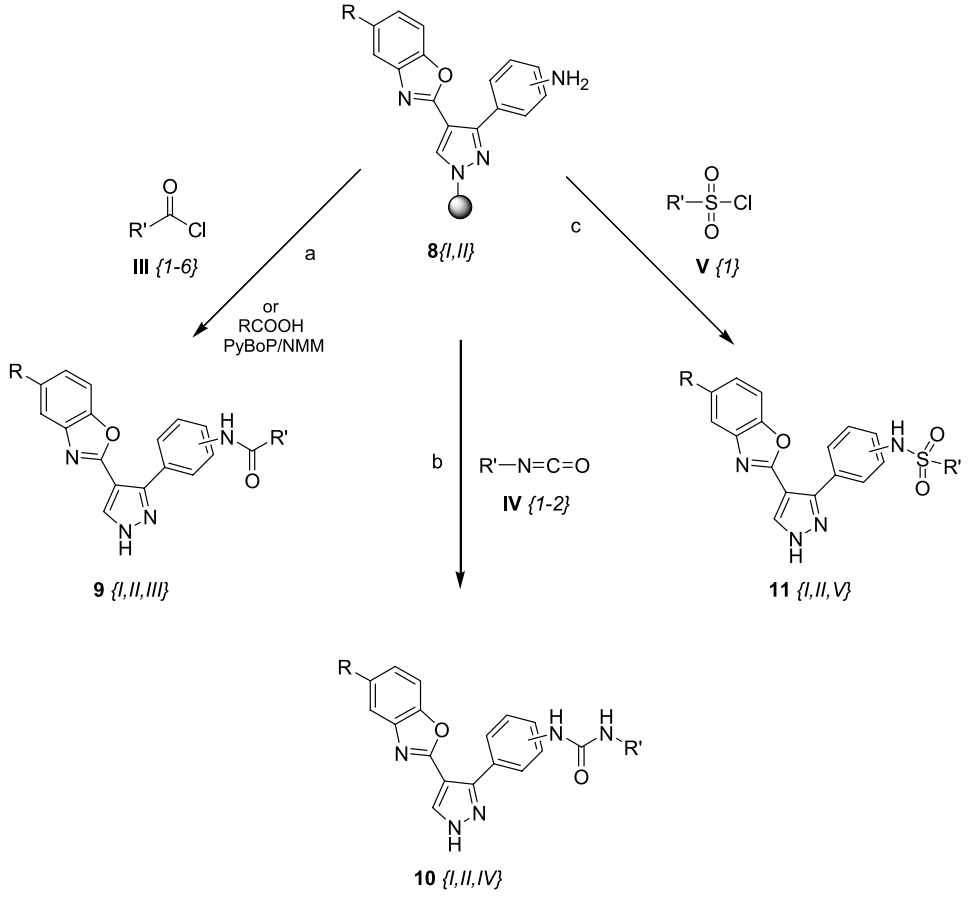


Figure 4. Utilized monomer sets (building blocks).

tetrafluoroborate *N*-oxide (TBTU) both aminophenol **II**{1}as well as *o*-amino-*p*-cresol **II**{2}coupled with resin **5** to give resin **6** as the only product. The intramolecular dehydrative cyclization of the 2-acylaminophenol **6** employing an excess of tri-*n*-butylphosphine (TBP) and diethyl azodicarboxylate (DEAD) in THF was used to provide resin **7**. The traditional conditions for the Mitsunobu reaction (triphenylphosphine TPP; DEAD) were not suitable for substrate **6** due to an incomplete conversion of the amide to the benzoxazole ring and the recovery of a high amount of the aminophenoxy-triphenylphosphonium salt (Fig. 3, structure **B**). Simple variations of the ratio of reagents, the reaction time and the number of treatments did not give satisfactory results. A dramatic improvement was achieved when replacing triphenylphosphine with tributylphosphine, which led to derivative **7** in a complete conversion. Reduction of the nitro group cleanly proceeded with stannous chloride ($SnCl_2$) in DMF and the obtained aromatic amine **8** was then functionalized with six acyl chlorides, two isocyanates and one sulfonyl chloride (Fig. 4) to give resins **9**, **10** and **11** (Scheme 2). Formation of amides was also performed by coupling resin **8** with carboxylic acids in the presence of PyBop. The outcome was similar for both methods. Cleavage with trifluoroacetic acid (TFA) in DCM afforded the final products.

All building blocks selected for aniline substitution showed a good reactivity leading to desired products with an



Scheme 2. Reagents and conditions: (a) (i) DIEA, DCM, rt, 16 h (ii) TFA 10% in DCM, rt, 1 h; (b) (i) DCM, rt, 16 h, (ii) TFA 10% DCM, rt, 1 h; (c) (i) DIEA, DCM, rt, 16 h, (ii) TFA 10% in DCM, rt, 1 h.

Table 1. Overall qualitative assessment of the validation library (36 examples)

	Crude (mg)	Purified (mg)	Chromatographic recovery (%)[a]	LC–MS purity crude[b]	LC–MS purity purified[b]
Average	27	11	60	67.3	94
Max	31.7	21	94.4	70.2	100
Min	21.2	2.5	18.8	62.7	83.8

[a] Weight purified/weight crude (theoretical based on 254 nm HPLC purity).
[b] Percent peak area by UV (254 nm).

average yield of 46% and an average purity of crudes of 67.3% (Table 1). All the crude mixtures from the cleavage were purified by preparative HPLC leading to compounds with high purity (Table 2).

3. Conclusion

We have developed a highly effective route for the synthesis of 2-(3-aryl-1*H*-pyrazol-4-yl)-1,3-benzoxazoles using a stepwise solid phase path with a dehydrative Mitsunobu cyclization as the key step. The preliminary docking analysis performed on the identified screening hit in its potential role as a combinatorial chemistry scaffold provided the rationale to develop this chemical class as a source of kinase inhibitors. The validated synthetic methodology described here can be applied to the production of a large kinase targeted library comprising thousands of molecules.[8]

Table 2. Purity data of the validation library members

Entry	M_W	LC–MS purity (purified)[a]	NMR purity[b]
9{I,II,III}			
9{1,1,1}	346.4	94.6	83
9{1,1,2}	344.4	97.1	86
9{1,1,3}	380.4	95	97
9{1,1,4}	410.4	95.9	88
9{1,1,5}	394.4	100	84
9{1,1,6}	428.9	97.8	92
9{1,2,1}	360.4	96.6	94
9{1,2,2}	358.4	98.8	85
9{1,2,3}	394.4	92.9	81
9{1,2,4}	424.5	97.7	81
9{1,2,5}	408.5	97.6	99
9{1,2,6}	442.9	100	94
9{2,1,1}	346.4	96.5	86
9{2,1,2}	344.4	87.1	73
9{2,1,3}	380.4	88.6	91
9{2,1,4}	410.4	92.4	86
9{2,1,5}	408.5	93.2	94
9{2,1,6}	428.9	78.2	66
9{2,2,1}	360.4	95.3	87
9{2,2,2}	358.4	94.2	83
9{2,2,3}	394.4	91.1	80
9{2,2,4}	424.5	90.6	87
9{2,2,5}	408.5	97.1	89
9{2,2,6}	442.9	94.6	92
10{I,II,IV}			
10{1,1,1}	395.4	95.7	89
10{1,1,2}	409.4	100	82
10{1,2,1}	409.4	100	95
10{1,2,2}	423.5	92.7	88
10{2,1,1}	395.4	90.1	93
10{2,1,2}	409.4	92.4	85
10{2,2,1}	409.4	93.7	92
10{2,2,2}	423.5	97.6	76
11{I,II,V}			
11{1,1,1}	430.5	97	81
11{1,2,1}	444.5	82.1	80
11{2,1,1}	430.5	83.8	81
11{2,2,1}	444.5	84.6	86

[a] Percent peak area by UV (254 nm).
[b] ^{1}H NMR quantitative purity determined using 1,4-bis-(trimethylsilyl) benzene as the standard Ref.11.

4. Experimental

4.1. Docking calculation of 1 into CDK2/Cyclin A

The crystal structure of CDK2/Cyclin A co-crystallized with a proprietary compound was taken from in-house X-ray data. The docking study was performed with QXP (the docking module of the Flo+program, Thistlesoft, version 2003),[12] using the docking algorithm, referred to as MCdock. The MCdock algorithm employs a user-defined number of repeated cycles of Monte Carlo followed by energy minimisation to generate and refine an ensemble of docked ligands. The ensemble is initiated with a single pose and is allowed to grow to 50 poses. For each search cycle the ligand pose is randomly chosen from the ensemble, and subjected to 1000 steps of Monte Carlo searching. The Monte Carlo variables are dihedrals of rotatable bonds, Cartesian coordinates of ring atoms, and molecular ligand rotation and translation. In each search cycle the best result is energy minimized, using a modified Amber force field.[13]

QXP allows the user to define parts of the binding site as flexible. These sections can move under the influence of the molecular mechanics force field during energy minimization. The sections designated for movement can be made fully flexible or partially flexible (using distance-based constraints). We made the CDK2 glycine-rich loop region (Gly11, Glu12, Gly16 and Val17) and Glu8 partially flexible and Lys33, Lys89, Tyr15 and Gln85 completely flexible.

The results were evaluated in terms of total estimated binding energy, internal strain energy of the ligand, van der Waals and electrostatic interaction energies. The calculation was performed on a 225 MHz Octane SGI workstation.

4.2. Synthetic procedures

Parallel reactions were run using an Argonaut Quest 210

All reagents and solvents were purchased from commercial suppliers of the best grade and used without further purification. Melting points were determined in open glass capillaries with a Büchi 535 melting point apparatus and are uncorrected. Flash chromatography was performed on silica gel (Merck grade 9385, 60 Å). Thin-layer chromatography

was performed on Whatman silica gel 60 plates coated with 250 μm layer with fluorescent indicator. Components were visualized either by UV light (λ: 254 nm) or by iodine vapor HPLC/MS was performed on a Waters X Terra RP 18 (4.6×50 mm, 3.5 μm) column using a Waters 2790 HPLC system equipped with a 996 Waters PDA detector and a Micromass mod. ZQ single quadrupole mass spectrometer, equipped with an electrospray (ESI) ion source. Mobile phase A was ammonium acetate 5 mm buffer (pH 5.5 with acetic acid/acetonitrile 95:5), and mobile phase B was H_2O–acetonitrile (5/95). Gradient from 10 to 90%B in 8 min, hold 90%B 2 min. UV detection at 220 and 254 nm. Flow rate 1 ml/min. Injection volume 10 μl. Full scan, mass range from 100 to 800 amu. Capillary voltage was 2.5 KV; source temperature was 120 °C; Cone was 10 V. Mass are given as *m*/*z* ratio.

All compounds have been purified by preparative HPLC on a Waters X-Terra RP18 (19×100 mm, 5 μm) column using a Waters preparative HPLC 2525 equipped with a 996 Waters PDA detector and a Micromass mod. ZQ single quadrupole mass spectrometer, electrospray ionisation, positive mode. Mobile phase A was water 0.01% formic acid, and mobile phase B was acetonitrile. Gradient from 10 to 90%B in 8 min, hold 90% B 2 min. Flow rate 20 ml/min.

^{1}H NMR spectroscopy was recorded on a Mercury VX 400 operating at 400.45 MHz equipped with a 5 mm double resonance probe (1*H* {15N–31P} ID_PFG Varian), using 1, 4-bis-(trimethylsilyl)benzene as internal standard; chemical shifts are expressed in ppm (δ).

The high resolution mass analyses were performed on a Micromass Q-TOF Ultima (Manchester, UK) hybrid quadrupole/orthogonal acceleration time of flight mass spectrometer equipped with an ESI ion source as described previously.[14] A Reserpine solution 250 pg/μl (about 100 counts/s) was used as the reference compound for TOF Lock Mass correction ($[M+H]^+$ ion 609.2806 *m*/*z*).

4.2.1. 3-(3-Nitro-phenyl)-1*H*-pyrazole-4-carboxylic acid ethyl ester 3{2}. A solution of hydrazine monohydrate (3.2 ml, 66 mmol) in dry ethanol (25 ml) was added dropwise at 0 °C to a solution of **I**{2} (17.9 g, 61 mmol) in ethanol (150 ml). The reaction mixture was stirred at rt for 3 h and the resulting solid was filtered, washed with water and cold ethanol, and dried to afford 11.5 g (72%) of **3**{2} as a pale yellow solid. Mp 160–161 °C.

^{1}H NMR (DMSO-d_6), (ppm): 13.69 (br s, 1H), 8.63 (t, J= 1.8 Hz, 1H), 8.45 (d, J=2.0 Hz, 1H), 8.23 (m, 2H), 7.70 (t, J=8.0 Hz, 1H), 4.19 (q, J=7.1 Hz, 2H), 1.21 (t, J=7.1 Hz, 3H).

4.2.2. 3-(4-Nitro-phenyl)-1*H*-pyrazole-4-carboxylic acid ethyl ester 3{1}. Using the above procedure the treatment of **I**{1} with hydrazine monohydrate afforded **3**{1} as a yellow solid (75%). Mp 191–192 °C.

^{1}H NMR (DMSO-d_6), ppm: 13.72 (br s, 1H), 8.44 (s, 1H), 8.25 (d, J=8.8 Hz, 2H), 8.02 (s, J=8.8 Hz, 2H), 4.18 (q, J=7.2 Hz, 2H), 1.22 (t, J=7.1 Hz, 3H).

4.2.3. Ethyl 3-(nitrophenyl)-1-trityl polystyrene-1*H*-pyrazole-4-carboxylate (4). DIEA (3.26 ml, 19.5 mmol) and a solution of the pyrazole **3** (2.5 g, 9.5 mmol) in DMF (12 ml) were added to a slurry of trityl chloride resin (5 g, 1.27 mmol/g loading, 6.35 mmol) in DCM (35 ml). The mixture was gently stirred at rt for 16 h and then filtered under reduced pressure. The resin was suspended in a mixture of DCM/MeOH/DIEA 85:10:5 (100 ml), stirred for 20 min and filtered. After washing consecutively with DCM, MeOH and Et_2O it was dried overnight in the oven at 35 °C under reduced pressure.

Both resins **4**{1} and **4**{2} gave rise to a loading of 1 mmol/g measured by weight increase.

4.2.4. 3-(3-(Nitrophenyl)-1-trityl polystyrene-1*H*-pyrazole-4-carboxylic acid (5). To a suspension of resin **4** (6.4 g, 1 mmol/g loading, 6.4 mmol) in 77 ml MeOH was added NaOH 35% (6.4 ml) and stirred at 70 °C for 16 h. After cooling, the slurry was filtered under reduced pressure and washed abundantly with MeOH to dissolve the NaOH precipitated during the reaction. The treatment was repeated three more times till starting material disappearance on LC–MS of a cleaved sample. The resin was afterwards washed with MeOH, DCM, Et_2O and dried at 35 °C under vacuum.

4.2.5. *N*-(2-Hydroxyphenyl)-3-(nitrophenyl)-1-trityl polystyrene-1*H*-pyrazole-4-carboxamide (6). A solution of HOBt (1.35 g, 10 mmol) and TBTU (3.2 g, 10 mmol) in 15 ml of dry DMF was added to a slurry of resin **6** (2 g, 1 mmol/g loading, 2 mmol, 1 equiv) in 5 ml of dry DMF. The mixture was stirred for 30 min then *o*-aminophenol (10 equiv) was added and the final suspension was stirred at rt for 20 h. The slurry was filtred under reduced pressure, the resin washed abundantly with DMF, DCM, MeOH and Et_2O and dried at 35 °C under vacuum.

4.2.6. 2-[3-(Nitrophenyl)-1-trityl polystyrene-1*H*-pyrazol-4-yl]-1,3-benzoxazole (7). Tributylphosphine (2.5 ml, 10 mmol) followed by DEAD (1.6 ml, 10 mmol) were added dropwise to a slurry of resin **6** (2.1 g, 2 mmol) in 20 ml of dry THF. The brown suspension was stirred at rt for 16 h. After filtering under reduced pressure the resin was washed with DMF (3×), DCM (3×), MeOH (3×) and Et_2O (3×) and dried at 35 °C under vacuum.

4.2.7. [4-(1,3-Benzoxazol-2-yl)-1-trityl polystyrene-1*H*-pyrazol-3-yl]aniline (8). A solution of $SnCl_2 \cdot H_2O$ (6.6 g, 30 mmol,) in DMF (10 ml) was added to a slurry of the resin **7** (2 g, 2 mmol) in DMF (10 ml). The suspension was stirred at rt for 16 h. After filtering under reduced pressure the resin was washed with DMF (3×), DCM (3×), MeOH (3×) and Et_2O (3×) and dried at 35 °C under vacuum.

4.3. Acylation with acyl chlorides

DIEA (137 μL, 0.08 mmol) and the appropriate acyl chloride (0.04 mmol) were added to the resin **8** (100 mg, 0.01 mmol), swelled in DCM (3 ml). The resulting suspension was stirred for 20 h at 22 °C, filtered, washed with DCM, MeOH and Et_2O, dried under nitrogen flux and used in the next step.

4.4. Acylation with carboxylic acids

A solution of NMM (55 μL, 0.05 mmol), PyBOP (260 mg, and the appropriate carboxylic acid (0.05 mmol) in 2 ml of DCM was stirred for 30 min and then added to a suspension of the resin **8** (100 mg, 0.01 mmol, 1 equiv) in DCM (1 ml). The obtained suspension was stirred for 20 h at 22 °C, filtered, washed with DCM (3×), MeOH (3×) and Et_2O (3×), dried under nitrogen flux and used in the next step.

4.5. Acylation with isocyanates

The appropriate isocyanate (0.04 mmol) was added to the resin **8** (100 mg, 0.01 mmol), swelled in DCM (3 ml) in the Quest vessel. The resulting suspension was stirred for 20 h at 22 °C, filtered, washed with DCM, MeOH and Et_2O, dried under nitrogen flux and used in the next step.

4.6. Sulfonylation

A solution of DIEA (103 μL, 0.06 mmol) and the appropriate sulfonyl chlorides (0.06 mmol) in 2 ml of DCM was added to a suspension of the resin **8** (100 mg, 0.01 mmol) in DCM (1 ml). The obtained suspension was stirred for 20 h at 22 °C, filtered, washed with DCM, MeOH and Et_2O, dried under nitrogen flux and used in the next step.

4.7. Cleavage

A solution of 2 ml of TFA 10% in DCM were added to 100 mg of the resins obtained after the derivatization of **8** in the Quest vessels. The red suspension was stirred for 1 h then filtered and the resin washed twice with 1 ml of DCM. The filtered solution was evaporated under nitrogen flux to give the products (**9**, **10**, **11**) as a crude solid or an oil, which was purified by preparative HPLC.

4.7.1. *N*-[4-(4-Benzooxazol-2-yl-1*H*-pyrazol-3-yl)-phenyl]-isobutyramide 9{1,1,1}. HPLC (254 nm): t_R 4.87 min (94.6%).

^{1}H NMR (DMSO-d_6), ppm: 13.63 and 13.56 (2br s, 1H, tautomers), 10.01 and 9.90 (2br s, 1H, tautomers), 8.60 and 8.18 (2s, 1H, tautomers), 7.76 (m, 3H) 7.67 (m, 2H), 7.62 (m, 1H), 7.32 (m, 2H), 2.62 (m, 1H), 1.12 (d, J= 6.6 Hz, 6H).

HRMS (ESI) calcd for $C_{20}H_{16}N_4O_2$ $[M+H]^+$347.1502, found 347.1500.

4.7.2. Cyclopropanecarboxylic acid [4-(4-benzooxazol-2-yl-1*H*-pyrazol-3-yl)-phenyl]-amide 9{1,1,2}. HPLC (254 nm): t_R 5.14 min (97.1%).

^{1}H NMR (DMSO-d_6), ppm: 13.65 (br s, 1H), 10.38 (br s, 1H), 8.27 (br s, 1H), 7.82 (d, J=8.7 Hz, 2H), 7.73 (m, 2H), 7.71 (m, 1H), 7.66 (m, 1H), 7.36 (m, 2H), 1.92 (m, 1H), 0.85 (m, 4H).

HRMS (ESI) calcd for $C_{20}H_{16}N_4O_2$ $[M+H]^+$345.1346, found 345.1330.

4.7.3. *N*-[4-(4-Benzooxazol-2-yl-1*H*-pyrazol-3-yl)-phenyl]-benzamide 9{1,1,3}. HPLC (254 nm): t_R 5.93 min (95%).

^{1}H NMR (DMSO-d_6), ppm: 13.65 (br s, 1H), 10.39 (br s, 1H), 8.32 (br s, 1H), 7.97 (d, J=6.8 Hz, 2H), 7.88 (m, 3H), 7.69 (m, 1H), 7.64 (m, 1H), 7.59 (m, 1H), 7.54 (t, J=7.5 Hz, 2H), 7.33 (m, 2H).

HRMS (ESI) calcd for $C_2H_{16}N_4O_2$ $[M+H]^+$381.1346, found 381.13273.

4.7.4. *N*-[4-(4-Benzooxazol-2-yl-1*H*-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide 9{1,1,4}. HPLC (254 nm): t_R 6.01 min (95.9%).

^{1}H NMR (DMSO-d_6), ppm: 13.64 (br s, 1H), 10.36 (br s, 1H), 8.35 (s, 1H), 7.88 (m, 4H), 7.69 (m, 1H), 7.64 (m, 1H), 7.56 (d, J=7.7 Hz, 1H), 7.50 (t, J=1.6 Hz, 1H), 7.45 (t, J= 7.7 Hz, 1H), 7.33 (m, 2H), 7.17 (m, 1H), 3.84 (s, 3H).

HRMS (ESI) calcd for $C_{24}H_{18}N_4O_3$ $[M+H]^+$411.1452, found 411.1441.

4.7.5. *N*-[4-(4-Benzooxazol-2-yl-1*H*-pyrazol-3-yl)-phenyl]-2-phenyl-acetamide 9{1,1,5}. HPLC (254 nm): t_R 5.48 min (100%).

^{1}H NMR (DMSO-d_6), ppm: 13.66 (br s, 1H), 10.38 (br s, 1H), 8.63 and 8.23 (2s, 1H, tautomers), 7.83 (m, 2H), 7.71 (m, 2H), 7.65 (m, 2H), 7.36 (m, 5H), 7.28 (m, 2H), 3.71 (s, 2H).

HRMS (ESI) calcd for $C_{24}H_{17}ClN_4O_2$ $[M+H]^+$395.1502, found 395.1502.

4.7.6. *N*-[4-(4-Benzooxazol-2-yl-1*H*-pyrazol-3-yl)-phenyl]-2-(4-chloro-phenyl)-acetamide 9{1,1,6}. HPLC (254 nm): t_R 6.50 min (97.8%).

^{1}H NMR (DMSO-d_6), ppm: 13.64 and 13.57 (2br s, 1H, tautomers), 10.37 and 10.27 (2br s, 1H, tautomers), 8.18 (s, 1H), 7.79 (m, 2H), 7.72 (m, 2H), 7.64 (m, 4H), 7.38 (m, 2H), 7.32 (m, 2H), 3.68 (s, 2H).

HRMS (ESI) calcd for $C_{24}H_{17}ClN_4O_2$ $[M+H]^+$429.1113, found 429.1104.

4.7.7. *N*-{4-[4-(5-Methyl-benzooxazol-2-yl)-1*H*-pyrazol-3-yl]-phenyl}-isobutyramide 9{1,2,1}. HPLC (254 nm): t_R 5.71 min (96.6%).

^{1}H NMR (DMSO-d_6), ppm: 13.59 and 13.53 (2br s, 1H, tautomers), 10.00 and 9.89 (2br s, 1H, tautomers), 8.15 (s, 1H), 7.71 (m, 4H), 7.53 (d, J=8.1 Hz, 1H), 7.44 (m, 1H), 7.14 (d, J=8.0 Hz, 1H), 2.62 (m, 1H), 2.42 (s, 3H), 1.12, (d, J=6.8 Hz, 6H).

HRMS (ESI) calcd for $C_{21}H_{20}N_4O_2$ $[M+H]^+$361.1659, found 361.1652.

4.7.8. Cyclopropanecarboxylic acid {4-[4-(5-methyl-benzooxazol-2-yl)-1*H*-pyrazol-3-yl]-phenyl}-amide 9{1,2,2}. HPLC (254 nm): t_R 5.55 min (98.8%).

^{1}H NMR (DMSO-d_6), ppm: 13.55 (s, 1H), 10.32 (s, 1H), 8.31 (s, 1H), 7.78 (d, J=8.8 Hz, 2H), 7.68 (d, J=8.8 Hz, 2H), 7.53 (d, J=8.0 Hz, 1H), 7.43 (m, 1H), 7.13 (d, J=8.0 Hz, 1H), 2.41 (s, 3H), 1.8 (m, 1H), 0.82 (m, 4H).

HRMS (ESI) calcd for $C_{21}H_{18}N_4O_2$ $[M+H]^+$359.1501, found 359.1492.

4.7.9. *N*-{4-[4-(5-Methyl-benzooxazol-2-yl)-1*H*-pyrazol-3-yl]-phenyl}-benzamide 9{1,2,3}. HPLC (254 nm): t_R 6.28 min (92.9%).

^{1}H NMR (DMSO-d_6), ppm: 13.65 and 13.55 (2br s, 1H, tautomers), 10.43 and 10.33 (2br s, 1H, tautomers), 8.17 (s, 1H), 7.97 (m, 2H), 7.92 (m, 1H), 7.85 (m, 2H), 7.60 (m, 1H), 7.54 (m, 4H), 7.45 (m, 1H), 7.15 (d, J=8.0 Hz, 1H), 2.42 (s, 3H).

HRMS (ESI) calcd for $C_{24}H_{18}N_4O_2$ $[M+H]^+$395.1502, found 395.1500.

4.7.10. 3-Methoxy-*N*-{4-[4-(5-methyl-benzooxazol-2-yl)-1*H*-pyrazol-3-yl]-phenyl}-benzamide 9{1,2,4}. HPLC (254 nm): t_R 5.94 min (97.7%).

^{1}H NMR (DMSO-d_6), ppm: 13.65 (br s, 1H), 10.38 (br s, 1H), 8.38 (s, 1H), 7.88 (m, 4H), 7.51 (m, 5), 7.17 (m, 2H), 3.86 (s, 3H), 2.42 (s, 3H).

HRMS (ESI) calcd for $C_{24}H_{18}N_4O_2$ $[M+H]^+$425.1608, found 425.1617.

4.7.11. *N*-{4-[4-(5-Methyl-benzooxazol-2-yl)-1*H*-pyrazol-3-yl]-phenyl}-2-phenyl-acetamide 9{1,2,5}. HPLC (254 nm): t_R 6.29 min (97.6%).

^{1}H NMR (DMSO-d_6), ppm: 13.61 (br s, 1H), 10.34 (br s, 1H), 8.29 (br s, 1H), 7.79 (d, J=8.2 Hz, 2H), 7.70 (d, J=8.2 Hz, 2H), 7.54 (d, J=8.2 Hz, 1H), 7.44 (s, 1H), 7.35 (m, 4H), 7.25 (m, 1H), 7.14 (d, J=7.3 Hz, 1H), 3.68 (s, 2H), 2.42 (s, 3H).

HRMS (ESI) calcd for $C_{25}H_{20}N_4O_2$ $[M+H]^+$409.1659, found 409.1668.

4.7.12. 2-(4-Chloro-phenyl)-*N*-{4-[4-(5-methyl-benzooxazol-2-yl)-1*H*-pyrazol-3-yl]-phenyl}-acetamide 9{1,2,6}. HPLC (254 nm): t_R 6.84 min (100%).

^{1}H NMR (DMSO-d_6), ppm: 13.66 and 13.58 (2br s, 1H, tautomers), 10.40 and 10.31 (2br s, 1H, tautomers), 8.20 (s, 1H), 7.82 (m, 2H), 7.72 (m, 2H), 7.52 (d, J=8.2 Hz, 1H), 7.50 (s, 1H), 7.41 (m, 4H), 7.16 (dd, J_1=8.2 Hz, J_2=1.1 Hz, 1H), 3.72 (s, 2H), 2.42 (s, 3H).

HRMS (ESI) calcd for $C_{25}H_{19}ClN_4O_2$ $[M+H]^+$443.1269, found 443.1279.

4.7.13. *N*-[3-(4-Benzooxazol-2-yl-1*H*-pyrazol-3-yl)-phenyl]-isobutyramide 9{2,1,1}. HPLC (254 nm): t_R 5.25 min (96.5%).

^{1}H NMR (DMSO-d_6), ppm: 13.70 (br s, 1H), 9.93 (br s, 1H), 8.43 (s, 1H), 8.03 (s, 1H), 7.73 (d, J=7.8 Hz, 1H), 7.67 (m, 1H), 7.62, (m, 1H), 7.48 (d, J=7.3 Hz, 1H), 7.89 (t, J=7.8 Hz, 1H), 7.33 (m, 2H), 2.59 (m, 1H), 1.10 (d, J=6.9 Hz, 6H).

HRMS (ESI) calcd for $C_{20}H_{18}N_4O_2$ $[M+H]^+$347.1502, found 347.1499.

4.7.14. Cyclopropanecarboxylic acid [3-(4-benzooxazol-2-yl-1*H*-pyrazol-3-yl)-phenyl]-amide 9{2,1,2}. HPLC (254 nm): t_R 5.15 min (87.1%).

^{1}H NMR (DMSO-d_6), ppm: 13.70 and 13.61 (2br s, 1H, tautomers), 10.32 and 10.21 (2br s, 1H, tautomers), 8.61 and 8.20 (2s, 1H, tautomers), 7.98 (s, 1H), 7.66 (m, 3H), 3.45 (m, 2H), 7.32 (m, 2H), 1.78 (m, 1H), 0.78 (d, J=4.6 Hz, 4H).

HRMS (ESI) calcd for $C_{20}H_{16}N_4O_2$ $[M+H]^+$345.1346, found 345.1341.

4.7.15. *N*-[3-(4-Benzoxazol-2-yl-1*H*-pyrazol-3-yl)-phenyl]-benzamide 9{2,1,3}. HPLC (254 nm): t_R 5.84 min (88.6%).

^{1}H NMR (DMSO-d_6), ppm: 13.79 and 13.69 (2br s, 1H, tautomers), 10.43 and 10.33 (2br s, 1H, tautomers), 8.25 (s, 1H), 7.98 (d, J=6.9 Hz, 2H), 7.90 (m, 1H), 7.66 (m, 4H), 7.55 (m, 3H), 7.45 (m, 1H), 7.35 (m, 2H).

HRMS (ESI) calcd for $C_{23}H_{16}N_4O_2$ $[M+H]^+$381.1346, found 381.1347.

4.7.16. *N*-[3-(4-Benzoxazol-2-yl-1*H*-pyrazol-3-yl)-phenyl]-3-methoxy-benzamide 9{2,1,4}. HPLC (254 nm): t_R 5.98 min (92.4%). ^{1}H NMR (DMSO-d_6), ppm: 13.78 and 13.69 (br s, 1H, tautomers), 10.39 and 10.29 (2br s, 1H, tautomers), 8.23 (m, 2H), 7.93 (m, 1H), 7.68 (m, 3H), 7.55 (m, 2H), 7.46 (t, J=7.9 Hz, 2H), 7.36 (m, 2H), 7.18 (d, J=8.9 Hz, 1H), 3.85 (s, 3H).

HRMS (ESI) calcd for $C_{24}H_{18}N_4O_3$ $[M+H]^+$411.1452, found 411.1464.

4.7.17. *N*-[3-(4-Benzooxazol-2-yl-1*H*-pyrazol-3-yl)-phenyl]-2-phenyl-acetamide 9{2,1,5}. HPLC (254 nm): t_R 5.52 min (93.2%).

^{1}H NMR (DMSO-d_6), ppm: 13.76 and 13.68 (2br s, 1H, tautomers), 10.36 and 10.25 (2br s, 1H, tautomers), 8.55 and 8.22 (2s, 1H, tautomers), 8.05 (s, 1H), 7.73 (m, 1H), 7.66 (m, 2H), 7.59 (m, 2H), 7.46 (m, 1H), 7.34 (m, 5H), 7.25 (m, 1H), 3.64 (d, J=7.8 Hz, 2H).

HRMS (ESI) calcd for $C_{24}H_{18}N_4O_2$ $[M+H]^+$395.1502, found 395.1519.

4.7.18. *N*-[3-(4-Benzooxazol-2-yl-1*H*-pyrazol-3-yl)-phenyl]-2-(4-chloro-phenyl)-acetamide 9{2,1,6}. HPLC (254 nm): t_R 6.41 min (78.2%).

^{1}H NMR (DMSO-d_6), ppm: 13.66 (br s, 1H), 10.26 (br s, 1H), 8.56 and 8.23 (2br s, 1H, tautomers), 8.03 (s, 1H), 7.64

(m, 3H), 7.58 (m, 1H), 7.50 (m, 1H), 7.34 (m, 6H), 3.64 (s, 2H).

HRMS (ESI) calcd for $C_{24}H_{17}ClN_4O_2$ $[M+H]^+$429.1113, found 429.1096.

4.7.19. *N*-{3-[4-(5-Methyl-benzooxazol-2-yl)-1*H*-pyrazol-3-yl]-phenyl}-isobutyramide 9{2,2,1}. HPLC (254 nm): t_R 5.66 min (95.3%).

^{1}H NMR (DMSO-d_6), ppm: 13. 67 and 13.59 (2br s, 1H, tautomers), 9.95 and 9.83 (br s, 1H), 8.16 (s, 1H), 8.01 (s, 1H), 7.71 (dd, J_1=23.6 Hz, J_2=8.5 Hz, 1H), 7.52 (d, J=8.0 Hz 1H), 7.41 (m, 2H), 7.33 (t, J=8.5 Hz, 1H), 7.14 (d, J=7.7 Hz, 1H), 2.58 (m, 1H), 2.41 (s, 3H), 1.09 (d, J=6.8 Hz, 6H).

HRMS (ESI) calcd for $C_{21}H_{20}N_4O_2$ $[M+H]^+$361.1659, found 361.1643.

4.7.20. Cyclopropanecarboxylic acid {3-[4-(5-methyl-benzooxazol-2-yl)-1*H*-pyrazol-3-yl]-phenyl}-amide 9{2,2,2}. HPLC (254 nm): t_R 5.58 min (94.2%).

^{1}H NMR (DMSO-d_6), ppm: 13.71 and 13.63 (2br s, 1H, tautomers), 10.35 and 10.24 (2br s, 1H, tautomers), 8.20 (s, 1H), 8.01 (s, 1H), 7.74 (m, 1H), 7.56 (d, J=8.2 Hz, 1H), 7.45 (m, 1H), 7.36 (m, 1H), 7.17 (d, J=8.0 Hz, 1H), 2.45 (s, 3H), 1.81 (m, 1H), 0.82 (d, J=4.5 Hz, 4H).

HRMS (ESI) calcd for $C_{21}H_{18}N_4O_2$ $[M+H]^+$359.1502, found 359.1509.

4.7.21. *N*-{3-[4-(5-Methyl-benzooxazol-2-yl)-1*H*-pyrazol-3-yl]-phenyl}-benzamide 9{2,2,3}. HPLC (254 nm): t_R 6.24 min (91.1%).

^{1}H NMR (DMSO-d_6), (ppm): 13.63 (br s, 1H), 10.36 and 10.29 (2br s, 1H, tautomers), 8.19 (s, 1H), 7.94 (m, 2H), 7.88 (m, 1H), 7.58 (m, 2H), 7.52 (m, 5H), 7.43 (m, 1H), 7.13 (d, J=8.0 Hz, 1H), 2.41 (s, 3H).

HRMS (ESI) calcd for $C_{24}H_{18}N_4O_2$ $[M+H]^+$395.1502, found 395.1493.

4.7.22. 3-Methoxy-*N*-{3-[4-(5-methyl-benzooxazol-2-yl)-1*H*-pyrazol-3-yl]-phenyl}-benzamide 9{2,2,4}. HPLC (254 nm): t_R 6.34 min (90.6%).

^{1}H NMR (DMSO-d_6), ppm: 13.69 and 13.62 (2br s, 1H, tautomers), 10.32 and 10.26 (2br s, 1H, tautomers), 8.18 (s, 1H), 7.88 (s, 1H), 7.58 (m, 1H), 7.53 (d, J=7.7 Hz, 2H), 7.47 (m, 2H), 7.43 (t, J=7.8 Hz, 2H), 7.14 (m, 2H), 3.82 (s, 3H), 2.41 (s, 3H).

HRMS (ESI) calcd for $C_{25}H_{20}N_4O_3$ $[M+H]^+$425.1608, found 425.1601.

4.7.23. *N*-{3-[4-(5-Methyl-benzooxazol-2-yl)-1*H*-pyrazol-3-yl]-phenyl}-2-phenyl-acetamide 9{2,2,5}. HPLC (254 nm): t_R 5.92 min (97.1%).

^{1}H NMR (DMSO-d_6), ppm: 13.73 and 13.64 (2br s, 1H, tautomers), 10.34 and 10.24 (2br s, 1H, tautomers), 8.61 and 8.20 (2s, 1H, tautomers), 8.03 (s, 1H), 7.71 (m, 1H), 7.54 (d, J=8.5 Hz, 2H), 7.43 (m, 2H), 7.36 (m, 4H), 7.27 (m, 1H), 7.18 (d, J=8.05 Hz, 1H), 3.67 (s, 2H), 2.44 (s, 3H).

HRMS (ESI) calcd for $C_{25}H_{20}N_4O_2$ $[M+H]^+$409.1659, found 409.1666.

4.7.24. 2-(4-Chloro-phenyl)-*N*-{3-[4-(5-methyl-benzooxazol-2-yl)-1*H*-pyrazol-3-yl]-phenyl}-acetamide 9{2,2,6}. HPLC (254 nm): t_R 6.77 min (94.6%).

^{1}H NMR (DMSO-d_6), ppm: 13.68 and 13.60 (2br s, 1H, tautomers), 10.32 and 10.21 (2br s, 1H, tautomers), 8.57 and 8.17 (2s, 1H, tautomers), 8.02 (s, 1H), 7.68 (m, 1H), 7.51 (m, 2H), 7.36 (m, 6H), 7.14 (d, J=8.0 Hz, 1H) 3.64 (s, 2H), 2.41 (s, 3H).

HRMS (ESI) calcd for $C_{25}H_{19}ClN_4O_2$ $[M+H]^+$443.1269, found 443.1273.

4.7.25. 1-[4-(4-Benzooxazol-2-yl-1*H*-pyrazol-3-yl)-phenyl]-3-phenyl-urea 10{1,1,1}. HPLC (254 nm): t_R 5.46 min (95.7%).

^{1}H NMR (DMSO-d_6), ppm: 13.65 and 13.57 (2br s, 1H, tautomers), 8.91 (br s, 1H), 8.77 (br s, 1H), 8.62 and 8.21 (2s, 1H), 7.82 (m, 2H), 7.70 (m, 1H), 7.63 (m, 3H), 7.53 (m, 2H), 7.30 (m, 4H), 6.99 (t, J=7.4 Hz, 1H).

HRMS (ESI) calcd for $C_{23}H_{17}N_5O_2$ $[M+H]^+$396.1455, found 396.1469.

4.7.26. 1-[4-(4-Benzooxazol-2-yl-1*H*-pyrazol-3-yl)-phenyl]-3-benzyl-urea 10{1,1,2}. HPLC (254 nm): t_R 5.28 min (100%).

^{1}H NMR (DMSO-d_6), ppm: 8.78 (s, 1H), 8.36 (br s, 1H), 7.77 (m, 2H), 7.70 (m, 1H), 7.66 (m, 1H), 7.56 (d, J=8.8 Hz, 2H), 7.35 (m, 6H), 7.27 (m, 1H), 6.73 (t, J=6.0 Hz, 1H), 4.35 (d, J=5.6 Hz, 2H).

HRMS (ESI) calcd for $C_{24}H_{19}N_5O_2$ $[M+H]^+$410.1611, found 410.1620.

4.7.27. 1-{4-[4-(5-Methyl-benzooxazol-2-yl)-1*H*-pyrazol-3-yl]-phenyl}-3-phenyl-urea 10{1,2,1}. HPLC (254 nm): t_R 6.43 min (100%).

^{1}H NMR (DMSO-d_6), ppm: 13.59 and 13.51 (2br s, 1H, tautomers), 8.88 (br s, 1H), 8.74 (br s, 1H), 8.56 and 8. 15 (2s, 1H, tautomers), 7.78 (m, 2H), 7.56 (m, 3H), 7.45 (m, 3H), 7.28 (t, J=7.5 Hz, 2H), 7.14 (d, J=8.8 Hz, 1H), 6.97 (t, J=7.5 Hz, 1H), 2.42 (s, 3H).

HRMS (ESI) calcd for $C_{24}H_{19}N_5O_2$ $[M+H]^+$410.1611, found 410.1616.

4.7.28. 1-Benzyl-3-{4-[4-(5-methyl-benzooxazol-2-yl)-1*H*-pyrazol-3-yl]-phenyl}-urea 10{1,2,2}. HPLC (254 nm): t_R 6.17 min (92.7%).

^{1}H NMR (DMSO-d_6), ppm: 13.52 (br s, 1H), 8.84 (br s, 1H),

8.28 (s, 1H), 7.72 (d, J=8.8 Hz, 2H), 7.54 (d, J=8 Hz, 2H), 7.50 (8s, 1H), 7.44 (m, 1H), 7.31 (m, 4H), 7.23 (m, 1H), 7.13 (m, 1H), 6.81 (br s, 1H), 4.31 (d, J=5.8 Hz, 2H), 2.41 (s, 3H).

HRMS (ESI) calcd for $C_{25}H_{21}N_5O_2$ $[M+H]^+$424.1768, found 424.1779.

4.7.29. 1-[3-(4-Benzooxazol-2-yl-1*H*-pyrazol-3-yl)-phenyl]-3-phenyl-urea 10{2,1,1}. HPLC (254 nm): t_R 5.52 min (90.1%).

^{1}H NMR (DMSO-d_6), ppm: 13.73 (br s, 1H), 9.00 (br s, 1H), 8.91 (br s, 1H), 8.53 (s, 1H), 7.88 (s, 1H), 7.69 (m, 1H), 7.64 (m, 1H), 7.61 (m, 1H), 7.45 (d, J=7.8 Hz, 2H), 7.42 (m, 2H), 7.35 (m, 2H), 7.27 (t, J=7.8 Hz, 2H), 6.96 (t, J=7.3 Hz, 1H).

HRMS (ESI) calcd for $C_{23}H_{17}N_5O_2$ $[M+H]^+$396.1455, found 396.1472.

4.7.30. 1-[3-(4-Benzooxazol-2-yl-1*H*-pyrazol-3-yl)-phenyl]-3-benzyl-urea 10{2,1,2}. HPLC (254 nm): t_R 5.78 min (92.4%).

^{1}H NMR (DMSO-d_6), ppm: 13.68 (br s, 1H), 8.71 (s, 1H), 8.32 (br s, 1H), 7.84 (s, 1H), 7.69 (m, 1H), 7.64 (m, 1H), 7.58 (m, 1H), 7.35 (m, 7H), 7.26 (m, 2H), 6.68 (br s, 1H), 4.31 (d, J=5.7 Hz, 2H).

HRMS (ESI) calcd for $C_{24}H_{19}N_5O_2$ $[M+H]^+$410.1611, found 410.1594.

4.7.31. 1-{3-[4-(5-Methyl-benzooxazol-2-yl)-1*H*-pyrazol-3-yl]-phenyl}-3-phenyl-urea 10{2,2,1}. HPLC (254 nm): t_R 6.42 min (93.7%).

^{1}H NMR (DMSO-d_6), ppm: 13.64 (br s, 1H), 8.79 (br s, 1H), 8.69 (s, 1H), 7.86 (s, 1H), 7.56 (m, 3H), 7.42 (m, 4H), 7.25 (t, J=7.3 Hz, 2H), 7.14 (d, J=8.0 Hz, 2H), 6.95 (t, J=7.3 Hz, 1H), 2.41 (s, 3H).

HRMS (ESI) calcd for $C_{24}H_{19}N_5O_2$ $[M+H]^+$410.1611, found 410.1608.

4.7.32. 1-Benzyl-3-{3-[4-(5-methyl-benzooxazol-2-yl)-1*H*-pyrazol-3-yl]-phenyl}-urea 10{2,2,2}. HPLC (254 nm): t_R 6.15 min (97.6%).

^{1}H NMR (DMSO-d_6), ppm: 13.64 and 13.56 (2br s, 1H, tautomers), 8.70 and 8.59 (2br s, 1H, tautomers), 8.16 (s, 1H), 7.79 (d, J=12.3 Hz, 1H), 7.52 (m, 3H), 7.42 (s, 1H), 7.37 (m, 1H), 7.29 (m, 4H), 7.22 (m, 1H), 7.14 (d, J=8.2 Hz, 1H), 6.61 (m, 1H), 4.29 (d, J=5.8 Hz, 2H), 2.41 (s, 3H).

HRMS (ESI) calcd for $C_{25}H_{21}N_5O_2$ $[M+H]^+$424.1768, found 424.1755.

4.7.33. *N*-[4-(4-Benzooxazol-2-yl-1*H*-pyrazol-3-yl)-phenyl]-4-methyl-benzenesulfonamide 11{1,1,1}. HPLC (254 nm): t_R 6.08 min (97.0%).

^{1}H NMR (DMSO-d_6), ppm: 13.61 (br s, 1H), 10.55 (br s, 1H), 8.58 and 8.20 (2s, 1H, tautomers), 7.74 (m, 4H), 7.67 (m, 1H), 7.59 (m, 1H), 7.35 (m, 4H), 7.20 (m, 2H), 2.34 (s, 3H).

HRMS (ESI) calcd for $C_{23}H_{18}N_4O_3S$ $[M+H]^+$431.1172, found 431.1187.

4.7.34. 4-Methyl-*N*-{4-[4-(5-methyl-benzooxazol-2-yl)-1*H*-pyrazol-3-yl]-phenyl}-benzenesulfonamide 11{1,2,1}. HPLC (254 nm): t_R 6.45 min (82.1%).

^{1}H NMR (DMSO-d_6), ppm: 13.54 (br s, 1H), 10.53 and 10.36 (2br s, 1H, tautomers), 8.54 and 8.13 (2s, 1H, tautomers), 7.71 (m, 4H), 7.52 (d, J=8 Hz, 1H), 7.39 (t, J=0.8 Hz, 1H), 7.36 (d, J=8.1 Hz, 2H), 7.19 (m, 2H), 7.13 (d, J=8.0 Hz, 1H), 2.42 (s, 3H), 2.33 (s, 3H).

HRMS (ESI) calcd for $C_{24}H_{20}N_4O_3S$ $[M+H]^+$445.1329, found 445.1326.

4.7.35. *N*-[4-(4-Benzooxazol-2-yl-1*H*-pyrazol-3-yl)-phenyl]-4-methyl-benzenesulfonamide 11{2,1,1}. HPLC (254 nm): t_R 5.73 min (83.8%).

^{1}H NMR (DMSO-d_6), ppm: 13.56 (br s, 1H), 10.50 (br s, 1H), 8.39 (s, 1H), 7.76 (m, 4H), 7.69 (m, 1H), 7.61 (m, 1H), 7.40 (d, J=8.0 Hz, 2H), 7.35 (m, 2H), 7.22 (d, J=8.4 Hz, 2H), 2.36 (s, 3H).

HRMS (ESI) calcd for $C_{23}H_{18}N_4O_3S$ $[M+H]^+$431.1172, found 431.1187.

4.7.36. 4-Methyl-*N*-{3-[4-(5-methyl-benzooxazol-2-yl)-1*H*-pyrazol-3-yl]-phenyl}-benzenesulfonamide 11{2,2,1}. HPLC (254 nm): t_R 6.37 min (84.6%).

^{1}H NMR (DMSO-d_6), ppm: 13.61 (br s, 1H), 10.28 (br s, 1H), 8.55 and 8.17 (2s, 1H, tautomers), 7.60 (d, J=8.3 Hz, 2H), 7.58 (s, 1H), 7.51 (d, J=8.1 Hz, 2H), 7.40 (s, 1H), 7.30 (s, 1H), 7.29 (d, J=8.5 Hz, 2H), 7.15 (d, J=8.1 Hz, 2H), 2.42 (s, 3H), 2.19 (s, 3H).

HRMS (ESI) calcd for $C_{24}H_{20}N_4O_3S$ $[M+H]^+$445.1329, found 445.1317.

References and notes

1. Levitzki, A. *Acc. Chem. Res.* **2003**, *36*, 462–469.
2. Noble, M. E.; Endicott, J. A.; Johnson, L. N. *Science* **2004**, *303*, 1800–1805.
3. Cohen, P. *Nature Rev. Drug. Discov.* **2002**, *1*, 309–315.
4. Fabbro, D.; Ruetz, S.; Buchdunger, E.; Cowan-Jacob, S. W.; Fendrich, G.; Liebetanz, J.; Mestan, J.; O'Reilly, T.; Traxler, P.; Chaudhuri, B. *Pharmacol. Therap.* **2002**, *93*, 79–98.
5. (a) Cohen, M. H.; Williams, G.; Johnson, J. R.; Duan, J.; Gobburu, J.; Rahman, A.; Benson, K.; Leighton, J.; Kim, S. K.; Wood, R.; Rothmann, M.; Chen, G.; Maung, U. K.; Staten, A. M.; Pazdur, R. *Clin. Cancer Res.* **2002**, *8*, 935–942. (b) Hernandez-Boluda, J. C.; Cervantes, F. *Drugs of Today* **2002**, *38*, 601–613.

6. Vansteenkiste, J. F. *Expert Rev. Anticancer Ther.* **2004**, *4*, 5–17.
7. Furet, P.; Meyer, T.; Strauss, A.; Raccuglia, S.; Rondeau, J. M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 221–224.
8. Berta, D.; Felder, E. R.; Villa, M.; Vulpetti, A. PCT Int. Appl., WO 0262804, 2002.
9. Okada, S.; Sawada, K.; Kuroda, A.; Watanabe, S.; Tanaka H. PCT Int. Appl., WO 9313099, 1993.
10. Wang, F. J.; Hauske, J. R.; Clayton, T.; Chrusciel, R. A. *Tetrahedron Lett.* **1997**, *38*, 6529–6532.
11. Pinciroli, V.; Biancardi, R.; Colombo, N.; Colombo, M.; Rizzo, V. *J. Comb. Chem.* **2001**, *3*, 434–440.
12. McMartin, C.; Bohacek, R. S. *J. Comput. Aided Mater. Des.* **1997**, *11*, 333–344.
13. Pearlman, D. A.; Case, D. A.; Caldwell, J. W.; Ross, W. S.; Cheatham, T. E.; DeBolt, S.; Ferguson, D.; Seibel, G.; Kollman, P. *Comp. Phys. Comm.* **1995**, *91*, 1–41.
14. Colombo, M.; Riccardi Sirtori, F.; Rizzo, V. *Rapid Commun. Mass Spectrom.* **2004**, *18*, 511–517.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 10811–10817

A new method for the synthesis of 2-cyclopenten-1-one-5-carboxylic ester derivatives via $Rh_2(OAc)_4$-mediated intramolecular C–H insertion reaction of 4*Z*-β-vinyl-α-diazo β-ketoesters

Guisheng Deng,[a,*] Baihua Xu[a] and Jianbo Wang[b]

[a]*College of Chemistry and Chemical Engineering, Hunan Normal University, Changsha 410081, People's Republic of China*
[b]*Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, Department of Chemical Biology, College of Chemistry, Peking University, Beijing 100871, People's Republic of China*

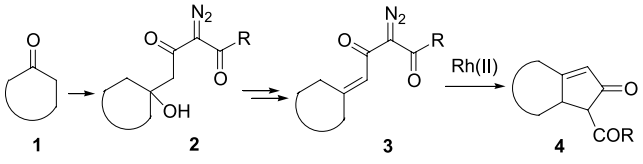
Received 14 March 2005; revised 23 May 2005; accepted 25 May 2005

Available online 23 September 2005

Abstract—2-Cyclopenten-1-one-5-carboxylic ester derivatives **14** are synthesized in a four-step-reaction sequence starting from alkynyl aldehydes **9** via 4*Z*-β-vinyl-α-diazo β-ketoesters intermediate **8**. The synthetic method for **8** is described. When the δ substituent is an alkyl group, Rh(II)-mediated decomposition of the diazo compounds **8** led to an intramolecular C–H insertion to afford 2-cyclopenten-1-one-5-carboxylic ester derivatives **14** in high yields. When the δ substituent is an aryl group, 2-hydroxynaphthoate **15** is obtained exclusively. In both cases, no Wolff rearrangement product was observed.

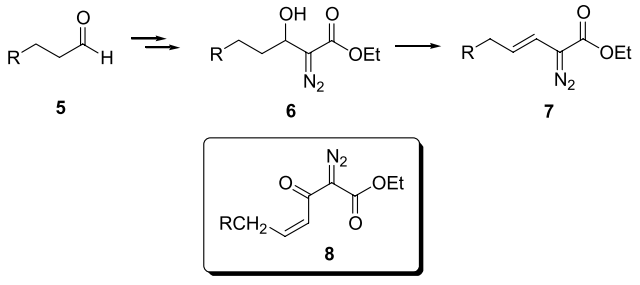
1. Introduction

2-Cyclopenten-1-one-5-carboxylic ester derivatives are useful intermediates in organic chemistry. The synthesis of these derivatives has been an attractive subject over the decades, and various methodologies have been developed for this purpose.[1] Intramolecular C–H insertion of Rh(II)-mediated α-diazo compounds has been an efficient approach to the formation of five-member ring structure.[2] However, this powerful approach has been so far limited to the synthesis of saturated cyclopentanone derivatives. We have recently reported a four-step sequence leading to bicyclic fused cyclopentanone derivatives **4** starting from cyclic ketones **1** via intermediates **2** and **3** (Scheme 1).[3] This study demonstrates the possibility of applying Rh(II)-carbene intramolecular C–H insertion in the synthesis of α,β-unsaturated cyclopentenone derivatives. Based on our interest in the synthetic application of α-diazo compounds and in connection with earlier research,[4] we conceived to develop a new method for the synthesis of 2-cyclopenten-1-one-5-carboxylic ester derivatives with intramolecular C–H insertion of Rh(II)-carbene as the key step.



Scheme 1.

Similar aldol condensation of a α-diazo-β-ketoester with aldehydes **5**, followed by a dehydration of the resulting δ-hydroxy-α-diazo-β-ketoester **6**, only gave the *E*-isomer **7** (Scheme 2).[5] Obviously, intramolecular C–H insertion will not occur from **7**. It has been reported that Wolff rearrangement occurred to generate vinylketenes when similar diazo compounds as **7** were decomposed with



Scheme 2.

Keywords: Synthesis; Insertion; 2-Cyclopenten-1-one-5-carboxylic ester derivatives; 4*Z*-β-vinyl-α-diazo β-ketoesters.
* Corresponding author. E-mail: gsdeng@hunnu.edu.cn

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.05.106

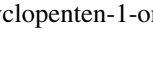
$Rh_2(OAc)_4$.[6] Therefore, the above reaction sequence is not suitable for the synthesis of 2-cyclopenten-1-one-5-carboxylic ester derivatives in general. In order to do that, the preparation of *Z*-isomer diazo compound **8** is crucial. We solved this problem by a three-step-reaction sequence starting from alkynyl aldehydes. Here we report our results concerning the preparation of intermediates **8** and the subsequent transformation to 2-cyclopenten-1-one-5-carboxylic ester derivatives.

2. Results and discussion

Initially, the requisite diazo compounds **8** were synthesized in four-steps starting from alkynyl aldehydes **9** (Scheme 3, (a)→(b)→(c)→(d)). Although the nucleophilic addition to aromatic aldehydes, aliphatic aldehydes, and α,β-unsaturated aldehydes by ethyl diazoacetate has been well developed,[7] the corresponding reaction with alkynyl aldehydes has not been reported. As anticipated, the compounds **10** were generated by aldol condensation of alkynyl aldehydes **9** with ethyl diazoacetate by treatment with a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). We found that 20% molar ratio of DBU to the substrates was the best suitable for the condensation reaction. Otherwise, the reaction of alkynyl aldehydes **9** with ethyl diazo acetate afforded the compounds **10a–e** in poorer yield. The aldol-type condensation was also carried out with NaH as base. The results are summarized in Table 1. As we can see the reaction with NaH as base gave better yields of the products **10a–e**.

Next, we studied the transformation of the diazo compounds **10** to the corresponding β-ketoesters **11**. Although the Rh(II)-mediated reactions of β-vinyl-β-hydroxy-α-diazo esters,[8] β-aryl-β-hydroxy-α-diazo esters,[9] and β-alkyl-β-hydroxy-α-diazo esters[10] have been reported, the corresponding reaction of β-alkynyl-β-hydroxy-α-diazo esters **10** has not been investigated. As expected, the diazo compounds **10a**, **10b**, and **10e** were converted to compounds **11a**, **11b**, and **11e**, respectively, in good yields upon exposure to rhodium(II) acetate in methylene chloride at room temperature (Table 2). The results are similar to the previously reported Rh(II)-mediated decomposition of β-vinyl-β-hydroxy-α-diazo esters.[8,11]

Table 1. The condensation of alkynyl aldehydes **9a–e** with ethyl diazoacetate

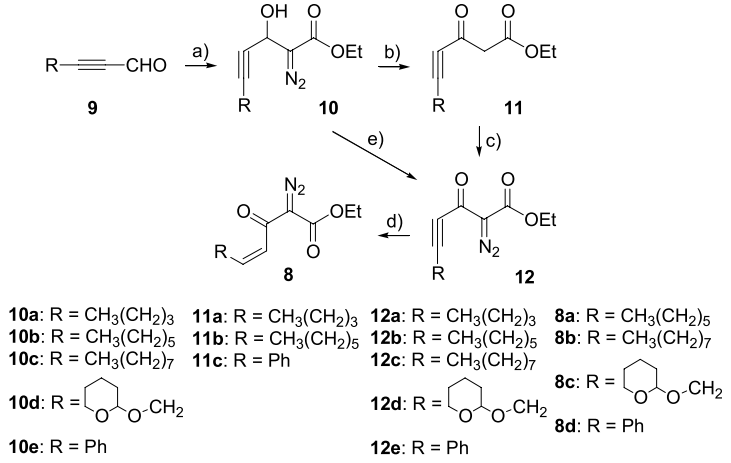
Entry	Aldehydes **9** R=	Product	Reaction time (h) (method A/method B)	Yield (%) (method A/method B)[a]
1	**a**, $CH_3(CH_2)_3$	**10a**	24/24	26/59
2	**b**, $CH_3(CH_2)_5$	**10b**	24/20	20/60
3	**c**, $CH_3(CH_2)_7$	**10c**	24/24	24/65
4	**d**, 	**10d**	—/22	—[b]/38
5	**e**, Ph	**10e**	18/24	55/62

[a] Isolated yield after column chromatography. Method A: the reaction carried in CH_3CN in the presence of 20% DBU at room temperature. Method B: the reaction carried in THF in the presence of NaH at 0 °C to room temperature.
[b] The reaction was not performed.

β-Keto esters **11a–c** were then transformed to the corresponding diazo compounds **12a–c** by treatment with TsN_3 in the presence of Et_3N in CH_3CN at room temperature in high yields (Table 3).

Although the above four-step transformation of **9** to **12** is efficient, we conceived that the diazo compounds **10a–e** may be directly oxidized to give the corresponding compounds **12a–e**, thereby the four-step sequence of the transformation can be shortened to a three-step synthetic sequence (Scheme 3, (a)→(e)→(d)). Therefore, we examined the oxidation of the β-hydroxy diazo compounds **10a–e** using MnO_2 as oxidant, because MnO_2 is a mild oxidant and has been used for the oxidation of a variety of compounds.[12] We were delighted to find that the hydroxy group of the compounds **10a–e** were efficiently oxidized to carbonyl group, while the diazo group kept intact (Table 4). Considering the fact that the diazo group can be easily oxidized,[13] it is rather astonishing to note the diazo group has tolerated the MnO_2 oxidation. This result may further broaden the scope of the chemical transformation of diazo carbonyl compounds.

Triple bond in compounds **12a–e** could be efficiently hydrogenated in the presence of Lindlar catalyst, giving



Scheme 3. (a) N_2CHCO_2Et, NaH, THF; (b) $Rh_2(OAc)_4$, CH_2Cl_2; (c) TsN_3, Et_3N, CH_3CN; (d) Lindlar catalyst, H_2, *n*-hexane; (e) MnO_2, CH_2Cl_2.

Table 2. The transformation of β-hydroxy-α-diazo esters **10a**, **10b**, **10e** to the compounds **11a–c**

Entry	β-Hydroxy diazo esters **10**	Product	Reaction time (h)	Yields (%)[a]
1	**a**, $CH_3(CH_2)_3$	**11a**	4	70
2	**b**, $CH_3(CH_2)_5$	**11b**	6	73
3	**e**, Ph	**11c**	6	78

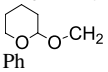
[a] Isolated yield after column chromatography.

Table 3. Reaction of β-keto esters **11b,c** with TsN_3

Entry	β-Keto ester **11** R=	Product	Reaction time (h)	Yields (%)[a]
1	**b**, $CH_3(CH_2)_5$	**12b**	14	90
2	**c**, Ph	**12e**	14	93

[a] Isolated yield after column chromatography.

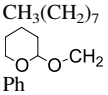
Table 4. The oxidation of **10a–e** with MnO_2

Entry	Diazo compounds **10**	Product	Reaction time (h)	Yield (%)[a]
1	**a**, $CH_3(CH_2)_3$	**12a**	6	88
2	**b**, $CH_3(CH_2)_5$	**12b**	15	90
3	**c**, $CH_3(CH_2)_7$	**12c**	10	89
4	**d**, 	**12d**	12	90
5	**e**, Ph	**12e**	10	92

[a] Isolated yield after column chromatography.

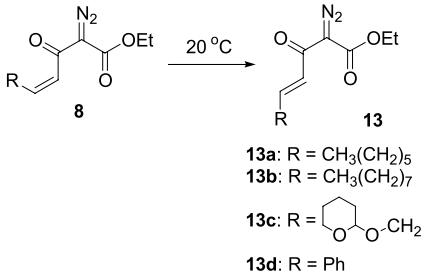
the corresponding 4*Z*-β-vinyl-α-diazo β-ketoesters **8a–d** in almost quantitative yields (Table 5). It is worth to note that the diazo group can be hydrogenated to methylene group with 10% Pd/C as the catalyst,[14] but in our study the diazo group remains intact in the hydrogenation reaction with Lindlar catalyst.

Table 5. The hydrogenation of **12b–e** with Lindlar catalyst

Entry	Diazo compound **9**	Product	Reaction time (h)	Yields (%)[a]
1	**b**, $CH_3(CH_2)_5$	**8a**	1	97
2	**c**, $CH_3(CH_2)_7$	**8b**	1	95
3	**d**, 	**8c**	1.5	94
4	**e**, Ph	**8d**	1.5	92

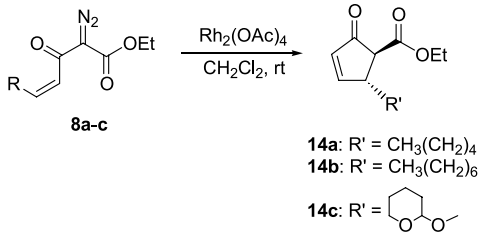
[a] Isolated yield after column chromatography.

It was noted that 4*Z*-β-vinyl-α-diazo β-ketoesters **8a–d** were unstable, and could be slowly isomerized into 4*E*-β-vinyl-α-diazo β-ketoesters **13a–d** at 20 °C (Scheme 4). Nevertheless, they could be stored for a month at −20 °C. This isomerisation could be monitored with ^1H NMR spectra (Table 6).

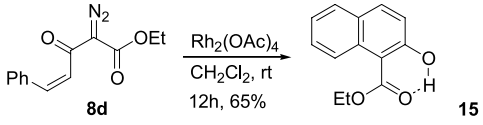


Scheme 4.

The $Rh_2(OAc)_4$-catalyzed decomposition of 4*Z*-β-vinyl-α-diazo β-ketoesters **8a–c**, in which the R is alkyl group, gave the corresponding 2-cyclopenten-1-one-5-carboxylic ester derivatives **14a–c** in excellent yields (Scheme 5, Table 7). In all the cases only one diastereoisomer was formed. When the R is aryl group, however, the corresponding $Rh_2(OAc)_4$-catalyzed decomposition resulted in 2-hydroxynaphthoate **15** (Scheme 6). This latter result is in accordance with the reported findings.[15] In all cases, no Wolff rearrangement product was detected.

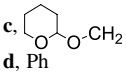


Scheme 5.



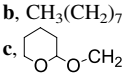
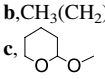
Scheme 6.

Table 6. The isomerisation of **8a–d** to **13a–d** monitored by ^1H NMR

Entry	R	^1H NMR of *Z*-isomer **8**	^1H NMR of *E*-isomer **13**	The molecular ratio[a] of *Z*-isomer **8** to *E*-isomer **13** (3/10/25 days)[b]
1	**a**, $CH_3(CH_2)_5$	γ-H: 6.18 (dt, *J*=11.4, 7.2 Hz); δ-H: 6.94 (dt, *J*=11.4, 1.5 Hz)	γ-H: 7.02 (dt, *J*=15.6, 6.6 Hz); δ-H: 7.14 (d, *J*=15.6 Hz)	70:30/25:75/10:90
2	**b**, $CH_3(CH_2)_7$	γ-H: 6.17 (dt, *J*=11.4, 7.5 Hz); δ-H: 6.93 (dt, *J*=11.4, 1.8 Hz)	γ-H: 7.06 (dt, *J*=15.6, 6.6 Hz); δ-H: 7.19 (d, *J*=15.6 Hz)	100:0/90:10/45:55
3	**c**, 	γ-H: 6.39 (dt, *J*=11.7, 4.8 Hz); δ-H: 7.06 (dt, *J*=11.7, 2.4 Hz)	γ-H: 7.08 (dt, *J*=15.3, 7.5 Hz); δ-H: 7.44 (dt, *J*=15.3, 2.1 Hz)	100:0/85:15/35:65
4	**d**, Ph	γ-H: 6.86 (d, *J*=12.6 Hz); δ-H: 6.91 (d, *J*=12.6 Hz)	γ-H: 7.76 (d, *J*=15.9 Hz); δ-H: 7.91 (d, *J*=15.9 Hz)	100:0/82:18/15:85

[a] The ratio was determined by ^1H NMR.
[b] The ^1H NMR spectra were measured when the diazo compounds **8a–d** were stored at 20 °C for 3, 10, and 25 days, respectively.

Table 7. The $Rh_2(OAc)_4$-catalyzed decomposition of 4*Z*-β-vinyl-β-keto-α-diazo esters **8a–c**

Entry	Diazo compound **8** R=	Product **14** R′=	Reaction time (h)	Yield (%)[a]
1	**a**, $CH_3(CH_2)_5$	**a**, $CH_3(CH_2)_4$	12	88
2	**b**, $CH_3(CH_2)_7$	**b**,$CH_3(CH_2)_6$	10	86
3	**c**, 	**c**, 	12	82

[a] Isolated yield after column chromatography.

In summary, we have found the diazo group has tolerated the MnO_2 oxidation and the hydrogenation with Lindlar catalyst. This remarkable observation leads to the development of a new approach to cyclopentenone ester derivatives, based on $Rh_2(OAc)_4$-mediated intramolecular C–H insertion of 4*Z*-β-vinyl-α-diazo β-ketoesters.

3. Experimental

3.1. General procedures

IR spectra were recorded on a WQF-200 spectraphotometer. NMR spectra were measured on Varian YH 300 apparatus in $CDCl_3$ solution using tetramethylsilane as an internal standard. MS spectra were recorded on ZAB-HS or +Q1 MCA spectrometer. Hexane, CH_3CN, and CH_2Cl_2 were dried on CaH_2, THF was distilled from sodium, and other solvents were distilled prior to use. Organic extracts were concentrated using a rotary evaporator at below 50 °C. Melting points were uncorrected. Column chromatography was performed using ZCX-α (200–300 mesh). Ethyl diazoacetate was prepared according to the known procedure.[16]

3.2. Typical procedure for the formation of 10a–e by aldol-type condensation

3.2.1. Ethyl 2-diazo-3-hydroxy-5-phenylpent-4-ynoate (10e). *Method A*. To a solution of ethyl diazo acetate (274 mg, 2.4 mmol) in anhydrous CH_3CN (10 mL) was added 1, 8-diazabicyclo[5.4.0]undec-7-ene (DBU) (60 mg, 0.4 mmol) in anhydrous CH_3CN (2 mL) and 3-phenylpropioaldehyde (260 mg, 2 mmol) in anhydrous CH_3CN (3 mL). The reaction mixture was stirred for 18 h at room temperature and then concentrated in vacuo. The residue was chromatographed on silica (petroleum ether/Et_2O 4:1) to give **10e** (268 mg, 55%) as brown yellow oil. *Method B*. To a suspension of NaH (58 mg, 2.4 mmol) in anhydrous THF (9 mL) at 0 °C was added dropwise ethyl diazo acetate (274 mg, 2.4 mmol) in anhydrous THF (3 mL). The reaction mixture was stirred for 30 min at 0 °C and then warmed to room temperature. The stirring was continued for another 30 min. 3-Phenylpropioaldehyde (260 mg, 2 mmol) in anhydrous THF (3 mL) was then added dropwise to this mixture. The reaction mixture was stirred for another 24 h at room temperature and then filtrated quickly. The filtrate was concentrated in vacuo and chromatographed on silica (petroleum ether/Et_2O 4:1) to give **10e** (302 mg, 62%) as brown yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.45–7.26 (m, 5H), 5.74 (s, 1H), 4.26 (q, *J*=7.1 Hz, 2H), 3.20 (br s, 1H), 1.28 (t, *J*=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.8, 131.8, 129.0, 128.3, 121.4, 87.2, 83.6, 77.2, 61.3, 58.8, 14.4; IR (KBr, cm^{-1}) 3419, 2983, 2235, 2102, 1693, 1672, 1491, 1400, 1373, 1342, 1292, 1111, 1018; EIMS (*m/z*) 216 [$(M-N_2)^+$], 197, 188, 170, 160, 142, 129, 126, 114 (100), 103, 89, 77, 63, 52, 29. Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.87; H, 5.03; N, 11.59.

3.2.2. Ethyl 2-diazo-3-hydroxynon-4-ynoate (10a). A yellow oil was obtained in 26 and 59% yields with method A and method B, respectively. ^1H NMR ($CDCl_3$, 300 MHz) δ 5.52 (t, *J*=1.8 Hz, 1H), 4.26 (q, *J*=7.2 Hz, 2H), 3.33 (br s, 1H), 2.25 (dt, *J*=7.1, 1.8 Hz, 2H), 1.54–1.34 (m, 4H), 1.29 (t, *J*=7.2 Hz, 3H), 0.91 (t, *J*=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.5, 88.5, 77.2, 75.1, 61.2, 58.5, 30.4, 21.8, 18.2, 14.4, 13.4; IR (KBr, cm^{-1}) 3425, 2960, 2935, 2875, 2227, 2102, 1701, 1672, 1466, 1375, 1344, 1290, 1109, 1016; EIMS (*m/z*) 224 [M^+], 207, 196, 182, 179, 167, 151, 139, 136, 121, 107, 97, 93, 79, 69, 55, 52, 41, 27 (100). Anal. Calcd for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19; N, 12.49. Found: C, 58.73; H, 7.29; N, 12.40.

3.2.3. Ethyl 2-diazo-3-hydroxyundec-4-ynoate (10b). A yellow oil was obtained in 20 and 60% yields with method A and method B, respectively. ^1H NMR ($CDCl_3$, 300 MHz) δ 5.52 (t, *J*=2.0 Hz, 1H), 4.26 (q, *J*=7.2 Hz, 2H), 2.24 (dt, *J*=7.1, 2.0 Hz, 2H), 1.53–1.46 (m, 2H), 1.42–1.26 (m, 6H), 1.29 (t, *J*=7.2 Hz, 3H), 0.89 (t, *J*=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.5, 88.5, 77.2, 75.2, 61.2, 58.5, 31.2, 28.4, 28.3, 22.4, 18.5, 14.4, 13.9; IR (KBr, cm^{-1}) 3433, 2956, 2931, 2860, 2227, 2100, 1697, 1676, 1466, 1373, 1342, 1290, 1105, 1016; EIMS (*m/z*) 252 [M^+], 207, 195, 182, 179, 163, 149, 135, 121, 109, 97, 93, 79, 67, 55, 52, 41, 29 (100). Anal. Calcd for $C_{13}H_{20}N_2O_3$: C, 61.88; H, 7.99; N, 11.10. Found: C, 61.81; H, 7.87; N, 11.19.

3.2.4. Ethyl 2-diazo-3-hydroxytridec-4-ynoate (10c). A yellow oil was obtained in 24 and 65% yields with method A and method B, respectively. ^1H NMR ($CDCl_3$, 300 MHz) δ 5.52 (t, *J*=2.1 Hz, 1H), 4.26 (q, *J*=7.2 Hz, 2H), 2.24 (dt, *J*=6.9, 2.1 Hz, 2H), 1.53–1.46 (m, 2H), 1.42–1.26 (m, 10H), 1.27 (t, *J*=7.2 Hz, 3H), 0.88 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.5, 88.8, 77.2, 75.1, 61.2, 58.7, 31.8, 29.7, 29.0, 28.8, 28.4, 22.6, 18.5, 14.4, 14.0; IR (KBr, cm^{-1}) 3406, 2956, 2931, 2858, 2229, 2104, 1697, 1678, 1466, 1373, 1344, 1290, 1107, 1018; EIMS (*m/z*) 252 [$(M-N_2)^+$], 207, 195, 182, 177, 165, 153, 149, 135, 121, 109, 95, 81, 67, 55, 41, 29 (100). Anal. Calcd for $C_{15}H_{24}N_2O_3$: C, 64.26; H, 8.63; N, 9.99. Found: C, 64.37; H, 8.56; N, 9.85.

3.2.5. Ethyl 2-diazo-3-hydroxy-6-(tetrahydro-2*H*-pyran-2-yloxy)hex-4-ynoate (10d). A yellow oil was obtained in 38% yield (method B). ^1H NMR ($CDCl_3$, 300 MHz) δ 5.56 (s, 1H), 4.80 (t, *J*=3.2 Hz, 1H), 4.33 (dd, *J*=3.2, 1.8 Hz, 2H), 4.26 (q, *J*=7.2 Hz, 2H), 3.87–3.79 (m, 1H), 3.56–3.53 (m, 1H), 1.83–1.71 (m, 2H), 1.63–1.57 (m, 4H), 1.30 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.2, 96.9, 83.4, 81.0, 77.2, 62.0, 61.3, 58.4, 53.9, 30.2, 25.3, 18.9, 14.4; IR (KBr, cm^{-1}) 3396, 2943, 2871, 2360, 2343, 2102, 1697, 1442, 1373, 1342, 1288, 1105, 1026, 903; EIMS (*m/z*) 282 [M^+], 253, 226, 198, 181, 167, 153, 135, 125, 107, 85

(100), 67, 43, 29. Anal. Calcd for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.43; N, 9.92. Found: C, 55.34; H, 6.55; N, 9.99.

3.3. Typical procedure for the formation of 11a–c by $Rh_2(OAc)_4$-mediated 1,2-hydrogen shift reaction

3.3.1. Ethyl 3-oxo-5-phenylpent-4-ynoate (11c). To a suspension of $Rh_2(OAc)_4$ (6.3 mg, 0.0143 mmol) in anhydrous CH_2Cl_2 (10 mL) at room temperature was added **10e** (348 mg, 1.43 mmol) in anhydrous CH_2Cl_2 (5 mL) over 5 min. The reaction mixture was stirred for another 6 h and then concentrated in vacuo. The residue was chromatographed on silica (petroleum ether/Et_2O 10:1) to give **11c** (240 mg, 78%) as yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.57–7.30 (m, 5H), 4.21 (q, $J=7.2$ Hz, 2H), 3.66 (s, 2H), 1.26 (t, $J=7.2$ Hz, 3H); IR (KBr, cm^{-1}) 2981, 2927, 2854, 2206, 1741, 1674, 1616, 1410, 1281, 1211, 1122, 1082, 1034.

3.3.2. Ethyl 3-oxonon-4-ynoate (11a). A colorless oil was obtained in 70% yield. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.17 (q, $J=7.2$ Hz, 2H), 3.51 (s, 2H), 2.34 (t, $J=6.9$ Hz, 2H), 1.57–1.47 (m, 2H), 1.44–1.32 (m, 2H), 1.24 (t, $J=7.2$ Hz, 3H), 0.88 (t, $J=7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.8, 166.1, 96.8, 80.3, 61.4, 51.4, 29.5, 21.8, 18.6, 14.0, 13.3; IR (KBr, cm^{-1}) 2962, 2935, 2875, 2216, 1745, 1680, 1614, 1466, 1414, 1321, 1248, 1176, 1034; EIMS (*m/z*) 197 [$(M+H)^+$], 179 (100), 123, 109, 95, 81, 67. Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.54; H, 8.13.

3.3.3. Ethyl 3-oxoundec-4-ynoate (11b). A colorless oil was obtained in 73% yield. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.14 (q, $J=7.2$ Hz, 2H), 3.49 (s, 2H), 2.31 (t, $J=7.1$ Hz, 2H), 1.55–1.43 (m, 2H), 1.38–1.08 (m, 6H), 1.22 (t, $J=7.2$ Hz, 3H), 0.80 (t, $J=6.9$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.7, 166.0, 96.7, 80.3, 61.3, 51.3, 31.1, 28.4, 27.4, 22.3, 18.9, 13.9, 13.8; IR (KBr, cm^{-1}) 2958, 2933, 2860, 2216, 1745, 1680, 1614, 1466, 1415, 1321, 1250, 1176, 1034; EIMS (*m/z*) 225 [$(M+H)^+$], 197, 179, 137, 109, 95 (100), 81, 67, 55. Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.70; H, 8.81.

3.4. Typical procedure for the formation of 12a, 12b, 12e from 11a–c by diazo transfer reaction

3.4.1. Ethyl 2-diazo-3-oxo-5-phenylpent-4-ynoate (12e). Et_3N (0.28 mL, 2 mmol) and *p*-toluene sulfonyl azide (237 mg, 1.2 mmol) in anhydrous CH_3CN (4 mL) were added dropwise to a solution of **8c** (216 mg, 1 mmol) in anhydrous CH_3CN (16 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 15 h at this temperature. Then, the solution was concentrated in vacuo and the residue was chromatographed on silica (petroleum ether/Et_2O 10:1) to give **9e** (225 mg, 93%) as yellow crystals: mp 78–80 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.62–7.59 (m, 2H), 7.44–7.34 (m, 3H), 4.33 (q, $J=7.2$ Hz, 2H), 1.32 (t, $J=7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.4, 160.0, 133.0, 130.9, 128.6, 120.0, 96.1, 85.5, 77.2, 61.7, 14.3; IR (KBr, cm^{-1}) 2983, 2935, 2210, 2152, 1718, 1589, 1466, 1442, 1371, 1331, 1215, 1171, 1130, 1039; EIMS (*m/z*) 242 [M^+], 214, 142, 129 (100), 114, 101, 87, 75, 63, 52, 29. Anal. Calcd for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.56. Found: C, 64.59; H, 4.30; N, 11.50.

3.4.2. Ethyl 2-diazo-3-oxoundec-4-ynoate (12b). A yellow oil was obtained in 90% yield. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.33 (q, $J=7.2$ Hz, 2H), 2.44 (t, $J=7.2$ Hz, 2H), 1.67–1.57 (m, 2H), 1.47–1.21 (m, 6H), 1.34 (t, $J=7.2$ Hz, 3H), 0.89 (t, $J=6.9$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.5, 160.1, 99.8, 78.1, 77.2, 61.6, 31.2, 28.5, 27.5, 22.4, 19.3, 14.3, 13.9; IR (KBr, cm^{-1}) 2956, 2933, 2860, 2222, 2139, 1734, 1697, 1610, 1466, 1371, 1315, 1259, 1105; EIMS (*m/z*) 251 [$(M+H)^+$], 222, 205, 193, 180, 165, 152, 147, 137, 125, 107, 97, 79, 67, 55, 43, 41, 29 (100). Anal. Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.30; H, 7.36; N, 11.28.

3.5. Typical procedure for the formation of 12b–e from 10b–e by MnO_2 oxidation reaction

3.5.1. Ethyl 2-diazo-3-oxo-5-phenylpent-4-ynoate (12e). Activated MnO_2 (2.175 g, 25 mmol, Aldrich) was added in 2 portions over 4 h to a solution of **10e** (610 mg, 2.5 mmol) in CH_2Cl_2 (15 mL). After stirring for 10 h at room temperature, the manganese dioxide was removed by filtration. The filtrate was concentrated in vacuo and chromatographed on silica (petroleum ether/Et_2O 6:1) to give **12e** (555 mg, 92%).

3.5.2. Ethyl 2-diazo-3-oxonon-4-ynoate (12a). A yellow oil was obtained in 88% yield. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.29 (q, $J=7.2$ Hz, 2H), 2.41 (t, $J=7.2$ Hz, 2H), 1.61–1.52 (m, 2H), 1.47–1.35 (m, 2H), 1.30 (t, $J=7.2$ Hz, 3H), 0.89 (t, $J=7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.4, 160.1, 99.8, 78.1, 77.2, 61.6, 31.5, 22.5, 19.3, 14.3, 14.0; IR (KBr, cm^{-1}) 2960, 2935, 2873, 2222, 2137, 1734, 1697, 1608, 1466, 1371, 1317, 1259, 1109; EIMS (*m/z*) 223 [$(M+H)^+$], 194, 165, 152, 147, 123, 107, 95, 79, 69, 55, 43, 41, 29 (100). Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.50; H, 6.41; N, 12.53.

3.5.3. Ethyl 2-diazo-3-oxoundec-4-ynoate (12b). A yellow oil was obtained in 90% yield.

3.5.4. Ethyl 2-diazo-3-oxotridec-4-ynoate (12c). A yellow oil was obtained in 89% yield. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.33 (q, $J=7.2$ Hz, 2H), 2.44 (t, $J=7.2$ Hz, 2H), 1.66–1.57 (m, 2H), 1.46–1.21 (m, 10H), 1.34 (t, $J=7.2$ Hz, 3H), 0.88 (t, $J=6.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.5, 160.1, 99.8, 78.1, 77.2, 61.6, 31.7, 29.0, 28.9, 28.8, 27.5, 22.6, 19.3, 14.3, 14.0; IR (KBr, cm^{-1}) 2954, 2924, 2854, 2224, 2135, 1736, 1701, 1614, 1464, 1371, 1313, 1259, 1103; EIMS (*m/z*) 279 [$(M+H)^+$], 203, 193, 180, 165, 153, 147, 123, 107, 95, 79, 69, 55, 43 (100), 41, 29. Anal. Calcd for $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N, 10.06. Found: C, 64.87; H, 7.90; N, 10.21.

3.5.5. Ethyl 2-diazo-3-oxo-6-(tetrahydro-2*H*-pyran-2-yloxy)hex-4-ynoate (12d). A yellow oil was obtained in 90% yield. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.82 (br s, 1H), 4.41 (s, 2H), 4.25 (q, $J=7.1$ Hz, 2H), 3.79–3.71 (m, 1H), 3.51–3.46 (m, 1H), 1.76–1.64 (m, 2H), 1.58–1.46 (m, 4H), 1.26 (t, $J=7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.8, 159.6, 96.9, 93.3, 81.9, 78.0, 61.9, 61.7, 53.7, 29.9, 25.1, 18.7, 14.1; IR (KBr, cm^{-1}) 2945, 2873, 2225, 2141, 1736, 1697, 1610, 1442, 1371, 1321, 1261, 1101, 1032, 903; EIMS (*m/z*) 262 [$(M-N_2)^+$], 179, 151 (100), 123, 101, 96,

85, 67, 55, 43, 41, 29. Anal. Calcd for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.99. Found: C, 55.69; H, 5.81; N, 10.10.

3.6. Typical procedure for the catalytic hydrogenation of 12b–e

3.6.1. Ethyl 2-diazo-3-oxoundec-4-enoate (8a). To a solution of **12b** (250 mg, 1 mmol) in hexane (10 mL) was added Lindlar catalyst (30 mg), and the reaction mixture was stirred vigorously for 1 h at room temperature under hydrogen gas balloon. The precipitate was filtrated and then the solvent was removed in vacuo. The residue was purified by chromatography (petroleum ether/Et_2O 8:1) to give **8a** (244 mg, 97%) as yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.93 (dt, $J=11.4$, 1.5 Hz, 1H), 6.18 (dt, $J=11.4$, 7.2 Hz, 1H), 4.25 (q, $J=7.1$ Hz, 2H), 2.66–2.58 (m, 2H), 1.61–1.53 (m, 2H), 1.32–1.22 (m, 6H), 1.30 (t, $J=7.1$ Hz, 3H), 0.83 (t, $J=6.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 182.5, 161.3, 150.2, 123.4, 77.2, 31.6, 30.0, 29.1, 29.0, 28.0, 22.5, 14.3, 14.0; IR (KBr, cm^{-1}) 2954, 2924, 2854, 2131, 1720, 1647, 1614, 1464, 1369, 1302, 1221, 1134, 1043; EIMS (*m/z*) 252 [M^+], 226, 224, 205, 195, 178, 167, 150, 139, 121 (100), 108, 94, 81, 69, 55, 43, 41, 28. Anal. Calcd for $C_{13}H_{20}N_2O_3$: C, 61.88; H, 7.99; N, 11.10. Found: C, 61.93; H, 7.89; N, 11.16.

3.6.2. Ethyl 2-diazo-3-oxotridec-4-enoate (8b). A yellow oil was obtained in 95% yield. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.93 (dt, $J=11.4$, 1.8 Hz, 1H), 6.17 (dt, $J=11.4$, 7.5 Hz, 1H), 4.25 (q, $J=7.1$ Hz, 2H), 2.65–2.57 (m, 2H), 1.43–1.36 (m, 2H), 1.21–1.32 (m, 10H), 1.28 (t, $J=7.1$ Hz, 3H), 0.83 (t, $J=6.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 182.5, 161.3, 150.1, 123.4, 77.2, 61.3, 31.8, 30.0, 29.6, 29.3, 29.2, 28.1, 22.6, 14.3, 14.0; IR (KBr, cm^{-1}) 2958, 2927, 2856, 2133, 1718, 1647, 1612, 1464, 1369, 1304, 1219, 1134, 1041; EIMS (*m/z*) 280 [M^+], 254, 252, 223, 206, 195, 178, 167, 156, 149, 135, 121, 108, 94, 81, 67, 55, 43, 41, 29 (100). Anal. Calcd for $C_{15}H_{24}N_2O_3$: C, 64.26; H, 8.63; N, 9.99. Found: C, 64.31; H, 8.70; N, 9.90.

3.6.3. Ethyl 2-diazo-3-oxo-6-(tetrahydro-2*H*-pyran-2-yloxy)hex-4-enoate (8c). A yellow oil was obtained in 94% yield. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.06 (dt, $J=11.7$, 2.4 Hz, 1H), 6.39 (dt, $J=11.7$, 4.8 Hz, 1H), 4.76–4.74 (m, 1H), 4.65–4.63 (m, 1H), 4.59–4.57 (m, 1H), 4.25 (q, $J=7.2$ Hz, 2H), 3.84–3.78 (m, 1H), 3.49–3.42 (m, 1H), 1.85–1.67 (m, 2H), 1.57–1.49 (m, 4H), 1.28 (t, $J=7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 182.0, 161.1, 148.2, 122.4, 98.8, 77.2, 66.9, 62.4, 61.5, 30.6, 25.4, 19.6, 14.3; IR (KBr, cm^{-1}) 2943, 2871, 2360, 2133, 1718, 1647, 1606, 1419, 1371, 1306, 1211, 1122, 1030, 968, 910 cm^{-1}; EIMS (*m/z*) 264 [$(M-N_2)^+$], 198, 181, 155, 141, 124, 109, 97, 85 (100), 67, 57, 43, 41, 29. Anal. Calcd for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.43; N, 9.92. Found: C, 55.40; H, 6.49; N, 9.83.

3.6.4. Ethyl 2-diazo-3-oxo-5-phenylpent-4-enoate (8d). A yellow oil was obtained in 92% yield. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.62–7.59 (m, 2H), 7.32–7.30 (m, 3H), 6.91 (d, $J=12.6$ Hz, 1H), 6.86 (d, $J=12.7$ Hz, 1H), 4.27 (q, $J=7.2$ Hz, 2H), 1.30 (t, $J=7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 182.5, 161.0, 141.6, 135.0, 129.8, 129.2, 128.0, 124.1, 77.2, 61.4, 14.2; IR (KBr) 2958, 2925, 2854, 2360, 2343, 2131, 1712, 1637, 1603, 1369, 1302, 1217, 1130, 1034 cm^{-1}; EIMS (*m/z*) 216 [$(M-N_2)^+$], 170 (100), 143, 131, 127, 115, 103, 89, 77, 65, 63, 52, 29. Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.88; H, 4.87; N, 11.49.

3.7. Typical procedure for the $Rh_2(OAc)_4$-catalyzed reaction of 8a–d

3.7.1. Ethyl 2-cyclopente-1-one-4-pentyl-5-carboxylate (14a). To a suspension of $Rh_2(OAc)_4$ (5.1 mg, 0.0115 mmol) in anhydrous CH_2Cl_2 (10 mL) at room temperature was added **8a** (290 mg, 1.15 mmol) in anhydrous CH_2Cl_2 (5 mL) over 5 min. After stirring for another 12 h, the reaction mixture was concentrated in vacuo. The residue was chromatographed on silica (petroleum ether/Et_2O 6:1) to give **14a** (228 mg, 88%) as colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.64 (dd, $J=5.7$, 2.4 Hz, 1H), 6.07 (dd, $J=5.7$, 2.1 Hz, 1H), 4.17 (q, $J=7.2$ Hz, 2H), 3.26–3.22 (m, 1H), 2.96 (d, $J=3.0$ Hz, 1H), 1.63–1.54 (m, 2H), 1.49–1.22 (m, 6H), 1.24 (t, $J=7.2$ Hz, 3H), 0.84 (t, $J=7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.5, 169.0, 168.0, 131.5, 61.4, 58.0, 46.0, 33.8, 31.5, 27.0, 22.3, 14.1, 13.8; IR (KBr, cm^{-1}) 2958, 2929, 2858, 1739, 1712, 1589, 1466, 1369, 1255, 1146, 1024; EIMS (*m/z*) 225 [$(M+H)^+$], 179 (100), 151, 123, 109, 95, 81, 67. Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.55; H, 9.01.

3.7.2. Ethyl 2-cyclopente-4-heptyl-1-one-5-carboxylate (14b). A colorless oil was obtained in 86% yield. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.63 (dd, $J=5.7$, 2.7 Hz, 1H), 6.06 (dd, $J=5.7$, 2.3 Hz, 1H), 4.16 (q, $J=7.1$ Hz, 2H), 3.25–3.21 (m, 1H), 2.95 (d, $J=2.7$ Hz, 1H), 1.62–1.53 (m, 2H), 1.47–1.21 (m, 10H), 1.23 (t, $J=7.1$ Hz, 3H), 0.82 (t, $J=7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.5, 168.9, 167.9, 131.5, 61.4, 58.0, 46.0, 33.9, 31.6, 29.3, 29.0, 27.3, 22.5, 14.1, 13.9; IR (KBr, cm^{-1}) 2958, 2929, 2856, 1739, 1709, 1591, 1466, 1369, 1252, 1146, 1032; EIMS (*m/z*) 253 [$(M+H)^+$], 225, 207, 179 (100), 151, 123, 109, 95, 81, 67. Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.35; H, 9.64.

3.7.3. Ethyl 2-cyclopente-1-one-4-(tetrahydro-2*H*-pyran-2-yloxy)-5-carboxylate (14c). A colorless oil was obtained in 82% yield. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.58 (dd, $J=6.0$, 2.4 Hz, 1H), 6.19 (dd, $J=6.0$, 2.7 Hz, 1H), 5.21 (m, 1H), 4.75–4.73 (m, 1H), 4.22 (q, $J=7.1$ Hz, 2H), 3.89–3.74 (m, 1H), 3.54–3.46 (m, 1H), 3.43 (d, $J=3.0$ Hz, 1H), 1.77–1.71 (m, 2H), 1.52–1.51 (m, 4H), 1.27 (t, $J=7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.0, 168.1, 162.4, 133.4, 100.3, 79.5, 63.2, 61.5, 59.2, 30.6, 25.2, 19.7, 14.2; IR (KBr, cm^{-1}) 2945, 2873, 1741, 1716, 1595, 1444, 1369, 1346, 1261, 1146, 1024, 906 cm^{-1}; EIMS (*m/z*) 254 [M^+], 225, 207, 179 (100), 151, 123, 107, 95, 81, 67, 55. Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.32; H, 7.25.

3.7.4. Ethyl 2-hydroxy-1-naphthoate (15). A colorless oil was obtained in 65% yield. ^1H NMR ($CDCl_3$, 300 MHz) δ 12.08 (s, 1H), 8.40 (d, $J=8.4$ Hz, 1H), 7.77 (d, $J=8.7$ Hz, 1H), 7.74–7.33 (m, 3H), 7.26 (d, $J=8.7$ Hz, 1H), 4.45 (q, $J=7.2$ Hz, 2H), 1.44 (t, $J=7.2$ Hz, 3H); IR (KBr, cm^{-1}) 2954, 2925, 2854, 1649, 1579, 1466, 1398, 1375, 1381, 1255, 1207, 1161, 1092, 829, 796, 773.

Acknowledgements

The project is supported by Education Department of Hunan Province, P. R. China (Grant 03C247). One of the authors (J. W.) thanks the financial support from NSFC (20225205, 20390050).

References and notes

1. For recent examples, see: (a) Barluenga, J.; Vicente, R.; Lopez, L. A.; Rubio, E.; Tomas, M.; Alvarez-Rua, C. *J. Am. Chem. Soc.* **2004**, *126*, 470–471. (b) Liu, Y.; Zhang, Y. *Tetrahedron Lett.* **2001**, *42*, 5745–5748. (c) Langer, P.; Kracke, B. *Synlett* **2001**, 1790–1792. (d) Aggarwal, V. K.; Belfield, A. J. *Org. Lett.* **2003**, *5*, 5075–5078. (e) Trost, B. M.; Jiang, C. *Org. Lett.* **2003**, *5*, 1563–1565. (f) He, W.; Sun, X.; Frontier, A. J. *J. Am. Chem. Soc.* **2003**, *125*, 14278–14279. (g) Schoop, A.; Greiving, H.; Gohrt, A. *Tetrahedron Lett.* **2000**, *41*, 1913–1916. (h) Hatanaka, M.; Ishida, A.; Tanaka, Y.; Ueda, I. *Tetrahedron Lett.* **1996**, *37*, 401–404. (i) Hatanaka, M.; Himeda, Y.; Tanaka, Y.; Ueda, I. *Tetrahedron Lett.* **1995**, *36*, 3211–3214. (j) Andrews, J. F. P.; Regan, A. C. *Tetrahedron Lett.* **1991**, *32*, 7731–7734.
2. For early reports, see: (a) Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808–4809. (b) Taber, D. F.; Ruckle, R. E., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7686–7693.
3. Deng, G.; Tian, X.; Wang, J. *Tetrahedron Lett.* **2003**, *44*, 587–589.
4. (a) Deng, G.; Tian, X.; Qu, Z.; Wang, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2773–2776. (b) Deng, G.; Jiang, N.; Ma, Z.; Wang, J. *Synlett* **2002**, 1913–1915.
5. (a) Calter, M. A.; Sugathapala, P. M.; Zhu, C. *Tetrahedron Lett.* **1997**, *38*, 3837–3840. (b) Calter, M. A.; Sugathapala, P. M. *Tetrahedron Lett.* **1998**, *39*, 8813–8816. (c) Calter, M. A.; Zhu, C. *J. Org. Chem.* **1999**, *64*, 1415–1419. (d) Shi, W.; Ma, M.; Wang, J. *Chin. Chem. Lett.* **2004**, *15*, 911–914.
6. (a) Collomb, D.; Deshayes, C.; Doutheau, A. *Tetrahedron* **1996**, *52*, 6665–6684. (b) Taylor, E. C.; Davies, H. M. L. *Tetrahedron Lett.* **1983**, *24*, 5453–5456. (c) Collomb, D.; Doutheau, A. *Tetrahedron Lett.* **1997**, *38*, 1397–1398.
7. Jiang, N.; Wang, J. *Tetrahedron Lett.* **2002**, *43*, 1285–1287 and references cited therein.
8. Nagao, K.; Chiba, M.; Kim, S. W. *Synthesis* **1983**, 197–199.
9. Kim, H. *J. Korean Chem. Soc.* **1996**, *40*, 549–556.
10. Pelliccirai, R.; Fringuelli, R.; Ceccherelli, P.; Sisani, E. *J. Chem. Soc., Chem. Commun.* **1979**, 959–960.
11. Padwa, A.; Kulkarni, Y. S.; Zhang, Z. *J. Org. Chem.* **1990**, *55*, 4144–4153.
12. (a) Fatiadi, A. J. In *Organic Synthesis by Oxidation with Metal Compounds*; Mijs, W. J., de Jonge, C. R. H. I., Eds.; Plenum: NY, USA, 1986; p 119. (b) Martinez, L. A.; Garcia, O.; Delgado, F.; Alvarez, C.; Patino, R. *Tetrahedron Lett.* **1993**, *34*, 5293.
13. (a) Curci, R.; Di Furia, F.; Ciabattoni, J.; Concannon, P. W. *J. Org. Chem.* **1974**, *39*, 3295–3297. (b) Ursini, A.; Pellicciari, R.; Tamburini, B.; Carlesso, R.; Gaviraghi, G. *Synthesis* **1992**, 363–364. (c) Ihmels, H.; Maggini, M.; Prato, M.; Scorrano, G. *Tetrahedron Lett.* **1991**, *32*, 6215–6218.
14. Pellicciari, R.; Natalini, B.; Cecchetti, S.; Fringuelli, R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 493–497.
15. Taylor, E. C.; Davies, H. M. L. *Tetrahedron Lett.* **1983**, *24*, 5453–5456.
16. (a) Searle, N. E. In *Organic Syntheses*, *Collect. Vol. 4*; Wiley: New York, 1963; p 424. (b) Womack, E. B.; Nelson, A. B. In *Organic Syntheses*, *Collect. Vol. 3*; Wiley: New York, 1955; p 392.