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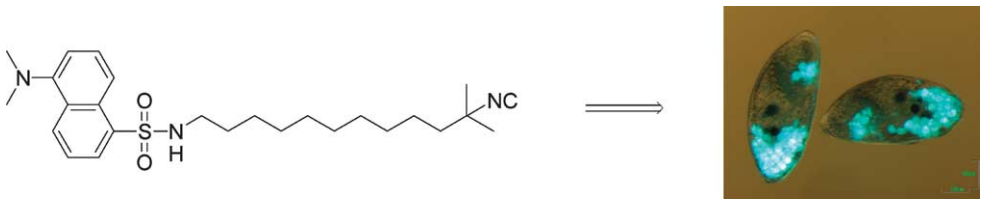
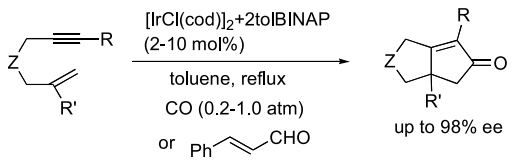
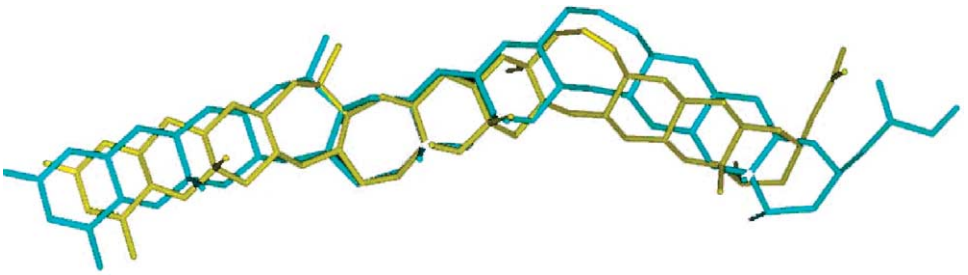
Contents

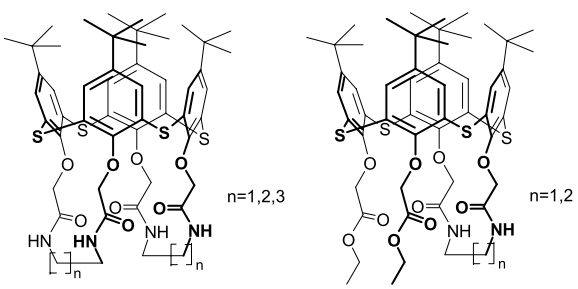


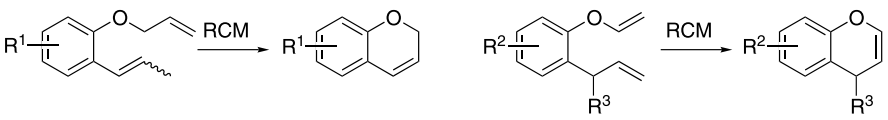


The X-ray crystal structure of brevetoxin B (yellow) and the 3D model of the best stereoisomer (blue) from a stereochemistry determination system are superimposed. Small differences in the bond angles of some of the more flexible rings are present, but all stereocenters have been properly oriented.

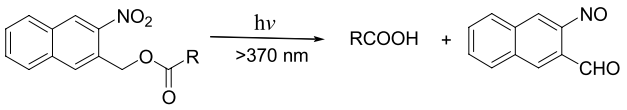


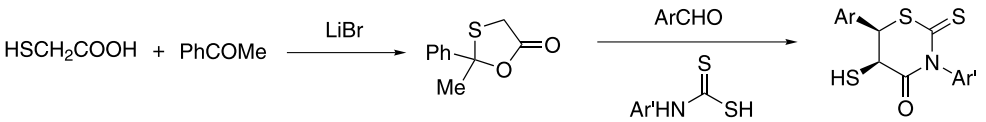
The formation of unusual lower rim proximally bridged thiacalix[4]arene derivatives in the cone conformation was observed during the aminolysis reaction of the corresponding tetraacetate derivative with aliphatic α,ω-diamines.

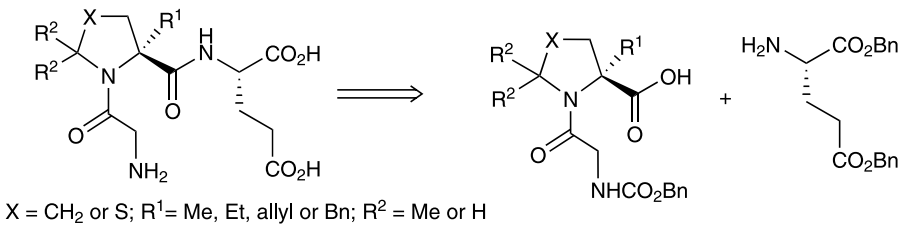




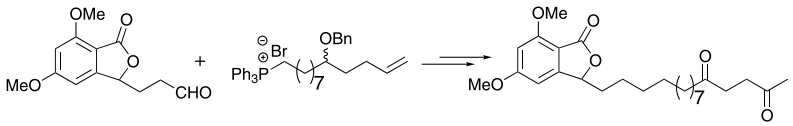
Six 4*H*-chromenes were synthesized from substituted phenols using vinylstannylation and ring-closing metathesis (RCM) as key steps. In addition, a different approach involving, amongst other steps, an aryl allyl isomerization and RCM afforded a set of seven 2*H*-chromenes from phenolic precursors.

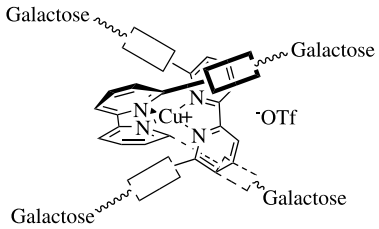




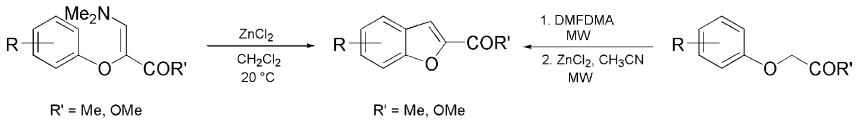


X = CH_2 or S; R^1= Me, Et, allyl or Bn; R^2 = Me or H

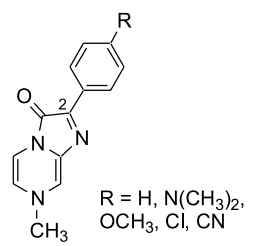


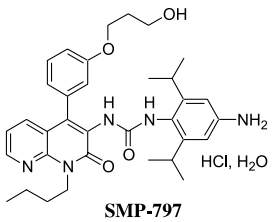


A new family of multivalent sugar ligands were assembled by combining oligopyridines with galactose units and by complexing these conjugates with metal ions.



A *para*-substitution of R on the phenyl group of a solvatochromic 2-phenylimidazopyrazinone (**1**) successively resulted in modulations of the spectroscopic properties; the UV/visible absorption and the fluorescence of **1** and the electronic absorption of charge-transfer complexes of **1** with TCNE and metal–ion complexes of **1**.





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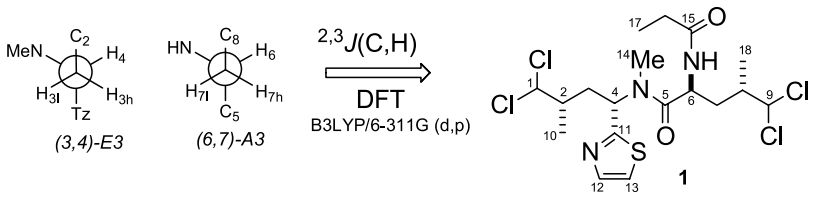
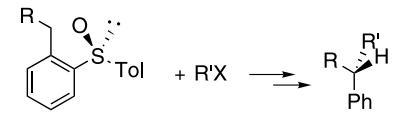
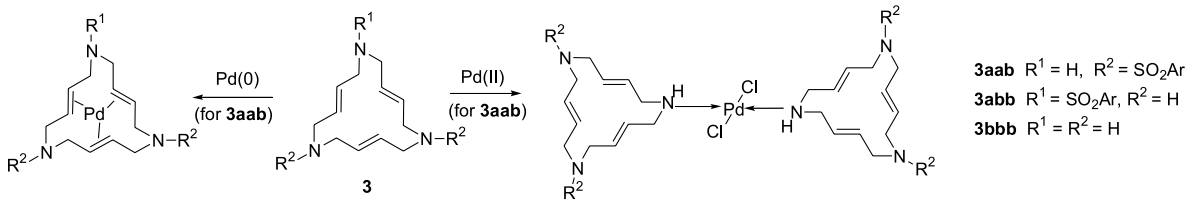


(3,4)-E3 *(6,7)-A3* **1**



R = Me, Et R' = Bn, Allyl, Me, Et



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Publisher's Announcement—New European Regional Editor for *Bioorganic & Medicinal Chemistry Letters*

Elsevier is pleased to announce the appointment of Professor Stephen Neidle who takes over from Professor Léon Ghosez as Regional Editor for Europe of *Bioorganic & Medicinal Chemistry Letters* on 1 September 2005.

Stephen Neidle is Professor of Chemical Biology at The School of Pharmacy, University of London, UK, where he also directs the Cancer Research UK Biomolecular Structure Group. He was educated at Imperial College, London, where he graduated in chemistry and then proceeded to do a PhD on crystallographic studies of natural products and antibiotics. After a period as an ICI Fellow, he joined the Biophysics Department at King's College. He was appointed as one of the first Cancer Research Campaign Career Development Awardees, becoming a Life Fellow on moving to the Institute of Cancer Research. In 1990, he was appointed to the Chair of Biophysics at the Institute of Cancer Research, where he was Academic Dean from 1997–2002. He moved to the new Chair of Chemical Biology at the School of Pharmacy in 2002.

Professor Neidle's research interests are primarily in nucleic acid structure and recognition by small molecules, and in exploiting this information for the rational design of new anticancer agents. In recent years, this has emphasised two principal classes of molecules: G-quadruplexes and duplex DNA. Together with colleagues at the University of Texas, he pioneered the concept of the selective targeting of telomeric DNA with small molecules that stabilise G-quadruplex formation at the telomere and inhibit the action of the enzyme telomerase, which is up-regulated in the majority of human cancers. More recently, this work has led him and his group to the design of a new class of anticancer molecules, Telomere Targeting Agents, which are currently in pre-clinical development.

Professor Stephen Neidle

Regional Editor for Europe of
Bioorganic & Medicinal Chemistry Letters

Starting 1 September 2005, submissions from Europe should be submitted to Professor Neidle via the journal's online submission page at: www.ees.elsevier.com/bmcl

Whilst welcoming the new Editor, we would like to take this opportunity of expressing our gratitude to Professor Léon Ghosez and his editorial office for their dedication and contribution to the journal during 13 years of service.

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Tetrahedron report number 736

Naphtho[2,3-*c*]furan-4,9-diones and related compounds: theoretically interesting and bioactive natural and synthetic products

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Dedicated to Associate Professor Dieter Wege on the occasion of his retirement

Contents

Keywords: Naphtho[2,3-*c*]furan-4,9-diones; Naphtho[2,3-*c*]furan-4(9*H*)-ones; Naphtho[2,3-*c*]furan; Isofuranonaphthoquinones.

Abbreviations: Ac, acetyl; AIBN, 2′-azobis(isobutyronitrile); Ar, aryl; Bn, benzyl; BOM, benzyloxymethyl; Bu^t, *tert*-butyl; CSA, camphor-10-sulfonic acid; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCM, dichloromethane; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DiBAL-H, diisobutylaluminium hydride; DMAP, *N*,*N*-dimethyl-4-aminopyridine; DMF, *N*,*N*-dimethylformamide; DMSO, dimethyl sulfoxide; Et, ethyl; FVP, flash vacuum pyrolysis; HMDS, hexamethyldisilazide; IBF, isobenzofuran; LDA, lithium diisopropylamide; *m*CPBA, *meta*-chloroperbenzoic acid; Me, methyl; MTPACl, Mosher's acid chloride=2-methoxy-2-(trifluoromethyl)phenylacetyl chloride; NBS, *N*-bromosuccinimide; *n*-Bu, 1-butyl; NIS, *N*-iodosuccinimide; NMO, *N*-methylmorpholine *N*-oxide; Ph, phenyl; PMB, *para*-methoxybenzyl; PMP, *para*-methoxyphenyl; Py, pyridyl or pyridine; TBAF, tetrabutylammonium fluoride; TBDPS, *tert*-butyldiphenylsilyl; TBS, *tert*-butyldimethylsilyl; *t*-Bu, *tert*-butyl; TEMPO, 2,2,6,6-tetramethylpiperidinyl 1-oxide; TFA, trifluoroacetic acid; TFPAA, trifluoroperacetic acid; THF, tetrahydrofuran; TIPS, triisopropylsilyl; TMEDA, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; TMS, trimethylsilyl; TPAP, tetrapropylammonium perruthenate; Ts, tosyl=*para*-toluenesulfonyl.

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1. Introduction

The furan moiety (**1**) occurs widely in synthetic and natural products, either as a simple structural unit or as part of a more complex annulated system.[1–3] With regard to the latter, there are two possible points of fusion to the furan ring, a fact that has important ramifications for the stability of the systems resulting from fusion with aromatic nuclei. Fusion of a benzene ring at the *b*-bond, as in benzofuran (**2**) (Fig. 1), does not perturb the benzene nucleus and thus gives rise to stable compounds. Accordingly, a vast number of *b*-fused synthetic and natural products[1,4] exist. In contrast, fusion at the *c*-bond, as in isobenzofuran (IBF) (**3**), interrupts the benzene π-sextet, reducing the aromaticity and, correspondingly, the stability of the system. The number of known *c*-fused compounds is therefore much smaller.

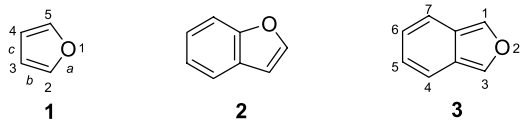


Figure 1.

Compounds incorporating the IBF structural unit display a propensity to undergo addition across the 1,3-positions, generating the more stable benzenoid aromatic systems. Thus, while benzofuran (**2**) is a stable compound, IBF (**3**) has been isolated only at low temperature, and rapidly polymerises on warming to room temperature.[5–7]

Stability can be imparted to the IBF moiety by incorporation of substituents into the 1- and 3-positions. Bulky substituents hinder the approach of reagents to the labile diene unit, thereby reducing the reactivity of the derivative. For example, 1,3-di-*t*-butylisobenzofuran (**4**)[8,9] (Fig. 2) is a crystalline solid, stable at room temperature over prolonged periods.[10] Aryl substituents also impart stability through conjugation. 1,3-Diphenylisobenzofuran (**5**), for example, is a commercially available, stable crystalline solid. The tri-*t*-butyl-substituted isobenzofurans **6** and **7**, although more open to attack at the 1,3-positions, are also stable at room temperature.[11,12] This is presumably due to the out-of-plane deformations induced by the bulky *o*-*t*-butyl groups, which reduce the π-conjugation, and thus the *o*-quinonedimethide (*o*-xylylenoid) character of the system.

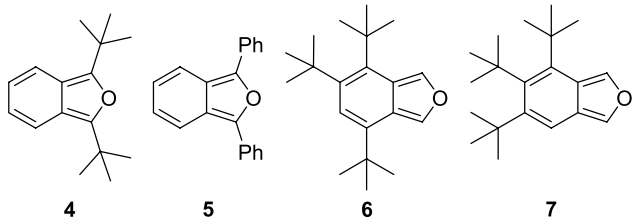


Figure 2.

Partially hydrogenated derivatives and those with carbonyl substituents in the benzenoid ring also have increased stability. In these compounds, addition across the 1,3-positions does not generate the dramatic increase in resonance energy observed with the parent species. Consequently, stable examples of this structural type exist, including 4,7-dihydroisobenzofuran (**8**),[13–15] isobenzofuran-4,7-dione (**9**)[16–19] and the natural product, albidin (**10**) (Fig. 3).[20,21]

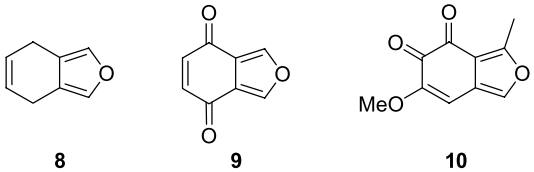


Figure 3.

The chemistry of isobenzofurans has been the subject of several reviews[22–27] and continues to be an active area of research.

On the basis of structure-reactivity considerations, naphtho[2,3-*c*]furan (**11**) (Fig. 4) should be even more reactive than IBF[24] and, whilst having being generated in solution and trapped in situ,[28,29] is probably too reactive to be isolated under normal laboratory conditions.[30] Introduction of carbonyl groups into the 4- and 9-positions generates the naphtho[2,3-*c*]furan-4,9-dione (isofuranonaphthoquinone) ring system (**12**), removing the *o*-quinonedimethide character present in **11** and thereby stabilising the system (Fig. 4).

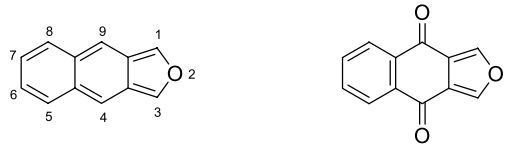


Figure 4.

It was the relationship of naphtho[2,3-*c*]furan-4,9-diones to naphtho[2,3-*c*]furan (**11**) that initially aroused the author's interest in this class of compounds. In particular, the natural products ventilone F and G, were originally formulated as **13** and **14**, comprising an IBF nucleus (Fig. 5).[31,32] As discussed below, it is likely that these structures are incorrect.[33]

The related naphtho[2,3-*c*]furan-4(9*H*)-ones, of which the parent compound **15** is unknown, comprise a relatively

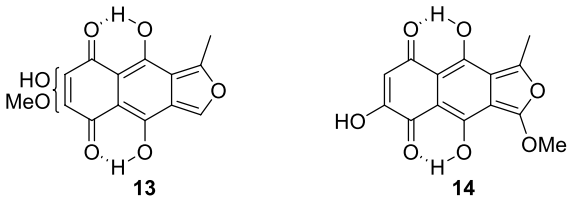
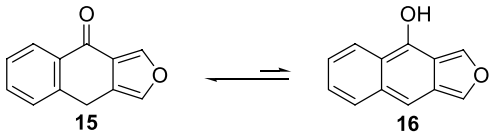


Figure 5.

small group of natural and synthetic products, which are particularly interesting because of their tautomeric relationship with naphtho[2,3-*c*]furan-4-ols (**16**), as exemplified by the parent compound in Scheme 1.



Scheme 1.

This report reviews the natural occurrence, biological activity, synthesis and chemistry of the naphtho[2,3-*c*]furan-4,9-diones, naphtho[2,3-*c*]furan-4(9*H*)-ones and related compounds. An attempt has been made to be comprehensive and apologies are extended to those whose work has been overlooked.

2. Natural products

The naphtho[2,3-*c*]furan-4,9-diones and naphtho[2,3-*c*]furan-4(9*H*)-ones form the largest subset of natural products containing a *c*-fused furan ring. They often co-occur, reflecting their common polyketide biosynthesis, probably originating from the heptaketide **17** (Fig. 6), in many cases where the terminal carboxyl group has been lost.[34]

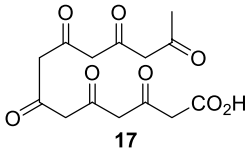


Figure 6.

The first reported naturally occurring isofuranonaphthoquinone, nectriafurone (**18**) (Fig. 7), was isolated in 1983 from the fungus *Nectria haematococca*.[35] Fungi have since proven to be the richest source of this class of natural products. Nectriafurone was subsequently isolated, along with the 5-methyl ether **19**, from *Fusarium oxysporum*, a

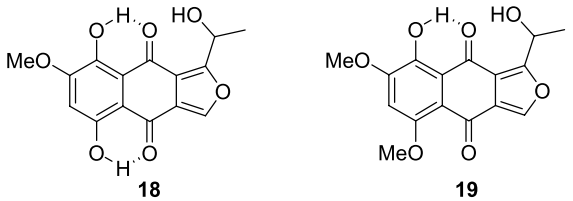


Figure 7.

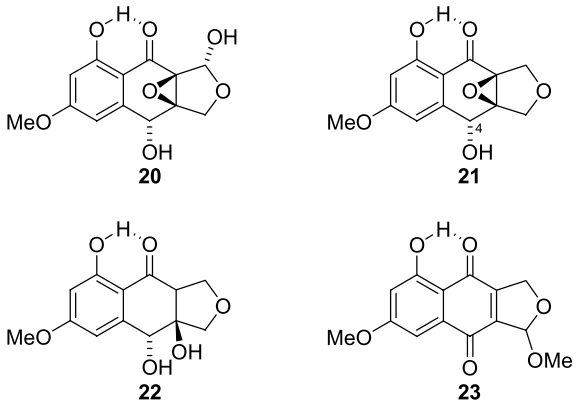


Figure 8.

citrus tree and cotton fungal pathogen.[36,37] More recently, other *Fusarium* species have been shown to contain nectriafurone, and weak antibiotic properties have been observed.[38,39] The configuration of the stereogenic centre in nectriafurone remains unknown; indeed, optical activity has not been established.[36]

Arthrinone (**20**) (Fig. 8) was originally isolated from an *Arthrinium* species and its relative stereochemistry was confirmed by X-ray crystallography.[40] It was subsequently found, along with dehydroxyarthrinone (**21**), 3a,9a-deoxy-3a-hydroxy-1-dehydroxyarthrinone (**22**) and cerdarin (**23**), in the coprophilous fungus *Cercophora sordarioides*.[41] The configuration of C4 in dehydroxyarthrinone (**21**) was established by Helmchen's method and the absolute stereochemistry of all other compounds is assumed based upon common biosynthesis. The relative stereochemistry of **21** and **22** was later established by synthesis (see Section 4).[42] All metabolites, but **22**, display antibacterial and antifungal activity and **20** and **21** exhibit limited cytotoxicity towards the NCI-60 tumour cell line.[41]

Dehydroxyarthrinone (**21**) has since been isolated from *Monosporascus cannonballus*, a serious cause of disease in muskmelon and watermelon, along with monosporascone (**24**), monosporascol A (**25**), demethylcerdarin (**26**) and the 2*H*-benzo[*f*]isoindole-4,9-dione, azamonosporascone (**27**) (Fig. 9).[43] Monosporascone (originally named GP-A) and its dihydro analogue GP-B (**28**) were earlier identified in

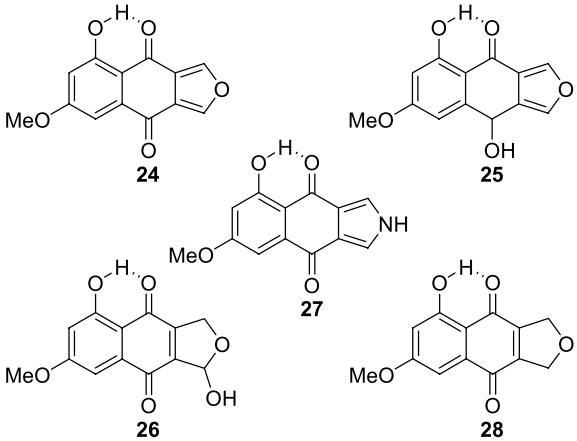


Figure 9.

Gelasinospora pseuodoreticulata and were shown to inhibit monoamine oxidase.[44]

The mycobiont of the lichen *Arthonia cinnabarina* has recently provided arthoniafurone A (**29**) and B (**30**), the first naphtho[2,3-*c*]furan-4,9-dione and naphtho[2,3-*c*]furan-4(9*H*)-one, respectively, bearing an acyl substituent in the furan ring (Fig. 10).[45]

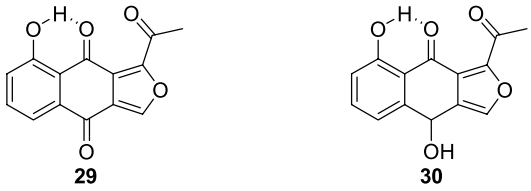


Figure 10.

Lolitrem B (**31**) (Fig. 11) is the most abundant member of the lolitremanes, a family of indole-diterpene neurotoxins produced by *Acremonium lolii* and various other endophytic fungi infecting important pasture grasses such as perennial ryegrass (*Lolium perenne*). They are thought to be the principal causative agents of perennial ryegrass staggers, a nervous disorder affecting livestock grazing on the infected pasture. The lolitremanes have recently been reviewed and are not covered further here.[46]

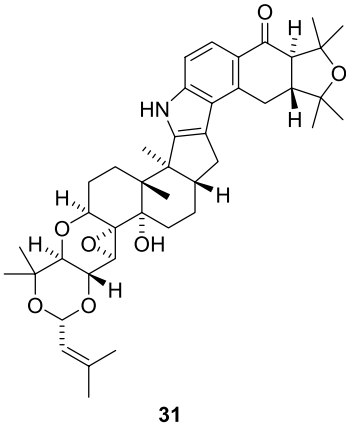


Figure 11.

In plants, naphtho[2,3-*c*]furan-4,9-diones were first identified in the root bark of *Ventilago maderaspatana*, an Indian species of the family Rhamnaceae. The compounds were thus named ventilone A (**32**), B (**33**), C (**34**), D (**35**) and E (**36**) (Fig. 12).[34] Ventilone B has since been shown to be an insect antifeedant.[47]

Subsequent investigation of the *Ventilago* genus yielded ventilone F from *V. goughii*,[31] and ventilone G from *V. vitiensis*, a Fijian species.[32] As mentioned in the introduction, these compounds were originally formulated as the naphtho[2,3-*c*]furan-5,8-diones **13** and **14** but based on structure-reactivity relationships and 2D NMR spectroscopic evidence from an analogous compound[33] (see Fig. 21), the tautomeric representations **37** and **38** are more appropriate (Fig. 13).

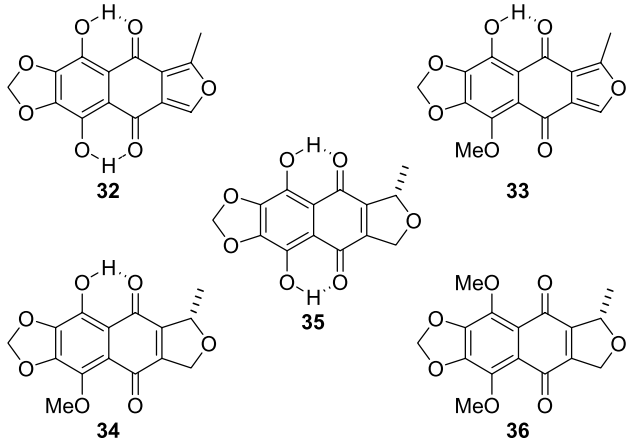


Figure 12.

Metabolites of this class have been found in other plant families, which have traditionally been used for therapeutic purposes. *Aloe ferox* (Cape aloe) was shown to produce **39** and the first reported naturally occurring naphtho[2,3-*c*]furan-4(9*H*)-one (**40**) and naphtho[2,3-*c*]furan-4(1*H*)-one (**41**).[48] Compounds **39** and **40** were later isolated from *Bulbine capitata*, along with six congeners (**42**–**47**)[49–51] (Fig. 14). The healing properties of plants of the *Aloe* genus are well known[52] and the milk decoction of the roots of *B. capitata* is used for the treatment of body rash and sexually transmitted diseases in its native Botswana.[49] Indeed, these compounds exhibit antioxidant and weak antiplasmodial activities.[51]

The lignan, aglacin D (**48**) (Fig. 15), although not biogenetically related to the other natural products discussed in this section, does contain a partially reduced naphtho[2,3-*c*]furan-4-one skeleton. Aglacin D was isolated from the Indonesian plant *Aglaia cordata* in 2001.[53]

Certain bacteria have also been shown to produce naphtho[2,3-*c*]furan derivatives. The first recorded example, MS-444 (**49**) (Fig. 16), has been isolated from several *Micromonospora* species.[54–57] MS-444 was shown to inhibit myosin light-chain kinase, a phosphorylating enzyme that interacts with actin to generate contractile force in smooth muscle fibres, and was thus patented as a potential vasodilator/bronchodilator.[56,57] Since its initial isolation,

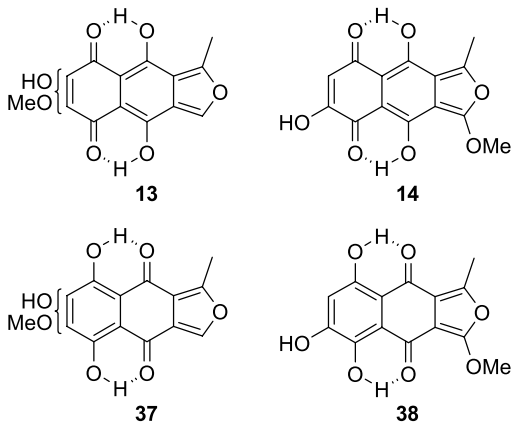


Figure 13.

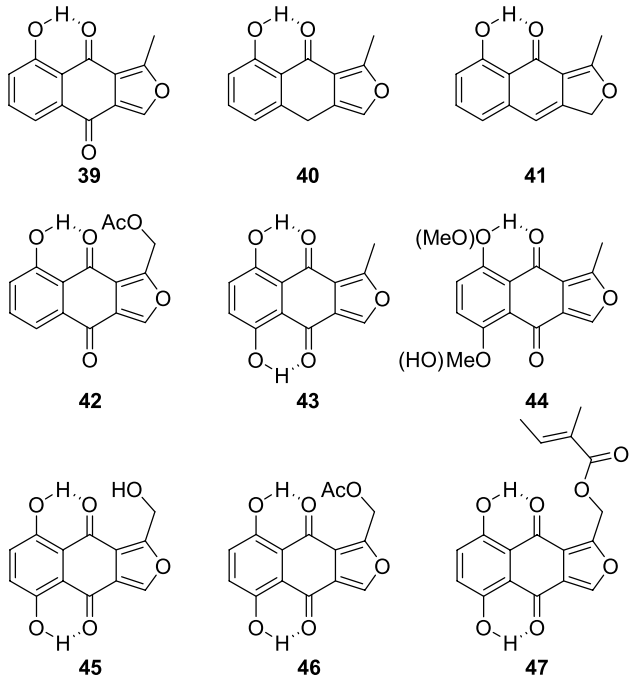


Figure 14.

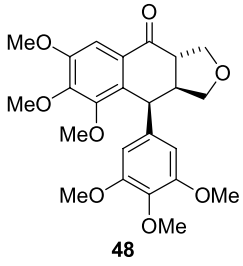


Figure 15.

MS-444 has been used in a patented anti-HIV drug[58] and its derivatives (e.g, **50**) have been assessed as immunosuppressive and anti-itching agents.[59] MS-444 has also been reported to strongly inhibit the growth of mammalian tumours.[55]

In 1996, lactonamycin (**51**), a more complex member of the family of naturally occurring compounds incorporating the naphtho[2,3-*c*]furan-4,9-dione skeleton, was isolated from *Streptomyces rishirienes* (Fig. 17).[60] Lactonamycin's powerful antibiotic activity against both methicillin- and vancomycin-resistant organisms, and cytotoxicity against various tumour cell lines,[61] combined with its novel and challenging architecture,[62] have inspired much synthetic interest (Section 3.8). *S. sanglier* has since yielded lactonamycin Z (**52**), the analogue bearing an α-2,6-dideoxyribohexose residue instead

Figure 16.

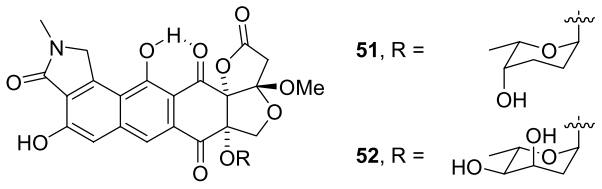


Figure 17.

of rhodinose.[63] Whilst the antibiotic activity of **52** against gram positive bacteria is relatively weak, it strongly inhibits the proliferation of gastric adenocarcinoma.

More recently, another *Streptomyces* species afforded bhimamycin A (**53**) and B (**54**), which both exhibited moderate antibiotic activity against *B. subtilis* and *E. coli* (Fig. 18).[64] The first reported naturally occurring 2*H*-benzo[*f*]isoindole-4,9-diones, bhimamycin C (**55**) and D (**56**), were also isolated from this source. The indoloquinones may arise by the addition of ethanolamine and anthranilic acid to **53** and **54**, respectively (see also Section 5.3), or to precursors common to all four natural products.

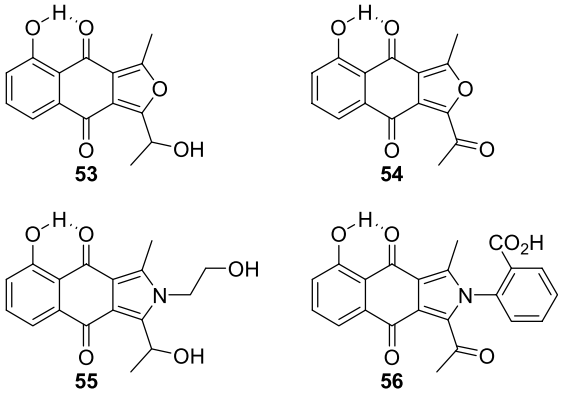


Figure 18.

The animal kingdom has provided a single *c*-fused naphthofuranone, furanaphin (**57**), which was isolated from the aphid *Aphis spiraecola* (Fig. 19).[65] Furanaphin was found to be cytotoxic to human promyelocytic leukemia Hl-60 cells.

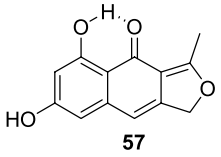


Figure 19.

Given that the aphid's food source, *Polygonum cuspidatum* Sieb. et Zucc., produces a yellow pigment,[66] the original source of **57** may be botanical. Indeed, the plant has been shown to contain quinonoid metabolites,[67,68] some of which co-occur with isofuranonaphthoquinones in other plant species.

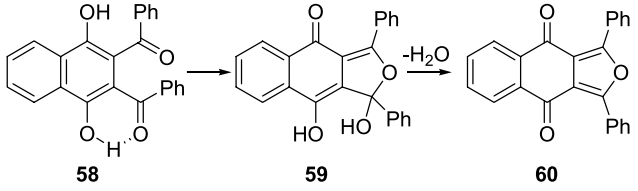
The stability of furanaphin, the second naturally occurring naphtho[2,3-*c*]furan-4(1*H*)-one (see also **41**, Fig. 14), is a reflection of the minimal resonance energy of the furan 'aromatic' ring.

3. Synthesis of naphtho[2,3-*c*]furan-4,9-diones

Several different strategies have been used to access the naphtho[2,3-*c*]furan-4,9-dione skeleton. For clarity, the syntheses are grouped by the key reaction in the following survey.

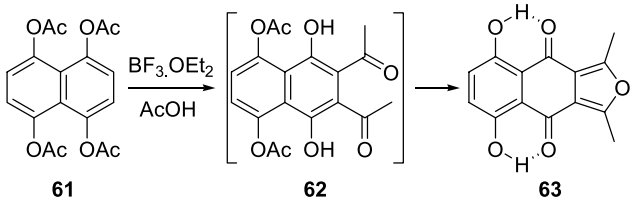
3.1. Cyclisation of 2,3-diacylnaphthalenes

Synthetic naphtho[2,3-*c*]furan-4,9-diones were known well before any natural products of this class had been discovered. The first literature preparation appeared in 1949, wherein the *o*-dibenzoylnaphthalene **58** or its diesters gave **60** upon heating or in the presence of acid (Scheme 2).[69] This transformation presumably proceeds via cyclisation, followed by dehydration of the intermediate hemiacetal **59**.



Scheme 2.

An analogous transformation was noted during the attempted Fries rearrangement of **61**.[70] The *o*-diketone **62** is the likely intermediate, but it was not observed, with cyclisation and dehydration proceeding under the reaction conditions to give **63** and its monoacetate in 63 and 36% yields, respectively (Scheme 3).

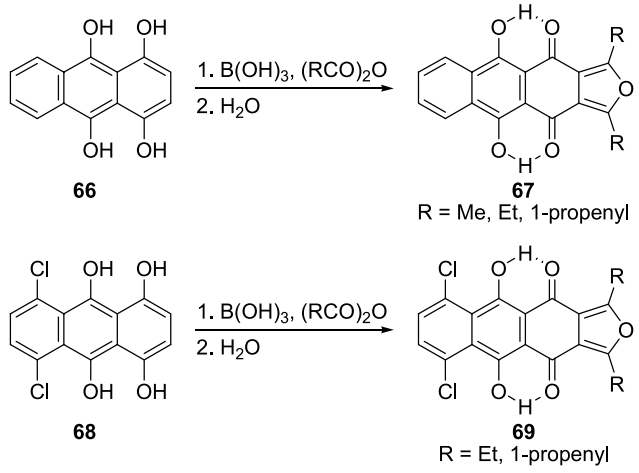


Scheme 3.

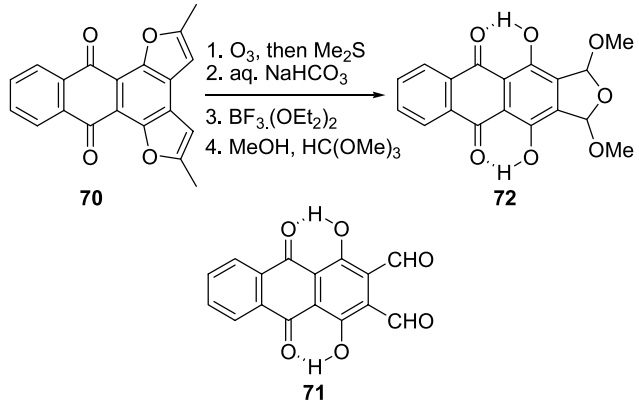
Similarly, **65** was produced in the Lewis acid-catalysed Fries rearrangement of the hexaacetate **64** (Scheme 4).[71]

The formation of the anthra[2,3-*c*]furan-4,11-diones **67** and **69**, from the reaction of leucoquinizarin (**66**) and the dichloro derivative **68** with triacyl borates (Scheme 5),[72] probably proceeds via a similar mechanism to that described above.

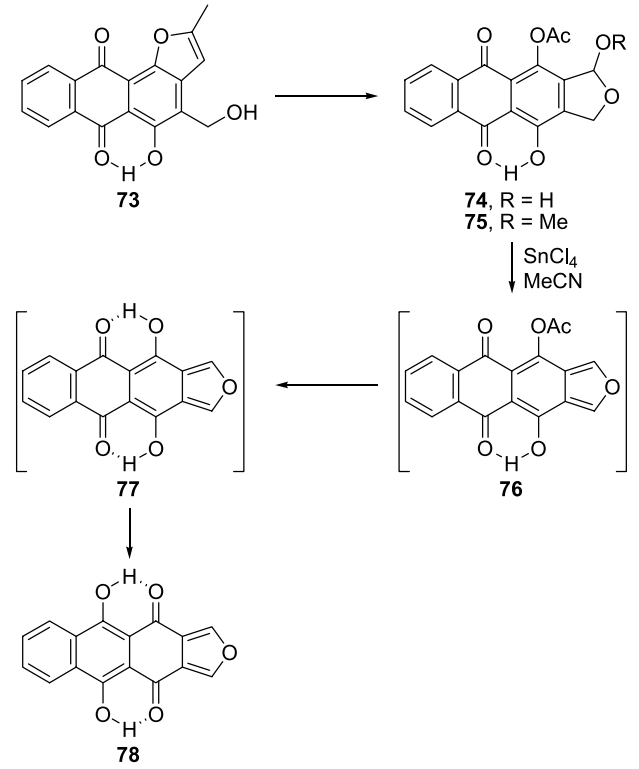
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7.

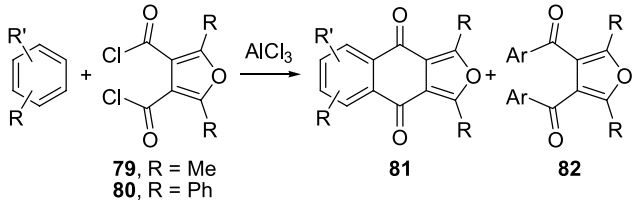
Compounds **67** and **69** were patented as textile dyes.[72] Naphtho[2,3-*c*]furan-4,9-diones are also coloured, ranging from pale brown for the parent compound to intense yellow, orange and red as the number of electron-releasing substituents is increased.

Ozonolysis of the bisanthrafuran **70**, followed by acetalisation, produced the dihydrofuran **72**, presumably via the *o*-dialdehyde **71** (Scheme 6).[73] In this case, the strong intramolecular H-bonds present in the product **72** probably inhibit aromatisation of the furan ring.

The anthrafuranol **73** gave lactol **74** under similar conditions to those described above (Scheme 7).[74] The corresponding acetal **75** readily eliminated methanol, giving a stable product, reportedly **77**, containing an IBF moiety[74] but, for the reasons explained above, this structure is unlikely. After cleavage of the acyl group of the initial product **76**, the IBF **77** would almost certainly tautomerise to the more stable **78**.

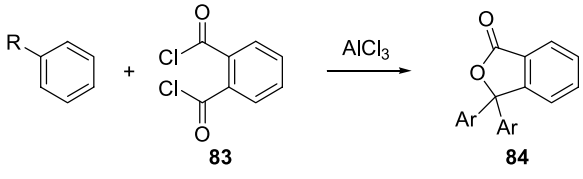
3.2. Friedel–Crafts acylation

Perhaps the most obvious route to naphtho[2,3-*c*]furan-4,9-diones is via bis-Friedel–Crafts acylation of benzenoid compounds with 3,4-furandicarbonyl dichlorides. Accordingly, this has been the most commonly used entry to this skeleton. The first literature example appeared in 1959,[75] wherein Friedel–Crafts acylation of benzene, toluene and the isomeric xylenes with **79** and **80** gave mainly the cyclic diones **81** and, on some occasions, the expected diaroylfurans **82** (Scheme 8). The yields and distribution of products are summarised in Table 1.



Scheme 8.

The preferential formation of the cyclic products was somewhat surprising, as phthaloyl chloride (**83**) had previously been shown to react with benzene and toluene in the presence of $AlCl_3$ to give mainly diarylphthalides **84** (Scheme 9).[76]



Scheme 9.

The Friedel–Crafts acylation study was later extended to several other aromatic hydrocarbons and various aryl ethers.[77] The results obtained are summarised in Table 1. It was noted that, contrary to the acylation of aromatic hydrocarbons, in a majority of cases the acylation of the aromatic ethers gave diaroylfurans instead of the quinonoid products. It should be pointed out, however, that the procedure of adding the dicarbonyl dichloride to an excess of the more reactive aromatic ethers favours diaroylfuran formation and the distribution of products may have been different if an equimolar ratio of reactants was used and the order of addition was reversed. Furthermore, $AlCl_3$ has been shown to cleave aromatic ethers *peri* to a carbonyl group in this series (see Scheme 26) and the workup involving a wash with aqueous NaOH would have removed any phenolic material formed, thereby distorting the final product distribution. Incidentally, concomitant demethylation of *peri*-methoxy substituents can be avoided by using the milder Lewis acid, tin tetrachloride.[78]

Since the initial studies described above, the $AlCl_3$-catalysed Friedel–Crafts acylation of benzenoid hydrocarbons, phenols and phenyl ethers with 3,4-furandicarbonyl dichloride (**85**) and the 2-methyl (**86**), 2,5-dimethyl (**79**) and 2,5-diphenyl (**80**) analogues (Fig. 20) has given naphtho[2,3-*c*]furan-4,9-diones in moderate to fair yields. The reaction conditions and results are summarised in Table 1.

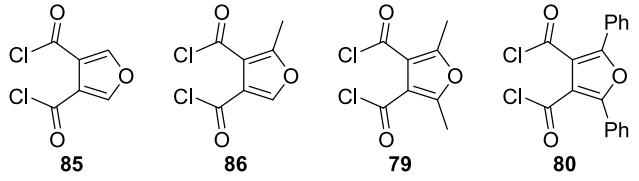
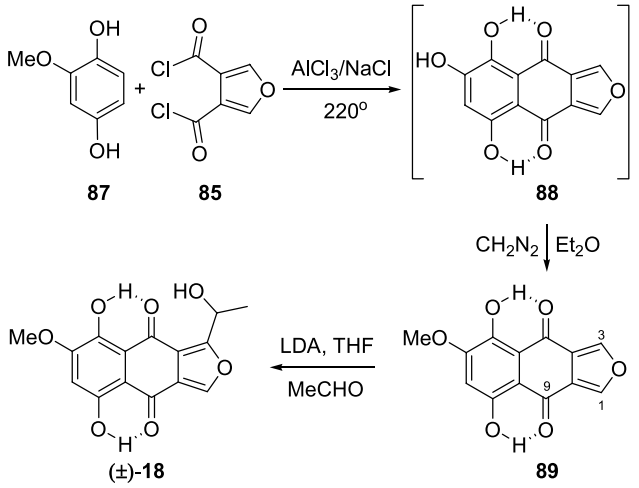


Figure 20.

The first synthesis of a natural product containing the naphtho[2,3-*c*]furan-4,9-dione ring system was that of (±)-nectriafurone [(±)-**18**] via the route depicted in Scheme 10. Acylation of the hydroquinone **87** with **85** under rather drastic conditions, gave the demethylated naphtho[2,3-*c*]furan-4,9-dione **88**. The crude product was selectively remethylated with diazomethane to give **89**. Treatment of **89** with a large excess of LDA then acetaldehyde gave (±)-nectriafurone [(±)-**18**] in 43% yield, in addition to smaller



Scheme 10.

Table 1. $AlCl_3$-catalysed Friedel–Crafts reaction of arenes with furan-3,4-dicarbonyl dichlorides

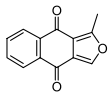
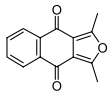
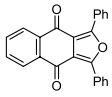
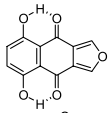
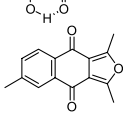
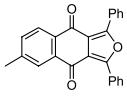
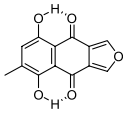
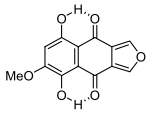
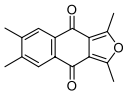
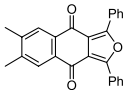
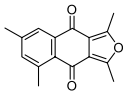
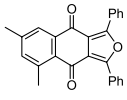
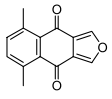
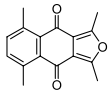
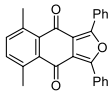
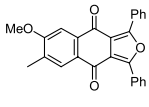
Arene	Furan	Conditions	Naphtho[2,3-*c*]furan-4,9-dione (%)		Diaroylfuran (%)	Refs.
	**85**	—	—		87	79
	86	—		17	50	79
	79	CS_2, 0 °C–rt		90	—	75
	80	0 °C–rt		71	—	75
	**85**	NaCl, 220 °C		20	—	80
	**79**	CS_2, 0 °C–rt		68	1	75
	80	CS_2, 0 °C–rt		61	1	75
	**79**	1. DCE, 0 °C–rt, 2. $NaOH/H_2O$	—		69	77
	80	1. DCE, 0 °C–rt, 2. $NaOH/H_2O$	—		57	77
	**85**	$PhNO_2$, 80 °C		45	—	81,82
	**85**	NaCl, 220 °C		18, crude product was remethylated	—	80
	**79**	0 °C–rt		82	—	75
	80	CS_2, 0 °C–rt		82	—	75
	**79**	CS_2, 0 °C–rt		13	67	75
	80	CS_2, 0 °C–rt		13	43	75
	**85**	DCE, 4–5 °C–rt		65	—	83
	79	CS_2, 0 °C–rt		72	—	75
	80	0 °C–rt		76	—	75
	**79**	1. DCE, 0 °C–rt, 2. $NaOH/H_2O$	—		56	77
	80	1. DCE, 0 °C–rt, 2. $NaOH/H_2O$		68	—	77

Table 1 (*continued*)

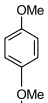
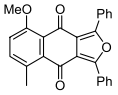
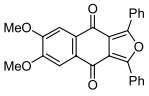
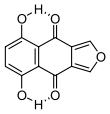
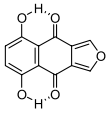
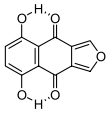
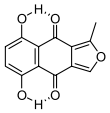
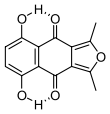
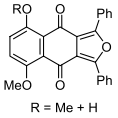
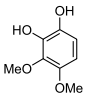
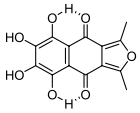
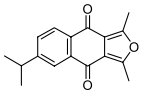
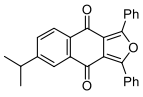
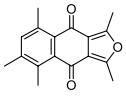
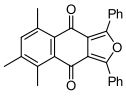
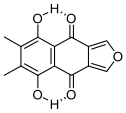
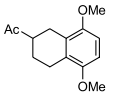
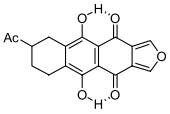
Arene	Furan	Conditions	Naphtho[2,3-*c*]furan-4,9-dione (%)	Diaroylfuran (%)	Refs.
	**79**	1. DCE, 0 °C–rt, 2. NaOH/H_2O	—	46	77
	**80**	1. DCE, 0 °C–rt, 2. NaOH/H_2O		70 —	77
	**80**	1. DCE, 0° C–rt, 2. NaOH/H_2O		74 —	77
	**79**	1. DCE, 0 °C–rt, 2. NaOH/H_2O	—	28	77
	**80**	1. DCE, 0 °C–rt, 2. NaOH/H_2O	—	60	77
	**85**	DCE		45 —	83
	85	DCM, reflux		63 —	84
	85	DCE		91 —	85
	86	DCE		32, +18 mono-methyl ethers —	33
	79	DCM, reflux		40 —	71
	80	DCE	 R = Me + H	65 —	83
	**79**	NaCl, 140 °C		22 —	71
	**79**	1. DCE, 0 °C–rt, 2. NaOH/H_2O		72 —	77
	80	1. DCE, 0 °C–rt, 2. NaOH/H_2O		76 —	77
	**79**	1. DCE, 0 °C–rt, 2. NaOH/H_2O		45 —	77
	80	1. DCE, 0 °C–rt, 2. NaOH/H_2O		59 —	77
	**85**	DCE		48 —	83

Table 1 (*continued*)

Arene	Furan	Conditions	Naphtho[2,3-*c*]furan-4,9-dione (%)	Diaroylfuran (%)	Refs.
	**85**	DCE		85	—	86

amounts of the 3- and 1,3-disubstituted products. The selectivity in lithiation of the heterocyclic ring was attributed to the electron-donating methoxy group, which diminishes the electron-withdrawing power of the C9 carbonyl group and thereby the acidity of H1, causing metallation at C3 to predominate.

More recently, the natural product **43** (Fig. 21) has also been prepared by a Friedel–Crafts cyclisation.[33] Like ventilone F and G (Fig. 13), **43** could potentially exist as the isobenzofuranoid tautomer **90**. Despite the vast difference in reactivity expected for the two tautomers, it is difficult to distinguish between the two possibilities based on standard spectroscopic data. However, 2D NMR experiments have established that, at least in solution, **43** is the correct structure.[33] By analogy, ventilone F and G are best represented by structures **37** and **38** (Fig. 13).

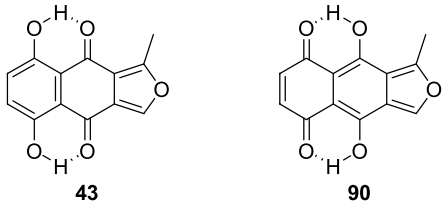
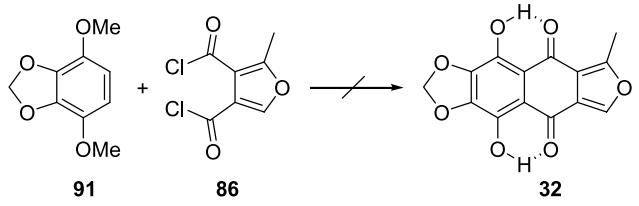


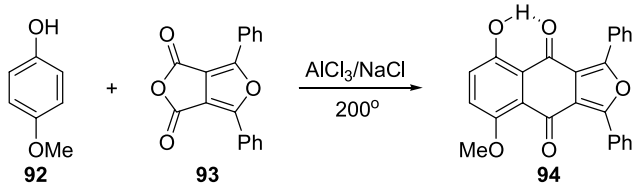
Figure 21.

The symmetry of the benzodioxole portion of ventilone A (**32**) makes it an obvious candidate for synthesis via the Friedel–Crafts reaction. However, attempts to effect the reaction of **91** with **86** under a variety of conditions have failed (Scheme 11).[87]



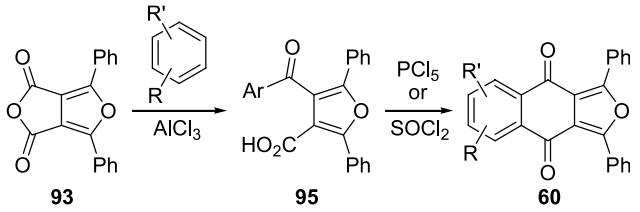
Scheme 11.

Anhydrides have also been used in the Friedel–Crafts approach to naphtho[2,3-*c*]furan-4,9-diones. For example, **93** cyclised with 4-methoxyphenol (**92**) in molten $AlCl_3$/NaCl to give **94** (Scheme 12).[83]



Scheme 12.

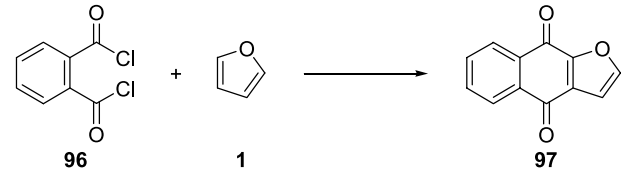
Conversely, under milder conditions, **93** reacted with aromatic hydrocarbons to give the 2,5-diphenyl-4-aroyl-3-furancarboxylic acids (**95**) in good yields (Scheme 13).[75] Attempts to prepare the acid chloride of the 4-benzoyl derivative **95** (Ar=Ph) yielded only the cyclised product **60** (R=R′=H).



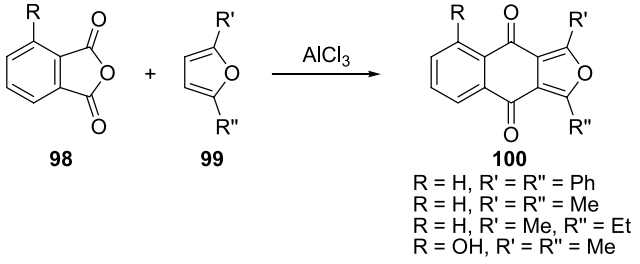
Scheme 13.

Other 3,4-furandicarboxylic acids are resistant to anhydride formation, presumably due to the strain imposed by the formation of the second five-membered ring, and therefore this technique has only limited application.

An alternative Friedel–Crafts acylation route to 1,3-disubstituted naphtho[2,3-*c*]furan-4,9-diones involves annulation of the heterocyclic ring. Furan (**1**) is activated towards electrophilic substitution, particularly at the α-positions, which are estimated to be 6×10^{11} fold more reactive than benzene.[88] Acylation with phthaloyl chloride (**96**), for example, would be expected to occur initially at the α-position and then at the β-position to give naphtho[2,3-*b*]furan-4,9-dione (**97**) (Scheme 14), although there appears to be no record of this reaction having been performed, perhaps due to the tendency of furan to resinify in the presence of $AlCl_3$.[88]



Scheme 14.

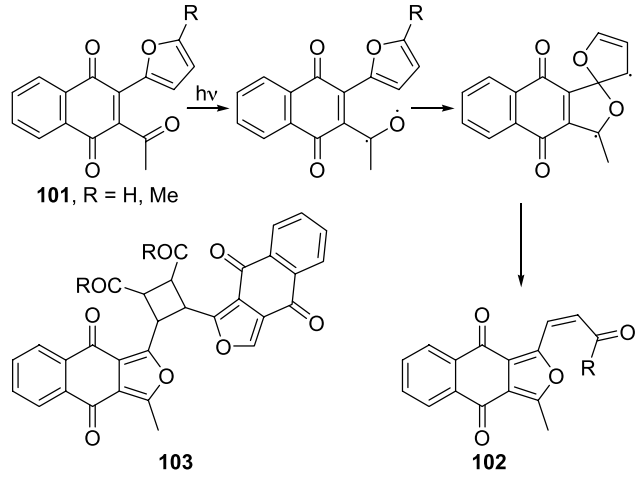


Scheme 15.

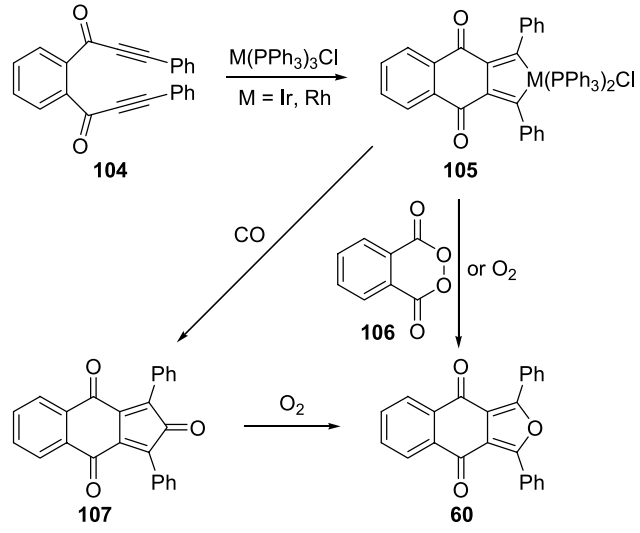
If attack at the α-positions is blocked by substituents, acylation can only occur across the 3,4-positions (which are still much more reactive than benzene[88]), resulting in the *c*-fused product. Surprisingly, phthaloyl chlorides have not been used to this end, but several 2,5-disubstituted furans (**99**) have been diacylated with phthalic anhydrides (**98**) to give the corresponding naphtho[2,3-*c*]furan-4,9-diones (**100**) in moderate yields (Scheme 15).[83,89]

3.3. Photo-isomerisation

An interesting route to the naphtho[2,3-*c*]furan-4,9-dione skeleton was discovered during an investigation of the photochemistry of α-furyl-substituted naphthoquinones **101**.[90] In dilute solution, the long-wavelength photolysis of **101** in aprotic solvents gave the products **102**, which are thought to arise via photo-excitation of the acetyl carbonyl group, followed by cyclisation and rearrangement (Scheme 16). In more concentrated solution, the dimers **103** resulting from [2+2] cycloaddition of the exocyclic double bonds of **102** were also isolated.



Scheme 16.

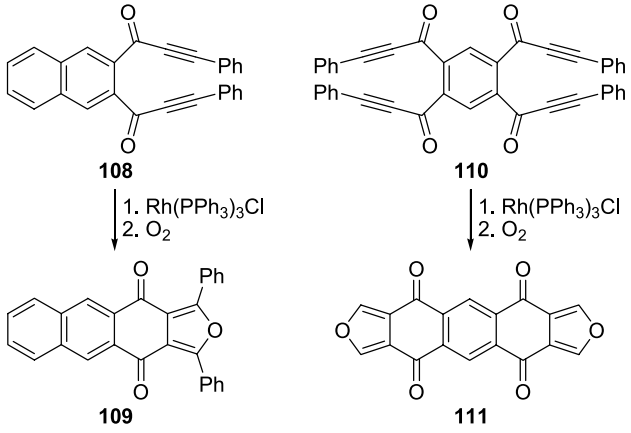


Scheme 17.

3.4. From metallocycles

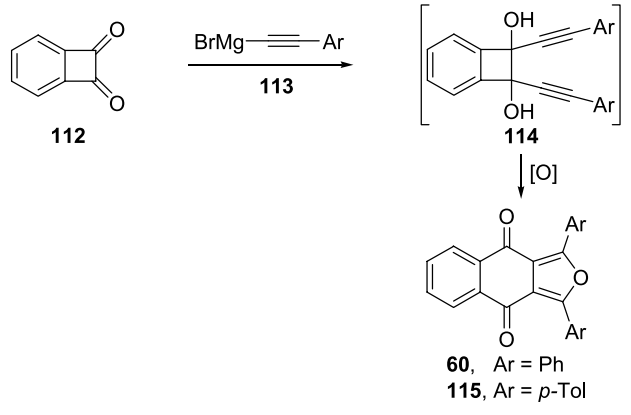
In their extensive studies of the reactions of transition metal complexes with diynes, Müller and co-workers found that the rhodium[91,92] and iridium[93] complexes **105**, formed from diynes **104**, react with oxygen to give **60** in low yield (15% for Rh) (Scheme 17). The rhodium complex was also oxidised to **60** by nitrous oxide[94] and in an attempt to react it with benzyne generated by the decomposition of phthaloyl peroxide (**106**).[95] Carbon monoxide was shown to displace the complexed rhodium, giving the cyclopentadienone **107**, which also reacted with oxygen to give **60**.[96]

The anthra[2,3-*c*]furan-4,11-dione **109**[92] and anthradifurantetrone **111**[74] were prepared by analogous reaction sequences, beginning with **108** and **110**, respectively (Scheme 18).



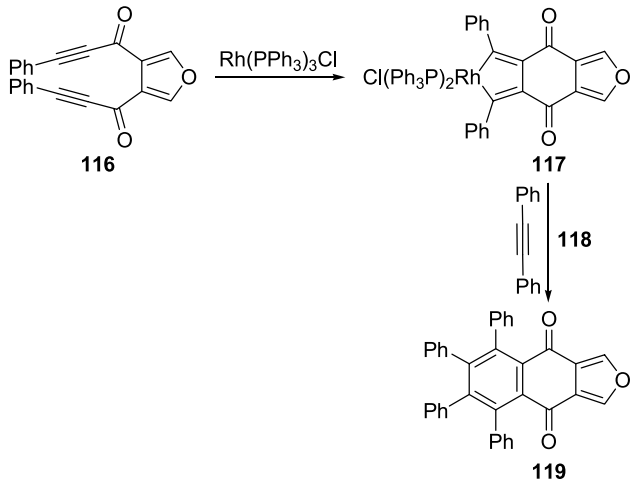
Scheme 18.

Similarly, naphtho[2,3-*c*]furan-4,9-diones **60** and **115** were produced in the reaction of the acetylides **113** with benzocyclobutene-1,2-dione (**112**) (Scheme 19),[96] presumably by rearrangement and oxidation of the initial diyne adducts **114**.



Scheme 19.

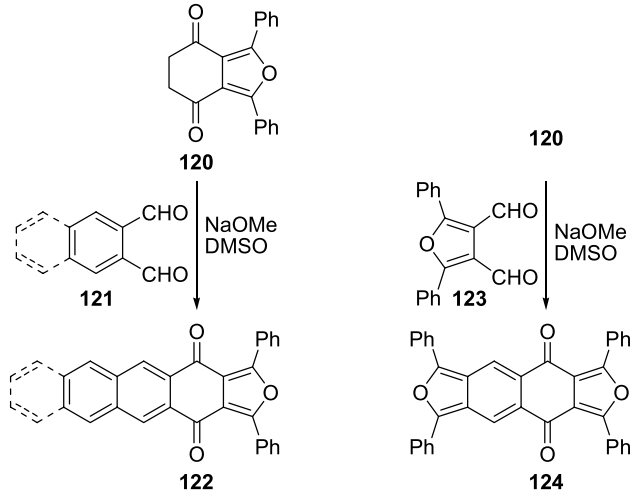
An alternative, but similar, approach was used to prepare the tetraphenyl derivative **119**, this time beginning with the 3,4-diacylfuran **116** (Scheme 20). The metallocycle **117** derived from **116** underwent a cycloaddition reaction with diphenylacetylene **118** to give the isofuranonaphthoquinone **119**.[97]



Scheme 20.

3.5. Crotonisation

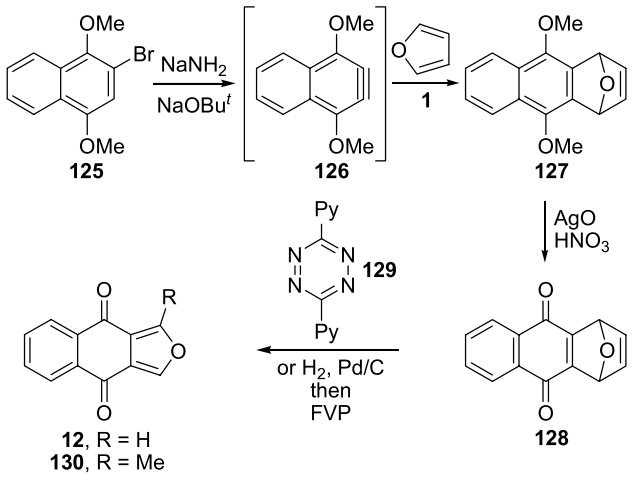
Under basic conditions the *o*-dialdehydes **121** undergo double aldol/dehydration reactions with the diketone **120** to give the aromatised products **122** (Scheme 21). The 3,4-diformylfuran **123** reacts similarly to give **124**.[98]



Scheme 21.

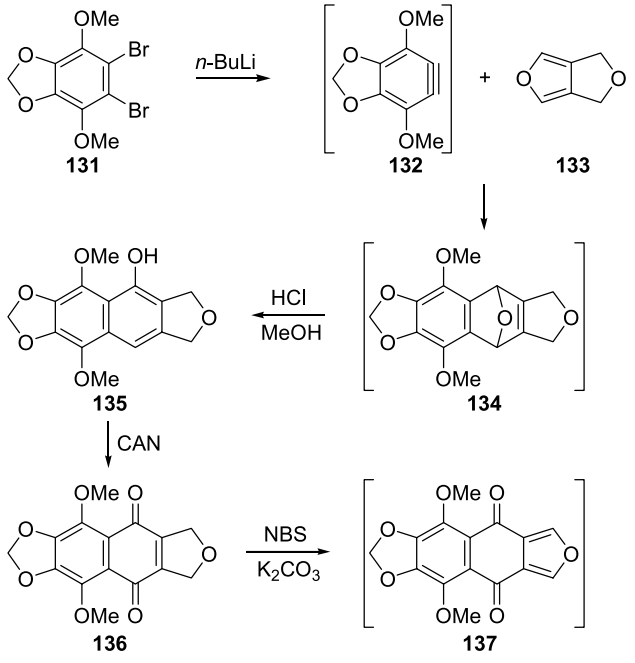
3.6. Diels–Alder reactions

Alder and Rickert's elegant Diels–Alder–retro-Diels–Alder strategy for the synthesis of 3,4-disubstituted furans[99–101] has been applied to the synthesis of the parent naphtho[2,3-*c*]furan-4,9-dione (**12**) (Scheme 22).[102] The aryne **126**, generated by dehydrobromination of **125** in the presence of furan (**1**), gave the adduct **127** and oxidative demethylation gave the corresponding quinone **128**. Selective hydrogenation of the unconjugated double bond of **128**, followed by a flash vacuum pyrolysis-induced retro-Diels–Alder reaction, gave **12**. Alternatively, following Warrener's tandem cycloaddition-cycloreversion protocol,[7] the more electron-rich double bond of **128** reacts with di-2-pyridyl-*s*-tetrazine (**129**) to give **12** via a similar Diels–Alder–retro-Diels–Alder domino process.[102] The same approach was used to prepare the 1-methyl-substituted derivative **130**.



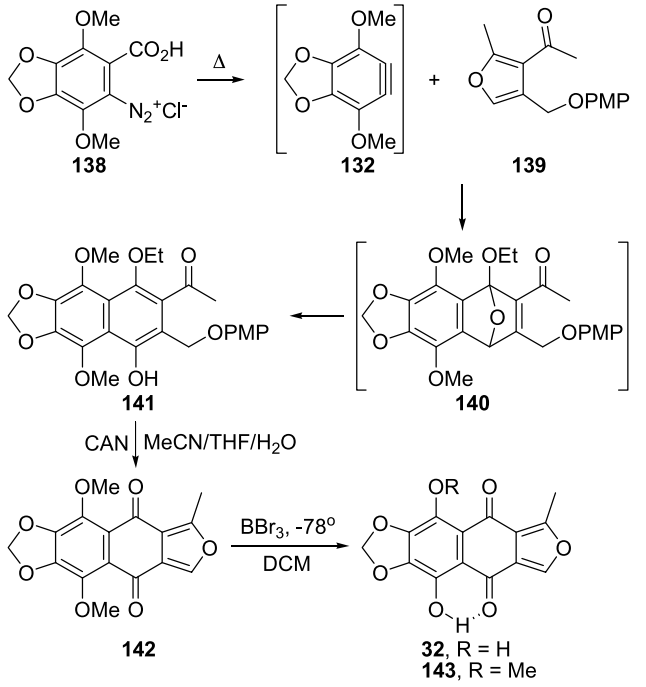
Scheme 22.

An alternative cycloaddition approach has been used to access the ring system of ventilone A (Scheme 23).[103] In situ generation of the aryne **132** by treatment of dibromide **131** with *n*-BuLi, in the presence of 4,6-dihydrofuro[3,4-*c*]furan (**133**), gave adduct **134**. This product could not be isolated due to the reactivity of the pyramidalised alkene linkage, but work-up under anaerobic conditions followed by acid treatment of the crude product, effected cleavage of the epoxy bridge, providing the phenol **135** in 56% yield. Oxidation gave the quinone **136** in 86% yield and subsequent aromatisation of the dihydrofuran ring gave **137**, lacking only the 1-methyl group of the dimethyl ether of ventilone A, in 79% yield.



Scheme 23.

A modified route in which the problems encountered above were avoided by formation of the furan ring late in the synthesis was used to make ventilone A (Scheme 24).[104] In this case, the highly substituted diazonium chloride **138** was chosen as the precursor to **132**, due to the incompatibility of



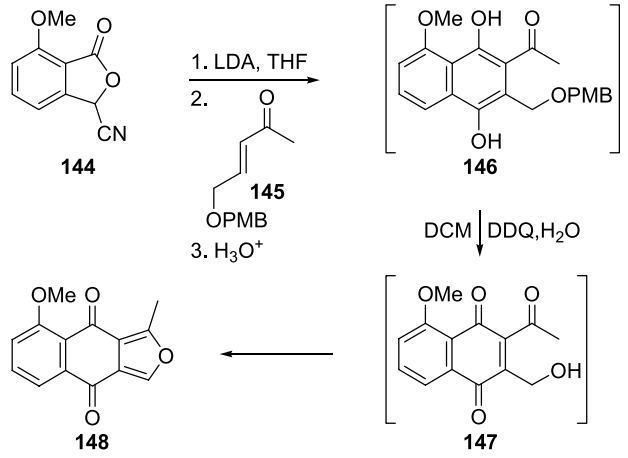
Scheme 24.

n-BuLi with the methyl ketone of **139**. Thermal decomposition of **138** in the presence of furan **139** presumably gave the expected cycloadduct **140**, although this was not observed, sufficient acid being generated by the initial reaction to open the epoxy bridge and provide the phenol **141** in 70% yield. Selective oxidative dealkylation of **141** to the corresponding quinone was accompanied by removal of the PMP protecting group, cyclisation of the resultant primary alcohol and transannular dehydration to generate the dimethyl ether of ventilone A (**142**) in one efficient (93%) step. Finally, selective demethylation with a large excess of boron tribromide afforded ventilone A (**32**) in low yield. Smaller excesses of BBr_3 gave the monomethyl ether **143**, isomeric to ventilone B (**33**, Fig. 12).

3.7. Cyanophthalide anion annulation

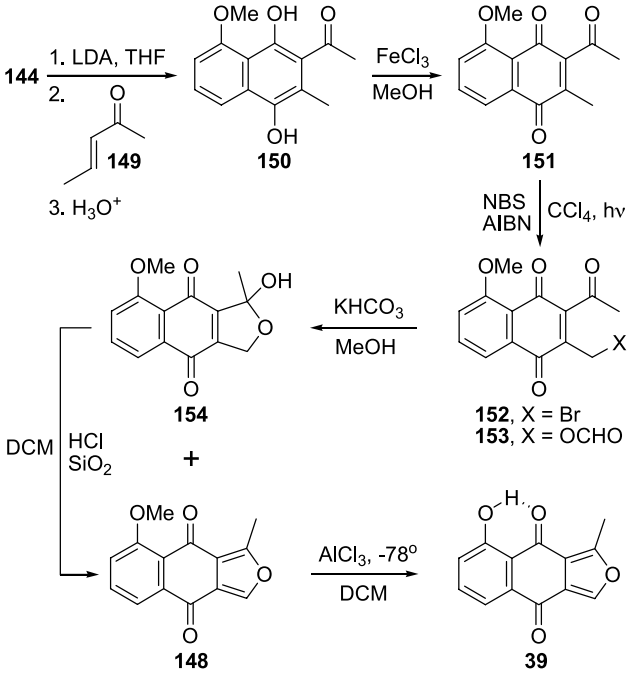
The strategy outlined in Section 3.6 (and also the Friedel–Crafts approach) suffers from regiochemical ambiguity when applied to isofuranonaphthoquinones with unsymmetrical substitution patterns in both the benzene and furan rings. An alternative approach, which makes use of a regiospecific annulation reaction (Scheme 25), has been applied to the natural product **39**.[33] Addition of the anion derived from the phthalide **144** to the α,β-unsaturated ketone **145**, followed by oxidation of the crude product, gave the methyl ether (**148**) of the natural product in 30% yield (Scheme 25), presumably by cyclisation and transannular dehydration of the hydroxymethylquinone **147**. The low yield was attributed to the propensity of the intermediate hydroquinone **146** to eliminate *p*-methoxybenzyl alcohol, generating a reactive *o*-quinonemethide.

The overall yield was improved by performing a similar reaction with *E*-3-penten-2-one (**149**) and subsequently functionalising the newly formed benzylic position



Scheme 25.

(Scheme 26). Thus, the annulation reaction of the unsubstituted Michael acceptor **149** gave the hydroquinone **150** in 79% yield and mild oxidation provided the corresponding quinone **151** quantitatively. Regioselective bromination with NBS gave **152** in 90% yield. Attempts to hydrolyse the bromide were unsuccessful, but substitution with sodium formate followed by mild hydrolysis of the resulting ester **153** gave a mixture of the desired product **148** and the intermediate lactol **154**. Dehydration was completed by stirring the mixture with acidified silica gel, affording **148** in 98% yield (from the bromide). Finally, demethylation with an excess of aluminium chloride provided the natural product **39** in 82% yield.[33]

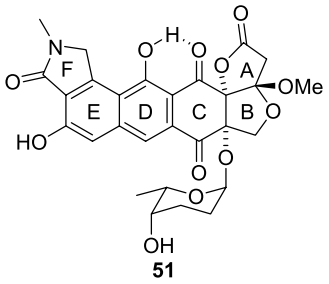


Scheme 26.

3.8. Lactonamycin

Lactonamycin (**51**) (Fig. 22) has inspired synthetic efforts in several laboratories, beginning with model chemistry that

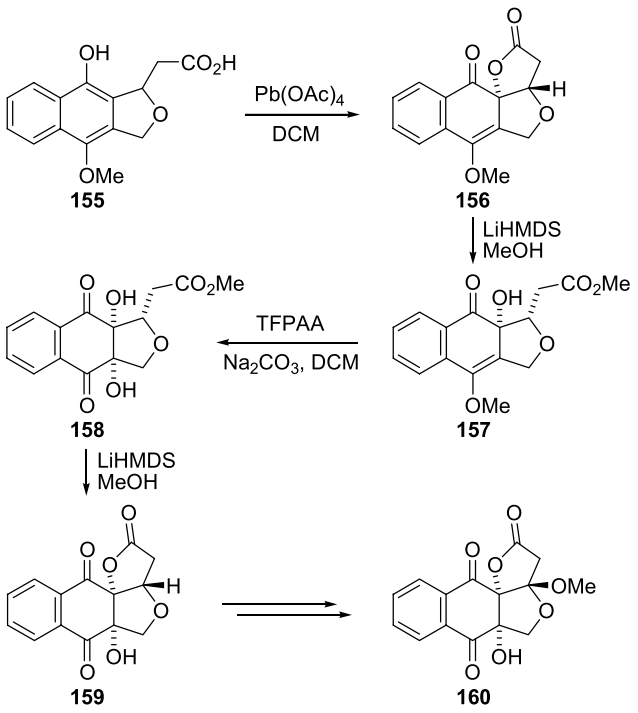
has provided the ABCD[105] and CDEF[106–108] ring systems[‡] and culminating in a total synthesis of the racemic aglycone by Danishefsky and co-workers.[109] Most recently, the Kelly group has prepared an enantiopure AB ring fragment with absolute stereochemistry matching that of the natural product.[110]



51

Figure 22.

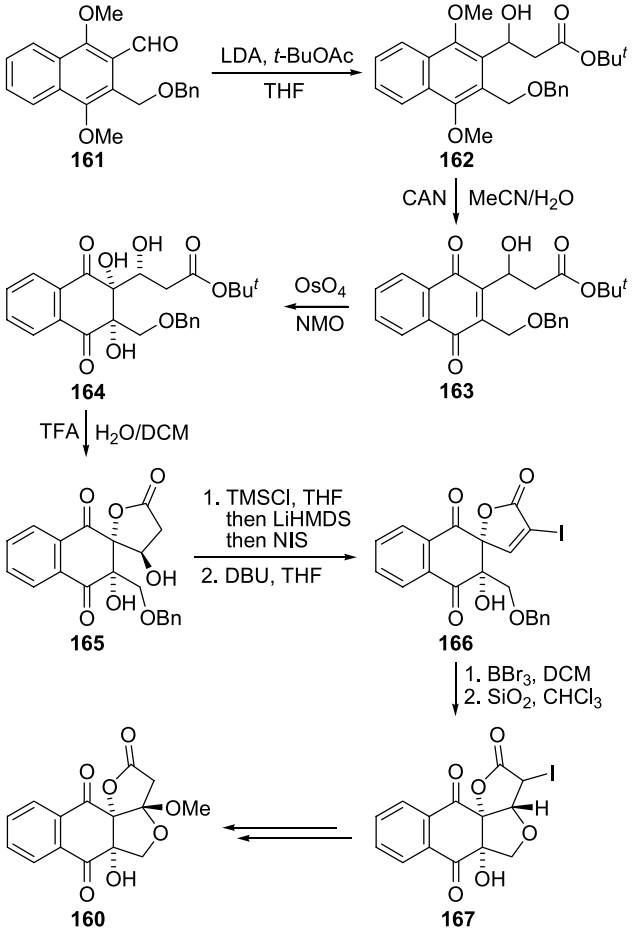
3.8.1. The ABCD ring system. Danishefsky and Cox's work towards a total synthesis of lactonamycin began with model chemistry that entailed successive oxidations of the advanced intermediate **155** (Scheme 27).[105] The key step was the intramolecular Wessely oxidative cyclisation of **155**, which gave the lactone **156** in 74% yield. Attempts to convert **156** into the required hydroxyketone by epoxidation of the enol ether favoured the undesired diastereomer. However, cleavage of the strained lactone to give **157** allowed selective epoxidation of the β-face through the directing influence of the neighbouring hydroxy group. The resulting *cis*-diol **158** was cyclised to give **159** and the angular methoxy group of **160** was installed via a series of reactions centered around the conjugate addition of methanol.



Scheme 27.

[‡] The ring system has been assigned letters in accord with the original structure elucidation reference.[61] Other workers have used a different lettering scheme.

Danishefsky and Cox followed up the work described above with an improved synthesis of the ABCD ring system (Scheme 28).[111] The enolate derived from *t*-butyl acetate added quantitatively to the naphthaldehyde **161** and the resulting secondary alcohol **162** was oxidatively demethylated to provide the quinone **163** in 97% yield. Dihydroxylation of the quinone double bond under standard conditions provided the triol **164** in 71% yield. This reaction is noteworthy, not only because it is the first such transformation of a complicated quinone, but because it is also completely diastereoselective. It follows that an asymmetric synthesis of lactonamycin should be possible if the configuration of the secondary alcohol **164** can be set by an enantioselective aldol reaction.

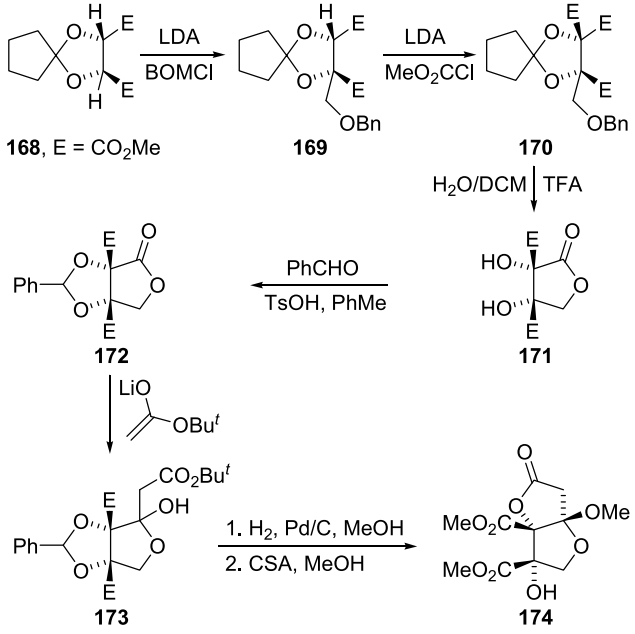


Scheme 28.

Protonolysis of the *t*-butyl ester **164** was accompanied by the desired cyclisation to give the lactone **165** in 83% yield. Attempts to oxidise the secondary alcohol to the corresponding ketone were unsuccessful, requiring the use of chemistry similar to that alluded to above. Thus, a one-pot protection of the alcohol/α-iodination (85%) was followed by the elimination of trimethylsilanol, giving the α,β-unsaturated enone **166** in 83% yield. Debenzylation, followed by treatment of the crude primary alcohol with silica gel in chloroform, effected the required conjugate

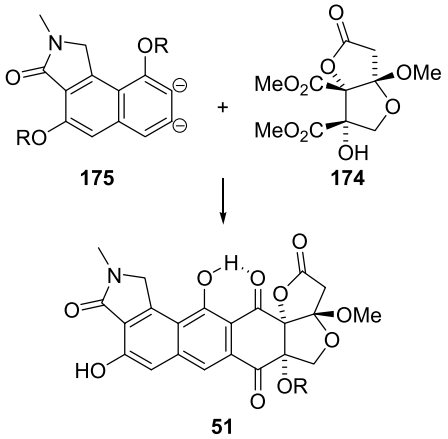
addition. The resulting mixture of epimeric α-iodolactones **167** was intermediate in the synthesis of **160** outlined in Scheme 27.

3.8.2. The AB ring system. Kelly and co-workers' asymmetric synthesis of the AB fragment of lactonamycin[110] began with D-tartaric acid, which was converted into the cyclopentylidene acetal **168** in two steps (Scheme 29).



Scheme 29.

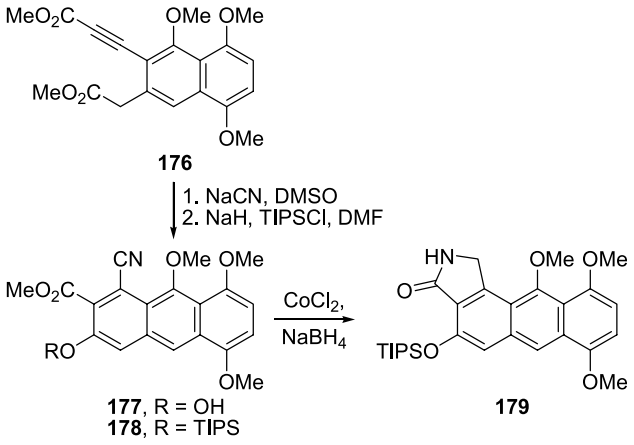
Alkylation with benzyloxymethyl chloride gave **169** in 60% yield and acylation with methyl chloroformate gave the triester **170** in 66% yield. Hydrolysis of the acetal was accompanied by debenzylation and cyclisation, providing the butyrolactone **171** in 60% yield. Reprotection of the glycol as the benzylidene acetal gave a 90% yield of a mixture of epimers (**172**), which were separately condensed with the anion of *t*-butyl acetate. Hydrogenolytic deprotection of the resulting products **173** gave the anomeric triols which, upon treatment with methanolic camphorsulfonic acid, underwent a cascade of events involving methyl acetal formation, anomerisation, and lactone closure to afford the target **174** in 63% yield.



Scheme 30.

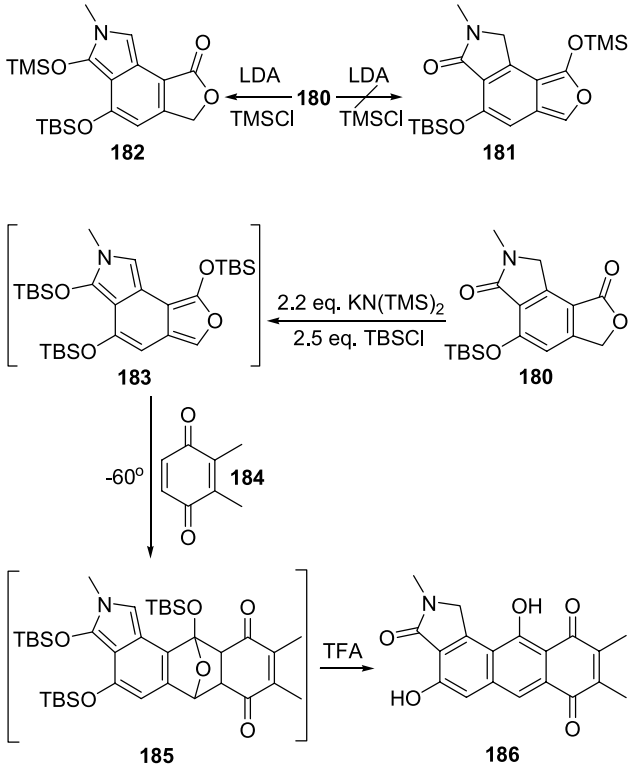
Kelly's proposed strategy to elaborate **174** involves the annulation of a synthon that would give rise (sequentially) to the dianion **175** (Scheme 30).

3.8.3. The CDEF ring system. Behar and Deville used a tandem Michael addition–Dieckmann condensation in their synthesis of the model system **179** (Scheme 31).[106] Thus,



Scheme 31.

1,4-addition of cyanide to the alkynyl ester **176** was accompanied by cyclisation to give the somewhat unstable anthrol **177**, which was immediately protected, giving the TIPS ether **178** in 68% yield over the two steps. Selective reduction of the nitrile was accompanied by the desired

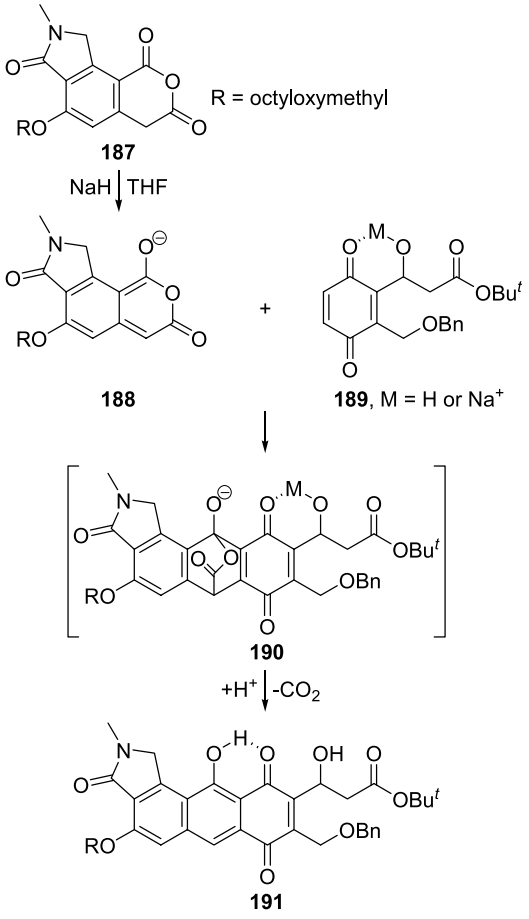


Scheme 32.

lactamisation to give the model compound **179** in 50% yield.

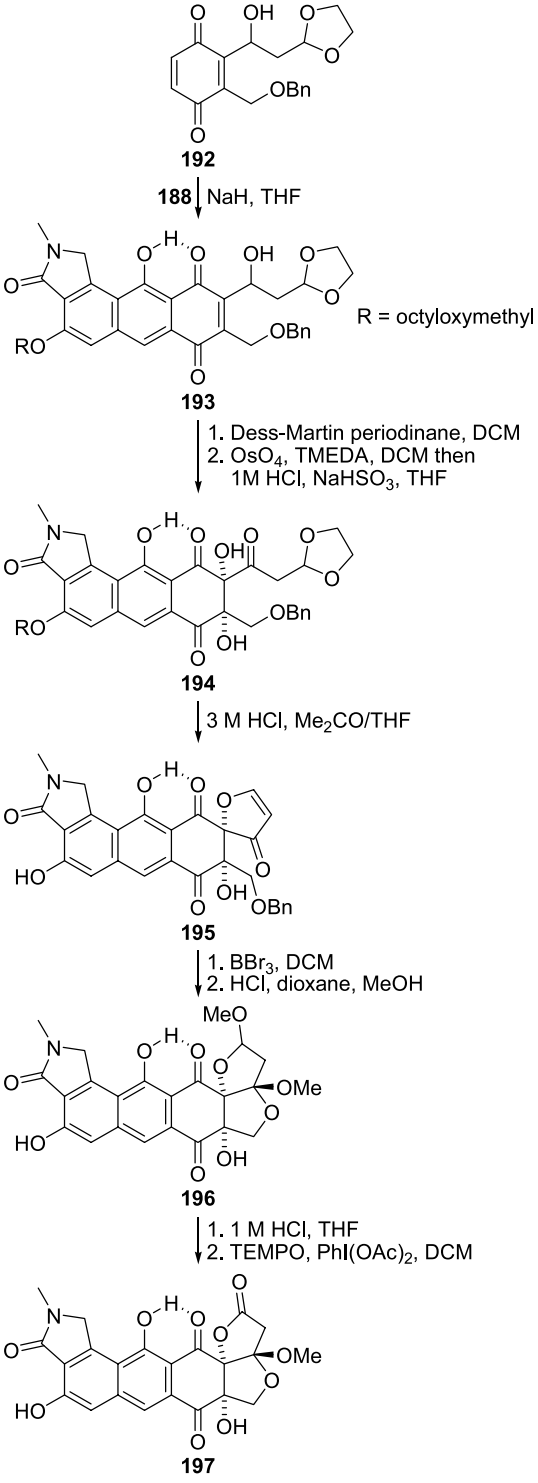
Kelly and co-workers used a Diels–Alder reaction as the key step in their synthesis of the CDEF-model system **186** (Scheme 32).[107] Their initial plan to use the isobenzofuran **181** was thwarted by the preferential formation of the isoindole **182**, but this was overcome by treatment of the phthalide precursor **180** with excess base and TBSCl. The resulting isofuranoisopyrrole **183** underwent the expected cycloaddition with 2,3-dimethylbenzoquinone **184** to give **185** and acid treatment of the crude product led to ring-opening, dehydration and deprotection, affording the desired product **186** in 74% yield from **180**.

The key step in Danishefsky and co-workers' synthesis of the CDEF ring system of lactonamycin was a regioselective Tamura-Diels–Alder reaction (Scheme 33).[108] The anion **188** derived from the homophthalic anhydride **187** underwent the annulation reaction with quinone **189** to give the desired tetracyclic system **191** in 40% yield, presumably by decarboxylation of the initially formed adduct **190**. The regioselectivity was attributed to internal activation of a carbonyl group by an intramolecular hydrogen bond or metal chelate. Despite the similarities of **191** to the model system **163** (Scheme 28), all attempts to fashion the AB ring system in this substrate were unsuccessful.



Scheme 33.

3.8.4. Lactonamycinone. The inability to convert **191** (Scheme 33) into the aglycone of lactonamycin necessitated a revised end-game (Scheme 34).[109] Again, Danishefsky and co-workers used a regioselective Tamura-Diels–Alder reaction, but this time with the quinone **192**, giving **193** in 42% yield. Oxidation of the secondary alcohol was succeeded by dihydroxylation of the electron-deficient quinone double bond, giving the diol **194** in 89% overall yield.



Scheme 34.

Hydrolysis of the dioxolane in **194** under acidic conditions was accompanied by cyclisation and dehydration, giving the

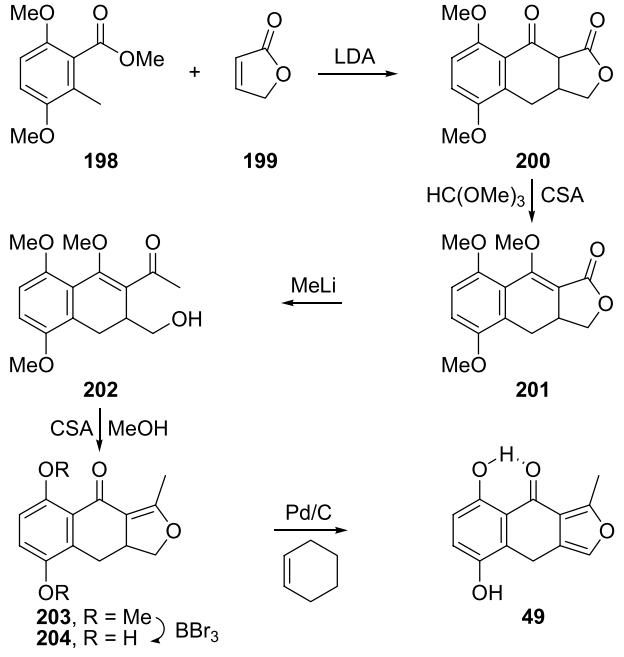
spiro butenolide **195** in 82% yield. Debenzylation, followed by treatment with methanolic HCl, led to intramolecular acetalisation and addition of methanol to the enol ether, affording **196**, the first synthetic compound possessing the complete hexacyclic framework of lactonamycinone, in a yield of 51%.

Selective hydrolysis of the acetal (in the presence of the ketal) occurred quantitatively, but oxidation of the resultant anomeric mixture of lactols proved to be more difficult. The required oxidation was eventually accomplished with TEMPO mediation, providing lactonamycinone (**197**) in 58% yield.

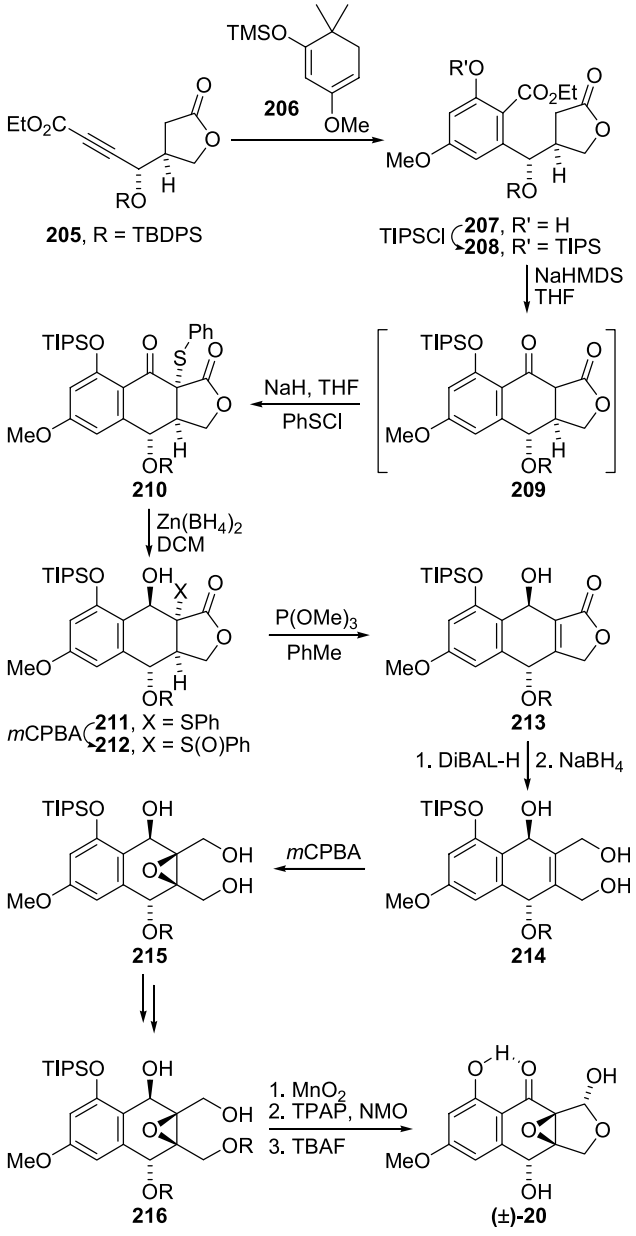
4. Synthesis of naphtho[2,3-*c*]furan-4(9*H*)-ones

In addition to the preparation of naphtho[2,3-*c*]furan-4(9*H*)-ones by reduction of the corresponding diones covered in Section 5.2, four natural product syntheses have been reported. The first, that of MS-444 (**49**),[112] began with the Michael–Dieckmann annulation reaction of **198** and butenolide (**199**), giving the lactone **200** as a mixture of enol and keto tautomers in 70% yield (Scheme 35). Formation of the enol ether **201** was followed by addition of methyllithium, providing the methyl ketone **202** in 87% yield. Acid treatment led to deprotection of the enol ether, cyclisation and dehydration, giving **203** in almost quantitative yield. Attempts to aromatise the furan ring led only to the formation of naphthalene byproducts. However, cleavage of the methyl ethers stabilised the carbonyl group through the strong *peri* H-bond, and transfer dehydrogenation of the hydroquinone **204** afforded the natural product **49** in 59% yield.

Uchiyama and co-workers achieved a stereoselective total synthesis of (±)-arthrinone [(±)-**20**] and the racemic forms of two co-occurring natural products [(±)-**21** and (±)-**22**] in 2000 (Scheme 36).[42] The synthesis involved the Diels–Alder reaction of the advanced intermediate **205**, the relative stereochemistry of which had been established earlier by a [2,3]-Wittig rearrangement. Heating **205** with the diene **206** led to cycloaddition-cycloreversion with extrusion of isobutylene, and hydrolytic workup afforded the phenol **207** in 81% yield. Reprotection of the phenol as the TIPS ether **208** was followed by a Dieckmann condensation, giving the unstable tricyclic ketone **209**, which was immediately sulfenylated, providing the thioether **210** in 87% yield over the two steps. Reduction of the ketone, which was presumed to be necessary to avoid aromatisation in the subsequent steps, afforded the alcohol **211** in 83% yield. Peracid oxidation of **211** gave the sulfoxide **212** as a mixture of epimers at sulfur in a combined yield of 90%. *syn*-Elimination of phenylsulfinic acid (separately from each epimer of **212**) installed the unsaturation necessary for the upcoming epoxidation, and



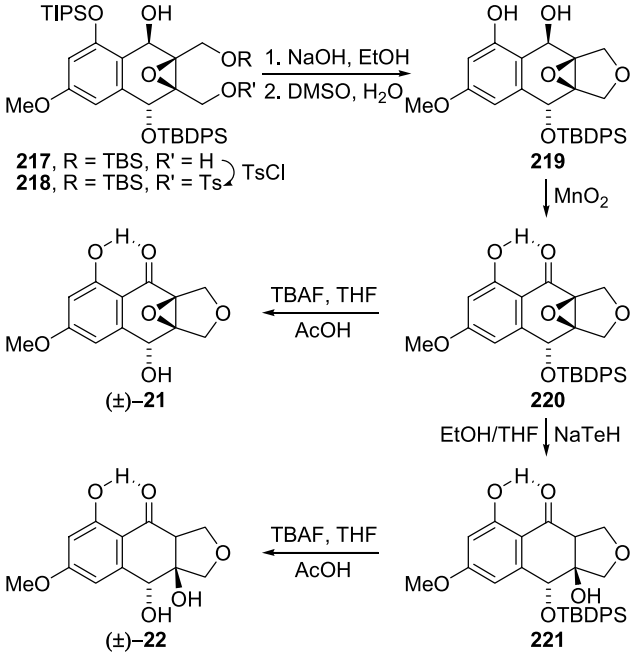
Scheme 35.



Scheme 36.

concurrently confirmed the stereochemistry of **211**. Attempts to epoxidise the resultant α,β-unsaturated lactone **213** were unsuccessful, but proceeded as required with the diol **214** produced by reduction of **213**. The diastereoselectivity of this epoxidation was revealed by the conversion of **213** into (±)-arthrinone [(±)-**20**]. Thus, a sequence of protection/deprotection reactions selectively provided the primary alcohol **216**, which was oxidised and deprotected to give the natural product.

The protected tetrol **217** (intermediate between **215** and **216**, in Scheme 36) was also a common precursor in the synthesis of (±)-dehydroxyarthrinone [(±)-**21**] and (±)-3a,9a-deoxy-3a-hydroxy-1-dehydroxyarthrinone [(±)-**22**] (Scheme 37). Selective and quantitative tosylation of the primary hydroxyl of **217** gave **218** which, after partial deprotection, cyclised to give the tetrahydrofuran **219** in 63% yield over both steps. Oxidation of the benzylic position gave the ketone **220** quantitatively, and deprotection afforded (±)-dehydroxyarthrinone [(±)-**21**]. Regioselective reductive ring-opening of the epoxide **220** with sodium hydrogen telluride gave the tertiary alcohol **221** in 77% yield and desilylation afforded the remaining natural product [(±)-**22**] in a yield of 87%.



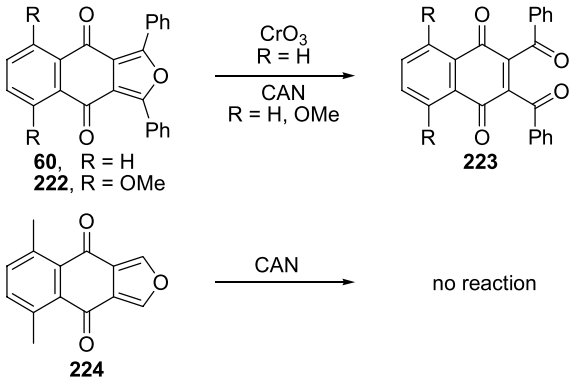
Scheme 37.

5. Reactivity

Some reactions of naphtho[2,3-*c*]furan-4,9-diones and related compounds have already been mentioned in the preceding sections. What follows is a more systematic survey of the topic grouped as much as possible by the type of reaction.

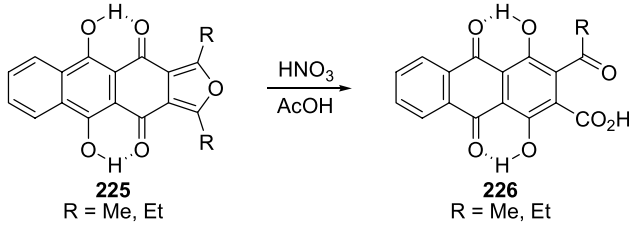
5.1. Oxidation

Strong oxidants have been shown to cleave the furan ring of naphtho[2,3-*c*]furan-4,9-diones to give *o*-diketones. For example, chromium trioxide or ceric ammonium nitrate (CAN) reacted with **60** to give **223** (R=H) (Scheme 38).[69] CAN brought about a similar transformation of the dimethoxy derivative **222**, but the analogue **224**, unsubstituted in the furan ring, was unaffected by this reagent.



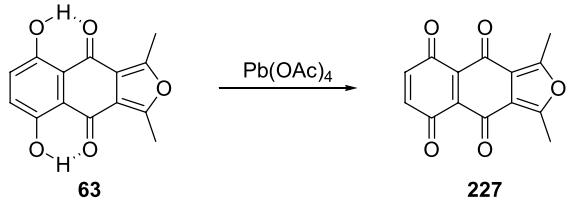
Scheme 38.

Nitric acid is also reported to oxidatively cleave the furan ring of isofuranoanthraquinones **225**, but in this case giving the corresponding 2-acylcarboxylic acids **226** (Scheme 39).[72]

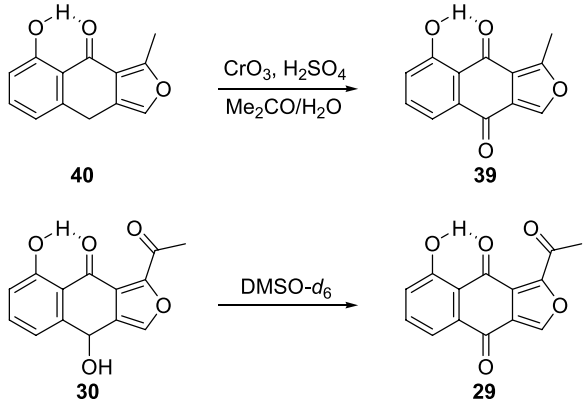


Scheme 39.

In contrast, oxidation of the dihydroxy derivative **63** with lead tetraacetate gave the corresponding tetrone **227** (Scheme 40).[78]



Scheme 40.



Scheme 41.

Table 2. Reduction of naphtho[2,3-*c*]furan-4,9-diones with metal hydrides

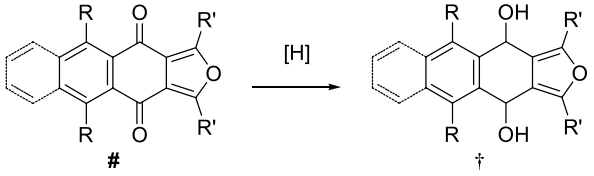
#	R	R′	Reductant	†	Yield (%)	Refs.
228	Me	H	KBH_4	**232**	—	113
229	OMe	H	$NaBH_4$	**233**	87	114
60	H	Ph	LAH	**234**	—	83
60	H	Ph	KBH_4	**234**	68	83
230	OH	Ph	KBH_4	**235**	—	115
231	OMe	Ph	LAH	**236**	55	83
109[a]	H	Ph	KBH_4	**237**	87	98

[a] Benzo fused analogue.

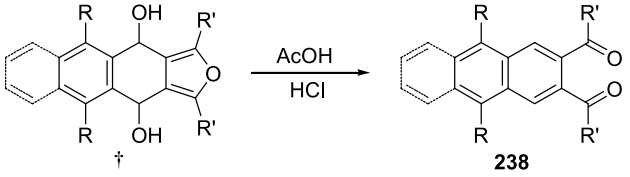
Jones oxidation of the naphtho[2,3-*c*]furan-4(9*H*)-one **40** gave the corresponding dione **39** (Scheme 41), reflecting the biosynthetic relationship of the two natural products. Similarly, arthoniafurone B (**30**) slowly oxidised to arthoniafurone A (**29**) in DMSO-d_6.

5.2. Reduction and dehydration of reduced derivatives

Naphtho[2,3-*c*]furan-4,9-diones (#) are reduced with metal hydrides to the corresponding diols (†). Examples of this transformation are summarised in Table 2.

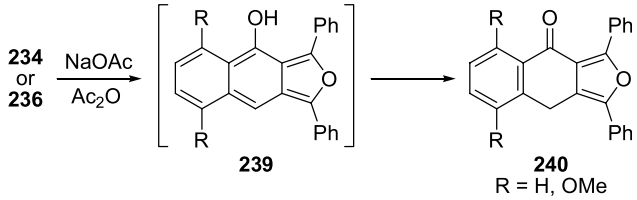


The diols (†) undergo acid-catalysed dehydration with concomitant opening of the furan ring to give the *o*-diacylnaphthalenes **238** (Scheme 42).[83,113]



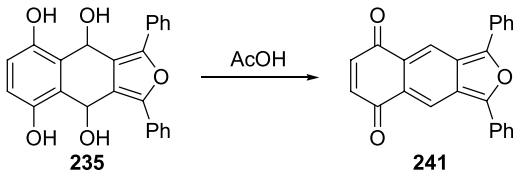
Scheme 42.

Under milder conditions transannular dehydration occurs to give the isonaphthofurans **239**, which tautomerise to the more stable naphtho[2,3-*c*]furan-4(9*H*)-ones **240** (Scheme 43).[83] The dimethoxy derivative (**240**, R=OMe) was also obtained directly from potassium borohydride reduction of the isofuranonaphthoquinone **231**.[83]



Scheme 43.

Conversely, dehydration of the reduced derivative bearing *peri*-hydroxyls **235** led to the formation of the naphtho[2,3-*c*]furan-5,8-dione **241** (Scheme 44).[115] Compound **241** is interesting in that it behaves as both a diene and a dienophile in the Diels–Alder reaction.



Scheme 44.

The polarographic behaviour of **60** and **119** (Fig. 23) has been investigated, both compounds undergoing two one-electron reduction steps. On the basis of the measured half wave potentials, the naphtho[2,3-*c*]furan-4,9-diones were shown to be more difficult to reduce than their anthraquinone counterparts, a property attributed to the presence of the π-excessive furan ring.[116]

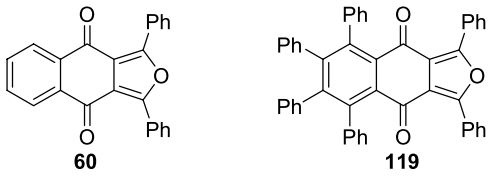
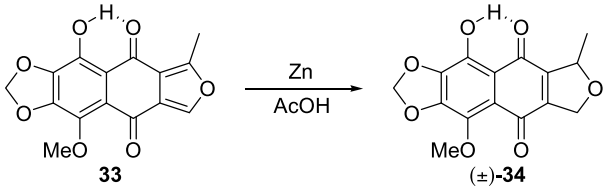


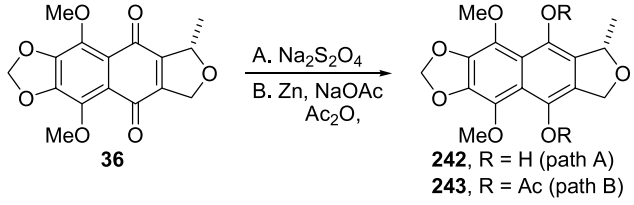
Figure 23.

Reduction has also been used as a tool in the structural elucidation of isofuranonaphthoquinone natural products. The position of the methoxy group in ventilone B (**33**) was revealed when partial reduction of the furan ring was found to give racemic ventilone C [(±)-**34**] (Scheme 45), of which a crystal structure had been obtained.[34]



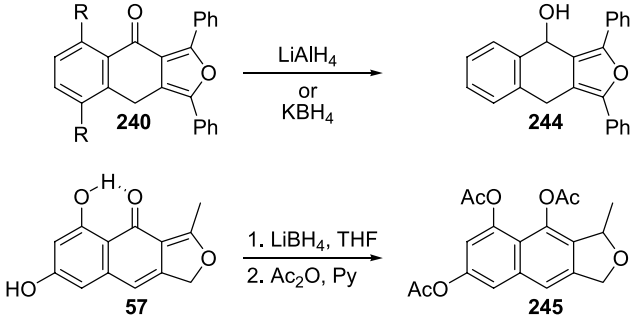
Scheme 45.

Ventilone E (**36**) was also reduced to the hydroquinone **242** with aqueous sodium dithionite and reductively acetylated to give **243** (Scheme 46).



Scheme 46.

The naphtho[2,3-*c*]furan-4(9*H*)-one **240** (R=H) was reduced to the corresponding secondary alcohol **244** by metal hydrides and reduction of furanaphin (**57**) with lithium borohydride followed by acetylation gave the triacetate **245** (Scheme 47).

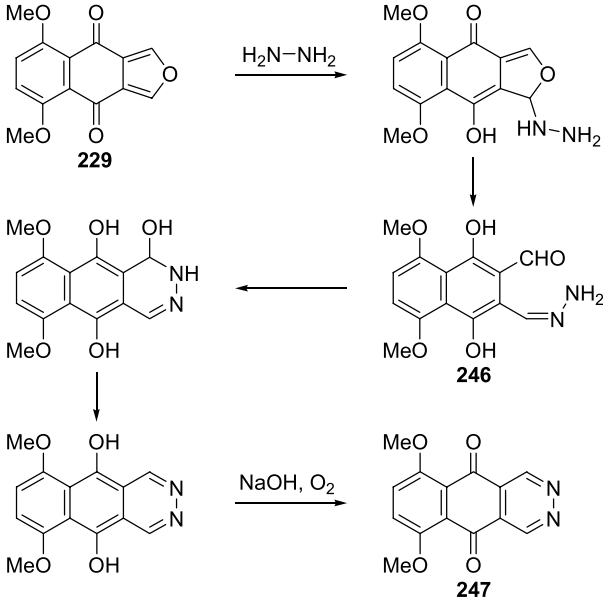


Scheme 47.

5.3. Conjugate addition

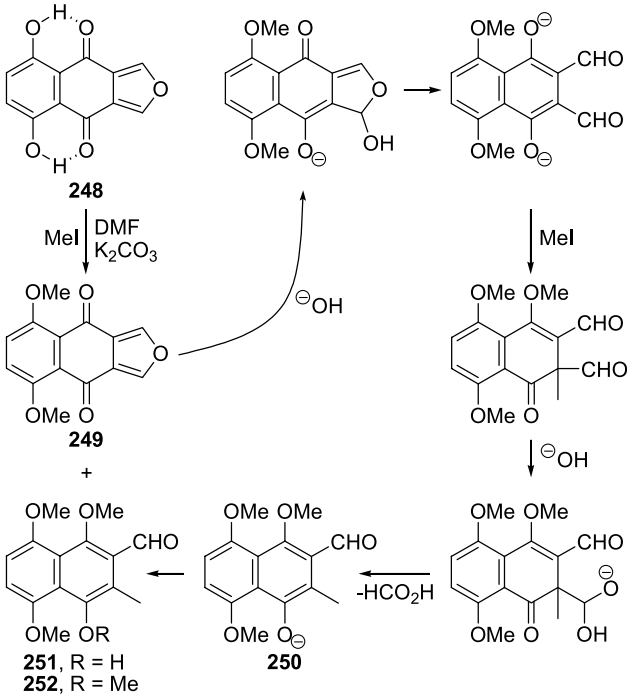
Naphtho[2,3-*c*]furan-4,9-diones are prone to conjugate addition of nucleophiles at the α-position of the furan ring. In this sense, they behave as attenuated *o*-quinonemethides, reactive species implicated in the mechanism of action of a number of important drugs.[117] Such reactivity may, in part, explain the biological activity of the naphtho[2,3-*c*]furan-4,9-diones.

For example, hydrazine reacted with **229** to give the phthalazinedione **247** after aerial oxidation (Scheme 48).[84] The first step in this transformation presumably involves 1,4-addition. Ring opening, followed by intramolecular condensation of the intermediate hydrazone **246** and oxidation, gives the observed product **247** in 89% yield.



Scheme 48.

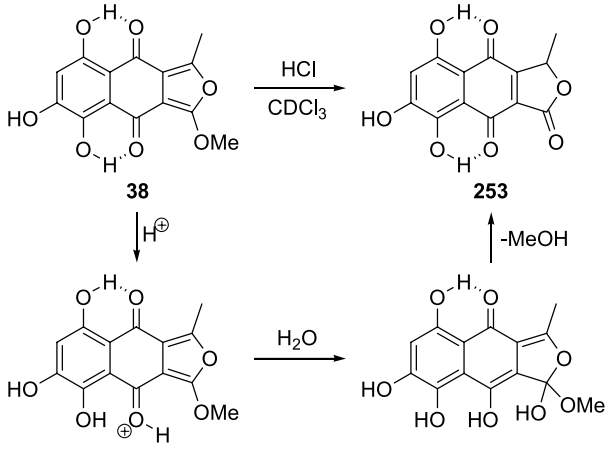
The unexpected byproducts **251** and **252** observed in the methylation of **248** (Scheme 49) were explained by conjugate addition of hydroxide (or carbonate) to the α-position of the initial product **249**.[85] Subsequent ring opening, *O*- and *C*-methylation and a retro-Claisen reaction



Scheme 49.

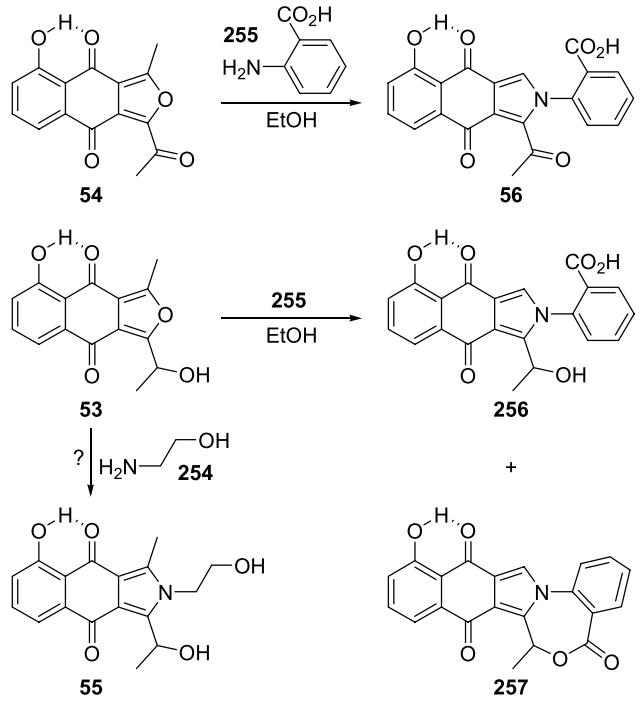
give the phenoxide **250**, which is methylated under the reaction conditions to give **252** or protonated on work-up to give **251**.

Furan ring-cleavage under acidic conditions can also be thought of as involving conjugate addition (Scheme 50). Such a reaction was used to aid the structural elucidation of ventilone G (**38**), which, upon treatment with strong acid, gave the lactone **253**, thereby placing the methoxy substituent in the furan ring (Scheme 50).[32]



Scheme 50.

It has been proposed that the isoindole natural products bhimamycin C (**55**) and D (**56**) may arise biogenetically via 1,4-addition of ethanolamine (**254**) and anthranilic acid (**255**) to bhimamycin A (**53**) and B (**54**), respectively (Scheme 51).[64] Indeed, a partial synthesis of bhimamycin D (**56**) was achieved by this method, albeit in only 2% yield.[64] Anthranilic acid also added to bhimamycin A (**53**) to give the non-natural analogues, bhimamycin F (**256**) and G (**257**) in respective yields of 24 and 13%.



Scheme 51.

5.4. 1,2-Addition

Nightingale and Sukornick, in the fashion of their time, attempted to prepare mono-2,4-dinitrophenylhydrazone derivatives of the array of isofuranonaphthoquinones that they had made (Table 1).[75] However, the reaction was only successful with **60**, **258** and **259** (Fig. 24).

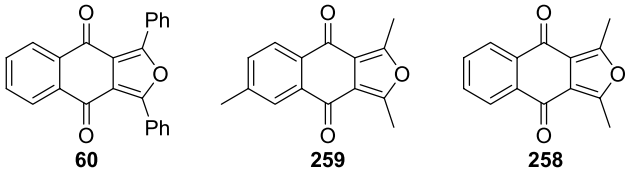
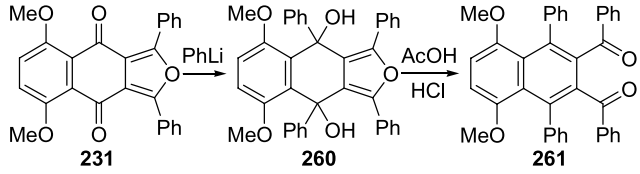


Figure 24.

The same authors found that the naphtho[2,3-*c*]furan-4,9-diones added 2 equiv of methylmagnesium iodide, although none of the addition products were isolated. In the case of some of the derivatives bearing α-methyl substituents, more than 2 equiv of the Grignard reagent were consumed, indicating the presence of active hydrogens, presumably those of the methyl groups, rendered acidic by the conjugated carbonyl groups.[75,77]

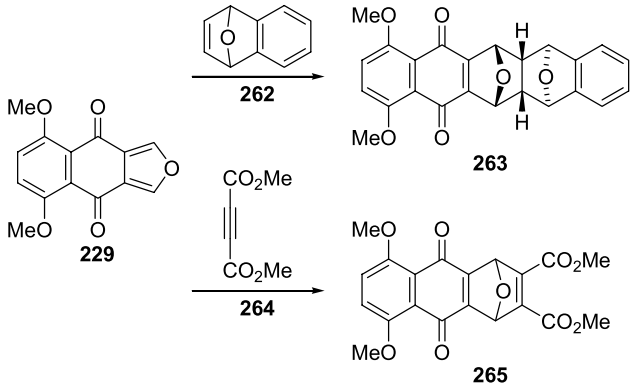
Excess phenyllithium added to **231** to give the expected dicarbinol **260**, which dehydrated in an analogous manner to that described in Section 5.2 to give the diketone **261** (Scheme 52).[83]



Scheme 52.

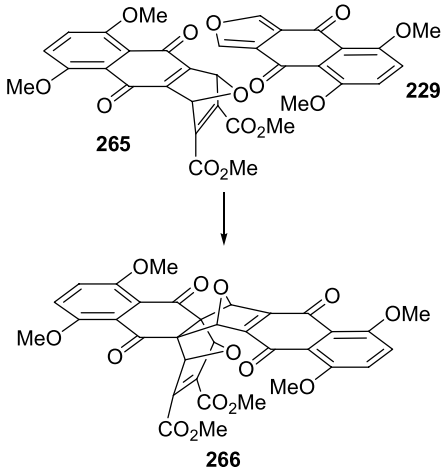
5.5. Cycloaddition reactions

Given the utility of furan as a diene in the Diels–Alder reaction, it is perhaps not surprising that naphtho[2,3-*c*]furan-4,9-diones also undergo [4+2] cycloadditions, although this was only demonstrated quite recently.[85] The readily prepared dimethoxy derivative **229** gave the expected cycloadducts **263** and **265** with the electron-rich dienophile, 1,4-dihydro-1,4-epoxynaphthalene (**262**), and the electron poor dienophile, dimethyl acetylenedicarboxylate (DMAD, **264**), respectively (Scheme 53).



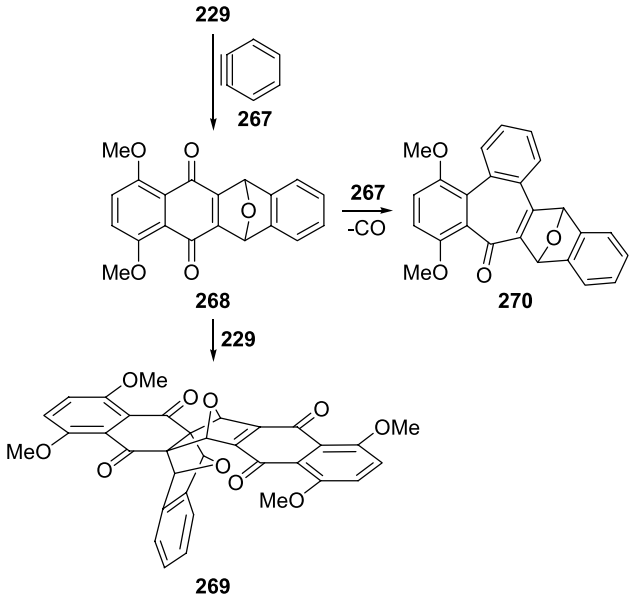
Scheme 53.

In the latter case, the double adduct **266** formed by a second cycloaddition of **229** to the strained conjugated double bond of the initial product **265** was also generated (Scheme 54).



Scheme 54.

When the dienophile was benzyne (**267**), the major monocycloadduct **268** was also accompanied by a small amount of the double adduct **269** (Scheme 55). In addition, a third product **270** was isolated in low yield. This tropolone **270** is thought to arise from a 1,3- or homo-Diels–Alder addition of benzyne to the initial product **268**, followed by expulsion of carbon monoxide. Indeed, in a separate experiment, generation of benzyne in the presence of **268** gave **270** in 45% yield.



Scheme 55.

The Diels–Alder reactivity of **229** contrasts with the report that the isobenzofurandione **9** fails to react with maleic anhydride (**271**)[18] (Fig. 25). However, compound **9** does undergo cycloaddition with the very electron-rich dienophile, 1,1,2,2-tetramethoxyethylene (**272**), to give adduct **273**. It is not immediately obvious why the differences in the Diels–Alder reactivity of **9** and **229** exist and the cycloaddition chemistry of both ring systems may warrant re-investigation.

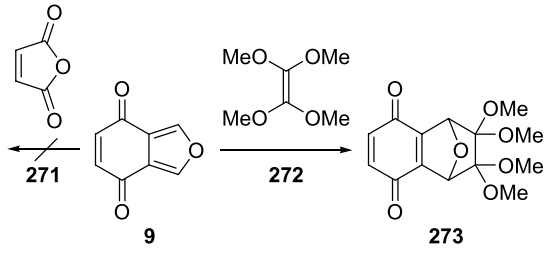
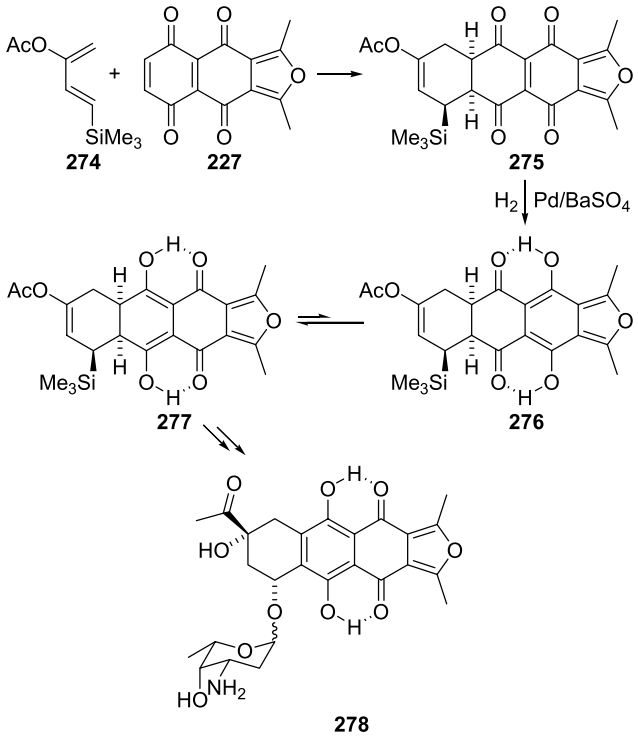


Figure 25.

The tetrone **227** has also been shown to take part in a Diels–Alder cycloaddition, this time as the dienophile.[78] Reaction with the diene **274** gave the expected *endo* adduct **275** (Scheme 56). Catalytic hydrogenation of the adduct reportedly gave the IBF derivative **276**, but for the reasons discussed in Section 3.2, the tautomer **277** is a more likely structure. The product of the hydrogenation reaction was elaborated via a number of steps into the dimethylfurano daunomycin analogue **278**, which exhibited anticancer activity in mice.[78]

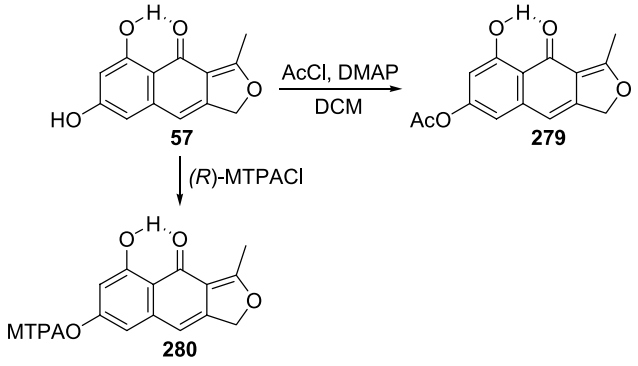
5.6. Miscellaneous

A number of simple acetylations[31,34,35,65,70,71,83] and methylations[32,34,36,70,71,80] of the phenolic hydroxyl groups of naphtho[2,3-*c*]furan-, 9-diones and partially reduced analogues have been conducted. It is worth noting that the strong intramolecular hydrogen-bond present in derivatives



Scheme 56.

with a hydroxy group *peri* to the carbonyl group permits these transformations to be carried out selectively; for example, treatment of furanaphtin (**57**) with an excess of acetyl chloride gave only the monoacetate **279** (Scheme 57).[65] Furanaphtin similarly formed a mono-Mosher's ester **280**. An analogous selective methylation was discussed earlier (Scheme 10).[80]

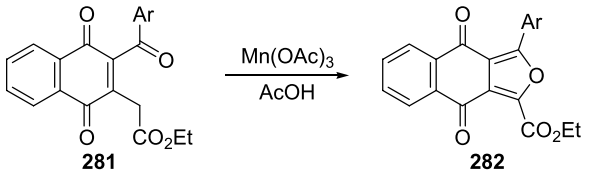


Scheme 57.

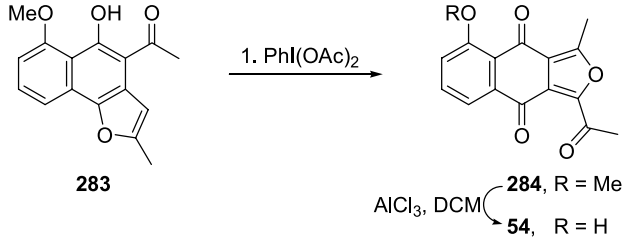
6. Recent developments

During the editing of this manuscript two papers relevant to this review were published and they are mentioned briefly here, for completeness. The (ethoxycarbonyl)naphtho[2,3-*c*]furan-4,9-diones **282** were formed as a minor by-product in the manganese(III) acetate-induced free-radical cyclisation of the naphthoquinones **281** (Scheme 58).[118]

Another novel naphtho[2,3-*c*]furan-4,9-dione synthesis was used to prepare bhimamycin B (**54**) (Scheme 59).[119] Thus, oxidative cleavage of the naphtho[1,2-*b*]furan **283** with



Scheme 58.



Scheme 59.

phenyliodonium diactetate gave **284** in 57% yield. Demethylation with $AlCl_3$ then gave the natural product **54** in 56% yield.

7. Conclusions

The naphtho[2,3-*c*]furan-4,9-diones and related compounds comprise a small but growing class of natural and synthetic products. Their structural diversity and reactivity has stimulated and challenged synthetic chemists and the biological activity associated with many of these compounds will ensure that they continue to attract interest for some time yet.

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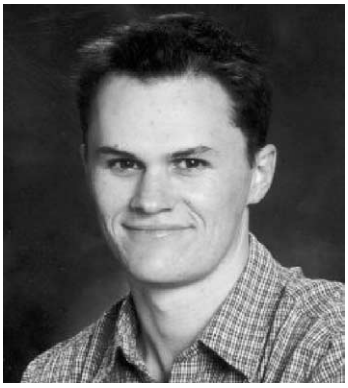
Biographical sketch



Matthew Piggott was born in Bunbury, Western Australia in 1974. He completed his undergraduate degree at The University of Western Australia in 1995 then studied for his PhD under the supervision of Associate Professor Dieter Wege. His research included the total synthesis of a number of natural products containing the naphtho[2,3-*c*]furan substructure. In 2000 he began his postdoctoral studies in the Research School of Chemistry at The Australian National University, where he worked on a medicinal chemistry project in collaboration with GlaxoSmithKline. The work, carried out under the supervision of Professors Martin Banwell and Chris Easton, involved the design and synthesis of inhibitors of tyrosine t-RNA synthetase as potential antibiotics. In 2002, he joined the group of Professor Ross Kelly as a postdoctoral associate at Boston College, where he worked towards the synthesis of a chemically powered molecular motor. In 2003 he returned to the ANU as a lecturer in the Department of Chemistry and then in 2005 moved to the School of Biomedical, Biomolecular and Chemical Sciences at UWA. His research interests include medicinal chemistry, particularly with respect to Parkinson's disease, and the synthesis of novel, naturally occuring and/or biologically active heteroaromatic and quinonoid compounds.

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Synthesis of azaphenanthridines via anionic ring closure

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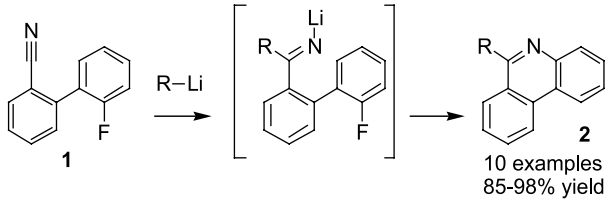
Abstract—A new and convergent synthesis of azaphenanthridines via an anionic ring closure is reported. *Ortho*-lithiation/in situ borylation of cyanopyridines produces the corresponding cyanopyridylboronic esters, which undergo a Suzuki–Miyaura cross-coupling to give the key intermediates. Addition of lithium morpholide produces the azaphenanthridines.

1. Introduction

We have previously reported a convergent synthetic protocol for the synthesis of 6-substituted phenanthridines (**2**) from biaryl **1** (see Scheme 1).[1] The reaction proceeds via attack of a lithiated species on the cyanogroup in **1** followed by intramolecular nucleophilic aromatic substitution of the fluorine.



Scheme 1. Synthesis of 6-substituted phenanthridines via anionic ring closure.[1]

We were interested in expanding the scope of our approach to the synthesis of heterocyclic phenanthridine derivatives, and set out to investigate whether it would be possible to synthesize the four isomeric 6-morpholinoaza-phenanthridines **3a–d** shown in Figure 1 using this strategy.

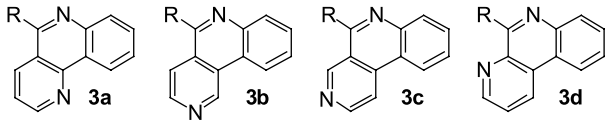


Figure 1. Targeted azaphenathridines. R = morpholine.

Keywords: Pyridines; Lithiation; Anionic ring closure.
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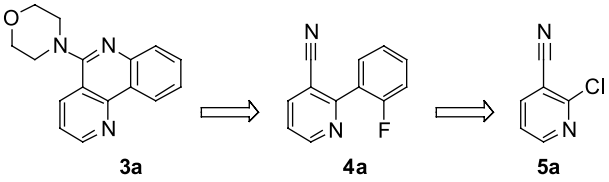
Substituted azaphenanthridines have a broad spectrum of biological activities, including antimalarial[2a–c] and analgesic activity.[2d] Furthermore, the 8-azaphenanthridine ring system in **3c** is the backbone of the pyridoacridine alkaloids,[2e] which exhibit anti-bacterial, anti-viral, anti-cancer activity,[2f] thus, a short and convergent approach to these ring systems would be highly desirable. Numerous different approaches to azaphenanthridines have been reported in the litterature,[3] but all lack the flexibility to produce all the targeted isomers in this study.

2. Results and discussion

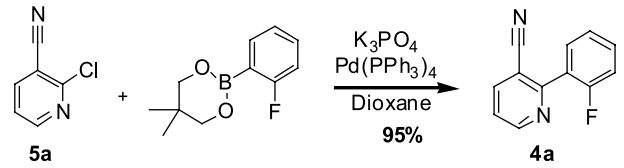
The retrosynthetic strategy is exemplified for the synthesis of **3a** from biaryl **4a**, which in turn should be accessible from commercially available 2-chloronicotinonitrile (**5a**) via a Suzuki–Miyaura cross-coupling[4] (see Scheme 2).



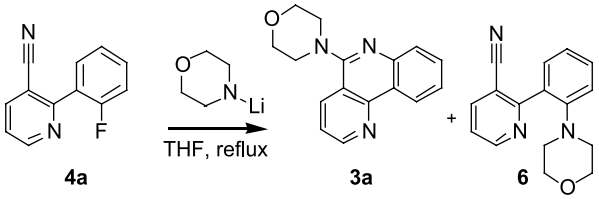
Scheme 2. Retrosynthetic analysis of **3a**.

Indeed, coupling of **5a** with the depicted 2-fluorophenylboronic ester[5] gave biaryl **4a** in 95% isolated yield (see Scheme 3).

With the desired biaryl in hand we were ready to test the proposed ring closure. Treating **4a** with lithium morpholide at reflux yielded a 37:63 mixture of the desired azaphenanthridine **3a** together with **6** resulting from nucleophilic



Scheme 3. Synthesis of **4a**.



Entry	Additive	3a	6
1	No additive	37%	63%
2	2 equiv DMPU	65%	35%
3	5 equiv DMPU	83%	17%
4	5 equiv LiCl	>99%(84%)[a]	<1%

Product ratio determined from GC-MS. a) Isolated yield

Scheme 4. Addition of lithium morpholide to **4a**.

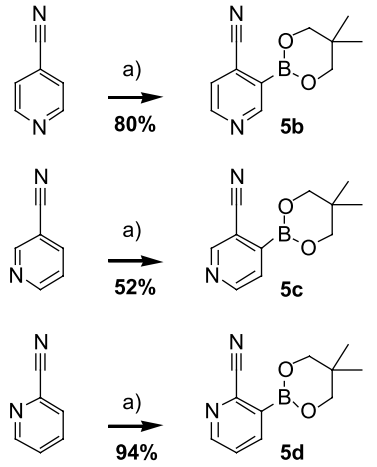
aromatic substitution of fluorine by lithium morpholide[6] (see Scheme 4, entry 1).

We speculated that coordination of lithium morpholide to the pyridine nitrogen was a prerequisite for the direct nucleophilic substitution as seen in the work by Meyers and co-workers on nucleophilic aromatic substitution on 2-fluoro-aryloxazolines.[7] If this coordination could be impeded, perhaps the ratio between **3a** and **6** would increase. Repeating the experiment with 2 equiv of DMPU[8] did improve the ratio (see Scheme 4, entry 2) and 5 equiv of DMPU accentuated the effect even more to give a 83:17 mixture of **3a** and **6** (see Scheme 4, entry 3). Increasing the amount of DMPU did not influence the ratio further and let to a decrease in conversion. LiCl was tried as additive in an attempt to pre-complex the pyridine nitrogen, preventing lithium morpholide from coordinating, and the result was remarkable (see Scheme 4, entry 4). With 5 equiv of LiCl the desired product was the only detectable species, and **3a** was obtained in 84% isolated yield.

Having established that the proposed synthetic route to azaphenanthridines was viable, we set out to prepare the three biaryl precursors (**4b–d**) needed for the remaining azaphenanthridines (**3b–d**). If the strategy shown in Scheme 2 was to be followed this would require the synthesis of the corresponding halocyanopyridines as these are not commercial available. Therefore, a different synthetic strategy was chosen.

2.1. Synthesis of cyanopyridylboronic esters

We have reported a new synthetic procedure for the synthesis of arylboronic esters via in situ trapping of unstable lithio-intermediates.[5] Following this method, benzonitrile was *ortho*-lithiated to give the corresponding cyanoarylboronic ester. Accordingly, **4b–d** were envisaged to be prepared via a *ortho*-lithiation/cross-coupling sequence of cyanopyridines.[9] Submitting 2-, 3- and 4-cyanopyridine to our standard conditions for in situ trapping with LiTMP/B(O^iPr)$_3$ produced the desired cyanopyridylboronic esters **5b–d** in 52–94% isolated yield (see Scheme 5). In all cases, GC–MS of the crude material showed full conversion to the desired cyanopyridylboronic esters.

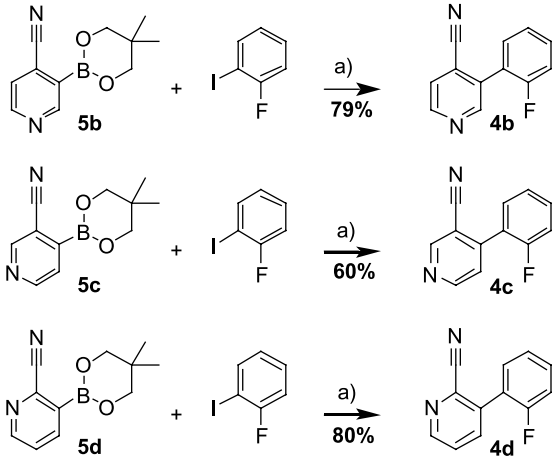


Scheme 5. Synthesis of cyanopyridylboronic esters **5b–d**.

2.2. Cross-coupling of cyanopyridylboronic esters

With the desired cyanopyridyl boronic esters in hand we set out to synthesize biaryls **4b–d**.

Suzuki–Miyaura coupling of pyridylboronic acids or esters is notoriously difficult as these derivatives are prone to deborylation.[10] Indeed, under standard Suzuki–Miyaura cross-coupling conditions we observed extensive deboryl-ation, and the parent cyanopyridines were isolated as the main product with only traces of the desired biaryls. Therefore, a range of conditions and additives were tested in order to optimize the coupling. After extensive

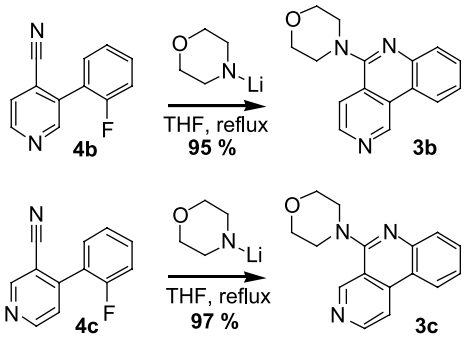


Scheme 6. Synthesis of biaryls via cross-coupling of cyanopyridylboronic esters.

experimentation we found that addition of CuI[11] in combination with CsF[12] in an aprotic solvent was crucial for the success of the reaction. Under these conditions the desired biaryls **4b–d** were isolated in 60–80% yield (see Scheme 6).

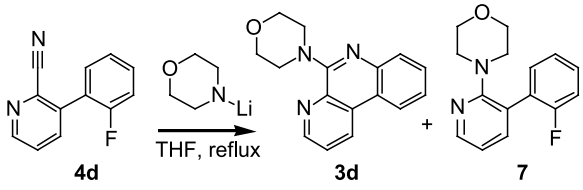
2.3. Synthesis of azaphenathridines

Treatment of **4b** and **4c** with lithium morpholide gave the desired azaphenanthridines in excellent yields (see Scheme 7). Compound **4b** gave **3b** in 95% yield and **4c** produced **3c** in 97% yield.



Scheme 7. Addition of lithium morpholide to **4b–c**.

The reaction of **4d** with lithium morpholide gave a 80:20 mixture of the desired product **3d** and a compound identified as **7** (see Scheme 8, entry 1). The identity of **7** was unequivocally established by synthesizing **7** in two steps from 3-bromo-2-chloropyridine.[13]

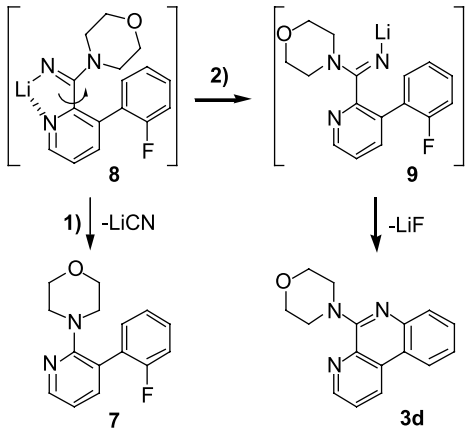


Entry	Additive	3d	7
1	No additive	80%	20%
2	5 equiv CsF	80%	20%
3	5 equiv LiCl	94%(88%)[a]	6%

Product ratio determined from GC-MS. a) Isolated yield

Scheme 8. Addition of lithium morpholide to **4d**.

Penney[14] reported the synthesis of aminopyridines via the addition of lithium amides to cyanopyridines, and we speculate that **7** is formed in a similar fashion from the initial adduct **8** (see Scheme 9) where the lithium presumably is coordinated to the pyridine nitrogen. This intermediate can then proceed via two different pathways: (1) elimination of LiCN to produce **7**, and (2) 'decoordination' of the lithium to the pyridine nitrogen leading to intermediate **9**, which then produces **3d** via intramolecular nucleophilic aromatic substitution of the fluorine. Penney reported that CsF promotes the formation of aminopyridines in the reaction, but we did not see any effect of CsF (see Scheme 8, entry 2). Encouraged by the effect of LiCl in the synthesis of **3a**, we though that LiCl might also have an effect on the course of this reaction as excess LiCl should



Scheme 9. Addition of lithium morpholide to **4d**.

promote the formation of intermediate **9**. Running the experiment with 5 equiv LiCl did indeed improve the ratio between **3d** and **7** to 94:6 (see Scheme 8, entry 3) and **3d** was subsequently isolated in 88% yield.

3. Conclusion

A short, convergent and high yielding synthetic approach to four isomeric azaphenanthridines has been developed. We are currently exploring the scope of this approach to the synthesis of other heterocyclic phenanthridine systems.

4. Experimental

4.1. General

All reactions involving air- and moisture sensitive reagents were performed under N_2 using syringe-septum cap techniques. All glassware was flame dried under vacuum prior to use. THF was distilled from Na/Benzophenone. LiCl was flame dried under vacuum. All other chemicals were used as received from commercial suppliers.

4.1.1. 2-(2-Fluorophenyl)nicotinonitrile (4a). A 100 mL Schlenk-flask was charged with 2-chloro-nicotinonitrile (**5a**) (1.39 g, 10 mmol), 2-(2-fluorophenyl)-5,5-dimethyl-[1,3,2]dioxaborinane[5] (2.50 g, 12.0 mmol), K_3PO_4 (4.25 g, 20.0 mmol), $Pd(PPh_3)_4$ (0.58 g, 5 mol%), then evacuated and refilled with N_2 three times before 1,4-dioxane (50 mL) was added. The reaction was stirred at 80 °C overnight, cooled to rt, evaporated on Celite and purified by FC to give 1.89 g **4a** as off white crystals (95%). Mp (heptane/EtOAc) 74–76 °C. R_f (heptane/EtOAc 3:1) 0.23. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.86 (1H, dd, J=5.0, 1.7 Hz), 8.08 (1H, dd, J=7.9, 1.7 Hz), 7.58 (1H, td, J=7.5, 1.8 Hz), 7.53–7.45 (m, 1H), 7.42 (1H, dd, J=7.9, 5.0 Hz), 7.30 (1H, td, J=7.5, 1.1 Hz), 7.21 (1H, d, J=8.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.6 (J_{C-F}=250 Hz), 157.1, 152.6, 140.7, 132.0 (J_{C-F}=8 Hz), 131.2 (J_{C-F}=3 Hz), 125.5 (J_{C-F}=14 Hz), 124.5 (J_{C-F}=4 Hz), 122.2, 116.4, 116.3 (J_{C-F}=22 Hz), 110.4. Anal. Calcd for $C_{12}H_7FN_2$: C, 72.72; H, 3.56; N, 14.13. Found C, 72.58; H, 3.76; N, 14.35.

4.2. General procedure for the synthesis of 5b–5d

In a flame dried 250 mL Schlenk-flask 2,2,6,6-tetramethylpiperidine (5.06 mL, 30 mmol) was dissolved in dry THF (50 mL) under N_2 and cooled to −30 °C before *n*-BuLi (30 mmol) was added via syringe over 2 min. The mixture was stirred at −30 °C for 5 min then cooled to −78 °C before $B(O^iPr)_3$ (8.08 mL, 35 mmol) was added via syringe over 2 min. The mixture was stirred at −78 °C for 5 min before the cyanopyridine (2.60 g, 25 mmol) dissolved in dry THF (50 mL) was added via syringe over 5 min. The reaction was left in the dry ice bath overnight slowly reaching rt. The reaction was quenched with glacial acetic acid (2.0 mL, 35 mmol) followed by addition of 2,2-dimethyl-1,3-propandiol (3.91 g, 37.5 mmol). The mixture was stirred for 1 h at rt then poured into 10% KH_2PO_4(aq) (75 mL). The water phase was extracted with CH_2Cl_2 (4× 50 mL) and the combined organic phase was washed with water (4×15 mL). The organic phase was dried ($MgSO_4$) and evaporated to give the crude product.

4.2.1. 3-(5,5-Dimethyl-[1,3,2]dioxaborinan-2-yl)isonicotinonitrile (5b). Following the general procedure, isonicotinonitrile yielded 4.32 g **5b** as analytically pure dark-red crystals (80%). Recrystallization from heptane/EtOAc gave white crystals. Mp 125–127 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.08 (1H, d, J=0.8 Hz), 8.76 (1H, d, J=5.1 Hz), 7.51 (1H, dd, J=5.1, 0.9 Hz), 3.84 (4H, s), 1.06 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.9, 151.5, 126.4, 124.5, 117.1, 72.5, 31.9, 21.9. Anal. Calcd for $C_{11}H_{13}BN_2O_2$: C, 61.15; H, 6.07; N, 12.97. Found C, 61.39; H, 5.86; N, 12.98.

4.2.2. 4-(5,5-Dimethyl-[1,3,2]dioxaborinan-2-yl)nicotinonitrile (5c). Following the general procedure, nicotinonitrile yielded 2.81 g **5c** as analytically pure dark-brown crystals (52%). Recrystallization from heptane/EtOAc gave off white crystals. Mp 96–98 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.88 (1H, d, J=0.7 Hz), 8.74 (1H, d, J=4.9 Hz), 7.77 (1H, dd, J=4.9, 0.7 Hz), 3.84 (4H, s), 1.05 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.8, 151.3, 128.2, 117.2, 113.1, 72.3, 31.7, 21.6. Anal. Calcd for $C_{11}H_{13}BN_2O_2$: C, 61.15; H, 6.07; N, 12.97. Found C, 60.85; H, 5.80; N, 13.26.

4.2.3. 3-(5,5-Dimethyl-[1,3,2]dioxaborinan-2-yl)picolinonitrile (5d). Following the general procedure, pyridine-2-carbonitrile yielded 5.08 g **5d** as analytically pure dark-brown crystals (94%). Recrystallization from heptane/EtOAc gave white crystals. Mp 47–49 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.69 (1H, dd, J=5.0, 1.7 Hz), 8.16 (1H, dd, J=7.7, 1.7 Hz), 7.44 (1H, dd, J=7.7, 5.0 Hz), 3.83 (4H, s), 1.05 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.5, 142.7, 137.2, 125.6, 117.6, 72.2, 31.6, 21.5. Anal. Calcd for $C_{11}H_{13}BN_2O_2$: C, 61.15; H, 6.07; N, 12.97. Found C, 60.93; H, 6.15; N, 12.85.

4.3. General procedure for the synthesis of 4b–4d

A Schlenk-flask was charged with the cyanopyridylboronic ester, 1-fluoro-2-iodobenzene (1.2 equiv), CsF (2 equiv), CuI (0.1 equiv), $Pd(PPh_3)_4$ (0.05 equiv), evacuated and refilled with N_2 three times. 1,4-Dioxane (4 mL/mmol) was added and the reaction was stirred vigorously under N_2 at 60 °C for 5 h. The reaction was quenched with water (4 mL/mmol) and the water phase was extracted with EtOAc (3× 20 mL), the organic phase was dried ($MgSO_4$), evaporated on Celite and purified by FC.

4.3.1. 3-(2-Fluorophenyl)isonicotinonitrile (4b). Following the general procedure, **5b** (1.94 g, 9.0 mmol) yielded 1.41 g **4b** as white crystals (79%). Mp (heptane/EtOAc) 50–52 °C. R_f (heptane/EtOAc 3:1) 0.25. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.84 (1H, s), 8.79 (1H, d, J=5.0 Hz), 7.65 (1H, dd, J=5.0, 0.7 Hz), 7.56–7.48 (1H, m), 7.45 (1H, td, J=7.5, 1.8 Hz), 7.32 (1H, td, J=7.5, 1.2 Hz), 7.28–7.23 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.5 (J_{C-F}= 249 Hz), 151.5 (J_{C-F}=2 Hz), 149.4, 133.2, 131.8 (J_{C-F}= 8 Hz), 131.1 (J_{C-F}=2 Hz), 125.7, 124.8 (J_{C-F}=4 Hz), 122.2 (J_{C-F}=15 Hz), 120.5, 116.4 (J_{C-F}=22 Hz), 115.7. Anal. Calcd for $C_{12}H_7FN_2$: C, 72.72; H, 3.56; N, 14.13. Found C, 72.42; H, 3.58; N, 13.92.

4.3.2. 4-(2-Fluorophenyl)nicotinonitrile (4c). Following the general procedure, **5c** (1.51 g, 7.0 mmol) yielded 832 mg **4c** as white crystals (60%). Mp (heptane/EtOAc) 102–103 °C. R_f (heptane/EtOAc 3:1) 0.29. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.96 (1H, s), 8.82 (1H, d, J= 5.2 Hz), 7.55–7.45 (3H, m), 7.30 (1H, td, J=7.6, 1.2 Hz), 7.24 (1H, td, J=8.8, 1.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2 (J_{C-F}=251 Hz), 153.5, 152.6, 147.1, 132.3 (J_{C-F}= 8 Hz), 130.7 (J_{C-F}=2 Hz), 125.0 (J_{C-F}=2 Hz), 124.9 (J_{CF}=4 Hz), 123.3 (J_{C-F}=14 Hz), 116.6 (J_{C-F}=22 Hz), 116.1, 110.1. HRMS $[M+H]^+$ calcd for $C_{12}H_7FN_2$: 199.0672, found: 199.0643.

4.3.3. 3-(2-Fluorophenyl)picolinonitrile (4d). Following the general procedure, **5d** (4.75 g, 22.0 mmol) yielded 3.49 g **4d** as white crystals (80%). Mp (heptane/EtOAc) 89–90 °C. R_f (heptane/EtOAc 3:1) 0.24. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.74 (1H, dd, J=4.7, 1.2 Hz), 7.88 (1H, d, J= 8.2 Hz), 7.60 (1H, dd, J=7.6, 4.7 Hz), 7.55–7.43 (2H, m), 7.30 (1H, td, J=7.6, 1.2 Hz), 7.21 (1H, d, J=8.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.3 (J_{C-F}=249 Hz), 149.9, 138.7 (J_{C-F}=2 Hz), 136.4, 133.2, 131.7 (J_{C-F}=8 Hz), 131.1(J_{C-F}=2 Hz), 126.5, 124.7 (J_{C-F}=4 Hz), 123.0 (J_{C-F}=15 Hz), 116.5, 116.3 (J_{C-F}=22 Hz). Anal. Calcd for $C_{12}H_7FN_2$: C, 72.72; H, 3.56; N, 14.13. Found C, 72.54; H, 3.71; N, 14.00.

4.4. General procedure for the reaction of 4a–d with lithium morpholide

In a flame dried Schlenk-flask under N_2 at rt, morpholine (1.2 equiv) was dissolved in dry THF (2 mL/mmol). *n*-BuLi (1.2 equiv) was added and the mixture was stirred for 5 min before the biaryl (**3a–d**) dissolved in dry THF (1 mL/mmol) was added. The mixture was heated to reflux for 30 min. After cooling, the reaction was quenched with satd NH_4Cl (aq) (20 mL) and extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$), evaporated on Celite and purified by FC.

4.4.1. 6-Morpholino-10-azaphenanthridine (3a). Following the general procedure, with the addition of dry LiCl (5 equiv) **4a** (396 mg, 2.0 mmol) yielded 413 mg **3a** as

white crystals (84%). Mp (heptane/EtOAc) 111–112 °C. R_f (heptane/EtOAc 2:1) 0.37. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.08 (1H, dd, J=4.1, 1.8 Hz), 8.96 (1H, dd, J=8.2, 1.8 Hz), 8.43 (1H, dd, J=8.2, 1.8 Hz), 7.94 (1H, d, J=8.2 Hz), 7.73 (1H, td, J=8.2, 1.2 Hz), 7.56 (1H, t, J=7.6 Hz), 7.53 (1H, dd, J=8.2, 4.1 Hz), 4.00 (4H, t, J=4.7 Hz), 3.51 (4H, t, J=4.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 152.3, 151.0, 145.4, 134.1, 130.5, 127.9, 125.4, 123.8, 123.6, 121.6, 116.3, 67.1, 51.9. Anal. Calcd for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.85. Found C, 72.44; H, 5.90; N, 15.86.

4.4.2. 6-Morpholino-9-azaphenanthridine (3b). Following the general procedure, **4b** (991 mg, 5.0 mmol) yielded 1.27 g **3b** as yellow crystals (95%). Mp (heptane/EtOAc) 124–125 °C. R_f (heptane/EtOAc 3:1) 0.16. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.97 (1H, s), 8.80 (1H, d, J=5.9 Hz), 8.54 (1H, dd, J=8.2, 1.8 Hz), 7.95 (1H, dd, J=8.2, 1.2 Hz), 7.90 (1H, dd, J=5.9, 1.2 Hz), 7.70 (1H, td, J=7.0, 1.2 Hz), 7.57 (1H, td, J=8.2, 1.8 Hz), 4.01 (4H, t, J=4.7 Hz), 3.54 (4H, t, J=4.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.1, 147.5, 145.7, 143.9, 129.6, 129.0, 128.7, 125.77, 124.9, 121.2, 120.5, 118.4, 67.0, 51.4. Anal. Calcd for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.85. Found C, 72.21; H, 5.66; N, 15.68.

4.4.3. 6-Morpholino-8-azaphenanthridine (3c). Following the general procedure, except the mixture was heated at reflux for 24 h, **4c** (793 mg, 4.0 mmol) yielded 1.03 g **3c** as yellow crystals (97%). Mp (heptane/EtOAc) 134–136 °C. R_f (heptane/EtOAc 3:1) 0.29. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.48 (1H, s), 8.83 (1H, d, J=5.3 Hz), 8.36 (1H, d, J=7.6, 1.2 Hz), 8.27 (1H, d, J=5.9 Hz,), 7.92 (1H, dd, J=8.2, 1.2 Hz), 7.72 (1H, td, J=7.0, 1.2 Hz), 7.51 (1H, td, J=8.2, 1.2 Hz), 4.01 (4H, t, J=4.7 Hz), 3.57 (4H, t, J=4.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 150.0, 148.2, 145.2, 140.4, 131.2, 128.7, 125.4, 122.6, 120.5, 116.0, 115.9, 67.0, 52.0. HRMS $[M+H]^+$ calcd for $C_{16}H_{15}N_3O$: 266.1293, found: 266.1293.

4.4.4. 6-Morpholino-7-azaphenanthridine (3d). Following the general procedure, with the addition of dry LiCl (5 equiv) **4d** (198 mg, 1.0 mmol) yielded 233 mg **3d** as yellow crystals (88%). Mp (heptane/EtOAc) 104–105 °C. R_f (heptane/EtOAc 3:1) 0.20. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.89 (1H, dd, J=4.1, 1.8 Hz), 8.77 (1H, dd, J=8.8, 1.8 Hz), 8.27 (1H, dd, J=8.2, 1.2 Hz), 7.89 (1H, d, J=8.2 Hz), 7.66–7.60 (2H, m), 7.43 (1H, td, J=7.0, 1.2 Hz), 4.03 (8H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.2, 148.1, 143.5, 137.7, 130.9, 130.0, 129.6, 128.0, 124.6, 124.3, 121.8, 121.0, 67.2, 50.3. Anal. Calcd for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.85. Found C, 72.15; H, 5.53; N, 15.75.

4.4.5. 2-(2-Morpholinophenyl)nicotinonitrile (6). A 5 mL vial for septum capping was charged with **4d** (180 mg, 0.91 mmol) and morpholine (3 mL, 35 mmol), capped and heated in a Biotage Initiator™ microwave system for 1 h at 225 °C. After cooling, the reaction was poured into satd NH_4Cl (aq) (15 mL) and CH_2Cl_2 (15 mL) and the organic phase was washed with satd NH_4Cl (aq) (2×15 mL) and the water phase was back extracted with CH_2Cl_2 (10 mL). The combined organic phases were dried ($MgSO_4$), evaporated on Celite and purified by FC to give 186 mg **6** as a white solid (78%). Mp (Et_2O) 133–134 °C. R_f (heptane/EtOAc 3:1) 0.18. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.86 (1H, dd, J=4.9, 1.7 Hz), 8.04 (1H, dd, J=7.8, 1.7 Hz), 7.45 (td, 1H, J=7.7, 1.7 Hz), 7.39 (1H, dd, J=7.2, 1.7 Hz), 7.36 (1H, dd, J=7.7, 5.0 Hz), 7.25–7.15 (2H, m), 3.55 (4H, t, J=4.4 Hz), 2.82 (4H, t, J=4.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.3, 152.6, 150.4, 140.1, 132.8, 130.9, 130.5, 123.9, 121.2, 119.4, 117.3, 110.9, 66.8, 51.9. Anal. Calcd for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84. Found C, 72.43; H, 5.77; N, 15.54.

4.4.6. 3-(2-Fluorophenyl)-2-morpholinopyridine (7). A 25 mL flask was charged with 3-bromo-2-chloropyridine (962 mg, 5.0 mmol), morpholine (871 mg, 10 mmol), K_2CO_3 (1.66 g, 12 mmol) and DMF (20 mL). The reaction was stirred overnight at 130 °C. After cooling to rt the reaction was poured into satd NH_4Cl (aq) (50 mL) and Et_2O (50 mL). The DMF-water phase was extracted with Et_2O (3×20 mL) and the combined organic phase was dried ($MgSO_4$), evaporated on Celite and purified by FC to give 840 mg 3-bromo-2-morpholinopyridine as white crystals (70%). Mp 94–95 °C. R_f (heptane/EtOAc 3:1) 0.42. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22 (1H, dd, J=4.7, 1.6 Hz), 7.78 (1H, dd, J=7.7, 1.6 Hz), 6.78 (1H, dd, J=7.7, 4.7 Hz), 3.89–3.84 (4H, m), 3.36–3.31 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 146.3, 142.2, 118.6, 112.7, 66.8, 49.9. Anal. Calcd for $C_9H_{11}BrN_2O$: C, 44.47; H, 4.56; N, 11.52. Found C, 44.47; H, 4.47; N, 11.44.

A Schlenk-flask was charged with 3-bromo-2-morpholinopyridine (729 mg, 3.0 mmol), 2-(2-fluorophenyl)-5,5-dimethyl-[1,3,2]dioxaborinane[5] (811 mg, 3.9 mmol), $Pd(PPh_3)_4$ (104 mg, 3 mol%) and evacuated and refilled with N_2 three times. Toluene (15 mL), EtOH (3 mL), 2 M K_2CO_3 (aq) (3 mL) was added and the reaction was stirred at 100 °C for 3 h. After cooling the mixture was poured into water (30 mL) and the water phase was extracted with CH_2Cl_2 (3×20 mL), dried ($MgSO_4$), evaporated on Celite and purified on FC to give 642 mg **7** as a colourless oil (83%). R_f (heptane/EtOAc 3:1) 0.27. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (1H, dd, J=4.8, 1.8 Hz), 7.54–7.47 (2H, m), 7.38–7.29 (1H, m), 7.20 (1H, m), 7.16 (1H, m), 6.94 (1H, dd, J=7.5, 4.9 Hz), 3.59 (4H, t, J=4.7 Hz), 3.13 (4H, t, J=4.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.5, 159.2 (J_{C-F}=248 Hz), 147.0, 140.7, 130.7 (J_{C-F}=3 Hz), 129.6 (J_{C-F}=8 Hz), 127.1 (J_{C-F}=15 Hz), 124.5 (J_{C-F}=4 Hz), 121.4, 116.7, 116.4 (J_{C-F}=22 Hz), 66.9, 49.4. Anal. Calcd for $C_{15}H_{15}FN_2O$: C, 69.75; H, 5.85; N, 10.85. Found C, 69.38; H, 5.84; N, 10.23.

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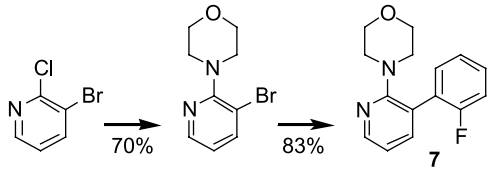

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Co-catalyzed autoxidation of alkene in the presence of silane. The effect of the structure of silanes on the efficiency of the reaction and on the product distribution

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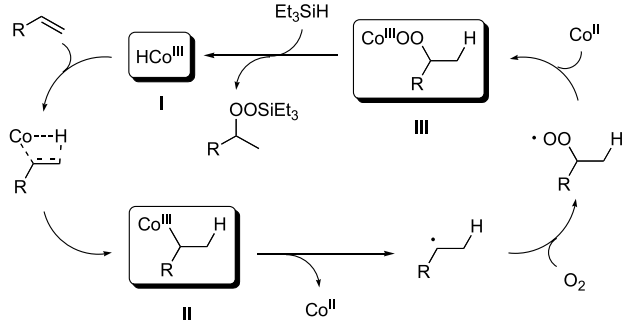
Abstract—A systematic investigation of the structural effect of silanes on the Co-catalyzed reductive oxygenation of alkene in the presence of silane (Mukaiyama–Isayama reaction) showed that the efficiency of the reaction decreases with the increase of the steric bulk of the silanes. A similar trend was observed for the metal-exchange reaction between Co(III)–alkylperoxo complex and silane, too. The peroxidation of (*S*)-limonene, followed by deprotection of the derived silyl peroxides, provides a mixture of the corresponding monocyclic hydroperoxide **24** and the bicyclic one **25**, the ratio being a marked function of the steric bulk of silanes.

1. Introduction

Much attention has been focused on selective oxygenations of the C=C double bond moiety by molecular oxygen.[1] Of these, Mukaiyama–Isayama reaction would be the most promising from the view of synthesis of the corresponding *sec*- and *tert*-alkyl hydroperoxides. They have reported that autoxidation of alkenes catalyzed by bis(1,3-diketonato)-cobalt(II) in the presence of triethylsilane (Et_3SiH) provides the corresponding triethylsilyl peroxides in high yield.[2,3] By treatment with one drop of concd HCl in MeOH, the triethylsilyl peroxides are easily desilylated to give the corresponding hydroperoxides. On the basis of a novel catalytic role of Co(III)–alkylperoxo complex **III** and Co(III)–alkyl complex **II** in the same peroxidation reaction of alkene with molecular oxygen and Et_3SiH, we have proposed a mechanism involving the Co(III)–hydride complex **I**, which would be produced by metal exchange between Co(III)–alkylperoxo complex **III** and silane (Scheme 1).[4] As a further insight, we report herein, that the steric bulk of silanes plays an important role in efficiency of both the peroxidation of alkene and the metal exchange between the isolated Co(III)–alkylperoxo complex and silane. In the synthesis of the antimalarial bicyclic peroxide from limonene, a similar substituent effect of silanes is observed.



Scheme 1. A proposed mechanism for Mukaiyama–Isayama reaction.

2. Results and discussion

2.1. Co(II)-catalyzed autoxidation of 3-methyl-3-butenyl benzoate in the presence of a series of silanes

We conducted bis(1-morpholinocarbamoyl-4,4-dimethyl-1,3-pentanedionato)cobalt(II) ($Co(modp)_2$)-catalyzed autoxidation of 3-methyl-3-butenyl benzoate **1** in the presence of a series of silanes **2a**–**g** in 1,2-dichloroethane (DCE) at room

Keywords: Co-catalyzed autoxidation; Silyl peroxide; Yingzhaosu A analogue; Antimalarial activity.
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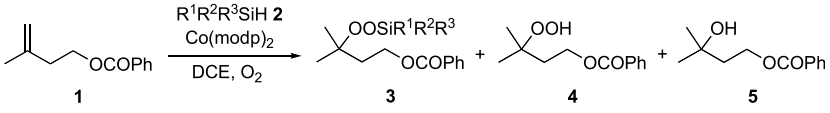
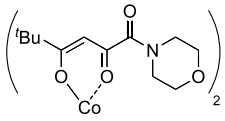
Table 1. Co(II)-catalyzed autoxidation of alkene **1** in the presence of silane[a]

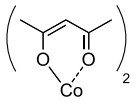


Run	Silane **2** (BDE, kcal/mol)[b]	Reaction time (h)	Conv. (%)	Products (%)		
				3	**4**	**5**
1	**a**: $PhSiH_3$ (88.2)	2	100		23	64
2	**b**: $PhMeSiH_2$	2	100		69	13
3	**c**: $PhMe_2SiH$	2	100	72	22	3
4	**d**: Et_3SiH (90.1)	2	100	89		
5[c]	**d**: Et_3SiH	3.5	95	80	5	9
6	**e**: Ph_2MeSiH	4	75	87		4
7	**f**: Ph_3SiH (83.0)	4	4[d]			
8	**g**: $^iPr_3SiH$	18	13[d]			

[a] The reaction of alkene **1** was undertaken in the presence of $Co(modp)_2$ (5 mol%) and a silane (2 equiv) at room temperature.
[b] BDE, bond dissociation energy, which was taken from the data in Ref. 10.
[c] $Co(acac)_2$ was used as the catalyst instead of $Co(modp)_2$.
[d] No oxidation product was identified.



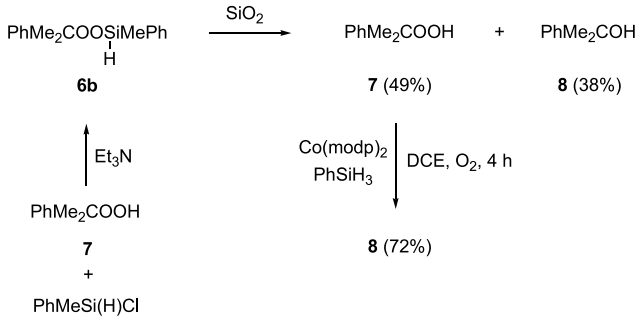
$Co(modp)_2$



$Co(acac)_2$

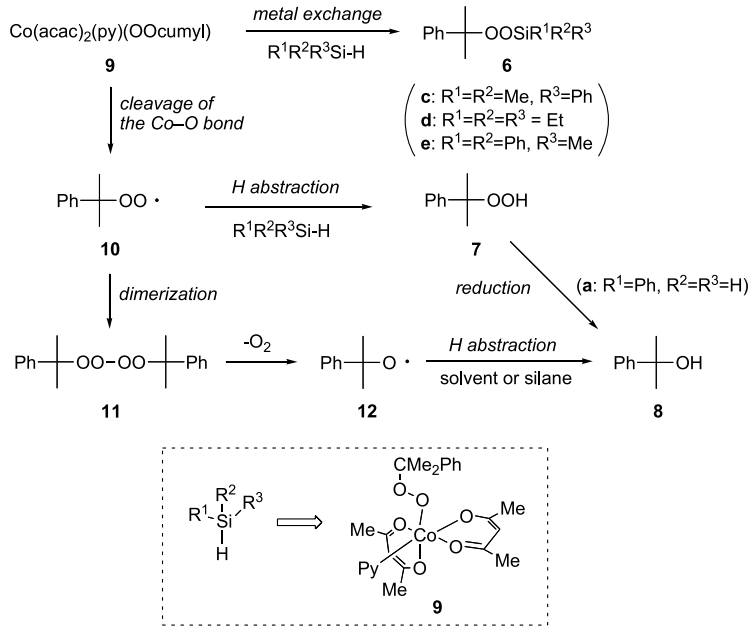
temperature (Table 1). By column chromatography of the crude mixture of products on silica gel, silyl peroxide **3**, hydroperoxide **4** and alcohol **5** were isolated (the yields of the products were calculated based on the consumed alkene **1**). Consistent with the result found by Isayama and Mukaiyama, $Co(modp)_2$- or $Co(acac)_2$-catalyzed peroxidation of **1** in the presence of Et_3SiH proceeded smoothly and regioselectively, affording the corresponding triethylsilyl peroxide **3d** in high yield (runs 4 and 5).[4] A similar trend was observed for $PhMe_2SiH$ **2c** (run 3). In the case of more bulky Ph_2MeSiH **2e** also the silyl peroxide **3e** was the major product (run 6), although the reaction rate was significantly slower than that in the presence of **2c** or **2d**. In the case of $PhSiH_3$ **2a** or $PhMeSiH_2$ **2b** the autoxidation proceeded smoothly. However, the isolated products were only hydroperoxide **4** and alcohol **5**; the corresponding silyl peroxide **3** was not isolated.[5] When the autoxidation was undertaken in the presence of the most bulky Ph_3SiH **2f** or $(isopropyl)_3SiH$ **2g**, no evidence was obtained for the formation of oxidation product. These results demonstrate that the structure of silane **2** plays an important role in determining both the efficiency of autoxidation[5a] and the product distribution.[5b]

Selective isolation of hydroperoxide **4** and alcohol **5** from the reaction of alkene **1** in the presence of $PhSiH_3$ **2a** or $PhMeSiH_2$ **2b** is discussed first. We thought that the corresponding silyl peroxide **3a** or **3b** is certainly produced by transmetallation between the corresponding Co(III)–alkylperoxo complex and the silane **2** (Scheme 1). This was confirmed by the measurement of the ^1H NMR spectrum of the crude product obtained from the reaction in the presence of $PhMeSiH_2$ **2b**; the silyl peroxide **3b** was found to be the major product. During column chromatography on silica gel or alumina, however, the decomposition occurred easily, thereby providing only hydroperoxide **4** and alcohol **5**. Exactly the same trend was observed for the reaction in the presence of $PhSiH_3$ **2a**. Consistent with this, treatment of (2-phenylpropan-2-ylperoxy)methyl(phenyl)silane **6b**, prepared by the reaction of cumyl hydroperoxide and PhMeSi(H)Cl in the presence of Et_3N,[6] also decomposed during the column chromatography on silica gel to give a mixture of hydroperoxide **7** (49%) and alcohol **8** (38%) (Scheme 2). In addition, the reaction of the hydroperoxide **7** with $PhSiH_3$ **2a** in the presence of a catalytic amount of $Co(modp)_2$ resulted in the complete decomposition into alcohol **8** (72%) (Scheme 2).



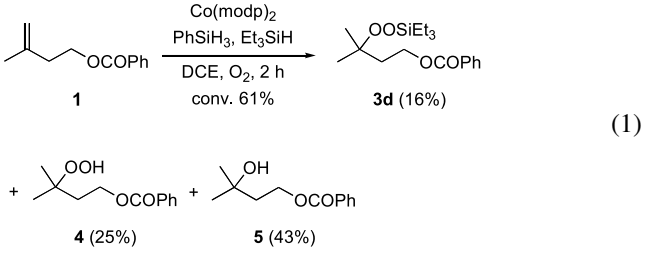
Scheme 2. Decomposition of silyl peroxide **6b** and hydroperoxide **7**.

The reaction in the presence of bulky Ph_3SiH **2f** or $(isopropyl)_3SiH$ **2g** did not give any oxidation product. This leads us to deduce that the difference in steric crowding rather than the difference in Si–H bond strength determines the efficiency of Mukaiyama–Isayama reaction. To obtain more clear-cut evidence for the effect of the steric bulk of silane on the reaction rate, we undertook a competitive reaction between $PhSiH_3$ **2a** and bulkier Et_3SiH **2d**. Since the products from the reaction with $PhSiH_3$ **2a** are hydroperoxide **4** and alcohol **5** and, in contrast, the reaction with Et_3SiH **2d** gives exclusively the silyl peroxide **3d**, it is reasonable to consider that the product composition (**4**+**5**)/**3d** indicates the relative reactivity between **2a** and **2d**. When the reaction of alkene **1** was undertaken in the



Scheme 3. The decomposition course of Co(III)–alkylperoxo complex **9** in the presence of silane.

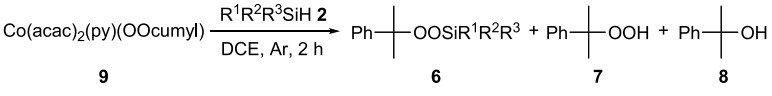
presence of **2a** and **2d** (2 mol equiv in each silane), a mixture of silyl peroxide **3d**, hydroperoxide **4** and alcohol **5** were obtained in yields of 16, 25 and 43%, respectively. In this respect, treatment of silyl peroxide **3d** with $PhSiH_3$ (2 mol equiv) in the presence of $Co(modp)_2$ (5 mol%) under an oxygen atmosphere for 2 h resulted in the complete recovery of **3d**, suggesting that silyl peroxide **3d** is stable under the reaction conditions. Thus, the (**4**+**5**)/**3d** ratio of 4:1 observed in the competitive reaction (Eq. 1) demonstrates that the reactivity of the relatively smaller $PhSiH_3$ **2a** is much larger than that of Et_3SiH **2d**.



(1)

Thus, we found that the steric bulk of silane is an important factor in determining the efficiency of the Mukaiyama–Isayama reaction. The origin would be that the Co(III)–alkylperoxo complex **III** is highly crowded and, therefore, approach of the sterically congested silane is quite difficult. To confirm this, we prepared the pyridine-coordinated Co(III)–alkylperoxo complex **9** (the structure of the *tert*-butylperoxo complex similar to **9** has been unambiguously determined by the X-ray analysis; see Scheme 3[7]) and tried the reaction with a series of silanes (Table 2). It would be reasonable to expect that the pyridine-coordinated complex **9** is more crowded than the relevant complex **III** generated during the Mukaiyama–Isayama reaction and, therefore, a larger steric effect would be observed in the metal exchange reaction between **9** and a silane. In connection with this, Talsi and his co-workers[8] have found that $Co(acac)_2$-$(OOCMe_2Ph)Py$ **9** is stable in the solid state (one month when kept at 0 °C) and in contrast, it decomposes very easily in organic solvents (in benzene $\tau_{1/2}=8$ h; in $CDCl_3$ $\tau_{1/2}=3$ h at 20 °C). By MS and ^1H NMR spectra, the volatile products in decomposition have been found to be cumyl alcohol,

Table 2. The reaction of Co(III)–alkylperoxy complex **9** with a silane[a]



Run	Silane **2**	Products (%)		
		6	**7**	**8**
1	**a**: $PhSiH_3$			54
2	**c**: $PhMe_2SiH$	37	5	19
3	**d**: Et_3SiH	23	24	26
4[b]	**d**: Et_3SiH	60		33
5	**e**: Ph_2MeSiH	15	18	38
6	**f**: Ph_3SiH		58	37
7	**g**: $^iPr_3SiH$		54	27
8	None			42

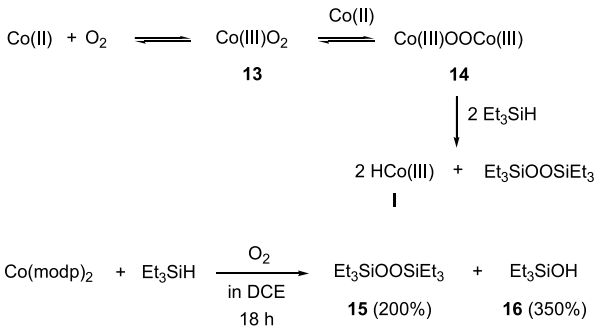
[a] Unless otherwise noted, the reaction was conducted in the presence of 2 mol equiv of a silane.
[b] The reaction in the presence of 20 mol equiv of the silane.[4]

acetophenone, acetylacetone, and pyridine (the yields have not been determined). Also, they have found that $Co(acac)_3$ is the main cobalt-containing product. We repeated the decomposition of **9** in DCE under an Ar atmosphere and found that only alcohol **8** was obtained in 42% yield (Table 2, run 8). In the presence of a silane, however, silyl peroxide **6** and hydroperoxide **7** were obtained together with alcohol **8**. Moreover, the product distribution is a marked function of the structure of silanes. Thus, in the case of the silane $PhMe_2SiH$ **2c** (run 2), Et_3SiH **2d** (run 3) or Ph_2MeSiH **2e** (run 5) the corresponding silyl peroxide **6** was certainly obtained, together with hydroperoxide **7** and alcohol **8**. When the reaction was performed in the presence of more bulky silane such as Ph_3SiH **2f** (run 6) or $(isopropyl)_3SiH$ **2g** (run 7), however, only a mixture of hydroperoxide **7** and alcohol **8** was obtained.

A reasonable mechanism for the formation of silyl peroxide **6**, hydroperoxide **7**, and alcohol **8** from the pyridine-coordinated Co(III)–alkylperoxo complex **9** is shown in Scheme 3. A probable mechanism for the formation of alcohol **8** in the absence of silane is discussed first. In solution the cleavage of the Co–O bond of the peroxo complex **9** is known to occur very easily yielding the cumylperoxyl radical **10** as determined by the measurement of ESR spectrum.[8] The reasonable mode of decay of the peroxyl radical **10** is dimerization to give the tetroxide **11**, which in turn ejects oxygen molecule to give the alkoxyl radical **12**.[9] Finally, the highly reactive oxy-radical **12** abstracts a hydrogen atom from solvent etc., thereby providing the corresponding alcohol **8** (Scheme 3).

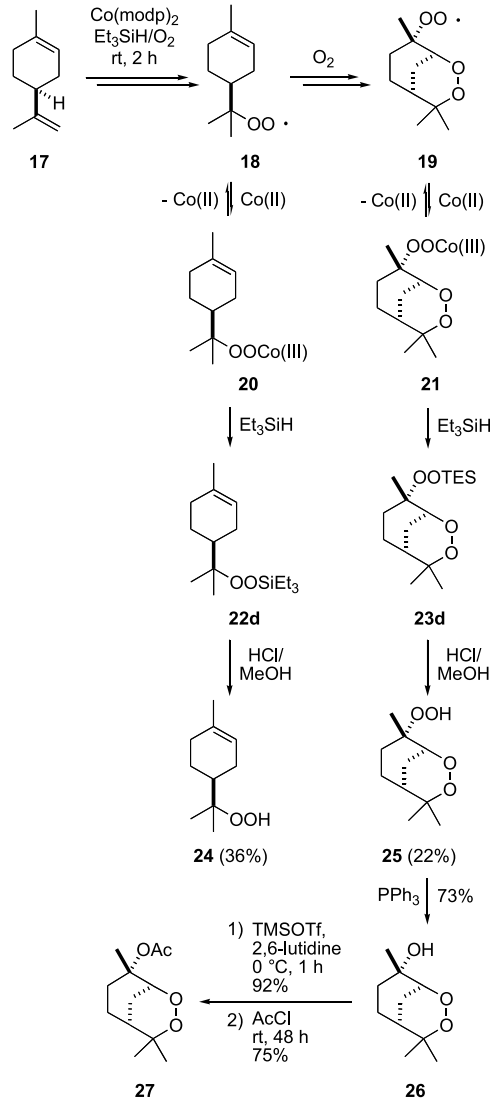
The formation of silyl peroxide **6** from the reaction with 2 mol equiv of silanes such as $PhMe_2SiH$ **2c**, Et_3SiH **2d** and Ph_2MeSiH **2e** may suggest that even in the case of the pyridine-coordinated Co(III)–alkylperoxy complex **9** metal exchange is possible to occur albeit inefficiently. When **9** was treated with 20 equiv of Et_3SiH, however, the corresponding triethylsilyl peroxide **6** was obtained in a substantial yield of 60%, together the alcohol **8** (33%) (Table 2, run 4).[4] Since the metal exchange reaction between **9** and silane is a slow process, cleavage of the Co–O bond competitively occurs to yield the peroxyl radical **10**, which in turn abstracts hydrogen from silanes **2** to give the hydroperoxide **7**. It should be noticed that the Si–H bond dissociation energies (BDE) of silanes (Table 2) are similar to that of the O–H bond of ROOH (ca. 89 kcal/mol).[10] In the case of the most bulky silanes **2f**,**g**, metal exchange is a disfavored process and, therefore, only the processes involving the formation of the peroxyl radical **10** can contribute, thereby yielding the hydroperoxide **7** and the alcohol **8**.

Thus, as an explanation for the inefficiency of the bulky silanes such as Ph_3SiH **2f** and $(isopropyl)_3SiH$ **2g** in the Mukaiyama–Isayama reaction, we propose slow metal exchange between the Co(III)–alkylperoxo complex **III** and the bulky silane. However, a similar but alternative explanation would be possible. That is, the initiation step leading to the formation of Co(III)–hydride complex **I** may be also difficult in the case of the bulky silanes, **2f** and **2g**. It is well known that Co(II) complexes such as $Co(acac)_2$ are oxidized by molecular oxygen to afford the corresponding



Scheme 4. Reaction of Co(II) with silane under an oxygen atmosphere.

superoxocobalt(III) **13** and μ-peroxocobalt(III) **14**.[11] Subsequent transmetallation of μ-peroxocobalt(III) **14** complex with a relatively small Et_3SiH would give the corresponding Co(III)–hydride complex **I** (Scheme 1). This has been confirmed by the fact that treatment of $Co(modp)_2$ with Et_3SiH (38 equiv) under an oxygen atmosphere for 18 h gave $Et_3SiOOSiEt_3$ **15** in 200% yield (based on the $Co(modp)_2$), together with Et_3SiOH **16** (350%) (Scheme 4).[4] The steric bulk of the μ-peroxocobalt(III) **14** is similar



Scheme 5. Peroxidation of (*S*)-limonene (**17**) in the presence of Et_3SiH **2d**.

to that of Co(III)–alkylperoxo complex **III** and, therefore, in the case of bulky silanes the formation of Co(III)–hydride complex **I** in the initiation step would be also quite difficult.

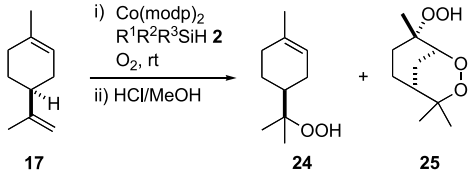
2.2. Preparation of yingzhaosu A analogue from (*S*)-limonene

Finally, the effect of the structure of silanes on the ratio of the monocyclic hydroperoxide **24** and the bicyclic one **25** in the peroxidation of (*S*)-limonene (**17**) is described. We have already reported that the $Co(modp)_2$-catalyzed autoxidation of **17** in the presence of Et_3SiH, followed by deprotection of the derived triethylsilyl peroxides, **22d** and **23d**, provides a mixture of monocyclic hydroperoxide **24** and the bicyclic one **25** in yields of 36 and 22%, respectively.[12] Reduction of **25** with PPh_3 gives the corresponding alcohol **26**, which is in turn acetylated to yield the yingzhaosu A analogue **27** having a remarkable antimalarial activity; the EC_{50} value of **27** (3.0×10^{-9} M) is superior to that of artemisinin, a natural antimalarial (1.0×10^{-8} M). The problem of this procedure is the low yield of the desired bicyclic hydroperoxide **25**, because of the concomitant formation of a larger amount of the monocyclic one **24** (Scheme 5).

As an approach to develop a more improved method in synthesis of the antimalarial acetate **27**, therefore, we investigated the effect of the structure of silanes **2b**,**d**,**e** on the composition of two hydroperoxides, **24** and **25** (Table 3). The $Co(modp)_2$-catalyzed autoxidation of (*S*)-limonene **17** in the presence of $PhMeSiH_2$ **2b** for 2 h gave only the monocyclic hydroperoxide **24** in 48% yield; no formation of the bicyclic one **25** was observed. When the same reaction was repeated in the presence of more bulky Ph_2MeSiH **2e** for 24 h, a mixture of the corresponding silyl peroxides, **22e** and **23e**, were obtained together with a substantial amount of the highly polar unidentified products. Subsequent deprotection gave the desired bicyclic hydroperoxide **25** in a yield of 21%, together with the monocyclic one **24** (14%). This clearly demonstrates that the ratio of **24/25** decreases with the increase in steric bulk of the silanes; $PhMeSiH_2$ **2b** > Et_3SiH **2d** > Ph_2MeSiH **2e**. This notable structural effect of silane on the product distribution would be explained in terms of the decrease in rate of the metal exchange between Co–alkylperoxo complex and silane with the increase in steric bulk of silane. In the case of small $PhMeSiH_2$ **2b**, the transmetallation with the Co–alkylperoxo complex **20**, derived from the regioselective oxidation of the less hindered double bond of (*S*)-limonene **17**, occurs very rapidly and as a result, the monocyclic silyl peroxide **22b** is produced exclusively (reference Scheme 5). In the case of bulky Ph_2MeSiH **2e**, however, the similar metal exchange must be very slow from steric reasons and, therefore, the reversible formation of the peroxyl radical **18** from the alkylperoxo complex **20**, followed by intramolecular cyclization leading to the formation of the bicyclic one **19**, becomes a favorable process. Thus, the bicyclic silyl peroxide **23e** is produced as the major product. From the view of an efficient synthesis of a bicyclic hydroperoxide **25**, however, the reaction in the presence of Ph_2MeSiH **2e** is similar to that in the presence of Et_3SiH **2d**. The former reaction using **2e** is very slow and, therefore, some competitive processes leading to the formation of undesired products seem to contribute in a larger extent (see Section 4).

In Table 4 are shown the in vivo antimalarial activities of the bicyclic acetate **27′**,[12] obtained by peroxidation of (*R*)-limonene (**17′**) and the subsequent transformations shown in Scheme 5, together with the data for artemisinin[13] and yingzhaosu A.[14] It is interesting to note that the activity of **27′** in po administration is very similar to that of artemisinin.

Table 3. Effect of the structure of silanes on the composition of the peroxidation products **24** and **25**



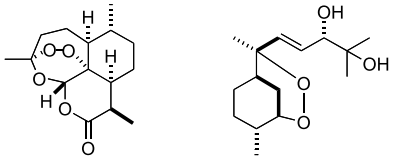
17 24 25

Silane **2**	Reaction time (h)	Yield (%)	
		24	**25**
b: $PhMeSiH_2$	2	48	
d: Et_3SiH	2	36	22
e: Ph_2MeSiH	24	14	21

Table 4. In vivo antimalarial activity of the yingzhaosu A analogue **27′** derived from (*R*)-limonene[a]

Compound	Method of administration	ED_{50} (mg/kg)	ED_{90} (mg/kg)
27′	ip	12	48
	po	38	>50
Artemisinin	ip	5	13
	po	32	89
Yingzhaosu A	sc	250[b]	

[a] ip, intraperitoneal; po, per oral; sc, subcutaneous injection.
[b] Taken from the data in Ref. 14.



artemisinin yingzhaosu A

3. Conclusion

Systematic study of the structural effect of silanes on the Co-catalyzed reductive oxygenation of alkene in the presence of silane (Mukaiyama–Isayama reaction) and on the metal-exchange reaction between Co(III)–alkylperoxo complex and silane demonstrates that the efficiency of both reactions decreases with the increase of the steric bulk of the silanes. Also, the product distributions are significantly influenced by the steric bulk of silanes. The in vivo antimalarial activity of (1*R*),(5*R*),(8*R*)-4,4,8-trimethyl-2,3-dioxabicyclo[3.3.1]nonan-8-yl acetate **27′** derived from (*R*)-limonene is very similar to that of artemisinin, a natural peroxidic antimalarial.

4. Experimental

4.1. General procedures

^{1}H (270 MHz) and ^{13}C (67.5 MHz) NMR spectra were obtained in $CDCl_3$ solution with $SiMe_4$ as the internal standard. Preparation of the cobalt(III) cumyldioxy complex **9** was already reported by Talsi et al.[8] The alkene **1** was prepared by the reported method.[4] Spectral data and elemental analysis of bicyclic acetate **27′** derived from (*R*)-limonene[12] and the method of determination of the in vivo antimalarial activity[13] have been already reported.

4.2. Caution

Since organic peroxides are potentially hazardous compounds, they must be handled with due care; avoid exposure to strong heat or light, or mechanical shock, or oxidizable organic materials, or transition metal ions. No particular difficulties were experienced in handling any of the new peroxides synthesized in this work using the reaction scales and procedures described below together with the safeguard mentioned above.

4.3. Co(modp)$_2$-catalyzed autoxidation of 3-methyl-3-buten-1-yl benzoate (1) in the presence of $PhMe_2SiH$ 2c

Into a two-neck 50 mL flask, charged with dioxygen, alkene **1** (198 mg, 1.04 mmol), Co(modp)$_2$ (27 mg, 0.05 mmol) and DCE (2.5 mL) were added, and then the flask was again charged with dioxygen. $PhMe_2SiH$ **2c** (272 mg, 2.0 mmol) was added via 1.0 mL gas-tight syringe, and the reaction mixture was stirred vigorously under an oxygen atmosphere at room temperature. After stirring for 2 h, the solvent was evaporated under reduced pressure. Hexane (10 mL) was added to the residue, and then the precipitated solid materials were removed by filtration over Celite. After concentration of the filtrate, the components of the residue were separated by column chromatography on silica gel. Elution with diethyl ether/hexane 2:98 gave the silyl peroxides **3c** (270 mg, 72%); the deprotection of the silyl group was easily undertaken by treatment with one portion of concd HCl in methanol for 2 min providing quantitatively the corresponding hydroperoxide **4**. From the second fraction (elution with ether/hexane 10:90) was obtained 3-hydroperoxy-3-methylbutyl benzoate **4**[4] (156 mg, 87%). Subsequent elution with diethyl ether/hexane 30:70 gave 3-hydroxy-3-methylbutyl benzoate **5**[4] (7 mg, 4%).

4.3.1. 3-(Dimethylphenylsilyl)dioxy-3-methylbutyl benzoate (3c). An oil; ^{1}H NMR δ 0.48 (s, 6H), 1.25 (s, 6H), 2.07 (t, J=7 Hz, 2H), 4.37 (t, J=7 Hz, 2H), 7.38–7.46 (m, 5H), 7.55 (t, J=7 Hz, 1H), 7.63 (d, J=7 Hz, 2H), 8.02 (d, J=7 Hz, 2H); ^{13}C NMR δ −2.6, 24.8, 37.3, 61.6, 81.7, 127.6, 128.2, 129.4, 129.8, 130.3, 132.7, 133.7, 136.2, 166.4. Anal. Calcd for $C_{20}H_{26}O_4Si$: C, 67.00; H, 7.31. Found: C, 67.02; H, 7.43.

4.3.2. 3-Hydroperoxy-3-methylbutyl benzoate (4). An oil; ^{1}H NMR δ 1.30 (s, 6H), 2.10 (t, J=7.1 Hz, 2H), 4.48 (t, J=7.1 Hz, 2H), 7.4–7.6 (m, 3H), 8.0–8.1 (m, 2H), 8.79 (br s, 1H); ^{13}C NMR δ 24.44 (2C), 36.57, 61.53, 81.16, 128.24 (2C), 129.39 (2C), 129.90, 132.92, 166.86. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.17; H, 7.25.

4.3.3. 3-Hydroxy-3-methylbutyl benzoate (5). An oil; ^{1}H NMR δ 1.33 (s, 6H), 1.89 (br s, 1H), 1.99 (t, J=6.8 Hz, 2H), 4.51 (t, J=6.8 Hz, 2H), 7.4–7.5 (m, 2H), 7.5–7.6 (m, 1H), 8.0–8.1 (m, 2H); ^{13}C NMR δ 29.78 (2C), 41.73, 61.96, 70.04, 128.27 (2C), 129.37 (2C), 130.05, 132.83, 166.45. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.29; H, 7.75.

4.3.4. Co(modp)$_2$-catalyzed autoxidation of alkene 1 in the presence of $PhMeSiH_2$ 2b. A mixture of alkene **1** (198 mg, 1.04 mmol), Co(modp)$_2$ (27 mg, 0.05 mmol), $PhMeSiH_2$ **2b** (272 mg, 2.0 mmol) in DCE (2.5 mL) were stirred at room temperature under an oxygen atmosphere for 2 h. After conventional work-up as described before, the ^{1}H NMR spectrum of the crude mixture of products was measured, which showed the presence of mainly 3-(methylphenylsilyl)dioxy-3-methylbutyl benzoate (**3b**); ^{1}H NMR δ 0.45 (t, J=4.05 Hz, 3H), 2.07 (t, J=7 Hz, 2H), 1.25 (s, 6H), 4.36 (q, J=4.05 Hz, 2H), 7.4 (m, 3H), 7.6 (m, 2H); ^{13}C NMR δ −7.5, 127.9, 129.4, 133.3, 134.7. However, the silyl peroxide **3b** was labile to the column chromatography on silica gel. Thus, elution with ether/hexane 10:90 gave the hydroperoxide **4** (155 mg, 70%). Subsequent elution with ether/hexane 30:70 gave the alcohol **5** (26 mg, 13%).

4.4. Co(modp)$_2$-catalyzed autoxidation of alkene 1 in the presence of two silanes 2a and 2d

A mixture of alkene **1** (160 mg, 1.1 mmol), Co(modp)$_2$ (27 mg, 0.05 mmol), $PhSiH_3$ **2a** (217 mg, 2.0 mmol), Et_3SiH **2d** (231 mg, 2.0 mmol), and 3,5-dimethylanisole (internal standard, 85 mg, 0.5 mmol) in DCE (2.5 mL) was stirred at room temperature for 2 h under an oxygen atmosphere. After the conventional workup as described above, the products were separated by column chromatography on silica gel. The first fraction (elution with ether/hexane 3:97) gave a mixture of alkene **1**, triethylsilyl peroxide **3d**[4] and 3.5-dimethylanisole (227 mg). By the comparison of the peak areas of the characteristic signals of these compounds in the ^{1}H NMR spectrum, the mixture was determined to contain **1** (145 mg, conv. 61%) and **3d** (34 mg, 16%). Subsequent elution with ether/hexane 10:90 gave hydroperoxide **4** (49 mg, 25%). From the final fraction (elution with ether/hexane 40:60) was obtained alcohol **5** (106 mg, 43%).

4.4.1. Decomposition of silyl peroxide 6b during the column chromatography on silica gel. (2-Phenylpropan-2-ylperoxy)methyl(phenyl)silane (**6b**) was prepared by the reported method.[6] To a solution of triethylamine (2.6 g, 26 mmol), cumyl hydroperoxide (3.6 g, 24 mmol) in hexane (50 mL), was added chloro(methyl)phenylsilane (3.9 g, 25 mmol) in hexane at 0 °C and the mixture was stirred at 0 C for 10 h. After filtration of the solid material over Celite, the residue was concentrated under reduced pressure to leave almost pure **6b** as an oil (1.7 g, 23%); ^{1}H NMR δ 0.55 (d, J=3 Hz, 3H), 1.58 (s, 6H), 5.11 (q, J=3 Hz, 1H), 7.3–7.7 (m, 10H); ^{13}C NMR δ −4.1, 26.4, 84.5, 124.2, 125.2, 125.5, 127.9, 128.5, 130.3, 134.4, 144.7. Then the column

chromatography of **6b** (194 mg, 0.66 mmol) on silica gel was undertaken. Elution with ether/hexane 20:80 gave cumyl hydroperoxide **7** (49 mg, 49%). From the second fraction (elution with ether/hexane 40:60) was obtained alcohol **8** (34 mg, 38%).

4.5. Co(modp)$_2$-catalyzed decomposition of cumyl hydroperoxide 7 in the presence of PhSiH$_3$ 2a

A mixture of hydroperoxide **7** (160 mg, 1.1 mmol), Co(modp)$_2$ (27 mg, 0.05 mmol) and PhSiH$_3$ **2a** (222 mg, 2.1 mmol) in DCE (2.5 mL) was stirred at room temperature for 4 h under an oxygen atmosphere. After the conventional workup, the products were separated by column chromatography on silica gel. Elution with ether/hexane 40:60 gave alcohol **8** (103 mg, 72%).

4.6. Decomposition of the Co(III)–alkylperoxo complex 9 in the presence of PhMe$_2$SiH 2c

To a solution of the complex **9** (245 mg, 0.50 mmol) in DCE (2.0 mL), was added PhMe$_2$SiH **2c** (136 mg, 1.0 mmol). After stirring for 2 h at room temperature under an argon atmosphere, solvent was evaporated under reduced pressure. Hexane (10 mL) was added to the residue, and the precipitated solid materials were removed by filtration over Celite. After concentration of the filtrate, products were separated by column chromatography on silica gel. Elution with ether/hexane 10:90 gave the silyl peroxide **6c** (52 mg, 37%). Subsequent elution with ether/hexane 18:82 gave the hydroperoxide **7** (4 mg, 5%). From the final fraction (elution with ether/hexane 40:60) was obtained the alcohol **8** (13 mg, 19%).

4.6.1. (2-Phenylpropan-2-ylperoxy)dimethyl(phenyl) silane (6c). An oil; ^{1}H NMR δ 0.45 (s, 6H), 1.52 (s, 6H), 7.15–7.42 (m, 8H), 7.62 (m, 2H); ^{13}C NMR δ −2.5, 26.5, 83.9, 125.5, 126.8, 127.8, 129.7, 133.8, 136.5, 145.2. Anal. Calcd for $C_{17}H_{22}O_2Si$: C, 71.28; H, 7.74. Found: C, 71.05; H, 7.74.

4.6.2. Co(modp)$_2$-catalyzed autoxidation of (*S*)-limonene (17) in the presence of PhMeSiH$_2$ 2b. Into a two-necked 50 mL flask, charged with dioxygen, were added (*S*)-limonene (**17**: 272 mg, 2.0 mmol), Co(modp)$_2$ (54 mg, 0.10 mmol), and DCE (5 mL), and then the flask was again charged with dioxygen. PhMeSiH$_2$ **2b** (513 mg, 4.2 mmol) was added via a 1.0 mL gastight syringe, and the reaction mixture was stirred vigorously under an oxygen atmosphere at room temperature for 2 h. After the conventional work-up, the ^{1}H NMR spectrum of the crude mixture of products was measured, which showed the presence of mainly 1-methyl-1-(4-methyl-3-cyclohexenyl)-ethyl methylphenylsilyl peroxide (**22b**); ^{1}H NMR δ 1.19 (s, 6H), 1.20–1.27 (m, 1H), 1.65 (s, 3H), 1.78–2.03 (m, 6H), 5.15 (d, J=2.7 Hz, 3H), 5.24 (q, J=2.7 Hz, 1H), 5.36 (m, 1H), 7.35–7.39 (m, 3H), 7.55–7.65 (m, 2H). The crude products were separated by column chromatography on silica gel. Elution with diethyl ether/hexane 10:90 gave the unsaturated hydroperoxide **24**[12] (164 mg, 48%).

4.6.3. Co(modp)$_2$-catalyzed autoxidation of (*S*)-limonene (17) in the presence of Ph$_2$MeSiH 2e. A mixture of (*S*)-limonene **17** (272 mg, 2.0 mmol), Co(modp)$_2$ (54 mg, 0.10 mmol), Ph$_2$MeSiH (775 mg, 4 mmol) in DCE (5 mL) was stirred at room temperature for 24 h under an oxygen atmosphere. After a conventional work-up, components of the residue were separated by column chromatography on silica gel. Elution with diethyl ether/hexane 2:98 gave a mixture of compounds (250 mg) containing mainly 1-methyl-1-(4-methyl-3-cyclohexenyl)ethyl methyldiphenylsilyl peroxide (**22e**); [^{1}H NMR δ 0.76 (s, 3H), 1.16 (s, 6H), 1.19–1.24 (m, 1H), 1.65 (s, 3H), 1.71–1.98 (m, 6H), 5.37 (m, 1H), 7.56 (m, 6H), 7.65 (m, 4H); ^{13}C NMR δ −3.5, 21.7, 21.9, 23.5, 24.1, 26.7, 31.0, 40.9, 88.5, 120.7, 127.6, 129.8, 134.7] and (1*S*),(5*S*),(8*S*)-4,4,8-trimethyl-2,3-dioxabicyclo[3.3.1]-nonan-8-yl methyldiphenylsilyl peroxide (**23e**); [^{1}H NMR δ 0.75 (s, 3H), 1.13 (s, 3H), 1.42 (s, 3H), 1.52 (s, 3H), 1.53–2.23 (m, 6H), 4.30 (m, 1H), 7.42 (m, 6H), 7.99 (m, 4H); ^{13}C NMR δ −3.7, 22.0, 23.8, 24.4, 24.6, 24.8, 31.9, 32.5, 40.9, 81.3, 83.8, 127.7, 130.0, 134.6], which could be separated by repeated column chromatography. Subsequent elution with ether gave a complex mixture of highly polar products (85 mg). After treatment of the mixture of the silyl peroxides, **22e** and **23e**, with a drop of concd HCl in methanol (2 mL) for 5 min, solid sodium bicarbonate and anhydrous MgSO$_4$ were added. The reaction mixture was stirred for an additional 10 min, and solid materials were removed by filtration over Celite. After evaporation of the solvent under reduced pressure, components of the residue were separated by column chromatography on silica gel. The unsaturated hydroperoxide **24**[12] (46 mg, 14%) was isolated by elution with diethyl ether/hexane 10:90. Subsequent elution with diethyl ether/hexane 15:85 gave the bicyclic hydroperoxide **25**[12] (85 mg, 21%).

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Design and synthesis of anti-barnacle active fluorescence-labeled probe compounds and direct observation of the target region in barnacle cypris larvae for dimethyl-isocyanoalkyl compounds

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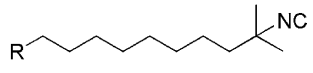
Abstract—Anti-barnacle active fluorescence-labeled probe compounds were synthesized, and the interaction between the synthesized probe compounds and the cypris larvae of barnacles was observed under a fluorescence microscope. The observation suggests that anti-fouling active isocyano substances would express activity by acting on the oil cell area in barnacle cypris larvae.

1. Introduction

Marine-fouling organisms, such as barnacles, mussels, and hydroids, cause serious problems by settling on ship hulls, cooling systems for power plants, and fishing equipment.[1] To protect these marine structures from such settlement, paints containing organo-tin and organo-copper compounds have been widely used as the most effective anti-fouling agents. However, numerous reports of environmental contamination have brought the use of these metal-based compounds to public attention.[2–6] The negative effect of organo-tin compounds, in particular, have led to regulations and bans of their use in various countries.[7] Therefore, environmentally benign alternatives are urgently required.

Natural anti-fouling active compounds are among the promising alternatives; however, their development has been hampered because of poor yields.[7–9] To create a potent anti-fouling agent, detailed structure–activity relationship studies must be conducted with respect to anti-fouling activity and toxicity. Recently, we studied structure–activity relationships with respect to anti-fouling activity based on natural anti-fouling active compounds.[10–13] The results of our studies suggest that the isocyano functional group is an important component that expresses potent anti-fouling activity. This suggestion is also supported by the fact that almost isolated compounds from nudibranch were isocyano-terpenes.[8,9,14] We synthesized several artificial anti-fouling active isocyano compounds. As shown in Figure 1, various simple linear alkyl isocyanides showed potent anti-fouling activity without significant toxicity.[12] However, it is not understood how these isocyano compounds express anti-fouling activity. Elucidation of the mechanism is an essential step toward the development of non-toxic anti-fouling agents. A fluorescence probe study is one of the most suitable methods to understand this mechanism since it allows the visualization of a site of action for anti-fouling compounds. We describe herein a direct observation study on a target region of the anti-barnacle active isocyano compounds in the cypris larvae of the barnacle *Balanus amphitrite* with fluorescence-labeled compounds.



1 R = $HC{=}CH_2$ EC_{50} = 0.046 μg/mL
2 R = CH_2NH_2 EC_{50} = 0.16 μg/mL
3 R = CH_2NHAc EC_{50} = 0.10 μg/mL

Figure 1. Structures and anti-barnacle activities of linear alkyl isocyanides **1**–**3**.

Keywords: Anti-foiling activity; Barnacle; Fluorescence-labeled probe; Isocyanide; Oil cell.
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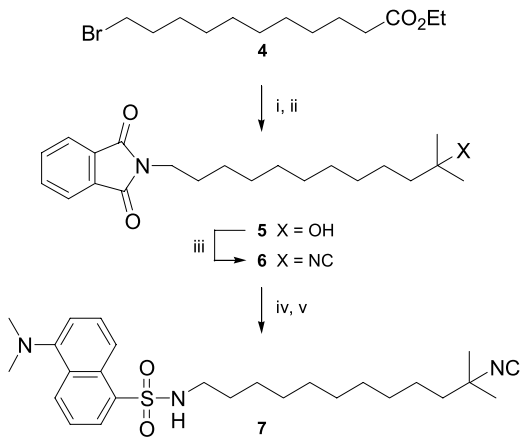
2. Results and discussion

Based on the results of the structure–activity relationships of simple linear alkyl isocyanides, we designed the synthesis of an isocyano compound **7** bearing a dansyl group as an anti-fouling active fluorescent probe because the fluorescence pattern of the dansyl group was assumed to be different from the autofluorescence of the barnacle *B. amphitrite*, which was observed under a filter set (EX 400–440 nm, EM 475 nm).[15] The synthesis of fluorescence-labeled compound **7** is shown in Scheme 1. Ester **4** was first converted to *tert*-alcohol with MeMgBr, which was then treated with phthalimide potassium salt to give hydroxyphthalimide **5**. The one-step construction of isocyanide from alcohol with TMSCN and $AgClO_4$[16] yielded isocyanophthalimide **6**. After the conversion of phthalimide **6** to amine with hydrazine monohydrate, the desired fluorescence-labeled isocyanide **7** was synthesized from the amine with dansyl chloride and triethylamine.



Scheme 1. Reagents and conditions: (i) MeMgBr, THF, 0 °C, 99%; (ii) phthalimide potassium salt, DMF, rt, 65%; (iii) TMSCN, $AgClO_4$, $MeNO_2$, rt, 76%; (iv) hydrazine monohydrate, MeOH, reflux, 99%; (v) dansyl chloride, Et_3N, CH_2Cl_2, rt, 59%.

Bioassays to evaluate the anti-fouling activity of the resulting probe were carried out with the cypris larvae of the barnacle *B. amphitrite*.[9,17] The cyprids in the test plate were observed after 120 h in accordance with a generally accepted method.[10–13] Probe compound **7** showed moderate anti-fouling activity (EC_{50} 2.80 μg/mL) without significant toxicity ($LD_{50} > 100$ μg/mL) against the *B. amphitrite* cyprids. Although the activity of probe **7** was weaker than those of compounds **1**–**3**, it was assumed that the activity was adequate for the observation of the target region because the mortality rate of the cyprids was 5% at 10 μg/mL at which the settlement inhibition rate was 75%. The interaction between the isocyano compound **7** and the cyprids was monitored under a fluorescence microscope with appropriate filters. Two kinds of filter sets, UV and Violet (EX 355–425 nm, EM 470 nm) and GFP (EX 470 nm, EM 525 nm), were used to clarify the difference between the autofluorescence of the cyprid and the fluorescence of the probe. Figure 2 shows photographs of the autofluorescence of the cyprids, and Figure 3 contains photographs of the cypris larvae in a cell of the bioassay.

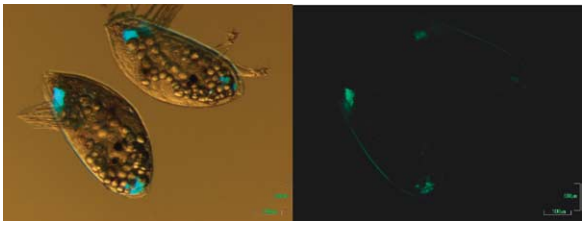


Figure 2. Fluorescence study of the barnacle *B. amphitrite* cyprids without compounds (autofluorescence), left: EX 355–425 nm, EM 470 nm; right: EX 470 nm, EM 525 nm.

The cell in which the concentration of the probe compound was adjusted to 10 μg/mL was observed since very few of the cyprids at that concentration had settled and died as described above. Living cyprids of *B. amphitrite* have several granules with autofluorescence in their bodies.[18] As shown in Figure 2, autofluorescence is localized at the anterior and posterior regions in cyprids and was detected under two kinds of filter sets, UV and Violet and GFP. When the cyprids were treated with probe **7** for 120 h, strong fluorescence was observed at a specific location of the larvae. This location is referred to as the oil cell area[18] and was observed with a UV and Violet filter (Fig. 3, left). On the other hand, autofluorescence was only observed under the GFP filter since the fluorescence of the dansyl group was not detected under identical conditions (Fig. 3, right). Considering that the specific fluorescence was not observed without compound **7** (Fig. 2, left), it was assumed to have originated from probe **7**. These results suggest that anti-fouling active isocyano substances would act on the oil cell area in the cypris larvae of barnacles.

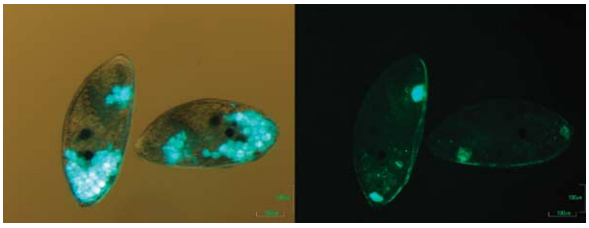
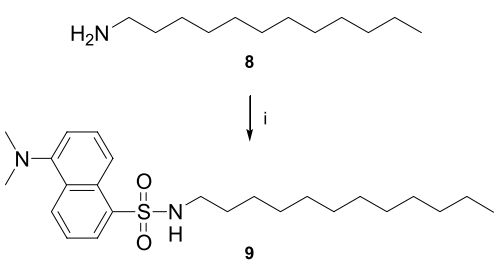


Figure 3. Fluorescence study of the barnacle *B. amphitrite* cyprids treated with probe **7**, left: EX 355–425 nm, EM 470 nm; right: EX 470 nm, EM 525 nm.

We next conducted a controlled study using fluorescence probe compound **9**, which lacked an isocyano group from compound **7** and had no specific functional group. The synthesis of fluorescence-labeled compound **9** is shown in Scheme 2. Treatment of dodecylamine **8** with dansyl



Scheme 2. Reagents and conditions: (i) dansyl chloride, Et_3N, CH_2Cl_2, rt, 84%.

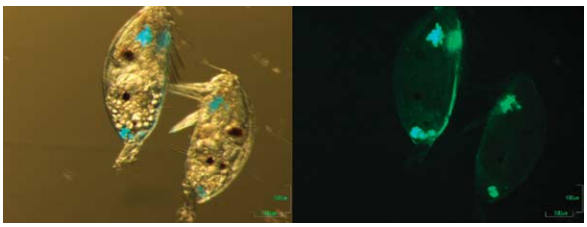


Figure 4. Fluorescence study of the barnacle *B. amphitrite* cyprids treated with probe **9**, left: EX 355–425 nm, EM 470 nm; right: EX 470 nm, EM 525 nm.

chloride and triethylamine afforded the desired fluorescence probe **9**.

Bioassays of the resulting probe compound **9** and observation under a fluorescence microscope were carried out by the same method as that used in the case of compound **7**. Compound **9** also showed moderate anti-fouling activity (EC_{50} 4.43 μg/mL) without significant toxicity (LD_{50} > 100 μg/mL) against the *B. amphitrite* cyprids, although the activity was slightly lower than that of compound **7**. Figure 4 contains photographs of the cyprids in the bioassay with probe **9** after 120 h. Compared with the photograph shown in Figure 3, the specific fluorescence signal on the oil cell area in the cypris larvae was obviously faint. Weak fluorescence was observed around the cyprids, but this was attributed to an interaction between hydrophobic compounds. This result could indicate that some natural hydrocarbon products showed effective anti-fouling activity.[14]

3. Conclusion

In conclusion, we have succeeded in the visualization of the binding site of the anti-fouling active isocyano compound in the barnacle cyprid. The results of the present study suggest that linear alkyl isocyanides express anti-fouling activity by acting on the oil cell area in the cypris larvae of barnacles. The role of the oil cell is reported as a food reserve providing an energy source during the non-feeding phase of the cypris larvae.[19] The present results will provide useful information for the future study of a mechanism to inhibit their settlement.

4. Experimental

4.1. General

Mps were determined on a MEL-TEMP (Laboratory Device) and are uncorrected. NMR spectra were obtained in $CDCl_3$ on a JEOL alpha-600 spectrometer. All ^1H NMR spectra are reported in ppm relative to TMS. All ^{13}C NMR spectra are reported in ppm relative to the central line of the triplet for $CDCl_3$ at 77.03 ppm. IR spectra were recorded on a JEOL WINSPEC-50 spectrometer. Mass spectra were recorded on an Applied Biosystems QSTER XL System. Chromatographic separations were carried out on a silica gel column (Fuji Silysia Chemical BW-127ZH; 100–270 mesh) unless otherwise stated.

4.1.1. 2-(11-Hydroxy-11-methyldodecyl)isoindole-1,3-dione (5). To a solution of MeMgBr (0.91 M in THF, 40.0 mL, 36.4 mmol) in THF (30 mL) cooled at 0 °C was added a solution of 11-bromoundecanoic acid ethyl ester **4** (5.0 g, 17.05 mmol) in THF (20 mL) under an argon atmosphere. After the reaction mixture was stirred at 0 °C for 1 h, the reaction was quenched with aqueous NH_4Cl (50 mL), and the resultant mixture was then extracted with EtOAc (300 mL). The combined extracts were washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The obtained crude alcohol (4.7 g, 99%) was used in the next experiment without purification. To a solution of the above alcohol (3.0 g, 10.7 mmol) in DMF (10 mL) was added phthalimide potassium salt (2.35 g, 12.4 mmol). After the reaction mixture was stirred at ambient temperature for 24 h, 1 M KOH (30 mL) was added, and the resultant mixture was then extracted with EtOAc (200 mL). The combined extracts were washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane = 1:2) to give alcohol **5** (2.4 g, 65%) as a white solid. Mp 46–47 °C; ^1H NMR δ 7.84 (2H, dd, J = 5.5, 2.9 Hz), 7.70 (2H, dd, J = 5.5, 2.9 Hz), 3.67 (2H, t, J = 7.3 Hz), 1.71–1.63 (2H, m), 1.47–1.42 (2H, m), 1.37–1.24 (14H, m), 1.21 (1H, br s), 1.20 (6H, s); ^{13}C NMR δ 168.50, 133.84, 132.25, 123.17, 71.07, 44.03, 38.12, 30.16, 29.57, 29.48, 29.45, 29.25, 29.16, 28.60, 26.87, 24.35; IR (KBr) 3504 (br), 2968, 2923, 2850, 1767, 1696, 1180, 719 cm^{-1}; MS (ESI) 346.2374 $[M+H]^+$, $C_{21}H_{32}NO_2$ requires 346.2376.

4.1.2. 2-(11-Isocyano-11-methyldodecyl)isoindole-1,3-dione (6). To a solution of alcohol **5** (1.8 g, 5.21 mmol) in nitromethane (20 mL) were added TMSCN (760 μL, 5.75 mmol) and then $AgClO_4$ (1.2 g, 5.79 mmol) in an argon atmosphere. The reaction mixture was stirred at ambient temperature for 2 h, and the reaction was then quenched with aqueous $NaHCO_3$ (20 mL). After being stirred for an additional 10 min, the mixture was filtered with Celite and washed with EtOAc (200 mL). The combined extracts were washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane = 1:2) to give isocyanide **6** (1.4 g, 76%) as a colorless oil. ^1H NMR δ 7.84 (2H, dd, J = 5.5, 2.9 Hz), 7.70 (2H, dd, J = 5.5, 2.9 Hz), 3.67 (2H, t, J = 7.3 Hz), 1.71–1.63 (2H, m), 1.57–1.51 (2H, m), 1.47–1.23 (22H, m) including 1.39 (6H, t, J = 1.8 Hz); ^{13}C NMR δ 168.45, 152.84 (t, J = 5.0 Hz), 133.81, 132.21, 123.12, 57.39 (t, J = 5.0 Hz), 42.48, 38.06, 29.46, 29.42, 29.40, 29.38, 29.12, 28.97, 28.57, 26.83, 24.11; IR (neat) 2981, 2927, 2854, 2130, 1772, 1712, 719 cm^{-1}; MS (ESI) 355.2380 $[M+H]^+$, $C_{22}H_{31}N_2O_2$ requires 355.2380.

4.1.3. 5-Dimethylamino-naphthalene-1-sulfonic acid (11-isocyano-11-methyldodecyl)amide (7). To a solution of isocyanide (1.35 g, 3.81 mmol) in methanol (20 mL) was added hydrazine monohydrate (400 μL, 8.24 mmol). After the reaction mixture was refluxed for 1 h, brine (50 mL) was added, and the resultant mixture was then extracted with EtOAc (200 mL). The combined extracts were washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The obtained crude amine (850 mg, 99%)

was used in the next experiment without purification. To a solution of the above amine (430 mg, 1.92 mmol) in dichloromethane (5 mL) were added dansyl chloride (520 mg, 1.92 mmol) and triethylamine (0.5 mL, 3.58 mmol). After the reaction mixture was stirred at ambient temperature for 12 h, the resultant mixture was concentrated under reduced pressure. The residue was purified by column chromatography on NH-silica gel (Fuji Silysia Chemical NH DM-1020; 100–200 mesh; EtOAc/hexane = 1:3) to give isocyano-dansyl amide **7** (520 mg, 59%) as a lime-green oil. ^{1}H NMR δ 8.54 (1H, d, J = 8.8 Hz), 8.29 (1H, d, J = 8.8 Hz), 8.25 (1H, dd, J = 7.3, 1.1 Hz), 7.57 (1H, dd, J = 8.8, 8.8 Hz), 7.53 (1H, dd, J = 8.8, 7.3 Hz), 7.19 (1H, d, J = 7.3 Hz), 4.52 (1H, t, J = 6.2 Hz), 2.89 (6H, s), 2.88 (2H, t, J = 6.2 Hz), 1.58–1.51 (4H, m), 1.46–1.05 (20H, m) including 1.39 (6H, t, J = 1.8 Hz); ^{13}C NMR δ 152.82 (t, J = 5.0 Hz), 152.05, 134.81, 130.35, 129.91, 129.66, 129.63, 128.32, 123.17, 118.70, 115.13, 57.40 (t, J = 5.0 Hz), 45.40, 43.31, 42.45, 29.50, 29.40, 29.30, 29.26, 29.23, 28.97, 28.89, 26.35, 24.07; IR (neat) 3290 (br), 2981, 2927, 2854, 2130, 1324, 1143, 790 cm^{-1}; MS (ESI) 458.2850 $[M+H]^+$, $C_{26}H_{40}N_3O_2S$ requires 458.2869.

4.1.4. 5-Dimethylamino-naphthalene-1-sulfonic acid dodecylamide (9). To a solution of dodecylamine **8** (185 mg, 1.0 mmol) in dichloromethane (5 mL) were added dansyl chloride (269 mg, 1.0 mmol) and triethylamine (0.3 mL, 2.15 mmol). After the reaction mixture was stirred at ambient temperature for 12 h, the resultant mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane = 1:4) to give dansyl amide **9** (350 mg, 84%) as a lime-green solid. Mp 57–58 °C; ^{1}H NMR δ 8.54 (1H, d, J = 8.8 Hz), 8.29 (1H, d, J = 8.8 Hz), 8.25 (1H, dd, J = 7.3, 1.1 Hz), 7.56 (1H, dd, J = 8.4, 7.7 Hz), 7.52 (1H, dd, J = 8.4, 7.3 Hz), 7.20 (1H, d, J = 7.3 Hz), 4.64–4.51 (1H, m), 2.89 (6H, s), 2.88 (2H, t, J = 7.0 Hz), 1.37–1.03 (20H, m), 1.39 (3H, t, J = 7.3 Hz); ^{13}C NMR δ 152.07, 134.84, 130.38, 129.94, 129.70, 129.67, 128.36, 123.19, 118.74, 115.16, 45.42, 43.34, 31.91, 29.60, 29.58, 29.52, 29.47, 29.36, 29.33, 28.97, 26.42, 22.69, 14.11; IR (KBr) 3297, 2958, 2915, 2846, 1324, 1149, 784 cm^{-1}; MS (ESI) 419.2720 $[M+H]^+$, $C_{24}H_{39}N_2O_2S$ requires 419.2726.

4.2. Cyprid larvae[20]

Adult barnacles, *B. amphitrite*, attached to bamboo poles were procured from oyster farms in Lake Hamana, Shizuoka, and maintained in an aquarium at 20 ± 1 °C by being fed with brine shrimp *Artemia salina* nauplii. Broods released I–II stage nauplii upon immersion in seawater after being dried for 1 day. Nauplii thus obtained were cultured in 2-L glass beakers at an initial density of 3 larvae mL^{-1} being fed with the diatom *Chaetoceros gracilis* at a concentration of 2.5×10^5 cells mL^{-1}. Cultures were maintained in filtered (0.2 μm) seawater diluted to 80% by deionized water (80% filtered seawater) at 25 °C with mild aeration. From day 1 to day 4, larvae were collected on 100 μm nylon nets, washed with 80% filtered seawater, and transferred to newly prepared algal diet suspensions. Larvae reached the cyprid stage in 5 days. The cyprids were stored in the dark at 5 °C until used. The day newly transformed cyprids were collected was designated as day 0.

4.3. Anti-fouling assay and observation of fluorescence

Test samples were dissolved in MeOH; aliquots of the solution were pipetted into wells of 24-well polystyrene tissue culture plates and air-dried. Two mL of 80% filtered seawater and six 2- or 3-day-old cyprids were added to each well. Four wells were used for each experiment. The plates were kept in the dark at 25 °C, and the number of larvae which attached, metamorphosed, died, or did not settle was counted under a microscope after 120 h. Cyprids that did not move, had extended appendages, and did not respond after a light touch by a metal probe were regarded as dead. The experiments were performed five times with different batches of larvae. The same assay of $CuSO_4$ was carried out as a positive control each time. The observation of fluorescence was carried out by using a Carl Zeiss Stemi SV-M2Bio with filter sets of UV and Violet Cube and GFP-Cube.

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Iridium-catalyzed enantioselective Pauson–Khand-type reaction of 1,6-enynes

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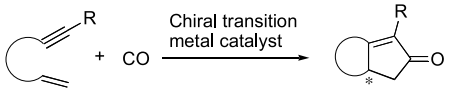
Abstract—Iridium–chiral diphosphine complex catalyzes an enantioselective intramolecular Pauson–Khand-type reaction to give various chiral bicyclic cyclopentenones. The enantioselective reaction proceeds more smoothly and enantioselectively under a lower partial pressure of carbon monoxide. Moreover, aldehyde can be used as a CO source in the enantioselective carbonylative coupling.

1. Introduction

The Pauson–Khand reaction is a carbonylative coupling of alkyne and alkene, which was originally reported using a stoichiometric amount of a cobalt carbonyl complex in 1973.[1] The reaction gives synthetically useful cyclopentenones; in fact, it has been used as a key reaction in natural product syntheses.[2] In the 1990s, efforts were extended toward developing a catalytic reaction, and Jeong reported a practical intramolecular reaction of enynes using a cobalt–phosphite complex;[3] many publications on catalytic reaction conditions followed.[4] Further progress was made by reactions using other transition metal complexes as catalysts, known as a Pauson–Khand-type reaction.[5] Since Buchwald reported Ti-catalyzed intramolecular reaction of enynes,[6] Ru[7] and Rh complexes[8] were found to be efficient catalysts. The first catalytic and enantioselective Pauson–Khand-type reaction was also realized by Buchwald using a chiral titanium complex, where various enynes were transformed into the corresponding chiral bicyclic cyclopentenones in high ee.[9] Further achievements include enantioselective reactions using a cobalt complex by Hiroi,[10] a rhodium one by Jeong[11] and an iridium one by us[12] in 2000 (Eq. 1), and the development of an enantioselective Pauson–Khand-type reaction is still an intriguing topic these days.[13]



(1)

This manuscript discloses further investigation of an iridium-catalyzed enantioselective Pauson–Khand-type reaction. Various types of enynes were submitted to the reaction under an atmospheric pressure or a lower partial pressure of carbon monoxide.[14] Moreover, an iridium-catalyzed Pauson–Khand-type reaction using an aldehyde as a CO source is also presented.

2. Results and discussion

2.1. Iridium complex-catalyzed enantioselective coupling with carbon monoxide

In order to investigate the catalytic activity of an iridium complex, we first examined an intramolecular Pauson–Khand-type reaction of enyne **1a** (Eq. 2). The iridium complex, possessing triphenylphosphine as an achiral ligand, operated as a more efficient catalyst than that without phosphine ligands. The results were opposite to those of a rhodium complex-catalyzed reaction, where the addition of triphenylphosphine deactivated the catalytic activity,[8c] and they prompted us to examine chiral ligands for iridium-catalyzed enantioselective intramolecular Pauson–Khand-type reaction.

Keywords: Iridium; Enynes; Carbonylation; Pauson–Khand reaction; Enantioselective.
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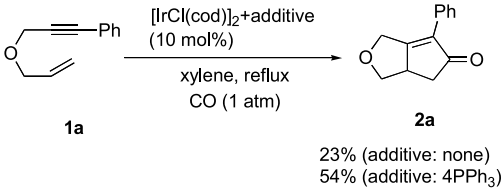


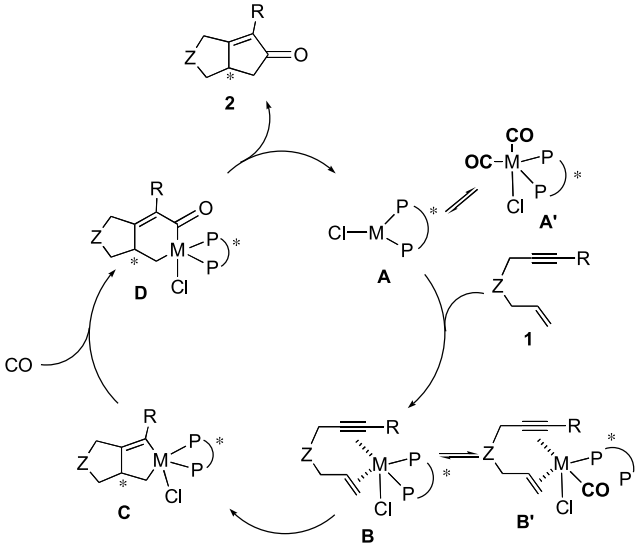
(2)

Next we investigated chiral diphosphines as chiral ligands (Table 1); with the increase of yield, enantioselectivity was improved and tolBINAP was found to be best among them. A good yield of 83% and high ee of 93% were achieved[15] (entries 1–5). Decreasing the amounts of catalyst to 5 mol% gave slightly poorer yield and enantioselectivity; however, drastic decrease of ee was observed, and a considerable amount of enyne **1** was recovered by 2 mol% catalyst (entries 6, 7). In order to increase the catalytic efficiency, the concentration of the chiral catalyst was found to be important: the higher yield and the same ee were achieved using 2 mol% catalyst when the reaction was examined for longer reaction time under the same concentration as that of entry 5 (entries 8, 9).

Various 1,6-enynes were submitted to the reaction using the chiral iridium catalyst,[16] which was prepared in situ from $[IrCl(cod)]_2$ and tolBINAP (Table 2). Electron-donating and -withdrawing substituents on the phenyl ring produced almost no effect, and the corresponding bicyclic enones **2b**,**c** were obtained in good yield with high ee (entries 1, 2). In place of aryl groups on the alkyne terminus of enyne, an isopropenyl group could be possible, yet with moderate yield (entry 3). Enynes, having alkyl groups on their alkyne termini, were also good substrates, and methyl-substituted enyne **1e** gave enone **2e** in the highest ee of 98% (entries 4–6). Not only oxygen-bridged enynes but also nitrogen-bridged enyne **1g** was enantiomerically transformed into bicyclic compound **2g** (entry 7); however, carbon-bridged enyne **1h** gave carbonylative product **2h** in moderate yield even over longer reaction time, and a considerable amount of enyne **1h** was recovered (entry 8). Decreasing a partial pressure of carbon monoxide accelerated the carbonylative coupling also in an iridium-catalyzed system,[8c] and higher yield was achieved under a 0.2 partial pressure of carbon monoxide without any lowering of ee.[17] Longer reaction time realized further better yield of ca. 90% (entries 9, 10).

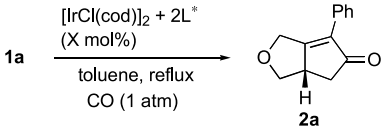
Also in the case of enyne **1i**, possessing a functionalized substituent on its alkyne terminus, decrease of a partial pressure of carbon monoxide worked well; moreover, ee was also significantly improved (entries 11, 12). Enyne, having 1,1-disubstituted olefin as an alkene moiety, is known to be rather inactive, and considerable amounts of enynes **1j**,**k** were recovered, respectively, under an atmospheric pressure of carbon monoxide (entries 13, 15). Due to the decrease of the partial pressure of CO, bicyclic cyclopentenones **2j**,**k**, having a chiral quaternary carbon, were obtained in acceptable yield and ee (entries 14, 16).

Scheme 1 depicts a possible mechanism: π-complexation of enyne **1** to chiral catalyst **A** induces an oxidative coupling to give metallacyclopentene **C**, where a chiral carbon is generated. Carbonyl insertion to **C** gives acyl complex **D**,[18] and the following reductive elimination provides enone **2** with regeneration of the active iridium species. In the reaction mixture, the mole amount of CO is much larger than that of the catalyst, which means that complex **A**′ and **B**′ could also exist by CO coordination. Complex **A**′ is less reactive than **A**, and an oxidative coupling of **B**′ lowers enantioselectivity. When the coupling is done under a lower



Scheme 1. A possible explanation for the effect of a partial pressure of CO.

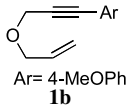
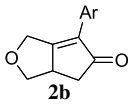
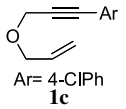
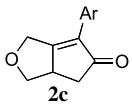
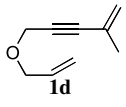
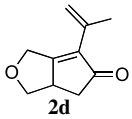
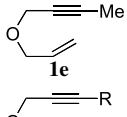
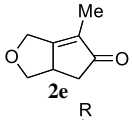
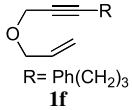
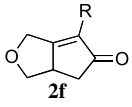
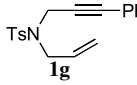
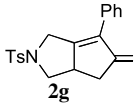
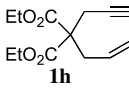
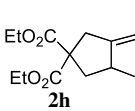
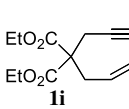
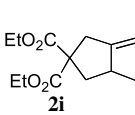
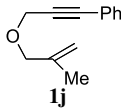
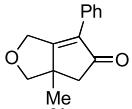
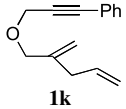
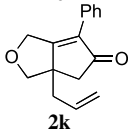
Table 1. Investigation of chiral ligands and amounts of catalyst in iridium-catalyzed enantioselective Pauson–Khand-type reaction



Entry	*X*	Chiral ligand[a]	[M]/mM[b]	Time/h	Yield/%	ee/%
1	10	CHIRAPHOS	15	12	13	<1
2	10	BDPP	15	12	23	22
3	10	DIOP	15	12	53	17
4	10	BINAP	15	12	64	86
5	10	tolBINAP	15	12	83	93
6	5	tolBINAP	7.5	24	75	91
7	2	tolBINAP	3	48	33	74
8	2	tolBINAP	15	48	59	93
9	2	tolBINAP	15	72	88	92

[a] (*S*,*S*)-isomers were used for entries 1–3. (*S*)-isomers were used for entries 4–10.
[b] Concentration of catalyst.

Table 2. Enantioselective Pauson–Khand-type reaction of various enynes under a CO atmosphere

Entry[a]	Enyne	Cyclopentenone	CO/atm	Time/h	Yield/%	ee/%
1	 Ar= 4-MeOPh **1b**	 **2b**	1.0	20	80	96
2	 Ar= 4-ClPh **1c**	 **2c**	1.0	20	78	95
3	 **1d**	 **2d**	1.0	20	54	97
4	 **1e**	 **2e**	1.0	20	60	98
5			1.0	48	75	97
6	 R= $Ph(CH_2)_3$ **1f**	 **2f**	1.0	20	54	90
7	 **1g**	 **2g**	1.0	12	85	95
8	 **1h**	 **2h**	1.0	36	51	88
9			0.2[b]	36	71	85
10			0.2[b]	72	89	86
11	 **1i**	 **2i**	1.0	72	15	84
12			0.2[b]	72	50	88
13	 **1j**	 **2j**	1.0	24	30	88
14			0.2[b]	72	86	93
15	 **1k**	 **2k**	1.0	96	22	86
16			0.2[b]	96	62	94

[a] $[IrCl(cod)]_2$ + 2(*S*)-tolBINAP (10 mol%), toluene, reflux.
[b] CO (0.2 atm) + Ar (0.8 atm).

partial pressure of CO, the content of **A** and **B** increases as compared with that of **A′** and **B′**, which probably brings about the acceleration of the coupling and the increase of ee.[19]

Table 2 shows wide generality of the present iridium-catalyzed enantioselective Pauson–Khand-type reaction; however, there is a limitation of enynes (Fig. 1): under the same reaction conditions as Table 2, enynes, containing 1,2-disubstituted olefin as an alkene moiety, a 1,7-enyne, and enynes with no substituent on the alkyne terminus met with failure, and only a trace amount of or no carbonylated product was detected.

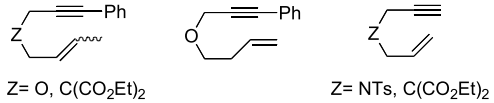
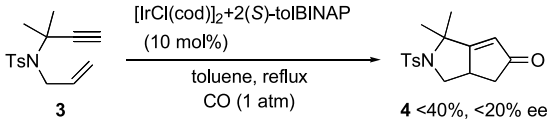


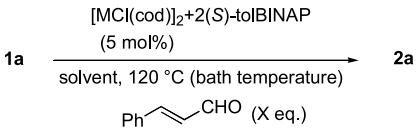
Figure 1. Enynes, which did not give carbonylated products.

We further examined enyne **3**, having no substituent on the alkyne terminus and having two methyls at the propargylic position, which deter isomerization of alkyne moiety to vinylidene complex.[20] Enone **4** was obtained yet only with low ee (Eq. 3). This result implies that the substituent on the alkyne terminus plays a pivotal role for high enantioselectivity.



(3)

Table 3. Examination of enantioselective Pauson–Khand-type reaction using cinnamaldehyde as a CO source



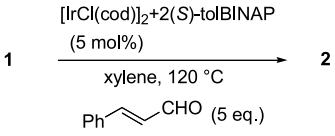
Entry	M	Solvent	*X*/equiv	Time/h	Yield/%	ee/%
1	Rh	None	20	5	89	82
2	Rh	Xylene	20	36	54	8
3	Ir	None	20	6	27	88
4	Ir	Xylene	20	12	52	86
5	Ir	Xylene	5	9	66	92
6	Ir	Toluene	5	24	25	95

2.2. Iridium complex-catalyzed enantioselective coupling using an aldehyde as a CO source

Recently, Morimoto and Kakiuchi[21] and we[22] independently reported a Rh-catalyzed Pauson–Khand-type reaction using aldehydes as a CO source in place of CO gas. Enantioselective reaction was also realized, where solvent-free condition is essential for high yield and ee (Table 3, entry 1).[22b] When the coupling was examined in xylene, it took much longer reaction time to consume enyne **1a** and enantioselectivity was extremely low (entry 2). We next examined an iridium-catalyzed coupling using an aldehyde as a CO source[23] and found that ee was high both with and without solvent; however, solvent was needed for high yield (entries 3, 4). Higher yield and ee were achieved by decreasing the amounts of cinnamaldehyde (entry 5). These results imply that the chiral rhodium complex would be stable and less reactive, and it works as a catalyst in harsh reaction conditions; on the contrary, the chiral iridium complex would be unstable, and solvent is needed for operating as an efficient catalyst.

Under the best reaction conditions (Table 3, entry 5), we examined an enantioselective coupling of several enynes (Table 4). In each entry, yield was moderate; however, ee was very high and exceeded that of rhodium-catalyzed coupling.[22b]

Table 4. Enantioselective Pauson–Khand-type reaction of various enynes using cinnamaldehyde as a CO source



Entry	Enyne	Time/h	Yield/%	ee/%
1	**1b**	5	57	91
2	**1c**	9	56	91
3	**1e**	24	30	85
4	**1g**	5	55	94
5	**1h**	24	51	87
6	**1j**	24	40	90

3. Conclusion

In summary, we have developed a catalytic and enantioselective Pauson–Khand-type reaction using a chiral iridium complex, which is readily prepared in situ from a commercially available and stable iridium complex and chiral diphosphine. Various enynes could be transformed into chiral bicyclic cyclopentenones in high ee. Especially, a low partial pressure of carbon monoxide facilitated the carbonylative coupling and improved the enantioselectivity. Furthermore, an enantioselective Pauson–Khand-type reaction using cinnamaldehyde as a CO source could be also achieved by chiral iridium complex and higher enantioselectivity was realized than that by the rhodium complex.

4. Experimental

4.1. General

Optical rotation was measured using Jasco DIP-370 polarimeter. IR spectra were recorded with Horiba FT210 spectrophotometer. NMR spectra were measured with JEOL AL-400 or Varian VXR-300S spectrometer using tetramethylsilane as an internal standard and $CDCl_3$ was used as solvent. Mass spectra were measured with JEOL JMS-SX102A and elemental analyses with Perkin Elmer PE2400II. Dehydrated toluene is commercially available and it was dried over molecular sieves 4 Å and degassed by carbon monoxide bubbling before use. All reactions were examined using a CO balloon or a balloon of CO and Ar (2:8). Spectral data of **2a–2c**, **2e–2h**, and **2j** were already published by others[4b,h,8b,c,9b,11,24,25] and us.[12,22]

4.2. Typical experimental procedure for enantioselective coupling with carbon monoxide (Table 2)

Preparation of a balloon with mixed gas of carbon monoxide and argon (2:8): CO (2 atm) was introduced into an autoclave (30 mL) then Ar (8 atm) was introduced into the autoclave; then the pressurized mixed gas (10 atm) was released into a balloon at an atmospheric pressure.

Under an atmosphere of carbon monoxide, tolBINAP (34.0 mg, 0.050 mmol) and $[Ir(cod)Cl]_2$ (16.8 mg, 0.025 mmol) were stirred in toluene (2.0 mL) at room temperature. After the addition of a toluene solution (2.0 mL) of enyne **1** (0.25 mmol), the reaction mixture was stirred under reflux for an appropriate time (cited in the table). The solvent was removed under reduced pressure, and the crude products were purified by thin-layer

chromatography to give chiral cycloadduct **2**. Enantiomeric excess was determined by HPLC analysis using a chiral column.

4.2.1. 2-Isopropenyl-7-oxabicyclo[3.3.0]oct-1-en-3-one (2d). Pale yellow oil. IR (neat) 2852, 1712, 1651, 1456, 1028, 903 cm^{-1}; ^1H NMR $\delta=1.80$ (s, 3H), 2.22 (dd, $J=3.0$, 17.4 Hz, 1H), 2.72 (dd, $J=3.0$, 17.4 Hz, 1H), 3.21–3.25 (m, 2H), 4.33 (dd, $J=5.8$, 5.8 Hz, 1H), 4.63 (d, $J=16.6$ Hz, 1H), 4.77 (d, $J=16.6$ Hz, 1H), 5.21 (s, 1H), 5.61 (s, 1H); ^{13}C NMR $\delta=22.2$, 40.2, 43.3, 66.4, 71.4, 118.0, 134.6, 135.1, 176.5, 206.6; HRMS (EI^+) for M found *m/e* 164.0824, calcd for $C_{10}H_{12}O_2$: 164.0837. $[\alpha]_D^{31}$ −178.3 (*c* 1.17, $CHCl_3$, 97% ee). Enantiomeric excess was determined by HPLC analysis using a chiral column (Daicel Chiralpak AD-H: 4×250 mm, 254 nm UV detector, room temperature, eluent: 3% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 15 min for major isomer and 16 min for minor isomer).

4.2.2. Diethyl 2-(benzyloxy)methyl-3-oxobicyclo[3.3.0]oct-1-en-7,7-dicarboxylate (2i). Pale yellow oil. IR (neat) 2982, 1730, 1672, 1267 cm^{-1}; ^1H NMR $\delta=1.21$–1.30 (m, 6H), 1.69 (dd, $J=12.7$, 12.7 Hz, 1H), 2.11 (dd, $J=3.3$, 17.9 Hz, 1H), 2.64 (dd, $J=6.2$, 17.9 Hz, 1H), 2.78 (dd, $J=7.7$, 12.7 Hz, 1H), 2.98–3.06 (m, 1H), 3.34 (d, $J=20.6$ Hz, 1H), 3.42 (d, $J=20.6$ Hz, 1H), 4.19–4.24 (m, 6H), 4.53 (s, 2H), 7.25–7.34 (m, 5H); ^{13}C NMR $\delta=14.1$, 34.7, 38.8, 41.6, 43.5, 61.1, 61.9, 62.0, 63.1, 73.1, 127.5, 128.2 133.6, 137.8, 170.6, 171.3, 181.2, 207.4; HRMS (FAB) for M+1 found *m/e* 387.1811, calcd for $C_{22}H_{27}O_6$: 387.1808. $[\alpha]_D^{31}$ −48.2 (*c* 1.11, $CHCl_3$, 88% ee). Enantiomeric excess was determined by HPLC analysis using a chiral column (Daicel Chiralpak AS-H: 4×250 mm, 254 nm UV detector, room temperature, eluent: 10% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 13 min for minor isomer and 17 min for major isomer).

4.2.3. 2-Phenyl-5-(2-propenyl)-7-oxabicyclo[3.3.0]oct-1-en-3-one (2k). IR (neat) 1711, 1021, 919, 764 cm^{-1}; ^1H NMR $\delta=2.25$ (dd, $J=6.6$, 13.5 Hz, 1H), 2.39 (d, $J=17.4$ Hz, 1H), 2.48 (dd, $J=8.1$, 13.5 Hz, 1H), 2.69 (d, $J=17.4$ Hz, 1H), 3.40 (d, $J=8.1$ Hz, 1H), 4.14 (d, $J=8.1$ Hz, 1H), 4.58 (d, $J=16.4$ Hz, 1H), 4.93 (d, $J=16.4$ Hz, 1H), 5.12 (d, $J=0.9$ Hz, 1H), 5.16 (d, $J=4.5$ Hz, 1H), 5.59–5.77 (m, 1H), 7.32–7.51 (m, 5H); HRMS (EI^+) for M found *m/e* 240.1160, calcd for $C_{16}H_{16}O_2$: 240.1150. $[\alpha]_D^{23}$ +5.28 (c 0.56, $CHCl_3$, 94% ee). Enantiomeric excess was determined by HPLC analysis using a chiral column (Daicel Chiralpak AD-H: 4×250 nm, 254 nm UV detecter, room temperature, eluent: 10% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 8 min for minor isomer and 10 min for major isomer).

4.3. Typical experimental procedure for enantioselective coupling using cinnamaldehyde as a CO source (Table 4)

Under an atmosphere of argon, tolBINAP (20.4 mg, 0.030 mmol) and $[Ir(cod)Cl]_2$ (10.1 mg, 0.015 mmol) were stirred in xylene (1.5 mL) at room temperature. After the addition of a xylene solution (0.5 mL) of enyne **1** (0.30 mmol) and cinnamaldehyde (198.0 mg, 1.5 mmol), the reaction mixture was stirred at 120 °C for an appropriate time (cited in the table). After the exclusion of excess cinnamaldehyde and xylene, the crude products were purified by thin-layer chromatography, and pure bicyclic enone **2** was obtained. Enantiomeric excess was determined by HPLC analysis using a chiral column.

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Computer-aided determination of relative stereochemistry and 3D models of complex organic molecules from 2D NMR spectra

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Abstract—A method for elucidation of the relative stereoconfiguration of natural product molecular structures and their 3D models based on NOE data and the application of a genetic algorithm is described. The method is applicable mainly for rigid polycyclic structures commonly encountered in natural products. It is demonstrated that the technique of simulated annealing cannot be easily used when dealing with low-weight fused ring molecules but the application of a genetic algorithm is proven successful. Examples of a typical genetic algorithm workflow and the optimization of the algorithmic parameters are discussed. The efficiency of the approach developed here is demonstrated on the complex natural products of both Taxol® ($C_{47}H_{51}NO_{14}$) and brevetoxin B ($C_{50}H_{70}O_{14}$).

1. Introduction

The biological activity of natural products and drug molecules is generally dependant on the relative stereochemistry of a molecule. Indeed, there are examples known where one stereoisomer can exhibit vastly different pharmacologic activity from the other stereoisomer. As an example, D-propoxyphene has analgesic activity while the other optical isomer, L-propoxyphene, has antihistaminic activity. Also thalidomide where one enantiomer is effective against morning sickness, while the other is teratogenic. Stereoisomer considerations can influence reaction pathways and certainly reaction kinetics, with one form being favored over another. Generally, the final step in contemporary structure characterization efforts is to define the relative, and if possible absolute stereochemistry. NMR methods are generally well suited to the former while the latter is generally obtained using chemical structure modification combined with NMR studies[1] or by X-ray crystallographic methods. NMR-based determination of relative stereochemistry is based on the nuclear Overhauser effect (NOE), which is dependant on the distance separating the cross-relaxing nuclides.[2] Typically NOESY or ROESY two-dimensional NMR experiments or their selective 1D analogs are used to provide the data for this analysis in rigid molecules. In the case of flexible molecules, considerable effort has been devoted to the development of *J*-based NMR methods that are used to measure long-range heteronuclear coupling constants that can then be used to assign the relative stereochemistry.[3]

In our previous work,[4–7] an expert system for molecular structure elucidation from 1D to 2D NMR spectra (mainly COSY, HSQC (or less desirably HMQC), and HMBC) was described. In this work, we describe an improvement to this software program that allows the determination of the relative stereochemistry of a molecular structure based on the nuclear Overhauser effect (NOE) constraints. The program extracts NOE information from either NOESY and/or ROESY spectra and determines the molecular stereochemistry accordingly. Results of selective NOE or ROE experiments can also be used for input to the program. This process can be carried out for several of the most likely structures produced during a structure elucidation by the expert system or performed on a chemical structure proposed by the chemist.

The utility of NOESY/ROESY spectra for relative stereochemistry determination is based on a direct

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correlation between both the crosspeak volume integration and the internuclear distance. Peak intensity in NOE/ROE measurements has an inverse sixth power relationship. Consequently,[8] what can be referred to as a 'strong' NOE is generally observed between pairs of hydrogens, which are 1.8–2.5 Å apart. Responses of 'medium' intensity usually correspond to an internuclear distance of 2.5–4.0 Å while 'weak' NOEs will generally be observed for larger distances if they are observed at all. NOE responses are not commonly observed for nuclei farther than 6.0 Å apart. A more detailed discussion of the correlation between NOE cross-peak intensity and internuclear distance will be given below.

Minimization algorithms deal with numerical values and, in this case, these numerical values are extracted from a set of NOEs overlaid on a 3D structure and examined for goodness of fit. The function describing this goodness of fit is called a penalty function. The better the solution then the lower the value of the function. The function must exhibit the lowest value for the best-matching stereoisomer.

In the present contribution, an appropriate function is suggested that can be minimized by calculation for all stereoisomeric structures or by using a genetic algorithm to limit the number of stereoisomers that need to be investigated.[9] To improve genetic algorithm convergence, efficient methods of parameter optimization are suggested and compared. Suggested methods for determining the relative stereochemistry of structures as well as the calculation of their 3D configurations are examined using complex structure examples. For this purpose, we have chosen to illustrate the proposed method using the complex natural products of Taxol ($C_{47}H_{51}NO_{14}$) and brevetoxin B ($C_{50}H_{70}O_{14}$).

2. Algorithms used for 3D structure determination

2.1. 3D structure optimization with molecular mechanics

Optimizing the three-dimensional geometry of an organic molecule from a molecular graph is a well-known problem that, in the case of small molecules, with less than 10–30 non-hydrogen atoms, can be performed using non-empirical quantum mechanical methods. These methods are computationally cumbersome and are rarely used in drug discovery applications. Fortunately, for most small organic molecules the task can be treated with a classical mechanics approach ('molecular mechanics').[10]

Falk et al.[11] reported a molecular modeling procedure to determine the relative configuration of a chiral molecule from NMR data. The procedure used constrained molecular mechanics with the constraints being interproton distances derived from the experimental nuclear Overhauser enhancement (NOE) data. High-temperature molecular dynamics allowed inversions at most stereocenters allowing the distance constraints to guide the molecule into configurations consistent with the NOE data. For molecules with complex ring systems this approach can fail to invert certain centers with sufficient frequency and this was countered by allowing additional inversions of selected stereocenters. The procedure was proven on organic molecules of known stereochemistry, with 5–17 chiral centers, provided that the number of available constraints was at least twice the number of stereocenters. The procedure was shown to be tolerant of large errors in the estimated interproton distances and is reasonably rapid.

In the current study, we used a molecular mechanical method with the popular CharMM parameterization[12] as a starting point that is subsequently minimized to obtain the optimal molecular geometry.

Commonly, the full molecular energy is estimated by the following sum:

$$E_{\text{Total}} = E_{\text{bonds}} + E_{\text{angles}} + E_{\text{dihedrals}} + E_{\text{improper}} + E_{\text{VdW}} \tag{1}$$

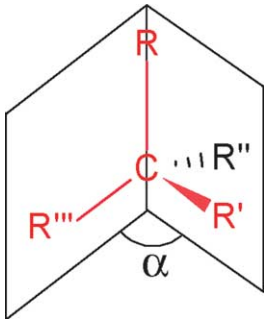
where E_{bonds}, E_{angles}, and $E_{\text{dihedrals}}$ stand for the energies of covalent bonds, valence, and dihedral angles, respectively, and are calculated as follows:

$$E_{\alpha} = \sum k_{\alpha}(\alpha_{\text{real}} - \alpha_{\text{ideal}})^2 \tag{2}$$

where α_{real} represents the current value of a structural parameter (i.e., bond length) and α_{ideal} is the 'ideal' value of the same parameter as defined and tabulated in the original article.[12] In this expression, the term k_{α} is a proportionality coefficient. E_{improper} corresponds to the energy of 'improper torsions', which are normal torsion angles with larger associated proportionality constants. The larger proportionality constants in this case serve to provide constraints that serve, for example, to keep benzene rings planar, etc.

We also make use of improper torsions to maintain stereocenter configurations while performing the molecular geometry optimizations.

For each chiral center, improper torsions, related to the energy value E_{improper} are introduced as indicated on the drawing below.



When a molecule is mirrored, the value of such a torsion change is energetically high so that freezing these angles prevents the stereocenters from being inverted. Finally, E_{VdW} is calculated as follows[12] (the sum is taken over all possible pairs of atoms):

$$E_{\text{VdW}} = \sum_{i \neq j} k_{\text{VdW}}\left(a_{ij}R_{ij}^{-12} - bR_{ij}^{-6}\right) \tag{3}$$

and is an approximation of van der Waals forces. Here, the

a_{ij} and b coefficients depend on atom types, R is an internuclear distance and k_{VdW} is a proportionality constant.

If distance restrictions derived from the NOE correlations are to be included into the calculation then we use $E_{GrandTotal}$ instead of E_{Total}:

$$E_{GrandTotal} = E_{Total} + E_{NOE} \quad (4)$$

where E_{NOE} is an NOE penalty function characterizing how consistent the current geometry is with the set of NOE restraints. The next Section 2.2 describes this penalty function.

2.2. NOE penalty function calculation

To make use of NOESY correlations we have chosen a penalty function for a given pair of atoms as follows.[13] The total penalty function is a sum of terms:

$$E_{ij}^{NOE} = k_{NOE}\begin{cases}\sqrt{1+\dfrac{(D^2-L^2)^2}{L^4}}-1, & \text{if} \quad D<L \\ 0, & \text{if} \quad L\le D\le U \\ \sqrt{1+\dfrac{(U^2-D^2)^2}{U^4}}-1, & \text{if} \quad U<D\end{cases} \quad (5)$$

where D is the current value of an internuclear distance and U and L are upper and lower estimates, respectively, for the internuclear distance. These estimates are derived from the NOESY crosspeak intensity, as will be shown below. The term k_{NOE} is a proportionality constant that is consistent with other proportionality constants used elsewhere in the force field. For the CharMM[12] parameterization values of 5–20 kcal/mol are suitable.

To obtain estimates for the values of U and L, we have implemented two schemes. The final choice, however, depends on the quality of the spectra and is ultimately left to the user.

- The first scheme was suggested by Wüthrich.[8] When this approach is used NOESY peaks are separated into three groups according to their volumes: 'strong' (15–100% of maximum the peak volume of the largest off-diagonal peak), 'medium' (1–15% of maximal peak volume) and 'weak' (everything else above noise level) according to the peak volumes. Corresponding internuclear distance restraints are assigned for the each group: 1.8–2.5 Å for strong, 2.5–4.0 Å for medium, and 4.0–6.0 Å for weak responses. Our experiments have shown that using peak heights instead of volumes decreases the calculation accuracy because of how substantially peak widths can differ.
- Through-space interactions between nuclei can be regarded as magnetic dipole–dipole interactions. The equations that govern dipole–dipole relaxation define the intensity of such an interaction to be proportional to r^{-6}, where r is the distance between the two protons engaged in the dipole–dipole relaxation process.[14] Consequently, the upper limit of the distance between two protons can be calculated as follows:

$$U = \left(\frac{r_{ref}^{-6}}{V_{ref}}V\right)^{-1/6} \quad (6)$$

where V_{ref} is the volume of the reference peak and r_{ref} is the corresponding internuclear distance between the reference peak and the peak of interest. In most cases we use the crosspeaks between anisochronous geminal protons in a CH_2 group as reference peaks since such peaks are almost always present, and the r_{ref} value is well-established ($\sim$1.8 Å). Because a crosspeak's intensity is sensitive to many experimental parameters, Eq. 6 can only be used to calculate the upper limit of an internuclear distance. The lower distance limit is usually set as the sum of the van der Waals radii of two hydrogen atoms, that is, 1.8 Å.

In proteins and larger peptides the concept of ambiguous assignment is widely used since it is difficult in these crowded spectra to unambiguously assign crosspeaks to a pair of atoms where there are chemical shift uncertainties due to overlap. Any ambiguous assignment is characterized by two sets of chemical shifts and any pair of items from either of these two sets may contribute to the observed crosspeak. For an ambiguously assigned peak, U and L values can be calculated in the same way as an unambiguous one. Some difficulties arise while calculating the D value. It was suggested to use the r^{-6}-summed distance $\bar{D}$:[15]

$$\overline{D} = \left(\sum_{a=1}^{Nb} r_a^{-6}\right)^{-1/6} \quad (7)$$

instead of D. In Eq. 7 summation is performed over all possible pairs of atoms. It can be shown that the final value is always smaller than the shortest internuclear distance. The contribution of any pair can be calculated as:[15]

$$\chi_{mk} = \frac{r_{mk}^{-6}}{\sum_{i,j} r_{ij}^{-6}} \quad (8)$$

(obviously, the sum of χ_{mk} terms is equal to unity). The bigger the contribution from a particular pair (i.e., χ_{mk} value) is the more probable it is that the assignment of an NOE peak will be made to it. In the current version of the software an ambiguous bond is treated as an unambiguous bond if one of the χ_{mk} values exceeds 95%.

2.3. Search by running over all stereoisomer structures

Natural product molecular structures run the gamut from conformationally rigid to highly flexible molecules. The most common, however, is the intermediate combination of both rigid and flexible substructures contained within a single molecule. For the molecules used in this study, Taxol and brevetoxin-B, there are a large number of unique conformers. Since many natural products include conformationally rigid fused ring units, such molecules are very amenable to study using NOE or ROE experiments. For the study of flexible components of the molecules J-based analysis NMR methods have been developed in order to

assign the configuration of the stereochemical centers.[3] For our purposes, we will assume from this point on that there is a single 'best' conformation assigned to each stereoisomer. Thus, in a case of a molecule with N stereocenters there are 2^N stereoisomers to be inspected.

Experience shows that direct evaluation of the target function for each possible stereoisomer is possible for small molecules with a molecular mass of 100–200 Da and 2–7 chiral centers.

In such simple cases we can follow three steps in order to obtain a result:

1. For a given covalent structure with N chiral centers generate the full set of 2^N isomers;
2. Optimize each 2D structure into a 3D model where the stereocenter configurations are kept fixed with the aid of improper torsions as detailed earlier;
3. All models are ranked according to their penalty function values. The top ranked stereoisomer is considered as the most probable.

Later in this manuscript, we will demonstrate the application of this approach to taxol (see Section 3).

2.4. The genetic algorithm (GA) approach

Genetic algorithms represent an attempt to model an evolutionary process using purely stochastic means. The central concept of the approach is encoding of a series of control variables. The control variables are assigned to a particular solution referred to as a 'chromosome'. Usually a set of chromosomes is generated and this results in a pool of structures as an output.[9,16] In the most general scenario, the application of a genetic algorithm for solving the problem posed above can be described by the following five steps:

1. Encode the stereochemical information associated with a solution, the stereoconfiguration of the analyzed molecule, in the form of a chromosome. Specifically, in the current work we encode a molecule within a chromosome by assigning a value of zero to R-stereocenters and a value of one to S-stereocenters. The length of a chromosome is equal to N, the total number of stereocenters in the structure.
2. Create a pool of chromosomes by random placement of ones and zeros in the N positions of the chromosome vectors.
3. *Perform crossovers*. Two offspring are created from a pair of ancestors by exchanging all the bits following after a selected locus. For example:

Ancestors	Locus selection	Offspring pair
0101101100011	**0101101** **100011**	**0101101** 100110
0111011100110	0111011 100110	0111011 **100011**

More precisely, the operation should be referred to as a one-point crossover, to differentiate it from a more sophisticated modification. A more realistic example can be found later in this report where benchmark calculations are discussed.

4. *Perform mutations*. Mutation is simply a random change in a chromosome vector with a given probability, P_M, of one of the adjustable parameters. The purpose of the mutation stage is to provide insurance against an irrevocable loss of genetic information and hence to maintain diversity within the population. An example is shown below.

Initial chromosome	Selecting bits for mutation	The result
0111011100110	011**1**01110**0**110	010101110**1**110

5. *Natural selection*. After a new solution (a set of chromosomes) is generated the offspring with the worst target function values are eliminated to maintain the pool size. This is denoted by the variable PoolSize.

The algorithm as described here is the simplest implementation of a genetic algorithm. The intrinsic challenge of this method is the possible degeneration of the pool. This is defined as the situation in which the whole pool evolves from only a few ancestors. As a consequence, the diversity of the pool drops and the algorithm may become trapped in a local minimum. This is characteristic for complex structures with more than 10 chiral centers. However, even for smaller molecules pool degradation may lead to the requirement of a bigger number of steps needed and therefore a longer run time. To increase the efficiency of this algorithm we have implemented enhancements that are crucial when dealing with very complex (>10 chiral centers) molecules, and which may be optionally used for simpler cases.

1. *Diversity guided crossover*. In the standard implementation, crossover is performed with a given probability, P_C, over randomly selected pairs of ancestors. In the present study, this step has been replaced with a diversity-guided crossover to maximize the genetic diversity of the offspring and to thereby minimize the number of generations needed to reach the solution. A similar approach has been taken in an earlier work.[17] First, we introduce a diversity function, F_{diff}, the so-called Hammond distance function (see the original report[17] for further details) for a given pair of ancestors:

$$F_{\mathrm{diff}}(\mathrm{Item1},\mathrm{Item2}) = \frac{1}{\mathrm{CLength}/2}\min\left(\sum_{i=1}^{\mathrm{CLength}} d_i; L - \sum_{i=1}^{\mathrm{CLength}} d_i\right), \quad d_i = \begin{cases} 1, & \text{if} \quad \mathrm{Item1}[i] = \mathrm{Item2}[i] \\ 0, & \text{if} \quad \mathrm{Item1}[i] \neq \mathrm{Item2}[i] \end{cases} \tag{9}$$

Item1 and Item2 denote two chromosomes and Item1[i] refers to the i-th bit). CLength refers to the chromosome length. It can be shown that both F_{diff}(Item1, Item1)=0 and F_{diff}(Item1, inversed Item1)=0. If half of the bits contained in the two chromosomes are different, then $F_{diff}=1$. PoolSize$\cdot P_C$ pairs with the highest possible diversity function values are selected and crossover is performed on this set.

2. *One-point crossover versus uniform crossover*. Uniform crossover implies an exchange at each bit position with a

probability of 0.5. Some authors strongly believe in the superiority of this approach,[18] but in this work the application of the GA approach to the solution of stereocenter determination has shown that one-point crossover exhibits much better results. The bottleneck in the implementation is chemically reasonable encoding of the chromosome. For instance, it is necessary to encode the stereocenters in a chromosome in accordance with their order and proximity in the real structure. The intention in this approach is to ensure that the local vicinity of most centers is not overly perturbed during the crossover process.

3. *Determining the local minima*. In general, crossovers can be thought of as tools to explore wide areas of conformational space and thereby assist in the determination of a global solution. Mutations, in turn, help to step down to a local minimum, which may be isolated after a serendipitous crossover event. In our experience, random mutations are computationally costly and not very efficient. The computational cost and lack of efficiency of random mutations is the primary reason that they have been replaced in the present study with a simple function that tries to find a local minimum. This process works as follows. Assume the existence of a set of chromosomes as a starting point. For a given chromosome, CLength offspring are produced by subsequent mutation of different bits. The target function is then evaluated for each of the modified offspring chromosomes. If one of them is better than the ancestor, the ancestor is replaced and the procedure is repeated on this 'best fit' offspring.

4. *Exponential selection*.[19] To encourage diversity, solutions with poor target function values are not immediately discarded. After a crossover, mutations and the determination of local minima proceed and the target function value is calculated for each item in the pool. As a target function the NOE penalty function (5) introduced above is applied. The pool is sorted to rank order the best values first and the j-th item is kept according to the following definition of probability:

$$P_j = \alpha \exp\left(\frac{-\beta j}{\text{PoolSize}}\right) \tag{10}$$

The first item is kept with α probability ($j=0\ldots$(PoolSize$-$1)). Preliminary experiments have shown that the optimal values are $\alpha=0.6$, $\beta=0.3$. For reference purposes the step responsible for the transition from crossover to natural selection is referred to as a 'generation' and several generations form a 'genetic run'.

The most powerful modification implemented in this work is a tournament selection scheme.[20] When two genetic runs are completed, a new pool of arbitrary size is produced by merging the two final pools and a new genetic run is performed. This process is referred to as one tournament stage. In the current version of software both one-stage and two-stage tournaments have been implemented. In the two-stage tournaments, four runs are performed in the first step, second in the second step, and one final run in the last step.

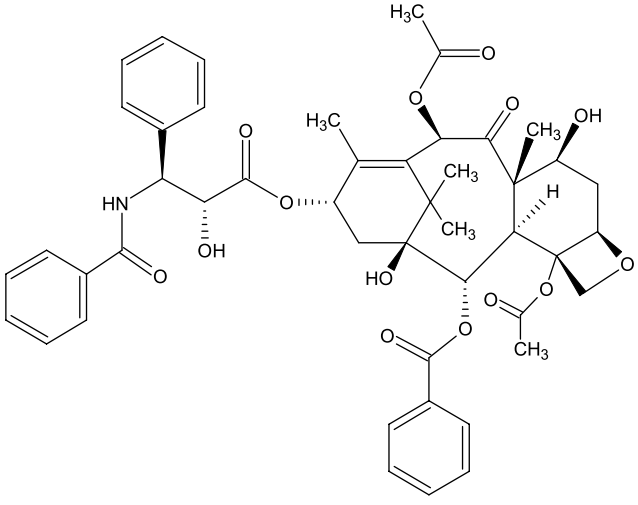
The algorithm developed to represent one genetic run is summarized below.

```
Randomly fill in population items;
For i = 1 to Generations Count do
    Calculate diversity function for each pair;
    Perform P_C·PoolSize crossovers;
    Randomly mutate P_M·PoolSize items (optional);
    Calculate the target function for each item;
    Select the 2–3 best chromosomes and perform a local
    minimum search (optional);
    Calculate the target function for new items;
    Sort pool;
    Delete items according to the exponential scheme;
End;
```

3. Results and discussion

3.1. An example of a genetic run and parameter optimization for Taxol

Taxol (**I**) is a complex polyoxygenated diterpene natural compound found in the stem bark of the western yew tree, *Taxus brevifolia Nutt*. Its anti-cancer activity has been extensively investigated.[21–23] Taxol exhibits activity against a number of leukeamias and solid tumors in the breast, ovary, brain, and lung[24] in humans. The first X-ray structure characterizing the stereochemistry of this compound was obtained in 1971.[25] Taxol has a 4:6:8:6 skeleton as well as pendant moieties. Complex stereochemistry is abundant throughout the molecule; there are 11 stereocenters. In the current study, we deal only with nine of 11 stereocenters since the other two are located on a flexible part of the molecule and this prevents NOE data from being observed for protons in this part of the structure. In such cases *J*-based analysis techniques[3] would be applied for the determination of stereochemical information but our approach does not yet account for such input data.



I

Initially all stereoisomers were produced ($2^9=512$) for the structure and the penalty function value (PFV) calculated

for every one in order to validate the accuracy of the penalty function calculation. These calculations were performed in 550 s using the computer described in the Section 5. The two lowest values from the penalty function were from the stereoisomer pictured here **I** and its mirrored twin, which would be expected to show similar interatomic distances after a 3D optimization. The difference in the PFV values of this pair of stereoisomers only differ by about 10% relative to their nearest neighbor in the rank order.

Following the protocol described earlier, the application of crossovers proceeds as represented in Table 1. Each stereocenter was associated with a chromosome locus and encoded with 0=R and 1=S as mentioned earlier. Initial chromosomes were generated randomly. This example illustrates that even after one generation the average penalty function value (PFV) in the pool drops. Quantitatively the decrease in the value of the PFV is a decrease of about 20% from 45.8 in the initial pool to 37.5 in the next. The best chromosome in the new pool has a PFV of 19. For taxol and other species of similar complexity PFVs of 5–10 are typically achieved for the correct stereoisomers. For the present case PFVs for **I** and mirrored **I** are 5.7 and 5.9, respectively. The structure ranked differs from **I** by one chiral center configuration and 3.1 PFV units. However, PFV never drops to zero because of the uncertainty in determination of exact conformation for a given stereoisomer.

To investigate how the number of generations and pool size influence the overall performance, as well as algorithm convergence, 100 tests were run using the taxol data as input. Ten generations were run with varying pool size. The results of testing three different modifications of the genetic algorithm and comparisons of their accuracy and speed are given below.

3.1.1. Plain algorithm. The 'plain algorithm' is the implementation of GA with no mutation or tournament selection and with the new pool formed only by the crossover. The results are summarized in Figure 1. With approximately eight generations and a pool size of 12–15 items the probability of success is >95%. We imply that a run is successful if the final pool contains the right stereoisomer.

3.1.2. Complex algorithm. In this implementation the pool is mutated after performing a crossover. Purely random mutations do not prove effective for this application. Mutations are performed with unity probability on degenerate positions in the chromosome. This modification can reduce the number of generations needed to five or six. As seen in the case of the plain algorithm described above, small pool sizes (4–6) continue to show poor results and are not recommended (see Fig. 2) whereas a pool size in the range of 8–10 again gave a >95% probability of success.

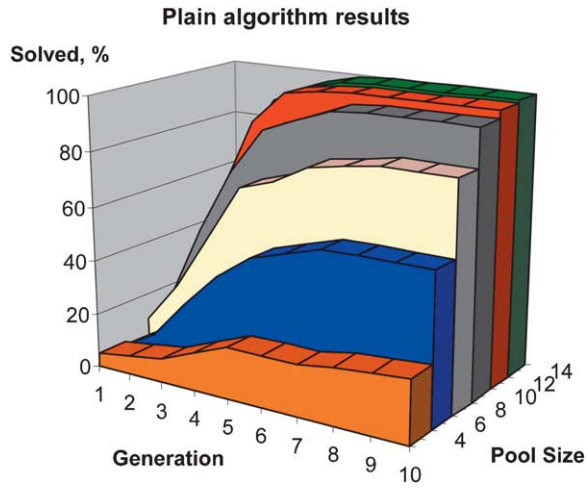


Figure 1. Results for the implementation of GA without mutation or tournament selection. The percentage of genetic runs where the structure is solved correctly is given as a function of the pool size and generation.

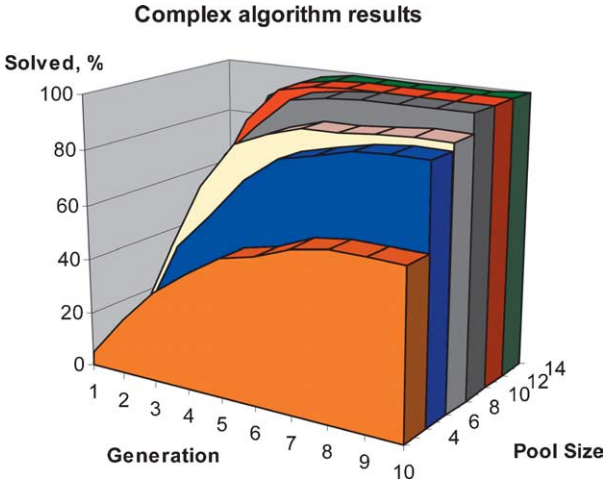


Figure 2. Results for the implementation of GA with mutation but without tournament selection. The percent of genetic runs where the structure is solved correctly is given as a function of the pool size and generation.

3.1.3. Tournament selection. Due to the different workflow

Table 1. A crossover example

Initial pool			New pool		
No.	Chromosome	Penalty function value	Parents	Chromosome	Penalty function value
(1)	111101 101	35	(5)+(6)	110100 100	19
(2)	011101101	40	(1)	111101101	35
(3)	1011 11000	44	(8)+(1)	1011 01101	39
(4)	000000111	45	(2)	011101101	40
(5)	1101 00111	47	(6)+(7)	1111 01001	41
(6)	1111 01100	50	(3)+(7)	1011 01001	42
(7)	0010 01001	53	(3)+(5)	1011 00111	43
(8)	1011 11001	53	(8)+(3)	1011 11000	44

The initial pool and the first set of offspring are indicated as well as which parents contribute to each offspring. For each chromosome, the PFV is given.

organization in the implementation of GA with tournament selection, it is difficult to directly compare the performance of this implementation to the previous two. Here, we tested the one-stage tournament selection for comparison (i.e., two runs on the first stage and the final genetic run). Each of the genetic runs included three generations resulting in nine generations from the entire workflow. In Figure 3, the performance of the tournament selection algorithm is compared with the first two algorithms described above.

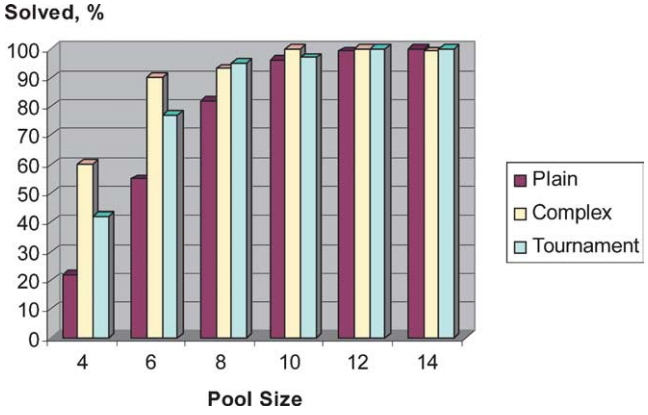


Figure 3. Performance of the two-stage tournament selection algorithm compared with the plain algorithm and complex algorithm (with mutations). Nine generations were used to produce these performance statistics.

From the results presented here it is concluded that adding mutations and/or arranging a tournament selection is the best implementation of the genetic algorithm for this work. However, there is one more metric to be considered in this evaluation. Table 2 summarizes the data related to the speed of the overall process. In the current version of software, up to 99% of computing time is spent on 3D optimization of the structures. The number of 3D optimizations may be used as an approximate measure of the total computing time. Since the quality of the results is the highest priority of the study only those parameter combinations that lead to success in 95% or more of the runs will be discussed. From Table 2 it may be concluded that the genetic algorithm is superior to a deterministic approach since the run with optimal parameter values is more than twice as fast as enumerating all possible isomers for this example—with optimal parameters around 200 3D optimizations are performed versus as many as $2^9=512$ needed for enumerating all possible stereoisomers. It is concluded that the plain algorithm (with 10 chromosomes in the pool) and the tournament selection modification (with a pool size equal to 8) are the best options.

Table 2. Comparison of the speed of different algorithm modifications and parameter sets (for runs where >95% are successful)

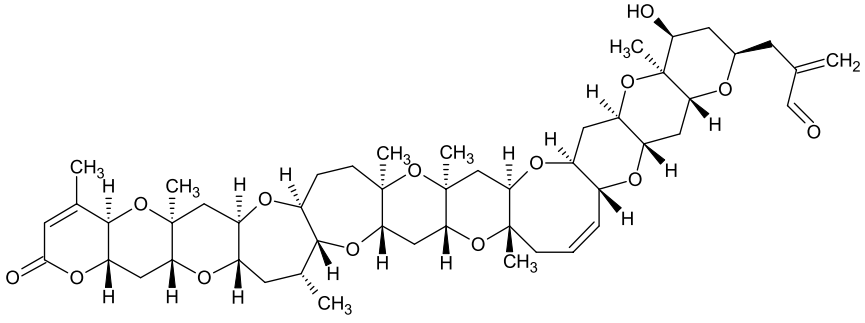
Algorithm modification	Pool size	Number of optimizations
Plain	10	201*
	12	327
	14	463
Mutations	10	275
	12	368
	14	471
Tournament	8	177*
	10	276
	12	397
	14	525

The fastest options are marked with an asterisk.

3.2. A challenging example: brevetoxin B

To challenge the system the structure of brevetoxin B (**2**) has been examined. Brevetoxin-B is the first and most prominent member of the brevetoxin family, produced by the dinoflaggelate *Ptychodiscus brevis* Davis (*Gymnodinium breve* Davis). This compound was isolated and characterized by spectroscopic and X-ray crystallographic means in 1981 by the groups of Lin, Nakanishi, and Clardy.[26,27] The highly complex molecular architecture is characterized by a novel array of ether oxygen atoms, regularly placed on a single carbon chain. This remarkable structure includes 11 rings, 23 stereogenic centers, and three carbon–carbon double bonds. The CPU time necessary for running over all ~8.4 million stereoisomers corresponding to this structure was estimated to be about one month.

In order to perform a comprehensive investigation of all the stereoisomers possible for brevetoxin-B, we attempted to solve this problem using both the genetic algorithm and by applying a simulated annealing algorithm.[28]



2

3.2.1. Simulated annealing (SA) algorithm.[27] Simulated annealing (SA) is a generic probabilistic heuristic approach for the global optimization problem, namely locating a good approximation to the global optimum of a given function in a large search space. In the SA method, each point s of the search space is compared to a state of an abstract physical system, and the function $E(s)$ to be minimized is interpreted as the internal energy of the system in that state. Therefore, the goal is to bring the system, from an arbitrary initial state,

to a state with the minimum possible energy. The implementation of the algorithm employs a random search and accepts not only the changes that decrease the objective function E, but also some that increase it. The latter are accepted with a probability of $p = \exp(-\delta E/T)$ where δE is the increase in E, and T is a control parameter, which by analogy with the original application, simulation of a metal solidifying, is known as the system 'temperature', irrespective of the objective function involved.

Programmatically, the algorithm consists of the following routines:

a. New solution generation. Applying relatively small, random changes to the previous solution.
b. Energy calculation. Accepting or rejecting an increase in E, if any, and updating the solution, if needed.
c. 'Annealing schedule'—this word-combination is introduced to refer to the degree to which the next minimization step in the process possesses a higher $E(s)$ value than the preceding step during the search. It includes the initial and final temperature estimates, as well as the rate of temperature change.

Since this type of approach is used routinely today for the determination of the biomolecular structures of DNA and proteins based on NOESY/ROESY data (see articles [29–31] for corresponding software package descriptions) an investigation into the efficacy of such an approach on the types of problems discussed here was deemed appropriate.

For the purposes of validation a stereoisomer of brevetoxin-B with seven stereocenters exhibiting wrong stereoconfiguration was generated. 3D coordinates and 120 distance restraints were introduced into the GROMACS software package,[31] a molecular dynamics simulation software package, which includes a simulated annealing energy minimization algorithm that is of value for this work.

The OPLS-AA force field[32] was used, with initial temperatures T_0 of 500, 1000, 3000, and 5000 K. A linear cooling scheme from T_0 down to 0 K was used while performing the simulated annealing. These experiments gave a series of resulting structures with 5–8 stereocenters with the incorrect chirality. By this process the conclusion was that simulated annealing is not as efficient in determining relative stereochemistry as it is in biomolecular structural chemistry, since it failed to find the correct unique stereoisomer configuration for brevetoxin-B.

The cause of such a profound failure can be explained by noting that a typical protein needs to cross a 5–15 kcal/mol barrier during a conformational change. The barrier for stereocenter inversion in a molecular structure with a rigid fused ring skeleton is much higher at an energy of 30 kcal/mol or more. To employ simulated annealing in this case the annealing temperature should be raised up to 10,000–50,000 K. Such parameters frequently lead to instability in the software package and are therefore avoided.

We are not questioning either the general utility or effectiveness of the simulated annealing algorithms, but rather have observed that in the specific case of low molecular weight rigid-skeleton molecules, for example, brevetoxin-B, with numerous stereocenters, that the parameters representing the annealing schedule and force-field parameterization need revisiting in order to achieve improved performance. In other words, direct application of the existing biopolymer-based SA approaches to molecules such as brevetoxin-B (**2**) is not straightforward. An alternative method to SA is therefore required.

3.2.2. Elucidation of the relative stereoconfiguration of brevetoxin-B by a genetic algorithm. The main problem with the genetic algorithm was the tendency of the algorithm to deteriorate toward pool degeneration. The search becomes trapped in a local minimum resulting in reasonably good, but not optimal solutions. In the case of simpler structures like taxol, random mutations of the pool vectors can be used help to overcome this problem. In more complex cases improvements in the algorithm are necessary.

The standard GA implementation utilizing crossover and mutation did not provide positive results. Introduction of exponential selection and tournament selection resulted in only 30–35% of the runs (twenty trials were performed for each algorithm modification, unless stated otherwise) being successful—that is, the right stereoisomer was present in the finally formed pool. Since performing random mutations exhibited no improvement, the random mutation step was enhanced by including an alternative local minima operation. To save run-time this stage is performed for only 2–4 of the best structures in the pool. All local minima searches take about 10 min—around 6% of the total run time for the task (around 2 h 50 min). The rest of the time is consumed by 3D optimizations related to crossover process.

Chemically-reasonable encoding (i.e., stereocenters in physically close proximity in the structure are placed as close as possible in the chromosome) proved to be the most efficient improvement in the algorithm. The implementation is run with exponential selection, tournament selection, local minima detection, and chemically-reasonable encoding 100 times and the right stereisomer is determined in each final pool. An example run is summarized in Table 3. A pool size of 20 with four generations for each genetic run gave 28 generations in total. The table indicates that the tournament selection scheme is necessary in the case of brevetoxin-B since the NOE penalty function steadily drops after each subsequent round of the tournament.

In Figure 4 the structure of brevetoxin-B from X-ray studies (yellow) and the structure obtained from the best chromosome in the final pool for our system for stereochemistry determination (blue) are shown as superimposed structures. In this case, the configuration of all of the stereocenters in both structures are the same. Even the conformations of the most 'flexible' seven- and eight-membered rings are similar. This demonstrates the power of the approach we have described to facilitate the identification of relative stereochemistry in a complex molecule containing multiple stereocenters.

Table 3. An example run workflow

		Tournament round 1				Round 2		Round 3
		Run 1-1	Run 1-2	Run 1-3	Run 1-4	Run 2-1	Run 2-2	Run 3-1
Penalty function	Best	32	36	15	38	13	12	10
	Average	43.2	46.9	37.9	54.7	20.3	22.3	15.5
Number of incorrect stereocenters	Best	3	2	5	3	1	1	0
	Average	7.8	8.0	8.4	6.3	5.8	6.9	5.7

Pool size=20; Four generations are treated during each genetic run. Here, the algorithms of tournament selection, exponential selection and local minima finding are used. For each genetic run, a penalty function value and the number of incorrect stereocenters (best and average in a pool) are given.

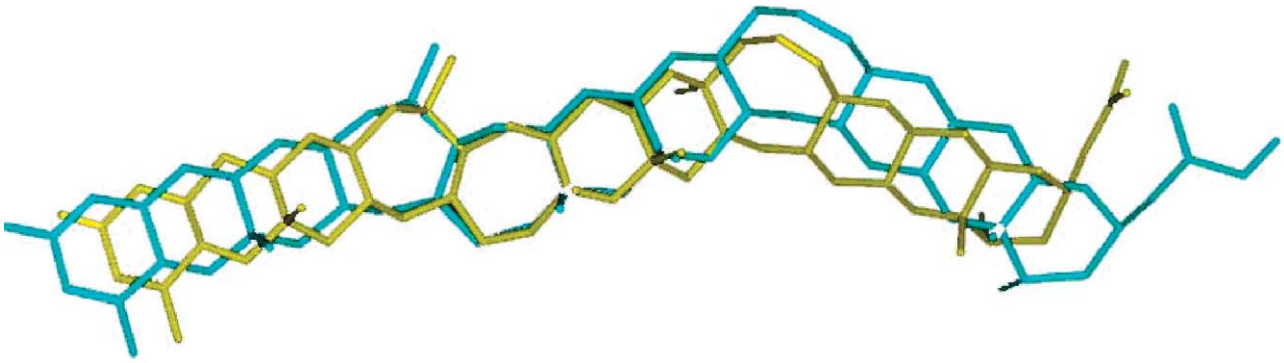


Figure 4. The X-ray crystal structure of brevetoxin B (yellow) and the 3D model of the best stereoisomer from the final pool (blue) of the stereochemistry determination system are superimposed. Small differences in the bond angles of some of the more flexible rings are present, but all stereocenters have been properly oriented.

4. Conclusions

A method for using a stochastic genetic algorithm for the determination of the 3D models of molecular structures is demonstrated by the application method to two complex natural products. Since the chromosomes used here only incorporate information about stereocenter configuration, and not information such as chair or boat ring conformations, conformational rigidity is essential to obtain accurate results. This requirement presently limits the algorithm to the fused ring portions of molecules. Relatively simple problems of 2–6 chiral centers may be solved in a straightforward manner by the enumeration of all stereoisomers and the calculation of the corresponding target function values. This process is fast and this approach is preferred over the use of genetic algorithms for molecules with smaller numbers of stereocenters.

Several genetic algorithm modifications have been tested on the more complex example of taxol that contains nine stereocenters in the rigid part of the molecule. A simple algorithm based only on crossovers was shown to be efficient in this case. More advanced algorithm implementations delivered approximately the same quality (i.e., percent of successful runs), while consuming more CPU time. Several improvements to the genetic algorithm were necessary to obtain high quality results on a very complex problem like brevetoxin-B, which contains 23 chiral centers. Such modifications included tournament selection and diversity-guided crossover. The results demonstrated to date are promising and the evaluation of the algorithms described here continues on a variety of complex natural products.

5. Experimental

The NMR spectra of taxol were acquired on a Varian INOVA 500 MHz spectrometer at 30 °C with $CDCl_3$ as a solvent. A set of 1D ^{13}C and ^{1}H experiments, two-dimensional experiments: COSY, HSQC, HMBC, and NOESY (mixing time: 700 ms) were obtained.[33] Spectral processing including peak peaking and peak volume measurement were performed with ACD/Labs' 1D NMR Processor and 2D NMR Processor software packages. The structure of the molecule was elucidated with ACD/Labs' Structure Elucidator expert system that has been described previously.[4–7] The assignments and the volumes of peaks in the NOESY spectrum (57 peaks) were included as inputs into the software.

The NMR spectra of brevetoxin-B were acquired using a Varian INOVA 600 MHz spectrometer at 25 °C with DMSO-d_6 as the solvent. The same experimental data sets as above: 1D ^{13}C and ^{1}H, COSY, HSQC, HMBC, and ROESY (mixing time: 400 ms) were used in the studies. The spectra were also processed in the same way as described above. Assignments were validated with literature data for the same[34] molecule and another member of brevetoxin family.[35] ROESY peak assignments resulted in producing 120 distance restraints.

All computations were performed on a PC Pentium IV computer operating at 2.8 GHz with 1 GB of RAM. A user-friendly interface was developed during this work to allow the user to visualize all of the stereoisomers presented in a conventional form along with the corresponding energies and NOESY/ROESY connectivities.

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Thiacalix[4]arene derivatives with proximally bridged lower rim

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Abstract—New types of lower rim proximally bridged thiacalix[4]arenes have been prepared by direct aminolysis of starting tetraacetate derivative in the cone conformation using aliphatic α,ω-diamines. X-ray crystallography revealed the highly preorganized array of –C(O)NH– bonds resulting in strong intramolecular hydrogen bonding between amide groups of both bridges. The length of the corresponding diamine was found to have an essential influence on the yield of these bridged molecules.

1. Introduction

Thiacalixarenes[1] have appeared recently as novel members of the well-known calixarene[2] family. The presence of four sulfur atoms results in many novel features[3] compared with 'classical' calixarenes, such as different complexation ability with sulfur contribution, easy chemical modification, different size and different conformational behaviour. Hence, thiacalix[4]arene exhibits a broad range of interesting functions, which make this compound a good candidate for many applications in supramolecular chemistry. Despite some recently described procedures for thiacalix[4]arene derivatization,[4,5] the chemistry of these compounds is still rather undeveloped.

In our recent papers, we have described the synthesis of thiacalix[4]arenes bearing amidic functions on the lower rim.[4q,r,t] These molecules represent potential building blocks suitable, for example, as the cores for dendritic structures or host systems preorganized for the complexation of various guests. The total number of described amide-functionalized thiacalix[4]arenes, however, still remains relatively low.[3] Until now the most frequent way of synthesising amide-functionalized thiacalix[4]arenes has been to use of the corresponding carboxylic acids together with appropriate coupling agents (DCC, CDI, HOBt etc.) or by application of reactive acyl chlorides. During our research connected with syntheses of thiacalix[4]arene-based dendritic cores,[4q,r] we also investigated the preparation of amide-functionalized thiacalix[4]arenes by means of the ester aminolysis reaction. Several examples of aminolysis of ethyl or methyl esters of 'classical' calix[4]arenes have been already reported.[6,7] Among them Wu et al. described the formation (unfortunately, without any specification of the yields) of unusual lower rim double 1,2-amide-bridged calix[4]arenes upon treatment of calix[4]arene tetraethyl acetate with an excess of appropriate diamines in ethanol.[7b] To the best of our knowledge there is no example of aminolysis reaction in the thiacalix[4]arene family so far with only one exception. In our recent paper we have mentioned aminolysis of the known tetraacetate cone **1** with an excess of ethylenediamine in THF at ambient temperature. However, only an intractable mixture containing the corresponding tetraamine derivative **4** ($n=2$) as major product together with partly substituted and bridged compounds has been obtained.[4r] Herein we wish to report the results of aminolysis of readily accessible *p-tert*-butylthiacalix[4]arene tetraethyl acetate **1** in the cone conformation[4e] with an excess of different aliphatic α,ω-diamines **2a–c** in refluxing ethanol.

2. Results and discussion

2.1. Synthesis

The aminolysis reaction was accomplished according to Scheme 1. Tetraacetate derivative **1** was refluxed with 10 equiv of appropriate α,ω-diamine **2a–c** in ethanol overnight to give the corresponding doubly-bridged compounds **3a–3c** fixed in the cone conformation in 36, 19 and 8% yields, respectively. These compounds were

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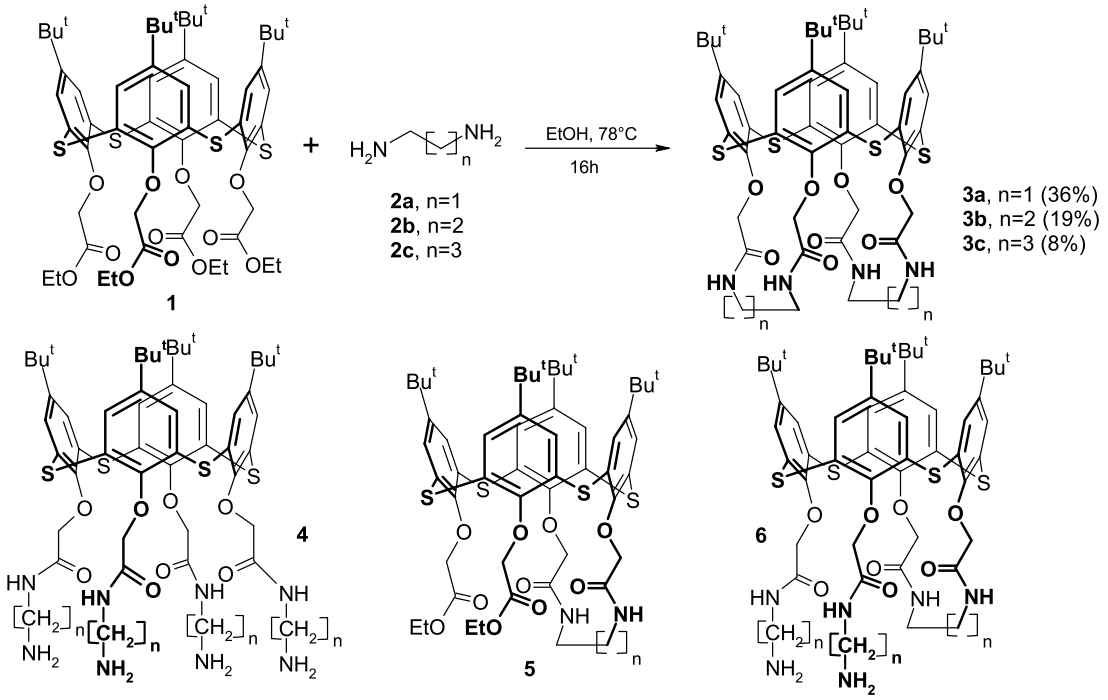

Scheme 1. Aminolysis reaction of *p-tert*-butylthiacalix[4]arene tetraacetate in cone conformation with aliphatic α,ω-diamines.

easily isolated by preparative TLC on silica gel, as their chromatographic behaviour is substantially different (highest R_f values) from the all other components of complicated reaction mixtures. Interestingly, the yield of doubly intramoleculary bridged cone conformers **3a**–**3c** depends on the excess of corresponding diamine. Thus, using less then 5 equiv of diamine led to a rapid decrease in the yield of doubly bridged molecules and the singly bridged compounds **5a** and **5b** in which two ethyl ester groups remained unreacted were also isolated in low yields (Table 1). However, we did not observe the formation of singly bridged derivatives **6** bearing two free amino groups as described Wu et al. in the case of classical calix[4]arene.[7b] On the other hand, increasing the excess of diamine over 10 equiv did not have any significant effect on the yield. Another interesting feature of this reaction is the fact that even a high excess of diamines **2a**–**c** did not lead to the formation of tetraamides **4**. The same results were obtained using dioxane at 80 °C as solvent instead of ethanol. As indicated in Scheme 1, the yield of doubly-bridged thiacalix[4]arenes **3a**–**3c** rapidly decreases with increasing length of the α,ω-diamine's chain. This clearly point out that an accurate length of the chain of the corresponding diamine is an essential prerequisite for the successful spanning of the two neighbouring (proximal) phenyl rings in *p-tert*-butylthiacalix[4]arene.

Table 1. Aminolysis of thiacalix[4]arene **1** with diamine **2a**–**c** in refluxing ethanol

α,ω-Diamine	Equiv	Product (yield %)
2a	10	**3a** (36)
	2.5	**3a** (10)+**5a** (16)
2b	10	**3b** (19)
	2.5	**3b** (8)+**5b** (9)
2c	10	**3c** (8)
	2.5	**3c** (5), **5c**-Not isolated

2.2. ^{1}H NMR and X-ray study

Very simple ^{1}H NMR spectra of doubly amide-bridged *p-tert*-butylthiacalix[4]arenes **3a**–**3c** precisely reflect their C_{2v} symmetry (Fig. 1a). Spanning of two proximal positions on the lower rim with symmetrical bridge causes the non-equivalence of geminal –O–CH_2–C(O)– (H_c, $H_{c'}$) protons. These protons form an AX spin system and each of them is, in ^{1}H NMR spectrum, represented by a doublet with a typical geminal coupling constant (J=13.7 Hz). Similarly, the aromatic protons (H_b, $H_{b'}$), are represented by two doublets with characteristic *meta*-splitting (J=2.2 Hz).

On the other hand, the accumulation of signals in ^{1}H NMR spectra of singly amide-bridged derivatives **5a** and **5b** is caused by the lower symmetry of these molecules. The presence of two singlets belonging to *tert*-butyl protons (H_a, $H_{a'}$) together with signals corresponding to the protons (H_f and H_g) of free ethyl ester groups is in agreement with the above shown structures. As depicted in Figure 1b, four doublets with geminal coupling constants in the range of 15.0–15.5 Hz belonging to reciprocally non-equivalent –O–CH_2–C(O)– protons of both amide-bridges (H_c and $H_{c'}$) and free acetate groups ($H_{c''}$ and $H_{c'''}$) can be observed in the region between 4.2 and 5.3 ppm. Four doublets with characteristic *meta*-splitting (J=2.4 Hz) patterns in the aromatic region represent further evidence for the singly amide-bridged structure.

The structures of the above described doubly-bridged thiacalix[4]arenes **3a**, **3b** and **3c** were unequivocally proven by single crystal X-ray analysis. Suitable single crystals were grown from CH_2Cl_2/MeOH mixture and were stable in air. As follows from Figure 2, amide-bridges on the lower rim represent a cyclic arrays of binding sites (–NH–C(O)–), potentially suitable for the complexation of selected

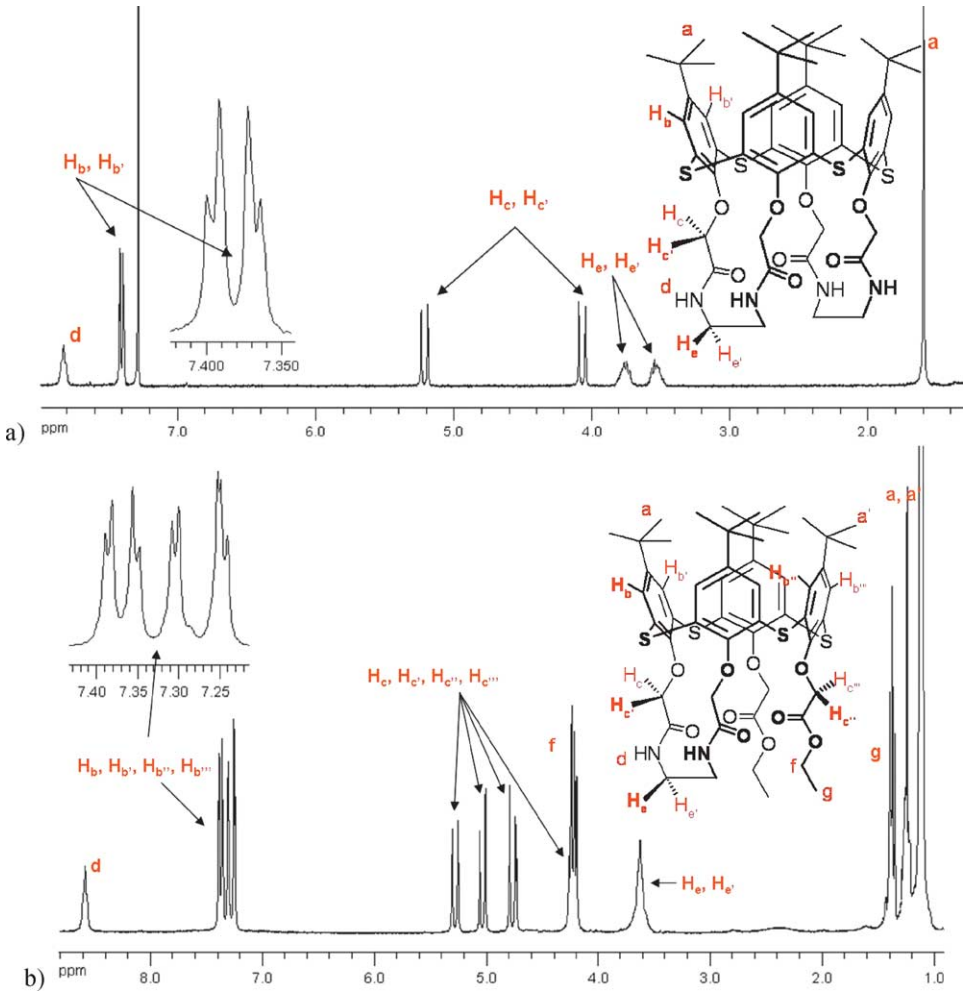

Figure 1. ^{1}H NMR spectra (300 MHz, $CDCl_3$, 25 °C) of derivatives **3a** (a) and **5a** (b).

substrates by means of hydrogen bonds. Thiacalix[4]arene units adopt the pinched cone conformation with two opposite aromatic rings pointing out of the cavity and the other two tilted towards each other. The conformation of amide-bridging units on the lower rim of derivative **3a** is held by three strong intramolecular hydrogen bonds: (S···H–N distance 2.73 Å, O···H–N distances 2.07 and 2.25 Å). Similarly, one of the amide –C(O)– groups in molecule **3b** is distorted into the cavity, forming strong intramolecular hydrogen bonds with both neighbour and opposite amide –NH– groups: (O···H–N distances 2.30 and 2.46 Å). Finally, the distortion of one of amide-bridging units in derivative **3c** is caused by three intramolecular hydrogen bonds employing both the hydrogen atoms of –NH– amide groups: (S···H–N distance 2.28 Å, O···H–N distances 1.97 and 2.73 Å).

In conclusion, we have demonstrated that the aminolysis of readily accessible thiacalix[4]arene tetraacetate **1** with various α,ω-diamines **2** does not lead to the proposed tetraamides **4** but rather gives unusual lower rim doubly-bridged molecules of type **3**. These compounds represent macrocyclic structures possessing well preorganised array of –NH–CO– binding sites on the lower rim. The potential applications of these compounds in supramolecular chemistry are currently under study.

3. Experimental

All moisture sensitive reactions were carried out under nitrogen atmosphere. All dry solvents were prepared according to standard procedures and stored over molecular sieves. Melting points are uncorrected and were determined using a Boetius Block apparatus (Carl Zeiss Jena, Germany). ^{1}H NMR spectra were recorded at 300 MHz. Elemental analyses were measured on Perkin-Elmer 240 instruments. All samples were dried in the desiccator over P_2O_5 under vacuum (1 Torr) at 80 °C for 8 h. Mass spectra were measured using FAB technique on ZAB-EQ (VG Analytical) spectrometer. The IR spectra were measured on an FT-IR spectrometer Nicolet 740 in KBr. The purity of the substances and the courses of reactions were monitored by TLC using TLC aluminum sheets with Silica gel 60 F_{254} (Merck). Preparative TLC chromatography was carried out on 20×20 cm glass plates covered by Silica gel 60 GF_{254} (Merck). The column chromatography was performed using Silica gel 60 (Merck).

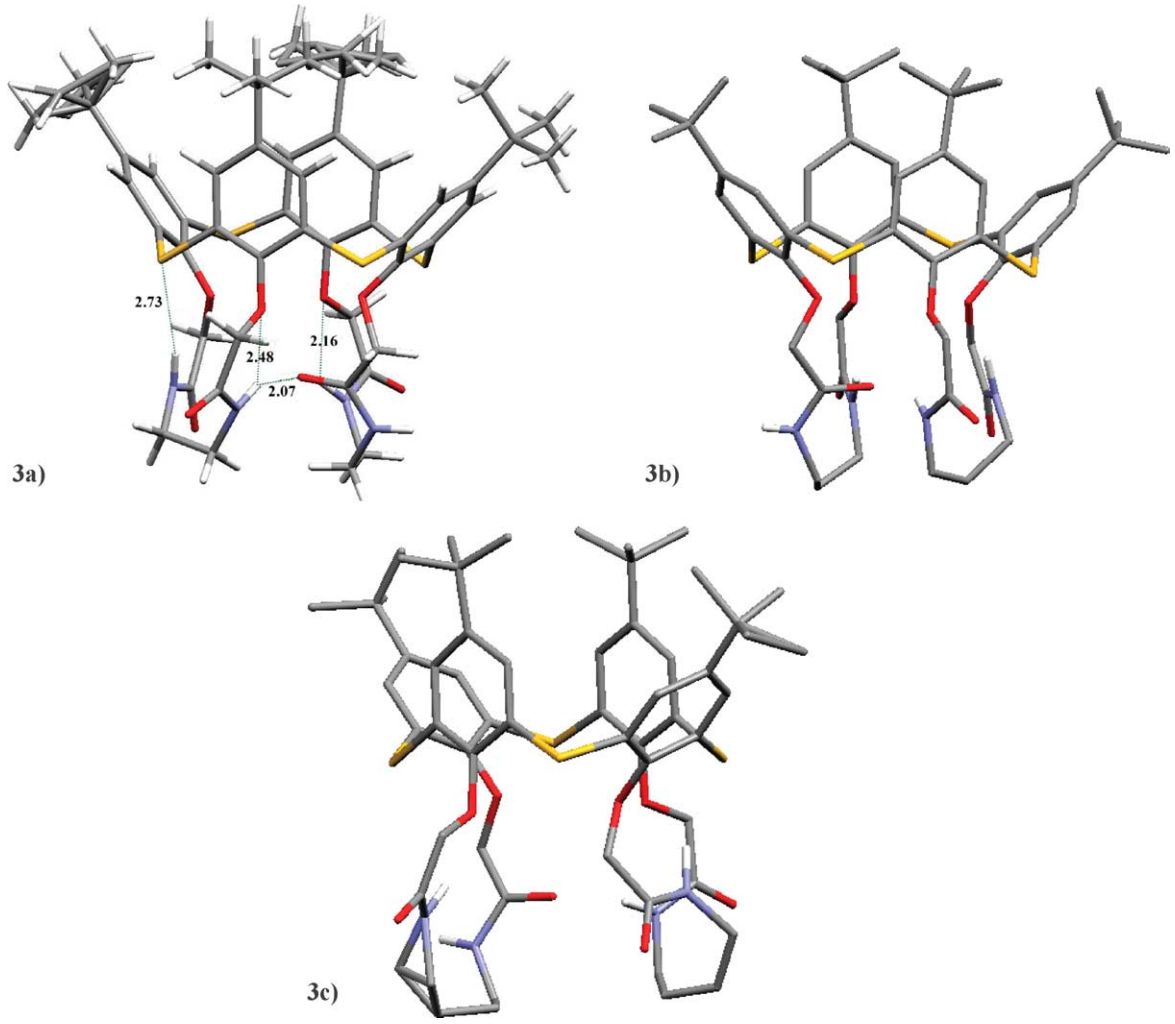

Figure 2. X-ray structures of doubly amide-bridged *p-tert*-butylthiacalix[4]arene derivatives **3a**, **3b** and **3c** (all distances in Å).

Compound **1**[4e] was prepared according to known procedure.

3.1. Aminolysis of *p-tert*-butylthiacalix[4]arene tetraethyl acetate 1 (cone) leading to doubly bridged products—general procedure

p-tert-Butylthiacalix[4]arene tetraethyl acetate **1** (1.00 g, 0.94 mmol) was suspended in 100 ml of ethanol and 9.4 mmol of the corresponding aliphatic α,ω-diamine was added in one portion. The reaction mixture was stirred under reflux for 16 h and then the solvent was evaporated under reduced pressure. The doubly bridged product was isolated by preparative TLC (SiO_2, $CHCl_3$/MeOH 10:1).

3.1.1. Doubly amide-bridged *p-tert*-butylthiacalix[4] arene 3a (cone). Isolated as a white crystalline compound (R_f=0.56, 338 mg, 36% yield). Mp >350 °C ($CHCl_3$–MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (s, 36H, –C(CH_3)$_3$); 3.49–3.52 (m, 4H, –CH$_2$–CH_2–NH–C(O)–); 3.72–3.74 (m, 4H, –C(O)–NH–CH_2–CH$_2$–); 4.04 (d, 4H, J=13.7 Hz, –O–CH_2–); 5.19 (d, 4H, J=13.7 Hz, –O–CH_2–); 7.37 (d, 4H, J=2.2 Hz, ArH); 7.40 (d, 4H, J=2.2 Hz, ArH); 7.79 (m, 4H, –C(O)–NH–); MS (FAB) m/z (rel intensity): 1002 [MH$^+$] (100); IR (KBr) ν_{max} (cm^{-1}): 3341, 1681, 1600, 1550. Calcd for $C_{52}H_{64}N_4O_8S_4$: C, 62.37; H, 6.44; N, 5.60 S, 12.81. Found: C, 62.47; H, 6.41; N, 5.10; S 12.52.

3.1.2. Doubly amide-bridged *p-tert*-butylthiacalix[4] arene 3b (cone). Obtained according to the general procedure as a white crystalline compound (R_f=0.62, 184 mg, 19% yield). Mp >350 °C ($CHCl_3$–MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (s, 36H, –C(CH_3)$_3$); 1.98 (m, 2H, –CH$_2$–CH_2–CH$_2$–NH–C(O)–); 2.15 (m, 2H, –CH$_2$–CH_2–CH$_2$–NH–C(O)–); 3.49–3.56 (m, 4H, –C(O)–NH–CH_2–CH$_2$–); 3.68–3.72 (m, 4H, –C(O)–NH–CH_2–CH$_2$–); 4.67 (d, 4H, J=14.6 Hz, –O–CH_2–); 4.90 (d, 4H, J=14.6 Hz, –O–CH_2–); 7.37 (d, 4H, J=2.5 Hz, ArH); 7.40 (d, 4H, J=2.5 Hz, ArH); 7.84 (t, 4H, J=5.2 Hz, –C(O)–NH–); MS (FAB) m/z (rel intensity): 1030 [MH$^+$] (100); IR (KBr) ν_{max} (cm^{-1}): 3336, 1682, 1676, 1533. Calcd for $C_{54}H_{68}N_4O_8S_4$: C, 63.01; H, 6.66; N, 5.44. Found: C, 62.77; H, 6.38; N, 5.41.

3.1.3. Doubly amide-bridged *p-tert*-butylthiacalix[4] arene 3c (cone). Prepared according to the general procedure and isolated as a beige crystalline compound (R_f=0.56, 79 mg, 8% yield). Mp >350 °C ($CHCl_3$–MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (s, 36H, –C(CH_3)$_3$); 1.87 (br s, 8H, –CH$_2$–CH_2–CH$_2$–NH–C(O)–);

3.51 (br s, 8H, –C(O)–NH–CH_2–CH_2–); 4.46 (d, 4H, J= 14.9 Hz, –O–CH_2–); 5.19 (d, 4H, J=15.1 Hz, –O–CH_2–); 7.37 (d, 4H, J=2.5 Hz, ArH); 7.41 (d, 4H, J=2.2 Hz, ArH); 7.78 (t, 4H, J=5.1 Hz, –C(O)–NH–); MS (FAB) m/z (rel intensity): 1058 [MH^+] (100); IR (KBr) ν_{max} (cm^{-1}): 3387, 1676, 1542. Calcd for $C_{56}H_{72}N_4O_8S_4$: C, 63.61; H, 6.86; N, 5.30. Found: C, 63.52; H, 6.73; N, 5.21.

3.2. Aminolysis of *p-tert*-butylthiacalix[4]arene tetraethyl acetate 1 (cone) leading to singly bridged products—general procedure

p-tert-Butylthiacalix[4]arene tetraethyl acetate **1** (0.50 g, 0.47 mmol) was suspended in 50 ml of ethanol and 1.18 mmol of the corresponding aliphatic α,ω-diamine was added in one portion. The reaction mixture was stirred under reflux for 24 h and then the solvent was evaporated under reduced pressure. The singly bridged product was isolated by preparative TLC (SiO_2, $CHCl_3$/MeOH 10:1).

3.2.1. Singly amide-bridged *p-tert*-butylthiacalix[4]arene diethyl acetate 5a (cone). Obtained as a beige crystalline compound (R_f=0.79, 78 mg, 16% yield). Mp 228–230 °C ($CHCl_3$–MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 18H, –C(CH_3)$_3$); 1.05 (s, 18H, –C(CH_3)$_3$); 1.15–1.22 (m, 6H, –O–CH$_2$–CH_3); 3.56 (m, 4H, –C(O)–NH–CH_2–CH$_2$–); 4.14–4.20 (m, 6H, –O–CH_2–CH$_3$ and –O–CH_2–); 4.71 (d, 2H, J=15.1 Hz, –O–CH_2–); 4.98 (d, 2H, J=15.1 Hz, –O–CH_2–); 5.22 (d, 2H, J=14.9 Hz, –O–CH_2–); 7.25 (d, 4H, J=2.4 Hz, ArH); 7.30 (d, 4H, J=2.4 Hz, ArH); 7.33 (d, 4H, J=2.4 Hz, ArH); 7.39 (d, 4H, J=2.4 Hz, ArH); 8.53 (m, 2H, –C(O)–NH–); MS (FAB) m/z (rel intensity): 1033 [MH^+] (100); IR (KBr) ν_{max} (cm^{-1}): 3351, 1766, 1733, 1683, 1541.

3.2.2. Singly amide-bridged *p-tert*-butylthiacalix[4]arene diethyl acetate 5b (cone). Isolated as a beige crystalline compound (R_f=0.71, 44 mg, 9% yield). Mp 292–294 °C ($CHCl_3$–MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 18H, –C(CH_3)$_3$); 1.05 (s, 18H, –C(CH_3)$_3$); 1.18 (t, 6H, J= 7.2 Hz, –O–CH$_2$–CH_3); 1.99 (m, 4H, –CH$_2$–CH_2–CH$_2$–NH–C(O)–); 3.46 (m, 4H, –C(O)–NH–CH_2–CH$_2$–); 3.56 (m, 4H, –C(O)–NH–CH_2–CH$_2$–); 4.16 (q, 4H, J=7.2 Hz, –O–CH_2–CH$_3$–); 4.50 (d, 2H, J=15.4 Hz, –O–CH_2–); 4.82 (d, 2H, J=15.1 Hz, –O–CH_2–); 4.93 (d, 2H, J=15.1 Hz, –O–CH_2–); 5.19 (d, 2H, J=15.4 Hz, –O–CH_2–); 7.23–7.27 (m, 8H, ArH); 8.27 (t, 2H, J=5.9 Hz, –C(O)–NH–); MS (FAB) m/z (rel intensity): 1047 [MH^+] (100); IR (KBr) ν_{max} (cm^{-1}): 3405, 1746, 1727, 1680, 1552.

3.3. Crystallographic study

X-ray data were collected on an Enraf Nonius CAD4 diffractometer with graphite monochromated Cu Kα radiation at 293 K. The structures were solved by direct methods. Mercury v.1.2.1. available as freeware at http://www.ccdc.cam.ac.uk/mercury/ was used for visualization.

X-ray data for **3a**: $C_{52}H_{64}N_4O_8S_4$, M=1001.3 g/mol, triclinic system, space group P -1, a=13.635(1), b= 13.915(1), c=18.115(2) Å, α=102.09(1), β=101.54(1), γ=112.23(1)°, V=2959.2(6) Å^3, Z=2, D_c=1.12 g cm^{-3}, μ(Cu Kα)=1.87 mm^{-1}, crystal dimensions of 0.2×0.3×0.8 mm. The structure was solved by direct method[8] and anisotropically refined by full matrix least-squares on F values[9] to final R=0.066 and R_w=0.064 using 5880 independent reflections (θ_{max}=64.95°, 656 parameters). Hydrogen atoms were located from expected geometry and were not refined. ψ-scan was used for absorption correction. Crystallographic data were deposited in CSD under CCDC registration number 268283.

X-ray data for **3b**: $C_{54}H_{68}N_4O_8S_4 \cdot 0.5CH_2Cl_2$, M= 1070.9 g/mol, monoclinic system, space group C 2/c, a= 28.993(2), b=13.9700(9), c=30.661(2) Å, β=103.23(1)°, V=12089(1) Å^3, Z=8, D_c=1.18 g cm^{-3}, μ(Cu Kα)= 2.26 mm^{-1}, crystal dimensions of 0.1×0.2×0.9 mm. The structure was solved by direct method[8] and anisotropically refined by full matrix least-squares on F values[9] to final R= 0.096 and R_w=0.072 using 3076 independent reflections (θ_{max}=67.94°, 591 parameters). Hydrogen atoms were located from expected geometry and were not refined. Molecule of dichloromethane was not able to refine, the SQUEEZE method was applied. Crystallographic data were deposited in CSD under CCDC registration number 268282.

X-ray data for **3c**: $C_{56}H_{72}N_4O_8S_4$, M=1057.4 g/mol, monoclinic system, space group P 2$_1$/c, a=12.705(3), b= 14.295(3), c=37.189(3) Å, β=95.00(2)°, V=6728(2) Å^3, Z=4, D_c=1.04 g cm^{-3}, μ(Cu Kα)=0.19 mm^{-1}, crystal dimensions of 0.2×0.3×0.6 mm. The structure was solved by direct method[8] and anisotropically refined by full matrix least-squares on F values[9] to final R=0.077 and R_w=0.039 using 5505 independent reflections (θ_{max}=59.95°, 662 parameters). Hydrogen atoms were located from expected geometry and were not refined. ψ-scan was used for absorption correction. Crystallographic data were deposited in CSD under CCDC registration number 268284.

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Ring-closing metathesis for the synthesis of 2*H*- and 4*H*-chromenes

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Abstract—Six 4*H*-chromenes were synthesized from substituted phenols using vinylstannylation and ring-closing metathesis (RCM) as key steps. In addition, a different approach involving amongst other steps, an aryl allyl isomerization and RCM afforded a set of seven 2*H*-chromenes from phenolic precursors.

1. Introduction

Compounds in which a benzene and pyran ring are fused together with various levels of saturation and oxidation are very common in Nature.[1] The 1-benzopyrans include structural skeletons such as chromane **1**, 4*H*-chromene **2** and 2*H*-chromene **3** as depicted in Figure 1.

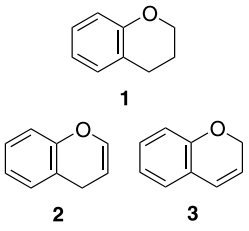

Figure 1.

As a class of compounds the 4*H*-chromenes **2** (also known as 4*H*-1-benzopyrans) are rather unusual and only a few examples of natural products containing this structure have been isolated.[2] An example of a naturally occurring 4*H*-chromene is 7-hydroxy-6-methoxy-4*H*-chromene **4**, which was efficiently synthesized by De Korte and co-workers (Fig. 2).[3] This natural product, which reportedly has interesting organoleptic properties, was isolated from the plant *Wisteria sinensis* along with the related compound, 6,7-dimethoxy-4*H*-chromene **5**.[2] In contrast to the paucity of 4*H*-chromene examples, the literature abounds with vast numbers of papers reporting the isolation and synthesis of naturally occurring 2*H*-chromenes **3**.[1] Examples reported recently include compounds **6** and **7**, both isolated from the leaf essential oil of *Calyptranthes tricona* (Fig. 2).[4]

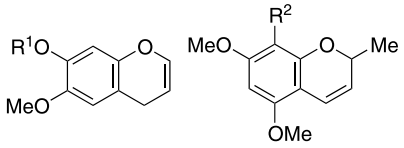

Figure 2.

The chromene skeletons have also elicited pharmaceutical interest as structural elements in drug-like compounds. Examples of artificial compounds bearing the 2*H*-chromene motif include 6-fluoro-2*H*-chromene **8**,[5] which exhibited the highest 5-HT_{1A} receptor affinity among a series of novel 6-fluorochromane derivatives; and 6-substituted 2*H*-chromenyl compound **9**,[6] which was tested for potential antidiabetic activity as a Na^+-glucose co-transporter inhibitor (Fig. 3). In addition, a series of hypoglycemic benzenesulfonylsemicarbazides with potential application in the treatment of diabetes mellitus included substituted 2*H*-chromene **10**.[7]

In recent years, the ring-closing metathesis (RCM) reaction[8] has been used to synthesize both the 2*H*-[9] and 4*H*-chromene[10] classes. Methodology for the synthesis of the 2*H*-chromenes normally involves the RCM of an

Keywords: 2*H*-chromenes; 4*H*-chromenes; Ring-closing metathesis; Isomerization.
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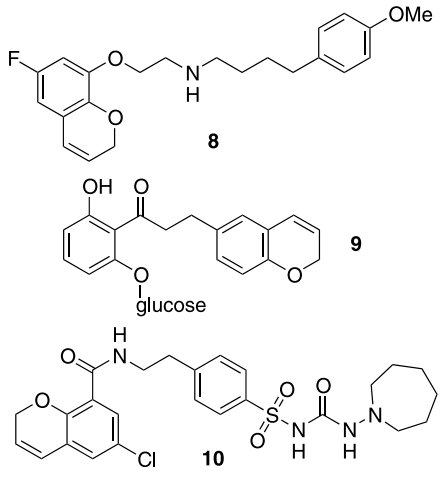


Figure 3.

o-allyloxystyrene [see disconnection (a) in Fig. 4]. On the other hand the synthesis of the 4*H*-chromenes using RCM, described only by ourselves in a communication[11] and by Lam and co-workers (one example),[10] has been accomplished by the RCM between a vinyloxy group and an arylallyl functionality (disconnection (b) in Fig. 4). In addition, our research group has been interested in the use of RCM and isomerization[12] methodology towards the synthesis of benzo-fused compounds.[11,13]

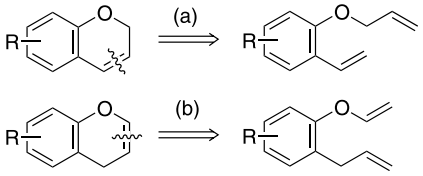


Figure 4.

In this publication we report in full novel syntheses to both the 4*H*- and 2*H*-chromene structures using RCM as the key step.[11] This paper describes in detail how the 4*H*-chromenes were synthesized by way of an *O*-vinylation followed by RCM using the second generation Grubbs catalyst **11** (Fig. 5). In addition, we disclose the synthesis of a small set of 2*H*-chromenes, which were obtained by first using a versatile aryl allyl isomerization step followed by the usual RCM reaction.[14]

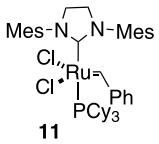
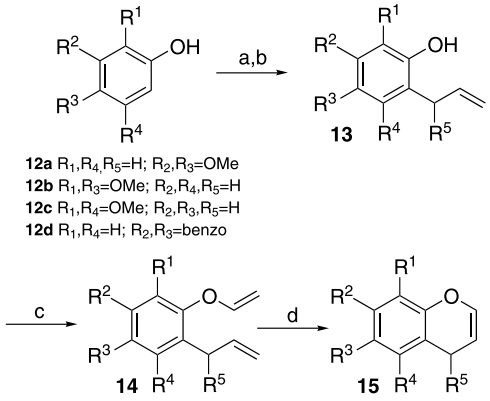


Figure 5.

2. Discussion: 4*H*-chromenes

Variably substituted phenols **12** were initially converted into their corresponding aryl allyl ethers. Subsequent thermal Claisen rearrangements then gave the substituted phenols **13** in acceptable yields over two steps (Scheme 1 and Table 1). The compounds were then converted into the respective aryl vinyl ethers **14**, also in excellent yield, using a copper-mediated procedure described in the literature.[15] The crucial ruthenium-mediated RCM reactions on compounds **14** were highly successful, affording the 4*H*-chromenes **15** in 63–98% yield. It is known that RCM using Grubbs' catalysts on substrates containing electron-rich vinylic olefins can be problematic[16] but that there are numerous literature examples demonstrating the application of RCM to alkyl vinyl ethers.[16b,17,18] However, our results are amongst the first describing the successful use of RCM on substrates bearing phenolic vinyl ethers.[9 g,h,10,19]

As mentioned in the introduction, 4*H*-chromene **15a** (=**5**) occurs naturally as a fragrance component from the plant *Wisteria sinensis* and the spectra of our synthesized product compared well to those obtained for the natural product.[2] The other substituted 4*H*-chromenes that were synthesized are described in Scheme 1 and Table 1 and it can be seen that most of the reaction yields were in an acceptable range. In addition, 4*H*-chromenes **15d** and **15e**, bearing a methyl functionality at position 5 of the pyran ring, were also obtained in good yields. Of interest was that relative to the 4-methyl-4*H*-chromenes **15b** and **15d**, the unsubstituted chromenes **15a**, **15c** and **15e** were much more prone to decomposition. This was evident by the rapid darkening of the oils, even within minutes under air, to afford deep green or blue oils after a number of weeks, which were difficult to characterize.



Scheme 1. (a) K_2CO_3, allyl bromide, acetone, 60 °C; (b) △ (180–240 °C), neat; (c) $Cu(OAc)_2$, $Sn(vinyl)_4$, acetonitrile, O_2, rt; (d) 5% catalyst **11**, toluene, 60 °C (for yields see Table 1 below).

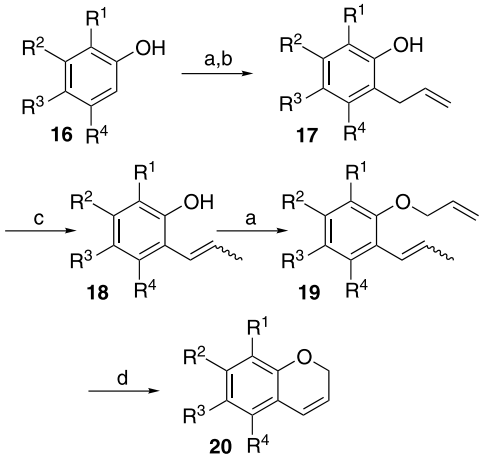
3. Discussion: 2*H*-chromenes

The synthesis of a small set of substituted 2*H*-chromenes required us to adopt a different approach. The 2-allylphenols **17** were synthesised as before, making use of the initial allylation of the substituted phenols **16** followed by a Claisen rearrangement (Scheme 2 and Table 2). The next step required the isomerization of the terminal alkene groups of **17** to the thermodynamically more favoured internal alkenes of the 2-(prop-1-enyl)phenols **18**. This was accomplished using the ruthenium-based catalyst, $[RuClH(CO)(PPh_3)_3]$, utilised by the group of Krompiec, and co-workers for a variety of isomerization applications.[20] For the most part, products **18** were obtained as a mixture of *E*- and *Z*-isomers with the *E*-isomers predominating. The only exception to this was that the isomerization of 1-allylnaphthalen-2-ol **17f** predominantly afforded the *Z*-isomer

Table 1. Yields for Scheme 1

	13[a]	13→14	14→15
a R^1,R^4,R^5=H; R^2,R^3=OMe	45%[b]	98%	90%
b R^1,R^4=H; R^2,R^3=OMe; R^5=Me	65%[b]	98%	98%
c R^1,R^3=OMe; R^2,R^4,R^5=H	91%[c]	99%	80%
d R^1,R^3=OMe; R^2,R^4=H; R^5=Me	42%[c]	98%	82%
e R^1,R^4=OMe; R^2,R^3,R^5=H	63%[d]	99%	85%
f R^1,R^2=H; R^3,R^4=benzo	90%[e]	74%	63%

[a] Yield over two steps.
[b] From compound **12a**.
[c] From compound **12b**.
[d] From compound **12c**.
[e] From compound **12d**.



Scheme 2. (a) K_2CO_3, allyl bromide, acetone, 60 °C; (b) Δ (180–240 °C) or microwave (150–200 °C), neat; (c) [$RuCl(CO)(PPh_3)_3$] (cat 1–4 mol%), toluene, 80 °C; (d) 5% catalyst **11**, toluene, rt −60 °C (for yields see Table 2 below).

of 1-(prop-1-enyl)naphthalen-2-ol **18f** after chromatography.[20b] A facile *O*-allylation on compounds **18a–g** then afforded the substituted 1-allyloxy-2-(prop-1-enyl)benzenes **19a–g** in acceptable yields. Compounds **19a–g** subsequently underwent RCM with Grubbs' second generation catalyst **11** to afford the desired 2*H*-chromenes **20a–g** in acceptable to good yields. The 2*H*-chromenes synthesized also contained a range of functional groups in varied positions on the aromatic portion, demonstrating the utility of this methodology. In particular the use of the nitro group, which can readily be reduced to an amine, and the versatile aldehyde substituents mean that subsequent modifications of the 2*H*-chromene skeletons should be readily attainable.

It is of interest to note that most of the previous RCM approaches to the 2*H*-chromene skeleton make use of an *O*-allyl group cyclizing onto a styrene. The presence of the styrene often necessitates an atom-inefficient Wittig reaction on the corresponding benzaldehyde,[9b,f] a transition metal-mediated vinylation of an aromatic halide[9d,j] or even a ketone to enol silyl ether transformation.[9g] Our methodology is thus different in that it enables the use of very simple precursors and reactions for the synthesis of the 2*H*-chromenes, utilizing the ruthenium-mediated isomerization as a key step.[21]

4. Conclusion

We have thus demonstrated a simple, versatile method of synthesizing the 4*H*-chromene skeleton using as key steps a copper-mediated aryl vinyl ether formation followed by a ruthenium-mediated RCM reaction. In addition this paper discloses our novel approach to the 2*H*-chromenes involving an aryl allyl isomerization and a RCM reaction. An advantage of both approaches is that they require substituted phenols as precursors. Since a wide variety of these compounds are commercially available or readily synthesized, it allows for a versatile approach to both classes of 1-benzopyrans.

5. Experimental

^1H and ^{13}C NMR spectra were recorded either on a Bruker

Table 2. Yields for Scheme 2

	16→17[a]	17→18	18→19	19→20
a $R^1=NO_2$; R^2,R^3,R^4=H	84%	96%	71%	90%
b R^1,R^2,R^4=H; $R^3=NO_2$	49%	96%	100%	100%
c R^1=OMe; R^2,R^3=H; R^4=CHO	68%	67%	81%	77%
d R^1=CHO; R^2,R^3,R^4=H	45%	89%	100%	80%
e R^1,R^2,R^4=H; R^3=CHO	41%	42%	64%	76%
f R^1,R^2=H; R^3,R^4=benzo[b]	90%	84%	65%	45%[c,d]
g R^1,R^2,R^3,R^4=H	[e]	90%	86%	80%[f,g]

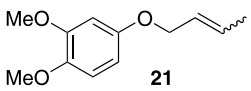
[a] Yields over two steps.
[b] For starting material **16a** R^1,R^4=H; R^2,R^3=benzo.
[c] Reaction on a 0.6 mmol scale.
[d] When reaction was repeated on a 0.3 mmol scale yield of **20f** obtained was 82%.
[e] 2-Allylphenol purchased from Aldrich.
[f] Yield >80% by ^1H NMR spectroscopy.
[g] Reaction performed on NMR spectroscopy scale as described in Ref. 13a.

AC-200, Bruker 300 or Bruker DRX 400 spectrometer at the frequency indicated. All ^{13}C signals in the aromatic/alkene region have been assigned as quaternary (C) or non-quaternary (CH). Infra-red spectra were recorded on either a Bruker IFS 25 Fourier Transform spectrometer or on a Bruker Vector 22 Fourier Transform spectrometer. Mass spectra were recorded on a Kratos MS 9/50, VG 70E MS or a VG 70 SEQ mass spectrometer. Macherey-Nagel kieselgel 60 (particle size 0.063–0.200 mm) was used for conventional silica gel chromatography. All solvents used for reactions and chromatography were distilled prior to use. All microwave reactions were performed in a CEM Corporation Discover Focused Microwave Synthesis system.

5.1. Experimental part A: 4*H*-chromenes

5.2. Known precursors for the synthesis of the 4*H*-chromenes 15a–f. 3,4-Dimethoxyphenol **12a** was allylated to afford 4-allyloxy-1,2-dimethoxybenzene.[22a] A Claisen rearrangement was performed on this compound to afford 2-allyl-4,5-dimethoxyphenol **13a**.[22b] Similarly, allylations on 3,4-dimethoxyphenol **12a** and 2,4-dimethoxyphenol **12b** with crotyl bromide afforded 4-(but-2-enyloxy)-1,2-dimethoxybenzene **21** (see below for experimental details and structure) and 1-(but-2-enyloxy)-2,4-dimethoxybenzene,[22c] respectively, which were converted to 4,5-dimethoxy-2-(1-methylallyl)phenol[22d] **13b** and 2,4-dimethoxy-6-(1-methylallyl)phenol[22c] **13d**, respectively, by way of the Claisen rearrangement. In a similar manner, 2-allyl-4,6-dimethoxyphenol **13c** (see below for experimental details) and 2-allyl-3,6-dimethoxyphenol[13e] **13e** were synthesized from 2,4-dimethoxyphenol **12b** and 2,5-dimethoxyphenol[13e] **12c**, respectively, by way of the intermediate allyl ethers; 1-allyloxy-2,4-dimethoxybenzene[22e] and 2-allyloxy-1,4-dimethoxybenzene.[13e] In a similar manner, 2-hydroxynaphthalene **12d** was converted into 2-allyloxynaphthalene[22f] and then into 1-allyl-naphthalen-2-ol[22f] **13f** by way of thermal Claisen rearrangement.

5.2.1. 4-(But-2-enyloxy)-1,2-dimethoxybenzene 21. Crotyl bromide (5.3 g, 39 mmol, 4.0 mL) and K_2CO_3 (8.1 g, 59 mmol) were added to 3,4-dimethoxyphenol **12a** (3.0 g, 18 mmol) dissolved in dry acetone (200 mL). The reaction mixture was then heated at reflux under nitrogen for 21 h. The K_2CO_3 was removed by filtration and the solvent was removed in vacuo. Purification by silica gel column chromatography (10% EtOAc/hexane) afforded the product 4-(but-2-enyloxy)-1,2-dimethoxybenzene **21** as a clear yellow oil (2.0 g, 53%, *E*:*Z* ratio 75:25). (Found: M^+, 208.1099, $C_{12}H_{16}O_3$ requires 208.1099); ^1H NMR (300 MHz, $CDCl_3$, only *E* isomer characterized): δ= 1.71–1.75 (3H, m, CH_3), 3.80 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 4.37 (2H, br d, J=5.8 Hz, OCH_2), 5.66–5.78 [1H, m, OCH_2=CHC*H*(CH_3)], 5.80–5.87 [1H, m OCH_2C*H*=CH(CH_3)], 6.37 (1H, dd, J=8.7, 2.5 Hz, 5-H), 6.52 (1H, d, J=2.5 Hz, 3-H), 6.73 (1H, d, J=8.7 Hz, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$, only *E* isomer characterized): δ=17.5 (CH_3), 55.4 (OCH_3), 56.1 (OCH_3), 68.8 (OCH_2), 100.8 (CH), 103.7 (CH), 111.6 (CH), 126.0 (CH), 129.9 (CH), 143.2 (C), 149.6 (C), 153.1 (C); ν_{max} ($CHCl_3$)/cm^{-1}: 1610, 1602, 1511, 1454; MS: m/z=208 (M^+, 51%), 196 (37), 182 (100), 165 (55), 154 (90), 139 (57), 79 (50), 55 (92), 39 (80), 27 (50).



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5.2.2. 2-Allyl-4,6-dimethoxyphenol 13c. 1-Allyloxy-2,4-dimethoxybenzene (1.1 g, 5.7 mmol) was heated without solvent at 220–236 °C for 45 min under a N_2 atmosphere. The resultant brown residue was then subjected to silica gel column chromatography (20% EtOAc/hexane) to afford 2-allyl-4,6-dimethoxyphenol **13c** (0.58 g, 53%) as a light yellow oily material. (Found: M^+, 194.0958, $C_{11}H_{14}O_3$ requires 194.0943); ^1H NMR (300 MHz, $CDCl_3$): δ=3.39–3.41 (2H, m, $ArCH_2$), 3.72 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 5.03–5.11 (2H, m, CH_2CH=CH_2), 5.50 (1H, s, OH), 5.92–6.06 (1H, m, CH_2CH=CH_2), 6.35 (1H, d, J=2.7 Hz, ArH), 6.46 (1H, d, J=2.7 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=33.9 ($ArCH_2$), 55.4 (OCH_3), 55.6 (OCH_3), 97.1 (CH), 105.4 (CH), 115.3 (CH), 125.7 (C), 136.4 (CH), 137.4 (C), 146.8 (C), 152.7 (C); ν_{max} ($CHCl_3$)/cm^{-1}: 3555 br, 1639, 1617, 1605, 1499, 1467, 1431; MS: m/z=194 (M^+, 100%), 179 (34), 161 (5), 151 (12), 137 (6), 133 (6), 119 (6), 91 (10), 69 (8), 65 (5).

5.3. General procedure for the vinylation of substituted 2-allyl-phenols 13 to 1-allyl-2-vinyloxy-benzenes 14

Anhydrous $Cu(OAc)_2$ (1.2 mol equiv) was added to a thoroughly degassed solution of substituted 2-allylphenol **13** (ca. 1.0 mmol) in CH_3CN (3.0 mL). The reaction vessel was then fitted with an O_2 balloon and tetravinyltin (1.2 mol equiv) was added through a septum. The mixture was left to react for 22 h at room temperature after, which aqueous NH_4OAc (0.3 M, 25 mL) was added. The aqueous layer was then extracted with EtOAc (5×20 mL). The combined organic extracts were dried with anhydrous $MgSO_4$, then filtered and the solvent removed in vacuo. The resultant residue was purified by column chromatography (2–30% EtOAc/hexane) to afford the product **14**. The following compounds were prepared using this procedure:

5.3.1. 1-Allyl-4,5-dimethoxy-2-(vinyloxy)benzene 14a. The product **14a** (0.23 g, quantitative) was isolated as a clear oil starting from substrate **13a** (0.20 g, 1.0 mmol). (Found: M^+, 220.1100, $C_{13}H_{16}O_3$ requires 220.1099); ^1H NMR (300 MHz, $CDCl_3$): δ=3.30–3.32 (2H, d m, J= 6.6 Hz, $ArCH_2$), 3.84 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.26 [1H, dd, J=6.2, 1.8 Hz, OCH=C(H)*H*], 4.47 [1H, dd, J=13.9, 1.8 Hz, OCH=C(*H*)H], 5.02–5.03 [1H, m, CH_2-CH=C(H)*H*], 5.06–5.08 [1H, m, CH_2CH=C(*H*)H], 5.86–5.97 (1H, m, CH_2CH=CH_2), 6.56 (1H, dd, J=13.9, 6.2 Hz, OC*H*=CH_2), 6.57 (1H, s, ArH), 6.69 (1H, s, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=33.5 (CH_2), 56.0 (OCH_3), 56.2 (OCH_3), 92.1 (CH), 103.7 (CH), 112.9 (CH), 115.5 (CH), 122.3 (C), 136.9 (CH), 145.5 (C), 147.1 (C), 147.9 (C), 150.4 (CH); IR ν_{max} ($CHCl_3$)/cm^{-1} 1635, 1609, 1510; MS: m/z=221 (M^++H, 18%), 220 (M^+, 100%), 205 (22), 194 (93), 191 (23), 179 (56), 91 (20), 69 (23).

5.3.2. 1-(But-3-en-2-yl)-4,5-dimethoxy-2-(vinyloxy)benzene 14b. The product **14b** (0.22 g, quantitative) was

isolated as a light yellow oil starting from substrate **13b** (0.20 g, 1.0 mmol). (Found: M^+, 234.1255, $C_{14}H_{18}O_3$ requires 234.1256); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.29 (3H, d, J=7.0 Hz, CH_3) 3.77–3.81 [1H, m, C*H*(CH_3)], 3.84 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.28 [1H, dd, J=6.2, 1.7 Hz, OCH=C(H)*H*], 4.50 [1H, dd, J=13.9, 1.7 Hz, OCH=C(*H*)H], 5.02–5.07 [2H, m, CH(CH_3)CH=CH_2], 5.94–6.05 [1H, m, CH(CH_3)C*H*=CH_2], 6.56 (1H, dd, J=13.9, 6.2 Hz, OC*H*=CH_2), 6.56 (1H, s, ArH), 6.69 (1H, s, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=20.6 (CH_3), 36.2 [*C*H(CH_3)], 56.9 (OCH_3), 57.1 (OCH_3), 93.2 (CH), 104.6 (CH), 111.6 (CH), 114.0 (CH), 128.7 (C), 143.3 (CH), 146.5 (C), 147.5 (C), 148.6 (C), 151.5 (CH); IR ν_{max} ($CHCl_3$)/cm^{-1} 1639, 1609, 1509; MS: m/z=235 (M^++H, 22%), 234 (M^+, 100%), 219 (20), 205 (41), 192 (21), 191 (77), 176 (19), 161 (17), 91 (18), 77 (19), 27 (22).

5.3.3. 1-Allyl-3,5-dimethoxy-2-(vinyloxy)benzene 14c. The product **14c** (0.22 g, quantitative) was obtained as a clear oil starting from substrate **13c** (0.19 g, 1.0 mmol). (Found: M^+, 220.1099, $C_{13}H_{16}O_3$ requires 220.1099); ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.32 (2H, d m, J=6.7 Hz, CH_2), 3.77 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 4.12 [1H, dd, J=6.3, 1.9 Hz, OCH=C(H)*H*], 4.24 [1H, dd, J=13.9, 1.9 Hz, OCH=C(*H*)H] 5.04–5.11 (2H, m, CH_2CH=CH_2), 5.85–5.96 (1H, m, CH_2C*H*=CH_2), 6.32 (1H, d, J=2.8 Hz, ArH), 6.39 (1H, d, J=2.8 Hz, ArH), 6.53 (1H, dd, J=13.9, 6.3 Hz, OC*H*=CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=34.2 (CH_2), 55.4 (OCH_3), 55.9 (OCH_3), 89.1 (CH), 98.3 (CH), 105.1 (CH), 116.1 (CH), 134.4 (C), 135.8 (C), 136.3 (CH), 151.5 (CH) 152.6 (C), 157.0 (C); IR ν_{max} ($CHCl_3$)/cm^{-1} 1633, 1610, 1594, 1486; MS: m/z=220 (M^+, 100%), 206 (48), 196 (38), 191 (60), 181 (71), 177 (32), 149 (34), 69 (30), 57 (77), 43 (45).

5.3.4. 1-(But-3-en-2-yl)-3,5-dimethoxy-2-(vinyloxy)benzene 14d. The product **14d** (0.21 g, quantitative) was isolated as a light yellow oil starting from substrate **13d** (0.20 g, 1.0 mmol). (Found: M^+, 234.1255, $C_{14}H_{18}O_3$ requires 234.1256); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.29 (3H, d, J=7.0 Hz, CH_3) 3.71–3.81 [1H, m under 2×OCH_3, C*H*(CH_3)], 3.78 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 4.13 [1H, dd, J=6.3, 1.8 Hz, OCH=C(H)*H*], 4.25 [1H, dd, J=13.9, 1.8 Hz, OCH=C(*H*)H], 5.02–5.09 [2H, m, CH(CH_3)-CH=CH_2], 5.92–6.03 [1H, m, CH(CH_3)C*H*=CH_2], 6.31 (1H, d, J=2.7 Hz, ArH), 6.38 (1H, d, J=2.7 Hz, ArH), 6.55 (1H, dd, J=13.9, 6.3, OC*H*=CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=19.9 (CH_3), 35.8 [*C*H(CH_3)], 55.5 (OCH_3), 56.0 (OCH_3), 89.3 (CH), 98.0 (CH), 103.1 (CH), 113.4 (CH), 135.3 (C), 139.9 (C), 142.2 (CH), 151.9 (CH), 152.5 (C), 157.1 (C); IR ν_{max} ($CHCl_3$)/cm^{-1} 1640, 1610, 1600, 1487; MS: m/z=235 (M^++H, 16%), 234 (M^+, 100%), 219 (20), 207 (29), 205 (77), 192 (28), 191 (54), 149 (32).

5.3.5. 2-Allyl-1,4-dimethoxy-3-(vinyloxy)benzene 14e. The product **14e** (0.22 g, quantitative) was isolated as a clear yellow oil starting from substrate **13e** (0.19 g, 1.0 mmol). (Found: M^+, 220.1099, $C_{13}H_{16}O_3$ requires 220.1099); ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.37 (2H, d m, J=6.2 Hz, CH_2), 3.77 (6H, s, 2×OCH_3), 4.14 [1H, dd, J=6.3, 1.9 Hz, OCH=C(H)*H*], 4.30 [1H, dd, J=13.9, 1.9 Hz, OCH=C(*H*)H], 4.92–5.01 (2H, m, CH_2CH=CH_2), 5.86–5.99 (1H, m, CH_2C*H*=CH_2), 6.56 (1H, dd, J=13.9, 6.3 Hz, OC*H*=CH_2), 6.62 (1H, d, J=8.9 Hz, ArH), 6.76 (1H, d, J=8.9 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=28.1 (CH_2), 55.8 (OCH_3), 56.4 (OCH_3), 89.6 (CH), 106.8 (CH), 110.6 (CH), 114.8 (CH), 123.2 (C), 136.1 (CH), 143.1 (C), 146.2 (C), 151.2 (CH), 152.1 (C); IR ν_{max} ($CHCl_3$)/cm^{-1} 1639, 1490; MS: m/z=221 (M^++H, 15%), 220 (M^+, 100%), 205 (21), 192 (45), 191 (33), 177 (21), 149 (58), 91 (43), 57 (50), 41 (63).

5.3.6. 1-Allyl-2-(vinyloxy)naphthalene 14f. The product **14f** (0.15 g, 74%) was isolated as a clear oil starting from substrate **13f** (0.18 g, 1.0 mmol). (Found: M^+, 210.10445, $C_{15}H_{14}O$ requires 210.10447); ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.84 (2H, br d, J=5.9 Hz, CH_2), 4.34 [1H, dd, J=6.2, 1.7 Hz, OC=C*H*(H)], 4.55 [1H, dd, J=13.9, 1.7 Hz, OC=CH(*H*)], 4.48 [1H, dd, J=9.1, 1.6 Hz, CH_2CH=CH(*H*)], 5.03 (1H, br s, CH_2CH=C*H*(H)], 5.95–6.09 (1H, m, CH_2C*H*=CH_2), 6.68 (1H, dd, J=13.9, 6.2 Hz, OC*H*=CH_2), 7.24 (1H, d, J=9.0 Hz, ArH), 7.38–7.43 (1H, m, ArH), 7.47–7.52 (1H, m, ArH), 7.72 (1H, d, J=8.9 Hz, ArH), 7.80 (1H, d, J=8.1 Hz, ArH), 7.98 (1H, d, J=8.5 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=29.5 (CH_2), 93.2 (OCH=*C*H_2), 115.5 (CH), 119.1 (CH), 124.1 (CH), 124.3 (ArC), 124.5 (CH), 126.4 (CH), 128.2 (CH), 128.5 (CH), 131.0 (ArC), 133.1 (ArC), 136.3 (CH), 150.1 (CH), 151.1 (ArC); IR ν_{max} ($CHCl_3$)/cm^{-1}: 1641, 1549, 1463; MS: m/z=210 (M^+, 100%), 181 (99), 165 (94), 152 (63), 128 (49), 115 (38), 77 (15), 63 (16).

5.4. General RCM procedure for the synthesis of substituted 4*H*-chromenes 15 from 1-allyl-2-vinyloxybenzenes 14

Typically, Grubbs catalyst **11** (4 mol%) was added to a degassed solution of the substituted 1-allyl-2-vinyloxybenzene **14** (ca. 0.5–1.0 mmol) dissolved in degassed, distilled toluene (ca. 30 mL, ca. 0.020 M). The reaction mixture was then heated at 60 °C for 1 h under a N_2 atmosphere. After removal of the solvent under reduced pressure the residue was purified by silica gel column chromatography (5–20% EtOAc/hexane) to afford the desired product **15**. The following compounds were obtained using this procedure:

5.4.1. 6,7-Dimethoxy-4*H*-chromene 15a (=5).[2,3] The product **15a** (0.12 g, 97%) was isolated as a light yellow oil starting from substrate **14a** (0.14 g, 0.64 mmol) and Grubbs catalyst **11** (20 mg, 0.024 mmol, 4 mol%) in toluene (30 mL, 0.020 M); ^{1}H NMR (200 MHz, $CDCl_3$): δ=3.31–3.33 (2H, m, 4-H), 3.82 (6H, s, 2×OCH_3), 4.86–4.93 (1H, m, 3-H), 6.42 (1H, s, ArH), 6.46 (1H, s, ArH), 6.42–6.46 (1H, m, 2-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=22.7 (CH_2), 55.8 (OCH_3), 56.1 (OCH_3), 99.7 (CH), 100.5 (CH), 110.2 (C), 111.2 (CH), 140.4 (CH), 144.7 (C), 144.8 (C), 148.0 (C).

5.4.2. 6,7-Dimethoxy-4-methyl-4*H*-chromene 15b. The product **15b** (0.15 g, 90%) was isolated as a dark yellow oil (that rapidly turned green upon drying under vacuum) starting from substrate **14b** (0.19 g, 0.81 mmol) and Grubbs catalyst **11** (27 mg, 0.031 mmol, 4 mol%) in toluene (40 mL, 0.02 M). (Found: M^+, 206.0940, $C_{12}H_{14}O_3$ requires 206.0943); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.32

(3H, d, $J=6.9$ Hz, CH_3), 3.44–3.48 (1H, m, 4-H), 3.83 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.84 (1H, dd, $J=6.2$, 3.9 Hz, 3-H), 6.43 (1H, s, ArH), 6.43–6.46 (1H, m, 2-H), 6.58 (1H, s, ArH); ^{13}C NMR (75 MHz, $CDCl_3$, 2 quaternary carbons not observed in spectrum): $\delta=25.6$ (CH_3), 28.2 (4-C), 55.6 (OCH_3), 56.0 (OCH_3), 98.0 (CH), 102.8 (CH), 105.7 (CH), 126.4 (C), 139.3 (CH), 155.4 (C); IR ν_{max} ($CHCl_3$)/cm^{-1}: 1664, 1618, 1509, 1452, 1406; MS: $m/z=206$ (M^+, 17%), 192 (14), 191 (100), 181 (15), 175 (10), 147 (22).

5.4.3. 6,8-Dimethoxy-4*H*-chromene 15c. The product **15c** (0.12 g, 68%) was isolated as a yellow oil that darkened rapidly with time, starting from substrate **14c** (0.20 g, 0.91 mmol) and Grubbs catalyst **11** (30 mg, 0.035 mmol, 4 mol%) in toluene (30 mL, 0.030 M). (Found: M^+, 192.0780, $C_{11}H_{12}O_3$ requires 192.0786); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=3.36$ (2H, br s, 4-H), 3.75 (3H, s, OCH_3), 3.85 (3H, s, OCH_3) 4.87–4.91 (1H, m, 3-H), 6.09 (1H, d, $J=2.5$ Hz, ArH), 6.34 (1H, d, $J=2.5$ Hz, ArH), 6.56 (1H, br d, $J=6.2$ Hz, 2-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=23.4$ (4-C), 55.5 (OCH_3), 55.9 (OCH_3), 98.3 (CH), 99.4 (CH), 103.3 (CH), 120.5 (C), 135.3 (C), 140.6 (CH), 148.5 (C), 155.2 (C); IR ν_{max} ($CHCl_3$)/cm^{-1}: 1664, 1601, 1491, 1457, 1428; MS: $m/z=192$ (M^+, 100%), 191 (83), 180 (10), 177 (25), 176 (14), 149 (42), 148 (11), 134 (10), 133 (11), 121 (12), 106 (11), 91 (11), 77 (13), 63 (10).

5.4.4. 6,8-Dimethoxy-4-methyl-4*H*-chromene 15d. The product **15d** (0.16 g, 91%) was isolated as a yellow oil (that rapidly turned green upon drying under vacuum) starting from substrate **14d** (0.20 g, 0.85 mmol) and Grubbs catalyst **11** (28 mg, 0.030 mmol, 4 mol%) in toluene (40 mL, 0.021 M). (Found: M^+, 206.0943, $C_{12}H_{14}O_3$ requires 206.0943); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.30$ (3H, d, $J=6.9$ Hz, CH_3), 3.42–3.48 (1H, m, 4-H), 3.73 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 4.80–4.86 (1H, m, 3-H), 6.18 (1H, d, $J=2.6$ Hz, ArH), 6.32 (1H, d, $J=2.6$ Hz, ArH), 6.53 (1H, dd, $J=6.2$, 0.8 Hz, 2-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=26.0$ (CH_3), 28.5 (4-C), 55.8 (OCH_3), 56.2 (OCH_3), 98.4 (CH), 103.1 (CH), 106.1 (CH), 126.7 (C), 139.7 (CH), 140.9 (C), 148.7 (C), 155.8 (C); IR ν_{max} ($CHCl_3$)/cm^{-1}: 1665, 1598, 1489; MS: $m/z=206$ (M^+, 45%), 192 (25), 191 (100), 181 (16).

5.4.5. 5,8-Dimethoxy-4*H*-chromene 15e. The product **15e** (0.14 g, 80%) was isolated as a light yellow oil starting from substrate **14e** (0.20 g, 0.91 mmol) and Grubbs catalyst **11** (30 mg, 0.035 mmol, 4 mol%) in toluene (30 mL, 0.030 M). (Found: M^+, 192.0785, $C_{11}H_{12}O_3$ requires 192.0786); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=3.22$–3.24 (2H, m, 4-H), 3.74 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 4.92–4.97 (1H, m, 3-H), 6.39 (1H, d, $J=8.9$ Hz, ArH), 6.53 (1H, dt, $J=6.3$, 1.9 Hz, 2-H), 6.67 (1H, d, $J=8.9$ Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=18.5$ (4-C), 55.5 (OCH_3), 56.3 (OCH_3), 100.3 (CH), 102.9 (CH), 109.4 (CH), 110.4 (C), 139.9 (CH), 141.5 (C), 141.9 (C), 151.2 (C); IR ν_{max} ($CHCl_3$)/cm^{-1}: 1676, 1640, 1599, 1494, 1454. MS: $m/z=193$ ($M^+ + 1$, 12%), 192 (100), 191 (40), 177 (62), 162 (16), 161 (35), 149 (10), 86 (20), 84 (32).

5.4.6. 1*H*-Benzo[*f*]chromene 15f.[23] The product **15f** (0.060 g, 63%) was isolated as a light-coloured semi-solid, which darkened rapidly with time, starting from substrate **14f** (0.11 g, 0.50 mmol) and Grubbs catalyst **11** (18 mg, 0.021 mmol, 4 mol%) in toluene (35 mL, 0.014 M); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=3.68$ (2H, br d, $J=1.9$ Hz, 1-H), 5.11–5.16 (1H, m, 2-H), 6.60 (1H, dt, $J=6.3$, 1.9 Hz, 3-H), 7.07 (1H, d, $J=8.9$ Hz, ArH), 7.39–7.44 (1H, m, ArH), 7.50–7.61 (1H, m, ArH), 7.65–7.70 (2H, m, 2×ArH), 7.78 (1H, d, $J=8.0$ Hz, 6-H).

5.5. Experimental part B: 2*H*-chromenes

5.5.1. Known precursors for the synthesis of the 2*H*-chromenes 20a–g. 2-Nitrophenol **16a**, 4-Nitrophenol **16b**, 3-hydroxy-4-methoxybenzaldehyde **16c**, 2-hydroxybenzaldehyde **16d**, 4-hydroxybenzaldehyde **16e** and 2-hydroxynaphthalene **16f** (=**12d**) were all converted to their allyl derivatives: 1-allyloxy-2-nitrobenzene,[24a] 1-allyloxy-4-nitrobenzene,[24b] 3-allyloxy-4-methoxybenzaldehyde,[24c] 2-allyloxybenzaldehyde,[24d] 4-allyloxybenzaldehyde,[24e] and 2-allyloxynaphthalene,[22f] respectively. A Claisen rearrangement was performed on these compounds to afford the rearranged products: 2-allyl-6-nitrophenol **17a**,[15b] 2-allyl-4-nitrophenol **17b**,[13e] 2-allyl-3-hydroxy-4-methoxybenzaldehyde **17c**,[15b] 3-allyl-2-hydroxybenzaldehyde **17d**,[24f] 3-allyl-4-hydroxybenzaldehyde[13e] **17e** and 1-allyl-naphthalen-2-ol[22f] **17f** (=**13f**), respectively. 2-Allylphenol **17g** was purchased from Aldrich and used without further purification.

5.6. General procedure for the isomerization of substituted 2-allylphenols 17 to 2-(prop-1-enyl)phenols 18

Typically, substituted 2-allylphenol **17** (ca. 3 mmol) and [RuClH(CO)(PPh_3)$_3$] (1–4 mol%) were dissolved in distilled, degassed toluene (5 mL). The reaction was heated at 65–90 °C for 24 h and the completion of the reaction was confirmed by NMR spectroscopy of a crude sample. The reaction solution was purified by filtration through a short silica gel pad (5% EtOAc/hexane) to afford the product, **18** as a mixture of *E*/*Z* isomers (predominantly *E*, which were then characterized by NMR spectroscopy). The following compounds were prepared using this procedure:

5.6.1. 2-Nitro-6-(prop-1-enyl)phenol 18a. The product **18a** (0.48 g, 96%, *E*:*Z* ratio 88:12) was obtained as an yellow oil from **17a** (0.50 g, 2.8 mmol). Found: M^+, 179.0556, $C_9H_9NO_3$ requires 179.0582); ^{1}H NMR (300 MHz, C_6D_6, only *E* isomer characterized, OH not observed in spectrum): $\delta=1.63$ (3H, dd, $J=6.7$, 1.7 Hz, CH_3), 5.92–6.04 (1H, m, CH=C*H*CH$_3$), 6.21–6.26 (1H, m, ArH), 6.71 (1H, dd, $J=15.9$, 1.6 Hz, C*H*=CHCH$_3$), 7.10–7.15 (1H, m, ArH), 7.53 (1H, dd, $J=8.5$, 1.4 Hz, ArH), 11.02 (1H, s, OH); ^{13}C NMR (75 MHz, C_6D_6, only *E* isomer characterized, one quaternary carbon obscured in spectrum): $\delta=18.8$ (CH_3), 119.2 (CH), 123.1 (CH), 124.1 (CH), 129.0 (CH), 133.3 (CH), 137.1 (C), 152.4 (C); IR ν_{max} ($CHCl_3$)/cm^{-1}: 3205 br, 1655, 1605, 1539, 1443, 1333; MS: $m/z=179$ (M^+, 21%), 162 (32), 149 (23), 132 (40), 131 (53), 103 (10), 81 (11), 77 (14), 69 (100), 55 (12), 43 (15), 41 (18).

5.6.2. 4-Nitro-2-(prop-1-enyl)phenol 18b. The product **18b** (0.17 g, 96%, *E*:*Z* ratio 87:13) was obtained as an

orange oil from **17b** (0.18 g, 1.0 mmol). Found: M^+, 179.0574, $C_9H_9NO_3$ requires 179.0582); ^1H NMR (300 MHz, $CDCl_3$, only *E* isomer characterized, OH not observed in spectrum): $\delta=1.95$ (3H, dd, $J=6.5$, 1.6 Hz, CH_3), 6.32–6.41 (1H, m, CH=C*H*CH_3), 6.57 (1H, dd, $J=$ 17.3, 1.4 Hz, C*H*=$CHCH_3$), 6.88 (1H, d, $J=8.9$ Hz, 6-H), 7.99 (1H, dd, $J=8.9$, 2.7 Hz, 5-H), 8.23 (1H, d, $J=2.7$ Hz, 3-H); ^{13}C NMR (75 MHz, $CDCl_3$, only *E* isomer characterized): $\delta=18.9$ (CH_3), 115.8 (CH), 123.2 (CH), 123.4 (CH), 123.8 (CH), 125.8 (C), 131.2 (CH), 141.6 (C), 158.0 (C); IR ν_{max} ($CHCl_3$)/cm^{-1}: 3384 br, 1655, 1614, 1583, 1519, 1493, 1434, 1338; MS: $m/z=179$ (M^+, 100%), 167 (18), 149 (14), 132 (11), 118 (12), 103 (10), 77 (18), 69 (15), 57 (20), 41 (13).

5.6.3. 3-Hydroxy-4-methoxy-2-(prop-1-enyl)benzaldehyde 18c. The product **18c** (0.38 g, 67%, *E*:*Z* ratio 66:34) was obtained as an orange oil from **17c** (0.57 g, 3.0 mmol). Found: M^+, 192.0787, $C_{11}H_{12}O_3$ requires 192.0786; ^1H NMR (300 MHz, $CDCl_3$): *E* isomer $\delta=1.99$ (3H, dd, $J=6.9$, 1.6 Hz, CH_3), 3.97 (3H, s, OCH_3), 5.95 (1H, s, OH), 6.05 (1H, dq, $J=15.9$, 6.6 Hz, CH=C*H*CH_3), 6.80 (1H, dd, $J=15.9$, 1.7 Hz, C*H*=$CHCH_3$), 6.86 (1H, d, $J=8.5$ Hz, 5-H), 7.48 (1H, d, $J=8.5$ Hz, 6-H), 10.08 (1H, s, CHO): *Z* isomer $\delta=1.59$ (3H, dd, $J=6.6$, 1.7 Hz, CH_3), 3.98 (3H, s, OCH_3), 5.81 (1H, s, OH), 6.17 (1H, dq, $J=11.3$, 6.9 Hz, CH=C*H*CH_3), 6.55 (1H, dd, $J=11.3$, 1.6 Hz, C*H*=$CHCH_3$), 6.91 (1H, d, $J=8.6$ Hz, 5-H), 7.54 (1H, d, $J=8.6$ Hz, 6-H), 10.02 (1H, s, CHO); ^{13}C NMR (75 MHz, $CDCl_3$, only *E* isomer characterized): $\delta=19.7$ (CH_3), 56.6 (OCH_3), 109.0 (CH), 122.2 (CH), 123.0 (CH), 128.6 (C), 132.7 (C), 136.4 (CH), 143.3 (C), 150.8 (C), 192.0 (CHO); IR ν_{max} ($CHCl_3$)/cm^{-1}: 3424 br, 1678, 1593, 1484, 1440; MS $m/z=192$ (M^+, 83%), 177 (100), 162 (20), 103 (21), 91 (18), 77 (21).

5.6.4. 2-Hydroxy-3-(prop-1-enyl)benzaldehyde 18d. The product **18d** (0.45 g, 89%, *E*:*Z* ratio 85:15) was obtained as an orange oil from **17d** (0.51 g, 3.5 mmol). Found: M^+, 162.0653, $C_{10}H_{10}O_2$ requires 162.0681); ^1H NMR (300 MHz, $CDCl_3$, only *E* isomer characterized): $\delta=1.93$ (3H, dd, $J=6.6$, 1.6 Hz, CH_3), 6.29–6.41 (1H, m, CH=C*H*CH_3), 6.70 (1H, dd, $J=15.9$, 1.6 Hz, C*H*=$CHCH_3$), 6.94–6.99 (1H, m, ArH), 7.41 (1H, dd, $J=$ 7.6, 1.5 Hz, ArH), 7.62 (1H, d, $J=7.6$ Hz, ArH), 9.87 (1H, s, CHO), 11.43 (1H, s, OH); ^{13}C NMR (75 MHz, $CDCl_3$, only *E* isomer characterized): $\delta=19.0$ (CH_3), 119.6 (CH), 120.6 (C), 123.9 (CH), 128.4 (CH), 132.2 (CH), 133.6 (CH), 137.1 (C), 158.4 (C), 196.8 (CHO); IR ν_{max} ($CHCl_3$)/cm^{-1}: 3250 br, 1951, 1654, 1608, 1486, 1431; MS: $m/z=162$ (M^+, 100%), 144 (14), 133 (12), 121 (14), 115 (17), 103 (7), 91 (10), 77 (15), 57 (12), 43 (14), 41 (14).

5.6.5. 4-Hydroxy-3-(prop-1-enyl)benzaldehyde 18e. The product **18e** (0.42 g, 42%, *E*:*Z* ratio 92:8) was obtained as a yellow solid (mp 88–91 °C, recrystalized from $CHCl_3$) from **17e** (1.0 g, 6.2 mmol). Found: M^+, 162.0680, $C_{10}H_{10}O_2$ requires 162.0681); ^1H NMR (300 MHz, $CDCl_3$, only *E* isomer characterized): $\delta=1.93$ (3H, dd, $J=6.6$, 1.7 Hz, CH_3), 6.27–6.37 (1H, m, CH=C*H*CH_3), 6.64 (1H, d, $J=$ 15.9 Hz, C*H*=$CHCH_3$), 6.96 (1H, d, $J=8.4$ Hz, 5-H), 7.17 (1H, br s, OH), 7.65 (1H, dd, $J=8.4$, 1.9 Hz, 6-H), 7.88 (1H, d, $J=1.9$ Hz, 2-H), 9.84 (1H, s, CHO); ^{13}C NMR (75 MHz, $CDCl_3$, only *E* isomer characterized): $\delta=18.9$ (CH_3), 116.2 (CH), 124.2 (CH), 126.1 (C), 129.5 (C), 129.7 (CH), 129.7 (CH), 130.4 (CH), 158.7 (C), 191.9 (CHO); IR ν_{max} ($CHCl_3$)/cm^{-1}: 3260 br, 1670, 1586, 1501, 1436; MS: $m/z=162$ (M^+, 100%), 133 (13), 115 (121), 105 (12), 91 (10), 77 (14), 65 (9), 51 (9), 39 (9).

5.6.6. 1-(Prop-1-enyl)naphthalen-2-ol 18f.[25] The product **18f** (0.42 g, 84%, *E*:*Z* ratio 33:67) was obtained as a clear oil from **17f** (0.5 g, 2.7 mmol). Found: M^+, 184.0886, $C_{13}H_{12}O$ requires 184.0888; ^1H NMR (300 MHz, $CDCl_3$): *Z* isomer $\delta=1.61$ (3H, br d, $J=6.7$ Hz, CH_3), 5.44 (1H, s, OH), 6.24–6.35 (1H, m, CH=C*H*CH_3), 6.56 (1H, br d, $J=$ 11.0 Hz, C*H*=$CHCH_3$), 7.20 (1H, d, $J=8.9$ Hz, ArH), 7.30–7.35 (1H, m, ArH), 7.41–7.46 (1H, m, ArH), 7.70–7.82 (3H, m, 3×ArH): *E* isomer $\delta=2.05$ (3H, br d, $J=6.4$ Hz, CH_3), 5.86 (1H, s, OH), 6.06–6.18 (1H, m, CH=C*H*CH_3), 6.66 (1H, br d, $J=16.3$ Hz, C*H*=$CHCH_3$), 7.19 (1H, d, $J=$ 8.7 Hz, ArH), 7.30–7.35 (1H, m, ArH), 7.41–7.46 (1H, m, ArH), 7.66 (1H, d, $J=8.9$ Hz, ArH), 7.70–7.82 (2H, m, 2× ArH); ^{13}C NMR (75 MHz, $CDCl_3$): *Z* isomer $\delta=14.8$ (CH_3), 115.3 (C), 117.0 (CH), 122.6 (CH), 123.3 (CH), 124.0 (CH), 126.3 (CH and C), 128.2 (CH), 129.1 (CH), 132.6 (C), 133.7 (CH), 149.7 (C): *E* isomer (some signals under those of *Z* isomer) $\delta=19.0$ (CH_3), 117.4 (CH), 123.7 (CH), 124.4 (CH), 128.7 (CH), 132.7 (C), 133.8 (CH), 150.3 (C); IR ν_{max} ($CHCl_3$)/cm^{-1}: 3350 br, 1689, 1641, 1588, 1569, 1550, 1515, 1463, 1431; MS $m/z=185$ ($M^+ + 1$, 18%), 184 (100), 183 (37), 181 (11), 173 (14), 172 (17), 170 (15), 169 (94), 168 (10), 167 (14), 165 (257), 155 (12), 153 (11), 152 (14), 141 (18), 139 (13), 128 (14), 127 (13), 115 (23), 83 (15).

5.6.7. 2-(Prop-1-enyl)-phenol 18g.[26] The product **18g** (0.90 g, 90%, *E*:*Z* ratio 89:11) was obtained as an orange oil from **17g** (1.0 g, 7.5 mmol); ^{1}NMR (300 MHz, $CDCl_3$, only *E* isomer characterized): $\delta=1.90$ (3H, dd, $J=6.6$, 1.7 Hz, CH_3), 5.06 (1H, br s, OH), 6.19 (1H, dq, $J=15.9$, 6.6 Hz, CH=C*H*CH_3), 6.58 (1H, br d, $J=15.9$ Hz, C*H*=$CHCH_3$), 6.77 (1H, d, $J=8.0$ Hz, ArH), 6.85–6.90 (1H, m, ArH), 7.05–7.11 (1H, m, ArH), 7.28 (1H, dd, $J=$ 7.6, 1.2 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$, only *E* isomer characterized): $\delta=18.9$ (CH_3), 115.6 (CH), 120.9 (CH), 125.1 (C), 125.3 (CH), 127.4 (CH), 127.9 (CH), 128.3 (CH), 152.3 (C).

5.7. General procedure for the allylation of substituted 2-(prop-1-enyl)phenols 18 to afford 1-allyloxy-2-(prop-1-enyl)benzenes 19

Typically, substituted 2-(prop-1-enyl)phenol **18** (ca. 2.6 mmol) and allyl bromide (2 mol equiv) were dissolved in acetone (10 mL) (or DMF for substrates containing an aldehyde functionality) containing K_2CO_3 (2 mol equiv). The resulting reaction mixture was then heated at reflux for 12–24 h (at 60 °C for DMF solutions). The reaction mixture was then cooled and the solvent removed under reduced pressure. H_2O (50 cm^3) was then added to the residue and the organic material, extracted using CH_2Cl_2 (4×40 mL). The organic layer was then separated and dried using $MgSO_4$ and then concentrated in vacuo. The organic residue obtained was then purified by column chromatography (10–30% EtOAc/hexane) to afford **19** as a mixture of *E*/*Z*

isomers (predominantly *E*, which were then characterized by NMR spectroscopy). The following compounds were prepared using this procedure:

5.7.1. 2-Allyloxy-1-nitro-3-(prop-1-enyl)benzene 19a. The product **19a** (0.25 g, 71%, *E*:*Z* ratio 90:10) was obtained as an orange oil from **18a** (0.18 g, 0.96 mmol). (Found: M^+, 219.0893, $C_{12}H_{13}NO_3$ requires 219.0895); ^{1}H NMR (300 MHz, $CDCl_3$, only *E* isomer characterized): δ= 1.93 (3H, dd, J=6.6, 1.6 Hz, CH_3), 4.49 (2H, br d, J= 5.8 Hz, OCH_2), 5.29 (1H, dd, J=10.4, 1.2 Hz, CH=C(H)*H*), 5.39 (1H, dd, J=17.1, 1.5 Hz, CH=C(*H*)H), 6.01–6.14 (1H, m, CH_2CH=CH_2), 6.26–6.38 (1H, m, CH=C*H*CH_3), 6.66 (1H, dd, J=15.9, 1.5 Hz, C*H*=$CHCH_3$), 7.12–7.17 (1H, m, ArH), 7.60–7.66 (2H, m, 2×ArH); ^{13}C NMR (75 MHz, $CDCl_3$, only *E* isomer characterized): δ=18.9 (CH_3), 77.0 (OCH_2 under $CDCl_3$ signals), 105.3 (CH), 122.9 (CH), 123.5 (CH), 124.5 (CH), 130.4 (CH), 130.5 (CH), 134.1 (C), 143.6 (C). 144.0 (CH), 147.1 (C); IR ν_{max} ($CHCl_3$)/cm^{-1}: 1670, 1655, 1602, 1531, 1444, 1359; MS: m/z=220 (M^++H, 29%), 219 (M^+, 44%), 204 (47), 190 (68), 186 (213), 172 (28), 162 (47), 132 (100), 115 (46), 103 (48), 77 (48), 39 (47).

5.7.2. 1-Allyloxy-4-nitro-2-(prop-1-enyl)benzene 19b. The product **19b** (0.18 g, quantitative, *E*:*Z* ratio 70:30) was obtained as an orange oil from **18b** (0.15 g, 0.83 mmol). Found: M^+, 219.0905, $C_{12}H_{13}NO_3$ requires 219.0895); ^{1}H NMR (300 MHz, $CDCl_3$): *E* isomer δ=1.94 (3H, dd, J= 6.6, 1.7 Hz, CH_3), 4.66–4.68 (2H, m, OCH_2), 5.35 [1H, dd, J=10.5, 1.3 Hz, CH=C(H)*H*], 5.44 [1H, dd, J=17.3, 1.3 Hz, CH=C(*H*)H], 6.01–6.14 (1H, m, CH_2CH=CH_3), 6.38 (1H, dq, J=15.9, 6.6 Hz, CH=C*H*CH_3), 6.70 (1H, dd, J=15.9, 1.6 Hz, C*H*=$CHCH_3$), 6.87 (1H, d, J=9.1 Hz, 6-H), 8.05 (1H, dd, J=9.1, 2.8 Hz, 5-H), 8.29 (1H, d, J= 2.8 Hz, 3-H): *Z* isomer δ=1.87 (3H, dd, J=7.2, 1.9 Hz, CH_3), 4.66–4.68 (2H, m, OCH_2), 5.34 [1H, dd, J=10.5, 1.4 Hz, CH=C(H)*H*], 5.40–5.46 [1H, m, CH=C(*H*)H], 5.91–6.11 (2H, m, CH_2CH=CH_3 and CH=C*H*CH_3), 6.51 (1H, dd, J=11.6, 1.7 Hz, C*H*=$CHCH_3$), 6.91 (1H, d, J= 9.0 Hz, 6-H), 8.12 (1H, dd, J=9.0, 2.7 Hz, 5-H), 8.16 (1H, d, J=2.7 Hz, 3-H); ^{13}C NMR (75 MHz, $CDCl_3$): *E* isomer δ=18.9 (CH_3), 69.6 (OCH_2), 111.4 (CH), 118.3 (CH), 121.9 (CH), 123.5 (CH), 123.8 (CH), 128.1 (C), 129.5 (CH), 132.0 (CH), 141.6 (C), 159.7 (C): *Z* isomer δ=14.6 (CH_3), 69.5 (OCH_2), 111.1 (CH), 118.2 (CH), 123.3 (CH), 124.0 (CH), 125.6 (CH), 127.2 (C), 129.3 (CH), 131.9 (CH), 141.0 (C), 160.9 (C); IR ν_{max} ($CHCl_3$)/cm^{-1}: 1676, 1585, 1565, 1511; MS: m/z=219 (M^+, 48%), 190 (10), 178 (67), 161 (14), 133 (11), 132 (100), 131 (64), 103 (23), 78 (12), 77 (22), 63 (11), 51 (13), 41 (71), 39 (25).

5.7.3. 3-Allyloxy-4-methoxy-2-(prop-1-enyl)benzaldehyde 19c. The product **19c** (0.13 g, 81%, *E*:*Z* ratio 74:26) was obtained as an orange oil from **18c** (0.13 g, 0.68 mmol). (Found: M^+, 232.1083, $C_{14}H_{16}O_3$ requires 232.1099); ^{1}H NMR (300 MHz, $CDCl_3$): *E* isomer δ=1.98 (3H, dd, J=6.6, 1.7 Hz, CH_3), 3.92 (3H, s, OCH_3), 4.41–4.46 (2H, m, OCH_2), 5.22 [1H, br d, J=10.1 Hz, CH=C(H)*H*], 5.34 [1H, dd, J=17.2, 1.5 Hz, CH=C(*H*)H], 5.86 (1H, dq, J=15.9, 6.6 Hz, CH=C*H*CH_3), 6.00–6.14 (1H, m, CH_2CH=CH_3), 6.73 (1H, dd, J=15.9, 1.7 Hz, C*H*=$CHCH_3$), 6.91 (1H, d, J=8.7 Hz, 5-H), 7.71 (1H, d, J=8.7 Hz, 6-H), 10.05 (1H, s, CHO): *Z* isomer δ=1.55 (3H, dd, J=6.8, 1.7 Hz, CH_3), 3.94 (3H, s, OCH_3), 4.41–4.46 (2H, m under *E*-isomer, OCH_2), 5.18–5.24 [1H, m under *E*-isomer, CH=C(H)*H*], 5.31 [1H, dd, J=17.2, 1.5 Hz, CH=C(*H*)H], 6.00–6.14 (2H, m under *E*-isomer, CH_2CH=CH_3 and CH=C*H*CH_3), 6.57 (1H, br d, J=11.4 Hz, C*H*=$CHCH_3$), 6.95 (1H, d, J= 8.8 Hz, 5-H), 7.75 (1H, d, J=8.7 Hz, 6-H), 9.99 (1H, s, CHO);^{13}C NMR (75 MHz, $CDCl_3$, only *E* isomer characterized): δ=19.1 (CH_3), 55.8 (OCH_3), 73.8 (OCH_2), 110.4 (CH), 117.7 (CH), 117.8 (CH), 122.2 (CH), 125.9 (CH), 128.3 (C), 133.9 (C), 136.5 (CH), 145.0 (C), 157.0 (C), 191.4 (CHO); IR ν_{max} ($CHCl_3$)/cm^{-1}: 1676, 1585, 1565, 1511, 1483, 1464, 1440, 1420; MS: m/z=232 (M^+, 37%), 191 (100), 175 (11), 164 (12), 163 (16), 148 (18), 135 (48), 119 (9), 103 (23), 91 (25), 77 (17), 65 (14), 41 (20).

5.7.4. 2-Allyloxy-3-(prop-1-enyl)benzaldehyde 19d. The product **19d** (0.53 g, quantitative, *E*:*Z* ratio 85:15) was isolated as a yellow oil from **18d** (0.43 g, 2.7 mmol). Found: M^+, 202.0997, $C_{13}H_{14}O_2$ requires 202.0994); ^{1}H NMR (300 MHz, $CDCl_3$, only *E* isomer characterized): δ=1.94 (3H, dd, J=6.6, 1.7 Hz, CH_3), 4.44–4.47 (2H, m, OCH_2), 5.29–5.37 [1H, m, CH=C(H)*H*], 5.38–5.44 [1H, m, CH=C(H)*H*], 6.07–6.15 (1H, m, OCH_2CHCH_2), 6.29–6.36 (1H, m, ArCH=C*H*), 6.67 (1H, dd, J=15.9, 1.5 Hz, ArC*H*=CH), 7.15–7.20 (1H, m, ArH), 7.67–7.72 (2H, m, 2×ArH), 10.39 (1H, s, CHO); ^{13}C NMR (75 MHz, $CDCl_3$, only *E* isomer characterized): δ=18.9 (CH_3), 77.0 (OCH_2), 118.7 (CH), 124.4 (CH), 124.5 (CH), 126.7 (CH), 128.6 (CH), 129.8 (C), 132.6 (CH), 132.7 (CH), 136.7 (C), 158.8 (C), 190.3 (CHO); IR ν_{max} ($CHCl_3$)/cm^{-1}: 1684, 1590, 1445; MS: m/z=202 (M^+, 16%), 178 (16), 177 (84), 176 (15), 161 (39), 159 (21), 149 (100), 145 (18), 133 (27), 132 (24), 120 (37), 115 (17), 105 (38), 103 (16), 77 (35), 65 (21), 63 (15), 51 (27), 41 (54), 38 (34).

5.7.5. 4-Allyloxy-3-(prop-1-enyl)benzaldehyde 19e. The product **19e** (0.81 g, 64%, *E*:*Z* ratio 93:7) was obtained as an orange oil from **18e** (1.0 g, 6.2 mmol). Found: M^+, 202.0993, $C_{13}H_{14}O_2$ requires 202.0994); ^{1}H NMR (300 MHz, $CDCl_3$, only *E* isomer characterized): δ=1.92 (3H, br d, J=6.6 Hz, CH_3), 4.65 (2H, br d, J=5.1 Hz, OCH_2), 5.33 [1H, br d, J=10.6 Hz, CH=C(H)*H*], 5.44 [1H, br d, J=17.3 Hz, CH=C(H)*H*], 6.01–6.15 (1H, m, OCH_2-C*H*CH_2), 6.36 (1H, dq, J=15.8, 6.6 Hz, ArCH=C*H*), 6.73 (1H, br d, J=15.8 Hz, ArC*H*=CH), 6.94 (1H, d, J=8.5 Hz, 5-H), 7.69 (1H, dd, J=8.5, 1.7 Hz, 6-H), 7.93 (1H, d, J= 1.7 Hz, 2-H), 9.88 (1H, s, CHO); ^{13}C NMR (75 MHz, $CDCl_3$, only *E* isomer characterized): δ=18.9 (CH_3), 69.2 (OCH_2), 111.7 (CH), 118.1 (CH), 124.5 (CH), 127.9 (CH), 128.1 (C), 128.4 (CH), 129.8 (C), 130.3 (CH), 132.4 (CH), 159.9 (C), 191.1 (CHO); IR ν_{max} ($CHCl_3$)/cm^{-1}: 1686, 1595, 1492; MS: m/z=202 (M^+, 58%), 173 (13), 161 (34), 159 (11), 133 (27), 115 (11), 106 (9), 105 (100), 103 (16), 79 (16), 77 (26), 51 (11), 41 (32), 39 (19).

5.7.6. 2-(Allyloxy)-1-(prop-1-enyl)naphthalene 19f.[25] The product **19f** (0.37 g, 65%, >95% *Z* isomer) was obtained as a clear oil from **18f** (0.30 g, 2.6 mmol). (Found: M^+, 224.1204, $C_{16}H_{16}O$ requires 224.1201); ^{1}H NMR (300 MHz, $CDCl_3$, only *Z* isomer characterized): δ=1.52 (3H, dd, J=6.8, 1.7 Hz, CH_3), 4.65–4.68 (2H, m, OCH_2), 5.23–5.27 (1H, m, CH=C(H)*H*), 5.38–5.45 [1H, m,

CH=C(*H*)H], 6.01–6.16 (2H, m, C*H*CH_3 and CH_2-C*H*=CH_2), 6.60 (1H, dd, J=11.2, 1.1 Hz, C*H*=$CHCH_3$), 7.26 (1H, d, J=9.0 Hz, ArH), 7.31–7.36 (1H, m, ArH), 7.41–7.47 (1H, m, ArH), 7.74–7.79 (2H, m, 2×ArH), 7.86 (1H, d, J=8.5 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$, only *Z* isomer characterized): δ=15.4 (CH_3), 70.2 (OCH_2), 115.2 (CH), 117.1 (CH), 121.1 (C), 123.6 (CH), 125.1 (CH), 126.1 (CH), 128.0 (CH), 128.4 (CH), 129.1 (C), 129.7 (CH), 129.8 (CH), 132.7 (C), 133.9 (CH), 153.0 (C); IR ν_{max} ($CHCl_3$)/cm^{-1}: 1672, 1623, 1596, 1511, 1465, 1435; MS: *m*/*z*=224 (M^+, 85%), 183 (100), 165 (49), 155 (93), 139 (31), 115 (33), 41 (35).

5.7.7. 1-Allyloxy-2-(prop-1-enyl)benzene 19g. The product **19g** (0.45 g, 86%, *E*:*Z* ratio 90:10) was obtained as a clear oil from **18g** (0.40 g, 3.0 mmol). Found: M^+, 174.1043, $C_{12}H_{14}O$ requires 174.1045); ^{1}H NMR (300 MHz, $CDCl_3$, only *E* isomer characterized): δ=1.89 (3H, dd, J=6.7, 1.5 Hz, CH_3), 4.54–4.55 (2H, m, OCH_2), 5.27 [1H, dd, J=10.5, 1.3 Hz, CH=C(H)*H*], 5.41 [1H, dd, J=17.3, 1.3 Hz, CH=C(H)*H*], 6.01–6.14 (1H, m, C*H*=CH_2), 6.16–6.29 (1H, m, CH=C*H*), 6.75 (1H, d, J=15.9 Hz, ArC*H*=CH), 6.81–6.92 (2H, m, 2×ArH), 7.11–7.16 (1H, m, ArH), 7.39 (1H, d, J=7.6 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$, only *E* isomer characterized): δ=19.3 (CH_3), 69.6 (OCH_2), 112.8 (CH), 117.6 (CH), 121.3 (CH), 126.1 (CH), 126.7 (CH), 126.8 (CH), 128.0 (CH), 130.6 (C), 134.0 (CH), 155.6 (C); IR ν_{max} ($CHCl_3$)/cm^{-1}: 1601; MS: *m*/*z*=174 (M^+, 51%), 145 (24), 133 (71), 121 (20), 105 (100), 91 (11), 77 (28), 65 (10), 51 (15), 41 (34), 39 (25).

5.8. General RCM procedure for the synthesis of substituted 2*H*-chromenes 20 from 1-allyloxy-2-(prop-1-enyl)benzenes 19

Typically, Grubbs catalyst **11** (4–6 mol%) was added to a degassed solution of the substituted 1-allyl-2-vinyloxybenzene **19** (ca. 0.5–1.0 mmol) dissolved in degassed, distilled toluene (ca. 30 mL, ca. 0.020 M). The reaction mixture was then heated at 60 °C for 1 h under a N_2 atmosphere. After removal of the solvent under reduced pressure the residue was purified by silica gel column chromatography (5–20% EtOAc/hexane) to afford the desired product **20**. The following compounds were obtained using this procedure:

5.8.1. 8-Nitro-2*H*-chromene 20a.[27] The product **20a** (0.14 g, 88%) was obtained as a light yellow oil from **19a** (0.20 g, 0.91 mmol). (Found: M^+, 177.0431, $C_9H_7O_3N$ requires 177.0426); ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.00 (2H, dd, J=3.4, 1.9 Hz, 2-H), 5.90 (1H, dt, J=10.0, 3.4 Hz, 3-H), 6.45 (1H, dt, J=10.0, 1.9 Hz, 4-H), 6.87–6.93 (1H, m, ArH), 7.14 (1H, dd, J=7.4, 1.4 Hz, ArH), 7.67 (1H, dd, J=8.3, 1.4 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$, one quaternary carbon not observed in spectrum): δ=66.5 (2-C), 120.4 (CH), 123.3 (CH), 123.4 (CH), 124.5 (C), 124.8 (CH), 130.9 (CH), 148.2 (C); IR ν_{max} ($CHCl_3$)/cm^{-1}: 1609, 1527, 1477, 1343; MS: *m*/*z*=177 (M^+, 100%), 176 (81), 130 (41), 103 (24), 102 (20), 77 (14), 51 (6).

5.8.2. 6-Nitro-2*H*-chromene 20b. The product **20b** (0.12 g, quantitative) was obtained as a fluffy yellow solid from **19b** (0.15 g, 0.68 mmol). This yellow solid (mp decomposition >210 °C with sweating at ca. 116 °C) decomposed rapidly (hours at room temperature) to a dark brown solid in air. (Found: M^+, 177.0434, $C_9H_7O_3N$ requires 177.0426); ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.99–5.00 (2H, m, 2-H), 5.88 (1H, dt, J=10.0, 3.3 Hz, 3-H), 6.43 (1H, d, J=10.0 Hz, 4-H), 6.78 (1H, d, J=8.9 Hz, 8-H), 7.83 (1H, d, J=2.5 Hz, 5-H), 7.99 (1H, dd, J=8.9, 2.5 Hz, 7-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=66.7 (2-C), 116.0 (CH), 121.7 (C), 122.1 (CH), 122.9 (CH), 123.6 (CH), 125.3 (CH), 141.8 (C), 159.5 (C); IR ν_{max} ($CHCl_3$)/cm^{-1}: 1650, 1613, 1578, 1506, 1488, 1435; MS: *m*/*z*=177 (M^+, 99%), 176 (100), 131 (24), 130 (57), 103 (25), 102 (23), 77 (44), 74 (10), 69 (10), 63 (10), 51 (26).

5.8.3. 8-Methoxy-2*H*-chromene-5-carbaldehyde 20c. The product **20c** (0.32 g, 77%) was obtained as an orange oil from **19c** (0.50 g, 2.2 mmol). (Found: M^+, 190.0639, $C_{11}H_{10}O_3$ requires 190.0630); ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.95 (3H, s, OCH_3), 4.86 (2H, dd, J=3.8, 1.8 Hz, 2-H), 6.00 (1H, dt, J=10.2, 3.8 Hz, 3-H), 6.89 (1H, d, J=8.5 Hz, ArH), 7.34 (1H, d, J=8.5 Hz, ArH), 7.53 (1H, dt, J=10.2, 1.8 Hz, 4-H), 9.97 (1H, s, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ=56.0 (OCH_3), 65.1 (2-C), 110.4 (CH), 121.4 (CH), 122.9 (C), 124.4 (CH), 124.4 (C), 128.8 (CH), 143.2 (C), 152.5 (C), 191.7 (CHO); IR ν_{max} ($CHCl_3$)/cm^{-1}: 1686, 1592, 1565, 1493, 1460, 1439, 1412; MS: *m*/*z*=190 (M^+, 100%), 189 (53), 175 (61), 161 (19), 147 (26), 119 (17), 91 (28), 65 (19).

5.8.4. 2*H*-Chromene-8-carbaldehyde 20d.[28] The product **20d** (0.21 g, 80%) was obtained as a light yellow oil from **19d** (0.34 g, 1.67 mmol). (Found: M^+, 160.0521, $C_{10}H_8O_2$ requires 160.0524); ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.96 (2H, br s, 2-H), 5.81–5.86 (1H, m, 3-H), 6.42 (1H, br d, J=10.0 Hz, 4-H), 6.87–6.92 (1H, m, ArH), 7.13 (1H, d, J=7.2 Hz, ArH), 7.61 (1H, d, J=7.8 Hz, ArH), 10.36 (1H, s, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ=66.0 (2-C), 120.9 (CH), 122.4 (CH), 123.0 (C), 123.5 (CH), 123.6 (C), 127.2 (CH), 132.2 (CH), 156.9 (C), 189.1 (CHO); IR ν_{max} ($CHCl_3$)/cm^{-1}: 1684, 1593, 1448, 1400; MS: *m*/*z*=160 (M^+, 80%), 159 (100), 148 (52), 120 (22), 118 (40), 103 (30), 102 (28), 91 (37), 89 (25), 77 (35), 63 (30), 57 (30), 55 (38), 51 (34), 41 (43), 39 (34).

5.8.5. 2*H*-Chromene-6-carbaldehyde 20e. The product **20e** (0.19 g, 76%) was obtained as an unstable orange oil from **19e** (0.31 g, 1.5 mmol). Found: M^+, 160.0531, $C_{10}H_8O_2$ requires 160.0524); ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.97 (2H, dd, J=3.3, 2.0 Hz, 2-H), 5.83 (1H, dt, J=10.0, 3.3 Hz, 3-H), 6.45 (1H, br d, J=10.0 Hz, 4-H), 6.84 (1H, d, J=8.3 Hz, 8-H), 7.47 (1H, d, J=1.9 Hz, 5-H), 7.62 (1H, dd, J=8.3, 1.9 Hz, 7-H), 9.82 (1H, s, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ=66.4 (2-C), 116.2 (CH), 117.8 (C), 122.1 (C), 122.7 (CH), 123.5 (CH), 127.8 (CH), 132.1 (CH), 159.0 (C), 190.7 (CHO); IR ν_{max} ($CHCl_3$)/cm^{-1}: 1686, 1595, 1578; MS: *m*/*z*=160 (M^+, 73%), 159 (100), 131 (33), 103 (19), 77 (25), 51 (18), 40 (10).

5.8.6. 3*H*-Benzo[*f*]chromene 20f.[23,29] The product **20f** (0.086 g, 45%) was obtained as a yellow oil from **19f** (0.13 g, 0.58 mmol). The reaction was repeated on a smaller scale (**19f**, 0.067 g, 0.30 mmol) to afford the product **20f**

(0.055 g, 82%) in a better yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.86 (2H, dd, J=3.8, 1.7 Hz, 3-H), 5.91 (1H, dt, J=9.8, 3.8 Hz, 2-H), 7.06 (1H, d, J=8.9 Hz, ArH), 7.13 (1H, d, J=9.8 Hz, 1-H), 7.31–7.36 (1H, m, ArH), 7.44–7.50 (1H, m, ArH), 7.64 (1H, d, J=8.9 Hz, ArH), 7.74 (1H, d, J=8.2 Hz, ArH), 7.92 (1H, d, J=8.5 Hz, ArH).

5.8.7. 2*H*-Chromene 20g.[29] This reaction was performed on **19g** (~20 mg) on a NMR spectroscopy scale in an NMR tube using $CDCl_3$ as solvent.[13a] The formation of product **20g** (conversion >80%) was confirmed by ^{1}H and ^{13}C NMR spectroscopy and the spectra compared well with that reported in the literature. ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.80 (2H, dd, J=3.5, 1.9 Hz, 2-H), 5.75 (1H, dt, J=9.8, 3.5 Hz, 3-H), 6.40 (1H, br d, J=9.8 Hz, 4-H), 6.76 (1H, d, J=8.0 Hz, ArH), 6.82–6.87 (1H, m, ArH), 6.93–6.96 (1H, m, ArH), 7.05–7.11 (1H, m, ArH).

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3-Nitro-2-naphthalenemethanol: a photocleavable protecting group for carboxylic acids

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Abstract—Photocleavable protecting groups are important in synthesis and caging. Among many such groups, 2-nitrobenzyl and related groups have been found useful in many applications. However, most of the known 2-nitrobenzyl-based caging chromophores show either low quantum yield or the photolysis wavelength is not suitable for various applications. In this paper, we report 2-nitro-3-naphthalenemethanol (NNM) as an efficient photocleavable protecting group for molecules containing a carboxylic function. NNM possesses photochemical properties better than the 2-nitrobenzyl chromophores as it is photoactivatable at 380 nm in aqueous medium (CH_3CN/H_2O, 3:2 v/v) showing the desired photochemistry. The carboxylic acids are efficiently photoreleased from NNM-based esters in almost quantitative yield.

1. Introduction

Light-induced deprotection of functional groups is important in synthesis and biomolecular caging.[1–5] For biomolecular caging applications, the photoactivation of the cage is required to be done with high rate and quantum efficiency under physiological conditions at wavelengths that are non-detrimental to biological systems. Several photoactivatable groups such as benzoin, cinnamoyl, coumaryl, 2-nitrobenzyl, phenacyl, polyaromatics etc. have been developed and employed in diverse synthetic and caging applications. Among these, the 2-nitrobenzyl derivatives have attracted much attention because of their compatibility with many functional groups (e.g., phosphate, carboxylates, hydroxyl and amines). Besides its application as an orthogonal protecting group in organic synthesis,[6] it has been extensively used in biology for photoactivation of antibodies,[7,8] synthesis of difficult cyclic peptide,[9] photo-release of Ca^{2+} ions,[10] synthesis of DNA arrays on glass substrates[11] and construction of a light-activated protein by unnatural amino acid mutagenesis.[12] However, most of the known 2-nitrobenzyl-based caging chromophores show either low quantum yield or photolysis wavelength is not suitable for various applications.[3] Recently, we have reported a new caging chromophore namely 2-nitro-3-naphthalenemethanol (NNM, **1**), which possesses photochemical properties better than the 2-nitrobenzyl chromophores.[8] NNM is photoactivatable at 380 nm in aqueous medium (0.9% aqueous NaCl) giving the desired photochemistry with quantum yield of ~0.60. We also demonstrated the application of NNM in protection and deprotection of $-NH_2$ group.[8] The improved photochemical properties of NNM prompted us to examine its usefulness in caging of molecules bearing the carboxyl group.

This paper describes photocleavable protecting group properties of NNM for carboxylic acids. For comparison purpose, we have also synthesized the widely used 4,5-dimethoxy-2-nitrophenyl methanol[3,13] (DMNM, **2**) and examined its efficacy for protection and deprotection of carboxylic acids.

2. Results and discussion

NNM[8] (**1**) and DMNM[14] (**2**) were prepared according to the given procedures. In order to investigate the photocleavable protecting group properties of NNM for carboxylic functional groups, it was attached to four different carboxylic acids to obtain esters **1a**–**1d** (Scheme 1) and photochemistry of these esters was examined. Similar studies were done on DMNM-based ester **2a** also.

The UV–vis absorption of NNM-based esters (**1a**–**1d**) is similar to the UV–vis absorption of NNM, with bands located at 214, 258, 302 and 352 nm. Hence, the presence of carboxylic acid moiety in NNM does not change its absorption wavelength. Similarly, the absorption spectrum of ester **2a** is similar to the absorption spectrum of DMNM,

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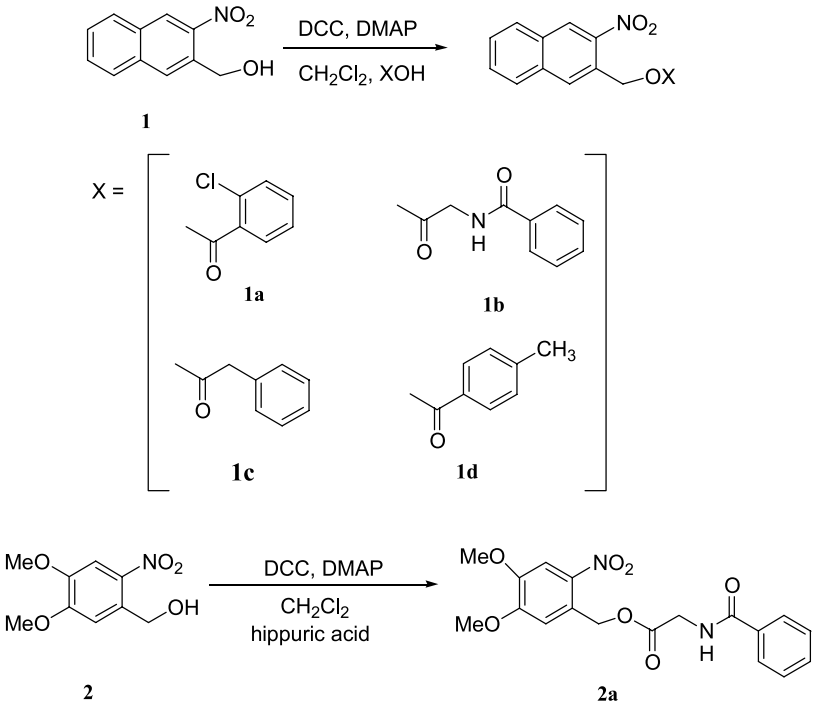


Scheme 1.

with bands located at 226 and 346 nm. However, a 1.0×10^{-3} M solution of these esters (**1a**–**1d**, **2a**) in CH_3CN–H_2O (3/2 v/v) shows absorption up to ~420 nm. Irradiation of a solution of **1a** in CH_3CN–H_2O (3/2 v/v) at ≥370 nm showed no considerable changes at 352 and 304 nm and it decreased at 258 (Fig. 1). When **2a** was photolysed under similar condition, absorbance at 346 nm decreased with concomitant increase at 220 nm (Fig. 2). HPLC analysis of the photomixture of ester **1a** revealed formation of parent carboxylic acids (*o*-chlorobenzoic acid), which can be generated if the ester undergoes the expected known photochemical reaction of NNM (Fig. 3).[8] Similarly, DMNM-based ester **2a** showed photorelease of parent carboxylic acid as evident by HPLC analysis (Fig. 4). This photorelease is again due to the expected photochemical reaction of DMNM.[3] The photochemical mechanism involved in these photoreleases is depicted in Scheme 2. The formation of nitrosoaldehyde is confirmed by proton NMR studies of the photomixture obtained from **1c**. The photomixture shows a peak at 11.20 ppm due –CHO group. It is similar to the mechanism observed in the case of 2-nitrobenzyl-based protecting groups.[2–4,8,15]

HPLC analysis showed formation of a few photoproducts in addition to the expected nirosoaldehyde. These could have generated from the secondary photoreaction of the primary photoproduct nitrosoaldehyde. The nitrosoaldehyde is known to undergo secondary photoreactions like dimerisation and oxidation.[13,16,17] Similar side reactions are also

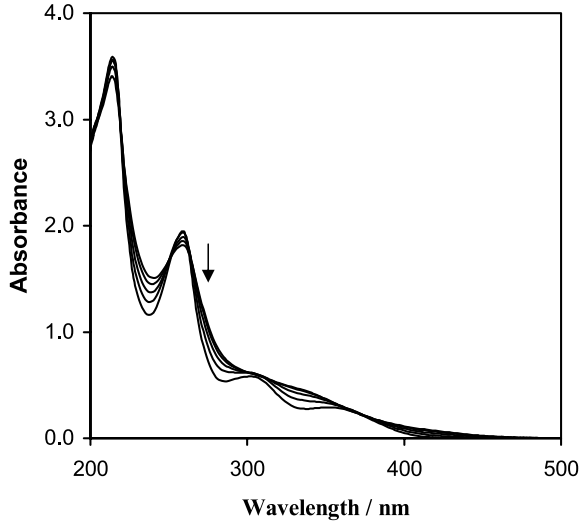


Figure 1. UV–vis absorption spectral changes during photolysis of **1a** (1.0×10^{-4} M) in acetonitrile–water (3/2, v/v).

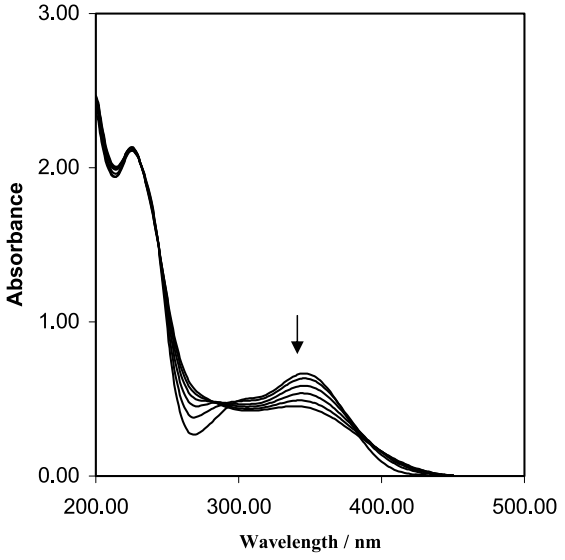


Figure 2. UV–vis absorption spectral changes during photolysis of **2a** (1.0×10^{-4} M) in acetonitrile–water (3/2, v/v).

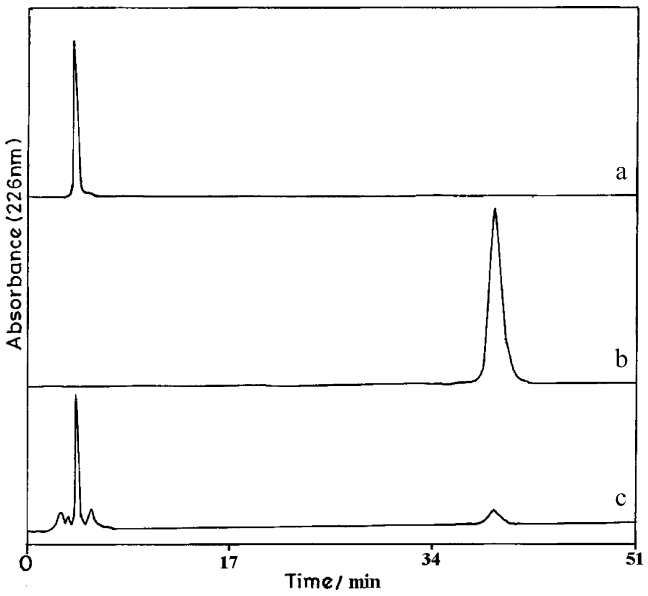


Figure 3. HPLC trace: (a) standard *o*-chlorobenzoic acid, R_t=4.3 min; (b) ester **1a**, R_t=37.6 min; (c) photomixture after 7 h photolysis of ester **1a** (>370 nm) with the released *o*-chlorobenzoic acid.

envisaged in NNM as well. However, these secondary reactions do not affect the percent release of the carboxylic acid, as the release is due to the primary photochemical process.

An action plot was constructed to obtain photodeprotection profiles for the esters. As shown in Figure 5 as a typical example, excellent deprotection yields of 96–100% were obtained in case of esters **1a–1d** (1.0×10^{-3} M) in about 6–7 h of photolysis at >370 nm. However, when **2a** was

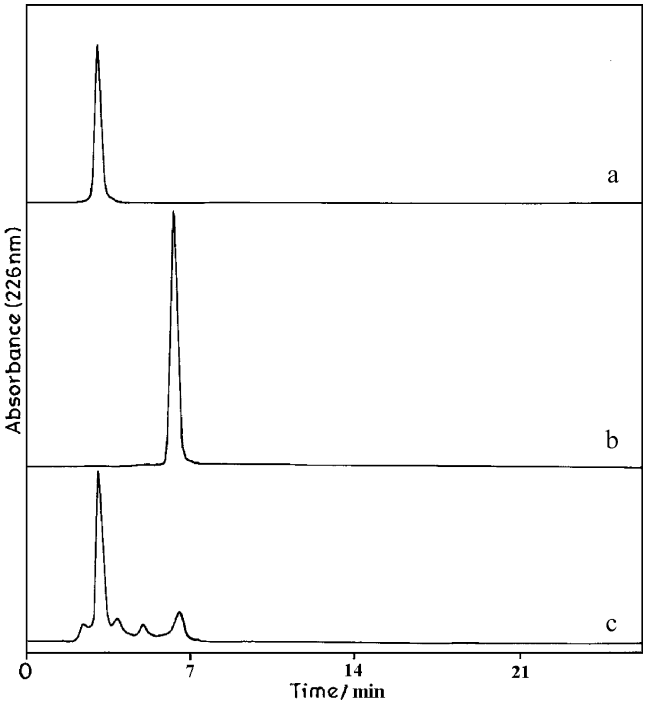
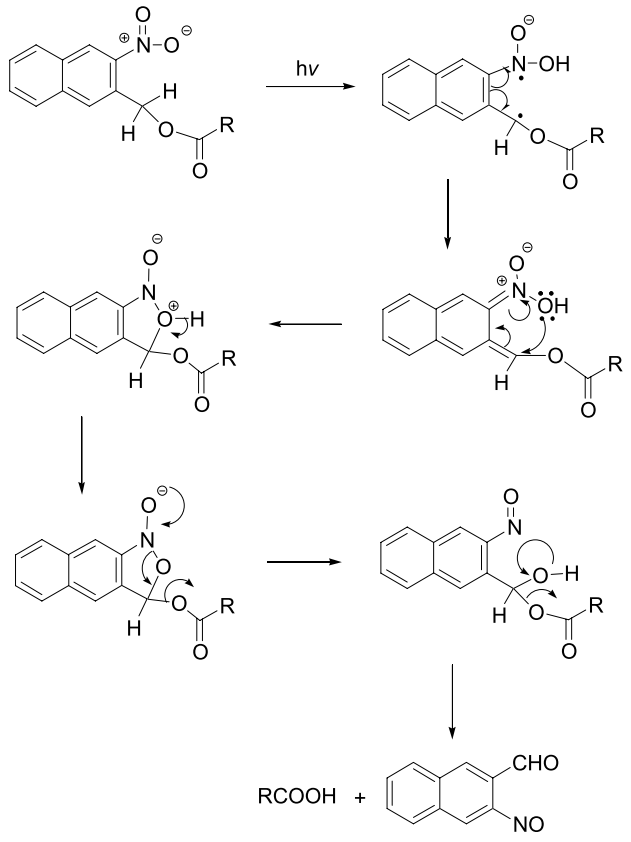


Figure 4. HPLC trace: (a) standard hippuric acid, R_t=2.9 min; (b) ester **2a**, R_t=6 min; (c) photomixture, after 12 h photolysis (>370 nm) of ester **2a** with the released hippuric acid.



Scheme 2.

irradiated under identical conditions the yield of deprotection was 88% but in about 12 h of photolysis. Quantum yields of disappearance (Φ) of the esters **1a–1d** were in range of 0.14–0.16 at 380 nm. However, ester **2a** disappeared under similar photochemical condition with a Φ of only 0.08 (Table 1). The acid moieties on NNM do not significantly affect the photochemical properties of NNM as no considerable differences in the quantum yield of disappearance of esters **1a–1d** have been observed.

Photolysis of esters was done in solvents like 1,4-dioxane, ethanol, and acetonitrile. The maximum photorelease

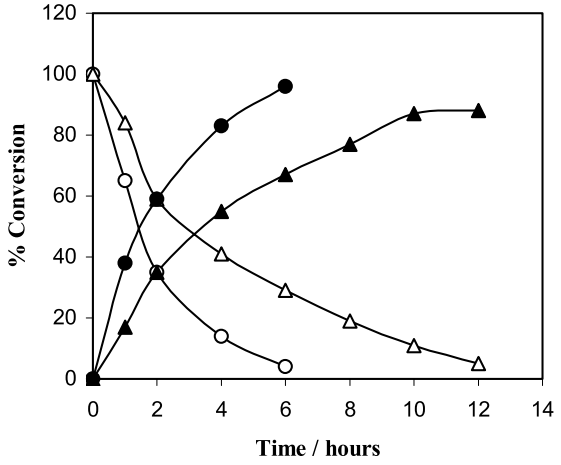
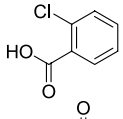
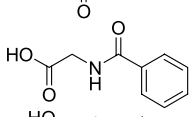
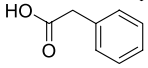
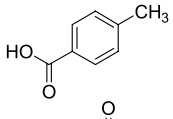
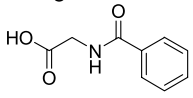


Figure 5. Time dependent decrease of esters (**1b** and **2a**) and release of hippuric acid. Ester **1b** (○); Ester **2a** (△); % Deprotection of hippuric acid from ester **1b** (●); % Deprotection of hippuric acid from ester **2a** (▲).

Table 1. Photochemical properties of esters **1a–1d** and **2a** (1.0×10^{-3} M in 3:2 acetonitrile/water)

Ester	Carboxylic acids	ε at 380 nm (mol^{-1} cm^{-1} L)	Photolysis time (h)[a]	Unreacted (%)[b]	Deprotection yield (%)[b]	Φ
1a		1626	7	3	97	0.16
1b		1280	6	4	96	0.15
1c		1886	6	0	100	0.15
1d		1755	6	4	96	0.13
2a		3180	12	5	88	0.08

[a] Time of disappearance of ester.
[b] Determined by HPLC.

(~75%) of the acid was observed in acetonitrile. However, the photorelease of acids in 1,4-dioxane and ethanol was only 25 and 35%, respectively. The photorelease of the acids can be further improved by irradiation of the esters in aqueous acetonitrile. Thus, the photoreleases could be maximized to >95% by irradiating the esters in acetonitrile containing water (up to 40%). Thus, polar solvents favour the photorelease. Control experiments showed that no thermal decomposition of the esters occurred as evidenced by HPLC analysis of the samples of esters solutions in CH_3CN–H_2O (3/2 v/v) kept in dark for about 8 days. Thus, NNM can be used to cage molecules bearing carboxyl functions. Its usage for other functional groups like phosphate and alcohol is also envisaged. It may, however, be noted that currently low solubility of NNM in water and additional synthetic work involved in its preparation limit its usage.

3. Conclusions

We have found that NNM is an efficient photocleavable protecting group for the carboxylic acids. It is photoactivatable in aqueous medium at 380–400 nm with the desired photochemical reaction. The carboxylic acids are released by irradiating the corresponding ester solution. Polar solvents like aqueous acetonitrile favour the photorelease of the acid. As compared to DMNM, the photorelease of acids in case of NNM-based esters is almost quantitative and with higher quantum efficiency.

4. Experimental

4.1. General

Starting materials for synthesis were from M/s. Lancaster (UK) and SRL India Ltd. All organic solvents were dried using standard procedures. Petroleum ether (pet-ether, 60–80 °C fraction) was procured in bulk from local suppliers and distilled before use. Other solvents (AR, UV–vis spectroscopic and HPLC grade) were purchased from SRL India Ltd, Mumbai. Thin-layer chromatography (TLC) was performed on silica gel (GF_{254} from SRL India Ltd, Mumbai) plates prepared by coating thin film of silica gel slurry prepared in ethyl acetate on glass plates. Column chromatography was performed on silica gel of 60–120 or 100–200 mesh (SRL India Ltd, Mumbai/Thomas Baker). All the organic extracts were dried over anhydrous sodium sulphate.

Melting points (Mp) were determined with a Veego melting point apparatus and are uncorrected. Electronic absorption spectra were recorded on Shimadzu UV-160 or Shimadzu UV-260 spectrophotometer. Nicolet Impact 400 series Fourier transform spectrometer (FTIR) was used to record the IR spectra of the compounds. NMR spectra were measured in a Fourier transform mode on Varian 300/400 MHz magnetic resonance spectrometer. The high-resolution mass spectra were recorded on Bruker Daltonics APEX 3 T Fourier Transform mass spectrophotometer and Q-Tof micro (YA-105) mass spectrometer. HPLC analyses were done using Hitachi L-6250 intelligent pump attached with U-2000 spectrophotometer under the following conditions: ALTEX ODS 5 μ, 4.6 mm×25 cm, 55% acetonitrile in water containing 0.1% phosphoric acid, 1.0 mL/min, 226 nm.

Irradiations were done using a 400 W medium pressure mercury lamp (Applied Photophysics Ltd, London UK, Model R-607), fitted either with a f/3.4 monochromator or with a glass filter (≥370 nm having 47 and 96% transmittance at 370 and 420 nm, respectively, with distance between sample and lamp being 2 cm) to isolate the desired wavelength for irradiation. UV–vis spectroscopic grade solvents were used for all photochemical works. The photochemical yield was defined as the ratio of ester molecules disappeared (calculated using HPLC as described above) to the amount of photons absorbed using the potassium ferrioxalate actinometer.[18]

NNM was prepared as described earlier.[8] It is a yellowish solid and remains as such under ambient laboratory light. However, the light yellowish solution of NNM in common organic solvents darkens under ambient laboratory light over a period of time. However, no significant absorption changes are observed in NNM solutions (10^{-3}–10^{-5} M) under ambient laboratory light for about a week.

Esters were prepared according to literature procedure.[19] In a typical case, solution of carboxylic acid (0.24 mmol), alcohol (0.24 mmol) and 4-(dimethylamino)pyridine (DMAP, 0.024 mmol) in anhydrous dichloromethane (5 mL) was stirred for 10 min. To the reaction mixture *N*,*N*-dicyclohexylcarbodiimide (DCC, 0.24 mmol) was added and stirred for 12 h at ambient temperature. Subsequently water (20 mL) was added into reaction mixture and compound was extracted with dichloromethane. The organic layer was washed with sodium bicarbonate solution and then with water and dried with anhydrous sodium sulphate. Solvent evaporation in vacuo gave solid, which was further purified by column chromatography.

4.1.1. 2-Chlorobenzoic acid-3-nitro-naphthalen-2-yl-methyl ester (1a). 2-Chlorobenzoic acid (0.038 g, 0.24 mmol), 3-nitro-naphthalenemethanol (0.049 g, 0.24 mmol) and DMAP (0.003 g, 0.024 mmol) in anhydrous dichloromethane (5 mL) was stirred for 10 min. To the reaction mixture DCC (0.049 g, 0.24 mmol) was added and stirred for 12 h at ambient temperature. Subsequently water (20 mL) was added into reaction mixture and compound was extracted with dichloromethane. The organic layer was washed with sodium bicarbonate solution and then with water and dried with anhydrous sodium sulphate. Solvent evaporation in vacuo gave light brown solid, which was further purified by column chromatography.

Yield: 89%. Mp: 94–96 °C; FTIR (KBr) ν_{max} (cm^{-1}): 1729 (OCO), 1525 and 1361 (NO_2); ES-MS: *m*/*z* 364.0367 ($M^+ + Na$) (found), 364.0353 ($M^+ + Na$) (calcd for $C_{18}H_{12}ClNO_4$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.73 (s, 1H, Ar-H), 8.14 (s, 1H, Ar-H), 8.02 (d, $J=8.4$ Hz, 1H, Ar-H), 7.95–7.89 (m, 2H, Ar-H), 7.73–7.64 (m, 2H, Ar-H), 7.50–7.43 (m, 2H, Ar-H), 7.37–7.33 (m, 1H, Ar-H) and 5.91 (s, 2H, CH_2O).

4.1.2. Benzoylamino acetic acid 3-nitro-naphthalen-2-yl-methyl ester (1b). Yield: 97%; light yellow solid. Mp: 152–154 °C; FTIR (KBr) ν_{max} (cm^{-1}): 3293 (NH), 1752 (OCO), 1639 (NHCO), 1530 and 1334 (NO_2); ES-MS: *m*/*z* 365.1130 ($M^+ + 1$) (found), 365.1137 ($M^+ + 1$) (calcd for $C_{20}H_{16}N_2O_5$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.72 (s, 1H, Ar-H), 8.04–7.93 (m, 3H, Ar-H), 7.85–7.82 (m, 2H, Ar-H), 7.75–7.66 (m, 2H, Ar-H), 7.56–7.43 (m, 3H, Ar-H), 6.72 (br s, 1H, NH), 5.87 (s, 2H, CH_2O) and 4.40 (d, $J=5.1$ Hz, 2H, CH_2NH).

4.1.3. Phenyl-acetic acid 3-nitro-naphthalen-2-yl-methyl ester (1c). Yield: 63%; light yellow solid. Mp: 90–92 °C; FTIR (KBr) ν_{max} (cm^{-1}): 1729 (OCO), 1525 and 1334 (NO_2); ES-MS: *m*/*z* 344.0911 ($M^+ + Na$) (found), 344.0899 ($M^+ + Na$) (calcd for $C_{19}H_{15}NO_4$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.66 (s, 1H, Ar-H), 7.97 (d, 1H, Ar-H), 7.72–7.60 (m, 4H, Ar-H), 7.40–7.26 (m, 5H, Ar-H), 5.64 (s, 2H, CH_2O) and 3.78 (s, 2H, CH_2).

4.1.4. 4-Methyl-benzoic acid 3-nitro-naphthalen-2-yl-methyl ester (1d). Yield: 94%; light yellow solid. Mp: 120–122 °C; FTIR (KBr) ν_{max} (cm^{-1}): 1716 (OCO), 1539 and 1341 (NO_2); ES-MS: *m*/*z* 344.0901 ($M^+ + Na$) (found), 344.0899 ($M^+ + Na$) (calcd for $C_{19}H_{15}NO_4$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.69 (s, 1H, Ar-H), 8.06–7.90 (m, 5H, Ar-H), 7.69–7.64 (m, 2H, Ar-H), 7.27 (d, $J=8.8$ Hz, 2H, Ar-H), 5.87 (s, 2H, CH_2O) and 2.43 (s, 3H, CH_3).

4.1.5. Benzoylamino-acetic acid 4, 5-dimethoxy-2-nitro-benzyl ester (2a). Yield: 63%; light brown solid. Mp: 158–160 °C; FTIR (KBr) ν_{max} (cm^{-1}): 3429 (NH), 1741 (OCO), 1659 (NHCO), 1528 and 1327 (NO_2); ES-MS: *m*/*z* 397.1024 ($M^+ + Na$) (found), 397.1012 ($M^+ + Na$) (cacld for $C_{18}H_{18}N_2O_7$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, $J=$ 8.4 Hz, 1H, Ar-H), 7.73 (s, 1H, Ar-H), 7.54 (t, $J=7.2$ Hz, 2H, Ar-H), 7.46 (t, $J=7.2$ Hz, 2H, Ar-H), 7.05 (s, 1H, Ar-H), 6.70 (br s, 2H, NH), 5.65 (s, 2H, CH_2O), 4.36 (d, $J=$ 4.8 Hz, 1H, CH_2NH), 4.00 (s, 3H, OCH_3) and 3.96 (s, 3H, OCH_3).

4.2. Photodeprotection of esters and calculation of deprotection yield by HPLC

In a typical experiment, 2 mL of 1.0×10^{-3} M solution of ester in solvents (e.g., acetonitrile–water, 3:2 v/v) was taken in a quartz cuvette. It was photolysed by a 400 W medium pressure mercury lamp and the progress of the photoreaction (deprotection) was monitored by HPLC. For the calculation of percent disappearance of ester and percent appearance of the corresponding acid (e.g., 2-chlorobenzoic acid in case of **1a**), aliquots of 20 μL of the photomixture was removed periodically and analysed by HPLC. The photochemical deprotection yields were calculated by comparing the HPLC trace (peak area) due to released acid (e.g., 2-chlorobenzoic acid in case of **1a**) with the corresponding peak area due to respective standard acid. The HPLC analysis data are average of three to four independent runs.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.08.019.

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Mercaptoacetic acid based expeditious synthesis of polyfunctionalised 1,3-thiazines

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Abstract—A novel three-component expeditious synthesis of 3,6-diaryl-5-mercaptoperhydro-2-thioxo-1,3-thiazin-5-ones from 2-methyl-2-phenyl-1,3-oxathiolan-5-one, an aromatic aldehyde and an *N*-aryldithiocarbamic acid is reported. The synthesis is diastereoselective and involves tandem Knoevenagel, Michael and ring transformation reactions under solvent-free microwave irradiation in a one-pot procedure.

1. Introduction

In general, polyfunctionalised heterocycles are interesting as potential biodegradable pharmaceuticals and agrochemicals.[1–3] It is well known that the presence of a thiol function in many enzymes (called '–SH enzymes') is essential for their enzyme activity. Likewise, incorporation of a thiol function in heterocycles, nucleosides, or nucleotides has led to a number of analogues possessing interesting biological and therapeutic properties.[4–11] The 1,3-thiazine nucleus is the active core of cephalosporins, which are among the most widely used β-lactam antibiotics. Owing to their chemical and biological interest, syntheses of various 1,3-thiazine derivatives have been reported in the literature[12–19] but 1,3-thiazine derivatives incorporating a thiol function are hitherto unreported and are not accessible through any one of the known synthetic routes for 1,3-thiazines[12–19] although they appear to be attractive scaffolds to be utilized for exploiting chemical diversity.

We have previously reported diastereoselective synthetic protocols for various highly functionalised 1,3-thiazines incorporating an amino, or acylamino function at C-5 employing glycine derivatives.[20–23] In a recent letter[24] we have reported a diastereoselective synthesis of 5-acylamino-3,6-diarylperhydro-2-thioxo-1,3-thiazin-4-ones via a multi-step one-pot reaction sequence starting from *N*-acylglycines, aromatic aldehydes and ammonium *N*-aryldithiocarbamates employing microwave (MW) irradiation.

As part of an ongoing programme of research, we had to develop a rapid and efficient synthesis of polyfunctionalised 1,3-thiazines **4** incorporating a thiol function at C-5. Thus, we devised a new mercaptoacetyl transfer agent, 2-methyl-2-phenyl-1,3-oxathiolan-5-one **1**, which leads to heterocyclisation and is the key element in the present successful synthetic strategy for the target compounds **4** (Scheme 1).

In view of achieving our goal expeditiously, we relied upon the significant advantages of multi-component reactions (MCRs)[25–29] under solvent-free MW irradiation.[30–34] Interestingly, the MCRs reported herein, yielding 5-mercapto-1,3-thiazines **4** from 1,3-oxathiolan-5-one **1** diastereoselectively (Scheme 1), are among the few examples showing increased stereoselectivity under MW irradiation compared to conventional heating.

2. Results and discussion

After some preliminary experimentation, it was found that the envisaged three-component synthesis (Scheme 1) was successful with an intimate mixture of 2-methyl-2-phenyl-1,3-oxathiolan-5-one **1**, an aromatic aldehyde **2** and an *N*-aryl dithiocarbamic acid **3** under intermittent MW irradiation of 480 W for the time specified in Table 1. Isolation and purification by recrystallisation from ethanol afforded the 1,3-thiazines **4** in 76–90% yield (Table 1) with >96% diastereoselectivity.

For comparison purposes, the final temperature of the reaction mixture was recorded immediately after the MW irradiation and found to be <85 °C. The reactions were also carried out using a thermostated oil bath at the same

Keywords: Solvent-free; Multi-component reactions; Microwaves; Stereoselective synthesis; 1,3-Thiazines.
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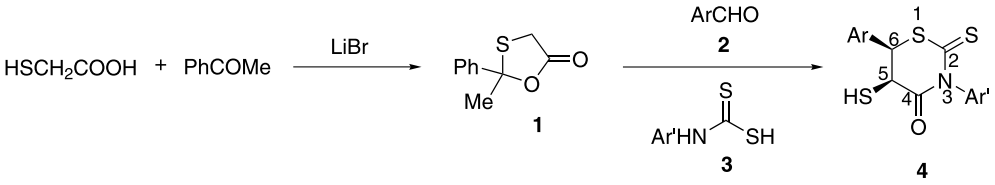


4, 6,7	Ar	Ar'	4,6,7	Ar	Ar'
a	Ph	Ph	**f**	4-$MeOC_6H_4$	2-MeC_6H_4
b	4-ClC_6H_4	Ph	**g**	Ph	4-$MeOC_6H_4$
c	4-$MeOC_6H_4$	Ph	**h**	4-ClC_6H_4	4-$MeOC_6H_4$
d	Ph	2-MeC_6H_4	**i**	4-$MeOC_6H_4$	4-$MeOC_6H_4$
e	4-ClC_6H_4	2-MeC_6H_4			

Scheme 1.

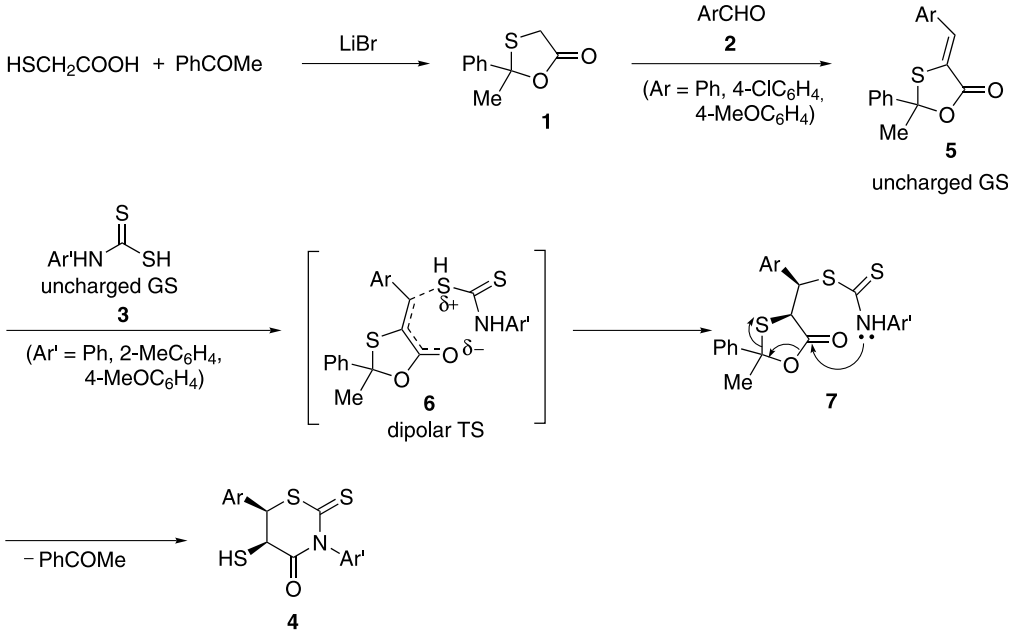
temperature (85 °C) as for the MW-activated method but for a longer (optimized) period of time (Table 1) to ascertain whether the MW method improves the yield or simply increases conversion rates. It was found that significantly lower yields (42–54%) were obtained using oil-bath heating rather than the MW-activated method (Table 1). This observation may be rationalized on the basis of the formation of a dipolar transition state (TS) from an uncharged ground state (GS) in these reactions (as an example, Scheme 2 shows a dipolar TS **6**), and the greater stabilisation of more polar TS by dipole–dipole interactions with the electric field of microwaves as compared to the less polar GS, which may reduce the activation energy ($\Delta G^{\neq}$) resulting in the rate enhancement.[30]

The formation of 1,3-thiazines **4** is best explained by Michael type addition of *N*-aryldithiocarbamic acid **3** to 4-arylidene-1,3-oxathiolan-5-one **5**, generated in situ, to

Table 1. Solvent-free three-component synthesis of products **7** and **4**

Product	Time		Yield (%)[a]	
	MW (min)[b]	Thermal (h)[c]	MW	Thermal
7a	6	2	48	40
7d	4	1	51	45
7h	4	1	55	48
4a	10	4	79	43
4b	8	4	83	45
4c	10	5	80	47
4d	8	3	84	49
4e	8	3	90	54
4f	10	5	76	42
4g	10	4	81	46
4h	8	3	90	52
7i	10	5	78	44

[a] Yield of isolated and purified product.
[b] Microwave irradiation power=480 W.
[c] Oil-bath heating at 85 °C.



Scheme 2.

afford the corresponding Michael adducts **7**, which undergo ring transformation to yield the final products **4** (Scheme 2). This conclusion is based on the observation that the representative intermediate compounds **7a**, **7d** and **7h** could be isolated in 48–55% yields, and that these could be converted into the corresponding 1,3-thiazines **4a**, **4d** and **4h** in quantitative yield.

The formation of Michael adducts **7** and their ring transformation to **4** were highly diastereoselective in favour of *cis* isomers. The diastereomeric ratios of the crude products were checked by ^{1}H NMR, prior to purification, to ensure accurate and true diastereomeric ratios are reported. The diastereomeric ratio in the case of MW activation was found to be $>96:<4$ and that from the oil-bath heating was $>55:<45$ as determined by ^{1}H NMR spectroscopy. The high diastereoselectivity ($>96\%$) in favour of *cis* isomers under MW irradiation may be explained by considering that MW irradiation favours the reactions occurring via a more polar TS,[30] and that the TS leading to the formation of *cis* isomers is more polar than that leading to the *trans* isomers because, in general, *cis* isomers are more polar than the *trans*.

3. Conclusion

In summary, we have developed a novel three-component one-pot mercaptoacetic acid-based synthetic protocol for an expeditious diastereoselective synthesis of potentially pharmaceutically and agrochemically useful polyfunctionalised 1,3-thiazines starting from readily and widely available simple substrates employing solvent-free microwave irradiation.

4. Experimental

4.1. General

Melting points were determined by open glass capillary method and are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 993 IR spectrophotometer, ^{1}H NMR spectra were recorded on a Bruker WM-40 C (400 MHz) FT spectrometer in DMSO-d_6 using TMS as internal reference. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz using the same solvent and internal reference. Mass spectra were recorded on a JEOL D-300 mass spectrometer. Elemental analyses were carried out in a Coleman automatic carbon, hydrogen and nitrogen analyser. A chemical laboratory microwave oven operating at 2450 MHz was used at an output of 480 W for all the experiments. All chemicals used were reagent grade and were used as received without further purification. Silica gel-G was for TLC.

4.1.1. 2-Methyl-2-phenyl-1,3-oxathiolan-5-one 1. A mixture of acetophenone (3.5 mL, 30 mmol), mercaptoacetic acid (2.1 mL, 30 mmol) and a catalytic amount of lithium bromide (2.61 g, 3 mmol) was stirred for 2 h at 70 °C and kept overnight at room temperature. Water (50 mL) was added to the reaction mixture and the product thus, obtained was recrystallized from water to give an analytically pure sample of **1** as white needles. Yield 4.77 g, 82%, mp 121–122 °C. IR (KBr) ν_{max} 3008, 2970, 1774, 1596, 1510, 1446, 1020 cm^{-1}. ^{1}H NMR (DMSO-d_6/TMS) δ: 1.98 (s, 3H, Me), 3.60 (d, 1H, $J=16.4$ Hz, CH_2), 3.69 (d, 1H, $J=16.4$ Hz, CH_2), 7.21–7.36 (m, 5H$_{arom}$). ^{13}C NMR (DMSO-d_6/TMS) δ: 17.4 (CH_2), 34.8 (2-C), 87.3 (4-C), 127.5, 128.9, 129.7, 136.2 (Ph), 173.4 (C=O). Mass (*m*/*z*): 194 (M^+). Anal. Calcd for $C_{10}H_{10}O_2S$: C, 61.83; H, 5.19%. Found: C, 61.53; H, 5.38%.

4.2. 3,6-Diaryl-5-mercaptoperhydro-2-thioxo-1,3-thiazin-4-ones 4. General procedure

Thoroughly mixed 2-methyl-2-phenyl-1,3-oxathiolan-5-one **1** (10.0 mmol), an aromatic aldehyde **2** (10.0 mmol) and an *N*-aryldithiocarbamic acid **3** (10.0 mmol) were taken in a 20 mL vial and subjected to MW irradiation at 480 W for 2 min. The reaction mixture was then thoroughly mixed outside the microwave oven for 2 min and again irradiated for another 2 min. This intermittent irradiation-mixing cycle was repeated for the total irradiation time (Table 1). After completion of the reaction as indicated by TLC (hexane/AcOEt 8:2, v/v), water (10 mL) was added to the reaction mixture and stirred well. The yellowish solid thus, obtained was washed with water to give the crude product, which was recrystallized from ethanol to afford a diastereomeric mixture ($>96:<4$; in the crude products the ratio was $>95:<5$ as determined by ^{1}H NMR spectroscopy). The product on second recrystallisation from ethanol furnished an analytically pure sample of a single diastereomer **4** (Table 1). On the basis of ^{1}H NMR spectra and literature precedent,[35–40] the *cis* stereochemistry was assigned to **4**, as the coupling constant ($J_{5,6}=5$ Hz) for **4** was lower than that for the very minor ($<4\%$) diastereomer (*trans*), $J_{5,6}=10$ Hz.

4.2.1. Compound 4a. Yellowish needles (2.61 g, 79%), mp 138–139 °C. IR (KBr) ν_{max} 3012, 2555, 1685, 1601, 1575, 1450, 1055 cm^{-1}. ^{1}H NMR (DMSO-d_6/TMS) δ: 1.59 (d, 1H, $J=8$ Hz, SH), 6.60 (d, 1H, $J=5$ Hz, 6-H), 6.74 (dd, 1H, $J=5$, 8 Hz, 5-H), 7.10–7.96 (m, 10H$_{arom}$). ^{13}C NMR (DMSO-d_6/TMS) δ: 25.8 (5-C), 42.4 (6-C), 127.0, 127.7, 128.6, 129.9, 130.7, 132.1, 132.8, 133.9 (2×Ph), 165.4 (C=O), 192.1 (C=S). Mass (*m*/*z*): 331 (M^+). Anal. Calcd for $C_{16}H_{13}NOS_3$: C, 57.97; H, 3.95; N, 4.23%. Found: C, 57.63; H, 4.20; N, 4.03%.

4.2.2. Compound 4b. Yellowish needles (3.03 g, 83%), mp 137–138 °C. IR (KBr) ν_{max} 3012, 2555, 1685, 1601, 1575, 1450, 1095 cm^{-1}. ^{1}H NMR (DMSO-d_6/TMS) δ: 1.59 (d, 1H, $J=8$ Hz, SH), 6.60 (d, 1H, $J=5$ Hz, 6-H), 6.74 (dd, 1H, $J=5$, 8 Hz, 5-H), 7.10–7.96 (m, 9H$_{arom}$). ^{13}C NMR (DMSO-d_6/TMS) δ: 26.3 (5-C), 42.9 (6-C), 127.1, 128.7, 129.3, 130.5, 131.5, 132.6, 133.6, 134.5 (Ph, 4-ClC_6H_4), 165.5 (C=O), 192.4 (C=S). Mass (*m*/*z*): 365 (M^+). Anal. Calcd for $C_{16}H_{12}ClNOS_3$: C, 52.52; H, 3.31; N, 3.83%. Found: C, 52.49; H, 3.07; N, 4.01%.

4.2.3. Compound 4c. Yellowish needles (2.89 g, 80%), mp 132–133 °C. IR (KBr) ν_{max} 3020, 2598, 1687, 1605, 1582, 1453, 1090 cm^{-1}. ^{1}H NMR (DMSO-d_6/TMS) δ: 1.60 (d, 1H, $J=8$ Hz, SH), 3.74 (s, 3H, OMe), 6.59 (d, 1H, $J=5$ Hz, 6-H), 6.72 (dd, 1H, $J=5$, 8 Hz, 5-H), 7.11–7.97 (m, 9H$_{arom}$).

^{13}C NMR (DMSO-d_6/TMS) δ: 26.1 (5-C), 42.7 (6-C), 54.7 (OMe), 127.2, 128.5, 129.4, 130.3, 131.2, 132.4, 133.3, 134.4 (Ph, 4-MeOC_6H_4), 165.4 (C=O), 192.2 (C=S). Mass (*m/z*): 361 (M^+). Anal. Calcd for $C_{17}H_{15}NO_2S_3$: C, 56.48; H, 4.18; N, 3.87%. Found: C, 56.14; H, 4.38; N, 3.65%.

4.2.4. Compound 4d. Yellowish needles (3.07 g, 84%), mp 139–140 °C. IR (KBr) ν_{max} 3018, 2561, 1682, 1602, 1579, 1448, 1092 cm^{-1}. ^{1}H NMR (DMSO-d_6/TMS) δ: 1.58 (d, 1H, J=8 Hz, SH), 2.30 (s, 3H, Me), 6.58 (d, 1H, J=5 Hz, 6-H), 6.70 (dd, 1H, J=5, 8 Hz, 5-H), 7.09–7.95 (m, 9H$_{arom}$). ^{13}C NMR (DMSO-d_6/TMS) δ: 20.2 (Me), 25.9 (5-C), 42.3 (6-C), 126.8, 127.5, 128.5, 129.2, 130.4, 131.3, 132.0, 132.6, 133.4, 134.0 (Ph, 2-MeC_6H_4), 165.3 (C=O), 192.1 (C=S). Mass (*m/z*): 345 (M^+). Anal. Calcd for $C_{17}H_{15}NOS_3$: C, 59.10; H, 4.38; N, 4.05%. Found: C, 58.75; H, 4.57; N, 3.80%.

4.2.5. Compound 4e. Yellowish needles (3.41 g, 90%), mp 143–144 °C. IR (KBr) ν_{max} 3022, 2590, 1683, 1604, 1568, 1452, 1091 cm^{-1}. ^{1}H NMR (DMSO-d_6/TMS) δ: 1.61 (d, 1H, J=8 Hz, SH), 2.33 (s, 3H, Me), 6.63 (d, 1H, J=5 Hz, 6-H), 6.74 (dd, 1H, J=5, 8 Hz, 5-H), 7.12–8.01 (m, 8H$_{arom}$). ^{13}C NMR (DMSO-d_6/TMS) δ: 20.8 (Me), 26.2 (5-C), 42.8 (6-C), 126.8, 127.6, 128.7, 129.4, 130.2, 131.3, 132.1, 132.7, 133.3, 134.1 (4-ClC_6H_4, 2-MeC_6H_4), 165.4 (C=O), 192.2 (C=S). Mass (*m/z*): 379 (M^+). Anal. Calcd for $C_{17}H_{14}ClNOS_3$: C, 53.74; H, 3.71; N, 3.69%. Found: C, 53.95; H, 3.55; N, 3.43%.

4.2.6. Compound 4f. Yellowish needles (2.85 g, 76%), mp 147–148 °C. IR (KBr) ν_{max} 3017, 2581, 1682, 1603, 1585, 1455, 1093 cm^{-1}. ^{1}H NMR (DMSO-d_6/TMS) δ: 1.60 (d, 1H, J=8 Hz, SH), 2.31 (s, 3H, Me), 3.76 (s, 3H, OMe), 6.61 (d, 1H, J=5 Hz, 6-H), 6.72 (dd, 1H, J=5, 8 Hz, 5-H), 7.13–7.98 (m, 8H$_{arom}$). ^{13}C NMR (DMSO-d_6/TMS) δ: 21.0 (Me), 26.1 (5-C), 42.6 (6-C), 55.1 (OMe), 126.9, 127.5, 128.9, 129.5, 130.1, 130.8, 131.6, 132.3, 132.9, 133.8 (4-MeOC_6H_4, 2-MeC_6H_4), 165.5 (C=O), 192.0 (C=S). Mass (*m/z*): 375 (M^+). Anal. Calcd for $C_{18}H_{17}NO_2S_3$: C, 57.57; H, 4.56; N, 3.73%. Found: C, 57.27; H, 4.36; N, 3.97%.

4.2.7. Compound 4g. Yellowish needles (2.92 g, 81%), mp 140–141 °C. IR (KBr) ν_{max} 3011, 2552, 1687, 1598, 1579, 1453, 1105 cm^{-1}. ^{1}H NMR (DMSO-d_6/TMS) δ: 1.59 (d, 1H, J=8 Hz, SH), 3.72 (s, 3H, OMe), 6.61 (d, 1H, J=5 Hz, 6-H), 6.73 (dd, 1H, J=5, 8 Hz, 5-H), 7.11–7.98 (m, 9H$_{arom}$). ^{13}C NMR (DMSO-d_6/TMS) δ: 25.9 (5-C), 42.4 (6-C), 54.8 (OMe), 127.2, 128.7, 129.3, 130.4, 131.4, 132.2, 133.4, 134.3 (Ph, 4-MeOC_6H_4), 165.7 (C=O), 192.5 (C=S). Mass (*m/z*): 361 (M^+). Anal. Calcd for $C_{17}H_{15}NO_2S_3$: C, 56.48; H, 4.18; N, 3.87%. Found: C, 56.73; H, 4.38; N, 3.52%.

4.2.8. Compound 4h. Yellowish needles (3.56 g, 90%), mp 163–165 °C. IR (KBr) ν_{max} 3019, 2596, 1687, 1601, 1581, 1452, 1123 cm^{-1}. ^{1}H NMR (DMSO-d_6/TMS) δ: 1.62 (d, 1H, J=8 Hz, SH), 3.74 (s, 3H, OMe), 6.63 (d, 1H, J=5 Hz, 6-H), 6.73 (dd, 1H, J=5, 8 Hz, 5-H), 7.13–7.98 (m, 8H$_{arom}$). ^{13}C NMR (DMSO-d_6/TMS) δ: 26.5 (5-C), 42.9 (6-C), 55.5 (OMe), 127.2, 128.8, 129.4, 131.3, 132.0, 132.8, 133.6, 134.4 (4-MeOC_6H_4, 4-ClC_6H_4), 165.9 (C=O), 192.6 (C=S). Mass (*m/z*): 395 (M^+). Anal. Calcd for $C_{17}H_{14}ClNO_2S_3$: C, 51.57; H, 3.56; N, 3.54%. Found: C, 51.21; H, 3.77; N, 3.35%.

4.2.9. Compound 4i. Yellowish needles (3.05 g, 78%), mp 155–156 °C. IR (KBr) ν_{max} 3013, 2592, 1685, 1603, 1586, 1458, 1118 cm^{-1}. ^{1}H NMR (DMSO-d_6/TMS) δ: 1.61 (d, 1H, J=8 Hz, SH), 3.73 (s, 3H, OMe), 3.79 (s, 3H, OMe), 6.62 (d, 1H, J=5 Hz, 6-H), 6.72 (dd, 1H, J=5, 8 Hz, 5-H), 7.12–7.97 (m, 8H$_{arom}$). ^{13}C NMR (DMSO-d_6/TMS) δ: 26.4 (5-C), 42.8 (6-C), 55.0, 55.4 (2×OMe), 127.3, 128.7, 129.5, 131.4, 132.1, 132.9, 133.6, 134.6 (2×4-MeOC_6H_4), 165.8 (C=O), 192.5 (C=S). Mass (*m/z*): 391 (M^+). Anal. Calcd for $C_{18}H_{17}NO_3S_3$: C, 55.22; H, 4.38; N, 3.58%. Found: C, 54.93; H, 4.58; N, 3.22%.

4.3. Isolation of the Michael adducts 7a, 7d and 7h and their conversion into the corresponding final products 4a, 4d and 4h

The procedure followed was the same as described above for the synthesis of **4** except that the time of MW irradiation in this case was 4–6 min instead of 8–10 min for **4**. The adducts **7** were recrystallized from ethanol to give a diastereomeric mixture (>97:<3; in the crude isolates the ratio was >94:<6 as determined by ^{1}H NMR spectroscopy), which was again recrystallized from ethanol to obtain an analytically pure sample of **7a**, **7d** and **7h**. The adducts **7a**, **7d** and **7h** were assigned the *erythro* stereochemistry, as their ^{1}H NMR spectra exhibited lower values of coupling constant, $J_{cyclicSCH,\ acyclicSCH}$=5 Hz, than that of the very minor (<3%) diastereomer (*threo*), $J_{cyclicSCH,\ acyclicSCH}$=10 Hz.[35–40] Finely powdered intermediate compounds **7a**, **7d** and **7h** were intermittently MW irradiated for 6 min in the same way as described for the synthesis of **4** to give the corresponding annulated products **4a**, **4d** and **4h** quantitatively.

4.3.1. Compound 7a. Yellowish needles (2.16 g, 48%), mp 127–128 °C. IR (KBr) ν_{max} 3148, 3008, 2971, 1776, 1604, 1574, 1455, 1108, 1020 cm^{-1}. ^{1}H NMR (DMSO-d_6/TMS) δ: 2.34 (s, 3H, Me), 6.64 (d, 1H, J=5 Hz, acyclic SCH), 6.77 (d, 1H, J=5 Hz, cyclic SCH), 7.14–8.00 (m, 15H$_{arom}$), 9.38 (br s, 1H, NH, exchanges with D_2O). ^{13}C NMR (DMSO-d_6/TMS) δ: 17.4 (Me), 35.0 (Me-*C*), 42.5 (Ar-*C*), 87.5 (O=C–*C*), 127.2, 128.6, 129.5, 130.6, 131.5, 132.7, 133.6, 134.5 (2×Ph), 173.7 (C=O), 192.3 (C=S). Mass (*m/z*): 451 (M^+). Anal. Calcd for $C_{24}H_{21}NO_2S_3$: C, 63.83; H, 4.69; N, 3.10%. Found: C, 63.53; H, 4.45; N, 3.35%.

4.3.2. Compound 7d. Yellowish needles (2.37 g, 51%), mp 128–129 °C. IR (KBr) ν_{max} 3147, 3010, 2970, 1775, 1603, 1579, 1460, 1109, 1021 cm^{-1}. ^{1}H NMR (DMSO-d_6/TMS) δ: 2.31 (s, 3H, Me), 2.34 (s, 3H, Me), 6.63 (d, 1H, J=5 Hz, acyclic SCH), 6.76 (d, 1H, J=5 Hz, cyclic SCH), 7.14–7.98 (m, 14H$_{arom}$), 9.36 (br s, 1H, NH, exchanges with D_2O). ^{13}C NMR (DMSO-d_6/TMS) δ: 17.3 (Me), 20.3 (Me), 34.9 (Me-*C*), 42.4 (Ar-*C*), 87.3 (O=C–*C*), 126.9, 127.6, 128.7, 129.2, 130.3, 131.4, 132.1, 132.7, 133.4, 134.1 (Ph, 2-Me C_6H_4), 173.6 (C=O), 192.1 (C=S). Mass (*m/z*): 465 (M^+). Anal. Calcd for $C_{25}H_{23}NO_2S_3$: C, 64.48; H, 4.98; N, 3.10%. Found: C, 64.14; H, 4.73; N, 3.37%.

4.3.3. Compound 7h. Yellowish needles (2.84 g, 55%), mp

142–143 °C. IR (KBr) ν_{max} 3150, 3012, 2973, 1779, 1605, 1580, 1459, 1112, 1023 cm^{-1}. ^1H NMR (DMSO-d_6/TMS) δ: 2.33 (s, 3H, Me), 3.72 (s, 3H, Me), 6.65 (d, 1H, $J=5$ Hz, acyclic SCH), 6.78 (d, 1H, $J=5$ Hz, cyclic SCH), 7.13–8.01 (m, $13H_{arom}$), 9.39 (br s, 1H, NH, exchanges with D_2O). ^{13}C NMR (DMSO-d_6/TMS) δ: 17.5 (Me), 35.1 (Me-*C*), 42.8 (Ar-*C*), 55.6 (OMe), 87.6 (O=C–*C*), 127.4, 128.7, 129.6, 131.4, 132.2, 133.0, 133.6, 134.7 (4-ClC_6H_4, 4-$MeoC_6H_4$), 173.8 (C=O), 192.5 (C=S). Mass (*m/z*): 516 (M^+). Anal. Calcd for $C_{25}H_{22}ClNO_3S_3$: C, 58.18; H, 4.30; N, 2.71%. Found: C, 57.85; H, 4.05; N, 2.91%.

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Synthesis of proline-modified analogues of the neuroprotective agent glycyl-L-prolyl-glutamic acid (GPE)

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Abstract—The synthesis of ten proline-modified analogues of the neuroprotective tripeptide GPE is described. Five of the analogues incorporate a proline residue with a hydrophobic group at C-2 and two further analogues have this side chain locked into a spirolactam ring system. The pyrrolidine ring was also modified by replacing the γ-CH_2 group with sulfur and/or incorporation of two methyl groups at C-5.

1. Introduction

The tripeptide Gly-Pro-Glu (GPE) is a naturally occurring peptide, which is proteolytically cleaved from insulin-like growth factor-1 (IGF-1).[1–7] IGF-1 is a potent neurotrophic factor[8,9] produced endogenously in damaged regions of the brain.[10] It has been postulated that some of the neuroprotective actions of IGF-1 are mediated by GPE[11] although the precise mechanism of action remains unclear. GPE has a different mode of action to IGF-1 as GPE does not bind to the IGF-1 receptor,[12,13] rather GPE has been shown to bind with low affinity to the *N*-methyl-D-aspartate (NMDA) receptor and also elicit a biological response via other mechanisms. GPE facilitates the release of dopamine through interaction with the NMDA receptor[16] but GPE stimulated acetyl choline release is via an unknown, non NMDA pathway.[14,16]

It has been demonstrated that GPE can act as a neuronal rescue agent following hypoxic-ischemic brain injury,[11,14] NMDA challenge[15] and in animal models of Parkinson's and Alzheimer's disease.[16,17] Analogues of GPE are thus of interest in the development of novel pharmaceutical agents for the treatment of central nervous system (CNS) injuries and neurodegenerative disorders.[18–21]

In our previous work, we have prepared GPE peptidomimetics modified at the glycine and glutamate residues in order to investigate structure–activity relationships and in an attempt to improve properties such as metabolic stability and oral bioavailability.[22–24] We herein, report the synthesis of analogues of GPE modified at the proline residue.

2. Results and discussion

In order to investigate the importance of the proline residue in GPE, ten analogues modified at either Pro or at the Pro-Glu bond were synthesized. In particular conformationally restricted analogues were prepared in order to gain insight into the receptor bound conformation. The general synthetic strategy employed involved the preparation of several modified proline residues that were then coupled to a glycine derivative and a glutamic acid di-ester (Scheme 1).

The presence of (*S*)-2-methylproline (2-MePro) is known to stabilize turns[25,26] and may also prevent peptidases recognizing the Pro-Glu amide bond resulting in resistance to proteolytic degradation.[27] Hence, the synthesis of glycyl-L-2-methylprolyl-L-glutamic acid (G-2MePE) **1** was undertaken. In order to further explore the influence of modifications at this position, four other 2-alkylproline analogues **2**–**5** were also synthesized (Scheme 2).

The 2-alkylproline derivatives were synthesized using Wang and Germanas's modification[28] of Seebach's method of self-reproducing chirality.[29,30] Condensation of L-proline **6** with choral (trichloroacetaldehyde) gave oxazolidinone **7**,[31] which was used for the synthesis of the five

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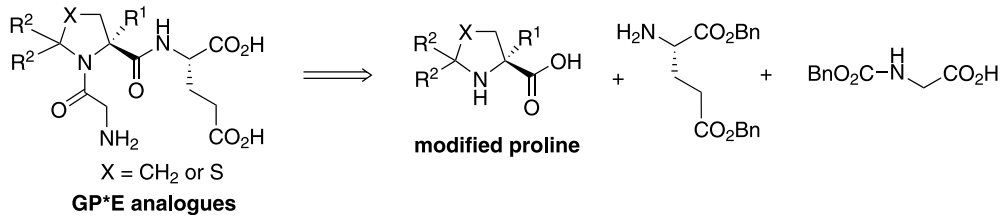
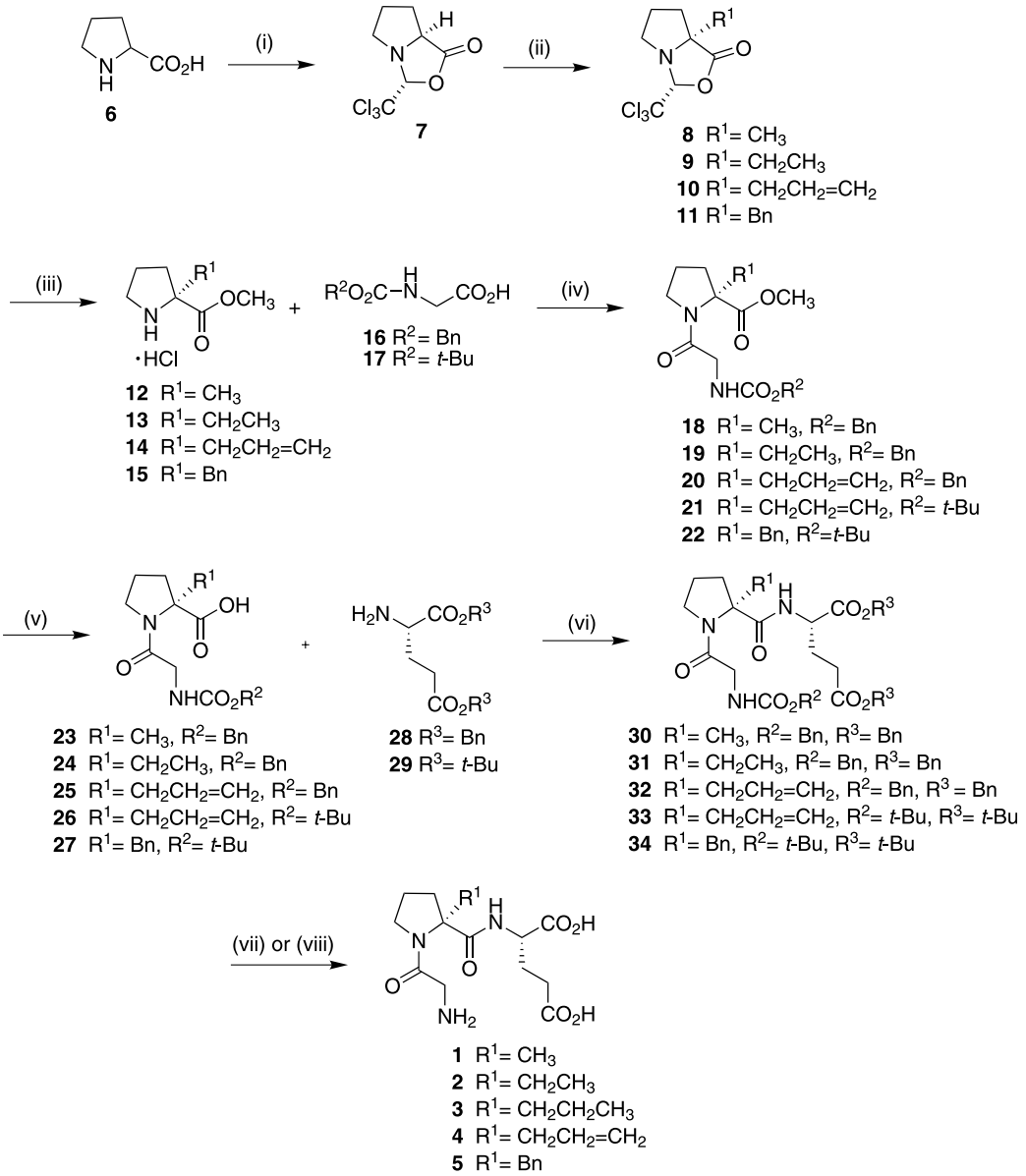
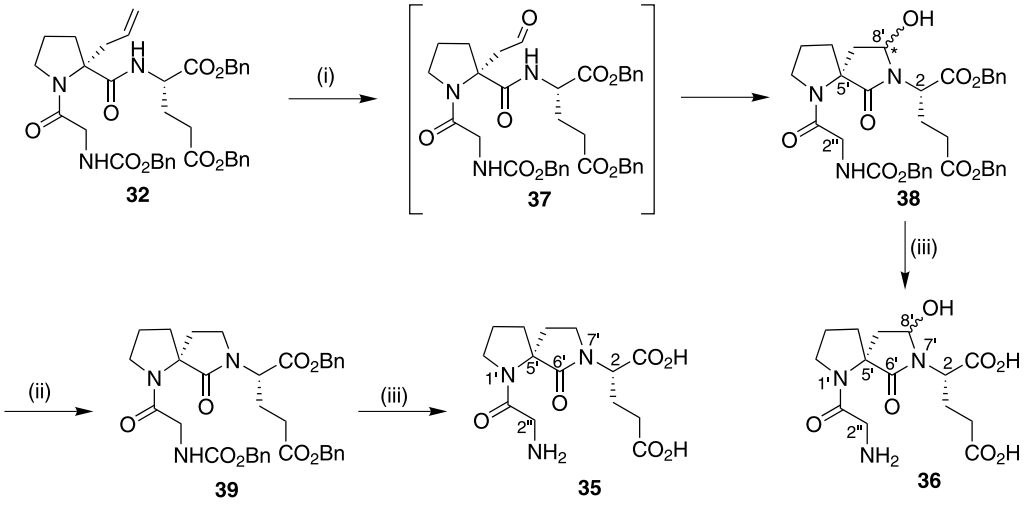


Scheme 1. General retrosynthesis for GP*E analogues.

2-alkylproline modified tripeptides **1**–**5**. Treatment of **7** with LDA to effect enolate formation followed by alkylation with iodomethane, iodoethane, allyl bromide or benzyl bromide, respectively, afforded alkylated oxazolidinones **8**–**11**. Esterification with thionyl chloride (for **8**,**9**) or acetyl chloride (for **10**,**11**) in methanol gave the methyl ester hydrochlorides **12**–**15**, which were coupled with *N*-benzyloxycarbonyl–glycine **16** (for **12**–**14**) or *N*-*tert*-butyloxycarbonyl-glycine **17** (for **14** and **15**) to give the dipeptides **18**–**22**.



Scheme 2. Reagents, conditions and yields: (i) chloral, $CHCl_3$, reflux, 6 h (77%); (ii) LDA, THF, −78 °C, MeI, EtI, $CH_3CH_2{=}CH_2Br$ or $PhCH_2Br$, −78–> −30 °C, 4 h, **8**, 63%, **9**, 46%, **10**, 60%, **11**, 2.5 h, 32%; (iii) $SOCl_2$, CH_3OH, reflux, 3 h, **12**, 100%, **13**, 71%, AcCl, CH_3OH, reflux, 24 h, **14**, 63%, **15**, 48%; (iv) for **18**, **19**, **20**: Et_3N, BoPCl, **16**, CH_2Cl_2, rt, **18**, 20.5 h, 92%, **19**, 19.5 h, 46%, **20**, 20 h, 30%; for **21**, **22**: Et_3N, BoPCl, **17**, CH_2Cl_2, rt, 19.5 h, **21**, 45%, **22**, 18.5 h, 22%; (v) dioxane, 1 M aqueous NaOH, rt, 15–20 h, **23**, 90%, **24**, 95%, **25**, 92%, **26**, 83%, **27**, 95%; (vi) for **30**, **31**, **32**: Et_3N, BoPCl, **28**, CH_2Cl_2, rt, 17 h, **30**, 89%, **31**, 17.5 h, 70%, **32**, 19.5 h, 76%; for **33**, **34**: Et_3N, BoPCl, **29**, CH_2Cl_2, rt, 17.5 h, **33**, 77%, **34**, 17 h, 68%; (vii) H_2, 10% Pd/C, CH_3OH/H_2O (90:10), rt, 23 h, **1**, 86%, **2**, 20 h, 99%, **3**, 19 h, 100%; (viii) CF_3CO_2H, CH_2Cl_2, rt, 6.5 h, **4**, 96%, **5**, 3.5 h, 100%.



Scheme 3. Reagents, conditions and yields: (i) O_3, $MeOH/CH_2Cl_2$ (1:1), 15 min then PPh_3, 24 h, then silica gel, 63%; (ii) $CF_3CO_2H/Et_3SiH/CH_2Cl_2$ (1:1:1), rt, 45 min, 96%; (iii) 10% Pd/C, CH_3OH/H_2O (88:12), 18 h, **35**, 78%, **36**, 99%.

The optimal conditions for the amide bond formation were investigated using the coupling between **12** and **16**; bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BoPCl) was found to be superior (92% yield compared to 66% with DCC) and was used for all subsequent coupling reactions. Hydrolysis of the methyl esters **18**,**19**,**20** (NaOH in dioxane) to the carboxylic acids **23**,**24**,**25** followed by coupling (BoPCl) with dibenzyl glutamate **28** afforded benzyl protected tripeptides **30**,**31**,**32**. Finally, global deprotection of the benzyl groups gave tripeptides **1**[32] and **2** whilst concomitant hydrogenolysis of the allyl group in **25** gave tripeptide **3**.

For the synthesis of the tripeptides **4** and **5** incorporating a 2-allylproline and a 2-benzylproline unit, respectively, Boc and *t*-butyl protecting groups were used. In these cases coupling of acids **26** and **27** with di-*tert*-butyl glutamate **29** gave tripeptides **33** and **34** affording tripeptides **4** and **5** as trifluoroacetate salts after deprotection with TFA.

In contrast to most peptide bonds that adopt exclusively the trans conformation, the amide bond between Xaa-Pro can exist as a mixture of cis and trans isomers.[33] The nature of the conformation about this bond can affect the biological activity of a peptide and there is evidence that some proteases only recognize the trans peptide bond.[34,35] The existence of specific peptidyl-prolyl cis-trans isomerases would seem to corroborate this evidence.[36] GPE is present as a 20:80 cis-trans mixture of isomers in D_2O solution as established by NMR analysis.[22] When an alkyl group is substituted at the 2-position of proline the trans conformation is preferred. Compounds **1**–**4** adopt the all trans conformation and the trans population also increased in compound **5** with only 10% adopting the cis conformation. The prevalence of the trans isomer in 2-methylproline compounds has been attributed to the bulky methyl group destabilizing the cis conformation.[37]

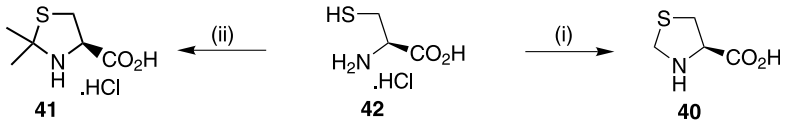
Another method of conformationally constraining a peptide is to synthesize a peptidomimetic containing a spirolactam ring system. It has been suggested that a spirolactam ring system may lock a compound into predominantly one conformation and different ring systems have been shown to mimic both β-[38] and γ-turns.[39] A spirocyclic γ-lactam bridge can be formed between the 2-position of the proline residue and the nitrogen of the glutamate residue in GPE thus, presenting an opportunity to investigate the effect of such conformational restriction in GPE analogues.

The synthesis of GP-[5.5]spirolactamE **35** and the corresponding GP-[5.5]hydroxyspirolactamE **36** is summarized in Scheme 3.

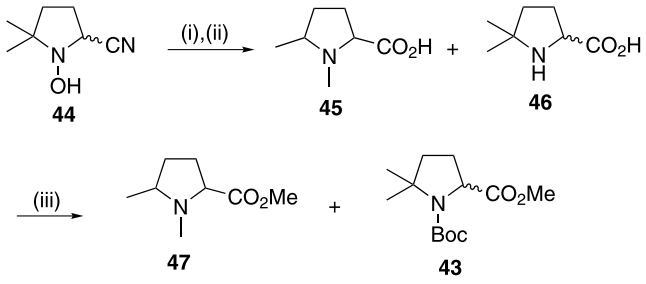
Ozonolysis of alkene **32** followed by treatment with triphenylphosphine proceeded via the intermediacy of aldehyde **37** to give alcohols **38** as a 1:1 mixture of diastereoisomers. Direct hydrogenation of **38** gave the hydroxyspirolactam **36** whereas initial reduction of the hydroxyl group (trifluoroacetic acid–triethylsilane–dichloromethane) to **39** before the hydrogenolysis step afforded spirolactam **35**. Both spirolactams adopted exclusively the trans conformation about the proline ring.

The pyrrolidine ring of proline is capable of adopting two distinct conformations. These down- and up-puckered conformations are defined as occurring when C^{γ} and the carbonyl group of proline lie on the same and opposite sides, respectively, of the plane defined by C^{δ}, N and C^{α}. The presence of a sulfur atom in the proline ring can affect the bond angles and bond lengths, in some cases altering the proline ring conformation. Kang found that replacement of the proline residue in AcProNHMe with 4-thiaproline **40** [(*R*)-thiozolidine-4-carboxylic acid (Thz)] resulted in a more puckered conformation.[40] Further conformational changes in the proline ring can be promoted by the addition of methyl groups at the 5 position of proline or Thz.[41–43] The next set of analogues incorporated such pseudo-proline moieties where the γ-CH_2 of Pro was replaced with sulfur and/or with dimethyl substitution at C^{δ}.

The pseudo-prolines: 4-thiaproline **40** [(*R*)-thiozolidine-4-carboxylic acid (Thz)] and 2,2-dimethylthiazolidine-4-carboxylic acid **41** were easily accessed by the reaction of



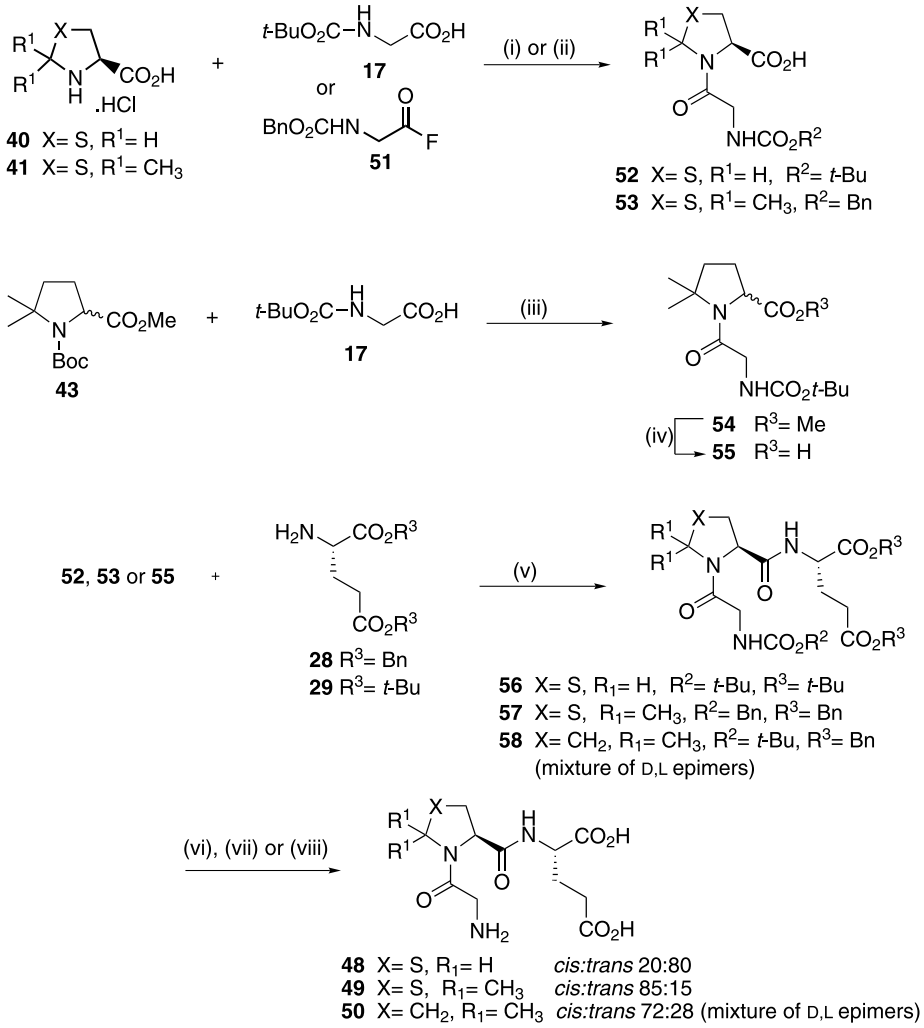
Scheme 4. Reagents, conditions and yields: (i) 37% aqueous HCHO, H_2O, rt, 22 h, then pyridine, 56%; (ii) dimethoxypropane, acetone, reflux, 2 h, 58%.



Scheme 5. Reagents, conditions and yields: (i) 32% aqueous HCl, 50 °C 5 h; (ii) H_2 (44 psi), 10% Pd/C, MeOH/H_2O (1:1), 20 h; (iii) $SOCl_2$, MeOH, 0 °C to rt, overnight then Boc_2O, *N*-methylmorpholine, CH_2Cl_2, reflux, 48 h [**43** (22%) **47** (42%)] over four steps.

cysteine **42** with formaldehyde[44] or 2,2-dimethoxypropane,[45,46] respectively (Scheme 4).

Boc-protected methyl D,L-5,5-dimethylprolinate **43** was prepared from nitrile **44** (Scheme 5). Nitrile **44** was prepared as described in the literature,[47,48] however, subsequent hydrolysis of the nitrile moiety and hydrogenation of the intermediate *N*-oxide as described[49] was concomitant with acid catalysed methyl migration yielding a mixture of **45** and **46**. (6:4 ratio, ^{1}H NMR). Extensive modification of the hydrolysis reaction could not overcome the formation of *N*-methyl compound **45**. It is interesting that this unwanted reaction has not been reported during the synthesis of 5,5-dimethylproline that has been described by several research groups.[49,50]



Scheme 6. Reagents, conditions and yields: (i) **17**, *i*-BuOCOCl, Et_3N, THF, 0 °C to rt, then **40**, Et_3N, H_2O, rt, 2 h, **52**, 81%; (ii) **51**, **41**, *i*-Pr_2EtN, DMF, rt, 18 h then MeOH, Me_3SiCl, rt, 15 h, **53**, 65%; (iii) **43**, CF_3CO_2H, CH_2Cl_2, rt, 2 h then **17**, BoPCl, *i*-Pr_2EtN, CH_2Cl_2, rt, 15 h, **54**, 52%; (iv) dioxane, 1 M aqueous NaOH, rt, 21 h, **55**, 94%; (v) for **56**: EtOCOCl, Et_3N, CH_2Cl_2, 0 °C, 35 min then **29**, Et_3N, CH_2Cl_2, 0 °C to rt, 15 h, **56**, 54%; for **57**, **58**: BoPCl, *i*-Pr_2EtN, CH_2Cl_2, **28**, rt, 7 h, **57**, 68%, **58**, 24 h, 67%; (vi) CF_3CO_2H, Et_3SiH, CH_2Cl_2, rt, 4 h, **48**, 61%; (vii) H_2(42 psi), 10% Pd/C, CH_3OH/H_2O (80:20), 24 h, **49**, 48%; (viii) CF_3CO_2H, CH_2Cl_2, rt, 75 min then H2, 10% Pd/C, CH_3OH/H_2O (80:20), 15 h, **50**, 93%.

Protection of both the acid and amine functionalities as a methyl ester and a *tert*-butyloxy carbamate (Boc), respectively, allowed facile separation and characterisation of the protected 5,5-dimethylproline **43** (22% yield over four steps) and the *N*-methyl by-product **47** (42% yield, over four steps). The desired protected 5,5-dimethylproline **43** existed as a mixture of epimers (55:45) exclusively as the cis conformer.

The tripeptides **48**–**50** were synthesized in a similar fashion to the 2-alkylproline analogues (Scheme 6). Coupling of the 4-thia-proline building block **40** to Boc-glycine **17** was carried out using a mixed anhydride activation procedure whereas the more hindered 5,5-dimethyl-4-thia-proline **41** required use of the more reactive acid fluoride **51** to afford **53**. In the case of the 5,5-dimethylproline **43** the Boc group was removed with trifluoroacetic acid before BoPCl coupling with Boc-glycine **17** to afford **54**. Hydrolysis of the methyl ester then afforded acid **55** in preparation for the second peptide coupling.

Coupling of the pseudo dipeptides **52**, **53** and **55** with either dibenzyl glutamate **28** or or di-*tert*-butyl glutamate **29** using either a mixed anhydride protocol or BoPCl gave the desired peptides **56**, **57** and **58**. The nature of the final deprotection step depended on the protecting groups employed in the synthesis thus, for **57** removal of the benzyloxycarbonyl and benzyl groups by hydrogenolysis provided tripeptide **49**. The Boc and *tert*-butyl ester groups in **56** were removed using trifluoroacetic acid to give tripeptide **48** as the trifluoroacetate salt whereas for the deprotection of **58**, treatment with trifluoroacetic acid followed by hydrogenolysis afforded tripeptide **50**.[51]

The presence of a sulfur atom at C-4 in the pyrrolidine ring of proline, by itself did not appear to significantly alter the conformation of the peptide about the Gly-Pro bond. In the GPE analogue **48** the cis:trans ratio was established to be 20:80, unchanged from the native peptide. The presence of the two methyl groups at C-5 had a more dramatic influence on the conformation with the cis:trans ratio dramatically shifted to favour the cis conformer. The population of the cis conformer in 5,5-dimethylated peptide **50** increased to 72% compared with the 20% seen with GPE. An even greater effect was observed with analogue **49**, which exhibited a 85:15 cis:trans ratio indicating that the presence of a sulphur atom at C-4 in combination with two methyl groups at C-5 in the proline ring plays a key role in determining the ratio of cis:trans isomers about the Gly-Pro bond. The high population of the cis conformer in related 5,5-dimethylprolines has been attributed to the effects of steric hindrance due to the methyl groups when the compound adopts the trans conformation.[41]

3. Conclusions

In summary, we herein report the synthesis of ten analogues of GPE. In five of these analogues the trans conformation about the Gly-Pro* bond was stabilized by either the presence of a hydrophobic alkyl group at C-2 on the proline (compounds **1**–**5**) or by a spirolactam bridge between the 2-position of the proline and the nitrogen of the glutamate (compounds **35** and **36**). In contrast, dimethylation at C-5 on the proline destabilises the trans conformation resulting in an increased population of the cis conformer (compounds **49** and **50**). These GP*E mimetics are valuable tools to provide information about the influence of the proline residue on the bioactivity of the parent peptide GPE.

4. Experimental

4.1. General details

All reactions were conducted in flame-dried or oven-dried glassware under a dry nitrogen atmosphere unless otherwise noted. All reagents were used as supplied. Tetrahydrofuran was dried over sodium/benzophenone and distilled prior to use. Flash chromatography was performed using Merck Kieselgel 60 (230–400 mesh) with the indicated solvents. Thin-layer chromatography (TLC) was carried out on precoated silica plates (Merck Kieselgel $60F_{254}$) and compounds were visualized by UV fluorescence and heating of plates dipped in anisaldehyde in ethanolic sulphuric acid or alkaline potassium permanganate solution. Melting points in degrees Celsius (°C) were measured on an Electrothermal® melting point apparatus and are uncorrected. Infrared spectra were recorded with a Perkin Elmer 1600 series Fourier-transform infrared spectrometer as thin films between sodium chloride plates. Absorption maxima are expressed in wavenumbers (cm^{-1}) with the following abbreviations: s = strong, m = medium, w = weak and br = broad nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AVANCE DRX400 (^1H, 400 MHz; ^{13}C, 100 MHz), a Bruker AVANCE 300 (^1H, 300 MHz; ^{13}C, 75 MHz) or a Bruker AC200 (^1H, 200 MHz; ^{13}C, 50 MHz) spectrometer at 298 K. For ^1H NMR data, chemical shifts are described in parts per million (ppm) relative to tetramethylsilane (δ 0.00), DOH (δ 4.75), CHD_2OD (δ 3.30) or $CHD_2S(O)CD_3$ (δ 2.50) and are reported consecutively as position (δ_H), relative integral, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, q = quintet, s = sextet, dd = doublet of doublets, m = multiplet, and where br = broad), coupling constant (*J*/Hz) and assignment. For ^{13}C NMR data, chemical shifts (ppm) are referenced internally to $CDCl_3$ (δ 77.0), CD_3OD (δ 49.1) and $(CD_3)_2S(O)$ (δ 39.4) or externally to 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt (DSS) and are reported consecutively as position (δ_C), degree of hybridisation and assignment. The asterisk* denotes resonances assigned to the minor conformer. High resolution mass spectra were recorded using a VG70-SE spectrometer operating at nominal accelerating voltage of 70 eV. Chemical ionisation (CI) mass spectra were obtained with ammonia as the reagent gas. Optical rotations were measured at 20 °C on a Perkin Elmer 341 polarimeter using 10 cm path length cells and are given in units of 10^{-1} degrees $cm^2\ g^{-1}$. Samples were prepared in the solvent indicated at the concentration specified (measured in g/100 cm^3).

4.1.1. (2*R*,5*S*)-2-Trichloromethyl-1-aza-3-oxabicyclo-[3.3.0]octan-4-one 7.[28,31] A suspension of L-proline (10.0 g, 86.8 mmol) and chloral hydrate (21.6 g, 130 mmol) were heated under reflux in chloroform

(100 cm^3) for 6 h with a reverse Dean-Stark trap. The solution was washed with water (2×30 cm^3) and the water washings were extracted with chloroform (50 cm^3). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed in vacuo to afford a light brown solid (19.8 g). The crude product was recrystallised from ethanol (80 cm^3) at 40 °C to form oxazolidinone **7** (16.1 g, 77%) as a white solid: mp 107–109 °C (lit.[31] ethanol, 107.6 °C): $[\alpha]_D$ +34.2 (*c* 2 in C_6H_6), lit.[28] $[\alpha]_D$ +33 (*c* 2.0 in C_6H_6); δ_H (200 MHz; $CDCl_3$) 1.67–2.29 (4H, m, Proβ-H_2 and Proγ-H_2), 3.08–3.20 (1H, m, Proβ-H_AH_B), 3.37–3.49 (1H, m, Proβ-H_AH_B), 4.09–4.15 (1H, m, Proα-H) and 5.17 (1H, s, NCH); δ_C (50 MHz; $CDCl_3$) 25.3 (CH_2, Proγ-C), 29.9 (CH_2, Proβ-C), 57.9 (CH_2, Proδ-C), 62.4 (CH, Proα-C), 100.6 [quat., *C*(Cl_3)], 103.6 (CH, N*C*H) and 175.5 (quat., CO); *m/z* (EI+) 244 (MH^+ 244).

4.1.2. (2*R*,5*S*)-5-Methyl-2-trichloromethyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one 8. *n*-Butyllithium (1.31 M, 4.68 cm^3, 6.14 mmol) was added dropwise to a stirred solution of diisopropylamine (0.86 cm^3, 6.14 mmol) in dry tetrahydrofuran (10 cm^3) at −78 °C under an atmosphere of nitrogen. The solution was stirred for 5 min, warmed to 0 °C and stirred for 15 min. The solution was added dropwise to a solution of oxazolidinone **7** (1.00 g, 4.09 mmol) in dry tetrahydrofuran (20 cm^3) at −78 °C over 20 min (reaction mixture turned dark), stirred for a further 30 min then iodomethane (0.76 cm^3, 12.3 mmol) added dropwise over 5 min. The solution was warmed to −50 °C over 2 h. Water (15 cm^3) was added, the solution warmed to room temperature and extracted with chloroform (3×40 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to dryness in vacuo to give a dark brown semi-solid. Purification of the residue by flash column chromatography (15% ethyl acetate–hexane) afforded oxazolidinone **8** (0.67 g, 63%) as a pale yellow solid: mp 55–57 °C (lit.[28] 57–60 °C); δ_H (300 MHz; $CDCl_3$) 1.53 (3H, s, CH_3), 1.72–2.02 (3H, m, Proβ-H and Proγ-H_2), 2.18–2.26 (1H, m, Proβ-H), 3.15–3.22 (1H, m, Proδ-H), 3.35–3.44 (1H, m, Proδ-H) and 4.99 (1H, s, NCH).

4.1.3. (2*R*,5*S*)-5-Ethyl-2-trichloromethyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one 9. The reaction was carried out following a similar procedure to that described for the preparation of oxazolidinone **8** using *n*-butyllithium (1.31 M, 28.3 cm^3, 37.1 mmol), diisopropylamine (5.2 cm^3, 37.1 mmol), oxazolidinone **7** (6.0 g, 24.7 mmol) and iodoethane (5.9 cm^3, 73.8 mmol) to afford oxazolidinone **9** (3.05 g, 46%) as a light red oil that solidified on standing to a pale brown solid: mp 76–77 °C: $[\alpha]_D$ +18.5 (*c* 0.25 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 1.04 (3H, t, *J*= 7.5 Hz, CH_3), 1.60–1.80 (1H, m, C$H_AH_B$$CH_3$), 1.72–1.99 (4H, m, $CH_AH_B$$CH_3$, Proβ-$H_AH_B$ and Proγ-H_2), 2.20–2.30 (1H, m, Proβ-H_AH_B), 3.22–3.29 (2H, m, Proδ-H_2) and 5.00 (1H, s, NCH); δ_C (75 MHz; $CDCl_3$) 8.4 (CH_3, CH_3), 25.5 (CH_2, *C*$H_2$$CH_3$), 30.9 ($CH_2$, Proγ-C), 35.6 ($CH_2$, Proβ-C), 58.6 ($CH_2$, Proδ-C), 72.5 (quat., Proα-C), 100.9 [quat., *C*(Cl_3)], 102.5 (CH, N*C*H) and 176.9 (quat., CO); *m/z* (EI+) 272.0014 (MH^+ $C_9H_{13}^{35}ClN_3O_2$ requires 272.0012).

4.1.4. (2*R*,5*R*)-5-Allyl-2-trichloromethyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one 10.[28] The reaction was carried out following a similar procedure to that described for the preparation of oxazolidinone **8** using *n*-butyllithium (1.31 M, 9.93 cm^3, 13.0 mmol), diisopropylamine (1.82 cm^3, 13.0 mmol), oxazolidinone **7** (2.10 g, 8.7 mmol) and allyl bromide (2.25 cm^3, 26.0 mmol) to afford oxazolidinone **10** (1.48 g, 60%) as a light orange oil for which the NMR data were in agreement with the literature.[28]

4.1.5. (2*R*,5*R*)-5-Benzyl-2-trichloromethyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one 11.[28] The reaction was carried out following a similar procedure to that described for the preparation of oxazolidinone **8** using *n*-butyllithium (1.31 M, 5.53 cm^3, 7.2 mmol), diisopropylamine (1.01 cm^3, 7.24 mmol), oxazolidinone **7** (1.18 g, 4.8 mmol) and benzyl bromide (1.72 cm^3, 14.5 mmol) to afford oxazolidinone **11** (0.52 g, 32%) as a colourless crystalline solid: mp 75–77 °C (lit.[28] 72–77); δ_H (400 MHz; $CDCl_3$) 1.32–1.55 (2H, m, Proγ-H_2), 1.93–2.13 (2H, m, Proβ-H_2), 2.58–2.65 (1H, m, Proδ-H_2), 2.92 (1H, d, *J*= 13.6 Hz, PhCH_AH_B), 2.98–3.03 (1H, m, Proδ-H_2), 3.32 (1H, d, *J*=13.6 Hz, $PhCH_AH_B$), 4.99 (1H, s, NCH) and 7.21–7.35 (5H, m, PhH); δ_C (100 MHz; $CDCl_3$) 24.8 (CH_2, Proγ-C), 34.6 (CH_2, Proβ-C), 41.6 (CH_2, Proδ-C), 58.4 (CH_2, Ph*C*H_2), 72.3 (quat., Proα-C), 100.6 (quat., CCl_3), 102.8 (CH, NCH), 127.0 (CH, Ph), 128.2 (CH, Ph), 130.9 (CH, Ph), 135.5 (quat., Ph) and 176.6 (quat., C=O); *m/z* (EI+) 333.0081 [$(M+H)^+$ $C_{14}H_{14}^{35}Cl_3NO_2$ requires 333.0090], 335.0069 [$(M+H)^+$ $C_{14}H_{14}^{35}Cl_2^{37}ClNO_2$ requires 335.0061], 337.0014 [$(M+H)^+$ $C_{14}H_{14}^{35}Cl$ $^{37}Cl_2NO_2$ requires 337.0031] and 339.0009 [$(M+H)^+$ $C_{14}H_{14}$ $^{37}Cl_3NO_2$ requires 339.0002].

4.1.6. Methyl L-2-methylprolinate hydrochloride 12. Thionyl chloride (4.30 mL, 58.9 mmol) was added dropwise cautiously to a stirred solution of **8** (7.57 g, 29.4 mmol) at 0 °C under a nitrogen atmosphere. The cooling bath was removed and mixture stirred at room temperature for 20 min then heated to reflux for 3 h. The volatiles were removed in vacuo, the residue suspended in toluene (20 mL) and concentrated at 50 °C to remove traces of thionyl chloride. Trituration with dry ether yielded a brown solid. The yellow/orange ether was decanted and the solid was shaken with dry ether, decanted and the procedure repeated until the ether was colourless. Removal of traces of ether in vacuo at 50 °C afforded **12** (ca. 5.0 g, 100%) as a free flowing, hygroscopic brown solid that was used without any further purification: mp 107–109 °C (lit.[52] 106–108 °C).

4.1.7. Methyl L-2-ethylprolinate hydrochloride 13. An ice-cooled solution of oxazolidinone **9** (2.86 g, 10.6 mmol) in dry methanol (35 cm^3) under an atmosphere of nitrogen was treated dropwise with a solution of thionyl chloride (2.3 cm^3, 31.5 mmol). The solution was heated under reflux for 3 h, cooled and the solvent removed under reduced pressure. The resultant brown oil was purified by flash column chromatography (10% methanol–dichloromethane) to afford hydrochloride **13** (1.45 g, 71%) as a light brown semi-solid: $[\alpha]_D$ −61.1 (*c* 0.3 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 1.07 (3H, t, *J*=7.3 Hz, CH_3), 1.95–2.33 (5H, m, C$H_2$$CH_3$, Proγ-$H_2$ and Proβ-H_AH_B), 2.43–2.47 (1H, Proβ-H_AH_B), 3.63 (3H, s, OCH_3) and 6.98–7.35 (2H, br s, NH_2); δ_C (75 MHz; $CDCl_3$) 9.9 (CH_3, *C*H_3), 22.8 (CH_2, *C*$H_2$$CH_3$), 28.9 ($CH_2$, Proγ-C), 35.1 ($CH_2$, Proβ-C), 45.7 ($CH_2$, Proδ-C), 53.8 ($CH_3$, OCH_3), 73.9 (quat., Proα-C) and 171.0

(quat., CO); *m/z* (EI+) 158.1181 (MH^+ $C_8H_{16}NO_2$ requires 158.1181).

4.1.8. Methyl L-2-allylprolinate hydrochloride 14.[28,53] An ice-cooled solution of oxazolidinone **10** (0.64 g, 2.24 mmol) in dry methanol (15 cm^3) was treated dropwise with a solution of acetyl chloride (0.36 cm^3, 5.0 mmol) in methanol (5 cm^3). The solution was heated under reflux for 24 h, cooled and the solvent removed under reduced pressure. The resultant brown oil was dissolved in toluene (40 cm^3) and concentrated to dryness to remove residual thionyl chloride and methanol, then purified by flash column chromatography (5–10% CH_3OH–CH_2Cl_2; gradient elution) to afford hydrochloride **14** (0.29 g, 63%) as a solid for which the NMR data were in agreement with that reported in the literature.[28,53] δ_H (300 MHz; $CDCl_3$) 1.72–2.25 (3H, m, Proβ-H_AH_B and Proγ-H_2), 2.32–2.52 (1H, m, Proβ-H_AH_B), 2.72–3.10 (2H, m, Proδ-H_2), 3.31–3.78 (2H, m, CH_2CH=CH_2), 3.84 (3H, s, CO_2CH_3), 5.20–5.33 (2H, m, CH=CH_2), 5.75–5.98 (1H, m, CH=CH_2) and 8.06 (1H, br s, N–H); *m/z* (CI+) 170.1183 [$(M+H)^+$ $C_9H_{16}NO_2$ requires 170.1181].

4.1.9. Methyl L-2-benzylprolinate hydrochloride 15.[54] An ice-cooled solution of oxazolidinone **11** (1.03 g, 3.07 mmol) in dry methanol (10 cm^3) was treated dropwise with a solution of acetyl chloride (0.71 cm^3, 10.0 mmol) in methanol (10 cm^3). The solution was heated under reflux for 24 h, cooled and the solvents removed under reduced pressure. The resultant brown oil was dissolved in toluene (80 cm^3), concentrated to dryness to remove residual thionyl chloride and methanol, then purified by flash column chromatography (5% CH_3OH–CH_2Cl_2) to afford hydrochloride **15**[28,53] (0.38 g, 48%) as a beige solid; δ_H (400 MHz; D_2O) 1.92–2.01 (1H, m, Proγ-H_AH_B), 2.11–2.23 (2H, m, Proβ-H_AH_B and Proγ-H_AH_B), 2.52–2.60 (1H, m, Proβ-H_AH_B), 3.19 (1H, d, J=14.3 Hz, PhCH_AH_B), 3.24–3.31 (1H, m, Proδ-H_AH_B), 3.37–3.43 (1H, m, Proδ-H_AH_B), 3.53 (1H, d, J=14.3 Hz, PhCH_AH_B), 3.83 (3H, s, CO_2CH_3) and 7.26–7.47 (5H, m, PhH); δ_C (100 MHz; D_2O) 24.4 (CH_2, Proγ-C), 36.8 (CH_2, Proβ-C), 43.8 (CH_2, PhCH_2), 47.6 (CH_2, Proδ-C), 56.0 (CH_3, OCH_3), 75.9 (quat., Proα-C), 130.4 (CH, Ph), 131.5 (CH, Ph), 131.7 (CH, Ph), 137.1 (quat., Ph) and 175.8 (quat., C=O); *m/z* (CI+) 220.1340 [$(M+H)^+$ $C_{13}H_{18}NO_2$ requires 220.1338].

4.1.10. Methyl *N*-benzyloxycarbonyl-glycyl-L-2-methylprolinate 18. Dry triethylamine (0.27 cm^3, 1.96 mmol) was added dropwise to a solution of hydrochloride **12** (0.11 g, 0.61 mmol) and *N*-benzyloxycarbonylglycine **16** (0.17 g, 0.79 mmol) in dry dichloromethane (35 cm^3) under an atmosphere of nitrogen at room temperature and the reaction mixture stirred for 10 min. Bis(2-oxo-3-oxazolidinyl)phosphinic chloride (0.196 g, 0.77 mmol) was added and the resultant colourless solution was stirred for 20.5 h. The solution was washed successively with 10% aqueous hydrochloric acid (30 cm^3) and saturated aqueous sodium hydrogen carbonate (30 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness in vacuo. Purification of the resultant residue by flash column chromatography (50–80% ethyl acetate–hexane; gradient elution) yielded ester **18** (0.18 g, 92%) as a colourless oil: $[\alpha]_D$ −33.0 (*c* 1.0 in MeOH); ν_{max} (film)/cm^{-1} 3406, 2952, 1732, 1651, 1521, 1434, 1373, 1329, 1310, 1284, 1257, 1220, 1195, 1172, 1135, 1107, 1082, 1052, 1029, 986, 965, 907, 876, 829, 775, 738 and 699; δ_H (300 MHz; $CDCl_3$) 1.49 (3H, s, CH_3), 1.77–2.11 (4H, m, Proβ-H_2 and Proγ-H_2), 3.43–3.48 (2H, m, Proδ-H_2), 3.61 (3H, s, OCH_3), 3.85–3.89 (2H, m, Glyα-H_2), 5.04 (2H, s, PhCH_2), 5.76 (1H, br s, N–H) and 7.21–7.28 (5H, s, ArH); δ_C (75 MHz; $CDCl_3$) 21.1 (CH_3, Proα-CH_3), 23.5 (CH_2, Proγ-C), 38.0 (CH_2, Proβ-C), 43.3 (CH_2, Glyα-C), 46.6 (CH_2, Proδ-C), 52.1 (CH_3, OCH_3), 66.0 (quat., Proα-C), 66.3 (CH_2, PhCH_2), 127.5 (CH, Ph), 127.6 (CH, Ph), 128.1 (CH, Ph), 136.2 (quat., Ph), 155.9 (quat., NCO_2), 166.0 (quat., Gly-CON) and 173.6 (quat., CO_2CH_3); *m/z* (EI+) 334.1535 (M^+ $C_{17}H_{22}N_2O_5$ requires 334.1529).

4.1.11. Methyl *N*-benzyloxycarbonyl-glycyl-L-2-ethylprolinate 19. Dry triethylamine (2.88 cm^3, 20.7 mmol) was added dropwise to a solution of hydrochloride **13** (1.14 g, 5.9 mmol) and *N*-benzyloxycarbonylglycine **16** (2.47 g, 11.8 mmol) in dry dichloromethane (100 cm^3) under an atmosphere of nitrogen at 0 °C, and the reaction mixture stirred for 10 min. Bis(2-oxo-3-oxazolidinyl)-phosphinic chloride (3.00 g, 11.8 mmol) was added and the solution was stirred for 2 h, warmed to room temperature and further stirred for 17.5 h. Dichloromethane (50 cm^3) was added and the solution washed successively with 0.5 M aqueous hydrochloric acid (2×50 cm^3) and saturated aqueous sodium hydrogen carbonate (2×50 cm^3), dried ($MgSO_4$), filtered and evaporated in vacuo to give a light orange gum. Purification of the resultant residue by flash column chromatography (40% ethyl acetate/hexane) yielded ester **19** (0.95 g, 46%) as a clear oil: $[\alpha]_D$ −9.2 (*c* 0.13 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 0.81 (3H, t, J=7.5 Hz, CH_3), 1.85–2.09 (5H, m, CH_2CH$_3$, Proγ-H_2 and Proβ-H_AH_B), 2.38 (1H, sextet, J=7.5 Hz, Proβ-H_AH_B), 3.43–3.47 (1H, m, Proδ-H_AH_B), 3.61–3.67 (1H, m, Proδ-H_AH_B), 3.70 (3H, s, OCH_3), 4.10–4.13 (2H, m, Glyα-H_2) 5.11 (2H, s, OCH_2Ph), 5.71 (1H, br s, Gly-NH) and 7.27–7.35 (5H, m, Ph); δ_C (75 MHz; $CDCl_3$) 8.3 (CH_3, CH_3), 24.1 (CH_2, CH_2CH_3), 26.5 (CH_2, Proγ-C), 35.3 (CH_2, Proβ-C), 44.1 (CH_2, Glyα-C), 48.2 (CH_2, Proδ-C), 52.9 (CH_3, OCH_3), 67.0 (CH_2, OCH_2Ph), 70.2 (quat., Proα-C), 128.2 (CH, Ph), 128.3 (CH, Ph), 128.7 (CH, Ph), 136.8 (quat., Ph), 156.5 (quat., NCO), 166.8 (quat., Gly-CON) and 174.5 (quat., CO_2CH_3); *m/z* (EI+) 348.1688 (MH^+ $C_{18}H_{24}N_2O_5$ requires 348.1685).

4.1.12. Methyl *N*-benzyloxycarbonyl-glycyl-L-2-allylprolinate 20. Dry triethylamine (1.07 cm^3, 7.70 mmol) was added dropwise to a solution of hydrochloride **14** (0.50 g, 2.41 mmol) and *N*-benzyloxycarbonyl-glycine **16** (0.65 g, 3.13 mmol) in dry dichloromethane (80 cm^3) under an atmosphere of nitrogen at room temperature, and the reaction mixture stirred for 10 min. Bis(2-oxo-3-oxazolidinyl)phosphinic chloride (0.772 g, 3.03 mmol) was added and the solution stirred for 20 h, then washed successively with 10% aqueous hydrochloric acid (80 cm^3) and saturated aqueous sodium hydrogen carbonate (80 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness in vacuo. Purification of the resultant residue by flash column chromatography (60% ethyl acetate–hexane, seven drops of Et_3N for every 200 cm^3) yielded ester **20** (0.26 g, 30%) as a yellow oil: $[\alpha]_D$ +46.0 (*c* 0.50 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 3405, 3066, 3032, 2953, 2877, 1723, 1655, 1586,

1507, 1434, 1373, 1333, 1309, 1248, 1169, 1121, 1083, 1047, 1027, 1002, 919, 866, 827, 776, 737 and 699; δ_H (300 MHz; $CDCl_3$) 1.92–2.17 (4H, m, Proβ-H_2 and Proγ-H_2), 2.60–2.67 (1H, m, C$H_A$$H_B$CH=$CH_2$), 3.09–3.16 (1H, m, $CH_A$$H_B$CH=$CH_2$), 3.35–3.42 (1H, m, Proδ-$H_A$$H_B$), 3.56–3.63 (1H, m, Proδ-$H_A$$H_B$), 3.70 (3H, s, OCH_3), 3.96 (2H, d, J=4.4 Hz, Glyα-H_2), 5.07–5.12 (4H, m, PhCH_2 and CH=CH_2), 5.58–5.70 (1H, m, CH=CH_2) and 7.27–7.35 (5H, s, PhH); δ_C (75 MHz; $CDCl_3$) 23.6 (CH_2, Proγ-C), 34.9 (CH_2, Proβ-C), 37.6 (CH_2, CH_2CH=CH_2), 43.6 (CH_2, Glyα-C), 47.5 (CH_2, Proδ-C), 52.5 (CH_3, OCH_3), 66.7 (CH_2, PhCH_2), 68.8 (quat., Proα-C), 119.4 (CH_2, CH=H_2), 127.9 (CH, Ph), 128.0 (CH, Ph), 128.4 (CH, Ph), 132.8 (CH, CH=CH_2), 136.4 (quat., Ph), 156.1 (quat., NCO_2), 166.4 (quat., Gly-CON) and 173.7 (quat., CO_2CH_3); *m/z* (EI+) 360.1682 (M^+ $C_{19}H_{24}N_2O_5$ requires 360.1685).

4.1.13. Methyl *N-tert*-butyloxycarbonyl-glycyl-L-2-allylprolinate 21. Dry triethylamine (0.28 cm^3, 2.02 mmol) was added dropwise to a solution of hydrochloride **14** (0.13 g, 0.63 mmol) and *N-tert*-butyloxycarbonylglycine **17** (0.14 g, 0.82 mmol) in dry dichloromethane (35 cm^3) under an atmosphere of nitrogen at room temperature, and the reaction mixture stirred for 10 min. Bis(2-oxo-3-oxazolidinyl)phosphinic chloride (0.20 g, 0.80 mmol) was added and the solution stirred for 19.5 h, then washed successively with 10% aqueous hydrochloric acid (35 cm^3) and saturated aqueous sodium hydrogen carbonate (35 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness in vacuo. Purification of the resultant residue by flash column chromatography (40% ethyl acetate–hexane) yielded ester **21** (0.09 g, 45%) as a light yellow oil: $[\alpha]_D$ +33.8 (*c* 0.83 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 3419, 3075, 2977, 2930, 2874, 1739, 1715, 1656, 1499, 1434, 1392, 1366, 1332, 1268, 1248, 1212, 1168, 1122, 1051, 1026, 1003, 943, 919, 867, 830, 779, 739, 699 and 679; δ_H (300 MHz; $CDCl_3$) 1.42 [9H, s, $C(CH_3)_3$], 1.93–2.08 (4H, m, Proβ-H_2 and Proγ-H_2), 2.59–2.67 (1H, m, C$H_A$$H_B$CH=$CH_2$), 3.09–3.16 (1H, m, $CH_A$$H_B$CH=$CH_2$), 3.35–3.44 (1H, m, Proδ-$H_A$$H_B$), 3.56–3.62 (1H, m, Proδ-$H_A$$H_B$), 3.70 (3H, s, OCH_3), 3.89 (2H, d, J=4.2 Hz, Glyα-H_2), 5.06–5.11 (2H, m, CH=CH_2), 5.42 (1H, br s, Gly-NH) and 5.58–5.72 (1H, m, CH=CH_2); δ_C (75 MHz; $CDCl_3$) 23.7 (CH_2, Proγ-C), 28.3 [CH_3, $C(CH_3)_3$], 35.0 (CH_2, Proβ-C), 37.6 (CH_2, CH_2CH=CH_2), 43.3 (CH_2, Glyα-C), 47.5 (CH_2, Proδ-C), 52.5 (CH_3, OCH_3), 68.8 (quat., Proα-C), 79.5 [quat., $C(CH_3)_3$], 119.4 (CH_2, CH=CH_2), 132.9 (CH, CH=CH_2), 155.7 (quat., NCO_2), 166.9 (quat., Gly-CON) and 173.8 (quat., CO_2CH_3); *m/z* (EI+) 326.1845 (M^+ $C_{16}H_{26}N_2O_5$ requires 326.1842).

4.1.14. Methyl *N-tert*-butyloxycarbonyl-glycyl-L-2-benzylprolinate 22. Dry triethylamine (0.59 cm^3, 4.22 mmol) was added dropwise to a solution of hydrochloride **15** (0.34 g, 1.32 mmol) and *N-tert*-butyloxycarbonylglycine **17** (0.30 g, 1.71 mmol) in dry dichloromethane (70 cm^3) under an atmosphere of nitrogen at room temperature, and the reaction mixture stirred for 10 min. Bis(2-oxo-3-oxazolidinyl)phosphinic chloride (0.42 g, 1.66 mmol) was added and the solution stirred for 18.5 h, then washed successively with 10% aqueous hydrochloric acid (70 cm^3) and saturated aqueous sodium hydrogen carbonate (70 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness in vacuo. Purification of the resultant residue by flash column chromatography (50% ethyl acetate–hexane) yielded ester **22** (0.11 g, 22%) as a pale yellow oil: $[\alpha]_D$ +105.3 (*c* 0.99 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 3419, 3061, 3028, 2977, 2873, 1799, 1739, 1715, 1655, 1582, 1497, 1454, 1432, 1392, 1366, 1330, 1250, 1167, 1121, 1093, 1049, 1026, 948, 915, 865, 819, 765, 736, 706 and 653; δ_H (300 MHz; $CDCl_3$) 1.08–1.12 (1H, m, Proγ-$H_A$$H_B$), 1.47 [9H, s, $C(CH_3)_3$], 1.67–1.72 (1H, m, Proγ-$H_A$$H_B$), 2.01–2.17 (2H, m, Proβ-H_2), 2.86–2.92 (1H, m, Proδ-$H_A$$H_B$), 3.08 (1H, d, J=13.8 Hz, PhC$H_A$$H_B$), 3.36–3.42 (1H, m, Proδ-$H_A$$H_B$), 3.75 (3H, s, OCH_3), 3.83 (1H, m, PhC$H_A$$H_B$), 3.90 (2H, d, J=3.6 Hz, Glyα-CH_2), 5.54 (1H, br s, N–H) and 7.06–7.30 (5H, m, PhH); δ_C (100 MHz; $CDCl_3$) 23.4 (CH_2, Proγ-C), 28.4 [CH_3, $C(CH_3)_3$], 34.7 (CH_2, Proβ-C), 37.8 (CH_2, PhCH_2), 43.6 (CH_2, Glyα-C), 47.4 (CH_2, Proδ-C), 52.6 (CH_3, OCH_3), 69.6 (quat., Proα-C), 79.6 [quat., $C(CH_3)_3$], 126.8 (CH, Ph), 128.3 (CH, Ph), 130.5 (CH, Ph), 136.7 (quat., Ph), 155.8 (quat., NCO_2), 167.2 (quat., Gly-CON) and 174.0 (quat., CO_2CH_3); *m/z* (EI+) 376.2001 (M^+ $C_{20}H_{28}N_2O_5$ requires 376.1998).

4.1.15. *N*-Benzyloxycarbonyl-glycyl-L-2-methylproline 23. To a solution of mthyl ester **18** (0.56 g, ca. 1.67 mmol) in 1,4-dioxane (33 cm^3) was added dropwise 1 M aqueous sodium hydroxide (10 cm^3, 10 mmol) and the mixture was stirred for 19 h at room temperature. Dichloromethane (100 cm^3) was then added and the organic layer extracted with saturated aqueous sodium hydrogen carbonate (2×100 cm^3). The combined aqueous layers were carefully acidified with dilute hydrochloric acid, extracted with dichloromethane (2×100 cm^3), and the combined organic layers dried ($MgSO_4$), filtered, and concentrated to dryness in vacuo. Purification of the ensuing residue (0.47 g) by flash column chromatography (50% ethyl acetate–hexane to 30% methanol–dichloromethane; gradient elution) gave acid **23** (0.68 g, 90%) as a white foam: $[\alpha]_D$ −62.3 (*c* 0.20 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 3583, 3324 br, 2980, 2942, 1722, 1649, 1529, 1454, 1432, 1373, 1337, 1251, 1219, 1179, 1053, 1027, 965, 912, 735 and 698; δ_H (300 MHz; $CDCl_3$) 1.59 (3H, s, Proα-CH_3), 1.89 (1H, 6 lines, J=18.8, 6.2, 6.2 Hz, Proβ-$H_A$$H_B$), 2.01 (2H, dtt, J=18.7, 6.2, 6.2 Hz, Proγ-H_2), 2.25–2.40 (1H, m, Proβ-$H_A$$H_B$), 3.54 (2H, t, J=6.6 Hz, Proδ-H_2), 3.89 (1H, dd, J=17.1, 3.9 Hz, Glyα-$H_A$$H_B$), 4.04 (1H, dd, J=17.2, 5.3 Hz, Glyα-$H_A$$H_B$), 5.11 (2H, s, OC$H_2$Ph), 5.84 (1H, br t, J=4.2 Hz, N–H), 7.22–7.43 (5H, m, Ph) and 7.89 (1H, br s, –COOH); δ_C (75 MHz; $CDCl_3$) 21.3 (CH_3, Proα-CH_3), 23.8 (CH_2, Proγ-C), 38.2 (CH_2, Proβ-C), 43.6 (CH_2, Glyα-C), 47.2 (CH_2, Proδ-C), 66.7 (quat., Proα-C), 66.8 (CH_2, OCH_2Ph), 127.9 (CH, Ph), 127.9 (CH, Ph), 128.4, (CH, Ph), 136.4 (quat., Ph), 156.4 (quat., NCO_2), 167.5 (quat., Gly-CON) and 176.7 (quat., CO); *m/z* (EI+) 320.1368 (M^+ $C_{16}H_{20}N_2O_5$ requires 320.1372).

4.1.16. *N*-Benzyloxycarbonyl-glycyl-L-2-ethylproline 24. To a solution of methyl ester **19** (0.39 g, 1.11 mmol) in dioxane (15 cm^3) was added dropwise 1 M NaOH (7.5 cm^3, 7.50 mmol) and the mixture was stirred for 20 h at room temperature. The solution was acidified with 1 M HCl and evaporated in vacuo. The resulting aqueous layer was extracted with dichloromethane (2×30 cm^3), dried ($MgSO_4$), filtered and evaporated in vacuo to form a clear gum, which solidified on standing to acid **24** (0.35 g, 95%)

as a colourless solid, which was used without further purification: $[\alpha]_D$ −9.9 (*c* 0.11 in MeOH); δ_H (300 MHz; $CDCl_3$) 0.83 (3H, t, *J*=7.4 Hz, CH_3), 1.93–2.22 (5H, m, CH_2CH_3, Proγ-H_2 and Pro-βH_AH_B), 2.35–2.40 (1H, m, Pro-βH_AH_B), 3.43–3.46 (1H, m, Proδ-H_AH_B), 3.57–3.62 (1H, m, Proδ-H_AH_B), 4.01 (2H, dd, *J*=4.3, 17.3 Hz, Glyα-H_2), 5.11 (2H, s, OCH_2Ph), 5.82 (1H, br s, Gly-NH), 7.26–7.36 (5H, m, Ph) and 7.70 (1H, br s, CO_2H); δ_C (75 MHz; $CDCl_3$) 8.5 (CH_3, CH_3), 23.9 (CH_2, CH_2CH_3), 26.7 (CH_2, Proγ-C), 34.8 (CH_2, Proβ-C), 44.1 (CH_2, Glyα-C), 48.7 (CH_2, Proδ-C), 67.3 (CH_2, OCH_2Ph), 71.9 (quat., Proα-C), 127.3 (CH, Ph), 127.9 (CH, Ph), 128.3 (CH, Ph), 128.4 (CH, Ph), 128.9 (CH, Ph), 136.7 (quat., Ph), 156.7 (quat., NCO_2), 168.9 (quat., Gly-CON) and 175.8 (quat., CO_2H); *m*/*z* (EI^+) 334.1523 (M^+ $C_{17}H_{22}N_2O_5$ requires 334.1529).

4.1.17. *N*-Benzyloxycarbonyl-glycyl-L-2-allylproline 25. To a solution of ester **20** (0.12 g, 0.34 mmol) in dioxane (7 cm^3) was added dropwise 1 M aqueous NaOH (2.06 cm^3, 2.06 mmol) and the mixture stirred for 20 h at room temperature. Dichloromethane (25 cm^3) was then added and the organic layer extracted with saturated aqueous sodium bicarbonate (3×25 cm^3). Careful acidification of the combined aqueous layers with dilute hydrochloric acid, extraction with dichloromethane (3×25 cm^3), drying of the combined organic layers ($MgSO_4$), filtration and concentration to dryness gave the acid **25** (0.11 g, 92%) as a yellow oil: $[\alpha]_D$ −3.16 (*c* 0.95 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 3408, 2957, 2923, 2850, 2622, 1715, 1650, 1531, 1453, 1375, 1333, 1259, 1214, 1173, 1121, 1083, 1056, 1028, 1002, 916, 823, 737 and 698; δ_H (300 MHz; $CDCl_3$) 1.93–2.07 (3H, m, Proβ-H_AH_B and Proγ-H_2), 2.22–2.26 (1H, m, Proβ-H_AH_B), 2.62–2.69 (1H, m, CH_AH_BCH=CH_2), 3.04–3.11 (1H, m, CH_AH_BCH=CH_2), 3.31–3.62 (2H, m, Proδ-H_2), 3.91–4.05 (2H, m, Glyα-H_2), 5.08–5.13 (3H, m, PhCH_2 and CH=CH_AH_B), 5.55–5.72 (1H, m, CH=CH_AH_B), 5.89 (1H, m, CH=CH_2), 7.29–7.45 (5H, m, PhH) and 8.12 (1H, br s, N–H); δ_C (75 MHz; $CDCl_3$) 23.5 (CH_2, Proγ-C), 34.6 (CH_2, Proβ-C), 37.5 (CH_2, CH_2CH=CH_2), 43.7 (CH_2, Glyα-C), 48.1 (CH_2, Proδ-C), 66.9 (CH_2, PhCH_2), 69.9 (quat., Proα-C), 119.8 (CH_2, CH=CH_2), 127.97 (CH, Ph), 128.04 (CH, Ph), 128.4 (CH, Ph), 132.3 (CH, CH=CH_2), 136.4 (quat., Ph), 156.4 (quat., NCO_2), 168.2 (quat., Gly-CON) and 176.1 (quat., CO_2H); *m*/*z* (EI+) 346.1526 (M^+ $C_{18}H_{22}N_2O_5$ requires 346.1529).

4.1.18. *N-tert*-Butyloxycarbonyl-glycyl-L-2-allylproline 26. To a solution of ester **21** (0.039 g, 0.12 mmol) in dioxane (2.4 cm^3) was added dropwise 1 M aqueous NaOH (0.72 cm^3, 0.72 mmol) and the mixture was stirred for 16 h at room temperature. Dichloromethane (10 cm^3) was then added and the organic layer extracted with saturated aqueous sodium bicarbonate (3×10 cm^3). Careful acidification of the combined aqueous layers with dilute hydrochloric acid, extraction with dichloromethane (3×10 cm^3), drying of the combined organic layers ($MgSO_4$), filtration and concentration to dryness gave acid **26** (0.031 g, 83%) as a yellow oil: $[\alpha]_D$ −15.8 (*c* 0.89 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 3414, 3076, 2978, 2931, 2620, 1713, 1654, 1510, 1454, 1434, 1392, 1367, 1268, 1250, 1213, 1169, 1121, 1056, 1028, 920, 869, 779, 736 and 701; δ_H (300 MHz; $CDCl_3$) 1.43 [9H, s, $C(CH_3)_3$], 1.95–2.15 (3H, m, Proβ-H_AH_B and Proγ-CH_2), 2.21–2.35 (1H, m, Proβ-H_AH_B), 2.63–2.70 (1H, m, CH_AH_BCH=CH_2), 3.04–3.11 (1H, m, CH_AH_BCH=CH_2), 3.35–3.47 (1H, m, Proδ-H_AH_B), 3.53–3.62 (1H, m, Proδ-H_AH_B), 3.92 (2H, m, Glyα-H_2), 5.08–5.13 (2H, m, CH=CH_2), 5.52 (1H, br s, Gly-NH), 5.56–5.71 (1H, m, CH=CH_2) and 8.31 (1H, br s, OH); δ_C (75 MHz; $CDCl_3$) 23.5 (CH_2, Proγ-C), 28.3 [CH_3, $C(CH_3)_3$], 34.6 (CH_2, Proβ-C), 37.5 (CH_2, CH_2CH=CH_2), 43.4 (CH_2, Glyα-C), 48.1 (CH_2, Proδ-C), 69.8 (quat., Proα-C), 79.8 [quat., $C(CH_3)_3$], 119.8 (CH_2, CH=CH_2), 132.3 (CH, CH=CH_2), 155.8 (quat., NCO_2), 168.5 (quat., Gly-CON) and 175.9 (quat., CO_2H); *m*/*z* (EI+) 312.1692 (M^+ $C_{15}H_{24}N_2O_5$ requires 312.1685).

4.1.19. *N-tert*-Butyloxycarbonyl-glycyl-L-2-benzylproline 27. To a solution of ester **22** (0.098 g, 0.26 mmol) in dioxane (5.2 cm^3) was added dropwise 1 M aqueous NaOH (1.56 cm^3, 1.56 mmol) and the mixture was stirred for 15 h at room temperature. Dichloromethane (20 cm^3) was then added and the organic layer extracted with saturated aqueous sodium bicarbonate (3×20 cm^3). Careful acidification of the combined aqueous layers with dilute hydrochloric acid, extraction with dichloromethane (3×20 cm^3), drying of the combined organic layers ($MgSO_4$), filtration and concentration to dryness gave the acid **27** (0.09 g, 95%) as a colourless glass-like solid: mp 74–77 °C: $[\alpha]_D$ +69.8 (*c* 0.99 in CH_2Cl_2); ν_{max} (CH_2Cl_2)/cm^{-1} 3415, 3060, 3028, 2978, 2879, 2621, 1711, 1655, 1497, 1454, 1392, 1367, 1252, 1167, 1120, 1092, 1081, 1049, 1029, 988, 942, 915, 887, 872, 814, 764, 736, 705 and 653; δ_H (400 MHz; $CDCl_3$) 1.14–1.21 (1H, m, Proγ-H_AH_B), 1.50 [9H, s, $C(CH_3)_3$], 1.72–1.78 (1H, m, Proγ-H_AH_B), 2.11–2.29 (2H, m, Proβ-H_2), 2.94–3.00 (1H, m, Proδ-H_AH_B), 3.13 (1H, d, *J*=13.9 Hz, PhCH_AH_B), 3.42–3.48 (1H, m, Proδ-H_AH_B), 3.83 (1H, d, *J*=13.9 Hz, PhCH_AH_B), 4.13 (2H, m, Glyα-H_2), 5.69 (1H, br s, Gly-NH), 7.10–7.33 (5H, m, PhH) and 8.37 (1H, br s, OH); δ_C (100 MHz; $CDCl_3$) 23.3 (CH_2, Proγ-C), 28.3 [CH_3, $C(CH_3)_3$], 34.5 (CH_2, Proβ-C), 37.8 (CH_2, PhCH_2), 43.7 (CH_2, Glyα-C), 47.8 (CH_2, Proδ-C), 70.3 (quat., Proα-C), 79.8 [quat., $C(CH_3)_3$], 126.9 (CH, Ph), 128.4 (CH, Ph), 130.5 (CH, Ph), 136.3 (quat., Ph), 156.0 (quat., NCO_2), 168.6 (quat., Gly-CON) and 176.9 (quat., CO_2H); *m*/*z* (EI+) 362.1834 (M^+ $C_{19}H_{26}N_2O_5$ requires 362.1842).

4.1.20. Dibenzyl *N*-benzyloxycarbonyl-glycyl-L-2-methylprolyl-L-glutamate 30. Triethylamine (0.50 cm^3, 3.59 mmol) was added dropwise to a solution of dipeptide **23** (0.36 g, 1.12 mmol) and L-glutamic acid dibenzyl ester *p*-toluenesulphonate **28** (0.73 g, 1.46 mmol) in dichloromethane (60 cm^3) under nitrogen at room temperature, and the reaction mixture stirred for 10 min. Bis(2-oxo-3-oxazolidinyl)phosphinic chloride (0.37 g, 1.41 mmol) was added and the colourless solution stirred for 17 h. The dichloromethane solution was washed successively with 10% aqueous hydrochloric acid (50 cm^3) and saturated aqueous sodium hydrogen carbonate (50 cm^3), dried ($MgSO_4$), filtered, and evaporated to dryness in vacuo. Purification of the resultant residue by repeated flash column chromatography (30–70% ethyl acetate–hexane; gradient elution) yielded protected tripeptide **30** (0.63 g, 89%) as a colourless oil. Tripeptide **30** was shown to adopt exclusively the trans conformer by NMR: R_f 0.55 (EtOAc): $[\alpha]_D$ −41.9 (*c* 0.29 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 3583,

3353 br, 2950, 1734, 1660, 1521, 1499, 1454, 1429, 1257, 1214, 1188, 1166, 1051, 911, 737 and 697; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.64 (3H, s, Proα-CH_3), 1.72 (1H, dt, J= 12.8, 7.6, 7.6 Hz, Proβ-H_AH_B), 1.92 (2H, 5 lines, J=6.7 Hz, Proγ-H_2), 2.04 (1H, 6 lines, J=7.3 Hz Gluβ-H_AH_B), 2.17–2.27 (1H, m, Gluβ-H_AH_B), 2.35–2.51 (3H, m, Proβ-H_AH_B and Gluγ-H_2), 3.37–3.57 (2H, m, Proδ-H_2), 3.90 (1H, dd, J=17.0, 3.6 Hz, Glyα-H_AH_B), 4.00 (1H, dd, J=17.1, 5.1 Hz, Glyα-H_AH_B), 4.56 (1H, td, J=7.7, 4.9 Hz, Gluα-H), 5.05–5.20 (6H, m, 3×OCH_2Ph), 5.66–5.72 (1H, br m, Gly-NH), 7.26–7.37 (15H, m, 3×Ph) and 7.44 (1H, d, J= 7.2 Hz, Glu-NH); δ_C (100 MHz; $CDCl_3$) 21.9 (CH_3, Proα-CH_3), 23.4 (CH_2, Proγ-C), 26.6 (CH_2, Gluβ-C), 30.1 (CH_2, Gluγ-C), 38.3 (CH_2, Proβ-C), 43.9 (CH_2, Glyα-C), 47.6 (CH_2, Proδ-C), 52.2 (CH, Gluα-C), 66.4 (CH_2, OCH_2Ph), 66.8 (CH_2, OCH_2Ph), 67.1 (CH_2, OCH_2Ph), 68.2 (quat., Proα-C), 127.9 (CH, Ph), 128.0 (CH, Ph), 128.1, (CH, Ph), 128.2, (CH, Ph), 128.2, (CH, Ph), 128.3, (CH, Ph), 128.4, (CH, Ph), 128.5, (CH, Ph), 128.5, (CH, Ph), 135.2 (quat., Ph), 135.7 (quat., Ph), 136.4 (quat., Ph), 156.1 (quat., NCO_2), 167.3 (quat., Gly-CO), 171.4 (quat., CO), 172.9 (quat., CO) and 173.4 (quat., CO); m/z (FAB+) 630.2809 (MH^+ $C_{35}H_{40}N_3O_8$ requires 630.2815).

4.1.21. Dibenzyl *N*-benzyloxycarbonyl-glycyl-L-2-ethyl-prolyl-L-glutamate 31. Dry triethylamine (0.44 cm^3, 3.16 mmol) was added to a solution of acid **24** (0.30 g, 0.91 mmol) and L-glutamic acid dibenzyl ester *p*-toluene sulphonate **28** (0.57 g, 1.13 mmol) in dry dichloromethane (50 cm^3) under an atmosphere of nitrogen at 0 °C, and the reaction mixture stirred for 10 min. Bis(2-oxo-3-oxazolidinyl)phosphinic chloride (0.29 g, 1.14 mmol) was added and the solution stirred for 2 h, warmed to room temperature and further stirred for 17.5 h. The solution was washed successively with 0.5 M aqueous hydrochloric acid (10 cm^3) and saturated aqueous sodium hydrogen carbonate (10 cm^3), dried ($MgSO_4$), filtered and evaporated in vacuo to form a light orange gum. Purification of the resultant residue by flash column chromatography (30% ethyl acetate/hexane) yielded protected tripeptide **31** (0.41 g, 70%) as a clear oil: $[\alpha]_D$ −52.7 (c 0.16 in MeOH); δ_H (300 MHz; $CDCl_3$) 0.78 (3H, t, J=7.4 Hz, CH_3), 1.25–2.24 (7H, m, CH_2CH_3, Gluβ-H_2, Proγ-H_2 and Proβ-H_AH_B), 2.34–2.40 (2H, m, Gluγ-H_2), 2.50–2.60 (1H, m, Proβ-H_AH_B), 3.34 (1H, q, J=9.4 Hz, Proδ-H_AH_B), 3.49–3.53 (1H, m, Proδ-H_AH_B), 3.96 (2H, ddd, J=4.9, 17.3 Hz, Glyα-H_2), 4.51–4.54 (1H, td, J=5.4, 7.8 Hz, Gluα-H), 5.06–5.19 (6H, m, 3×OCH_2Ph), 5.70 (1H, br s, Gly-NH), 7.26–7.36 (15H, 3×Ph) and 8.09 (1H, d, J=7.3 Hz, Glu-NH); δ_C (75 MHz; $CDCl_3$) 8.8 (CH_3, CH_3), 23.6 (CH_2, CH_2CH_3), 27.2 (CH_2, Proγ-C), 27.7 (CH_2, Gluβ-C), 30.6 (CH_2, Gluγ-C), 34.3 (CH_2, Proβ-C), 44.5 (CH_2, Glyα-C), 49.0 (CH_2, Proδ-C), 52.6 (CH, Gluα-C), 66.9 (CH_2, OCH_2Ph), 67.3 (CH_2, OCH_2Ph), 67.5 (CH_2, OCH_2Ph), 73.9 (quat., Proα-C), 128.4 (CH, Ph), 128.5 (CH, Ph), 128.6 (CH, Ph), 128.7 (CH, Ph), 128.8 (CH, Ph), 128.9 (CH, Ph), 135.7 (quat., Ph), 136.1 (quat., Ph), 136.8 (quat., Ph), 156.6 (quat., NCO_2), 168.7 (quat., Gly-CON), 171.8 (quat., Pro-CON), 172.9 (quat., Gluα-CO) and 173.6 (quat., Gluγ-CO); m/z (FAB+) 644.2981 (MH^+ $C_{36}H_{42}N_3O_8$ requires 644.2972).

4.1.22. Dibenzyl *N*-benzyloxycarbonyl-glycyl-L-2-allyl-prolyl-L-glutamate 32. Dry triethylamine (0.07 cm^3, 0.49 mmol) was added dropwise to a solution of acid **25** (0.05 g, 0.15 mmol) and L-glutamic acid dibenzyl ester *p*-toluenesulphonate **28** (0.10 g, 0.20 mmol) in dry dichloromethane (8.2 cm^3) under an atmosphere of nitrogen at room temperature, and the reaction mixture stirred for 10 min. Bis(2-oxo-3-oxazolidinyl)phosphinic chloride (0.05 g, 0.19 mmol) was added and the solution was stirred for 19.5 h. The solution was washed successively with 10% aqueous hydrochloric acid (7 cm^3) and saturated aqueous sodium hydrogen carbonate (7 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness in vacuo. Purification of the resultant residue by flash column chromatography (50–80% ethyl acetate–hexane; gradient elution) yielded protected tripeptide **32** (0.08 g, 76%) as a colourless oil: $[\alpha]_D$ −27.8 (c 0.79 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 3943, 3583, 3413, 3055, 3032, 2982, 2956, 2880, 2685, 2411, 2305, 1955, 1732, 1668, 1586, 1499, 1454, 1423, 1388, 1329, 1265, 1214, 1169, 1170, 1081, 1058, 1028, 994, 924, 897, 824, 737 and 701; δ_H (400 MHz; $CDCl_3$) 1.85 (3H, m, Proβ-H_AH_B and Proγ-H_2), 1.99–2.08 (1H, m, Gluβ-H_AH_B), 2.17–2.25 (1H, m, Gluβ-H_AH_B), 2.32–2.49 (3H, m, Proβ-H_AH_B and Gluγ-H_2), 2.71–2.76 (1H, m, CH_AH_BCH=CH_2), 3.05–3.10 (1H, m, CH_AH_BCH=CH_2), 3.33 (1H, m, Proδ-H_AH_B), 3.51 (1H, m, Proδ-H_AH_B), 3.96 (2H, d, J=3.9 Hz, Glyα-H_2), 4.55 (1H, dd, J=7.6, 5.1 Hz, Gluα-H), 5.07–5.19 (8H, m, 3×PhCH_2 and CH=CH_2), 5.53–5.63 (1H, m, CH=CH_2), 5.71 (1H, br s, Gly-NH), 7.32–7.36 (15H, m, 3×Ph) and 7.90 (1H, d, J=7.2 Hz, Glu-NH); δ_C (100 MHz; $CDCl_3$) 23.1 (CH_2, Proγ-C), 26.7 (CH_2, Gluβ-C), 30.2 (CH_2, Gluγ-C), 34.2 (CH_2, Proβ-C), 37.9 (CH_2, CH_2-CH=CH_2), 44.1 (CH_2, Glyα-C), 48.5 (CH_2, Proδ-C), 52.2 (CH, Gluα-C), 66.4 (CH_2, PhCH_2), 66.9 (CH_2, PhCH_2), 67.2 (CH_2, PhCH_2), 71.9 (quat., Proα-C), 119.9 (CH_2, CH=CH_2), 127.9 (CH, Ph), 128.05 (CH, Ph), 128.1 (CH, Ph), 128.2 (CH, Ph), 128.3 (CH, Ph), 128.4 (CH, Ph), 128.45 (CH, Ph), 128.5 (CH, Ph), 132.1 (CH, CH=CH_2), 135.3 (quat., Ph), 135.7 (quat., Ph), 136.4 (quat., Ph), 156.2 (quat., NCO_2), 168.1 (quat., Gly-CO), 171.3 (quat., Gluα-CO), 172.7 (quat., Gluγ-CO) and 173.0 (quat., Pro-CON); m/z (FAB+) 656.2970 (MH^+ $C_{37}H_{42}N_3O_8$ requires 656.2992).

4.1.23. Di-*tert*-butyl *N*-*tert*-butyloxycarbonyl-glycyl-L-2-allylprolyl-L-glutamate 33. Dry triethylamine (0.044 cm^3, 0.32 mmol) was added dropwise to a solution of acid **26** (0.031 g, 0.10 mmol) and L-glutamic acid di-*tert*-butyl ester hydrochloride **29** (0.038 g, 0.129 mmol) in dry dichloromethane (5.30 cm^3) under an atmosphere of nitrogen at room temperature, and the reaction mixture stirred for 10 min. Bis(2-oxo-3-oxazolidinyl)phosphinic chloride (0.032 g, 0.13 mmol) was added and the solution stirred for 17.5 h. The solution was washed successively with 10% aqueous hydrochloric acid (5 cm^3) and saturated aqueous sodium hydrogen carbonate (5 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness in vacuo. Purification of the resultant residue by flash column chromatography (50% ethyl acetate–hexane) yielded protected tripeptide **33** (0.43 g, 77%) as a light yellow oil: $[\alpha]_D$ −29.9 (c 0.90 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 3583, 3417, 3076, 2978, 2931, 1728, 1664, 1522, 1453, 1426, 1392, 1367, 1329, 1251, 1158, 1056, 1028, 949, 919, 846 and 735; δ_H (300 MHz; $CDCl_3$) 1.26 [9H, s, $C(CH_3)_3$], 1.42 [9H, s, $C(CH_3)_3$], 1.43 [9H, s, $C(CH_3)_3$], 1.85–1.94 (4H, m, Proβ-H_AH_B, Gluβ-H_AH_B and Proγ-H_2), 2.02–2.12 (1H, m, Gluβ-H_AH_B),

2.16–2.33 (2H, m, Gluγ-H_2), 2.48–2.53 (1H, m, Proβ-H_AH_B), 2.69–2.77 (1H, m, 0.5 CH_AH_BCH=CH_2), 3.08–3.15 (1H, m, CH_AH_BCH=CH_2), 3.29–3.38 (1H, m, Proδ-H_AH_B), 3.53–3.56 (1H, m, Proδ-H_AH_B), 3.91 (2H, d, J=4.0 Hz, Glyα-H_2), 4.33 (1H, dd, J=7.5, 5.2 Hz, Gluα-H), 5.08–5.14 (2H, m, CH=CH_2), 5.47 (1H, br s, Gly-NH), 5.52–5.66 (1H, m, CH=CH_2) and 7.77 (1H, d, J=7.4 Hz, Glu-NH); δ_C (75 MHz; $CDCl_3$) 23.1 (CH_2, Proγ-C), 27.4 (CH_2, Gluβ-C), 27.9 [CH_3, C(CH_3)$_3$], 28.0 [CH_3, C(CH_3)$_3$], 28.3 [CH_3, C(CH_3)$_3$], 31.5 (CH_2, Gluγ-C), 34.2 (CH_2, Proβ-C), 38.0 (CH_2, CH_2CH=CH_2), 43.7 (CH_2, Glyα-C), 48.4 (CH_2, Proδ-C), 52.7 (CH, Gluα-C), 71.8 (quat., Proα-C), 79.5 [quat., C(CH_3)$_3$], 80.6 [quat., C(CH_3)$_3$], 81.9 [quat., C(CH_3)$_3$], 119.8 (CH_2, CH=CH_2), 132.3 (CH, CH=CH_2), 155.7 (quat., NCO_2), 168.4 (quat., Gly-CO), 170.8 (quat., Gluα-CO), 172.3 (quat., Gluγ-CO) and 172.8 (quat., Pro-CON); m/z (EI+) 553.3359 (M^+ $C_{28}H_{47}N_3O_8$ requires 553.3363).

4.1.24. Di-*tert*-butyl *N*-*tert*-butyloxycarbonyl-glycyl-L-2-benzylprolyl-L-glutamate 34. Dry triethylamine (0.11 cm^3, 0.77 mmol) was added dropwise to a solution of acid **27** (0.09 g, 0.24 mmol) L-glutamic acid di-*tert*-butyl ester hydrochloride **29** (0.09 g, 0.31 mmol) in dry dichloromethane (13 cm^3) under an atmosphere of nitrogen at room temperature, and the reaction mixture stirred for 10 min. Bis(2-oxo-3-oxazolidinyl)phosphinic chloride (0.08 g, 0.30 mmol) was added and the solution stirred for 17 h, then washed successively with 10% aqueous hydrochloric acid (12 cm^3) and saturated aqueous sodium hydrogen carbonate (12 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness in vacuo. Purification of the resultant residue by flash column chromatography (40% ethyl acetate–hexane) yielded protected tripeptide **34** (0.10 g, 68%) as a colourless oil: $[\alpha]_D$ +15.7 (c 1.15 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 3418, 3357, 3060, 3028, 2978, 2933, 2875, 1727, 1663, 1582, 1519, 1497, 1454, 1426, 1392, 1367, 1330, 1251, 1158, 1093, 1051, 1029, 949, 914, 846, 736, 705 and 651; δ_H (400 MHz; $CDCl_3$) 1.28–1.39 (1H, m, Proγ-H_AH_B), 1.43 [27H, s, C(CH_3)$_3$], 1.47 [27H, s, C(CH_3)$_3$], 1.48 [27H, s, C(CH_3)$_3$], 1.69–1.74 (1H, m, Proγ-H_AH_B), 1.89–1.99 (2H, m, Proβ-H_2), 2.08–2.17 (1H, m, Gluβ-H_AH_B), 2.23–2.41 (3H, m, Gluβ-H_AH_B and Gluγ-H_2), 2.89–2.95 (1H, m, Proδ-H_AH_B), 3.13 (1H, d, J=13.4 Hz, PhCH_AH_B), 3.40–3.46 (1H, m, Proδ-H_AH_B), 3.85 (1H, d, J=13.4 Hz, PhCH_AH_B), 3.92 (2H, d, J=3.8 Hz, Glyα-H_2), 4.33 (1H, td, J=7.5, 5.2 Hz, Gluα-H), 5.58 (1H, br s, Gly-NH), 7.07–7.28 (5H, m, PhH) and 7.71 (1H, d, J=7.2 Hz, Glu-NH); δ_C (100 MHz; $CDCl_3$) 23.0 (CH_2, Proγ-C), 27.4 (CH_2, Gluβ-C), 28.0 [CH_3, C(CH_3)$_3$], 28.1 [CH_3, C(CH_3)$_3$], 28.3 [CH_3, C(CH_3)$_3$], 31.5 (CH_2, Gluγ-C), 34.2 (CH_2, Proβ-C), 38.0 (CH_2, PhCH_2), 44.1 (CH_2, Glyα-C), 48.2 (CH_2, Proδ-C), 52.9 (CH, Gluα-C), 72.4 (quat., Proα-C), 79.6 [quat., C(CH_3)$_3$], 80.7 [quat., C(CH_3)$_3$], 82.1 [quat., C(CH_3)$_3$], 126.8 (CH, Ph), 128.3 (CH, Ph), 130.4 (CH, Ph), 136.3 (quat., Ph), 155.8 (quat., NCO_2), 168.6 (quat., Gly-CO), 171.0 (quat., Gluα-CO), 172.5 (quat., Gluγ-CO) and 173.1 (quat., Pro-CON); m/z (FAB+) 604.3592 (MH^+ $C_{32}H_{50}N_3O_8$ requires 604.3598).

4.1.25. Glycyl-L-2-methylprolyl-L-glutamic acid 1. A mixture of the protected tripeptide **30** (0.63 g, 1.00 mmol) and 10% palladium on activated carbon (0.32 g, 0.30 mmol) in 90:10 methanol–water (22 cm^3) was stirred under an atmosphere of hydrogen at room temperature, protected from light, for 23 h. The reaction mixture was filtered through a Celite™ pad and the pad washed with 75:25 methanol–water (200 cm^3). The filtrate was concentrated to dryness under reduced pressure and the residue triturated with anhydrous diethyl ether to afford tripeptide **1** (0.27 g, 86%) as an hygroscopic colourless solid. Tripeptide **1** was shown to adopt the trans conformation by NMR analysis: mp 144 °: $[\alpha]_D$ −52.4 (c 0.19 in H_2O); δ_H (400 MHz; D_2O) 1.62 (3H, s, Proα-CH_3), 1.97–2.25 (6H, m, Proβ-H_2, Proγ-H_2 and Gluβ-H_2), 2.45 (2H, t, J=7.3 Hz, Gluγ-H_2), 3.62–3.70 (2H, m, Proδ-H_2), 3.96 (1H, d, J=16.5 Hz, Glyα-H_AH_B), 4.02 (1H, d, J=16.4 Hz, Glyα-H_AH_B) and 4.28 (1H, dd, J=8.4, 4.7 Hz, Gluα-H); δ_C (100 MHz; D_2O) 19.9 (CH_3, Proα-CH_3), 23.0 (CH_2, Proγ-C), 26.9 (CH_2, Gluβ-C), 30.9 (CH_2, Gluγ-C), 38.8 (CH_2, Proβ-C), 40.7 (CH_2, Glyα-C), 47.5 (CH_2, Proδ-C), 54.4 (CH, Gluα-C), 67.8 (quat., Proα-C), 164.6 (quat., Gly-CO), 175.3 (quat., Pro-CON), 177.2 (quat., Gluα-CO), and 178.5 (quat., Gluγ-CO); m/z (FAB+) 316.1508 (MH^+ $C_{13}H_{22}N_3O_6$ requires 316.1509).

4.1.26. Glycyl-L-2-ethylprolyl-L-glutamic acid 2. A mixture of protected tripeptide **31** (0.51 g, 0.80 mmol) and 10% palladium on activated carbon (0.09 g, 0.08 mmol) in 90:10 methanol–water (50 cm^3) was stirred under an atmosphere of hydrogen at room temperature for 20 h. The solution was filtered through a Celite™ pad, the pad washed with methanol (2×30 cm^3) and the filtrate evaporated to dryness to give a clear gum. The gum was placed under vacuum for 30 min then triturated with anhydrous diethyl ether to tripeptide **2** (0.26 g, 99%) as an hygroscopic colourless solid. Tripeptide **2** was shown to be exclusively the trans conformer by ^1H and ^{13}C NMR analysis: mp 82–85 °C: $[\alpha]_D$ −43.8 (c 0.1 in MeOH); δ_H (400 MHz; D_2O) 0.86 (3H, t, J=7.4 Hz, CH_3), 1.94–2.40 (8H, m, C$H_2$$CH_3$, Gluβ-$H_2$, Proβ-$H_2$ and Pro-γH_2), 2.52–2.56 (2H, m, Gluγ-H_2), 3.55–3.61 (1H, td, J=6.9, 9.7 Hz, Proδ-H_AH_B), 3.75–3.80 (1H, m, Proδ-H_AH_B), 4.08 (2H, q, J=16.6 Hz, Glyα-H_2) and 4.44 (1H, q, J=4.9 Hz, Gluα-H); δ_C (100 MHz; $CDCl_3$) 6.9 (CH_3, CH_3), 22.8 (CH_2, CH_2CH_3), 25.3 (CH_2, Proγ-C), 25.5 (CH_2, Gluβ-C), 30.11 (CH_2, Gluγ-C), 35.0 (CH_2, Proβ-C), 40.7 (CH_2, Glyα-C), 48.6 (CH_2, Proδ-C), 52.6 (CH, Gluα-C), 71.7 (quat., Proα-C), 164.9 (quat., Gly-CON), 175.2 (quat., Pro-CON) 176.0 (quat., Gluα-CO) and 177.3 (quat., Gluγ-CO); m/z (FAB+) 330.1667 (MH^+ $C_{14}H_{24}N_3O_6$ requires 330.1665).

4.1.27. Glycyl-L-2-propylprolyl-L-glutamic acid 3. A mixture of protected tripeptide **32** (64 mg, 0.097 mmol) and 10% palladium on activated carbon (20 mg, 0.19 mmol) in 90:10 methanol–water (9.8 cm^3) was stirred under an atmosphere of hydrogen at room temperature, protected from light, for 19 h. The reaction mixture was filtered through a Celite™ pad and the pad washed with 75:25 methanol–water (50 cm^3). The filtrate was concentrated to dryness under reduced pressure to afford tripeptide **3** (33 mg, 100%) as a colourless solid. Tripeptide **3** was shown to be exclusively the trans conformer by NMR analysis: mp 278–280 °C (dec.): $[\alpha]_D$ −16.7 (c 0.18 in H_2O); δ_H (300 MHz; D_2O) 0.98 (3H, t, CH_2CH_3), 1.09 (1H, m, C$H_AH_BCH_3$), 1.44 (1H, m, C$H_AH_BCH_3$), 1.82–2.31 (8H, m, Proβ-H_2, Proγ-H_2, Gluβ-H_2 and C$H_2CH_2CH_3$),

2.40 (1H, m, Gluγ-H_2), 3.55–3.63 (1H, m, Proδ-H_AH_B), 3.80 (1H, m, Proδ-H_AH_B), 4.03 (1H, d, J=16.6 Hz, Glyα-H_AH_B), 4.15 (1H, d, J=16.6 Hz, Glyα-H_AH_B) and 4.27 (1H, dd, J=8.2, 4.8 Hz, Gluα-H); δ_C (100 MHz; D_2O) 16.0 (CH_3, CH_2CH_3), 19.0 (CH_2, CH_2CH_3), 25.4 (CH_2, Proγ-C), 30.9 (CH_2, Gluβ-C), 36.3 (CH_2, Gluγ-C), 37.4 (CH_2, $CH_2CH_2CH_3$), 38.3 (CH_2, Proβ-C), 43.3 (CH_2, Glyα-C), 51.2 (CH_2, Proδ-C), 58.1 (CH, Gluα-C), 74.1 (quat., Proα-C), 167.7 (quat., NCO), 177.8 (quat., Pro-CON), 180.9 (quat., Gluα-CO) and 184.7 (quat., Gluγ-CO); m/z (FAB+) 344.1827 (MH^+ $C_{15}H_{26}N_3O_6$ requires 344.1822).

4.1.28. Glycyl-L-2-allylprolyl-L-glutamic acid trifluoroacetate 4. To a solution of the protected tripeptide **33** (41 mg, 0.073 mmol) in dichloromethane (4.5 cm^3) at room temperature was added trifluoroacetic acid (0.75 cm^3, 9.74 mmol) dropwise and the reaction mixture was stirred for 6.5 h. The solution was evaporated under reduced pressure to form tripeptide **4** (32 mg, 96%) as a pale yellow solid. Tripeptide **4** was shown to exist exclusively as the trans-conformer by NMR analysis: mp 105–108 °C: $[\alpha]_D$ −7.64 (c 0.39 in H_2O); δ_H (400 MHz; D_2O) 1.90–2.02 (1H, m, Proγ-H_AH_B), 2.03–2.14 (2H, m, Proγ-H_AH_B and Gluβ-H_AH_B), 2.19–2.32 (3H, m, Proβ-H_2 and Gluβ-H_AH_B), 2.54 (2H, ddd, J=8.1, 7.3, 2.0 Hz, Gluγ-H_2), 2.74 (1H, dd, J=13.7, 7.3 Hz, CH_AH_BCH=CH_2), 3.12 (1H, dd, J=13.7, 7.3, 0.5 Hz CH_AH_BCH=CH_2), 3.48–3.55 (1H, m, Proδ-H_AH_B), 3.72–3.77 (1H, m, Proδ-H_AH_B), 3.98 (1H, d, J=16.7 Hz, Glyα-H_AH_B), 4.10 (1H, d, J=16.7 Hz, Glyα-H_AH_B), 4.46 (1H, dd, J=4.9, 9.5 Hz, Gluα-H) 5.20–5.26 (2H, m, CH=CH_2) and 5.73–5.82 (1H, m, CH=CH_2); δ_C (100 MHz; D_2O) 25.4 (CH_2, Proγ-C), 28.1 (CH_2, Gluβ-C), 32.7 (CH_2, Gluγ-C), 38.1 (CH_2, Proβ-C), 39.1 (CH_2, CH_2CH=CH_2), 43.3 (CH_2, Glyα-C), 51.0 (CH_2, Proδ-C), 55.1 (CH, Gluα-C), 73.2 (quat., Proα-C), 120.3 (quat., CF_3), 122.6 (CH_2, CH=CH_2), 134.4 (CH, CH=CH_2), 165.4 (quat., CF_3CO_2), 167.5 (quat., Gly-CO), 177.5 (quat., Pro-CON), 178.0 (quat., Glyα-CO) and 179.8 (quat., Gluγ-CO); m/z (EI+) 342.1653 ($M^+ - CF_3CO_2$ $C_{15}H_{24}N_3O_6$ requires 342.1665).

4.1.29. Glycyl-L-2-benzylprolyl-L-glutamic acid trifluoroacetate 5. To a solution of the protected tripeptide **34** (98 mg, 0.16 mmol) in dichloromethane (4 cm^3) at room temperature was added trifluoroacetic acid (0.75 cm^3) dropwise and the reaction mixture was stirred for 3.5 h. The solution was evaporated under reduced pressure to give tripeptide **5** (82 mg, 100%) as an hygroscopic colourless solid. Tripeptide **5** was shown to be a 90:10 trans:cis mixture of conformers by ^{1}H NMR analysis (the ratio was estimated from the relative intensities of the double doublets and multiplet at δ 4.51 and 4.33, assigned to the Gluα-H protons of the major and minor conformers, respectively): mp 73–82 °C: $[\alpha]_D$ +41.0 (c 1.61 in MeOH); δ_H (300 MHz; D_2O) 1.27–1.39 (1H, m, Proγ-H_AH_B), 1.68–1.83 (1H, m, Proγ-H_AH_B), 2.07–2.42 (4H, m, Proβ-H_2 and Gluβ-H_2), 2.57 (2H, t, J=7.1 Hz, Gluγ-H_2), 2.82–2.92 (1H, m, Proδ-H_AH_B), 3.24 (1H, d, J=13.3 Hz, PhCH_AH_B), 3.50–3.59 (1H, m, Proδ-H_AH_B), 3.70 (1H, d, J=13.3 Hz, PhCH_AH_B), 3.91 (1H, d, J=16.7 Hz, Glyα-H_AH_B), 4.09 (1H, d, J=16.7 Hz, Glyα-H_AH_B), 4.33* (0.1H, m, Gluα-H), 4.51 (0.9H, dd, J=4.8, 9.6 Hz, Gluα-H) and 7.21–7.44 (5H, m, PhH); δ_C (100 MHz; D_2O) 25.0 (CH_2, Proγ-C), 27.9 (CH_2, Gluβ-C), 32.5 (CH_2, Gluγ-C), 37.7 (CH_2, Proβ-C), 39.2 (CH_2, PhCH_2), 43.5 (CH_2, Glyα-C), 50.6 (CH_2, Proδ-C), 54.9 (CH, Gluα-C), 56.0* (CH, Gluα-C), 73.8 (quat., Proα-C), 117.0 (quat., CF_3), 129.6 (CH, Ph), 131.1 (CH, Ph), 132.9 (CH, Ph), 138.3 (quat., Ph), 165.4 (quat., CF_3CO_2), 167.7 (quat., Gly-CO), 177.2 (quat., Pro-CON), 178.0 (quat., Gluα-CO) and 179.7 (quat., Gluγ-CO); m/z (FAB+) 392.1817 ($M^+ - CF_3CO_2$ $C_{19}H_{26}N_3O_6$ requires 392.1822).

4.1.30. Dibenzyl (2*S*,5′*R*,8′*R*)- and (2*S*,5′*R*,8′*S*)-[1′-(2″-benzyloxycarbonylamino-acetyl)-8′-hydroxy-6′-oxo-1′,7′-diazaspiro[4.4]non-7′-yl]-1,5-pentanedioate 38. Alkene **32** (96 mg, 0.15 mmol) was dissolved in dry dichloromethane–methanol (6 cm^3, 1/1) and the solution cooled to −78 °C. A slow stream of ozone was bubbled through the solution for 15 min, followed by O_2 to remove excess ozone. Triphenylphosphine (57.5 mg, 0.22 mmol) was added and the resulting mixture vigorously stirred for 24 h, then a small amount of silica was added to the reaction mixture (containing aldehyde **37**) and the solvent removed under reduced pressure. The resulting residue was purified by flash column chromatography (100% ethyl acetate) to afford hydroxyspirolactam **38** (61 mg, 63%) as a pale yellow oil. Hydroxyspirolactam **38** was shown to be a 7:3 mixture of diastereomers by ^{1}H NMR analysis. The ratio was estimated from the relative intensities of the multiplet at δ 4.76–4.79 and the doublet of doublets at δ 5.00, assigned to the 2-H protons of the minor and major isomers, respectively) with the isomers being inseparable: $[\alpha]_D$ −44.4 (c 0.90 in MeOH); ν_{max} (film)/cm^{-1} 3410, 3064, 3034, 2953, 2881, 2083, 1718, 1649, 1498, 1454, 1332, 1267, 1215, 1170, 1121, 1082, 1048, 1028, 1003, 984, 909, 776, 736 and 698; δ_H (400 MHz; $CDCl_3$) 1.74–1.77[1] (0.3H, m, 9′-H_AH_B), 1.93–2.04 (1.3H, m, 9′-H_AH_B and 3′-H_A*H_B), 2.11–2.39 [4.4H, m, 4′-H_AH_B, 3′-H_AH_B, 3-H_AH_B and 3-H_AH_B(major)], 2.42–2.66 (3.3H, m, 3-H_AH_B*, 4-H_2 and 4′-H_AH_B), 2.76 (0.7H, dd, J=12.9, 6.1 Hz, 9′-H_AH_B), 3.46–3.58 (2H, m, 2′-H_2), 3.80–3.85* (0.3H, obscured, 2″-H_AH_B), 3.87 (0.7H, dd, J=17.5, 3.3 Hz, 2″-H_AH_B), 4.02 (0.7H, dd, J=17.5, 5.1 Hz, 2″-H_AH_B), 3.99–4.05* (0.3H, obscured, 2″-H_AH_B), 4.69 (1H, s, OH), 4.76–4.79* (0.3H, m, 2-H), 5.00 (0.7H, dd, J=10.8, 4.8 Hz, 2-H), 5.09–5.21 (6H, m, 3×OCH_2Ph), 5.25* (0.3H, dd, J=12.3, 7.1 Hz, 8′-H), 5.42 (0.7H, dd, J=6.0, 2.4 Hz, 8′-H), 5.48* (0.3H, m, NH), 5.58–5.59 (0.7H, m, NH) and 7.27–7.39 (15H, m, 3× Ph); δ_C (100 MHz; $CDCl_3$) 24.1* (CH_2, 3-C), 24.2 (CH_2, 3-C), 24.5 (CH_2, 3′-C), 25.3* (CH_2, 3′-C), 30.2 (CH_2, 4′-C), 30.7* (CH_2, 4′-C), 37.9 (CH_2, 4-C), 39.4 (CH_2, 9-C), 39.7* (CH_2, 9-C), 43.0* (CH_2, 2″-C), 43.7 (CH_2, 2″-C), 47.0 (CH_2, 2-C), 47.7* (CH_2, 2-C), 54.3 (CH, 2′-C), 54.7* (CH, 2′-C), 65.6* (quat., 5-C), 66.2* (CH_2, OCH_2Ph), 66.4 (CH_2, OCH_2Ph), 66.8 (CH_2, OCH_2Ph), 67.0* (CH_2, OCH_2Ph), 67.2* (CH_2, OCH_2Ph), 67.3 (CH_2, OCH_2Ph), 68.1 (quat., 5-C), 77.7 (CH, 8-C), 80.6* (CH, 8-C), 128.05 (CH, Ph), 128.09 (CH, Ph), 128.2 (CH, Ph), 128.4 (CH, Ph), 128.5 (CH, Ph), 128.6 (CH, Ph), 128.7 (CH, Ph), 134.5 (quat., Ph), 135.3* (quat., Ph), 135.8 (quat., Ph), 136.0* (quat., Ph), 136.4 (quat., Ph), 156.1 (quat., NCO_2), 166.0 (quat., 1″-C), 167.1* (quat., 1″-C), 170.1* (quat., 1′-C), 172.5 (quat., 1′-C), 172.7* (quat., 5′-C), 173.6 (quat., 5′-C), 173.8* (quat., 6-C) and 175.1 (quat., 6-C); m/z (FAB+) 658.2749 (MH^+ $C_{36}H_{40}N_3O_9$ requires 658.2765).

4.1.31. Dibenzyl (2*S*,5′*R*)-[1′-(2″-benzyloxycarbonyl-amino-acetyl)-6′-oxo-1′,7′-diazaspiro[4.4]non-7′-yl]-1,5-pentanedioate 39. A solution of hydroxyspirolactam **38** (33 mg, 0.05 mmol) in trifluoroacetic acid–triethylsilane–dichloromethane (1.0 cm^3, 1/1/1), at room temperature, was stirred for 45 min then concentrated in vacuo to give an opaque white oil, which was purified by flash column chromatography (100% ethyl acetate) to afford spirolactam **39** (31 mg, 96%) as a colourless oil: $[\alpha]_D$ −18.0 (*c* 0.67 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 3583, 3412, 3032, 2952, 1734, 1654, 1497, 1454, 1432, 1289, 1259, 1215, 1171, 1048, 982, 738 and 698; δ_H (300 MHz; $CDCl_3$) 1.76–2.19 (6H, m, 9′-H_AH_B, 4′-H_2, 3′-H_AH_B and 3-H_2), 2.31–2.63 (4H, m, 9′-H_AH_B, 3′-H_AH_B and 4-H_2), 3.31 (1H, dd, *J*=16.8, 8.1 Hz, 8′-H_AH_B), 3.40–3.47 (1H, m, 8′-H_AH_B), 3.51–3.55 (2H, m, 2′-H_2), 3.86 (1H, dd, *J*=17.1, 3.3 Hz, 2″-H_AH_B), 4.05 (1H, dd, *J*=17.1, 5.4 Hz, 2″-H_AH_B), 4.90 (1H, dd, *J*=11.3, 4.5 Hz, 2-H), 5.07–5.18 (6H, m, 3×OCH_2Ph), 5.63 (1H, br s, N–H) and 7.27–7.34 (15H, m, 3Ph); δ_C (75 MHz; $CDCl_3$) 23.4 (CH_2, 3′-C), 24.0 (CH_2, 3-C), 29.8 (CH_2, 9′-C), 30.4 (CH_2, 4-C), 36.2 (CH_2, 4′-C), 39.8 (CH_2, 8′-C), 43.7 (CH_2, 2″-C), 47.1 (CH_2, 2′-C), 53.8 (CH, 2-C), 66.3 (CH_2, OCH_2Ph), 66.9 (CH_2, OCH_2Ph), 67.2 (CH_2, OCH_2Ph), 68.2 (quat., 5-C), 128.0 (CH, Ph), 128.05 (CH, Ph), 128.1 (CH, Ph), 128.3 (CH, Ph), 128.49 (CH, Ph), 128.5 (CH, Ph), 128.7 (CH, Ph), 135.2 (quat., Ph), 136.0 (quat., Ph), 136.5 (quat., Ph), 156.2 (quat., NCO_2), 166.1 (quat., 1″-C), 170.1 (quat., 1-C), 172.7 (quat., 5-C) and 174.4 (quat., 6′-C); *m*/*z* (FAB+) 642.2802 (MH^+ $C_{36}H_{40}N_3O_8$ requires 642.2815).

4.1.32. (2*S*,5′*R*)-[1′-(2″-amino-acetyl)-6′-oxo-1′,7′-diazaspiro[4.4]non-7′-yl]-1,5-pentanedioic acid 35. A mixture of protected spirolactam **39** (30 mg, 0.047 mmol) and 10% palladium on activated carbon (9.6 mg, 0.09 mmol) in 88:12 methanol–water (6.6 cm^3) was stirred under an atmosphere of hydrogen at room temperature, protected from light, for 18 h. The reaction mixture was filtered through a Celite™ pad with 75:25 methanol–water (30 cm^3), and the filtrate concentrated to dryness under reduced pressure to give a yellow solid that was purified by reverse-phase C18 flash column chromatography (H_2O) to afford spirolactam **35** (12 mg, 78%) as a colourless solid: mp 238–239 °C (dec.): $[\alpha]_D$ −23.5 [*c* 1.15 in MeOH–H_2O (1/1)]; δ_H (400 MHz; D_2O) 1.97–2.61 (10H, m, 9′-H_2, 4′-H_2, 3′-H_2, 3-H_2 and 4-H_2), 3.44–3.78 (4H, br m, 8′-H_2 and 2′-H_2) 3.81–4.12 (2H, br m, 2″-H_2) and 4.41 (1H, m, 2-H); δ_C (100 MHz; D_2O) 25.8 (CH_2, 3′-C), 27.8 (CH_2, 3-C), 31.4 (CH_2, 9′-C), 37.3 (2×CH_2, 4′-C and 4-C), 43.1 (2×CH_2, 8′-C and 2″-C), 50.1 (CH_2, 2′-C), 60.2 (CH, 2-C), 72.5 (quat., 5′-C), 173.6 (quat., 1″-C), 178.9 (quat., 6′-C) 179.1 (quat., 1-C) and 184.9 (quat., 5-C); *m*/*z* (FAB+) 328.1521 (MH^+ $C_{14}H_{21}N_3O_6$ requires 328.1509).

4.1.33. (2*S*,5′*R*,8′*R*)- and (2*S*,5′*R*,8′*S*)-[1′-(2″-amino-acetyl)-8′-hydroxy-6′-oxo-1′,7′-diazaspiro[4.4]non-7′-yl]-1,5-pentanedioic acid 36. A mixture of protected hydroxyspirolactam **38** (27 mg, 0.041 mmol) and 10% palladium on activated carbon (8.4 mg, 0.079 mmol) in 88:12 methanol–water (5.8 cm^3) was stirred under an atmosphere of hydrogen at room temperature, protected from light, for 18 h. The reaction mixture was filtered through a Celite™ pad with 75:25 methanol–water (30 cm^3) and the filtrate concentrated to dryness under reduced pressure to afford spirolactam **36** (14 mg, 99%) as a colourless solid. Spirolactam **36** was shown to be a 7:3 mixture of two diastereomers by ^1H NMR analysis (the ratio was estimated from the relative intensities of the doublet of doublets at δ 4.47 and 4.53, assigned to 2-H of the minor and major isomers, respectively): mp 216–218 °C (dec.): $[\alpha]_D$ +0.86 [*c* 0.35 in MeOH–H_2O (1:1)]; δ_H (400 MHz; D_2O) 2.10–2.46 (9H, m, 9′-H_AH_B, 4′-H_2, 3′-H_2, 3-H_2 and 4-H_2), 2.65* (0.3H, dd, *J*=13.8, 7.0 Hz, 9′-H_AH_B), 2.75 (0.7H, dd, *J*=13.6, 6.2 Hz, 9′-H_AH_B), 3.55–3.61 (1H, m, 2′-H_AH_B), 3.69–3.73 (1H, m, 2′-H_AH_B), 3.94–4.09 (2H, d, *J*=16.5 Hz, 2″-H_2), 4.47* (0.3H, dd, *J*=9.9, 5.8 Hz, 2-H), 4.53 (0.7H, dd, *J*=10.4, 5.0 Hz, 2-H), 5.49* (0.3H, dd, *J*=6.8, 5.1 Hz, 8′-H) and 5.59 (0.7H, d, *J*=6.1 Hz, 8′-H); δ_C (100 MHz; D_2O) 26.0* (CH_2, 3′-C), 26.1 (CH_2, 3′-C), 27.4 (CH_2, 3-C), 29.6* (CH_2, 3-C), 39.3* (CH_2, 4-C), 40.1 (CH_2, 4-C), 40.7 (2×CH_2, 4′-C and 9′-C), 42.2* (CH_2, 9′-C), 43.1 (CH_2, 2″-C), 49.8 (CH_2, 2′-C), 49.9* (CH_2, 2′-C), 60.2* (CH, 2-C), 60.7 (CH, 2-C), 70.1* (quat., 5′-C), 70.9 (quat., 5′-C), 80.6 (CH, 8′-C), 83.2* (CH, 8′-C), 166.9 (quat., 1″-C), 167.1* (quat., 1″-C), 178.2* (quat., 6′-C), 179.7 (2×quat., 1-C and 6′-C), 180.4 (quat., 1-C), 182.5 (quat., 5-C) and 182.8* (quat., 5-C); *m*/*z* (FAB+) 344.1467 (MH^+ $C_{14}H_{22}N_3O_7$ requires 344.1458).

4.1.34. Methyl *N*-*tert*-butyloxycarbonyl-(D,L)-5,5-dimethylprolinate 43.[49] Nitrile **44**[49,55] (2 g, 14.3 mmol) was dissolved in 32% hydrochloric acid (6 cm^3) and heated to 50 °C for 5 h. Evaporation of the solvent afforded a residue that was dissolved in methanol–water (1/1, 30 cm^3) and hydrogenated over 10% palladium on activated carbon (0.3 g) under 44 psi of hydrogen for 20 h. The catalyst was removed by filtration through Celite™ and the solvent removed in vacuo to yield a 6:4 mixture of *N*-methyl-5-methylproline* **45**, and the desired 5,5-dimethylproline **46**; δ_H (300 MHz; D_2O) 1.34–1.40 (8.6H, m, 4×CH_3), 1.67–1.74 (1.3H, m) 1.91 (1.6H, t, *J*=12.2 Hz), 2.07–2.32 (3.5H, m), 2.40–2.54 (2H, m), 2.90* (3.6H, s, *N*-CH_3), 3.45–3.53 (1.3H, m), 4.23* (1.3H, dd, *J*=9.7, 7.5 Hz, Proα-H) and 4.47 (1H, d, *J*=8.4 Hz, Proα-H); δ_C (75 MHz; D_2O) 14.6* (CH_3), 24.5 (CH_3), 24.7 (CH_3), 25.9* (CH_2), 27.2 (CH_2), 29.9* (CH_2), 37.0 (CH_2), 39.1* (CH_3, *N*-CH_3), 58.9* (CH, Proδ-C), 67.1 (quat., Proδ-C), 67.6* (CH, Proα-C), 69.2 (CH, Proα-C), 171.5* (quat., Proα-CO) and 172.4 (quat., Proα-CO). The mixture was subsequently dissolved in dry methanol (60 cm^3), cooled to 0 °C and thionyl chloride (4.2 cm^3, 57.2 mmol) was added dropwise over 5 min. The reaction was allowed to warm to room temperature and stirred overnight. The solvent was removed, the residue was dissolved in saturated sodium hydrogen carbonate solution and the products extracted with chloroform to yield a mixture of inseparable methyl esters (1.53 g), which were dissolved in dry dichloromethane (20 cm^3). *N*-Methylmorpholine (1.56 cm^3, 14.2 mmol) and di-*tert*-butyldicarbonate (3.1 g, 14.2 mmol) were added and the reaction was heated at reflux under nitrogen for 48 h. After cooling to room temperature the reaction mixture was washed with water, 1 M aqueous hydrochloric acid (2×30 cm^3), brine and dried ($MgSO_4$). The aqueous layer was concentrated in vacuo to give methyl *N*-methyl-5-methylprolinate **47** (1.093 g, 42%, four steps) as its hydrochloride salt. This was neutralized with saturated sodium hydrogen carbonate and purified by chromatography (silica gel, 4:1,

dichloromethane/ethyl acetate); δ_H (200 MHz; $CDCl_3$; Me_4Si) 1.06 (3H, d, $J=6.0$ Hz, Proδ-CH_3), 1.35–1.55 (1H, m), 1.70–2.01 (3H, m), 2.17–2.27 (1H, m), 2.24 (3H, s, *N*-CH_3), 2.90 (1H, t, $J=7.8$ Hz, Proα-H) and 3.65 (3H, s, 2-CO_2CH_3); δ_C (75 MHz; $CDCl_3$) 18.2 (CH_3, Proδ-CH_3), 26.4 (CH_2), 31.3 (CH_2), 38.9 (CH_3, *N*-CH_3), 51.3 (CH_3, Proα-CO_2CH_3) 61.8 (CH, Proδ-C), 68.4 (CH, Proα-C) and 173.6 (quat., Proα-CO); *m/z* (CI+) 158.1176 (MH^+. $C_8H_{16}NO_2$ requires 158.1181); The organic layer was concentrated in vacuo and purified by chromatography (silica gel, dichloromethane then chloroform) to give methyl *N*-*tert*-butyloxycarbonyl-(D,L)-5,5-dimethylprolinate **43** (0.795 g, 22%, four steps) as a yellow oil. This compound existed as a mixture of epimers (55:45) almost exclusively as the cis conformer; δ_H (300 MHz; $CDCl_3$) 1.26–1.53 [15H, m, $C(CH_3)_2$, $C(CH_3)_3$], 1.60–1.90 (4H, m, Proβ-H_2 and Proγ-H_2), 3.66 (3H, CO_2CH_3), 4.24 (0.55H, dd $J=8.9$, 3.5 Hz, Proα-H) and 4.35 (0.45H, dd $J=8.5$, 2.6 Hz, Proα-H); δ_C (75 MHz; $CDCl_3$) 25.7 (CH_3, Proδ-CH_3), 25.9 (CH_2, Proγ-C), 26.0 (CH_3, Proδ-CH_3), 26.5 (CH_2, Proγ-C), 26.6 (CH_3, Proδ-CH_3), 27.2 (CH_3, Proδ-CH_3), 28.2 [CH_3, $C(CH_3)_3$], 28.3 [CH_3, $C(CH_3)_3$], 39.8 (CH_2, Proβ-C), 40.7 (CH_2, Proβ-C), 51.6 (CH_3, Proα-CO_2CH_3), 51.7 (CH_3, Proα-CO_2CH_3), 60.5 (quat., Proδ-C), 61.16 (CH, Proα-C), 61.2 (CH, Proα-C), 61.3 (quat., Proδ-C), 79.1 [quat., $C(CH_3)_3$], 79.6 [quat., $C(CH_3)_3$], 152.4 (quat., NCO_2), 154.0 (quat., NCO_2), 173.4 (quat., Proα-CO) and 173.8 (quat., Proα-CO); *m/z* (EI+) 257.1624 (M^+ $C_{13}H_{23}NO_4$ requires 257.1627).

4.1.35. *N*-*tert*-Butyloxyglycyl-L-4-thiaproline 52. *iso*-Butyl chloroformate (0.154 g, 1.12 mmol) was added to a stirred solution of *N*-*tert*-butyloxycarbonylglycine **17** and triethylamine (0.215 g, 1.15 mmol) in tetrahydrofuran (6 cm^3) at 0 °C. A white precipitate was observed, the cooling bath was removed and the mixture stirred at room temperature for 10 min. A solution of 4-thiaproline hydrochloride **40**[44] (0.150 g, 1.12 mmol) and triethylamine (0.215 g, 1.15 mmol) in water (2 cm^3) was added and the resultant solution was stirred for 1 h. The mixture was acidified with 2 M HCl and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo to yield an oil (0.39 g) that was purified by flash chromatography (hexane/ethyl acetate/acetic acid 2:1:0.3 then 1:1:0.2) gave dipeptide **52** (0.264 g, 81%) as a hygroscopic white foam. **52** was shown to be a 62:38 trans:cis mixture of conformers by ^1H NMR analysis (the ratio was estimated from the integration of the GlyN–H protons at δ 5.65 and 5.75 assigned to major and minor conformers, respectively): $[\alpha]_D$ −93.5 (*c* 0.25 in CH_2Cl_2); δ_H (400 MHz; $CDCl_3$) 1.43[2] [3.4H, s, $C(CH_3)_3$], 1.44 [5.6H, s, $C(CH_3)_3$], 3.31 (1.24H, d, $J=5.1$ Hz, 3-H_AH_B), 3.37* (0.38H, dd, $J=11.8$, 5.2 Hz, 3-H_AH_B), 3.49* (0.38H, dd, $J=11.7$, 1.4 Hz, 3-H_AH_B), 3.90–4.20 (2H, m, Glyα-H_2), 4.55–4.62 (1.62H, m 5-H_2, *5-H_AH_B), 4.79* (0.38H, d, $J=9.7$ Hz, 5-H_AH_B), 4.86* (0.38H, d, $J=5.7$ Hz, 2-H), 5.11 (0.62H, t, $J=4.9$ Hz, 2-H), 5.65 (0.62H, br s, GlyN–H) and 5.75* (0.38H, br s, GlyN–H); δ_C (100 MHz; $CDCl_3$) 28.2 [CH_3, $C(CH_3)_3$], 32.3 (CH_2, 3-C), 34.4* (CH_2, 3-C), 43.1 (CH_2, Glyα-C), 43.4* (CH_2, Glyα-C), 47.6 (CH_2, 5-C), 48.9* (CH_2, 5-C), 60.7* (CH, 2-C), 61.6 (CH, 2-C), 80.3* [quat., $C(CH_3)_3$], 80.7 [quat., $C(CH_3)_3$], 156.1 (quat., NCO_2), 156.4* (quat., NCO_2), 167.8 (quat., Gly-CO), 168.0* (quat., Gly-CO), 171.6 (quat., 2-CO) and 172.0* (quat., 2-CO); *m/z* (EI+) 290.0938 (M^+ $C_{11}H_{18}N_2O_5S$ requires 290.0936).

4.1.36. Di-*tert*-Butyl *N*-*tert*-butyloxycarbonylglycyl-L-4-thiaprolyl-L-glutamate 56. Ethyl chlorofomate (0.048 g, 0.445 mmol) was added dropwise to a solution of acid **52** (0.129 g, 0.445 mmol) and triethylamine (0.050 g, 0.49 mmol) in dichloromethane (3 cm^3) at 0 °C. The solution was stirred for 35 min at 0 °C then a solution of glutamic acid di-*tert*-butyl ester hydrochloride **29** (0.132 g, 0.445 mmol) and triethylamine (0.050 g, 0.49 mmol) in dichloromethane (3 cm^3) was added. The mixture was stirred overnight, washed successively with 2 M aqueous hydrochloric acid, saturated sodium hydrogen carbonate solution, dried (Na_2SO_4), filtered and the solvent removed. Purification by flash chromatography (dichloromethane/ethyl acetate, 3:1) afforded protected tripeptide **56** (0.128 g, 54%) as a colourless solid. **56** was shown to be a 66:34 trans:cis mixture of conformers by ^1H NMR analysis (the ratio was estimated from the integration of the thiaProN–H protons at δ 7.20 and 7.43 assigned to major and minor conformers, respectively): mp 99–100 °C: $[\alpha]_D$ −70 (*c* 0.6 in CH_2Cl_2); δ_H (400 MHz; $CDCl_3$) 1.25–1.45 [27H, m, $C(CH_3)_3$], 1.80–1.95 (1H, m, Gluβ-H_AH_B), 1.97–2.14 (1H, m, Gluβ-H_AH_B), 2.18–2.35 (2H, m, Gluγ-H_2), 3.14 (0.66H, dd, $J=11.2$, 7.0 Hz, 3-H_AH_B), 3.22–3.35[3] (0.34H, br m, 3-H_AH_B), 3.38 (1H, dd, $J=12.3$, 3.6 Hz, 3-H_AH_B), 3.85–4.05 (2H, m, Glyα-H_2), 4.38 (1H, br t, $J=4.8$ Hz, Gluα-H), 4.49–4.57 (1.66H, 5-H_AH_B and *5-H_AH_B), 4.69–4.77* (0.72H, *5-H_AH_B and *2-H), 4.98 (0.66H, br s, 2-H), 5.51 (1H, br s, GlyN–H), 7.20 (0.66H, d, $J=7.2$ Hz, thiaProN–H), 7.20* (0.34H, br s, thiaProN–H); δ_C (100 MHz; $CDCl_3$) 26.4* (CH_2, Gluβ-C), 27.1 (CH_2, Gluβ-C), 27.8 [CH_3, $C(CH_3)_3$], 27.9 [CH_3, $C(CH_3)_3$], 28.2 [CH_3, $C(CH_3)_3$], 31.3 (CH_2, Gluγ-C), 32.2 (CH_2, 3-C), 35.4* (CH_2, 3-C), 43.2 (CH_2, Glyα-C), 43.5* (CH_2, Glyα-C), 48.2 (CH_2, 5-C), 49.7* (CH_2, 5-C), 52.5 (CH, Gluα-C), 62.3* (CH, 2-C), 62.5 (CH, 2-C), 79.7 [quat., $C(CH_3)_3$], 80.6 [quat., $C(CH_3)_3$], 80.9* [quat., $C(CH_3)_3$], 82.1 [quat., $C(CH_3)_3$], 82.2* [quat., $C(CH_3)_3$], 155.7 (quat., NCO_2), 167.9 (quat., Gly-CO), 168.6* (quat., 2-CO), 168.9 (quat., 2-CO), 170.4 (quat., Gluα-CO) and 172.4 (quat., Gluγ-CO); *m/z* (FAB+) 532.2628 (MH^+ $C_{24}H_{42}N_3O_8S$ requires 532.2693).

4.1.37. Glycyl-L-4-thiaprolyl-L-glutamic acid trifluoroacetate 48. Trifluoroacetic acid (1 cm^3) was added to a stirred solution of protected tripeptide **56** (0.128 g, 0.241) and triethylsilane (0.084 g, 0.723 mmol) in dichloromethane (3 cm^3). The resultant solution was stirred for 4 h at room temperature and the volatiles removed in vacuo. Purification of the residue by chromatography (reverse phase C_{18}, water, 10–20% acetonitrile/water) and lyophilisation gave **48** (0.066 g, 61%) as a hygroscopic off white solid. **48** was shown to be a 80:20 trans:cis mixture of conformers by ^1H NMR analysis (the ratio was estimated from the integration of the Glyα protons at δ 3.80–3.92 and 3.58 assigned to major and minor conformers, respectively): no mp due to hygroscopic sample: $[\alpha]_D$ −88.6 (*c* 0.203 in H_2O); δ_H (400 MHz; D_2O) 1.73–1.82 (1H, m, Gluβ-H_AH_B), 1.96–2.06 (1H, m, Gluβ-H_AH_B), 2.28 (2H, t, $J=6.9$ Hz, Gluγ-H_2), 2.96 (0.8H, dd, $J=12.4$, 3.7 Hz, 3-H_AH_B), 3.13* (0.2H, d, 12.2, 3-H_AH_B), 3.20 (0.8H, dd, $J=12.4$, 7.3 Hz,

3-H_AH_B), 3.27* (0.2H, dd, J=12.4, 6.9 Hz, 3-H_AH_B), 3.58 (0.2H, d, J=16.4 Hz, Glyα-H_AH_B), 3.80–3.92 (1.8H, m, Glyα-H_2 and *Glyα-H_AH_B), 4.25 (0.8H, dd, 9.4 and 4.8, Gluα-H), 4.30* (0.2H, dd, 10.0 and 4.8, Gluα-H), 4.35–4.49 (2H, m, 5-H_2) and 4.67 (1H, dd, J=6.9 Hz, 3.8 Hz, 2-H); δ_C (100 MHz; $CDCl_3$) 24.8* (CH_2, Gluβ-C), 25.3 (CH_2, Gluβ-C), 29.5 (CH_2, Gluγ-C), 29.8* (CH_2, Gluγ-C), 32.8 (CH_2, 3-C), 34.9* (CH_2, 3-C), 40.3 (CH_2, Glyα-C), 40.5* (CH_2, Glyα-C), 48.4 (CH_2, 5-C), 49.6* (CH_2, 5-C), 51.7 (CH, Gluα-C), 51.9* (CH, Gluα-C), 61.6* (CH, 2-C), 62.6 (CH, 2-C), 115.7 (quat., q, J=290.7 Hz, CF_3CO_2H), 161.9 (quat., q, J=36.2 Hz, CF_3CO_2H), 165.0 (quat., Gly-CO), 165.6* (quat., Gly-CO), 171.0* (quat., 2-CO), 171.5 (quat., 2-CO), 174.0* (quat., Gluα-CO), 174.1* (quat., Gluα-CO) and 176.7 (quat., Gluγ-CO); m/z (FAB+) 320.0921 [M(free base)H^+ $C_{11}H_{18}N_3O_6S$ requires 320.0916].

4.1.38. *N*-Benzyloxycarbonylglycyl-L-thia-5,5-dimethylproline 53. To a stirred solution of 5,5,-dimethyl-4-thiaproline hydrochloride **41**[45,46] (0.354 g, 1.79 mmol) under nitrogen in dry dimethylformamide (35 cm^3) was added diisopropylethylamine (0.594 cm^3, 1.9 mmol) and acid fluoride **51**[56,57](0.341 g, 1.61 mmol). The solution was stirred for 18 h, the solvent was removed in vacuo and the residue was redissolved in ethyl acetate, washed with 10% citric acid solution, brine and dried ($MgSO_4$). The solvent was removed and the residue purified by flash chromatography (4:1:0.5, ethyl acetate/hexane/acetic acid, then 3:1.0.4) to give the desired compound contaminated with *N*-benzyloxycarbonylglycine **16** (14%, ^{1}H NMR). This mixture was dissolved in methanol, trimethylsilyl chloride (0.07 cm^3) added and the solution stirred overnight. Removal of the solvent in vacuo and subsequent flash chromatography (3:1, ethyl acetate/hexane [to remove *N*-benzyloxycarbonylglycine methyl ester] then 3:1.0.4 ethyl acetate/hexane/acetic acid) gave dipeptide **53** (0.320 g, 65%, based on amount of acid fluoride reacted) as a white solid. This compound existed purely as the cis conformer: mp 130–132 °C: $[\alpha]_D$ −51.7 (c 0.116 in dichloromethane); δ_H (300 MHz; $CDCl_3$) 1.85 (3H, s, [†]Pδ-CH_3) 1.91 (3H, s, Pδ-CH_3), 3.30 (1H, dd, J=12.1, 5.6 Hz, Pβ-H_AH_B), 3.40 (1H, d, J=12.1 Hz, Pβ-H_AH_B), 3.87 (1H, dd, J=16.6, 3.7 Hz, Glyα-H_AH_B), 4.09 (1H, dd, J=16.6, 3.7 Hz, Glyα-H_AH_B), 4.82 (1H, d, J=5.2 Hz, Pα-H), 5.13 (2H, s, OCH_2Ph), 6.10 (1H, br t, J=3.8 Hz, GlyN–H) and 7.29–7.39 (5H, m, Ph); δ_C (75 MHz; $CDCl_3$) 27.0 (CH_3, Pδ-CH_3) 29.4 (CH_3, Pδ-CH_3), 31.6 (CH_2, Pβ-C), 44.8 (CH_2, Glyα-C), 64.3 (CH, Pα-C), 67.3 (CH_2, OCH_2Ph), 74.2 (quat., Pδ-C), 127.9 (CH, Ph), 128.1 (CH, Ph), 128.4 (CH, Ph), 135.8 (quat., Ph), 156.8 (quat., NCO_2), 166.6 (quat., Gly-CO) and 172.0 (quat., Pα-CO); m/z (EI+) 352.1088 (M^+ $C_{16}H_{20}N_2O_5S$ requires 352.1093).

4.1.39. Dibenzyl *N*-benzyloxycarbonyl-glycyl-L-thia-5,5-dimethylprolyl-L-glutamate 57. To a stirred solution of dipeptide **53** (0.398 g, 1.11 mol), L-glutamic acid dibenzyl ester *p*-toluenesulfonate **28** (0.670 g, 1.34 mol) and diisopropylethylamine (0.51 cm^3, 2.90 mmol) in dry dichloromethane (40 cm^3) was added bis(2-oxo-3-oxazolidinyl)phosphinic chloride (0.370 g, 1.45 mmol) in one portion. The solution was stirred for 7 h under nitrogen and the solvent removed. The residue was suspended in ethyl acetate, washed with 10% citric acid solution, saturated sodium hydrogen carbonate, brine and dried ($MgSO_4$). Removal of the solvent and subsequent chromatography (2:1, hexane/ethyl acetate, then 1:1) gave protected tripeptide **57** (0.5 g, 68%) as a colourless oil. Protected tripeptide **57** was shown to be a 90:10 cis:trans mixture of conformers by ^{1}H NMR analysis (the ratio was estimated from the integration of the broad singlets at δ 5.69 and 5.80 and assigned to the GlyN–H protons of the major and minor conformers, respectively): $[\alpha]_D$ −35.6 (c 0.399 in dichloromethane); δ_H (300 MHz; $CDCl_3$) 1.85 (3H, Pδ-CH_3) 1.97 (3H, Pδ-CH_3), 2.08–2.15 (1H, m, Gluβ-H_AH_B), 2.29–2.38 (1H, m, Gluβ-H_AH_B), 2.47 (2H, t, J=5.4 Hz, Gluγ-H_2), 3.32 (2H, m, Pβ-H_2), 3.85 (1H, d, J=16.6 Hz, Glyα-H_AH_B), 3.91 (1H, dd, J=17.0, 8.0 Hz, Glyα-H_AH_B), 4.72 (2H, br s, Pα-H, Gluα-H), 5.20–5.08 (6H, m, 3×OCH_2Ph), 5.69 (0.9H, br s, Gly-NH), 5.80* (0.1H, br s, Gly-NH) and 7.33–7.39 (15H, m, Ph); δ_C (75 MHz; $CDCl_3$) 26.3 (CH_2, Gluβ-C), 26.45* (CH_2, Gluβ-C), 27.21* (CH_3, Pδ-CH_3), 27.43 (CH_3, Pδ-CH_3), 28.4 (CH_3, Pδ-CH_3), 29.91 (CH_2, Gluγ-C), 30.09* (CH_2, Gluγ-C), 32.3 (CH_2, Pβ-C), 44.7 (CH_2, Glyα-C), 45.1* (CH_2, Glyα-C), 52.1 (CH, Gluα-C), 52.3* (CH, Gluα-C), 65.8 (CH, Pα-H), 66.4 (CH_2, OCH_2Ph), 66.8 (CH_2, OCH_2Ph), 67.4 (CH_2, OCH_2Ph), 74.5 (quat., Pδ-C), 127.8 (CH, Ph), 127.9 (CH, Ph), 128.1, (CH, Ph), 128.14 (CH, Ph), 128.2 (CH, Ph), 128.3 (CH, Ph), 128.5 (CH, Ph), 134.8 (quat., Ph), 135.5 (quat., Ph), 136.2 (quat., Ph), 156.4 (quat., NCO_2), 167.1 (quat., Gly-CO), 169.6 (quat., P-CON), 170.9 (quat., Gluα-CO) and 172.7 (quat., Gluγ-CO); m/z (FAB+) 662.2536 (MH^+ $C_{35}H_{40}N_3O_8S$ requires 662.2536).

4.1.40. Glycyl-L-thia-5,5-dimethylprolyl-L-glutamic acid 49. Protected tripeptide **57** (0.44 g, 0.66 mmol) was dissolved in methanol–water (4/1, 50 cm^3), placed in a Parr bottle. The vessel was flushed with nitrogen, 10% palladium on activated carbon (70 mg, 0.066 mmol) was added and the mixture was pressurized to 40 psi with hydrogen and shaken for 3 h. Further 10% palladium on activated carbon (70 mg) was added and the reaction continued for 21 h. The reaction mixture was filtered through Celite,™ washed with methanol–water (4/1) and the solvent removed to yield an oil, which by TLC and ^{1}H NMR analysis contained the desired product and products containing varying amounts of debenzylation. The mixture was dissolved in water and passed through a C_{18} column eluting with water, then 10% methanol–water. The relevant fractions were combined, the solvent removed and the residue was triturated with dry ether to yield tripeptide **49** (0.110 g, 48%) as a white solid. Tripeptide **49** was shown to be a 85:15 cis:trans mixture of conformers by ^{1}H NMR analysis (the ratio was estimated from the integration of the doublets at δ 4.95 and 5.02 and assigned to the Pα-H protons of the major and minor conformers, respectively): mp 145–150 °C: $[\alpha]_D$ −75 (c 0.064 in water); δ_H (300 MHz; D_2O) 1.84 (2.55H, s, Pδ-CH_3). 1.90* (0.45H, s, Pδ-CH_3) 1.93 (3H, s, Pδ-CH_3), 1.96–2.05 (1H, m, Gluβ-H_AH_B), 2.18–2.27 (1H, m, Gluβ–H_AH_B), 2.42 (2H, t, J=7.5 Hz, Gluγ-H_2), 3.36 (1H, d, J=12.7 Hz, Pβ-H_AH_B) 3.59 (1H, dd, J=12.8, 6.4 Hz, Pβ-H_AH_B),, 3.70 (1H, d, J=16.2 Hz, Glyα-H_AH_B), 4.01 (1H, d, J=16.3 Hz, Glyα-CH_AH_B), 4.23* (0.15H, dd, J=9.1, 4.9 Hz, Gluα-H), 4.32 (0.85H, dd, J=9.1, 4.9 Hz,

[†] P refers to the proline analogue portion in question.

Gluα-H), 4.95 (0.85H, d, $J=6.2$ Hz, Pα-H) and 5.02* (0.15H, d, $J=6.0$ Hz, Pα-H); δ_C (75 MHz; D_2O) 26.1* (CH_3, Pδ-CH_3), 26.3 (CH_3, Pδ-CH_3), 26.56 (CH_2, Gluβ-C), 27.6 (CH_3, Pδ-CH_3), 27.9* (CH_3, Pδ-CH_3), 31.1 (CH_2, Gluγ-C), 30.3* (CH_2, Gluγ-C), 32.1 (CH_2, Pβ-C), 32.3* (CH_2, Pβ-C), 41.1* (CH_2, Glyα-C), 41.6 (CH_2, Glyα-C), 54.4 (CH, Gluα-C), 55.0* (CH, Gluα-C), 65.3* (CH, Pα-H), 65.5 (CH, Pα-H), 74.3* (quat., Pδ-C), 74.6 (quat., Pδ-C), 164.4* (quat., Gly-CO), 164.6 (quat., Gly-CO), 170.5 (quat., P-CON), 170.8* (quat., P-CON), 176.9 (quat., Gluα-CO) and 178.3 (quat., Gluγ-CO); *m/z* (FAB+) 348.1249 (MH^+ $C_{12}H_{22}N_3O_6S$ requires 348.1229).

4.1.41. Methyl *N-tert*-buyltoxycarbonylglycyl-(D,L)-5,5-dimethylprolinate 54. Trifluoroacetic acid (1 cm^3) was added to a stirred solution of carbamate **43** (0.584 g, 2.27 mmol) in dichloromethane (6 cm^3). The solution was stirred for 2 h after which time the volatiles were removed in vacuo and traces of trifluoroacetic acid were removed by placing the sample on an oil pump for 2 h. The salt was then dissolved in dichloromethane (20 cm^3) and diisopropylethylamine (1.3 cm^3, 7.49 mmol) was added (white fumes) followed by *N-tert*-butyloxycarbonylglycine **17** (0.477 g, 2.73 mmol) and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (0.691 g, 2.28 mmol). Additional dichloromethane (5 cm^3) was added and the solution was stirred overnight under nitrogen. The solvent was then removed in vacuo, the residue was dissolved in ethyl acetate and washed sequentially with 2 M aqueous hydrochloric acid, saturated sodium hydrogen carbonate and dried ($MgSO_4$). Removal of the solvent gave an oil (0.440 g) that was purified by chromatography (silica gel, hexane/ethyl acetate, 2:1, then 1:1) to give dipeptide **54** (0.368 g, 52%) as a colourless oil. Dipeptide **54** was shown to be 80:20 cis:trans mixture of conformers by ^{1}H NMR analysis (the ratio was estimated from the integration of the chemical shifts at δ 4.28 and 4.46 assigned to the Proα-H protons of the major and minor conformers, respectively); δ_H (300 MHz; $CDCl_3$) 1.26 (2.4H, s, Proδ-CH_3), 1.28 [9H, s, $C(CH_3)_3$], 1.31[5] (0.6H, s, Proδ-CH_3), 1.44* (0.6H, s, Proδ-CH_3), 1.46 (2.4H, s, Proδ-CH_3), 1.59–2.15 (4H, m, Proβ-H_2, Proγ-H_2), 3.37 (0.8H, dd, $J=16.7$, 3.3 Hz, Glyα-H_AH_B), 3.57* (0.6H, s, Proα-CO_2CH_3), 3.61 (2.4H, s, Proα-CO_2CH_3), 3.74 (0.8H, dd, $J=16.7$, 3.3 Hz, Glyα-H_AH_B), 3.84* (0.2H, dd, $J=16.9$, 3.9 Hz, Glyα-H_AH_B), 3.39–4.01* (0.2H, m, Glyα-H_AH_B), 4.28 (0.8H, d, $J=8.3$ Hz, Proα-H), 4.46* (0.2H, dd, $J=8.0$, 2.2 Hz, Proα-H) and 5.40 (1H, br s, 1H, Gly-NH); δ_H (75 MHz; $CDCl_3$) 24.5 (CH_3, Proδ-CH_3), 25.0* (CH_2, Proβ-C), 26.1 (CH_3, Proδ-CH_3), 26.9* (CH_3, Proδ-CH_3), 27.2* (CH_3, Proδ-CH_3), 27.4 (CH_2, Proβ-C), 27.9 [CH_3, $C(CH_3)_3$], 38.9 (CH_2, Proγ-C), 41.7* (CH_2, Proγ-C), 42.8* (CH_2, Glyα-C), 43.1 (CH_2, Glyα-C), 51.7* (CH_3, Proα-CO_2CH_3), 52.3 (CH_3, Proα-CO_2CH_3), 60.1 (CH, Proα-C), 60.9* (quat., Proδ-C), 61.7* (CH, Proα-C), 63.8 (CH, Proα-C), 78.0 [quat., $C(CH_3)_3$], 155.3 (quat., NCO_2), 155.4* (quat., NCO_2), 166.5 (quat., Gly-CO), 167.7* (quat., Gly-CO), 171.9 (quat., Proα-CO) and 172.4* (quat., Proα-CO); *m/z* (CI+) 315.1927 (MH^+ $C_{15}H_{27}N_2O_5$ requires 315.1920).

4.1.42. *N-tert*-Butoxycarbonylglycyl-(D,L)-5,5-dimethylproline 55. To a solution of dipeptide **54** (0.362 g, 1.16 mmol) in dioxane (12 cm^3) was added 1 M aqueous sodium hydroxide (5.91 cm^3, 5.91 mmol) and the mixture stirred for 21 h. The reaction was acidified with solid citric acid and the product was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvent removed in vacuo to yield an oil, which was purified by chromatography (silica gel, hexane/ethyl acetate, 2:1, 1:1, 4:6), to give acid **55** (0.324 g, 94%) as a white foam, which liquified rapidly. Acid **55** was shown to be an 80:20 cis:trans mixture of conformers by ^{1}H NMR analysis (the ratio was estimated from the integration of the broad singlets at δ 5.81 and 5.66 assigned to the GlyN–H protons of the major and minor conformers, respectively); δ_H (300 MHz; $CDCl_3$) 1.40 (2.4H, s, Proδ-CH_3), 1.43 [7.2H, s, $C(CH_3)_3$], 1.44* [1.8H, s, $C(CH_3)_3$], 1.47* (0.6H, s, Proδ-CH_3), 1.58* (0.6H, s, Proδ-CH_3), 1.61 (2.4H, s, Proδ-CH_3), 1.74–2.33 (4H, m, Proβ-H_2, Proγ-H_2), 3.37 (0.8H, dd, $J=16.7$, 3.3 Hz, Glyα-H_AH_B), 3.65 (0.8H, dd, $J=16.8$, 3.6 Hz, Glyα-H_AH_B), 3.96 (1H, dd, $J=16.9$, 3.9 Hz, Glyα-H_AH_B, Glyα-H_AH_B* partially obscured), 4.21* (0.2H, dd, $J=17.0$, 5.9 Hz, Gyα-H_AH_B), 4.42 (0.8H, d, $J=7.2$ Hz, Proα-H), 4.67* (0.2H, d, $J=7.9$ Hz Proα-H), 5.66* (0.2H, br s, Gly-NH), 5.81 (0.8H, br s, Gly-NH) and 6.2 (1H, br s, OH); δ_H (75 MHz; $CDCl_3$) 24.8 (CH_3, Proδ-CH_3), 25.1* (CH_2, Proβ-C), 26.3 (CH_3, Proδ-CH_3), 27.1* (CH_3, Proδ-CH_3), 27.6* (CH_3, Proδ-CH_3), 28.0 (CH_2, Proβ-C), 28.2 [CH_3, $C(CH_3)_3$], 39.2 (CH_2, Proγ-C), 42.0* (CH_2, Proγ-C), 43.0* (CH_2, Glyα-C), 43.5 (CH_2, Glyα-C), 60.5 (CH, Proα-C), 61.8* (quat., Proδ-C), 62.2* (CH, Proα-C), 64.3 (CH, Proα-C), 79.7* [quat., $C(CH_3)_3$], 80.2 [quat., $C(CH_3)_3$], 156.0* (quat., NCO_2), 156.4 (quat., NCO_2), 166.8 (quat., Gly-CO), 169.5* (quat., Gly-CO), 173.9 (quat., Proα-CO) and 174.5* (quat., Proα-CO); *m/z* (CI+) 315.1927 (MH^+ $C_{15}H_{27}N_2O_5$ requires 315.1920).

4.1.43. Dibenzyl *N-tert*-butoxycarbonylglycyl-(D,L)-5,5-dimethylprolyl-L-glutamate 58. To a stirred solution of acid **55** (0.298 g, 1 mmol) in dry dichloromethane (40 cm^3) was added successively diisopropylethylamine (0.453 cm^3, 2.6 mmol), L-glutamic acid dibenzyl ester *p*-toluenesulphonate **28** (0.648 g, 1.3 mmol) and bis(2-oxo-3-oxazolidinyl)-phosphinic chloride (0.330 g, 1.3 mmol). The resultant solution was stirred at room temperature under nitrogen overnight and the solvent removed. The residue was dissolved in ethyl acetate, washed with 10% aqueous citric acid solution, saturated sodium hydrogen carbonate, brine and dried ($MgSO_4$). The solvent was evaporated and the product purified by chromatography (silica gel, hexane/ethyl acetate, 1:1) to give protected tripeptide **58** (0.408 g, 67%) as a yellow oil (1:1 mixture of Proα-C epimers). Tripeptide **58** was shown to be 85:15 cis:trans mixture of conformers by ^{1}H NMR analysis (the ratio was estimated from the integration of the chemical shifts at δ 5.31–5.38 and 5.48 assigned to the Gly-NH protons of the major and minor conformers, respectively); δ_H (300 MHz; $CDCl_3$) 1.41 [9H, s, $C(CH_3)_3$], 1.44 (2.55H, s, Proδ-CH_3), 1.52* (0.45H, s, Proδ-CH_3), 1.54* (0.45H, s, Proδ-CH_3), 1.64 (2.55H, s, Proδ-CH_3), 1.67 (2.55H, s, Proδ-CH_3), 1.70–2.24 (6H, m, Proβ-H_2, Proγ-H_2, Gluβ-H_2), 2.35–2.45 (2H, m, Gluγ-H_2), 3.58–3.69 (0.85H, m, Glyα-H_AH_B), 3.85 (0.85H, m, Glyα-H_AH_B), 3.88–3.98* (0.15H, m, Glyα-H_AH_B), 4.12–4.17* (0.15H, m, Glyα-H_AH_B), 4.20–4.31 (1H, m, Proα-H), 4.59–4.71 (1H, m, Gluα-H), 5.10–5.22 (m, 4H, 2×OCH_2Ph), 5.31–5.38 (0.85H, m, Gly-NH) and 5.48*

(0.15H, m, Gly-NH); δ_C (75 MHz; $CDCl_3$) 24.38 (CH_3, Proδ-CH_3), 24.46 (CH_3, Proδ-CH_3), 25.1* (CH_2, Proβ-C), 25.2* (CH_2, Proβ-C), 26.2 (CH_2, Gluβ-C), 26.3 (CH_2, Gluβ-C), 26.6 (CH_3, Proδ-CH_3), 26.8* (CH_2, Proβ-C), 27.0* (CH_3, Proδ-CH_3), 27.1* (CH_3, Proδ-CH_3), 27.9* (CH_3, Proδ-CH_3), 28.2 [CH_3, $C(CH_3)_3$], 28.5 (CH_2, Proβ-C), 28.8 (CH_2, Proβ-C), 30.05* (CH_2, Gluγ-C), 30.1* (CH_2, Gluγ-C), 30.2 (CH_2, Gluγ-C), 30.25 (CH_2, Gluγ-C), 38.9 (CH_2, Proγ-C), 39.1 (CH_2, Proγ-C), 42.4** (CH_2, Proγ-C), 43.1* (CH_2, Glyα-C), 43.3* (CH_2, Glyα-C), 43.5 (CH_2, Glyα-C), 43.6 (CH_2, Glyα-C), 51.7* (CH, Gluα-C), 52.0 (CH, Gluα-C), 52.1 (CH, Gluα-C), 61.5* (quat., Proδ-C), 61.6* (quat., Proδ-C), 61.9 (CH, Proα-C), 62.0 (CH, Proα-C), 63.0* (CH, Proα-C), 63.05* (CH, Proα-C), 64.3 (quat., Proδ-C), 64.3 (quat., Proδ-C), 66.3* (CH_2, OCH_2Ph), 66.4* (CH_2, OCH_2Ph), 66.41 (CH_2, OCH_2Ph), 66.5 (CH_2, OCH_2Ph), 67.0* (CH_2, OCH_2Ph), 67.1* (CH_2, OCH_2Ph), 67.21 (CH_2, OCH_2Ph), 67.24 (CH_2, OCH_2Ph), 79.3 [quat., $C(CH_3)_3$], 128.1 (CH, Ph), 128.2 (CH, Ph), 128.3 (CH, Ph), 128.4* (CH, Ph), 128.43 (CH, Ph), 128.5 (CH, Ph), 135.03 (quat., Ph), 135.07, (quat., Ph), 153.13* (quat., Ph), 135.18* (quat., Ph), 135.6 (quat., Ph), 135.7* (quat., Ph), 155.8* (quat., NCO_2), 155.9 (quat., NCO_2), 156.0 (quat., NCO_2), 167.6 (quat., Gly-CO), 167.7 (quat., Gly-CO), 168.8* (quat., Gly-CO), 169.3* (quat., Gly-CO), 171.1 (quat., Pro-CON), 171.3* (quat., Pro-CON), 171.4* (quat., Pro-CON), 171.6 (quat., Gluα-CO), 171.8 (quat., Gluα-CO), 172.4 (quat., Gluγ-CO), 172.5* (quat., Gluγ-CO) and 172.6 (quat., Gluγ-CO); *m/z* (EI+) 609.3035 (M^+ $C_{33}H_{43}N_3O_8$ requires 609.3050).

4.1.44. Glycyl-(D,L)-5,5-dimethylprolyl-L-glutamic acid 50. To a stirred solution of protected tripeptide **58** (0.276 g, 0.454 mmol) in dichloromethane (10 cm^3) was added trifluoroacetic acid (1 cm^3) and the mixture stirred for 75 min. The solvent was removed in vacuo, the residue was dissolved in saturated sodium hydrogen carbonate and the product extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$) and the solvent removed to yield an oil (0.244 g), which was dissolved in methanol–water (4/1, 50 cm^3). The flask was flushed with nitrogen, 10% palladium on activated carbon (0.048 mg, 0.454 mmol) was added and the mixture was then stirred overnight under one atmosphere of hydrogen. Filtration through Celite™ followed by removal of the solvent yielded an oil that was triturated with dry diethyl ether to yield tripeptide **50** (0.139 g, 93%) as an off white solid. Tripeptide **50** was shown to be a 72:28 cis:trans mixture of conformers by ^1H NMR analysis (the ratio was estimated from the integration of the chemical shifts at δ 3.57 and 4.15–4.16 assigned to the Glyα-H protons of the major and minor conformers, respectively). Approximately 10% of the final product was tentatively assigned as the hydrochloride salt**: mp 145–150 °C; δ_H (400 MHz; D_2O) 1.43 (2.16H, s, Proδ-CH_3), 1.49* (0.84H, s, Proδ-CH_3), 1.57* (0.84H, s, Proδ-CH_3), 1.58* (0.84H, s, Proδ-CH_3), 1.60 (2.16H, s, Proδ-CH_3), 1.61 (2.16H, s, Proδ-CH_3), 1.90–2.48 (8H, m, Proβ-H_2, Proγ-H_2, Gluβ-H_2, Gluγ-H_2), 3.57 (0.72H, dd, J=16.1, 2.8 Hz, Glyα-H_AH_B), 3.75–3.82** (0.2H, m, Glyα-H_AH_B, Gluα-H), 3.94 (0.72H, dd, J=16.1, 6.5 Hz, Glyα-H_AH_B), 4.11** (0.1H, d, J=2.5 Hz, Glyα-H_AH_B), 4.15–4.16* (0.56H, m, Glyα-H_2), 4.24–4.30 (1H, m, Gluα-H), 4.46–4.51** (0.1H, m, Proα-H), 4.60 (0.72H, t, J=10.1 Hz, Proα-H) and 4.68* (0.28H, dd, J=13.5, 4.3 Hz, Proα-H); δ_C (400 MHz; D_2O) 23.56 (CH_3, Proδ-CH_3), 23.76 (CH_3, Proδ-CH_3), 24.1** (CH_3, Proδ-CH_3), 25.0 (CH_2, Gluβ-C), 25.2 (CH_3, Proδ-CH_3), 25.6 (CH_2, Gluβ-C), 25.7** (CH_3, Proδ-CH_3), 26.0 (CH_2, Gluβ-C), 26.1* (CH_3, Proδ-CH_3), 26.2* (CH_3, Proδ-CH_3), 26.4 (CH_2, Gluβ-C), 26.8* (CH_2, Gluβ-C), 28.4, (CH_2, Proβ-C), 28.7, (CH_2, Proβ-C), 30.8* (CH_2, Gluγ-C), 31.0* (CH_2, Gluγ-C), 31.2 (CH_2, Gluγ-C), 38.7 (CH_2, Proγ-C), 38.8 (CH_2, Proγ-C), 40.6* (CH_2, Glyα-C), 40.7 (CH_2, Glyα-C), 40.8 (CH_2, Glyα-C), 41.1* (CH_2, Proγ-C), 41.2* (CH_2, Proγ-C), 46.1** (CH_2, Glyα-C), 54.1 (CH, Gluα-C), 54.5 (CH, Gluα-C), 59.7* (CH, Proα-C), 61.7 (CH, Proα-C), 61.8 (CH, Proα-C), 62.6** (quat., Proδ-C), 62.7* (quat., Proδ-C), 63.4* (CH, Proα-C), 63.9** (quat., Proδ-C), 65.0 (quat., Proδ-C), 65.1 (quat., Proδ-C), 164.8 (quat., Gly-CO), 164.9 (quat., Gly-CO), 165.6* (quat., Gly-CO), 165.8* (quat., Gly-CO), 166.0** (quat., Gly-CO), 172.3** (quat., Pro-CON), 172.8 (quat., Pro-CON), 173.1 (quat., Pro-CON), 173.3* (quat., Pro-CON), 173.6* (quat., Pro-CON), 176.9 (quat., Gluα-CO), 177.3 (quat., Gluα-CO) and 178.1 (quat., Gluγ-CO); *m/z* (FAB+) 330.1666 (MH^+ $C_{14}H_{24}N_3O_6$ requires 330.1666).

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Synthesis of the phthalide-containing anti-*Helicobacter pylori* agents CJ-13,015, CJ-13,102, CJ-13,103, CJ-13,104 and CJ-13,108

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Abstract—Flexible racemic syntheses of the phthalide-containing antibiotics CJ-13,015, CJ-13,102, CJ-13,103, CJ-13,104 and CJ-13,108 that inhibit *Helicobacter pylori* have been carried out in a convergent fashion by Wittig coupling of a phthalide-containing aldehyde fragment with an appropriate phosphorous ylide.

1. Introduction

Helicobacter pylori is a microaerophilic Gram-negative bacterium that infects over 50% of the human population worldwide. Infection has been associated with chronic superficial gastritis, chronic active gastritis, peptic ulcer disease and gastric cancer in humans.[1] As a result of the latter, the International Agency for Research in Cancer classified *H. pylori* as a class I carcinogen in 1994.[2]

The current first-line triple-therapy for *H. pylori*-associated gastrointestinal diseases, using a combination of antibiotics with a proton-pump inhibitor, fails to fully eradicate *H. pylori* in approximately 10–23% of patients. As a result, second-line or rescue treatments are often required.[3] Treatment failure is associated with the emergence of *H. pylori* strains that are resistant to the broad-spectrum antibiotics used.[2]

Consequently, there is an urgent need for the development of more effective and selective anti-*H. pylori* agents. In a screening program designed to discover such compounds, Dekker et al.[4] isolated seven new phthalide antibiotics with specific anti-*H. pylori* activity (**1**–**7**) from the basidiomycete *Phanerochaete velutina* CL6387 (Fig. 1). Two structurally related compounds, spirolaxine **8a**[5a] and its methyl ether **8b**,[5b] isolated from *Sporotrichum laxum*, *S. pruinosum* and *Phanerochaete*, *chrysosporium* have also been reported. These phthalide-containing compounds provide promising new leads for the treatment of *H. pylori*-related diseases.

To date, CJ-13,015 **3** is the only member of the *P. velutina* series of antibiotics to have been synthesized.[6] The synthetic strategy used a 5-methylfuranyl bromide as a latent 1,4-dicarbonyl system and was efficient requiring only six steps. However, the synthetic route did not possess the intrinsic flexibility necessary to access the other compounds in the series. We herein report a flexible synthetic strategy that has been used to prepare five of these antibiotics **3**–**7** as racemates.

Our recent enantioselective total synthesis of spirolaxine methyl ether **8b**[7] unequivocally established the absolute stereochemistry at C-3 of the phthalide unit to be of the (*R*)-configuration. It is therefore, likely that C-3 of the phthalide unit in compounds **1**–**7** will also exhibit the (*R*)-configuration. To this end the enantioselective total syntheses of the more complex and helicobactericidal spiroacetal containing antibiotics CJ-12,954 **1** and CJ-13,014 **2**, are currently being investigated.

2. Results and discussion

The work reported herein, describes the racemic total syntheses of five of the *P. velutina* series of phthalide antibiotics (**3**–**7**). The highly convergent and flexible synthetic strategy adopted hinged on the Wittig reaction of a key phthalide aldehyde **9**, derived from 2,4-dimethoxybenzoic acid **10**, with the ylide generated from the appropriate phosphonium salt **11**, **12** or **13** (Scheme 1).

Keywords: Phthalides; *Helicobacter pylori*; Wittig reaction.
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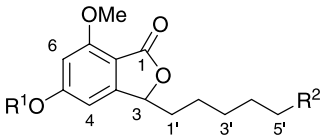
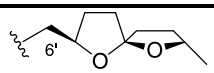
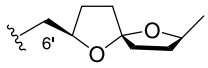
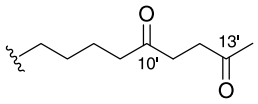
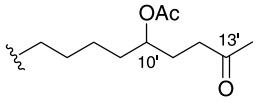
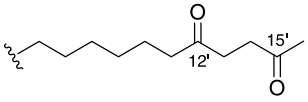
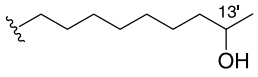
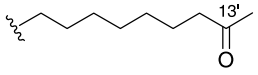
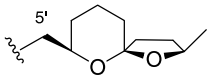


Antibiotic	R^1	R^2	Activity[a]
CJ-12,954 **1**	Me		0.02
CJ-13,014 **2**	Me		0.02
CJ-13,015 **3**	Me		2
CJ-13,102 **4**	Me		0.5
CJ-13,103 **5**	Me		50
CJ-13,104 **6**	Me		500
CJ-13,108 **7**	Me		10
Spirolaxine **8a**	H		0.01
Spirolaxine methyl ether **8b**	Me		No data

a. μg/disk that gives a 15 mm zone of inhibition.

Figure 1. Structure and anti-*H. pylori* activity of phthalide antibiotics (**1–7**) and spirolaxine **8** isolated from *P. velutina*.

The alcohol functionality in CJ-13,104 **6** was easily obtained from reduction of the ketone in CJ-13,108 **7**, that in turn was derived from the 11-carbon phosphonium salt **13**, (Scheme 3). CJ-13,015 **3** and CJ-13,102 **4** were prepared from a common hydroxyketone intermediate **14** starting from the 11-carbon phosphonium salt **11** (Scheme 4). CJ-13,103 **5** was available from the union of the ylide derived from the 13-carbon phosphonium salt **12** with phthalide aldehyde **9** (Scheme 5).

2.1. Synthesis of phthalide aldehyde 9

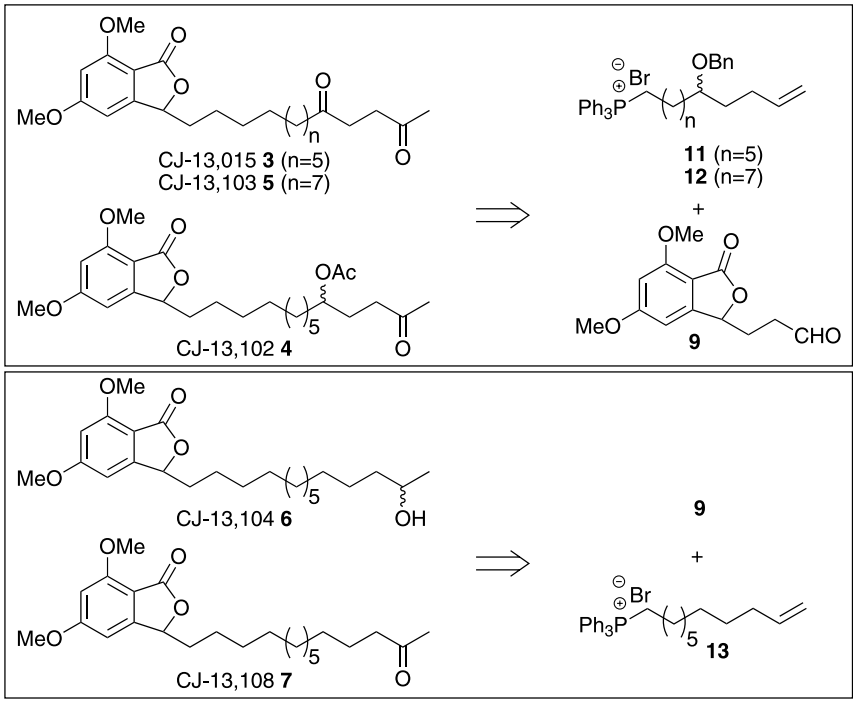
Phthalide aldehyde **9** was the core building block used to prepare all five of the desired compounds. It was prepared from commercially available 2,4-dimethoxybenzoic acid **10** (Scheme 2) firstly by conversion to the corresponding amide **15**. *ortho*-Lithiation followed by formylation provided aldehyde **16**, which furnished alkene **17** upon treatment with but-3-en-1-ylmagnesium bromide. Acid-catalysed cyclisation furnished phthalide **18** that upon ozonolysis of the terminal olefin gave the desired phthalide aldehyde **9** in 65% overall yield.

2.2. Synthesis of CJ-13,104 6 and CJ-13,108 7

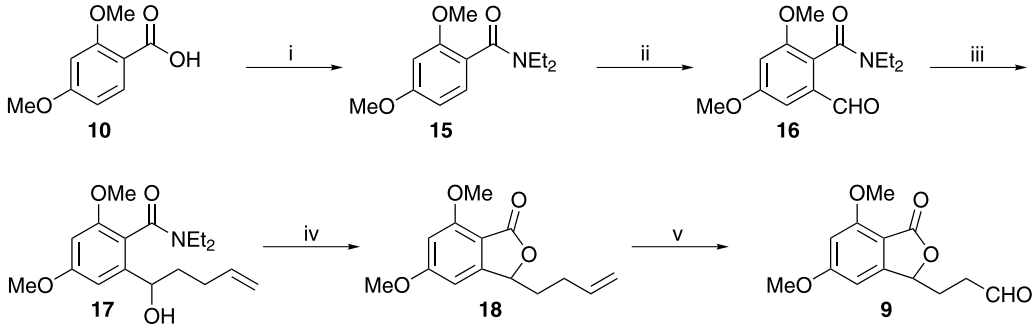
The synthesis of CJ-13,104 **6** and CJ-13,108 **7** (Scheme 3) began with the preparation of phosphonium salt **13**, obtained from commercially available 10-undecen-1-yl bromide **19** in 96% yield. Wittig reaction of the ylide generated from phosphonium salt **13**, with aldehyde **9** gave the desired olefin **20** in 86% yield, as a mixture of (*E*)- and (*Z*)-isomers, the relative ratios of which were unable to be determined. Selective Wacker oxidation of the terminal olefin afforded methyl ketone **21**, which upon hydrogenation of the internal olefin furnished CJ-13,108 **7** in 62% yield. Reduction of the C-13′ ketone in CJ-13,108 **7** with sodium borohydride gave CJ-13,104 **6** in 95% yield.

2.3. The synthesis of CJ-13,015 3 and CJ-13,102 4

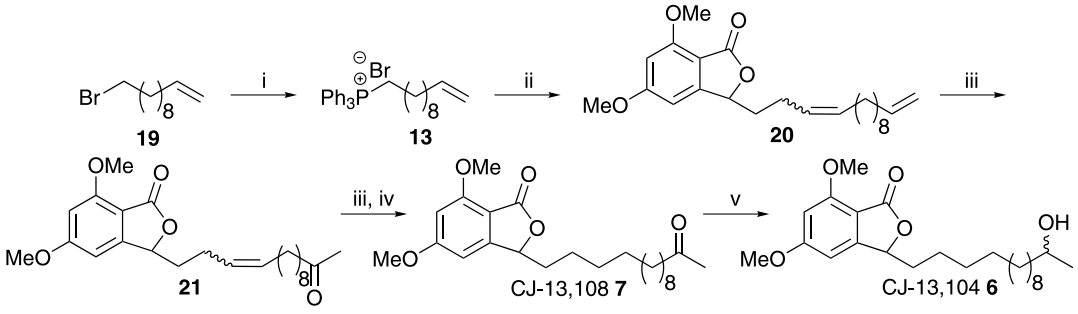
The synthesis of CJ-13,015 **3** and CJ-13,102 **4** (Scheme 4) started from a common hydroxyketone intermediate **14** that was prepared from commercially available 7-octen-1-ol **22**. Protection of the alcohol as a *tert*-butyldimethylsilyl ether **23** followed by epoxidation of the terminal olefin provided oxirane **24** in quantitative yield. Ring-opening of the epoxide using a higher-order allyl-cuprate afforded alcohol **25**, which was protected as a benzyl ether **26**. Cleavage of the *tert*-butyldimethylsilyl ether yielded alcohol **27** that underwent conversion to bromide **28** followed by reaction with triphenylphosphine to furnish the desired phosphonium



Scheme 1. Retrosynthetic analysis of CJ-13,015, CJ-13,102, CJ-13,103, CJ-13,104 and CJ-13,108.

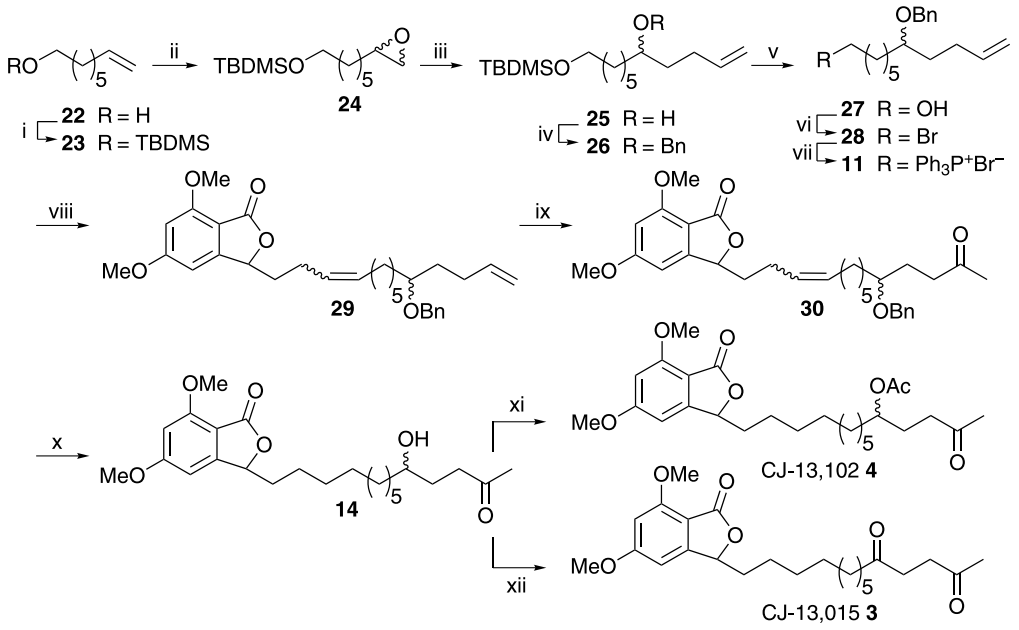


Scheme 2. Reagents and conditions: (i) $SOCl_2$, reflux, 2.5 h, then Et_2NH, CH_2Cl_2, rt, 12 h, 96%; (ii) *t*-BuLi (1.1 equiv), THF, −78 °C, 15 min, then DMF, rt, 16 h, 99%; (iii) but-3-en-1-ylmagnesium bromide, Et_2O, rt, 30 min; (iv) *p*TSA, PhMe, reflux, 6 h, 87% from **16**; (v) O_3, MeOH, −50 °C, 10 min, then Me_2S, rt, 1 h, 79%.

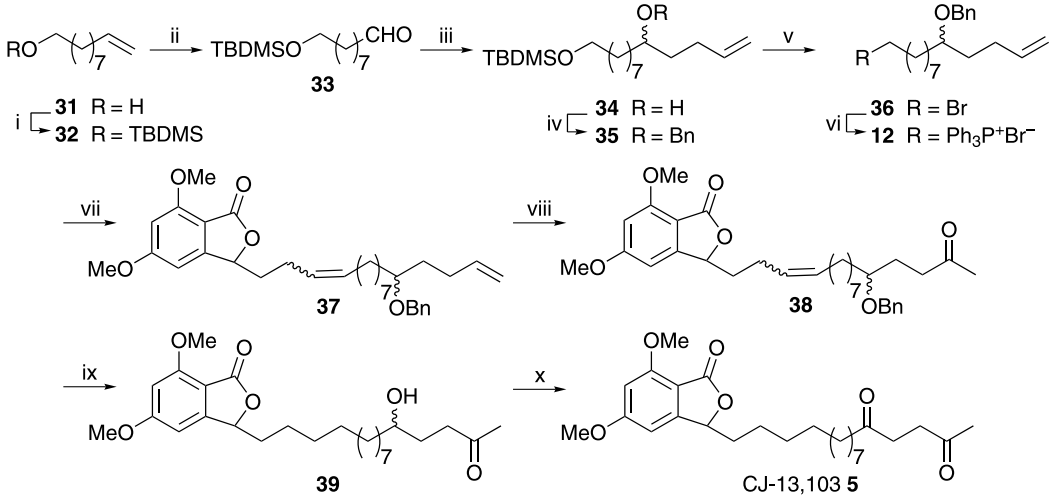


Scheme 3. Reagents and conditions: (i) PPh_3, MeCN, reflux, 24 h, 96%; (ii) *n*-BuLi, THF, −78 °C to rt, 30 min, then **9**, −78 °C to rt, 2 h, 86% (iii) $PdCl_2$, CuCl, DMF–H_2O (8/1), O_2, rt, 3 h, 62%; (iv) 10% Pd/C, H_2, EtOAc, rt, 1 h, 100% (v) $NaBH_4$, MeOH, rt, 10 min, 95%.

salt **11** in 34% overall yield (seven steps). Wittig reaction of the ylide generated from phosphonium salt **11** with phthalide aldehyde **9** gave olefin **29** in 72% yield, as a mixture of (*E*)- and (*Z*)-isomers, the relative ratios of which were unable to be determined. Selective Wacker oxidation of the terminal olefin afforded ketone **30** which, upon simultaneous hydrogenation of the internal olefin and hydrogenation of the benzyl ether, furnished hydroxyketone **14**. Direct acetylation of alcohol **14** provided CJ-13,102 **4**, whereas TPAP oxidation furnished the diketone CJ-13,015 **3**.



Scheme 4. Reagents and conditions: (i) TBDMSCl, imidazole, DMAP, CH_2Cl_2, 0 °C, 3 h, 99%; (ii) *m*CPBA, NaOAc, CH_2Cl_2, rt, 18 h, 99%; (iii) 5% CuCN, allylmagnesium bromide, Et_2O, −78 °C, 10 h, 55%; (iv) NaH, TBAI, DMF, 0 °C, 75 min, then BnBr, rt, 18 h, 81%; (v) TBAF, THF, 0 °C, 2 h, 97%; (vi) CBr_4, PPh_3, MeCN, 0 °C, 30 min, 100%; (vii) PPh_3, MeCN, reflux, 26 h, 80%; (viii) *n*-BuLi, THF, −78 °C to rt, 30 min, then **9**, −78 °C to rt, 2 h, 72%; (ix) $PdCl_2$, CuCl, DMF–H_2O (8/1), O_2, rt, 3 h, 54%; (x) 10% Pd/C, H_2, EtOAc, rt, 3 h; (xi) Ac_2O, DMAP, pyridine, rt, 8 h, 83% from **30**; (xii) TPAP, NMO, CH_2Cl_2, rt, 30 min, 37% over two steps.



Scheme 5. Reagents and conditions: (i) TBDMSCl, imidazole, DMAP, CH_2Cl_2, 0 °C, 3 h, 96%; (ii) O_3, MeOH, −50 °C, 10 min, then Me_2S, rt, 1 h, 95%; (iii) but-3-en-1-ylmagnesium bromide, Et_2O, rt, 30 min, 96%; (iv) NaH, TBAI, DMF, 0 °C, 75 min, then BnBr, rt, 18 h, 95%; (v) PPh_3Br_2, CH_2Cl_2, rt, 24 h, 91%; (vi) PPh_3, MeCN, reflux, 24 h, 80%; (vii) *n*-BuLi, THF, −78 °C to rt, 30 min, then **9**, −78 °C to rt, 2 h, 73%; (viii) $PdCl_2$, CuCl, DMF–H_2O (8/1), O_2, rt, 3 h, 61% (ix) 10% Pd/C, H_2, EtOAc, rt, 3 h; (x) TPAP, NMO, CH_2Cl_2, rt, 30 min, 44% over two steps.

2.4. Synthesis of CJ-13,103 5

Following a similar strategy to that used for the synthesis of CJ-13,015 **3**, the preparation of CJ-13,103 **5** started with commercially available 9-decen-1-ol **31** (Scheme 5). Protection of the alcohol as a *tert*-butyldimethylsilyl ether **32** followed by ozonolysis of the terminal olefin provided aldehyde **33**. Treatment of **33** with but-3-en-1-ylmagnesium bromide afforded alcohol **34** in quantitative yield. Protection of the alcohol as a benzyl ether **35** followed by a one-pot desilylation–bromination procedure[8] using triphenylphosphine–bromine complex, afforded bromide **36**, that furnished the desired phosphonium salt **12** upon reaction with triphenylphosphine. Wittig reaction of the ylide generated from phosphonium salt **12** with phthalide aldehyde **9** gave olefin **37** in 73% yield, as a mixture of (*E*) and (*Z*) isomers, the relative ratios of which were unable to be determined. Selective Wacker oxidation of the terminal olefin afforded ketone **38** which, upon simultaneous hydrogenation of the internal olefin and

hydrogenation of the benzyl ether, furnished hydroxyketone **39**. Finally, oxidation of alcohol **39** afforded CJ-13,103 **5**.

3. Conclusions

An efficient and flexible strategy has been developed to prepare five anti-*Helicobacter pylori* agents (**3**–**7**). The convergent strategy developed, involving union of phthalide aldehyde **9** with an appropriately functionalized ylide, is readily amenable to the construction of analogues.

4. Experimental

4.1. General

All reactions were carried out in flame dried or oven dried glassware under a dry nitrogen atmosphere. Tetrahydrofuran was distilled from sodium benzophenone while dichloromethane and *N*,*N*-dimethylformamide were dried over calcium hydride and distilled prior to use. Flash chromatography was carried out using 0.063–0.1 mm silica gel with the appropriate solvent. Thin-layer chromatography was performed using silica coated aluminium plates (60 F254). Compounds were identified using UV fluorescence and or staining with vanillin in ethanolic sulphuric acid. Low resolution mass spectra were recorded using a VG-70SE spectrometer operating at a nominal accelerating voltage of 70 eV. High resolution mass spectra were recorded at a nominal resolution of 5000–10,000. Infrared spectra were obtained using a Perkin-Elmer Spectrum 1000 series Fourier Transform IR spectrometer as a thin film between sodium chloride plates. NMR spectra were recorded on either the Bruker DRX300 spectrometer operating at 300 MHz for ^{1}H nuclei and 75 MHz for ^{13}C nuclei or using a Bruker DRX400 spectrometer operating at 400 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei. Melting points were determined on a Kofler hot-stage apparatus, and are uncorrected.

4.2. Procedure for the synthesis of phthalide aldehyde 9

4.2.1. *N*,*N*-Diethyl 2,4-dimethoxybenzamide 15. A solution of 2,4-dimethoxybenzoic acid **10** (5.15 g, 28.27 mmol) in thionyl chloride (20 mL) was heated at reflux for 2.5 h. The solvent was removed in vacuo. Benzene (3×10 mL) was added to the residue then removed in vacuo. A solution of diethylamine (9 mL, 87.00 mmol) in dichloromethane (10 mL) was added dropwise to a stirred solution of the crude acid chloride in dichloromethane (40 mL) at 0 °C. After stirring at room temperature for 12 h, the reaction mixture was diluted with dichloromethane (50 mL), washed with 10% w/v aqueous sodium bicarbonate (3×10 mL), brine (3×10 mL), and the organic layer dried over magnesium sulfate. Removal of the solvent in vacuo followed by flash column chromatography using diethyl ether–hexane (3/1) as eluent gave the title compound **15** (6.71 g, 96%) as a viscous yellow oil. The ^{1}H NMR data obtained were in agreement with the literature values.[9]

4.2.2. *N*,*N*-Diethyl 2-formyl-4,6-dimethoxybenzamide 16. *tert*-Butyllithium (23 mL of a 1.05 M solution in hexanes, 24.15 mmol) was added dropwise to a stirred solution of *N*,*N*-diethyl 2,4-dimethoxybenzamide **15** (5.20 g, 21.91 mmol) in tetrahydrofuran (193 mL) at −78 °C. After stirring for 25 min, *N*,*N*-dimethylformamide (6.7 mL, 86.16 mmol) was added dropwise. The reaction mixture was warmed to room temperature, stirred for 12 h and the solvent removed in vacuo. The residue was dissolved in dichloromethane (30 mL), washed with brine (3×15 mL) and the organic layer dried over magnesium sulfate. Removal of the solvent in vacuo followed by flash column chromatography using diethyl ether as eluent gave the title compound **16** (5.71 g, 99%) as a viscous yellow oil. ν_{max} (film) 2971, 1702, 1633, 1602, 1461, 1320, 1290, 1223, 1201, 1155, 1097, 1045, 955, 936 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 0.96 (3H, t, J=7.1 Hz, NCH_2CH_3), 1.22 (3H, t, J=7.1 Hz, NCH_2CH_3), 3.07 (2H, q, J=7.1 Hz, NCH_2CH_3), 3.41–3.55 (1H, m, $NCH_AH_BCH_3$), 3.58–3.70 (1H, m, $NCH_AH_BCH_3$), 3.78 (3H, s, OMe), 3.81 (3H, s, OMe), 6.65 (1H, d, J=2.3 Hz, 5-H), 6.97 (1H, d, J=2.3 Hz, 6-H), 9.90 (1H, s, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) 12.6 (CH_3, NCH_2CH_3), 13.7 (CH_3, NCH_2CH_3), 39.0 (CH_2, NCH_2CH_3), 42.8 (CH_2, NCH_2CH_3), 55.6 (CH_3, OMe), 55.9 (CH_3, OMe), 102.4 (CH, C-5), 104.7 (CH, C-3), 123.3 (quat., C-1), 134.2 (quat., C-2), 156.8 (quat., C-6), 160.9 (quat., C-4), 165.7 (quat., $CONEt_2$), 190.2 (CH, CHO); *m*/*z* (FAB+, %) 266 (M^+, 65), 238 (12), 236 (23), 193 (100), 167 (13), 165 (16), 154 (15), 71 (19); HRMS (FAB+): found MH^+, 266.1383. $C_{14}H_{19}NO_4$ requires 266.1392.

4.2.3. *N*,*N*-Diethyl 4,6-dimethoxy-2-(1′-hydroxypent-4′-en-1′-yl)benzamide 17. A solution of aldehyde **16** (900 mg, 3.39 mmol) in diethyl ether (15 mL) was added dropwise to the stirred solution of but-3-en-1-ylmagnesium bromide (11.75 mL of a 0.63 M solution in diethyl ether, 7.41 mmol) at 0 °C and the reaction mixture allowed to warm to room temperature. After stirring for 30 min, saturated aqueous ammonium chloride (20 mL) was added, the reaction mixture extracted with diethyl ether (3×10 mL) and the organic layer dried over magnesium sulfate. Removal of the solvent in vacuo followed by flash column chromatography using ethyl acetate–hexane (1/1) as eluent afforded the title compound **17** (1.01 g) as a 1:1 mixture of rotamers and as a viscous yellow oil. ν_{max} (film) 3390, 2937, 1614, 1455, 1317, 1202, 1154, 1049, 912, 732, 635 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 1.04 (3H, t, J=7.0 Hz, NCH_2CH_3), 1.23 (3H, t, J=7.0 Hz, NCH_2CH_3), 1.70–2.30 (4H, m, 2′-H, 3′-H), 3.15 (2H, q, J=7.0 Hz, NCH_2CH_3), 3.47 (2H, t, J=7.0 Hz, NCH_2CH_3), 3.77 (3H, s, OMe), 3.82 (3H, s, OMe), 4.45–4.59 (1H, m, 1′-H), 4.92–5.15 (2H, m, 5′-H), 5.74–5.88 (1H, m, 4′-H), 6.36 (1H, d, J=2.2 Hz, 5-H), 6.59 (1H, d, J=2.2 Hz, 3-H), 6.64 (1H, d, J=2.2 Hz, 3-H); ^{13}C NMR (75 MHz, $CDCl_3$) 12.5, 12.6 (CH_3, NCH_2CH_3), 13.6, 15.2 (CH_3, NCH_2CH_3), 30.4 (CH_2, C-3′), 37.3 (CH_2, C-2′) 38.7 (CH_2, NCH_2CH_3), 42.8 (CH_2, NCH_2CH_3), 55.3 (CH_3, OMe), 55.4 (CH_3, OMe), 69.6, 73.1 (CH, C-1′), 97.4, 97.5 (CH, C-5), 102.0, 103.4 (CH, C-3), 114.7, 114.8 (CH_2, C-5′), 117.0 (quat., C-1), 138.1, 138.3 (CH, C-4′), 144.0 (quat., C-2), 156.1 (quat., C-6), 161.0, 161.2 (quat., C-4), 168.5 (quat., C=O); *m*/*z* (EI+, %) 321 (M^+, 17), 266 (18), 249 (38), 236 (11), 231 (25), 207 (59), 193 (100), 165 (29), 74 (32), 58 (33), 41 (12); HRMS (EI+): found M^+, 321.1938. $C_{18}H_{27}NO_4$ requires 321.1940.

4.2.4. 3-(But-3′-en-1′-yl)-5,7-dimethoxy-(3*H*)-isobenzofuran-1-one 18. To a crude sample of alcohol **17** (1.10 g, 3.42 mmol) in toluene (20 mL) was added *p*-toluenesulfonic acid monohydrate (100 mg, 0.50 mmol). The mixture was heated under reflux for 6 h. Removal of the solvent in vacuo followed by flash column chromatography using ethyl acetate–hexane (1/1) as eluent yielded the title compound **18** (800 mg, 87% over two steps) as a yellow oil. ν_{max} (film) 2942, 1739, 1606, 1463, 1340, 1218, 1160, 1033, 913, 816, 732, 670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 1.72–1.85 (1H, m, 1′-H_A), 2.02–2.14 (1H, m, 1′-H_B), 2.20–2.30 (2H, m, 2′-H), 3.90 (3H, s, OMe), 3.95 (3H, s, OMe), 5.00–5.12 (2H, m, 4′-H), 5.28–5.35 (1H, m, 3-H), 5.75–5.89 (1H, m, 3′-H), 6.43 (1H, s, 6-H), 6.43 (1H, s, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) 28.8 (CH_2, C-2′), 34.0 (CH_2, C-1′), 55.8 (CH_3, OMe), 55.8 (CH_3, OMe), 78.9 (CH, C-3), 97.4 (CH, C-6), 98.6 (CH, C-4), 105.8 (quat., C-7a), 115.7 (CH_2, C-4′), 136.8 (CH, C-3′), 154.8 (quat., C-3a), 159.5 (quat., C-7), 166.6 (quat., C-5), 168.2 (quat., C=O); *m/z* (EI+, %) 248 (M^+, 7), 194 (34), 193 (100), 165 (31), 91 (12); HRMS (EI+): found M^+, 248.1055. $C_{13}H_{14}O_4$ requires 248.1049.

4.2.5. 5,7-Dimethoxy-3-(3′-oxoprop-1′-yl)-(3*H*)-isobenzofuran-1-one 9. A solution of olefin **18** (200 mg, 0.81 mmol) in methanol (15 mL) was cooled to −50 °C under nitrogen. Ozone was bubbled through the solution for 10 min at a rate of 1 L/min. The mixture was flushed with nitrogen and dimethyl sulfide (3 mL) was added. The resulting mixture was warmed to room temperature, further dimethyl sulfide added (1 mL) and the mixture stirred for 1 h. The solvent was removed in vacuo and the resulting yellow residue dissolved in water (5 mL), extracted with diethyl ether (3×10 mL) and the organic layer dried over magnesium sulfate. Removal of the solvent in vacuo followed by flash column chromatography using ethyl acetate–hexane (1/1) as eluent afforded the title compound **9** (160 mg, 79%) as a yellow oil. ν_{max} (film) 2928, 2951, 1755, 1602, 1463, 1338, 1218, 1158, 1028, 837, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 1.88 (1H, dddd, J=14.4, 8.3, 8.3, 5.1 Hz, 1′-H_A), 2.44 (1H, dddd, J=14.4, 7.4, 7.4, 3.2 Hz, 1′-H_B), 2.54 (1H, ddd, J=18.7, 8.2, 5.1 Hz, 2′-H_A), 2.75 (1H, td, J=18.7, 7.4 Hz, 2′-H_B), 3.88 (3H, s, OMe), 3.94 (3H, s, OMe), 5.34 (1H, dd, J=8.3, 3.2 Hz, 3-H), 6.42 (1H, s, 4-H), 6.43 (1H, s, 6-H), 9.80 (1H, apparent s, 3′-H); ^{13}C NMR (75 MHz, $CDCl_3$) 26.9 (CH_2, C1′), 38.9 (CH_2, C2′), 56.0 (CH_3, OMe), 56.0 (CH_3, OMe), 78.4 (CH, C3), 97.4 (CH, C6), 99.1 (CH, C4), 106.7 (quat., C7a), 154.3 (quat., C3a), 159.7 (quat., C7), 167.0 (quat., C5), 168.0 (quat., C1), 200.7 (CH, C3′); *m/z* (EI+, %) 250 (M^+, 30), 206 (61), 193 (100), 165 (21), 135 (20) and 77 (10); HRMS (EI+): found M^+, 250.0833. $C_{13}H_{14}O_5$ requires 250.0841.

4.3. Procedure for the synthesis of CJ-13,104 6 and (±)-CJ-13,108 7

4.3.1. Triphenyl(undec-10-en-1-yl)phosphonium bromide 13. Triphenylphosphine (3.2 g, 12.3 mmol) was added in one portion to a solution of 11-bromoundec-1-ene **19** (2.8 mL, 12.9 mmol) in benzene (20 mL). The solution was heated under nitrogen at reflux for 24 h. The solvent was removed in vacuo leaving a viscous white residue that was triturated with diethyl ether (2×5 mL). Removal of the solvent in vacuo afforded the title compound **13** (6.15 g, 96%) as a viscous colourless oil. The ^{31}P NMR data obtained was in agreement with the literature value. ^{31}P NMR (300 MHz, $CDCl_3$) 24.2 (lit. ^{31}P 24.3).[10]

4.3.2. 5,7-Dimethoxy-3-(tetradec-3′,13′-dien-1′-yl)-(3*H*)-isobenzofuran-1-one 20. *n*-Butyllithium (0.56 mL of a 1.6 M solution in hexanes, 0.90 mmol) was added dropwise to a stirred solution of triphenyl(undec-10-en-1-yl)-phosphonium bromide **13** (370 mg, 0.75 mmol) in tetrahydrofuran (10 mL) at −78 °C. The resulting deep orange solution was warmed to room temperature, re-cooled to −78 °C and a solution of phthalide aldehyde **9** (150 mg, 0.60 mmol) in tetrahydrofuran (5 mL) added dropwise with stirring. The mixture was warmed to room temperature, stirred for 2 h and the solvent removed in vacuo. The resulting residue was dissolved in dichloromethane (20 mL), washed with brine (3×5 mL) and the organic layer dried over magnesium sulfate. Removal of the solvent in vacuo followed by flash column chromatography using ethyl acetate–hexane (4/1) as eluent afforded the title compound **20** (200 mg, 86%) as a greasy colourless oil. ν_{max} (film) 2926, 2853, 1759, 1614, 1463, 1433, 1338, 1217, 1158, 1056, 1029, 910, 837, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 1.25–1.42 (12H, m, 6′-H, 7′-H, 8′-H, 9′-H, 10′-H, 11′-H), 1.62–1.78 (1H, m, 1′-H_A), 1.91–2.08 (5H, m, 1′-H_B, 5′-H, 12′-H), 2.09–2.36 (2H, m, 2′-H), 3.89 (3H, s, OMe), 3.94 (3H, s, OMe), 4.90–5.01 (2H, m, 14′-H), 5.27–5.48 (3H, m, 3-H, 3′-H, 4′-H), 5.73–5.87 (1H, m, 13′-H), 6.42 (1H, s, 6-H), 6.42 (1H, s, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) 22.5 (CH_2, C-2′), 27.0 (CH_2, C-5′), 28.7 (CH_2, C-11′), 28.9 (CH_2, C-6′), 29.1 (CH_2, C-10′), 29.3 (CH_2, C-9′), 29.3 (CH_2, C-8′), 29.4 (CH_2, C-7′), 33.6 (CH_2, C-12′), 34.8 (CH_2, C-1′), 55.7 (CH_3, OMe), 55.8 (CH_3, OMe), 79.1 (CH, C-3), 97.3 (CH, C-6), 98.5 (CH, C-4), 106.7 (quat., C-7a), 113.9 (CH_2, C-14′), 127.4 (CH, C-3′), 131.6 (CH, C-4′), 139.0 (CH, C-13′), 154.9 (quat., C-3a), 159.4 (quat., C-7), 166.6 (quat., C-5), 168.2 (quat., C=O); *m/z* (EI+, %) 386 (M^+, 23), 261 (25), 247 (24), 208 (100), 193 (50); HRMS (EI+): found M^+, 386.2457. $C_{24}H_{34}O_4$ requires 386.2451.

4.3.3. 5,7-Dimethoxy-3-(13′-oxotetradec-3′-en-1′-yl)-(3*H*)-isobenzofuran-1-one 21. Palladium(II) chloride (46 mg, 0.26 mmol) and copper(I) chloride (61 mg, 0.62 mmol) were added to a stirred solution of diene **20** (200 mg, 0.52 mmol) in *N*,*N*-dimethylformamide–water (4 mL/0.5 mL) at room temperature. The reaction mixture was bubbled with oxygen gas with stirring for 3 h. The mixture was filtered through a pad of Celite® and the solvent removed in vacuo. The resulting residue was dissolved in dichloromethane (10 mL), washed with brine (3×2 mL) and the organic layer dried over magnesium sulfate. Removal of the solvent in vacuo followed by flash column chromatography using ethyl acetate–hexane (1/1) as eluent afforded the title compound **21** (130 mg, 62%) as a greasy colourless oil. ν_{max} (film) 3498, 2926, 2853, 1756, 1712, 1613, 1464, 1432, 1338, 1217, 1158, 1054, 1028, 837, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 1.22–1.36 (10H, m, 6′-H, 7′-H, 8′-H, 9′-H, 10′-H), 1.49–1.62 (2H, m, 11′-H), 1.68–1.79 (1H, m, 1′-H_A), 1.90–2.07 (3H, m, 1′-H_B, 5′-H), 2.12 (3H, s, 14′-H), 2.15–2.33 (2H, m, 2′-H), 2.41 (2H, t, J=7.3 Hz, 12′-H), 3.89 (3H, s, OMe), 3.94 (3H, s, OMe), 5.26–5.50 (3H, m, 3-H, 3′-H, 4′-H), 6.42 (1H, s, 6-H), 6.42

(1H, s, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) 22.6 (CH_2, C-2′), 23.7 (CH_2, C-11′), 27.1 (CH_2, C-5′), 29.0 (CH_2, C-10′), 29.0 (CH_2, C-9′), 29.2 (CH_2, C-6′), 29.2 (CH_2, C-8′), 29.5 (CH_2, C-7′), 29.7 (CH_2, C-14′), 34.9 (CH_2, C-1′), 43.7 (CH_2, C-12′), 55.8 (CH_3, OMe), 55.9 (CH_3, OMe), 79.1 (CH, C-3), 97.4 (CH, C-6), 98.6 (CH, C-4), 106.8 (quat., C-7a), 127.5 (CH, C-3′), 131.6 (CH, C-4′), 155.0 (quat., C-3a), 159.5 (quat., C-7), 166.6 (quat., C-5), 168.3 (quat., C-1), 209.3 (quat., C-13′); *m/z* (EI+, %) 402 (M^+, 25), 384 (18), 345 (14), 208 (100), 207 (88), 194 (75), 193 (72), 43 (46); HRMS (EI+): found M^+, 402.2403. $C_{24}H_{34}O_5$ requires 402.2406.

4.3.4. (±)-CJ-13,108 7. Palladium 10% on carbon (20 mg, 0.036 mmol) was added in one portion to a stirred solution of olefin **21** (130 mg, 0.32 mmol) in ethyl acetate (5 mL) at room temperature. The reaction mixture was stirred under an atmosphere of hydrogen for 1 h and filtered through a pad of Celite®. Removal of the solvent in vacuo followed by flash column chromatography using ethyl acetate–hexane (1/1) as eluent afforded the title compound **7** (130 mg, 100%) as a colourless solid. The ^{1}H and ^{13}C NMR data obtained were in agreement with the literature values.[4] Mp 104–106 °C; ν_{max} (film) 3462, 2915, 1758, 1701, 1600, 1469, 1336, 1220, 1162, 1053, 1026, 837 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 1.22–1.36 (16H, m, 3′-H, 4′-H, 5′-H, 6′-H, 7′-H, 8′-H, 9′-H, 10′-H), 1.41–1.46 (2H, m, 2′-H), 1.52–1.59 (2H, m, 11′-H), 1.64–1.73 (1H, m, 1′-H_A), 1.94–1.99 (1H, m, 1′-H_B), 2.13 (3H, s, 14′-H), 2.42 (2H, t, J=7.4 Hz, 12′-H), 3.90 (3H, s, OMe), 3.95 (3H, s, OMe), 5.30 (1H, dd, J=7.8, 3.9 Hz, 3-H), 6.42 (1H, s, 6-H), 6.42 (1H, s, 4-H); ^{13}C NMR (100 MHz, $CDCl_3$) 23.7 (CH_2, C-11′), 24.5 (CH_2, C-2′), 29.0 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.7 (CH_2, C-14′), 34.7 (CH_2, C-1′), 43.6 (CH_2, C-12′), 55.8 (CH_3, OMe), 55.8 (CH_3, OMe), 79.8 (CH, C-3), 97.3 (CH, C-6), 98.4 (CH, C-4), 106.7 (quat., C-7a), 155.1 (quat., C-3a), 159.4 (quat., C-7), 166.5 (quat., C-5), 168.4 (quat., C-1), 209.3 (quat., C-13′); *m/z* (EI+, %) 404 (M^+, 32), 347 (65), 207 (57), 193 (100), 43 (19); HRMS (EI+): found M^+, 404.2559. $C_{24}H_{36}O_5$ requires 404.2563.

4.3.5. CJ-13,104 6. Sodium borohydride (116 mg, 3.07 mmol) was added in one portion to a stirred solution of CJ-13,108 **7** (310 mg, 0.77 mmol) in methanol (10 mL) at 0 °C. The reaction mixture was stirred at room temperature under an atmosphere of nitrogen for 10 min and the solvent removed in vacuo. The residue was dissolved in dichloromethane (10 mL), washed with brine (3×2 mL) and the organic layer dried over magnesium sulfate. Removal of the solvent in vacuo followed by flash column chromatography using ethyl acetate–hexane (1/1) as eluent afforded the title compound **6** (296 mg, 95%) as a colourless solid. The ^{1}H and ^{13}C NMR data obtained were in agreement with the literature values.[4] Mp 100–102 °C; ν_{max} (film) 3413, 3054, 2928, 2854, 1752, 1604, 1495, 1463, 1422, 1337, 1265, 1219, 1159, 1058, 896, 840, 737, 704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 1.18 (3H, d, J=6.2 Hz, 14′-H), 1.20–1.38 (18H, m, 3′-H, 4′-H, 5′-H, 6′-H, 7′-H, 8′-H, 9′-H, 10′-H, 11′-H), 1.38–1.45 (4H, m, 2′-H, 12′-H), 1.67–1.71 (1H, m, 1′-H_A), 2.00–1.96 (1H, m, 1′-H_B), 3.81 (1H, sextet, J=6.1 Hz, 13′-H), 3.89 (3H, s, OMe), 3.95 (3H, s, OMe), 5.30 (1H, dd, J=7.9, 3.7 Hz, 3-H), 6.41 (1H, s, 6-H), 6.41 (1H, s, 4-H); ^{13}C NMR (100 MHz, $CDCl_3$) 23.4 (CH_3, C-14′), 24.6 (CH_2, C-2′), 25.7 (CH_2, C-11′), 29.3 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.5 (CH_2) 29.5 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 34.8 (CH_2, C-1′), 39.3 (CH_2, C-12′), 55.9 (CH_3, OMe), 55.9 (CH_3, OMe), 68.1 (CH, C-13′), 79.9 (CH, C-3), 97.3 (CH, C-6), 98.5 (CH, C-4), 106.9 (quat., C-7a), 155.2 (quat., C-3a), 159.5 (quat., C-7), 166.6 (quat., C-5), 168.5 (quat., C=O); *m/z* (EI+, %) 406 (M^+, 1), 388 (38), 362 (48), 207 (60), 193 (100), 165 (13), 55 (19), 45 (16), 41 (18); HRMS (EI+): found M^+, 406.2713. $C_{24}H_{38}O_5$ requires 406.2719.

4.4. Procedure for the synthesis of (±)-CJ-13,015 3 and CJ-13,102 4

4.4.1. 1-(*tert*-Butyldimethylsilyloxy)-oct-7-ene 23. A solution of 7-octen-1-ol **22** (1.51 g, 11.8 mmol) in dichloromethane (10 mL) was added dropwise to a stirred mixture of imidazole (850 mg, 12 mmol), 4-dimethylaminopyridine (69 mg, 0.57 mmol) and *tert*-butyldimethylsilyl chloride (1.88 g, 12.4 mmol) in dry dichloromethane (30 mL) at 0 °C. After stirring at for 3 h, saturated aqueous sodium bicarbonate (10 mL) was added, the reaction mixture extracted with dichloromethane (3×5 mL) and the organic layer dried over magnesium sulfate. Removal of the solvent in vacuo followed by flash column chromatography using heptane–diethyl ether (99/1) as eluent afforded the title compound **23** (2.74 g, 100%) as a colourless oil. ν_{max} (film) 2955, 2929, 2857, 1641, 1471, 1463, 1414, 1387, 1361, 1255, 1102, 1030, 1005, 993, 937, 909, 836, 811, 775, 660 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 0.05 (6H, s, Si^{t}Bu*Me*$_2$), 0.90 (9H, s, Si^t*Bu*Me$_2$), 1.27–1.32 (4H, m, 3-H, 4-H), 1.36–1.46 (2H, m, 5-H), 1.50 (2H, quintet, J=6.8 Hz, 2-H), 2.05 (2H, dt, J=7.0, 7.0 Hz, 6-H), 3.60 (2H, t, J=6.5 Hz, 1-H), 4.96 (1H, d, J=11.4 Hz, 8-H_A), 4.99 (1H, d, J=19.2 Hz, 8-H_B), 5.76–5.84 (1H, m, 7-H); ^{13}C NMR (100 MHz, $CDCl_3$) −5.3 (CH_3, Si^{t}Bu*Me*$_2$), 17.5 (quat., Si^t*Bu*Me$_2$) 25.0 (CH_2, C-3), 25.3 (CH_3, Si^t*Bu*Me$_2$), 28.3 (CH_2, C-4), 28.3 (CH_2, C-5), 32.2 (CH_2, C-2), 33.2 (CH_2, C-6), 63.1 (CH_2, C-1), 114.7 (CH_2, C-8), 140.0 (CH, C-7); *m/z* (CI, NH_3, %) 243 (MH^+, 100), 202 (4), 185 (29), 132 (12), 91 (13), 71 (12); HRMS (CI, NH_3): found MH^+, 243.2144. $C_{14}H_{30}OSi$ requires 243.2144.

4.4.2. 1-(*tert*-Butyldimethylsilyloxy)-7-epoxyoctane 24. A solution of 1-(*tert*-butyldimethylsilyloxy)-oct-7-ene **23** (2.79 g, 11.5 mmol) in dry dichloromethane (5 mL) was added dropwise to a stirred mixture of 3-chloroperoxybenzoic acid (3.40 g, 20 mmol) and sodium acetate (2.00 g, 23 mmol) in dichloromethane (50 mL) at 0 °C and the mixture stirred for 1 h. After stirring at room temperature for 18 h, the reaction mixture was filtered, washed with saturated aqueous sodium sulfite (3×10 mL), extracted with dichloromethane (3×5 mL) and the organic layer dried over magnesium sulfate. Removal of the solvent in vacuo followed by flash column chromatography using hexane–diethyl ether (3/1) as eluent afforded the title compound **24** (2.77 g, 99%) as a pale yellow oil. ν_{max} (film): 2928, 2856, 1471, 1463, 1409, 1387, 1361, 1255, 1098, 1006, 938, 917, 835, 812, 775, 659 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 0.03 (6H, s, Si^{t}Bu*Me*$_2$), 0.88 (9H, s, Si^t*Bu*Me$_2$), 1.32–1.34 (4H, m, 3-H, 4-H), 1.43–1.54 (6H, m, 2-H, 5-H, 6-H), 2.45 (1H, dd, J=5.0, 2.7 Hz, 8-H_A), 2.73 (1H, dd, J=5.0, 4.1 Hz, 8-H_B), 2.85–2.88 (1H, m, 7-H),

3.59 (2H, t, J=6.5 Hz, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$) −5.3 (CH_3, Si^{t}Bu*Me*$_2$), 18.3 (quat., Si^t*Bu*Me$_2$), 25.8 (CH_2), 26.0 (CH_3, Si^t*Bu*Me$_2$), 26.1 (CH_2), 29.3 (CH_2, C-4), 32.5 (CH_2, C-6), 32.8 (CH_2, C-2), 47.0 (CH_2, C-8), 52.3 (CH, C-7), 63.2 (CH_2, C-1); *m/z* (CI, NH_3, %) 259 (MH^+, 100), 243 (6), 127 (19), 109 (13), 92 (12), 71 (7); HRMS (CI, NH_3): found MH^+, 259.2087. $C_{14}H_{30}O_2Si$ requires 259.2093.

4.4.3. 1-(*tert*-Butyldimethylsilyloxy)undec-10-en-7-ol 25. A solution of allylmagnesium bromide (1.53 mL of a 1 M solution in diethyl ether, 1.53 mmol) was added dropwise to a stirred suspension of copper(I) cyanide (37.6 mg, 0.33 mmol) in diethyl ether (4 mL) at −78 °C. To the resulting stirred cuprate reagent was added a solution of epoxide **24** (198 mg, 0.77 mmol) in diethyl ether (6 mL) at −78 °C. After stirring for 10 h, saturated aqueous ammonium chloride (30 mL) was added and the mixture allowed to warm to room temperature. The reaction mixture was extracted with diethyl ether (3×20 mL) and the organic layer dried over magnesium sulfate. Removal of the solvent in vacuo followed by flash column chromatography using hexane–diethyl ether (4/1) as eluent gave the title compound **25** (1.02 g, 55%) as a pale yellow oil. ν_{max} (film) 3350, 3077, 2929, 2856, 1641, 1471, 1463, 1412, 1388, 1360, 1255, 1100, 1005, 938, 910, 836, 812, 775, 710, 661 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 0.03 (6H, s, Si^{t}Bu*Me*$_2$), 0.88 (9H, s, Si^t*Bu*Me$_2$), 1.26–1.37 (6H, m, 3-H, 4-H, 5-H), 1.38–1.61 (6H, m, 2-H, 6-H, 8-H), 2.09–2.23 (2H, m, 9-H), 3.59 (2H, t, J=6.6 Hz, 1-H), 3.53–3.62 (1H, m, 7-H), 4.96 (1H, dd, J=10.2, 1.7 Hz, 11-H$_A$), 5.04 (1H, dd, J=17.1, 1.7 Hz, 11-H$_B$), 5.78–5.89 (1H, m, 10-H); ^{13}C NMR (100 MHz, $CDCl_3$) −5.3 (CH_3, Si^{t}Bu*Me*$_2$), 18.4 (quat., Si^t*Bu*Me$_2$), 25.6 (CH_2), 25.8 (CH_2) 26.0 (CH_3, Si^t*Bu*Me$_2$), 29.5 (CH_2), 30.1 (CH_2, C-9), 32.8 (CH_2, C-2), 36.5 (CH_2), 37.4 (CH_2), 63.2 (CH_2, C-1), 71.5 (CH, C-7), 114.7 (CH_2, C-11), 138.6 (CH, C-10); *m/z* (CI, NH_3, %) 301 (MH^+, 18), 283 (20), 151 (14), 109 (50), 95 (100), 83 (20), 81 (42), 75 (49); HRMS (CI, NH_3): found MH^+, 301.2561. $C_{17}H_{36}O_2Si$ requires 301.2563.

4.4.4. 7-(Benzyloxy)-1-(*tert*-butyldimethylsilyloxy) undec-10-ene 26. A solution of alcohol **25** (161 mg, 0.53 mmol) in *N*,*N*-dimethylformamide (1 mL) was added dropwise to a stirred suspension of sodium hydride (15 mg, 0.64 mmol) and tetrabutylammonium iodide (51 mg, 0.15 mmol) in *N*,*N*-dimethylformamide (1 mL) at 0 °C. After stirring for 75 min, benzyl bromide (0.08 mL, 0.64 mmol) was added dropwise and the reaction mixture stirred at room temperature for 18 h. Saturated aqueous ammonium chloride (5 mL) was added, the reaction mixture extracted with diethyl ether (3×5 mL) and the organic layer dried over magnesium sulfate. Removal of the solvent in vacuo followed by flash column chromatography using hexane–diethyl ether (49/1) as eluent gave the title compound **26** (170 mg, 81%) as a yellow oil. ν_{max} (film) 3065, 3030, 2929, 2857, 1640, 1496, 1471, 1462, 1454, 1387, 1360, 1254, 1206, 1098, 1071, 1028, 1005, 994, 938, 910, 836, 813, 775, 734, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 0.05 (6H, s, Si^{t}Bu*Me*$_2$), 0.90 (9H, s, Si^t*Bu*Me$_2$), 1.25–1.43 (6H, m, 3-H, 4-H, 5-H), 1.46–1.65 (6H, m, 2-H, 6-H, 8-H), 2.01–2.17 (2H, m, 9-H), 3.39 (1H, quintet, J=5.9 Hz, 7-H), 3.60 (2H, t, J=6.6 Hz, 1-H), 4.49 (2H, s, OC*H*$_2$Ph), 4.94 (1H, dd, J=8.8, 2.0 Hz, 11-H$_A$), 5.00 (1H, dd, J=17.2, 2.0 Hz, 11-H$_B$), 5.77–5.87 (1H, m, 10-H), 7.24–7.38 (5H, m, OCH$_2$*Ph*); ^{13}C NMR (100 MHz, $CDCl_3$) −5.3 (CH_3, Si^{t}Bu*Me*$_2$), 18.4 (quat., Si^t*Bu*Me$_2$), 25.3 (CH_2), 25.8 (CH_2), 26.0 (CH_3, Si^t*Bu*Me$_2$), 29.6 (CH_2), 29.6 (CH_2), 32.8 (CH_2), 33.1 (CH_2, C-8), 33.7 (CH_2), 63.3 (CH_2, C-1), 70.8 (CH_2, O*C*H$_2$Ph), 78.4 (CH, C-7), 114.4 (CH_2, C-11), 127.4 (CH, OCH$_2$*Ph*), 127.7 (CH, OCH$_2$*Ph*), 128.3 (CH, OCH$_2$*Ph*), 138.8 (CH, C-10), 139.0 (quat., OCH$_2$*Ph*); *m/z* (CI, NH_3, %) 391 (MH^+, 7), 283 (17), 216 (28), 108 (18), 92 (45), 91 (100); HRMS (CI, NH_3): found MH^+, 391.3034. $C_{24}H_{42}O_2Si$ requires 391.3032.

4.4.5. 7-(Benzyloxy)undec-10-en-1-ol 27. Tetrabutylammonium fluoride (4.13 mL of a 1 M solution in tetrahydrofuran, 4.13 mmol) was added dropwise to a stirred mixture of silyl ether **26** (1.08 g, 2.75 mmol) and 4 Å molecular sieves (200 mg) in tetrahydrofuran (15 mL) at 0 °C. After stirring for 2 h, saturated aqueous ammonium chloride (10 mL) was added, the reaction mixture extracted with diethyl ether (3×5 mL) and the organic layer dried over magnesium sulfate. Removal of the solvent in vacuo followed by flash column chromatography using hexane–diethyl ether (4/1) as eluent gave the title compound **27** (613 mg, 97%) as a yellow oil. ν_{max} (film): 3368, 3065, 3030, 2931, 2857, 1640, 1496, 1454, 1414, 1396, 1350, 1307, 1257, 1206, 1067, 1028, 994, 910, 735, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 1.30–1.44 (6H, m, 3-H, 4-H, 5-H), 1.50–1.70 (6H, m, 2-H, 6-H, 8-H), 2.11–2.15 (2H, m, 9-H), 3.40 (1H, quintet, J=5.8 Hz, 7-H), 3.63 (2H, t, J=6.6 Hz, 1-H), 4.50 (2H, s, OC*H*$_2$Ph), 4.95 (1H, dd, J=10.2, 1.6 Hz, 11-H$_A$), 5.01 (1H, dd, J=17.2, 1.6 Hz, 11-H$_B$), 5.77–5.85 (1H, m, 10-H), 7.25–7.36 (5H, m, OCH$_2$*Ph*); ^{13}C NMR (100 MHz, $CDCl_3$) 25.2 (CH_2), 25.7 (CH_2), 29.6 (CH_2), 29.6 (CH_2, C-9), 32.7 (CH_2), 33.1 (CH_2, C-8), 33.7 (CH_2), 63.0 (CH_2, C-1), 70.8 (CH_2, O*C*H$_2$Ph), 78.3 (CH, C-7), 114.4 (CH_2, C-11), 127.4 (CH, OCH$_2$*Ph*), 127.8 (CH, OCH$_2$*Ph*), 128.3 (CH, OCH$_2$*Ph*) 138.8 (CH, C-10), 139.0 (quat., OCH$_2$*Ph*); *m/z* (EI+, %) 276 (M^+, 1), 175 (4), 107 (9), 92 (10), 91 (100), 65 (4), 55 (5), 41 (4); HRMS (EI+): found M^+, 276.2089. $C_{18}H_{28}O_2$ requires 276.2089.

4.4.6. 7-(Benzyloxy)-1-bromoundec-10-ene 28. A solution of carbon tetrabromide (1.44 g, 4.34 mmol) in acetonitrile (2 mL) was added dropwise to a stirred mixture of alcohol **27** (0.60 g, 2.17 mmol) and triphenylphosphine (1.14 g, 4.34 mmol) in acetonitrile (20 mL) at 0 °C. After stirring the reaction mixture at room temperature for 30 min, saturated aqueous sodium bicarbonate (10 mL) was added and the reaction mixture extracted with diethyl ether (3×5 mL). The organic layer was washed with brine (2×10 mL) and dried over magnesium sulfate. Removal of the solvent in vacuo followed by flash column chromatography using hexane–diethyl ether (49/1) as eluent gave the title compound **28** (0.72 g, 98%) as a colourless oil. ν_{max} (film): 3064, 3029, 2933, 2857, 1640, 1496, 1453, 1349, 1306, 1260, 1206, 1093, 1067, 1028, 993, 910, 734, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 1.25–1.47 (6H, m, 3-H, 4-H, 5-H), 1.48–1.70 (4H, m, 6-H, 8-H), 1.83 (2H, quintet, J=7.2 Hz, 2-H), 2.08–2.22 (2H, m, 9-H), 3.37–3.43 (3H, m, 1-H, 7-H), 4.49 (2H, s, OC*H*$_2$Ph), 4.95 (1H, dd, J=10.2, 1.6 Hz, 11-H$_A$), 5.01 (1H, dd, J=17.2, 1.6 Hz, 11-H$_B$), 5.77–5.85 (1H, m, 10-H), 7.25–7.36 (5H, m, OCH$_2$*Ph*);

^{13}C NMR (100 MHz, $CDCl_3$) 25.1 (CH_2), 28.1 (CH_2), 28.9 (CH_2), 29.6 (CH_2, C-9), 32.7 (CH_2), 33.1 (CH_2, C-8), 33.6 (CH_2), 33.9 (CH_2, C-1), 70.8 (CH_2, O*C*H_2Ph), 78.3 (CH, C-7), 114.5 (CH_2, C-11), 127.4 (CH, OCH$_2$*Ph*), 127.7 (CH, OCH$_2$*Ph*), 128.3 (CH, OCH$_2$*Ph*), 138.7 (CH, C-10), 139.0 (quat., OCH$_2$*Ph*); *m/z* (EI+, %) 339 (M^+, 0.1), 175 (9), 107 (9), 92 (10), 91 (100), 65 (4), 55 (5), 41 (5); HRMS (EI+): found M^+, 338.1243, 340.1219. $C_{18}H_{27}BrO$ requires 338.1245, 340.1225.

4.4.7. [7-(Benzyloxy)undec-10-en-1-yl]triphenylphosphonium bromide 11. Triphenylphosphine (1.18 g, 4.51 mmol) was added in one portion to a stirred solution of bromide **28** (765 mg, 2.26 mmol) in acetonitrile (10 mL) at room temperature. The mixture was heated under an atmosphere of nitrogen at reflux for 26 h. Removal of the solvent in vacuo followed by flash column chromatography using dichloromethane–methanol (19/1) as eluent gave the title compound **11** (1.08 g, 80%) as a wax. ν_{max} (film) 3377, 3055, 3031, 3007, 2989, 2934, 2859, 2791, 1639, 1618, 1587, 1495, 1485, 1453, 1438, 1413, 1344, 1315, 1273, 1190, 1161, 1113, 1066, 1027, 996, 912, 788, 725, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 1.20–1.36 (4H, m, 4-H, 5-H), 1.41–1.68 (8H, m, 2-H, 3-H, 6-H, 8-H), 2.04–2.17 (2H, m, 9-H), 3.35 (1H, quintet, J=5.8 Hz, 7-H), 3.84–3.91 (2H, m, 1-H), 4.45 (2H, s, O*CH*$_2$Ph) 4.94 (1H, dd, J=10.2, 1.6 Hz, 11-H$_A$), 4.99 (1H, dd, J=17.1, 1.6 Hz, 11-H$_B$), 5.74–5.85 (1H, m, 10-H), 7.25–7.31 (5H, m, OCH$_2$*Ph*), 7.65–7.89 (15H, m, P*Ph*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 22.5 (CH_2, d, J=7 Hz, C-2), 22.7 (CH_2, d, J=49 Hz, C-1), 24.8 (CH_2, C-5), 29.4 (CH_2, C-4), 29.6 (CH_2, C-9), 30.3 (CH_2, d, J=15 Hz, C-3), 33.0 (CH_2, C-8), 33.6 (CH_2, C-6), 70.7 (CH_2, O*C*H$_2$Ph), 78.2 (CH, C-7), 114.4 (CH_2, C-11), 118.4 (quat., d, J=85 Hz, P*Ph*$_3$), 127.4 (CH, OCH$_2$*Ph*), 127.7 (CH, OCH$_2$*Ph*), 128.3 (CH, OCH$_2$*Ph*), 130.4 (CH, d, J=12 Hz, P*Ph*$_3$), 133.7 (CH, d, J=10 Hz, P*Ph*$_3$), 134.9 (CH, P*Ph*$_3$) 138.7 (CH, C-10), 139.0 (quat., OCH$_2$*Ph*); *m/z* (FAB+, %) 521 (M^+−Br, 100), 429 (4), 413 (5), 373 (6), 275 (4), 262 (8), 183 (6), 91 (15); HRMS (FAB): found M^+−Br, 521.2965. $C_{36}H_{42}BrOP$ requires 521.2973.

4.4.8. 3-(10′-Benzyloxytetradec-3′,13′-dien-1′-yl)-5,7-dimethoxy-(3*H*)-isobenzofuran-1-one 29. *n*-Butyllithium (0.23 mL of a 1.6 M solution in hexanes, 0.37 mmol) was added dropwise to a stirred solution of phosphonium salt **11** (200 mg, 0.33 mmol) in dry tetrahydrofuran (5 mL) at −78 °C. The resulting deep orange solution was warmed to room temperature, re-cooled to −78 °C, and a solution of phthalide aldehyde **9** (69 mg, 0.28 mmol) in dry tetrahydrofuran (2 mL) was added dropwise with stirring. The mixture was warmed to room temperature, stirred for 2 h and the solvent removed in vacuo. The resulting residue was dissolved in dichloromethane (20 mL), washed with brine (3×5 mL) and the organic layer dried over magnesium sulfate. Removal of the solvent in vacuo followed by flash column chromatography using hexane–diethyl ether (4/6) as eluent gave the title compound **29** (98 mg, 72%) as a viscous colourless oil. ν_{max} (film) 3505, 3065, 3005, 2931, 2855, 1759, 1639, 1613, 1495, 1462, 1455, 1432, 1360, 1338, 1216, 1158, 1108, 1062, 1028, 911, 837, 735, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 1.23–1.46 (6H, m, 6′-H, 7′-H, 8′-H), 1.48–1.66 (4H, m, 9′-H, 11′-H), 1.67–1.78 (1H, m, 1′-H$_A$), 1.94–2.05 (3H, m, 1′-H$_B$, 5′-H), 2.09–2.21 (3H, m, 2′-H$_A$, 12′), 2.22–2.35 (1H, m, 2′-H$_B$), 3.40 (1H, quintet, J=5.8 Hz, 10′-H), 3.86 (3H, s, OMe), 3.92 (3H, s, OMe), 4.49 (2H, s, O*CH*$_2$Ph), 4.94 (1H, dd, J=10.2, 1.8 Hz, 14′-H$_A$), 5.00 (1H, dd, J=17.2, 1.8 Hz, 14′-H$_B$), 5.22–5.28 (1H, m, 3-H), 5.30–5.47 (2H, m, 3′-H, 4′-H), 5.72–5.88 (1H, m, 13′-H), 6.40 (2H, br s, 4-H, 6-H), 7.21–7.36 (5H, m, OCH$_2$*Ph*); ^{13}C NMR (100 MHz, $CDCl_3$) 22.8 (CH_2, C-2′), 25.2 (CH_2, C-8′), 27.2 (CH_2, C-5′), 29.4 (CH_2), 29.6 (CH_2), 29.6 (CH_2, C-12′), 33.1 (CH_2, C-11′), 33.7 (CH_2, C-9′), 35.0 (CH_2, C-1′), 55.9 (CH_3, OMe), 56.0 (CH_3, OMe), 70.8 (CH_2, O*C*H$_2$Ph), 78.4 (CH, C-10′), 79.3 (CH, C-3), 97.3 (CH, C-6), 98.7 (CH, C-4), 106.9 (quat., C-7a), 114.4 (CH_2, C-14′), 127.4 (CH, OCH$_2$*Ph*), 127.6 (CH, C-3′), 127.7 (CH, OCH$_2$*Ph*), 128.3 (CH, OCH$_2$*Ph*), 131.7 (CH, C-4′), 138.8 (quat., OCH$_2$*Ph*), 139.0 (CH, C-13′), 155.1 (quat., C-3a), 159.6 (quat., C-7), 166.7 (quat., C-5), 168.5 (quat., C=O); *m/z* (FAB+, %) 493 (MH^+, 9), 385 (8), 219 (5), 120 (11), 91 (22); HRMS (FAB): found MH^+, 493.2953. $C_{31}H_{40}O_5$ requires 493.2954.

4.4.9. 3-(10′-Benzyloxy-13′-oxotetradec-3′-en-1′-yl)-5,7-dimethoxy-(3*H*)-isobenzofuran-1-one 30. Palladium(II) chloride (11 mg, 0.06 mmol) and copper(I) chloride (15 mg, 0.16 mmol) were added in one portion to a stirred solution of diene **29** (64 mg, 0.13 mmol) in *N*,*N*-dimethylformamide–water (4 mL/0.5 mL) at room temperature. The reaction mixture was bubbled with oxygen gas with stirring for 3 h. The mixture was filtered through Celite® and the solvent removed in vacuo. The resulting residue was dissolved in dichloromethane (10 mL), washed with brine (3×2 mL) and dried over magnesium sulfate. Removal of the solvent in vacuo followed by flash column chromatography using hexane–ethyl acetate (1/1) as eluent afforded the title compound **30** (35 mg, 54%) as a viscous colourless oil. ν_{max} (film) 3503, 3061, 3005, 2930, 2855, 1755, 1713, 1605, 1494, 1456, 1432, 1359, 1338, 1271, 1217, 1158, 1108, 1062, 1028, 972, 837, 735, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 1.20–1.50 (6H, m, 6′-H, 7′-H, 8′-H), 1.53–1.65 (2H, m, 9′-H), 1.67–1.78 (2H, m, 1′-H$_A$, 11′-H$_A$), 1.82–1.93 (1H, m, 11′-H$_B$), 1.94–2.05 (3H, m, 1′-H$_B$, 5′-H), 2.11 (3H, s, 14′-H), 2.13–2.23 (1H, m, 2′-H$_A$,), 2.23–2.35 (1H, m, 2′-H$_B$), 2.48–2.53 (2H, m, 12′-H), 3.38–3.40 (1H, m, 10′-H), 3.89 (3H, s, OMe), 3.95 (3H, s, OMe), 4.43 (1H, d, J=11.5 Hz, O*CH*$_A$H$_B$Ph), 4.51 (1H, d, J=11.5 Hz, OCH$_A$*H*$_B$Ph), 5.28–5.30 (1H, m, 3-H), 5.35–5.45 (2H, m, 3′-H, 4′-H), 6.41 (1H, s, 4-H), 6.42 (1H, s, 6-H), 7.30–7.34 (5H, m, OCH$_2$*Ph*); ^{13}C NMR (100 MHz, $CDCl_3$) 22.8 (CH_2, C-2′), 25.2 (CH_2, C-8′), 27.2 (CH_2, C-5′), 27.5 (CH_2, C-11′), 29.4 (CH_2), 29.6 (CH_2), 30.0 (CH_3, C-14′), 33.7 (CH_2, C-9′), 35.0 (CH_2, C-1′), 39.3 (CH_2, C-12′), 55.9 (CH_3, OMe), 56.0 (CH_3, OMe), 70.8 (CH_2, O*C*H$_2$Ph), 77.9 (CH, C-10′), 79.3 (CH, C-3), 97.3 (CH, C-6), 98.7 (CH, C-4), 106.9 (quat., C-7a), 127.5 (CH, OCH$_2$*Ph*), 127.6 (CH, C-3′), 127.8 (CH, OCH$_2$*Ph*), 128.3 (CH, OCH$_2$*Ph*), 131.7 (CH, C-4′), 138.8 (quat., OCH$_2$*Ph*), 155.1 (quat., C-3a), 159.6 (quat., C-7), 166.7 (quat., C-5), 168.5 (quat., C-1), 209.1 (quat., C-13′); *m/z* (FAB+, %) 509 (MH^+, 2), 401 (9), 219 (4), 124 (7), 120 (8), 91 (19), 89 (22); HRMS (FAB+): found MH^+, 509.2904. $C_{31}H_{40}O_6$ requires 509.2903.

4.4.10. 5,7-Dimethoxy-3-(10′-hydroxy-13′-oxotetradec-1′-ly)-(3*H*)-isobenzofuran-1-one 14. Palladium 10% on

carbon (20 mg, 0.036 mmol) was added in one portion to a stirred solution of benzyl ether **30** (35 mg, 0.07 mmol) in ethyl acetate (5 mL) at room temperature. The reaction mixture was bubbled with hydrogen gas for 3 h and filtered through a pad of Celite®. Removal of the solvent in vacuo afforded the title compound **14** as a colourless oil (25 mg) that was not purified further before use in the subsequent steps.

4.4.11. (±)-CJ-13,015 3. Tetra-*n*-propylammonium perruthenate (5 mg, 0.01 mmol) and *N*-methylmorpholine *N*-oxide (10 mg, 0.09 mmol) were added to a stirred solution of crude alcohol **14** (11 mg) in dichloromethane (2 mL) at room temperature. The reaction mixture was stirred for 30 min then filtered through a pad of silica. Removal of the solvent in vacuo followed by flash column chromatography using hexane–ethyl acetate (1/1) as eluent afforded the title compound **3** (4 mg, 37% over two steps) as a colourless solid. The ^{1}H and ^{13}C NMR data obtained were in agreement with the literature values.[4] Mp 103–104 °C; ν_{max} (film) 3584, 2925, 2852, 1756, 1710, 1603, 1494, 1465, 1431, 1413, 1360, 1337, 1218, 1159, 1099, 1053, 1028, 836, 689 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 1.18–1.39 (10H, m, 3′-H, 4′-H, 5′-H, 6′-H, 7′-H), 1.37–1.52 (2H, m, 2′-H), 1.52–1.74 (3H, m, 1′-H_A, 8′-H), 1.92–2.03 (1H, m, 1′-H_B), 2.19 (3H, s, 14′-H), 2.44 (2H, t, J=7.4 Hz, 9′-H), 2.67–2.72 (4H, m, 11′-H, 12′-H), 3.90 (3H, s, OMe), 3.95 (3H, s, OMe), 5.30 (1H, dd, J=7.9, 3.7 Hz, 3-H), 6.41 (1H, s, 4-H), 6.42 (1H, s, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$) 23.8 (CH_2, C-8′), 24.6 (CH_2, C-2′), 29.1 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 30.0 (CH_3, C-14′), 34.8 (CH_2, C-1′), 36.0 (CH_2, C-12′), 36.9 (CH_2, C-11′), 42.8 (CH_2, C-9′), 55.9 (CH_3, OMe), 56.0 (CH_3, OMe), 79.9 (CH, C-3), 97.3 (CH, C-6), 98.6 (CH, C-4), 106.9 (quat., C-7a), 155.2 (quat., C-3a), 159.6 (quat., C-7), 166.6 (quat., C-5), 168.6 (quat., C-1), 207.4 (quat., C-13′), 209.7 (quat., C-10′); *m/z* (FAB+, %) 419 (MH^+, 5), 403 (73), 120 (14), 89 (19); HRMS (FAB+): found MH^+, 419.2431. $C_{24}H_{34}O_6$ requires 419.2434.

4.4.12. CJ-13,102 4. Acetic anhydride (2 mL, 21.16 mmol) was added dropwise to a stirred mixture of crude alcohol **14** (11 mg) and *N*,*N*-dimethyl-4-aminopyridine (5 mg, 0.04 mmol) in pyridine (2 mL) at room temperature. The reaction mixture was stirred for 8 h and the solvent removed in vacuo. Flash column chromatography using hexane–ethyl acetate (1/1) as eluent afforded the title compound **4** (10 mg, 83% over two steps) as a colourless oil. ^{1}H and ^{13}C NMR data obtained were in agreement with the literature values.[4] ν_{max} (film) 3504, 2927, 2853, 1756, 1718, 1603, 1494, 1464, 1432, 1359, 1337, 1241, 1218, 1159, 1104, 1052, 1028, 837, 732, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 1.20–1.35 (10H, m, 3′-H, 4′-H, 5′-H, 6′-H, 7′-H), 1.35–1.58 (4H, m, 8′-H, 2′-H), 1.61–1.80 (3H, m, 1′-H_A, 9′-H), 1.84–2.02 (3H, m, 1′-H_B, 11′-H), 2.05 (3H, s, O*Ac*) 2.15 (3H, s, 14′-H), 2.45 (2H, t, J=7.4 Hz, 12′-H), 3.90 (3H, s, OMe), 3.95 (3H, s, OMe), 4.82–4.88 (1H, m, 10′-H), 5.29 (1H, dd, J=7.8, 3.7 Hz, 3-H), 6.41 (1H, s, 4-H), 6.42 (1H, s, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$) 21.2 (CH_3, O*Ac*), 24.6 (CH_2, C-2′), 25.2 (CH_2, C-8′), 27.9 (CH_2, C-11′), 29.3 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.4 (CH_2) 30.0 (CH_3, C-14′), 34.2 (CH_2, C-9′), 34.8 (CH_2, C-1′), 39.5 (CH_2, C-12′), 55.9 (CH_3, OMe), 56.0 (CH_3, OMe), 73.5 (CH, C-10′), 80.0 (CH, C-3), 97.3 (CH, C-6), 98.6 (CH, C-4), 106.9 (quat., C-7a), 155.2 (quat., C-3a), 159.6 (quat., C-7), 166.6 (quat., C-5), 168.6 (quat., C-1), 170.9 (quat., O*Ac*), 208.0 (quat., C-13′); *m/z* (FAB+, %) 463 (MH^+, 3), 403 (11), 120 (15), 89 (23), 73 (12); HRMS (FAB+): found MH^+, 463.2703. $C_{26}H_{38}O_7$ requires 463.2696.

4.5. Procedure for the synthesis of (±)-CJ-13,103 5

4.5.1. 1-(*tert*-Butyldimethylsilyloxy)dec-9-ene 32. Using a similar method to that described above for the preparation of sily ether **23**, alcohol **31** (3.6 g, 23.04 mmol) was reacted with *tert*-butyldimethylsilyl chloride (5.53 g, 29.90 mmol) to afford the the title compound **32** (6.00 g, 96%) as a colourless oil. The ^{1}H and ^{13}C NMR data obtained were in agreement with the literature values.[11]

4.5.2. 9-(*tert*-Butyldimethylsilyloxy)nonanal 33. A solution of alkene **32** (5.00 g, 18.5 mmol) in methanol (20 mL) was cooled to −50 °C under nitrogen. Ozone was bubbled through the solution for 10 min at a rate of 1 L/min. The mixture was flushed with nitrogen and dimethyl sulfide (5 mL) was added. The resulting mixture was warmed to room temperature, further dimethyl sulfide added (2 mL) and the mixture stirred for 1 h. The solvent was removed in vacuo and the resulting yellow residue dissolved in water (5 mL), extracted with diethyl ether (3×10 mL) and the organic layer dried over magnesium sulfate. Removal of the solvent in vacuo followed by flash column chromatography using ethyl acetate–hexane (1/1) as eluent afforded the title compound **33** (4.80 g, 95%) as an oil. The ^{1}H NMR data obtained was in agreement with the literature values.[12]

4.5.3. 1-(*tert*-Butyldimethylsilyloxy)tridec-12-en-9-ol 34. A solution of aldehyde **33** (5.00 g, 18.3 mmol) in diethyl ether (15 mL) was added dropwise to a stirred solution of but-3-en-1-ylmagnesium bromide (56 mL of 0.5 M solution in diethyl ether, 28 mmol) at 0 °C and the reaction mixture allowed to warm to room temperature. After stirring for 30 min, saturated aqueous ammonium chloride (20 mL) was added, the reaction mixture extracted with diethyl ether (3× 10 mL) and the organic layer dried over magnesium sulfate. Removal of the solvent in vacuo followed by flash column chromatography using ethyl acetate–hexane (1/1) as eluent afforded the title compound **34** as a yellow oil. ν_{max} (film) 3361, 2929, 2856, 1641, 1471, 1463, 1387, 1361, 1255, 1100, 1006, 938, 909, 835, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 0.02 (6H, s, Si^{t}Bu*Me*$_2$), 0.87 (9H, s, Si^{t}*Bu*Me$_2$), 1.22–1.34 (8H, m, 3-H, 4-H, 5-H, 6-H), 1.38–1.66 (8H, m, 2-H, 7-H, 8-H, 10-H), 2.10–2.20 (2H, m, 11-H), 3.56–3.59 (3H, m, 1-H, 9-H), 4.94 (1H, d, J=10.2 Hz, 13-H_A), 5.02 (1H, d, J=17.2 Hz, 13-H_B), 5.78–5.85 (1H, m, 12-H); ^{13}C NMR (100 MHz, $CDCl_3$) −5.3 (CH_3, Si^{t}Bu*Me*$_2$), 18.3 (quat., Si^{t}*Bu*Me$_2$), 25.6 (CH_2), 25.7 (CH_2), 25.9 (CH_3, Si^{t}*Bu*Me$_2$), 29.3 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 30.0 (CH_2, C-11), 32.8 (CH_2, C-2), 36.4 (CH_2), 37.4 (CH_2), 63.2 (CH_2, C-1), 71.5 (CH, C-7), 114.7 (CH_2, C-11), 138.6 (CH, C-10); *m/z* (FAB+, %) 329 (MH^+, 27), 311 (17), 123 (14), 115 (16), 109 (21), 95 (40), 89 (27), 81 (37), 75 (83); HRMS (FAB+): found MH^+, 329.2883. $C_{19}H_{40}O_2Si$ requires 329.2876.

4.5.4. 9-Benzyloxy-1-(*tert*-butyldimethylsilyloxy)tridec-12-ene 35. Using a similar method to that described above

for the preparation of benzyl ether **26**, alcohol **34** (944 mg, 2.87 mmol) was reacted with benzyl bromide (0.48 mL, 4.02 mmol) to afford the title compound **35** (1.14 g, 95%) as a yellow oil. ν_{max} (film) 3065, 3031, 2929, 2856, 1641, 1496, 1471, 1462, 1454, 1387, 1360, 1306, 1254, 1207, 1098, 1071, 1028, 1005, 938, 909, 835, 814, 775, 733, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 0.05 (6H, s, Si^{t}BuMe_2), 0.90 (9H, s, Si^t*Bu*Me$_2$), 1.22–1.38 (8H, m, 3-H, 4-H, 5-H, 6-H), 1.44–1.70 (8H, m, 2-H, 7-H, 8-H, 10-H), 2.10–2.29 (2H, m, 11-H), 3.38–3.47 (1H, m, 9-H), 3.59–3.67 (2H, m, 1-H), 4.53 (2H, s, *OCH*$_2$Ph) 4.88–5.05 (2H, m, 13-H), 5.87–5.92 (1H, m, 12-H), 7.27–7.38 (5H, m, OCH$_2$*Ph*); ^{13}C NMR (100 MHz, $CDCl_3$) −5.3 (CH_3, Si^{t}Bu*Me*$_2$), 18.3 (quat., Si^t*Bu*Me$_2$), 25.2 (CH_2), 25.7 (CH_2), 25.9 (CH_3, Si^t*Bu*Me$_2$), 29.3 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 32.8 (CH_2), 33.1 (CH_2), 33.7 (CH_2), 63.2 (CH_2, C-1), 70.7 (CH_2, O*C*H$_2$Ph), 78.3 (CH, C-9), 114.4 (CH_2, C-13), 127.3 (CH, OCH$_2$*Ph*), 127.7 (CH, OCH$_2$*Ph*), 128.2 (CH, OCH$_2$*Ph*), 138.7 (CH, C-12), 139.0 (quat., OCH$_2$*Ph*); *m/z* (FAB+, %) 419 (MH^+, 5), 311 (11), 95 (13), 91 (100), 89 (14), 81 (13), 75 (81); HRMS (FAB+): found MH^+, 419.3341. $C_{26}H_{46}O_2Si$ requires 419.3345.

4.5.5. 1-Bromo-9-(benzyloxy)tridec-12-ene 36. Bromine (1.71 mL, 33.4 mmol) was added dropwise to a stirred solution of triphenylphosphine (8.89 g, 33.9 mmol) in dichloromethane (100 mL) at 0 °C. The mixture was warmed to room temperature resulting in formation of a white suspension to which was added a solution of silyl ether **35** (2.00 g, 4.78 mmol) in dichloromethane dropwise with stirring. The resulting mixture was stirred for 24 h at room temperature then filtered through a plug of silica using hexane–ethyl acetate (9/1) as eluent, affording the title compound **36** (1.60 g, 4.40 mmol) as a colourless oil. ν_{max} (film) 3064, 3029, 2929, 2854, 1639, 1496, 1453, 1349, 1305, 1252, 1206, 1093, 1067, 1027, 994, 910, 733, 696, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 1.25–1.32 (6H, m, 4′-H, 5′-H, 6′-H), 1.34–1.45 (4H, m, 3′-H, 7′-H), 1.46–4.70 (4H, m, 8′-H, 10′-H), 1.84 (2H, quintet, J=7.2 Hz, 2-H), 2.06–2.20 (2H, m, 11-H), 3.35–3.43 (3H, m, 1-H, 9-H), 4.49 (2H, s, OC*H*$_2$Ph), 4.93–4.96 (1H, m, 13-H$_A$), 5.01 (1H, dd, J=17.2, 1.6 Hz, 13-H$_B$), 5.78–5.85 (1H, m, 10-H), 7.22–7.36 (5H, m, OCH$_2$*Ph*); ^{13}C NMR (100 MHz, $CDCl_3$) 25.1 (CH_2), 28.1 (CH_2), 28.6 (CH_2), 29.3 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 32.7 (CH_2), 33.0 (CH_2), 33.6 (CH_2), 34.0 (CH_2, C-1), 70.7 (CH_2, O*C*H$_2$Ph), 78.3 (CH, C-9), 114.4 (CH_2, C-13), 127.3 (CH, OCH$_2$*Ph*), 127.7 (CH, OCH$_2$*Ph*), 128.2 (CH, OCH$_2$*Ph*), 138.7 (CH, C-12), 139.0 (quat., OCH$_2$*Ph*); *m/z* (EI+, %) 368 (M^+, 0.1), 366 (M^+, 0.1), 175 (11), 92 (11), 91 (100); HRMS (EI+): found M^+, 366.1550, 368.1537. $C_{20}H_{31}BrO$ requires 366.1558, 368.1538.

4.5.6. [9-(Benzyloxy)tridec-12-en-1-yl]triphenylphosphonium bromide 12. Using a similar method to that described above for the preparation of phosphonium salt **11**, bromide **36** (730 mg, 1.99 mmol) was reacted with triphenylphosphine (680 mg, 2.58 mmol) to afford the title compound **12** (1.0 g, 80%) as a wax. ν_{max} (film) 3390, 3056, 3007, 2989, 2928, 2856, 2792, 2174, 1639, 1615, 1587, 1485, 1463, 1454, 1439, 1413, 1340, 1317, 1271, 1190, 1162, 1113, 1069, 1027, 996, 923, 787, 723, 691, 638 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 1.16–1.36 (8H, m, 3′-H, 4′-H, 5′-H, 6′-H), 1.41–1.56 (2H, m, 7′-H), 1.57–1.71 (4H, m, 2′-H, 8′-H), 1.72–2.36 (4H, m, 10′-H, 11′-H), 3.35–3.45 (1H, m, 9-H), 3.64–3.82 (2H, m, 1-H), 4.48 (2H, s, OC*H*$_2$Ph), 4.89–5.07 (2H, m, 13-H), 5.71–5.89 (1H, m, 12-H), 7.20–7.40 (5H, m, OCH$_2$*Ph*), 7.65–7.94 (15H, m, P*Ph*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 22.3 (CH_2, d, J=9 Hz, C-2), 22.6 (CH_2, d, J=46 Hz, C-1), 24.8 (CH_2), 27.1 (CH_2), 28.7 (CH_2), 28.8 (CH_2), 29.3 (CH_2, d, J=5 Hz, C-4), 30.1 (CH_2, d, J=16 Hz, C-3), 32.8 (CH_2), 33.4 (CH_2), 70.4 (CH_2, O*C*H$_2$Ph), 78.1 (CH, C-9), 114.1 (CH_2, C-13), 118.0 (quat., d, J=86 Hz, P*Ph*$_3$), 127.0 (CH, OCH$_2$*Ph*), 127.4 (CH, OCH$_2$*Ph*), 127.9 (CH, OCH$_2$*Ph*), 130.2 (CH, d, J=13 Hz, P*Ph*$_3$), 133.3 (CH, d, J=10 Hz, P*Ph*$_3$), 134.8 (CH, d, J=3 Hz, P*Ph*$_3$), 138.4 (CH, C-12), 138.7 (quat., OCH$_2$*Ph*); *m/z* (FAB+, %) 549 (M^+−Br, 100), 523 (28), 521 (28), 459 (18), 441 (92), 401 (51), 275 (12), 262 (27), 183 (15), 91 (14).

4.5.7. 3-(12′-Benzyloxyhexadec-3′,15′-dien-1′-yl)-5,7-dimethoxy-(3*H*)-isobenzofuran-1-one 37. Using a similar method to that described above for the preparation of diene **29**, phosphonium salt **12** (300 mg, 0.48 mmol) was reacted with phthalide aldehyde **9** (120 mg, 0.48 mmol) to afford the title compound **37** (181 mg, 73%) as a viscous colourless oil. ν_{max} (film) 3514, 3075, 3006, 2927, 2853, 1759, 1640, 1614, 1495, 1463, 1455, 1434, 1360, 1338, 1217, 1158, 1109, 1061, 1029, 912, 837, 735, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 1.22–1.42 (10H, m, 6′-H, 7′-H, 8′-H, 9′-H, 10′-H), 1.45–1.88 (5H, m, 1′-H$_A$, 11′-H, 13′-H), 1.92–2.07 (3H, m, 1′-H$_B$, 5′-H), 2.08–2.21 (3H, m, 2′-H$_A$, 14′-H), 2.22–2.37 (1H, m, 2′-H$_B$), 3.37–3.43 (1H, m, 12′-H), 3.89 (3H, s, OMe), 3.95 (3H, s, OMe), 4.49 (2H, OC*H*$_2$Ph), 4.89–5.11 (2H, m, 16′-H$_A$), 5.29 (1H, dd, J=8.5, 3.3 Hz, 3-H), 5.33–5.48 (2H, m, 3′-H, 4′-H), 5.71–5.87 (1H, m, 15′-H), 6.41 (2H, br s, 4-H, 6-H), 7.22–7.37 (5H, m, OCH$_2$*Ph*); ^{13}C NMR (75 MHz, $CDCl_3$) 22.7 (CH_2), 25.2 (CH_2), 27.2 (CH_2), 27.4 (CH_2), 29.2 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 31.6 (CH_2), 33.1 (CH_2), 33.7 (CH_2), 34.9 (CH_2, C-1′), 55.8 (CH_3, OMe), 55.9 (CH_3, OMe), 70.7 (CH_2, O*C*H$_2$Ph), 78.4 (CH, C-12′), 79.2 (CH, C-3), 97.3 (CH, C-6), 98.6 (CH, C-4), 106.9 (quat., C-7a), 114.3 (CH_2, C-16′), 127.3 (CH, OCH$_2$*Ph*), 127.5 (CH, C-3′), 127.7 (CH, OCH$_2$*Ph*), 128.2 (CH, OCH$_2$*Ph*), 131.7 (CH, C-4′), 138.7 (CH, C-15′), 139.0 (quat., OCH$_2$*Ph*), 155.0 (quat., C-3a), 159.6 (quat., C-7), 166.6 (quat., C-5), 168.3 (quat., C=O); *m/z* (FAB+, %) 521 (MH^+, 12), 413 (24), 373 (10), 207 (10), 193 (10), 120 (12), 91 (30); HRMS (FAB+): found MH^+, 521.3260. $C_{33}H_{44}O_5$ requires 521.3267.

4.5.8. 3-(12′-Benzyloxy-15′-oxohexadec-3′-en-1′-yl)-5,7-dimethoxy-(3*H*)-isobenzofuran-1-one 38. Using a similar method to that described above for the preparation of methyl ketone **30**, Wacker oxidation of alkene **37** (111 mg, 0.21 mmol) afforded the title compound **38** (70 mg, 61%) as a viscous colourless oil. ν_{max} (film) 2928, 2853, 1755, 1713, 1676, 1613, 1494, 1463, 1433, 1339, 1217, 1159, 1059, 1029, 914, 837, 733, 697, 500 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 1.20–1.48 (10H, m, 6′-H, 7′-H, 8′-H, 9′-H, 10′-H), 1.49–1.62 (2H, m, 11′-H), 1.65–1.90 (3H, m, 1′-H$_A$, 13′-H), 1.92–2.08 (3H, m, 1′-H$_B$, 5′-H), 2.10 (3H, s, 16′-H), 2.12–2.22 (1H, m, 2′-H$_A$), 2.23–2.35 (1H, m, 2′-H$_B$), 2.42–2.53 (2H, m, 14′-H), 3.35–3.42 (1H, m, 12′-H), 3.89 (3H, s, OMe), 3.95 (3H, s, OMe), 4.42 (1H, d, J=11.6 Hz, OC*H*$_A$H$_B$Ph), 4.50 (1H, d, J=11.6 Hz,

OCH_AH_BPh), 5.29 (1H, d, $J=8.6$, 3.3 Hz, 3-H), 5.33–5.48 (2H, m, 3′-H, 4′-H), 6.41 (1H, s, 4-H), 6.42 (1H, s, 6-H), 7.30–7.37 (5H, m, OCH_2Ph); ^{13}C NMR (75 MHz, $CDCl_3$) 22.7 (CH_2, C-2′), 25.3 (CH_2), 27.2 (CH_2), 27.5 (CH_2), 29.2 (CH_2), 29.5(CH_2), 29.6 (CH_2), 29.7 (CH_2), 29.9 (CH_3, C-14′), 33.7 (CH_2), 35.0 (CH_2, C-1′), 39.3 (CH_2, C-14′), 55.9 (CH_3, OMe), 56.0 (CH_3, OMe), 70.7 (CH_2, CH_2Ph), 77.9 (CH, C-12′), 79.3 (CH, C-3), 97.4 (CH, C-6), 98.7 (CH, C-4), 106.9 (quat., C-7a), 127.5 (CH, OCH_2Ph), 127.5 (CH, C-3′), 127.8 (CH, OCH_2Ph), 128.3 (CH, OCH_2Ph), 131.7 (CH, C-4′), 138.8 (quat., OCH_2Ph), 155.1 (quat., C-3a), 159.6 (quat., C-7), 166.7 (quat., C-5), 168.4 (quat., C-1), 208.9 (quat., C-15′); *m/z* (FAB+, %) 537 (MH^+, 5), 429 (75), 389 (10), 207 (11), 191 (17), 165 (10), 120 (11), 91 (52), 89 (32); HRMS (FAB+): found MH^+, 537.3226. $C_{33}H_{44}O_6$ requires 537.3216.

4.5.9. 5,7-Dimethoxy-3-(12′-hydroxy-15′-oxohexadec-1-yl)-(3*H*)-isobenzofuran-1-one 39. Using a similar method to that described above for the preparation of alcohol **14**, benzyl ether **38** (60 mg, 0.11 mmol) was reacted with hydrogen over 10% palladium on charcoal to afford the title compound **39** as a colourless oil (48 mg) that was not purified further before use in the subsequent steps.

4.5.10. (±)-CJ-13,103 5. Using a similar method to that described above for the preparation of CJ-13,015 **3**, TPAP oxidation of alcohol **39** (40 mg, 0.09 mmol) afforded the title compound **5** (25 mg, 44% from **38**) as a colourless solid. ^1H and ^{13}C NMR data obtained were in agreement with the literature values.[4] Mp 103–104 °C; ν_{max} (film) 2921, 2848, 2100, 1757, 1641, 1470, 1337, 1218, 1160, 837, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 1.20–1.37 (14H, m, 3′-H, 4′-H, 5′-H, 6′-H, 7′-H, 8′-H, 9′-H), 1.38–1.49 (2H, m, 2′-H), 1.52–1.61 (2H, m, 10′-H), 1.64–1.75 (1H, m, 1′-H_A), 1.93–2.02 (1H, m, 1′-H_B) 2.19 (3H, s, 16′-H), 2.44 (2H, t, $J=7.4$ Hz, 11′-H), 22.66–2.72 (4H, m, 13′-H, 14′-H), 3.89 (3H, s, OMe), 3.95 (3H, s, OMe), 5.30 (1H, dd, $J=8.0$, 3.7 Hz, 3-H), 6.41 (1H, s, 4-H), 6.41 (1H, s, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$) 23.8 (CH_2, C-10′), 24.6 (CH_2, C-2′), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.5 (CH_2) 30.0 (CH_3, C-16′), 34.8 (CH_2, C-1′), 36.0 (CH_2, C-14′), 36.9 (CH_2, C-13′), 42.8 (CH_2, C-11′), 55.9 (CH_3, OMe), 56.0 (CH_3, OMe), 80.0 (CH, C-3), 97.4 (CH, C-6), 98.6 (CH, C-4), 107.0 (quat., C-7a), 155.2 (quat., C-3a), 159.6 (quat., C-7), 166.6 (quat., C-5), 168.6 (quat., C-1), 207.4 (quat., C-15′), 209.8 (quat., C-12′); *m/z* (EI+, %) 446 (M^+, 9), 428 (18), 375 (23), 348 (12), 333 (87), 207 (46), 193 (100), 165 (14), 99 (17), 71 (11), 57 (12), 55 (20), 43 (27); HRMS (EI+): found M^+, 446.2678. $C_{26}H_{38}O_6$ requires 446.2668.

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Synthesis of some oligopyridine–galactose conjugates and their metal complexes: a simple entry to multivalent sugar ligands

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Abstract—Some galactose–oligopyridine conjugates were readily assembled by combining differently functionalized oligopyridines with peracetylated galactose derivatives. Variation in the structure of the components and of the linkers employed for their connection afforded adducts of different size, shape, and conformational mobility. Complexation of the bipyridine ligands with CuOTf and of the terpyridine ligand with $Zn(OTf)_2$ afforded the corresponding peracetylated 2:1 and 1:1 complexes, respectively, as single species. Their structures were determined to be tetrahedral (Cu complexes) and trigonal-bipyramidal (Zn complex), on the basis of spectroscopic evidence. Removal of the acetyl protecting groups from the ligands afforded the corresponding polyols. The terpyridine–Zn(II) complex, unlike the bipyridine–Cu(I) complexes maintained their structures upon removal of the acetyl protecting groups.

1. Introduction

Protein–carbohydrate interactions control a variety of fundamental biological processes.[1] In many instances several carbohydrate units are involved in the binding event,[2] to take advantage of the so-called 'glycoside cluster effect'.[3,4] Artificial multivalent glycoside ligands have been synthesized with the aim of better understanding the protein–carbohydrate interaction processes and of developing inhibitors of these phenomena when they are involved in infectious cycles.

The vast majority of the multivalent sugar ligands reported so far have been assembled around dendritic or polymeric frameworks to exploit the high number of functional groups presented by these scaffolds.[3] Among the studied systems falling outside these classes of compounds, examples of metal saccharide–ligand conjugates have been particularly scarce.[5–7] This is surprising, because the metal-assisted association of carbohydrate components modified with a metal-binding ligand can open a straightforward access to carbohydrate clusters in which the number and the relative orientation of the carbohydrate residues can be modulated almost at will by changing the structure of the ligand and the nature of the metal.

As a part of a project devoted to explore the potential of metal saccharide–ligand conjugates in the field of multivalent sugar presentation, we wish to report some preliminary results on the synthesis of galactose-containing oligopyridine derivatives and their complexes with metal ions.

2. Results and discussion

Synthesis of the modified galactose residues. On the basis of its ubiquitous involvement in protein–carbohydrate interactions,[1–3] galactose was selected as the sugar component of the designed oligopyridine–carbohydrate conjugates. Derivatives **2**–**4**, featuring different spacers and handles for the connection to the oligopyridine ligands, were synthesized starting from *O*-(2,3,4,6-*O*-tetracetyl-D-galactopyranosyl) trichloroacetimidate **1**[8] and using trimethylsilyl triflate promoted glycosidation reactions (Scheme 1). In particular, amine **2** was obtained as a single β-isomer in 50% overall yield by reaction with benzyl *N*-(2-hydroxyethyl)carbamate followed by reductive cleavage of the nitrogen-protecting group; phenol **3** was prepared in 33% overall yield by β-selective glycosidation with

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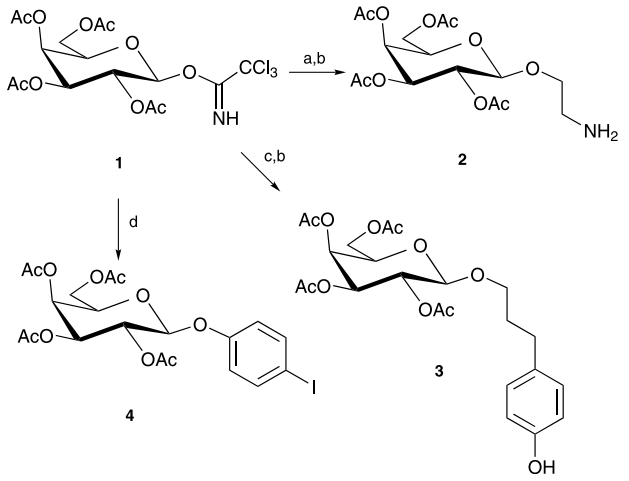


Scheme 1. Synthesis of galactose derivatives **2**–**4**. Reagents and conditions: (a) TMSOTf, $HOCH_2CH_2NHCOBn$, DCM, 0 °C, 2 h; (b) 10% Pd/C, 1 atm H_2, EtOH, rt, 2 h; (c) TMSOTf, 4-BnO–C_6H_4–$(CH_2)_3OH$, DCM, 0 °C, 2 h; (d) TMSOTf, 4-I-C_6H_4OH, DCM, 0 °C, 2 h.

3-(4-benzyloxyphenyl)-1-propanol,[9] followed by hydrogenolysis of the benzyl group; reaction of **1** with 4-iodophenol afforded (85% yield) a 78:22 mixture of anomers, from which the pure β-isomer **4** was readily obtained by chromatography in 66% yield.

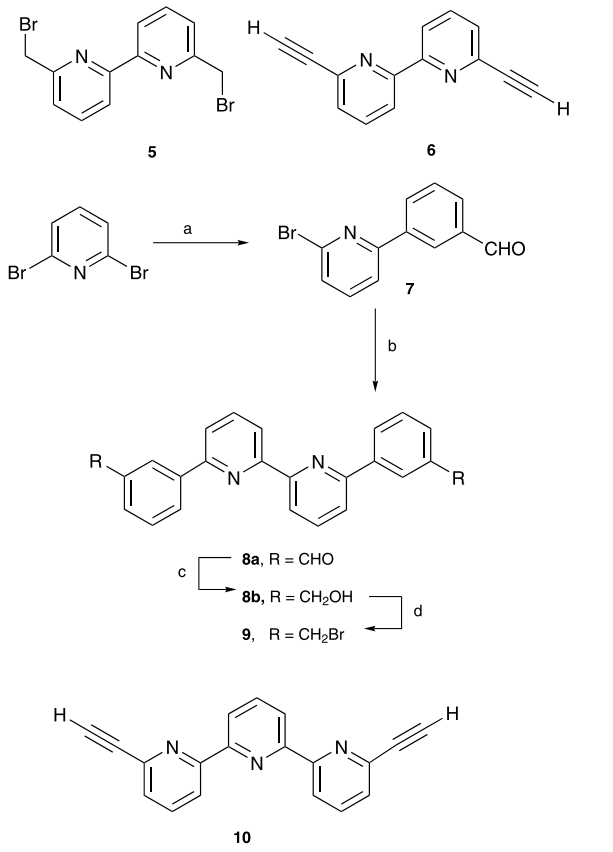
Synthesis of the oligopyridines. Oligopyridines **5**, **6**, **8**, **9**, and **10** carrying functional groups of different size and conformational mobility were selected for this study (Scheme 2). Compounds **5**,[10] **6**,[11] and **10**[12] were prepared according to literature procedures. Bis-aldehyde **8a** was obtained in two steps involving first Suzuki-type coupling of 2,6-dibromopyridine with 3-formylphenylboronic acid to afford compound **7** (56% yield),[13] and then nickel promoted homocoupling of the latter (47% yield).[14] From **8a**, dibromide **9** was readily prepared by reduction to the corresponding diol **8b** with $NaBH_4$ (96% yield) and bromination with PBr_3 (82% yield).

Synthesis of the oligopyridine–galactose conjugates and their metal complexes. By combining bipyridines **5**, **6**, **8a**, and **9** with functionalized galactose derivatives **2**-**4**, acetates **11**–**14** were obtained (Scheme 3).

Reaction of phenol **3** with dibromides **5** and **9**, carried out in the presence of cesium carbonate, afforded adducts **11** and **13** in 55 and 30% yields, respectively. The bis-acetylene derivative **12** was obtained in 33% yield by coupling bipyridine **6** with aryliodide **4** under standard Sonogashira conditions.

Imine **14** was synthesized in 90% yield by adding 6 equiv of amine **2** to a 5 mM solution of bis-aldehyde **8a** in 80:20 CH_2Cl_2/MeOH. Terpyridine **15** was obtained in 60% yield by combining galactose derivative **4** with 2″,6-diethynyl-2,2′:6′,6″-terpyridine **10** following the procedure employed for the preparation of conjugate **12**.

Formation of complexes **Cu(11)$_2$**–**Cu(14)$_2$** was performed in 92–98% yields by addition of 1 mol equiv of $CuOTf \cdot 0.5C_6H_6$ to 2 mol equiv of ligands **11**–**14** in 50:50

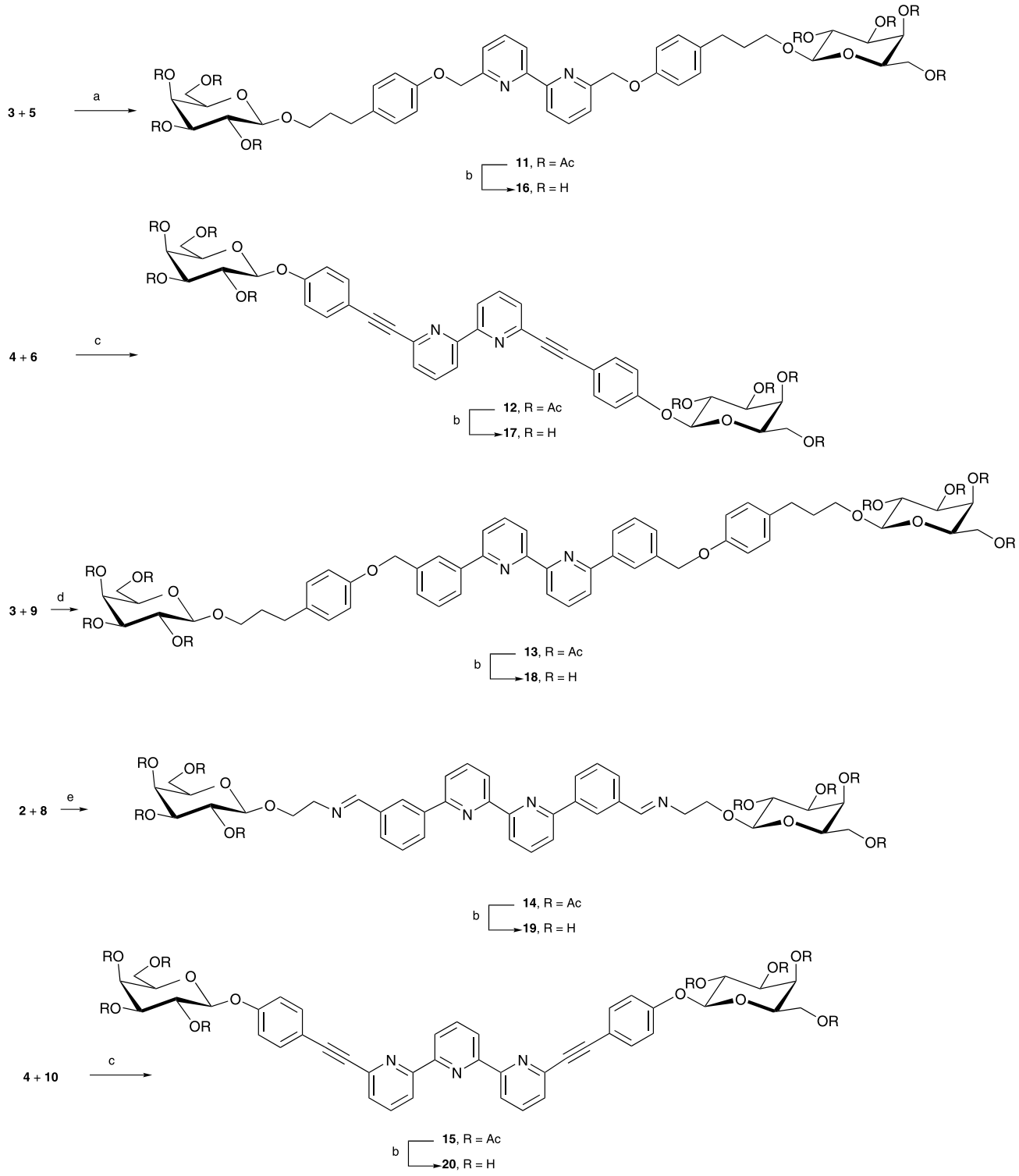


Scheme 2. Structure of oligopyridines **5**, **6**, and **10** and synthesis of bipyridines **8** and **9**. Reagents and conditions: (a), 3-formylphenyboronic acid, $Pd(OAc)_2$, PPh_3, DME, $NaHCO_3$, reflux, 22 h; (b), $NiCl_2$ hexahydrate, PPh_3, Zn, DMF, 50 °C, 22 h; (c), $NaBH_4$, EtOH, 0 °C, 5 h; (d), PBr_3, DCM, 0 °C to rt, 16 h.

acetonitrile/$CHCl_3$ to afford, after solvent evaporation, dark red solids. **Cu(11)$_2$**–**Cu(13)$_2$** were purified by filtration through a short silica gel column. Mass spectroscopy (MS-FAB) indicated the formation of adducts containing two ligands for each copper cation.

The assignment of structures to these complexes was based on NMR evidence. For instance, in all cases the ^{13}C NMR signals of the bipyridine carbons in positions 5/5′ and 3/3′ were shifted downfield by 4.3–4.6 and 1.1–1.9 ppm, respectively, upon complexation. An opposite shift was experienced by the quaternary 2/2′ carbons of bipyridine, that were shifted upfield by 2.8–3.7 ppm. These trends are in agreement with those generally observed when two 6,6′-disubstituted bipyridine units complex a Cu(I) cation to afford a tetrahedral adduct.[15,16]

Further support in favor of the formation of tetrahedrally arranged complexes **Cu(11)$_2$**–**Cu(14)$_2$** also came from the variation in the chemical shift observed for the protons of the residues in the vicinity of the bipyridine nuclei. Inspection of molecular models showed that upon formation of a tetrahedral complex protons of one ligand molecule fell in the shielding cone of the bipyridine moiety of the other ligand molecule (Fig. 1). As a consequence, strong upfield shifts were expected and indeed observed. For instance, the signal of the methylene groups bound to bipyridine C-6 and C-6′ in ligand **11** were shifted by about 0.5 ppm upfield in



Scheme 3. Synthesis of oligopyridine–galactose conjugates **11**–**20**. Reagents and conditions: (a), Cs_2CO_3, MeCN, rt, 18 h; (b), 0.1 M MeONa, MeOH, rt, 15 h; (c), CuI, $PdCl_2(PPh_3)_2$, *i*-Pr_2NH, THF, reflux, 24 h; (d), Cs_2CO_3, DMF/MeCN 80:20, rt, 18 h; (e), MeOH/DCM 20:80, rt, 18 h.

complex **Cu(11)$_2$**. Similarly, the protons of the phenyl rings connected to the same bipyridine carbons in ligands **13** and **14** experienced large upfield shifts (up to more than 1 ppm) upon formation of **Cu(13)$_2$** and **Cu(14)$_2$** (see Section 4).

On the other hand, the chemical shifts of the the H and C atoms of the glactose units remained virtually unchanged upon complex formation. This showed that these residues, being isolated from the bipyridine nucleus by the spacer, were not affected by the complexation event and maintained their conformational freedom. This observation is important because it suggests that the galactose units in **Cu(11)$_2$**–**Cu(14)$_2$** were not limited by the complexation in their potential ability to interact with a biological target.

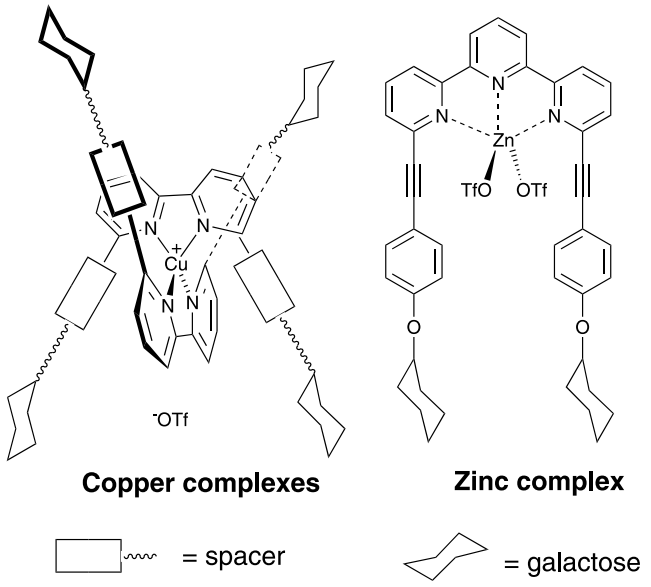


Figure 1. Schematic representation of copper(I)- and zinc(II)-complexes.

Reaction of ligand **15** with 1 mol equiv of $Zn(OTf)_2$ in chloroform afforded the corresponding 1:1 complex **Zn(15)**, to which, on the basis of literature data collected for related complexes[17] and of NMR and mass spectroscopic evidence, the trigonal bipyramidal structure reported in Figure 1 was assigned.

Having performed the synthesis of the acetylated complexes, we turned our attention to the preparation of their unprotected analogs required for biological evaluation. In principle these compounds could be obtained by two different approaches: (i) by deprotection of the acetylated complexes, and (ii) by complexation of the deacetylated ligands.

Reaction of ligands **11**–**15** with excess sodium methoxide in methanol readily gave the corresponding fully deprotected, crude polyols **16**–**20** that were isolated by simple evaporation of the reaction solvent. The extremely poor solubility of these compounds in most organic solvents[18] made their purification very difficult. Removal of sodium methoxide was only achieved by stirring a suspension of the crude polyols in water. Filtration of the mixture, however, afforded products containing large and undetermined amounts of water. These products were fully characterized by ^{1}H and ^{13}C NMR analysis and mass spectroscopy.[18]

The poor solubility of the polyhydroxylated ligands **16**–**20** made quite unpractical the synthesis of their complexes by reaction with metal triflates, requiring the use of very dilute methanol solution of the ligands.[19] However, by deacetylation of the corresponding adducts $\mathbf{Cu(11)_2}$, $\mathbf{Cu(12)_2}$, and $\mathbf{Cu(14)_2}$ (see above) unprotected complexes $\mathbf{Cu(16)_2}$, $\mathbf{Cu(17)_2}$, and $\mathbf{Cu(19)_2}$ were obtained and fully characterized.[20] The trends in the chemical shift difference between the polyhydroxylated ligands and their complexes observed in the ^{1}H and ^{13}C NMR spectra in combination with mass spectroscopy data (MS-ESI) indicated that $\mathbf{Cu(16)_2}$, $\mathbf{Cu(17)_2}$, and $\mathbf{Cu(19)_2}$ maintained the tetrahedral structure of their parent species. However, deacetylation of complex **Zn(15)** resulted in complex decomposition to afford the deprotected ligand **20**.

3. Conclusions

In conclusion, this work has demonstrated that galactose–oligopyridine conjugates could readily be assembled by combining four differently functionalized bipyridines and one terpyridine with three peracetylated galactose derivatives. Variation in the structure of the components and of the linkers employed for their connection afforded adducts of different size, shape, and conformational mobility, thus showing the generality of this approach.

Complexation of the bipyridine ligands with CuOTf and of the terpyridine ligand with $Zn(OTf)_2$ afforded the corresponding peracetylated 2:1 and 1:1 complexes, respectively, as single species. Their structures were determined to be tetrahedral (Cu complexes) and trigonal-bipyramidal (Zn complex), on the basis of NMR and mass spectroscopic evidence. Removal of the acetyl protecting groups from the ligands was possible, affording polyols that turned out to be poorly soluble in most organic solvents and in water. In contrast to the terpyridine–Zn(II) complex, the bipyridine/Cu(I) complexes survived the removal of the acetyl protecting groups and maintained their structure.

Studies dedicated to assess the binding ability[21] of these multivalent glycosylated ligands on macromolecular receptors such as lectins[22] by turbidimetric analysis[23] will be reported in due course.

4. Experimental

4.1. General methods

^{1}H NMR spectra were recorded on Bruker instruments at 300 or 500 MHz in chloroform-*d* ($CDCl_3$) unless otherwise stated, and were referenced to tetramethylsilane (TMS) at 0.00 ppm; ^{13}C NMR spectra were recorded at 75 or 125 MHz and were referenced to 77.0 ppm in $CDCl_3$. $^{13}C\{^1H\}$ NMRspectra were obtained using Waltz decoupling and were exponentially multiplied to give 0.8 Hz line broadening before Fourier transformation. All two dimensional experiments were acquired with a Bruker inverse 5 mm z-gradient probe. The 90° pulse widths were 9.2 and 13.1 μs for ^{1}H and ^{13}C, respectively. The gradient was shaped by a waveform generator and amplified by a Bruker B-AFPA-10 amplifier. A sinusoidal gradient of 1 ms length and a recovery time of 0.1 ms was used. The 2D COSY spectra were recorded with a 1024×1024 data matrix and 512 increments of 1 scan each, in magnitude mode, with a relaxation delay of 1.0 s and using a 1:1 gradient combination, then processed with zero-filling in f_1 and unshifted sine-bell apodization function. The HMQC and HMBC spectra were recorded using standard Bruker software sequences inv4gs and inv4gslplrnd, respectively. The following acquisition parameters were applied in both experiments: spectral widths in f_1 (^{13}C) and f_2 (^{1}H) dimensions 16,000 and 3000 Hz, respectively, a 1024× 1024 data matrix, 512 time increments of 200 scans each

and a 5:3:4 gradient combination. We set $\Delta_1 = 3.5$ ms in both experiments and $\Delta_2 = 60$ ms only in HMBC, as interpulse delay for the evolution of long-range coupling. The Fourier transformations were performed with shifted and unshifted sine-bell apodization functions in f_1 (^{13}C) and f_2 (^{1}H) dimension, respectively.

Optical rotations were measured at the Na-D line in a 1 dm cell at 22 °C. IR spectra were recorded on thin film or as solution in CH_2Cl_2 or as KBr pellets. 3-(4-Benzyloxyphenyl)-1-propanol,[9] and compounds **1**,[9] **5**,[10] **6**,[11] and **10** were prepared according to literature procedures. 3-(4-Benzyloxyphenyl)-1-propanol had mp 63–65 °C (lit.,[9] 64–65 °C); the β- and α-anomers of imidate **1** had mp 145–146 and 121–123 °C, respectively (lit.,[8] 146–147 and 122–123 °C); 6,6′-bis(bromomethyl)-2,2′-bipyridine had mp 180–181 °C (lit.,[10] 180–181 °C); 6,6′-diethynyl-2,2′-bipyridine had mp 190–192 °C (lit.,[11] 192–193 °C); 2″,6-diethynyl-2,2′:6′,6″-terpyridine (mp 220 °C, decomposition) had NMR data identical to those reported in the literature.[14]

4.2. Synthesis of the galactose dendrons 2–4

4.2.1. *O*-(2-Aminoethyl)-(2,3,4,6-*O*-tetracetyl)-β-D-galactopyranose (2). *Glycosidation reaction*. To a solution of a 2:1 mixture of β and α anomers of *O*-(2,3,4,6-*O*-tetracetyl-D-galactopyranosyl) trichloroacetimidate **1** (1.40 g, 2.84 mmol) and benzyl *N*-(2-hydroxyethyl)carbamate (0.98 g, 4.76 mmol) in dry CH_2Cl_2 (30 mL) stirred under nitrogen and cooled at 0 °C, a solution of trimethylsilyl triflate (0.25 mL, 1.30 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise. After 1 h stirring at 0 °C, the reaction was quenched by the addition of triethylamine (2 mL), and the resulting mixture was concentrated under vacuum. The residue was purified by flash chromatography with a 50:50 hexane/ethyl acetate mixture as eluant. The product *O*-(2-*N*-carbobenzyloxyaminoethyl)-(2,3,4,6-*O*-tetracetyl)-β-D-galactopyranose (0.75 g, 1.43 mmol, 50% yield) was obtained as a thick pale yellow oil. (Found: C, 55.0; H, 6.0; N, 2.5. $C_{24}H_{31}NO_{12}$ requires C, 54.8; H, 5.9; N, 2.7%); $[\alpha]_D^{22}$ +4.4 (*c* 1.2 in CH_2Cl_2); IR: ν_{max} (film)/cm^{-1} 3250, 1751, 1722, 1230; ^{1}H NMR: δ 2.00 (3H, s, Me), 2.02 (3H, s, Me), 2.05 (3H, s, Me), 2.17 (3H, s, Me), 3.35–3.50 (2H, m, CH_2NH), 3.68–3.77 (2H, m, CH_2CH_2O), 3.85–3.95 (1H, m, H-C5), 4.16 (2H, d, J=6.6 Hz, H-C6), 4.47 (1H, d, J=7.9 Hz, H-C1), 5.03 (1H, dd, J=3.4, 7.1 Hz, H-C3), 5.12 (2H, s, CH_2Ar), 5.17-5.22 (1H, m, H-C2), 5.40 (1H, d, J=3.4 Hz, H-C4), 7.32–7.40 (5H, m, aromatic H); ^{13}C NMR: δ 20.4 (2×Me), 20.5 (2×Me), 40.8 (CH$_2$–NH), 61.2 (galactose C-6), 66.7 (CH$_2$–Ar), 66.9 (galactose C-4), 68.8 (galactose C-2), 69.3 (CH$_2$ bound to anomeric O), 70.5 (galactose C-3), 70.8 (galactose C-5), 101.5 (galactose C-1), 128.0 (2 *ortho* C of aryl ring), 128.1 (*para* C of aryl ring), 128.4 (2, *meta* C of aryl ring), 136.5 (quaternary C of aryl ring), 169.5 (C=O), 170.0 (2 C=O), 170.1 (C=O), 170.2 (C=O).

Removal of the Cbz group. To a solution of *O*-(2-*N*-carbobenzyloxyaminoethyl)-(2,3,4,6-*O*-tetracetyl)-β-D-galactopyranose (0.26 g, 0.50 mmol) in absolute EtOH (20 mL), 10% Pd/C (0.03 g) was added. The resulting slurry was shaken under a hydrogen atmosphere for 2 h. The mixture was then filtered through a Celite cake and the filtrate was concentrated under vacuum to afford the pure product **2** (0.195 g, 0.5 mmol, 99% yield) as a thick oil. (Found: C, 48.9; H, 6.2; N, 3.8. $C_{16}H_{25}NO_{10}$ requires C, 49.1; H, 6.4; N, 3.6%); $[\alpha]_D^{22}$ +13.1 (*c* 0.6 in CH_2Cl_2); IR: ν_{max}(film)/cm^{-1} 3320, 1751; ^{1}H NMR: δ 1.75 (2H, bs, NH_2), 1.92 (3H, s, Me), 1.98 (3H, s, Me), 2.00 (3H, s, Me), 2.09 (3H, s, Me), 2.70–2.85 (2H, m, CH_2N), 3.53–3.60 (1H, m, one H of CH_2CH_2O), 3.80–3.90 (2H, m, H-C5 and one H of CH_2CH_2O), 4.06–4.14 (2H, m, H-C6), 4.46 (1H, d, J=7.9 Hz, H-C1), 4.97 (1H, dd, J=3.2, 7.1 Hz, H-C3), 5.14 (1H, dd, J=8.1, 8.3 Hz, H-C2), 5.33 (1H, d, J=3.2 Hz, H-C4); ^{13}C NMR: δ 20.4 (Me), 20.5 (2 Me), 20.6 (Me), 41.6 (CH_2–N), 61.2 (galactose C-6), 67.0 (galactose C-4), 68.9 (galactose C-2), 69.3 (CH$_2$ bound to anomeric O), 70.6 (galactose C-5), 70.8 (galactose C-3), 101.4 (galactose C-1), 169.3 (C=O), 169.9 (C=O), 170.0 (C=O), 170.2 (C=O); MS-ESI$^+$: m/z 392 $[M+H]^+$.

4.2.2. *O*-[3-(4-Hydroxyphenyl)-1-propyl)]-(2,3,4,6-*O*-tetracetyl)-β-D-galactopyranose (3). *Glycosidation reaction*. To a solution of a 2:1 mixture of β and α anomers of *O*-(2,3,4,6-*O*-tetracetyl-D-galactopyranosyl) trichloroacetimidate **1** (0.49 g, 1.0 mmol) and 3-(4-benzyloxy-phenyl)-1-propanol (0.36 g, 1.5 mmol) in dry CH_2Cl_2 (8 mL) stirred under nitrogen and cooled at 0 °C, a solution of trimethylsilyl triflate (0.08 mL, 0.46 mmol) in dry CH_2Cl_2 (1 mL) was added dropwise. After 2 h stirring at 0 °C, the reaction was quenched by the addition of triethylamine (0.5 mL), and the resulting mixture was concentrated under vacuum. The residue was purified by flash chromatography with a 70:30 hexane/ethyl acetate mixture as eluant. The product *O*-[3-(4-phenylmethoxyphenyl)-1-propyl)]-(2,3,4,6-*O*-tetracetyl)-β-D-galacto-pyranose (0.19 g, 0.33 mmol, 33% yield) was obtained as a thick oil. (Found: C, 63.2; H, 6.5. $C_{30}H_{36}O_{11}$ requires C, 62.9; H, 6.3%); $[\alpha]_D^{22}$ −4.4 (*c* 0.6 in CH_2Cl_2); IR: ν_{max} (film)/cm^{-1} 1752, 1224; ^{1}H NMR: δ 1.80–2.00 (2H, m, $CH_2CH_2CH_2$), 2.02 (3H, s, Me), 2.05 (3H, s, Me), 2.08 (3H, s, Me), 2.17 (3H, s, Me), 2.57–2.70 (2H, m, CH_2CH_2Ar), 3.45–3.60 (1H, m, one H of CH_2 bound to anomeric O), 3.87–3.99 (2H, m, H-C5 and one H of CH_2 bound to anomeric O), 4.10–4.25 (2H, m, H-C6), 4.48 (1H, d, J=7.9 Hz, H-C1), 5.00–5.10 (3H, m, H-C3 and OCH_2Ar), 5.26 (1H, dd, J=7.9, 9.3 Hz, H-C2), 5.41 (1H, d, J=3.4 Hz, H-C4), 6.92 (2H, A part of AB system, J=8.5 Hz, aromatic H *ortho* to O), 7.10 (2H, B part of AB system, J=8.5 Hz, aromatic H *meta* to O); 7.25–7.40 (5H, m, aromatic H of benzyloxy group); ^{13}C NMR: δ 20.4 (2×Me), 20.5 (2 Me), 30.9 (CH_2–C–CH_2), 31.2 (Ar–C–CH_2), 61.2 (galactose C-6), 67.0 (d, galactose C-4), 68.9 (d, galactose C-2), 69.0 (CH$_2$ bound to anomeric O), 70.0 (O–C–Ar), 70.6 (galactose C-3), 70.9 (galactose C-5), 101.3 (galactose C-1), 114.8 (2×aromatic C *ortho* to O), 127.4 (*para* C of benzyloxy ring), 127.8 (2×*meta* C of benzyloxy ring), 128.5 (2×*ortho* C of benzyloxy ring), 129.3 (2×C of aryl ring *meta* to O), 133.9 (quaternary aromatic C *para* to O), 137.0 (quaternary C of benzyloxy ring), 158.0 (quaternary aromatic C bound to O), 169.0 (C=O), 170.2 (2×C=O), 170.5 (C=O).

Removal of the benzyl group. To a solution of *O*-[3-(4-phenylmethoxyphenyl)-1-propyl)]-(2,3,4,6-*O*-tetracetyl)-β-D-galactopyranose (0.30 g, 0.52 mmol) in absolute EtOH (20 mL), 10% Pd/C (0.02 g) was added. The resulting slurry

was shaken under a hydrogen atmosphere for 2 h. The mixture was then filtered through a Celite cake and the filtrate was concentrated under vacuum to afford the pure product **3** (0.25 g, 0.52 mmol, 99% yield) as a gum-like material. (Found: C, 57.0; H, 6.1. $C_{23}H_{30}O_{11}$ requires C, 57.2; H, 6.3%); $[\alpha]_D^{22}$ 0.0, $[\alpha]_{436}^{22}$ +0.8 (*c* 1 in CH_2Cl_2); IR: ν_{max}(film)/cm^{-1} 3436, 1751, 1225; ^{1}H NMR: δ 1.83–1.96 (2H, m, $CH_2CH_2CH_2$), 2.00 (3H, s, Me), 2.04 (3H, s, Me), 2.07 (3H, s, Me), 2.16 (3H, s, Me), 2.55–2.70 (2H, m, CH_2CH_2Ar), 3.41–3.55 (1H, m, one H of CH_2 bound to anomeric C), 3.80–3.95 (2H, m, H-C5 and one H of CH_2 bound to anomeric O), 4.10–4.25 (2H, m, H-C6), 4.47 (1H, d, *J*=7.8 Hz, H-C1), 5.04 (1H, dd, *J*=3.4, 10.5 Hz, H-C3), 5.25 (1H, dd, *J*=7.8, 8.3 Hz, H-C2), 5.40 (1H, d, *J*=3.4 Hz, H-C4), 5.70 (1H, b s, OH), 6.77 (2H, A part of AB system, *J*=8.5 Hz, aromatic H *ortho* to O), 7.03 (2H, B part of AB system, *J*=8.5 Hz, aromatic H *meta* to O); ^{13}C NMR: δ 20.4 (2×Me), 20.7 (2×Me), 30.8 (CH_2–*C*–CH_2), 31.2 (t, Ar–*C*–CH_2), 61.2 (galactose C-6), 67.1 (galactose C-4), 68.9 (methylene bound to anomeric O), 69.0 (galactose C-2), 70.6 (galactose C-3), 70.9 (galactose C-5), 101.3 (galactose C-1), 115.2 (2×C of aryl ring *ortho* to O), 129.4 (2×C of aryl ring *meta* to O), 132.0 (quaternary aromatic C *para* to O), 154.0 (quaternary aromatic C bound to O), 170.1 (2×C═O), 170.2 (2×C═O). MS-ESI$^+$: *m*/*z* 505.6 [M+Na]$^+$.

4.2.3. *O*-(4-Iodophenyl)-(2,3,4,6-*O*-tetracetyl)-β-D-galactopyranose (4). To a solution of a 2:1 mixture of β and α anomers of *O*-(2,3,4,6-*O*-tetracetyl-D-galactopyranosyl) trichloroacetimidate **1** (0.49 g, 1.0 mmol) and 4-iodophenol (0.22 g, 1.0 mmol) in dry CH_2Cl_2 (8 mL) stirred under nitrogen and cooled at 0 °C, a solution of trimethylsilyl triflate (0.08 ml, 0.46 mmol) in dry CH_2Cl_2 (1 mL) was added dropwise. After 2 h stirring at 0 °C, the reaction was quenched by the addition of triethylamine (0.5 mL), and the resulting mixture was concentrated under vacuum. The residue was purified by flash chromatography with a 70:30 hexane/ethyl acetate mixture as eluant. The first eluted product (0.104 g, 0.19 mmol, 19% yield) was a pale yellow solid with mp 88–90 °C, $[\alpha]_D^{22}$ +23.0 (*c* 1 in CH_2Cl_2). On the basis of the H–C1/H–C2 coupling constant value (*J*=3.4 Hz) the α-anomeric configuration was assigned to this compound. The second eluted product (0.363 g, 0.66 mmol, 66% yield) was the β-anomer. It was obtained as a white solid with mp 44–45 °C. (Found: C, 43.3; H, 4.5. $C_{20}H_{23}IO_{10}$ requires C, 43.6; H, 4.2%); $[\alpha]_D^{22}$ +8.7 (*c* 0.7 in CH_2Cl_2); IR: ν_{max}(KBr)/cm^{-1} 1752, 1227, 1087; ^{1}H NMR: δ 2.00 (3H, s, Me), 2.05 (6H, s, 2 Me), 2.17 (3H, s, Me), 4.02–4.10 (1H, m, H-C5), 4.15–4.25 (2H, m, H-C6), 5.02 (1H, d, *J*=7.9 Hz, H–C1), 5.13 (1H, dd, *J*=3.5, 10.5 Hz, H–C3), 5.43–5.51 (2H, m, H–C4 and H–C2), 6.80 (2H, A part of AB system, *J*=8.8 Hz, aromatic H *ortho* to O), 7.60 (2H, B part of AB system, *J*=8.8 Hz, aromatic H *meta* to O); ^{13}C NMR: δ 20.4 (2×Me), 20.5 (2×Me), 61.3 (galactose C-6), 66.8 (galactose C-4), 68.5 (galactose C-2), 70.7 (galactose C-3), 71.1 (galactose C-5), 86.0 (quaternary aromatic C bound to iodine) 99.5 (galactose C-1), 119.2 (2×C of aryl ring *ortho* to O),138.4 (2×C of aryl ring *meta* to O), 156.7 (quateranry aromatic C bound to O), 170.1 (2×C═O), 170.2 (2×C═O). MS-ESI$^+$: *m*/*z* 573.2 [M+Na]$^+$.

4.3. Synthesis of oligopyridines

4.3.1. 2-Bromo-6-(3-formylphenyl)pyridine (7). To a solution of 2,6-dibromopyridine (2.00 g, 8.44 mmol), triphenylphosphine (0.44 g, 1.67 mmol), and palladium acetate (0.19 g, 0.83 mmol) in dry DME (100 mL) stirred under nitrogen at room temperature, 3-formylphenylboronic acid (1.37 g, 9.17 mmol) was added followed by a 2 M aqueous solution of sodium carbonate (25 mL, 40.8 mmol). The resulting mixture was refluxed for 22 h, and the solvent was evaporated under vacuum. The remaining aqueous phase was extracted with CH_2Cl_2 (3×50 mL), and the combined organic phases were washed with water and dried over sodium sulfate. Filtration and evaporation of the solvent under vacuum afforded the crude product that was purified by flash chromatography with a 80:20 hexane/ethyl acetate mixture as eluant. The product **7** (1.24 g, 4.72 mmol, 56% yield) was a white solid, mp 90–91 °C. (Found: C, 55.3; H, 2.9; N, 5.5. $C_{12}H_8BrNO$ requires C, 55.0; H, 3.1; N, 5.3%); IR: ν_{max}(KBr)/cm^{-1} 1688, 1552, 1430, 1188, 1125; ^{1}H NMR: δ 7.50 (1H, d, *J*=7.8 Hz, pyridine H–C3), 7.64–7.70 (2H, m, pyridine H–C4 and H *meta* to CHO), 7.79 (1H, d, *J*=7.8 Hz, pyridine H–C5), 7.98 (1H, dt, *J*=1.4, 7.8 Hz, H *para* to CHO), 8.31 (1H, dd, *J*=1.4, 7.9 Hz, H *ortho* to CHO), 8.52 (1H, t, *J*=1.4 Hz, H between pyridine and CHO), 10.15 (1H, s, CHO); ^{13}C NMR: δ 119.1 (pyridine C-5), 127.1 (pyridine C-3), 128.2 (C between pyridine ring and CHO), 129.6 (C *meta* to pyridine ring), 130.6 (C *para* to CHO), 132.7 (C *ortho* to CHO and *para* to pyridine ring), 137.0 (quaternary C bound to pyridine ring), 138.6 (quaternary carbon bound to CHO), 139.2 (pyridine C-4), 142.2 (pyridine C-2), 157.0 (pyridine C-6) 191.9 (CHO). MS-ESI$^+$: *m*/*z* 263.9 [M+H]$^+$.

4.3.2. 6,6′-Bis(3-formylphenyl)-2,2′-bipyridine (8a). A suspension of nickel dichloride hexahydrate (1.06 g, 3.87 mmol), triphenylphosphine (4.06 g, 15.47 mmol), and zinc powder (0.38 g, 5.8 mmol) in dry DMF (30 mL) was stirred at 60 °C under nitrogen for 1 h. A DMF (10 mL) solution of 2-bromo-6-(3-formylphenyl)pyridine (1.01 g, 3.86 mmol) was then added and the mixture was stirred at 60 °C for 23 h. After addition of diluted aqueous ammonia (50 mL) to the cooled mixture, this was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were washed twice with brine and dried over sodium sulfate. Filtration and evaporation of the solvent under vacuum, afforded the crude product as a cream-colored solid. This was purified by several washings with a 90:10 hexane/ethyl acetate mixture to remove the unreacted aldehyde, excess triphenylphosphine, and some triphenylphosphineoxide. The resulting solid **8a** (0.70 g, 1.9 mmol, 47% yield), mp 197–198 °C, was pure enough for analysis and subsequent manipulation. (Found: C, 78.9; H, 4.2; N, 7.9. $C_{24}H_{16}N_2O_2$ requires C, 79.1; H, 4.4; N, 7.7%); IR: ν_{max}(KBr)/cm^{-1} 1680, 1589, 1437, 1199; ^{1}H NMR: δ 7.73 (2H, t, *J*=8.5 Hz, H *meta* to CHO), 7.91 (2H, d, *J*=7.8 Hz, pyridine H-5), 8.00–8.05 (4H, m, H *para* to CHO and pyridine H-4), 8.50 (2H, d, *J*=8.5 Hz, H *ortho* to CHO and *para* to pyridine ring), 8.67 (2H, d, *J*=7.8 Hz, pyridine H-3), 8.72 (2H, s, H between CHO and pyridine ring), 10.20 (2H, s, CHO); ^{13}C NMR: δ 121.0 (2×pyridine C-3), 121.5 (2×pyridine C-5), 128.2 (2×C between CHO and pyridine ring), 129.8 (2×C *meta* to CHO and to pyridine ring), 130.8 (2×C *ortho* to

CHO and *para* to pyridine ring), 132.8 (2×C *para* to CHO), 137.1 (2×pyridine C-4), 139.0 (2×quaternary C bound to CHO), 139.1 (2×quaternary C *meta* to CHO), 154.8 (2×pyridine C-6), 155.7 (2×pyridine C-2), 192.1 (2×C of CHO). MS-ESI$^+$: *m/z* 387.1 $[M+Na]^+$.

4.3.3. 6,6′-Bis(3-hydroxymethylphenyl)-2,2′-bipyridine (8b). To a sirred suspension of dialdehyde **8a** (0.365 g, 1 mmol) in absolute EtOH (10 mL) cooled at 0 °C, $NaBH_4$ (0.08 g, 2 mmol) was added in one portion. The reaction mixture was warmed up to room temperature and stirring was continued until a clear solution was obtained (about 3 h). A few drops of water were then added and the solvent was evaporated under vacuum. The residue was dissolved in water (10 mL) and the aqueous phase was extracted with CH_2Cl_2 (2×20 mL). The combined organic phases were dried over sodium sulfate. Filtration and evaporation of the solvent under vacuum, afforded the crude product as a cream-colored solid that was purified by flash chromatography with a 98:2 CH_2Cl_2:MeOH mixture as eluant to give the product **8b** (0.353 g, 0.96 mmol, 96% yield), as a white solid, mp 142 °C. (Found: C, 78.0; H, 5.6; N, 7.9. $C_{24}H_{20}N_2O_2$ requires C, 78.2; H, 5.5; N, 7.6%); IR: ν_{max}(KBr)/cm^{-1} 3270, 1568, 1437, 1039; ^{1}H NMR: δ 3.60 (2H, bs, OH), 4.26 (4H, s, CH_2O), 7.48 (2H, d, J=8.5 Hz, H *ortho* to CH_2OH and *para* to pyridine ring), 7.55 (2H, t, J=8.4 Hz, H *meta* to CH_2OH), 7.83 (2H, d, J=8.5 Hz, pyridine H-C5), 7.95 (2H, t, J=8.5 Hz, pyridine H-C4), 8.11 (2H, d, J=8.5 Hz, H *para* to CH_2OH), 8.23 (2H, s, H between CH_2OH and pyridine ring), 8.63 (2H, d, J=8.5 Hz, pyridine H–C3); ^{13}C NMR: δ 65.1 (2×CH_2–O), 119.8 (2×pyridine C-3), 120.5 (2×d, pyridine C-5), 125.6 (2×C *para* to CH_2OH), 126.3 (2×C between CH_2OH and pyridine ring), 127.6 (2×C *meta* to CH_2OH), 129.0 (2×C *ortho* to CH_2OH and *para* to pyridine ring), 137.7 (2×pyridine C-4 and 2×quaternary C *meta* to CH_2OH), 141.8 (2×quaternary C bound to CH_2OH), 155.7 (2×pyridine C-6), 156.0 (2×pyridine C-2). MS-ESI$^+$: *m/z* 391.1 $[M+Na]^+$.

4.3.4. 6,6′-Bis(3-bromomethylphenyl)-2,2′-bipyridine (9). To a stirred solution of the diol **8b** (0.30 g, 0.81 mmol) in dry CH_2Cl_2 (10 mL) cooled at 0 °C, a solution of PBr_3 (0.46 mL) in dry CH_2Cl_2 (2 mL) was slowly added. After 30 min stirring at 0 °C the reaction mixture was warmed up to room temperature, and stirring was continued for 16 h. The reaction was quenched by the addition of a 0.1 M solution of sodium hydroxide until neutrality of the aqueous phase was obtained. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2×10 mL). The combined organic phases were dried over sodium sulfate. Filtration and evaporation of the solvent under vacuum, afforded the crude product that was purified by flash chromatography with CH_2Cl_2 as eluant to give the product **9** (0.33 g, 0.66 mmol, 82% yield), as a white solid, mp 209–211 °C. (Found: C, 58.1; H, 3.6; N, 5.4. $C_{24}H_{18}Br_2N_2$ requires C, 58.3; H, 3.7; N, 5.7%); IR: ν_{max}(KBr)/cm^{-1} 1568, 1437, 1218; ^{1}H NMR: δ 4.66 (4H, s, CH_2Br), 7.45–7.60 (4H, m, H *ortho* to CH_2Br and *para* to pyridine ring, and H *meta* to CH_2Br and *meta* to pyridine ring), 7.84 (2H, d, J=8.5 Hz, pyridine H-C5), 7.98 (2H, t, J=8.5 Hz, pyridine H-C4), 8.11 (2H, d, J=8.5 Hz, H *para* to CH_2Br), 8.24 (2H, s, H between pyridine ring and CH_2Br), 8.65 (2H, d, J=8.5 Hz, pyridine H–C3); ^{13}C NMR: δ 33.6 (2×CH_2Br), 120.5 (2×pyridine C-3), 120.8 (2×pyridine C-5), 127.2 (2×C *ortho* to CH_2Br and *para* to pyridine ring), 127.9 (2×C between CH_2Br and pyridine ring), 129.3 (2×C *meta* to CH_2Br and *meta* to pyridine ring), 129.7 (2×C *para* to CH_2Br), 138.2 (2×pyridine C-4, and 2×quaternary C *meta* to CH_2Br), 139.8 (2×quaternary C bound to CH_2Br), 155.7 (4×pyridine C-2 and C-6). MS-ESI$^+$: *m/z* 495.1 $[M+H]^+$.

4.4. Synthesis of oligopyridine–galactose conjugates

4.4.1. 6,6′-Bis-[4-[3-[(2,3,4,6-*O*-tetracetyl)-β-D-galactopyranosyl]-prop-1-yl]-phenyloxy-methyl]-2,2′-bipyridine (11). To a stirred solution of bipyridine **5** (51 mg, 0.15 mmol) and phenol **3** (166 mg, 0.34 mmol) in dry acetonitrile (4 mL), cesium carbonate (0.3 g, 0.84 mmol) was added. The mixture was stirred at room temperature for 18 h. The solvent was then evaporated under vacuum and the residue was purified by flash chromatography with a 50:50 hexane/ethyl acetate mixture as eluant to give **11** as a light brown, gum-like material (95 mg, 0.083 mmol, 55% yield). (Found: C, 60.5; H, 5.7; N, 2.7. $C_{58}H_{68}N_2O_{22}$ requires C, 60.8; H, 6.0; N, 2.4%); $[\alpha]_D^{22}$ −2.5 (*c* 0.8 in CH_2Cl_2); IR: ν_{max}(film)/cm^{-1} 2932, 1746, 1510, 1223, 1048; ^{1}H NMR (CD_3OD): δ 1.83–1.95 (4H, m, CH_2CH_2-CH_2O), 2.00 (6H, s, Me), 2.04 (6H, s, Me), 2.07 (6H, s, Me), 2.17 (6H, s, Me), 2.56–2.72 (4H, m, $CH_2CH_2CH_2O$), 3.50 (2H, A part of an AB system, J=6.0, 10.0 Hz, one H of $CH_2CH_2CH_2O$), 3.86–3.95 (4H, m, one H of $CH_2CH_2CH_2O$ and galactose H-5), 4.17 (4H, AB system, J=6.2 Hz, galactose H-6), 4.48 (2H, d, J=8.0 Hz, galactose H-1), 5.04 (2H, dd, J=3.4, 10.4 Hz, galactose H-3), 5.23 (2H, dd, J=8.0, 10.4 Hz, galactose H-2), 5.30 (4H, s, PyCH_2O), 5.41 (2H, d, J=3.4 Hz, galactose H-4), 6.97 (4H, A part of an AB system, J=8.5 Hz, H *ortho* to O), 7.11 (4H, B part of an AB system, J=8.5 Hz, H *meta* to O), 7.57 (2H, d, J=7.6 Hz, pyridine H-5), 7.87 (2H, t, J=7.6 Hz, pyridine H-4), 8.37 (2H, d, J=7.6 Hz, pyridine H-3); ^{13}C NMR (CD_3OD): δ 20.5 (4×Me), 20.6 (2×Me), 20.8 (2×Me), 30.9 (2×CH_2–*C*–CH_2), 31.2 (2×Ar–*C*–CH_2), 61.3 (2×galactose C-6), 67.1 (2×galactose C-4), 69.0 (2×galactose C-2, and 2×CH_2 bound to anomeric O), 70.6 (2×galactose C-5), 71.0 (2×galactose C-3), 77.0 (2×CH_2 bound to pyridine), 101.3 (2×galactose C-1), 114.8 (4×aromatic C *ortho* to O), 120.3 (2×pyridine C-3), 121.4 (2×pyridine C-5), 129.4 (4×aromatic C *meta* to O), 134.1 (2×quaternary aromatic C of phenyl ring bound to CH_2), 137.9 (2×pyridine C-4), 155.0 (2×pyridine C-2), 156.8 (2×quaternary aromatic C of phenyl ring bound to O), 157.0 (2×pyridine C-6), 170.1 (8×C=O); MS-ESI$^+$: *m/z* 1145 $[M+H]^+$, 1167 $[M+Na]^+$.

4.4.2. 6,6′-Bis-[2-[4-[(2,3,4,6-*O*-tetracetyl)-β-D-galactopyranosyl]-phenyl]-ethynyl]-2,2′-bipyridine (12). In a stirred mixture of dry THF (4.4 mL) and diisopropylamine (3.1 mL) kept under a nitrogen atmosphere, bipyridine **6** (47 mg, 0.23 mmol) and iodide **4** (251 mg, 0.46 mmol) were added. After 10 min stirring at room temperature, $PdCl_2(PPh_3)_2$ (5 mg, 0.007 mmol) and CuI (4 mg, 0.02 mmol) were added in this order. The mixture was refluxed for 24 h. Evaporation of the solvent under vacuum afforded a residue that was purified by flash chromatography

with a 50:50 hexane/ethyl acetate mixture as eluant to give **12** as a light brown, gum-like material (80 mg, 0.076 mmol, 33% yield). (Found: C, 62.0; H, 5.3; N, 2.4. $C_{54}H_{52}N_2O_{20}$ requires C, 61.8; H, 5.0; N, 2.7%); $[\alpha]_D^{22}$ +18.6 (*c* 0.2 in CH_2Cl_2); IR: ν_{max}(film)/cm^{-1} 2925, 2217, 1747, 1260, 1043; ^1H NMR (CD_3OD): δ 1.97 (6H, s, Me), 2.04 (6H, s, Me), 2.06 (6H, s, Me), 2.17 (6H, s, Me), 4.13 (4H, d, J= 6.2 Hz, galactose H-6), 4.49 (2H, t, J=6.2 Hz, galactose H-5), 5.26 (2H, A part of an AB system, J=8.0, 10.0 Hz, galactose H-2), 5.31 (2H, B part of an AB system, J=3.0, 10.0 Hz, galactose H-3), 5.38 (2H, d, J=3.0 Hz, galactose H-4), 5.61 (2H, d, J=8.0 Hz, galactose H-1), 7.10 (4H, A part of an AB system, J=8.6 Hz, H *ortho* to O), 7.68 (4H, B part of an AB system, J=8.6 Hz, H *meta* to O), 7.74 (2H, d, J=7.7 Hz, pyridine H-3), 8.04 (2H, t, J=7.7 Hz, pyridine H-4) and 8.39 (2H, d, J=7.7 Hz, pyridine H-5); ^{13}C NMR (CD_3OD): 19.0 (8×Me), 61.1 (2×galactose C-6), 67.3 (2×galactose C-4), 68.7 (2×galactose C-2), 70.8 (2× galactose C-3, and 2×galactose C-5), 87.6 (2×s, one acetylenic C), 88.3 (2×s, other acetylenic C), 98.2 (2× galactose C-1), 116.5 (4×aromatic C *ortho* to O, and 2× quaternary phenyl *C* bound to acetylenic C), 120.4 (2×pyridine C-3), 127.1 (2×pyridine C-5), 133.2 (4× aromatic C *meta* to O), 137.4 (2×pyridine C-4), 142.6 (2× pyridine C-6), 155.7 (2×pyridine C-2), 157.4 (2×aromatic C bound to O), 169.9 (4×C=O), 170.5 (4×C=O); MS-ESI$^+$: *m*/*z* 1049 $[M+H]^+$, 1071 $[M+Na]^+$.

4.4.3. 6,6′-Bis-[3-[4-[3-[(2,3,4,6-*O*-tetracetyl)-β-D-galactopyranosyl]-prop-1-yl]-phenyloxy-methyl]phenyl]-2,2′-bipyridine (13). To a stirred solution of bipyridine **9** (74 mg, 0.15 mmol) and phenol **3** (166 mg, 0.34 mmol) in a mixture of dry DMF (4 mL) and dry acetonitrile (1 mL), cesium carbonate (0.3 g, 0.84 mmol) was added. The mixture was stirred at room temperature for 18 h. Water (5 mL) was then added and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (2×10 mL). The combined organic phases were dried over sodium sulfate. Filtration and evaporation of the solvent under vacuum, afforded the crude product that was purified by flash chromatography with a 50:50 hexane/ethyl acetate mixtures as eluant to give **13** as a light brown, gum-like solid (58 mg, 0.045 mmol, 30% yield). (Found: C, 64.5; H, 5.6; N, 2.5. $C_{70}H_{76}N_2O_{22}$ requires C, 64.8; H, 5.9; N, 2.2%); $[\alpha]_D^{22}$ −3.4 (*c* 0.15 in CH_2Cl_2); ν_{max}(CH_2Cl_2)/cm^{-1} 2948, 1747, 1510, 1223, 1050; ^1H NMR (CD_3OD): δ 1.85 (4H, quintet, J=6.5 Hz, $CH_2CH_2CH_2O$), 1.95 (6H, s, Me), 1.99 (6H, s, Me), 2.08 (6H, s, Me), 2.17 (6H, s, Me), 2.63 (4H, t, J=6.5 Hz, $CH_2CH_2CH_2O$), 3.52 (2H, A part of an AB system, J=6.5, 9.8 Hz, one H of $CH_2CH_2CH_2O$), 3.83 (2H, B part of an AB system, J=6.5, 9.8 Hz, one H of $CH_2CH_2CH_2O$), 4.04 (2H, quartet, J=6.2 Hz, galactose H-5), 4.12 (4H, AB system, J=3.6, 6.2 Hz, galactose H-6), 4.58 (2H, d, J=4.4 Hz, galactose H-1), 5.04–5.14 (4H, m, galactose H-2 and H-3), 5.23 (4H, s, $ArCH_2O$), 5.38 (2H, br s, galactose H-4), 6.99 (4H, A part of an AB system, J= 8.6 Hz, H *ortho* to OCH_2Ar), 7.14 (4H, B part of an AB system, J=8.6 Hz, H *meta* to OCH_2Ar), 7.55 (4H, d, J= 5.1 Hz, H *para* to CH_2OAr and H *para* to pyridine ring), 7.95 (2H, d, J=7.2 Hz, pyridine H-5), 8.02 (2H, t, J= 7.5 Hz, pyridine H-4), 8.16 (2H, t, J=5.1 Hz, H *meta* to pyridine ring), 8.31 (2H, br s, H between pyridine ring and OCH_2Ar), 8.54 (2H, d, J=7.5 Hz, pyridine H-3); ^{13}C NMR (CD_3OD): 19.5 (8×Me), 30.9 (2×CH_2–*C*–Ar), 31.6 (2× CH_2–*C*–CH_2), 61.6 (2×galactose C-6), 67.9 (2×galactose C-4, and 2×CH_2–*C*H_2–O–anomeric C), 69.6 (2×galactose C-2), 70.0 (2×Ar–*C*–O), 70.7 (2×galactose C-5), 71.4 (2×galactose C-3), 101.2 (2×galactose C-1), 115.1 (4× aromatic C *ortho* to O), 119.8 (2×pyridine C-3), 120.6 (2× pyridine C-5), 126.1 (2×aromatic C of phenyl ring between pyridine ring and CH_2–OAr), 126.3 (2×aromatic C *meta* to pyridine ring and CH_2–OAr), 128.2 (2×aromatic *para* to pyridine ring), 129.0 (2×aromatic C *para* to CH_2–OAr), 129.5 (4×aromatic C *meta* to O), 134.0 (2×quaternary aromatic C *para* to O), 138.2 (2×quaternary aromatic C bound to CH_2–OAr, and 2×pyridine C-4), 138.5 (2× quaternary C bound to pyridine ring), 156.8 (2×quaternary aromatic C bound to O),157.0 (4×pyridine C-2 and C-6), 170.0 (4×C=O), 171.0 (4×C=O); MS-ESI$^+$: *m*/*z* 1297 $[M+H]^+$, 1319 $[M+Na]^+$.

4.4.4. 6,6′-Bis-[3-[*N*-2-[(2,3,4,6-*O*-tetracetyl)-β-D-galactopyranosyl]-ethyl]-imminomethyl] phenyl]-2,2′-bipyridine (14). A solution of dialdehyde **8a** (35 mg, 0.09 mmol) and amine **2** (241 mg, 0.61 mmol) in a mixture of CH_2Cl_2 (14 mL) and MeOH (3.5 mL) was stirred overnight at room temperature. The solvent was then evaporated under vacuum and water (2 mL) and Et_2O (10 mL) were then added. The organic phase was separated and the aqueous phase was extracted with Et_2O (2×10 mL). The combined organic phases were dried over sodium sulfate. Filtration and evaporation of the solvent under vacuum, afforded the product **14** as a light brown solid (87 mg, 0.081 mmol, 90% yield) that softened into a very thick oil when heated at 48 °C and remained like that up to 220 °C. (Found: C, 60.2; H, 5.5; N, 5.3. $C_{56}H_{62}N_4O_{20}$ requires C, 60.5; H, 5.6; N, 5.0%); $[\alpha]_D^{22}$ +2.3 (*c* 0.4 in CH_2Cl_2); IR: ν_{max}(CH_2Cl_2)/ cm^{-1} 2925, 1747, 1651, 1370, 1226, 1060; ^1H NMR (CD_3CN): δ 1.97 (6H, s, Me), 2.07 (12H, s, Me), 2.16 (6H, s, Me), 3.75–3.84 (2H, m, one H of NCH_2CH_2O), 3.89–3.97 (6H, m, galactose H-5, one H of NCH_2CH_2O, and one H of NCH_2CH_2O), 4.12–4.22 (6H, m, one hydrogen of NCH_2-CH_2O and galactose H-6), 4.56 (2H, d, J=8.0 Hz, galactose H-1), 5.00 (2H, dd, J=3.5, 11.5 Hz, galactose H-3), 5.20 (2H, dd, J=8.0, 11.5 Hz, galactose H-2), 5.50 (2H, br s, galactose H-4), 7.60 (2H, t, J=7.7 Hz, aromatic H *meta* to pyridine ring), 7.86 (2H, dt, J=1.1, 7.7 Hz, aromatic H *para* to pyridine ring), 7.89 (2H, dd, J=0.8, 7.2 Hz, pyridine H-5), 7.98 (2H, t, J=7.2 Hz, pyridine H-4), 8.33 (2H, dt, J=1.1, 7.7 Hz, aromatic H *para* to CH=N), 8.42 (2H, s, CH=N), 8.50 (2H, t, J=1.1 Hz, aromatic H *ortho* to CH=N and *ortho* to pyridine ring), 8.66 (2H, dd, J=0.8, 7.2 Hz, pyridine H-3); ^{13}C NMR (CD_3CN): δ 20.3 (2×Me), 20.5 (2×Me), 20.6 (4×Me), 60.5 (2×CH_2–N), 61.2 (2× galactose C-6), 67.0 (2×galactose C-4), 68.6 (2×galactose C-2), 68.9 (2×CH_2–O–galactose C-1), 70.6 (2×galactose C-5), 70.8 (2×galactose C-3), 101.3 (2×galactose C-1), 119.9 (2×pyridine C-3), 120.4 (2×pyridine C-5), 126.8 (2×aromatic C between pyridine ring and CH=N), 128.5 (2×aromatic C *para* to pyridine ring), 129.0 (2×aromatic C *meta* to pyridine ring and *meta* to CH=N), 129.3 (2× aromatic C *para* to CH=N), 136.4 (2×quaternary C bound to CH=N), 137.7 (2×pyridine C-4), 139.7 (2×aromatic C bound to pyridine ring), 155.5 (2×pyridine C-6), 155.8 (2×pyridine C-2), 163.3 (2×CH=N), 170.0 (4×C=O),

170.1 (2×C═O), 170.3 (2×C═O); MS-ESI$^+$: *m/z* 1111 $[M+H]^+$, 1133 $[M+Na]^+$.

4.4.5. 2″,6-Bis-[2-[4-[(2,3,4,6-*O*-tetracetyl)-β-D-galactopyranosyl]-phenyl]-ethynyl]-2,2′:6′,6″-terpyridine (15). In a stirred mixture of dry THF (4.6 mL) and diisopropylamine (3.1 mL) kept under a nitrogen atmosphere, terpyridine **10** (63 mg, 0.22 mmol) and iodide **4** (260 mg, 0.47 mmol) were added. After 10 min stirring at room temperature, $PdCl_2(PPh_3)_2$ (5 mg, 0.007 mmol) and CuI (4 mg, 0.02 mmol) were added in this order. The mixture was refluxed for 24 h. Evaporation of the solvent under vacuum afforded a residue that was purified by flash chromatography with a 50:50 hexane/ethyl acetate mixture as eluant to give **15** as a light brown solid (150 mg, 0.13 mmol, 60%) that softened into a very thick oil when heated at 145 °C and remained like that up to 220 °C. (Found: C, 62.6; H, 4.6; N, 4.0. $C_{59}H_{55}N_3O_{20}$ requires C, 62.9; H, 4.9; N, 3.7%); $[\alpha]_D^{22}$ +11.0 (*c* 0.4 in CH_2Cl_2); IR: $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2936, 2220, 1752, 1229, 1077; ^{1}H NMR (CD_3OD): δ 2.00 (6H, s, Me), 2.08 (6H, s, Me), 2.07 (6H, s, Me), 2.09 (6H, s, Me), 4.20 (4H, d, J=6.4 Hz, galactose H-6), 4.14 (2H, t, J=6.4 Hz, galactose H-5), 5.30 (2H, dd, J=3.2, 10.0 Hz, galactose H-3), 5.35–5.45 (4H, m, galactose H-1 and H-2), 5.50 (2H, d, J=3.2 Hz, galactose H-4), 7.10 (4H, A part of an AB system, J=8.8 Hz, aromatic H *ortho* to O), 7.55–7.65 (6H, m, terpyridine H-5 and H-3″, and aromatic H *meta* to O), 7.98 (2H, t, J=7.9 Hz, terpyridine H-4 and H-4″), 8.08 (1H, t, J=7.9 Hz, terpyridine H-4′), 8.47 (2H, d, J=7.9 Hz, terpyridine H-3′ and H-5′), 8.57 (2H, d, J=7.9 Hz, terpyridine H-3 and H-5″); ^{13}C NMR (CD_3OD): 20.5 (8×Me), 61.0 (2×galactose C-6), 66.8 (2×galactose C-4), 68.5 (2×galactose C-2), 70.7 (2×galactose C-3), 71.2 (2×galactose C-5), 88.2 (4×acetylenic C), 99.0 (2×galactose C-1), 116.8 (4×aromatic C *ortho* to O and 2×quaternary phenyl *C* bound to acetylenic C), 120.6 (2×terpyridine C-3 and C-5″), 121.8 (2×terpyridine C-3′ and C-5′), 127.4 (2×terpyridine C-5 and C-3″), 133.2 (4×aromatic C *meta* to O), 137.6 (2×terpyridine C-4 and C-4″), 138.1 (1×terpyridine C-4′), 143.0 (2×terpyridine C-6 and C-2″), 155.0 (2×terpyridine C-2′ and C-6′), 156.7 (2×terpyridine C-2 and C-6″), 158.0 (2×aromatic C bound to O), 170.5 (8×C═O); MS-ESI$^+$: *m/z* 1126 $[M+H]^+$.

4.5. Deprotection of the acetylated ligands 11-14 to polyols 16-19

General procedure. A solution of ligand (typical amount 0.015 mmol) in 0.1 M MeONa in MeOH (2 mL, 0.2 mmol) was stirred overnight under nitrogen. The solvent was evaporated under vacuum from the resulting suspension, and the residue was shaken with water (2 mL) for 3 h. The solid was filtered and washed with water until the filtered water was neutral. All the crude products obtained by filtration were insoluble in most organic solvents and soluble in DMSO. The solubility in MeOH was enough to record NMR spectra on very diluted solutions of these compounds. ^{1}H NMR (CD_3OD) showed the presence of large but difficult to determine amount of water in the samples. Satisfactory analytical data could not be obtained.

4.5.1. 6,6′-Bis-[4-[3-(β-D-galactopyranosyl)-prop-1-yl]-phenyloxymethyl]-2,2′-bipyridine (16). White solid. ^{1}H NMR (CD_3OD): δ 1.91 (4H, quintet, J=7.0 Hz, CH_2CH_2-CH_2O), 2.68 (4H, t, J=7.0 Hz, $CH_2CH_2CH_2O$), 3.45–3.60 (6H, m, galactose H-5, H-2, and H-3), 3.57 (2H, A part of an AB system, J=6.4, 9.7 Hz, one H of $CH_2CH_2CH_2O$), 3.74 (4H, AB system, J=6.0 Hz, galactose H-6), 3.85 (2H, d, J=3.4 Hz, galactose H-4), 3.92 (2H, B part of an AB system, J=6.4, 9.7 Hz, one H of $CH_2CH_2CH_2O$), 4.22 (2H, d, J=7.4 Hz, galactose H-1), 5.27 (4H, s, $PyCH_2O$), 6.97 (4H, A part of an AB system, J=8.5 Hz, aromatic H *ortho* to O), 7.17 (4H, B part of an AB system, J=8.5 Hz, aromatic H *meta* to O), 7.60 (2H, d, J=7.6 Hz, pyridine H-5), 7.94 (2H, t, J=7.6 Hz, pyridine H-4), 8.33 (2H, d, J=7.6 Hz, pyridine H-3); ^{13}C NMR (CD_3OD): δ 31.2 (2×CH_2–*C*–Ar), 31.8 (2×CH_2–*C*–CH_2Ar), 61.4 (2×galactose C-6), 68.9 (2×CH_2 bound to anomeric O), 69.3 (2×galactose C-4), 70.8 (2×Py*C*H_2O), 71.6 (2×galactose C-2), 74.0 (2×galactose C-3), 75.5 (2×galactose C-5), 104.1 (2×galactose C-1), 114.9 (4×aromatic C of phenyl ring *ortho* to O), 120.3 (2×pyridine C-3), 121.7 (2×pyridine C-5), 129.6 (4×aromatic C of phenyl ring *meta* to O), 135.0 (2×quaternary C of phenyl ring bound to CH_2), 138.0 (2×pyrdine C-4), 156.0 (2×pyridine C-2), 156.8 (2×quaternary C of phenyl ring bound to O), 157.7 (2×pyridine C-6); MS-ESI$^+$: *m/z* 831 $[M+Na]^+$. HRMS *m/z* 808.34278.

4.5.2. 6,6′-Bis-[2-[4-(β-D-galactopyranosyl)-phenyl]-ethynyl]-2,2′-bipyridine (17). White solid ^{1}H NMR (CD_3OD): δ 3.63 (2H, dd, J=3.4, 9.8 Hz, galactose H-3), 3.71–3.79 (2H, m, galactose H-5), 3.81 (4H, AB system, J=5.0, 8.0 Hz, galactose H-6), 3.85 (2H, dd, J=7.8, 9.9 Hz, galactose H-2), 3.95 (2H, d, J=3.4 Hz, galactose H-4), 4.97 (2H, d, J=7.8 Hz, galactose H-1), 7.18 (4H, A part of an AB system, J=8.6 Hz, aromatic H *ortho* to O), 7.60 (4H, B part of an AB system, J=8.6 Hz, aromatic H *meta* to O), 7.65 (2H, d, J=7.7 Hz, pyridine H-3), 7.97 (2H, t, J=7.7 Hz, pyridine H-4), 8.35 (2H, d, J=7.7 Hz, pyridine H-5); ^{13}C NMR (CD_3OD): δ 61.0 (2×galactose C-6), 68.8 (2×galactose C-4), 70.8 (2×galactose C-2), 73.4 (2×galactose C-3), 75.7 (2×galactose C-5), 87.2 (2×acetylenic C bound to pyridine), 88.8 (2×acetylenic C bound to ArO), 101.2 (2×galactose C-1), 115. (2×quaternary aromatic C bound to acetylenic C), 116.6 (4×aromatic C *ortho* to O), 120.4 (2×pyridine C-3), 127.1 (2×pyridine C-5), 133.1 (4×aromatic C *meta* to O), 137.5 (2×pyridine C-4), 143.0 (2×pyridine C-6), 155.0 (2×pyridine C-2),158.0 (2×quaternary aromatic C bound to O); MS-ESI$^+$: *m/z* 735 $[M+Na]^+$. HRMS *m/z* 712.22595.

4.5.3. 6,6′-Bis-[3-[4-[3-(β-D-galactopyranosyl)-prop-1-yl]-phenyloxymethyl]phenyl]-2,2′-bipyridine (18). White solid. ^{1}H NMR (CD_3OD): δ 1.91 (4H, quintet, J=8.0 Hz, $CH_2CH_2CH_2O$), 2.69 (4H, t, J=8.0 Hz, $CH_2CH_2CH_2O$), 3.45–3.60 (6H, m, galactose H-3, H-5, and H-2), 3.57 (2H, A part of an AB system, J=8.0, 9.8 Hz, one H of $CH_2CH_2CH_2O$), 3.76 (4H, d, J=6.6 Hz, galactose H-6), 3.86 (2H, d, J=3.5 Hz, galactose H-4), 3.92 (2H, B part of an AB system, J=8.0, 9.8 Hz, one H of $CH_2CH_2CH_2O$), 4.22 (2H, d, J=7.6 Hz, galactose H-1), 5.20 (4H, s, $ArCH_2O$), 6.98 (4H, A part of an AB system, J=8.6 Hz, aromatic H *ortho* to O), 7.18 (4H, B part of an AB system, J=8.6 Hz, aromatic H *meta* to O), 7.55 (4H, d, J=5.1 Hz,

aromatic H *para* to CH_2OAr and aromatic H *para* to pyridine ring), 7.95 (2H, d, $J=7.8$ Hz, pyridine H-5), 8.03 (2H, t, $J=7.8$ Hz, pyridine H-4), 8.16 (2H, t, $J=5.1$ Hz, aromatic H *meta* to pyridine ring), 8.31 (2H, br s, aromatic H between pyridine ring and CH_2OAr), 8.55 (2H, d, $J=7.8$ Hz, pyridine H-3); ^{13}C NMR (CD_3OD): δ 30.9 (2× CH_2–*C*–Ar), 31.4 (2×CH_2–*C*–CH_2), 61.1 (2×galactose C-6), 68.6 (2×CH_2–CH_2–*C*), 69.0 (2×galactose C-4), 69.8 (2×Ar–*CH_2*–O), 71.3 (2×galactose C-2), 73.7 (2× galactose C-3), 75.2 (2×galactose C-5), 103.0 (2× galactose C-1), 114.7 (4×aromatic C *ortho* to O), 119.4 (2×pyridine C-3), 120.2 (2×pyridine C-5), 125.8 (2× aromatic C between pyridine ring and CH_2OAr), 126.0 (2×aromatic C *meta* to pyridine ring and CH_2OAr), 128.0 (2×aromatic C *para* to pyridine ring), 128.5 (2×aromatic C *para* to CH_2OAr), 129.1 (4×aromatic C *meta* to O), 135.0 (2×quaternary aromatic C *para* to O), 137.7 (2× pyridine C-4), 138.0 (2×s, quaternary aromatic C *meta* to pyridine ring), 156.0 (4×pyridine C-2 and C-6) and 157.5 (2×quaternary aromatic C bound to O); MS-ESI$^+$: *m/z* 983 $[M+Na]^+$. HRMS *m/z* 960.40331.

4.5.4. 6,6′-Bis-[3-[*N*-2-(β-D-galactopyranosyl)-ethyl]-imminomethyl]-phenyl]-2,2′-bipyridine (19). White solid. ^1H NMR (CD_3OD): δ 3.41–3.60 (6H, m, galactose H-2, H-3, and H-5), 3.72–3.78 (4H, m, galactose H-6), 3.85 (2H, br d, $J=3.0$ Hz, galactose H-4), 3.90–4.00 (6H, m, N*CH_2*CH_2O and one H of NCH_2*CH_2*O), 4.20–4.30 (2H, m, one H of NCH_2*CH_2*O), 4.35 (2H, d, $J=8.0$ Hz, galactose H-1), 7.63 (2H, t, $J=7.8$ Hz, aromatic H *meta* to pyridine ring and *meta* to CH=N), 7.85 (2H, d, $J=7.7$ Hz, aromatic H *para* to pyridine ring), 8.01 (2H, d, $J=7.2$ Hz, pyridine H-5), 8.06 (2H, t, $J=7.2$ Hz, pyridine H-4), 8.34 (2H, d, $J=7.8$ Hz, aromatic H *para* to CH=N), 8.57 (2H, s, *CH*=N), 8.65 (2H, br s, aromatic C between pyridine ring and CH=N), 8.76 (2H, d, $J=7.2$ Hz, pyridine H-3); ^{13}C NMR (CD_3OD): δ 60.3 (2×*CH_2*–N), 61.2 (2×galactose C-6), 68.8 (2×N–CH_2*CH_2*–O), 69.1 (2×galactose C-4), 71.2 (2×galactose C-2), 73.6 (2×galactose C-3), 75.3 (2× galactose C-5), 103.8 (2×galactose C-1), 119.7 (2× pyridine C-3), 120.2 (2×pyridine C-5), 126.3 (2×aromatic C between pyridine ring and CH=N), 128.8 (4×aromatic C *para* to pyridine ring and aromatic C *meta* to pyridine ring and *meta* to CH=N), 129.2 (2×aromatic C *para* to CH=N), 136.2 (2×quaternary aromatic C bound to CH=N), 137.9 (2×pyridine C-4), 139.7 (2×quaternary aromatic C bound to pyridine ring), 155.5 (2×pyridine C-2), 156.0 (2×pyridine C-6), 164.8 (2×CH=N); MS-ESI$^+$: *m/z* 797 $[M+Na]^+$. HRMS *m/z* 774.31085.

4.6. Synthesis of Cu(I) and Zn(II) complexes

4.6.1. Synthesis of the Cu(I) complexes. *General procedure*. To a stirred solution of ligand (typical amount 0.01 mmol) in $CHCl_3$ (0.5 mL), kept under nitrogen at room temperature, $CuOTf\cdot 0.5C_6H_6$ (0.36 mL of a 0.01 M solution in acetonitrile, 0.005 mmol) was added. The red solution was stirred at room temperature for 24 h. The solvent was then evaporated under vacuum to afford a red solid that was purified by a filtration on a short column of silica gel for flash chromatography with a 95:5 CH_2Cl_2/MeOH mixture as eluant (when attempted, this purification degraded complex **Cu(14)$_2$** that was isolated as crude product). In all cases the recovery of the complex was virtually quantitative.

Compound **Cu(11)$_2$**. Red solid. ^1H NMR (CD_3OD): δ 1.75–1.86 (8H, m, 2×CH_2*CH_2*CH_2O), 1.98 (12H, s, Me), 2.01 (12H, s, Me), 2.07 (12H, s, Me), 2.16 (12H, s, Me), 2.45–2.61 (8H, m, *CH_2*CH_2CH_2O), 3.52 (4H, A part of an AB system, $J=6.0$, 10.0 Hz, one H of CH_2CH_2*CH_2*O), 3.82 (4H, B part of an AB system, $J=6.0$, 10.0 Hz, H of CH_2CH_2*CH_2*O), 4.06–4.22 (12H, m, galactose H-5 and H-6), 4.64 (4H, d, $J=7.8$ Hz, galactose H-1), 4.82 (8H, s, 2×Ar*CH_2*O), 5.08–5.19 (8H, m, galactose H-2 and H-3), 5.41 (4H, br s, galactose H-4), 6.25 (8H, A part of an AB system, $J=8.3$ Hz, aromatic H *ortho* to O), 6.80 (8H, B part of an AB system, $J=8.3$ Hz, aromatic H *meta* to O), 7.78 (4H, d, $J=7.6$ Hz, pyridine H-5), 8.09 (4H, t, $J=7.6$ Hz, pyridine H-4), 8.20 (4H, d, $J=7.6$ Hz, pyridine H-3); ^{13}C NMR (CD_3OD): δ 19.0 (8×Me), 19.4 (8×Me), 30.3 (4× Ar–*C*–CH_2), 31.3 (4×CH_2–*C*–CH_2), 61.1 (4×galactose C-6), 67.4 (4×galactose C-4), 68.4 (4×CH_2 bound to anomeric O), 69.2 (4×galactose C-2), 70.3 (4×galactose C-5), 70.4 (4×ArO–*CH_2*), 70.9 (4×galactose C-3), 100.8 (4×galactose C-1), 113.2 (8×aromatic C *ortho* to O), 121.4 (4×pyridine C-3), 125.7 (4×pyridine C-5), 128.9 (8×aromatic C *meta* to O), 134.3 (4×quaternary aromatic C *para* to O), 138.9 (4×pyridine C-4), 151.5 (4×pyridine C-2), 155.0 (4×pyridine C-6), 155.8 (4×quaternary aromatic C bound to O), 169.9 (8×C=O), 170.5 (8× C=O); MS-FAB: *m/z* 2353 $[M-OTf]^+$; HRMS *m/z* 2351.79451 $[M-OTf]^+$.

Compound **Cu(12)$_2$**. Red solid. ^1H NMR (CD_3OD): δ 2.00 (12H, s, Me), 2.06 (12H, s, Me), 2.08 (12H, s, Me), 2.21 (12H, s, Me), 4.20–4.26 (8H, m, galactose H-6), 4.34 (4H, t, $J=6.5$ Hz, galactose H-5), 5.25–5.41 (12H, m, galactose H-3, H-2, and H-1), 5.51 (4H, d, $J=3.2$ Hz, galactose H-4), 6.73 (8H, A part of an AB system, $J=8.7$ Hz, aromatic H *meta* to O), 6.85 (8H, B part of an AB system, $J=8.6$ Hz, aromatic H *meta* to O), 7.77 (4H, d, $J=7.6$ Hz, pyridine H-5), 8.00 (4H, t, $J=7.8$ Hz, pyridine H-4), 8.12 (4H, d, $J=8.0$ Hz, pyridine H-3); ^{13}C NMR (CD_3OD): δ 19.1 (8×Me), 19.3 (8×Me), 61.1 (4×galactose C-6), 67.3 (4×galactose C-4), 68.7 (4×galactose C-2), 70.7 (4×galactose C-3), 70.9 (4×galactose C-5), 86.4 (4×acetylenic C bound to pyridine), 92.0 (4×acetylenic C bound to phenyl ring), 98.0 (4×galactose C-1), 115.0 (4×quaternary aromatic C bound to acetylenic C), 116.3 (8×aromatic C *ortho* to O), 121.1 (4×pyridine C-3), 128.4 (4×pyridine C-5), 132.5 (8× aromatic C *meta* to O), 137.7 (4×pyridine C-4), 141.4 (4×pyridine C-6), 151.6 (4×pyridine C-2), 157.5 (4×aromatic C bound to O), 169.8 (4×C=O), 170.0 (4×C=O), 170.5 (4×C=O), 170.6 (2×C=O); MS-FAB: *m/z* 2161 $[M-OTf]^+$; HRMS *m/z* 2159.56450 $[M-OTf]^+$.

Compound **Cu(13)$_2$**. Red solid. ^1H NMR (CD_3OD): δ 1.71 (8H, quintet, $J=6.5$ Hz, CH_2*CH_2*CH_2O), 1.95 (12H, s, Me), 1.99 (12H, s, Me), 2.00 (12H, s, Me), 2.14 (12H, s, Me), 2.47 (8H, t, $J=6.5$ Hz, *CH_2*CH_2CH_2O), 3.43 (4H, A part of an AB system, $J=6.5$, 9.8 Hz, one H of CH_2CH_2*CH_2*O), 3.75 (4H, B part of an AB system, $J=6.5$, 9.8 Hz, one H of CH_2CH_2*CH_2*O), 4.04 (4H, q, $J=6.2$ Hz, galactose H-5), 4.12 (8H, AB system, $J=3.6$, 6.2 Hz, galactose H-6), 4.39

(8H, s, ArCH_2O), 4.53 (4H, d, J=7.8 Hz, galactose H-1), 5.02–5.13 (8H, m, galactose H-2 and H-3), 5.38 (4H, br s, galactose H-4), 6.36 (8H, A part of an AB system, J=8.6 Hz, aromatic H *ortho* to OCH_2Ar), 6.83 (8H, B part of an AB system, J=8.6 Hz, aromatic H *meta* to OCH_2Ar), 7.03–7.09 (8H, m, aromatic H of phenyl ring in *meta* and *para* position to pyridine ring), 7.24 (8H, d, J=6.7 Hz, aromatic H of phenyl ring *para* to CH_2OAr), 7.38 (8H, d, J=7.7 Hz, pyridine H-5), 7.75 (4H, t, J=7.7 Hz, pyridine H-4), 7.97 (4H, d, J=7.7 Hz, pyridine H-3), 8.06 (4H, br s, aromatic H of phenyl ring between pyridine and CH_2OAr); ^{13}C NMR (CD_3OD): δ 19.5 (12×Me), 19.8 (4×Me), 30.8 (4×Ar–*C*–CH_2), 31.6 (4×CH_2*C*–CH_2), 61.5 (4×galactose C-6), 67.8 (4×galactose C-4), 68.6 (4×Ar–*C*–O), 68.8 (4×CH_2 bound to anomeric O), 69.6 (4×galactose C-2), 70.7 (4×galactose C-5), 71.4 (4×galactose C-3), 101.2 (4×galactose C-1), 114.5 (8×aromatic C *ortho* to O), 121.3 (4×pyridine C-3), 125.2 (4×pyridine C-5), 125.6 (4×aromatic C between pyridine and CH_2OAr), 127.3 (4×aromatic C *meta* to CH_2OAr), 127.5 (4×aromatic C *para* to pyridine), 128.1 (4×aromatic C *ortho* to pyridine and *para* to CH_2OAr), 129.2 (4×aromatic C *meta* to O), 134.0 (4×quaternary aromatic C *para* to O), 137.4 (4×quaterrnary C bound to CH_2OAr), 138.2 (4×pyridine C-4), 139.0 (4×quaternary aromatic C bound to pyridine), 153.3 (4×pyridine C-2), 156.9 (4×aromatic C bound to O, and 4×pyridine C-6), 170.5 (8×C=O), 171.0 (8×C=O); MS-FAB: *m/z* 2658 $[M-OTf]^+$; HRMS *m/z* 2655.91478 $[M-OTf]^+$.

Compound **Cu(14)$_2$**. Red solid. ^{1}H NMR (CD_3CN): δ 1.80 (12H, s, Me), 1.89 (12H, s, Me), 1.98 (12H, s, Me), 1.99 (12H, s, Me), 3.46–3.57 (4H, m, one H of N*C*$H_2$$CH_2O$), 3.80–3.96 (8H, m, one H of N*C*$H_2$$CH_2O$, and one hydrogen of NCH_2*C*H_2O), 4.02–4.12 (12H, m, galactose H-6 and one hydrogen of NCH_2*C*H_2O), 4.48 (4H, d, J=7.8 Hz, galactose H-1), 4.90–5.02 (12H, m, galactose H-2, H-3, and H-5), 5.28 (4H, br s, galactose H-4), 7.14 (4H, t, J=7.5 Hz, aromatic H *meta* to pyridine), 7.36 (4H, d, J=7.5 Hz, aromatic H *para* to pyridine), 7.58 (4H, d, J=7.5 Hz, aromatic H *para* to CH=N), 7.65 (4H, d, J=7.0 Hz, pyridine H-5), 7.72 (4H, br s, CH=N), 7.95–8.04 (8H, m, pyridine H-4 and H-3), 8.21 (4H, br s, aromatic H between CH=N and pyridine ring); ^{13}C NMR (CD_3CN): δ 19.7 (8×Me), 19.8 (8×Me), 60.0 (4×NCH_2), 61.2 (4×galactose C-6), 67.3 (4×galactose C-4), 68.7 (4×galactose C-2), 69.1 (4×CH_2 bound to anomeric O), 70.5 (8×galactose C-3 and C-5), 100.8 (4×galactose C-1), 121.5 (4×pyridine C-3), 124.8 (4×pyridine C-5), 126.4 (4×aromatic C between pyridine ring and CH=N), 128.0 (4×aromatic C *meta* to pyridine ring), 128.8 (4×aromatic *para* to pyridine ring), 130.4 (4×aromatic C *para* to CH=N), 135.5 (4×quaternary aromatic C bound to CH=N), 138.2 (4×pyridine C-4), 138.7 (4×quaternary aromatic C bound to pyridine ring), 152.8 (4×pyridine C-2), 156.0 (4×pyridine C-6), 161.1 (4×CH=N), 169.7 (8×C=O), 170.0 (8×C=0); MS-FAB: *m/z* 2284 $[M\text{-}OTf]^+$; HRMS *m/z* 2283.73221 $[M-OTf]^+$.

4.6.2. Deprotection of the acetylated complexes Cu(11)$_2$, Cu(12)$_2$, and Cu(14)$_2$ to Cu(16)$_2$, Cu(17)$_2$, and Cu(19)$_2$. This was performed following the procedure described above for the deprotection of the acetylated ligands.

Compound **Cu(16)$_2$**. Red solid. ^{1}H NMR (CD_3OD): δ 1.83–190 (8H, m, CH_2*C*$H_2$$CH_2O$), 2.56 (8H, t, J=7.4 Hz, *C*$H_2$$CH_2$*C*$H_2$O), 3.47–3.60 (16H, m, galactose H-3, galactose H-5, galactose H-2, and one H of CH_2CH_2*C*H_2O), 3.77 (8H, d, J=6.0 Hz, galactose H-6), 3.88 (4H, d, J=3.3 Hz, galactose H-4), 3.90 (4H, B part of an AB system, J=6.4, 9.7 Hz, one H of CH_2CH_2*C*H_2O), 4.25 (4H, d, J=7.7 Hz, galactose H-1), 4.80 (8H, s, PyCH_2O), 6.22 (8H, A part of an AB system, J=8.5 Hz, aromatic H *ortho* to O), 6.81 (8H, B part of an AB system, J=8.5 Hz, aromatic H *meta* to O), 7.76 (4H, d, J=8.1 Hz, pyridine H-3), 8.08 (4H, t, J=8.1 Hz, pyridine H-4), 8.18 (4H, d, J=8.1 Hz, pyridine H-5); ^{13}C NMR (CD_3OD): δ 30.6 (4×CH_2–*C*–Ar), 31.5 (4×CH_2–*C*–CH_2), 61.1 (4×galactose C-6), 68.5 (4×CH_2–CH_2–*C*–O), 68.9 (4×galactose C-4), 70.5 (4×Py*C*H_2O), 71.2 (4×galactose C-2), 73.7 (4×galactose C-3), 75.3 (4×galactose C-5), 103.7 (4×galactose C-1), 113.0 (8×aromatic C *ortho* to O), 121.5 (4×pyridine C-3), 125.8 (4×pyridine C-5), 128.9 (8×aromatic H *meta* to O), 134.7 (4×quaternary aromatic C *para* to O), 139.0 (4×pyridine C-4), 151.6 (4×pyridine C-2), 155.0 (4×pyridine C-6), 155.8 (4×quaternary aromatic C bound to O); MS-ESI$^+$: *m/z* 1679 $[M-OTf]^+$; HRMS *m/z* 1679.61973 $[M-OTf]^+$.

Compound **Cu(17)$_2$**. Red solid. ^{1}H NMR (CD_3OD): δ 3.63 (4H, dd, J=3.4, 9.6 Hz, galactose H-3), 3.79–3.90 (16H, m, galactose H-5, H-6, and H-2), 3.95 (4H, d, J=3.0 Hz, galactose H-4), 4.90 (4H, d, J=7.7 Hz, galactose H-1), 6.70 (8H, A part of an AB system, J=8.6 Hz, aromatic H *ortho* to O), 6.90 (8H, B part of an AB system, J=8.6 Hz, aromatic H *meta* to O), 7.71 (4H, d, J=7.5 Hz, pyridine H-3), 7.96 (4H, t, J=7.7 Hz, pyridine H-4), 8.08 (4H, d, J=7.7 Hz, pyridine H-5); ^{13}C NMR (CD_3OD): δ 61.3 (4×galactose C-6), 68.9 (4×galactose C-4), 70.6 (4×galactose C-2), 73.4 (4×galactose C-3), 75.8 (4×galactose C-5), 86.2 (4×acetylenic C bound to pyridine ring), 92.2 (4×acetylenic C bound to phenyl ring), 100.9 (4×galactose C-1), 109.0 (4×quaternary aromatic C bound to acetylenic carbon), 116.2 (8×aromatic C *ortho* to O), 121.0 (4×pyridine C-3), 128.0 (4×pyridine C-5), 132.3 (8×aromatic C *meta* to O), 137.6 (4×pyridine C-4), 143.0 (4×pyridine C-6), 152.0 (4×pyridine C-2), 158.0 (4×quaternary aromatic C bound to O); MS-ESI$^+$: *m/z* 1487 $[M-OTf]^+$; HRMS *m/z* 1487.39145 $[M-OTf]^+$.

Compound **Cu(19)$_2$**. Red solid. ^{1}H NMR (CD_3OD): δ 3.35–3.58 (20H, m, galactose H-3, H-5, and H-2, and N*C*$H_2$$CH_2$-O), 3.65–3.80 (12H, m, one hydrogen of NCH_2*C*H_2O and galactose H-6), 3.87 (4H, d, J=3.0 Hz, galactose H-4), 3.90–4.10 (4H, m, one hydrogen of NCH_2*C*H_2O), 4.21 (4H, d, J=7.2 Hz, galactose H-1), 7.11 (4H, t, J=7.8 Hz, aromatic H *meta* to pyridine ring and *meta* to CH=N), 7.45 (4H, d, J=7.8 Hz, aromatic H *para* to pyridine ring), 7.61 (4H, d, J=7.8 Hz, aromatic H *para* to CH=N), 7.73 (4H, d, J=7.2 Hz, pyridine H-3), 7.82 (4H, s, CH=N), 8.03–8.20 (12H, m, pyridine H-4 and H-5, and aromatic H between pyridine ring and CH=N); ^{13}C NMR (CD_3OD): δ 60.0 (4×CH_2–N), 61.1 (4×galactose C-6), 68.6 (4×CH_2*C*H_2–O), 68.8 (4×galactose C-4), 71.0 (4×galactose C-2), 73.5 (4×galactose C-3), 75.2 (4×galactose C-5), 103.7 (4×galactose C-1), 121.6 (4×pyridine C-3), 124.9 (4×pyridine C-5), 127.1 (4×aromatic C between pyridine

ring and CH=N), 127.9 (4×aromatic C *para* to pyridine ring), 128.4 (4×aromatic C *meta* to pyridine ring and *meta* to CH=N), 130.4 (4×aromatic C *para* to CH=N), 135.1 (4×aromatic C bound to CH=N), 138.6 (4×pyridine C-4), 138.9 (4×quaternary aromatic C bound to pyridine ring), 152.7 (4×pyridine C-2), 156.1 (4×pyridine C-6), 162.7 (4×CH=N); MS-ESI$^+$: *m/z* 1611 $[M-OTf]^+$; HRMS *m/z* 1611.56120 $[M-OTf]^+$.

4.6.3. Synthesis of the Zn(15) complex. To a stirred solution of ligand **15** (30 mg, 0.026 mmol) in $CHCl_3$ (0.5 mL), kept under nitrogen at room temperature, $Zn(OTf)_2$ (9.6 mg, 0.026 mmol) was added. The solution was stirred at room temperature for 15 h. The solvent was then evaporated under vacuum to afford a pale yellow solid in quantitative yield. ^{1}H NMR (CD_3OD): δ 2.02 (6H, s, Me), 2.08 (6H, s, Me), 2.09 (6H, s, Me), 2.23 (6H, s, Me), 4.25 (4H, d, $J=6.4$ Hz, galactose H-6), 4.39 (2H, t, $J=6.4$ Hz, galactose H-5), 5.32 (2H, dd, $J=3.2$, 10.0 Hz, galactose H-3), 5.46–5.58 (4H, m, galactose H-1 and H-2), 5.53 (2H, d, $J=3.2$ Hz, galactose H-4), 6.93 (4H, A part of an AB system, $J=8.7$ Hz, aromatic H *meta* to O), 7.04 (4H, B part of an AB system, $J=8.7$ Hz, aromatic H *ortho* to O), 7.56 (1H, t, $J=7.9$ Hz, terpyridine H-4′), 7.75 (2H, d, $J=7.9$ Hz, terpyridine H-5 and H-3″), 8.17 (2H, d, $J=7.9$ Hz, terpyridine H-3′ and H-5′), 8.24 (2H, t, $J=7.9$ Hz, terpyridine H-4 and H-4″), 8.55 (2H, d, $J=7.9$ Hz, pyridine H-3 and H-5″); ^{13}C NMR (CD_3OD): δ 19.1 (4×Me), 19.2 (4×Me), 61.0 (2×galactose C-6), 67.2 (2×galactose C-4), 68.6 (2×galactose C-2), 70.7 (2×galactose C-3), 71.0 (2×galactose C-5), 83.7 (2×acetylenic C bound to terpyridine), 94.9 (2×acetylenic C bound to phenyl), 98.0 (2×galactose C-1), 114.3 (2×quaternary phenyl *C* bound to acetylene), 116.6 (4×aromatic C *ortho* to O), 122.2 (2×terpyridine C-3 and C-5″), 124.1 (2×terpyridine C-3′ and C-5′), 132.3 (2×terpyridine C-5 and C-3″), 133.1 (4×aromatic C *meta* to O), 141.1 (2×pyridine C-4 and C-4″), 142.8 (2×pyridine C-6 and C-2″), 142.9 (1×pyridine C-4′), 149.7 (2×pyridine C-2′ and C-6′), 149.9 (2×pyridine C-2 and C-6″), 158.2 (2×aromatic C bound to O), 169.8 (2×C=O), 169.9 (2×C=O), 170.4 (2×C=O), 170.5 (2×C=O); MS-FAB: *m/z* 1339 $[M-OTf]^+$; HRMS *m/z* 1338.21783 $[M-OTf]^+$.

4.6.4. 2″,6-Bis-[2-[4-(β-D-galactopyranosyl)-phenyl]-ethynyl]-2,2′:6′,6″-terpyridine 20. This compound was obtained attempting the deacetylation of **Zn(15)** (see above for condition and isolation). White solid. ^{1}H NMR (DMSO-d_6): δ 3.44 (2H, dd, $J=3.2$, 9.6 Hz, galactose H-3), 3.53-3.68 (8H, m, galactose H-2, H-5, and H-6), 3.74 (2H, d, $J=3.2$ Hz, galactose H-4), 4.93 (2H, d, $J=7.6$ Hz, galactose H-1), 7.13 (4H, A part of AB system, $J=8.7$ Hz, aromatic H *ortho* to O), 7.62 (4H, B part of AB system, $J=8.7$ Hz, aromatic H *meta* to O), 7.74 (2H, d, $J=7.7$ Hz, terpyridine H-5 and H-3″), 8.07 (2H, t, $J=7.8$ Hz, terpyridine H-4 and H-4″), 8.16 (1H, t, $J=7.9$ Hz, terpyridine H-4′), 8.49 (2H, d, $J=7.8$ Hz, terpyridine H-3′ and H-5′), 8.63 (2H, d, $J=8.0$ Hz, terpyridine H-3 and H-5″); ^{13}C NMR (DMSO-d_6): δ (2×galactose C-6), 68.9 (2×galactose C-4), 70.8 (2×galactose C-2), 73.5 (2×galactose C-3), 75.7 (2×galactose C-5), 87.1 (2×acetylenic C bound to terpyridine), 89.0 (2×acetylenic C bound to phenyl), 101.3 (2×galactose C-1), 116.6 (2×quaternary carbon of phenyl ring bound to acetylenic C), 116.7 (4×aromatic C *ortho* to O), 120.3 (2×C-5 and C-3″ of terpyridine), 121.3 (2×C-3′ and C-5′ of terpyridine), 127.5 (2×C-3 and C-5″ of terpyridine), 133.0 (4×aromatic C *meta* to O), 137.4 (2×C-4 and C-4″ of terpyridine), 138.0 (terpyridine C-4′), 143.1 (2×terpyridine C-2 and C-6″), 155.0 (2×terpyridine C-2′ and C-6′), 157.0 (2×terpyridine C-6 and C-2″), 158.0 (2×aromatic C bound to O); MS-ESI$^+$: *m/z* 812 $[M+yNa]^+$.

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16. It must be noted that ligand **14** contains two additional nitrogen atoms as potentially competing binding sites for Cu(I). It has been shown however, that the imine nitrogens of some imine-bridged olygobipyridine ligands were not involved in the complexation with Cu(I) cations, that occurred exclusively at the bipyridine nitrogens. On the basis of NMR evidence we believe that this is also the case for the complexation of ligand **14**. For a leading reference see: Stiller, R.; Lehn, J.-M. *Eur. J. Inorg. Chem.* **1998**, 977–982.
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18. Compounds **16**-**19** were scarcely soluble in MeOH and reasonably soluble in DMSO, that was the only solvent for ligand **20**. Analytically pure samples of **16**-**20** could not be obtained.
19. Attempts of running the complexation reaction of **16–20** in DMSO met with no success, probably because of the strongly coordinating nature of this solvent.
20. Complexes $\mathbf{Cu(16)_2}$, $\mathbf{Cu(17)_2}$, and $\mathbf{Cu(19)_2}$ were enough soluble in CD_3OD to obtain NMR data. $\mathbf{Cu(18)_2}$ was insoluble in CD_3OD. When the NMR spectra of these complexes were recorded in DMSO extensive complex decomposition was observed. As in the case of the polyols, from which they formally derive, isolation of analytically pure compounds was not possible. These solubility properties may represent a problem in the biological studies of such a compounds. Studies are currently underway in order to solve this problem.
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An efficient synthesis of benzofurans and their application in the preparation of natural products of the genus *Calea*

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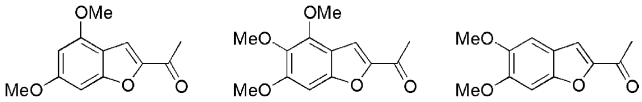
Dedicated to Professor Gustavo García de la Mora on his 60th birthday

Abstract—The intramolecular cyclization of the β-substituted olefins methyl 2-aryloxy-3-dimethylaminopropenoates **3a**–**3f** catalyzed by Lewis acids leads to a short and novel synthesis of benzofurans **2a**–**2f**. When the olefins 4-dimethylamino-3-aryloxy-3-buten-2-ones **4a**–**4f** were used, the cyclization process was faster and provided the corresponding substituted 2-acetylbenzofurans **1a**–**1f**. Among the latter, naturally occurring compounds calebertin (**1a**), caleprunin A (**1b**), and caleprunin B (**1c**) were prepared in good overall yields. These benzofurans were also obtained by direct treatment under MW irradiation of the precursors 1-aryloxypropan-2-ones **7a**–**7c** with DMFDMA, followed by addition of the catalyst, resulting in a route that was one step shorter.

1. Introduction

An intense effort has been made directed towards the synthesis of benzofurans,[1] due to their biological activity as potential pharmacological agents,[2] and to their occurrence in nature.[3] Among the reported synthetic strategies, those approaches designed for building the heterocyclic ring have been widely preferred, because of their simplicity when the starting materials are already carrying the functionalized benzene moiety. Thus, a great number of methods have been developed for the heterocyclic ring closure,[1,4] being particularly versatile those approaches leading to the C3–C3a bond formation as the key step.[5]

Natural 2-acetylbenzofurans calebertin (**1a**), caleprunin A (**1b**), and caleprunin B (**1c**) have been isolated from *Calea* species.[6] Caleprunin B (**1c**) had been previously isolated from *Eupatorium sternbergianum* and called eupatarone.[7] The syntheses of these compounds were carried out through an aldolic condensation of the corresponding *ortho*-formylphenoxyketone.[8] Partial synthesis of compound **1c** has also been reported by oxidation of natural 5,6-dimethoxy-2-isopropylbenzofuran.[9]



1a **1b** **1c**

Recently, we reported our preliminary results about a new straightforward synthesis of benzofurans **2**,[10] taking advantage of the high reactivity of captodative olefins in Friedel–Crafts reactions.[11] Thus, the intramolecular cyclization of the previously functionalized methyl 2-aryloxy-3-dimethylaminopropenoates (**3**) promoted by a Lewis acid ($ZnCl_2$) allowed for the preparation of benzofurans **2** in good yields (Scheme 1). Compounds **3** are acting as enaminones, which have proved to be privileged Michael acceptors for the addition of a large number of nucleophiles.[12]

With the aim of optimizing and extending our methodology, we hereby describe the development of some alternative conditions for the preparation of benzofurans **2**, and the study of preparation and intramolecular cyclization of 3-aryloxy-4-dimethylamino-3-buten-2-ones **4** as versatile and reactive precursors of compounds **1** (Scheme 1), including the total synthesis of natural products **1a**–**1c**.

Keywords: 2-Aryloxy-3-dimethylaminopropenoates; Natural 2-acetylbenzofurans; Cyclization; Lewis acid catalysis; Microwaves.
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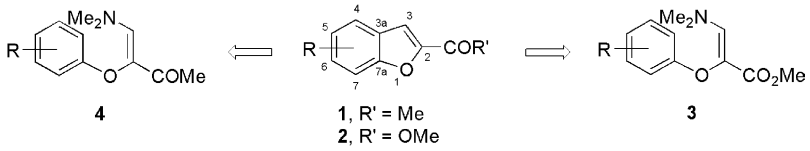
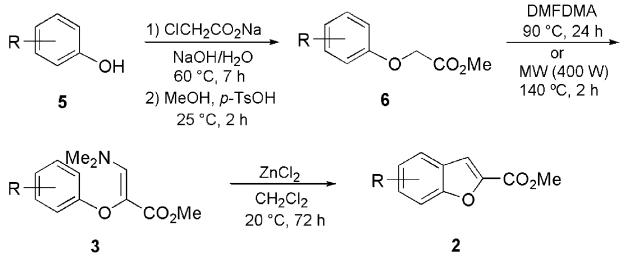


Scheme 1.

2. Results and discussion

Scheme 2 depicts the synthesis of benzofurans **2** starting from phenols **5**. Thus, phenols **5a–5i** were converted to methyl phenoxyacetates **6a–6i** in good yields (81–92%) by reacting with the sodium salt of chloroacetic acid or with chloroacetic acid in aqueous NaOH, and heating at 60 °C for 7 h, followed by esterification in the presence of dry methanol and 10 mol% of *p*-TsOH.[13]



Scheme 2.

Methyl 3-dimethylaminopropenoates **3a–3i** were readily obtained by treatment of methyl phenoxyacetates **6a–6i** with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) at 90 °C for 24 h (Scheme 2; Table 1, entries 1–9).[14] The reaction times were reduced by increasing the temperature, but the yields were not significantly enhanced (Table 1, entries 10–12). This conversion could be also carried out by MW irradiation in comparable yields, but in shorter reaction times (Table 1, entries 13–15). Other advantage of the latter method was the fact that the crude mixtures were cleaner and then the purification process by column chromatography on silica gel was easier. In all cases, the propenoates **3** were only obtained as the *Z* stereoisomers, as shown by NOE experiments (irradiation of the signal assigned to protons of dimethylamino group produced an enhancement of the signals corresponding to the aromatic protons). This stereoisomeric preference is probably due to the higher stability gained by the efficient resonance effect of the β-amino unsaturated ester system when the bulky dimethylamino group is located *trans* to the methoxycarbonyl group.[15]

Cyclization of the corresponding 2-aryloxy-3-dimethylaminopropenoates **3a–3c** under thermal conditions (100 °C, 48 h) provided benzofurans **2a–2c** in fair yields (40–45%) (Table 2, entries 1–3). The yields were improved for the series **3a–3f** when a Lewis acid catalyst ($ZnCl_2$) was used (Table 2, entries 4–9). The reaction was regioselective, since we were unable to detect by NMR the isomers with the ring closure towards the *ortho* position of the substituent in the benzene ring. We also found that under microwave (MW) irradiation,[16] the cyclization of compounds **3b** and **3c** took place in modest yields (Table 2, entries 10 and 11). It is noteworthy that analogs **3g–3i**, whose aryl ring is substituted by methyl groups or corresponds to the β-naphthyl ring, were unable to be cyclized by any of the methods described in Table 2. This is probably due to the weak electron-releasing activation of the aryl ring by their substituents, during the intramolecular Friedel–Crafts process.

We investigated the preparation of benzofurans **2a–2c** by a one-step tandem reaction, starting from the phenoxyacetic methyl esters **6a–6c** with DMFDMA (2 mol equiv) in acetonitrile under thermal conditions, either with ($ZnCl_2$) or without catalyst. The desired benzofurans **2a–2c** were obtained in low yields (<25%) along with a higher proportion of their corresponding methyl propenoates **3a–3c** (<58%) (Eq. 1). Looking to improve the yields of

Table 1. Preparation of methyl 2-aryloxy-3-dimethylaminopropenoates **3a–3i**[a]

Entry	**6** (R)	Temperature (°C)	Time *t* (h)	**3**	Yield (%)[b]
1	**6a** (3-OMe)	90	24	**3a**	61
2	**6b** (3,4-$(OMe)_2$)	90	24	**3b**	68
3	**6c** (3,4-OCH_2O)	90	24	**3c**	60
4	**6d** (3-OMe, 4-OEt)	90	24	**3d**	74
5	**6e** (3-OMe, 4-OBn)	90	24	**3e**	63
6	**6f** (2,3,4-$(OMe)_3$)	90	24	**3f**	76
7	**6g** (3-Me)	90	24	**3g**	64
8	**6h** (2,5-$(Me)_2$)	90	24	**3h**	65
9	**6i** (3,4-C_4H_4)	90	24	**3i**	66
10	**6a** (3-OMe)	140	16	**3a**	56
11	**6b** (3,4-$(OMe)_2$)	140	16	**3b**	68
12	**6c** (3,4-OCH_2O)	140	16	**3c**	71
13	**6a** (3-OMe)	140[c]	2	**3a**	65
14	**6b** (3,4-$(OMe)_2$)	140[c]	2	**3b**	67
15	**6c** (3,4-OCH_2O)	140[c]	2	**3c**	70

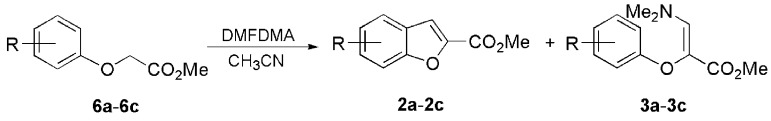
[a] Under N_2 atmosphere, with 3.0 mol equiv of DMFDMA.
[b] After column chromatography and recrystallization.
[c] Under MW irradiation (400 W).

Table 2. Preparation of benzofurans **2a–2h**

Entry	**3** (R)	Conditions	Solvent	Temperature (°C)	Time *t* (h)	**2**	Yield (%)[a]
1	**3a** (3-OMe)	Thermal	MeCN	100	48	**2a**	40
2	**3b** (3,4-$(OMe)_2$)	Thermal	MeCN	100	48	**2b**	42
3	**3c** (3,4-OCH_2O)	Thermal	MeCN	100	48	**2c**	45
4	**3a** (3-OMe)	$ZnCl_2$[b]	CH_2Cl_2	20	72	**2a**	62
5	**3b** (3,4-$(OMe)_2$)	$ZnCl_2$[b]	CH_2Cl_2	20	72	**2b**	68
6	**3c** (3,4-OCH_2O)	$ZnCl_2$[b]	CH_2Cl_2	20	72	**2c**	68
7	**3d** (3-OMe, 4-OEt)	$ZnCl_2$[b]	CH_2Cl_2	20	72	**2d**	65
8	**3e** (3-OMe, 4-OBn)	$ZnCl_2$[b]	CH_2Cl_2	20	72	**2e**	70
9	**3f** (2,3,4-$(OMe)_3$)	$ZnCl_2$[b]	CH_2Cl_2	20	72	**2f**	72
10	**3b** (3,4-$(OMe)_2$)	MW[c]	MeCN	100	5	**2b**	48
11	**3c** (3,4-OCH_2O)	MW[c]	MeCN	100	5	**2c**	51

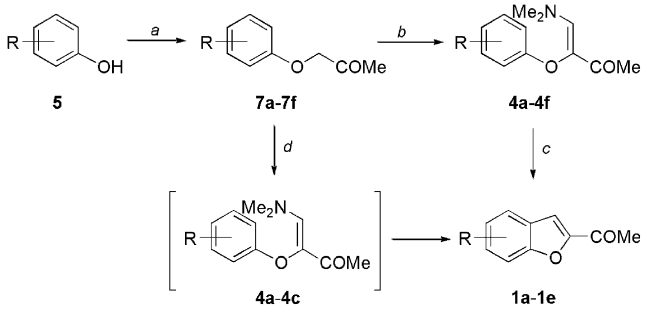
[a] After column chromatography and recrystallization.
[b] Three mole equivalents.
[c] Four hundred watts.

the desired benzofurans, the reactions were also carried out under MW irradiation, but the ratios of **2a–2c/3a–3c** were similar.



(1)

For the synthesis of 2-acetylbenzofurans **1**, it was necessary to prepare the corresponding 1-aryloxypropan-2-ones **7**, followed by the intramolecular cyclization of 3-aryloxy-4-dimethylamino-3-buten-2-ones **4** (Scheme 3). Compounds **7a–7f** were prepared in good yields (70–87%) by a base-promoting Williamson reaction between the substituted phenols, **5**, and chloroacetone (**8**) in refluxing acetone.[17] The series of compounds **4a–4f** was prepared in high yields (81–88%) by reacting the corresponding 1-aryloxypropan-2-ones **7a–7f** with 1.0 mol equiv of DMFDMA (Scheme 3). A larger amount of DMFDMA can lead to a mixture of the mono- and bis-dimethylaminomethylene derivatives. Of the complete series of compounds **4a–4f**, only derivatives **4a–4e** were able to undergo cyclization to obtain benzofurans **1a–1e** under Lewis acid catalysis efficiently (Table 3, entries 1–5). Although other catalysts such as $BF_3 \cdot OEt_2$ were used (Table 3, entries 6 and 7), $ZnCl_2$ was more efficient to promote such a process. Like compound **3h**, derivative **4f** (R = 2,5-$(Me)_2$) was not enough reactive to carry out the cyclization process.



Scheme 3. Reagents and conditions: (a) $ClCH_2COCH_3$ (**8**), K_2CO_3, acetone, reflux, 12 h; (b) DMFDMA (1.0 mol equiv), 80 °C, 6 h; (c) $ZnCl_2$, CH_2Cl_2, 20 °C, 48 h; (d) (i) DMFDMA (1.0 mol equiv), MW (200 W), 80 °C, 10 min; (ii) $ZnCl_2$, CH_3CN, MW (200 W), 80 °C, 30 min.

It is noteworthy that derivatives **4a–4e** cyclized to the corresponding benzofurans much faster (48 h) than the 3-dimethylaminopropenoates **3a–3e** (72 h) did under similar conditions (Table 2). This difference in reactivity is a consequence of the enone moiety of derivatives **4** being

Table 3. Preparation of 2-acetylbenzofurans **1a–1e**[a]

Entry	Precursor (R)	Conditions	Solvent	Temperature (°C)	Time *t* (h)	**1**	Yield (%)[b]
1	**4a** (3,5-$(OMe)_2$)	$ZnCl_2$	CH_2Cl_2	20	48	**1a**	60
2	**4b** (3,4,5-$(OMe)_3$)	$ZnCl_2$	CH_2Cl_2	20	48	**1b**	61
3	**4c** (3,4-$(OMe)_2$)	$ZnCl_2$	CH_2Cl_2	20	48	**1c**	62
4	**4d** (3,4-OCH_2O)	$ZnCl_2$	CH_2Cl_2	20	48	**1d**	61
5	**4e** (3-OMe)	$ZnCl_2$	CH_2Cl_2	20	48	**1e**	62
6	**4c** (3,4-$(OMe)_2$)	$BF_3 \cdot OEt_2$	CH_2Cl_2	20	24	**1c**	52
7	**4d** (3,4-OCH_2O)	$BF_3 \cdot OEt_2$	CH_2Cl_2	20	24	**1d**	55
8	**7a** (3,5-$(OMe)_2$)	DMFDMA	MeCN	90	48	**1a**	19
9	**7b** (3,4,5-$(OMe)_3$)	DMFDMA	MeCN	90	48	**1b**	18
10	**7c** (3,4-$(OMe)_2$)	DMFDMA	MeCN	90	48	**1c**	21
11	**7a** (3,5-$(OMe)_2$)	[c]	[c]	[c]	[c]	**1a**	35
12	**7b** (3,4,5-$(OMe)_3$)	[c]	[c]	[c]	[c]	**1b**	38
13	**7c** (3,4-$(OMe)_2$)	[c]	[c]	[c]	[c]	**1c**	42

[a] Under N_2 atmosphere, with 3.0 mol equiv of $ZnCl_2$ or $BF_3 \cdot OEt_2$ and 1.0 mol equiv of DMFDMA.
[b] After column chromatography and recrystallization.
[c] Under N_2 atmosphere: (a) MW irradiation (400 W), with DMFDMA at 100 °C for 10 min; (b) addition of $ZnCl_2$ in MeCN, and MW irradiation (400 W) at 100 °C for 30 min.

more activated than the methyl propenoate moiety in compounds **3** towards a nucleophilic conjugate addition.[18]

Therefore, natural benzofurans **1a–1c** were obtained in good overall yields starting from phenols **5a–5c** in a three-step synthesis: calebertin (**1a**) was obtained in 35%, caleprunin A (**1b**) in 37%, and caleprunin B (**1c**) in 48%. However, we investigated a shorter strategy by the tandem reaction of condensation–cyclization of 1-aryloxypropan-2-ones **7a–7c** with DMFDMA (Scheme 3). A first method consisted of heating this mixture in acetonitrile at 90 °C for 48 h. Although the desired products were obtained, the yields were low (Table 3, entries 8–10), and a large amount of the intermediates 3-dimethylaminopropan-2-ones **4a–4c** was found. These results prompted us to follow a one-pot two-step sequence in order to achieve the cyclization of the latter to obtain the benzofurans. Thus, the second method included, as the first step, the free-solvent MW irradiation (400 W) of the mixture of **7** and DMFDMA at 100 °C for 10 min, followed by the addition of $ZnCl_2$ in MeCN and irradiation at the same temperature for 30 min. The natural products **1a–1c** were readily isolated from the crude mixtures in better yields (Table 3, entries 11–13) than the first tandem method, but they were lower than the overall yields obtained by the two-step methodology.

3. Conclusions

We have described the full details of the new methodology for the preparation of the 2-carbomethoxybenzofurans **2a–2f** series via intramolecular cyclization of the methyl 2-aryloxy-3-dimethylaminopropenoates **3a–3f**, respectively. We are also reporting an alternative method for the tandem thermal condensation–cyclization process between phenoxyacetates **6** and DMFDMA, based on a solvent-free process under MW irradiation. As an extension of this synthetic route, a series of 2-acetylbenzofurans, **1a–1e**, was prepared through analogous reaction conditions from **4a–4e**, a cyclization process which was faster than that when obtaining benzofurans **2a–2f** from **3a–3f**. Among the compounds **1a–1e**, the naturally occurring benzofurans **1a–1c** were prepared in good overall yields, starting from 1-aryloxypropan-2-ones **7a–7c**. A shorter method for the preparation of these natural products consisted of a one-pot two-step reaction promoted by MW irradiation, which involved the in situ preparation of the precursors **4a–4c** and their cyclization in the presence of Lewis acid catalysts.

4. Experimental

4.1. General

Melting points (uncorrected) were determined with an Electrothermal capillary melting point apparatus. IR spectra were recorded on a Perkin-Elmer 1600 spectrophotometer. ^1H (300 MHz) and ^{13}C (75.4 MHz) NMR spectra were recorded on a Varian Mercury-300 instrument, in $CDCl_3$ or acetone-d_6 as solvents and TMS as an internal standard. Mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained, in electron impact (EI) (70 eV) mode, on a Hewlett-Packard 5971A and on a Jeol JMS-AX 505 HA spectrometers, respectively. Microwave (MW) irradiation was performed on a SEV/MIC-1 (Puebla, Mexico) MW reactor.[19] Microanalyses were performed by M-H-W Laboratories (Phoenix, AZ, USA), and Centro de Investigaciones Químicas, Universidad Autónoma de Hidalgo (Pachuca, Hgo., Mexico). Analytical thin-layer chromatography was carried out using E. Merck silica gel 60 F_{254} coated 0.25 plates, visualized by long- and short-wavelength UV lamps. Flash column chromatography was performed on silica gel (230–400 mesh) from Natland International Co. All air moisture sensitive reactions were carried out under nitrogen using oven-dried glassware. Toluene was freshly distilled over sodium, and methylene chloride, ethyl acetate, acetonitrile, and DMSO over calcium hydride, prior to use. Acetone was distilled after refluxing over $KMnO_4$ for 4 h. K_2CO_3 was dried overnight at 200 °C before use. Triethylamine was distilled over sodium hydroxide. All other reagents were used without further purification. For the preparation and spectroscopic data of **2b**, **3b**, and **6b**, see Ref. 10.

4.2. Preparation of phenols 5d, 5e, and 5f

4.2.1. 4-Ethoxy-3-methoxyphenol (5d). (i) A mixture of 3.0 g (19.7 mmol) of vanillin and 4.08 g (29.5 mmol) of dry K_2CO_3 in 30 mL of dry acetone was stirred and heated to reflux for 30 min, and 2.35 g (21.6 mmol) of ethyl bromide were added dropwise. The mixture was refluxed for 8 h, then filtered, and the solvent was removed under vacuum. The residue was dissolved in EtOAc (30 mL), successively washed with saturated solutions of $NaHCO_3$ and NaCl (3×5 mL), and dried (Na_2SO_4). The solvent was removed under vacuum, and the residue was purified by column chromatography over silica gel (80 g, hexane/EtOAc 95:5) to give 3.19 g (90%) of 4-ethoxy-3-methoxybenzaldehyde as a white solid: R_f 0.38 (hexane/EtOAc 8:2); mp 59–60 °C (hexane/EtOAc 9:1) [lit.[20] 58 °C]. (ii) To a solution of 3.0 g (16.6 mmol) of the latter in dry CH_2Cl_2 (40 mL) 4.09 g (16.6 mmol) of MCPBA was added, and the mixture was stirred at room temperature for 3 h. The mixture was filtered, the solution was washed with a saturated solution of $NaHCO_3$ until neutral, and the organic layer was dried (Na_2SO_4). The solvent was removed under vacuum, the residue was purified by column chromatography over silica gel (15 g, hexane/EtOAc 9:1) to give 2.34 g (72%) of 4-ethoxy-3-methoxyphenyl formate as a white solid: R_f 0.36 (hexane/EtOAc 8:2); mp 61–62 °C (hexane/EtOAc 9:1); IR (KBr) 1736, 1698, 1601, 1508, 1263, 1189, 1125, 1158, 1101, 1032, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (t, $J=7.1$ Hz, 3H, OCH_2CH_3), 3.81 (s, 3H, OMe), 4.04 (t, $J=7.1$ Hz, 2H, OCH_2CH_3), 6.60–6.66 (m, 2H, ArH), 6.78–6.84 (m, 1H, ArH), 8.25 (s, 1H, OCHO); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.6 (OCH_2CH_3), 55.9 (OMe), 64.6 (OCH_2CH_3), 105.3 (C-2), 112.2 (C-6), 112.7 (C-5), 143.4 (C-4), 146.4 (C-1), 149.8 (C-3), 159.6 (OCHO). (iii) Under an N_2 atmosphere and at room temperature, 1.0 mL of a 5% aqueous solution of K_2CO_3 was slowly added to a solution of 1.0 g (5.1 mmol) of 4-ethoxy-3-methoxyphenyl formate in methanol (10 mL). The mixture was stirred at room temperature for 30 min and the solvent was removed under vacuum. The residue was saturated with 1.0 g of NaCl and extracted with EtOAc (3×5 mL). The organic extracts were washed with brine (3×5 mL), the organic layer was dried

(Na_2SO_4), and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (15 g, hexane/EtOAc 8:2) to give 0.754 g (88%) of **5d** as a yellow oil: R_f 0.40 (hexane/EtOAc 6:4); IR (film) 3424, 2978, 1605, 1512, 1457, 1288, 1218, 1160, 1127, 1033, 954 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, J= 7.0 Hz, 3H, OCH_2CH_3), 3.68 (s, 3H, OMe), 3.98 (t, J= 7.1 Hz, 2H, OCH_2CH_3), 6.32 (dd, J=8.7, 2.7 Hz, 1H, H-6), 6.43 (d, J=2.7 Hz, 1H, H-2), 6.65 (br s, 1H, OH), 6.70 (d, J=8.7 Hz, 1H, H-5); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.7 (OCH_2CH_3), 55.4 (OMe), 65.4 (OCH_2CH_3), 100.6 (C-2), 105.0 (C-6), 114.7 (C-5), 141.5 (C-4), 150.0 (C-3), 150.6 (C-1). Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.41; H, 7.38.

4.2.2. 4-Benzyloxy-3-methoxyphenol (5e). Following the procedures as for **5d**: (i) With 3.0 g (19.7 mmol) of vanillin, 4.08 g (29.5 mmol) of dry K_2CO_3, and 2.72 g (21.6 mmol) of benzyl chloride, to yield 4.1 g (86%) of 4-benzyloxy-3-methoxybenzaldehyde as a white solid: R_f 0.34 (hexane/EtOAc 8:2); mp 74–75 °C (hexane/EtOAc 9:1); IR (KBr) 1682, 1588, 1508, 1460, 1267, 1133, 1023, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.92 (s, 3H, OMe), 5.23 (s, 2H, OCH_2), 6.98 (d, J=8.2 Hz, 1H, H-5), 7.28–7.46 (m, 7H, H-2, H-6, PhH), 9.82 (s, 1H, CHO); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 55.9 (OMe), 70.7 (OCH_2), 109.3 (C-5), 112.3 (C-2), 126.4 (C-6), 127.1 (PhCH), 128.1 (PhCH), 128.6 (PhCH), 130.2 (C-1), 135.9 (PhC), 150.0 (C-3), 153.5 (C-4), 190.8 (CHO); MS (70 eV) m/z 242 (M^+, 9), 151 (1), 91 (100), 79 (6), 65 (19), 51 (8). (ii) With 3.0 g (12.4 mmol) of 4-benzyloxy-3-methoxybenzaldehyde and 3.06 g (12.4 mmol) of MCPBA to yield 1.92 g (60%) of 4-benzyloxy-3-methoxyphenyl formate as a white solid: R_f 0.40 (hexane/EtOAc 8:2); mp 69–71 °C (hexane/EtOAc 9:1); IR (KBr) 1736, 1604, 1508, 1452, 1218, 1192, 1159, 1128, 1104, 1028, 953 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.84 (s, 3H, OMe), 5.11 (s, 2H, OCH_2), 6.59 (dd, J=8.7, 2.4 Hz, 1H, H-6), 6.68 (d, J=2.4 Hz, 1H, H-2), 6.85 (d, J= 8.7 Hz, 1H, H-5), 7.24–7.44 (m, 5H, PhH), 8.25 (s, 1H, OCHO); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 56.0 (OMe), 71.3 (OCH_2), 105.5 (C-2), 112.3 (C-6), 114.1 (C-5), 127.2 (PhCH), 127.8 (PhCH), 128.5 (PhCH), 136.7 (PhC), 143.8 (C-4), 146.2 (C-1), 150.2 (C-3), 159.6 (OCHO). (iii) With 1.0 g (3.9 mmol) of 4-benzyloxy-3-methoxyphenyl formate to yield 0.762 g (85%) of **5e** as a white solid: R_f 0.46 (hexane/EtOAc 6:4); mp 85–86 °C (hexane/EtOAc 7:3); IR (KBr) 3417, 3038–2978, 1606, 1510, 1456, 1288, 1210, 1160, 1225, 1024, 925 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.75 (s, 3H, OMe), 5.04 (s, 2H, OCH_2), 5.46 (br s, 1H, OH), 6.24 (dd, J=8.7, 2.7 Hz, 1H, H-6), 6.43 (d, J=2.7 Hz, 1H, H-2), 6.70 (d, J=8.7 Hz, 1H, H-5), 7.20–7.42 (m, 5H, PhH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 55.7 (OMe), 72.3 (OCH_2), 100.8 (C-2), 106.0 (C-6), 116.2 (C-5), 127.5 (PhCH), 127.7 (PhCH), 128.4 (PhCH), 137.2 (PhC), 141.7 (C-4), 150.7 (C-3), 150.8 (C-1). Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 72.85; H, 6.21.

4.2.3. 2,3,4-Trimethoxyphenol (5f).[21] Following the procedures as for **5d**: (ii) With 3.0 g (15.3 mmol) of 2,3,4-trimethoxybenzaldehyde and 3.77 g (15.3 mmol) of MCPBA to yield 2.33 g (72%) of 2,3,4-trimethoxyphenyl formate. (iii) With 2.33 g of the latter to yield 1.66 g (82%) of **5f** as a colorless oil: R_f 0.29 (hexane/EtOAc 8:2); IR (film) 3407, 2941, 1711, 1488, 1431, 1266, 1201, 1161, 1091, 1052, 903 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 3H, OMe), 3.86 (s, 3H, OMe), 3.90 (s, 3H, OMe), 6.10–6.30 (br s, 1H, OH), 6.52 (d, J=8.7 Hz, 1H, H-5), 6.60 (d, J=8.7 Hz, 1H, H-6); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 56.4 (OMe), 60.8 (OMe), 61.1 (OMe), 107.6 (C-5), 108.6 (C-6), 130.0 (C-3), 140.4 (C-2), 143.3 (C-1), 146.8 (C-4).

4.3. Preparation of the phenoxyacetic methyl esters 6a–6i (For spectral data, see Supplementary data)

4.3.1. Methyl 3-methoxyphenoxyacetate (6a).[22] (i) An aqueous solution (5 mL) of 1.1 g (27.5 mmol) of NaOH and 3.2 g (27.5 mmol) of sodium chloroacetate in water (5 mL) were successively added dropwise to 3.1 g (25.0 mmol) of 3-methoxyphenol (**5a**) at room temperature. The mixture was stirred at 60 °C for 7 h. A concentrated aqueous solution of HCl (36%) was added until pH 2, and the precipitate was filtered. The solid was recrystallized from hexane/EtOAc 1:4, giving 3.64 g (80%) of 3-methoxyphenoxyacetic acid as a white solid: R_f 0.51 (hexane/EtOAc 1:1); mp 117–119 °C [lit.[23] 116–118 °C]; IR (KBr) 3300–2350, 1744, 1599, 1495, 1431, 1246, 1208, 1161, 1047, 924 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.79 (s, 3H, OMe), 4.67 (s, 2H, CH_2O), 6.48–6.60 (m, 3H, ArH), 7.17–7.23 (m, 1H, ArH), 8.92 (br s, 1H, CO_2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 55.3 (MeO), 64.7 (CH_2O), 101.3 (ArH), 106.3 (ArH), 107.8 (ArH), 130.1 (ArH), 158.5 (Ar), 160.9 (Ar), 174.0 (CO_2H). (ii) A mixture of 1.0 g (5.5 mmol) of 3-methoxyphenoxyacetic acid and 0.095 g (0.55 mmol) of *p*-toluenesulfonic acid in dry methanol (5 mL) was stirred at room temperature for 2 h. The solvent was removed under vacuum. The residue was dissolved in EtOAc (5 mL) and washed with saturated solution of $NaHCO_3$ until neutral. The organic layer was dried (Na_2SO_4) and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (15 g, hexane/EtOAc 9:1), to give 0.99 g (92%) of **6a** as a colorless oil: R_f 0.30 (hexane/EtOAc 8:2).

4.3.2. Methyl (benzo[1,3]dioxol-5-yloxy)acetate (6c). Following the procedures as for **6a**: (i) With an aqueous solution (20 mL) of 5.0 g (72.4 mmol) of NaOH, 4.1 g (43.4 mmol) of chloroacetic acid in 20 mL of H_2O, and 5.0 g (36.2 mmol) of benzo[1,3]dioxol-5-ol (**5c**), to give 6.6 g (80%) of (benzo[1,3]dioxol-5-yloxy)acetic acid as a pale brown solid: R_f 0.38 (hexane/EtOAc/AcOH 2:3:0.1); mp 104–105 °C (hexane/EtOAc 1:4); IR (KBr) 3230–2400, 1732, 1487, 1424, 1264, 1190, 1146, 1035, 922, 783 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 4.62 (s, 2H, CH_2O), 5.93 (s, 2H, OCH_2O), 6.10–6.30 (br, 1H, CO_2H), 6.38 (dd, J= 8.7, 3.0 Hz, 1H, H-6), 6.57 (d, J=3.0 Hz, 1H, H-4), 6.73 (d, J=8.7 Hz, 1H, H-7); ^{13}C NMR (75.4 MHz, acetone-d_6) δ 65.6 (CH_2O), 98.1 (C-4), 101.5 (OCH_2O), 106.0 (C-6), 107.9 (C-7), 142.3 (C-7a), 148.5 (C-3a), 153.8 (C-5), 169.8 (CO_2H); MS (70 eV) m/z 196 (M^+, 100), 137 (99), 109 (11), 79 (14), 65 (6). (ii) With 5.0 (25.5 mmol) of (benzo[1,3]dioxol-5-yloxy)acetic acid and 0.44 g (2.55 mmol) of *p*-toluenesulfonic acid in dry methanol (25 mL), to give 4.72 g (88%) of **6c** as a white solid: R_f 0.42 (hexane/EtOAc 7:3); mp 152–154 °C (hexane/EtOAc 9:1). Anal. Calcd for $C_{10}H_{10}O_5$: C, 57.14; H, 4.79. Found: C, 57.03; H, 4.74.

4.3.3. Methyl 4-ethoxy-3-methoxyphenoxyacetate (6d). Following the procedures as for **6a**: (i) With an aqueous solution (5 mL) of 1.42 g (35.6 mmol) of NaOH, 2.02 g (21.4 mmol) of chloroacetic acid in 5 mL of H_2O, and 3.0 g (17.8 mmol) of 4-ethoxy-3-methoxyphenol (**5d**), to give 3.15 g (78%) of 4-ethoxy-3-methoxyphenoxyacetic acid as colorless crystals: R_f 0.32 (hexane/EtOAc/AcOH 2:3:0.1); mp 122–123 °C (hexane/EtOAc 1:4); IR (KBr) 3300–2300, 1738, 1709, 1597, 1513, 1472, 1434, 1267, 1223, 1195, 1086, 955 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 1.31 (t, $J=6.9$ Hz, 3H, OCH_2CH_3), 3.78 (s, 3H, OMe), 3.95 (q, $J=6.9$ Hz, 2H, OCH_2CH_3), 4.62 (s, 2H, CH_2O), 6.39 (dd, $J=9.0$, 3.0 Hz, 1H, H-6), 6.60 (d, $J=3.0$ Hz, 1H, H-2), 6.82 (d, $J=9.0$ Hz, 1H, H-5); ^{13}C NMR (75.4 MHz, acetone-d_6) δ 14.7 (OCH_2CH_3), 55.3 (OMe), 65.0 (OCH_2CH_3), 65.2 (OCH_2), 101.4 (C-2), 104.4 (C-6), 114.7 (C-5), 143.5 (C-4), 151.0 (C-3), 153.1 (C-1), 169.9 (CO_2H); MS (70 eV) *m/z* 226 (M^+, 100), 197 (58), 169 (11), 139 (89), 125 (33), 111 (40), 95 (11), 65 (9). (ii) With 3.0 (13.3 mmol) of 4-ethoxy-3-methoxyphenoxyacetic acid, and 0.23 g (1.33 mmol) of *p*-toluenesulfonic acid in dry methanol (15 mL), to give 2.87 g (90%) of **6d** as a white solid: R_f 0.72 (hexane/EtOAc 7:3); mp 53–54 °C (hexane/EtOAc 8:2). Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.90; H, 6.87.

4.3.4. Methyl 4-benzyloxy-3-methoxyphenoxyacetate (6e). Following the procedures as for **6a**: (i) With an aqueous solution (5 mL) of 1.04 g (26.05 mmol) of NaOH, 1.48 g (15.66 mmol) of chloroacetic acid in 5 mL of H_2O, and 3.0 g (13.0 mmol) of 4-benzyloxy-3-methoxyphenol (**5e**), to give 2.7 g (72%) of 4-benzyloxy-3-methoxyphenoxyacetic acid as a white solid: R_f 0.34 (hexane/EtOAc/AcOH 2:3:0.1); mp 114–115 °C (hexane/EtOAc 1:4); IR (KBr) 3600–2400, 1737, 1600, 1511, 1451, 1262, 1220, 1196, 1165, 1081, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.84 (s, 3H, OMe), 4.60 (s, 2H, OCH_2), 5.07 (s, 2H, OCH_2Ph), 6.27 (dd, $J=8.7$, 3.0 Hz, 1H, H-6), 6.61 (d, $J=3.0$ Hz, 1H, H-2), 6.77 (d, $J=8.7$ Hz, 1H, H-5), 7.20–7.44 (m, 5H, PhH), 10.29 (br s, 1H, CO_2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 55.9 (OMe), 65.2 (OCH_2), 71.7 (OCH_2Ph), 101.4 (C-2), 103.6 (C-6), 114.9 (C-5), 127.3 (PhH), 127.8 (PhH), 128.4 (PhH), 137.1 (Ph), 143.3 (C-4), 150.8 (C-3), 152.3 (C-1), 174.6 (CO_2H). Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.38; H, 6.02. (ii) With 3.0 g (10.4 mmol) of 4-benzyloxy-3-methoxyphenoxyacetic acid and 0.18 g (1.04 mmol) of *p*-toluenesulfonic acid in dry methanol (15 mL), to give 2.86 g (91%) of **6e** as a white solid: R_f 0.72 (hexane/EtOAc 6:4); mp 72–73 °C (hexane/EtOAc 7:3). Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.53; H, 6.00. Found: C, 67.39; H, 5.95.

4.3.5. Methyl 2,3,4-trimethoxyphenoxyacetate (6f). Following the procedures as for **6a**: (i) With an aqueous solution (5 mL) of 0.78 g (19.5 mmol) of NaOH, 2.27 g (19.5 mmol) of sodium chloroacetate in 5 mL of H_2O, and 3.0 g (16.3 mmol) of 2,3,4-trimethoxyphenol (**5f**), to give 3.16 g (80%) of 2,3,4-trimethoxyphenoxyacetic acid as a white solid: R_f 0.46 (hexane/EtOAc 2:8); mp 90–91 °C (hexane/EtOAc 1:4); IR (KBr) 3650–2300, 1738, 1491, 1430, 1268, 1244, 1201, 1117, 1094, 1014 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 3.76 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.85 (s, 3H, OMe), 4.65 (s, 2H, OCH_2), 4.95–5.40 (br, 1H, CO_2H), 6.61–6.70 (m, 2H, H-5, H-6); ^{13}C NMR (75.4 MHz, acetone-d_6) δ 55.8 (OMe), 60.4 (OMe), 60.6 (OMe), 66.1 (OCH_2), 106.9 (ArCH), 109.0 (ArCH), 143.7 (ArC), 144.1 (ArC), 146.4 (ArC), 148.9 (ArC), 169.9 (CO_2H). (ii) With 2.0 g (8.26 mmol) of 2,3,4-trimethoxyphenoxyacetic acid and 0.144 g (0.83 mmol) of *p*-toluenesulfonic acid in dry methanol (10 mL), to give 1.84 g (87%) of **6f** as a colorless oil: R_f 0.23 (hexane/EtOAc 7:3). Anal. Calcd for $C_{12}H_{16}O_5$: C, 56.24; H, 6.29. Found: C, 56.04; H, 6.92.

4.3.6. Methyl 3-methylphenoxyacetate (6g). Following the procedures as for **6a**: (i) With an aqueous solution (10 mL) of 3.7 g (92.5 mmol) of NaOH, 4.8 g (50.8 mmol) of chloroacetic acid in 10 mL of H_2O, and 5.0 g (46.3 mmol) of 3-methylphenol (**5g**), to give 6.5 g (85%) of 3-methylphenoxyacetic acid as white needles: R_f 0.57 (hexane/EtOAc/AcOH 1:1:0.2); mp 104–105 °C (hexane/EtOAc 1:4) [lit.[24] 102 °C]; IR (KBr) 3175–2350, 1733, 1709, 1609, 1584, 1485, 1459, 1422, 1290, 1275, 1254, 1161, 1098, 1088, 920, 771 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H, Me), 4.67 (s, 2H, OCH_2), 6.70 (dd, $J=8.2$, 2.3 Hz, 1H, H-6), 6.75 (br s, 1H, H-2), 6.83 (br d, $J=7.7$ Hz, 1H, H-4), 7.18 (dd, $J=8.2$, 7.7 Hz, 1H, H-5), 9.43 (br s, 1H, CO_2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.4 (Me), 64.6 (OCH_2), 111.2 (C-6), 115.4 (C-2), 122.8 (C-4), 129.3 (C-5), 139.8 (C-3), 157.3 (C-1), 175.1 (CO_2H); MS (70 eV) *m/z* 166 (M^+, 100), 121 (96), 108 (19), 91 (90), 77 (15), 65 (17). Anal. Calcd for $C_9H_{10}O_3$: C, 65.06; H, 6.06. Found: C, 65.08; H, 6.08. (ii) With 1.0 g (6.02 mmol) of 3-methylphenoxyacetic acid and 0.11 g (0.64 mmol) of *p*-toluenesulfonic acid in dry methanol (4.7 mL), to give 0.97 g (90%) of **6g** as a colorless oil: R_f 0.50 (hexane/EtOAc 8:2). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.35; H, 6.83.

4.3.7. Methyl 2,5-dimethylphenoxyacetate (6h). Following the procedures as for **6a**: (i) With an aqueous solution (10 mL) of 3.3 g (81.0 mmol) of NaOH, 4.25 g (49.1 mmol) of chloroacetic acid in 10 mL of H_2O, and 5.0 g (40.0 mmol) of 2,5-dimethylphenol (**5h**), to give 6.0 g (82%) of 2,5-dimethylphenoxyacetic acid as white needles: R_f 0.43 (hexane/EtOAc/AcOH 2:3:0.1); mp 138–139 °C (hexane/EtOAc 1:4) [lit.[25] 113–114 °C]; IR (KBr) 3024–2363, 1722, 1615, 1583, 1509, 1429, 1292, 1273, 1242, 1158, 1136, 1078, 938, 812 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 2.18 (s, 3H, Me), 2.25 (s, 3H, Me), 4.69 (s, 2H, OCH_2), 6.29 (br s, 1H, CO_2H), 6.64–6.72 (m, 2H, H-4, H-6), 7.00 (d, $J=8.1$ Hz, 1H, H-3); ^{13}C NMR (75.4 MHz, acetone-d_6) δ 15.3 (Me-2), 20.6 (Me-5), 64.7 (OCH_2), 112.2 (C-6), 121.6 (C-4), 123.5 (C-2), 130.6 (C-3), 136.5 (C-5), 156.3 (C-1), 169.9 (CO_2H); MS (70 eV) *m/z* 180 (M^+, 100), 162 (5), 136 (23), 135 (22), 122 (15), 121 (94), 106 (21), 105 (22), 91 (54), 77 (35), 65 (6). (ii) With 5.0 g (27.8 mmol) of 2,5-dimethylphenoxyacetic acid and 0.48 g (2.78 mmol) of *p*-toluenesulfonic acid in dry methanol (25 mL), to give 4.6 g (85%) of **6h** as a colorless oil: R_f 0.60 (hexane/EtOAc 7:3). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.89; H, 7.39.

4.3.8. Methyl (naphthalen-2-yloxy)acetate (6i). Following the procedures as for **6a**: (i) With an aqueous solution (5 mL) of 1.66 g (41.5 mmol) of NaOH, 2.36 g (25.0 mmol)

of chloroacetic acid in 5 mL of H_2O, and 3.0 g (20.8 mmol) of 2-naphthol (**5i**), to give 3.78 g (90%) of (naphthalen-2-yloxy)acetic acid as a white solid: R_f 0.32 (hexane/EtOAc/AcOH 2:3:0.1); mp 154–155 °C (hexane/EtOAc 1:4) [lit.[26] 154 °C]. (ii) With 5.0 g (24.7 mmol) (naphthalen-2-yloxy)-acetic acid and 0.427 g (2.47 mmol) of *p*-toluenesulfonic acid in dry methanol (25 mL), to give 4.92 g (92%) of **6i** as a white solid: R_f 0.50 (hexane/EtOAc 7:3); mp 76–77 °C (hexane/EtOAc 8:2) [lit.[27] 75–77 °C].

4.4. General procedure for the preparation of methyl 2-aryloxy-3-dimethylaminopropenoates 3a–3i (Table 4).

Method A. A mixture of 1.0 mol equiv of the methyl phenoxyacetates **6a–6i** and 3.0 mol equiv of *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) was heated to 90 °C for 24 h. The crude mixture was evaporated under vacuum until dried and purified by column chromatography over silica gel (20 g/g sample, hexane/EtOAc 8:2) to give the corresponding compounds **3a–3i**.

Method B. The same procedure as method A for substrates **6a–6c**, and heating the reaction mixture to 140 °C for 2 h under MW irradiation (400 W) to give products **3a–3c** (Table 4).

4.4.1. Methyl (*Z*)-3-dimethylamino-2-(3-methoxyphenoxy)propenoate (3a). Using method A with 0.5 g (2.55 mmol) of **6a** and 0.91 g (7.65 mmol) of DMFDMA, to give 0.39 g (61%) of **3a** as a colorless oil: R_f 0.37 (hexane/EtOAc 6:4). Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.26; H, 6.68; N, 5.43.

4.4.2. Methyl (*Z*)-2-(benzo[1,3]dioxol-5-yloxy)-3-dimethylaminopropenoate (3c). Using method A with 0.5 g (2.38 mmol) of **6c** and 0.85 g (7.14 mmol) of DMFDMA, to give 0.38 g (60%) of **3c** as a white solid: R_f 0.72 (hexane/EtOAc 6:4); mp 99–100 °C (hexane/EtOAc 1:1). Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.73; H, 5.62; N, 5.48.

4.4.3. Methyl (*Z*)-3-dimethylamino-2-(4-ethoxy-3-methoxyphenoxy)propenoate (3d). Using method A with 0.5 g (2.08 mmol) of **6d** and 0.742 g (6.24 mmol) of DMFDMA, to give 0.45 g (74%) of **3d** as a white solid: R_f 0.30 (hexane/EtOAc 6:4); mp 80–82 °C (hexane/EtOAc 7:3). Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 61.22; H, 6.88; N, 4.60.

4.4.4. Methyl (*Z*)-2-(4-benzyloxy-3-methoxyphenoxy)-3-dimethylaminopropenoate (3e). Using method A with 0.5 g (1.65 mmol) of **6e** and 0.59 g (4.97 mmol) of DMFDMA, to give 0.37 g (63%) of **3e** as a white solid: R_f 0.25 (hexane/EtOAc 6:4); mp 73–74 °C (hexane/EtOAc 7:3). Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.12; H, 6.39; N, 3.82.

4.4.5. Methyl (*Z*)-3-dimethylamino-2-(2,3,4-trimethoxyphenoxy)propenoate (3f). Using method A with 0.5 g (1.95 mmol) of **6f** and 0.697 g (5.86 mmol) of DMFDMA, to give 0.46 g (76%) of **3f** as a white solid: R_f 0.20 (hexane/EtOAc 6:4); mp 72–73 °C (hexane/EtOAc 7:3). Anal. Calcd for $C_{15}H_{21}NO_6$: C, 57.87; H, 6.80; N, 4.50. Found: C, 57.64; H, 6.69; N, 4.39.

4.4.6. Methyl (*Z*)-3-dimethylamino-2-(3-methylphenoxy)propenoate (3g). Using method A with 0.5 g (2.78 mmol) of **6g** and 0.99 g (8.3 mmol) of DMFDMA, to give 0.41 g (64%) of **3g** as a white solid: R_f 0.44 (hexane/EtOAc 7:3); mp 42–43 °C (hexane/EtOAc 7:3). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.51; H, 7.07; N, 5.78.

4.4.7. Methyl (*Z*)-3-dimethylamino-2-(2,5-dimethylphenoxy)propenoate (3h). Using method A with 0.5 g (2.58 mmol) of **6h** and 0.92 g (7.73 mmol) of DMFDMA, to give 0.42 g (65%) of **3h** as a white solid: R_f 0.38 (hexane/EtOAc 7:3); mp 93–94 °C (hexane/EtOAc 7:3). Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.53; H, 7.76; N, 5.49.

4.4.8. Methyl (*Z*)-3-dimethylamino-2-(naphthalen-2-yloxy)propenoate (3i). Using method A with 0.5 g (2.31 mmol) of **6i** and 0.825 g (6.93 mmol) of DMFDMA, to give 0.41 g (66%) of **3i** as a white solid: R_f 0.32 (hexane/EtOAc 7:3); mp 120–121 °C (hexane/EtOAc 7:3). Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.64; H, 6.12; N, 5.35.

4.5. General procedures for the preparation of methyl benzofuran-2-carboxylates 2a–2f

See Table 5.

Method A. Under an N_2 atmosphere at room temperature, a mixture of 1.0 mol equiv of the corresponding 3-dimethylaminopropenoate **3a–3f**, 3.0 mol equiv of $ZnCl_2$ in dry CH_2Cl_2 (50 mL) was stirred at the same temperature for 72 h. The mixture was filtered, washed with H_2O (2× 20 mL), and dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (10 g, hexane/EtOAc 95:5) to give the corresponding benzofurans **2a–2f**.

Method B. A mixture of 1.0 mol equiv of the methyl phenoxyacetate **6a–6c** and 3.0 mol equiv of DMFDMA in dry acetonitrile (10 mL) was heated to 100 °C for 48 h. The solvent was evaporated under vacuum, and the residue was purified by column chromatography over silica gel (15 g, hexane/EtOAc 95:5) to give the corresponding compounds **2a–2c**.

Method C. A mixture of 1.0 mol equiv of the methyl phenoxyacetate **6a–6c** and 2.0 mol equiv of DMFDMA in dry acetonitrile (20 mL) was heated to 140 °C for 16 h. Then, 1.0 mol equiv of $ZnCl_2$ was added and the mixture was heated to 140 °C for 20 h. The mixture was filtered and the solvent was evaporated under vacuum. The residue was purified by column chromatography over silica gel (15 g, hexane/EtOAc 95:5) to give the corresponding compounds **2a–2c**.

Method D. A mixture of 1.0 mol equiv of the methyl phenoxyacetate **6a–6c**, 2.0 mol equiv of DMFDMA, and 2.0 mol equiv of $ZnCl_2$ in dry acetonitrile (20 mL) was

Table 4. Spectral data of compounds **3a–3i** and **4a–4f**[a]

Compound	IR (cm^{-1})	GC–MS *m/z*	^1H NMR ($CDCl_3$) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$) δ
3a	1759, 1598, 1491, 1439, 1294, 1197, 1153, 1087, 917, 839, 764		2.91 (s, 6H, NMe), 3.60 (s, 3H, CO_2Me), 3.74 (s, 3H, OMe), 6.46–6.54 (m, 3H, ArH), 7.10–7.16 (m, 1H, ArH), 7.11 (s, 1H, H-3)	42.0 (NMe), 51.0 (CO_2CH_3), 55.1 (MeO), 101.1 (C-2′), 106.7 (C-6′), 107.0 (C-4′), 114.6 (C-2), 129.8 (C-5′), 139.6 (C-3), 160.5 (C-1′ or C-3′), 160.7 (C-3′ or C-1′), 166.2 (CO_2CH_3)
3c	1695, 1634, 1482, 1436, 1300, 1219, 1173, 1125, 1086, 1036	265 (M^+), 234, 206 (100), 188, 178, 149, 116, 107, 84, 65	2.93 (s, 6H, NMe), 3.60 (s, 3H, CO_2Me), 5.86 (s, 2H, OCH_2O), 6.34 (dd, J=8.7, 2.4 Hz, 1H, H-6′), 6.50 (d, J=2.4 Hz, 1H, H-4′), 6.64 (d, J=8.7 Hz, 1H, H-7′), 7.08 (s, 1H, H-3)	42.0 (NMe), 51.0 (CO_2CH_3), 97.5 (C-4′), 101.1 (OCH_2O), 106.1 (C-6′), 107.9 (C-7′), 115.2 (C-2), 139.6 (C-3), 141.9 (C-7a′), 148.1 (C-3a′), 154.6 (C-5′), 166.3 (CO_2CH_3)
3d	1695, 1633, 1506, 1440, 1358, 1299, 1220, 1190, 1154, 1120, 1087, 1034	295 (M^+), 236 (100), 208, 190, 179, 153, 139, 116, 88, 84, 57, 42	1.34 (t, J=7.0 Hz, 3H, OCH_2CH_3), 2.90 (s, 6H, NMe), 3.57 (s, 3H, CO_2Me), 3.77 (s, 3H, OMe), 3.95 (q, J=7.0 Hz, 2H, OCH_2CH_3), 6.33 (dd, J=8.9, 2.9 Hz, 1H, H-6′), 6.53 (d, J=2.9 Hz, 1H, H-2′), 6.70 (d, J=8.9 Hz, 1H, H-5′), 7.08 (s, 1H, H-3)	14.7 (OCH_2CH_3), 42.0 (NMe), 50.9 (CO_2CH_3), 55.6 (OMe), 64.7 (OCH_2CH_3), 100.1 (C-2′), 104.4 (C-6′), 113.6 (C-5′), 114.9 (C-2), 139.5 (C-3), 142.7 (C-4′), 150.1 (C-3′), 153.6 (C-1′), 166.3 (CO_2Me)
3e	1695, 1634, 1505, 1445, 1358, 1299, 1218, 1189, 1119, 1086, 1025	357 (M^+), 298, 266, 238, 210, 153, 116, 91 (100), 65	2.93 (s, 6H, NMe), 3.61 (s, 3H, CO_2Me), 3.83 (s, 3H, OMe), 5.04 (s, 2H, OCH_2Ph), 6.35 (dd, J=8.8, 2.7 Hz, 1H, H-6′), 6.59 (d, J=2.7 Hz, 1H, H-2′), 6.76 (d, J=8.8 Hz, 1H, H-5′), 7.11 (s, 1H, H-3), 7.23–7.44 (m, 5H, PhH)	42.0 (NMe), 51.0 (CO_2CH_3), 55.7 (OMe), 71.7 (OCH_2Ph), 100.3 (C-2′), 104.5 (C-6′), 114.9 (C-2), 115.1 (C-5′), 127.2 (PhCH), 127.6 (PhCH), 128.3 (PhCH), 137.4 (PhC), 139.6 (C-3), 142.7 (C-4′), 150.6 (C-3′), 154.2 (C-1′), 166.2 (CO_2Me)
3f	1696, 1638, 1483, 1432, 1359, 1299, 1245, 1220, 1093, 1054	311 (M^+), 252 (100), 224, 195, 166, 137, 116, 84, 56, 42	2.95 (s, 6H, NMe), 3.59 (s, 3H, CO_2Me), 3.77 (s, 3H, OMe), 3.90 (s, 3H, OMe), 3.95 (OMe), 6.46–6.55 (m, 2H, H-5′, H-6′), 7.13 (s, 1H, H-3)	42.0 (NMe), 51.0 (CO_2CH_3), 56.1 (OMe), 61.1 (OMe), 61.2 (OMe), 106.2 (ArCH), 107.7 (ArCH), 114.9 (C-2), 139.7 (C-3), 142.8 (ArC), 143.2 (ArC), 147.0 (ArC), 147.8 (ArC), 166.2 (CO_2Me)
3g	1697, 1634, 1486, 1434, 1358, 1299, 1253, 1218, 1146, 1116, 1087, 775	235 (M^+), 204, 176 (100), 158, 148, 119, 116, 84, 77, 65	2.30 (s, 3H, Me), 2.95 (s, 6H, NMe), 3.62 (s, 3H, CO_2Me), 6.70–6.80 (m, 3H, ArH), 7.10–7.18 (m, 1H, H-5′), 7.14 (s, 1H, H-3)	21.5 (Me), 42.0 (NMe), 51.2 (CO_2CH_3), 111.7 (C-6′), 114.9 (C-2), 115.5 (C-2′), 122.3 (C-4′), 129.2 (C-5′), 139.5 (C-3′), 139.6 (C-3), 159.2 (C-1′), 166.1 (CO_2Me)
3h	1698, 1637, 1506, 1434, 1359, 1299, 1253, 1218, 1123, 1085	249 (M^+, 100), 218, 190, 174, 162, 144, 129, 114, 98, 84, 70	2.26 (br s, 6H, Me), 2.95 (s, 6H, NMe), 3.61 (s, 3H, CO_2Me), 6.59 (d, J=1.5 Hz, 1H, H-6′), 6.67 (dd, J=7.8, 1.5 Hz, 1H, H-4′), 7.01 (d, J=7.8 Hz, 1H, H-3′), 7.16 (s, 1H, H-3)	15.8 (Me-2), 21.3 (Me-5), 42.0 (NMe), 51.1 (CO_2CH_3), 113.1 (C-6′), 115.1 (C-2), 121.7 (C-4′), 122.8 (C-2′), 130.5 (C-3′), 136.5 (C-5′), 139.5 (C-3), 157.2 (C-1′), 166.7 (CO_2Me)
3i	1696, 1631, 1511, 1435, 1356, 1299, 1215, 1118, 1085, 848, 746	271 (M^+), 240, 212 (100), 194, 184, 155, 141, 127, 115, 84, 56, 42	2.96 (s, 6H, NMe), 3.63 (s, 3H, CO_2Me), 7.22 (d, J=2.4 Hz, 1H, H-1′), 7.24 (s, 1H, H-3), 7.26 (dd, J=8.7, 2.4 Hz, 1H, H-3′), 7.29–7.36 (m, 1H, H-6′), 7.38–7.45 (m, 1H, H-7′), 7.70 (d, J=8.1 Hz, 1H, H-8′), 7.74–7.80 (m, 2H, H-4′, H-5′)	42.1 (NMe), 51.2 (CO_2CH_3), 108.8 (C-1′), 114.8 (C-2), 117.7 (C-3′), 123.7 (C-6′), 126.3 (C-8′), 126.8 (C-5′), 127.6 (C-7′), 129.4 (C-4a′), 129.6 (C-4′), 134.4 (C-8a′), 139.8 (C-3), 157.2 (C-2′), 166.6 (CO_2Me)
4a	1667, 1595, 1470, 1350, 1309, 1203, 1138, 1062, 951		1.92 (br s, 3H, COMe), 2.91 (br s, 6H, NMe_2), 3.67 (br s, 6H, 2OMe), 6.05 (br s, 3H, H-2′, H-4′, H-6′), 7.20 (br s, 1H, H-4)	24.6 ($COCH_3$), 42.7 (NMe), 55.1 (2MeO), 93.5 (C-2′, C-4′, C-6′), 125.5 (C-3), 138.5 (C-4), 161.0 (C-1′), 161.5 (C-3′, C-5′), 194.1 ($COCH_3$)
4b	1666, 1592, 1501, 1463, 1422, 1311, 1222, 1126, 1008, 955		1.95 (br s, 3H, COMe), 2.95 (s, 6H, NMe_2), 3.71 (s, 3H, OMe), 3.75 (s, 6H, 2OMe), 6.11 (s, 2H, H-2′, H-6′), 7.23 (br s, 1H, H-4)	24.7 ($COCH_3$), 42.3 (NMe), 55.9 (2MeO), 60.7 (MeO), 91.8 (C-2′, C-6′), 125.5 (C-3), 132.3 (C-4′), 138.7 (C-4), 153.8 (C-3′, C-5′), 155.5 (C-1′), 194.5 ($COCH_3$)
4c	1666, 1588, 1507, 1436, 1308, 1226, 1191, 1153, 1122, 1025, 949		1.96 (br s, 3H, COMe), 2.95 (s, 6H, NMe_2), 3.78 (s, 3H, OMe), 3.81 (s, 3H, OMe), 6.33–6.40 (m, 1H, H-6′), 6.52 (d, J=3.0 Hz, 1H, H-2′), 6.72 (d, J=8.7 Hz, 1H, H-5′), 7.23 (br s, 1H, H-4)	24.7 ($COCH_3$), 42.0 (NMe), 55.8 (MeO), 56.2 (MeO), 99.8 (C-2′), 104.5 (C-6′), 111.8 (C-5′), 125.9 (C-3), 138.6 (C-4), 143.7 (C-4′), 149.9 (C-3′), 153.4 (C-1′), 192.6 ($COCH_3$)
4d	1667, 1588, 1481, 1307, 1173, 1125, 1035		1.96 (br s, 3H, COMe), 2.96 (s, 6H, NMe_2), 5.89 (s, 2H, OCH_2O), 6.32 (dd, J=8.1, 2.4 Hz, 1H, H-6′), 6.49 (d, J=2.4 Hz, 1H, H-4′), 6.66 (d, J=8.1 Hz, 1H, H-7′), 7.22 (br s, 1H, H-4)	24.7 ($COCH_3$), 42.0 (NMe), 97.5 (C-4′), 101.2 (OCH_2O), 106.0 (C-6′), 108.1 (C-7′), 126.1 (C-3), 138.5 (C-4), 142.0 (C-7a′), 148.4 (C-3a′), 153.4 (C-5′), 194.2 ($COCH_3$)
4e	1666, 1603, 1589, 1577, 1488, 1434, 1352, 1310, 1140, 1119, 1042, 963		1.84 (br s, 3H, COMe), 2.83 (s, 6H, NMe_2), 3.62 (s, 3H, OMe), 6.32–6.47 (m, 3H, H-2′, H-4′, H-6′), 6.97–7.08 (m, 1H, H-5′), 7.14 (br s, 1H, H-4)	24.3 ($COCH_3$), 41.9 (NMe), 54.8 (MeO), 100.7 (C-2′), 106.5 (C-4′ or C-6′), 106.7 (C-6′ or C-4′), 125.2 (C-3), 129.8 (C-5′), 138.1 (C-4), 159.9 (C-1′ or C-3′), 160.6 (C-3′ or C-1′), 193.8 ($COCH_3$)
4f	1666, 1589, 1505, 1434, 1353, 1313, 1253, 1123, 959		1.93 (br s, 3H, COMe), 2.24 (s, 3H, Me-5′), 2.25 (s, 3H, Me-2′), 2.96 (s, 6H, NMe_2), 6.58 (br s, 1H, H-6′), 6.67 (br d, J=7.5 Hz, 1H, H-4′), 7.02 (d, J=7.5 Hz, 1H, H-3′), 7.30 (br s, 1H, H-4)	15.8 (CH_3-2′), 21.2 (CH_3-5′), 24.5 ($COCH_3$), 42.0 (NMe), 112.8 (C-6′), 121.8 (C-2′), 122.5 (C-4′), 125.5 (C-3), 130.7 (C-3′), 136.9 (C-5′), 138.4 (C-4), 156.7 (C-1′), 194.8 ($COCH_3$)

[a] For spectral data of **3b**, see Ref. 10.

Table 5. Spectral data of compounds **1a**–**1e** and **2a**–**2f**[a]

Compound	IR (cm^{-1})	GC–MS *m/z*	^1H NMR ($CDCl_3$) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$) δ
1a	1672, 1618, 1547, 1501, 1461, 1272, 1217, 1148, 1114	220 (M^+, 100), 205, 177, 149, 135, 119	2.53 (s, 3H, COMe), 3.85 (s, 3H, OMe), 3.90 (s, 3H, OMe), 6.30 (d, *J*=2.1 Hz, 1H, H-5), 6.63 (dd, *J*=2.1, 0.9 Hz, 1H, H-7), 7.52 (d, *J*=0.9 Hz, 1H, H-3)	26.0 ($COCH_3$), 55.6 (OMe), 55.8 (OMe), 87.8 (C-7), 95.1 (C-5), 112.0 (C-3a), 112.2 (C-3), 150.9 (C-2), 155.1 (C-4), 158.0 (C-7a), 162.5 (C-6), 187.2 ($COCH_3$)
1b	1675, 1618, 1547, 1486, 1468, 1425, 1299, 1265, 1216, 1196, 1137, 1110	250 (M^+, 100), 235, 207, 177, 151, 135	2.53 (s, 3H, COMe), 3.83 (s, 3H, OMe), 3.90 (s, 3H, OMe), 4.11 (s, 3H, OMe), 6.77 (d, *J*=0.9 Hz, 1H, H-7), 7.56 (d, *J*=0.9 Hz, 1H, H-3)	26.1 ($COCH_3$), 56.3 (OMe), 60.7 (OMe), 61.4 (OMe), 90.1 (C-7), 112.3 (C-3), 113.2 (C-3a), 137.4 (C-5), 147.1 (C-4 or C-6), 151.4 (C-2), 153.1 (C-7a), 155.9 (C-6 or C-4), 187.5 ($COCH_3$)
1c	1670, 1620, 1547, 1490, 1466, 1295, 1218, 1134, 1005	220 (M^+, 100), 205, 177, 149, 135, 121	2.55 (s, 3H, COMe), 3.92 (s, 3H, OMe), 3.94 (s, 3H, OMe), 7.04 (s, 1H, H-4), 7.05 (br d, *J*=0.9 Hz, 1H, H-7), 7.42 (d, *J*=0.9 Hz, 1H, H-3)	26.2 ($COCH_3$), 56.3 (2OMe), 95.0 (C-7), 102.6 (C-4), 113.9 (C-3), 119.0 (C-3a), 147.7 (C-5), 151.4 (C-6), 151.6 (C-2), 152.3 (C-7a), 187.7 ($COCH_3$)
1d	1667, 1558, 1458, 1318, 1297, 1242, 1185, 1146, 1035, 939	204 (M^+, 100), 189, 161, 133, 75	2.53 (s, 3H, COMe), 6.03 (s, 2H, OCH_2O), 6.98 (s, 1H, H-4), 7.00 (br s, 1H, H-7), 7.38 (d, *J*=0.9 Hz, 1H, H-3)	26.1 ($COCH_3$), 93.8 (C-7), 100.2 (OCH_2O), 101.9 (C-4), 114.1 (C-3), 120.5 (C-3a), 145.8 (C-5), 149.8 (C-6), 152.0 (C-2), 152.7 (C-7a), 187.5 ($COCH_3$)
1e	1740, 1677, 1620, 1551, 1494, 1461, 1304, 1265, 1222, 1153, 1112, 1023	190 (M^+), 175 (100), 147, 119, 77	2.56 (s, 3H, COMe), 3.86 (s, 3H, OMe), 6.93 (dd, *J*=8.8, 2.1 Hz, 1H, H-5), 7.03 (br d, *J*=2.1 Hz, 1H, H-7), 7.44 (d, *J*=0.9 Hz, 1H, H-3), 7.55 (d, *J*=8.8 Hz, 1H, H-4)	26.2 ($COCH_3$), 55.7 (OMe), 95.5 (C-7), 113.8 (C-3), 114.4 (C-5), 120.3 (C-3a), 123.6 (C-4), 152.2 (C-2), 157.2 (C-7a), 161.1 (C-6), 187.5 ($COCH_3$)
2a	1726, 1620, 1593, 1567, 1494, 1440, 1315, 1269, 1225, 1178, 1154, 1112, 1025, 840, 763		3.85 (s, 3H, CO_2Me), 3.94 (s, 3H, OMe), 6.92 (dd, *J*=8.7, 2.1 Hz, 1H, H-5), 7.04 (br d, *J*=2.1 Hz, 1H, H-7), 7.45 (d, *J*=0.9 Hz, 1H, H-3), 7.52 (d, *J*=8.7 Hz, 1H, H-4)	52.2 (CO_2CH_3), 55.7 (MeO), 95.6 (C-7), 114.0 (C-5), 114.3 (C-3), 120.1 (C-3a), 123.0 (C-4), 145.5 (C-2), 157.0 (C-6), 160.0 (C-7a), 160.5 (CO_2CH_3)
2c	1730, 1563, 1489, 1462, 1302, 1244, 1181, 1108, 1038, 940, 855	220 (M^+), 189, 177, 162, 133 (100), 103, 75, 74	3.93 (s, 3H, CO_2Me), 6.02 (s, 2H, OCH_2O), 6.96 (s, 1H, H-4), 7.01 (br s, 1H, H-7), 7.40 (d, *J*=0.9 Hz, 1H, H-3)	52.2 (CO_2CH_3), 93.8 (C-7), 100.0 (OCH_2O), 101.8 (C-4), 114.6 (C-3), 120.3 (C-3a), 145.0 (C-5), 145.6 (C-6), 149.2 (C-2), 151.7 (C-7a), 159.7 (CO_2CH_3)
2d	1724, 1619, 1555, 1486, 1445, 1296, 1205, 1141, 1013, 924, 864	250 (M^+), 222, 207 (100), 193, 179, 161, 135, 119, 92, 77, 63	1.48 (t, *J*=6.9 Hz, 3H, OCH_2CH_3), 3.91 (s, 3H, CO_2Me), 3.93 (s, 3H, OMe), 4.10 (t, *J*=6.9 Hz, 3H, OCH_2CH_3), 7.02 (s, 1H, H-4), 7.05 (s, 1H, H-7), 7.41 (s, 1H, H-3)	14.7 (OCH_2CH_3), 52.1 (CO_2CH_3), 56.2 (OMe), 64.8 (OCH_2CH_3), 95.2 (C-7), 104.0 (C-4), 114.4 (C-3), 118.8 (C-3a), 144.4 (C-5), 146.8 (C-2), 151.3 (C-7a), 151.4 (C-6), 159.9 (CO_2CH_3)
2e	1722, 1620, 1559, 1488, 1445, 1295, 1197, 1137, 1005, 742	312 (M^+), 281, 221, 193, 178, 161, 137, 119, 105, 91 (100), 65	3.930 (s, 3H, OMe), 3.932 (s, 3H, OMe), 5.16 (s, 2H, OCH_2Ph), 7.06 (s, 1H, H-4), 7.07 (br s, 1H, H-7), 7.27–7.47 (m, 6H, H-3, ArH)	52.1 (CO_2CH_3), 56.2 (OMe), 71.5 (OCH_2Ph), 95.3 (C-7), 105.6 (C-4), 114.5 (C-3), 118.8 (C-3a), 127.3 (PhCH), 127.9 (PhCH), 128.6 (PhCH), 136.7 (PhC), 144.4 (ArC), 146.5 (ArC), 151.5 (ArC), 151.7 (ArC), 159.9 (CO_2CH_3)
2f	1728, 1571, 1487, 1460, 1426, 1356, 1316, 1254, 1225, 1196, 1134, 1046	266 (M^+), 251 (100), 235, 193, 167, 137, 121	3.88 (s, 3H, OMe-5), 3.91 (s, 3H, OMe-6), 3.93 (s, 3H, CO_2Me), 4.21 (s, 3H, OMe-7), 6.76 (s, 1H, H-4), 7.42 (s, 1H, H-3)	52.2 (CO_2CH_3), 56.3 (OMe-5), 61.0 (OMe-7), 61.6 (OMe-6), 97.0 (C-4), 114.4 (C-3), 123.0 (C-3a), 139.2 (C-7), 141.4 (C-6), 142.9 (C-7a), 145.6 (C-2), 151.6 (C-5), 159.7 (CO_2CH_3)

[a] For spectral data of **2b**, see Ref. 10.

heated to 100 °C under MW irradiation (400 W) for 5 h. The mixture was filtered and the solvent was evaporated under vacuum. The residue was purified by column chromatography over silica gel (15 g, hexane/EtOAc 95:5) to give the corresponding compounds **2a**–**2c**.

4.5.1. Methyl 6-methoxybenzofuran-2-carboxylate (2a). Using the general procedures: method A: with 0.05 g (0.199 mmol) of **3a**, and 0.081 g (0.59 mmol) of $ZnCl_2$, and stirring for 72 h, to give 0.025 g (62%) of **2a**; method B: with 0.05 g (0.25 mmol) of **6a** and 0.089 g (0.75 mmol) of DMFDMA, to yield 0.01 g (20%) of **2a**; method C: with 0.05 g (0.25 mmol) of **6a**, 0.059 g (0.50 mmol) of DMFDMA, and 0.035 g (0.25 mmol) of $ZnCl_2$, to yield 0.011 g (22%) of **2a**; method D: with 0.05 g (0.25 mmol) of **6a**, 0.059 g (0.50 mmol) of DMFDMA, and 0.069 g (0.50 mmol) of $ZnCl_2$, to yield 0.0095 g (19%) of **2a** as a white solid: R_f 0.63 (hexane/EtOAc 7:3); mp 93–95 °C (hexane/EtOAc 9:1) [lit.[28] 92–95 °C].

4.5.2. Methyl 1,3,5-trioxa-*s*-indacene-2-carboxylate (2c). Using the general procedures: method A: with 0.05 g (0.188 mmol) of **3c**, and 0.077 g (0.565 mmol) of $ZnCl_2$, and stirring for 72 h, to give 0.028 g (68%) of **2c**; method B: with 0.05 g (0.23 mmol) of **6c** and 0.085 g (0.714 mmol) of DMFDMA, to yield 0.013 g (25%) of **2c**; method C: with 0.05 g (0.23 mmol) of **6c**, 0.055 g (0.46 mmol) of DMFDMA, and 0.032 g (0.23 mmol) of $ZnCl_2$, to yield 0.01 g (20%) of **2c**; method D: with 0.05 g (0.23 mmol) of **6c**, 0.055 g (0.46 mmol) of DMFDMA, and 0.064 g (0.46 mmol) of $ZnCl_2$, to yield 0.01 g (20%) of **2c** as a white solid: R_f 0.44 (hexane/EtOAc 7:3); mp 181–182 °C (hexane/EtOAc 9:1). Anal. Calcd for $C_{11}H_8O_5$: C, 60.01; H, 3.66. Found: C, 60.21; H, 3.90.

4.5.3. Methyl 5-ethoxy-6-methoxybenzofuran-2-carboxylate (2d). Using the general procedure of method A with 0.05 g (0.169 mmol) of **3d**, and 0.069 g (0.508 mmol) of $ZnCl_2$, and stirring for 72 h, to give 0.028 g (65%) of **2d** as a white solid: R_f 0.43 (hexane/EtOAc 7:3); mp 159–160 °C (hexane/EtOAc 8:2). Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.37; H, 5.88.

4.5.4. Methyl 5-benzyloxy-6-methoxybenzofuran-2-carboxylate (2e). Using the general procedure of method A with 0.05 g (0.14 mmol) of **3e**, and 0.057 g (0.42 mmol) of $ZnCl_2$, and stirring for 72 h, to give 0.035 g (70%) of **2e** as a white solid: R_f 0.48 (hexane/EtOAc 7:3); mp 102–104 °C (hexane/EtOAc 8:2). Anal. Calcd for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found: C, 69.10; H, 5.30.

4.5.5. Methyl 5,6,7-trimethoxybenzofuran-2-carboxylate (2f). Using the general procedure of method A with 0.05 g (0.16 mmol) of **3f**, and 0.066 g (0.48 mmol) of $ZnCl_2$, and stirring for 72 h, to give 0.03 g (72%) of **2f** as a white solid: R_f 0.42 (hexane/EtOAc 7:3); mp 66–67 °C (hexane/EtOAc 8:2). Anal. Calcd for $C_{13}H_{14}O_6$: C, 58.65; H, 5.30. Found: C, 58.83; H, 5.54.

4.6. General procedure for the preparation of the 1-aryloxypropan-2-ones 7a–7f (For spectral data, see Supplementary data)

Under an N_2 atmosphere, a mixture of phenol **5** and anhydrous K_2CO_3 (1.5 mol equiv) in dry acetone (30 mL) was heated to 60 °C for 1 h. α-Chloroacetone (**8**) (1.1 mol equiv) was added dropwise, and the mixture was heated to 60 °C for 12 h. The mixture was filtered and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (20 g/g sample, hexane/EtOAc 9:1), to give the corresponding products **7a**–**7f**.

4.6.1. 1-(3,5-Dimethoxyphenoxy)propan-2-one (7a). Using the general procedure with 3.0 g (19.5 mmol) of **5j**, 4.04 g (29.2 mmol) of K_2CO_3, and 1.98 g (21.4 mmol) of (**8**) to give 2.94 g (72%) of **7a** as a colorless oil: R_f 0.31 (hexane/EtOAc 6:4). Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 63.02; H, 6.90.

4.6.2. 1-(3,4,5-Trimethoxyphenoxy)propan-2-one (7b). Using the general procedure with 3.0 g (16.3 mmol) of **5k**, 3.37 g (24.4 mmol) of K_2CO_3, and 1.66 g (17.9 mmol) of **8** to give 2.74 g (70%) of **7b** as a white solid: R_f 0.24 (hexane/EtOAc 6:4); mp 26–27 °C (hexane/EtOAc 7:3) [lit.[17] 26.8 °C].

4.6.3. 1-(3,4-Dimethoxyphenoxy)propan-2-one (7c). Using the general procedure with 3.0 g (19.5 mmol) of **5b**, 4.04 g (29.2 mmol) of K_2CO_3, and 1.98 g (21.4 mmol) of **8** to give 3.48 g (85%) of **7c** as a white solid: R_f 0.35 (hexane/EtOAc 6:4); mp 45–46 °C (hexane/EtOAc 7:3) [lit.[17] 45 °C].

4.6.4. 1-(Benzo[1,3]dioxol-5-yloxy)propan-2-one (7d). Using the general procedure with 3.0 g (21.7 mmol) of **5c**, 4.5 g (32.6 mmol) of K_2CO_3, and 2.21 g (23.9 mmol) of **8** to give 3.67 g (87%) of **7d** as a colorless oil: R_f 0.28 (hexane/EtOAc 8:2). Anal. Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.66; H, 5.27.

4.6.5. 1-(3-Methoxyphenoxy)propan-2-one (7e).[29] Using the general procedure with 3.0 g (24.2 mmol) of **5a**, 5.01 g (36.3 mmol) of K_2CO_3, and 2.46 g (26.6 mmol) of **8** to give 3.57 g (82%) of **7e** as a colorless oil: R_f 0.33 (hexane/EtOAc 8:2).

4.6.6. 1-(2,5-Dimethylphenoxy)propan-2-one (7f).[30] Using the general procedure with 3.0 g (24.6 mmol) of **5h**, 5.09 g (36.9 mmol) of K_2CO_3, and 2.5 g (27.1 mmol) of **8** to give 3.75 g (86%) of **7f** as a colorless oil: R_f 0.55 (hexane/EtOAc 8:2).

4.7. General procedure for the preparation of the (*Z*)-3-aryloxy-4-dimethylamino-3-buten-2-ones 4a–4f

Under an N_2 atmosphere, a mixture of one of the 1-aryloxypropan-2-ones, **7a**–**7f**, and of DMFDMA (1.0 mol equiv) was heated to 80 °C for 6 h. The mixture was evaporated under vacuum and the residue was purified by column chromatography over silica gel (20 g/g sample, hexane/EtOAc 1:1), to give the corresponding products **4a**–**4f** (Table 4).

4.7.1. (*Z*)-4-Dimethylamino-3-(3,5-dimethoxyphenoxy)-3-buten-2-one (4a). Using the general procedure with 1.0 g (4.76 mmol) of **7a** and 0.57 g (4.76 mmol) of DMFDMA, to give 1.04 g (82%) of **4a** as a yellow solid: R_f 0.21 (hexane/EtOAc 6:4); mp 102–103 °C (hexane/EtOAc 1:4). Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.50; H, 7.05; N, 5.40.

4.7.2. (*Z*)-4-Dimethylamino-3-(3,4,5-trimethoxyphenoxy)-3-buten-2-one (4b). Using the general procedure with 0.5 g (2.08 mmol) of **7b** and 0.25 g (2.08 mmol) of DMFDMA, to give 0.53 g (86%) of **4b** as an orange solid: R_f 0.20 (hexane/EtOAc 6:4); mp 107–108 °C (hexane/EtOAc 1:4). Anal. Calcd for $C_{15}H_{21}NO_4$: C, 61.00; H, 7.17; N, 4.74. Found: C, 61.15; H, 6.97; N, 4.68.

4.7.3. (*Z*)-3-(3,4-Dimethoxyphenoxy)-4-dimethylamino-3-buten-2-one (4c). Using the general procedure with 0.5 g (2.38 mmol) of **7c** and 0.28 g (2.38 mmol) of DMFDMA, to give 0.53 g (85%) of **4c** as an orange solid: R_f 0.22 (hexane/EtOAc 6:4); mp 94–95 °C (hexane/EtOAc 1:4). Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.26; H, 7.35; N, 5.26.

4.7.4. (*Z*)-3-(Benzo[1,3]dioxol-5-yloxy)-4-dimethylamino-3-buten-2-one (4d). Using the general procedure with 1.0 g (5.15 mmol) of **7d** and 0.61 g (5.15 mmol) of DMFDMA, to give 1.05 g (81%) of **4d** as a yellow solid: R_f 0.23 (hexane/EtOAc 4:6); mp 166–167 °C (hexane/EtOAc 1:4). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.58; H, 5.93; N, 5.69.

4.7.5. (*Z*)-4-Dimethylamino-3-(3-methoxyphenoxy)-3-buten-2-one (4e). Using the general procedure with 0.5 g (2.78 mmol) of **7e** and 0.33 g (2.78 mmol) of DMFDMA, to give 0.57 g (88%) of **4e** as a reddish solid: R_f 0.25 (hexane/EtOAc 6:4); mp 77–78 °C (hexane/EtOAc 3:7). Anal. Calcd

for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.50; H, 7.17; N, 6.00.

4.7.6. (*Z*)-4-Dimethylamino-3-(2,5-dimethylphenoxy)-3-buten-2-one (4f). Using the general procedure with 1.0 g (5.62 mmol) of **7f** and 0.67 g (5.62 mmol) of DMFDMA, to give 1.1 g (84%) of **4f** as an orange solid: R_f 0.36 (hexane/EtOAc 6:4); mp 148–149 °C (hexane/EtOAc 3:7). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.28; H, 7.97; N, 6.12.

4.8. General procedures for the preparation of 2-acetylbenzofurans 1a–1e (Table 5)

Method A. Under an N_2 atmosphere at room temperature, a mixture of 1.0 mol equiv of the corresponding 3-dimethylaminopropan-2-one **4a**–**4e**, 3.0 mol equiv of $ZnCl_2$ in dry CH_2Cl_2 (50 mL) was stirred at the same temperature for 48 h. The mixture was filtered, washed with H_2O (2× 20 mL), and dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (10 g, hexane/EtOAc 95:5) to give the corresponding benzofurans **1a**–**1e**.

Method B. A mixture of 1.0 mol equiv of the 1-aryloxypropan-2-ones **7a**–**7c** and 1.0 mol equiv of DMFDMA was heated to 100 °C under MW irradiation (400 W) for 10 min; then 3.0 mol equiv of $ZnCl_2$ in dry acetonitrile (20 mL) were added and the mixture was heated 100 °C under MW irradiation (400 W) for 30 min. The mixture was filtered and the solvent was evaporated under vacuum. The residue was purified by column chromatography over silica gel (15 g, hexane/EtOAc 95:5) to give the corresponding compounds **1a**–**1c**.

4.8.1. Calebertine (2-acetyl-4,6-dimethoxybenzofuran) (1a). Using method A with 0.05 g (0.189 mmol) of **4a**, and 0.077 g (0.567 mmol) of $ZnCl_2$, and stirring for 48 h, to give 0.025 g (60%) of **1a**; method B: with 0.1 g (0.476 mmol) of **7a**, 0.057 g (0.476 mmol) of DMFDMA, and 0.196 g (1.43 mmol) of $ZnCl_2$, to give 0.037 g (35%) of **1a** as a white solid: R_f 0.32 (hexane/EtOAc 7:3); mp 111–112 °C (hexane/EtOAc 8:2) [lit.[8a] 112–113 °C].

4.8.2. Caleprunine A (2-acetyl-4,5,6-trimethoxybenzofuran) (1b).[8a] Using method A with 0.05 g (0.17 mmol) of **4b**, and 0.069 g (0.508 mmol) of $ZnCl_2$, and stirring for 48 h, to give 0.026 g (61%) of **1b**; method B: with 0.1 g (0.417 mmol) of **7b**, 0.05 g (0.417 mmol) of DMFDMA, and 0.17 g (1.25 mmol) of $ZnCl_2$, to give 0.04 g (38%) of **1b** as a yellow oil: R_f 0.30 (hexane/EtOAc 7:3).

4.8.3. Caleprunine B (2-acetyl-5,6-dimethoxybenzofuran) (1c). Using method A with 0.05 g (0.189 mmol) of **4c**, and 0.077 g (0.567 mmol) of $ZnCl_2$, and stirring for 48 h, to give 0.026 g (62%) of **1c**; method B: with 0.1 g (0.476 mmol) of **7c**, 0.057 g (0.476 mmol) of DMFDMA, and 0.196 g (1.43 mmol) of $ZnCl_2$, to give 0.044 g (42%) of **1a** as a white solid: R_f 0.36 (hexane/EtOAc 7:3); mp 115–116 °C (hexane/EtOAc 8:2) [lit.[6] 115–117 °C].

4.8.4. 6-Acetyl-1,3,5-trioxa-*s*-indacene (1d). Using the general procedure for the preparation of **2a**–**2e** (method A) with 0.05 g (0.20 mmol) of **4d**, and 0.082 g (0.60 mmol) of $ZnCl_2$, and stirring for 48 h, to give 0.025 g (61%) of **1d** as a white solid: R_f 0.37 (hexane/EtOAc 7:3); mp 132–133 °C (hexane/EtOAc 8:2) [lit.[31] 156–157.5 °C]. Anal. Calcd for $C_{11}H_8O_4$: C, 64.71; H, 3.95. Found: C, 64.95; H, 4.07.

4.8.5. 2-Acetyl-6-methoxybenzofuran (1e). Using the general procedure for the preparation of **2a**–**2e** (method A) with 0.05 g (0.21 mmol) of **4e**, and 0.087 g (0.64 mmol) of $ZnCl_2$, and stirring for 48 h, to give 0.025 g (62%) of **1e** as a white solid: R_f 0.42 (hexane/EtOAc 7:3); mp 97–98 °C (hexane/EtOAc 8:2) [lit.[32] 98–99 °C].

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.08.015

Spectral data (IR, GC–MS, ^{1}H NMR, and ^{13}C NMR) of compounds **6a**–**6h** and **7a**–**7f**.

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Substituent effects on the spectroscopic properties of solvatochromic 2-phenylimidazo[1,2-*a*]pyrazin-3(7*H*)-ones: an effective control for the colorimetric sensor properties

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Abstract—Substituent effects on the spectroscopic properties of a solvatochromic compound, 7-methyl-2-phenylimidazo[1,2-*a*]pyrazin-3(7*H*)-one (**1c**), using derivatives **1** with a *para*-substituent R on the phenyl group, were investigated systematically. In the UV/visible absorption spectra, the solvatochromic property of **1** originating from hydrogen-bonding interactions was effectively regulated by the substituent effects. In particular, the cyano derivative **1e** showed significant solvatochromism with a wide color variation range and a high sensitivity toward solvents. Similarly, the fluorescence of **1** showed a redshift as the electron-withdrawing property of R increased. The substituent effects were evaluated by AM1-COSMO calculations, which also suggested that derivatives **1** are good electron donors and that the electron-donating ability is regulated by R. This was confirmed by the observation of low oxidation potentials and the formation of charge-transfer complexes with tetracyanoethylene. Absorption-spectrum changes of **1c** and **1e** caused by metal–ion complexation were also compared, showing that the cyano derivative **1e** is a good colorimetric sensor for the Lewis acidity of the metal ions. From these observations, it was established that *para*-substitution of R on the phenyl group of **1c** caused successive modulations of the colorimetric sensor properties.

1. Introduction

Derivatives of imidazo[1,2-*a*]pyrazin-3(7*H*)-one (imidazopyrazinone, Chart 1) are important bio- and chemiluminescent compounds. They appear as the luminescent substrates of bioluminescent marine organisms such as the crustacean *Vargula* (*Cypridina*),[1] the jellyfish *Aequorea*,[2] and the luminous squid *Symplectoteuthis*.[3] Imidazopyrazinone derivatives also have chemiluminescent reactivity in aprotic solvents.[4,5] In addition to their luminescent properties, a series of imidazopyrazinone derivatives show a unique solvatochromism originating from hydrogen-bonding interaction with protic solvent molecules. The imidazopyrazinone ring has a zwitterionic character, and the negatively charged carbonyl group of imidazopyrazinone functions as a hydrogen-bond acceptor to bond with protic solvent molecules.[6] The color of imidazopyrazinone derivatives in solution changes depending on the strength of the hydrogen bonding with solvent molecules. Among the various imidazopyrazinone derivatives, 7-methyl-2-phenylimidazo[1,2-*a*]pyrazin-3(7*H*)-one (**1c**) shows a significant solvatochromic color change. Thus, 2-phenylimidazopyrazinone derivatives are applicable as colorimetric sensors for the proton-donor ability of solvents.[6,7]

To gain further insight into controlling color variation range and sensitivity toward the proton-donor ability of solvents, we studied substituent effects on the spectroscopic property of **1c** using *para*-substituted derivatives (Chart 1; **1a**, R = $N(CH_3)_2$; **1b**, R = OCH_3; **1d**, R = Cl; **1e**, R = CN).[7] We found that in the solvatochromic properties of **1**, the cyano

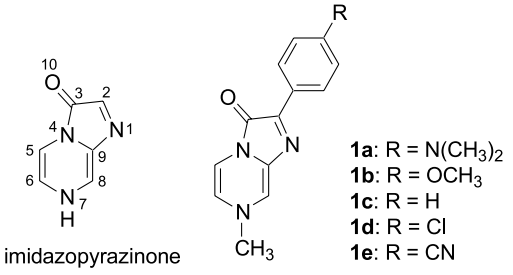

Chart 1.

Keywords: Substituent effect; Solvatochromism; Fluorescence; Charge-transfer complex; Metal–ion complexation.
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derivative **1e** is preferable as a colorimetric sensor.[7] We also investigated the fluorescence of **1**, the electronic absorption of charge-transfer (CT) complexes of **1** with a typical electron acceptor compound, tetracyanoethylene (TCNE), and the electronic absorption of metal–ion complexes of **1**. We found that these spectroscopic properties of **1** are readily modulated by the *para*-substitution of R on the phenyl group.

2. Results and discussion

2.1. Solvatochromic property of imidazopyrazinones 1

2-Phenylimidazopyrazinone derivatives **1** were prepared by *N*-methylation of the corresponding 7-NH derivatives.[8] *N*-methyl derivatives were chosen as stable substrates because the *N*-methylation inhibits possible generation of the imidazopyrazinone anion, which has a high chemiluminescent reactivity.[6a] The UV/visible absorption spectra of **1** were measured in DMSO, acetonitrile (MeCN), chloroform ($CHCl_3$), 2-propanol (2-PrOH), methanol (MeOH), acetic acid (AcOH), H_2O, and 2,2,2-trifluoroethanol (TFE). The selected spectra of **1a**, **1c**, and **1e** are shown in Figure 1. The colors of **1b**, **1c**, and **1d** in solutions varied from red to yellow depending on the solvent. In the case of **1e**, the color changed from pink to orange, while that of **1a** showed a small change from dark to pale orange. The solution of **1a** in AcOH looked dark orange and the spectrum of the solution of **1a** in AcOH showed a weak absorption band around 570 nm. The behavior of **1a** may be due to a partial protonation at the dimethylamino group. Absorption maxima (λ_{max}) and molar absorption coefficients (ε) of **1** are summarized in Table 1.

To evaluate the substituent effects on the solvatochromic property, the wavenumbers (ν in cm^{-1}) of the lowest energy bands of **1** are correlated to Kamlet–Taft's α value, which is a parameter for the proton-donor (hydrogen-bond donor) ability of solvents (Fig. 2).[9,10] The linear relationships between α and ν obtained were as follows: **1a**: $\nu=550\alpha+19{,}920$ ($r=0.94$), **1b**: $\nu=1110\alpha+19{,}970$ ($r=0.99$), **1c**: $\nu=1360\alpha+19{,}690$ ($r=0.99$), **1d**: $\nu=1340\alpha+19{,}540$ ($r=0.99$), and **1e**: $\nu=1420\alpha+18{,}770$ ($r=0.98$). These observed linear correlations indicate that the hydrogen-bonding interaction between **1** (acceptor) and the solvent molecules (donor) regulates the solvatochromism, as reported previously.[6,7] In the α-ν correlations, the slope gradually increases with increase in the electron-withdrawing property of R: **1a** ≪ **1b** < **1c** ≈ **1d** < **1e**. On the other hand, the intercept gradually decreases with increase in the electron-withdrawing property of R: **1a** ≈ **1b** > **1c** > **1d** ≫ **1e**. In particular, a significantly small intercept was found for **1e**. Thus, the cyano derivative **1e** has a wide color

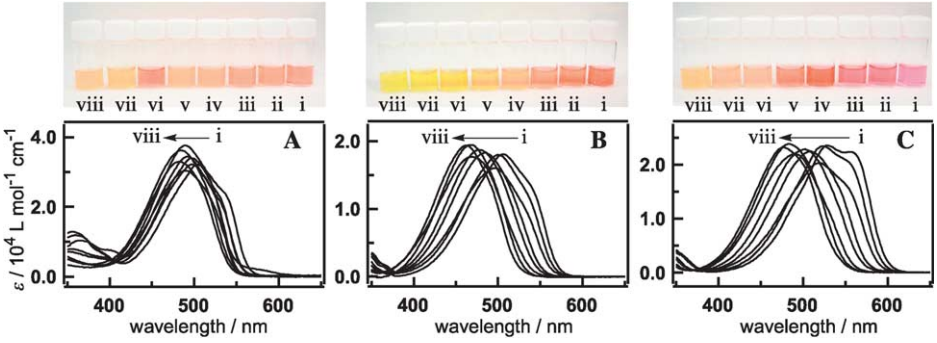


Figure 1. Graduated changes of colors and the UV/visible absorption spectra of **1a** (**A**, R = $N(CH_3)_2$), **1c** (**B**, R = H), and **1e** (**C**, R = CN) in various solvents at 25 °C: (i) DMSO, (ii) MeCN, (iii) $CHCl_3$, (iv) 2-PrOH, (v) MeOH, (vi) AcOH, (vii) H_2O, (viii) TFE.

Table 1. UV/visible absorption data of 2-phenylimidazopyrazinone derivatives **1** in various solvents

Compounds (R)	λ_{max}/nm (ε/10^4 L mol^{-1} cm^{-1})							
	DMSO (0.00)[a]	MeCN (0.19)[a]	$CHCl_3$ (0.44)[a]	2-PrOH (0.76)[a]	MeOH (0.93)[a]	AcOH (1.12)[a]	H_2O (1.17)[a]	TFE (1.51)[a]
1a ($N(CH_3)_2$)	504 (3.22)	498 (3.22)	497 (3.40)	491 (3.44)	490 (3.76)	490 (3.76)	482 (3.30)	484 (3.62)
	359 (1.20)	254 (1.99)	267 (2.09)	260 (2.16)	259 (2.28)	261 (1.63)	251 (1.94)	257 (2.09)
	328 (1.16)							
1b (OCH_3)	500 (2.02)	495 (1.94)	493 (1.74)	480 (2.11)	476 (2.16)	470 (2.21)	468 (2.20)	464 (1.94)
	304 (2.00)	302 (1.69)	307 (1.18)	322 (1.23)	297 (2.21)	293 (0.94)	293 (1.04)	316 (0.93)
		237 (1.70)		300 (1.29)	241 (2.06)		237 (1.88)	292 (0.90)
				243 (2.09)				238 (2.08)
1c (H)	507 (1.81)	500 (1.80)	497 (1.61)	485 (1.83)	478 (1.87)	470 (1.77)	467 (1.95)	463 (1.94)
	300 (1.93)	296 (2.08)	298 (1.74)	293 (1.82)	291 (1.64)	289 (1.30)	288 (1.39)	285 (1. 28)
		238 (1.61)		239 (1.84)	232 (1.95)		230 (1.90)	229 (2.01)
		223 (1.63)						
1d (Cl)	509 (2.34)	505 (2.31)	500 (2.12)	489 (2.31)	483 (2.35)	475 (2.33)	470 (2.29)	462 (2.54)
	303 (2.76)	300 (2.80)	303 (2.41)	297 (2.41)	297 (2.27)	294 (1.96)	291 (1.89)	289 (1.90)
		228 (2.10)		241 (2.27)	233 (2.39)		231 (2.34)	229 (2.55)
1e (CN)	528 (2.36)	524 (2.35)	518 (2.03)	509 (2.25)	500 (2.29)	492 (2.20)	483 (2.39)	477 (2.32)
	308 (2.29)	307 (2.51)	313 (2.42)	304 (2.37)	302 (2.34)	300 (2.14)	297 (2.13)	297 (2.28)
		237 (1.73)		239 (2.04)	239 (2.04)		239 (2.30)	235 (2.46)

[a] Kamlet–Taft's α value.

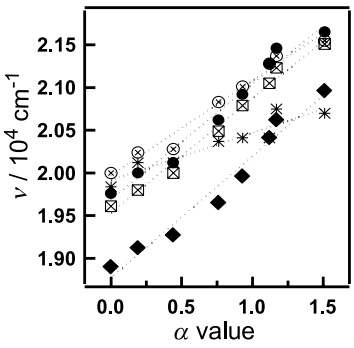


Figure 2. Plots of wavenumbers ν (cm^{-1}) of the lowest energy bands for **1** against Kamlet–Taft's α values: **1a** (✳), **1b** (⊗), **1c** (●), **1d** (⊠), and **1e** (◆).

variation range of solvatochromism and a high sensitivity toward the proton-donor ability of solvents, indicating that **1e** is the preferred colorimetric sensor for the proton-donor ability of solvents.

2.2. Fluorescent property of imidazopyrazinones 1

The substituent and solvent effects on the absorption spectra of **1** described above suggest that the fluorescence spectra of **1** also depend on the substituent and solvent. Therefore, we observed fluorescence emission spectra of **1** in MeCN and MeOH (Fig. 3). One of the spectral characteristics for **1** is to display structured emission. The maxima (λ_{fl}) and quantum yields (Φ_{fl}) are summarized in Table 2. The λ_{fl} values showed a bathochromic shift with increase in the electron-withdrawing property of the substituent R. The observed shift of the fluorescence spectra with change of R corresponds to that of the UV/visible absorption spectra. In particular, **1e** (R=CN) shows a significant redshift, with the λ_{fl} values around 600 nm. In contrast to the solvatochromism observed in the absorption spectra, only a small difference in λ_{fl} was observed between that in MeCN and

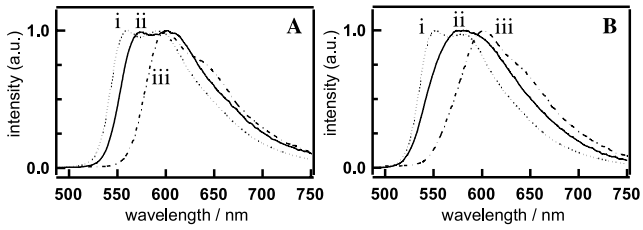


Figure 3. Fluorescence emission spectra of **1a** (i, R=$N(CH_3)_2$), **1c** (ii, R=H), and **1e** (iii, R=CN) in MeCN (**A**) and MeOH (**B**) at 25 °C. Excitation wavelengths in MeCN are 495, 494, and 522 nm for **1a**, **1c**, and **1e**, respectively, and those in MeOH are 485, 470, and 494 nm for **1a**, **1c**, and **1e**, respectively.

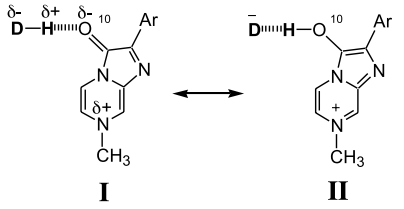
Table 2. Fluorescence of **1** in MeCN and MeOH

Compounds (R)	MeCN		MeOH	
	λ_{fl}/nm	Φ_{fl}	λ_{fl}/nm	Φ_{fl}
1a ($N(CH_3)_2$)	561, 591	0.070	552, 579	0.160
1b (OCH_3)	566, 597	0.038	573	0.052
1c (H)	574, 600	0.029	581	0.032
1d (Cl)	577, 607	0.033	577	0.034
1e (CN)	599, 640 sh	0.057	601, 640 sh	0.045

that in MeOH. This result indicates that the fluorescence emission of **1** is not much affected by the hydrogen-bonding interactions with protic solvent molecules, which cause the solvatochromism of **1** in the ground states (S_0). It is likely that the singlet-excited states (S_1) of **1** have a π-electronic character, which is less zwitterionic as compared with the corresponding S_0 states. Therefore, the hydrogen-bonded S_1 states generated by electronic excitations in MeOH dissociate the hydrogen bonds before fluorescence emission.[11] Then, the $S_1 \rightarrow S_0$ transitions of the molecules without the hydrogen bonds in MeOH gave the fluorescence emission spectra similar to those in MeCN. The Φ_{fl} values, except that of **1a** in MeOH, depend somewhat on the substituent R and the solvent.

2.3. Molecular orbital (MO) considerations of the π-electronic character of imidazopyrazinones 1

The hydrogen bonded structure of **1** with a solvent molecule (D–H) is considered a hybrid of the resonance structures **I** and **II**, as depicted in Scheme 1.[6a] We postulated that the resonance structure **I** contains the free molecule **1** as a chromophore part, while the protonated molecule $\mathbf{1}H^+$ is involved with the resonance structure **II** (Chart 2). Therefore, to evaluate the spectroscopic properties of **1**, we carried out AM1-COSMO semi-empirical MO calculations on **1** and $\mathbf{1}H^+$ using the dielectric constant of DMSO (ε=46.5).[6a,12,13] The selected data are summarized in Tables 3 and 4. All of the free molecules **1** had the negatively charged oxygen atom (O-10, net atomic charge=ca. −0.6) and a large dipole moment (μ), supporting the conclusion that the O-10 of the imidazopyrazinone moieties of **1** effectively make hydrogen bonds with solvent molecules.



Scheme 1.

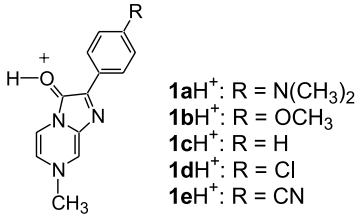


Chart 2.

In the solvatochromism of **1**, the dimethylamino derivative **1a** shows the smallest slope value for the α-ν correlation. As depicted in Figure 4, the HOMO–LUMO energy gap ($\Delta E_{HOMO-LUMO}$) of $\mathbf{1a}H^+$ is the smallest among $\mathbf{1}H^+$ because of a steep rise in the HOMO level. On the other hand, the $\Delta E_{HOMO-LUMO}$ of **1** does not change very much. The resulting difference (0.57 eV) in $\Delta E_{HOMO-LUMO}$ between **1a** and $\mathbf{1a}H^+$ is much smaller than that (0.8–

Table 3. Properties of **1** evaluated with the AM1-COSMO method (ε=46.5)

Compounds (R)	ΔH_f[a]/kJ mol^{-1}	HOMO (eV)	LUMO (eV)	$\Delta E_{HOMO-LUMO}$[b]/eV	Net atomic charge on O-10	μ[c]/D
1a ($N(CH_3)_2$)	291.0	−7.92	−1.19	6.73	−0.59	15.9
1b (OCH_3)	98.6	−7.99	−1.19	6.80	−0.59	18.4
1c (H)	273.3	−8.06	−1.19	6.87	−0.59	17.8
1d (Cl)	242.4	−8.07	−1.24	6.83	−0.58	20.1
1e (CN)	390.7	−8.11	−1.32	6.79	−0.58	23.6

[a] Heat of formation.
[b] HOMO–LUMO energy gap.
[c] Dipole moment.

Table 4. Properties of the protonated species $\mathbf{1}H^+$ evaluated with the AM1-COSMO method (ε=46.5)

Compounds (R)	ΔH_f[a]/kJ mol^{-1}	HOMO (eV)	LUMO (eV)	$\Delta E_{HOMO-LUMO}$[b]/eV
$\mathbf{1a}H^+$ ($N(CH_3)_2$)	725.7	−8.65	−1.35	7.30
$\mathbf{1b}H^+$ (OCH_3)	532.3	−8.98	−1.36	7.62
$\mathbf{1c}H^+$ (H)	708.6	−9.15	−1.36	7.79
$\mathbf{1d}H^+$ (Cl)	678.8	−9.18	−1.38	7.80
$\mathbf{1e}H^+$ (CN)	829.0	−9.21	−1.42	7.79

[a] Heat of formation.
[b] HOMO–LUMO energy gap.

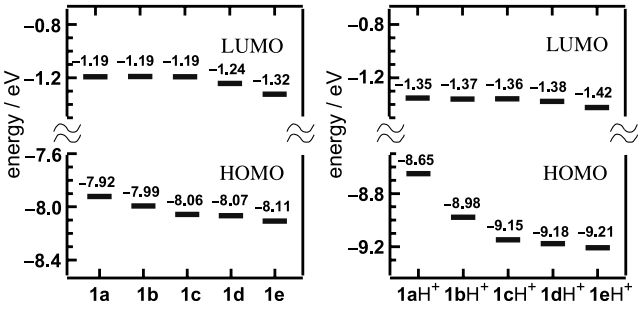


Figure 4. Energy levels of HOMO and LUMO for **1** (left) and protonated species $\mathbf{1}H^+$ (right) calculated by the AM1-COSMO method (ε=46.5 for DMSO).

1.0 eV) of other derivatives, reasonably explaining the observation that **1a** had the smallest slope value for the α-ν correlation.

The significantly small intercept of the cyano derivative **1e** in the α-ν correlation, however, cannot be explained by changes of $\Delta E_{HOMO-LUMO}$ alone. The $\Delta E_{HOMO-LUMO}$ of **1e** (6.79 eV), for instance, is smaller than that of **1c** (6.87 eV) and larger than that of **1a** (6.73 eV). As a remarkable MO characteristic, the LUMO level of **1e** is 0.13 eV lower than that of **1c** (R=H), while the HOMO level of **1e** is 0.05 eV lower than that of **1c**. Thus, the difference in the LUMO levels between **1c** and **1e** is much larger than that in the HOMO levels, resulting in the small intercept of **1e** with an electron-withdrawing cyano group. Further, the small intercept of **1e** may be attributed to the effect of a specific solvation, which is not considered in the AM1-COSMO calculation. It may be possible that **1e** is affected by a strong electrostatic interaction with solvent molecules induced by the large dipole moment (24 D) of **1e**.

2.4. Spectroscopic property of the charge-transfer complexes of imidazopyrazinones 1 with TCNE

The relatively high HOMO levels of **1** calculated with the AM1-COSMO method suggest that derivatives **1** are good enough electron donors to make CT complexes by mixing with an appropriate electron acceptor. Therefore, we investigated next the electron-donating properties and the electronic absorption of the CT complexes of **1** with TCNE, as another spectroscopic property. First, we measured the oxidation potentials of **1** in MeCN with cyclic voltammetry (CV) and square wave voltammetry (SWV), as shown in Figure 5. The half-wave oxidation potentials ($E^{ox}_{1/2}$) of **1** determined with reversible CV data matched the corresponding peak potentials observed with SWV. The $E^{ox}_{1/2}$ values are in the range from +0.43 to +0.74 V versus SCE (Table 5). This result indicates that derivatives **1** serve as electron donors having an electron-donating ability stronger than 1,2,4,5-tetramethoxybenzene ($E^{ox}_{1/2}$ = +0.81 V vs SCE)[14] but weaker than tetrathiafulvalene ($E^{ox}_{1/2}$ = +0.33 V vs SCE).[15] Next, we observed the absorption bands (λ_{ct} in Table 5) of the CT complexes of **1** with TCNE in MeCN, as

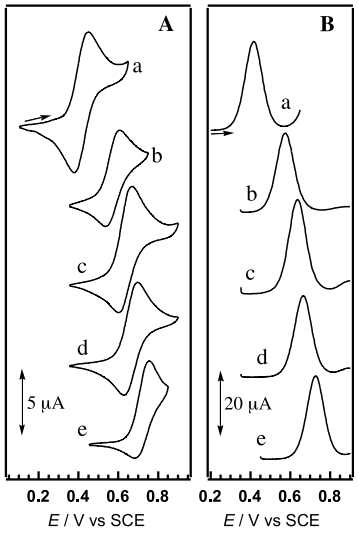


Figure 5. CV (**A**) and SWV (**B**) of **1** (1.0×10^{-3} mol L^{-1}) in MeCN containing 0.1 mol L^{-1} n-Bu_4NClO_4 at 25 °C under Ar: **1a** (a), **1b** (b), **1c** (c), **1d** (d), and **1e** (e).

Table 5. Oxidation potentials ($E^{ox}_{1/2}$) of **1** and absorption maxima (λ_{ct}) of the CT complexes of **1** with TCNE in MeCN

Compound (R)	$E^{ox}_{1/2}$/V versus SCE	λ_{ct}/nm
1a ($N(CH_3)_2$)	+0.43	ca. 1100
1b (OCH_3)	+0.59	889
1c (H)	+0.65	865
1d (Cl)	+0.68	850
1e (CN)	+0.74	821

shown in Figure 6. The colors of the CT complexes varied from near IR to purple. The λ_{ct} value gradually blue-shifted with increase in the electron-withdrawing property of R. The wavenumbers (ν_{ct} in cm^{-1}) of the CT bands for the complexes of **1** and TCNE were well correlated to the $E^{ox}_{1/2}$ values, as shown in Figure 7. Therefore, derivatives **1** are good electron donors, and the electron-donating ability of **1** is effectively regulated by the *para*-substituent R.

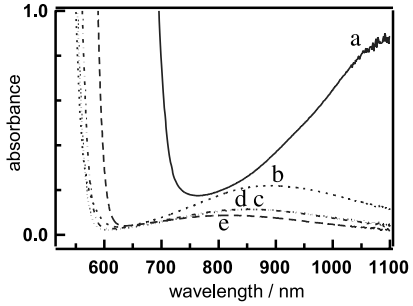


Figure 6. Absorption bands of the CT complexes of **1** (2×10^{-4} mol L^{-1}) with TCNE (0.05 mol L^{-1}) in MeCN at 25 °C: the complexes of **1a** (a), **1b** (b), **1c** (c), **1d** (d), and **1e** (e).

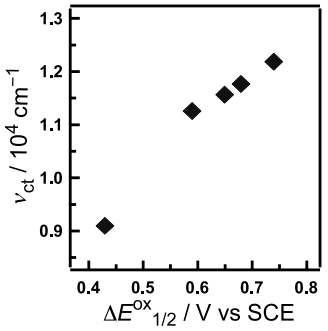


Figure 7. Plot of wavenumbers ν_{ct} of the CT bands for the complexes of **1** and TCNE against the oxidation potentials $E^{ox}_{1/2}$ of **1**.

2.5. Metal–ion complexation of the cyano derivative 1e: a colorimetric sensor of the Lewis acidity of metal ions

The solvatochromism observed in the absorption spectra of **1** indicated that the cyano derivative **1e** is useful as a colorimetric sensor for the proton-donor ability of solvents. To develop the usefulness of **1e** as a colorimetric sensor toward another interaction in solution, we additionally studied the absorption-spectrum changes induced by metal–ion complexation of **1e** as well as those in **1c** (R=H). We previously found that metal–ion complexes of 2-phenylimidazopyrazinone derivatives show a characteristic spectral change depending on the Lewis acidity of the metal ions.[16] Similarly, we observed the UV/visible absorption spectra of the complexes of **1c** and **1e** with various metal ions (Li^+, Ba^{2+}, $Ca.^{2+}$, Mg^{2+}, La^{3+} and Sc^{3+}) in MeCN, as shown in Figure 8. The experimental conditions including the initial concentrations of the metal ions shown in Figure 8 were cited in the reference of the previous report.[16] Under the conditions, the complex becomes the major component in the equilibrium of the metal–ion complexation. The solution color of **1e** changed from pink to pale yellow, while that of **1c** changed from red to pale yellow. The lowest energy bands (λ_m) of the complexes of **1c** and **1e** are summarized in Table 6. To evaluate the change of the λ_m value correlated with the metal ions, the transition energies [ΔE_m (eV)] converted from the λ_m values were correlated with the Fukuzumi parameters [ΔE (eV)] for the Lewis acidity of the metal ions (Fig. 9).[17] The plots show that the ΔE_m values for the complexes of **1c** and **1e** correlate linearly with the ΔE parameters and the ΔE–ΔE_m correlations for the complexes of **1c** and **1e** are $\Delta E_m = 0.57\Delta E + 2.33$ ($r=0.97$) and $\Delta E_m = 0.67\Delta E + 2.18$ ($r=0.96$), respectively. In the metal–ion complexes, derivatives **1** make a coordinate bond with a metal ion (M^{n+}) at the negatively charged oxygen atom, O-10 (Scheme 2), resulting in a change of the π-electronic character of the imidazopyrazinone moiety.[16,18] As the Lewis acidity of the metal ion increases, the Lewis acid/base interaction in the complexes is enhanced, resulting in a blue-shift of the λ_m values. The ΔE–ΔE_m correlation of **1e** has a large slope and a small intercept compared to those of **1c**, indicating that **1e** has a wide color-variation range and a high sensitivity toward the Lewis acidity. Therefore, **1e** is an excellent colorimetric sensor for the Lewis acidity of the metal ions. The difference in the ΔE–ΔE_m correlations between **1e** and **1c** is similar to that in the α-ν correlations for the solvatochromism, indicating that the π-electronic character of the imidazopyrazinone moiety in the metal–ion complex is regulated similarly to the hydrogen-bonding interactions with protic solvent molecules.

3. Conclusion

In conclusion, it was confirmed that a *para*-substitution of R on the phenyl group of **1c** produced successive modulations of the spectroscopic properties, the UV/visible absorption and fluorescence of **1**, and the electronic absorption of CT complexes of **1** with TCNE and metal–ion complexes of **1**. The *para*-substituent R on the phenyl group efficiently modulated the various spectroscopic properties of 2-phenylimidazopyrazinone **1**. In UV/visible absorption spectra, **1** showed the solvatochromic property originating from the hydrogen-bonding interactions, which was effectively regulated by the substituent effect of R. In particular, the cyano derivative **1e** showed a wide color variation range and a high sensitivity toward the proton-donor ability of solvents. The fluorescence of **1** showed a redshift with increase in the electron-withdrawing property of R in a manner similar to the UV/visible absorption, while fluorescence showed only a small dependency on solvent. The substituent effect on solvatochromism was substantiated by the results of the AM1-COSMO calculations, which also suggest that derivatives **1** are good electron donors and that the electron-donating ability of **1** is effectively regulated by R. This was confirmed by the observation of low oxidation potentials and the formation of CT complexes of TCNE. Absorption-spectrum changes of **1c**

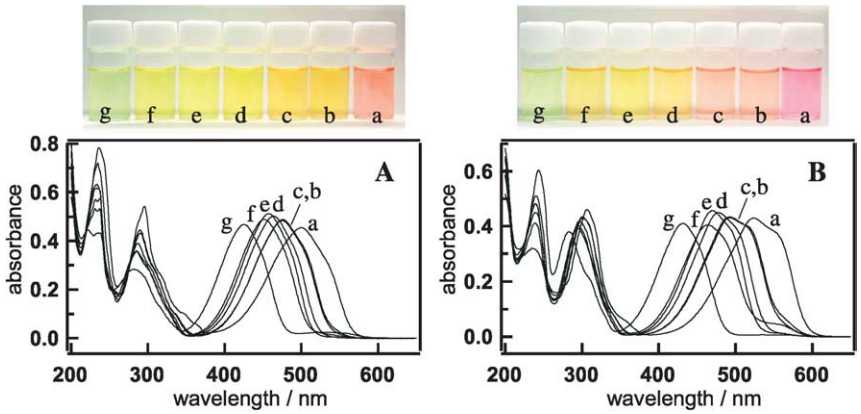


Figure 8. Graduated changes of colors and UV/visible absorption spectra of **1c** (**A**, 2.5×10^{-5} mol L^{-1}) and **1e** (**B**, 2.5×10^{-5} mol L^{-1}) in MeCN containing various metal ions at 25 °C; free (a), Li^{+} (b), Ba^{2+} (c), Ca^{2+} (d), Mg^{2+} (e), La^{3+} (f), and Sc^{3+} (g) ($[Li^{+}]=5.0\times10^{-2}$ mol L^{-1}, $[Ba^{2+}]=2.0\times10^{-2}$ mol L^{-1}, $[Ca^{2+}]=[Mg^{2+}]=1.0\times10^{-2}$ mol L^{-1}, $[La^{3+}]=[Sc^{3+}]=1.0\times10^{-4}$ mol L^{-1}).

Table 6. Wavelengths (λ_m) of the lowest energy bands of the metal–ion complexes of **1c** and **1e** in MeCN at 25 °C

Compound (R)	λ_m/nm						
	Free	Li^{+} (0.53)[a]	Ba^{2+} (0.49)[a]	Ca^{2+} (0.58)[a]	Mg^{2+} (0.65)[a]	La^{3+} (0.82)[a]	Sc^{3+} (1.00)[a]
1c (H)	501	475	474	464	457	451	425
1e (CN)	523	493	493	477	470	464	431

[a] The Fukuzumi parameters [ΔE (eV)] for the Lewis acidity. See Ref. 17.

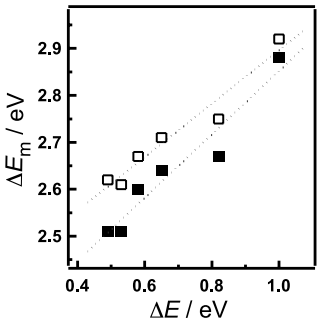
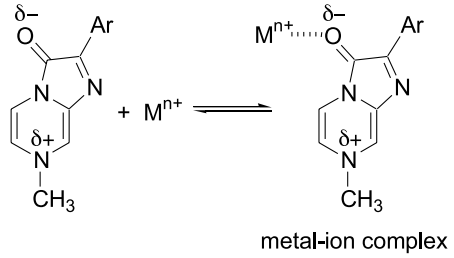


Figure 9. Plots of the energies ΔE_m of the metal–ion complexes of **1c** (□) and **1e** (■) against the Fukuzumi parameters ΔE for the Lewis acidity.



Scheme 2.

and **1e** induced by metal–ion complexation were also compared, showing that the cyano derivative **1e** is a good colorimetric sensor for the Lewis acidity of the metal ions.

4. Experimental

4.1. General

Melting points were obtained with a Yamato MP-21 apparatus, and were uncorrected. IR spectra were measured with a Horiba FT-720 spectrometer. Electron ionization mass spectra were recorded with a JEOL JMS-600 mass spectrometer. Elemental analysis was performed by the Research Centre for Giant Molecules, Graduate School of Science, Tohoku University. ^{1}H NMR spectra were recorded on a JEOL GX-270 instrument (270 MHz). UV/visible absorption spectra were measured with a Varian Cary 50 spectrophotometer. Fluorescence spectra were measured with a JASCO FP-6500 fluorescence spectrophotometer (excitation and emission bandpasses, 3 nm; scan speed, 200 nm/min) and were corrected according to manufacturer's instructions. Fluorescence quantum yields were determined relative to quinine sulfate in 0.10 mol L^{-1} H_2SO_4 ($\Phi_F=0.55$, λ_{ex} 366 nm) as the standard. Spectroscopic measurements were made in a quartz cuvette (1 cm path-length) at 25 ± 1 °C. Spectral grade solvents were used for measurements of UV/visible absorption and fluorescence spectra. CV and SWV measurements were performed on a Cypress Systems CS-1200 computer control potentiostat. A three-electrode arrangement was used for the measurements: an Ag/AgCl electrode as the reference electrode and Pt wires as the auxiliary and working electrodes. The scan rate for CV was set at 100 mV s^{-1}. For SWV measurements, the square wave height, step height, and square wave period were set at 50 mV, 2 mV, and 20 ms, respectively. The sample solutions (ca. 1.0×10^{-3} mol L^{-1}) were prepared in MeCN containing tetrabutylammonium perchlorate (0.1 mol L^{-1}) as a supporting electrolyte, and were bubbled with Ar before each measurement. All potentials are referenced to the potential of the ferrocene/ferricinium couple ($E_{ox}^{\circ}=+0.45$ V vs SCE).[19] Semi-empirical MO calculations were carried out with the AM1 Hamiltonian[12] and the COSMO method[13] in the MOPAC package.[20]

4.2. Synthesis of imidazopyrazinone derivatives

4.2.1. 2-(4-Dimethylaminophenyl)-7-methylimidazo[1,2-*a*]pyrazin-3(7*H*)-one (1a). A mixture of 2-(4-dimethylaminophenyl)imidazo[1,2-*a*]pyrazin-3(7*H*)-one (108 mg, 0.43 mmol), methyl iodide (1.1 g, 8.3 mmol), and K_2CO_3 (174 mg, 1.26 mmol) in EtOH (10 mL) was stirred at room temperature under Ar for 20 h. Insoluble salts were filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH=10:1) and silica gel TLC ($CHCl_3$/MeOH=10:1), to give **1a** as red cubes (28 mg, 24% yield). **1a**: mp 220 °C (dec); ^{1}H NMR (CD_3OD) δ 8.32 (2H, m), 7.69 (1H, d, J=1.3 Hz), 7.48 (1H, d, J=5.9 Hz), 6.88 (1H, dd, J=5.9, 1.3 Hz), 6.82 (2H, m), 3.71 (3H, s), 3.04 (6H, s); IR (KBr) 1675, 1604, 1533 cm^{-1}; EIMS *m*/*z* 268 (M^+, 100), 94 (98). Anal. Calcd for $C_{15}H_{16}N_4O\cdot\frac{1}{4}H_2O$: C, 66.04; H, 6.10; N, 20.54. Found: C, 65.95; H, 6.17; N, 20.72.

4.2.2. 2-(4-Methoxyphenyl)-7-methylimidazo[1,2-*a*]pyrazin-3(7*H*)-one (1b). The synthesis of **1b** followed that of **1a**. **1b**: red powder, mp 205 °C (dec); ^{1}H NMR (CD_3OD) δ 8.39 (2H, m), 7.85 (1H, d, J=1.3 Hz), 7.54 (1H, d, J=5.6 Hz), 7.01 (2H, m), 6.93 (1H, dd, J=5.6, 1.3 Hz), 3.86 (s, 3H), 3.74 (s, 3H); IR (KBr) 1670, 1587, 1515 cm^{-1}; EIMS *m*/*z* 255 (M^+, 100), 94 (70). Anal. Calcd for $C_{14}H_{13}N_3O_2\cdot\frac{1}{4}H_2O$: C, 64.73; H, 5.24; N, 16.18. Found: C, 65.00; H, 5.38; N, 15.83.

4.2.3. 7-Methyl-2-phenylimidazo[1,2-*a*]pyrazin-3(7*H*)-one (1c). Compound **1c** was prepared according to the literature.[6a]

4.2.4. 2-(4-Chlorophenyl)-7-methylimidazo[1,2-*a*]pyrazin-3(7*H*)-one (1d). The synthesis of **1d** followed that of **1a**. **1d**: red powder, mp >250 °C; ^{1}H NMR (CD_3OD) δ 8.43 (2H, m), 8.05 (1H, d, J=1.3 Hz), 7.64 (1H, d, J=5.9 Hz), 7.45 (2H, m), 6.99 (1H, dd, J=5.9, 1.3 Hz), 3.80 (3H, s); IR (KBr) 1668, 1592, 1494 cm^{-1}; EIMS *m*/*z* 259 (M^+, 62), 94 (100). Anal. Calcd for $C_{13}H_{10}ClN_3O$: C, 60.12; H, 3.88; N, 16.18; O. Found: C, 59.77; H, 4.14; N, 16.10.

4.2.5. 2-(4-Cyanophenyl)-7-methylimidazo[1,2-*a*]pyrazin-3(7*H*)-one (1e). The synthesis of **1e** followed that of **1a**. **1e**: gold powder, mp >250 °C; ^{1}H NMR (CD_3OD) δ 8.61 (2H, m), 8.20 (1H, d, J=1.3 Hz), 7.79 (2H, m), 7.72 (1H, d, J=5.9 Hz), 7.03 (1H, dd, J=5.9, 1.3 Hz), 3.84 (3H, s); IR (KBr) 2223, 1666, 1594, 1506 cm^{-1}; EIMS *m*/*z* 250 (M^+, 81), 94 (100). Anal. Calcd for $C_{14}H_{10}N_4O$: C, 67.19; H, 4.03; N, 22.39. Found: C, 67.00; H, 4.35; N, 22.29.

4.3. Measurements of the electronic absorption of the CT complexes of 1 with TCNE

TCNE was purified by sublimation under vacuum. Stock solutions (1 mL) of **1** (4.0×10^{-4} mol L^{-1}) and TCNE (0.10 mol L^{-1}) in MeCN were mixed at 25 °C. UV/visible absorption spectra of solutions were measured immediately after mixing.

4.4. Measurements of the electronic absorption of the metal–ion complexes of 1c and 1e

For the metal–ion complexation, perchlorate salts of Li^+, Ba^{2+}, Ca^{2+} and Mg^{2+}, and trifluoromethanesulfonate salts of La^{3+} and Sc^{3+} were used. These were dried at 180 °C under vacuum and were used to prepare stock solutions in MeCN ($[Li^+]=0.10$ mol L^{-1}, $[Ba^{2+}]=4.0\times10^{-2}$ mol L^{-1}, $[Ca.^{2+}]=[Mg^{2+}]=2.0\times10^{-2}$ mol L^{-1}, $[La^{3+}]=[Sc^{3+}]=2.0\times10^{-4}$ mol L^{-1}). Two millilitres of each stock solution of the salt was added to a solution of **1c** or **1e** (5.0×10^{-5} mol L^{-1}) in 2 mL of MeCN at 25 °C. UV/visible absorption spectrum of the mixed solution was measured immediately after mixing.

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Synthesis of SMP-797: a new potent ACAT inhibitor

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Abstract—A potent ACAT (acyl-CoA: cholesterol acyltransferase) inhibitor SMP-797 was effectively synthesized by the urea formation of 3-amino-4-aryl-1,8-naphthyridin-2(1*H*)-one and 4-amino-2,6-diisopropylamine. The synthesis of the former compound involved the Suzuki coupling reaction as a key step, and the latter was prepared by the 4-selective nitration of 2,6-diisopropylaniline using 2,3,5,6-tetrabromo-4-methyl-4-nitro-2,5-cyclohexadienone.

1. Introduction

An enzyme acyl-CoA: cholesterol acyltransferase (ACAT), which catalyzes the intracellular cholesterol esterification,[1] plays important roles in several physiological processes: (1) absorption of dietary and biliary cholesterol in the intestines;[2] (2) determination of cholesteryl ester content and the secretion of hepatic very low density lipoprotein (VLDL);[3] (3) accumulation of cholesteryl esters in macrophage in the arterial wall.[4] Inhibition of ACAT, therefore, is expected to reduce plasma lipid levels by inhibiting intestinal cholesterol absorption and hepatic VLDL secretion, and to prevent progression of atherosclerotic lesions by inhibiting the accumulation of cholesteryl esters in macrophage. For this reason, ACAT inhibitor is an attractive target for the treatment of hypercholesterolemia and atherosclerosis.[5]

It was previously found in our group that urea derivatives derived from 3-amimo-4-aryl-1,8-naphthyridin-2(1*H*)-one and anilines, in paticular, SM-32504 exhibited potent ACAT inhibitory activity.[6] However, this compound was poorly absorpted by oral absorption due to its low aqueous solubility. Extensive studies then lead to the development of SMP-797, which possesses 4-amino group on the aniline and 3-hydroxypropoxy group on the 4-phenyl group of the naphthyridinone moiety (Fig. 1).[7] SMP-797 decreased the serum total cholesterol level by 53% compared with control at the dosage of 1.0 mg/kg/day orally for 3 weeks in a rabbit model fed a casein-rich diet. This effect can be compared with atrovastatin, which decreased 54% by a dose of 10 mg/kg/day orally for 6 weeks.[8]

SMP-797 was synthesized by the urea coupling reaction of 3-amino-4-phenylnaphthyridine **4** and 4-amino-2,6-diisopropylaniline **8**.[7] Initial preparation of **4** and **8**, however, employed relatively long synthetic methods. The compound **4** was obtained according to the synthesis of SM-32504,[6] which involved benzoylation of 2′-aminopyridine **1** via directed ortho-metalation and the Friedländer reaction of 2-amino-3-(3-methoxybenzoyl)pyridine **3**. The synthesis required 10 steps from commercially available **1**. Use of expensive BuLi reagent in the synthesis of **2** and one carbon removal from **3** using the Crutius reaction were other drawbacks.

The other unit **8** of SMP-797 was obtained by nitration of protected 2,6-diisopropylaniline **5** followed by functional manipulation, which resulted in a five-step synthesis from commercially available **5**.[7,9] In addition, **8** was gradually oxidized in air, and was not easy to handle. An improved synthesis of **4** and **8**, therefore, was required for the effective preparation of SM-797 (Scheme 1).

In the improved synthesis of the naphthyridine unit, hydroxy protecting group was changed from acetate to benzyl, because we first examined naphthyridine construction in the synthesis of **16**. The Skraup reaction and the Friedländer

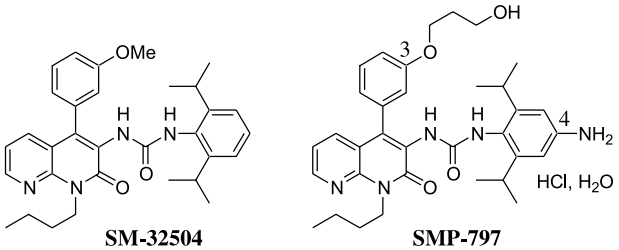

Figure 1.

Keywords: Cyclization; Friedländer reaction; Suzuki coupling; 4-Selective nitration; SMP-797.
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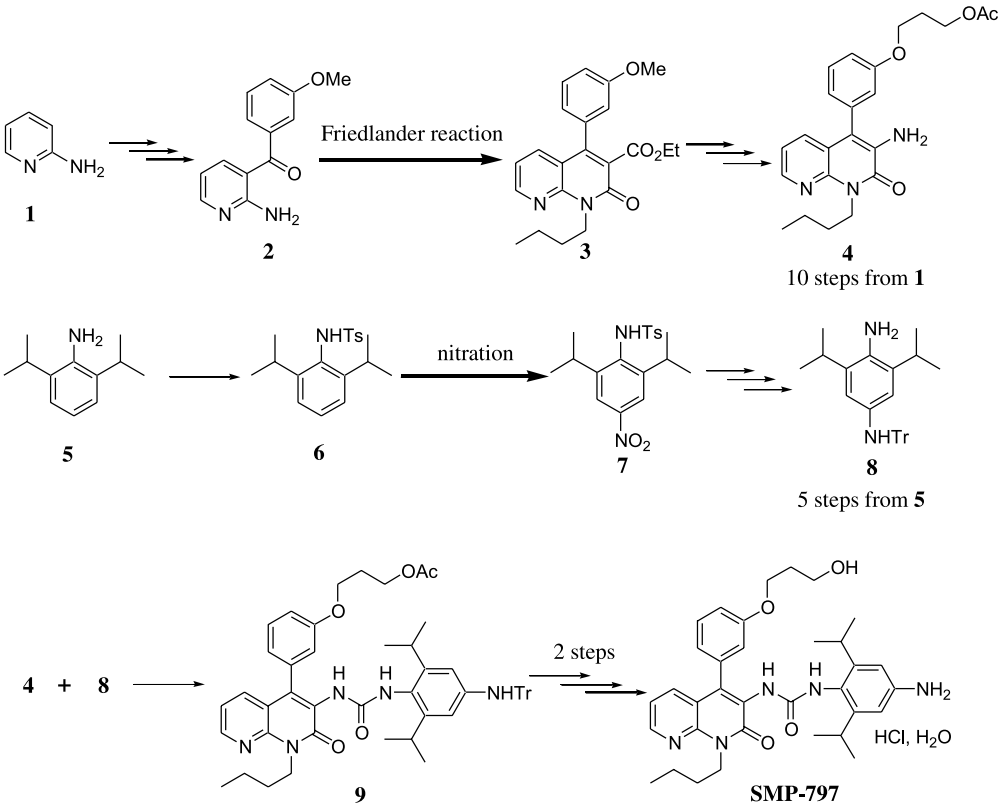
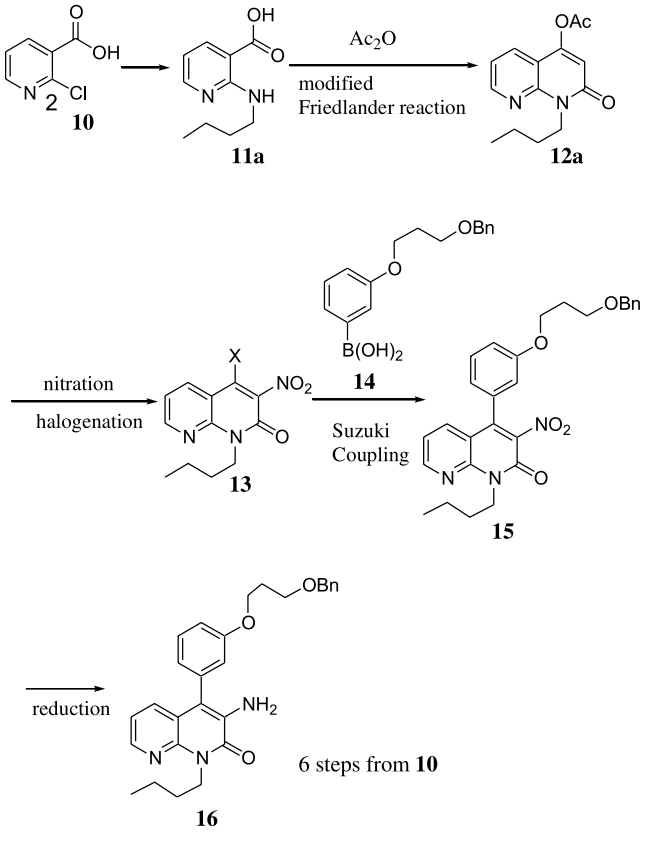


Scheme 1.

reaction are classical methods to prepare 1,8-naphthyridin-2(1*H*)-ones.[10] The former is the condensation reaction of 2-aminopyridine with a three-carbon unit such as β-ketoester. The latter is the condensation of a 2-amino-3-carbonylpyridine with a two-carbon unit typically enolizable carbonyl compounds. Preparation of 4-arylated 1,8-naphtyhyridin-2(1*H*)-ones by these methods, however, has been rare: condensation reaction of 6-amino-4-phenylpyridin-2(1*H*)-ones and β-ketoesters[11,12] (Skraup reaction); condensation of 2-amino-3-benzoylpyridine and activated methylenes[11,13] (Friedländer reaction); cyclization of 2-[(2,2-dimethyl-1-oxopropyl)amino]-β-hydroxy-β-phenyl-3 pyridinepropanoic acids.[14] We, therefore, explored a new method for the synthesis of 4-aryl-1,8-naphthyridin-2(1*H*)-ones:[15] It was planned that aryl group was introduced by the Suzuki coupling reaction. Only two precedents of the Suzuki coupling were reported for naphthyridines.[16,17] In spite of few precedents, the organometallic method appeared to be effective for a preparation of naphthyridine derivatives. As a result of the present study, a synthesis involving shorter than the original method, and overcoming the drawbacks noted above was developed: (1) condensation of 2-chloro-3-carboxypyridine **10** with primary amine giving 2-amino-3-carboxypyridine; (2) construction of 1,8-naphthyridin-2(1*H*)-one nuclei by the modified Friedländer reaction using acetic anhydride. Such cyclization of 2-aminobenzoic acid with acetic anhydride has been used only to synthesize quinolines;[18] (3) nitration at the 3-position; (4) the Suzuki coupling[19] of 4-halo-1,8-naphthyridin-2(1*H*)-ones **13** (Scheme 2).



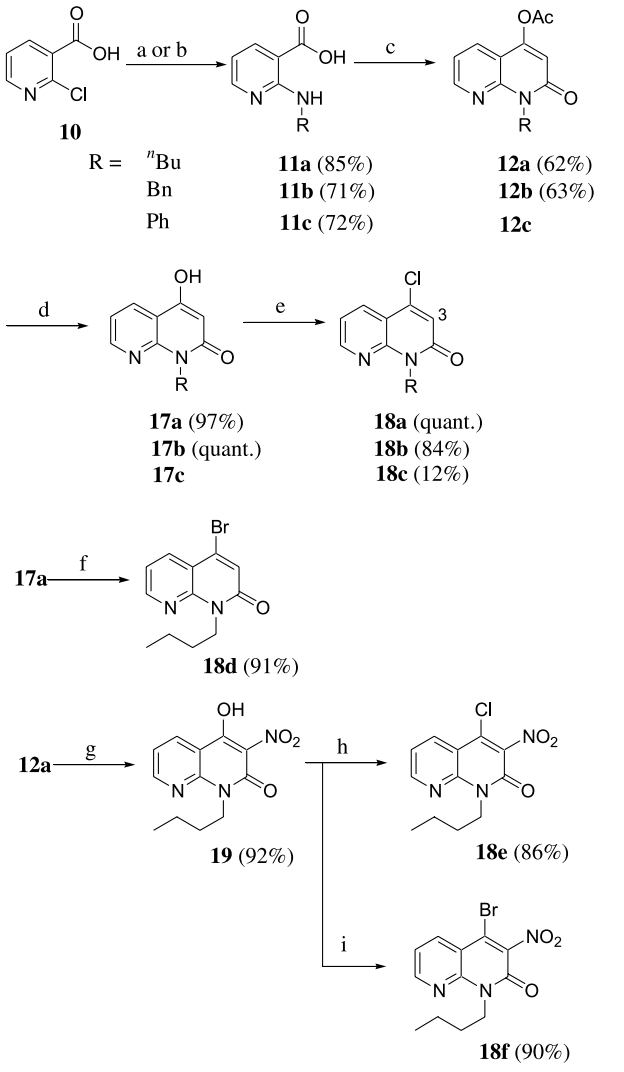
Scheme 2.

2. Results and discussion

Heating neat 2-chloronicotinic acid **10** and butylamine under reflux for 2 days or benzylamine at 90 °C for 10 h gave 2-aminonicotinic acids **11a** and **11b**, respectively.[20,21] The reaction of **11a** or **11b** with acetic anhydride in boiling acetic acid for 2 h gave the cyclized products 4-acetoxy-1,8-naphthyridines **12a** and **12b** in good yields. Thus, the 1,8-naphthyridine structure could be constructed in two-steps from commercially available **10** using inexpensive reagents. It may be likely that the intramoleculer C–C bond formation takes place via the Claisen condensation of acetamide and mixed anhydride formed from pyridinecarboxylate and acetic anhydride.

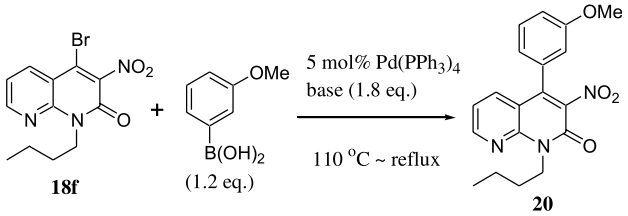
The compounds **17a** and **17b** obtained by deacetylation of **12a** and **12b**, respectively, were converted to 4-chloro-naphthyridines **18a** and **18b** by reacting with $POCl_3$. Treatment of **17a** with $POBr_3$ gave a bromide **18d**. *N*-Phenyl derivative **11c** obtained according to the literature[22] was converted analogously to **18c** without isolating the intermediates **12c** and **17c**. Although the yield of **18c** was low due to the formation of various by-products in the cyclizaion step, the method provided a sufficient amount of **18c** for our study. It should be noted that these syntheses provide 1-alkyl- or 1-aryl-3-halo-naphthyridin-2(1*H*)-ones lacking the 3-substituent, which have not appeared in literature. 4-Halo-3-nitronaphthyridine **18e**[23] and **18f** were obtained from **12a** by nitration and halogenation (Scheme 3).

Organometallic 4-arylation was examined using 4-halo-1,8-naphthyridin-2-ones. 4-Bromo-3-nitro-1,8-naphthyridine **18f** was initially reacted with zinc or Grignard reagent prepared from 3-bromoanisole in the presence of metal catalysts such as CuI, $Pd(PPh_3)_4$, $PdCl_2$(dppf), $Ni(PPh_3)_4$, $NiCl_2(PPh_3)_2$, $NiCl_2$(dppp).[24] Immediate decomposition of **18f**, however, took place, and no desired coupling product **20** was obtained. We, therefore, focused our attention to the palladium catalyzed Suzuki coupling of **18f** and 3-methoxyphenylboronic acid (Table 1).



Scheme 3. Reagents and conditions: (a) butylamine, reflux, 2 days; (b) benzylamine, 90 °C, 10 h; (c) Ac_2O, AcOH, reflux, 2 h; (d) K_2CO_3, H_2O–MeOH, rt, 3 h; (e) $POCl_3$, 90 °C, 0.5–2 h; (f) $POBr_3$, 100 °C, 30 min; (g) concd HNO_3, concd H_2SO_4, rt, overnight; (h) $POCl_3$, 90 °C, 45 min; (i) $POBr_3$, 100 °C, 30 min.

Table 1. The Suzuki coupling reaction of 4-halo-3-nitronaphthyridines **18f** with 3-methoxyphenylboronic acid

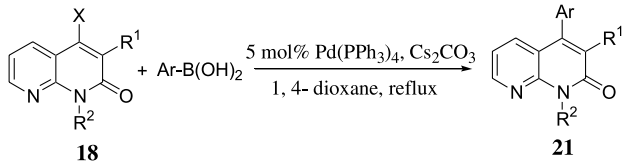


Entry	Solvent	Base	Time (h)	Yield (%)	Recovered SM (%)
1	DME–H_2O	Na_2CO_3	4	52	—
2	DME	Na_2CO_3	4	5	77
3	1,4-Dioxane	Na_2CO_3	4	11	63
4	1,4-Dioxane	K_2CO_3	4	42	33
5	1,4-Dioxane	Cs_2CO_3	4	87	—
6	1,4-Dioxane	$^iPr_2NEt$	4	0	—
7	Toluene	Cs_2CO_3	8	83	5
8	DME	Cs_2CO_3	8	62	27
9	DME	Cs_2CO_3	4	12	—

In the presence of 5 mol% $Pd(PPh_3)_4$, **18f** and 3-methoxyphenylboronic acid were reacted in the presence of Na_2CO_3 in DME/H_2O 4:1 at reflux for 4 h, and **20** was obtained in 52% yield (entry 1). The moderate yield of **20** was due to hydrolysis of 4-bromonaphthyridine **18f** to 4-hydroxynaphthyridine **19**. Anhydrous conditions in DME or 1,4-dioxane prevented the hydrolysis, although yield lowered (entries 2 and 3). Then, several bases were examined, and Cs_2CO_3 turned out to give satisfactory results (entries 3–6). As for solvent, 1,4-dioxane and toluene gave better results than DME and DMF. Considerable decomposition of **18f** took place in DMF (entries 7–9).

Based on the studies, the Suzuki coupling reaction of **18** with several arylboronic acids (1.2 equiv) was conducted under 1,4-dioxane reflux using 5 mol% $Pd(PPh_3)_4$ in the presence of cesium carbonate (1.8 equiv), and 4-aryl-1,8-naphthyridin-2(1*H*)-ones were obtained in high yields. The coupling reaction proceeded equally well using chloride **18e** or bromide **18f** (entry 5). As indicated by the reactions of **18a**, **18b**, and **18c**, 1-substituent did not affect the yield (entries 1–3). Fortunately 3-nitro group of **18e**, which is essential for the synthesis of SM-32504, did not interfere with the reaction (entries 5, 7, 9, 11, 13, 15, 17, 19, and 21) (Table 2). A variety of arylboronic acids possessing either electron-donating or electron-withdrawing substituent underwent the Suzuki coupling, although the reaction of 3-acetyl and 3-cyanophenylboronic acid required slightly prolonged reaction time (entries 18–21). The Suzuki coupling method facilitated the synthesis of various 4-aryl-1,8-naphthyridin-2(1*H*)-one derivatives.[15]

Table 2. The Suzuki coupling reaction of 4-halonaphthyridines **18** with substituted aryl boronic acid

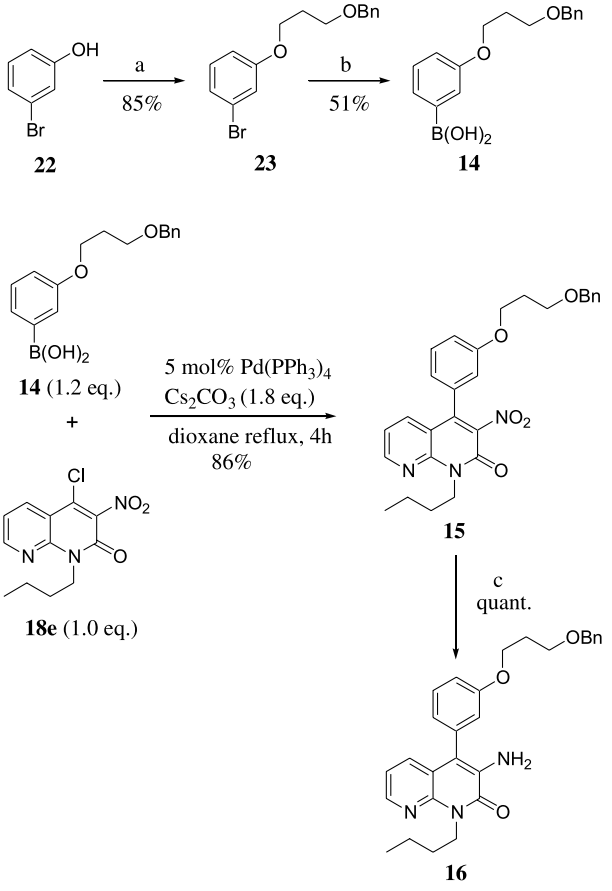


18 **21**

Entry	Ar	18	Time (h)	Yield (%)
1		**18a**	4	90
2		**18b**	4	91
3		**18c**	4	88
4		**18d**	3	95
5		**18e**	5	82
6	OMe	**18a**	4	91
7	OMe	**18e**	5	80
8	OMe	**18a**	4	86
9	OMe	**18e**	5	83
10	OMe	**18a**	4	80
11	OMe	**18e**	5	79
12	CF_3	**18a**	4	92
13	CF_3	**18e**	5	79
14	CF_3	**18a**	4	98
15	CF_3	**18e**	5	82
16	F	**18a**	4	86
17	F	**18e**	5	73
18	O	**18a**	5	85
19	O	**18e**	7	82
20	CN	**18a**	10	83
21	CN	**18e**	12	75

Then, this new synthetic method was applied to the preparation of **16**, an intermediate for SMP-797. Boronic acid **14** was obtained from *m*-bromophenol **22** by O-alkylation and organometallic boronic acid formation. The key Suzuki coupling of 4-chloro-3-nitronaphthyridine **18e** with **14** proceeded smoothly in 86% yield giving **15**. Reduction of the nitro group of **15** with zinc dust in AcOH and MeOH provided 1-alkyl-3-amino-4-aryl-1,8-naphthyridin-2(1*H*)-one **16** (Scheme 4). Thus, the improved synthesis provided **16** in six-steps from commercially available **10**.

The next study was directed to the preparation of the aniline part **26** of SMP-797. Previous synthesis of **26** involved

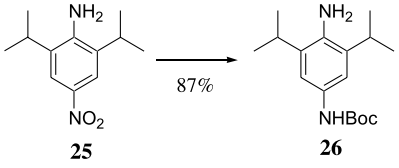


Scheme 4. Reagents and conditions: (a) benzyl 3-bromopropyl ether (1.1 equiv), K_2CO_3 (3.0 equiv), DMF, 60 °C, 3 h; (b) Mg (1.1 equiv), cat I_2, $B(OMe)_3$ (1.0 equiv), THF, rt, overnight; (c) Zn (10 equiv), AcOH (2.5 equiv), MeOH, reflux, 1.5 h.

N-protection of 2,6-diisopropylaniline **5**.[7,9] In the present study, direct 4-selective nitration of 2,6-diisopropylaniline **5** was examined, although such reaction was not known in literature. Nitration of aniline under strong acid conditions is known to take place at the 3-position because of the protonation of the amino group.[25] In accordance, 2,6-diisopropyl-3-nitroaniline was obtained as the only product by the nitration of 2,6-diisopropylaniline **5** with concd HNO_3 in concd H_2SO_4.[7] In order to direct the reaction at the 4-position, it was considered that bulky and neutral nitrating reagent would be suitable, and reactions of *N*-nitropyridinium salts[26] and nitrocyclohexadienones[27] were examined.

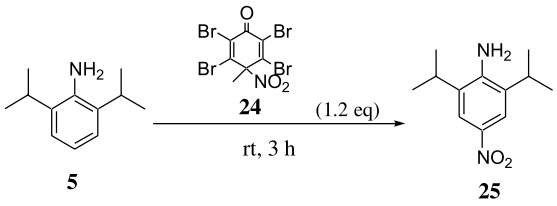
When 2,6-diisoproylaniline **5** was treated with **24** in acetic acid at rt, a very small amount of 4-nitro-2,6-diisopropylaniline **25**, starting material **5**, and unknown by products were obtained. Use of strong acid trifluoroacetic acid as solvent resulted in the complex mixture. The low yield was considered to be due to nitration of amino group activated by dialkyl group. In order to decrease the reactivity of **24**, use of less acidic alcohol solvents were examined, which considerably improved the yield of **25**.[27] The reaction in ethanol gave higher yield of 68% than in methanol and 2-propanol (Table 3). The nitration using 2,4,6-trimethyl-1-nitropyridinium tetrafluoroborate or 2,6-dimethyl-1-nitropyridinium tetrafluoroborate did not proceed under various conditions.

Pd/C-catalyzed hydrogenation of **25** in MeOH followed by treatment with $(Boc)_2O$ in situ gave stable key intermediate **26** in a high yield. These procedures avoided isolation of unstable 4-amino-2,6-diisopropylaniline (Scheme 5). Thus, monoprotected phenylenediamine **26** was obtained from **5** in two-steps.



Scheme 5. Reagents and conditions: H_2, cat Pd/C, MeOH, rt, 5 h and then $(Boc)_2O$ (1.1 equiv), 2 h.

Table 3. The nitration of **5** by using nitrating reagent **24**

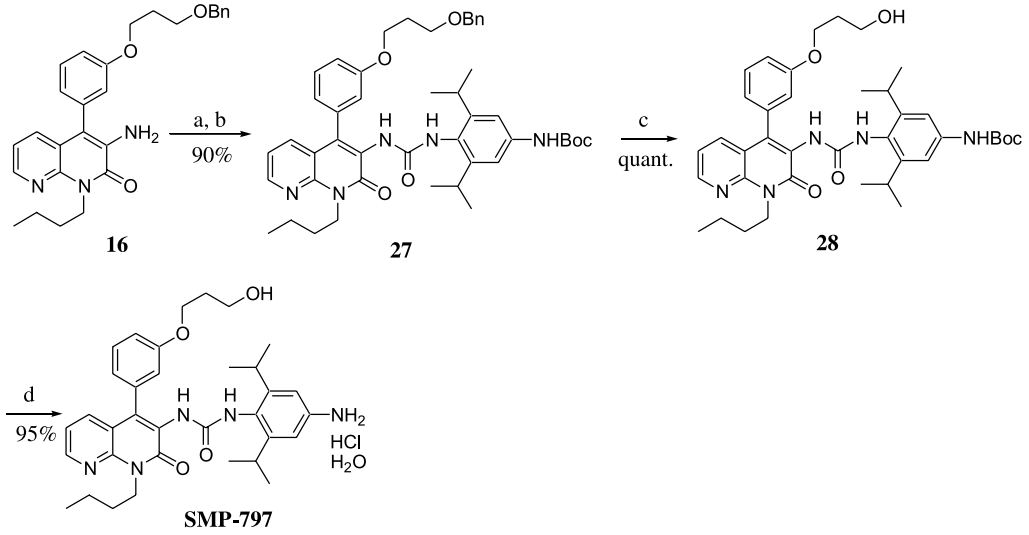


Entry	Solvent	Yield (%)
1	AcOH	Trace
2	CF_3CO_2H	Dec
3	MeOH	50
4	EtOH	68
5	^{i}PrOH	43

The final urea formation from **16** and **26** was conducted as follows. Urea **27** was prepared from **16** in a high yield via the phenyl carbamate formation followed by teratment with **26** in the presence of DMAP in DMF. Then, **27** was transformed into SMP-797 by hydrogenolysis of the benzyl group, and the removal of the Boc group with 10% methanolic HCl (Scheme 6).

3. Conclusion

In summary, we developed an efficient method to synthesize potent ACAT inhibitor SMP-797 using novel syntheses of 4-aryl-3-animo-1,8-naphthyridin-2(1*H*)-one via modified Friedländer reaction and the Suzuki coupling reaction. An efficient preparative method of 2,6-diisopropyl-4-amino-aniline via direct nitration of 2,6-diisopropylamine was also developed.



Scheme 6. Reagents and conditions: (a) phenyl chloroformate (2.0 equiv), THF, rt, overnight; (b) **26** (1.2 equiv), DMAP (3.0 equiv), DMF, rt, overnight; (c) H_2, cat Pd/C, MeOH, rt, 5 h; (d) 10% HCl/MeOH, rt, overnight.

4. Experimental

4.1. General

Melting points were determined on a Thomas-Hoover melting point apparatus without correction. ^{1}H NMR spectra were recorded on a JEOL JNM-LA300 spectrometer in the stated solvents using tetramethylsilane as an internal standard. IR spectra were obtained on a JEOL JIR-SPX60 or a Perkin-Elmer 1600 FT-IR spectrometer. Elemental analyses and high resolution mass spectra were conducted at Sumitomo Analytical Center Inc. Thin layer chromatography and flash column chromatography were performed on silica gel glass-backed plates (5719, Merck&Co.) and silica gel 60 (230–400 or 70–230 mesh, Merck&Co.), respectively. Unless otherwise noted, all the materials were obtained from commercial suppliers, and were used without further purification. All solvents were commercially available grade. All reactions were carried out under nitrogen atmosphere unless otherwise mentioned.

4.1.1. 2-(Butylamino)nicotinic acid (11a). A mixture of 2-chloronicotinic acid **10** (10.0 g, 63.5 mmol) and butylamine (20 mL) was heated at reflux for 2 days. The reaction mixture was concentrated in vacuo, and the residue was diluted with Et_2O. The organic materials were extracted twice with 1 M NaOH, and the combined aqueous layers were acidified to pH 3 by adding concd HCl. The resulting crystals were collected by filtration, washed with AcOEt, and dried in vacuo to give **11a** (10.5 g, 85%) as colorless crystals.

Mp 160–161 °C, lit.[20] mp 157 °C (benzene); ^{1}H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.91 (3H, t, J=7.3 Hz), 1.35 (2H, qt, J=7.3, 7.3 Hz), 1.55 (2H, tt, J=7.3, 7.3 Hz), 3.44 (2H, t, J=7.3 Hz), 6.57 (1H, dd, J=4.8, 7.7 Hz), 8.05 (1H, dd, J=2.0, 7.7 Hz), 8.11 (1H, br), 8.24 (1H, dd, J=2.0, 4.8 Hz), 13.0 (1H, br).

4.1.2. 2-(Benzylamino)nicotinic acid (11b). A mixture of 2-chloronicotinic acid **10** (5.00 g, 31.7 mmol) and benzylamine (17 mL) was stirred at 90 °C for 10 h. NaOH (2 M) and Et_2O were added, and the aqueous layer was separated. The organic layer was extracted twice with 2 M NaOH. The combined aqueous layers were acidified by concd HCl to pH 3. The resulting crystals were collected by filtration, washed with AcOEt, and dried in vacuo to give **11b** (5.14 g, 71%) as colorless crystals.

Mp 230–231 °C, lit.[21] mp 238–240 °C (EtOH); ^{1}H NMR (DMSO-d_6, 300 MHz), δ (ppm) 4.68 (2H, d, J=4.8 Hz), 6.61 (1H, dd, J=4.7, 7.7 Hz), 7.19–7.31 (5H, m), 8.08 (1H, dd, J=1.8, 7.7 Hz), 8.23 (1H, dd, J=1.8, 4.7 Hz), 8.47 (1H, br), 13.1 (1H, br).

4.1.3. 1-Butyl-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl acetate (12a). 2-(Butylamino)nicotinic acid **11a** (2.80 g, 14.4 mmol) was suspended in a mixture of acetic anhydride (35 mL) and acetic acid (18 mL), and the mixture was stirred under reflux for 2 h. After cooled, volatile materials were evaporated in vacuo, and the residue was purified by silica gel chromatography to give **12a** (2.48 g, 66%) as colorless crystals.

Mp 73–74 °C (Et_2O/hexane). IR (film): ν 1762, 1662, 1581 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.91 (3H, t, J=7.3 Hz), 1.33 (2H, qt, J=7.3, 7.3 Hz), 1.60 (2H, tt, J=7.3, 7.3 Hz), 2.42 (3H, s), 4.36 (2H, t, J=7.3 Hz), 6.61 (1H, s), 7.34 (1H, dd, J=4.8, 8.1 Hz), 8.20 (1H, dd, J=1.7, 8.1 Hz), 8.71 (1H, dd, J=1.7, 4.8 Hz). Anal. Calcd for $C_{18}H_{18}N_2O$: C, 64.41; H, 6.09; N, 10.61. Found: C, 64.60; H, 6.20; N, 10.76.

4.1.4. 1-Benzyl-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl acetate (12b). 2-(Benzylamino)nicotinic acid **11b** (2.00 g, 8.76 mmol) was suspended in a mixture of acetic anhydride (25 mL) and acetic acid (17 mL), and the mixture was stirred under reflux for 2 h. After cooled, volatile materials were evaporated in vacuo, and the residue was purified by silica gel chromatography to give **12b** (1.62 g, 63%) as pale brown crystals.

Mp 133–134 °C (Et_2O/hexane). IR (film): ν 1770, 1651 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz), δ (ppm) 2.44 (3H, s), 5.60 (2H, s), 6.70 (1H, s), 7.20–7.30 (5H, m), 7.37 (1H, dd, J=4.6, 7.9 Hz), 7.26 (1H, dd, J=1.7, 7.9 Hz), 8.68 (1H, dd, J=1.7, 4.6 Hz). Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.53; H, 4.65; N, 9.63.

4.1.5. 1-Butyl-4-hydroxy-1,8-naphthyridin-2(1*H*)-one (17a). To a solution of **12a** (200 mg, 0.768 mmol) in MeOH (8 mL) was added a solution of K_2CO_3 (106 mg, 1.15 mmol) in water (2 mL). The mixture was stirred at rt for 3 h. Volatile materials were evaporated in vacuo, and to the residue was added 3 M HCl. The resulting crystals were collected by filtration, washed with AcOEt, and dried in vacuo to give **17a** (162 mg, 97%) as white crystals.

Mp 210–211 °C. IR (film): ν 1554, 1508 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.89 (3H, t, J=7.3 Hz), 1.30 (2H, qt, J=7.3, 7.3 Hz), 1.55 (2H, tt, J=7.3, 7.3 Hz), 4.29 (2H, t, J=7.3 Hz), 5.87 (1H, s), 7.26 (1H, dd, J=4.7, 7.9 Hz), 8.21 (1H, dd, J=1.8, 7.9 Hz), 8.63 (1H, dd, J=1.8, 4.7 Hz), 11.6 (1H, s). Anal. Calcd for $C_{18}H_{18}N_2O$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.82; H, 6.44; N, 12.70.

4.1.6. 1-Benzyl-4-hydroxy-1,8-naphthyridin-2(1*H*)-one (17b). To a solution of **12b** (1.10 g, 3.74 mmol) in MeOH (40 mL) was added a solution of K_2CO_3 (775 mg, 5.61 mmol) in water (10 mL). The mixture was stirred at rt for 3 h. Volatile materials were evaporated in vacuo, and to the residue was added 3 M HCl. The resulting crystals were collected by filtration, washed with AcOEt and dried in vacuo to give **17b** (940 mg, quant.) as white crystals.

Mp 258–259 °C. IR (film): ν 1558, 1523 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz), δ (ppm) 5.53 (3H, s), 5.95 (1H, s), 7.15–7.30 (6H, m), 8.25 (1H, dd, J=1.8, 7.9 Hz), 8.59 (1H, dd, J=1.8, 4.8 Hz), 11.2 (1H, s). Anal. Calcd for $C_{17}H_{14}N_2O_3\cdot H_2O$: C, 71.16; H, 4.82; N, 11.06. Found: C, 71.08; H, 4.74; N, 10.93.

4.1.7. 1-Butyl-4-chloro-1,8-naphthyridin-2(1*H*)-one (18a). A mixture of **17a** (200 mg, 0.916 mmol) and $POCl_3$ (0.342 mL, 3.67 mmol) was stirred at 100 °C for 2 h. The reaction mixture was neutralized by adding saturated

aqueous $NaHCO_3$ under ice-cooling, and the organic materials were extracted with AcOEt. The organic layer was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography to give **18a** (218 mg, quant.) as a colorless oil.

IR (film): ν 1645, 1577, 1550 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.89 (3H, t, J=7.3 Hz), 1.32 (2H, qt, J=7.3, 7.3 Hz), 1.58 (2H, tt, J=7.3, 7.3 Hz), 4.34 (2H, t, J=7.3 Hz), 7.01 (1H, s), 7.42 (1H, dd, J=4.6, 7.9 Hz), 8.30 (1H, dd, J=1.1, 7.9 Hz), 8.73 (1H, dd, J=1.1, 4.6 Hz). Anal. Calcd for $C_{12}H_{13}ClN_2O\cdot H_2O$: C, 60.43; H, 5.58; N, 11.84. Found: C, 60.25; H, 5.41; N, 11.62.

4.1.8. 1-Benzyl-4-chloro-1,8-naphthyridin-2(1*H*)-one (18b). A mixture of **17b** (640 mg, 2.54 mmol) and $POCl_3$ (0.946 mL, 10.1 mmol) was stirred at 90 °C for 30 min. The reaction mixture was neutralized by adding saturated aqueous $NaHCO_3$ under ice-cooling, and the organic materials were extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography to give **18b** (580 mg, 84%) as pale green crystals.

Mp 131–132 °C (Et_2O/hexane). IR (film): ν 1650, 1573 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 5.60 (2H, s), 7.12 (1H, s), 7.19–7.29 (5H, m), 7.44 (1H, dd, J=4.6, 7.9 Hz), 8.36 (1H, dd, J=1.5, 7.9 Hz), 8.71 (1H, dd, J=1.5, 4.6 Hz); HRMS (ESI) $(M+H)^+$ calcd for $C_{15}H_{12}ClN_2O$ 271.0638, found 271.0631.

4.1.9. 4-Chloro-1-phenyl-1,8-naphthyridin-2(1*H*)-one (18c). 2-(Phenylamino)nicotinic acid **11c** (200 mg, 0.934 mmol) was suspended in a mixture of acetic anhydride (20 mL) and acetic acid (2 mL), and the mixture was stirred under reflux for 8 h. After cooled, volatile materials were evaporated in vacuo, and the residue was purified by short silica gel chromatography. The product was dissolved in MeOH (15 mL), and a solution of K_2CO_3 (645 mg, 4.67 mmol) in water (5 mL) was added. The mixture was stirred at rt for 2 h, and concentrated in vacuo. The residue was diluted with AcOEt, and the organic materials were extracted twice with 2 M NaOH. The combined aqueous layers were acidified by adding concd HCl, and the organic materials were extracted three times with $CHCl_3$. The combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. To the residue was added $POCl_3$ (1.5 mL), and the mixture was heated at reflux for 1.5 h. The reaction mixture was neutralized by adding saturated aqueous $NaHCO_3$ under ice-cooling, and the organic materials were extracted with AcOEt. The organic layer was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography to give **18c** (28.2 mg, 12% for three-steps) as colorless crystals.

Mp 192–193 °C (Et_2O/hexane). IR (film): ν 1655, 1577 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 7.13 (1H, s), 7.27–7.29 (2H, m), 7.39–7.54 (4H, m), 8.37 (1H, dd, J=1.3, 7.9 Hz), 8.50 (1H, dd, J=1.3, 4.4 Hz); HRMS (ESI) $(M+H)^+$ calcd for $C_{14}H_{10}ClN_2O$ 257.0482, found 257.0427.

4.1.10. 4-Bromo-1-butyl-1,8-naphthyridin-2(1*H*)-one (18d). A mixture of **17a** (300 mg, 1.37 mmol) and $POBr_3$ (1.18 g, 4.12 mmol) was stirred at 100 °C for 30 min. Then, the reaction was quenched by adding saturated aqueous $NaHCO_3$ under ice-cooling, and the organic materials were extracted with AcOEt. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography to give **18d** (351 mg, 91%) as a colorless oil.

IR (film): ν 1647, 1578, 1547 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.90 (3H, t, J=7.5 Hz), 1.32 (2H, qt, J=7.5, 7.5 Hz), 1.60 (2H, tt, J=7.5, 7.5 Hz), 4.35 (2H, t, J=7.5 Hz), 7.23 (1H, s), 7.43 (1H, dd, J=4.6, 7.9 Hz), 8.27 (1H, dd, J=1.8, 7.9 Hz), 8.72 (1H, dd, J=1.8, 4.6 Hz). Anal. Calcd for $C_{12}H_{13}BrN_2O$: C, 51.26; H, 4.66; Br, 28.42; N, 9.96. Found: C, 51.25; H, 4.67; Br, 28.56; N, 9.96.

4.1.11. 1-Butyl-4-hydroxy-3-nitro-1,8-naphthyridin-2(1*H*)-one (19). To a solution of **12a** (500 mg, 1.92 mmol) in concd H_2SO_4 (5 mL) was added concd HNO_3 (0.130 mL, 2.11 mmol) at 0 °C. The mixture was stirred at rt overnight, and was poured into ice-water. The resulting crystals were collected by filtration, and dried to give **19** (467 mg, 92%) as pale yellow crystals.

Mp 110 °C, lit.[28] mp 106–109 °C (^{i}PrOH/H_2O); ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.91 (3H, t, J=7.3 Hz), 1.33 (2H, qt, J=7.3, 7.3 Hz), 1.57 (2H, tt, J=7.3, 7.3 Hz), 4.31 (2H, t, J=7.3 Hz), 7.32 (1H, dd, J=4.6, 7.9 Hz), 8.44 (1H, dd, J=1.8, 7.9 Hz), 8.69 (1H, dd, J=1.8, 4.6 Hz).

4.1.12. 1-Butyl-4-chloro-3-nitro-1,8-naphthyridin-2(1*H*)-one[23] (18e) A mixture of **19** (800 mg, 3.04 mmol) and $POCl_3$ (3 mL) was stirred at 100 °C for 45 min. The mixture was poured into ice-water, and was neutralized with saturated aqueous $NaHCO_3$ under ice-cooling. The organic materials were extracted with AcOEt. The organic layer was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography to give **8e** (734 mg, 86%) as pale yellow crystals.

Mp 93–94 °C (Et_2O/hexane). IR (neat): ν 1660, 1535 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.92 (3H, t, J=7.3 Hz), 1.37 (2H, qt, J=7.3, 7.3 Hz), 1.67 (2H, tt, J=7.3, 7.3 Hz), 4.44 (2H, t, J=7.3 Hz), 7.60 (1H, dd, J=4.6, 8.0 Hz), 8.54 (1H, dd, J=1.7, 8.0 Hz), 8.92 (1H, dd, J=1.7, 4.6 Hz). Anal. Calcd for $C_{12}H_{12}ClN_3O_3$: C, 51.16; H, 4.29; N, 14.92. Found: C, 51.00; H, 4.27; N, 14.84.

4.1.13. 4-Bromo-1-butyl-3-nitro-1,8-naphthyridin-2(1*H*)-one (18f). A mixture of **19** (200 mg, 0.759 mmol) and $POBr_3$ (1.00 g, 3.80 mmol) was stirred at 100 °C for 30 min. After diluted with toluene, the suspension was poured into ice-water. The mixture was neutralized by adding saturated aqueous $NaHCO_3$ under ice-cooling. The organic materials were extracted with toluene. The organic layer was washed with saturated aqueous $NaHCO_3$, dried

over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography to give **18f** (222 mg, 90%) as pale brown crystals.

Mp 120–121 °C (Et_2O/hexane). IR (film): ν 1655, 1543 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.90 (3H, t, J=7.3 Hz), 1.35 (2H, qt, J=7.3, 7.3 Hz), 1.65 (2H, tt, J=7.3, 7.3 Hz), 4.42 (2H, t, J=7.3 Hz), 7.57 (1H, dd, J=4.6, 8.0 Hz), 8.46 (1H, dd, J=1.7, 8.0 Hz), 8.86 (1H, dd, J=1.7, 4.6 Hz). Anal. Calcd for $C_{12}H_{12}BrN_3O_3$: C, 44.19; H, 3.71; N, 12.88. Found: C, 44.10; H, 3.63; N, 12.76.

4.2. General procedure for the Suzuki coupling reaction

1-Alkyl-4-halo-1,8-naphthyridin-2(1*H*)-one (1.0 equiv), arylboronic acid (1.2 equiv), Cs_2CO_3 (1.8 equiv), and $Pd(PPh_3)_4$ (5 mol%) were suspended in 1,4-dioxane, and the mixture was stirred under reflux. After cooling to rt, water was added. The organic materials were extracted with AcOEt, washed with brine, and dried over $MgSO_4$. The solvent was evaporated in vacuo, and the residue was purified by silica gel chromatography to give 1-alkyl-4-aryl-1,8-naphthyridin-2(1*H*)-one.

4.2.1. 1-Butyl-4-phenyl-1,8-naphthyridin-2(1*H*)-one. The title compound was prepared from phenylboronic acid (56.2 mg, 0.461 mmol) and **18a** (100 mg, 0.384 mmol), and was obtained as colorless crystals (96.4 mg, 90%).

Mp 96–97 °C (Et_2O/hexane), lit.[28] mp 96–97 °C ($^iPr_2O$); ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.93 (3H, t, J=7.1 Hz), 1.37 (2H, qt, J=7.1, 7.1 Hz), 1.64 (2H, tt, J=7.1, 7.1 Hz), 4.42 (2H, t, J=7.1 Hz), 6.60 (1H, s), 7.28 (1H, dd, J=4.6, 7.4 Hz), 7.50–7.54 (5H, m), 7.85 (1H, d, J=7.4 Hz), 8.67 (1H, d, J=4.6 Hz).

4.2.2. 1-Benzyl-4-phenyl-1,8-naphthyridin-2(1*H*)-one. The title compound was prepared from phenylboronic acid (43.9 mg, 0.360 mmol) and **18b** (81.2 mg, 0.300 mmol), and was obtained as pale yellow crystals (85.0 mg, 91%).

Mp 150–152 °C (Et_2O/hexane), lit.[28] mp 154–155 °C ($^iPr_2O$); ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 5.67 (2H, s), 6.68 (1H, s), 7.18–7.32 (6H, m), 7.51–7.55 (5H, m), 7.89 (1H, dd, J=1.5, 7.9 Hz), 8.64 (1H, dd, J=1.5, 4.6 Hz).

4.2.3. 1,4-Diphenyl-1,8-naphthyridin-2(1*H*)-one. The title compound was prepared from phenylboronic acid (43.9 mg, 0.360 mmol) and **18c** (77.0 mg, 0.300 mmol), and was obtained as pale yellow crystals (79.2 mg, 88%).

Mp 203–204 °C (Et_2O/hexane), lit.[29] mp 210–212 °C (AcOEt); ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 6.70 (1H, s), 7.26–7.32 (3H, m), 7.44–7.61 (8H, m), 7.90 (1H, dd, J=1.8, 8.0 Hz), 8.44 (1H, dd, J=1.8, 4.6 Hz).

4.2.4. 1-Butyl-3-nitro-4-phenyl-1,8-naphthyridin-2(1*H*)-one. The title compound was prepared from phenylboronic acid (44.9 mg, 0.368 mmol) and **18e** (86.5 mg, 0.307 mmol), and was obtained as pale yellow crystals (81.6 mg, 82%).

Mp 149–150 °C (Et_2O/hexane). IR (film): ν 1662, 1535 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.94 (3H, t, J=7.5 Hz), 1.40 (2H, qt, J=7.5, 7.5 Hz), 1.71 (2H, tt, J=7.5, 7.5 Hz), 4.50 (2H, t, J=7.5 Hz), 7.38–7.45 (3H, m), 7.55–7.68 (4H, m), 8.81–8.84 (1H, m). Anal. Calcd for $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30; N, 13.00. Found: C, 66.68; H, 5.27; N, 12.90.

4.2.5. 1-Butyl-4-(4-methoxyphenyl)-1,8-naphthyridin-2(1*H*)-one. The title compound was prepared from 4-methoxyphenylboronic acid (70.0 mg, 0.461 mmol) and **18a** (100 mg, 0.384 mmol), and was obtained as colorless crystals (95.8 mg, 91%).

Mp 114–115 °C (Et_2O/hexane). IR (film): ν 1655, 1581 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.93 (3H, t, J=7.5 Hz), 1.37 (2H, qt, J=7.5, 7.5 Hz), 1.64 (2H, tt, J=7.5, 7.5 Hz), 3.83 (3H, s), 4.42 (2H, t, J=7.5 Hz), 6.56 (1H, s), 7.10 (2H, d, J=7.5 Hz), 7.28 (1H, dd, J=4.7, 8.0 Hz), 7.45 (1H, d, J=7.5 Hz), 7.92 (1H, d, J=8.0 Hz), 7.67 (1H, d, J=4.7 Hz). Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.32; H, 6.49; N, 8.85.

4.2.6. 1-Butyl-4-(4-methoxyphenyl)-3-nitro-1,8-naphthyridin-2(1*H*)-one. The title compound was prepared from 4-methoxyphenylboronic acid (56.0 mg, 0.368 mmol) and **18e** (86.5 mg, 0.307 mmol), and was obtained as pale yellow crystals (87.2 mg, 80%).

Mp 124–125 °C (Et_2O/hexane). IR (film): ν 1655, 1535 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.94 (3H, t, J=7.5 Hz), 1.39 (2H, qt, J=7.5, 7.5 Hz), 1.70 (2H, tt, J=7.5, 7.5 Hz), 3.83 (3H, s), 4.49 (2H, t, J=7.5 Hz), 7.13 (2H, d, J=8.8 Hz), 7.36 (2H, d, J=8.8 Hz), 7.40 (1H, dd, J=4.6, 8.1 Hz), 7.74 (1H, dd, J=1.6, 8.1 Hz), 8.82 (1H, dd, J=1.6, 4.6 Hz). Anal. Calcd for $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89. Found: C, 64.29; H, 5.40; N, 11.78.

4.2.7. 1-Butyl-4-(3-methoxyphenyl)-1,8-naphthyridin-2(1*H*)-one. The title compound was prepared from 3-methoxyphenylboronic acid (46.6 mg, 0.368 mmol) and **18a** (79.9 mg, 0.307 mmol), and was obtained as a colorless amorphous solid (81.6 mg, 86%).

IR (film): ν 1651, 1578 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.93 (3H, t, J=7.5 Hz), 1.37 (2H, qt, J=7.5, 7.5 Hz), 1.65 (2H, tt, J=7.5, 7.5 Hz), 3.80 (3H, s), 4.43 (2H, t, J=7.5 Hz), 6.62 (1H, s), 7.03–7.10 (3H, m), 7.28 (1H, dd, J=4.6, 8.1 Hz), 7.46 (1H, dd, J=7.3, 7.3 Hz), 7.89 (1H, d, J=8.1 Hz), 8.67 (1H, d, J=4.6 Hz); HRMS (ESI) $(M+H)^+$ calcd for $C_{19}H_{22}N_2O_2$ 309.1603, found 309.1612.

4.2.8. 1-Butyl-4-(3-methoxyphenyl)-3-nitro-1,8-naphthyridin-2(1*H*)-one (15). The title compound was prepared from 3-methoxyphenylboronic acid (56.0 mg, 0.368 mmol) and **18e** (86.5 mg, 0.307 mmol), and was obtained as pale yellow crystals (89.5 mg, 83%).

Mp 124–125 °C (Et_2O/hexane). IR (film): ν 1662, 1535 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.94 (3H, t, J=7.5 Hz), 1.40 (2H, qt, J=7.5, 7.5 Hz), 1.70 (2H, tt, J=7.5, 7.5 Hz), 3.77 (3H, s), 4.50 (2H, t, J=

7.5 Hz), 6.96–7.01 (2H, m), 7.15 (1H, dd, J=2.8, 8.4 Hz), 7.40 (1H, dd, J=4.2, 8.0 Hz), 7.49 (1H, dd, J=7.9, 7.9 Hz), 7.72 (1H, dd, J=1.5, 8.0 Hz), 8.82 (1H, dd, J=1.5, 4.2 Hz). Anal. Calcd for $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89. Found: C, 64.33; H, 5.33; N, 11.76.

4.2.9. 1-Butyl-4-(2-methoxyphenyl)-1,8-naphthyridin-2(1*H*)-one. The title compound was prepared from 2-methoxyphenylboronic acid (70.0 mg, 0.461 mmol) and **18a** (100 mg, 0.384 mmol), and was obtained as a colorless amorphous solid (95.3 mg, 80%).

IR (film): ν 1650, 1581 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.94 (3H, t, J=7.5 Hz), 1.38 (2H, qt, J=7.5, 7.5 Hz), 1.65 (2H, tt, J=7.5, 7.5 Hz), 3.68 (3H, s), 4.42 (2H, t, J=7.5 Hz), 6.53 (1H, s), 7.01–7.12 (3H, m), 7.19–7.30 (1H, m), 7.19–7.30 (3H, m), 7.49–7.51 (2H, m), 8.64 (1H, d, J=4.6 Hz); HRMS (ESI) $(M+H)^+$ calcd for $C_{19}H_{22}N_2O_2$ 309.1603, found 309.1590.

4.2.10. 1-Butyl-4-(2-methoxyphenyl)-3-nitro-1,8-naphthyridin-2(1*H*)-one. The title compound was prepared from 2-methoxyphenylboronic acid (56.0 mg, 0.368 mmol) and **18e** (86.5 mg, 0.307 mmol), and was obtained as pale yellow crystals (85.4 mg, 79%).

Mp 189–190 °C (Et_2O/hexane). IR (film): ν 1655, 1535 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.95 (3H, t, J=7.1 Hz), 1.46 (2H, qt, J=7.1, 7.1 Hz), 1.71 (2H, tt, J=7.1, 7.1 Hz), 3.69 (3H, s), 4.49 (2H, t, J=7.1 Hz), 7.12 (1H, t, J=7.5 Hz), 7.24–7.28 (2H, m), 7.37 (1H, dd, J=4.6, 8.0 Hz), 7.54–7.60 (2H, m), 8.82 (1H, dd, J=1.7, 4.6 Hz). Anal. Calcd for $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89. Found: C, 64.23; H, 5.34; N, 11.64.

4.2.11. 1-Butyl-4-[4-(trifluoromethyl)phenyl]-1,8-naphthyridin-2(1*H*)-one. The title compound was prepared from 4-(trifluoromethyl)phenylboronic acid (87.6 mg, 0.461 mmol) and **18a** (100 mg, 0.384 mmol), and was obtained as colorless crystals (123 mg, 92%).

Mp 150–151 °C (Et_2O/hexane). IR (film): ν 1655, 1581 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.93 (3H, t, J=7.1 Hz), 1.38 (2H, qt, J=7.1, 7.1 Hz), 1.66 (2H, tt, J=7.1, 7.1 Hz), 6.69 (1H, s), 7.28 (1H, dd, J=4.7, 7.1 Hz), 7.74 (2H, d, J=8.3 Hz), 7.81 (1H, d, J=7.1 Hz), 7.92 (1H, d, J=8.3 Hz), 8.69 (1H, d, J=4.7 Hz). Anal. Calcd for $C_{19}H_{17}F_3N_2O$: C, 65.89; H, 4.95; N, 8.09. Found: C, 65.70; H, 4.92; N, 7.88.

4.2.12. 1-Butyl-3-nitro-4-[4-(trifluoromethyl)phenyl]-1,8-naphthyridin-2(1*H*)-one. The title compound was prepared from 4-(trifluoromethyl)phenylboronic acid (58.3 mg, 0.368 mmol) and **18e** (86.3 mg, 0.307 mmol), and was obtained as pale yellow crystals (95.1 mg, 79%).

Mp 119–120 °C (Et_2O/hexane). IR (film): ν 1655, 1535 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.95 (3H, t, J=7.5 Hz), 1.41 (2H, qt, J=7.5, 7.5 Hz), 1.72 (2H, tt, J=7.5, 7.5 Hz), 4.52 (2H, t, J=7.5 Hz), 7.39 (1H, dd, J=4.7, 8.0 Hz), 7.66 (1H, dd, J=0.93, 8.0 Hz), 7.71 (2H, d, J=8.0 Hz), 7.98 (1H, d, J=8.0 Hz), 8.84 (1H, dd, J=0.93, 4.7 Hz). Anal. Calcd for $C_{19}H_{16}F_3N_3O_3$: C, 58.31; H, 4.12; N, 10.74. Found: C, 58.06; H, 4.09; N, 10.45.

4.2.13. 1-Butyl-4-[3-(trifluoromethyl)phenyl]-1,8-naphthyridin-2(1*H*)-one. The title compound was prepared from 3-(trifluoromethyl)phenylboronic acid (87.6 mg, 0.461 mmol) and **18a** (100 mg, 0.384 mmol), and was obtained as colorless crystals (131 mg, 98%).

Mp 127–128 °C (Et_2O/hexane). IR (film): ν 1655, 1581 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.94 (3H, t, J=7.3 Hz), 1.38 (2H, qt, J=7.3, 7.3 Hz), 1.66 (2H, tt, J=7.3, 7.3 Hz), 4.44 (2H, t, J=7.3 Hz), 6.71 (1H, s), 7.30 (1H, dd, J=4.6, 7.9 Hz), 7.76–7.92 (5H, m), 8.68–8.70 (1H, m). Anal. Calcd for $C_{19}H_{17}F_3N_2O$: C, 65.89; H, 4.95; N, 8.09. Found: C, 65.75; H, 4.91; N, 8.01.

4.2.14. 1-Butyl-3-nitro-4-[3-(trifluoromethyl)phenyl]-1,8-naphthyridin-2(1*H*)-one. The title compound was prepared from 3-(trifluoromethyl)phenylboronic acid (58.3 mg, 0.368 mmol) and **18e** (86.5 mg, 0.307 mmol), and was obtained as pale yellow crystals (98.9 mg, 82%).

Mp 130–131 °C (Et_2O/hexane). IR (film): ν 1659, 1527 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.95 (3H, t, J=7.5 Hz), 1.41 (2H, qt, J=7.5, 7.5 Hz), 1.71 (2H, tt, J=7.5, 7.5 Hz), 4.52 (2H, t, J=7.5 Hz), 7.41 (1H, dd, J=4.6, 8.4 Hz), 7.64 (1H, dd, J=1.1, 8.4 Hz), 7.78–7.86 (2H, m), 7.90 (1H, s), 7.98 (1H, d, J=7.3 Hz), 8.84 (1H, dd, J=1.1, 4.6 Hz). Anal. Calcd for $C_{19}H_{16}F_3N_3O_3$: C, 58.31; H, 4.12; N, 10.74. Found: C, 58.17; H, 4.07; N, 10.77.

4.2.15. 1-Butyl-4-(3-fluorophenyl)-1,8-naphthyridin-2(1*H*)-one. The title compound was prepared from 3-fluorophenylboronic acid (56.2 mg, 0.461 mmol) and **18a** (100 mg, 0.384 mmol), and was obtained as colorless crystals (98.0 mg, 86%).

Mp 97–98 °C (Et_2O/hexane). IR (film): ν 1647, 1578 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.93 (3H, t, J=7.3 Hz), 1.37 (2H, qt, J=7.3, 7.3 Hz), 1.64 (2H, tt, J=7.3, 7.3 Hz), 4.43 (2H, t, J=7.3 Hz), 6.70 (1H, s), 7.29 (1H, dd, J=4.7, 6.8 Hz), 7.73–7.86 (3H, m), 8.00–8.02 (2H, m), 8.69 (1H, d, J=4.7 Hz). Anal. Calcd for $C_{18}H_{17}FN_2O$: C, 72.95; H, 5.78; N, 9.45. Found: C, 72.85; H, 5.68; N, 9.27.

4.2.16. 1-Butyl-4-(3-fluorophenyl)-3-nitro-1,8-naphthyridin-2(1*H*)-one. The title compound was prepared from 3-fluorophenylboronic acid (51.5 mg, 0.368 mmol) and **18e** (86.5 mg, 0.307 mmol), and was obtained as pale yellow crystals (76.5 mg, 73%).

Mp 172–173 °C (Et_2O/hexane). IR (film): ν 1666, 1539 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.95 (3H, t, J=7.5 Hz), 1.40 (2H, qt, J=7.5, 7.5 Hz), 1.71 (2H, tt, J=7.5, 7.5 Hz), 4.51 (2H, t, J=7.5 Hz), 7.29 (1H, d, J=7.7 Hz), 7.39–7.49 (3H, m), 7.60–7.72 (2H, m), 8.83 (1H, dd, J=1.1, 4.0 Hz). Anal. Calcd for $C_{18}H_{16}FN_3O_3$: C, 63.34; H, 4.72; N, 12.31. Found: C, 63.05; H, 4.67; N, 12.01.

4.2.17. 4-(3-Acethylphenyl)-1-butyl-1,8-naphthyridin-2(1*H*)-one. The title compound was prepared from 3-acethylphenylboronic acid (75.6 mg, 0.461 mmol) and

18a (100 mg, 0.384 mmol), and was obtained as a colorless amorphous solid (105 mg, 85%).

IR (film): ν 1651, 1581 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.94 (3H, t, J=7.1 Hz), 1.38 (2H, qt, J=7.1, 7.1 Hz), 1.66 (2H, tt, J=7.1, 7.1 Hz), 2.63, (3H, s), 4.45 (2H, t, J=7.5 Hz), 6.70 (1H, s), 7.29 (1H, dd, J=4.7, 8.0 Hz), 7.68–7.85 (3H, m), 8.05–8.11 (2H, m), 8.70 (1H, dd, J=1.7, 4.6 Hz); HRMS (ESI) $(M+H)^+$ calcd for $C_{20}H_{22}N_2O_2$ 321.1603, found 321.1609.

4.2.18. 4-(3-Acethylphenyl)-1-butyl-3-nitro-1,8-naphthyridin-2(1*H*)-one. The title compound was prepared from 3-acethylphenylboronic acid (60.3 mg, 0.368 mmol) and **18e** (86.5 mg, 0.307 mmol), and was obtained as pale yellow crystals (80.2 mg, 82%).

Mp 151–152 °C (Et_2O/hexane). IR (film): ν 1662, 1531 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.95 (3H, t, J=7.5 Hz), 1.41 (2H, qt, J=7.5, 7.5 Hz), 1.72 (2H, tt, J=7.5, 7.5 Hz), 2.60 (3H, s), 4.52 (2H, t, J=7.5 Hz), 7.40 (1H, dd, J=4.8, 8.1 Hz), 7.66 (1H, dd, J=1.1, 8.1 Hz), 7.70–7.78 (2H, m), 8.02 (1H, s), 8.15–8.18 (1H, m), 8.84 (1H, dd, J=1.1, 4.8 Hz). Anal. Calcd for $C_{20}H_{19}N_3O_4$: C, 65.74; H, 5.24; N, 11.50. Found: C, 65.41; H, 5.17; N, 11.10.

4.2.19. 3-(1-Butyl-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)benzonitrile. The title compound was prepared from 3-cyanophenylboronic acid (67.7 mg, 0.461 mmol) and **18a** (100 mg, 0.384 mmol), and was obtained as colorless crystals (97.1 mg, 83%).

Mp 144–145 °C (Et_2O/hexane). IR (film): ν 2233, 1651, 1581 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.93 (3H, t, J=7.5 Hz), 1.37 (2H, qt, J=7.5, 7.5 Hz), 1.64 (2H, tt, J=7.5, 7.5 Hz), 4.43 (2H, t, J=7.5 Hz), 6.70 (1H, s), 7.29 (1H, dd, J=4.6, 7.9 Hz), 7.72–7.86 (3H, m), 8.00–8.02 (2H, m), 8.69 (1H, d, J=4.6 Hz). Anal. Calcd for $C_{19}H_{17}N_3O$: C, 75.23; H, 5.65; N, 13.85. Found: C, 74.92; H, 5.65; N, 13.71.

4.2.20. 3-(1-Butyl-3-nitro-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl)benzonitrile. The title compound was prepared from 3-cyanophenylboronic acid (54.1 mg, 0.368 mmol) and **18e** (86.5 mg, 0.307 mmol), and was obtained as pale yellow crystals (80.3 mg, 75%).

Mp 160–161 °C (Et_2O/hexane). IR (film): ν 2233, 1659, 1531 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.95 (3H, t, J=7.5 Hz), 1.40 (2H, qt, J=7.5, 7.5 Hz), 1.71 (2H, tt, J=7.5, 7.5 Hz), 4.52 (2H, t, J=7.5 Hz), 7.41 (1H, dd, J=4.6, 8.1 Hz), 7.68 (1H, dd, J=1.7, 8.1 Hz), 7.79–7.82 (2H, m), 8.02–8.03 (1H, m), 8.07–8.10 (1H, m), 8.85 (1H, dd, J=1.7, 4.6 Hz). Anal. Calcd for $C_{19}H_{16}N_4O_3$: C, 65.51; H, 4.63; N, 16.08. Found: C, 65.43; H, 4.57; N, 15.84.

4.2.21. 1-[3-(Benzyloxy)propoxy]-3-bromobenzene (23). To a suspension of 3-bromophenol (3.00 g, 17.3 mmol) and K_2CO_3 (7.19 g, 52.0 mmol) in DMF (20 mL) was added benzyl 3-bromopropyl ether (3.92 g, 19.1 mmol) at rt. The mixture was stirred at 60 °C for 3 h. After cooling to rt, water was added. The organic materials were extracted with AcOEt, washed with water, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography to give **23** (4.71 g, 85%) as a colorless oil.

IR (film): ν 1589, 1466 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 1.98 (2H, tt, J=6.2, 6.2 Hz), 3.57 (2H, t, J=6.2 Hz), 4.06 (2H, t, J=6.2 Hz), 4.48 (2H, s), 6.92–6.96 (1H, m), 7.10–7.13 (2H, m), 7.21–7.36 (6H, m); HRMS (ESI) $(M+H)^+$ calcd for $C_{16}H_{19}BrO_2$ 321.0490, found 321.0512.

4.2.22. {3-[3-(Benzyloxy)propoxy]phenyl}boronic acid (14). To a suspension of Mg (2.50 g, 10.3 mmol) and a catalytic amount of I_2 in THF (15 mL), a solution of **23** (3.00 g, 9.34 mmol) in THF (3 mL) was added dropwise at rt. The mixture was stirred for 1.5 h at reflux. After cooled to −10 °C, $B(OMe)_3$ (1.05 mL, 9.34 mmol) was added. The mixture was warmed to rt, and stirred overnight. Then, 10% H_2SO_4 (10 mL) was added, and the organic materials were extracted with Et_2O. The extracts were washed twice with 10% H_2SO, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography to give **14** (1.35 g, 51%) as a colorless amorphous solid.

IR (film): ν 3267, 1346 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 2.00 (2H, tt, J=6.2, 6.2 Hz), 3.36 (1H, br d), 3.60 (2H, t, J=6.2 Hz), 4.05 (2H, t, J=6.2 Hz), 4.49 (2H, s), 6.93–6.96 (1H, m), 7.21–7.46 (8H, m), 8.03 (1H, br); HRMS (ESI) $(M+H)^+$ calcd for $C_{16}H_{21}BO_4$ 287.1457, found 287.1478.

4.2.23. 4-{3-[3-(Benzyloxy)propoxy]phenyl}-1-butyl-3-nitro-1,8-naphthyridin-2(1*H*)-one (15). The compound **18e** (100 mg, 0.355 mmol), **14** (122 mg, 0.426 mmol), Cs_2CO_3 (208 mg, 0.640 mmol), and $Pd(PPh_3)_4$ (20.6 mg, 5 mol%) were suspended in 1,4-dioxane (10 mL), and the mixture was stirred under reflux for 4 h. After cooling to rt, water was added. The organic materials were extracted with AcOEt, washed with brine, and dried over $MgSO_4$. The solvent was evaporated in vacuo, and the residue was purified by silica gel chromatography to give **15** (148 mg, 86%) as a pale yellow oil.

IR (film): ν 1662, 1587, 1539 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.96 (3H, t, J=7.1 Hz), 1.41 (2H, qt, J=7.1, 7.1 Hz), 1.71 (2H, tt, J=7.1, 7.1 Hz), 2.00 (2H, tt, J=6.2, 6.2 Hz), 3.58 (2H, t, J=6.2 Hz), 4.04–4.12 (2H, m), 4.47 (2H, s), 4.51 (2H, t, J=7.1 Hz), 6.97–7.02 (2H, m), 7.13–7.16 (1H, m), 7.23–7.33 (5H, m), 7.41 (1H, dd, J=4.8, 8.1 Hz), 7.49 (1H, t, J=8.3 Hz), 7.73 (1H, dd, J=1.7, 8.1 Hz); HRMS (ESI) $(M+H)^+$ calcd for $C_{28}H_{31}N_3O_5$ 488.2185, found 488.2204.

4.2.24. 3-Amino-4-{3-[3-(benzyloxy)propoxy]phenyl}-1-butyl-1,8-naphthyridin-2(1*H*)-one (16). A suspension of **15** (156 mg, 0.320 mmol), Zn dust (209 mg, 3.20 mmol), and AcOH (0.046 mL, 0.800 mmol) in MeOH (10 mL) was heated at reflux for 1.5 h. The mixture was made basic with saturated aqueous $NaHCO_3$, and the precipitate was removed by passing through Celite. The organic materials were extracted with AcOEt, washed with saturated aqueous $NaHCO_3$, and dried over $MgSO_4$. The solvents were

evaporated in vacuo, and the residue was purified by silica gel chromatography to give **16** (154 mg, quant.) as colorless crystals.

Mp 100–101 °C (AcOEt/hexane). IR (film): ν 3446, 3344, 1585, 1571 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.95 (3H, t, J=7.3 Hz), 1.39 (2H, qt, J=7.3, 7.3 Hz), 1.69 (2H, tt, J=7.3, 7.3 Hz), 2.00 (2H, tt, J=6.2, 6.2 Hz), 3.59 (2H, t, J=6.2 Hz), 4.09 (2H, t, J=6.2 Hz), 4.47 (2H, s), 4.53 (2H, t, J=7.3 Hz), 5.12 (2H, s), 6.86–6.89 (2H, m), 7.04 (1H, dd, J=2.6, 9.7 Hz), 7.13 (1H, dd, J=4.6, 7.9 Hz), 7.24–7.33 (6H, m), 7.48 (1H, t, J=7.9 Hz), 8.34 (1H, dd, J=1.8, 4.6 Hz); HRMS (ESI) $(M+H)^+$ calcd for $C_{28}H_{33}N_3O_3$ 458.2444, found 458.2455.

4.2.25. 2,6-Diisopropyl-4-nitroaniline (25). To a solution of 2,6-diisopropylaniline **5** (0.0940 mL, 0.500 mmol) in EtOH (2.5 mL) was added, 2,3,5,6-tetrabromo-4-methyl-4-nitro-2,5-cyclohexadienone **24** (234 mg, 0.500 mmol) at rt. The mixture was stirred at rt for 3 h, and poured into water. The organic materials were extracted with AcOEt, washed twice with water, and dried over $MgSO_4$. The solvents were evaporated in vacuo, and the residue was purified by silica gel chromatography to give **25** (75.6 mg, 68%) as yellow crystals.

Mp 125–126 °C (Et_2O/hexane), lit.[9] mp 105–108 °C (CH_2Cl_2/petroleum ether); ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 1.18 (12H, d, J=6.6 Hz), 3.05–3.14 (2H, m), 6.29 (2H, br), 7.80 (2H, s).

4.2.26. *tert*-Butyl (4-amino-3,5-diisopropylphenyl)carbamate (26). A suspension of **25** (275 mg, 1.24 mmol) and 10% Pd/C (20 mg) in MeOH (20 mL) was stirred at rt for 2 h under a hydrogen atmosphere. Hydrogen was replace with nitrogen, and 2 M NaOH (0.310 mL, 0.620 mmol) was added. The reaction mixture was stirred for 2 h. The catalyst was removed by passing through Celite, and $(Boc)_2O$ (0.313 mL, 1.36 mmol) was added to the solution. After the mixture was stirred for 2 h at rt, the solvent was evaporated in vacuo. Separated crystals were washed with hexane, and dried in vacuo to give **26** (292 mg, 81%) as colorless powder.

Mp 158–159 °C. IR (film): ν 3329, 1689, 1537, 1157 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 1.11 (12H, d, J=6.8 Hz), 1.44 (9H, s), 2.94–3.03 (2H, m), 4.26 (2H, br), 6.99 (2H, br), 8.68 (1H, br d); HRMS (ESI) $(M+H)^+$ calcd for $C_{17}H_{30}N_2O_2$ 293.2229, found 293.2231.

4.2.27. *tert*-Butyl [4-({[(4-{3-[3-(benzyloxy)propoxy]phenyl}-1-butyl-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl)amino]carbonyl}amino)-3,5-diisopropylphenyl]carbamate (27). To a solution of **16** (300 mg, 0.656 mmol) in THF (15 mL) was added phenyl chloroformate (0.0905 mL, 0.721 mmol) at rt. The mixture was stirred at rt overnight. Volatile materials was evaporated, and the residue was dissolved by DMF (15 mL). To the solution, were added **26** (210 mg, 0.718 mmol) and DMAP (168 mg, 1.38 mmol) at rt, and the mixture was stirred at rt overnight. Saturated aqueous NH_4Cl was added, and the organic materials were extracted with AcOEt. The organic layer was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography to give **27** (456 mg, 90% for two-steps) as a colorless amorphous solid.

IR (film): ν 1637, 1603, 1581, 1157 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.94–0.99 (15H, m), 1.42 (2H, qt, J=7.1, 7.1 Hz), 1.45 (9H, s), 1.71 (2H, tt, J=7.1, 7.1 Hz), 2.01 (2H, tt, J=6.2, 6.2 Hz), 2.85 (2H, tt, J=7.1, 7.1 Hz), 3.59 (2H, t, J=6.2 Hz), 4.06 (2H, t, J=6.2 Hz), 4.46 (2H, s), 4.52 (2H, t, J=7.1 Hz), 6.88–6.91 (2H, m), 7.00–7.03 (1H, m), 7.15 (2H, s), 7.22–7.31 (6H, m), 7.39 (1H, t, J=8.3 Hz), 7.59–7.61 (2H, m), 7.70 (1H, s), 8.61 (1H, dd, J=1.8, 4.6 Hz), 9.09 (1H, s); HRMS (ESI) $(M+H)^+$ calcd for $C_{46}H_{59}N_5O_6$ 776.4387, found 776.4389.

4.2.28. *tert*-Butyl (4-{[({1-butyl-4-[3-(3-hydroxypropoxy)phenyl]-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl}amino)carbonyl]amino}-3,5-diisopropylphenyl)carbamate (28). A suspension of **27** (239 mg, 0.308 mmol), 10% Pd/C (24 mg), and AcOH (0.0264 mL, 0.462 mmol) in MeOH (20 mL) was stirred at rt for 5 h under a hydrogen atmosphere. The catalyst was removed by passing through Celite, and the solvent was evaporated in vacuo. The residue was purified by silica gel chromatography to give **28** (211 mg, quant.) as a colorless amorphous solid.

IR (film): ν 3320, 1635, 1600, 1583, 1157 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.85–0.99 (15H, m), 1.42 (2H, qt, J=7.0, 7.0 Hz), 1.45 (9H, s), 1.71 (2H, tt, J=7.0, 7.0 Hz), 1.88 (2H, tt, J=6.2, 6.2 Hz), 2.86 (2H, tt, J=7.0, 7.0 Hz), 3.56 (2H, t, J=6.2 Hz), 4.04 (2H, t, J=6.2 Hz), 4.52 (2H, t, J=7.0 Hz), 6.88–6.90 (2H, m), 7.01 (1H, dd, J=2.2, 8.3 Hz), 7.15 (2H, s), 7.25 (1H, dd, J=4.8, 8.3 Hz), 7.39 (1H, t, J=7.9 Hz), 7.60–7.63 (2H, m), 7.69 (1H, s), 8.61 (1H, dd, J=2.2, 4.8 Hz), 9.90 (1H, s); HRMS (ESI) $(M+H)^+$ calcd for $C_{39}H_{53}N_5O_6$ 686.3918, found 686.3930.

4.2.29. *N*-(4-amino-2,6-diisopropylphenyl)-*N'*-{1-butyl-4-[3-(3-nydroxypropoxy)phenyl]-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl}urea hydrochloride hydrate (SMP-797). To a solution of **28** (3.00 g, 4.37 mmol) in MeOH (7 mL) was added 10% HCl/MeOH (30 mL) at rt. The mixture was stirred at rt overnight. Volatile materials was evaporated, and the residue was dissolved in MeOH (5 mL) by heating at 70 °C. Acetone (50 mL) was added to the solution, and the mixture was stirred under reflux for 1 h. After cooled, separated white crystals were filtered, and dried to give SMP-797 (2.59 g, 95%), which was recrystallized from MeOH giving colorless crystals.

Mp 196–197 °C (MeOH).[7] IR (KBr): ν 2966, 1636, 1584, 1546 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.85–0.99 (15H, m), 1.41 (2H, qt, J=7.3, 7.3 Hz), 1.70 (2H, tt, J=7.3, 7.3 Hz), 1.87 (2H, tt, J=6.1, 6.1 Hz), 2.95 (2H, tt, J=7.3, 7.3 Hz), 3.54 (2H, t, J=6.1 Hz), 4.03 (2H, t, J=6.1 Hz), 4.50 (2H, t, J=7.0 Hz), 6.88–6.89 (2H, m), 7.00–7.03 (3H, m), 7.25 (1H, dd, J=4.6, 7.9 Hz), 7.40 (1H, t, J=7.9 Hz), 7.60 (1H, dd, J=1.5, 7.9 Hz), 7.79 (1H, s), 7.87 (1H, s), 8.61 (1H, dd, J=1.5, 4.6 Hz), 9.88 (2H, br). Anal. Calcd for $C_{34}H_{43}N_5O_4 \cdot HCl \cdot H_2O$: C, 63.79; H, 7.24; Cl, 5.54; N, 10.94. Found: C, 63.85; H, 7.21; Cl, 5.74; N, 10.96.

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NMR *J*-based analysis of nitrogen-containing moieties and application to dysithiazolamide, a new polychlorinated dipeptide from *Dysidea* sp.

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Dedicated to Professor Joaquín Plumet, Universidad Completense de Madrid, on the occasion on his 60th birthday

Abstract—The methodology of *J*-based analysis applied to 1,3-methylcarboamido systems allowed us to deduce the relative configurations of the two leucine-like fragments of a new tetrachloro amino acid derivative dysithiazolamide, which was isolated from an unidentified sponge of the genus *Dysidea*. Furthermore, the absolute configuration was also proposed by comparison with analogous systems.

1. Introduction

One of the most important problems in organic structure analysis is to elucidate the configuration of adjacent stereocenters in a carbon skeleton. This challenge is easily met when a three- to six-membered ring is present, because their well-defined conformational behavior allows simple NMR parameters, such as scalar (*J* couplings) or dipolar (NOE) interactions, to be unambiguously translated into configurations. Conversely, stereochemical analysis on open polysubstituted acyclic systems is considerably more demanding. The *J*-based configuration analysis, recently devised by Murata et al.[1] relies on the extensive use of $^{2,3}J$(C,H)/^{3}J(H,H) couplings in combination with NOE data. This technique has been widely applied in the elucidation of relative configurations of natural compounds featuring acyclic chains bearing substituents such as hydroxyl, alkoxy, methyl,[2] halogens,[3] or even pyridinyl[4] groups. To date, a few reports have been published in which Murata's methodology were applied to chiral nitrogen-substituted acyclic systems.[5] Reliable curves—obtained by ab initio methods—describing the angular dependence in fragments containing nitrogen and oxygen substituents suggested similar behavior but with a slightly different range for ^{2}J(CH).[6] Nonetheless, a more systematic, and hence reliable, application of this methodology to nitrogen-containing acyclic compounds with an unknown relative configuration requires the collection of more $^{2,3}J$(CH) experimental data from suitable models.

Table 1. NMR data for dysithiazolamide (**1**)[a]

No.	δ_C	δ_H (m, *J* in Hz)
1	78.55 d	5.84 d, 3.0
2	40.84 d	2.10 dddd, 6.3, 2.6, 3.0, 10.3
3	31.18 t	H3l: 2.55 ddd, 2.6, 11.5, 14.3, H3h: 2.22 ddd, 4.2, 10.3, 14.3
4	52.05 d	6.21 dd, 4.2, 11.5
5	172.82 s	—
6	47.03 d	5.04 ddd, 2.8, 8.6, 10.4
7	35.19 t	H7l: 1.96 ddd, 2.6, 10.4, 13.7, H7h: 1.67 ddd 2.8, 9.9; 13.7
8	40.64 d	2.27 dddd, 6.7, 2.6, 3.0, 9.9
9	78.60 d	5.79 d, 3.0
10	15.81 q	1.22 d, 6.3
11	168.37 s	—
12	142.57 d	7.76 d, 3.4
13	119.96 d	7.36 d, 3.4
14	29.61 q	2.94 s
15	174.08 s	—
16	29.61 t	2.30 q, 7.7
17	9.66 q	1.18 t, 7.7
18	15.53 q	1.26 d, 6.7
NH	—	6.33 d, 8.6

[a] Recorded in $CDCl_3$ at 600 MHz for ^{1}H and 150 MHz for ^{13}C.

Keywords: *J*-Based analysis; *Dysidea*; DFT.
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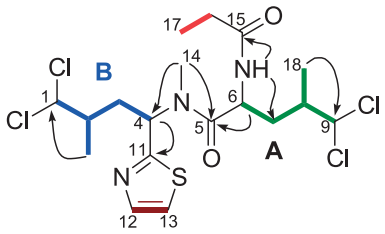
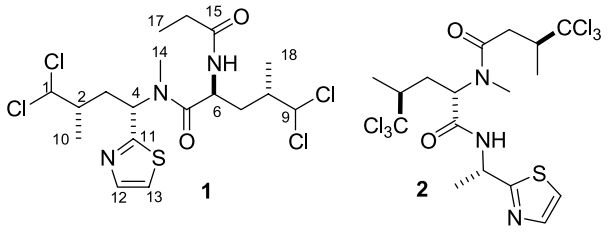


Figure 1. COSY spin-systems (bolded) and selected HMBC correlations found in **1**.

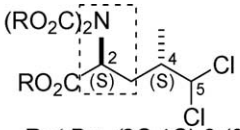


2. Results and discussion

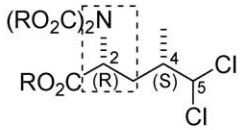
In the course of our continuing program on the isolation of new bioactive metabolites from marine organisms, the organic extract of a sponge of the genus *Dysidea* (Dictyoceratidae) collected by hand on the reefs off Mayo Island (Sulawesi, Indonesia) using SCUBA, afforded a new compound, which we have named dysithiazolamide (**1**) along with the known compound dysidenin (**2**).[7]

Analysis of the APCIMS data of **1** quickly led us to envision a tetrachloride metabolite based on the diagnostic isotopic cluster at *m/z* 492, 494, 496 and 498 in a ratio 7.8:10:4.8:1. ^{13}C NMR and DEPT-135 experiments (see Table 1) showed the presence of eighteen well-resolved resonances observed as four methyls, three methylenes, eight methines and three quaternary carbons. The molecular formula of **1** ($C_{18}H_{27}Cl_4N_3SO_2$) was completed on the basis of the (+)-HRESIMS, ^{13}C, and ^{1}H NMR data. The ^{1}H–^{1}H gCOSY and gHMQC cross peaks allowed us to build-up two leucine-like fragments following correlations from two characteristic dichloromethyl moieties, from H1/C1(5.84/78.55) and H9/C9 (5.79/78.60) to H4/C4 (6.21/52.05) and H6/C6 (5.04/47.03). The presence of a thiazol-2-yl and a propionamidyl moieties were located at C4 and C6, respectively, based on the key gHMBC correlations observed from δ_C 168.37 (C11) to δ_H 6.21 (H4) and from 174.08 (C15) to 6.33 (NH). In addition, an *N*-methyl group was placed at C4 due to the HMBC correlation from δ_C

Table 2. Data sets of calculated versus experimental *J* values for the C2–C3 conformational arrangements of the structural models **3a**–**c**[a]



R=*t*-Bu, *(2S,4S)*-**3** (**3a**)
R=Me, *(2S,4S)*-**3** (**3b**)



R=Me, *(2R,4S)*-**3** (**3c**)

Experimental [a]		*Calculated* [e]					
3a *(anti)*		**3b** *(anti)*			**3c** *(syn)*		
		anti	**gauche (–)**	**gauche (+)**	**anti**	**gauche (–)**	**gauche (+)**
C2–C3							
^3J (H3*l*, H2)	11.0[b]	11.3	3.6	1.8	4.8	4.5	6.5
^3J (H3*h*, H2)	4.3[b]	3.5	4.9	9.8	11.1	1.7	2.6
^3J (H3*l*, C1)	2.4[c]	2.4	1.1	7.3	0.4	0.8	8.6
^3J (H3*h*, C1)	0.8[c]	0.8	8.7	4.7	2.8	2.2	1.4
^3J (H2, C4)	2.8[d]	2.1	7.4	3.9	1.3	5.5	6.3
^2J (H3*l*, C2)	-6.9[d]	-6.5	-2.1	-4.8	-0.6	-3.4	-2.7
^2J (H3*h*, C2)	-2.5[d]	-1.3	-4.0	-5.5	-6.2	-3.3	0.3
TAD[f]	-	***5.0***	*35.9*	*39.7*	*30.9*	*20.3*	*31.5*
	C2-C3	anti	gauche (-)	gauche (+)	anti	gauche (-)	gauche (+)
			anti			*syn*	

[a] All NMR data were recorded at 300 K in $CDCl_3$.
[b] $^3J_{H,H}$ obtained from first-order analysis of the ^{1}H NMR spectrum at 600 MHz.
[c] PS-HMBC or *J*-HMBC.
[d] HETLOC.
[e] DFT-B3LYP/6-311G for minimization and B3LYP/6-311G (d,p) for coupling constant calculations.
[f] Total absolute deviation (TAD) values express the overall numerical distance between calculated and experimental values for a given structural arrangement.

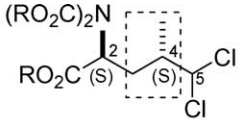
52.04 to δ_H 2.94 (Me14). The final link between the two fragments C1–C4 and C6–C9 was established by two key HMBC heteronuclear connectivities from C5 (δ_C 172.82) to H6 (δ_H 5.04) and to H14 (δ_H 2.94).

The acyclic chain of **1** was considered a good example to apply our own hybrid QM theoretical/experimental extension of Murata's methodology to determine its relative configuration. For the sake of clarity, we divided the structure into two different fragments, depicted as A and B (see Fig. 1). We recognized that the enantiopure amino acid derivative (2*S*,4*S*)-**3** (**3a**) (Tables 2 and 3, R=*t*-Bu), very recently synthesized by us,[8] which bears a methyl and an *N*,*N*-bis-Boc-protected nitrogen function in a 1,3-acyclic relationship would serve as a good model for both fragments A and B. We therefore initially measured all relevant ^3J(H,H) and $^{2,3}J$(C,H) couplings on this model through ^{1}H NMR, HETLOC[9], PS-HMBC[10] and *J*-HMBC[11] spectra. At the same time, in an effort to strengthen our assignments, experimental *J*-values were subsequently compared with their theoretically derived counterparts. On the basis on our experience, QM calculations at the DFT level to accurately predict the homo- and heteronuclear coupling constants constitute a valid supplement to the original *J*-based Murata's methodology.[12] Accordingly, theoretical QM data were calculated for (2*S*,4*S*)-**3** (**3b**), (2*R*,4*S*)-**3** (**3c**), and (2*S*,4*R*)-**3** (**3d**) diastereoisomers (see Tables 2 and 3). These compounds were chosen because they represent the different configurations at C2 and C4.

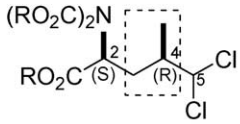
The main staggered rotamers among the six possible systems (three for each of the two relative configurations *anti* and *syn*) were firstly minimized using the B3LYP or mPW1PW91 functionals with 6-31G (d) or 6-311G (d) basis sets.[13,14] In order to save computational time, R=Me was used for both models, since preliminary tests confirmed that changes did not occur in the theoretical values obtained. The dominant *anti* conformers found for both C2–C3 and C3–C4 fragments are outlined in the first column of Tables 2 and 3 (gray background) and their sets of coupling constants were in perfect agreement between the experimental and the calculated data.

In order to corroborate our assignments, a ROESY experiment was also performed. The large NOE effect between H2 and H3h, in comparison with H3l, confirmed

Table 3. Data sets of calculated versus experimental *J* values for the C3–C4 conformational arrangements of the structural models **3a–d**[a]

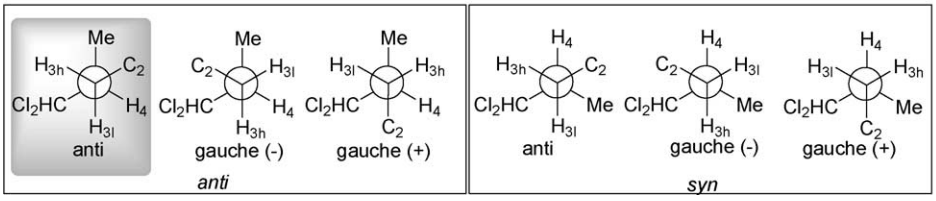


R=*t*-Bu, (2*S*,4*S*)-**3** (**3a**)
R=Me, (2*S*,4*S*)-**3** (**3b**)



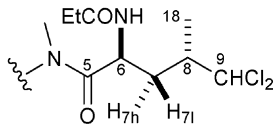
R=Me, (2*S*,4*R*)-**3** (**3d**)

Experimental [a]		*Calculated* [e]					
3a *(anti)*		**3b** *(anti)*			**3d** *(syn)*		
		anti	**gauche (–)**	**gauche (+)**	**anti**	**Gauche (–)**	**Gauche (+)**
C3–C4							
^3J (H3*l*, H4)	3.0[b]	2.2	2.7	9.9	8.5	2.6	3.6
^3J (H3*h*, H4)	11.0[b]	10.3	5.8	5.2	0.8	10.8	4.0
^3J (H3*l*, Me)	6.2[d]	7.0	3.2	3.6	5.3	3.0	2.8
^3J (H3*h*, Me)	3.0[d]	3.4	7.4	1.5	5.6	1.6	7.4
^3J (H3*h*, C5)	3.2[c]	3.9	0.8	12.3	7.5	3.3	14.1
^3J (H3*l*, C5)	3.4[c]	1.9	11.2	1.4	0.0	11.6	2.6
^2J (H3*h*, C4)	-5.4[d]	-2.7	-1.6	-4.7	-2.6	-2.5	-2.2
^2J (H3*l*, C4)	-4.5[d]	-3.7	-3.5	-2.0	-4.4	0.1	-3.0
TAD[f]	-	*7.6*	*26.9*	*28.6*	*28.8*	*21.4*	*31.8*

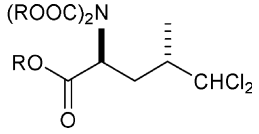


[a] All NMR data were recorded at 300 K in $CDCl_3$.
[b] $^3J_{H,H}$ obtained from first-order analysis of the ^{1}H NMR spectrum at 600 MHz.
[c] PS-HMBC or *J*-HMBC.
[d] HETLOC.
[e] DFT-B3LYP/6-311G for minimization and B3LYP/6-311G (d,p) for coupling constant calculations.
[f] Total absolute deviation (TAD) values express the overall numerical distance between calculated and experimental values for a given structural arrangement.

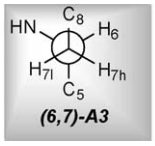
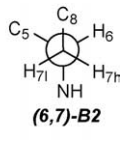
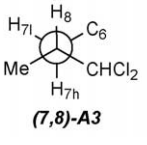
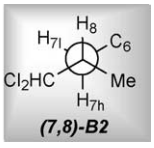
Table 4. ^{3}J(H,H) and $^{2,3}J$(C,H) (Hz) values of the corresponding conformers for fragment A of dysithiazolamide (**1**) and comparison with those of the synthetic model **3a**



Fragment A



R=*t*-Bu, **3a**

Bond	Possible conformers		^{3}J(H,H)	**1**	**3a**	$^{2,3}J$(C,H)	**1**	**3a**	NOE (**1**)	
C6–C7			H_6–H_{7l} H_6–H_{7h}	2.8 10.4	4.3 11.0	^{2}J(C_6, H_{7l}) ^{2}J(C_6,H_{7h})	Large Small	−6.9 −2.5	NH–H_{7l} NH–H_{7h}	Strong Weak
	(6,7)-A3	*(6,7)-B2*								
C7–C8			H_8–H_{7l} H_8–H_{7h}	2.6 9.9	3.0 11.0	^{3}J(C_9, H_{7h}) ^{3}J(C_9, H_{7l}) ^{3}J(Me_{18}, H_{7l}) ^{3}J(Me_{18},H_{7h})	Small Small Large Small	3.2 3.4 6.2 3.0	Me_{18}–H_{7h} Me_{18}–H_{7l} H_9–H_{7h} H_9–H_{7l} Me_{18}–H_6	Strong Weak Medium Strong Strong
	(7,8)-A3	*(7,8)-B2*								

the presence of the predicted rotamer around the C2–C3 bond. Similarly, the weak NOE between H3l and Me10, in comparison to that between H3h and the same methyl, was consistent with the staggered rotamer predicted for the C3–C4 carbon fragment.

Having successfully applied the *J*-based analysis, augmented by key NOE interactions, to the synthetic model, we set out to elucidate the relative configuration of the novel natural compound. The small amount isolated (1.2 mg) only allowed us to obtain ROESY and PS-HMBC spectra.

Fragment A. For the C6–C7 moiety, the values found for ^{3}J(H6–H7l) and ^{3}J(H6–H7h) left two possible rotamers, which are denoted as (6,7)-A3 and (6,7)-B2 (see Table 4). A large PS-HMBC crosspeak was found for ^{2}J(C6–H7l) in comparison to ^{2}J(C6–H7h). This pair large/small was also present in our synthetic model, aminoacid (2*S*,4*S*)-**3** (**3a**), −6.9 and −2.5 Hz, respectively, which again corroborates in being a good model for our purpose. In addition, a large NOE effect was observed between NH/H7l in comparison to NH–H7h. These observations are only compatible with the (6,7)-A3 rotamer as is depicted in Table 4. The proton–proton coupling constants around the C7–C8 bond again led us to consider only two rotamers. PS-HMBC comparisons were made between Me18–H7l (large) and Me18–H7h (small), which along with the ROESY experiment indicated the prevalence of the (7,8)-B2 rotamer. NOE effects were found between Me18–H6 (strong), Me18–H7h (strong) and Me18–H7l (weak). All six carbon–proton and proton–proton coupling constants were in perfect agreement with those found for the aminoacid model. The combination of these two diastereomeric relationships led us to assign an *anti* configuration between the NHCOEt and the methyl group in fragment A.

Fragment B. Once again the homonuclear coupling constants (see Table 5) suggested that there is one staggered rotamer for each bond: H4 should be in a *gauche* disposition to H3h and *anti* to H3l in the C3–C4 bond, while for the C2–C3 bond H2 should be *anti* to H3h and *gauche* to H3l.

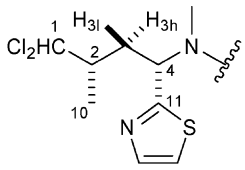
Although information concerning the C3–C4 bond could not be extracted from the PS-HMBC, the strong NOE interaction between NMe–H3l and the lack of NOE between NMe–H3h in the ROESY spectrum of **1** suggested the presence of the (3,4)-E3 rotamer. For the C2–C3 bond, PS-HMBC correlations provided only a small Me10–H3l coupling, while no other couplings could be observed. The ROESY experiment showed a stronger NOE for the pair H3l–$CHCl_2$ in comparison with H3l–Me10. A dipolar effect was not observed between H4–$CHCl_2$. Finally, the strong H2–H3l NOE suggested the presence of (2,3)-B2 as the major rotamer. The assembly of these two segments into a *syn* configuration between the thiazole ring and the methyl group gave the relative configuration of fragment B.

The sponge *Dysidea* sp. yielded structurally diverse secondary metabolites and, among these, polychlorinated compounds have been proven to have a sponge-cyanobacterial complex origin. All of these compounds are characterized by the presence of fragments derived from leucine in which several CH_3 groups are replaced by $CHCl_2$ or CCl_3 moieties. It has been demonstrated that the addition occurs at the pro-*R*-methyl group, which always generates the *S* configuration at the new chiral center.[15] Some studies have confirmed the influence of the *S* configuration of the tri- or dichloromethyl groups in the cytotoxic activity of this kind of compound.[16] Bearing in mind that all known compounds possessing this unit have been described with the *S* absolute configuration, we propose the absolute configuration for the new compound to be (2*S*, 4*S*, 5*S*, 7*S*).

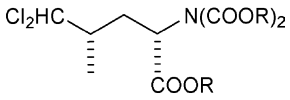
3. Conclusions

The relative configurations of two leucine-like fragments of a new compound, dysithiazolamide **1**, isolated from *Dysidea* sp. were determined by using NOE and the

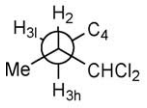
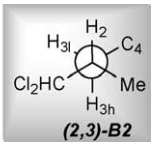
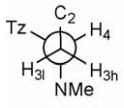
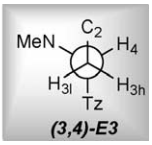
Table 5. ^{3}J(H,H) and $^{2,3}J$(C,H) (Hz) values and corresponding conformers for fragment B of dysithiazolamide (**1**) and comparison with those of the synthetic model **3a**

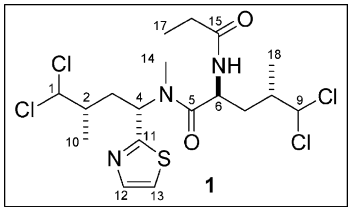


Fragment B



R=*t*-Bu, **3a**

Bond	Possible conformers		^{3}J(H,H)	**1**	**3a**	$^{2,3}J$(C,H)	**1**	**3a**	NOE (**1**)	
C2–C3			H_2–H_{3l}	2.6	4.3	$^{3}J(C_{10}, H_{3l})$	Large	6.2	Me_{10}–H_{3l}	Weak
	(2,3)-A3	***(2,3)-B2***	H_2–H_{3h}	10.3	11.0	$^{3}J(C_1,H_{3l})$	Small	3.4	H_1–H_{3l}	Strong
									Me_{10}–H_4	Medium
									H_2–H_3	Strong
C3–C4			H_4–H_{3l}	11.5	11.0				H_{3l}–NMe	Strong
	(3,4)-D2	***(3,4)-E3***	H_4–H_{3h}	4.2	3.0					



$^{2,3}J$(C,H) methodology. The final absolute configuration of **1** was also proposed by comparison with analogous compounds isolated from *Dysidea* sponges. An extensive set of Quantum Mechanical theoretical calculations for the various possible conformers and their coupling constants, were compared with those measured by NMR experiments, and the aminoacid **3a** helped to confirm the configurational relationships at the 1,3-methylcarboamido systems.

Although the *J*-based methodology has proved to be very useful for analysis of polyoxygenated or poplymethylated framework, no many studies for nitrogen-containing acyclic compounds have been conducted. A systematic, and hence reliable collection of more $^{2,3}J$(C,H) experimental data from suitable models, as **3a** and others very recently published by us,[5c] will cover this gap in order to be applied to unknown natural compounds with these nitrogen motifs.

4. Experimental

4.1. Biological material

Specimens of *Dysidea* sp. were collected in October 1996 in the Mayo Island near Sulawesi Island (Indonesia) (Coordinates: 1°19′699 N, 126°25′129 E.) at depth range 40 feet and identified by Dr. Cristina Díaz. Voucher samples are deposited at the Departamento de Química Fundamental, Universidade de A Coruña, under reference UDC 96015. A picture can be obtained from the authors.

4.2. Extraction and isolation

Specimens of the sponge (500 g) were homogenized in MeOH (3×2.5 L), and the solvent was evaporated under reduced pressure. The crude extract was partitioned between CH_2Cl_2 and H_2O (1:1). The fraction soluble in CH_2Cl_2 was evaporated under pressure and partitioned between 10% aqueous MeOH (400 mL) and hexane (2×400 mL). Water was added to the polar fraction until the mixture became 50% aqueous MeOH and then was extracted with CH_2Cl_2 (3×400 mL). The viscous oil (0.76 g) obtained from the CH_2Cl_2 fraction was repeated submited to flash column chromatography (eluting with hexane/EtOAc mixtures of increasing polarity) to give five fractions. First fraction was purified by reversed-phase HPLC eluting with MeOH–H_2O (8/2) to obtain 1.2 mg of compound **1** along with 25 mg of the known compound dysidenin (**2**).

4.2.1. Dysithiazolamide (1). ^{1}H and ^{13}C see Table 1. (+)-HR-ESIMS: exact mass 490.0661, calcd for $C_{18}H_{28}Cl_4N_3O_2S$ 490.0684. (+)-LR-APCIMS *m/z* (int.): 490 (53), 492 (66), 494 (37). $[\alpha]_D$ −35 (*c* 0.08, CH_2Cl_2).

4.3. QM calculations

Calculations were carried out using the Gaussian03W, version C-2 software package.[14] Structures and energies of the species considered were optimized at the DFT levels using the functionals B3LYP and mPW1PW91 and the 6-31G(d) or 6-311G(d) basis set.

The coupling constants were calculated using a GIAO

approach by DFT methods employing the B3LYP and mPW1PW91 functionals. For each of the approaches considered, the 6-31G(d,p) and 6-311G(d,p) basis sets were utilized.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.08.011. One- and two-dimensional NMR and ESIMS for the new compound along with QM calculations.

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Remote stereocontrol by sulfinyl groups: asymmetric alkylation of chiral 2-*p*-tolylsulfinyl benzyl carbanions

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Abstract—Alkylation reactions of the benzyllithiums derived from enantiomerically pure 2-*p*-tolylsulfinyl alkylbenzenes have been carried out with excellent yields and high de. A lithiation-substitution sequence, stereochemically controlled by a remote sulfoxide, accounts for the experimental results.

1. Introduction

Many important classes of natural products with biological significance have benzylic carbon stereocenters that lack heteroatoms and bear an alkyl group, which is usually methyl.[1] The absence of any functionality at a such position reduces the number of possibilities for synthesizing them and converts the creation of these benzylic chiral centers in a significant challenge in asymmetric synthesis.[2] Enantioselective deprotonation/substitution processes of benzylic positions have been widely investigated in the last years.[3] The alkylation of benzylcarbanions with heteroatom-containing substituents at α position (O, N, Si, S) has been intensively explored employing several chiral auxiliaries such as formamidines,[4] oxazolines,[5] (*S*)-methoxymethyl pyrrolidine derivatives[6] or carbamates.[7] Tricarbonylchromium arene complexes[8] or chiral ligands, such as bis (oxazolines)[9] and (−)-sparteine,[10] have been also applied. The observed ee were variable and dependent on the alkylating agent.

In our continuing search for new applications of sulfoxides in asymmetric synthesis,[11] we found that *ortho*-*p*-tolylsulfinyl group can stabilize benzyllithium carbanions and promote highly diastereoselective reactions, according to asymmetric 1,4-induction processes. Their nucleophilic addition to carbonyl compounds[12] and *N*-sulfinyl imines[13] evolved with a complete control at the configuration of the benzylic center. The success of these reactions was attributed to the coordination of the electrophile to the benzyllithium as a previous step to the nucleophilic attack. The importance of these reactions for the asymmetric synthesis of benzylic centers prompted us to investigate the behavior of these prochiral benzyl carbanions in other type of reactions, such as those of nucleophilic substitution, where the electrophiles are not coordinating. Moreover, these reactions would provide compounds lacking of any other functionality. In this paper, we describe the results obtained in reactions of 2-*p*-tolylsulfinyl alkylbenzenes with different alkylating agents in the presence of LDA.

2. Results and discussion

Sulfoxides **1** and **2** were prepared in high ee (>98%) according to the procedure previously reported[12a] starting from *ortho*-bromo derivatives of ethylbenzene and *n*-propylbenzene, respectively. The last one is not commercially available and was prepared by reductive deoxygenation of benzylic alcohol **3** employing the combination of chlorodimethylsilane and a catalytic amount of $InCl_3$[14] (Scheme 1).[15]

We first studied the alkylation reactions on sulfoxide **1** (Table 1). The addition of LDA (1.2 equiv) to a solution of **1** in THF at −78 °C, immediately produces a colored solution indicative of formation of the anion. We further added the alkylating reagents and maintained the same temperature during 3 h. The alkylation with benzyl or allyl bromide proceeded with high yields and stereoselectivities to afford **5a** or **6a** as the major products, respectively (entries 1 and 4). Diastereoselectivity was not improved by decreasing the temperature till −90 °C (entries 2 and 5). Remarkable decreases in the de are observed when alkyl chlorides are

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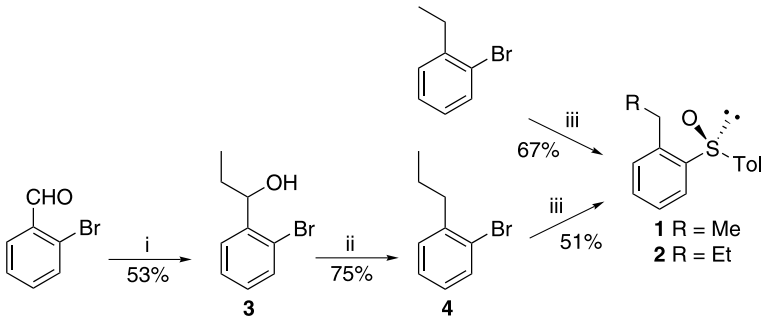
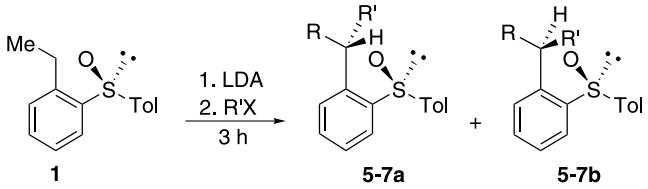


Scheme 1. Synthesis of the starting sulfoxides **1** and **2**.

Table 1. Alkylation of (*S*)-1-*p*-tolylsulfinyl-2-ethylbenzene (**1**)



Entry	RX	Temperature (°C)	Compound	a:b	Overall yield
1	BnBr	−78	**5**	92:8	87 (78)[a]
2	BnBr	−90	**5**	92:8	[b]
3	BnCl	−78	**5**	70:30	78
4	AllylBr	−78	**6**	87:13	86 (55)[a]
5	AllylBr	−90	**6**	86:14	[b]
6	AllylCl	−78	**6**	52:48	74
7	EtI	−78		—	—
8	EtOTf	−78	**7**	86:14	86

[a] Isolated yield of the major epimer.
[b] Yield not determined.

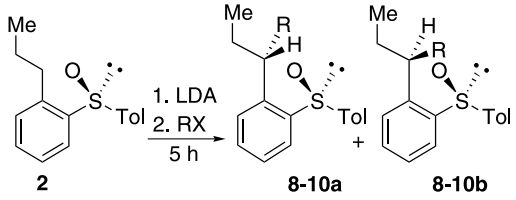
used as electrophiles instead of bromides (entries 3 and 6). This influence of the leaving group on the stereoselectivity had been also observed by Beak.[10e,f] These results show that the stereoselectivity is dependent on the leaving group of the alkyl halide. Less reactive alkylating agents are not efficient enough and thus ethyl triflate had to be used (entry 8) instead ethyl iodide, which afforded a complex mixture (entry 7).

Sulfoxide **2** was treated under the same conditions as **1**. Reactivity of **2** is clearly lower than that of **1** as it can be deduced from the presence of a significant amount of unreacted **2**, detected by ^{1}H NMR, in the crudes of all the performed experiences. After several modifications of the experimental conditions (temperature, solvent and reaction time) we determined that the best results were obtained by adding the electrophile in two batches with 2 h between the additions. However, even in these conditions, a variable residue of **2** remains unreacted. The results are collected in Table 2.

The previously commented lower reactivity of **2** is compensated by its higher stereoselectivity. Benzylation and allylation proceeded with around 90% de (entries 1 and 2) whereas methylation with MeOTf took place with 78% de (entry 3). Both, yield and diastereoselectivity slightly decreased with MeI (70% de, entry 4). The conversion was not complete in any case even when the reaction time is enlarged until 28 h. As it was expected, the ^{1}H NMR spectra for diastereoisomers **10a** and **7b** are identical, as well as those for **10b** and **7a**.

The separation of the obtained diastereoisomers was not an easy task. Compound **5a** was achieved diastereomerically pure by flash chromatography, whereas **6a** was separated from **6b** by crystallization. Diastereoisomers **7**–**10** had to be separated by chiral HPLC (see Section 4).

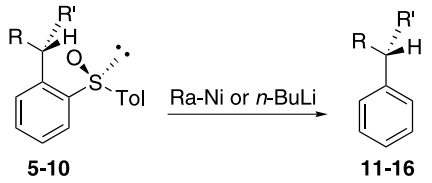
Table 2. Alkylation of (*S*)-1-*p*-tolylsulfinyl-2-propylbenzene (**2**)



Entry	RX	Product	a:b	Overall yield
1	BnBr	**8**	95:5	75[a]
2	AllylBr	**9**	94:6	80[b]
3	MeOTf	**10**	89:11	74[b]
4	MeI	**10**	85:15	65[b]

[a] Starting material (4%) was recovered.
[b] Starting material (10%) was recovered.

Table 3. Desulfinylation of *ortho*-sulfinyl alkylbenzenes **5–10**



Entry	R, R' (sulfoxide)	Method	Product	Yield	Configuration
1	Me, Bn (**5a**)	Ra-Ni	**11**	60	*R*
2	Et, Bn (**8a**:**8b**, 95:5)	Ra-Ni	**12**	59	*R*
3	Me, Et (**7a**:**7b**, 65:35)	*n*-BuLi	**13**	43	*R*
4	Et, Me (**10a**:**10b**, 93:7)	*n*-BuLi	**14**	22	*S*
5	Me, Allyl (**6a**)	*n*-BuLi	**15**	38	*R*
6	Et, Allyl (**9a**:**9b**, 91:9)	*n*-BuLi	**16**	52	*R*

2.1. Desulfinylation reactions: configurational assignment

The configuration of the predominant diastereoisomers was established by conversion of compounds **5–10** into optically active alkylbenzenes. The structure determination had been established by comparison with authentic samples (ee), see Section 4. Desulfinylation of benzylic derivatives **5** and **8** with Raney nickel gave (*R*)-**11** and (*R*)-**12**, respectively (Table 3, entries 1 and 2). The reactions of dialkyl derivatives **7** and **10** with Ra-Ni only progress till sulfenyl derivatives even enlarging the reaction times. Therefore, it was necessary to perform the hydrogenolysis with *n*-BuLi[16] (entries 3 and 4) to afford (*R*)-**13** and (*S*)-**14**.[†] The low yields obtained with *n*-BuLi are not surprising on the basis of the large similarity of the aryl groups joined to the sulfinyl group. Treatment of allylic derivatives **6** and **9** with Ra-Ni afforded complex mixtures, being the sulfenyl derivatives with reduced double bound the major products. By enlarging the reaction times desulfurated products with no double bond could be isolated in low yields. The reactions of **6** and **9** with *n*-Bu–Li afforded better yields of **15** and **16**, respectively (entries 5 and 6).

2.2. Stereochemical discussion

The stereochemical outcome of the alkylations is in accordance with that previously proposed for reaction of *ortho*-*p*-tolylsulfinyl benzyllithium carbanions with aldehydes.[12] Taking into account steric effects, benzyllithium derivative **A** must be the most stable among all diastereomers and conformers since the most sized groups at sulfur (*p*-Tol) and benzyl carbon (*R*) lack of allylic strain with the *ortho* protons (Fig. 1). In the reactions of these species with aldehydes, the carbonyl oxygen becomes associated with the lithium as a previous step to the nucleophilic addition. As this association is not possible with alkyl halides or triflates, their reactivity is clearly lower (longer reaction times). However, the fact that the configuration at the benzylic carbon for the major diastereoisomer for alkylations was the same than that obtained in nuclephilic additions to aldehydes, suggests that both reactions proceed with retention in the configuration of the carbanions. The

[†] Compounds **13** and **14** are enantiomers of the same product. They are achieved from the use of enriched mixtures of diastereoisomers **7a** or **10a**, respectively.

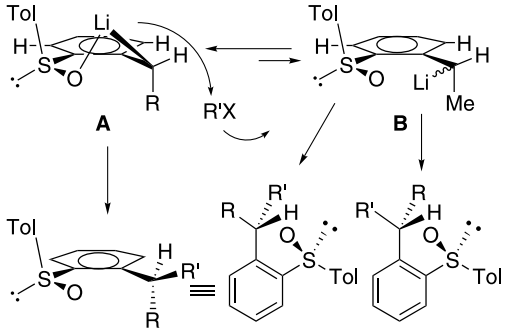


Figure 1. Stereochemical course of the reaction.

incomplete stereoselectivity observed for alkylations (de ranged between 70–90%) may be explained by assuming the lower reactivity of these electrophiles. This fact determines that they partially require to be attacked by the less stable but more reactive species **B**, without defined configuration (Fig. 1).

3. Conclusion

We have described the asymmetric alkylation of 2-*p*-tolylsulfinyl alkylbenzenes controlled by the remote sulfinyl group. Reactions are highly stereoselective and their de is higher by increasing the reactivity of the electrophiles and the length of the chain of the starting material. Desulfuration with Ra-Ni or *n*-BuLi yields compounds with chiral benzylic centers in high but not complete optical purity, which is probably due to some problems in the purification of the intermediates.

4. Experimental

4.1. General experimental methods

Solvents were purified according to standard procedures. Reactions were monitored by TLC on commercially available precoated plates (Merck silica gel 60 F_{254}). Flash chromatography was performed with Merck silica gel 60 (230–400 mesh ASTM). Melting points were measured using a Gallemkamp apparatus in open capillary tubes. Specific rotations were measured at room temperature on a Perkin-Elmer 241 MC polarimeter and concentrations

are expressed in g/100 mL. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AC-300 spectrometer (300 and 75 MHz, respectively). Chemical shifts are reported in ppm and *J* values are given in Hz. The attributions are supported by double resonance experiments. IR spectra were obtained in film with a Bruker Vector 22 spectrometer (4000–400 cm^{-1}). Mass spectra were measured by electron impact (EI, 70 eV) or FAB with a VG AutoSpec spectrometer. Elemental analyses were obtained with a Perkin-Elmer 2400 CHNS/O series II. Daicel Chiralcel OD or Chiralpack AD columns and hexane/isopropanol as eluant by using an Agilent 1100 HPLC equipment.

4.2. Synthesis of 2-*p*-tolylsulfinyl alkylbenzenes

4.2.1. 1-(2-Bromophenyl)-1-propanol (3). A solution of ethylmagnesium bromide, previously formed by addition of bromoethane (6.5 mL, 88.0 mmol) over Mg (1.9 g, 80.0 mmol) in anhydrous ether (20 mL), was added slowly over a solution of 2-bromobenzaldehyde (9.8 mL, 84.0 mmol) in anhydrous ether (10 mL) at 0 °C. After 5 h stirring at room temperature, the mixture was hydrolyzed (30 mL of saturated NH_4Cl), extracted (3×30 mL of ether), dried ($MgSO_4$), washed with brine and the solvent evaporated. The residue was purified by flash column chromatography (eluant, hexane/AcOEt 9:1). Yield: 53% as colorless oil. IR: 3385, 2967, 1466, 1020, 741 cm^{-1}. ^{1}H NMR: δ 7.52 (m, 2H, Ar), 7.33 (t, 1H, J=7.5 Hz, Ar), 7.11 (dt, 1H, J=1.6, 7.5 Hz, Ar), 5.00 (dd, 1H, J=4.8, 7.5 Hz, –C*H*–OH), 2.09 (broad s, 1H, –O*H*), 1.94–1.59 (m, 2H, CH_3–CH_2—), 1.00 (t, 3H, J=7.5 Hz, CH_3–CH_2–). ^{13}C NMR: δ 143.5, 132.6, 128.7, 127.6, 127.3, 122.1, 74.2, 30.5, 10.1. Anal. Calcd for $C_9H_{11}BrO$: C, 50.26; H, 5.15. Found: C, 50.36; H, 5.12. *m/z* (EI$^+$): 214 (M^+, 12), 185 (100), 157 (22), 105 (14), 84 (42), 77 (88). HRMS calcd for $C_9H_{11}BrO$: 213.9993. Found: 213.9986.

4.2.2. 1-Bromo-2-propylbenzene (4). A solution of alcohol **3** (4.3 g, 20.1 mmol) in freshly distilled CH_2Cl_2 (30 mL) was added to a solution of $InCl_3$ (5–10 mol%) and Me_2SiClH (6.0 mL, 54.2 mmol) in CH_2Cl_2 (50 mL) at room temperature under Ar atmosphere. After 45 min stirring, the mixture was hydrolyzed (50 mL of H_2O), extracted (3×50 mL of ether), dried ($MgSO_4$), washed with brine and the solvent evaporated. The residue was purified by flash column chromatography (eluant, hexane). Yield: 75% as colorless oil. IR: 2960, 2871, 1469, 1439, 1021, 748 cm^{-1}. ^{1}H NMR: δ 7.52 (d, J=7.5 Hz, 1H, Ar), 7.21 (m, 2H, Ar), 7.04 (m, 1H, Ar), 2.71 (m, 2H, –CH_2–Ar), 1.65 (sx, 2H, J=7.3 Hz, CH_3–CH_2–), 0.98 (t, 3H, J=7.3 Hz, CH_3–CH_2–). ^{13}C NMR: δ 141.8, 132.6, 130.3, 127.3, 127.2, 124.4, 38.2, 23.0, 13.8. Anal. Calcd for $C_9H_{11}Br$: C, 54.30; H, 5.57. Found: C, 54.49; H, 5.15.

4.2.3. (*S*)-1-*p*-Tolylsulfinyl-2-propylbenzene (2). The synthesis of this compound was performed starting from **4** according to the procedure previously reported for **1**.[12a] Yield: 51% as white solid. Mp: 29–30 °C (Et_2O/hexane). (α($^{20}_{D}$ −128.2 (*c* 1, $CHCl_3$). IR: 2961, 1642, 1467, 1085, 1033 cm^{-1}. ^{1}H NMR: δ 7.92 (m, 1H, Ar), 7.47 and 7.23 (AA′BB′ system, 4H, Tol), 7.39 (m, 2H, Ar), 7.19 (m, 1H, Ar), 2.82–2.55 (m, 2H, –CH_2–Ar), 2.35 (s, 3H, CH_3–Ar), 1.57 (m, 2H, –CH_2–CH_3), 1.14 (t, 3H, J=7.5 Hz, CH_3–CH_2). ^{13}C NMR: δ 142.7, 142.1, 141.9, 141.5, 130.9, 129.9, 129.5, 127.1, 125.9, 124.8, 33.8, 24.0, 21.3, 13.9. Anal. Calcd for $C_{16}H_{18}OS$: C, 74.38; H, 7.02; S, 12.41. Found: C, 74.38; H, 7.09; S, 12.26. *m/z* (EI$^+$): 258 (M^+, 6), 241 (100), 211 (44), 166 (41), 149 (74), 91 (51), 77 (18). HRMS calcd for $C_{16}H_{18}OS$: 258.1078. Found: 258.1070.

4.3. General procedure for alkylations

A solution of *n*-BuLi 2.5 M in hexane (0.60 mmol, 1.2 equiv) was added over *i*-Pr_2NH (0.90 mmol, 1.8 equiv) in THF (3 mL) at 0 °C. After 45 min stirring, the mixture was cooled at −78 °C and a solution of the sulfoxide **1** or **2** (0.50 mmol, 1.0 equiv) in THF (2 mL) was added and purple anion formed. After 1 h stirring, the electrophile (1.5 mmol, 3.0 equiv) was added. 3 h later, the mixture was hydrolyzed at that temperature (5 mL of saturated NH_4Cl), extracted (3×5 mL of CH_2Cl_2), dried (Na_2SO_4), washed with brine and the solvent evaporated. The residue was purified by flash column chromatography. For sulfoxide **2** two further equivalents were added after 2 h of reaction and 3 h later the mixture was hydrolyzed. Conditions of separation by HPLC are indicated in any case.

4.3.1. [2*R*,(*S*)*S*]-2-[2-(*p*-Tolylsulfinyl)phenyl]-1-phenylpropane (5a). This compound was obtained starting from sulfoxide **1**. Eluant for chromatography: hexane/AcOEt 1:3. Yield **5a**+**5b** (92:8): 87%. The mixture of **5a** and **5b** resulting from the chromathography of the crude reaction was newly chromatographied (eluant:hexane/EtOAc 3:2) to give **5a** with de>98% (yield 78%). Daicel Chiralpack AD (hexane/*i*-PrOH 90:10, flow rate 1 mL/min): t_S=23.4 min and t_R=24.9 min. (α($^{20}_{D}$ −174.7 (*c* 2, $CHCl_3$). IR: 3026, 2963, 2925, 1595, 1493, 1083, 1030 cm^{-1}. ^{1}H NMR: δ 7.79 (d, 1H, J=7.4 Hz, Ar), 7.50–7.35 (m, 3H, Ar), 7.25–7.16 (m, 7H, Ar), 6.91 (m, 2H, Ar), 3.60 (sx, 1H, J=6.9 Hz, CH_3–C*H*–), 2.72 (d, 2H, J=7.5 Hz, Ph-CH_2–), 2.36 (s, 3H, CH_3–Ar), 1.26 (d, 3H, J=6.9 Hz, CH_3–CH–). ^{13}C NMR: δ 145.5, 142.2, 141.7, 141.3, 139.7, 131.3, 129.8, 129.0, 128.1, 127.3, 126.5, 125.9, 125.7, 43.1, 36.3, 21.9, 21.3. Anal. Calcd for $C_{22}H_{22}OS$: C, 79.00; H, 6.63; S, 9.59. Found: C, 78.89; H, 6.68; S, 9.99. *m/z* (EI$^+$): 334 (M^+, <1), 317 (100), 243 (24), 225 (95), 211 (31), 135 (24), 91 (79), 77 (15). HRMS calcd for $C_{22}H_{22}OS$: 334.1391. Found: 334.1379.

4.3.2. [4*R*,(*S*)*S*]-4-[2-(*p*-Tolylsulfinyl)phenyl]-1-pentene (6a). This compound was obtained starting from sulfoxide **1**. Eluant for chromatography: hexane/AcOEt 4:1. Yield **6a**+**6b** (87:13): 86%. The mixture of **6a** and **6b** resulting from the chromathography of the crude reaction was crystallized to give **6a** with de>98% (yield 55%). Mp: 67–68 °C (Et_2O/hexane, white solid). Daicel Chiralpack AD (hexane/*i*-PrOH 87:13, flow rate 1 mL/min): t_S=11.4 min and t_R=12.4 min. (α($^{20}_{D}$ −120.0 (*c* 1, $CHCl_3$). IR: 2961, 2931, 1593, 1472, 1081, 1027 cm^{-1}. ^{1}H NMR: δ 7.96 (m, 1H, Ar), 7.48 and 7.23 (AA′BB′ system, 4H, Tol), 7.47–7.38 (m, 2H, Ar), 7.28 (m, 1H, Ar), 5.49–5.35 (m, 1H, –C*H*=CH_2), 4.86–4.81 (m, 2H, CH_2=CH–), 3.26 (sx, 1H, J=6.7 Hz, CH_3–C*H*–), 2.36 (s, 3H, CH_3–Ar), 2.15–1.92 (m, 2H, –CH_2–CH–), 1.25 (d, 3H, J=6.9 Hz, CH_3–CH–). ^{13}C NMR: δ 145.1, 142.0, 141.6, 135.8, 131.1, 129.9, 127.2, 126.4, 126.3, 124.7, 116.5, 41.2, 34.2, 21.6, 21.3. Anal.

Calcd for $C_{18}H_{20}OS$: C, 76.01; H, 7.09; S, 11.27. Found: C, 76.38; H, 7.22; S, 11.12. *m/z* (EI^+): 284 (M^+, 2), 267 (91), 243 (30), 225 (100), 211 (24), 143 (55), 135 (32), 91 (47), 77 (20). HRMS calcd for $C_{18}H_{20}OS$: 284.1235. Found: 284.1233.

4.3.3. [2*R*,(*S*)*S*]-2-[2-(*p*-Tolylsulfinyl)phenil]-butane (7a). This compound was obtained from the reaction of sulfoxide **1** with ethyl triflate. Eluant for chromatography: hexane/AcOEt 4:1. Yield **7a**+**7b** (86:14): 86%. Daicel Chiralcel OD (hexane/*i*-PrOH 98:2, flow rate 1 mL/min): t_S= 27.9 min and t_R=30.3 min. Only the NMR parameters of major diastereoisomer **7a** are indicated. IR: 2957, 1463, 1082, 1057, 1028 cm^{-1}. ^1H NMR: δ 7.97 (m, 1H, Ar), 7.49 and 7.24 (AA′BB′ system, 4H, Tol), 7.45–7.36 (m, 2H, Ar), 7.28 (m, 1H, Ar), 3.10 (sx, 1H, J=6.9 Hz, CH_3–C*H*–), 2.36 (s, 3H, C*H*$_3$-Ar), 1.52–1.26 (m, 2H, CH_3–C*H*$_2$–), 1.24 (d, 3H, J=6.9 Hz, C*H*$_3$–CH–), 0.60 (t, 3H, J=7.3 Hz, C*H*$_3$–CH_2–). ^{13}C NMR: δ 145.6, 141.9, 141.2, 130.9, 129.5, 126.6, 125.9, 124.4, 123.9, 35.5, 29.4, 21.5, 20.9, 11.5. Anal. Calcd for $C_{17}H_{20}OS$: C, 75.50; H, 7.24; S, 11.52. Found: C, 75.21; H, 7.46; S, 11.76.

4.3.4. [2*R*,(*S*)*S*]-2-[2-(*p*-Tolylsulfinyl)phenyl]-1-phenyl-butane (8). This compound was obtained starting from sulfoxide **2**. Eluant for chromatography: hexane/AcOEt 3:1. Yield **8a**+**8b** (95:5): 75%. Daicel Chiralpack AD (hexane/*i*-PrOH 87:13, flow rate 1 mL/min): t_2=18.5 min, t_S= 19.6 min and t_R=23.2 min. The ^1H NMR parameters of minor diastereoisomer are indicated in italics. These values are required to establish the de. ($\alpha(^{20}_{D}$ −190.6 (*c* 1, $CHCl_3$). IR: 2961, 1644, 1454, 1083, 1032 cm^{-1}. ^1H NMR: δ 7.96 (m, 1H, Ar, minor diastereoisomer), 7.75 (m, 1H, Ar), 7.51–7.34 (m, 3H, Ar), 7.17–7.10 (m, 7H, Ar), 6.87 (m, 2H, Ar), 3.44 (m, 1H, –CH_2–C*H*–CH_2–), 2.80 and 2.69 (d AB system, 2H, J=7.5, 13.5 Hz, Ph-C*H*$_2$–), 2.35 (s, 3H, C*H*$_3$-Ar), 1.83–1.15 (m, 2H, CH_3–C*H*$_2$–), 0.81 (t, 3H, J=7.5 Hz, C*H*$_3$–CH_2–), 0.39 (t, 3H, J=7.3 Hz, C*H*$_3$–CH_2, minor diastereoisomer). ^{13}C NMR: δ 143.9, 143.7, 141.7, 141.1, 139.8, 131.2, 129.8, 129.1, 128.1, 127.4, 126.7, 125.9, 125.7, 43.5, 42.0, 29.2, 21.3, 11.7. *m/z* (EI^+): 348 (M^+, <1), 331 (100), 241 (36), 211 (37), 91 (62), 77 (9). HRMS calcd for $C_{23}H_{24}OS$: 348.1548. Found: 348.1521.

4.3.5. [4*R*,(*S*)*S*]-4-[2-(*p*-Tolylsulfinyl)phenil]-1-hexene (9). This compound was obtained starting from sulfoxide **2**. Eluant for chromatography: hexane/AcOEt 3:1. Yield **9a**+**9b** (94:6): 80%. Daicel Chiralpack AD (hexane/*i*-PrOH 90:10, flow rate 1 mL/min): t_S=13.1 min, t_R=14.0 min and t_2=15.9 min. The ^1H NMR parameters of minor diastereoisomer are indicated in italics. These values are required to establish the de. ($\alpha(^{20}_{D}$ −94.2 (*c* 1, $CHCl_3$). IR: 2962, 2929, 1640, 1469, 1084, 1033 cm^{-1}. ^1H NMR: δ 7.98 (m, 1H, Ar), 7.91 (m, 1H, Ar, minor diastereoisomer), 7.47 and 7.22 (AA′BB′ system, 4H, Tol), 7.45–7.39 (m, 2H, Ar), 7.25–7.20 (m, 1H, Ar), 5.37–5.24 (m, 1H, –C*H*=CH_2), 4.79–4.75 (m, 2H, C*H*$_2$=CH–), 3.05 (m, 1H, CH_2–C*H*–), 2.35 (s, 3H, C*H*$_3$-Ar), 2.19–1.90 (m, 2H, –C*H*$_2$–CH–), 1.87–1.45 (m, 2H, CH_3–C*H*$_2$–), 0.82 (t, 3H, J=7.3 Hz, C*H*$_3$–CH_2–), 0.47 (t, 3H, J=7.3 Hz, C*H*$_3$–CH_2, minor diastereoisomer). ^{13}C NMR: δ 143.4, 142.1, 141.7, 135.9, 131.1, 129.9, 127.2, 126.6, 126.5, 124.5, 116.4, 41.3, 39.8, 29.1, 21.4, 11.7. *m/z* (EI^+): 298 (M^+, 1), 281 (100), 257 (10), 241 (70), 239 (53), 149 (46), 91 (52), 77 (27). HRMS calcd for $C_{19}H_{22}OS$: 298.1391. Found: 298.1389.

4.3.6. [2*S*,(*S*)*S*]-2-[2-(*p*-Tolylsulfinyl)phenil]-butane (10a). This compound was obtained from the reaction of sulfoxide **2** with methyl triflate. Eluant for chromatography: hexane/AcOEt 4:1. Yield **10a**+**10b** (89:11): 86%. Only the NMR parameters of major diastereoisomer **10a** are indicated. ^1H NMR: δ 7.99 (m, 1H, Ar), 7.46 and 7.22 (AA′BB′ system, 4H, Tol), 7.41 (m, 2H, Ar), 7.25 (m, 1H, Ar), 3.06 (sx, 1H, J=6.9 Hz, CH_3–C*H*–), 2.35 (s, 3H, C*H*$_3$–Ar), 1.63 (quint, 2H, J=7.3 Hz, CH_3–C*H*$_2$–), 0.88 (d, 3H, J=6.9 Hz, C*H*$_3$–CH–), 0.84 (t, 3H, J=7.3 Hz, C*H*$_3$–CH_2–). ^{13}C NMR: δ 145.3, 142.7, 142.4, 141.5, 131.1, 129.9, 127.0, 126.1, 126.0, 124.1, 35.9, 31.3, 21.3, 20.9, 12.0.

4.4. General procedure for desulfynilations summarized in Table 3

Method A The sulfoxide was dissolved in a minimal amount of ethanol and excess of Raney nickel was added. The reaction mixture was vigorously stirred at room temperature and was monitored by TLC. When no starting material remained, stirring was stopped and the solvent was carefully decanted and filtered on Celite. The solvent was evaporated and the product was obtained from the residue in high purity (Table 3).

Method B A solution of *n*-BuLi in hexane (10 equiv) was added over a solution of sulfoxide in THF at −78 °C under Ar atmosphere. After 3 min stirring, the mixture was hydrolyzed at that temperature (saturated NH_4Cl), extracted (CH_2Cl_2), dried (Na_2SO_4), washed with brine and the solvent evaporated. The residue was purified by flash column chromatography with hexane as eluant.

4.4.1. (*R*)-1,2-Diphenylpropane (11).[17] This compound was obtained according to method A starting from sulfoxide **5a**. Yield: 60%. ($\alpha(^{20}_{D}$ −73.7 (*c* 1, $CHCl_3$). Lit.[17b] ($\alpha(^{20}_{D}$ −78.6 (*c* 2.02, $CHCl_3$) to ee>99%. ^1H NMR: δ 7.34–7.08 (m, 10H, Ar), 3.11–2.91 (m, 2H, Ph–C*H*$_2$–), 2.84–2.71 (m, 1H, CH_3–C*H*–), 1.25 (d, 3H, J=7.0 Hz, C*H*$_3$–CH–). ^{13}C NMR: δ 146.9, 140.8, 129.1, 128.2, 128.1, 127.0, 126.0, 125.8, 45.0, 41.8, 21.1.

4.4.2. (*R*)-1,2-Diphenylbutane (12).[18] This compound was obtained according to method A starting from a mixture of sulfoxides **8a**:**8b** (95:5). Yield: 59%. ($\alpha(^{20}_{D}$ −101.9 (*c* 1, $CHCl_3$). Lit.[18] ($\alpha(^{20}_{D}$ +12.5 (*c* 0.3, $CHCl_3$) to *S* configuration. The ee was not determined by the authors in that report. ^1H NMR: δ 7.43–7.18 (m, 10H, Ar), 3.04 (m, 2H, Ph–C*H*$_2$–), 2.92–2.83 (m, 1H, CH_2–C*H*–CH_2–), 1.96–1.69 (m, 2H, CH_3–C*H*$_2$–), 0.92 (t, 3H, J=7.3 Hz, C*H*$_3$–CH_2). ^{13}C NMR: δ 145.0, 140.8, 129.1, 128.1, 128.0, 127.8, 125.9, 125.7, 49.8, 43.5, 28.3, 12.1.

4.4.3. (*R*)-2-Rhenylbutane (13).[19] This compound was obtained according to method B starting from a mixture of sulfoxides **7a**:**7b** (65:35). Yield: 43%. ($\alpha(^{20}_{D}$ −6.2 (*c* 0.5, $CHCl_3$). Lit.[19a] ($\alpha(^{20}_{D}$ +28.4 (neat) to *S* configuration. The ee was not determined by the authors in that report. ^1H NMR: δ 7.35–7.14 (m, 5H, Ar), 2.60 (sx, 1H, J=7.0 Hz,

CH_3–C*H*–), 1.61 (quint, 2H, –CH_2–CH–), 1.25 (d, 3H, J= 7.0 Hz, CH_3–CH–), 0.84 (t, 3H, J=7.5 Hz CH_3–CH_2–).

4.4.4. (*S*)-2-Phenylbutane (14).[19] This compound was obtained according to method B starting from a mixture of sulfoxides **10a**:**10b** (3:97). Yield: 22%. (α($^{20}_{D}$ +10.4 (*c* 0.5, $CHCl_3$). Lit.[19a] (α($^{20}_{D}$ +28.4 (neat). The ee was not determined by the authors in that report.

4.4.5. (*R*)-4-Phenylpentene (15).[20] This compound was obtained according to method B starting from sulfoxide **6a**. Yield: 38%. (α($^{20}_{D}$ −21.4 (*c* 1, $CHCl_3$). Lit.[20a] (α($^{20}_{D}$ −19.3 (neat) to ee=97.4%. ^{1}H NMR: δ 7.32–7.14 (m, 5H, Ar), 5.75–5.61 (m, 1H, –C*H*=CH_2), 5.00–4.89 (m, 2H, CH_2=CH–), 2.57–2.34 (m, 3H, –CH_2–C*H*–), 1.81–1.49 (m, 2H, CH_3–CH_2–), 0.79 (t, 3H, J=7.3 Hz, CH_3–CH_2–). ^{13}C NMR: δ 145.2, 137.2, 128.2, 127.8, 125.9, 115.7, 47.6, 40.9, 28.8, 12.0.

4.4.6. (*R*)-4-Fenilhexeno (16).[19a,21] This compound was obtained according to method B starting from a mixture of sulfoxides **9a**:**9b** (95:5). Yield: 52%. (α($^{20}_{D}$ −8.0 (*c* 1, $CHCl_3$). Lit.[19a] (α($^{20}_{D}$ −8.99 (neat), ee∼86–89%. ^{1}H NMR: δ 7.32–7.14 (m, 5H, Ar), 5.75–5.61 (m, 1H, –C*H*=CH_2), 5.00–4.89 (m, 2H, CH_2=CH–), 2.57–2.34 (m, 3H, –CH_2–C*H*–), 1.81–1.49 (m, 2H, CH_3–CH_2–), 0.79 (t, 3H, J= 7.3 Hz, CH_3–CH_2–). ^{13}C NMR: δ 145.2, 137.2, 128.2, 127.8, 125.9, 115.7, 47.6, 40.9, 28.8, 12.0.

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Preparation of 15-membered unsaturated N–H containing azamacrocycles and their differential coordination with Pd(0) and Pd(II)

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Abstract—The use of 2-(trimethylsilylethyl)sulfonamide (SES-NH_2) has permitted the selective and efficient synthesis of new triolefinic 15-membered azamacrocycles **3**. Differential coordination mode with palladium has been observed when macrocycle **3aab** [(*E*,*E*,*E*)-1,6-bis(*p*-tolylsulfonyl)-1,6,11-triazacyclopentadeca-3,8,13-triene] was treated with a palladium(0) or a palladium(II) source.

1. Introduction

In the last 5 years we have studied 15-membered triolefinic macrocycles of type **1** and their capacity to coordinate palladium(0) giving the air- and moisture stable Pd^0-complexes of type **2** (Fig. 1).[1,2] The three olefinic double bonds in **1** are the only coordinating centers for the palladium atom because the three nitrogen atoms are devoid of coordinating ability due to lone pair conjugation with the SO_2 group. Palladium(0) complexes **2** were obtained by interchange of ligand using either $Pd(PPh_3)_4$ or $Pd(dba)_2$ as metal source. The palladium atom perfectly fit inside of the macrocyclic cavity being the coordination mode with the three olefins planar trigonal.[3]

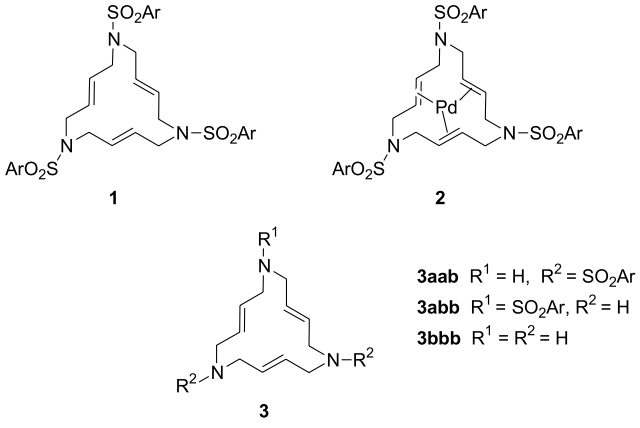

Figure 1.

On the other hand, azamacrocycles are important and powerful ligands in transition metal coordination chemistry.[4–7] Special attention has been paid to the coordination properties of cyclam[8] and porphyrin[9] derivatives. Since macrocycles **1** are structurally related to macrocyclic structures mentioned above, the preparation of N–H macrocycles **3** and the study of their coordinative properties was an interesting point of analysis. Unfortunately, the first attempts in our group to prepare unsaturated triolefinic azamacrocycles **3** by detosylation of **1** (Ar = *p*-tolyl) proved to be troublesome.

We present in this paper, the preparation of new unsaturated azamacrocycles **3** by selective removal of *N*-sulfonamide SE groups and their coordination with Pd^0 and Pd^{II}.

Moreover, introduction of two different metals—or the same metal in two different oxidation states—within the framework of an organic molecule in an ordered way at well-defined distances is a target that has interest in metal–metal interactions studies[10,11] and in metal deposition on solid supports for heterogeneous catalysis.[12–14] Our macrocycles **3** have the appropriate features for such an ordered distribution of metals.

Keywords: Macrocycles; Azamacrocycles; Sulfonamides; Protecting groups; Palladium.
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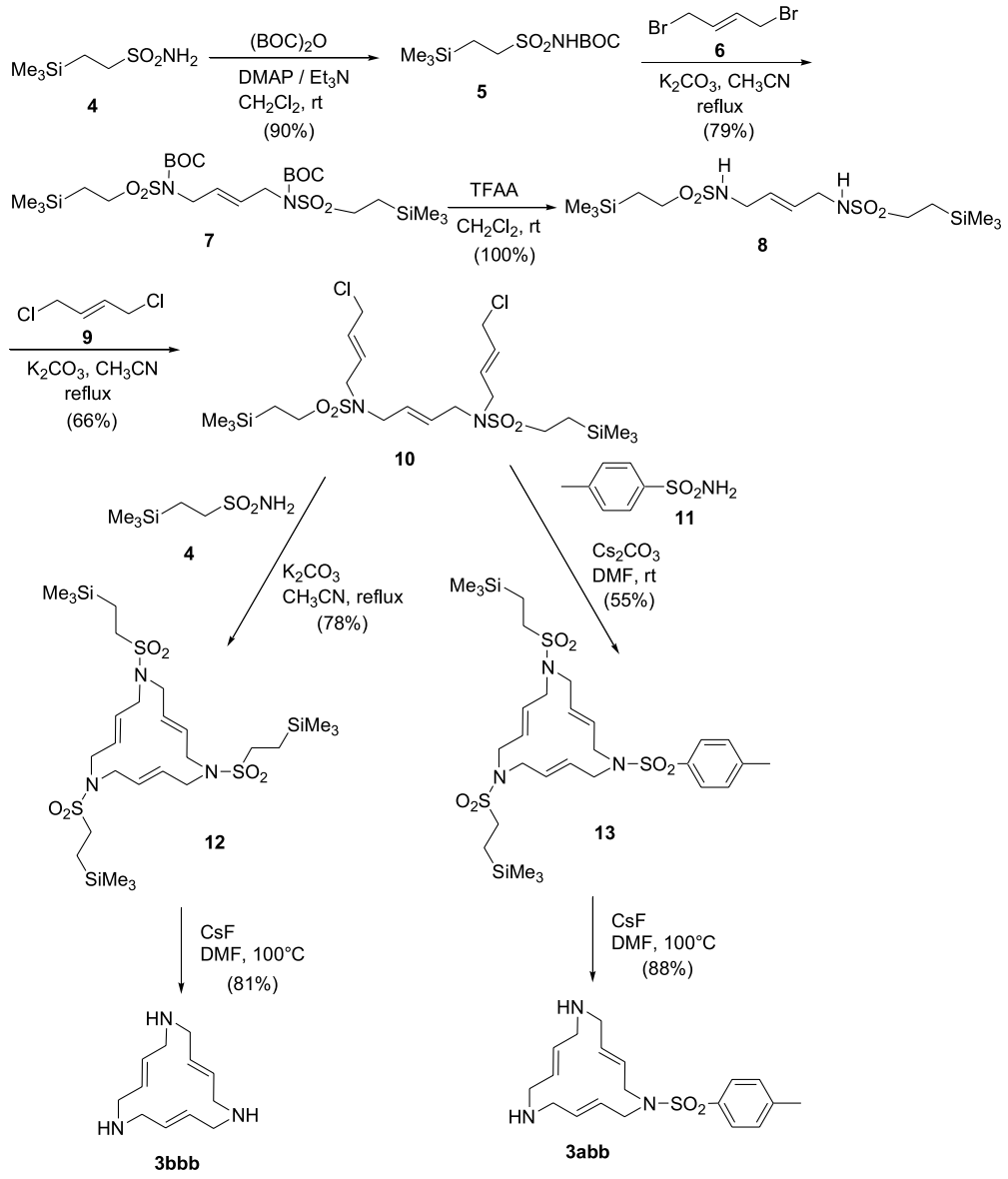


Scheme 1. Synthesis of 15-membered triolefinic azamacrocycles **3bbb** and **3abb**.

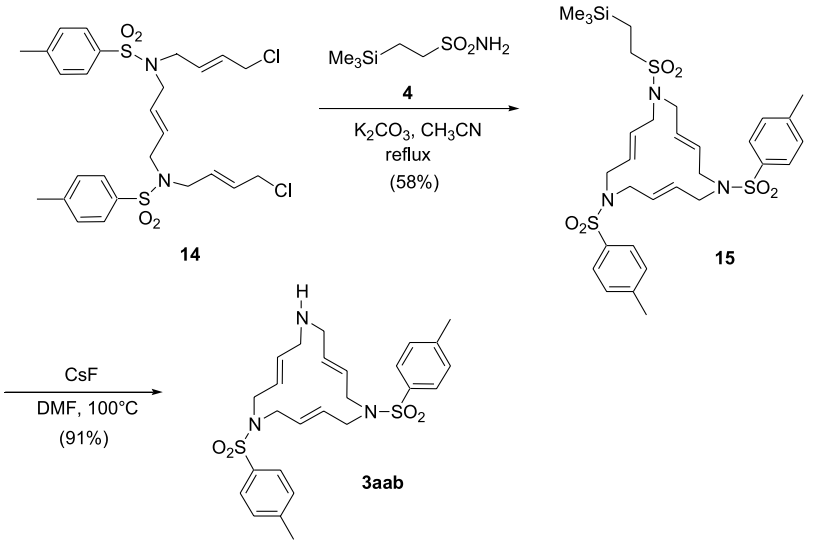
2. Results and discussion

The use of the 2-(tri-methylsilylethyl)sulfonyl (or SES) group as an amine protecting group has been reported in the literature.[15,16] SES-sulfonamides are easily deprotected under mild reaction conditions tolerating sensitive functionality in the compound and, in addition, the deprotection process leaves the free amine rather than the salt.[17,18] The selective and easy removal of the SES protecting group offers us the opportunity to prepare different types of unsaturated azamacrocycles **3** (Fig. 1). Preparation of macrocycles **3abb**, **3bbb** and **3aab** are outlined in Schemes 1 **and** 2.

2-(Trimethylsilylethyl)sulfonamide (SES-NH_2) **4** was prepared according to the procedure described in the literature.[18] Compound **4** was converted into its *N*-*tert*-butyloxycarbonyl (BOC) derivative **5**. Reaction of **5** with 0.5 equiv of *trans*-1,4-dibromo-2-butene (**6**) afforded the protected disulfonamide **7**. Treatment of **7** with trifluoroacetic acid selectively removed the BOC group to afford **8** in 100% yield. Conversion of **8** into **10** required an excess of dichloride **9** (8 equiv). After some optimizing work,[†] treatment of bis-sulfonamide **10** with one equiv of either SES-NH_2 **4** or *p*-tolylsulfonamide **11** gave, respectively, the two macrocycles **12** and **13**. The SES groups in macrocycles **12** and **13** were cleaved with cesium fluoride in anhydrous DMF at 100 °C affording azamacrocycles **3bbb** and **3abb** in 81 and 88% yield, respectively, (Scheme 1).

Macrocycle **3aab** was prepared as outlined in Scheme 2. Following the same pathway as for macrocycles **3bbb** and **3abb**, reaction of (*E*,*E*,*E*)-1,14-dichloro-*N*,*N*′-bis(*p*-tolylsulfonyl)-5,10-diazatetradeca-2,7,12-triene **14**[19] with SES-NH_2 **4** in the presence of potassium carbonate in refluxing

[†] The cyclisation step to **12** was also tried using Cs_2CO_3 as a base in DMF affording 45% yield when the reaction was run at room temperature and 58% yield when the reaction was run at 80 °C. The cyclisation step to **13** was also tried using K_2CO_3 in refluxing CH_3CN. Under these reaction conditions **13** was obtained in 45% yield.

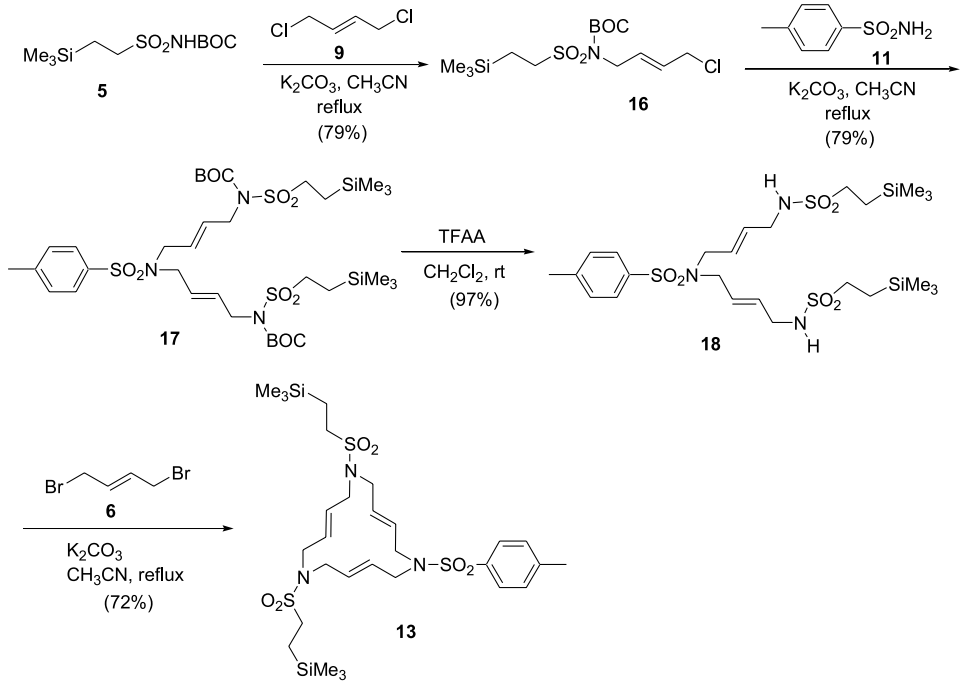


Scheme 2. Synthesis of 15-membered triolefinic azamacrocycle **3aab**.

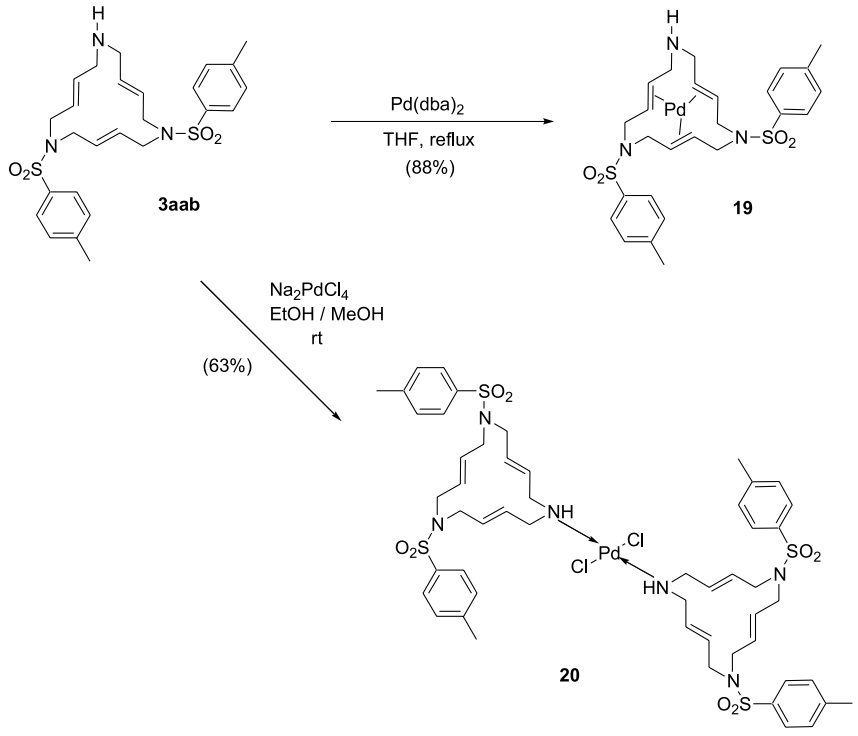
acetonitrile afforded macrocycle **15** in 58% yield. Deprotection of SES group using cesium fluoride in anhydrous DMF at 100 °C led to azamacrocycle **3aab** in 91% yield.

An alternative and more efficient way to prepare protected macrocycles, as for example **13**, is outlined in Scheme 3. The synthesis started with the BOC-protected SES-sulfonamide **5**, which was treated with an excess of dichloride **9** (4 equiv) to afford chlorosulfonamide **16** in 79% yield. Condensation of 2 equiv of **16** with 1 equiv of *p*-tolylsulfonamide **11** led to intermediate **17**. Again, treatment of **17** with trifluoroacetic acid removed selectively and efficiently (97% yield) the two BOC-protecting groups leaving the two SES-groups unaffected. Finally, cyclisation of **18** with 1 equiv of dibromobutene **6** in the presence of potassium carbonate in refluxing acetonitrile gave the macrocycle **13** in 72% yield. Comparing the two pathways for the synthesis of **13** the overall yield of five steps improves from 26% (Scheme 1) to 39% (Scheme 3).

Once we had azamacrocycles of type **3** in hand we decided to study their complexating ability towards palladium metal in its different oxidation states. Macrocycle **3aab** turned out to be the most soluble compound in classical organic solvents, therefore, it was the compound chosen for coordination studies. The results are summarized in Scheme 4. Owing to the high insolubility of macrocycles containing two or three NH groups (**3abb** and **3bbb**) no complexation studies with palladium could be done with them.



Scheme 3. Alternative pathway for the synthesis of protected macrocycle **13**.



Scheme 4. Complexation ability of azamacrocycle **3aab** in front of Pd^0 and Pd^{II} complexes.

Palladium(0) complex **19** was prepared in 88% yield by reaction of **3aab** with bis(dibenzylideneacetone)palladium(0) in refluxing THF. On the other hand, when **3aab** was treated with an alcoholic solution (EtOH–MeOH, 4:1) of sodium tetrachloropalladate(II) at room temperature, Pd^{II} complex **20** was obtained in 63% yield. Unfortunately, all attempts to obtain X-ray quality crystals of complexes **19** and **20** failed. However, the structure of Pd^0 complex **19** could be unequivocally assigned based on our previous structural analysis by means of NMR spectroscopy of Pd^0 complexes **2** (Fig. 1).[3] Upfield shift of the ^1H and ^{13}C NMR signals of the olefinic protons is an inequivocal proof of the triolefinic coordination mode of **19**.

Thus, the ^1H NMR spectrum of **3aab** showed a broad singlet at δ 5.69 ppm corresponding to the six olefinic protons and the ^{13}C NMR spectrum presented three signals at δ 129.4, 130.3 and 131.0 ppm for the olefinic carbon atoms. In contrast, the olefinic protons in Pd^0-complex **19**, compared to **3aab**, shifted strongly upfield ($\delta = 1.5$–4.8 ppm) following the normal behavior observed for complexes **2**,[3] as well as for other Pd^0-olefin complexes.[20–24] ^{13}C NMR spectrum of **19** showed the olefinic carbon atoms shifted by $\Delta\delta = 50$ ppm upfield as compared to the free ligand **3aab**. In contrast, this behavior is not observed for Pd^{II}-complex **20** (most probably *trans*-**20**). The ^1H NMR data for the olefins of Pd^{II}-complex **20** showed two broad signals at δ 5.5 and 5.8 ppm for the twelve olefinic protons and the ^{13}C NMR spectrum presented three signals in the same range (δ 128–132 ppm) as for the free ligand **3aab**. Furthermore, 2D heteronuclear (^1H–^{13}C HMQC) correlation spectrum has been done to confirm assignment of the ring protons (See Supplementary data)

In addition, complexes **19** and **20** presented correct elemental analysis and their molecular weight was confirmed by Electrospray Ionization Mass Spectrometry (ESI-MS). Compounds **19** and **20** were easily identified by the characteristic isotope distribution of the metal. Isotope abundance of clusters was compared with calculated values. The ESI mass spectra of **19** showed a cluster centered at *m*/*z* 622 assigned to the $[M+H]^+$ ion. The ESI mass spectra of **20** showed a cluster centered at *m*/*z* 1173 attributed to the cationic species $[M-Cl]^+$. Figure 2 shows the ESI-MS spectra of complexes **19** and **20**. The two insets show the isotope distribution pattern for the *m*/*z* 621 ion corresponding to $[M]^+$ of **19** and for the *m*/*z* 1173 ion corresponding to $[M-Cl]^+$ of **20**, respectively.

With all these data in hand, we can conclude that when macrocycle **3aab** is treated with a palladium(0) source, the metal atom is introduced into the macrocyclic cavity, being coordinated by the three olefins, whereas, when it is treated with palladium(II), the nitrogen donor atoms are responsible for the coordination.

Further studies on the complexation properties of this novel macrocycles are in progress in our laboratories.

3. Experimental

3.1. General remarks

2-(Trimethylsilylethyl)sulfonamide **4** was prepared according to the procedure of Robins et al.[18] (*E*,*E*,*E*)-1,14-dichloro-*N*,*N*′-bis(*p*-tolylsulfonyl)-5,10-diazatetradeca-2,7,12-triene **14** was prepared as previously reported by us for the 1,14-dibromo analogue.[19] 1,4-dibromo-2-butene, **6**,

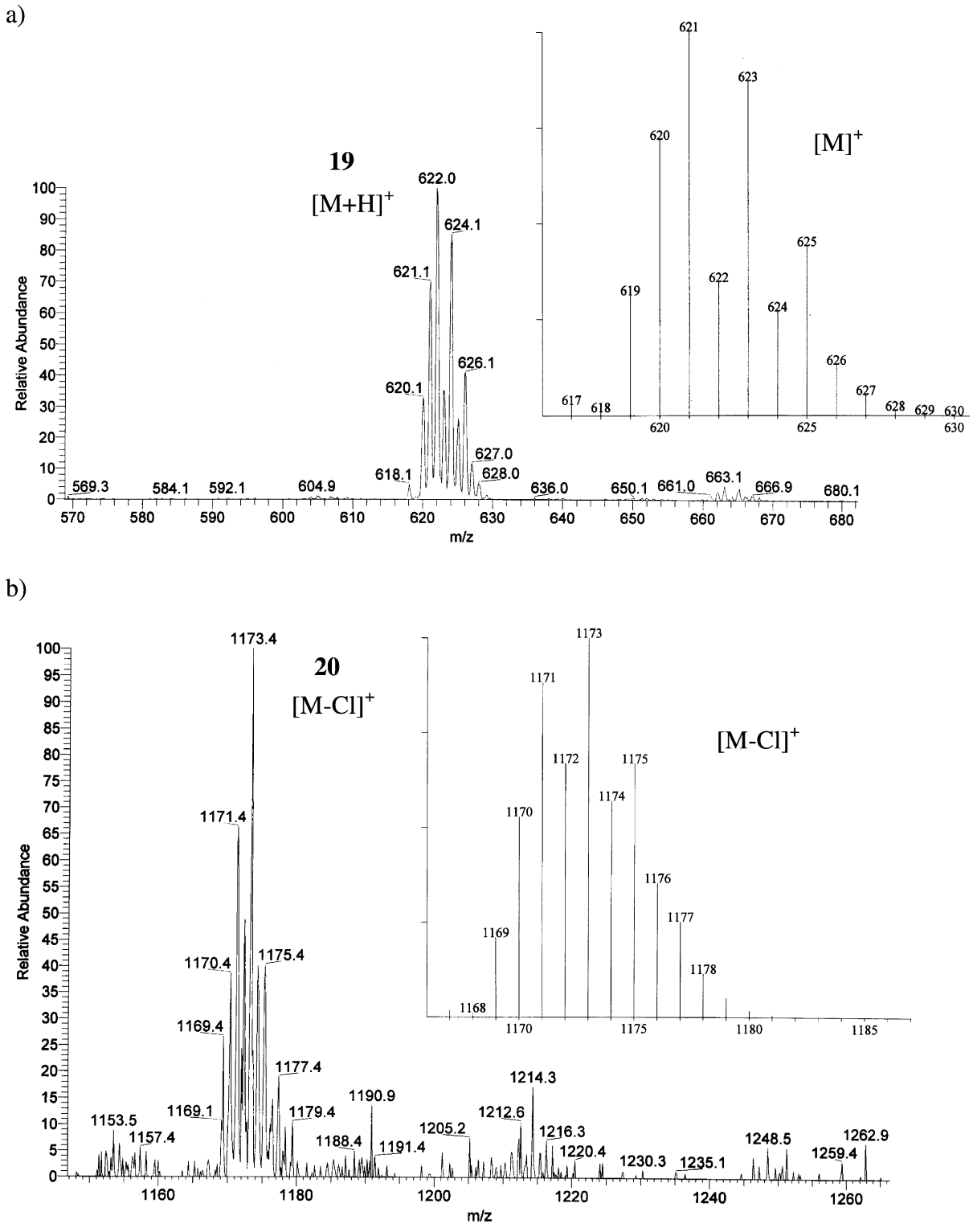


Figure 2. ESI(+) mass spectra of (a) complex **19** and (b) complex **20** compared with theoretical isotope distribution (the inset).

1,4-dichloro-2-butene, **9**, and *p*-tolylsulfonamide, **11**, are commercially available and were used as received.

^{1}H NMR (^{13}C NMR) spectra were recorded at 200 MHz (50 MHz) using Me_4Si as internal standard. Chemical shifts are given in δ units. ESI (electrospray ionization) mass spectra were acquired using a quadrupole mass spectrometer equipped with an electrospray ion source. The instrument was operated in the positive-ion mode (ESI+) at a probe tip voltage of 3 kV. Elemental analyses were determined at 'Servei d'Anàlisi de la Universitat de Girona'. TLC analyses were performed on silica gel 60 F 256 plates, and column chromatographies were performed on silica gel 60 (70–230 mesh).

3.1.1. *N*-(*tert*-Butyloxycarbonyl)(2-trimethylsilylethyl) sulfonamide (5). It was prepared according to the general method of ref.[25] Colorless solid. Mp 79–81 °C (*n*-hexane) (lit.[26] 82–82.5 °C). IR (ATR): ν 3258, 2984, 1710, 1432, 1341, 1245, 1130 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ 0.06 (s, 9H), 0.99–1.08 (m, 2H), 1.50 (s, 9H), 3.27–3.36 (m, 2H), 7.66 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS): δ −1.5, 10.8, 28.4, 49.9, 84.6, 150.6. ESI-MS (*m/z*): 299 $[M+NH_4]^+$, 580 $[2M+NH_4]^+$.

3.1.2. (*E*)-*N*,*N*′-Bis(*tert*-butyloxycarbonyl)-*N*,*N*′-bis[(2-trimethylsilylethyl)sulfonyl]-2-butene-1,4-diamine (7). A stirred mixture of **5** (0.74 g, 2.63 mmol), (*E*)-1,4-dibromo-2-butene (**6**) (0.28 g, 1.31 mmol), potassium carbonate (0.66 g, 4.77 mmol), and acetonitrile (10 mL) was refluxed for 27 h (TLC monitoring). The salts were filtered off and the filtrate was evaporated to afford a residue, which was purified by column chromatograpy on silica gel (*n*-hexane–EtOAc, 9:1) to afford **7** (0.64 g, 79%) as a colorless solid. A sample specially purified for elemental analysis was obtained by digestion with *n*-hexane. Mp 120–121 °C (*n*-hexane). IR (ATR): ν 2954, 1723, 1346, 1137 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ 0.07 (s, 18H), 0.93–1.02 (m, 4H), 1.52 (s, 18H), 3.35–3.44 (m, 4H), 4.24 (br abs, 4H), 5.78 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS): δ −1.4, 10.9, 28.6, 48.0, 51.5, 85.0, 129.5, 152.0. ESI-MS (*m/z*): 632 $[M+NH_4]^+$. Anal. Calcd for $C_{24}H_{50}N_2O_8S_2Si_2$ (614.96): C, 46.87; H, 8.20; N, 4.56. Found: C, 47.03 and 47.02; H, 8.53 and 8.33; N, 4.51 and 4.50.

3.1.3. (*E*)-*N*,*N*′-Bis[(2-trimethylsilylethyl)sulfonyl]-2-butene-1,4-diamine (8). A mixture of **7** (0.41 g, 0.67 mmol), trifluoroacetic acid (0.31 mL, 4.02 mmol), and dichloromethane (6 mL) was stirred at room temperature for 24 h. Then, a second portion of trifluoroacetic acid (0.47 mL, 6.10 mmol) was added and the mixture was stirred 24 h more until completion of the reaction (TLC monitoring). The solution was washed with aqueous $NaHCO_3$ (2×10 mL), water (2×10 mL), dried over anhydrous sodium sulfate and evaporated. Compound **8** (0.28 g, 100%) was obtained as a colorless solid. A sample specially purified for elemental analysis was obtained by crystallization from CH_2Cl_2–*n*-hexane. Mp 119.5–120.5 °C (CH_2Cl_2–*n*-hexane). IR (ATR): ν 3283, 2954, 1310, 1248, 1134 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ 0.06 (s, 18H), 0.97–1.06 (m, 4H), 2.90–2.99 (m, 4H), 3.72 (br abs, 4H), 4.98 (br s, 2H), 5.78 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS): δ −1.3, 11.2, 45.3, 49.9, 129.8. ESI-MS (*m/z*): 415 $[M+H]^+$, 432 $[M+NH_4]^+$. Anal. Calcd for $C_{14}H_{34}N_2O_4S_2Si_2$ (414.73): C, 40.54; H, 8.26; N, 6.75. Found: C, 40.56 and 40.84; H, 8.34 and 8.53; N, 6.73 and 6.72.

3.1.4. (*E*,*E*,*E*)-*N*,*N*′-Bis[(2-trimethylsilylethyl)sulfonyl]-1,14-dichloro-5,10-diazatetradeca-2,7,12-triene (10). A stirred mixture of **8** (2.43 g, 5.86 mmol) and potassium carbonate (3.64 g, 26.34 mmol) was heated at 70 °C in acetonitrile (25 mL) for 10 min. Then, (*E*)-1,4-dichloro-2-butene (**9**) (5.43 mL, 49.72 mmol) was added. The mixture was refluxed for 18 h (TLC monitoring). The salts were filtered off and the solvent was evaporated under vacuum. The residue was crystallized from CH_2Cl_2–EtOAc–*n*-hexane to afford **10** (2.28 g, 66%) as a colorless solid. Mp 79.5–80.5 °C (*n*-hexane). IR (ATR): ν 2951, 1321, 1247, 1142 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ 0.09 (s, 18H), 0.98–1.07 (m, 4H), 2.88–2.97 (m, 4H), 3.87 (d, J=4.2 Hz, 8H), 4.09 (d, J=5.6 Hz, 4H), 5.60–5.95 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS): δ −1.4, 11.0, 44.4, 48.6, 49.1, 50.0, 130.0, 130.3, 131.0. ESI-MS (*m/z*): 591–593 $[M+H]^+$, 608–610 $[M+NH_4]^+$. Anal. Calcd for $C_{22}H_{44}Cl_2N_2O_4S_2Si_2$ (591.80): C, 44.65; H, 7.49; N, 4.73. Found: C, 44.34 and 44.33; H, 7.85 and 7.88; N, 4.68 and 4.66.

3.1.5. (*E*,*E*,*E*)-1-6,11-Bis[(2-trimethylsilylethyl)sulfonyl]-1,6,11-triazacyclopentadeca-3,8,13-triene (12). A stirred mixture of **10** (0.63 g, 1.06 mmol), **4** (0.24 g, 1.32 mmol), potassium carbonate (0.59 g, 4.27 mmol), and acetonitrile (50 mL) was refluxed for 24 h (TLC monitoring). The salts were filtered off and the filtrated was evaporated. The residue was purified by column chromatography on silica gel (*n*-hexane–EtOAc, polarity from 9:1 to 8:2) to afford **12** (0.58 g, 78%) as a colorless solid. A sample specially purified for elemental analysis was obtained by digestion with *n*-hexane. Mp 150.5–151.5 °C (*n*-hexane). IR (ATR): ν 2955, 1328, 1249, 1134 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ 0.06 (s, 27H), 0.95–1.04 (m, 6H), 2.86–2.95 (m, 6H), 3.88 (br s, 12H), 5.76 (br s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS): δ −1.3, 11.0, 48.7, 51.3, 130.9. ESI-MS (*m/z*): 717 $[M+NH_4]^+$. Anal. Calcd for $C_{27}H_{57}N_3O_6S_3Si_3$ (700.21): C, 46.31; H, 8.21; N, 6.00. Found: C, 46.44 and 46.60; H, 8.49 and 8.50; N, 5.92 and 5.91.

3.1.6. (*E*,*E*,*E*)-1-(*p*-Tolylsulfonyl)-6,11-bis[(2-trimethylsilylethyl)sulfonyl]-1,6,11-triazacyclopentadeca-3,8,13-triene (13). A mixture of **10** (0.77 g, 1.30 mmol), **11** (0.22 g, 1.28 mmol), cesium carbonate (1.70 g, 5.20 mmol), and DMF (50 mL) was stirred at room temperature for 24 h (TLC monitoring). The solvent was evaporated and CH_2Cl_2 (50 mL) was added. The salts were filtered of through Celite and the organic layer was dried and evaporated. The residue was purified by column chromatography on silica gel (*n*-hexane–EtOAc, polarity from 9:1 to 8:2) to afford **13** (0.49 g, 55%) as a colorless solid. A sample specially purified for elemental analysis was obtained by digestion with *n*-hexane. Mp 113–114 °C (*n*-hexane). IR (ATR): ν 2954, 1330, 1250, 1136 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ 0.06 (s, 18H), 0.95–1.04 (m, 4H), 2.43 (s, 3H), 2.85–2.94 (m, 4H), 3.75 (br s, 4H), 3.84 (br s, 8H), 5.70 (br s, 6H), 7.32 (d, J=8 Hz, 2H), 7.68 (d, J=8 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS): δ −1.4, 10.9, 22.1, 48.5, 51.0, 51.5, 127.7, 130.4, 130.5, 130.6, 130.7, 136.8, 144.1. ESI-MS (*m/z*): 690 $[M+H]^+$, 707 $[M+NH_4]^+$. Anal. Calcd for $C_{29}H_{51}N_3O_6S_3Si_2 \cdot CH_3OH$ (722.14): C, 50.47; H, 7.45; N, 6.09. Found: C, 49.84 and 49.63; H, 7.92 and 8.09; N, 5.91 and 5.92. HRMS Calcd *m/z* for (M+Na) 712.2370. Found: 712.2387.

3.1.7. (*E*,*E*,*E*)-1,6-Bis(*p*-tolylsulfonyl)-11-[(2-trimethylsilylethyl)sulfonyl]-1,6,11-triazacyclopentadeca-3,8,13-triene (15). This was obtained as for **12**. Colorless solid. Mp 118–120 °C (*n*-hexane–diethyl ether). IR (ATR): ν 2923, 1328, 1155, 1090 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ 0.06 (s, 9H), 0.95–1.04 (m, 2H), 2.43 (s,

6H), 2.83–2.95 (m, 2H), 3.72 (br s, 8H), 3.81 (br s, 4H), 5.64 (br s, 6H), 7.32 (d, $J=7.6$ Hz, 4H), 7.67 (d, $J=7.6$ Hz, 4H). ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS): δ −1.4, 10.8, 22.0, 48.5, 50.8, 51.3, 51.4, 127.7, 130.1, 130.2, 130.4, 136.7, 144.1. ESI-MS (*m/z*): 680 $[M+H]^+$, 697 $[M+NH_4]^+$. Anal. Calcd for $C_{31}H_{45}N_3O_6S_3Si.Et_2O$ (754.10): C, 55.74; H, 7.35; N, 5.57; S, 12.76. Found: C, 55.71 and 55.63; H, 7.42 and 7.38; N, 5.76 and 5.75; S, 12.64 and 13.06.

3.1.8. General procedure for deprotection of macrocycles 12, 13, and 15. Preparation of (*E*,*E*,*E*)-1,6,11-triazacyclopentadeca-3,8,13-triene (3bbb). A stirred mixture of macrocycle **12** (0.53 g, 0.76 mmol), anhydrous cesium fluoride (1.15 g, 7.57 mmol), and anhydrous DMF (15 mL) was heated at 100 °C for 19 h (TLC and RMN monitoring). Methanol (1 mL) was added and the solvents were evaporated under vacuum. The oily residue was purified by bulb-to-bulb distillation affording **3bbb** (0.13 g, 81%) as a colorless oil. Bp 175–185 °C/3 mmHg. IR (ATR): ν 3293, 2907 cm^{-1}. ^{1}H NMR (200 MHz, CD_3OD, 25 °C, TMS): δ 3.20–3.27 (m, 12H), 5.55–5.70 (m, 6H). ^{13}C NMR (50 MHz, CD_3OD, 25 °C, TMS): δ 51.7, 132.7. ESI-MS (*m/z*): 208 $[M+H]^+$, 249 $[M+CH_3CN+H]^+$. HRMS Calcd *m/z* for (M+H) 208.1810. Found: 208.1803.

3.1.9. (*E*,*E*,*E*)-1-(*p*-Tolylsulfonyl)-1,6,11-triazacyclopentadeca-3,8,13-triene (3abb). Colorless solid. Mp 91.5–92.5 °C (*n*-hexane). IR (ATR): ν 3251, 2890, 1323, 1150, 1088 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ 2.43 (s, 3H), 3.25–3.34 (m, 8H), 3.74 (d, $J=5$ Hz, 4H), 5.50–5.75 (m, 6H), 7.30 (d, $J=8.2$ Hz, 2H), 7.70 (d, $J=8.2$ Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS): δ 22.1, 51.0, 51.5, 51.8, 127.6, 127.8, 130.4, 131.6, 134.4, 137.2, 143.9. ESI-MS (*m/z*): 362 $[M+H]^+$. HRMS Calcd *m/z* for (M+H) 362.1900. Found: 362.1892.

3.1.10. (*E*,*E*,*E*)-1,6-Bis(*p*-tolylsulfonyl)-1,6,11-triazacyclopentadeca-3,8,13-triene (3aab). Colorless solid. Mp 144–145 °C (*n*-hexane). IR (ATR): ν 1331, 1154 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ 2.43 (s, 6H), 3.42 (br s, 4H), 3.73 (br s, 8H), 4.87 (br s, 1H), 5.69 (br s, 6H), 7.31 (d, $J=8$ Hz, 4H), 7.67 (d, $J=8$ Hz, 4H). ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS): δ 22.1, 49.1, 51.4, 51.9, 127.8, 129.4, 130.3, 130.4, 131.1, 136.8, 144.1. ESI-MS (*m/z*): 516 $[M+H]^+$. Anal. Calcd for $C_{26}H_{33}N_3O_4S_2\cdot{}^1/_2$MeOH (531.70): C, 59.86; H, 6.63; N, 7.90; S, 12.06. Found: C, 59.99 and 59.80; H, 6.71 and 6.83; N, 8.00 and 8.01; S, 12.00 and 11.87.

3.1.11. *N*-[(*E*)-4-Chloro-2-butenyl]-*N*-(*tert*-butyloxycarbonyl)(2-trimethylsilylethyl)sulfonamide (16). A stirred mixture of **5** (3.32 g, 11.80 mmol), dichlorobutene **9** (5.15 mL, 47.16 mmol), potassium carbonate (8.14 g, 58.90 mmol), and acetonitrile (80 mL) was refluxed for 6 h (TLC monitoring). The salts were filtered off and the filtrated was evaporated. The oily residue was purified by column chromatography on silica gel (*n*-hexane–EtOAc, 15:1) to afford **16** (3.44 g, 79%) as a colorless oil. IR (ATR): ν 2955, 1727, 1355 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ 0.09 (s, 9H), 0.95–1.04 (m, 2H), 1.57 (s, 9H), 3.38–3.47 (m, 2H), 4.08 (d, $J=4.5$ Hz, 2H), 4.30 (d, $J=4.5$ Hz, 2H), 5.85–5.92 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS): δ −1.4, 11.2, 28.7, 44.7, 47.7, 51.5, 85.2, 130.3, 130.4, 152.0. ESI-MS (*m/z*): 370 $[M+H]^+$, 387 $[M+NH_4]^+$.

3.1.12. (*E*,*E*)-1,11-Bis(*tert*-butyloxycarbonyl)-1,11-bis[(2-trimethylsilylethyl)sulfonyl]-6-(*p*-tolylsulfonyl)-1,6,11-triazaundeca-3,8-diene (17). A stirred mixture of **16** (2.29 g, 6.19 mmol), **11** (0.54 g, 3.15 mmol), potassium carbonate (2.62 g, 18.96 mmol), and acetonitrile (60 mL) was refluxed for 19 h (TLC monitoring). The salts were filtered off and the filtrated was evaporated. The residue was purified by column chromatography on silica gel (*n*-hexane–EtOAc, 9:1) to afford **17** (2.06 g, 79%) as a colorless oil. IR (ATR): ν 2953, 1723, 1349, 1133 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ 0.06 (s, 18H), 0.90–0.99 (m, 4H), 1.51 (s, 18H), 2.42 (s, 3H), 3.33–3.45 (m, 4H), 3.77 (d, $J=6$ Hz, 4H), 4.17 (d, $J=6$ Hz, 4H), 5.45–5.70 (m, 4H), 7.29 (d, $J=8.2$ Hz, 2H), 7.67 (d, $J=8.2$ Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS): δ −1.4, 11.0, 22.2, 28.6, 48.1, 48.5, 51.5, 85.0, 127.8, 128.5, 130.4, 130.7, 137.8, 143.9, 152.0. ESI-MS (*m/z*): 855 $[M+NH_4]^+$. Anal. Calcd for $C_{35}H_{63}N_3O_{10}S_3Si_2\cdot 2Et_2O$ (986.49): C, 52.35; H, 8.48; N, 4.26. Found: C, 52.50 and 51.58; H, 8.62 and 8.82; N, 4.63 and 4.83.

3.1.13. (*E*,*E*)-1,11-Bis[(2-trimethylsilylethyl)sulfonyl]-6-(*p*-tolylsulfonyl)-1,6,11-triazaundeca-3,8-diene (18). A mixture of **17** (1.97 g, 2.35 mmol), trifluoroacetic acid (1.08 mL, 14.02 mmol), and dichloromethane (30 mL) was stirred at room temperature for 24 h. Then, a second portion of trifluoroacetic acid (1.63 mL, 21.16 mmol) was added and the mixture was stirred 24 h more until completion of the reaction (TLC monitoring). The crude solution was washed with aqueous $NaHCO_3$ (2×30 mL), water (2×30 mL), dried over anhydrous sodium sulfate and evaporated. Compound **18** (1.45 g, 97%) was obtained as a colorless solid. A sample specially purified for elemental analysis was obtained by digestion with *n*-hexane. Mp 123–124 °C (*n*-hexane). IR (ATR): ν 3280, 2954, 1314, 1134 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ 0.09 (s, 18H), 0.99–1.08 (m, 4H), 2.47 (s, 3H), 2.92–3.01 (m, 4H), 3.68–3.79 (m, 8H), 4.73 (t, $J=6.2$ Hz, 2H), 5.64–5.72 (m, 4H), 7.35 (d, $J=8.0$ Hz, 2H), 7.71 (d, $J=8.0$ Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS): δ −1.4, 10.9, 22.0, 44.9, 49.7, 49.8, 127.7, 128.3, 130.4, 131.1, 137.1, 144.4. ESI-MS (*m/z*): 638 $[M+H]^+$, 655 $[M+NH_4]^+$. Anal. Calcd for $C_{25}H_{47}N_3O_6S_3Si_2$ (638.02): C, 47.06; H, 7.42; N, 6.59. Found: C, 46.78; H, 7.85; N, 6.33.

3.1.14. (*E*,*E*,*E*)-1-(*p*-Tolylsulfonyl)-6,11-bis(2-trimethylsilylethyl)sulfonyl-1,6,11-triazacyclopentadeca-3,8,13-triene (13). A stirred mixture of **18** (1.39 g, 2.18 mmol), dibromobutene **6** (0.48 g, 2.24 mmol), potassium carbonate (1.51 g, 10.92 mmol), and acetonitrile (180 mL) was refluxed for 22 h (TLC monitoring). The salts were filtered off and the filtrated was evaporated. The residue was purified by column chromatography on silica gel (*n*-hexane–EtOAc, 8:2) to afford **13** (1.08 g, 72%) as a colorless solid.

3.1.15. (*E*,*E*,*E*)-1,6-Bis(*p*-tolylsulfonyl)-1,6,11-triazacyclopentadeca-3,8,13-trienepalladium(0) (19). A magnetically stirred solution of macrocycle **3aab** (0.14 g,

0.27 mmol) and bis(dibenzylideneacetone)palladium(0) (0.16 g, 0.28 mmol) in THF (14 mL) was refluxed for 3.5 h (TLC monitoring). The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (EtOAc–CH_2Cl_2–methanol, 8:1:1) to afford **19** as a colorless solid (0.15 g, 88%). Mp 150–152 °C (dec). IR (ATR): ν 2918, 1329, 1156 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ 1.55–1.95 (m, 4H), 2.39 (s, 6H), 2.80 (q, $J=11.6$ Hz, 2H), 3.13 (dt, $J=13.0$, 2.8 Hz, 2H), 3.53–4.10 (m, 6H), 4.55–4.87 (m, 4H), 7.25–7.32 (m, 4H), 7.60–7.75 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS): δ 22.0, 45.8, 46.0, 48.8, 49.1, 50.2, 50.3, 77.6, 77.7, 78.4, 81.3, 81.7, 82.5, 127.5, 127.6, 130.3, 130.4, 135.9, 136.6, 143.8, 143.9. ESI-MS (*m/z*): 622 $[M+H]^+$. Anal. Calcd for $C_{26}H_{33}N_3O_4S_2Pd\cdot\frac{1}{2}CHCl_3$ (681.78): C, 46.68; H, 4.95; N, 6.16; S, 9.40. Found: C, 46.63 and 46.76; H, 5.21 and 5.26; N, 5.93 and 5.93; S, 9.17 and 9.32.

3.1.16. *trans*-(*E*,*E*,*E*)-Dichlorobis[1,6-bis(*p*-tolylsulfonyl)-1,6,11-triazacyclopentadeca-3,8,13-triene]palladium(II) (20). Macrocycle **3aab** (0.10 g, 0.19 mmol) was stirred in a mixture of EtOH–MeOH (20–5 mL) until complete dissolution. Then, a solution of sodium tetrachloropalladate (II) (0.058 g, 0.20 mmol) in MeOH (3 mL) was added slowly to the previous one and the mixture was stirred 10 min until precipitation of a yellow solid. The reaction mixture was stored in the freeze overnight to assure the complete precipitation of the complex. Then, the solid residue was filtered, washed with cold methanol to give Pd(II) complex **20** (0.074 g, 63%) as a yellow solid. A sample specially purified for elemental analysis was obtained by crystallization from *n*-hexane–$CHCl_3$. Mp 137–139 °C (dec). IR (ATR): ν 1332, 1155 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ 2.45 (s, 12H), 3.15–3.45 (m, 4H), 3.50–3.90 (m, 20H), 5.40–5.95 (m, 12H), 7.33 (d, $J=8$ Hz, 8H), 7.68 (d, $J=8$ Hz, 8H). ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS): δ 22.2, 51.4, 51.9, 54.7, 127.9, 128.3, 130.4, 130.6, 132.3, 136.7, 144.4. ESI-MS (*m/z*): 1173 $[M-Cl]^+$. Anal. Calcd for $C_{52}H_{66}N_6O_8S_4Cl_2Pd\cdot CHCl_3$ (1328.06): C, 47.93; H, 5.08; N, 6.33; S, 9.66. Found: C, 47.87 and 47.76; H, 5.49 and 5.46; N, 6.23 and 6.20; S, 9.36 and 9.34.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.08.013

NMR spectroscopic data for macrocycle **3aab** Palladium(0) complex **19** and Palladium(II) complex **20**.

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Synthesis of new crosslinkable co-polymers containing a push–pull zinc porphyrin for non-linear optical applications

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Abstract—In this paper, the synthesis of a crosslinkable co-polymer containing new push–pull arylethynyl zinc porphyrins is described. The synthesis of porphyrin chromophores, analogous to Therien's porphyrin (*J. Am. Chem. Soc.* **1996**, *118*, 1497–1503) functionalized with a methacrylic polymerizable group and a carboxylic acid crosslinking group was achieved with a new synthetic procedure leading to a higher overall yield compared to what was previously reported in the literature for similar and simpler structures. Radical copolymerization of the porphyrin chromophore with glycidyl methacrylate has then been carried out with success. This work opens a perspective on the possibility to integrate porphyrinic chromophore with high first-order molecular quadratic hyperpolarizability coefficient in opto-electronic devices.

1. Introduction

The increasing need of optoelectronic devices for telecommunications, optical switching and information storage has led to a tremendous research activity in the area of non-linear optic (NLO) materials.[1,2] Amongst the wide range of NLO chromophores investigated in the last 15 years, organometallic and coordination compounds probably appear as the most promising.[3–6] Therien and co-workers have reported a push–pull arylethynyl porphyrin chromophore with exceptional first-order molecular quadratic hyperpolarizability coefficient (β).[7–9] The presence of zinc inside the porphyrin core appears to be essential to guarantee high β value, as demonstrated by other studies on push–pull nickel or copper porphyrins.[10–12] However, to consider practical applications, the active NLO chromophores must be inserted in a matrix to be subsequently cast into films. Polymeric materials are, by far, the most convenient matrix used to host NLO chromophores for the development of materials exhibiting macroscopic electro-optic properties.[1,2] Besides this, long-term stability of the macroscopic electro-optic activity of the material is of a high importance for its future commercial development.[13,14] Increasing stability of the nonlinear response consists in limiting the relaxation of the field-induced orientation of the chromophores in the matrix. This is generally achieved by two strategies. The first one consists in grafting the chromophore into a polymeric matrix of high glass-transition temperature. Many examples using polyimide matrices have proved the efficiency of such approach.[1,2,15] Its main drawback stems from the need to perform the poling process at high temperature, which can cause partial thermal decomposition of the chromophores. A less severe approach consists in locking the chromophore orientation after the poling process by a crosslinking reaction. Some recent examples using different crosslinkable strategies have been reported and have fully demonstrated the validity of such an approach.[1,2,16–20] More particularly, a cross-linking reaction based on the opening of an epoxy group by a carboxylic acid carried by the chromophore proved to be quite efficient to lock the chromophores orientation after poling.[21–23]

In spite of its numerous qualities (large β value and high thermal stability), Therien's chromophore has never been, up to now, covalently integrated into a polymeric material. Herein, we report on a new synthetic strategy to prepare gram-scale of new push–pull porphyrins and their successful copolymerization with glycidyl methacrylate (GMA). The introduction of a methacrylate group and a carboxylic

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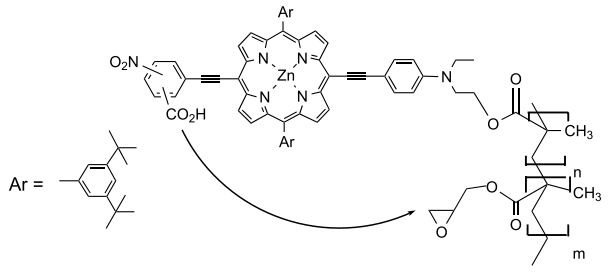


Figure 1. Structures of the electro-optic materials described in this study.

acid group on the porphyrins makes it possible to copolymerize them with GMA and to produce a material that could be subsequently thermally crosslinked after poling (Fig. 1).

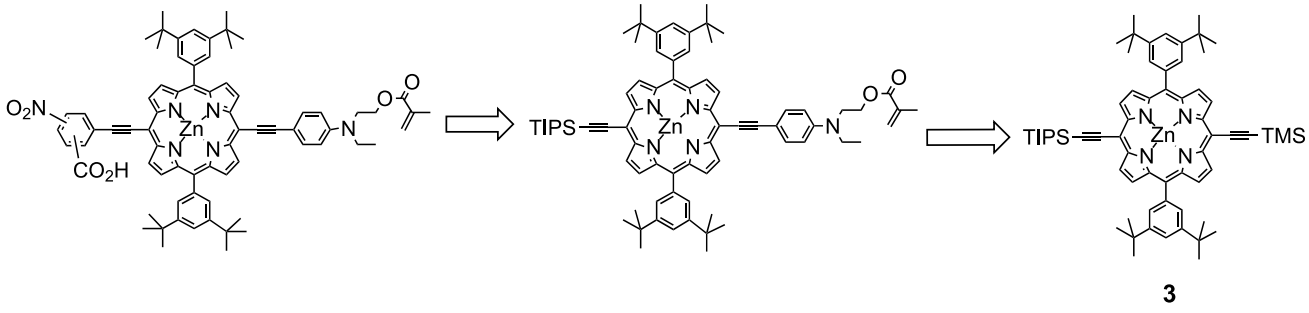
2. Results and discussion

The synthesis of the donor–acceptor porphyrins was performed using a new converging approach, which differs from the procedures originally described by Therien[7] and later used by Plater[24] for the preparation of other arylethynyl porphyrins.

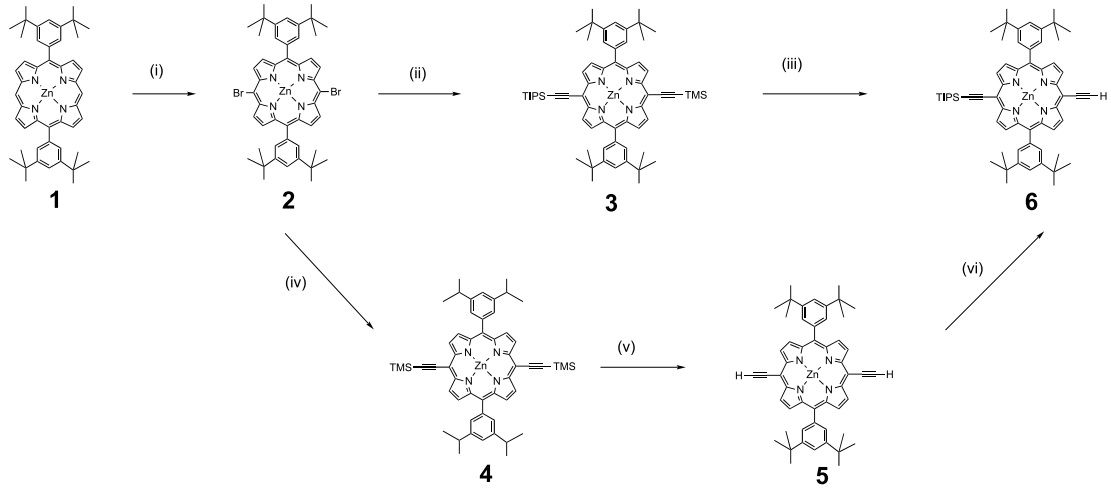
The synthetic approach relies on a key synthon: the bisethynyl porphyrin **3** in which the ethynyl groups are protected with silyl groups of different labilities (trimethylsilyl: TMS and trisisopropylsilyl: TIPS). The selective cleavage of the ethynyl protective groups allows for successive Sonogashira cross-coupling reactions of the porphyrin with the electron donor moiety and then with the electron acceptor unit (Scheme 1). The preparation of the starting porphyrin **6** is depicted in Scheme 2.

The bisbrominated porphyrin **2** is readily synthesized in gram-scale following literature methodology. The conditions used here were mostly inspired by those reported by Plater,[24] with a slight modification on the bis bromination step. This reaction offers a higher yield when the *N*-bromosuccinimide (NBS) was added dropwise and at low temperature (90% yield) instead of in one fraction at room temperature (70% yield).

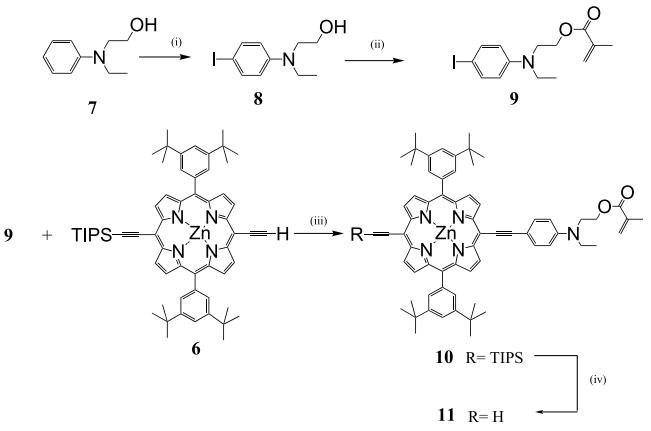
We tested two different routes to prepare porphyrin **6** (Scheme 2). A straightforward approach consists in a statistical Sonogashira cross-coupling reaction of porphyrin **2** with a mixture of trisisopropylsilyl acetylene and trimethylsilyl acetylene, followed by a selective deprotection of the trimethylsilyl group under basic conditions, as described by Therien.[25] The second route requires the preparation of the symmetrical bis trimethylsylilacetylene porphyrin **4**, followed by the cleavage of both trimethylsilyl groups by fluoride. Then, the deprotonation of one ethynyl group of **5** with lithium bis(trimethylsilyl)amide (LiHMDS) and the quenching of the resulting anion with trisisopropylsilyl chloride also afforded porphyrin **6**[24] as analogous to



Scheme 1. Retrosynthetic scheme for the synthesis of the push–pull porphyrin.



Scheme 2. Synthesis of the porphyrin **6**. Reagents and conditions: (i) NBS (2 equiv), CH_2Cl_2, 0 °C, 90%; (ii) trisisopropylsilyl acetylene (6 equiv)/trimethylsilyl acetylene (2 equiv), $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, THF, 20 h, 40 °C, 40%; (iii) NaOH (1 M aq), THF/MeOH, rt, 88%; (iv) trimethylsilylacetylene (5 equiv), $Pd(PPh)_3Cl_2$, THF, Et_3N, 20H, 45 °C, 95%; (v) BuN_4F, THF, rt, 92%; (vi) LiHMDS (1.4 equiv), THF, 10 min, then *iso*Pr_3SiCl (1.4 equiv), 38%.

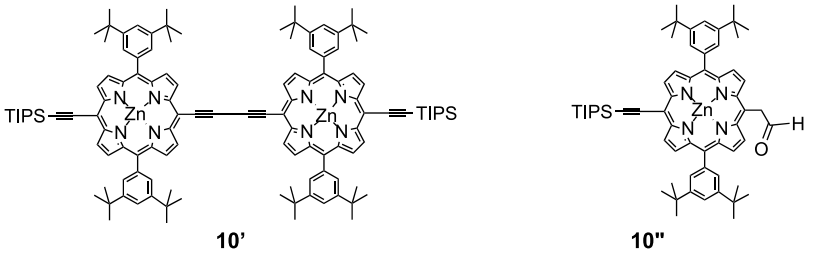


Scheme 3. Synthesis of the donor moiety **9** and its coupling with porphyrin **6**. Reagents and conditions: (i) iodine (3 equiv), pyridine, dioxane, 1 h, 0 °C, 96%; (ii) methacryloyl chloride, $CHCl_3$, Et_3N, 0 °C, 70%; (iii) $Pd_2(dba)_3 \cdot CHCl_3$, $AsPh_3$, THF/toluene/Et_3N, 40 °C, 20 h, 85%; (iv) Bu_4NF, THF, rt, 99%.

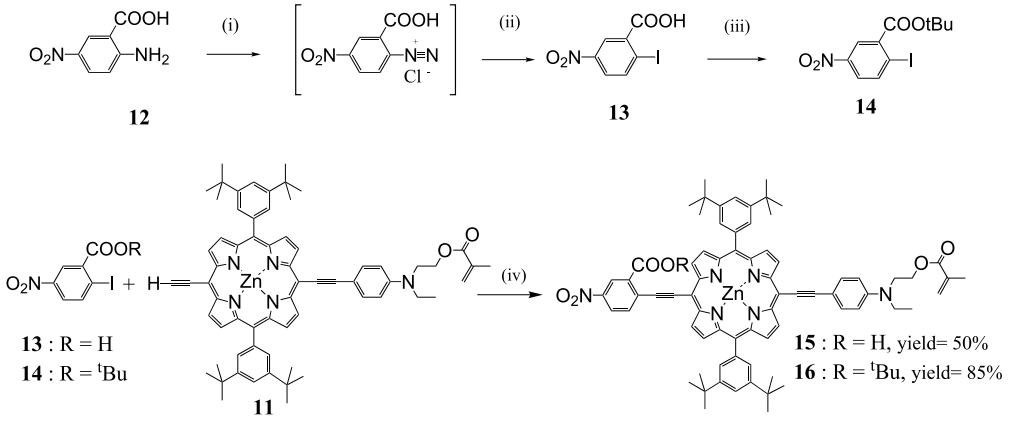
Anderson's similar species with trihexylsilylethynyl and unsubsituted ethynyl groups.[26] The two routes gave a similar overall yield (38%), but the second route avoids the utilization of the costly trisisopropylsylil acetylene reagent, on the other hand the first route is one step shorter.

Various attempts to couple the easily available 4-bromo-*N*-ethyl-*N*-hydroxyaniline with the porphyrin **6** failed. This can be explained by the inefficient oxidative addition of electron rich amino phenyl bromide on the Pd^0 center of the catalyst. This failure prompted us to replace the bromo group by the more reactive iodo halogen. Numerous approaches for the iodination in the *para* position of aniline derivatives already exist in literature[27,28], but few of them operate in mild and neutral conditions compatible with the free alcoholic group of **7**. The iodination reaction used in the synthesis of **8** was inspired by a method originally described by Irie for the iodination of indole derivatives.[29] It consists in reacting an excess of iodine on the *N*-ethyl-*N*-hydroxyethyl-aniline **7**, in a mixture of pyridine–dioxane (1/1). It appeared that these simple and mild conditions were perfectly suitable for the selective iodination of compound **7** with an excellent 96% yield (Scheme 3). Compound **8** was then reacted with methacryloyl chloride in the presence of Et_3N, affording **9** with a 70% yield. The Sonogashira cross-coupling reaction of **9** with the porphyrin **6** was carried out using Lindsey's conditions[30] because they gave higher yield and higher reproducibility than those used by Plater.[24] We attribute this to the formation of two undesired by-products, namely the compound **10′** resulting from the Glaser's homocoupling and the compound **10″** in which the acetylenic was transformed into vinyl alcohol group following an anti-Markovnikov hydration type reaction[31,32] (Scheme 4). Purification of the porphyrin **10** was not possible by column chromatography on silica gel or alumina due to the degradation of the zinc porphyrin. A size exclusion chromatography on Sephadex LH20 stationary phase was instead performed after a flash filtration on silica gel initially neutralized by triethylamine. The trisisopropylsilyl group of **10** was finally cleaved by tetrabutylammonium fluoride in a quantitative yield.

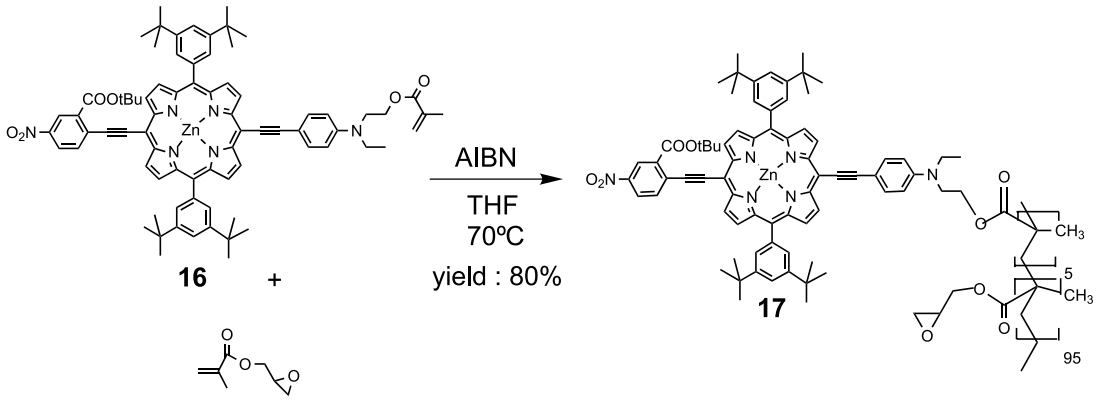
The iodinated acceptor moiety **13** was prepared from the commercially available 2-amino-5-nitro-benzoic acid **12** according to a Sandmeyer reaction from the diazonium salt of **12** and potassium iodide (Scheme 5). The Sonogashira



Scheme 4. Structure of the by-products **10′** and **10″** formed during the reaction of **6** and **9** using the catalyst $Pd(PPh_3)_4$.



Scheme 5. Synthesis of the acceptor moieties **13** and **14** and coupling with porphyrin **11**. Reagents and conditions: (i) NaOH (O, 5 N aq), 70 °C, then HCl (12 N), then $NaNO_2$, 0 °C; (ii) KI (satd aq), H_2O, 0 °C, 65% for the two steps; (iii) *tert*-BuOH, DCC/DMAP, THF, 70 °C, 51%; (iv) $Pd_2(dba)_3 \cdot CHCl_3$, $AsPh_3$, THF/toluene/Et_3N, 40 °C, 20 h.



Scheme 6. Polymerization reaction of the esterified push–pull porphyrin **17**.

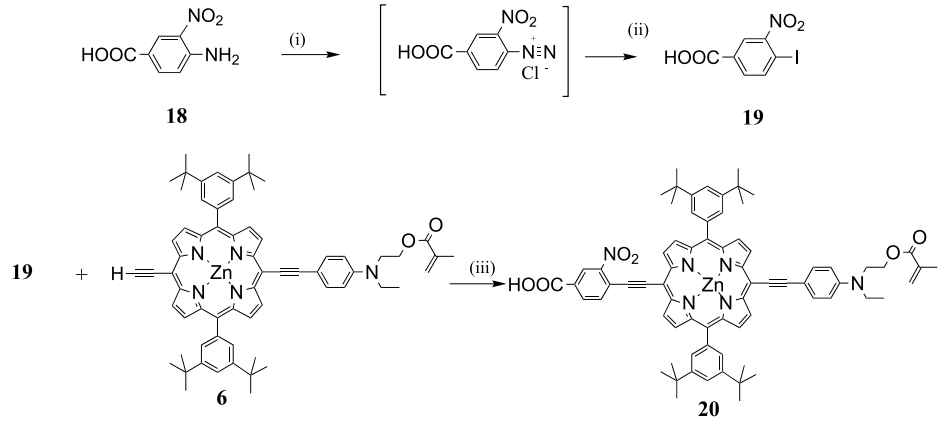
cross-coupling reaction of porphyrin **6** with **13** afforded the expected product **15** with a 50% yield, but unfortunately the lack of reproducibility of this reaction prevented us from preparing the expected push–pull porphyrin **15** in large quantity. This problem was not surprising, since Mioskowsky and co-workers[33] have shown that a carboxylic acid in *ortho* position of an iodo group prevents Sonogashira cross-coupling, most probably by the irreversible chelation of the Pd catalyst by COOH after oxidative addition of aryl iodide. We decided therefore, to protect the acid group by a *tert*-butyl ester group. The esterification was carried out by reacting **13** and *tert*-butanol in THF in the presence of dicyclohexylcarbodiimide and a catalytic amount of dimethylaminopyridine and afforded **14** in a quite satisfying yield of 65%. Compound **14** was then successfully coupled with porphyrin **11** in a Sonogashira cross-coupling reaction, to give **16** in 85% yield (Scheme 5). Unfortunately, all our attempts to deprotect selectively the *tert*-butyl group without affecting the methacrylate function (including the use of mild basic condition, trifluoroacetic acid, or cerium chloride) failed. The best results were obtained using cerium chloride chloroform but with only 15% yield.

Still, we decided to copolymerize the protected esterified porphyrin **16** with glycidyl methacrylate. The copolymerization was performed in THF with a molar ratio GMA/chromophore of 95:5, using 10% mol AIBN as an initiator, and leads to a total conversion of the monomer **16** (Scheme 6). A size exclusion chromatography (polystyrene standards) was performed on **17** and it showed a $\overline{M_w}$ of only 2400 D with a polydispersity index (PDI) = 1.2, indicating an oligomeric structure rather than polymeric.

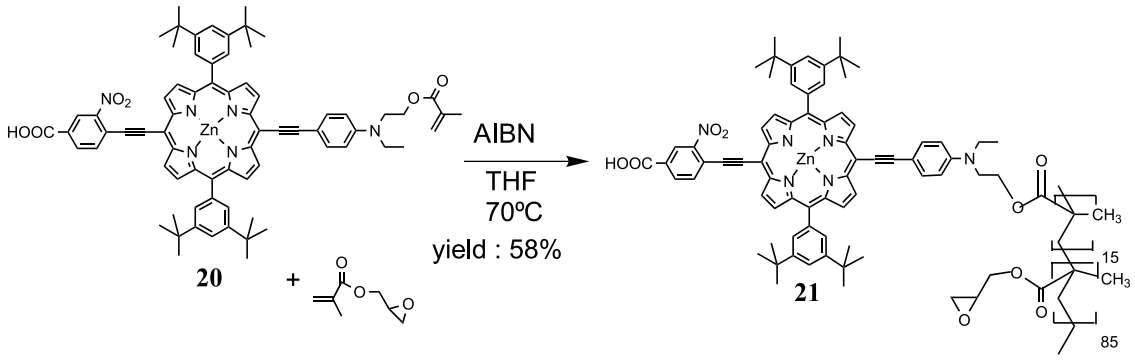
These unsatisfying results prompted us to direct our efforts to a new porphyrin chromophore in which the position of the respective nitro and carboxylic acid groups on the electron acceptor moiety were inverted (compound **20**). Previous works on azo push–pull chromophores have indeed shown that such a change did not affect significantly the value of the electro-optic coefficient.[34–36] In compound **19**, the new position of the carboxylic acid group with respect to the iodo group should avoid the problem encountered in the final Sonogashira cross-coupling step. In addition, the more accessible carboxylic acid group, compared to that in the original target **15**, could facilitate the crosslinking reaction with epoxy functions of the polymer.

The new acceptor moiety **19** was synthesized according to a similar Sandmeyer reaction to that previously used for **13**, but using the commercially available 4-amino-3-nitrobenzoic acid **18** as a starting material (Scheme 7). The iodinated acceptor **19** was finally coupled with porphyrin **6** leading to **20** with an excellent 85% yield with high reproducibility.

Copolymerization of **20** with GMA was performed in THF with 10% mol. AIBN as an initiator and with an increased amount of porphyrin **16** (15% mol) compared to that used in



Scheme 7. Synthesis of the acceptor moietie **19** and its coupling with porphyrin **11**. Reagents and conditions: (i) NaOH (O, 5 N aq), 70 °C, then HCl (12 N), then $NaNO_2$, 0 °C; (ii) KI (satd aq), H_2O, 0 °C, 65% for the two steps; (iii) $Pd_2(dba)_3 \cdot CHCl$, $AsPh_3$, THF/toluene/Et_3N, 40 °C, 20 h, 85%.



Scheme 8. Polymerization reaction of the chromophore **20** with glycidyl methacrylate.

the case of **17**. Precipitation of the crude reaction mixture with methanol followed by a vacuum filtration afforded polymer **21** with a 60% yield (Scheme 8). A size exclusion chromatography was performed and indicated a satisfying molecular weight $\overline{M}_w = 8600$ D with a polydispersity index = 1.6.

ATG measurements performed on the push–pull chromophore **20** and on the corresponding polymer **21** indicated no degradation of both materials until 220 °C confirming the high thermal stability of these substances.

3. Conclusion

This work is the first example of incorporation of a porphyrin displaying NLO properties into a crosslinkable polymeric matrix. Notably, the satisfying overall yield of 22% from the free base bis-aryl porphyrin **1** to the push–pull chromophore **20**, has been increased compared to that reported in previous papers for simpler push–pull porphyrin chromophores. The push–pull porphyrin **20** has been successfully copolymerized with glycidyl methacrylate leading to a soluble material. It is noteworthy that the synthetic strategy described herein, allows for the preparation of significant quantity of both monomeric porphyrin **20** and polymer **17** permitting thus, a complete study of the electro-optical properties of these new materials. The investigation of the magnitude and the stability of the electro-optical properties of these new materials is under way and will be reported in due course.

4. Experimental

4.1. General methods

^{1}H NMR spectra were recorded on a ARX 400 MHz Bruker spectrometer. Chemical shifts for ^{1}H NMR spectra are referenced relative to residual protium in the deuterated solvent ($CDCl_3$, $\delta = 7.26$ ppm; *d*-THF $\delta_1 = 3.57$ ppm–$\delta =$ 1.72 ppm). UV–vis absorption spectra were recorded on a Cary 5G Varian spectrophotometer. Mass spectra were recorded on a EI-MS HP 5989A spectrometer or on a JMS-700 (JEOL LTD, Akishima, Tokyo, Japan) double focusing mass spectrometer of reversed geometry equipped with electrospray ionization (ESI) source. Thin-layer chromatography (TLC) was performed on aluminum sheets precoated with Merck 5735 Kieselgel 60F_{254}. Column chromatography was carried out either with Merck 5735 Kieselgel 60F (0.040–0.063 mm mesh). Air sensitive reactions were carried out under argon in dry solvents and glassware. Chemicals were purchased from Aldrich and used as received. 5,15-Bis-(3,5-di-*tert*-butylphenyl)porphyrin was prepared according to literature method.[37]

UV–vis absorption spectra were recorded on a UV-2401PC Shimadzu spectrophotometer. Fourier transform infrared spectra were recorded in pressed KBr pellets on a Bruker Vector 22 spectrometer.

Molecular masses and molecular mass distributions were measured using size exclusion chromatography (SEC) on a system equipped with a SpectraSYSTEM AS1000 autosampler, with a guard column (Polymer Laboratories, PL gel 5 m Guard, 50×7.5 mm) followed by two columns (Polymer Laboratories, 2 PL gel 5 m MIXED-D columns, 2×300×7.5 mm), with a SpectraSYSTEM RI-150 detector and a SpectraSYSTEM UV2000 detector. The eluent used was THF at a flow rate of 1 mL min^{-1} at 35 °C. Polystyrene standards [(580–483)×10^3 g mol^{-1}] were used to calibrate the SEC. The purity of the compounds was better than 95% as judged by ^{1}H NMR spectroscopy.

4.1.1. [5,15-Dibromo-10,20-bis-(3,5-di-*tert*-butylphenyl) porphyrinato] zinc (II): 2. Porphyrin **1** (1.21 g, 1.62 mmol) was dissolved in 60 mL of dichloromethane. The mixture was cooled to 0 °C and NBS (560 mg, 3.16 mmol in 10 mL of dichloromethane) was added dropwise with an addition funnel. The ice bath was removed and methanol (200 mL) was added and the volume of the resulting solution was reduced (roughly 20 mL). The precipitate was filtered and intensively washed with methanol to give a violet powder (1.31 g, 90%). The analytical data of this compound agreed completely with those reported by Plater.[24]

^{1}H NMR (300 MHz, DMSO), δ (ppm): 9.60 (d, 4H, $^3J =$ 4.2 Hz); 8.77 (d, 4H, $^3J = 4.2$ Hz); 7.97 (d, 4H, $^4J = 1.5$ Hz); 7.83 (t, 2H, $^4J = 1.5$ Hz); 1.57 (s, 36H).

4.1.2. [5,15-Bis-(3,5-di-*tert*-butylphenyl)-10-(trisisopropylsilyl)ethynyl-20-(trimethylsilyl)ethynyl-porphyrinato] zinc (II): 3. Porphyrin **2** (300 mg, 0.33 mmol), $Pd(PPh_3)_2Cl_2$ (24 mg), CuI (7 mg), trimethylsilylacetylene (100 μL, 0.7 mmol), trisisopropylsilyl acetylene (0.4 mL,

1.78 mmol) were loaded in a sealed tube. THF (10 mL) and Et_3N (3 mL) were added and the mixture was stirred for 20 h at 40 °C. After evaporation of the solvents, the residue was purified by flash column chromatography on silica gel eluted with a gradient of petroleum ether/dichloromethane: from 90:10 to 70:30. The middle green fraction was isolated giving, after evaporation, the pure asymmetric disilylated porphyrin **3** (135 mg, 40%).

^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 9.74 (d, 2H, ^3J= 4.8 Hz); 9.69 (d, 2H, ^3J=4.8 Hz); 8.98 (d, 2H, ^3J=4.8 Hz); 8.95 (d, 2H, ^3J=4.8 Hz); 8.03 (d, 4H, ^4J=1.8 Hz); 7.81 (t, 2H, ^4J=1.8 Hz); 1.54 (s, 36H); 1.51–1.42 (m, 21H); 0.59 (s, 9H). UV–vis (CH_2Cl_2): λ_{max}, nm (ε, mol^{-1} L cm^{-1}) 434 (210,000); 576 (9500); 629 (17,000). FT-IR (cm^{-1}): 2960 (s, *tert*-Bu); 2141 (m, C≡C); 1592 (m, Ar); 1213 (m); 852 (s). HR-ESMS, *m/z*: calcd for $C_{64}H_{80}N_4Si_2Zn$: 1024.521 ($M^+\cdot$), found: 1024.520 ($M^+\cdot$).

4.1.3. [5,15-Bis-(3,5-di-*tert*-butylphenyl)-10,20-bis-ethynyl-porphyrinato] zinc (II): 5. Porphyrin **2** (1.01 g, 1.11 mmol), trimethylsilylacetylene (560 μL, 4.44 mmol), CuI (21 mg), $Pd(PPh_3)_2Cl_2$ (84 mg) were dissolved in THF (40 mL) and Et_3N (10 mL) in a Schlenk tube set under argon atmosphere. The mixture was heated at 45 °C for 20 h. The solvents were evaporated and the residue was filtered through silica gel, eluted with dichloromethane/petroleum ether: 50:50. The green solid was dissolved in THF (100 mL) and Bu_4NF 1 M in THF (2.5 mL, 2.5 mmol) was added. The solvents were evaporated to 1/4 of the initial volume and MeOH was added to precipitate the porphyrin. After filtration and washing with methanol, porphyrin **5** was obtained as a green-blue powder (790 mg, 90%).

^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 9.68 (d, 4H, ^3J= 4.8 Hz); 8.90 (d, 4H, ^3J=4.8 Hz); 8.10 (d, 4H, ^4J=1.5 Hz); 7.92 (t, 2H, ^4J=1.5 Hz); 4.63 (s, 2H); 1.59 (s, 36H). HR-ESMS, *m/z*: calcd for $C_{52}H_{52}N_4Zn$: 796.351 ($M^+\cdot$), found: 796.353 ($M^+\cdot$).

4.1.4. [5,15-Bis-(3,5-di-*tert*-butylphenyl)-10-ethynyl-20-(trisisopropylsilyl)ethynyl-porphyrinato] zinc (II): 6. *Route 1*. Porphyrin **3** was dissolved in a mixture of THF/MeOH (15 mL/15 mL). 1 M aq NaOH (2 mL) was added and the mixture was stirred at room temperature for 15 min. Dichloromethane and water were then added and the organic layer was extracted, dried and rotary-evaporated. The residue was dissolved in a minimum amount of dichloromethane, precipitated with methanol and filtered. Porphyrin **6** was obtained as a green solid (110 mg, 88%).

Route 2. Porphyrin **5** (500 mg, 0.63 mmol) was dissolved in distilled THF (60 mL). Bistrimethylsilyl-lithium bis(trimethylsilyl)amide (LiHMDS) 1 M in THF (0.9 mL, 0.9 mmol) was rapidly added (in one portion) to the stirred mixture. After 10 min at room temperature, trisisopropylsilyl chloride (0.25 mL) was added and the mixture was further stirred for 10 min. 30 mL of 1 M aq KOH were added and the mixture was extracted with dichloromethane. After removal of the solvent, the residue was purified by flash chromatography on silica gel eluted with the mixture petroleum ether/dichloromethane: 80:20 leading to the awaited porphyrin **6** (230 mg, 38%).

^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 9.78 (d, 2H, ^3J= 4.8 Hz); 9.69 (d, 2H, ^3J=4.8 Hz); 8.99 (d, 2H, ^3J=4.8 Hz); 8.98 (d, 2H, ^3J=4.8 Hz); 8.03 (d, 4H, ^4J=1.8 Hz); 7.81 (t, 2H, ^4J=1.8 Hz); 4.19 (s, 1H); 1.55 (s, 36H); 1.51–1.42 (m, 21H). UV–vis (CH_2Cl_2): λ_{max}, nm (ε, mol^{-1} L cm^{-1}): 435 (205,000); 576 (9000); 630 (15,000). HR-ESMS, *m/z*: calcd for $C_{61}H_{72}N_4SiZn$: 952.484 ($M^+\cdot$), found: 952.485 ($M^+\cdot$).

4.1.5. 1-Iodo-4-[*N*-ethyl,*N*-(2-hydroxyethyl)amino]benzene: 8. To a solution of *N*-ethyl,*N*-hydroxyethylaniline (4 g, 24.2 mmol) in dioxane (180 mL) and pyridine (180 mL) cooled in an ice bath, iodine (9.22 g, 36.2 mmol) was added. After 1 h of stirring the mixture was warmed to room temperature for one further hour. Then iodine (3 g, 13 mmol) was added and the mixture was stirred for one supplementary hour. The crude reaction mixture was washed with 10% aq $Na_2S_2O_3$ until the brown color disappeared. After addition of water, the mixture was extracted with dichloromethane. The solvent was rotary-evaporated and the residue was purified by flash column chromatography on silica gel eluted with dichloromethane. White crystals were obtained (6.52 g, 96%).[38]

^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.44 (d, 2H, ^3J= 8.7 Hz); 6.52 (d, 2H, ^3J=8.7 Hz); 3.77 (t, 2H, ^3J=5.7 Hz); 3.37–3.45 (m, 4H); 1.7 (s(broad), 1H); 1.14 (t, 3H, ^3J= 6.9 Hz). ^{13}C NMR (300 MHz, $CDCl_3$), δ (ppm): 147.72; 137.81; 123.94; 114.92; 59.97; 52.44; 45.58; 11.72. EI-MS: $M^+\cdot$ (%): 293 (100); 263 (22); 247 (18); 136 (28); 92 (37). Mp=33 °C.

4.1.6. 2-[Ethyl(4-iodophenyl)amino]ethyl methacrylate: 9. A two necked flask equipped with a reflux condenser and an argon outlet was charged with **8** (5 g, 17.2 mmol) and THF (75 mL). Et_3N (3.62 mL) was added and the mixture was cooled at 0 °C. Methacryloyl chloride (1.95 mL, 17.2 mmol) was added dropwise with a syringe over a period of 1 h and the solution was then heated for 20 h at 40 °C. The solution was filtered, evaporated and the residue was chromatographed on silica gel eluted with the mixture dichloromethane/petroleum ether: 50:50. The pure desired product was isolated as a colorless oil (4.25 g, 75%).

^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.47 (d, 2H, ^3J= 9.0 Hz); 6.54 (d, 2H, ^3J=9.0 Hz); 6.08 (s, 1H); 5.58 (s, 1H); 4.28 (t, 2H, ^3J=6.3 Hz); 3.58 (t, 2H, ^3J=6.3 Hz); 3.45 (q, 2H, ^3J=7.2 Hz); 1.91 (s, 3H); 1.14 (t, 3H, ^3J=7.2 Hz). ^{13}C NMR (300 MHz, $CDCl_3$), δ (ppm): 166.25; 146.13; 136.76; 134.96; 127.99; 124.92; 113.25; 60.78; 47.46; 44.11; 17.30; 11.01. FT-IR (cm^{-1}): 2895–2970 (w, alk); 1717 (s, C=O); 1637 (w, CH_2=C); 1587 (m, Ar); 1163 (s). EI-MS: $M^+\cdot$ (%): 359 (24); 260 (100).

4.1.7. {5,15-Bis-(3,5-di-*tert*-butylphenyl)-10-[ethyl-(methacryloyloxyethyl)aminophenylethynyl]-20-(trisisopropylsilyl)ethynyl-porphyrinato} zinc (II): 10. Porphyrin **6** (300 mg, 0.315 mol) and compound **9** (224 mg, 0.630 mol) were placed in a schlenk tube and toluene (30 mL), THF (10 mL) and Et_3N (10 mL) were added. The solution was deaerated by three freeze–pump–thaw cycles and $Pd_2(dba)_3\cdot CHCl_3$ (30 mg) and triphenylarsine (30 mg) were added. The solution was stirred 30 min at room temperature. After solvents removal, the residue was

dissolved in THF and chromatographied on LH 20 Sephadex stationary phase and the major green band was collected. Finally, the green powder was dissolved in a minimum volume of dichloromethane and precipitated with methanol. After filtration, a green powder was obtained (320 mg, 85%).

^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 9.77 (d, 2H, ^3J= 4.8 Hz); 9.72 (d, 2H, ^3J=4.5 Hz); 8.94 (m, 4H); 8.05 (d, 4H, ^4J=1.8 Hz); 7.87 (d, 2H, ^3J=9.0 Hz); 7.81 (t, 2H, ^4J= 1.8 Hz); 6.88 (d, 2H, ^3J=9.0 Hz); 6.14 (s, 1H); 5.62 (s, 1H); 4.38 (t, 2H, ^3J=6.3 Hz); 3.72 (t, 2H, ^3J=6.3 Hz); 3.55 (q, 2H, ^3J=7.2 Hz); 1.97 (s, 3H); 1.4–1.6 (m, 57H); 1.25 (t, 3H, ^3J=7.2 Hz). FT-IR (cm^{-1}): 2960 (s, *t*-Bu); 2930 (s, *i*-Pr); 2863 (m, –CH_2–); 2183 (m, C≡C); 2136 (m, C≡C); 1718 (m, C=O); 1212 (s). HR-ESMS, *m/z*: calcd for $C_{75}H_{89}N_5O_2SiZn$: 1183.608 ($M^+\cdot$), found: 1183.609 ($M^+\cdot$).

When Plater's conditions were used (mixture of tetrahydrofurane (6 mL) and pyrrolidine (20mL) as solvents) and the above catalyst ($Pd_2(dba)_3\cdot CHCl_3$ and triphenylarsine) was replaced by $Pd(PPh_3)_4$ (6 mg) and CuI (3 mg)) the two major products were formed. These two products were the porphyrins **10′** and **10″** that were isolated in variable yields from one run to the other **10′** (70–50%) and **10″** (10–30%).

Porphyrin dimer **10′**. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 9.73 (m, 8H); 8.91 (m, 8H); 8.02 (d, 8H, ^4J=1.8 Hz); 7.80 (t, 4H, ^4J=1.8 Hz); 1.4–1.6 (m, 114H).

Porphyrin **10″**. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 10.44 (s, 1H, CHO); 9.78 (d, 2H, ^3J=4.5 Hz); 9.42 (d, 2H, ^3J= 4.5 Hz); 9.05 (d, 2H, ^3J=4.5 Hz); 9.01 (d, 2H, ^3J=4.5 Hz); 8.04 (d, 4H, ^4J=1.8 Hz); 7.80 (t, 2H, ^4J=1.8 Hz); 5.98 (s, 2H); 1.4–1.6 (m, 57H). FT-IR (cm^{-1}): 2956–2900 (vs, *t*-Bu, *i*-Pr); 2864 (m, –CH_2–); 2810 and 2710 (w, CO–H); 2138 (m, C≡C); 1724 (m, C=O). MS(MALDI-TOF), *m/z*: calcd for $C_{61}H_{72}N_4OSiZn$: 970.492 ($M^+\cdot$), found: 970 (77%), 971 (48%), 972 (100%), 973 (72%), 974 (74%), 975 (35%).

4.1.8. {5,15-Bis-(3,5-di-*tert*-butylphenyl)-10-ethynyl-20-[ethyl(methacryloyloxyethyl) aminophenylethynyl]-porphyrinato} zinc (II): 11. One hundred and fifty microlitres of 1 M Bu_4NF in THF (0.15 mmol) was added to a solution of porphyrin **10** (150 mg, 0.126 mmol in 150 mL of THF). The mixture was stirred for 30 min at room temperature. The solvent was partly removed, water was added and the mixture was extracted with dichloromethane. After evaporation of the solvents, the residue was redissolved in a minimum amount of dichloromethane, petroleum ether was added to precipitate the porphyrin (130 mg, 100%).

^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 9.74 (d, 2H, ^3J= 4.8 Hz); 9.64 (d, 2H, ^3J=4.5 Hz); 8.96 (m, 4H); 8.06 (d, 4H, ^4J=1.8 Hz); 7.82 (d, 2H, ^3J=9.0 Hz); 7.80 (t, 2H, ^4J= 1.8 Hz); 6.85 (d, 2H, ^3J=9.0 Hz); 6.13 (s, 1H); 5.61 (s, 1H); 4.38 (t, 2H, ^3J=6.3 Hz); 4.06 (s, 1H); 3.71 (t, 2H, ^3J= 6.3 Hz); 3.54 (q, 2H, ^3J=7.2 Hz); 1.97 (s, 3H); 1.4–1.6 (m, 57H); 1.28 (t, 3H, ^3J=7.2 Hz). FT-IR (cm^{-1}): 2960 (s, *tert*-Bu); 2863 (m, –CH_2–); 2138 (m, C≡C); 1718 (m, C=O); 1212 (s). UV–vis (CH_2Cl_2): λ_{max}, nm (ε, mol^{-1} L cm^{-1}): 432 (205,000); 568 (11,000); 616 (10,000).

4.2. General procedure for iodination of amino nitrobenzoic acid (compound 13 or 19)

A solution of the amino nitrobenzoic acid **12** or **18** (4.5 g, 24.7 mmol) in 45 mL of 0.5 M aq NaOH was heated at 70 °C until complete dissolution. Then, 10 mL of 12 N HCl were added dropwise, giving rise to a fine precipitate. The mixture was then cooled at 0 °C with an ice bath and $NaNO_2$ (1.7 g, 21.7 mmol) in 5 mL of water was added. The precipitate partly dissolved and the mixture was stirred for 1 h at 0 °C. The mixture was filtered while the filtrate was carefully kept at 0 °C. Then, a saturated solution of KI (8.4 g, 50 mmol) was added dropwise on the precipitate causing a strong release of N_2. The mixture turned to red and a precipitate appeared. The ice bath was removed and the mixture was stirred for two additional hours. After filtration and washing with water, the iodo nitrobenzoic acid was obtained as an orange solid (4.7 g, 65%).

4.2.1. 2-Iodo-5-nitrobenzoic acid 13.[39,40] ^{1}H NMR **13** (300 MHz, $CDCl_3$), δ (ppm): 8.83 (d, 1H, ^4J=2.7 Hz); 8.30 (d, 1H, ^3J=8.7 Hz); 8.02 (dd, 1H, ^3J=8.7 Hz, ^4J=2.7 Hz); 6.3 (s broad, 1H). FT-IR (cm^{-1}): 1710 (s, C=O); 1526 (s, ν_{asym} NO_2); 1347 (s, ν_{sym} NO_2). EI-MS: $M^+\cdot$ (%): 293 (100); 263 (36); 92 (35). Mp=197 °C.

4.2.2. 4-Iodo-3-nitrobenzoic acid 19.[41,42] ^{1}H NMR **18** (300 MHz, $CDCl_3$), δ (ppm): 8.52 (d, 1H, ^4J=1.5 Hz); 8.21 (d, 1H, ^3J=6.0 Hz); 7.94 (dd, 1H, ^3J=6.0 Hz, ^4J=1.5 Hz); 4.8 (s broad, 1H). FT-IR (cm^{-1}): 1700 (s, C=O); 1535 (s, ν_{asym} NO_2); 1351 (s, ν_{sym} NO_2). EI-MS: $M^+\cdot$ (%): 293 (100); 263 (25); 136 (32); 92 (40). Mp=201 °C.

4.2.3. *tert*-Butyl 2-iodo-5-nitrobenzoate: 14. Compound **13** (1.75 g, 6 mmol) was dissolved in THF (36 mL). Dicyclohexylcarbodiimide (DCC, 1.85 g, 6.9 mmol) and *tert*-BuOH (2.83 mL, 30 mmol) were added. DMAP (20 mg) were added and the mixture was heated for 20 h at 70 °C. The solvents were removed and the residue was purified by a column chromatography on silica gel eluted with the mixture dichloromethane/petroleum ether: 30:70. The pure product **14** was isolated as white crystals (1.35 g, 65%).

^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 8.47 (d, 1H, ^4J= 3.1 Hz); 8.16 (d, 1H, ^3J=8.7 Hz); 7.93 (dd, 1H, ^3J=8.7 Hz, ^4J=3.1 Hz); 1.65 (s, 9H). ^{13}C NMR (300 MHz, $CDCl_3$), δ (ppm): 164.22; 147.69; 142.30; 138.71; 125.69; 124.89; 101.83; 84.20; 28.07. FT-IR (cm^{-1}): 2980 (m, *tert*-Bu); 1713 (s, C=O); 1526 (s, ν_{asym} NO_2); 1341 (s, ν_{sym} NO_2). EI-MS: $M^+\cdot$ (%): 349 (16); 293 (97); 276 (38); 75 (36); 57 (89); 56 (100). Mp=107 °C.

4.2.4. {5,15-Bis-(3,5-di-*tert*-butylphenyl)-10-(4-nitro-2-carboxyphenyl)ethynyl-20-[ethyl (methacryloyloxyethyl)aminophenylethynyl]-porphyrinato} zinc (II): 15. Porphyrin **11** (75 mg, 0.073 mmol) and compound **13** (25 mg, 0.085 mmol) were dissolved in THF (2 mL), Et_3N (2 mL) and toluene (6 mL). The mixture was intensively degassed with three freeze–pump–thaw cycles. $Pd_2(dba)_3\cdot CHCl_3$ (7 mg) and $AsPh_3$ (7 mg) were added and the mixture was heated for 2 h at 50 °C. The crude reaction mixture was filtered through a short plug of celite and the

solvents were removed. The crude porphyrin was dissolved in a minimum amount of dichloromethane and was precipitated with petroleum ether. Porphyrin **15** was obtained as a green-brown powder upon vacuum filtration. (43 mg, 51%).

^{1}H NMR (300 MHz, THF), δ (ppm): 10.03 (d, 2H, ^3J= 4.2 Hz); 9.68 (d, 2H, ^3J=4.2 Hz); 8.98 (d, 1H, ^3J=1.8 Hz); 8.85 (d, 2H, ^3J=4.2 Hz); 8.82 (d, 2H, ^3J=4.2 Hz); 8.48 (dd, 1H, ^3J=4.8 Hz, ^4J=1.8 Hz); 8.45 (d, 1H, ^3J=4.8 Hz); 8.08 (d, 4H, ^4J=1.2 Hz); 7.85–7.92 (m, 4H); 6.98 (d, 2H, ^3J= 8.7 Hz); 6.08 (s, 1H); 5.61 (s, 1H); 4.42 (t, 2H, ^3J=5.2 Hz); 3.75 (t, 2H, ^3J=5.2 Hz); 3.57 (m, 2H); 1.94 (s, 3H); 1.58 (s, 36H); 1.35 (t, 3H, ^3J=5.7 Hz). UV–vis (CH_2Cl_2): λ_{max}, nm (ε, mol^{-1} L cm^{-1}) 458 (123,000); 686 (48,000). FT-IR (cm^{-1}): 2961 (s, *tert*-Bu); 2867 (m, –CH_2–); 2181 (s, C≡C); 1750 (s, C=O acid); 1718 (m, C=O ester) ; 1525 (s, ν_{asym} NO_2); 1348 (s, ν_{sym} NO_2); 1191 (s, ν_s, C–O). HR-ESMS, *m/z*: calcd for $C_{73}H_{72}N_6O_6Zn$: 1193.488 ([M+H]$^+$·), found: 1193.486 ([M+H]$^+$·).

4.2.5. {5,15-Bis-(3,5-di-*tert*-butylphenyl)-10-(4-nitro-2-*tert*-butylcarboxyphenyl)ethynyl-20-[ethyl (methacryloyloxyethyl)aminophenylethynyl]-porphyrinato} zinc (II): 16. Porphyrin **11** (225 mg, 0.22 mmol) and **14** (114 mg, 0.33 mmol) were dissolved in THF (6 mL), Et_3N (6 mL) and toluene (20 mL). The mixture was intensively degassed with three freeze–pump–thaw cycles. $Pd_2(dba)_3\cdot CHCl_3$ (20 mg) and $AsPh_3$ (20 mg) were added and the mixture was heated for 12 h at 50 °C. The crude reaction mixture was evaporated and the residue was purified by flash chromatography on silica gel using the mixture petroleum ether/dichloromethane: 30:70. The porphyrin was dissolved in a minimum amount of dichloromethane and was precipitated with methanol affording a green-brown powder (235 mg, 85%).

^{1}H NMR (300 MHz, THF), δ (ppm): 9.94 (d, 2H, ^3J= 4.5 Hz); 9.66 (d, 2H, ^3J=4.5 Hz); 8.85 (m, 3H); 8.77 (d, 2H, ^3J=4.5 Hz); 8.50 (dd, 1H, ^3J=4.8 Hz, ^4J=1.8 Hz); 8.40 (d, 1H, ^3J=4.8 Hz); 8.05 (d, 2H, ^4J=1.2 Hz); 7.8 (m, 4H); 6.92 (d, 2H, ^3J=8.7 Hz); 6.04 (s, 1H); 5.54 (s, 1H); 4.32 (t, 2H, ^3J=5.2 Hz); 3.72 (t, 2H, ^3J=5.2 Hz); 3.57 (q, 2H, ^3J=5.2 Hz); 1.88 (s, 3H); 1.75 (s, 9H); 1.52 (s, 36H); 1.22 (t, 3H, ^3J=5.2 Hz). UV–vis (CH_2Cl_2): λ_{max}, nm (ε, mol^{-1} L cm^{-1}) 465 (110,000); 689 (56,000). FT-IR (cm^{-1}): 2960 (vs, *t*-Bu); 2867 (m, –CH_2–); 2183 (s, C≡C); 1724 (s, COO*t*Bu); 1718 (m, C=O); 1524 (s, ν_{asym} NO_2); 1348 (s, ν_{sym} NO_2); 1200 (s, ν_s, C–O). HR-ESMS, *m/z*: calcd for $C_{77}H_{81}N_6O_6Zn$: 1249.551 ([M+H]$^+$·), found: 1249.552 ([M+H]$^+$·).

4.2.6. {5,15-Bis-(3,5-di-*tert*-butylphenyl)-10-(2-nitro-4-carboxyphenyl)ethynyl-20-[ethyl (methacryloyloxyethyl)aminophenylethynyl]-porphyrinato} zinc (II): 20. The same protocol as used for **15** was applied, with 200 mg of porphyrin **11**, 65 mg of **19**, 20 mL of toluene, 6 mL of Et_3N and 6 mL of THF. Porphyrin **20** was obtained as a brown solid (208 mg, 87%).

^{1}H NMR (300 MHz, THF), δ (ppm): 9.86 (d, 2H, ^3J= 4.5 Hz); 9.70 (d, 2H, ^3J=4.5 Hz); 8.90 (m, 3H); 8.82 (d, 2H, ^3J=4.5 Hz); 8.46 (m, 2H); 8.10 (s, 4H); 7.90 (s, 2H); 7.87 (d, 2H, ^3J=9 Hz); 6.97 (d, 2H, ^3J=9 Hz); 6.11 (s, 1H); 5.60 (s, 1H); 4.40 (t, 2H, ^3J=6 Hz); 3.78 (t, 2H, ^3J=6 Hz); 3.58 (q, 2H, ^3J=5 Hz); 1.95 (s, 3H); 1.58 (s, 36H); 1.28 (t, 3H, ^3J=5 Hz). UV–vis (CH_2Cl_2): λ_{max}, nm (ε, mol^{-1} L cm^{-1}): 463 (125,000); 691 (52,000). FT-IR (cm^{-1}): 2961 (s, *t*-Bu); 2867 (m, –CH_2–); 2168 (m, C≡C); 1742 (s, C=O acid); 1718 (m, C=O); 1518 (s, ν_{asym} NO_2); 1342 (s, ν_{sym} NO_2); 1212 (s, ν_s, C–O). HR-ESMS, *m/z*: calcd for $C_{73}H_{72}N_6O_6Zn$: 1193.488 ([M+H]$^+$·), found: 1193.487 ([M+H]$^+$·)

4.3. General procedure for porphyrin polymerization with glycidyl methacrylate (polymers 17 and 21)

A mixture of porphyrin (**16** or **20**) and glycidyl methacrylate (with a molar ratio porphyrin/GMA of 1:19 and 1:6, for respectively **17** and **21**) was dissolved in THF (25 mL/ 1 mmol porphyrin) in a sealed tube. AIBN was added (10% weight of the monomers) and the mixture was degassed by three freeze–pump–thaw cycles. The mixture was heated at 70 °C for 20 h. The mixture was added dropwise in 10 volumes of methanol to precipitate the polymer. The precipitate was filtered and intensively washed with methanol affording the polymer as a green powder.

4.3.1. Polymer 17. Yield: 80%, 280 mg. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 9.7–9.9 (m, 4H); 8.7–8.9 (m, 4H); 7.95–8.05 (m, 4H); 7.7–7.8 (m, 4H); 6.8–6.9 (m, 2H); 4.4–4.2 (m, 19H); 3.8–3.6 (m, 21H); 3.05–3.2 (m, 19H); 2.7–2.9 (m, 19H); 2.5–2.6 (m, 19H); 1.8–2.0 (m, 20H); 0.8–1.6 (m, 140H). FT-IR (cm^{-1}): 2961 (m); 2181 (w, C≡C); 1731 (s); 1148 (s); 907 (m, n_{as}, epoxy). GPC averages: ($\overline{M_n}$)=1900; ($\overline{M_w}$)=2400; PDI=1.2.

4.3.2. Polymer 21. Yield: 58%, 250 mg. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 9.7–9.9 (m, 4H); 8.8–9.0 (m, 4H); 7.6–8.2 (m, 8H); 6.8–7.0 (m, 2H); 4.4–4.2 (m, 11H); 3.8–3.6 (m, 13H); 3.05–3.2 (m, 11H); 2.5–2.9 (m, 22H); 0.8–2 (m, 80H). FT-IR (cm^{-1}): 2956 (m); 2178 (w, C≡C); 1730 (s); 1150 (s); 908 (m, n_{as}, epoxy). GPC averages: ($\overline{M_n}$)=5100; ($\overline{M_w}$)=8618; PDI=1.6.

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Glucofuranose derivatives as a library for designing and investigating low molecular mass organogelators

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Abstract—We designed and synthesized a class of saccharide-based gelators having three free OH groups in the glucofuranose fragment. The gelating abilities of fourteen compounds were examined to systematically study the influence of the hydrophobic fragment connected to the C2′ carbon. Also the correlation between the saccharide crystal structure and its gelating properties was examined, showing limited usefulness in this particular case. SEM observations were carried out in order to investigate the hierarchical structure of xerogels and changes depending on different gel concentration.

1. Introduction

In recent years, the development of new gelators of organic solvents as well as the investigation of the gelating process and gel structure has received much attention.[1–6] Gels derived from low-molecular-mass compounds have attracted special interest on account of their unique features, potential applications and relative simplicity of the gelator molecules. Low-molecular-mass gelators form gels, which fall within the physical gels (in contradistinction to chemical gels) since only non-covalent interactions between the gelator molecules are involved. The formation of the gel based on spontaneous self-assembly of gelator molecules under non-equilibrium conditions such as the cooling of oversaturated solutions is used as the typical preparation method. According to the type of driving forces of molecular aggregation, low-molecular-mass gelators can be classified into two categories: non-hydrogen-bond-based and hydrogen-bond-based gelators. The title saccharides having free OH groups fall within the latter group. The presence of intermolecular hydrogen bonds is responsible for self-assembling of the gelator molecules, which leads to the formation of a fibrous superstructure, as can be observed in TEM and SEM pictures of xerogels. The structure of a particular fibril as well as the process of gel formation can be investigated by small angle X-ray scattering (SAXS).[7] Analysis of the crystal structure of the pure gelator can shed light on its gelating ability. Despite significant progress in this field during the last decade, the accurate design of a new gelator is still a hard task. The basic feature of the gelator molecules is their ability to stack into one-dimensional chains. Thus, the prediction of a new gelator can often be made per analogy according to the rule that if the molecule looks similar to already known good gelators it will stack in similar way and thus, also possess gelating abilities. The bis-urea compounds are an excellent example of this concept.[1b] The correlation between the hydrogen-bond network in the bulk crystal and gelating ability was also shown for the class of pyranoside derivatives.[8] On the other hand, saccharides having three free OH groups can form different hydrogen-bond-based networks even if the configuration of the saccharide ring remains unchanged: in other words they look similar but can pack in quite a different manner, which seems to be responsible for increasing the margin of unpredictability. This inspired us to collect and study a large and consistent group of relatively similar compounds having different gelating abilities.[9] Glucofuranose derivatives were chosen as they are one of the simplest, smallest and most efficient gelators. Moreover, having an unchanged furanose ring with three unprotected OH groups, they can be easily modified by changing the hydrophobic fragment connected to the dioxolane C-2′ carbon atom.

2. Results and discussion

2.1. Gelation tests for various gelator/solvent systems

The class of furanose derivatives were synthesized as potential gelators. What these compounds have in common

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are unprotected 3, 5 and 6 OH groups. All, except one (**1**, allo), contain a glucofuranose ring and the only difference is the hydrophobic part connected to the dioxolane C-2′ carbon atom bridging dioxolane oxygen atoms (Fig. 1). By changing this fragment the gelator–gelator and gelator–solvent interactions can be modified, which can ultimately influence the gelation abilities. As can be seen from Table 1, glucofuranose derivatives can gel a huge spectrum of solvents, the only weakness is that they do not act as gelators for polar solvents like alcohols and water. This, however, may be understood when the aggregation mode of gelator molecules, based on intermolecular hydrogen bonds, is considered. Thus, polar solvents containing strong proton donor or proton acceptor groups can influence the speed and way in which the hydrogen bond network forms. A comparison of **1** and **3** reveals the dependence between the absolute configuration of the furanose ring and the gelating abilities. A similar dependence already has been shown for the series of methyl glycosides of 4,6-*O*-benzylidene monosaccharides[10] and fits the general finding that a tendency to form infinite one-dimensional hydrogen bond chains is one of the prerequisites for a good gelator. It is clear from Table 1 that gelating abilities can also be tuned by changing the substituent on the C2′ carbon atom. While the configuration changes of the furanose ring influence the gelator–gelator interactions most (leading to the different intermolecular H-bonds) the hydrophobic part of the gelator molecules is mostly responsible for gelator–solvent interactions. The aliphatic chains can stabilize the gelating abilities (as **9**, **10** and **2** are poor gelators). Moreover, longer chains can stabilize gels with more polar solvents as in the case of **5**, **6** and **14** gels with ethyl acetate. This solvent can act as competing hydrogen bond donor and, therefore, suppress the hydrogen bond based mechanism of saccharide self-agregation. Consequently, the hydrophobic–hydrophilic effects can start to play an important role. This may explain why the hydrophobic part of the saccharide molecule has to be relatively large and well defined.

2.2. Molecular arrangement in a single crystal

As a rule, the better the gelator is, the worse quality crystals it forms (if any). Since the examined saccharides tend to grow mostly as poor quality needles, the X-ray structures can be obtained just for a few compounds. The crystal structures for **1**[11] **3**,[12] and **9**[13] are available from the Cambridge Structural Database. Those for **10**, **7**, have been measured and solved during our investigations. Structures were inspected in respect of the way in which molecules pack, in particular the hydrogen bond network was analyzed (Fig. 2). The differences between the crystal structure of **1** and **3** (allo and gluco) match their gelation abilities well. **1** (poor gelator) exhibits a two-dimensional hydrogen bond network, while molecules of **3** are assembled in one-dimensional chain as may be expected for good gelators. However, on the other hand, within the gluco-set this relationship is not clear. **10** exhibits similar chains as **3**, while **9** molecules form chains having three-fold screw axis symmetry. Both **9** and **10** are poor gelators. The hydrogen bond network in **7** may be described as layered, with the layers having distinct hydrophobic and hydrophilic faces. In spite of the two-dimensional hydrogen bond network, which should not be suitable for a good gelator, **7** forms clear and

Table 1. Organic solvents tested for gelation by **1**–**14**[a]

Solvent	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Toluene	P	P	G	G*	G*	G*	P	P	I→P	I→P	G*	G*	G*	G*
Benzene	P	P	G	G*	G*	G*	P	P	I→P	I→P	G*	G*	G*	G*
p-Xylene	P	P	G	G*	G*	G*	P	P	P	I→P	G*	G*	G*	G*
Carbon tetrachloride	P	P	G*	G*	P, PG	G*	P	I→P	I→P	I→P	PG	G*	G*	P
Nitrobenzene	P	P, SSP	G	G*	G*	G*	P	P	P	SSP	SSP	P	P	G
Chloroform	P	P	G*	G	P, PG	G, PG	G*	G*	P	I→P	G*	P	G, PG	P, PG
Dibenzyl ether	P	P	G*	G*	G*	P	P	P	SSP	SSP	P, SSP	P	PG	PG
Cyclohexane	P	P	G*	P	P	PG, SSP	I→P	P	I→P	I→P	P	P	G*	G*
n-Hexane	P	I→P	P	P	G*	P	I→P	I→P	I→P	I→P	P	P	P	P
n-Heptane	P	I→P	P	P	G*	P	I→P	I→P	I→P	I→P	P	P	P	P
Methanol	S→P	S→P	S	S	S	S	S→P	S→P	S	P	S→P	S	S→P	S
Ethanol	S→P	S→P	S	S→P	S→P	S	S→P	S→P	S→P	P	S→P	S	S→P	S
Acetonitrile	S→P	P	P	S→P	S	S	P	P	S→P	P	P	P	S→P	P
Ethyl acetate	P	P	P	P	S→G	P→G	P	P	S→P	P	P	P	P	S→G
1,4-Dioxane	S→P	S	S	S→P	S→P	S	S→P	S→P	S→P	P	S	S	S	S
THF	S→P	P	S	S	S→P	S	S→P	S	S→P	P	S→P	S	S	S
Water	S→P	S	S	S	S	P	S→P	P	P	P	S→P	P	P	S
Acetone	P	P	P	S	S→SSP	S	P	P	P	P	S	S	S→P	S

[a] Abbreviations used: G, gel at 3.0 wt vol% $^{-1}$; G*, gel even under 1.0 wt vol% $^{-1}$; PG, partial gel; S, solution; P, precipitation; SSP, self supporting precipitation; I, insoluble (not fully soluble at 3.0 wt vol% $^{-1}$). In the case of 'S' at 3% starting mixture higher concentrations were checked to obtain either gel (S→G) or precipitation (S→P). In the case of 'I' at 3% starting mixture the lower concentrations were used in order to fully dissolve the saccharide, as the presence of the crystals can influence gelation.

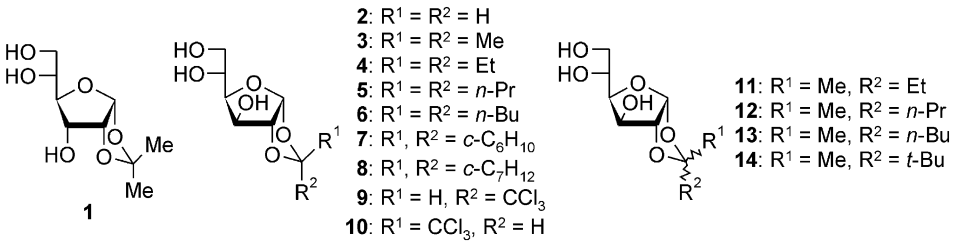

Figure 1. Investigated compounds.

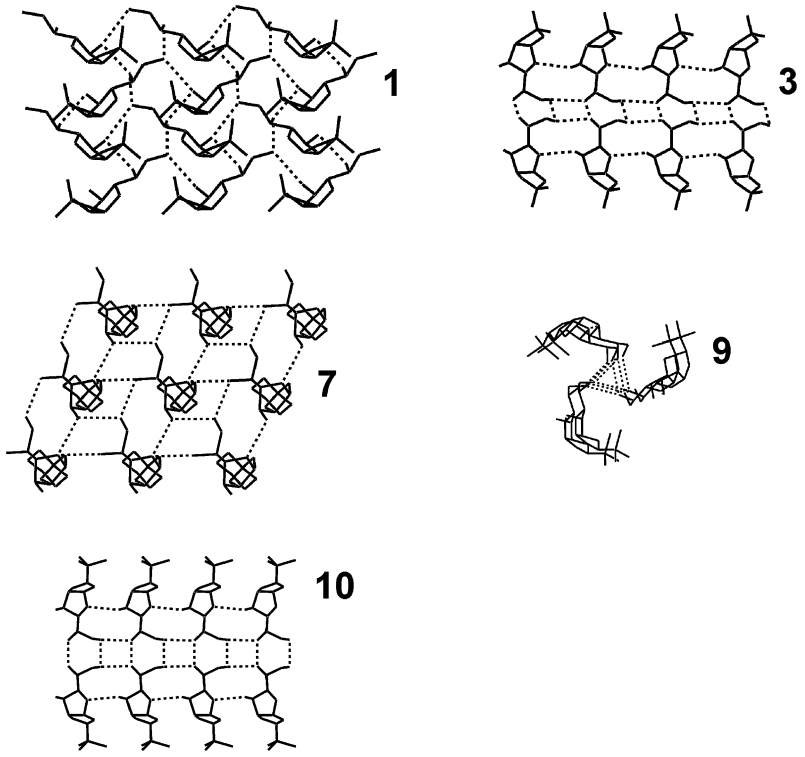

Figure 2. Hydrogen bond networks in bulk crystals as observed in compounds **1**, **3**, **7**, **9**, and **10**. Hydrogen bonds represented by dotted lines, hydrogen atoms were omitted for clarity.

stable gels with $CHCl_3$. The possible explanation is the different molecular arrangement in chloroform. The crystal structure for **7** was solved for crystals grown from methanol (the solvent was not included into the structure). The same structure (checked by XRD) was observed for acetonitrile, acetone, ethanol and water but the material obtained by solvent evaporation from the chloroform solution gave totally amorphous powder diffraction spectra. Moreover, the analysis of the molecular geometry showed a surprising similarity between all investigated furanose fragments (except allo **1**, see Fig. 3), that is almost the same building blocks can form different hydrogen-bond networks. Thus, the molecular stacking in **7**/$CHCl_3$ gel can be totally different that in the bulk crystal. Although this may explain the gel formation, it also shows the limitation of the 'structural approach' for this class of low molecular mass organogelators.

2.3. SEM observations of xerogels

In order to obtain visual insight into the aggregation mode in the micrometre scale, SEM studies were performed on dry samples of xerogels. The pictures were taken from xerogels

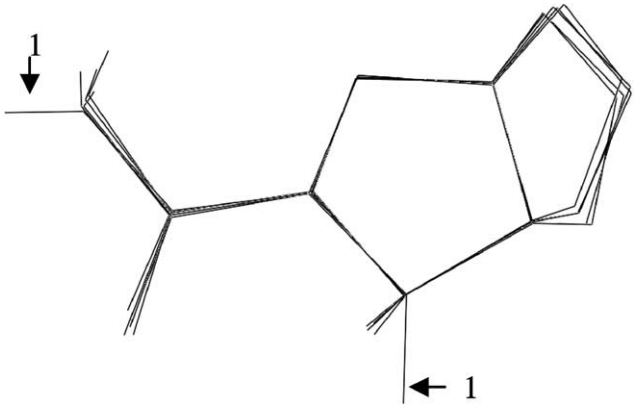

Figure 3. Overlayed molecules of **1**, **3**, **9**, **10** and **7**. Fitting based on furanose five-membered ring. The only one significant difference is that connected with allo (**1**). Non-polar fragments connected to the C2′ carbon atom were not included.

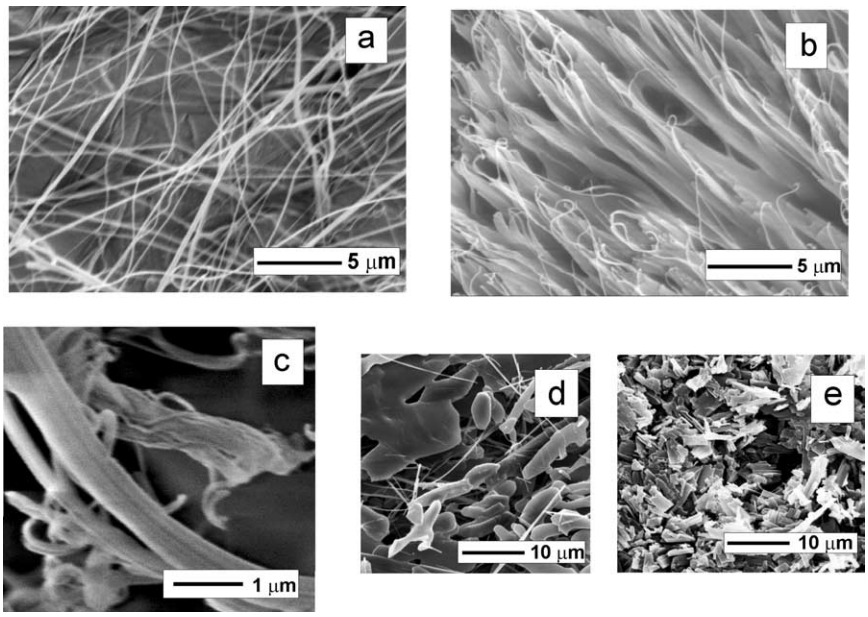

Figure 4. SEM images of the xerogels obtained from: (a) **4**/CCl_4 1.0% gel; (b) **4**/CCl_4 0.03% gel; (c) **3**/benzene 2% gel; (d) **7**/$CHCl_3$ 3% gel; (e) **4**/$CHCl_3$ 2% gel.

of **3**, **4** and **7** obtained from benzene CCl_4 and $CHCl_3$. Typical pictures showing fibrils or ribbons were observed both for benzene and CCl_4. Moreover the xerogel morphology shows a strong dependence on the gel concentration, showing fibrils in the case of diluted systems, while ribbons were typical for concentrated gels. This is clearly visible in the two SEM images of 0.03 and 1.0% of **4**/CCl_4 xerogels (see Fig. 4). The hierarchical structure (fibrils can arrange together to form larger objects (ribbons)) can also be observed in a highly enlarged structure of **3**/benzene xerogel. On the other hand, the **7**/$CHCl_3$ xerogels exhibit quite a different picture more similar to crystallization. This effect is probably due to the xerogel preparation. In the case of **7**/$CHCl_3$ xerogel two methods were used: The gel was frozen in liquid nitrogen and then the solvent was sublimated using a vacuum pomp (while the frozen gel was still being cooled by the dry ice) or a small amount of the gel was dried over normal pressure and room temperature. In both cases similar SEM pictures were obtained, which seemed close to those obtained for self-supporting precipitation materials.[8b] The XRD measurements of the **7**/$CHCl_3$ xerogel show a significant percentage of crystallinity but for the gel no peaks were obtained. This kind of SEM picture seems to be characteristic for xerogels obtained from $CHCl_3$ and can also be seen for **4**/CHCl3. The problem is currently under investigation.

3. Conclusion

The present study has introduced a new class of low molecular mass organogelators based on glucofuranose derivatives. These compounds can gel several organic solvents, some of them even in very low concentrations. The gelating abilities strongly depend on the size and character of the fragment connected to the carbon atom C2′. Saccharides containing relatively long aliphatic chains in this position exhibit a clear tendency for gelating more polar solvents, which may be a good starting point for designing furanose-based hydrogelators. No clear relationship between molecular packing in a single crystal and the gelation abilities can be found, however, this is probably caused by the possibility of the glucofuranose fragment making several topologically different but energetically similar hydrogen-bond networks.

4. Experimental

4.1. General

Reagents were used as obtained from supplier. Solvents were purified and dried according to literature methods. TLC was performed on silica gel HF-254 and column chromatography on silica gel 230–400 mesh (Merck). NMR spectra were recorded with a Varian AC-200 (200 MHz), and Varian Mercury 400BB (400 MHz) spectrometers in chloroform-d_1 ($CDCl_3$), methanol-d_4 (CD_3OD) or chloroform-d_1/methanol-d_4 mixture (approx. 10:1) with Me_4Si as internal standard. High resolution mass spectra (HR-MS) were measured with a MARINER mass spectrometer. Optical rotations were measured with a JASCO P-1020 automatic polarimeter.

Compounds **4**, **11**–**13** were prepared according to literature procedure.[9]

4.1.1. 6-*O*-Acetyl-1,2:3,5-di-*O*-methylene-α-D-glucofuranose. The title compound was obtained by modified literature procedure.[14] To a solution of D-glucose (50 g) in water (20 mL) glacial acetic acid (200 mL), paraformaldehyde (55 g) and (with caution) concd sulfuric acid (96%, 25 mL) were added. The mixture was heated under reflux for 1 h, cooled to room temperature and ice water (250 mL) was added. Product was extracted with chloroform (3×100 mL), combined organic extracts were washed with water (3×

100 mL), 5% aq $NaHCO_3$ until neutral and water (100 mL), dried (Na_2SO_4) and evaporated to dryness. Column chromatography of the residue (hexane/ethyl acetate 7:3 → 1:2 as eluents) gave crude product (11.2 g), which was used in the next reaction step without further purification. ^{1}H NMR ($CDCl_3$) δ: 6.07 (d, 1H, $J_{1,2}$=2.8 Hz, H-1), 2.14 (s, Ac). ^{13}C NMR ($CDCl_3$) δ: 105.0 (C-1), 97.1 (CH_2), 87.7 (CH_2), 84.1, 76.8, 75.6, 71.1, 63.1 (C-6), 21.4 (CH_3).

4.1.2. 1,2:3,5-Di-*O*-methylene-α-D-glucofuranose. The title compound was obtained by modified literature procedure.[14] 6-*O*-Acetyl-1,2:3,5-di-*O*-methylene-α-D-glucofuranose (11.2 g) was deacetylated under standard conditions (MeONa, MeOH). Column chromatography of the residue (hexane/ethyl acetate 5:1 → 1:1 as eluents) gave crude product (5.6 g), which was used in the next reaction step without further purification. ^{1}H NMR ($CDCl_3$) δ: 6.06 (d, 1H, $J_{1,2}$=3.8 Hz, H-1). ^{13}C NMR ($CDCl_3$) δ: 104.9 (C-1), 97.0 (CH_2), 87.7 (CH_2), 84.2, 77.0, 76.1, 73.7, 62.2 (C-6).

4.1.3. 3,5,6-Tri-*O*-acetyl-1,2-*O*-methylene-α-D-glucofuranose. A solution of crude 1,2:3,5-di-*O*-methylene-α-D-glucofuranose obtained above (5.6 g) in 2% HCl (80 mL) was heated at 105–110 °C (bath temperature) for 2 h, neutralized with satd $NaHCO_3$ and evaporated to dryness.[15] Column chromatography of the residue (hexane/ethyl acetate 2:1 → hexane/ethyl acetate/methanol 4:3:1 as eluents) gave recovered starting material (2.95 g, 53%) followed by an unseparable mixture of 1,2-*O*-methylene-α-D-glucofuranose and 3,5-*O*-methylene-α,β-D-glucofuranose (1.11 g, 21%). This mixture was acetylated under standard conditions (Ac_2O, pyridine) and purified by column chromatography (hexane/ethyl acetate 7:3 → 1:1 as eluents) to afford the title compound (0.26 g, oil) followed by crude acetylated 3,5-methylene isomer (1.15 g, as anomeric mixture). The title compound had $[\alpha]_D^{25}$ 39.8 (*c* 0.6, chloroform). ^{1}H NMR ($CDCl_3$) δ: 5.95 (d, 1H, $J_{1,2}$=3.7 Hz, H-1), 5.44 (d, 1H, $J_{3,4}$=3.2 Hz, H-3), 5.13 and 5.05 (2s, CH_2), 5.17 (m, 1H, H-5), 4.58 (dd, 1H, $J_{6,5}$=2.4 Hz, $J_{6,6'}$=12.4 Hz, H-6), 4.40 (d, 1H, H-2), 4.29 (dd, 1H, $J_{4,5}$=9.3 Hz, H-4), 4.09 (dd, 1H, $J_{6',5}$=5.4 Hz, H-6′), 2.06 (s, 6H, 2×Ac), 2.00 (s, 3H, Ac). ^{13}C NMR ($CDCl_3$) δ: 104.6 (C-1), 96.7 (CH_2), 83.2, 78.5, 74.4, 67.5, 63.2 (C-6), 20.8 (Ac), 20.7 (Ac), 20.6 (Ac). HR-MS(EI) calcd for $C_{13}H_{18}O_9$ $[M-CH_2O-Ac]^+$: HR-MS(EI) calcd for $C_{10}H_{13}O_7$ $[M-C_3H_5O_2]^+$: 245.0661. Found: 245.0659.

4.1.4. 1,2-*O*-Methylene-α-D-glucofuranose (2). 3,5,6-Tri-*O*-acetyl-1,2-*O*-methylene-α-D-glucofuranose (250 mg) was deacetylated under standard conditions (MeONa, MeOH) for 1 h, neutralized by passage through Amberlyst 15 (H^+ form) and evaporated to dryness to yield 145 mg (97%) of the title compound.[16] ^{1}H NMR (CD_3OD) δ: 5.87 (d, 1H, $J_{1,2}$=3.7 Hz, H-1), 5.04 and 4.96 (2s, 2H, CH_2), 4.35 (dd, 1H, $J_{2,3}$=0.7 Hz, H-2), 4.28 (m, 1H, H-3), 3.89 (dd, 1H, $J_{4,3}$=2.7 Hz, $J_{4,5}$=8.4 Hz, H-4), 3.85 (m, 1H, H-5), 3.75 (dd, 1H, $J_{6,5}$=3.0 Hz, $J_{6,6'}$=11.6 Hz, H-6), 3.59 (dd, 1H, $J_{6',5}$=5.6 Hz, H-6′). ^{13}C NMR (CD_3OD) δ: 105.7 (C-1), 97.2 (CH_2), 86.5, 83.1, 75.4, 70.5, 65.1 (C-6).

4.2. α-Chloralose (9) and β-chloralose (10)

Pure α- and β-chloraloses were obtained from commercially available mixture (Fluka, α:β=85:15) by acetylation (Ac_2O, pyridine)—chromatographic separation (hexane/ethyl acetate 7:3)—deacetylation (MeONa, MeOH) sequence.[17]

4.3. General procedure

To a mixture of ketone (20–30 equiv), anhydrous zinc chloride (1.5 equiv) and 85% phosphoric acid (0.05 equiv), D-glucose (50 mM) was added and stirred at room temperature for 2–6 days. Undissolved D-glucose was filtered off and washed with a small portion of ketone. The filtrate was made slightly alkaline with 40% aqueous sodium hydroxide, insoluble material was removed by filtration through a Celite pad and washed with acetone. The filtrate was evaporated to dryness and purified by column chromatography.

From 4-heptanone (hexane/ethyl acetate 9:1, then hexane/ethyl acetate 7:3, then ethyl acetate as eluents) two products were obtained.

4.3.1. 1,2:5,6-Di-*O*-(1-ethylbutylidene)-α-D-glucofuranose. Faster moving fractions contained the title compound (3%, pale yellow crystalline mass). $[\alpha]_D^{25}$ +10.5 (*c* 1.1, chloroform). ^{1}H NMR ($CDCl_3$) δ: 5.96 (d, 1H, $J_{1,2}$=3.7 Hz, H-1), 4.54 (d, 1H, H-2), 4.35 (m, 2H, H-3,5), 4.20 (dd, 1H, $J_{6,5}$=6.2 Hz, $J_{6,6'}$=8.2 Hz, H-6), 4.11 (dd, 1H, $J_{4,3}$=2.9 Hz, $J_{4,5}$=7.7 Hz, H-4), 3.95 (dd, 1H, $J_{6',5}$=5.6 Hz, H-6′), 1.28–1.75 (m, 16H), 0.95 (m, 12H). ^{13}C NMR ($CDCl_3$) δ: 115.76 (O–C–O), 113.45 (O–C–O), 105.82 (C-1), 86.00, 82.24, 76.00, 74.02, 68.70 (C-6), 40.57 (CH_2), 40.25 (CH_2), 40.16 (CH_2), 39.52 (CH_2), 17.90 (CH_2), 17.84 (CH_2), 17.57 (CH_2), 17.43 (CH_2), 14.88 (CH_3), 14.80 (CH_3). HR-MS (ESI) calcd for $C_{20}H_{36}NaO_6$ $[M+Na]^+$: 395.2404. Found: 395.2423.

4.3.2. 1,2-*O*-(1-Ethylbutylidene)-α-D-glucofuranose (5). Slower moving fractions comprised the title compound (5%, amorphous glass). $[\alpha]_D^{25}$ −0.45 (*c* 0.6, chloroform/methanol 9:1). ^{1}H NMR ($CDCl_3+CD_3OD$) δ: 5.87 (d, 1H, $J_{1,2}$=3.8 Hz, H-1), 4.43 (d, 1H, H-2), 4.23 (d, 1H, $J_{3,4}$=2.6 Hz, H-3), 3.99 (dd, 1H, $J_{4,5}$=7.5 Hz, H-4), 3.90 (m, 1H, H-5), 3.75 (dd, 1H, $J_{5,6}$=3.2 Hz, $J_{6,6'}$=11.7 Hz, H-6), 3.60 (dd, 1H, $J_{6',5}$=6.0 Hz, H-6′), 1.60 (m, 2H), 1.18–1.52 (m, 6H), 0.86 (m, 6H, 2×CH_3). ^{13}C NMR ($CDCl_3+CD_3OD$) δ: 115.62 (O–C–O), 105.33 (C-1), 85.98, 80.73, 75.38, 70.24, 64.48 (C-6), 40.16 (CH_2), 40.07 (CH_2), 17.82 (CH_2), 17.39 (CH_2), 14.61 (CH_3). HR-MS (ESI) calcd for $C_{13}H_{24}NaO_6$ $[M+Na]^+$: 299.1465. Found: 299.1481.

From 5-nonanone (hexane/ethyl acetate 9:1, then hexane/ethyl acetate 7:3, then ethyl acetate as eluents) two products were obtained.

4.3.3. 1,2:5,6-Di-*O*-(1-propylpentylidene)-α-D-glucofuranose. Faster moving fractions contained the title compound (4%, pale yellow crystalline mass). $[\alpha]_D^{25}$ −8.2 (*c* 1.8, chloroform). ^{1}H NMR ($CDCl_3$) δ: 5.97 (d, 1H, $J_{1,2}$=3.8 Hz, H-1), 4.55 (d, 1H, H-2), 4.36 (m, 2H, H-3,5), 4.25 (dd, 1H,

$J_{6,5}$=6.1 Hz, $J_{6,6'}$=8.2 Hz, H-6), 4.11 (dd, 1H, $J_{4,3}$= 2.8 Hz, $J_{4,5}$=7.7 Hz, H-4), 3.94 (dd, 1H, $J_{6',5}$=5.6 Hz, H-6′), 2.55 (d, 1H, J=3.7 Hz, OH), 1.62 (m, 8H, 4×CH_2), 1.34 (m, 16H, 8×CH_2), 0.93 (m, 12H, 4×CH_3). ^{13}C NMR ($CDCl_3$) δ: 115.98 (O–C–O), 113.60 (O–C–O), 105.86 (C-1), 86.01, 82.36, 76.01, 74.00, 68.76 (C-6), 38.01 (CH_2), 37.82 (CH_2), 37.63 (CH_2), 36.98 (CH_2), 26.71 (CH_2), 26.52 (CH_2), 26.40 (CH_2), 26.31 (CH_2), 23.49 (CH_2), 23.44 (CH_2), 23.38 (2×CH_2), 14.54 (2×CH_3), 14.50 (CH_3), 14.38 (CH_3). HR-MS (ESI) calcd for $C_{24}H_{44}NaO_6$ [M+Na]$^+$: 451.3030. Found: 451.3054.

4.3.4. 1,2-*O*-(1-Propylpentylidene)-α-D-glucofuranose (6). Slower moving fractions comprised the title compound (8%, amorphous glass). $[\alpha]_D^{25}$+0.4 (*c* 0.7, chloroform/methanol 9:1). ^{1}H NMR ($CDCl_3$+CD_3OD) δ: 5.88 (d, 1H, $J_{1,2}$=3.7 Hz, H-1), 4.46 (d, H, H-2), 4.26 (d, 1H, $J_{3,4}$= 2.4 Hz, H-3), 4.00 (dd, 1H, $J_{4,5}$=7.3 Hz, H-4), 3.93 (m, 1H, H-5), 3.78 (dd, 1H, $J_{6,5}$=3.2 Hz, $J_{6,6'}$=11.7 Hz, H-6), 3.63 (dd, 1H, $J_{6',5}$=5.9 Hz, H-6′), 1.62 (m, 2H), 1.47 (m, 2H), 1.26 (m, 8H), 0.86 (m, 6H). ^{13}C NMR ($CDCl_3$+CD_3OD) δ: 115.91 (O–C–O), 105.32 (C-1), 85.95, 80.67, 75.41, 70.24, 64.43 (C-6), 37.63 (CH_2), 37.54 (CH_2), 26.65 (CH_2), 26.27 (CH_2), 23.27 (2×CH_2), 14.38 (CH_3), 14.32 (CH_3). HR-MS (ESI) calcd for $C_{15}H_{28}NaO_6$ [M+Na]$^+$: 327.1778. Found: 327.1787.

From cycloheptanone (hexane/ethyl acetate 3:2, then ethyl acetate, then ethyl acetate/methanol 3:1 as eluents) two products were obtained.

4.3.5. 1,2:5,6-Di-*O*-cycloheptylidene-α-D-glucofuranose. Faster moving fractions contained crude title compound (7%). Mp: 112–114 °C. $[\alpha]_D^{25}$+13.1 (*c* 1.7, chloroform). ^{1}H NMR (CD_3OD) δ: 5.81 (d, 1H, $J_{1,2}$=3.6 Hz, H-1), 4.39 (dd, 1H, $J_{2,3}$=0.4 Hz, H-2), 4.25 (m, 1H), 4.10 (m, 1H), 4.03 (dd, 1H, J=2.8, 11.5 Hz), 4.01 (dd, 1H, $J_{6,5}$=6.2 Hz, $J_{6,6'}$=8.6 Hz, H-6), 3.88 (dd, 1H, $J_{6',5}$=5.8 Hz, H-6′), 1.45–1.95 (other protons). ^{13}C NMR (CD_3OD) δ: 117.4 (C), 114.6 (C), 106.2 (C-1), 86.3, 82.7, 75.3, 73.7, 67.5 (C-6), 41.3 (CH_2), 40.9 (CH_2), 39.4 (CH_2), 38.8 (CH_2), 30.4 (CH_2), 30.3 (CH_2), 30.1 (CH_2), 29.9 (CH_2), 23.6 (CH_2), 23.4 (CH_2), 23.3 (CH_2), 23.0 (CH_2). HR-MS (ESI) calcd for $C_{20}H_{32}NaO_6$ [M+Na]$^+$: 391.2091. Found: 391.2085.

4.3.6. 1,2-*O*-Cycloheptylidene-α-D-glucofuranose (8). Slower moving fractions comprised the title compound (8%). Mp: 149–150 °C (lit. mp: 151.5–152.5 °C)[18]. ^{1}H NMR (CD_3OD) δ: 5.83 (d, 1H, $J_{1,2}$=3.7 Hz, H-1), 4.41 (d, 1H, H-2), 4.20 (d, 1H, $J_{3,4}$=2.7 Hz, H-3), 3.98 (dd, 1H, $J_{4,5}$=8.6 Hz, H-4), 3.87 (m, 1H, H-5), 3.74 (dd, 1H, $J_{6,5}$= 3.2 Hz, $J_{6,6'}$=11.6 Hz, H-6), 3.58 (dd, 1H, $J_{6',5}$=6.0 Hz, H-6′), 1.5–1.98 (m, other protons). ^{13}C NMR (CD_3OD) δ: 117.2 (C), 106.1 (C-1), 86.0, 81.3, 75.5, 70.4, 65.2 (C-6), 41.1 (CH_2), 39.4 (CH_2), 30.1 (CH_2), 29.9 (CH_2), 23.4 (CH_2), 23.0 (CH_2).

4.3.7. 1,2-*O*-(1,2,2-Trimethylpropylidene)-α-D-glucofuranose (14) (as a mixture of diastereoisomers). The title compound was obtained from 3,3-dimethyl-2-butanone (pinacolone). Hexane/ethyl acetate 7:3, then ethyl acetate as eluents, yield 8%. Major diastereoisomer had ^{1}H NMR ($CDCl_3$+CD_3OD) δ: 5.87 (d, 1H, $J_{1,2}$=3.8 Hz, H-1), 4.48 (d, 1H, H-2), 4.27 (d, 1H, $J_{3,4}$=2.9 Hz, H-3), 4.08 (dd, 1H, $J_{4,5}$=7.6 Hz, H-4), 3.88 (m, H-5), 3.74 (dd, 1H, $J_{6,5}$=3.4 Hz, $J_{6,6'}$=11.7 Hz, H-6), 3.61 (dd, 1H, $J_{6',5}$=6.2 Hz, H-6′), 1.20 (s, 3H, CH_3), 0.95 (s, 9H, *tert*-Bu). ^{13}C NMR ($CDCl_3$+CD_3OD) δ: 119.35, 104.78 (C-1), 85.31, 80.66, 74.92, 69.92, 64.36 (C-6), 37.95, 25.18, 22.23. Minor diastereoisomer had ^{1}H NMR ($CDCl_3$+CD_3OD) δ: 5.90 (d, 1H, $J_{1,2}$=3.7 Hz, H-1), 4.42 (d, 1H, H-2), 4.24 (d, 1H, $J_{3,4}$= 2.7 Hz, H-3), 4.03 (dd, 1H, $J_{4,5}$=7.7 Hz, H-4), 3.88 (m, H-5), 3.76 (dd, 1H, $J_{6,5}$=3.4 Hz, $J_{6,6'}$=11.5 Hz, H-6), 3.57 (dd, 1H, $J_{6',5}$=6.3 Hz, H-6′), 1.37 (s, 3H, CH_3), 0.87 (s, 9H, *tert*-Bu). ^{13}C NMR ($CDCl_3$+CD_3OD) δ: 116.54, 106.50 (C-1), 88.06, 81.05, 75.13, 69.96, 64.27 (C-6), 40.62, 25.22, 19.05. HR-MS (ESI) calcd for $C_{12}H_{22}NaO_6$ [M+Na]$^+$: 285.1309. Found: 285.1324.

4.4. Gelation test procedure

The gelation test was carried out as follows: the gelator was mixed in the closed-capped tube with the appropriate amount of solvent to result in a concentration of 3% [g mL^{-1}] (about 15 mg of gelator and 0.5 mL of solvent were used). The mixture was heated until the solid was dissolved and then about one further minute. By this procedure usually the solvent bp was reached. The test tube was cooled in air to 20 °C, left for 24 h at this temperature and then turned upside down. When the gel was formed the whole procedure was repeated with the concentration below 1%. Once we found by chance the gel formation in **5**/ethyl acetate system in concentration over 3% (while at 3% it was marked as 'S') all the 'S' marked systems in Table 1 (solution in 3%) were checked in higher concentration until we get either G (S→G) or P (S→P). In some cases, however, the solubility was so high and the amount of the gelator limited that a final answer cannot be given. In the case of 'I' at starting 3% concentration the lower concentrations were used in order to fully dissolve the saccharide, as the presence of the crystals can influence gelation (to get finally either I→G or I→P). All gels were also, in addition to usual 'invert vial test', examined using an optical microscope to exclude self-supporting precipitation.

4.5. X-ray crystallography

Diffraction data for **7** and **10** were collected at 100 K by using Kappa CCD diffractometer with graphite monochromated Mo Kα radiation. Lorentz and polarization corrections but not absorption corrections were applied. Structures were solved by direct methods (SHELXS-97) and refined on F^2 by full-matrix least-squares method (SHELXL-97)[19]. All atoms except hydrogens were refined as anisotropic. **7**: triclinic, space group $P1$, a=5.5010(3), b=6.1960(4), c=10.4990(7) Å, α=79.285(3), β=85.502(4), γ=65.609(4)°, V=320.23(3) Å^3, $R1$=0.042 [$I>2\sigma(I)$], $wR2$=0.094 (all data), **10**: monoclinic, space group $C2$, a=10.0600(8), b=5.6470(3), c=20.5190(16) Å, β=100.637(3)°, V=1145.63(14) Å^3, $R1$=0.042 [$I>2\sigma(I)$], $wR2$=0.097 (all data). Crystallographic data for compounds **7** and **10** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC268574 and CCDC268575, respectively. 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].

4.6. SEM observations

SEM observations were performed using a scanning electron microscope type DSM 942 (Zeiss, Germany) and Philips 515 in the secondary electron (SE) mode. The gel was prepared in a sample tube and frozen in liquid nitrogen. The frozen specimen was evaporated by a vacuum pump for about 8 h. Samples were fixed with conductive glue to the SEM holder. Then samples were coated with a thin layer of Au to protect the sample from heat destruction and to keep real parameters of the observed details.

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Solvent-free condensation of arylacetonitrile with aldehydes

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Abstract—The condensation of a series of arylacetonitriles with aldehydes can be carried out by mixing equivalent amounts of reagents with neat powdered KOH at room temperature for 3–60 min depending on the aldehyde steric hindrance. At higher temperature (110 °C), yields were generally higher and purity increased within very short reaction times (1–5 min). With pentamethylphenylacetonitrile, a phase transfer agent was necessary to give a satisfactory yield.

1. Introduction

Unsaturated nitriles play a key role in several pathways proposed for the prebiotic synthesis of biological molecules.[1] Arylacrylonitriles are important synthons of the synthesis of several biologically active molecules in the preparation of flagrances,[2] flavonoïd pigments,[3] sexual pheromones[4] and vitamin A.[5] They are directly concerned for increasing soybean yield as plant growth regulators,[6] and as inhibitors of prostaglandin synthetase.[7] Recently, they were used in the field of organic materials in order to obtain high-electron affinity polymers, which can be used to produce light-emitting diodes (LEDs) with air stable electrodes.[8,9]

The usual preparation of arylacrylonitriles involves the reaction of aromatic aldehydes with arylacetonitriles (Meyer and Frost reaction).[10] Indeed, they can be obtained under basic conditions in a polar solvent (NaOH, KOH, NaOEt, K_2CO_3 in MeOH or EtOH)[11–15] or under liquid–liquid phase transfer catalysis conditions.[3,16]

Very recently, we have proposed solvent-free procedures using neat powdered base.[17] When applied to the reaction of phenylacetonitrile with 4-methoxybenzaldehyde, excellent results were obtained using KOH at room temperature (Method I). The reactions were performed at higher temperatures (Method II, 110 °C), eventually in the presence of a phase transfer agent (PTA) (Method III). When a PTA catalyst was added (TBAB, Aliquat 336, TDA-1 or 18-C-6), under microwave irradiation (MW), new acrylonitriles with phenyl or alkyl group were obtained (whatever the base) according to a multi-step proposed mechanism.[17] With nonanenitrile, the PTA is necessary to obtain satisfactory yields, which were enhanced when using excesses of base ($KOCH_3$ or KOH) and nonanenitrile. However, a rather high temperature (130–150 °C) is needed, either under MW irradiation or conventional heating.

Strengthened by these results and in order to generalize the method, we now extend this study to the reaction of a series of aliphatic and aromatic aldehydes, including hindered ones, with substituted phenylacetonitriles.

2. Results and discussions

2.1. Reactions with phenylacetonitrile

Reactions were first carried out by mixing equivalent molar amounts of aldehyde (10 mmol), phenylacetonitrile and finely ground KOH. The main product was the α,β-unsaturated nitriles **3**(*Z*+*E*), contaminated by compound **4** resulting from Michael addition of **2a** to **3** (Eq. 1), and sometimes **5** coming from competitive Cannizzaro reaction.

Keywords: Solvent-free condensation; Microwave irradiation; Phase transfer catalysis; X-ray crystallography.
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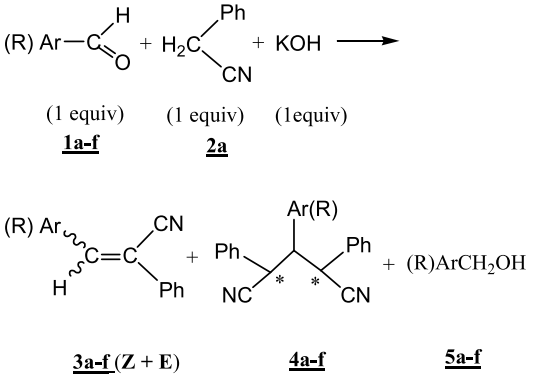


(1)

The main results are given in Table 1.

In all the cases, the major isomer was **3*Z*** with only traces of **3*E*** ($\leq$2%). The *Z* configuration of the carbon=carbon double bond in the major stereoisomer of compounds **3** was determined by X-ray single crystal analysis and by ^{13}C NMR. The ^{3}J coupling constant between the ethylenic proton and the carbon of the nitrile group was measured. In all cases, ^{3}J(C–H) values larger than 14 Hz were found.[18]

With the less hindered aromatic aldehydes **1a**–**c**, good yields (75–86%, entries 1, 3 and 6) were obtained within very short reaction time (3 min), needing a slight excess of aldehyde (1.3 equiv) when bearing a CF_3 group in position 4 (entry 6). Extended reaction times up to 10 min induced only a slight improvement, presumably due to the inefficacy of stirring as the reaction mixture became too solid (entries 2 and 4).

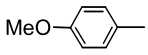
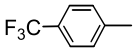
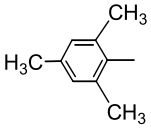
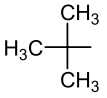
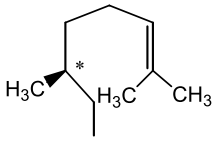
With aldehyde **1c**, an important amount of compound **4c** resulting from the Michael addition of **2a** to **3c*Z*** is obtained (8–12%, entries 5 and 6). When using an excess of nitrile (entry 7), the yield in **4c** is increased up to 20%. Furthermore, **1c** was among the tested aldehydes the only one giving amounts of the Cannizzaro product **5c**.

Where a highly hindered aromatic aldehyde such as mesitaldehyde **1d** is concerned, reaction time had to be extended up to 60 min to give a quasi-quantitative yield (98%, entry 10). Pivalaldehyde **1e**, in spite of steric hindrance due to *tert*-butyl group, led to a good yield in 10 min when using a slight excess of aldehyde (1.5 equiv) (87%, entry 12). No by-products were observed in these two last cases.

A yield of 87% in **3f*Z*** was obtained from L-(−)-citronellal **1f** in 10 min (entry 13), together with small amounts of **4f** (4%). Extension of reaction time did not allow any improvement.

The same reactions were next carried out at higher temperatures ($\geq$110 °C) under MW irradiation for very short times (1–2 min) and compared systematically with conventional heating (Δ) under strictly similar conditions (time, temperature, stirring,…) in order to check the possible non-thermal MW specific effects.[19]

Table 1. Solvent-free condensation of phenylacetonitrile **2a** with aromatic **1a**–**d** and aliphatic **1e**–**f** aldehydes, at room temperature, in the presence of KOH [Method I]

Entry	Aldehyde	(R) Ar	Reaction time (min)	Conversion[a] (%)	Yields (%)[a]			
					3*Z*	**3*E***	**4**	**5**
1	**1a**	Ph	3	96	77	1	4	0
2			10	96	81	1	6	0
3	**1b**		3	95	86	1	2	0
4			10	98	90	1	2	0
5	**1c**		3	94	63	2	12	7
6			3[b]	92	75	2	8	7
7			3[c]	—	67	2	20	5
8	**1d**		10	75	62	0	0	0
9			30	87	87	0	0	0
10			60	100	98	0	0	0
11	**1e**		10	79	77	0	0	0
12			10[d]	89	87	0	0	0
13	**1f**		10	94	87	1	4	0

[a] Conversions (based on consumption of **2a**) and yields were measured by GC using an internal standard (diethyl phthalate).
[b] **1c** (1.3 equiv).
[c] **2a** (1.2 equiv).
[d] **1e** (1.5 equiv).

Table 2. Solvent-free condensation of **2a** with a series of aldehydes **1a–f**, in the presence of KOH under MW irradiation or in a thermostated oil bath (Δ) [Method II]

Entry	Aldehyde	Activation method	Reaction time (min)	Temperature[a] (°C)	Conversion[b] (%)	Yields (%)[b]		
						3Z	**3E**	**4**
14	**1a**	MW	1	113	100	90	3	0
15		Δ	1	112	99	88	3	2
16	**1b**	MW	1	120	95	92	2	0
17		Δ	1	120	95	93	2	0
18	**1c**	MW	1	111	97	87	3	4
19		MW	2	125	99	94	1	2
20		Δ	1	101	97	83	2	5
21	**1d**	MW	1	111	42	42	0	0
22		MW	2	131	90	80	4	0
23		Δ	2	134	91	74	1	0
24	**1e**	MW	1	77	67	66	< 1	0
25		MW	2	115	84	83	< 1	0
26		Δ	1	80	60	58	< 1	0
27	**1f**	MW	1	123	98	95	3	0
28		Δ	1	107	96	90	4	2

[a] Optimal values obtained under MW (assigned temperature = 100 °C for **1a–d** and **1f**, 60 °C for **1e**) and consequently used for reactions under conventional heating Δ (values evaluated inside the reaction mixtures).
[b] Conversions and yields measured by GC using an internal standard (diethyl phthalate).

In Table 2 the results obtained under these conditions (MW and Δ) are given.

Yields were quite good (≥80%) within very short reaction times (1–2 min). Two opposite behaviours were shown:

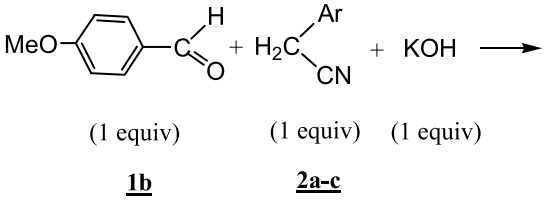
- a significant decrease in yield in the case of mesitaldehyde **1d** (80% within 2 min, entry 22) remained significantly less than the one resulting from reaction at room temperature. The yield was not next improved by extending reaction time up to 3 and 5 min as the isomer *E* was appearing (ex 3 min MW **3d*Z***: 80% **3d*E***: 10%).
- a clear increase with benzaldehyde **1a** (88–90% instead of 77–81% by Method I). The improvement is even more important with **1c** as yield was 94% versus only 63% according to Method I. Furthermore, it is of interest here to recover much less by-products (3% instead of 15–25%).

Aliphatic aldehydes **1e** and **1f** led to comparable yields but now without any traces of by-products (compare entries 25–27, respectively, with entries 11 and 13 in Table 1).

Finally, as a general rule, Method II seems to be more suitable than Method I improving the yield and reducing the secondary reactions. Nevertheless, in all these cases, results were practically identical whatever the activation mode, that is, no specific MW effects intervene here. The absence of such MW effects is justified as expected when considering the only slight modification of the polarity of the system during the reaction from the ground state to the transition state. The increase in polarity (necessary to observe MW effects) is here evidently limited due to the involvement of $PhCHCN^{-},M^{+}$ loose ion pairs concerning a charge delocalized (soft) anion.[20]

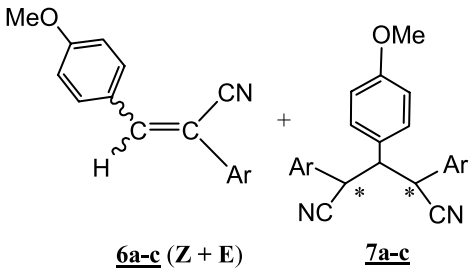
2.2. Reactions of several aromatic acetonitriles with 4-methoxybenzaldehyde

Reactions were carried out by mixing equivalent amounts of 4-methoxybenzaldehyde **1b** (10 mmol), arylacetonitrile **2a–c** and finely ground KOH. The main product was the α,β-unsaturated nitrile **6**, essentially with *Z* geometry, eventually accompanied in certain cases of compound **7** derived from Michael addition of **2** to **6** (Eq. 2).



(1 equiv) (1 equiv) (1 equiv)

1b **2a-c**



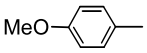
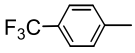
6a-c (**Z** + **E**) **7a-c** (2)

The main results are given in Table 3.

Satisfactory yields were obtained (≥74%) after short reaction times (≤10 min). The *Z* isomer was preponderant and accompanied by traces of **6*E***. However, extension of the reaction time induced slight modification presumably due to the heterogeneity of the reaction mixture. This reaction was next foreseen under MW irradiation and, for sake of comparison, with classical heating under similar conditions. Results are given in Table 4.

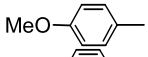
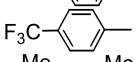
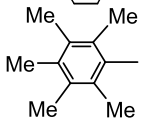
With nitriles **2a–c**, we isolated **6a–c*Z*** in high yields under

Table 3. Solvent-free condensation at room temperature of arylacetonitriles **2a–c** with 4-methoxybenzaldehyde **1b** in the presence of solid KOH [Method I]

Entry	Nitrile	Ar	Reaction time (min)	Conversion[a] (%)	Yields (%)[a]		
					6*Z*	**6*E***	**7**
3	**2a**	Ph	3	95	86	1	2
4			10	98	90	1	2
29	**2b**		3	83	65	2	0
30			10	94	74	1	0
31	**2c**		10	92	88	2	0

[a] Conversions and yields were evaluated by GC using an internal standard (diethyl phthalate).

Table 4. Solvent-free condensation of $ArCH_2CN$ **2a–c** with **1b** in the presence of solid KOH under MW irradiation or in a thermostated oil bath (Δ) [Method II]

Entry	Nitrile	Ar	Activation mode	Reaction time (min)	Temperature[a] (°C)	Conversion[a] (%)	Yields (%)[b]		
							6*Z*	**6*E***	**7**
14	**2a**	Ph	MW	1	113	100	90	3	0
15			Δ	1	112	99	88	3	2
32	**2b**		MW	1	124	99	89	3	0
33			Δ	1	124	93	83	2	0
34	**2c**		MW	1	119	99	92	1	0
35			Δ	1	119	100	93	1	0
36	**2d**		MW	5	122	47	19	14	0
37			Δ	5	120	45	24	14	0
38			MW	3	140	43	17	13	0

[a] Optimal values obtained under MW (assigned temperature = 100 °C for entries 14, 32 and 34, 120 °C for 36 and 140 °C for 38) and consequently used for reactions under conventional heating Δ (values evaluated inside the reaction mixtures).
[b] Conversions and yields were measured by GC using an internal standard (diethyl phthalate).

MW within 1 min (≥89%), even with nitrile **2b** (89%), which proved to be lower at room temperature (74% after 10 min, entry 30).

With the especially hindered nitrile **2d**, the yields remained very low (33%, entry 36), even when increasing temperature to 140 °C (entry 38).

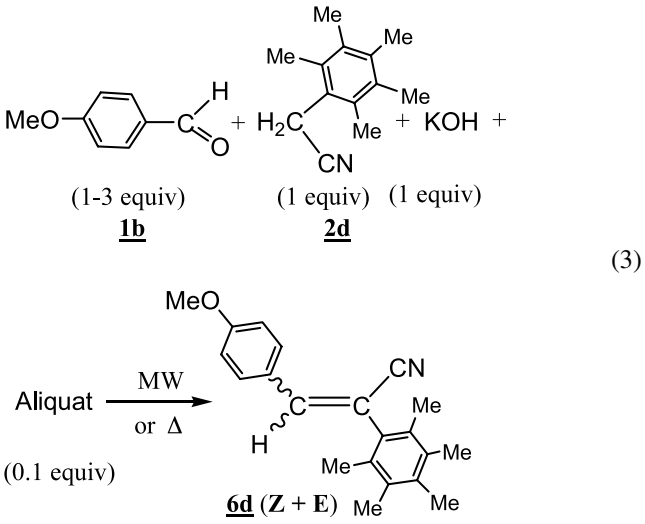
Changing the MW heating to conventional heating (entry 37) did not change the yield. In fact, as before, we did not observe any MW effects (Table 4), since yields and conversions were quite similar under conventional heating for the four nitriles (**2a**–**2d**). In order to try to improve the yield with the hindered **2d**, we also performed the reaction after addition of Aliquat 336 (Eq. 3), of which we report in Table 5 the main results obtained either under MW irradiation or classical heating with similar conditions.

The addition of Aliquat 336 allowed to noticeably increase the yields in ***6Z*** + ***E*** from 33% (entry 36, Table 4) up to 56% (entry 40, Table 5) under similar conditions (5 min at 120 °C). Yields were even more significantly improved up to 86% (entry 43) using an excess of aldehyde (1.5–3 equiv) with an optimal yield for 2 equiv. In all cases, ***Z*** is the predominant isomer. However, as discussed above, no noticeable MW specific effects were evidenced (MW = 86% versus Δ = 76%).

Table 5. Solvent-free condensation of pentamethylphenylacetonitrile **2d** with **1b** under solid–liquid phase transfer catalysis (PTC) conditions and MW irradiation or in a thermostated oil bath (Δ) [Method III]

Entry	**1b** (equiv)	Activation mode	Reaction time (min)	Temperature[a] (°C)	Conversion[b] (%)	Yields (%)[b]	
						6d*Z*	**6d*E***
39	1	MW	3	117	73	36	16
40		MW	5	120	96	36	20
41	1.5	MW	5	120	86	48	20
42	2	MW	3	120	91	55	20
43		MW	5	120	90	64	22
44		Δ	5	120	100	57	19
45		MW	7	120	91	56	20
46	3	MW	5	120	75	47	22

[a] Optimal values obtained under MW (assigned temperature = 120 °C) and consequently used for under conventional heating Δ (values evaluated into the reaction mixtures).
[b] Conversions and yields were measured by GC using an internal standard (diethyl phthalate).



2.3. Crystallographic study

The structures of compounds **3dZ**, **6cZ**, **6dZ** and **6dE** have been established by X-ray crystallography (Fig. 1). The crystal data were collected using a Bruker X8-APEX II-CCD area detector diffractometer. Intensities were given with graphite-monochromated Mo Kα radiation (0.71073 Å). The data were recorded at room temperature for **6dE** and at 100 K($\pm$1 K) for the three others (**3dZ**, **6cZ** and **6dZ**). The structures were solved by direct methods SHELX 86[21] and refined using SHELX 97[22] suite of programs. Non-H atoms were refined anisotropically by full-matrix least-squares techniques. H atoms were calculated geometrically and included in the refinement.

Crystal's data, details of data collections and structures refinements are given in the Section 4.

3. Conclusions

We have shown that solvent-free conditions, as previously established for the condensation of phenylacetonitrile with 4-methoxybenzaldehyde,[17] can be generalized to a series of aromatic and aliphatic aldehydes and to more or less hindered nitriles. At room temperature (Method I), reactions required from 3–60 min depending of the aldehyde steric hindrance. At higher temperatures ($\geq$110 °C, Method II), either under MW irradiation or conventional heating, reaction times are very short (1–5 min) and yields are generally higher and less by-products are recovered. With

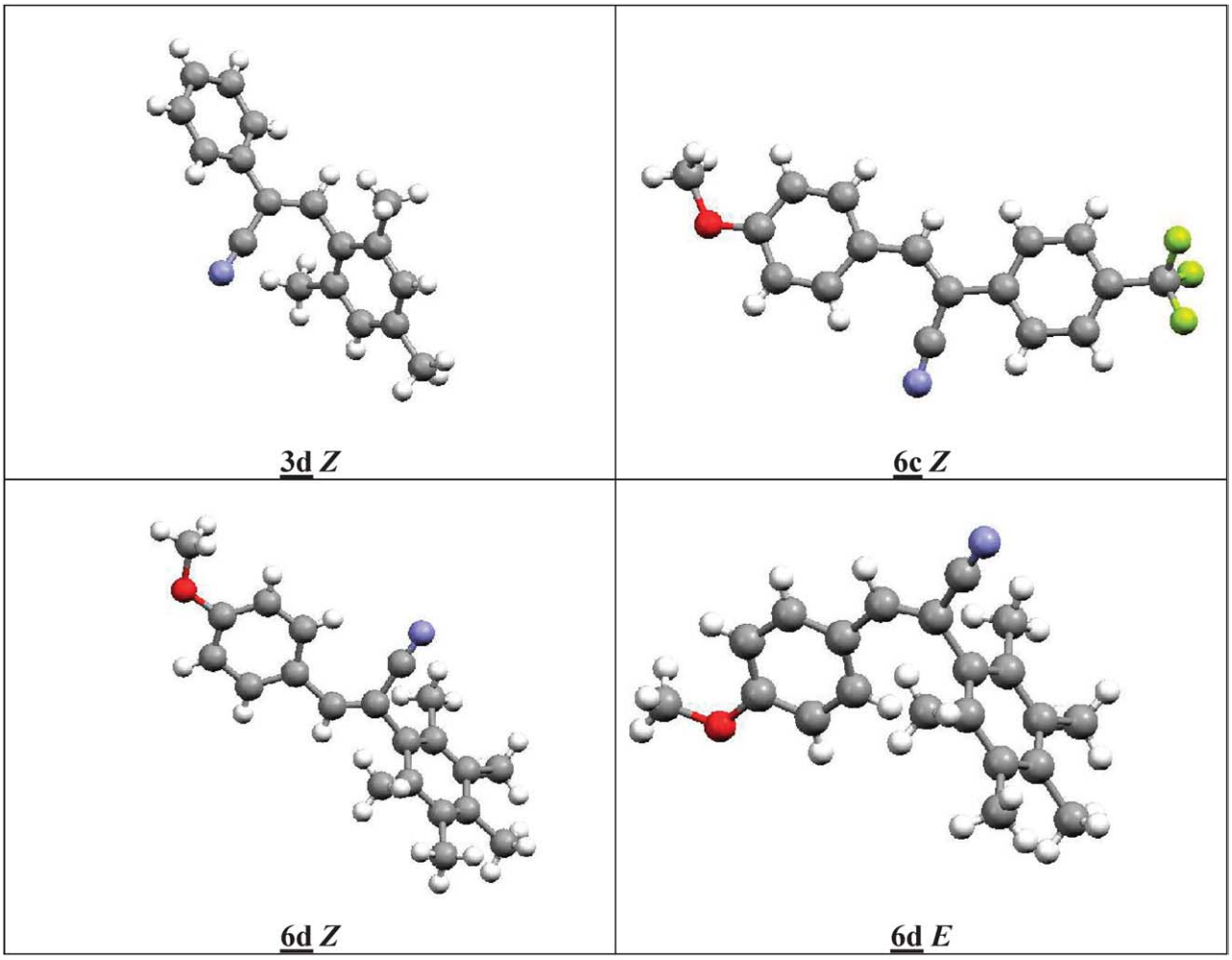


Figure 1. Crystal structures for **3dZ**, **6cZ**, **6dZ** and **6dE**.

pentamethylphenylacetonitrile, a phase transfer agent (Method III) is necessary to obtain a satisfactory yield at 120 °C. We have not observed any special MW effects neither on yields or conversions nor on the selectivity ***Z/E*** of the formed acrylonitriles.

4. Experimental

Microwave equipment

Reactions were performed in a monomode reactor Synthewave 402 microwave device from Prolabo.[23] The temperature was measured during the reaction by infrared detection, which indicates the surface temperature after previous calibration of emissivity in each case with an optical fiber thermometer (FTI-10 device from Fiso, optical fiber up to 250 °C). All reactions were conducted in a cylindrical Pyrex tube with mechanical stirring to ensure homogeneity in temperature. The power was monitored during irradiation to maintain a constant temperature.

Characterization of products

Solid products were characterized by their melting points. All the products were also characterized by GC–MS (Delsi-NerMag spectrometer with an ionising energy of 70 eV coupled to a gas chromatography fitted with a capillary column DB5, 30 m, ID = 0.25 mm).

Their ^{1}H and ^{13}C NMR spectra were registered on a Bruker instrument (AC 200, AC 250 and DRX 400) as $CDCl_3$ solutions. Chemical shifts are expressed in δ units (ppm) and quoted downfield from TMS as an internal standard. Proton-coupled ^{13}C NMR experiments were performed on a Bruker DRX 400 NMR spectrometer using a classical gated decoupling technique.

X-ray crystallography

Crystallographic data:

	3dZ	**6cZ**	**6dZ**	**6d*E***
Chemical formula	$C_{18}H_{17}N$ NO	$C_{17}H_{12}F_3$ NO	$C_{21}H_{23}$ NO	$C_{21}H_{23}$ NO
Crystal system	Monoclinic	Monoclinic	Triclinic	Orthorhombic
Space Group	$P2_1/n$	$C2/c$	P-1	$Pbca$
a (Å)	10.27(1)	15.98(1)	12.16(1)	13.31(1)
b (Å)	9.02(1)	31.32(1)	18.27(1)	13.38(1)
c (Å)	14.72(1)	13.68(1)	18.64(1)	19.40(1)
α (°)	90	90	61.49(1)	90
β (°)	90.17(1)	125.019(1)	70.99(1)	90
γ (°)	90	90	89.87(1)	90
V (Å^3)	1363(1)	5607(1)	3382(2)	3454(2)
Z	4	16	4	8
μ (Mo Kα) (mm^{-1})	0.070	0.117	0.073	0.071
Crystal size (mm)	0.200, 0.180, 0.130	0.200, 0.120, 0.060	0.100, 0.080, 0.020	0.250, 0.300, 0.300
F (000)	528	2496	1312	1312
2θ range (°)	2.42–30.89	1.30–30.98	1.29–24.05	2.10–27.48
T (K)	100(1)	100(1)	100(1)	293(2)
Number of data collected	11,553	35,396	18,750	7461
Number of unique data	3382	8051	9317	3950
Observed data [$I>2\sigma(I)$] (nobs)	2998	5169	2757	2928
Rint (%)	2.01	4.51	8.90	2.03
Number of parameters (nvar)	176	397	365	212
R a(%)	6.67	5.71	21.94	6.03
wR b(%)	9.82	12.69	30.10	8.17
Sc	1.024	0.978	1.225	1.035
$\Delta\rho$min (e$^-$ Å^{-3})	−0.564	−0.410	−0.785	−0.282
$\Delta\rho$max (e$^-$ Å^{-3})	0.433	0.559	0.939	0.331

The dimensions of the crystal **6dZ** (20 microns thickness) did not permit to obtain data of satisfying quality to carry out a perfect refinement. The factor R for this structure is 21.94%. This structure is not deposited on Cambridge Crystallographic Data Center but this result is sufficient to prove that the compound is the expected one.

Crystallographic data for the structures reported in this paper, have been deposited with the Cambridge Crystallographic Data Center, CCDC Nos. 269684–269685 and 269686. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

GC Analyses

All the yields were determined by GC with diethyl phthalate as internal standard. The GC devices (GC 9000 series Fisons, GC 5160 Vega series 2 Carlo Erba) were fitted with a non-polar capillary column, film thickness = 0.1 μm, carrier gas = helium.

GC equipment is fitted with a hardware (NCI 900 series interface) and software (Turbochrom) system developed by Perkin Elmer Co.

GC conditions and retention times for reagents and products are given in Table 6.

Typical experiment

Aldehydes, arylacetonitriles, Aliquat 336 were purchased from commercial sources (Acros, Aldrich or Avocado Chemical Co.). Aldehydes **1a**, **1b** and **1c** were distilled before use. All others were used without any further purification. Commercial solid KOH (containing 15% H_2O) was finely grounded.

Table 6. GC conditions and retention times (RT) for reagents and products

Products or reagents	GC column	GC conditions	RT (min)	Internal standard RT (min)
1a	OV1, 12 m	100→250 °C (10 min)	1.18	5.87
2a	ID=0.25 mm	10 °C/min	1.73	
3a*Z*		P_{He}=50 kPa	9.78	
3a*E*			8.40	
4a			15.17+15.57	
1c	12QC2/BP1, 12 m	80→250 °C (5 min)	1.15	6.46
2a	ID=0.22 mm	10 °C/min	1.86	
3c*Z*		P_{He}=50 kPa	9.88	
3c*E*			8.53	
4c			14.44+15.03	
5c			2.27	
1b	DB1, 30 mm	100→280 °C (10 min)	5.58	9.38
2a	ID=0.25 mm	10 °C/min	4.50	
3b*Z*≡6a*Z*		P_{He}=70 kPa	16.40	
3b*E*≡6a*E*			15.12	
4b≡7a			22.43+23.24	
1d			6.33	
3d*Z*			15.17	
3d*E*			14.05	
1f		100→250 °C (10 min)	4.74	9.38
3f*Z*		10 °C/min	14.25	
3f*E*			13.93	
4f			23.00+23.42+23.80	
1e		80→250 °C (10 min)	In the solvent	11.14
2a		10 °C/min	5.40	
3e*Z*			9.71	
3eE			9.39	
1b		120→280 °C (10 min)	4.75	7.65
2b		10 °C/min	5.63	
6b*Z*			17.22	
6b*E*			15.60	
2c			4.09	
6c*Z*			13.91	
6c*E*			12.29	
2d			9.78	
6d*Z*			19.44	
6d*E*			17.69	

4.1. Solvent-free uncatalyzed reaction (Tables 1–4)

A mixture of phenylacetonitrile **2a** (10 mmol; 1.17 g), solid KOH (10 mmol; 0.65 g) and aldehyde **1a–f** (10 mmol) were introduced into a Pyrex vessel adapted to the microwave equipment fitted with a mechanical stirrer. At room temperature [Method I] or at temperatures ≥110 °C [Method II], the reactions were carried out in Pyrex vessels according to the conditions indicated in the Tables. At the end of the reaction, organic products were extracted with organic solvent (ethyl acetate) and the mixture was then filtered through sintered-glass.

The products **3a–f**(*Z*+*E*), **4a–c**, **4f** and **5c** were identified by GC–MS, NMR, X-ray crystallography, retention time by comparison with authentic samples, and analyzed by GC with an internal standard. Under conventional heating conditions (Δ) (Tables 2 and 4), the same Pyrex vessel as for MW experiments was used in the reactions carried out in the thermostated oil bath, at the same temperature as under MW irradiation. The same treatments were performed in both cases.

4.2. PTC solvent-free reaction (Tables 5 and 6)[Method III].

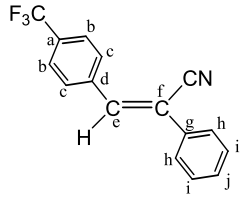
A mixture of arylacetonitrile **2a–d** (10 mmol), solid KOH (10 mmol; 0.65 g), Aliquat 336 (1 mmol; 0.4 g) and 4-methoxybenzaldehyde **1b** (10 mmol; 0.68 g) were introduced into a Pyrex vessel adapted to the microwave equipment, fitted with a mechanical stirrer.

Treatment remained exactly the same whatever the catalyzed or non-catalyzed nature of the reactions, under MW irradiation or conventional heating.

4.2.1. *Z*-2,3-Diphenylacrylonitrile 3a*Z* (RN: 2510-95-4). Commercial product (Lancaster Chemical Co.)

4.2.2. *Z*-2-Phenyl-3-(4-methoxyphenyl)acrylonitrile 3b*Z* or 6a*Z* (RN: 5432-07-5). This product was already described in earlier work.[17]

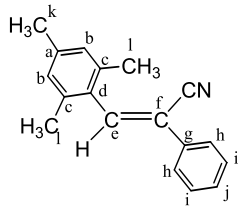
4.2.3. *Z*-2-Phenyl-3-(4-trifluoromethylphenyl]acrylonitrile 3c*Z* (RN: 147728-28-7).



Purified by flash chromatography (ether/*n*-pentane/ethanol 3:15:0.5). White crystals. Mp=112–114 °C. MS: *m*/*z* 273

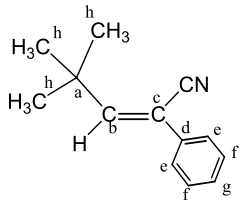
(M^+, 100%), 258 (10.7), 252 (11.4), 204 (78.2), 177 (11), 88 (11), 51 (13.5). ^{1}H NMR: 7.40–7.55 (m, 3H, H_i+H_j), 7.58 (s, 1H, H_e), 7.62–7.70 (m, 2H, H_h), 7.70–7.78 (m, 2H, H_b), 7.95–8.05 (m, 2H, H_c). ^{13}C NMR: 114.49 (C_f), 117.39 (CN) ($J_{He-CN}=14.5$ Hz), 122.22 (CF_3), 125.95 (C_b), 126.17 (C_h), 129.12 (C_i)+129.40 (C_c), 129.85 (C_j), 131.33 (C_a), 133.80 (C_g), 137.02 (C_d), 140.11 (C_e).

4.2.4. *Z*-2-Phenyl-3-(2,4,6-trimethylphenyl)acrylonitrile 3d*Z* (RN: 173975-31-0).



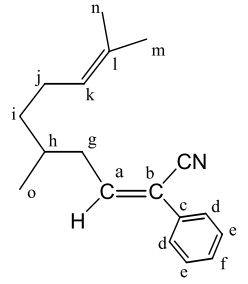
Purified by washing the crude product with cold *n*-pentane. Yellow crystals. Mp=103 °C. MS: *m/z* 247 (M^+, 100%), 231 (59.7), 205 (10.2), 115 (17.1), 91 (14.1), 77 (17.4), 51 (12.2). ^{1}H NMR: 2.31 (s, 9H, H_k+H_l), 6.91 (s, 2H, H_b), 7.34–7.45 (m, 3H, H_i+H_j), 7.64 (s, 1H, H_e), 7.65–7.70 (m, 2H, H_h). ^{13}C NMR: 20.10 (C_k), 20.97 (C_l), 116.72 (C_f), 118.50 (CN) ($J_{He-CN}=14.5$ Hz), 125.72 (C_h), 129.55 (C_b), 128.94 (C_i)+129.23 (C_j), 130.69 (C_a), 133.21 (C_g), 135.81 (C_c), 138.32 (C_d), 142.75 (C_e).

4.2.5. *Z*-2-Phenyl-3-*tert*-butylacrylonitrile 3e*Z* (RN: 110327-47-4).



Purified by distillation under reduced pressure. Colourless liquid. Bp=120–122/0.55 mbar. MS: *m/z* 185 (M^+, 73.5), 170 (100), 154 (18.6), 143 (67.4), 128 (46.3), 115 (33.7), 77 (34.2), 41 (31.6). ^{1}H NMR: 1.35 (s, 9H, H_h), 6.75 (s, 2H, H_b), 7.33–7.43 (m, 3H, H_f+H_g), 7.52–7.58 (m, 2H, H_e). ^{13}C NMR: 29.53 (C_h), 34.42 (C_a), 112.10 (C_c), 117.20 (CN) ($J_{Hb-CN}=15.0$ Hz), 125.73 (C_e), 128.63 (C_g), 128.76 (C_f), 135.08 (C_d), 157.31 (C_b).

4.2.6. *Z*-2-Phenyl-3-[(2,6-dimethyl)hept-5-en]acrylonitrile 3f*Z*.

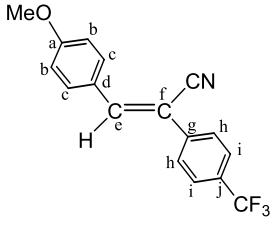


Purified by flash column chromatography on silica gel (*n*-pentane). Colourless liquid. MS: *m/z* 253 (M^+, 18.1), 238 (20.1), 154 (18.1), 115 (59.2), 109 (77.7), 81 (22.9), 69 (100), 55 (27.4), 41 (87.8). ^{1}H NMR: 0.98 (d, 3H, H_o), 1.15–1.55 (m, 2H, H_i), 1.61+1.68 (2s, 2×3H, H_n+H_m), 1.70–1.85 (m, 1H, H_h), 1.9–2.15 (m, 2H, H_j), 2.37–2.70 (m, 2H, H_g), 5.09 (m, 1H, H_k), 6.83 (t, 1H, H_a), 7.30–7.48 (m, 3H, H_e+H_f), 7.48–7.60 (m, 2H, H_d). ^{13}C NMR: 17.53 (C_n), 19.36 (C_o), 25.36 (C_j), 25.58 (C_m), 32.69 (C_h), 36.54 (C_i), 39.21 (C_g), 116.46 (CN) ($J_{Ha-CN}=14.4$ Hz), 116.55 (C_b), 124.06 (C_k), 125.41 (C_d), 128.65 (C_f), 128.73 (C_e), 131.37+133.13 (C_c+C_l), 145.83 (C_a).

4.2.7. *Z*-2-(4-Methoxyphenyl)-3-(4-methoxyphenyl)-acrylonitrile 6b*Z* (RN: 6443-74-9).

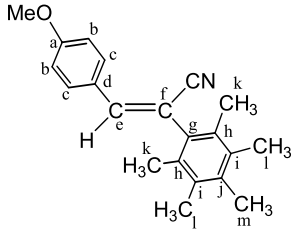
This product was already described in earlier work.[17]

4.2.8. *Z*-2-(4-Trifluoromethylphenyl)-3-(4-methoxyphenyl)acrylonitrile 6c*Z* (RN: 146725-29-3).



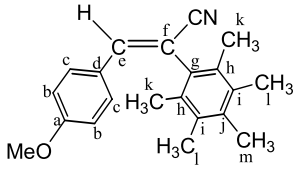
Purified by flash column chromatography on silica gel (*n*-pentane then *n*-pentane/ether 98:2). Yellow crystals. Mp=127–128 °C. MS: *m/z* 303 (M^+, 100), 284 (13,4), 272 (12.7), 240 (13.7), 234 (29), 233 (55.8), 219 (12.1), 191 (29.1), 190 (57.1). ^{1}H NMR: 3.89 (s, 3H, OCH_3), 6.94–7.06 (m, 2H, H_b), 7.54 (s, 1H, H_e), 7.64–7.85 (m, 2×2H, H_h+H_i), 7.85–8.01 (m, 2H, H_c). ^{13}C NMR: 55.24 (CH_3O), 107.07 (C_f), 114.52 (C_b), 118.03 (CN) ($J_{He-CN}=15.0$ Hz), 121.03 (CF_3), 124.00 (C_d), 125.99 (C_h), 128.43 (C_i), 129.39 C_j), 131.56 (C_c), 138.34 (C_g), 143.70 (C_e), 161.96 (C_a).

4.2.9. *Z*-2-(2,3,4,5,6-Pentamethylphenyl)-3-(4-methoxyphenyl)acrylonitrile 6d*Z*.



Purified by flash column chromatography on silica gel (*n*-pentane then *n*-pentane/ether 99:1–95:5). White solid. Mp=157 °C. MS: *m/z* 305 (M^+, 100%), 290 (37.9), 275 (29.6), 263 (8.9), 197 (10.1), 182 (17.2), 121 (16.2). ^{1}H NMR: 2.24+2.27+2.28 (3s, 15H, $H_k+H_l+H_m$), 3.87 (s, 3H, OCH_3), 6.79 (s, 1H, H_e), 6.95–7.06 (m, 2H, H_b), 7.81–7.94 (m, 2H, H_c). ^{13}C NMR: 16.59 (C_l), 16.87 (C_m), 17.87 (C_k), 55.40 (CH_3O), 108.07 (C_f), 114.28 (C_b), 118.68 (CN) ($J_{He-CN}=15.5$ Hz), 126.51 (C_d), 130.62 (C_c), 132.19 (C_h), 132.90 (C_g), 133.05 (C_i), 135.70 (C_j), 146.37 (C_e), 161.23 (C_a).

4.2.10. *E*-2-(2,3,4,5,6-Pentamethylphenyl)-3-(4-methoxyphenyl)acrylonitrile 6d*E*.



Purified by flash column chromatography on silica gel (pentane then pentane/ether 99:1–95:5). White solid. Mp = 153 °C. MS: *m/z* 305 (M^+, 100%), 290 (38.5), 275 (26), 263 (7.6), 197 (6.8), 182 (11), 121 (10.2). ^{1}H NMR: 2.19 + 2.22 + 2.28 (3s, 6H + 6H 3H, $H_k + H_l + H_m$), 3.74 (s, 3H, OCH_3), 6.66–6.74 (m, 2H, H_b), 6.89–6.98 (m, 2H, H_c), 7.31 (s, 1H, H_e). ^{13}C NMR: 16.63 (C_l), 16.94 (C_m), 17.08 (C_k), 55.20 (CH_3O), 111.05 (C_f), 114.11 (C_b), 120.46 (CN) ($J_{He-CN} = 9.3$ Hz), 127.11 (C_d), 129.58 (C_g), 131.22 (C_h), 131.35 (C_c), 133.42 (C_i), 135.94 (C_j), 144.19 (C_e), 160.87 (C_a).

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Facile preparation of cyclopropanes from 2-iodoethyl-substituted olefins and 1,3-dihalopropanes with zinc powder

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Abstract—Two efficient, simple, cheap, and environmentally benign preparations of cyclopropanes were achieved. One is the formation via 3-*exo-trig* manner from various electron-deficient 2-iodoethyl-substituted olefins with zinc powder in a mixture of *t*-butyl alcohol and water, and the other is the formation via 3-*exo-tet* manner from various 1,3-dihalopropanes with zinc powder in ethanol.

1. Introduction

A wide variety of naturally occurring cyclopropane derivatives bearing potent utility and biological activity are known.[1] Therefore, synthetic study of the cyclopropane ring is still important. Practical methods for the construction of cyclopropanes with olefinic groups have been carried out with free carbene derived from haloform under basic conditions,[2] diazo-olefins with the Rh-catalyst,[3] the Simmons–Smith reactions[4] and others.[5] Among them, cyclopropanation with diazo-olefins using the Rh-catalyst and the Simmons–Smith reaction are the most common and useful. However, generally, electron-rich olefins are required, since these reactions proceed via an electrophilic manner. On the other hand, the formation of cyclopropanes via radical pathways is challenging and interesting, since the cyclopropane rings are thermodynamically much disfavoured because of their ring strain,[6] and the carbon-centered radicals are generally nucleophilic, and, therefore, electron-deficient olefins are required.[7] There are three approaches for the construction of cyclopropane rings through a radical pathway. The first one is the formation of cyclopropanes via radical 3-*exo-trig* cyclization, the second one is that via radical 3-*exo-dig* cyclization, and the third one is that via radical 3-*exo-tet* cyclization. Today, to the best of our knowledge, studies on the formation of cyclopropanes via radical pathways are extremely limited, though a few radical 3-*exo-trig* cyclizations, which are favoured in Baldwin's rule, are known.[8] Thus, for the typical radical reagent system, Bu_3SnH with AIBN in refluxing benzene, Jung reported an interesting study in that the introduction of a *gem*-dialkoxy group to the 5-position of 6-bromo-2-hexenoate esters dramatically promoted radical 4-*exo-trig* cyclization to provide the corresponding cyclobutanes (α-cyclobutylacetate esters).[9] Based on this result, methyl 5-bromo-4,4-dimethoxy-2-pentenoate was treated with Bu_3SnH and AIBN in refluxing benzene. However, the expected cyclopropane derivative was not formed,[10] since ring-opening reaction of the formed cyclopropylmethyl radical occurred rapidly. On the other hand, electrochemical reductive cyclization of ethyl 5-methanesulfonyloxy-4,4-dimethyl-2-pentenoate was effectively carried out to form the corresponding cyclopropane.[11] Photolysis of 2-substituted butyrophenones gave the corresponding cyclopropyl phenyl ketones through a Norrish II type pathway.[12] As metal-induced radical 3-*exo-trig* cyclization, formation of 11β-hydroxy-5,9-cyclopregnane-3,20-dione by SET reduction of 9α-bromo-11β-hydroxyprogestrone bearing a δ-bromo-α,β-unsaturated ketone group, with chromous acetate was reported.[13] Treatment of δ-iodo- and δ-bromo-α,β-unsaturated esters with SmI_2 in the presence of *t*-butyl alcohol in THF gave the corresponding cyclopropanes.[14] The same treatment of γ,γ-disubstituted δ-*oxo*-α,β-unsaturated esters with SmI_2 in the presence of *t*-butyl alcohol in THF provided the corresponding cyclopropanols via the ketyl radicals.[15] Among these cyclopropanation methods, SmI_2-mediated radical 3-*exo-trig* cyclization to cyclopropanes is effective and useful. However, SmI_2 is extremely air-sensitive and, therefore, careful experimental operation is required. For the radical 3-*exo-dig* cyclization, the cyclization generally does not proceed. This is in agreement with Baldwin's rule, since

Keywords: Cyclopropane; 3-*exo-trig*; 3-*exo-tet*; Zinc.
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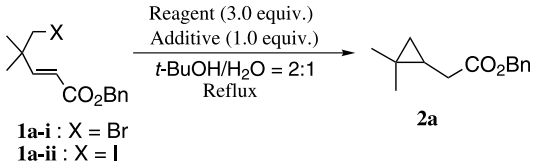
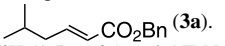
Table 1. 3-*exo-trig* Cyclization of benzyl 5-halo-4,4-dimethyl-2-pentenoate



1a-i : X = Br
1a-ii : X = I

2a

Entry	X	Reagent	Additive	Time (h)	Yield (%)
1	Br[a]	Zn	—	6	15
2	Br[b]	Zn	—	18	42 (37)[c]
3	Br[d]	Zn	—	5	0
4	I[a]	Zn	—	4	67
5	I	Zn	—	4	77
6	I	Zn	$ZnBr_2$	2	63
7	I	Zn	$Yb(OTf)_3$	3	21
8	I	Zn	$FeCl_3$	3	67
9	I	Zn	$Mg(ClO_4)_2$[e]	2	76
10	I	In	—	4	17 (26)[c]
11	I	Mg	—	10	0 (83)[c]
12	I	Fe	—	9	0 (86)[c]
13	I	Bu_3SnH[f]	—	1	0 (83)[g]
14	I	$(Me_3Si)_3SiH$[h]	—	2	0 (36)[g]

[a] A mixture of *t*-amyl alcohol and H_2O (2:1) was used as a solvent, instead of a mixture of *t*-BuOH and H_2O (2:1).
[b] KI (2.0 equiv) was added.
[c] Yield of recovered starting material **1a**.
[d] Sonication was carried out at 40 °C in an ultrasonic cleaner bath.
[e] $Mg(ClO_4)_2$ (2.0 equiv) was added.
[f] A mixture of Bu_3SnH (1.5 equiv) and AIBN (0.3 equiv) in *t*-BuOH was added dropwise over 1 h.
[g] Yield of compound **3a**,  (**3a**).
[h] A mixture of $(Me_3Si)_3SiH$ (1.5 equiv) and AIBN (0.5 equiv) in *t*-BuOH was added dropwise over 2 h.

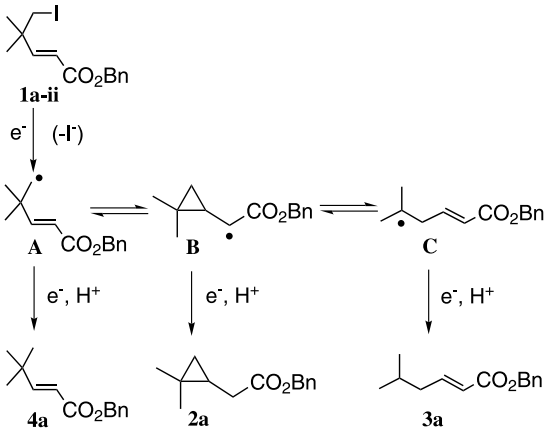
3-*exo-dig* cyclization is disfavoured. For the radical 3-*exo-tet* cyclization, the study is extremely limited, though radical 3-*exo-tet* cyclization is favoured in Baldwin's rule.[8] 1,3-Dihalides, mainly 1,3-diiodopropane derivatives, can be reductively cyclized to cyclopropanes by metal reduction such as Na,[16a–c] halogen–metal exchange such as *t*-BuLi,[17] and metal hydride such as $LiAlH_4$,[16b,c] and it is proposed that some of these reactions proceed through a radical pathway. Treatment of 1,3-diiodopropane with benzoyl peroxide at 110 °C gave cyclopropane in quite good yield.[18] Treatment of 2,2-disubstituted 1,3-diiodopropane with Bu_3SnH in refluxing benzene gave the corresponding cyclopropane in good yield.[16c] Recently, an interesting study for the formation of substituted cyclopropanes from the reaction of 2-substituted 1,3-diiodopropanes with $(C_6F_{13}CH_2CH_2)_3SnH$ or Ph_3SnH and AIBN under highly diluted conditions through homolytic substitution of the intermediate 3-iodoalkyl radicals was reported, and radical cyclization proceeds in the range of $5\times10^5\ s^{-1}$.[19]

Previously, we reported zinc- and indium-mediated radical ring-expansion reaction of α-halomethyl cyclic β-keto esters in aqueous alcohol to give the corresponding ring-expanded products in good yields, as an environmentally benign method.[20h] Here, as a part of our study toward environmentally benign organic synthesis via a radical pathway,[20] we would like to report an efficient, simple, cheap, and environmentally benign zinc-mediated radical 3-*exo-trig* cyclization of electron-deficient 2-haloethyl-substituted olefins to provide cyclopropanes in a mixture of *t*-butyl alcohol and water, and zinc-mediated 3-*exo-tet* cyclization of 1,3-dihalopropanes to provide cyclopropanes in ethanol.[21]

2. Results and discussion

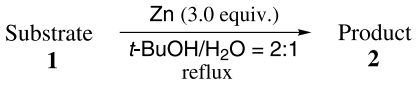
2.1. Formation of cyclopropanes from 2-haloethyl-substituted olefins via 3-*exo-trig* manner

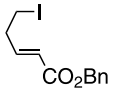
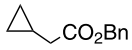
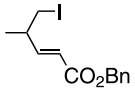
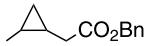
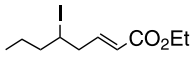
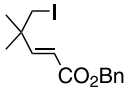
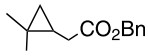
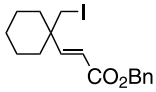
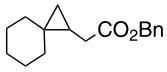
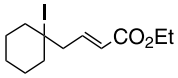
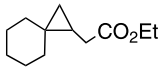
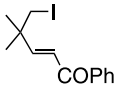
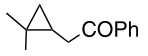
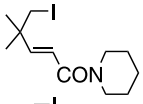
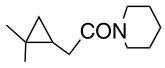
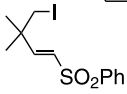
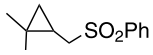
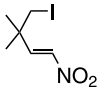
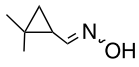
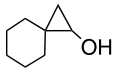
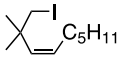
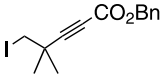
As a preliminary study, benzyl 5-bromo-4,4-dimethyl-2-pentenoate (**1a–i**) and benzyl 5-iodo-4,4-dimethyl-2-pentenoate (**1a–ii**) were treated with zinc powder in a mixture of *t*-butyl alcohol and water under refluxing conditions as shown in Table 1. Reactivity of the bromide **1a–i** was poor (entries 1–3), even though the reaction was carried out in the presence of KI or under sonication conditions, and the starting material was recovered mainly. However, the iodide **1a–ii** showed good reactivity to give the corresponding cyclopropane, benzyl (2,2-dimethylcyclopropyl)acetate, in

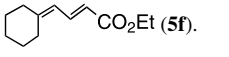


Scheme 1. Plausible reaction pathway.

Table 2. 3-*exo-trig* Cyclization of 2-iodoethyl-subtituted olefins



Entry	Substrate	Time (h)	Product	Yield (%)
1		5		5 (**2b**)
2		3		6 (**2c**)
3		1		13 (**2d**)
4		4		77 (**2a**)
5		3		99 (**2e**)
6		0.5		55 (**2f**)[a]
7		3		84 (**2g**)
8		4		75 (**2h**)
9		2		62 (**2i**)
10		2		66 (**2j**)[b]
11		2		90 (**2k**)
12		3		0 (64)[c]
13		1		0 (70)[c]
14		2		0 (88)[c]

[a] Compound **5f** was also obtained in 35% yield  (**5f**).

[b] *Syn*/*anti*=2:1.

[c] Yield of the direct reduction product.

good yield (entry 5). The addition of a Lewis acid for activation of the olefinic group by coordination onto the carbonyl oxygen atom of the iodide **1a**–**ii**, did not affect the yield (entries 6–9). Instead of zinc powder, the addition of indium showed poor reactivity (entry 10), and magnesium and iron powder did not provide any cyclized product (entries 11, 12). As typical radical reagents, tributyltin hydride and tris(trimethylsilyl)silane were treated with iodide **1a**–**ii** in the presence of AIBN, respectively. However, the cyclized cyclopropane **2a** was not obtained at all; instead, indirect reduction product **3a** was obtained in 83 and 36% yields, respectively (entries 13, 14). This result supports Jung's report.[10] Radical cyclization of primary carbon-centered radical **A** via 3-*exo-trig* manner is rapid, however, ring opening of the cyclized cyclopropylmethyl radical **B** is more rapid than the ring closure to generate a more stable tertiary carbon-centered radical **C**, as shown in Scheme 1. It is known that the rate constant for ring opening

of a cyclopropylmethyl radical is $1.3\times10^{8}\ s^{-1}$ (25 °C), and that of the ring closure via 3-*exo-trig* manner is $1.0\times10^{4}\ s^{-1}$ (25 °C).[22] The rate constants for the hydrogen atom abstraction from tributyltin hydride and tris(trimethylsilyl)-silane by a primary carbon-centered radical are $2.4\times10^{6}\ M^{-1}\ s^{-1}$ (25 °C) and $3.8\times10^{5}\ M^{-1}\ s^{-1}$ (25 °C), respectively.[23] Therefore, in tributyltin hydride and tris-(trimethylsilyl)silane systems, before the hydrogen atom abstraction from them by the cyclized cyclopropylmethyl radical **B**, ring opening rapidly occurred to give the indirect reduction product **3a** through the hydrogen atom abstraction by stable tertiary carbon-centered radical **C**. However, with zinc powder, the cyclized carbon-centered radical **B** is rapidly reduced to the corresponding anion and is protonated to provide cyclopropane, benzyl (2,2-dimethyl-cyclopropyl)acetate, in good yield.

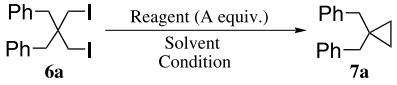
Based on these results, various 2-iodoethyl-substituted olefins were treated with zinc powder under the same conditions as shown in Table 2. Thus, electron-withdrawing groups such as ester, ketone, amide, sulfone, and nitro groups accelerate the radical 3-*exo-trig* cyclization to give the corresponding cyclopropanes effectively (entries 4–10), while phenyl and pentyl groups did not provide any cyclized products at all, respectively (entries 12, 13). Moreover, it is obvious that the introduction of dialkyl groups to the 4-position or 5-position of 5-iodo-2-pentenoate esters promotes the radical 3-*exo-trig* cyclization, while, the introduction of a monoalkyl group to the 4- or 5-position of 5-iodo-2-pentenoate esters reduces dramatically the cyclization product, similar to the parent 5-iodo-2-pentenoate esters (entries 1–6). This is the same effect, which was observed for the radical 4-*exo-trig* cyclization of 6-bromo-2-hexenoate ester with Bu_3SnH.[9] Thus, introduction of two alkyl groups to the 4- or 5-position of 2-pentenoate esters is important for the efficient 3-*exo-trig* cyclization. Instead of an activated olefinic group, radical 3-*exo-trig* cyclization onto an electron-deficient formyl group proceeded effectively to form the corresponding cyclopropanol in good yield (entry 11).

2.2. Formation of cyclopropanes from 1,3-dihalopropanes via 3-*exo-tet* manner

Reaction of compound **6a** with zinc powder (3.0 equiv) was carried out in refluxing mixtures of *t*-BuOH/H_2O and EtOH/H_2O to give the corresponding cyclopropane **7a** in 93 and 98% yields, respectively, as shown in Table 3 (entries 1, 2). When the amount of zinc powder was reduced to 1.2 equiv, the reaction also proceeded under the same conditions. However, the yield was decreased and the starting material **6a** was partly recovered (entry 3). The reaction in refluxing EtOH proceeded again cleanly, even though the amount of zinc powder was reduced to 1.2 equiv (entry 4). When the reaction was carried out in EtOH or in a mixture of EtOH/H_2O at room temperature, cyclopropane **7a** was not formed at all, and the starting material **6a** was recovered quantitatively (entries 5, 6). On the other hand, the reaction in a mixture of THF/satd aq NH_4Cl at room temperature proceeded, though the reaction requires long reaction time and 3.0 equiv of zinc powder for effective cyclization (entries 7, 8). Instead of zinc powder, the addition of indium powder showed poor reactivity (entry 11), and magnesium and iron powder did not provide any cyclopropane **7a** (entries 9, 10). As typical radical reagents, Bu_3SnH and $(Me_3Si)_3SiH$ were treated with 1,3-diiodopropane **6a** in the presence of AIBN in refluxing EtOH to give cyclopropane **7a** in 99 and 22% yields, respectively (entries 12–14). Additionally, as a typical SET reagent, SmI_2 was treated with 1,3-diiodopropane **6a** in THF at room temperature to give cyclopropane **7a** in good yield (entry 15).

Based on these results, various 1,3-diiodopropanes **6** bearing methoxy, bromo, ester, and olefinic groups were treated with zinc powder to provide the corresponding cyclopropanes **7** in good yields as shown in Table 4. Thus, 1,3-diiodopropanes bearing dibenzyl, bis-*p*-methylbenzyl,

Table 3. Cyclization of 2,2-dibenzyl-1,3-diiodopropane with zinc powder

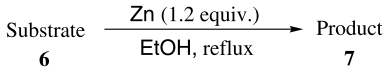


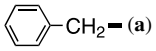
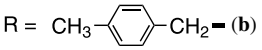
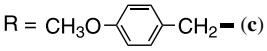
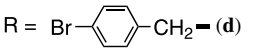
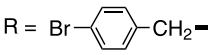
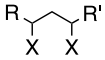
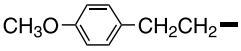
6a **7a**

Entry	Reagent	A	Solvent	Condition	Time (h)	Yield (%)
1	Zn	3.0	*t*-BuOH/H_2O (2:1)	Reflux	1	93
2	Zn	3.0	EtOH/H_2O (2:1)	Reflux	2	98
3	Zn	1.2	EtOH/H_2O (2:1)	Reflux	3	60 (36)[a]
4	Zn	1.2	EtOH	Reflux	3	97
5	Zn	1.2	EtOH	rt	22	0 (97)[a]
6	Zn	1.2	EtOH/H_2O (3:1)	rt	24	0 (99)[a]
7	Zn	3.0	aq NH_4Cl (satd)/THF (1:1)	rt	24	92
8	Zn	1.2	aq NH_4Cl (satd)/THF (1:1)	rt	24	43 (46)[a]
9	Fe	1.2	EtOH	Reflux	21	0 (99)[a]
10	Mg	1.2	EtOH	Reflux	18	0 (94)[a]
11	In	1.2	EtOH	Reflux	6	10 (68)[a]
12	Bu_3SnH[b]	2.4	EtOH	Reflux	5	99
13	Bu_3SnH	2.4	EtOH	Reflux	3	99
14	$(Me_3Si)_3SiH$[c]	2.4	EtOH	Reflux	4	22
15	SmI_2	3.0	THF	rt	1	83

[a] Yield of recovered starting material **6a**.
[b] A mixture of Bu_3SnH (2.4 equiv) and AIBN (0.2 equiv) in EtOH was added dropwise over 4 h.
[c] A mixture of $(Me_3Si)_3SiH$ (2.4 equiv) and AIBN (0.2 equiv) in EtOH was added dropwise over 3 h.

Table 4. Cyclization of various 1,3-dihalopropane with zinc powder



Entry	Substrate		Time (h)	Yield (%)
1	 R =  (**a**)		3	97
2	R =  (**b**)		1	99
3	R =  (**c**)		3	96
4	R =  (**d**)		3	91
5	R = $C_2H_5O_2C$– (**e**)		5	86
6	 R = 	X=I (**f**)	2	98
7		X=Br (**f–i**)	15[a]	81
8	R = 	X=I (**g**)	1	99
9		X=Br (**g–i**)	15[a]	83 (5)[b]
10	R = 	X=I (**h**)	2	94
11		X=Br (**h–i**)	15[a]	76
12		X=Cl (**h–ii**)	18[a]	27
13	 R = 	X=I (**i**)	2	94
14		X=I (**j**)	2	98
15	R = 	X=Br (**j–i**)	16[a]	46 (45)[c]
16	 R = CH_3–	X=I (**k**)	3	93 (1:0.8)[d]
17	R' = CH_3O– 	X=I (**k**)	5[e]	29 (61)[c] (1:2)[d]
18		X=I (**k**)	5[f]	42 (47)[c] (1:2)[d]

[a] Zn (3.0 equiv) and NaI (3.0 equiv) were added.
[b] Yield of recovered starting material **6g–i**.
[c] Yield of direct reduction product.
[d] Ratio of diastereomers.
[e] A mixture of Bu_3SnH (2.4 equiv) and AIBN (0.2 equiv) in EtOH was added dropwise over 4 h.
[f] A mixture of $(Me_3Si)_3$ SiH (2.4 equiv) and AIBN (0.2 equiv) in EtOH was added dropwise over 4 h.

bis-*p*-methoxybenzyl, bis-*p*-bromobenzyl, and diethoxycarbonyl groups at the 2-position, generated cyclopropanes **7** in good yields (entries 1–5). 1,3-Diiodopropanes bearing *p*-bromobenzyl, dodecyl, and 10-undecenyl groups at the 2-position, and bearing dodecyl and 10-undecenyl groups at the 1-position, also gave cyclopropanes in good yields (entries 6, 8, 10, 13, 14). When 1,3-dibromopropanes were treated in the presence of NaI under the same conditions, the corresponding cyclopropanes were again formed in good yields (entries 7, 9, 11). However, 1,3-dibromopropane bearing a 10-undecenyl group at the 1-position gave the cyclopropane in moderate yield (entry 15). This result probably comes from the fact that the nucleophilic substitution at the secondary carbon-bromine bond by the iodide anion does not proceed effectively. When 1,3-disubstituted 1,3-diiodopropane **6k**, which is a diastereomeric mixture (2:5) was treated with zinc powder, Bu_3SnH initiated by AIBN, and $(Me_3Si)_3SiH$ initiated by AIBN under the same conditions, the corresponding cyclopropane **7k** was obtained in good yield with zinc powder, in poor yield with Bu_3SnH, and in moderate yield with $(Me_3Si)_3$-SiH, respectively, and the ratio of the diastereomers was a little different (entries 16–18). The present cyclization mechanism with zinc powder is still not clear, and it may not be completely the same as that with Bu_3SnH and $(Me_3Si)_3$-SiH, that is, radical 3-*exo*-*tet* manner.

3. Conclusion

Thus, zinc-mediated cyclopropanation of electron-deficient 2-iodoethyl-substituted olefins in a mixture of *t*-butyl alcohol and water, and zinc-mediated cyclopropanation of 1,3-dihalopropanes in ethanol were successfully achieved. The present methods are efficient, simple, and environmentally benign for the preparation of cyclopropanes.

4. Experimental

4.1. General

^1H NMR spectra were recorded on 400 and 500 MHz spectrometers, and ^{13}C NMR spectra were recorded on 100

and 125 MHz spectrometers. Chemical shifts are expressed in ppm downfield from TMS in δ units. In the ^{13}C NMR spectra, p, s, t, and q means primary, secondary, tertiary, quaternary. Mass spectra were recorded on HX-110 and JMS-AT II 15 spectrometers. IR spectra were measured with an FT/IR-200 spectrometer. Silica Gel 60 was used for column chromatography, and Wakogel B-5F was used for preparative TLC. Zinc powder (no. 48005-30) was obtained from Kanto Kagaku Co, and used directly without any pretreatment.

4.2. General procedure for zinc-mediated cyclopropanation of electron-deficient 2-iodoethyl-substituted olefins

Zinc powder (1.2 mmol) was added to a refluxing solution of 2-iodoethyl olefin (0.4 mmol) in a mixture of *t*-BuOH (2 mL) and water (1 mL) under an argon atmosphere. After 0.5–5 h at the same temperature, the mixture was filtered through Celite®, then the solvent was removed, and the residue was purified by preparative TLC or column chromatography on silica gel.

4.2.1. Benzyl (2,2-dimethylcyclopropyl)acetate (2a). Colorless oil; IR (neat) 2950, 1740, 750, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=7.40–7.28 (5H, m), 5.14 (2H, s), 2.37 (2H, d, J=7.6 Hz), 1.05 (3H, s), 1.02 (3H, s), 0.94–0.84 (1H, m), 0.51 (1H, dd, J=8.5, 4.6 Hz), 0.03 (1H, t, J=4.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ=173.6 (q), 136.2 (q), 128.5 (t), 128.1 (t), 66.1 (s), 35.0 (s), 27.0 (p), 20.0 (p), 19.9 (t), 19.5 (s), 15.4 (q); MS (FAB): *m/z* 218; HRMS (EI) found: 218.1297 *m/z*, calcd for $C_{14}H_{18}O_2$: M^+=218.1307.

4.2.2. Benzyl 2-spiro[2.5]octylacetate (2e). Colorless oil; IR (neat) 2930, 1740, 750, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=7.40–7.27 (5H, m), 5.14 (2H, s), 2.45 (1H, dd, J=16.3, 7.2 Hz), 2.34 (1H, dd, J=16.3, 7.6 Hz), 1.58–1.12 (10H, m), 0.94–0.85 (1H, dddd, J=8.5, 7.6, 7.2, 4.7 Hz), 0.48 (1H, dd, J=8.5, 4.7 Hz), 0.03 (1H, t, J=4.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ=173.4 (q), 136.1 (q), 128.4 (t), 128.1 (t), 128.0 (t), 66.0 (s), 37.5 (s), 34.1 (s), 30.6 (s), 26.3 (s), 25.6 (s), 25.4 (s), 22.8 (q), 19.5 (t), 17.8 (s); MS (FAB): *m/z* 259; HRMS (FAB) found: 259.1679 *m/z*, calcd for $C_{17}H_{23}O_2$: M+H=259.1698.

4.2.3. Ethyl 2-spiro[2.5]octylacetate (2f). Colorless oil; IR (neat) 2930, 1740, 1180 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=4.15 (2H, q, J=7.2 Hz), 2.38 (1H, dd, J=16.2, 7.3 Hz), 2.27 (1H, dd, J=16.2, 7.3 Hz), 1.27 (3H, t, J=7.2 Hz), 1.60–1.24 (10H, m), 0.91–0.81 (1H, m), 0.47 (1H, dd, J=8.4, 4.5 Hz), 0.01 (1H, t, J=4.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ=173.8 (q), 60.2 (s), 37.6 (s), 34.2 (s), 30.7 (s), 26.4 (s), 25.6 (s), 25.1 (s), 22.8 (q), 19.5 (t), 17.8 (s), 14.2 (p); MS (FAB): *m/z* 197; HRMS (EI) found: 196.1467 *m/z*, calcd for $C_{12}H_{20}O_2$: M^+=196.1463.

4.2.4. (2,2-Dimethylcyclopropyl)acetophenone (2g). Colorless oil; IR (neat) 2940, 1690, 750, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=7.96 (2H, m), 7.55 (1H, tt, J=7.4, 1.6 Hz), 7.46 (2H, m), 3.03 (1H, dd, J=17.0, 7.0 Hz), 2.93 (1H, dd, J=17.0, 7.2 Hz), 1.11 (3H, s), 1.06 (3H, s), 1.02–0.94 (1H, dddd, J=8.7, 7.2, 7.0, 4.6 Hz), 0.56 (1H, dd, J=8.7, 4.6 Hz), 0.06 (1H, t, J=4.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ=200.3 (q), 137.0 (q), 132.8 (t), 128.5 (t), 128.0 (t), 39.2 (s), 27.1 (p), 20.2 (p), 19.8 (s), 19.6 (t), 15.4 (q); MS (FAB): *m/z* 189; HRMS (FAB) found: 189.1268 *m/z*, calcd for $C_{13}H_{17}O$: M+H=189.1279.

4.2.5. 2-(2′,2′-Dimethylcyclopropyl)-1-piperidinylethanone (2h). Colorless oil; IR (neat) 2940, 1640, 1440, 1250, 1220 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=3.56 (2H, dt, J=5.3, 5.1 Hz), 3.40 (2H, m), 2.44 (1H, dd, J=15.5, 6.3 Hz), 2.24 (1H, dd, J=15.5, 7.5 Hz), 1.68–1.50 (6H, m), 1.08 (3H, s), 1.05 (3H, s), 0.90–0.79 (1H, dddd, J=8.6, 7.5, 6.3, 4.7 Hz), 0.52 (1H, dd, J=8.6, 4.7 Hz), 0.04 (1H, t, J=4.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ=171.4 (q), 46.8 (s), 42.7 (s), 34.0 (s), 27.1 (p), 26.6 (s), 25.6 (s), 24.6 (s), 20.5 (t), 20.2 (p), 19.8 (s), 15.4 (q); MS (FAB): *m/z* 196; HRMS (FAB) found: 196.1718 *m/z*, calcd for $C_{12}H_{22}O_{14}N$: M+H=196.1701.

4.2.6. (2,2-Dimethylcyclopropyl)methanesulfonylbenzene (2i). Colorless oil; IR (neat) 2950, 1300, 1150, 750, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=7.93 (2H, m), 7.66 (1H, tt, J=7.4, 1.5 Hz), 7.57 (2H, m), 3.22 (1H, dd, J=14.5, 7.0 Hz), 3.05 (1H, dd, J=14.5, 7.2 Hz), 0.98 (3H, s), 0.91–0.83 (1H, dddd, J=8.7, 7.2, 7.0, 5.0 Hz), 0.78 (3H, s), 0.52 (1H, dd, J=8.7, 5.0 Hz), 0.00 (1H, t, J=5.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ=139.1 (q), 133.5 (t), 129.0 (t), 128.4 (t), 57.5 (s), 26.4 (p), 19.9 (p), 19.2 (s), 17.6 (t), 16.1 (q); MS (FAB): *m/z* 225; HRMS (FAB) found: 225.0935 *m/z*, calcd for $C_{12}H_{17}O_2S$: M+H=225.0949.

4.2.7. 2,2-Dimethyl cyclopropanecarbaldehyde oxime (2j). ^1H NMR (400 MHz, $CDCl_3$) *syn* form: δ=6.68 (1H, d, J=8.6 Hz), 2.14 (1H, td, J=8.6, 5.1 Hz), 1.18 (3H, s), 1.17 (3H, s), 0.96 (1H, dd, J=8.6, 5.1 Hz), 0.65 (1H, t, J=5.1 Hz); *anti* form: δ=7.22 (2H, d, J=8.5 Hz), 1.44 (1H, td, J=8.5, 5.1 Hz), 1.14 (6H, s), 0.84 (1H, dd, J=8.5, 5.1 Hz), 0.66 (1H, t, J=5.1 Hz).

4.2.8. Spiro[2.5]octan-1-ol (2k). Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ=3.28 (1H, dd, J=6.1, 3.0 Hz), 1.62–1.38 (8H, m), 1.21–1.10 (2H, m), 0.47 (1H, t, J=6.1 Hz), 0.33 (1H, dd, J=6.1, 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ=56.5 (t), 34.7 (s), 28.8 (s), 26.3 (s), 25.9 (s), 25.0 (s), 24.3 (q), 20.2 (s).

4.3. General procedure for zinc-mediated cyclopropanation of 1,3-diiodopropanes

Zinc powder (1.2 mmol) was added to a refluxing solution of 1,3-diiodopropane (0.4 mmol) in EtOH (3 mL) under an argon atmosphere. After 1–5 h at the same temperature, the mixture was filtered through Celite®, then the solvent was removed, and the residue was purified by preparative TLC or column chromatography on silica gel.

4.3.1. 1,1-Dibenzylcyclopropane (7a). Colorless oil; IR (neat) 3030, 2920, 1500, 1460, 1080, 1020, 760, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=7.31–7.25 (4H, m), 7.24–7.16 (6H, m), 2.56 (4H, s), 0.52 (4H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ=140.1 (q), 129.5 (t), 128.0 (t), 126.0 (t), 41.5 (s), 20.8 (q), 10.7 (s); MS (FAB): *m/z* 222; HRMS (EI) found: 222.1422 *m/z*, calcd for $C_{17}H_{18}$: M^+=222.1409.

4.3.2. 1,1-Bis(*p*-methylbenzyl)cyclopropane (7b). Colorless oil; IR (neat) 3000, 2920, 1520, 1020, 810 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) $\delta=7.08$ (8H, d, $J=1.7$ Hz), 2.51 (4H, s), 2.33 (6H, s), 0.48 (4H, s); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta=137.0$ (q), 135.3 (q), 129.4 (t), 128.7 (t), 41.1 (s), 21.0 (p), 20.9 (q), 10.6 (s); MS (FAB): *m/z* 250; HRMS (EI) found: 250.1734 *m/z*, calcd for $C_{19}H_{22}$: $M^+=250.1722$.

4.3.3. 1,1-Bis(*p*-methoxybenzyl)cyclopropane (7c). Colorless oil; IR (neat) 2910, 2840, 1610, 1510, 1250, 1180, 1040, 820 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) $\delta=7.09$ (4H, d, $J=8.7$ Hz), 6.83 (4H, d, $J=8.7$ Hz), 3.80 (6H, s), 2.49 (4H, s), 0.47 (4H, s); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta=157.8$ (q), 132.2 (q), 130.3 (t), 113.5 (t), 55.2 (p), 40.6 (s), 21.1 (q), 10.5 (s); MS (FAB): *m/z* 283; HRMS (FAB) found: 282.1620 *m/z*, calcd for $C_{19}H_{22}O_2$: M+H=282.1620.

4.3.4. 1,1-Bis(*p*-bromobenzyl)cyclopropane (7d). Colorless oil; IR (neat) 2920, 1490, 1400, 1070, 1010, 800 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) $\delta=7.40$ (4H, d, $J=8.2$ Hz), 7.02 (4H, d, $J=8.2$ Hz), 2.47 (4H, s), 0.53 (4H, s); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta=138.8$ (q), 131.2 (t), 131.1 (t), 119.9 (q), 40.8 (s), 20.5 (q), 10.8 (s); MS (FAB): *m/z* 379; HRMS (FAB) found: 379.9577 *m/z*, calcd for $C_{17}H_{16}Br_2$: M+H=379.9599.

4.3.5. Diethyl cyclopropane-1,1-dicarboxylate (7e). Colorless oil; IR (neat) 1730, 1320, 1210, 1140 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) $\delta=4.20$ (4H, q, $J=7.0$ Hz), 1.43 (4H, s), 1.28 (6H, t, $J=7.0$ Hz). This compound is available from Aldrich.

4.3.6. *p*-Bromobenzylcyclopropane (7f). Colorless oil; IR (neat) 3080, 3000, 1490, 1070, 1010, 820 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) $\delta=7.40$ (2H, d, $J=8.5$ Hz), 7.13 (2H, d, $J=8.5$ Hz), 2.49 (2H, d, $J=7.0$ Hz), 0.99–0.90 (1H, m), 0.52 (2H, ddd, $J=7.9$, 5.7, 4.5 Hz), 0.18 (2H, dt, $J=5.7$, 4.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta=141.1$ (q), 131.3 (t), 130.1 (t), 119.6 (q), 39.7 (s), 11.7 (t), 4.6 (s); MS (FAB): *m/z* 210; HRMS (EI) found: 210.0049 *m/z*, calcd for $C_{10}H_{11}Br$: $M^+=210.0044$.

4.3.7. Dodecylcyclopropane (7g). Colorless oil; IR (neat) 2920, 2850, 1460, 1020, 820, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) $\delta=1.45$–1.20 (20H, m), 1.19 (2H, dt, $J=7.3$, 7.0 Hz), 0.89 (3H, t, $J=6.9$ Hz), 0.72–0.60 (1H, m), 0.39 (2H, ddd, $J=8.1$, 5.5, 4.1 Hz), −0.01 (2H, dt, $J=5.5$, 4.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta=34.8$ (s), 31.9 (s), 29.67 (s), 29.64 (s), 29.5 (s), 29.3 (s), 22.7 (s), 14.1 (p), 10.9 (t), 4.3 (s); MS (EI): *m/z* 210; HRMS (EI) found: 210.2361 *m/z*, calcd for $C_{15}H_{30}$: $M^+=210.2348$.

4.3.8. 10-Undecenylcyclopropane (7h). Colorless oil; IR (neat) 2930, 2850, 1640, 1460, 1020, 910, 820 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) $\delta=5.82$ (1H, ddt, $J=17.2$, 10.2, 6.8 Hz), 5.04–4.97 (1H, ddt, $J=17.2$, 2.1, 1.7 Hz), 4.96–4.91 (1H, ddt, $J=10.2$, 2.1, 1.2 Hz), 2.05 (2H, m), 1.45–1.22 (14H, m), 1.18 (2H, dt, $J=7.5$, 7.0 Hz), 0.72–0.60 (1H, m), 0.39 (2H, ddd, $J=8.2$, 5.8, 4.0 Hz), −0.01 (2H, dt, $J=5.8$, 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta=139.2$ (t), 114.0 (s), 34.7 (s), 33.8 (s), 29.66 (s), 29.63 (s), 29.59 (s), 29.51 (s), 29.48 (s), 29.1 (s), 28.9 (s), 10.9 (t), 4.3 (s); MS (EI): *m/z* 194; HRMS (EI) found: 194.2046 *m/z*, calcd for $C_{14}H_{26}$: $M^+=194.2035$.

4.3.9. 1-(2′-(*p*-Methoxyphenyl)ethyl)-2-methylcyclopropane (7k). Colorless oil; IR (neat) 2930, 1510, 1240, 1040, 820 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *syn* form: $\delta=7.10$ (2H, d, $J=8.7$ Hz), 6.82 (2H, d, $J=8.7$ Hz), 3.78 (3H, s), 2.64 (2H, t, $J=7.7$ Hz), 1.65–1.40 (2H, m), 1.01 (3H, d, $J=6.3$ Hz), 0.82–0.65 (2H, m), 0.60 (1H, td, $J=8.4$, 4.1 Hz), −0.31 (1H, td, $J=5.2$, 4.1 Hz); *anti* form: $\delta=7.10$ (2H, d, $J=8.7$ Hz), 6.82 (2H, d, $J=8.7$ Hz), 3.78 (3H, s), 2.62 (2H, m), 1.65−1.40 (2H, m), 0.99 (3H, d, $J=5.8$ Hz), 0.45–0.33 (2H, m), 0.18 (1H, dt, $J=7.8$, 4.6 Hz), 0.13 (1H, dt, $J=7.8$, 4.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta=157.6$ (q), 134.9 (q), 134.8 (q), 129.3 (t), 113.6 (t), 55.2 (p), 36.5 (s), 35.5 (s), 35.0 (s), 30.9 (s), 19.5 (t), 19.0 (p), 15.4 (t), 13.2 (p), 12.9 (s), 12.8 (t), 11.9 (s), 9.5 (t); MS (FAB): *m/z* 190; HRMS (FAB) found: 190.1341 *m/z*, calcd for $C_{13}H_{18}O$: M+H=190.1358.

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