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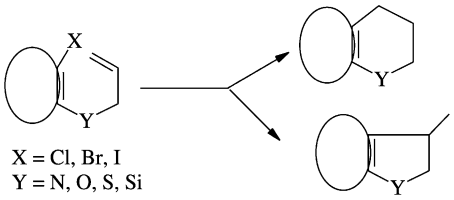
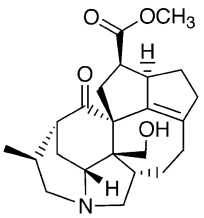
Contents

REPORT



ARTICLES



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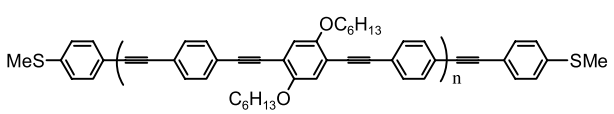
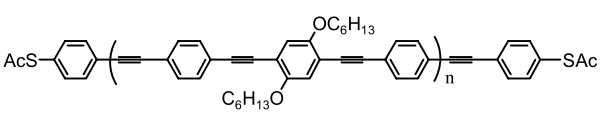
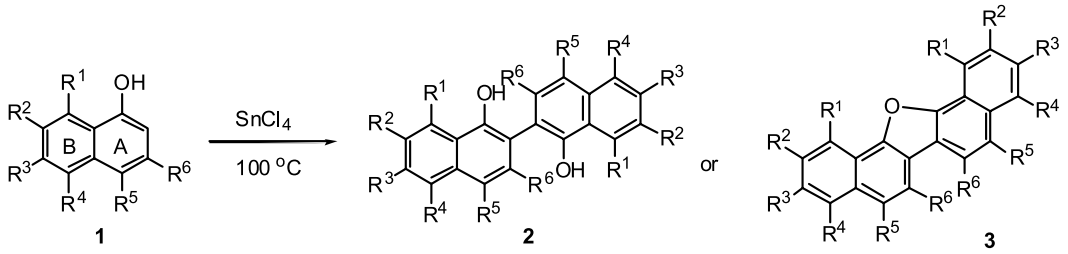
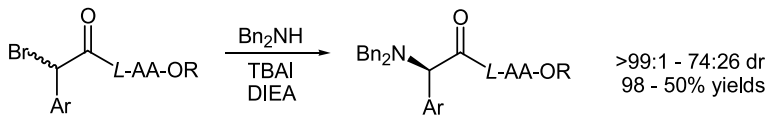
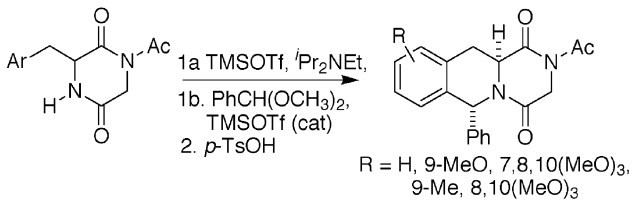
Five new fused-hexacyclic alkaloids, daphniglaucins D (**1**), E (**2**), F (**3**), G (**4**), and H (**5**), and two new yuzurimine-type alkaloids, daphniglaucins J (**6**) and K (**7**), have been isolated from the leaves of *Daphniphyllum glaucescens*, and the structures and relative stereochemistry were elucidated on the basis of spectroscopic data and chemical means.





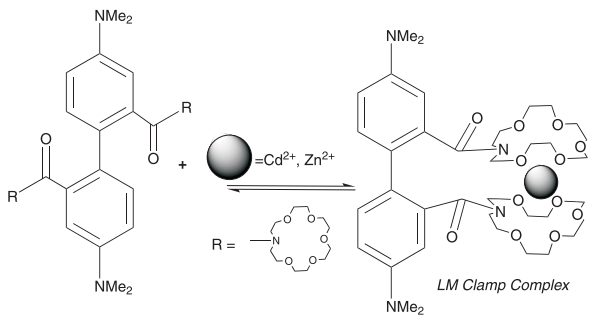


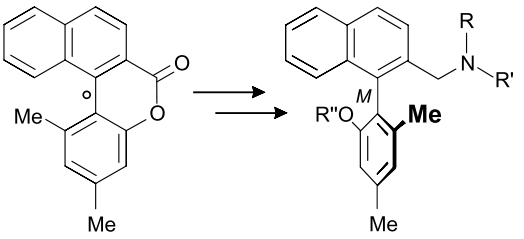


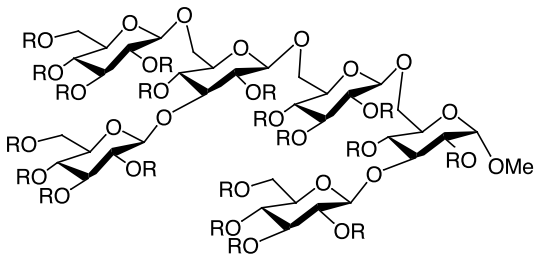


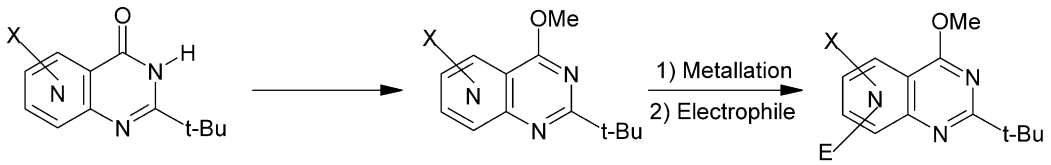
N-Alkylation of the lactam function of title compounds gave *O*,*N*-amidoacetals. Subsequent diastereoselective Pictet Spengler-type reactions afforded 6-phenyl-pyrazinoisoquinolinediones and a thieno analog while paraformaldehyde gave 6-unsubstituted compounds or benzo[*f*]pyrazino[1,2-*c*]1,3-oxazepine-1,4-diones.

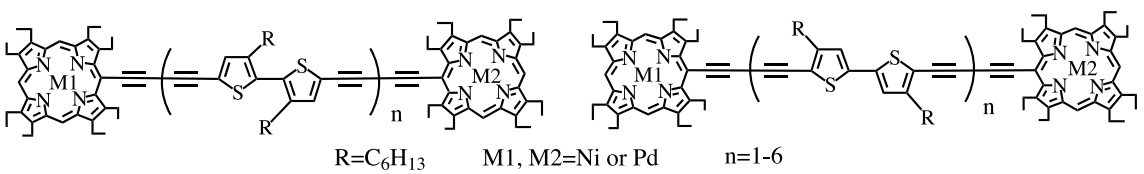
Azacrown ligands derived from bipheyl have shown that the selective sensing of Cd^{2+} exhibit by the monoazacrown derivatives is reversed when using the bisazacrown-tetramethylbenzidine derivative. In this case, both azacrown moieties form a sandwich type 1:1 complex allowing a selective sensing of Zn^{2+}.

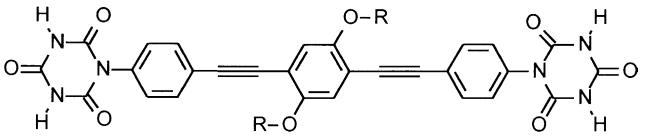












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Formation of five- and six-membered heterocyclic rings under radical cyclisation conditions

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Contents

1. Introduction

A few years ago, radicals were the subject of mechanistically oriented research and there has been increasing interest for several years in the chemistry of radical cyclisation. Important efforts have been made towards the synthesis of various heterocycles and many new methodologies have been developed in the field of radical cyclisations. Since their first appearance in literature, various types of *exo*- and *endo*-cyclisations of radicals onto internal unsaturated bonds have been described. The kinetics of various radical processes was known in the mid

Keywords: Radical cyclisation; Five- and six-membered heterocycles; Tributyltin hydride; Cascade cyclisation; Sulphur heterocycles.

Abbreviations: TBTH/Bu_3SnH, tributyltin hydride; Me_3SnH, trimethyltin hydride; Ph_3SnH, triphenyltin hydride; TTMSH/$(TMS)_3SiH$, tris(trimethylsilyl)silane; Bu_3GeH, tributylgermanium hydride; Bu_3SnCl, tributyltin chloride; Bu_3SnF, tributyltin fluoride; AIBN, azobis(isobutyronitrile); AMBN, azobis(methylisobutyronitrile); ACN, 1,1′-azobis(cyclohexanecarbonitrile); VA-061, 2,2′-azobis[2-(2-imidazoline-2-yl)propane]; EPHP, *N*-ethylpiperidine hypophosphite; CTAB, cetyltrimethylammonium bromide; $Zn(OTf)_2$, zinc(II)triflate; $(EtO)_2P(O)H$, diethylphosphite; TMEDA, *N*,*N*,*N*,*N*-tetramethyl-1,2-ethylenediamine; $Mn(OAc)_3$, manganese triacetate; $Cu(OAc)_2$, copper diacetate; HOMO, highest occupied molecular orbital; $Na(CN)BH_3$, sodiumcyanoborohydride; PhSH, thiophenol; THF, tetrahydrofuran; $Cp_2Zr(H)Cl$, Schwartz reagent; SmI_2, samarium diiodide; DLP, dilauroyl peroxide; DFT, density functional theorem; ATRC, atom transfer radical cyclisation; HPLC, high-performance liquid chromatography.

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1970s. The kinetic and structural information on various reactive intermediates was the first step in modern synthetic radical chemistry.[1–9] Beckwith[10] and Stork[11] reported that, under tin hydride annulated reaction conditions, a 5-*exo*/6-*endo* type of vinyl radical **1** cyclisation onto a C=C bond gives a mixture of both 5-*exo* and 6-*endo* products. The kinetic study of Beckwith[10] also showed that the initially formed five-membered ring radical **2** undergoes further isomerisation to produce the six-membered ring **3**. The fact that the five-membered ring closure is kinetically favoured is further supported by the work of Crich et al.[12] They pointed out the preferential formation of the 5-*exo* products by carrying out the reaction in a very rapid radical quenching system using PhSeSePh–Bu_3SnH (Fig. 1).

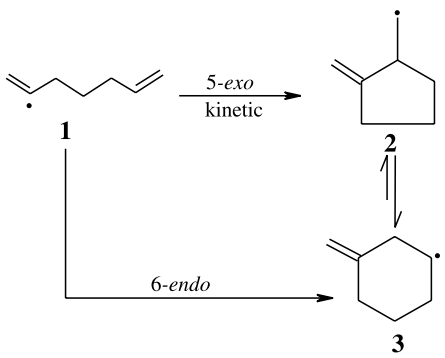


Figure 1. Vinyl radical cyclisations onto C=C bonds.

Similarly, a 5-*exo*/6-*endo* cyclisation of acyl radical **4** also gives a mixture of both 5-*exo* and 6-*endo* products (**5** and **6**, respectively) and, accordingly, the 5-*exo* cyclisation of acyl radicals onto a C=C bond is a kinetically favoured process[13a,b] (Fig. 2).

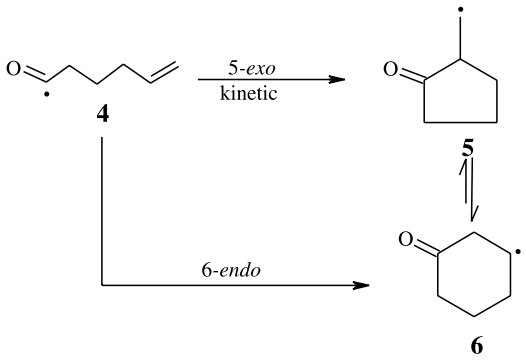


Figure 2. Acyl radical cyclisations onto C=C bonds.

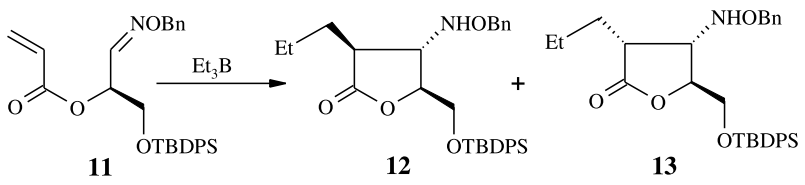
Among the numerous approaches and systems, which have been developed, some representative examples related to the formation of five- and six-membered heterocycles[13c] are discussed in this review.

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

Tin hydrides (Bu_3SnH, Me_3SnH and Ph_3SnH)[14] have been successfully employed in the synthesis of heterocycles using radical cyclisation. Generally, an excess of the tin hydrides with a smaller equivalent of a radical initiator like azobisisobutyronitrile (AIBN) are used in this type of reaction. An alternative procedure involves the use of a small amount of tri-*n*-butyltin chloride with sodium cyanoborohydride for the in situ generation of tri-*n*-butyltin hydride. Certain organotin compounds such as the trimethyltin derivatives are highly toxic,[15] whilst tributyl- and triphenyltins are only moderately toxic for mammals and moreover, it is very difficult to completely remove the toxic triorganotin byproducts, which are produced in stoichiometric amounts during the reaction. One of the most useful processes is the transformation of the excess, unreacted trialkyltin or triphenyltin halides to the corresponding easily removable, non-volatile, insoluble polymeric triorganotin fluoride by using aqueous potassium fluoride.[16] Purification of the product is, therefore, very difficult and various attempts have been made to overcome this problem. Due to this difficulty, various efforts have been directed towards tin-free radical chemistry.[17] Tris(trimethylsilyl)silane [$(TMS)_3SiH$] is commonly used in place of Bu_3SnH[18–22] and is slightly less reactive than Bu_3SnH, but very expensive,[23–26] and the reaction conditions are analogous to the tin hydride-mediated reductions using AIBN as initiator in refluxing benzene or toluene. Tributylgermanium hydride (Bu_3GeH) is another expensive reagent that can be used for an improved cyclisation yield. One such example is the cyclisation of perfluoroalkenyl radicals[27] using Bu_3GeH. Generally germanes are more reactive than silanes, but less reactive than tin hydrides. In most cases, AIBN is used as the radical initiator. There are, however, other diazine initiators, for example, azobis(methylisobutyronitrile) [AMBN], which is more soluble and can be used in cyclohexane as well as in toluene as the solvent. Cyclohexane is found to be the preferred solvent for Bu_3SnH-mediated reactions because toluene and benzene not only act as a solvent, but may also participate in the radical reactions.

The use of water as a solvent is a tremendous development in the field of radical cyclisation. The radical reaction in aqueous media is advantageous from the point of view of cost, safety and environmental concern. Additionally, most of the organic radical species are stable in water. Water-soluble initiators are used for carrying out the radical reactions in water. Mono- and bicyclic tetrahydrofurans and dihydrobenzofurans have been synthesised by the use of tri-2-furylgermanium hydride as the radical mediator in water.[28]

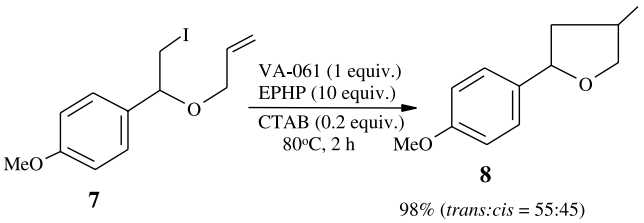
Recently, the radical cyclisations of hydrophobic substrates in water using the combination of 2,2′-azobis[2-(2-imidazolin-2-yl)propane] (VA-061), 1-ethylpiperidine hypophosphite (EPHP) and cetyltrimethylammonium bromide (CTAB) have been reported by Nambu et al.,[29] who observed that, when 2-iodo-1-(4-methoxyphenyl)-1-prop-2-enyloxy ethane **7** was treated with VA-061 as the water-soluble initiator and EPHP as the chain carrier, the cyclised product, 1-methoxy-4-(4-methyl-2-oxolanyl)benzene **8** was formed in 64% yield. By using 1–10 equiv. of NaCl as a 'salting out' salt, however, the reaction of the compound **7** proceeded more effectively and the yield of the product **8** was found to increase. It is important to note that a large quantity of a 'salting in' salt such as guanidine hydrochloride was necessary to facilitate the cyclisation reaction



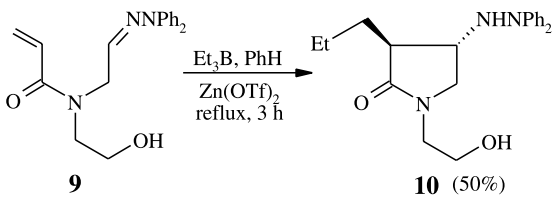
Solvent	T°C	Yield	Selectivity (**12**:**13**)
i) PhMe	reflux	70%	8:1
ii) PhH	reflux	64%	12:1
iii) PhMe	20°C	53%	18:1
iv) CH_2Cl_2	20°C	53%	10:1
v) H_2O/MeOH (1:4, v/v)	reflux	55%	9:1

Scheme 1.

of compound **7**. On the other hand, the reaction of **7** was best observed by using various surfactants (e.g., CTAB) in the presence of VA-061 and EPHP. The reaction did not go to completion in the presence of the commonly used radical initiator, AIBN.

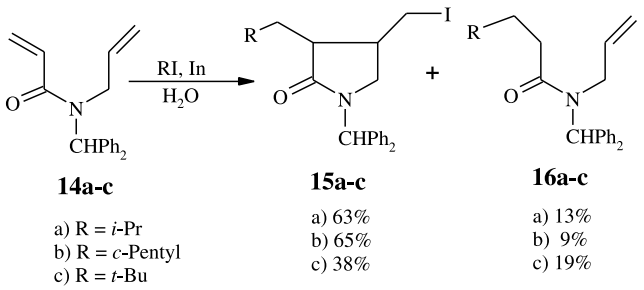


Triethylborane (Et_3B) is a useful reagent for radical cyclisation. The novel tandem radical addition cyclisation of oxime ethers and hydrazones intramolecularly concerted with the α,β-unsaturated carbonyl group is reported[30] by Miyabe et al. to give the heterocycles via a tandem C–C bond-forming process. The tandem reaction of the hydrazone **9** in the presence of the Lewis acid, $Zn(OTf)_2$, furnished only the *trans* cyclic product **10** and no *cis* isomer was formed.



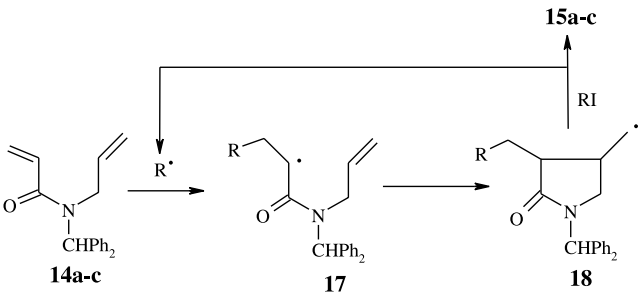
The radical addition cyclisation reaction of substrates having two different radical acceptors such as acrylate and aldoxime ether moieties has also been described. The reaction of the chiral oxime ether **11** in the presence of triethylborane in refluxing toluene proceeded smoothly to give a major diastereomer **12** in 70% yield, along with a small amount of another diastereomer **13**. The tandem reaction of **11** proceeded smoothly, even in aqueous media, providing a novel method for the asymmetric synthesis of γ-butyrolactones and β-amino acid derivatives[30] (Scheme 1).

Indium metal can be used for tandem carbon–carbon bond forming reactions as a single-electron-transfer (SET) radical initiator in aqueous media.[31] The radical addition–cyclisation reaction of hydrazones gave the functionalised cyclic products. The tandem addition–cyclisation trap reaction[31] of the substrate **14a** having acrylate and olefin moieties gives the desired cyclic product **15a** in 63% yield as a *trans*/*cis*-mixture in 3.2:1 ratio, along with 13% yield of the addition product **16a** (Scheme 2).



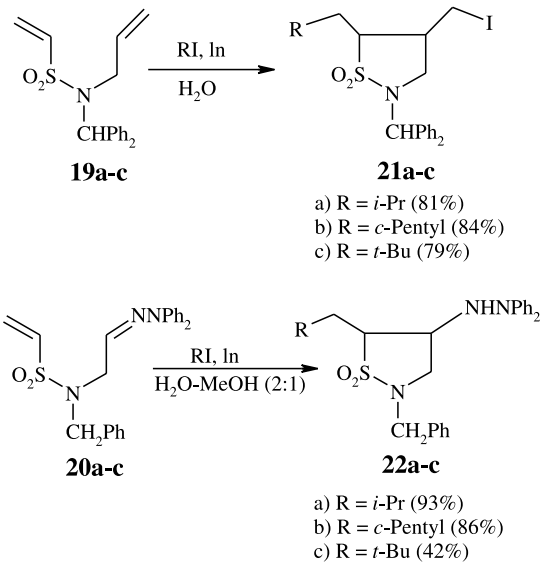
Scheme 2.

The preferential formation of the cyclic products **15a-c** over the addition products **16a-c** from **14a-c** could be explained by a radical mechanism. The indium-mediated reaction was initiated by single-electron-transfer to RI, with the generation of an alkyl radical. This radical then attacked the electrophilic acrylate moiety of **14** to generate the carbonyl-stabilised radical **17**. The cyclic products **15a-c** were obtained via the intramolecular reaction of the radical **17** with the olefin moiety, followed by an iodine atom transfer reaction from RI to the intermediate primary radical **18** (Scheme 3).



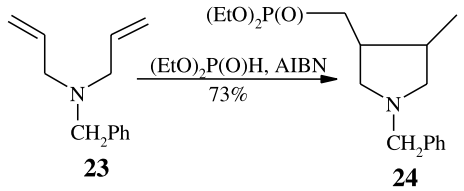
Scheme 3.

Similarly, the sulphonamides **19a-c** and the hydrazones **20a-c** produced only the cyclic products **21a-c** and **22a-c**, respectively. In these cases, other byproducts are not formed, due to the good reactivities of the sulphonamides and hydrazones as electron-deficient olefins (Scheme 4).

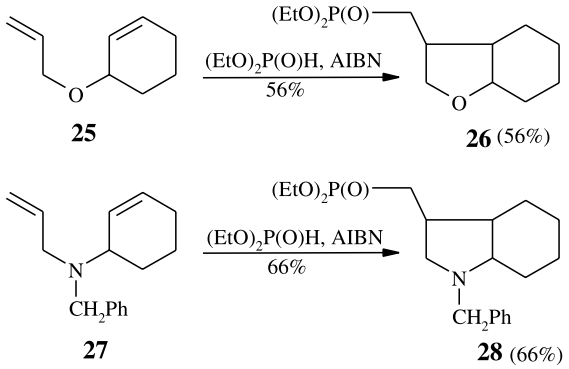


Scheme 4.

Diethyl phosphite, $(EtO)_2P(O)H$, an alternative and more versatile reagent for radical cyclisation was recently investigated by Parsons et al.[32] The reaction of the benzamide **23** with diethyl phosphite gave the pyrrolidine **24** in 73% yield when AIBN was used as the initiator or in 75% yield with Et_3B/O_2[33] at room temperature.



Bicyclic oxygen and nitrogen heterocycles could also be prepared by applying this methodology.[32] The cyclisation of the compounds **25** and **27** involved the reaction of diethyl phosphite with intermediate secondary (rather than primary) carbon-centred radicals to furnish **26** and **28** in 56 and 66% yield, respectively (Scheme 5).



Scheme 5.

The reaction of diethyl phosphite with tertiary carbon-centred radicals has also been demonstrated.[32] The yield for the cyclisations involving the intermediate tertiary carbon-centred radicals was rather lower and this may be explained by the greater stability of the tertiary carbon-centred radicals, which results in lower rates of hydrogen-atom transfer from diethyl phosphite.[34] In comparison to tin hydrides, phosphorous hydrides such as diethyl phosphite are inexpensive and non-toxic and it is also much easier to change the substituents on phosphorous.

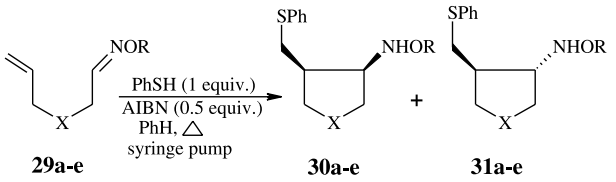
3. Synthesis of nitrogen heterocycles

3.1. Imine and enamine substrates and related systems

Bowman et al. have reported[35] alkyl radical cyclisations onto imino groups. Ryu et al. elaborated[36] the fact that a 5-*exo*/6-*endo* type of acyl radical cyclisation onto an N=C bond furnished 2-pyrrolidinones in a selective 5-*exo* manner. Recently, they also observed[37] that a 5-*exo*/6-*endo* type of vinyl radical cyclisation onto an aldimine N=C bond proceeds selectively in a 6-*endo* manner, to produce the methylenepiperidines.

9-(2-Bromoanilino)acridine was reported[38] to cyclise with tributyltin hydride and AIBN in boiling toluene to produce the pentacyclic acridines in very low yield (31%). The yield may be increased in the radical cyclisation reaction of *N*-alkylacridines to furnish 8-alkylquinoacridines.

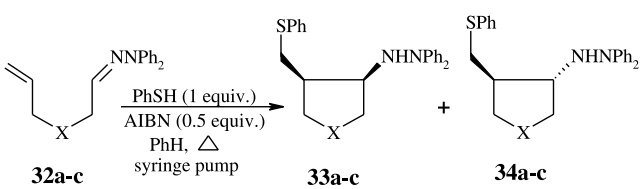
Naito et al. investigated[39] the radical cyclisation of various oxime ethers **29a-e** and obtained a mixture of the *cis* **30a-e** and *trans* compounds **31a-e** in combined yield (Scheme 6).



a) X = C(COOEt)$_2$, R = Me 76% (*cis*:*trans* = 4.0:1)
b) X = CH$_2$, R = Me 49% (*cis*:*trans* = 3.3:1)
c) X = NTs, R = Me 88% (*cis*:*trans* = 2.0:1)
d) X = NBoc, R = Me 62% (*cis*:*trans* = 3.0:1)
e) X = O, R = Bn 72% (*cis*:*trans* = 3.0:1)

Scheme 6.

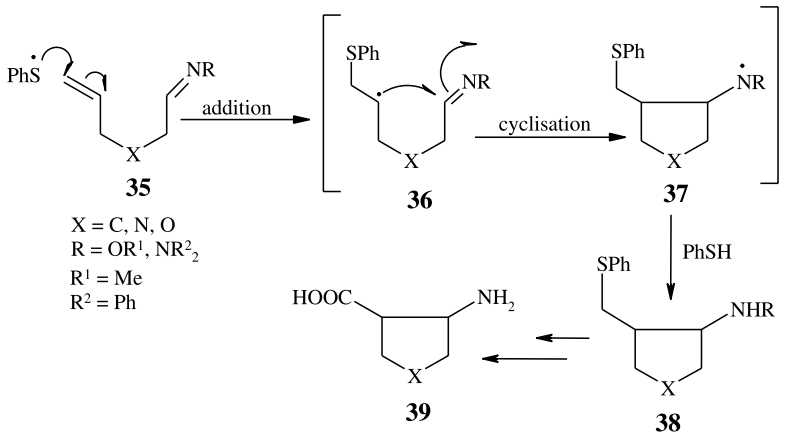
After the successful cyclisation of the oxime ethers **29a-e**, they investigated[39] the sulphanyl radical addition–cyclisation of various hydrazones **32a-c** to give a mixture of the *cis* **33a-c** and *trans* compounds **34a-c** in good combined yield (Scheme 7).



a) X = CH$_2$ 73% (*cis*:*trans* = 2.0:1)
b) X = NTs 75% (*cis*:*trans* = 1.5:1)
c) X = O 84% (*cis*:*trans* = 1.3:1)

Scheme 7.

Naito et al. then synthesised[39] the cyclic β-amino acids by a combination of sulphanyl radical addition–cyclisation of



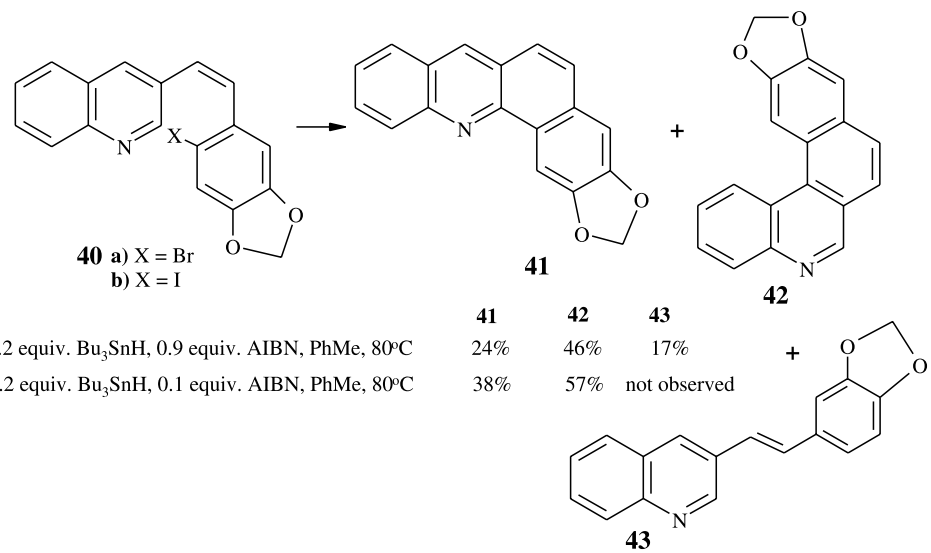
Scheme 8.

oxime ethers or hydrazones connected with alkenes and subsequent conversion of a phenylsulphanylmethyl group to a carboxyl unit. In this approach, a sulphanyl radical would attack the terminal alkenyl group in the substrates **35** to provide the alkyl radical species **36**, which are expected to form the substituted cyclic amines **38** via the aminyl radicals **37** as a result of 5-*exo-trig* cyclisation of **36**. Subsequent conversion of the phenylsulphanylmethyl group into the carbocyclic moiety would furnish the desired β-amino acid **39** (Scheme 8). This methodology has been successfully applied for the synthesis of a wide range of both natural and unnatural cyclic β-amino acids.

Radical additions to C-2, C-3 and C-4 of a quinoline have all been shown to proceed under neutral conditions.[40] In each case, the formation of heteroaromatic products, rather than dihydroquinolines, was observed by an oxidative tin hydride pathway. Treatment of the *cis*-azastilbene **40a** with tributyltin hydride under radical-forming conditions led to a separable mixture of the C-2 addition product **41** (24%) and the C-4 addition product **42** (46%), along with some *trans*-azastilbene **43** (17%). Similarly the iodo compound **40b** gave a mixture of compound **41** and **42** in 38 and 57% yield, respectively. In this case compound **43** was not obtained (Scheme 9).

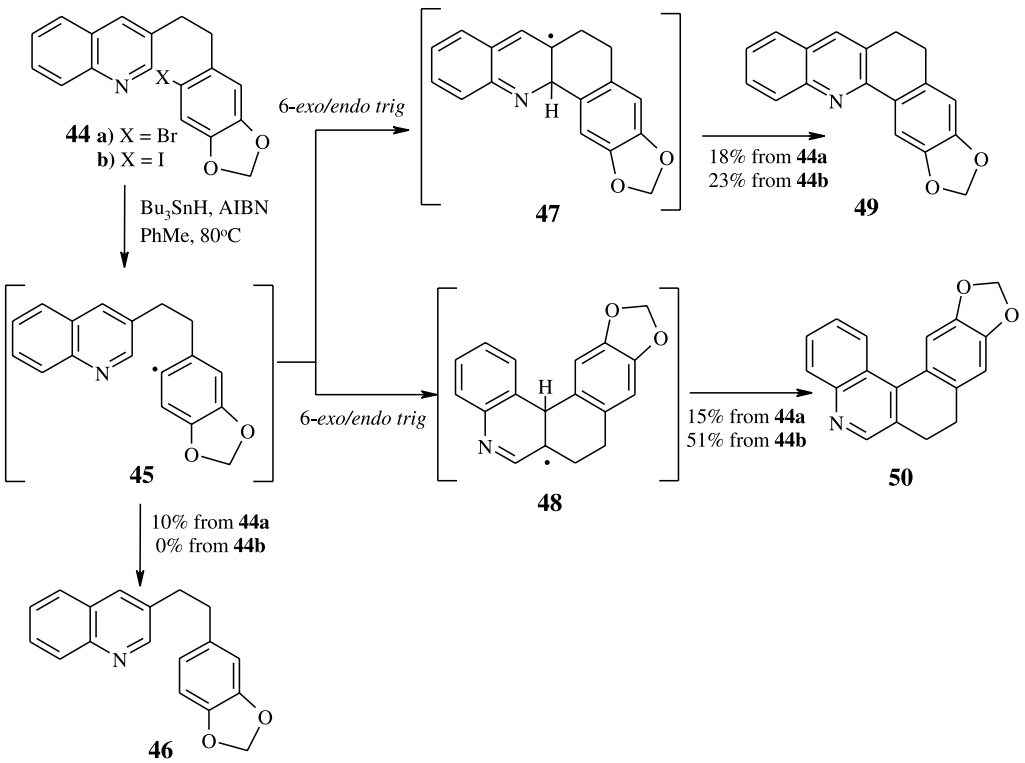
The cyclisation of **44a**,**b**, where a saturated two-carbon chain conjoined the quinoline and the aryl halide, led to a complex product mixture. The bromo derivative, 3-[2-(6-bromo-1,3-benzodioxol-5-yl)-ethyl]quinolone **44a** furnished the cyclisation product **49** in 18% via intermediate **47** and compound **50** (15%) via intermediate **48**. Additionally some recovered starting material (27%) and the dihydroazastilbene **46** (10%) following intermediate **45** could also be isolated. The reaction with the corresponding iodo compound **44b** proceeded more efficiently, however, yielding dihydrobenzo[*c*]acridine **49** and dihydrobenzo[*k*]-phenanthridine **50** in 23 and 51% yield, respectively in the same manner (Scheme 10). It is important to note that 5-*exo*/5-*endo-trig* radical cyclizations to quinolines fail and therefore appear to be more akin to 5-*endo-trig* processes than 5-*exo-trig* processes.

The radical addition to C-3 of quinoline can occur in different ways, for example, substrates in which the radical precursor was tethered at C-2 or C-4 of the quinoline moiety



	41	42	43
40 a: 1.2 equiv. Bu_3SnH, 0.9 equiv. AIBN, PhMe, 80°C	24%	46%	17%
b: 1.2 equiv. Bu_3SnH, 0.1 equiv. AIBN, PhMe, 80°C	38%	57%	not observed

Scheme 9.



Scheme 10.

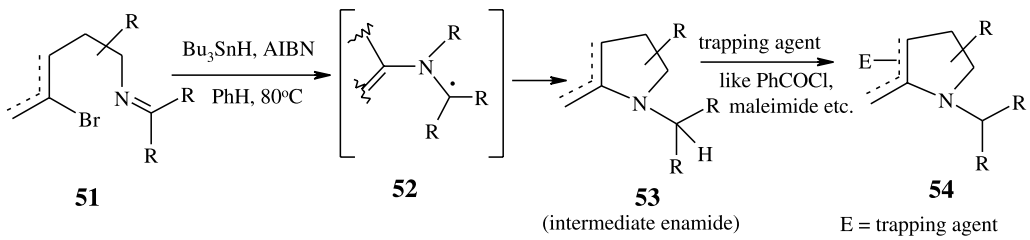
afforded different six-membered cyclised products in variable yields.

Ketimines derived from *o*-bromophenethylamine were reported[41] to cyclise to the *N*-substituted indolines under *n*-Bu_3SnH-mediated radical cyclisation conditions.

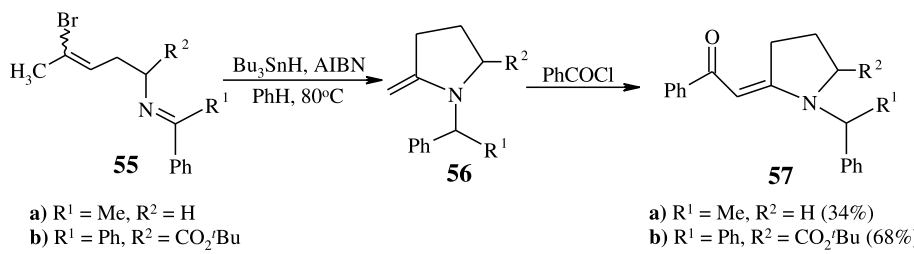
Johnston et al. have described[42,43] the free radical-mediated vinyl amination by non-conventional vinyl radical addition to azomethine nitrogen, following 5-*exo-trig* cyclisation, and this protocol is shown in Scheme 11, this involve sequential conversion of compound **51** to **54** via the intermediate **52** and **53**, respectively.

It was observed that compounds **55** on treatment with Bu_3SnH–AIBN furnished compounds **56**, which were trapped with benzoyl chloride to generate the final compound **57** (Scheme 12).

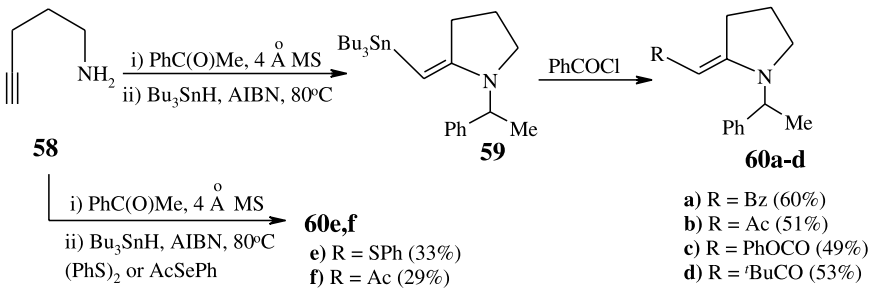
This new vinyl amination protocol is very useful for synthetic access to non-stabilised *N*,*N*-dialkyl enamines and tandem bond-forming processes.[42] Vinyl radicals might also



Scheme 11.



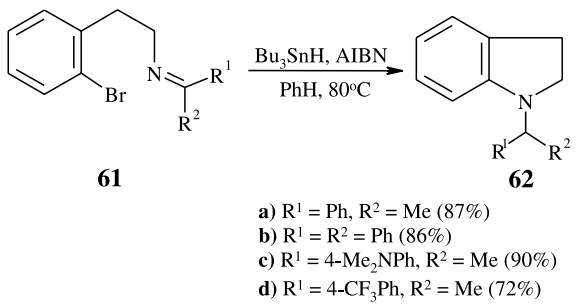
Scheme 12.



Scheme 13.

be produced by the addition of heteroatom-centred radicals to alkyne π-bonds and, accordingly, aminostannation was achieved by the addition of a stannyl radical to the ketimine obtained from the alkyne **58** in a highly regio- and stereoselective manner to give the β-stannyl enamine **59**. This enamine **59** was acylated at low temperature without the use of additives. A variety of acid chlorides varying in oxidation state and steric hindrance furnished the vinylogous amides and carbamates **60a-d**, ranging from 49 to 60% yield. Again, aminothiolation of the intermediate iminoalkyne provided the β-arylthioenamine **60e** in 33% yield with diphenyl disulphide as the thiyl radical precursor. Similarly, phenylselenoacetate and tributylstannane gave the product of aminoacylation **60f** in 29% yield (Scheme 13).

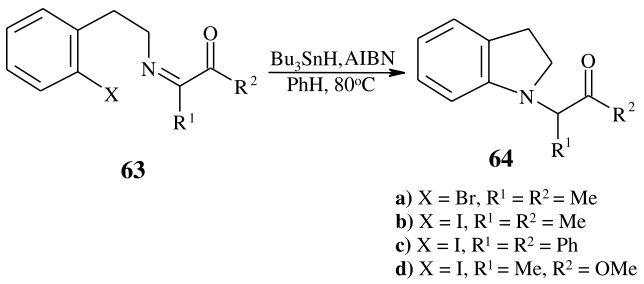
Recently, the tributyltin hydride-mediated radical cyclisation of various ketimines **61a-d** to provide **62a-d** was carried out to analyse the aryl radical additions to the nitrogen of azomethines.[44] Aryl, trifluoromethyl, alkyl and α,β-unsaturated ketimines are engaged in regioselective aryl nitrogen bond formation via 5-*exo* cyclisations of an aryl radical to the azomethine nitrogen. C–N bond formation is more selective than C–C bond formation and competes only with direct aryl radical reduction by the stannane (Scheme 14).



Scheme 14.

In the case of α-ketoimines **63a-d**, no such competitive aryl radical reduction was observed. The reaction conditions are pH 7 and are therefore the mildest methods available for the amination of an aromatic ring. Here, only indoline products **64a-d** were isolated and the reduction products arising of the aryl halides could not be identified in the crude reaction mixture (>200:1 cyclised/ArH) (Scheme 15).

Oxime benzoates have already been found to be convenient precursors for iminyl radicals.[45] Analogously, amidoxime



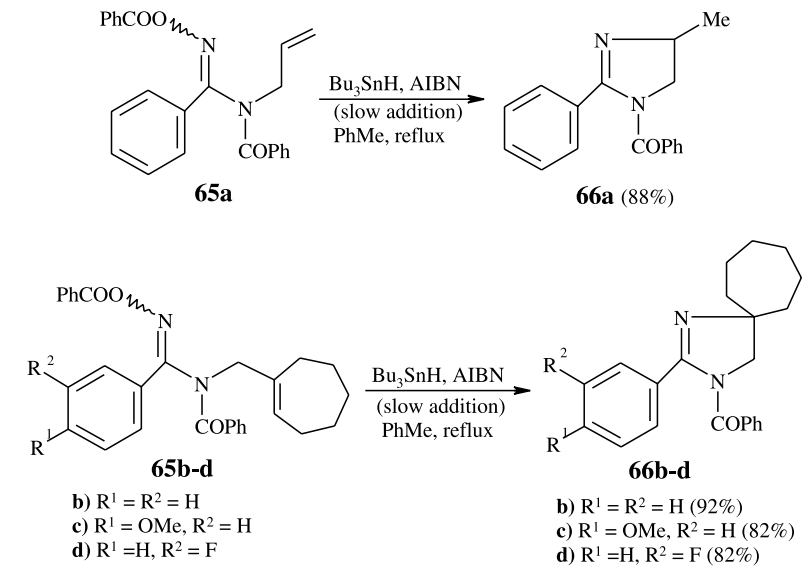
Scheme 15.

benzoates could act as substrates for generating the corresponding amidinyl radicals. The tri-*n*-butylstannane-mediated reactions of various amidoxime benzoates **65a-d** resulted in the smooth formation of the corresponding imidazolines **66a-d** in excellent yield.[46] Some reported examples are shown in Scheme 16.

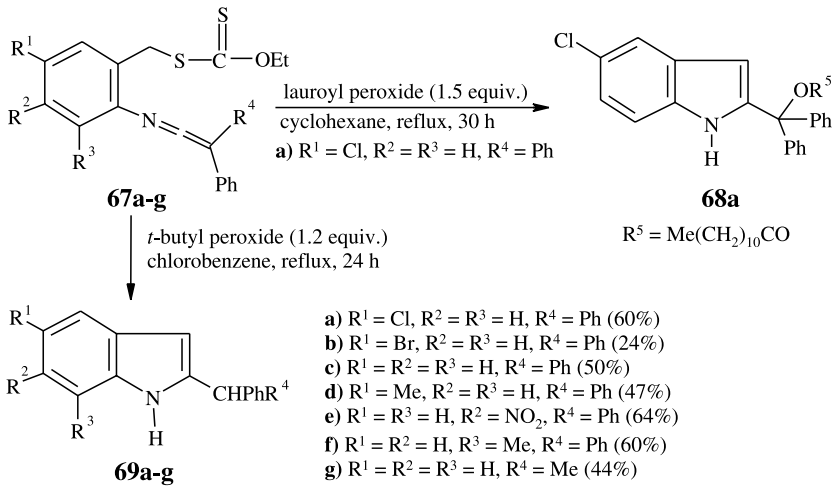
3.2. Substrates with ketenimine functions

A novel radical annulated synthesis of 2-alkyl indoles based on the intramolecular addition of benzylic radicals onto the central carbon atom of a ketenimine function following a 5-*exo-dig* cyclisation was described very recently.[47] Here, the radical cyclisation of the ketenimine **67a** was initiated by lauroyl peroxide in refluxing cyclohexane to furnish the indole-containing lauroyloxy fragment **68a** in 38% yield, along with a small amount of 5-chloro-2-diphenylmethylindole **69a**. On the other hand, if the reaction of the ketenimine **67a** was carried out in boiling chlorobenzene with stoichiometric amount of *t*-butyl peroxide, compound **69a** was obtained in 60% yield as the only product. When the ketenimine **67b-g** were initiated by *t*-butyl peroxide (1.2 equiv.) in refluxing chlorobenzene compounds **69b-g** were isolated in varying yield (Scheme 17).

The mechanism for the formation of **68** and **69** from **67** may be explained as follows. The radical $(R_o)^{\cdot}$ produced by the thermal decomposition of the peroxide initiator exchanges the xanthate group with the ketenimines **67** to give the expected benzylic radicals **70**, which then undergo a 5-*exo* addition of the radical moiety onto the central carbon of the ketenimine function, followed by a prototropic imine–enamine equilibrium, favouring the indole from **73**. The stabilised tertiary radicals **73** may undergo reduction to give indoles **69** or electron transfer to the lauroyl peroxide to produce the carbocations **74**. These carbocations **74** were then quenched by the carboxylate anion generated in the redox process to give the compounds **68**. The conversion of



Scheme 16.



Scheme 17.

67 to **69** is a reductive process and the source of hydrogen atom that quenched the radicals **73** is not obvious[48] (Scheme 18).

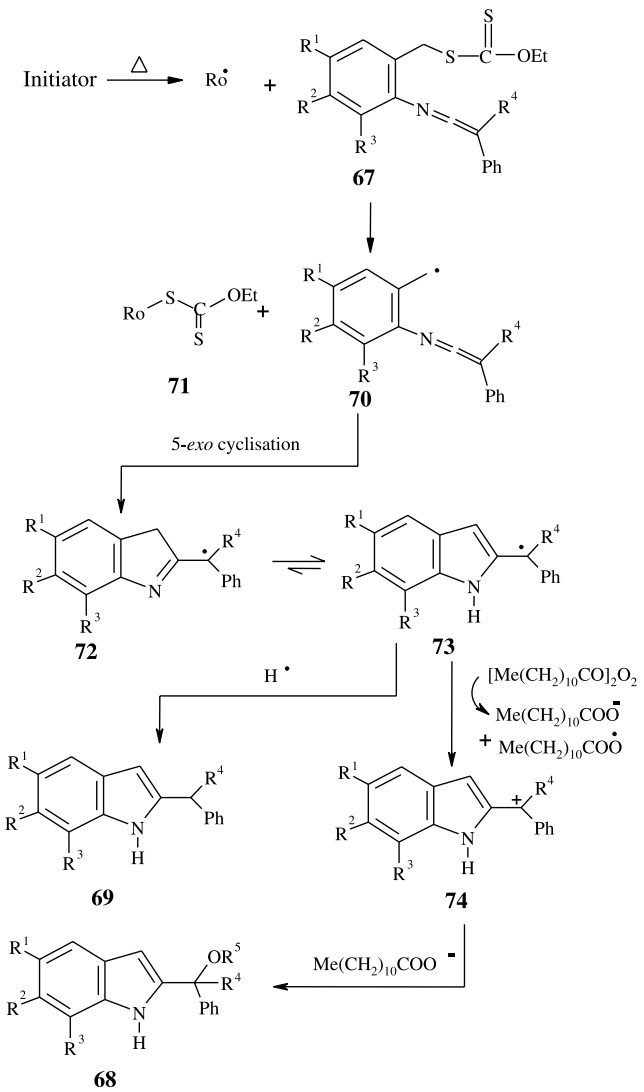
1-(2-Bromoethyl)-2-isocyanatobenzene **75** was allowed to react with tributyltin hydride by using thermal initiation with AIBN, photochemical initiation and conditions of slow organotin addition.[49] The main product, 3,4-dihydro-1*H*-quinolin-2-one **80**, was evidently formed by 6-*endo* cyclisation of the radical **76** to give the acylaminyl radical **77** that abstracted a hydrogen atom from the tin hydride. Alternatively, the cyclisation might be considered as 6-*exo*. Hydrogen atom abstraction by the O-centred mesomer of **77** might afford an iminol that would tautomerise to **80**. 2,3-Dihydroindole-1-carbaldehyde **81** was formed by 5-*exo* cyclisation at the *N*-terminus of the isocyanate group via **78** and this is followed by the abstraction of a hydrogen atom from tin hydride. A small amount of the direct reduction product **79** was also formed. The rate constants for the two processes were estimated and compared with reaction enthalpies computed by the density functional theorem (DFT) method (Scheme 19).

3.3. *N*-Vinylic substrates and related systems

9-(2-Bromo-*N*-methylanilino)acridine was cyclised[38] under normal radical cyclisation conditions to produce the 1,3-methylquinoacridine as the major product (50%). Similarly, 1-bromo-9-(*N*-methylanilino)acridine undergoes radical cyclisation to furnish the same product in 56% yield.

Aryl radicals generated by the homolysis of the Ar–Br bond by *n*-Bu_3SnH–AIBN have been used extensively as the key step in the establishment of the C_{aryl}–C_{alkyl} bond. This method has been applied to construct a variety of systems such as dihydroindoles,[50] benzofurans,[51] tetrahydro-β-naphthols[52] and oxindoles.[53]

In the synthesis of pyrrolophenanthridine alkaloids, *N*-(2-bromo-4,5-dimethoxybenzyl)-*N*-(2′-β-hydroxyethylphenyl)-



Scheme 18.

amine was prepared[54] in one of the steps and it was then refluxed for 12–13 h in benzene in the presence of AIBN by the slow addition of TBTH in benzene. Cyclisation of the tin-free residue obtained after chromatography furnished the phenanthridine alcohol as a colourless solid (27% yield).

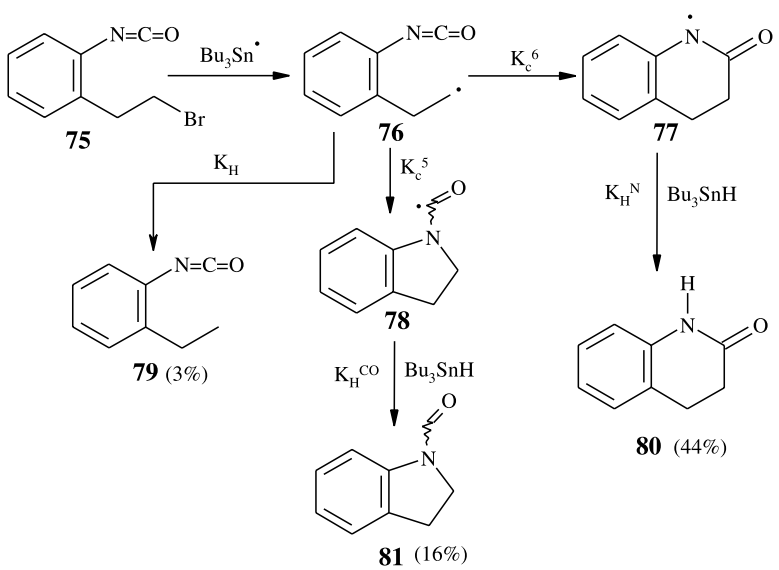
Tamura et al. have examined[55] the effect of a halogen atom in the 5-*endo* radical cyclisation of α-haloamides by employing the *N*-benzyl amides **82a**-**c**. The cyclisation ability decreased from the chloro to bromo to iodo amide (**82a→b→c**). $(TMS)_3SiH$ annulated reactions have exhibited the same tendency (Scheme 20).

The compound **82a** under normal radical cyclisation conditions (Bu_3SnH in the presence of AIBN in boiling toluene) afforded the cyclisation product **83** in 92% yield, while the compound **82b** gave a mixture of compound **83**, enamide **84** and the α,β-unsaturated product **85** in 55, 11 and 11% yield, respectively. The reaction of the α-iodo amide **82c** furnished the simple reduction product **86** in 68% yield, along with very small amount of the cyclisation products **84** and **85**. The effectiveness of the cyclisation of the α-iodo amides was restored by using Bu_3SnCl[56] or Bu_3SnF as additives (Scheme 20).

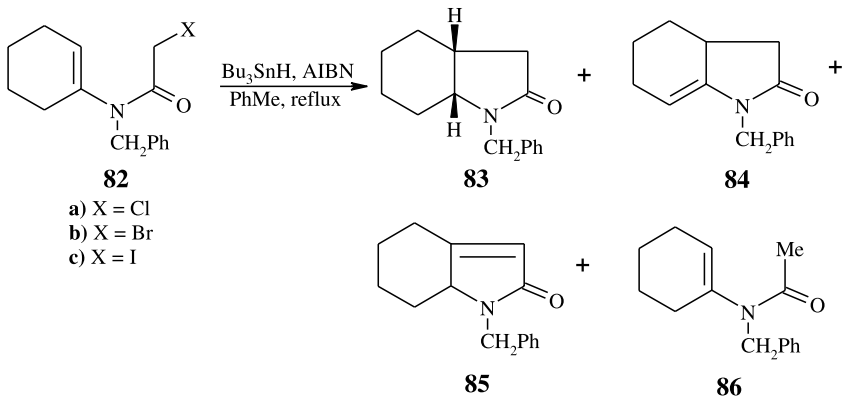
N-(α-Haloacetamido)dehydroalanine derivatives on treatment with tributyltin hydride in boiling benzene or toluene afforded the pyroglutamates in a disfavoured 5-*endo-trig* manner.[57] The *N*-benzyl substituent was found to be essential for this type of cyclisation, because the corresponding N–H derivatives furnished no pyroglutamate.

Dichloro and trichloroamides are found to be more efficient for the effective formation of pyroglutamate. The cyclisation of the S-phenyl derivative also furnished the pyrrolidinone as a 2:1 mixture of diastereomers in only 28% yield. Parsons et al. have explored[58] the Bu_3SnH-mediated radical cyclisation of various *N*-acryloxy-2-amino-2-cyclohexanones to afford the bicyclic lactams.

Influenced by radical-stabilising substituents such as



Scheme 19.



82
a) X = Cl
b) X = Br
c) X = I

83 **84** **85** **86**

Scheme 20.

methyl, phenyl, phenylthio, dimethyl or dichloro groups, the γ-lactam was prepared exclusively via 5-*endo-trig* cyclisation from a range of 2-halo-*N*-(3,4-dihydro-2-naphthyl)-acetamides.[59]

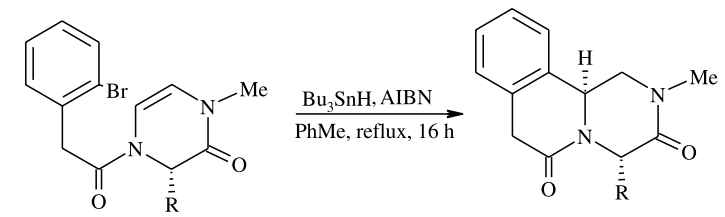
Ikeda et al. reported[60] the Bu_3SnH- or $(TMS)_3SiH$-mediated 5-*endo-trig* radical cyclisation of *N*-(cyclohex-1-enyl)-*N*-(4-methoxybenzyl)-2-(3,4-methylenedioxyphenyl)-2-(phenylseleno)acetamide to give a mixture of *cis*-fused (3*R**,3*aS**,7*aS**)- and *trans*-fused (3*R**,3*aS**,7*aR**)-3-aryloctahydroindol-2-ones, respectively. On the other hand, 5-*exo-trig* radical cyclisation of *N*-(cyclohex-2-enyl)-*N*-(4-methoxybenzyl)-2-(3,4-methylenedioxyphenyl)-2-(phenylthio)acetamide furnished *cis*-fused (3*R**,3*aS**,7*aR**)-3-aryloctahydroindol-2-ones in a stereoselective manner.

A novel radical cyclisation involving tributyltin hydride has been demonstrated[61] to form tri- and tetracyclic ring systems related to the Amaryllidaceae or Erythrina family of alkaloids. The radical cyclisation of dichloroethanamides was reported to generate a 5,6-bicyclic ring system.

The chloroethanamide having a ketone group at C-3 (instead of C-6) under tributyltin hydride-mediated radical cyclisation conditions furnished a very small amount (16%) of octahydroindolone. This clearly suggests that the efficiency of the 5-*endo* cyclisation is influenced only when the ketone group is placed at C-6.

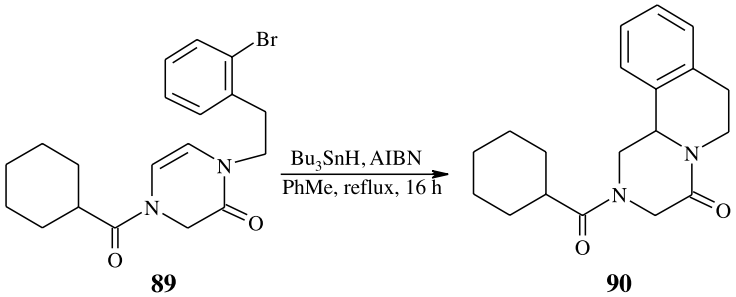
The tributyltin hydride-mediated radical cyclisation of *N*-(2-phenylthiocyclohex-1-enyl)-α-haloamides has also been reported.[62] Bromoacetamides having no substituent α- to the halogen atom cyclised exclusively in a 4-*exo-trig* manner, whereas the fully substituted haloamides gave the 5-*endo-trig* cyclization products. This clearly indicates that the mode of cyclisation is affected by the size of the substituents around the radical centre.

Radical cyclisations providing five-membered rings are



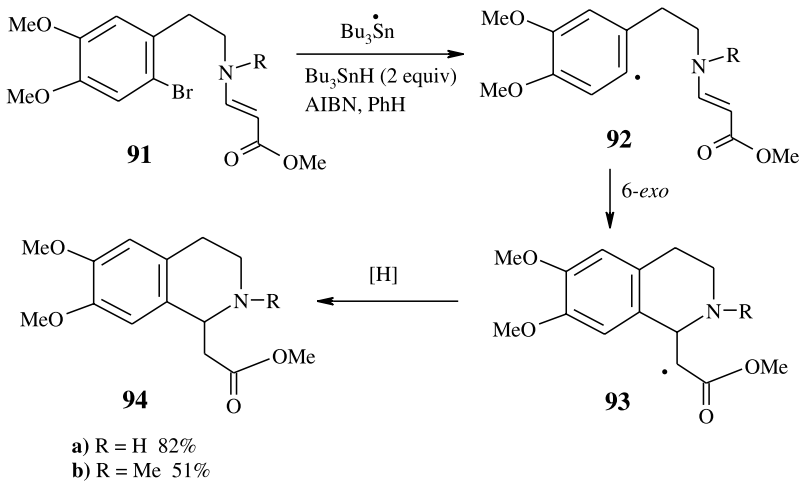
87

88
a) R = Bn (80%)
b) R = *i*-Pr (70%)
c) R = Me (71%)



89 **90**

Scheme 21.



Scheme 22.

highly stereoselective.[63–66] Although the formation of six-membered rings via radical cyclisations is less common compared to the five-membered rings, it still has an important role in synthesis. The Bu_3SnH-mediated radical cyclisation of *o*-iodobenzamide was reported to produce phenanthridone via 6-*endo* cyclisation.[67]

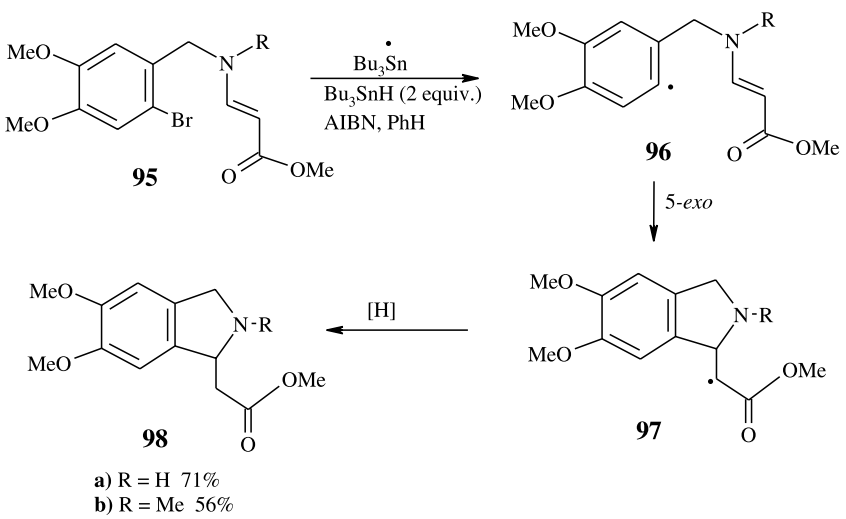
Ishibashi et al. reported[68] that *N*-vinylic-*o*-iodobenzamides upon treatment with Bu_3SnH–ACN gave mainly the 5-*exo* cyclisation product. The enamide having a phenyl substituent on the vinyl carbon atom α- to the nitrogen atom, however, gave predominantly the 6-*endo* cyclisation product.

Todd et al. encountered difficulty in developing a general synthesis of the fused-ring system via the acyliminium intermediate and therefore turned their attention to radical cyclisation as an alternative approach. Influenced by the success of Rigby et al.[69] and Ishibashi et al.[70] with the ring closure of aryl radicals onto acyclic enamides, Todd et al. applied a similar protocol to the acyl pyrazinone intermediate **87**.[71] Tri-*n*-butyltin hydride-mediated radical cyclisation of the bromophenyl dihydropyrazinone **87** furnished the peptide mimics **88** in good yield via 6-*exo* selectivity (Scheme 21).

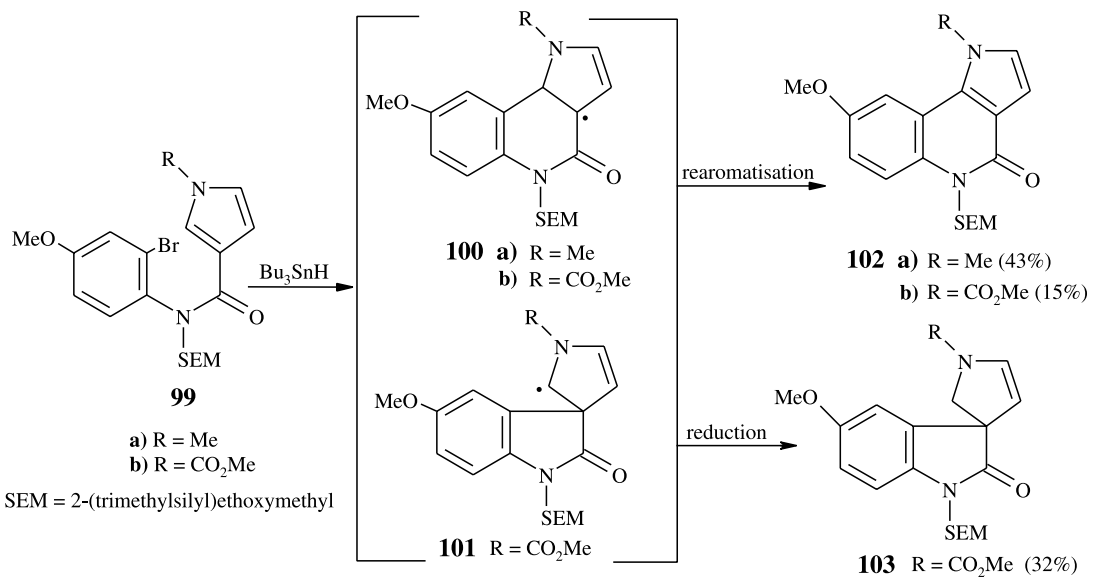
The anthelmintic drug praziquantel **90** has been synthesised[71] following the radical-initiated cyclisation of the pyrazinone **89**. The tetracyclic galanthan alkaloid ring system has also been prepared by a Bu_3SnH-mediated radical cyclisation of aryl radicals[72] (Scheme 21).

Radical cyclisations of highly reactive aryl radicals onto double and triple bonds are very useful to construct carbocycles and heterocycles[1,8a,73] and especially aza heterocycles.[73b] Various sizes of aza heterocycles have been obtained by radical addition to *N*-vinyl amides (enamides).[70,74,75] *N*-Vinyl unit-containing compounds like enamines,[76] *N*-sulfonyl enamines[77] and enaminones[78,79] are less common substrates for the additions.

Aryl radical cyclisation in *N*-phenyl, *N*-benzyl and *N*-phenethyl enaminones has been developed.[80] The tetrahydroisoquinolines **94** have been produced from the *N*-phenethyl enaminones **91** via aryl radical **92** and H-abstraction of the 6-*exo* ring closure product **93** (Scheme 22).



Scheme 23.



Scheme 24.

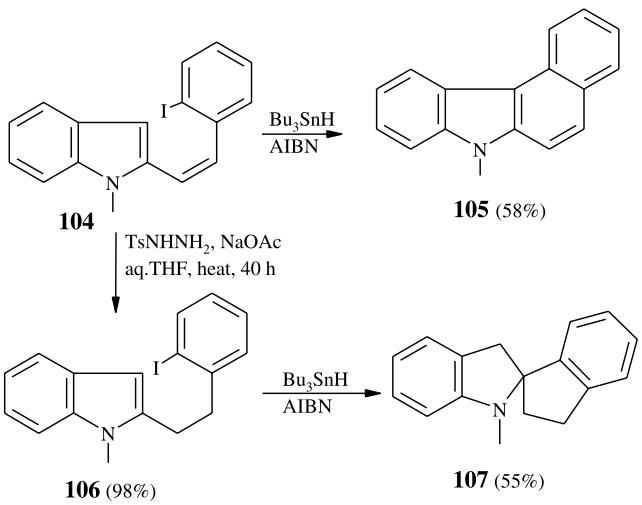
Similarly, the radical cyclisation of *N*-benzyl enaminones **95** afforded isoindoles **98** via intermediate radical **96** and H-abstraction of the 5-*exo*-ring closure product **97** in good yield (Scheme 23). No cyclised product was obtained from the *N*-phenyl enaminones.

Aryl radical cyclisation has been proved to be very useful in the development of modern heterocyclic chemistry and also in the synthesis of natural products.[81] Jones et al. have reported[82] that the regiochemistry of the cyclisation of aryl radicals onto pyrroles attached through an amide at the C-3 position is influenced by the *N*-substituent on the pyrrole. Pyrroles substituted with an electon-donating group (methyl) on nitrogen, for example, **99a**, gave exclusively 8-methoxy-1-methyl-5-(2-trimethylsilylethoxymethyl)-4,5-dihydro-1*H*-pyrrolo[3,2-*c*]quinolin-4-one **102a** in 43% yield arising from 6-*endo* cyclisation following intermediate **100a**. No 5-*exo* or 6-*exo* cyclisation product was isolated from the reaction. On the other hand, pyrroles substituted on nitrogen with an elecron-withdrawing group (carbamate) such as **99b** gave cyclisation product **103** (32%) via intermediate radical **101**, along with a small amount of aromatised product **102b** in 15% yield via radical **100b** (Scheme 24). From the consideration of the above results, it has been concluded that the formation of either the spiropyrrolidinyloxindole or pyrrolo[3,2-*c*]qinoline nucleus from a common intermediate can be controlled by changing the substituent on the pyrrole, and the regiochemistry is not influenced by the substituents on the benzene ring.

2-Bromo-3-carboxamide was found to provide hexahydro-pyrrolo[3,4-*b*]indole[83] when refluxed in toluene in the presence of Bu_3SnH and a catalytic amount of AIBN. Some reduction product was also encountered from the reaction. This reaction is believed to involve the generation of the expected C-2 radical, followed by [1,5]-H atom abstraction to give the α-amidoyl radical and then 5-*endo-trig* cyclisation to the indole double bond, followed by hydrogen abstraction to give the indoline. Snieckus and Curran termed the first two steps in this process as radical translocation.[84]

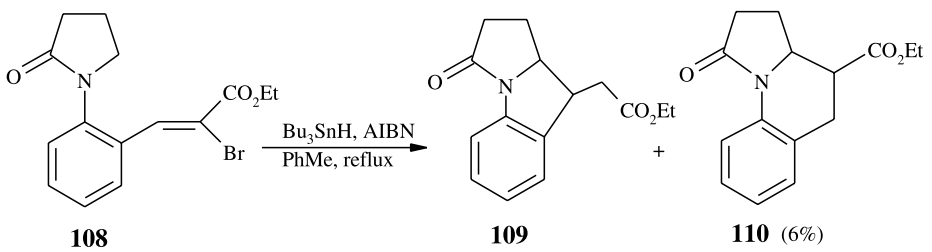
A few years ago, the synthesis of 2-stannylindoles was reported[85] by the radical cyclisation of 2-alkenyl-phenyl-isonitriles. With this result in view, Tokuyama et al. have synthesised[86] 2,3-disubstituted indoles by a Bu_3SnH annulated radical cyclisation of 2-alkenylthioanilides. The *cis*-isomer of the 2-alkenylthioanilide on treatment with Bu_3SnH–AIBN in toluene at 80 °C for 5 min furnished the expected 2-*n*-pentyl-3-(acetoxymethyl)indole in 93% yield. The same product was obtained within 5 min at room temperature by using Et_3B as the radical initiator.[87]

Recently, it was observed[88] that the tributyltin hydride-mediated radical cyclisation of the 2-styrylindole **104** took place at C-3 of the indole via a 6-*endo-trig* pathway to produce the benzo[*c*]carbazole **105** in 58% yield as the major product. On the other hand, the radical cyclisation of the indole **106** generated the spirocycle **107** as the major product in 55% yield (Scheme 25).



Scheme 25.

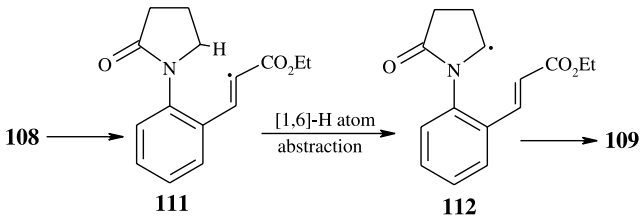
Parsons et al. have shown[89] that the 5,5,6-ring system present in mitomycins can be prepared via tandem radical



Scheme 26.

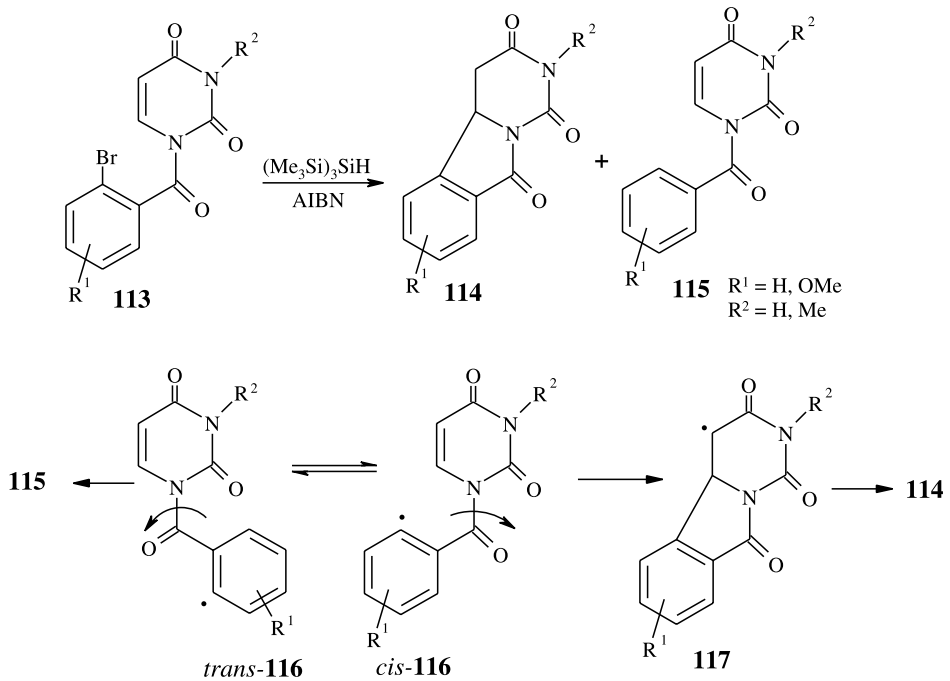
cyclisation sequences involving either a tandem 5-*endo*/5-*exo* radical cyclisation or, alternatively, a [1,6]-hydrogen-atom transfer, followed by a 5-*exo* cyclisation sequence. The reaction of compound **108** with tributyltin hydride and AIBN furnished the desired 5,5,6-tricycle **109** in 64% isolated yield as a 1.4:1 mixture of diastereomers. It is very important to note that the 6-*endo* product **110** was formed in only 6% yield (as a single diastereomer) and no simple reduced product was isolated (Scheme 26).

The ability to control the ratio of 5-*exo*/6-*endo* radical cyclisation pathways by appropriate substitution of the precursor is of particular mechanistic interest, as is the novel [1,6]-hydrogen-atom transfer reaction. The formation of the product **109** from **108** is based on the following mechanistic approach. Reaction of the compound **108** with the tributyltin radical should produce a reactive vinyl radical **111**, which could undergo a rearrangement reaction to form the more stable pyrrolidinone radical **112**. Such an intermediate pyrrolidinone radical **112** could not be formed from a classical halogen-atom transfer route because of the difficulty in preparing the requisite 5-halopyrrolidinone precursor (Scheme 27).

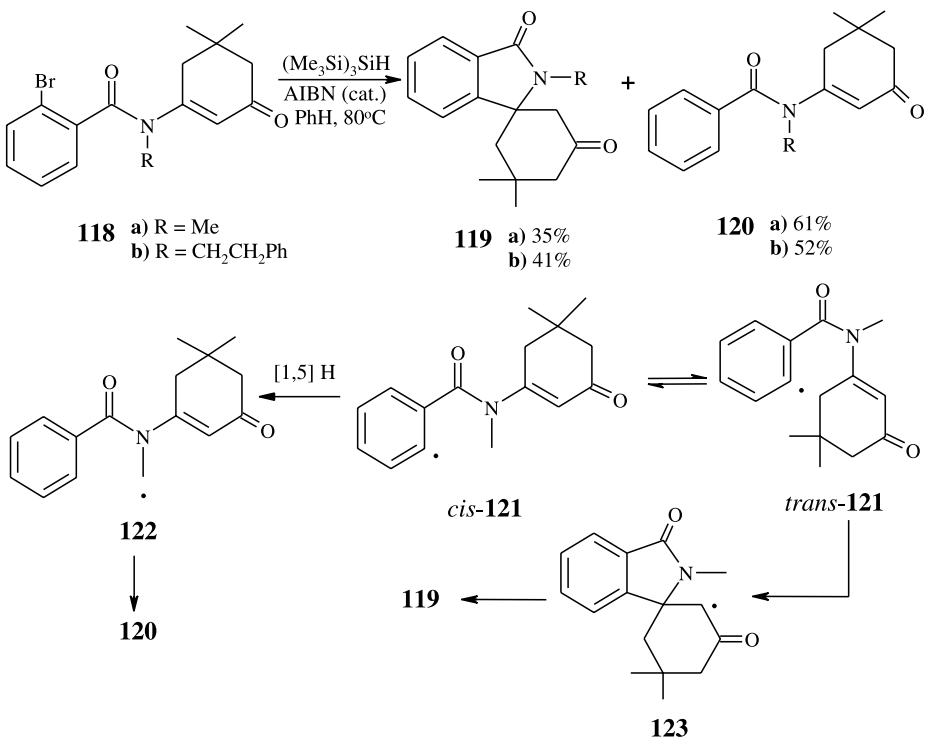


Scheme 27.

Recently, Zhang et al. have described[90] a general method for constructing a variety of nitrogen heterocycles. They treated the *N*-acylated cyclic nitrogen compounds **113** with $(TMS)_3SiH$ and AIBN to generate the tricyclic isoindolinones **114** as the major product via radical **117**, along with some reduction product **115**. In this case, the initial radical **116** is generated from **113** and is equilibrated between the *cis*- and *trans*-amide conformation. Only the *cis*-amide conformation (*cis*-**116**) underwent the conjugate radical cyclisation to give **114**. The *trans*-amide conformation (*trans*-**116**) gave the direct reduction product **115** (Scheme 28).



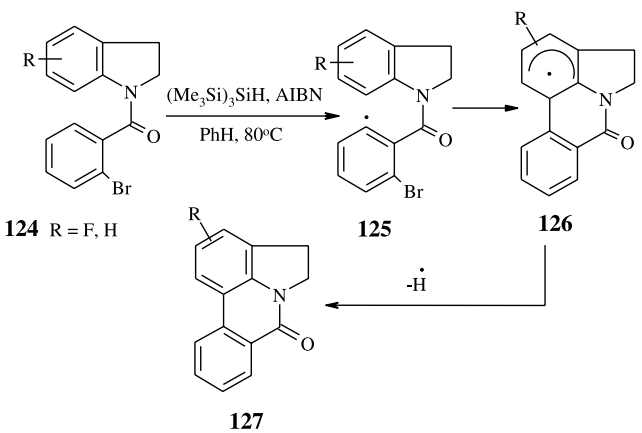
Scheme 28.



Scheme 29.

By the application of a similar protocol,[90] they prepared the spiroisoindolinones **119** from **118** via intermediate radical **123**. In this case, the yields of the cyclisation products were very low (35–41%) and significant amounts of the direct reduction products **120** were obtained (52–61%). It was proposed that the equilibrium between *cis*-**121** and *trans*-**121** favours the formation of *cis*-**121** and the relatively stable α-amidomethyl radical **122** is generated from *cis*-**121** by a [1,5]-H atom transfer (Scheme 29).

Zhang et al. then extended their protocol to the synthesis of various tetracyclic isoquinolinones[90] **127** from compound **124** through the intermediates **125** and **126**. One such reported case is depicted in Scheme 30.

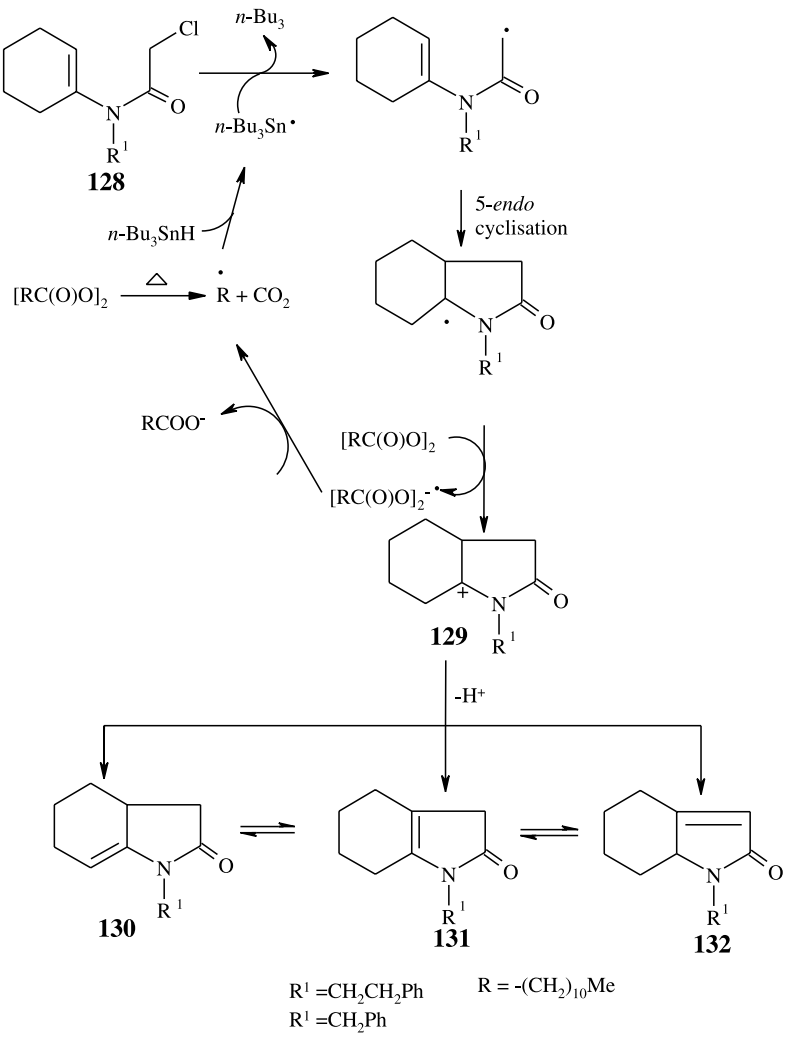


Scheme 30.

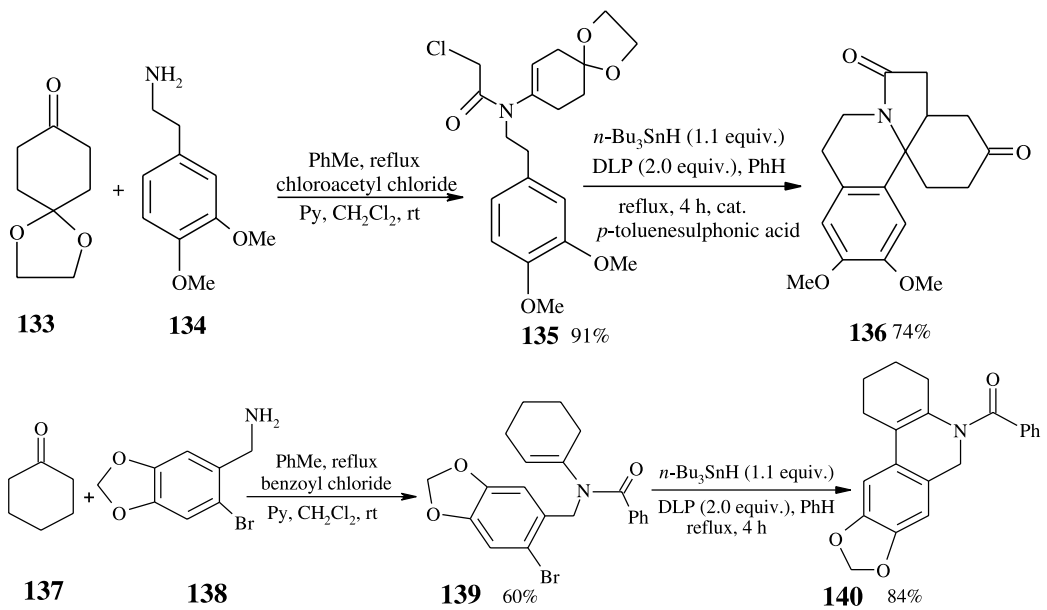
The oxidative radical cyclisation of enamides **128** by using *n*-Bu_3SnH and dilauroyl peroxide has recently been reported by Miranda et al.[91] and an efficient 5-*endo* and 6-*endo* oxidative radical cyclisation was observed. *n*-Bu_3SnH and dilauroyl peroxide were used both as radical initiator and oxidant in cyclisations onto enamide systems. Dibenzoyl peroxide and dicumyl peroxide were also tested in the same reaction and the product yields were very similar to those obtained with dilauroyl peroxide.

The effectiveness of dibenzoyl peroxide and dicumyl peroxide in this process was also examined. The combined product yields were quite similar to those obtained with dilauroyl peroxide (DLP), but the product distribution was rather different with the dibenzoyl peroxide-mediated reaction. The tendency for the latter reaction to give mainly the most stable olefin **132** may be explicable by a faster conversion of **130** and **131** into **132** by the more acidic benzoic acid produced in this reaction (Scheme 31).

The erythrina and phenanthridine framework was constructed in a two-step sequence featuring the novel cyclisation. The chloroacetamide **135** was prepared in a two-step process from commercially available ketone **133** and amine **134**. The dibenzoyl peroxide mediated reaction failed to effect cyclisation of **135**, in the absence of *n*-Bu_3SnH. However, erythrina derivative **136** was isolated in 74% yield by adding a catalytic amount of *p*-toluenesulphonic acid to the reaction mixture after **135** had been consumed in the *n*-Bu_3SnH–DLP mediated radical cyclisation. The new *n*-Bu_3SnH–DLP oxidative radical cyclisation process was extended to an aryl bromide. The bromide **139** was prepared in two steps from the piperonal derived amine **138** and cyclohexanone **137** in moderate yield. Reaction of **139** under the above mentioned oxidative radical conditions furnished the thermodynamically stable olefins **140** exclusively in good yield (Scheme 32).

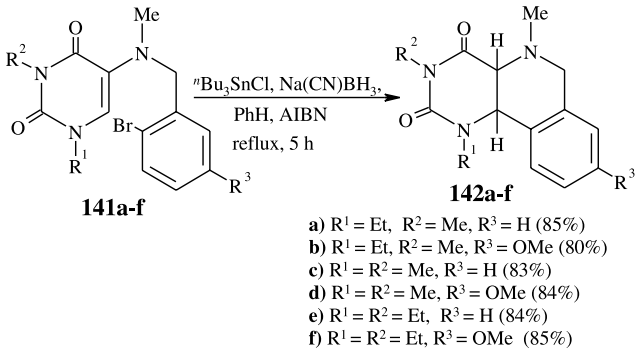


Scheme 31.



Scheme 32.

Recently we have reported[92] the regioselective synthesis of a number of pyrimidino[3,2-*c*]tetrahydroisoquinolin-2,4-diones **142a-f** from the 1,3-dialkyl-5-(*N*-2′-bromobenzyl,*N*-methyl)amino pyrimidine-2,4-diones **141a-f** by the intramolecular addition of an aryl radical to the uracil ring bearing the amino nitrogen atom (Scheme 33).



Scheme 33.

The formation of a six-membered heterocyclic ring in the products **142a-f** from the substrates **141a-f** may be easily explained by the initial formation of the aryl radical **143**, followed by a 6-*endo* ring closure to give a tertiary radical **146**, which may then accept a hydrogen radical to afford the final products **142a-f**. In an alternative route, the aryl radical **143** may undergo a 5-*exo*-ring closure to generate a spiroheterocyclic radical[93] **144**, which may be converted into the tertiary radical **146** via the radical **145** by a neophyl rearrangement[94] (Scheme 34).

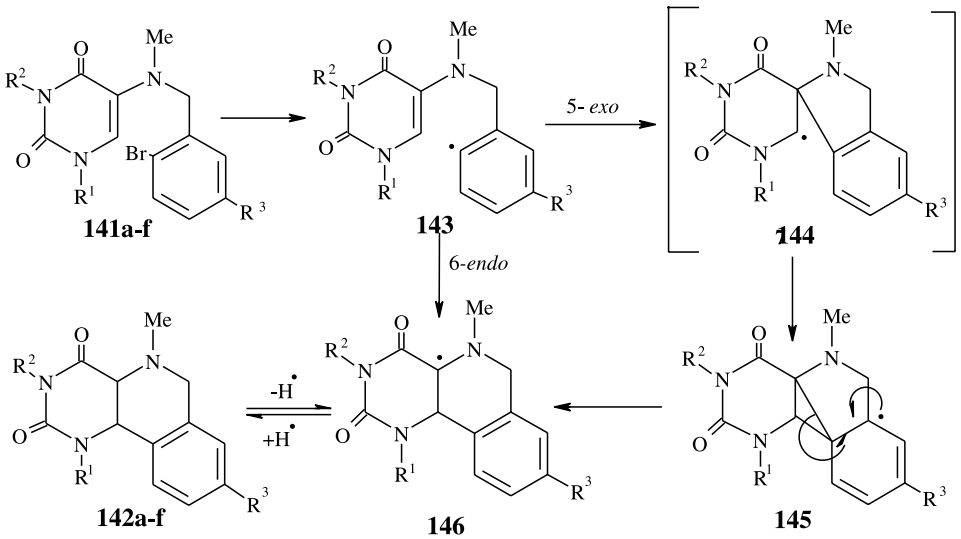
An interesting feature of this reaction sequence is that the usual aerial oxidation in this type of cyclisation with $^{n}Bu_3SnH$ is not observed and the dihydro compounds are isolated in excellent yield. The usual course during this type of cyclisation is that the initially formed dihydro products give oxidized products by aerial oxidation, that is, an oxidation step in the *n*-Bu_3SnH-mediated cyclisation.[9b,54,95]

3.4. *N*-Allylic substrates and related systems

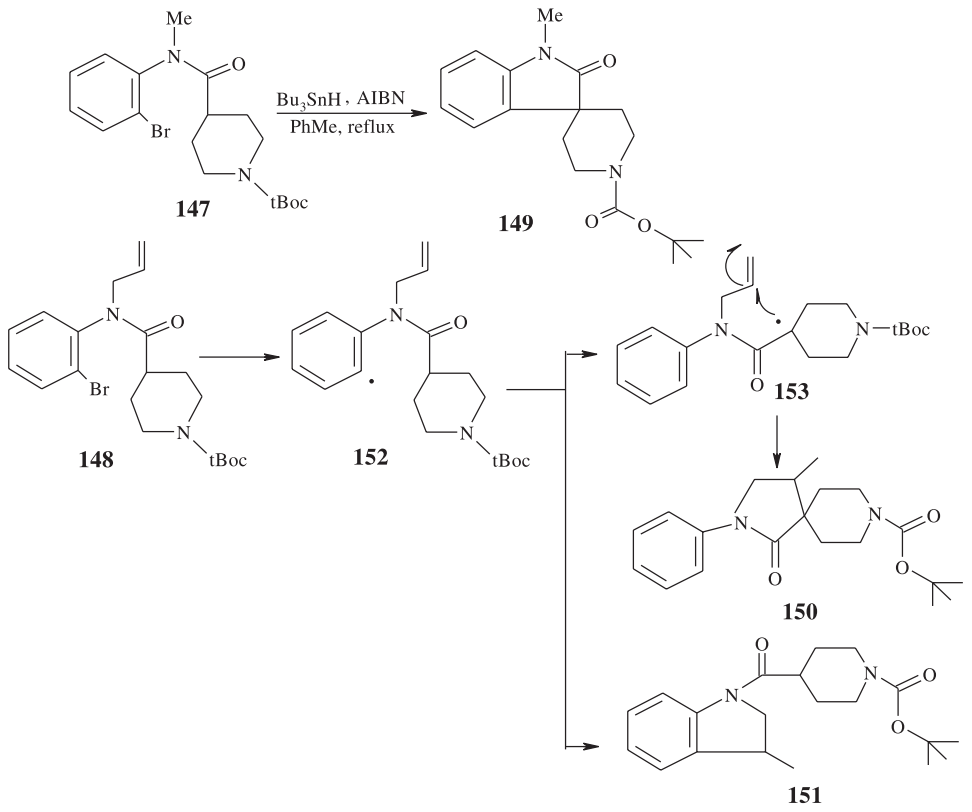
Several methods have been employed for the preparation of γ-lactams.[96,97] The formation of γ-lactams by the use of 5-*exo* or 5-*endo* cyclisation of a carbamoylmethyl radical has received considerable attention by researchers and the interest continues to grow.[1,5,8a,13c,95a,b,98] It is now well established that, in the Bu_3SnH-mediated radical cyclisations of ω-haloalkenes, an iodine atom is a better leaving group than a bromine or chlorine atom,[5] because of the lower C–I bond dissociation energy compared to that of a C–Br or C–Cl bond.[5] The result of using a chlorine atom as a leaving group for the radical cyclisation of ω-haloalkenes is therefore, an increase in the amount of the uncyclised reduction products. This trend was proved to be true in the Bu_3SnH-mediated 5-*exo* radical cyclisation of *N*-(cyclohex-2-enyl)-α-haloacetamides.[99,100] The fact that an iodine atom is a better leaving group for the Bu_3SnH-mediated radical cyclisation of ω-haloalkenes is not applicable to the 5-*endo-trig* cyclisation of α-haloamides having an alkenic sp^2 carbon atom α- to the amide nitrogen atom.

Storey[101] has described a novel synthesis of a series of spirocyclic pyrrolidin-2-ones under standard radical cyclisation conditions. The pyrrolidin-2-ones were obtained in excellent yield and are the result of a [1,5]-hydrogen atom transfer, followed by 5-*exo-trig* cyclisation.

The reaction of the compound **147** has been explored[102] in toluene solution with TBTH in the presence of AIBN at 100 °C for 2 h to synthesise the compound **149**. The formation of compound **149** in this study is difficult to rationalise, but there are several reported examples in the literature[103] relating to the formation of oxidation products during TBTH-mediated reactions. Under similar reaction conditions, the compound **148** produced a mixture of two compounds **150** (75% yield) and **151** (8% yield). Reaction of the compound **148** to give **150** and **151** could be rationalised as follows. The initial radical **152** undergoes *exo*-cyclisation, followed by abstraction of the newly formed radical by hydride to give **151**. The compound



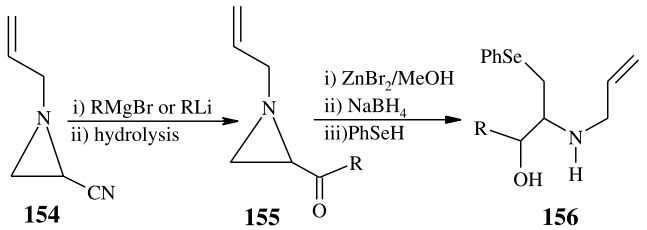
Scheme 34.



Scheme 35.

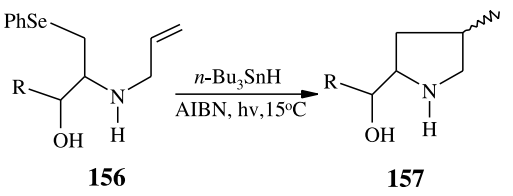
150, on the other hand, was formed by the rearrangement of **152** to the more stable radical **153**, followed by *exo*-cyclisation (Scheme 35).

Diasterocontrol by a hydroxyl auxiliary in the synthesis of pyrrolidines via radical cyclisation has been demonstrated by Engman et al.[104] Organoselenium radical precursors of 3-aza-5-hexenyl radicals carrying a 1-hydroxyalkyl group in the 2-position were prepared by the addition of organometallic reagents to *N*-allyl-2-aziridinecarbonitrile **154**, reduction of the resulting aziridine ketones **155** and regioselective benzeneselenol ring opening of the aziridines (Scheme 36).



Scheme 36.

Reductive radical cyclisation of compound **156** was achieved by photolysis in benzene in the presence of tributyltin hydride and AIBN at 15 °C. This cyclisation was highly selective, affording the corresponding *trans*-2,4-disubstituted pyrrolidine **157** (*cis*/*trans* ca. 1:10) as the major diastereomer (Scheme 37). Recrystallisation afforded material that was substantially more enriched in the *trans*-isomer (*cis*/*trans*<1:25). In this connection, it is important to note that cyclisation of radical precursors carrying a



a) R = Ph 82% (*cis*:*trans* = 1:9)
b) R = 2-thienyl 80% (*cis*:trans = 1:9)
c) R = *n*-Pentyl, 96% (*cis*:*trans* = 1:10)
d) R = *i*-Pr 81% (*cis*:*trans* = 1:12)
e) R = 2-(1,3-diox- 84% (*cis*:*trans* = 1:9)
olan-2-yl)ethyl

Scheme 37.

hydroxyl auxiliary in the side chain are much more *trans*-selective than they would be if the hydroxyl group was missing.

The high *trans*-selectivity (*cis*/*trans*=1:14) for the phenoxymethyl substituent could be due to intramolecular hydrogen bonding,[105] favouring an equatorial orientation of the 2-substituent in a chair-like transition state **A** (Fig. 3).

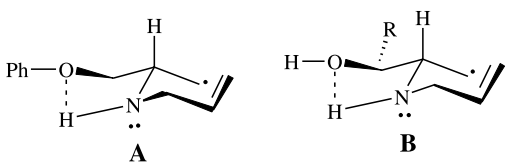
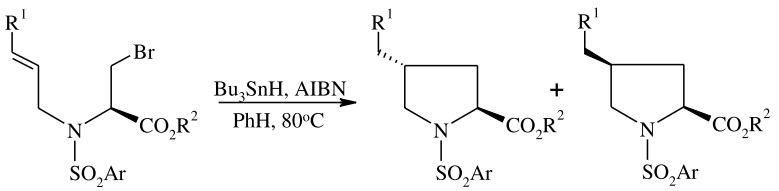


Figure 3. Hydrogen bonding in the transition state of the radical ring closure.



158a-f **159a-f** **160a-f**

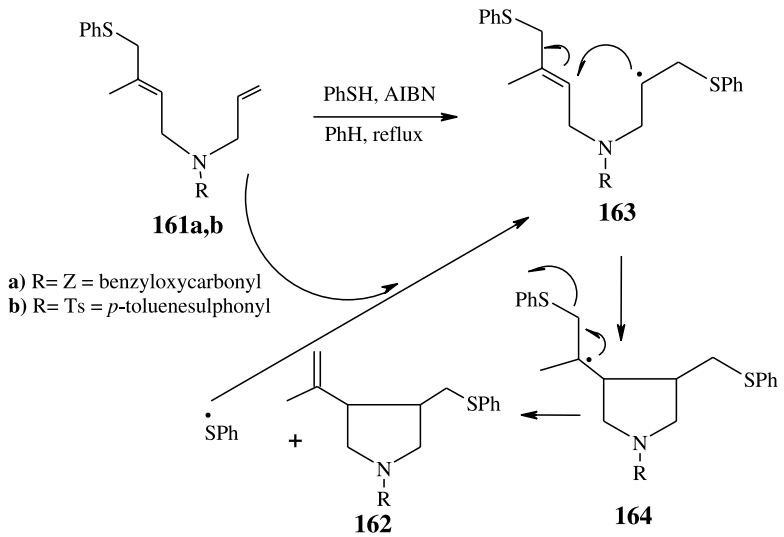
a) R^1 = H, R^2 = Bn, Ar = *p*-Tolyl	159a:160a = 3:1	80%
b) R^1 = H, R^2 = Bn, Ar = *p*-Nitrophenyl	159b:160b = 4:1	83%
c) R^1 = H, R^2 = Bn, Ar = *p*-Chlorophenyl	159c:160c = 4:1	85%
d) R^1 = H, R^2 = Bn, Ar = 2-Naphthyl	159d:160d = 8:1	85%
e) R^1 = H, R^2 = $CHPh_2$, Ar = *p*-Tolyl	159e:160e = 3:1	82%
f) R^1 = Ph, R^2 = Bn, Ar = *p*-Tolyl	159f:160f = 1.7:1	85%

Scheme 38.

Engman et al. have used a similar protocol to employ a hydroxyl substituent in the side chain as an auxiliary (favouring the transition state **B** in Figure 3) to increase the *trans*-selectivity in the cyclisation of 2-substituted 3-aza-5-hexenyl radicals.

Basak et al. subjected[106] the *N*-arylsulphonyl-*N*-allyl-3-bromo-L-alanines **158a-f** to tributyltin hydride-mediated intramolecular radical cyclisation to obtain enantiopure 4-substituted L-proline derivatives **159a-f** and **160a-f** in excellent yield. The predominant product was the *trans* isomers **160a-f** and the reaction followed an exclusive 5-*exo*-addition in all cases (Scheme 38).

The radical cyclisation of the carbamate **161a** has been demonstrated[107] in the presence of 1 equiv. of thiophenol and 0.5 equiv. of AIBN in benzene under refluxing condition to produce a mixture of the *cis*- and *trans*-pyrrolidines **162a** having an isopropenyl group in 22% combined yield as an inseparable mixture. The same reaction with 2 equiv. of thiophenol furnished the compound **162a** in 63% yield. Treatment of **161b**



161a,b

a) R= Z = benzyloxycarbonyl
b) R= Ts = *p*-toluenesulphonyl

163 **162** **164**

Substrate	PhSH (equiv.)	AIBN (equiv.)	Yield (%)
161a	1.0	0.5	22
161a	2.0	1.0	63
161a	0.2	0.2	16
161b	0.2	0.2	50

Scheme 39.

containing *N*-tosyl group with 0.2 equiv. of thiophenol afforded a 1:1 mixture of the *cis*- and *trans*-pyrrolidines **162b** in moderate yield. The mechanism of the reaction is shown in Scheme 39.

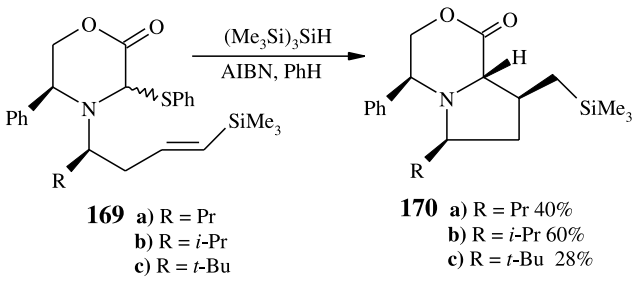
The first step of the reaction is the intermolecular addition of a phenylsulphanyl radical to the terminal olefin of **161**, producing the carbon-centred radical **163**, and then ring closure to the radical **164**, followed by subsequent β-elimination, leading to the isopropenylpyrrolidine **162** and a sulphanyl radical, which reacts with **161** to give back the radical **163**.

3.5. *N*-Propargylic substrates and related systems

The radical cyclisation of dipeptides proceeds smoothly to give five- and seven-membered rings in good to moderate total yield using Stork's catalytic tin hydride method.[108] The *N*,*N*-substituted dipeptides **165a-h** having a triple bond on a side chain were allowed to react with Bu_3SnH to furnish the products **167a-h** in good to moderate yield. Two types of side products were associated with the main product, one of which reflected the direct reduction of the radicals before any further cyclisation (**166a-h**). The second type of products (**168a-h**) resulted from a possible [1,5]-H transfer from the *N*-methyl group, followed by 7-*exo* cyclisation (Scheme 40).

3.6. Diastereoselective 5-*exo-trig* radical cyclisation

Recently, Agami et al. carried out[109] the transformation of β-amino alcohols having a vinylsilane functionality **169a-c** into the bicyclic derivatives **170a-c** via a diastereoselective 5-*exo-trig* radical cyclisation. The yield of **170c** may, however, be increased to 40% by using triethylborane as initiator and tris(trimethylsilyl)silane as hydrogen donor in refluxing benzene (Scheme 41).



Scheme 41.

It is important in this connection that two stereogenic centres are generated during these cyclisations. Here, the radical reacts with the double bond of the vinylsilane moiety by assuming a chair-like transition state[110] according to an axial approach[111] in a relative *anti* position to both the phenyl group and the R substituent. The radical undergoes 5-*exo-trig* cyclisation[112] and the chair-like transition state in which the vinylsilane adopts a pseudoequatorial position explains the absolute configuration of the second centre (Fig. 4).

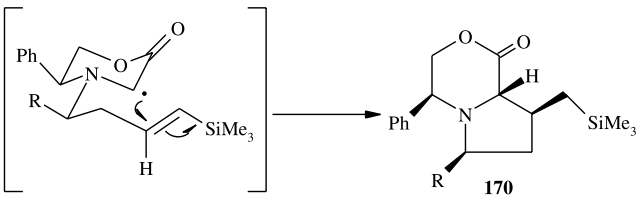
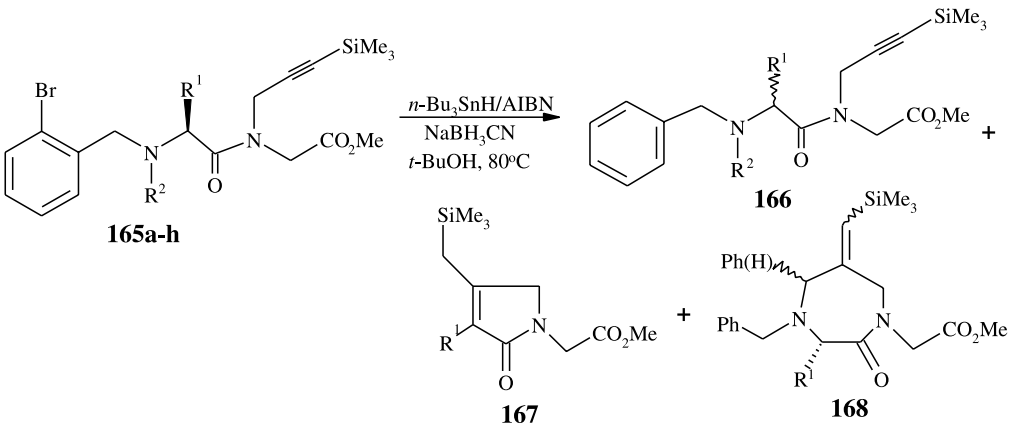


Figure 4. Stereochemical view point for the synthesis of enantiopure proline derivative.

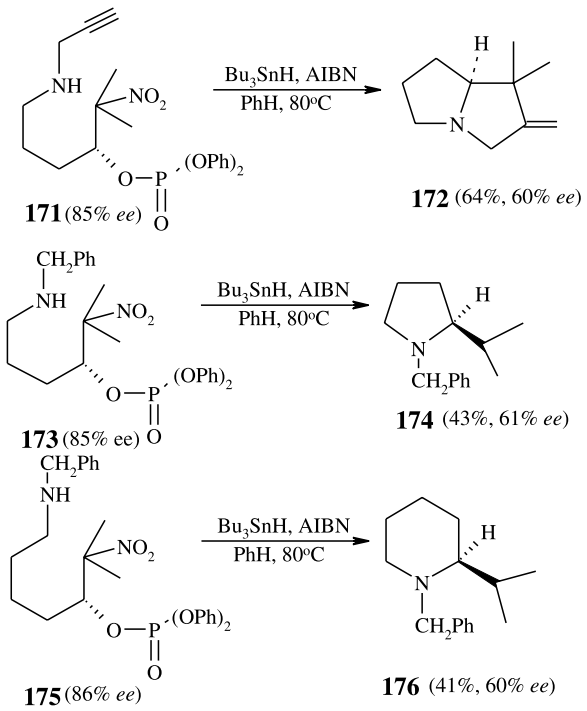
3.7. Enantioselective radical cyclisation

Crich et al. synthesised[113] pyrrolidines and piperidines with



	R^1	R^2	**166** (%)	**167**(%)	**168**(%)
165a)	H	Me	4	90	
165b)	Me	Me	17	68	9
165c)	Me	Bn	8	39	49
165d)	Et	Me	14	45	11
165e)	CH_2Ph	Me	17	37	10
165f)	*i*-Pr	Me	22	32	13
165g)	*i*-Bu	Me	36	32	11
165h)	$-CH_2CH_2CH_2-$		23	39	

Scheme 40.



Scheme 42.

significant enantioselectivity (~60% ee) from enantiomerically enriched β-(diphenylphosphatoxy)nitroalkanes by radical ionic fragmentation, induced by tributyltin hydride and AIBN in refluxing benzene. Substrate **171** (85% ee) under a tandem polar radical cross over reaction furnished the pyrrolizidine **172** in 64% yield (60% ee). Compound **173** on treatment with tributyltin hydride and AIBN in refluxing benzene resulted in the isolation of the pyrrolidine **174** in 43% yield and 61% ee. Considering the 85% ee of the substrate, it is readily calculated that **174** with 71% ee would be obtained if enantiomerically pure **173** were used in the cyclisation. The cyclisation of the next higher homologue **175** provided **176** in a very similar enantiomeric excess, demonstrating the extension of the model to the formation of piperidines (Scheme 42).

The absolute configuration of compound **173** and **175** is consistent with the model shown in Figure 5 in which nucleophilic attack occurs within the initial contact of the radical ions pair and on the face of the alkene radical cation opposite to that shielded by the departing phosphate group (as shown in the intermediate **177**).

3.8. Cascade/tandem cyclisation

Ishibashi et al. investigated[114] the radical cyclisation of enamide **178a** in the presence of 1.5 equiv. of Bu_3SnH and a catalytic amount of 1,1′-azobis(cyclohexanecarbonitrile) (ACN) in refluxing toluene to give a complex mixture of products from which **179a**, **180a** and **181a** were isolated in 11, 13 and 3% yield, respectively. Unfortunately, no expected radical cascade product was obtained from **178a**. The formation of **180a** and **181a** might be the result of 6-*exo* and 7-*endo* aryl radical cyclisations with the *N*-acryloyl group, respectively. The *N*-crotonoyl congener **178b** also furnished no cascade product; only the 6-*endo* and 6-*exo* aryl radical cyclisation products **179b** and **180b** were formed in 39 and 28% yield, respectively. In this case, no 7-*endo* cyclisation product **181b** was formed (Scheme 43).

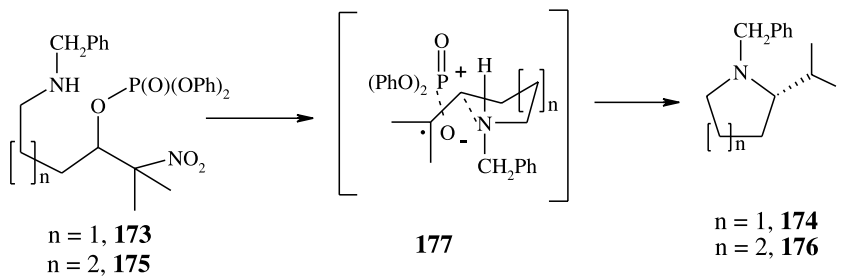
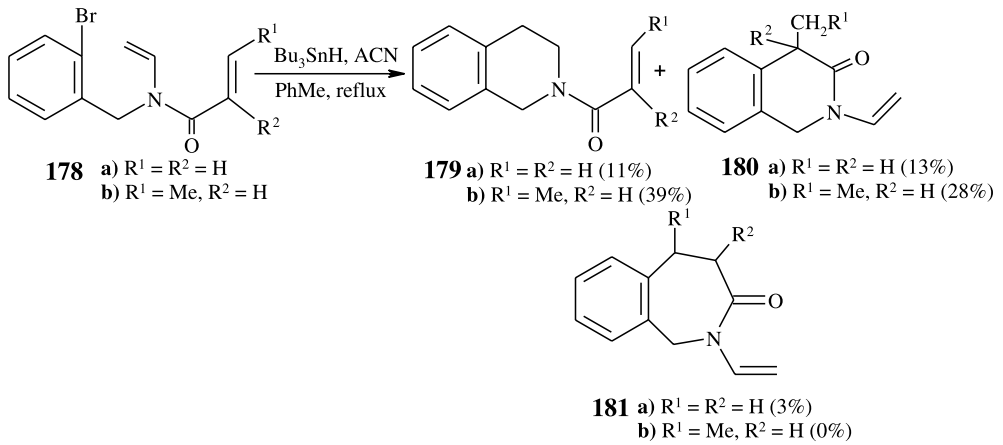
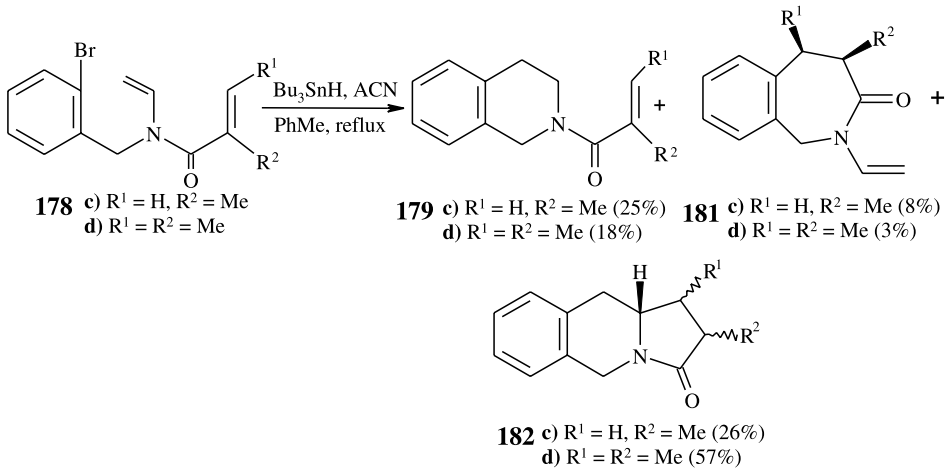


Figure 5. Enantioselective formation of heterocycles.



Scheme 43.

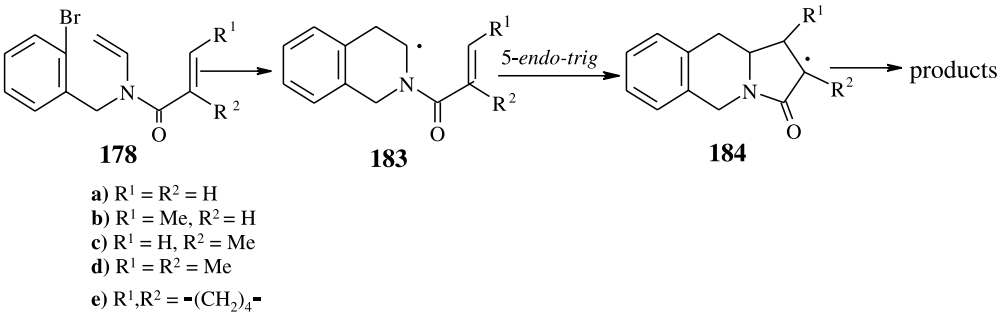


Scheme 44.

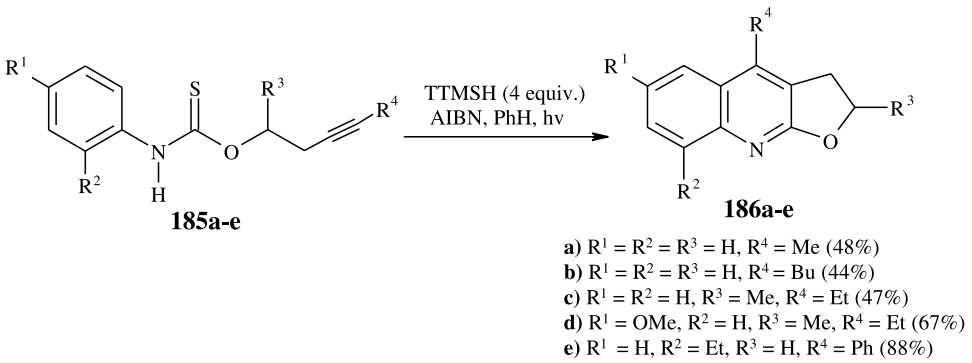
Treatment of the *N*-methacryloyl congener **178c** with Bu_3SnH/ACN, however, afforded the expected radical cascade product, 1,2,3,5,10,10*a*-hexahydro-2-methyl-pyrrolo[1,2-*b*]isoquinolin-3-one **182c**, in 26% yield as a mixture of two stereoisomers in a ratio of ca. 3:2, along with **179c** and **181c** in 25 and 8% yield, respectively. The same workers, encouraged by the above results, treated compound **178d** under similar radical cyclisation conditions, to furnish **179d**, **181d** and **182d** in 18, 3 and 57% yield, respectively (Scheme 44).

The formation of **182c** strongly suggests that the methyl substituent at the α-position of the *N*-acryloyl group in **178c** acts as an effective radical-stabilising group for the radical **184** (R^1=H, R^2=Me) generated by 5-*endo-trig* cyclisation of the α-amidoyl radical **183** (R^1=H, R^2=Me). The formation of the 6-*exo* cyclisation product **180** (R=Me) might be prevented due to the steric interference of the methyl group (Scheme 45).

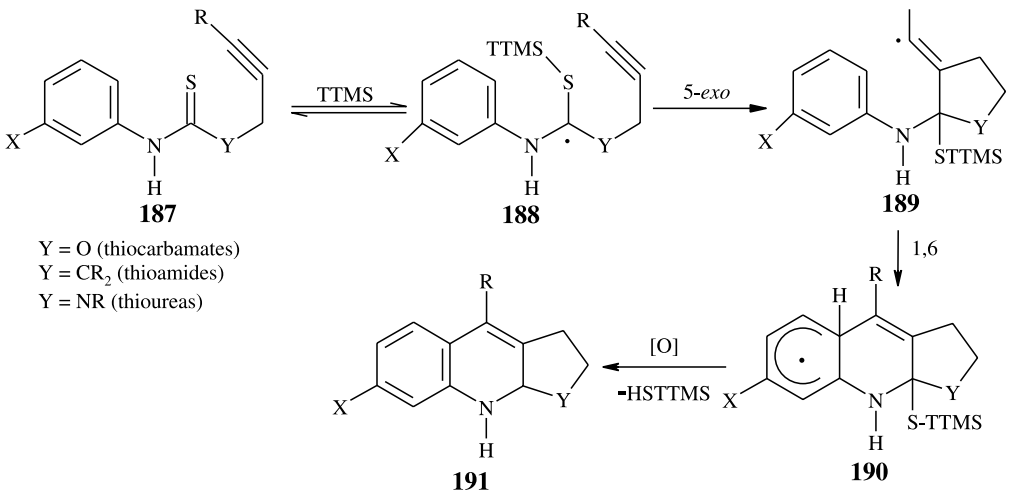
Curran et al. observed[115] that phenylcarbamic acid pent-3-ynyl esters **185a-e** in the presence of AIBN (1 equiv.) and tristrimethylsilylsilane (TTMSH) (4 equiv.) in benzene under standard conditions involving UV irradiation furnished the furoquinolines **186a-e** (Scheme 46). Additionally, the same workers focused the standard radical cyclisation of various thioamides and thioureas to furnish 2,3-dihydro-1*H*-cyclopenta[*b*]quinoline and indoloquinoline derivatives, respectively.



Scheme 45.



Scheme 46.



Scheme 47.

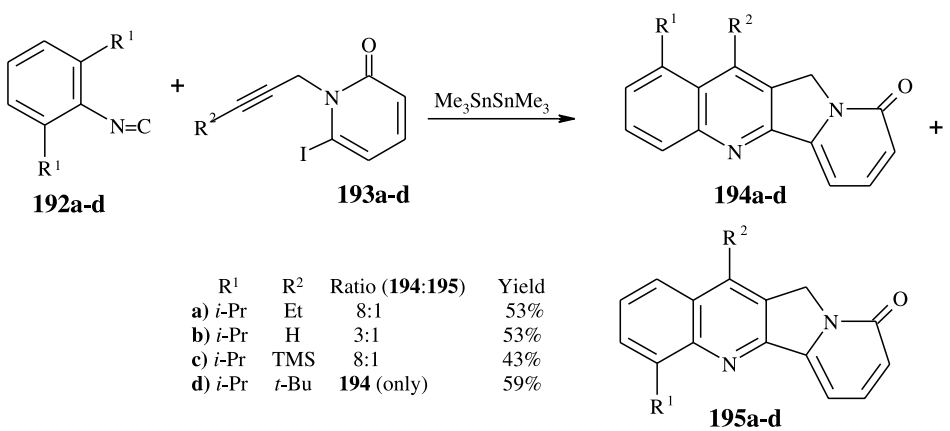
The suggested mechanism for this reaction is the reversible addition of the TTMS radical to the thiocabonyl group of **187** to give the stabilised radical **188**, which undergoes cyclisation to the vinylic radical **189**. 1,6-Cyclisation to one of the vacant *ortho* sites provides the delocalised radical **190**, from which oxidative re-aromatisation[103] is followed by ionic loss of the thiol to give **191** (Scheme 47).

Cascade [4+1] radical annulation of *o*,*o*′-dialkyl-substituted aryl isonitriles **192a-d** with *N*-propargyl-6-iodopyridones **193a-d** furnished a mixture of the 7,9-isomers **194a-d** and 7,12-isomers **195a-d** of 11*H*-indolizino[1,2-*b*]quinolin-9-ones with significant regioselectivity in favour of the more crowded product[116] (Scheme 48). The usefulness of the method is illustrated with a regioselective synthesis of (20*S*)-7-trimethylsilyl-9-isopropyl camptothecin. The 11*H*-indolizino[1,2-*b*]quinolin-9-one ring forms the core of the camptothecin and mappicine families of natural products. Camptothecin is the parent of one of the most important families of antitumour agents,[117] while analogues of mappicine exhibit antiviral activity.[118]

The formation of the products **194** and **195** by the annulation of *o*,*o*′-dialkyl-substituted aryl isonitriles with *N*-propargyl-6-iodopyridones may be explained as follows. The vinyl radical **197** was produced by the standard addition of the 6-pyridinyl radicals **196** to the isonitrile **197a** followed by 5-*exo*-cyclisation. This vinyl radical **197** partitions between 1,6-cyclisation to the *ortho* carbon to give **198** and 1,5-cyclisation to the *ipso* carbon to give **199**. β-Fragmentation of the isopropyl group from **198** provided the minor 7,12-isomer **195a**. Fragmentation of **199** to the iminyl radical **200**, followed by reclosure in a 1,6-fashion, furnished the rearranged radical **201**, which, upon loss of the isopropyl radical, provided the major 7,9-isomer **194a**. As the size of the *ortho* aryl substituent on the isonitrile increases, the partitioning of the radical **197** is directed away from 1,6-cyclisation due to the crowding in the intermediate **198** and this results in the formation of the less-crowded spirocycle **199** via 1,5-cyclisation.

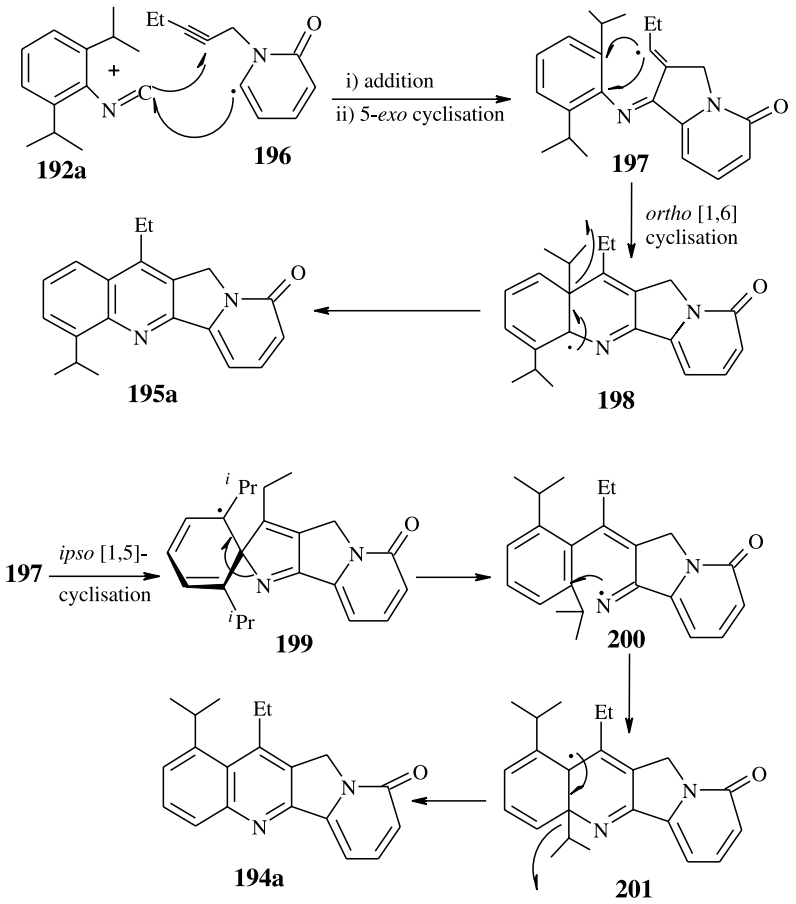
As the fates of the products are determined by the partitioning of **197**, the end result is the formation of the more-crowded 7,9-isomer **194a** by subsequent ring cleavage, reclosure and loss of the isopropyl group (**199→200→201→194a**) (Scheme 49).

Cascade radical reactions via α-(arylsulphanyl)imidoyl radicals were successfully applied[119] for the competitive [4+2] and [4+1] radical annulations of alkynyl isothiocyanates such as **204** with aryl radicals **203** (from **202**) leading to a new class of compounds, the thiochromeno[2,3-*b*]indoles. These derivatives were formed as a mixture of the substituted analogues **205** and **206** (Scheme 50).



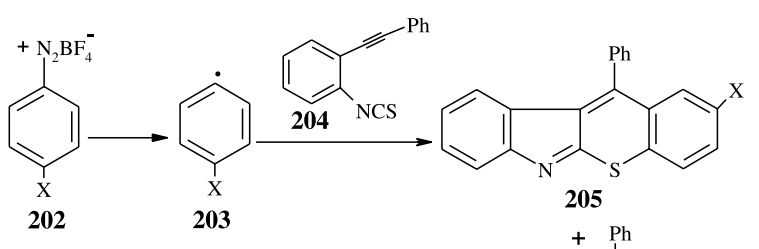
R1	R2	Ratio (**194**:**195**)	Yield
a) *i*-Pr	Et	8:1	53%
b) *i*-Pr	H	3:1	53%
c) *i*-Pr	TMS	8:1	43%
d) *i*-Pr	*t*-Bu	**194** (only)	59%

Scheme 48.



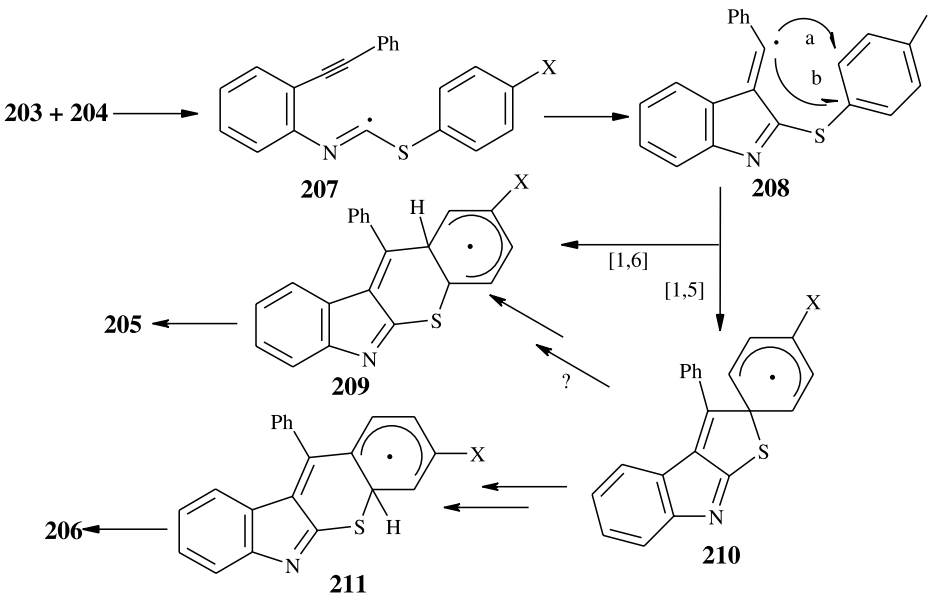
Scheme 49.

The isomer ratio is strongly dependent on the aryl substituent and has been correlated to its ability to delocalise the spin density. The presence of a methylsulphanyl group in the *ortho* position of the initial aryl radical results in complete regioselectivity and better yield. This is due to both strong spin delocalisation effect, which promotes exclusive [4+1] annulation, and a good radical leaving group ability, which facilitates the aromatisation of the final cyclohexadienyl radical. The reaction outcome can be accounted for through the initial addition of the aryl radical to the sulphur atom of the isothiocyanate to give the imidoyl radical **207**, with the subsequent cyclisation of **207** onto the C–C triple bond leading to the vinyl radical **208**. This radical eventually undergoes two competitive 1,5- and 1,6-cyclisations onto the aromatic ring of the starting aryl radical. In one route, 1,6-ring closure leads directly to the formation of the thiochromeno ring, the sulphurated part of which can be taken as arising from a [4+2] radical annulation between the radical **203** and the isothiocyanate **204**. Aromatisation of the cyclohexadienyl radical **209** eventually gives the compound **205**. In another route, 1,5-cyclisation produces the spirohexadienyl radical **210**, the thiophene ring of which is the result of [4+1] annulation between **203** and the isothiocyanate **204**. Ring expansion of



Series	X	**205** (%)	**206** (%)
a)	H	50	
b)	CF_3	27	23
c)	Cl	27	23
d)	OMe	20	20
e)	SMe	8	32
f)	N_3	4	40
g)	C(O)Me	2	43

Scheme 50.



Scheme 51.

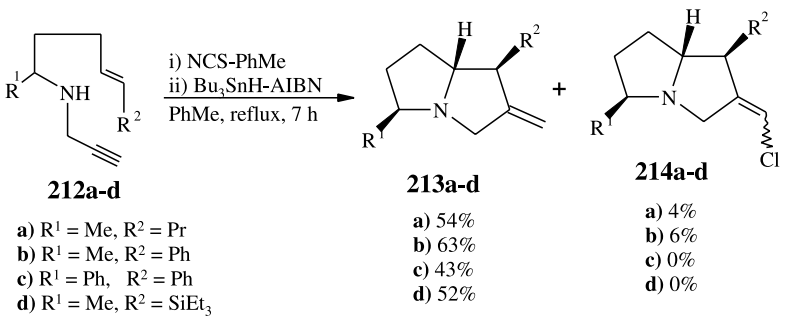
the radical **210** onto the sulphur atom to **211**, followed by aromatisation, affords the isomeric compound **206** (Scheme 51).

Theoretical calculations support the hypothesis of competitive, independent [4+2] and [4+1] annulation pathways and suggest that rearrangement onto the sulphur atom of the [4+1] intermediate does not occur via a sulphuranyl radical, but rather through either a transition state or a sulphur-centred (thioamidyl) radical. The latter is possibly the preferred route in the presence of an *o*-methylsulphanyl moiety that can act as a leaving group in the final *ipso*-cyclisation process.

Tandem cyclisation of *N*-propargylaminyl radicals produced by *N*-chlorination of (*E*)-alk-4-enylamines **212a-d**, followed by treatment with the tributyltin radical using *n*-Bu_3SnH and catalytic AIBN, afforded the 2-methylene-pyrrolizidines[120] **213a-d** and the reaction is highly stereoselective. The atom-transferred products **214a** and **214b** were also obtained in low yield in the case of **212a** and **212b** (Scheme 52).

The transition state **C** for the aminyl radical cyclisation is found to be chair-like, in which R^1 possesses a pseudo-equatorial position.[64b,121] The first ring closure produces a *trans*-2,5-disubstituted pyrrolidine intermediate **D**, and this is then followed by 5-*exo* cyclisation on to the C≡C bond efficiently to give the pyrrolizidine intermediate **E** as a diastereomer. This then abstracts a hydrogen atom from the tributyltin hydride to give the product **213** (Fig. 6).

The synthesis of the spiropyrrolidinyloxindoles, horsfiline and coerulescine, has been described,[122] in which the key



Scheme 52.

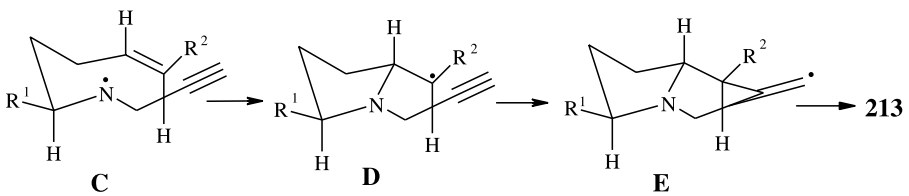
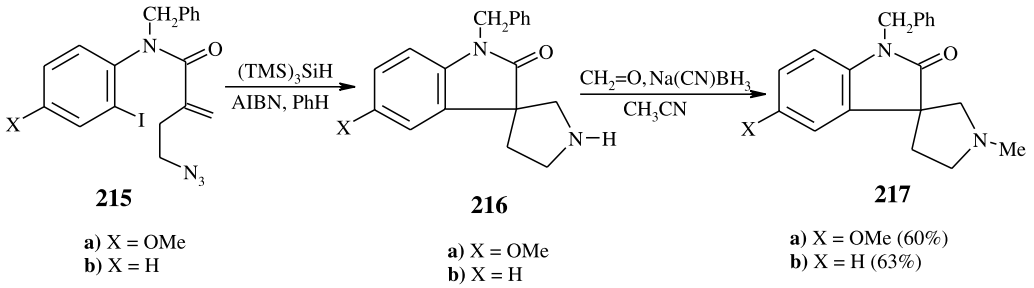
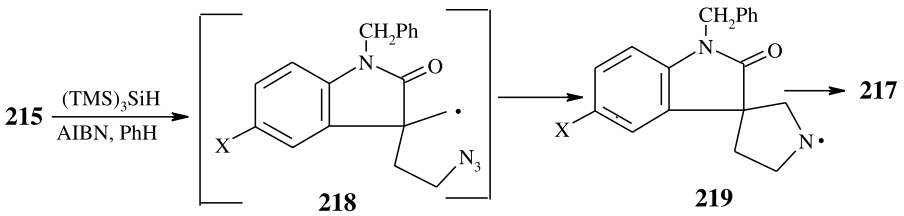


Figure 6. Chair-like transition state of aminyl radical in which R^1 possesses a pseudo-equatorial position.



Scheme 53.



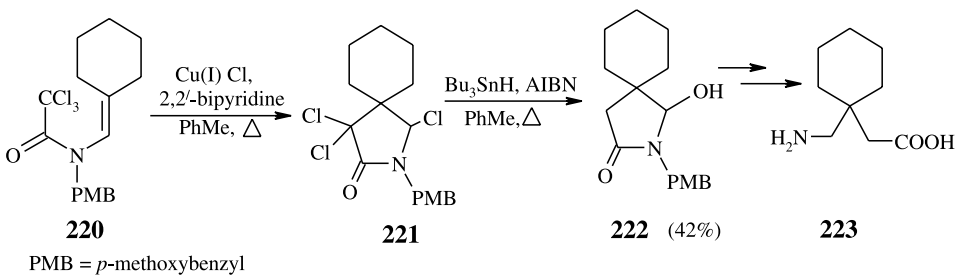
Scheme 54.

step was the tandem radical cyclisation of iodoaryl alkenyl azides. The radical cyclisation of 2-(2-azidoethyl)-*N*-benzyl-*N*-(2-iodo-4-methoxyphenyl)acrylamide **215a** by using $(TMS)_3SiH$ and AIBN in refluxing benzene furnished 1-benzyl-5-methoxy-1*H*-spiro[indole-3,3′-pyrrolidin]-2-one **216a** and this was subjected to in situ methylation to produce 1-benzyl-5-methoxy-1′-methyl-1*H*-spiro[indole-3,3′-pyrrolidin]-2-one **217a** in 60% yield. A similar protocol was followed for the conversion of **215b** to **217b** via **216b** (Scheme 53).

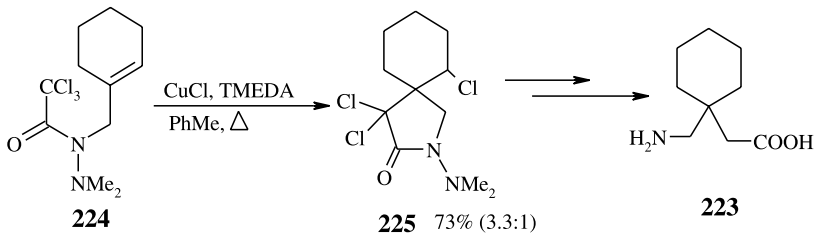
Compound **215** after passing through two intermediates **218** and **219** (nitrogen radical intermediate) furnished the final product **217**. The mechanism for the conversion of **215** to **217** is depicted in Scheme 54.

3.9. Synthesis of nitrogen heterocycles with non-conventional reagents

The radical cyclisation of unsaturated organohalides[95a,123] is very common for preparing five-membered nitrogen heterocycles and a variety of pyrrolidinones[124] have been prepared following the favoured 5-*exo-trig* pathway. Recently, it was reported that the 5-*endo-trig* radical cyclisation of haloenamides[125] also furnished pyrrolidinones. This cyclisation is unusual in the sense that the initial carbamoylmethyl radical reacts to form a five-membered, rather than a four-membered (or a β-lactam), ring. The formation of a β-lactam ring following the favoured 4-*exo-trig* cyclisation is generally observed when radical-stabilising (aromatic) groups are introduced on the enamide C=C bond.[126] Tributyltin hydride annulated 5-*endo* cyclisations have provided efficient approaches to substituted pyroglutamates.[57,127] It is very difficult to use tributyltin hydride, as the tin-containing byproducts are often difficult to remove and the cyclisation leads to the reduction of C–halogen and C=C bonds. In view of these circumstances, Parsons et al. have developed[128] a more straightforward and versatile approach, in which the 5-*endo-trig* radical cyclisation reaction of enamides with manganese(III) acetate or copper(I) chloride/bipyridine have been utilised to produce functionalised pyrrolidinones. Both of the reagents are cheaper, the metal byproducts are more easily removed and a functional group (generally a double bond or a halogen atom) is introduced into the product after cyclisation. The copper(I)-mediated cyclisations are very efficient and the bicyclic dienes can be isolated in >80% yield, while the corresponding manganese(III) reactions are generally more problematic, producing the dienes in lower yield (35–52%). Bryans et al. carried out[129] the radical cyclisation of a variety of haloenamides with copper(I) or ruthenium(II) complexes. They observed that the copper(I)/bipyridine reactions gave predominantly the γ-lactams via a 5-*endo* route, whereas the β-lactams were mainly produced via a 4-*exo* pathway by using dichlorotris(triphenyl phosphine)-ruthenium(II) or copper(I)/TMEDA(*N*,*N*,*N*,*N*-tetramethyl-1,2-ethylenediamine). *N*-Allyl-*N*,*N*-dimethyl-2,2-dichlorohydrazides were found to react with CuCl/TMEDA in



Scheme 55.



224 **225** 73% (3.3:1) **223**

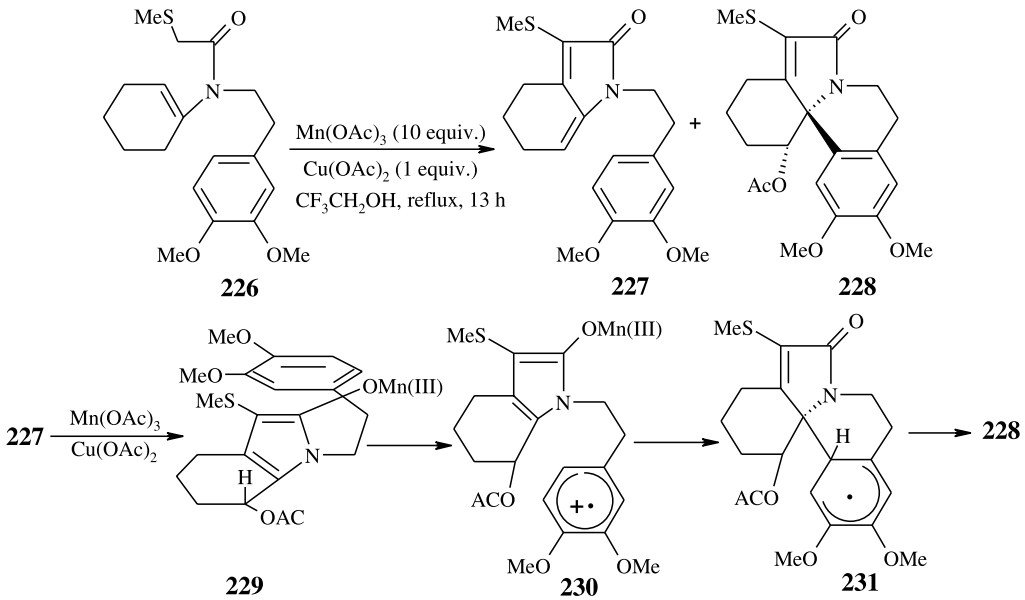
Scheme 56.

ethyl acetate to afford *N*-(dimethylamino)-2-pyrrolidinones[130] as a mixture of inseparable diastereomers.

In another report,[131] the radical cyclisation of halo-amides has been utilised to afford functionalised pyrrolidinones via 5-*endo-trig* and 5-*exo-trig* radical cyclisation pathways. The trichloro-enamide **220** was heated with copper(I) chloride/bipyridine to give the desired trichlorinated spirocycle **221**, following 5-*endo-trig* cyclisation. The spirocycle **221** was then reacted with tributyltin hydride (3.3 equiv.) to remove all three chlorine atoms. It is very important to note that hydrolysis, rather than reduction, of the chlorine atom α- to the nitrogen occurs to give the hydroxypyrrolidinone **222** in 42% yield. By applying this methodology, Parsons et al.[131] have synthesised the anti-epileptic drug, gabapentin **223**, after several multistep synthetic reactions (Scheme 55).

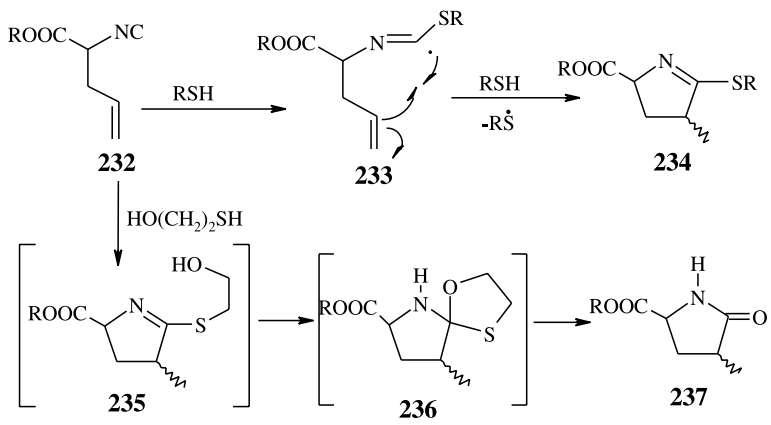
Although the formation of gabapentin **223** following a 5-*endo-trig* approach offers an alternative strategy, the overall yield of **223** from the copper(I)-catalysed reaction is only 2%, mainly because of the inefficient formation of the trichloroenamide **221**. A more efficient synthesis of **223** has been achieved by using 5-*exo* radical cyclisation, in which the key step involved the radical cyclisation of the cyclohexene derivative **224**, bearing an *N*-dimethylamino protecting group. The trichloride **224**, on treatment with copper(I) chloride and TMEDA resulted in the formation of the desired heterocycles **225** in 73% yield as a 3.3:1 mixture of separable diastereomers (Scheme 56). Following the successful formation of spirocyclic compounds using copper(I)-mediated atom transfer radical cyclisation (ATRC) reactions, Parsons et al. also succeeded in forming the unsaturated pyrrolidinone, pulchellalactam, by using 5-*endo* cyclisation.[131]

Ishibashi et al. observed[132] that the treatment of *N*-[2-(3,4-dimethoxyphenyl)ethyl]-α-(methylthio) acetamide **226** with $Mn(OAc)_3$ in the presence of $Cu(OAc)_2$ gave the tetrahydroindol-2-one **227**, which then cyclised with $Mn(OAc)_3$ to give 4-acetoxyerythrinane **228**. The formation of **228** from **227** may be depicted as follows. When the 3,4-dimethoxyphenyl and pyrrole rings of the acetoxy-substituted intermediate **229** were brought very close together, a mutual π−π interaction[133] between the two aromatic rings becomes evident. If the HOMO level of this system is enhanced, either the 3,4-dimethoxyphenyl or pyrrole ring would be readily oxidised. A more rapid oxidation of the electron-rich 3,4-dimethoxyphenyl ring than that of the pyrrole ring might result in the formation of the cation radical **230**. This is then followed by a nucleophilic attack of the pyrrole ring on the cation radical **230** to give the radical **231**. A further oxidation of **231** and deprotonation of the resulting cation would give **228** (Scheme 57). Mn(III)/Cu(II)-mediated oxidative radical cyclisation was applied to a formal synthesis of 3-demethoxyerythratidinone, a naturally occurring Erythrina alkaloid.



226 **227** **228** **229** **230** **231**

Scheme 57.



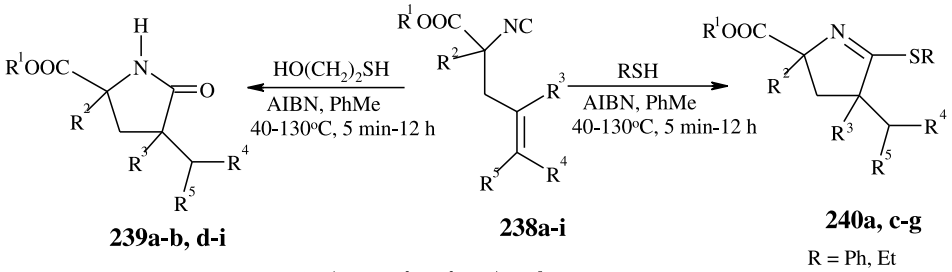
Scheme 58.

Kilburn et al. have reported[134] the microwave-assisted free radical cyclisation of alkenyl and alkynyl isocyanides with thiols to give the five-membered nitrogen heterocycles. In a typical reaction a thiyl radical (RS) was found to add to an alkenyl isocyanide **232**, generating a thioimidoyl radical **233** which underwent 5-*exo* cyclisation and subsequent hydrogen atom abstraction to afford *cis*- and *trans*-pyrrolines **234**. By using 2-mercaptoethanol *cis*- and *trans*-pyroglutamates **237** were obtained, through the intermediate **235** and also through the intermediate of a cyclic derivative **236** which underwent hydrolysis during the reaction (Scheme 58).

Microwave flash heating was found to give a better yield than the traditional thermal heating techniques. Alkanethiols and 2-mercaptoethanol were found to provide different products when treated with alkenyl isocyanides. Cyclisation of the isocyanides, **238a** and **238g**, afforded the *cis*- and *trans*-pyrrolines **240a** and **240g** in satisfactory yield (60 and 40%, respectively) under thermal conditions. The yield of the same products **240a** and **240g** may be increased to 75 and 78%, respectively, by the use of microwave flash-heating within 5 min. When 2-mercaptoethanol was used *cis*- and *trans*-pyroglutamates **239a**-**b** and **239d**-**f** were obtained in excellent yield, both under thermal and microwave conditions. However, the microwave reactions furnished slightly better yield and were completed in much shorter times. Cyclisation were also attempted by the use of benzenethiol and 2-mercaptoethanol in the absence of radical initiator. Isocyanides **238a**-**d** and **238f** all cyclised in good yield. However, the yields were lower than with radical initiator but still comparable to thermal methods. In order to carry out such reactions the reaction time had to be increased to 10 min with 4 equiv. of thiol (Scheme 59).

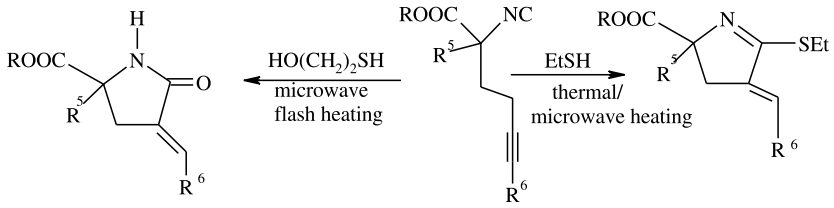
Similarly ethanethiol and 2-mercaptoethanol also provided different cyclised products from alkynyl isocyanides under standard thermal conditions, cyclisation of alkynyl isocyanides **241a**, **241c** and **241d**, using 2-mercaptoethanol, gave surprisingly poor yield of the corresponding pyroglutamates **242a**, **242c** and **242d**. However, with microwave flash-heating dramatically good yields were obtained. Again, high yield of pyrrolines (**243a**, **243c** and **243d**) were also obtained under thermal and microwave assisted condition by the use of ethanethiol (Scheme 60).

Pyrrolines and pyroglutamates have been synthesised in good to excellent yield by employing the microwave flash heating technique. The reaction times were dramatically reduced and the cyclisations of alkynyl isocyanides, which gave poor results under traditional thermal conditions, were improved.



a) R^1 = Et, R^2 = R^3 = R^4 = R^5 = H
b) R^1 = Et, R^2 = $CH_2CH{=}CH_2$, R^3 = R^4 = R^5 = H
c) R^1 = Et, R^2 = R^4 = R^5 = H, R^3 = Me
d) R^1 = Et, R^2 = $CH_2C(Me){=}CH_2$, R^3 = Me, R^4 = R^5 = H
e) R^1 = Et, R^2 = R^3 = H, R^4 = R^5 = Me
f) R^1 = PMB, R^2 = R^3 = R^4 = R^5 = H
g) R^1 = Bn, R^2 = R^3 = R^5 = H, R^4 =Ph
h) R^1 = Bn, R^2 = R^4 = R^5 = H, R^3 =Me
i) R^1 = Bn, R^2 = $CH_2C(Me){=}CH_2$, R^3 = Me, R^4 = R^5 = H

Scheme 59.



242a-d **241a-d** **243a, c-d**

a) R = Et, R^5 = H, R^6 =TMS
b) R = $PhCH_2$, R^5 = H, R^6 = TMS
c) R = $PhCH_2$, R^5 = $CH_2C{\equiv}CTMS$, R^6 = TMS
d) R = Et, R^5 = $CH_2C{\equiv}CH$, R^6 = H

Scheme 60.

4. Synthesis of oxygen heterocycles

γ-Lactams have been prepared by several methods.[96,97] The formation of these heterocycles by tin hydride-mediated radical cyclisation is often practical.[135,136] A general route to γ-lactones has been developed by Stork[137–139] and by Ueno[140–142] and this has been increasingly applied in their synthesis.[143–145]

The synthesis of tetrahydrofurans by the radical cyclisation of bromo acetals and bromo ketals is well known. Srikrishna et al. have utilised[146] the tributyltin hydride annulated radical cyclisation reaction to produce 2-alkoxy-4-methylenetetrahydrofurans from the suitable bromo acetals. Srikrishna et al. also reported[147] the radical cyclisation reactions of various bromo acetals, followed by aromatisation, to produce the 2,3,5-tri- and 2,3,4,5-tetrasubstituted furans, respectively. They also demonstrated[148] the tributyltin hydride-mediated radical cyclisation of the bromo ketal, 3-[(2-bromo-1-methoxy-1-phenyl)-ethoxy-propyne, with tri-*n*-butyltin chloride and $Na(CN)BH_3$ in the presence of a catalytic amount of AIBN. Tributylchlorostannane acts as a Lewis acid in the presence of sodium cyanoborohydride in the regioselective reductive demethoxylation of dimethyl and mixed ketals.[149]

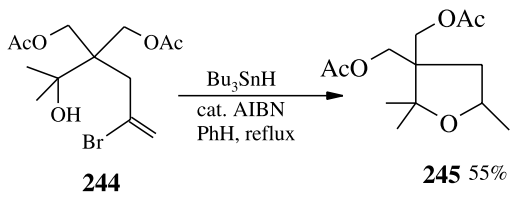
Beckwith et al. have pointed out[150] the Bu_3SnH-prompted radical cyclisation of various acyclic bromo acetals. One of the methods for the synthesis of tetrahydrofurans by radical cyclisation is the 5-*exo* cyclisation of alkoxy radicals. A novel method for the generation of alkoxy radicals has been introduced[151] from *N*-alkoxydithiocarbamates by a radical reaction with Bu_3SnH/AIBN in refluxing benzene for 3 h to furnish 4-phenoxy-1-butanol in 95% yield. The alkoxy radical was also generated under tin-free conditions[152,153] using PhSH as a radical mediator in the presence of AIBN in refluxing benzene.

A combination of sulphanyl radical addition–cyclisation of dienes connected with hydroximates, followed by conversion of the resulting cyclic hydroximate to the lactone, has proved to be an unique method for the construction of α,β-disubstituted γ-lactones.[154] The radical cyclisation of (*Z*)-hydroximates in the presence of thiophenol and AIBN furnished a mixture of the cyclised *cis*- and *trans*-products in 82% combined yield. No such cyclised product was, however, obtained from the corresponding (*E*)-hydroximates. Clive et al. have described[155] a method for making spiro enones from bromo acetals such that the stereochemistry at the spiro centre is controlled by the stereochemistry of an adjacent hydroxyl group. Several novel bridged spiro lactones can be prepared by the tandem radical cyclisations of α,β-unsaturated cyclohexanone derivatives bearing an appropriate allyl side chain via a double radical cyclisation of the enol ester radical.[156]

Acyl radicals participate in a wide range of inter- and intramolecular reactions and they are therefore very useful synthetic intermediates.[157] A few years ago, Evans et al. reported[158] the $(TMS)_3SiH$ annulated radical cyclisation of acyl selenides to furnish the cyclic ethers in 90–96% yield, with 33:1 diastereoselectivity (by HPLC) at C-3′. Acyl radicals have also been used in the synthesis of five-, six- and seven-membered oxygen heterocycles. Substituted tetrahydrofuran-3-ones can be easily prepared[159] from *o*-vinylated-β-hydroxyalkyl phenyl chalcogenides via carbonylation or reductive cyclisation. The initially formed alkyl radical is carbonylated using a high pressure of CO to give an acyl radical, which facilitates 5-*exo-trig* cyclisations onto vinyl ethers with electron-withdrawing groups.

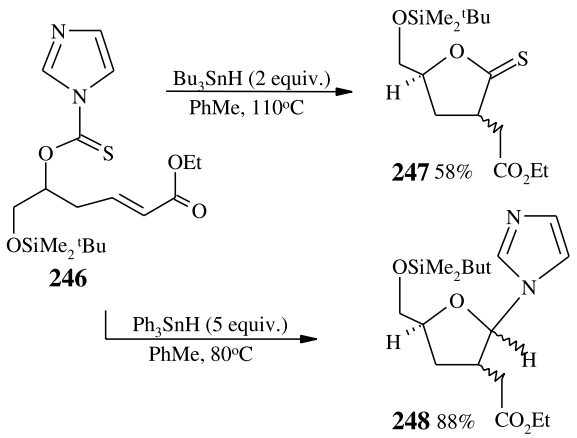
Recently, the Bu_3SnH-mediated radical cyclisation of unsaturated organohalides has attracted considerable interest to synthetic organic chemists.[95a,b,123a,160] Under mild, neutral reaction conditions, a large number of five- and six-membered rings may be prepared by employing this methodology. Various hydroxy-tetrahydrofurans[161] have been prepared under normal radical cyclisation conditions. The use of an allylic *o*-stannylketyl radical cyclisation to form a chroman by the 6-*exo-trig* cyclisation of the diene was also reported.[162]

In 2003, Yokota et al. have achieved[163] the tri-*n*-butyltin hydride-mediated radical cyclisation of the hydroxy vinyl bromide **244** via a 5-*exo-trig* cyclisation of an alkoxy radical and it is thought to be produced by an unusual [1,5]-hydrogen shift from the hydroxyl group to vinyl radical to generate an unusual furan **245** in 55% yield as the major product (Scheme 61). Similar results were obtained by using primary and secondary alcohols as the substrates. The conformation of the carbon chain is controlled by the presence of the quaternary carbon centre at the β-position to the hydroxyl group.



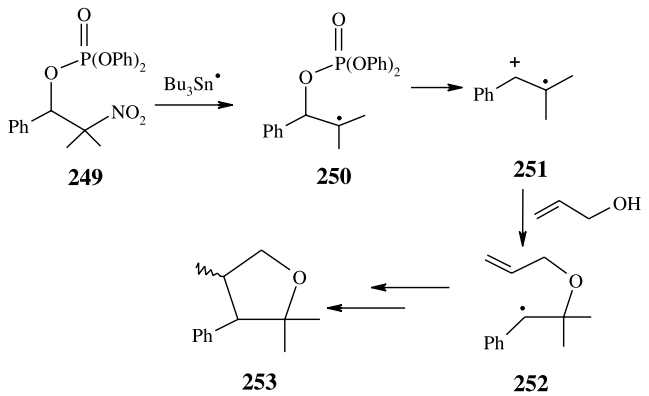
Scheme 61.

The thiolactone **247** (*cis*/*trans*=2.1:1.0) was produced[164] in 58% yield by a Bu_3SnH-mediated radical cyclisation reaction of a simple carbohydrate-derived imidazole thioate **246**. When a dilute solution of the substrate **246** in benzene was added to an excess of Ph_3SnH at 80 °C (reverse addition), however, the immediate result was the formation of an imidazole glycoside **248** in 88% yield (Scheme 62).



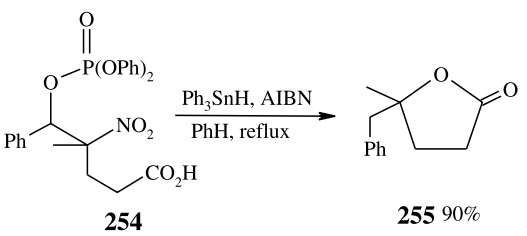
Scheme 62.

The diphenyl phosphate **249** was synthesised[165] and was then subjected to reflux with tributyltin hydride in 3:1 mixture of benzene and allyl alcohol. The immediate result was the formation of a (1:10) *trans*/*cis* mixture of 2,2,4-trimethyl-3-phenyltetrahydrofuran **253** via **250**, **251** and **252**, respectively. The reaction sequence is depicted in Scheme 63.



Scheme 63.

The formation of the γ-lactone **255** in 90% yield was achieved by refluxing the phosphorylated nitro acid **254** with triphenyltin hydride and AIBN in benzene[165] (Scheme 64).

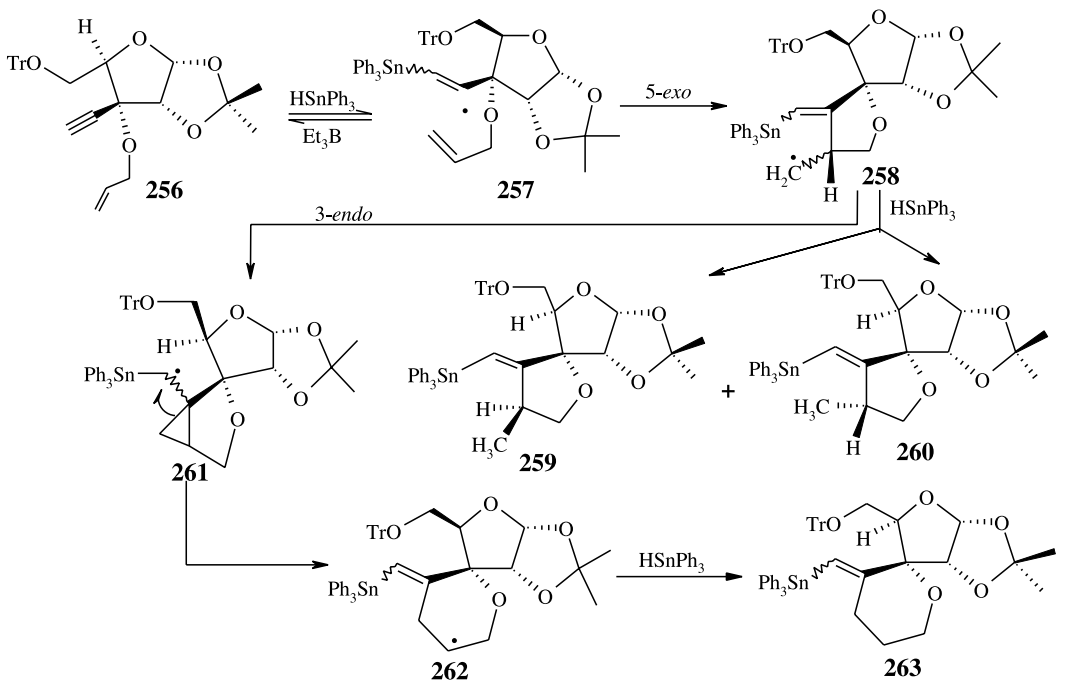


Scheme 64.

The triphenyltin hydride-mediated free radical cyclisation of the radical precursor **256**, a new stereoselective entry into the 1,7-dioxaspiro[4,4]nonane ring system, has recently come to light.[166] The cyclisation of the precursor **256** gave a mixture of products, two 5-*exo* products **259** and **260** (via **257** and **258**) and one 6-*endo* product **263** following the sequential route (**258→261→262→263**), in a 1:1:1 ratio. The cyclisation of compound **256** was modelled using semi-empirical PM 3 calculations, while taking into account the preferred conformers in the transition state for the eight possible structures, the *E*/*Z* stereochemistry at the *exo*-double bond and the *R*/*S* configuration at the newly formed stereocenters, via either chair or boat conformations, to give the 5-*exo* products. From the energy calculations at a density functional theorem (DFT) level on these optimised structures to obtain more accurate differences in energy between all the possible structures in the transition state, it is clear that the chair forms were more stable than the boat forms (Scheme 65).

Intramolecular homolytic *ipso* substitution has already been used for the preparation of benzo-fused ring systems such as phenanthridinones[67,103] and benzochromenes.[167] Here, Zhang et al. achieved a novel double *ipso* substitution process for the synthesis of azabenzoisocoumarins.[90] In this case, the initial radical **265**, generated from the radical precursor **264**, underwent 1,5-*ipso* substitution by a radical attack at the 2-position of the pyridine ring to produce the carbonyloxy radical **267** through **266**. This then underwent a second 1,6-*ipso* substitution to displace the methoxy group from **268** to furnish 10-oxa-4-azaphenanthren-9-one **269**. The yield of the rearrangement product **269** was decreased to <10% in the absence of the methoxy group and this suggests the important role of the methoxy group in the promotion of the double *ipso* rearrangement (Scheme 66).

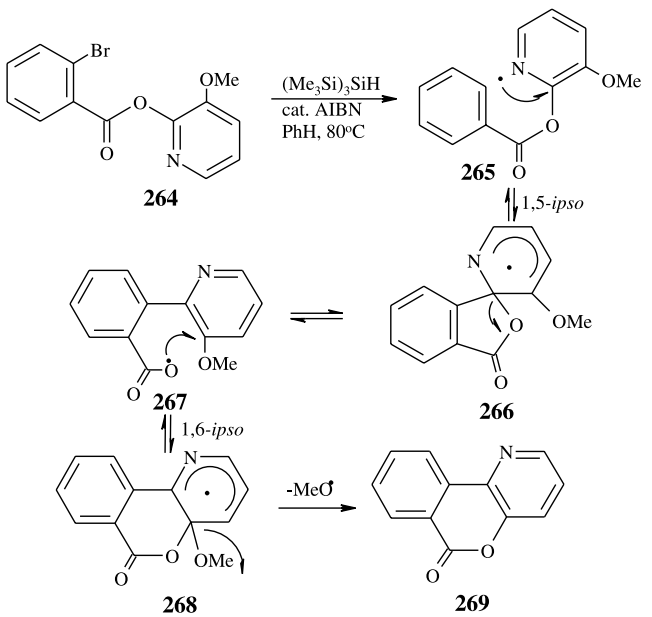
The cyclization of aryl radicals onto 2-bromo-*N*-alkyl-*N*-(3-oxocyclohex-1-enyl)benzamides furnished the ketospiro-2,3-dihydroisoindol-1-ones.[168] Analogously, 2-bromobenzoic acid 3-oxocyclohex-1-enyl esters gave the keto-spiro-γ-lactones.[168,169] Recently, Zhang et al. described[170] a straightforward two-step parallel synthesis for structurally diversified spiro compounds, where 2-bromobenzoic acids **270** were used as common building blocks to couple with a series of conjugated enols or enamines. Sequential intramolecular free-radical Michael additions lead to the formation of spirobenzolactones, spirobenzolactams, spirobenzolactone-lactams, spirobenzolactone-thiolactones, spirodilactones and bridged-spirolactones. Substituted 2-bromobenzoic acids (**270**) reacted with teronic acid (**271**) to give the intermediate enol ester **272**. Compounds **272** were reported to have antifungal activity and cyclised in the presence of $(Me_3Si)_3SiH$ and catalytic amount of AIBN



Scheme 65.

to afford spirodilactones **273**. Compounds **273** possess a unique heterocyclic system that was also found in natural product altenuic acid II. Again, substituted 2-bromobenzoic acids (**270**) on reaction with thiotetronic acid (**274**) furnished the intermediates **275**. These then underwent radical spirocyclisation to give spirolactone–thiolactone **276**.

In a similar manner spirolactone ester **279** was synthesised by coupling of 2-bromobenzoic acid (**270**) with a β-keto ester **277** followed by radical cyclisation of **278** (Scheme 67).



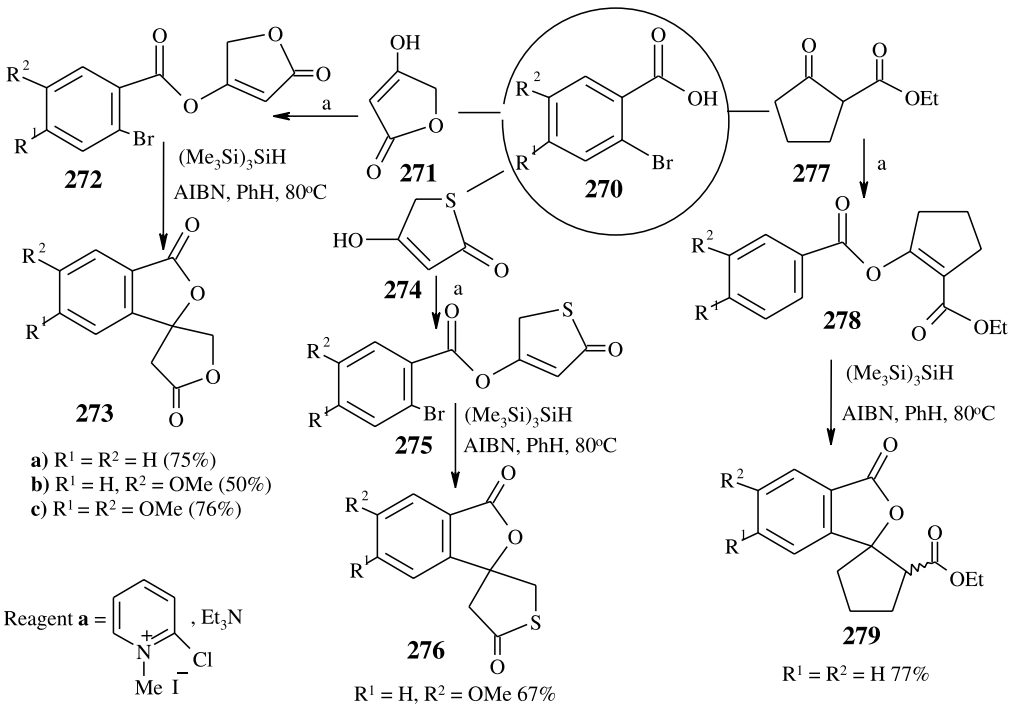
Scheme 66.

Recently, we have reported[171] the regioselective synthesis of 1*H*,3*H*,6*H*-[2]benzopyrano[4,3-*d*]pyrimidine-2,4-diones **281a-f** (75–85%) and 12*H*-benzopyrano[3,2-*c*][1]benzopyran-5-ones **283a-h** (70–85%), respectively, by radical cyclisation reactions. The starting materials, the 5-(2′-bromobenzyloxy)pyrimidine2,4-diones **280a-f** or 4-(2′-bromobenzyloxy)benzopyran-7-ones **282a-h**, were separately refluxed in benzene under a nitrogen atmosphere with tri-*n*-butyltin chloride and sodium cyanoborohydride in the presence of a catalytic amount of azobisisobutyronitrile (AIBN) for 3–4 h to give the cyclic products **281a-f** or **283a-h**, respectively (Scheme 68).

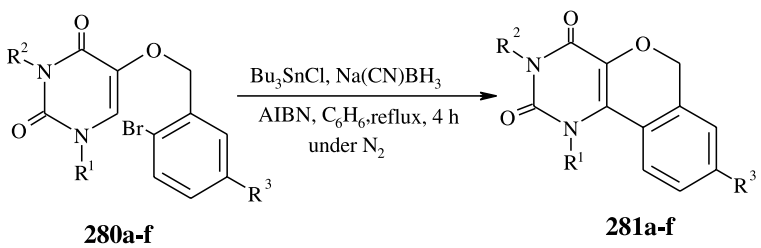
The exact reason why the 6-*endo*-cyclisation product is exclusively formed is not clear at present. The formation of the products **281a-f** from **280a-f** may, however, be explained by the generation of an aryl radical **284**. Subsequent 5-*exo* cyclisation may give a spiroheterocyclic radical[93] **285** (not isolated), followed by neophyl rearrangement,[94] to give the more stable intermediate radical **286** (benzylic radical) or by a 6-*endo* route directly to give the intermediate radical **286**, which then re-aromatises to yield the products **281a-f**, by an unknown mechanism, which is usual for this type of synthetic sequence, that is, an oxidation step in *n*-Bu_3SnH-mediated cyclisations[9b,54,95] (Scheme 69).

A similar mechanism is also operative for the formation of the products **283a-h** from **282a-h**.

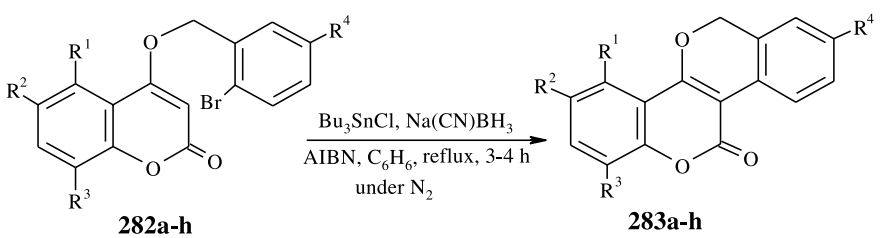
Recently, we have extended our efforts[172] in the regioselective synthesis of 2*H*-benzopyrano[3,2-*c*]quinolin-7(8*H*)-ones **288a-f** by a Bu_3SnH-mediated radical cyclisation of 4-(2′-bromobenzyloxy)quinolin-2(1*H*)-one derivatives **287a-f** (Scheme 70).



Scheme 67.

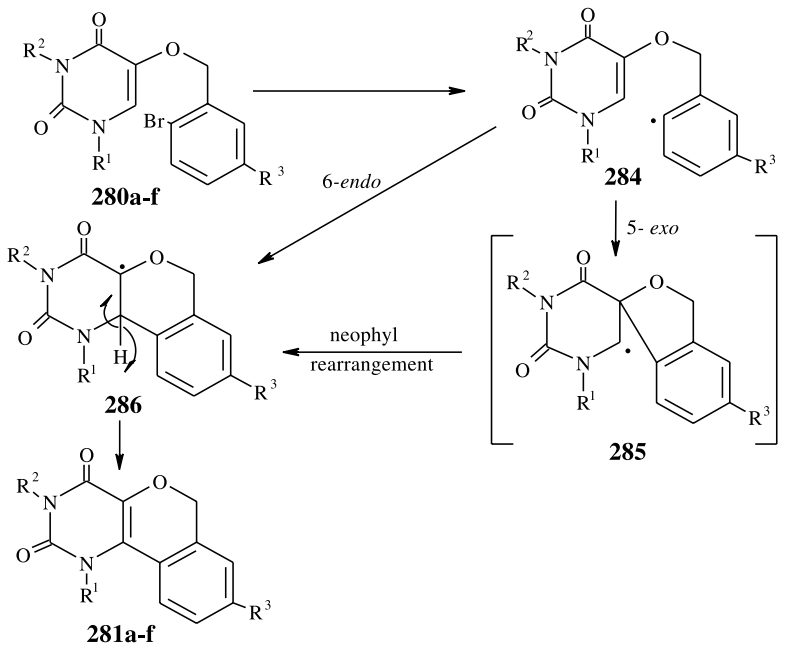


a) $R^1 = R^2 = Me$, $R^3 = H$ (80%)
b) $R^1 = R^2 = Me$, $R^3 = OMe$ (75%)
c) $R^1 = R^2 = Et$, $R^3 = H$ (85%)
d) $R^1 = R^2 = Et$, $R^3 = OMe$ (80%)
e) $R^1 = Et$, $R^2 = Me$, $R^3 = H$ (82%)
f) $R^1 = Et$, $R^2 = Me$, $R^3 = OMe$ (84%)



a) $R^1 = R^2 = R^3 = R^4 = H$ (75%)
b) $R^1 = R^2 = R^3 = H$, $R^4 = OMe$ (78%)
c) $R^1 = R^3 = R^4 = H$, $R^2 = Me$ (70%)
d) $R^1 = R^3 = H$, $R^2 = Me$, $R^4 = OMe$ (72%)
e) $R^1 = R^3 = Me$, $R^2 = R^4 = H$ (76%)
f) $R^1 = R^3 = Me$, $R^2 = H$, $R^4 = OMe$ (85%)
g) $R^1 = R^2 = R^4 = H$, $R^3 = Me$ (82%)
h) $R^1 = R^2 = H$, $R^3 = Me$, $R^4 = OMe$ (78%)

Scheme 68.



Scheme 69.

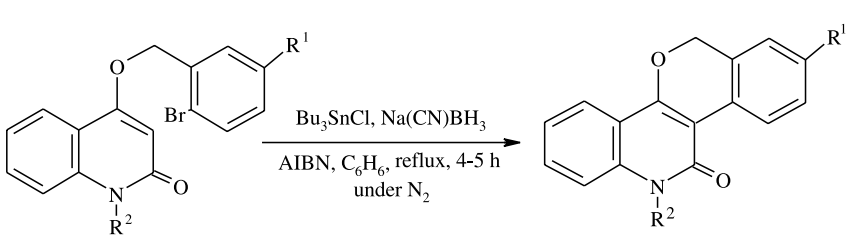
We have also synthesised[173] various spiroheterocycles **292a**,**b** by the tri-*n*-butyltin hydride-induced radical cyclisation of 5-(*o*-bromoaryloxymethylene)-6,7,8-trihydropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **289a**,**b**. These heterocycles can additionally be obtained under acid-catalysed enol–ether cleavage conditions. The formation of the products **292a**,**b** from **289a**,**b** may be explained by the formation of an aryl radical **290**, followed by 5-*endo-trig* cyclisation, to give the spirocyclic radical **291**, which may then give the final spiroheterocycles **292a**,**b** (Scheme 71).

4.1. Synthesis of oxygen heterocycles with non-conventional reagents

The reduction of halides with bis(cyclopentadienyl)zirconium chloride hydride [$Cp_2Zr(H)Cl$; Schwartz reagent] proceeded smoothly via a radical process, which is similar to the reduction with *n*-Bu_3SnH, in the presence of triethylborane as an initiator.[174] It was reported[175] that the haloacetals[137,141] on treatment with $Cp_2Zr(H)Cl$ in the presence of Et_3B in THF at 25 °C for 3 h furnished the cyclised products in excellent yield.

Hypophosphorous acid (H_3PO_2) and the corresponding 1-ethylpiperidine salt, *N*-ethylpiperidine hypophosphite (EPHP), are now well established for the generation of radicals in both aqueous and organic media.[72,176,177] This method has a good potential to replace the moderately toxic Bu_3SnH.[167a]

The samarium diiodide-induced reductive radical cyclisation of various haloalkenes has been developed.[178] Jiang et al. have synthesised[179] (±) cryptotanshinone and tanshinone IIA from the readily available 1,5-naphthalenediol **293**, in which the key step is the SmI_2-promoted intramolecular radical cyclisation of the compound **294** to produce the cyclic product **295** in 88% yield.[180] The compound **295** is found to serve as a suitable precursor to cryptotanshinone and tanshinone IIA (Scheme 72).

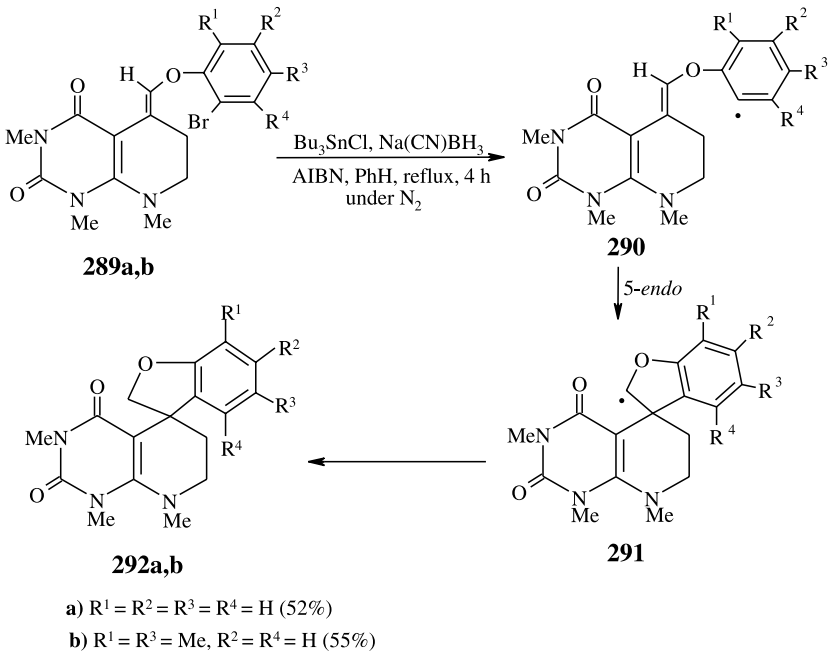


287a-f

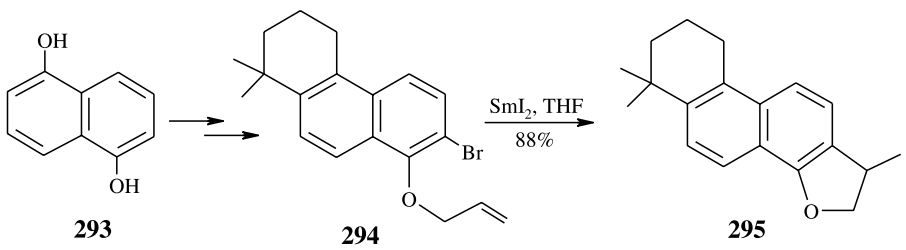
288a-f

a) R^1 = H, R^2 = Ph (80%)
b) R^1 = OMe, R^2 = Ph (76%)
c) R^1 = H, R^2 = Me (70%)
d) R^1 = OMe, R^2 = Me (73%)
e) R^1 = H, R^2 = Et (70%)
f) R^1 = OMe, R^2 = Et (76%)

Scheme 70.



Scheme 71.



Scheme 72.

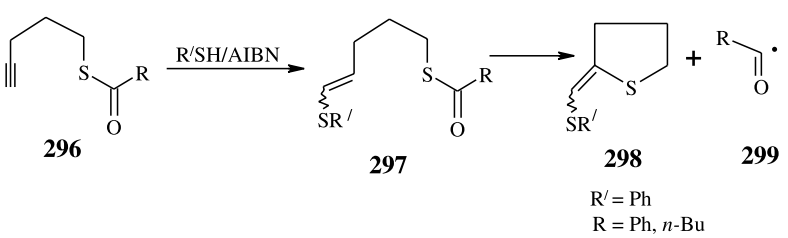
5. Synthesis of sulphur heterocycles

A few years ago, the Bu_3SnH-mediated radical cyclisation of di-isophenol-ω-haloalkyl ethers from oxapolycycloalkanones was reported.[181] Influenced by this result, Ponaras et al. extended this methodology to the sulphur-containing 2-(ω-haloalkylthio)enones to produce predominantly the fused thiapolycycloalkanones.[182]

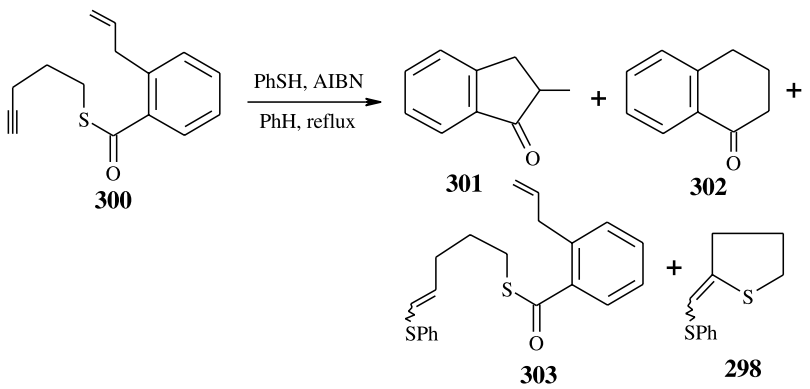
Acyl and aryl selenides are often the precursors of choice for acyl radicals, due to their capability to take part in chain sequences with tri-*n*-butylstannane and tris(trimethylsilyl)-silane.[183–185] The replacement of acyl selenides by thiol esters has been carried out, but these are normally very poor sources of acyl radicals[183] and this lack of reactivity may be increased by the inclusion of an additional propagation step, in which an aryl radical brings about an intramolecular homolytic substitution at sulphur.

Crich et al. prepared[157e] the iodothiol ester precursors by the reaction of (iodophenyl)ethanethiol with appropriate acyl chlorides. Benati et al. have utilised[186] this idea to prepare the thiophene **298** by the reaction of thiol ester **296** with R′SH and AIBN in refluxing benzene via the intermediate formation of **297**. In this case aryl radical **299** was also generated (Scheme 73).

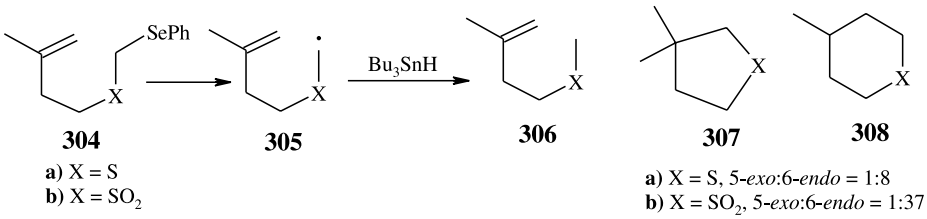
The radical reactions of some thiol esters were carried out[187] by adding a benzene solution of PhSH and AIBN under refluxing conditions. The thiol ester **300** led to the isolation of the cyclised indanone **301** and tetralone **302** in ca. 96:4 ratio (overall 73% yield), along with comparable amounts of



Scheme 73.



Scheme 74.



Scheme 75.

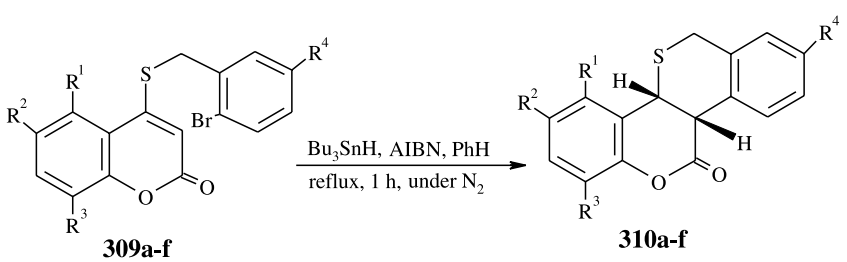
the (*E*)- and (*Z*)-dihydrothiophene **298**. Small amounts of the (*E*)- and (*Z*)-vinyl sulphide adduct **303** were the additional products (Scheme 74).

A few years ago, Della et al. reported[188] the results of a parallel study of the cyclisation of the 2-thia- and 2-sulphonyl-5-hexenyl radicals and obtained mixtures containing substantial quantities of both the 5-*endo* and 6-*exo* products, respectively. Recently, Della et al. also pointed out[189] the regioselectivity of the ring closure of 2-thia- and 2-sulphonyl-5-methyl-5-hexenyl radicals. The selenides **304** were the selected precursors to the radicals **305**. Ring closure of the α-substituted radicals **305** (X=S, SO_2) was found to be irreversible and led to significant amounts of the 6-*endo*-cyclisation products **308**. In the case of the sulphonyl radical **305** (X=SO_2), the extent of 6-*endo*- versus 5-*exo*-ring closure was enormously enhanced and the ratio of the 5-*exo* to 6-*endo* (**307/308**) product was 1:37. Very little acyclic reduced species **306** (X=SO_2) was detected. The high regioselectivity in the case of the radical ring closure of the sulphone **305** (X=SO_2) is a combination of two predominant factors, the steric effect and the frontier molecular orbital interaction (Scheme 75).

Recently, we have described[190] a simple convergent synthesis of the *cis*-benzothiopyrano[3,2-*c*]benzopyran-7(2*H*)-ones **310a-f** (70–75%) through the implementation of a regioselective 6-*endo-trig* aryl radical cyclisation of the respective 4-(2′-bromobenzyl)thiobenzopyran-7-ones **309a-f** with tributyltin hydride in the presence of a radical initiator (AIBN) (Scheme 76).

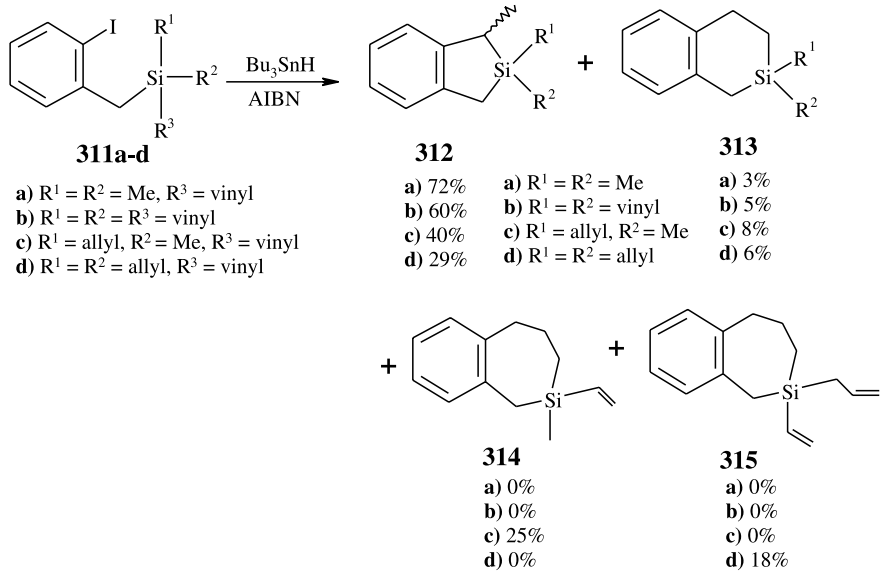
6. Synthesis of silicon-containing heterocycles

The intramolecular free-radical mediated formation of C–C bonds has been studied for a long time and is one of the most important methods for the synthesis of carbocyclic compounds.[123a] Tributyltin radical-induced intramolecular radical reactions of *ortho*-substituted phenyl halides have



a) $R^1 = R^2 = R^3 = H$, R^4 = OMe (75%)
b) $R^1 = R^2 = R^3 = R^4 = H$ (72%)
c) $R^1 = H$, R^2 = Me, $R^3 = H$, R^4 = OMe (72%)
d) $R^1 = H$, R^2 = Me, $R^3 = R^4 = H$ (70%)
e) R^1 = Me, $R^2 = H$, R^3 = Me, R^4 = OMe (74%)
f) R^1 = Me, $R^2 = H$, R^3 = Me, $R^4 = H$ (70%)

Scheme 76.



Scheme 77.

been explored for the preparation of indanes, dihydroindoles, dihydrobenzofurans and tetrahydrobenzopyrans.[180,191–195] It was reported[196] that, when *o*-iodobenzyldimethylvinylsilane **311a** was treated with tributyltin hydride and AIBN, the siloles **312a** and **313a** were obtained in 72 and 3% yield, respectively, that is, the 5-*exo-trig* cyclised product was exclusive. A similar result was obtained in the cyclisation of compound **311b**. Treatment of the *o*-iodobenzylallylvinylmethylsilane **311c** under radical cyclisation conditions furnished the products **312c** (mixture of diastereomers) and **313c**, as well as **314** in 40, 8 and 25% isolated yield, respectively. In this case, the 7-*endo* cyclisation is competitive with the 5-*exo* cyclisation, while the 6-*endo* reaction seems to be rather slow. The compound **311d** under similar reaction conditions furnished the siloles **312d** and **313d** via a 5-*exo* and 6-*endo* cyclisation in 29 and 6% yield, respectively. In the case of **311d**, the compound **315d** was additionally formed in 18% yield via a 7-*endo* cyclisation. The results with **311c**,**d** are indicative of the fact that the vinyl group reacts in preference to the allyl group (Scheme 77).

7. Conclusions

As already stated, the literature on the synthesis of heterocycles by radical cyclisation is vast and it is beyond the scope of this review to include all aspects of the topic. Therefore, only the introduction, mechanism and recent representative examples have been included. The application of the radical cyclisation for the formation of the pyran and furan rings in heterocycles is incorporated. Mechanistic aspects of various radical cyclisation reactions have been studied in detail. In recent years, there has been a considerable study of the cyclisation of radicals on heterocyclic compounds, a reaction that had previously been ignored. Radical cyclisation reactions, however, still offer enormous challenges to synthetic organic chemists.

Acknowledgements

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Biographical sketch

Krishna C. Majumdar received his BSc (1966) and MSc (1968) degrees from the University of Calcutta and PhD from the university of Idaho, completing his doctoral thesis in 1972 as a teaching fellow under the direction of Professor B. S. Thyagarajan. He was then awarded a research associateship with professor Thyagarajan at the same University and in 1974 he moved to the University of Alberta as a postdoctoral fellow with Professor R. K. Brown. Next year he joined the group of Professor J. William Lown at the same University to study the mode of action of cancer antibiotics. After returning to India (1977) he was with the Birla Institute of Technology and Science as reader for a brief stint. He then moved to the University of Kalyani first as lecturer (1977) and then as reader (1984), professor (1995) and professor and Head (2003). He also served the Indian Institute of Technology (Kharagpur) for a short period as an associate professor (1990–91) and also North Eastern Hill University as a visiting professor (1996). His research interests centered around synthetic organic chemistry with more than 160 publications mainly based on [1,3], [1,5], [2,3], [3,3] and [3,4]-sigmatropic rearrangements of which Claisen rearrangement is specially notable. His recent research interests also include radical reactions and design and synthesis of liquid crystals. Under his guidance 26 students already received their PhD degrees. He is associated with the discovery of sulphoxide and amine oxide rearrangements for the synthesis of fused thiophenes and pyrroles. He has affiliation with a number of professional bodies. He has also authored a number of review articles and a book chapter. He is a recipient of the Chemical Research Society of India medal (2004).

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

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Daphniglaucins D–H, J, and K, new alkaloids from *Daphniphyllum glaucescens*

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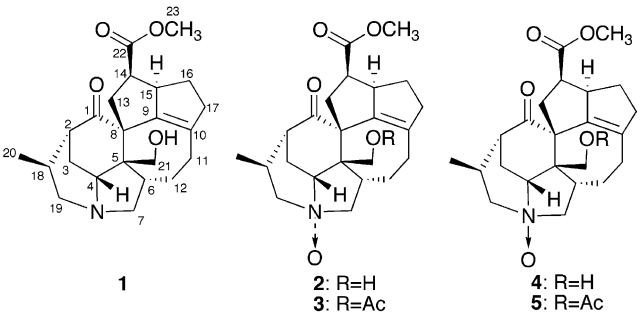
Abstract—Five new fused-hexacyclic alkaloids, daphniglaucins D (**1**), E (**2**), F (**3**), G (**4**), and H (**5**), and two new yuzurimine-type alkaloids, daphniglaucins J (**6**) and K (**7**), have been isolated from the leaves of *Daphniphyllum glaucescens*, and the structures and relative stereochemistry were elucidated on the basis of spectroscopic data and chemical means.

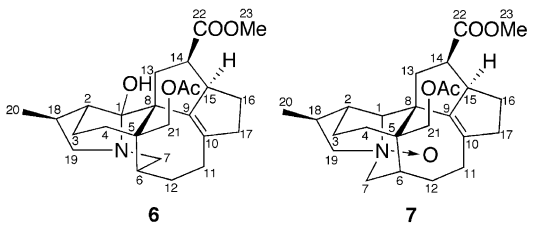
The *Daphniphyllum* alkaloids represent a series of structurally diverse alkaloids with unusual polycyclic skeletons obtained from *Daphniphyllum* species.[1,2] These ring systems have attracted great interest as challenging targets for total synthesis as well as biosynthetic studies.[3] Heathcock and co-workers have proposed a biogenetic pathway for *Daphniphyllum* alkaloids and demonstrated a biomimetic total synthesis of several *Daphniphyllum* alkaloids.[3,4]

Recently, we have isolated some novel types of *Daphniphyllum* alkaoids[5–13] such as daphnezomines A and B[5] with a unique aza-adamantane core and daphnezomines F and G[6] with an 1-azabicyclo[5.2.2]undecane ring system as well as daphnicyclidins A–H,[8] J, and K[9] with unique hexa- or pentacyclic ring system, daphmanidin A[10] with an unprecedented fused-hexacyclic skeleton from the leaves and stems of *D. teijismanni* and/or *D. humile*, daphniglaucin A[11] with a fused-heptacyclic skeleton and a quaternary nitrogen and daphniglaucin C[12] with a tetracyclic ring system consisting of an octahydroindole and a hexahydroazulene rings from the leaves of *D. glaucescens*, and calyciphyllines A and B[13] with a novel hexacyclic skeleton from the leaves of *D. calycinum*. In our continuing search for structurally unique and biogenetically interesting *Daphniphyllum* alkaloids from *D. glaucescens*, five new alkaloids with a fused-hexacyclic skeleton, daphniglaucins D–H (**1**–**5**), were isolated together with two new yuzurimine-type alkaloids, daphniglaucins J and K (**6** and **7**, respectively), from the leaves of *D. glaucescens*. This paper describes the isolation and structural elucidation of **1**–**7**.

1. Isolation of daphniglaucins D–H (1–5), J (6), and K (7)

The leaves of *D. glaucescens* were extracted with MeOH, and the extract was partitioned between EtOAc and 3% tartaric acid. Water-soluble materials, which were adjusted at pH 9 with sat. Na_2CO_3, were extracted with $CHCl_3$. $CHCl_3$-soluble materials were subjected to an amino silica gel column (hexane/EtOAc, 9:1→1:1 and then $CHCl_3$/MeOH, 1:0→0:1), from which a fraction eluted with $CHCl_3$/MeOH (7:3) was purified by C_{18} HPLC (30% CH_3CN/0.1%TFA) to afford daphniglaucins D (**1**, 0.002% yield), E (**2**, 0.002%), G (**4**, 0.002%), J (**6**, 0.002%), and K (**7**, 0.002%) together with a known alkaloid, macrodaphniphyllidine (0.003%).[14] A fraction eluted with $CHCl_3$/MeOH





Keywords: Alkaloid; *Daphniphyllum glaucescens*; Daphniglaucin.
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(4:1) in the amino silica gel column described above was purified by an LH-20 column [$CHCl_3$/MeOH (7:3)] and then a silica gel column [$CHCl_3$/MeOH (4:1)] followed by C_{18} HPLC (30% CH_3CN/0.1%TFA) to give daphniglaucins F (**3**, 0.002%) and H (**5**, 0.003%).

2. Structures of daphniglaucins D–H (1–5)

Daphniglaucin D (**1**) was shown to have the molecular formula of $C_{23}H_{31}NO_4$ by HRFABMS [*m/z* 386.2317, $(M+H)^+$, Δ −1.5 mmu]. IR absorptions implied the presence of hydroxyl, ester carbonyl and ketone (3410, 1735, and 1700 cm^{-1}, respectively) functionalities. ^{13}C NMR data (Table 2) revealed twenty-three carbon signals due to one tetrasubstituted olefin, two carbonyls, two sp^3 quaternary carbons, six sp^3 methines, nine sp^3 methylenes, one methyl, and one methoxy. Among them, two methylenes (δ_C 59.5; δ_H 2.92 and 3.52, δ_C 51.1; δ_H 3.07 and 3.24) and one methine (δ_C 65.4; δ_H 4.19) were ascribed to those bearing a nitrogen.

The $^1H-^1H$ COSY and HOHAHA spectra revealed connectivities of three partial structures **a** (C-2 to C-4, C-2 to C-18, and C-18 to C-19 and C-20), **b** (C-6 to C-7 and C-12, and C-11 to C-12), and **c** (C-13–C-17) as shown in Figure 1. HMBC correlations were observed for H-19b to C-7 (δ_C 59.5) and H-7b and H-19a to C-4 (δ_C 65.4), suggesting that C-4, C-7, and C-19 were connected to each other through a nitrogen atom. The connectivity of C-21 to C-4, C-6, and C-8 through C-5 was implied by HMBC correlations for H_2-21 to C-4, C-5 (δ_C 61.7), C-6 (δ_C 44.8), and C-8 (δ_C 56.8). HMBC cross-peaks for H_2-11 and H_2-17 to C-10 (δ_C 140.7) indicated connectivities of units **b** and **c** through C-10. The presence of a ketone at C-1 was suggested by the HMBC correlation for H-2 to C-1 (δ_C 214.5). The connectivity of C-1 and C-13 to C-9 through C-8 was implied by HMBC correlations for H_2-13 to C-1, C-8, and C-9 (δ_C 141.0). In addition, the HMBC correlation for H-15 to C-9 indicated the connectivity of C-9 to C-15. A methoxy group was attached to C-22 by HMBC correlations for H_3-23 and H-14 to C-22 (δ_C 176.4). Thus, the gross structure of daphniglaucin D was assigned as **1** having the same fused-hexacyclic ring system as that of calyciphylline A[13] as shown in Figure 1.

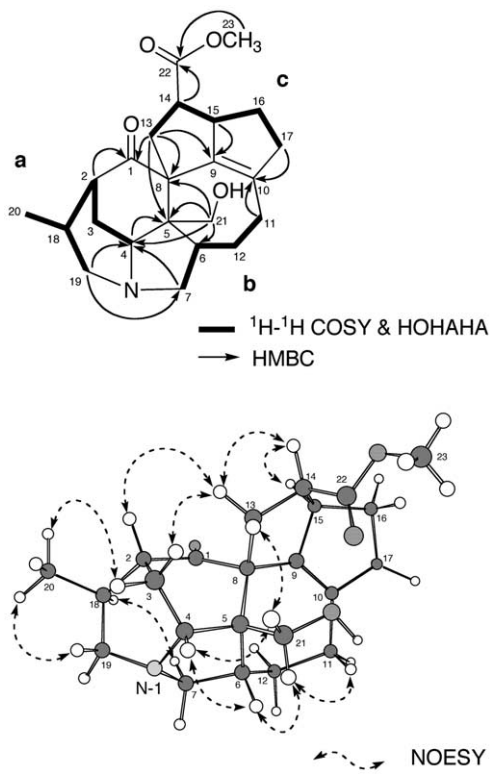


Figure 1. Selected 2D NMR correlations for daphniglaucin D (**1**).

The relative stereochemistry of **1** was deduced from NOESY correlations as shown in Figure 1. The NOESY correlation of H-3b/H-13a suggested that the cyclohexane ring (C-1∼C-5 and C-8) took a boat form. Conformational calculations of daphniglaucin D (**1**) by Monte Carlo simulation suggested that conformer **A** with outside direction of nitrogen lone pair was energetically more stable than conformer **B** with inside direction of nitrogen lone pair. A NOESY correlation of H-7a/H-18 also supports the stable conformer **A** (Fig. 2).

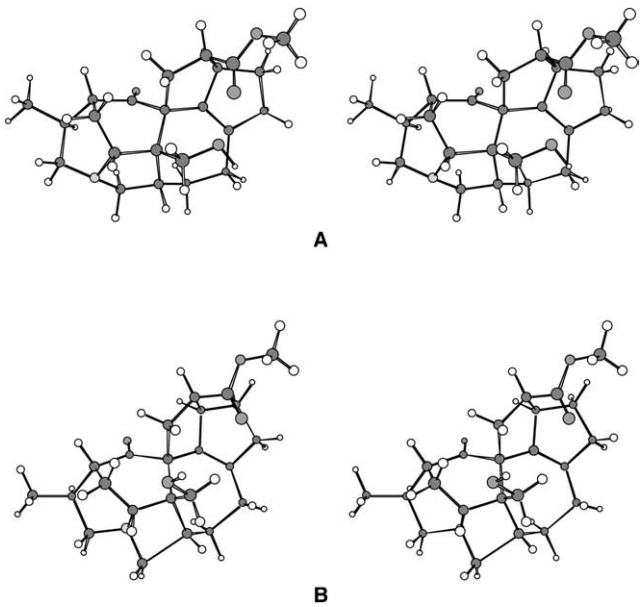


Figure 2. Stereoscopic view of two representative stable conformers (**A** and **B**) for daphniglaucin D (**1**) analyzed by Monte Carlo simulation followed by minimization and clustering analysis. Direction of nitrogen lone pair was different from each other.

Daphniglaucins E (**2**) and G (**4**) were shown to have the molecular formula of $C_{23}H_{31}NO_5$ by HRFABMS [**2**: *m/z* 402.2289, $(M+H)^+$, Δ +0.9 mmu; **4**: *m/z* 402.2225, $(M+H)^+$, Δ −5.5 mmu]. The NMR data of **2** and **4** were analogous to those of **1** except for the following observation: the chemical shifts of C-4 (δ_C **2**: 81.6, **4**: 80.7), C-7 (δ_C **2**: 77.3, **4**: 75.1), and C-19 (δ_C **2**: 67.1, **4**: 66.1) which resonated at lower field than those of carbons of **1** [δ_C 65.4 (C-4), 59.5 (C-7), and 51.1 (C-19)] bearing a nitrogen were observed.[15] Detailed 2D NMR analysis indicated that daphniglaucins E (**2**) and G (**4**) were the N-oxide forms of daphniglaucin D (**1**). The relative stereostructures of **2** and **4** were elucidated by NOESY cross-peaks as depicted in the computer-generated 3D drawing as shown in Figure 3. NOESY correlations of H-3α/H-19β and H-18/H-19α

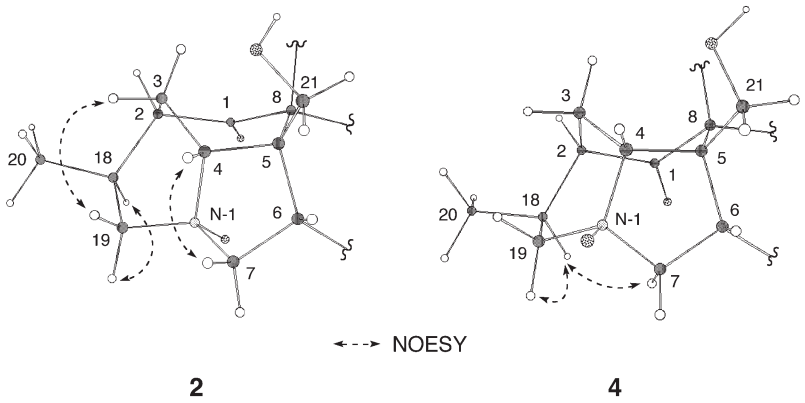


Figure 3. Selected NOESY correlations for parts of daphniglaucins E (**2**) and G (**4**).

indicated that piperidine ring in **2** (C-2–C-4, C-18–C-19, and N) took boat form. Whereas, a NOESY correlation of H-18/H-7α in **4** argued well for the conformation with outside direction of nitrogen lone pair like as that of daphniglaucin D (**1**).

Daphniglaucins F (**3**) and H (**5**) were shown to have the molecular formula of $C_{25}H_{33}NO_6$ by HRFABMS [**3**: *m/z* 444.2393, $(M+H)^+$, Δ +0.7 mmu; **5**: *m/z* 444.2373, $(M+H)^+$, Δ −1.3 mmu]. NMR data of **3** and **5** were analogous to those of **2** and **4**, respectively, except for the acetyl moiety (**3**: δ_H 2.14, δ_C, 20.9 and 172.5; **5**: δ_H 2.14, δ_C 20.8 and 172.2). Acetylation of daphniglaucins E (**2**) and G (**4**) afforded the mono acetates of **2** and **4**, respectively, whose spectral data and the $[\alpha]_D$ value were identical with those of natural daphniglaucins F (**3**) and H (**5**).

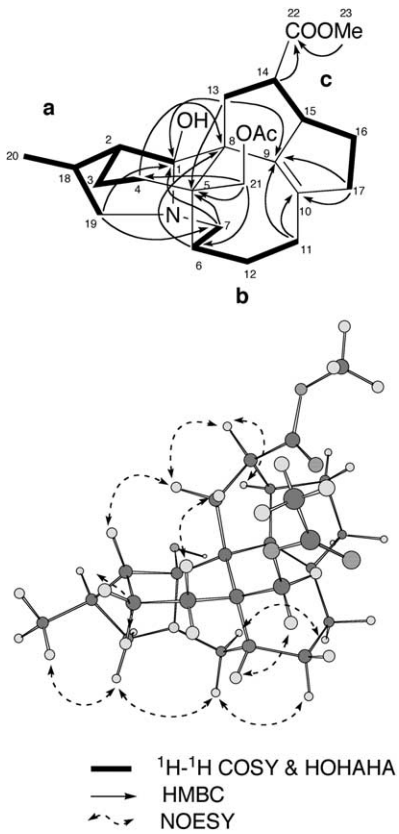
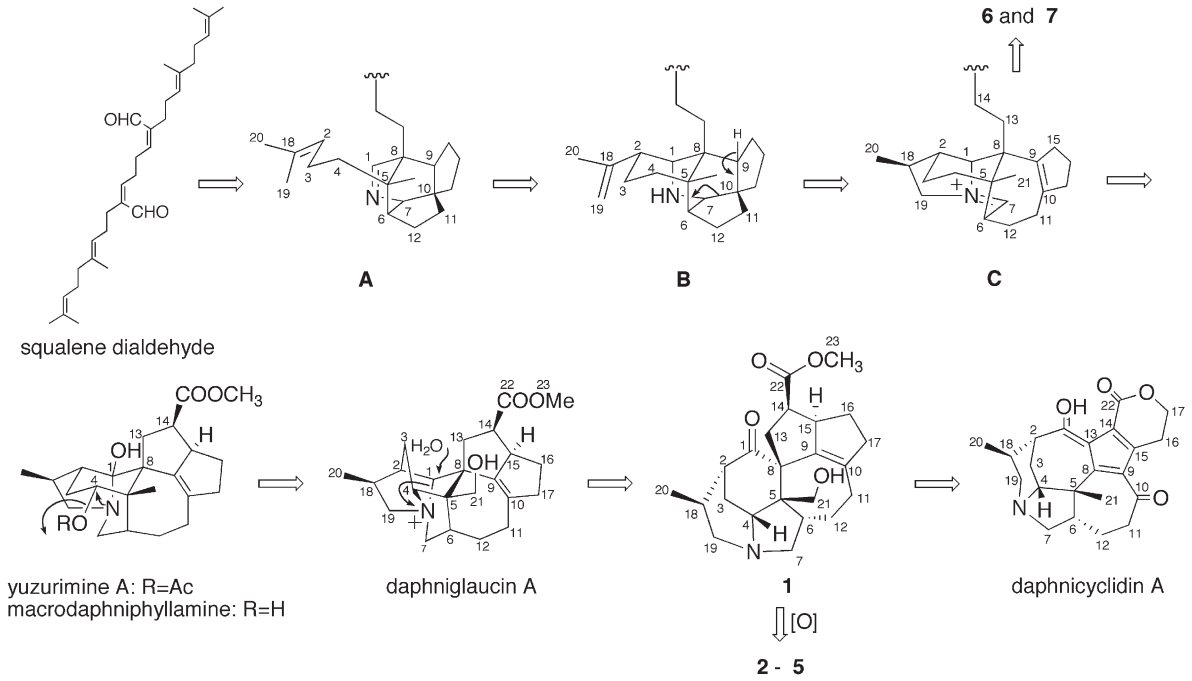


Figure 4. Selected 2D NMR correlations and relative configurations for daphniglaucin J (**6**).

3. Structures of daphniglaucins J (6) and K (7)

Daphniglaucin J (**6**) was shown to have the molecular formula of $C_{25}H_{35}NO_5$ by HRFABMS [*m/z* 430.2610, $(M+H)^+$, Δ +1.7 mmu]. IR absorptions implied the presence of hydroxyl and ester carbonyl (3400 and 1730 cm^{-1}, respectively) functionalities. The ^{13}C NMR spectra of **6** (Table 2) revealed signals due to 7 quaternary carbons (sp^2×4 and sp^3×3), 5 methines (sp^3), 10 methylenes, and 3 methyls, suggesting that **6** had a similar backbone skeleton to that of macrodaphniphyllidine.[14] The structure of **6** was elucidated by 2D NMR (^{1}H–^{1}H COSY, HOHAHA, HMQC, and HMBC) data (Fig. 4). The ^{1}H–^{1}H COSY and HOHAHA spectra revealed connectivities of C-1 to C-4, C-2 to C-18, C-18 to C-20 (unit **a**), C-6 to C-7, C-6 to C-12, and C-11 to C-12 (unit **b**), and C-13 to C-17 (unit **c**). These three partial units were connected on the basis of HMBC correlations and the relative stereochemistry was deduced from NOESY correlations. The conformation of the piperidine ring (N-1, C-1, C-8, and C-5–C-7) in the 2-azabicyclo[3.3.1]nonane moiety was assigned as boat form from NOESY correlations (Fig. 4). Thus, daphniglaucin J (**6**) was assigned to be 1-hydroxy form of macrodaphniphyllidine.

HRFABMS data [*m/z* 430.2610, $(M+H)^+$, Δ +1.7 mmu] of daphniglaucin K (**7**) indicated the molecular formula, $C_{25}H_{35}NO_5$, which was larger than that of macrodaphniphyllidine[14] by one oxygen unit. Detailed analyses of the 2D NMR (^{1}H–^{1}H COSY, HOHAHA, HMQC, and HMBC) spectra of **7** and comparison of the ^{13}C chemical shifts of C-1, C-7, and C-19 (δ 79.3, 69.7, and 83.8, respectively) in **7** with those of macrodaphniphyllidine indicated the presence of an N-oxide functionality for **7**. Oxidation of macrodaphniphyllidine with *m*-chloroperbenzoic acid (*m*-CPBA) afforded the N-oxide derivative, whose spectral data and the $[\alpha]_D$ value were identical with those of natural daphniglaucin K (**7**). The stereochemistry of the N-oxide was assigned as *R* from a NOESY correlation between H-3 and H-7. Thus, daphniglaucin K (**7**) was concluded to be the N-oxide of macrodaphniphyllidine.



Scheme 1. Plausible biogenetic path of daphniglaucins D–H (**1**–**5**).

4. Plausible biogenesis of daphniglaucins D–H (1–5)

A plausible biogenetic pathway for daphniglaucins D–H (**1**–**5**) is proposed as shown in Scheme 1. The biogenetic origin of daphniglaucin D (**1**) seems to be yuzurimine-type alkaloids such as yuzurimine A[16] and macrodaphniphyllamine[14] with an appropriate leaving group at C-4. Cleavage of C-1–N-1 bond of daphniglaucin A, which might be produced by loss of the leaving group at C-4 by attack of the nitrogen to form the N-1–C-4 bond, will give the skeleton of daphniglaucin D (**1**).

5. Experimental

5.1. General methods

^{1}H and ^{13}C NMR spectra were recorded on 600 MHz spectrometer equipped with an X32 computer and an Eurotherm temperature control unit. The NMR samples of daphniglaucins D–H (**1**–**5**), J (**6**) and K (**7**) were prepared by dissolving 1.5 mg in 30 μL of CD_3OD in 2.5 mm micro cells (Shigemi Co. Ltd.) and chemical shifts were reported using residual CD_3OD (δ_H 3.31 and δ_C 49.0) as internal standards. 1D NMR spectra were measured at 300 K with 16 K data points, which were multiplied by a Gaussian filter and zero filled to 32 K data points before Fourier transformation. Standard pulse sequences were employed for the 2D NMR experiments. COSY, HOHAHA, and NOESY spectra were measured with spectral widths of both dimensions of 4800 Hz, and 32 scans with two dummy scans were accumulated into 1 K data points for each of 256 t_1 increments. NOESY and HOHAHA spectra in the phase sensitive mode were measured with a mixing time of 800 and 30 ms, respectively. For HMQC spectra in the phase sensitive mode and HMBC spectra, a total of 256 increments of 1 K data points were collected. For HMBC spectra with *Z*-axis PFG, a 50 ms delay time was used for long-range C–H coupling. Zero-filling to 1 K for F_1 and multiplication with squared cosine-bell windows shifted in both dimensions were performed prior to 2D Fourier transformation. FABMS was measured by using glycerol as a matrix.

5.2. Material

The stems of *D. glaucescens* Blume (Daphniphyllaceae) were collected at Hen-Chung, Ping-tong, Taiwan in 2002. The botanical identification was made by Ya-Ching Shen, National Sun Yat-Sen University. Voucher specimens (no. 020412) have been deposited in the herbarium of Hokkaido University.

5.3. Extraction and isolation

The leaves of *D. glaucescens*(1.65 kg) were extracted with MeOH, and the extract (555 g) was partitioned between EtOAc and 3% tartaric acid. Water-soluble materials, which were adjusted at pH 9 with sat. Na_2CO_3, were extracted with $CHCl_3$. A part (4.6 g) of the $CHCl_3$-soluble materials (9.6 g) was subjected to an amino silica gel column (hexane/EtOAc, 9:1→1:1 and then $CHCl_3$/MeOH, 1:0→0:1), from which a fraction eluted with $CHCl_3$/MeOH (7:3) was purified by C_{18} HPLC (30% CH_3CN/0.1%TFA) to afford daphniglaucins D (**1**, 0.002% yield), E (**2**, 0.002%), G (**4**, 0.002%), J (**6**, 0.002%), and K (**7**, 0.002%) together with a known alkaloid, macrodaphniphyllidine (0.003%).[14] A fraction eluted with $CHCl_3$/MeOH (4:1) in the amino silica gel column was purified by an LH-20 column [$CHCl_3$/MeOH (7:3)] and then a silica gel column [$CHCl_3$/MeOH (4:1)] followed by C_{18} HPLC (30% CH_3CN/0.1%TFA) to give daphniglaucins F (**3**, 0.002%) and H (**5**, 0.003%).

5.3.1. Daphniglaucin D (1). Colorless solid; $[\alpha]_D^{24}=-21°$

(c 0.5, CH_3OH); IR (neat) ν_{max} 3410, 2930, 1735, 1700, 1205, and 1130 cm^{-1}; ^1H and ^{13}C NMR data (Tables 1 and 2, respectively); FABMS m/z 386 $(M+H)^+$; HRFABMS m/z 386.2317 (M+H; calcd for $C_{23}H_{32}NO_4$, 386.2332).

5.3.2. Daphniglaucin E (2). Colorless solid; $[\alpha]_D^{24}=-23°$ (c 0.7, CH_3OH); IR (neat) ν_{max} 3410, 2930, 1730, 1650, 1455, 1380, and 1200 cm^{-1}; ^1H and ^{13}C NMR data (Tables 1 and 2, respectively); FABMS m/z 402 $(M+H)^+$; HRFABMS m/z 402.2289 (M+H; calcd for $C_{23}H_{32}NO_5$, 402.2280).

5.3.3. Daphniglaucin F (3). Colorless solid; $[\alpha]_D^{24}=-18°$ (c 0.2, CH_3OH); IR (neat) ν_{max} 3422, 2952, 1730, 1650, 1455, 1380, and 1200 cm^{-1}; ^1H and ^{13}C NMR data (Tables 1 and 2, respectively); FABMS m/z 444 $(M+H)^+$; HRFABMS m/z 444.2393 (M+H; calcd for $C_{25}H_{34}NO_6$, 444.2386).

5.3.4. Daphniglaucin G (4). Colorless solid; $[\alpha]_D^{24}=-40°$ (c 0.5, CH_3OH); IR (neat) ν_{max} 3390, 2930, 1730, 1680, 1205, and 1140 cm^{-1}; ^1H and ^{13}C NMR data (Tables 1 and 2, respectively); FABMS m/z 402 $(M+H)^+$; HRFABMS m/z 402.2225 (M+H; calcd for $C_{23}H_{32}NO_5$, 402.2280).

5.3.5. Daphniglaucin H (5). Colorless solid; $[\alpha]_D^{24}=-11°$ (c 0.2, CH_3OH); IR (neat) ν_{max} 3383, 2926, 1732, 1709, 1455,

Table 2. ^{13}C NMR data (δ_C) of daphniglaucins D–H, J, and K (**1**–**7**) in CD_3OD at 300 K

Carbon	1	2	3	4	5	6	7
1	214.5	214.8	214.2	213.4	212.6	101.7	79.3
2	43.8	44.1	43.7	43.4	43.0	43.5	37.3
3	19.4	18.4	18.7	18.3	18.7	22.1	20.2
4	65.4	81.6	82.4	80.7	81.2	32.7	32.7
5	61.7	61.2	61.2	61.0	60.9	51.3	44.3
6	44.8	45.2	45.9	44.8	45.6	37.9	39.5
7	59.5	77.3	76.4	75.1	73.9	58.3	69.7
8	56.8	56.3	55.0	56.3	55.4	43.6	38.6
9	141.0	141.5	141.1	141.1	140.6	143.6	141.0
10	140.7	139.9	140.4	140.1	140.6	138.2	137.8
11	27.8	30.0	29.3	29.6	29.0	25.3	26.7
12	30.3	31.5	31.0	31.1	30.7	28.4	28.1
13	40.5	41.0	41.5	40.9	41.5	39.0	40.8
14	42.9	42.7	42.9	42.8	43.1	44.4	43.7
15	55.1	55.4	55.3	55.5	55.0	59.5	55.3
16	27.9	28.1	27.9	27.9	27.6	29.9	28.2
17	42.0	41.7	41.7	41.7	41.8	44.4	43.6
18	30.6	33.2	33.2	32.6	32.5	34.0	33.8
19	51.1	67.1	67.4	66.1	66.0	64.1	83.8
20	18.5	18.9	19.0	18.4	18.4	14.2	12.9
21	64.1	66.7	69.5	65.4	68.5	69.9	73.4
22	176.4	176.8	176.0	176.5	175.9	176.8	176.4
23	51.9	51.9	52.0	51.9	52.0	51.8	51.8
24			172.5		172.2	172.7	172.7
25			20.9		20.8	20.8	20.8

Table 1. ^1H NMR data (δ_H) of daphniglaucins D–H, J, and K (**1**–**7**) in CD_3OD at 300 K

Proton	1	2	3	4	5	6	7
1							3.93 (1H, d, 4.3)
2	2.61 (1H, brs)	2.58 (1H, brs)	2.06 (1H, m)	2.70 (1H, brs)	2.76 (1H, m)	2.48 (1H, m)	2.79 (1H, m)
3a	2.47 (1H, m)	2.61 (1H, dd, 3.4, 15.9)	2.62 (1H, dd, 3.5, 15.9)	2.46 (1H, brd, 16.2)	2.55 (1H, m)	1.88 (1H, m)	1.74 (2H, m)
3b	2.30 (1H, dd, 3.5, 15.9)	2.30 (1H, m)	2.34 (1H, dd, 3.5, 17.7)	2.62 (1H, dd, 3.8, 16.2)	2.62 (1H, m)	1.80 (1H, m)	
4a	4.19 (1H, brs)	4.02 (1H, brs)	3.97 (1H, brd, 2.3)	4.40 (1H, brs)	4.42 (1H, m)	2.02 (1H, m)	1.75 (1H, m)
4b						1.77 (1H, m)	2.03 (1H, m)
6	2.94 (1H, m)	3.00 (1H, m)	2.92 (1H, m)	3.13 (1H, m)	3.03 (1H, m)	2.44 (1H, m)	2.52 (1H, m)
7a	2.92 (1H, m)	3.33 (1H, m)	3.35 (1H, dd, 6.7, 12.3)	3.58 (1H, dd, 5.7, 12.2)	3.64 (1H, m)	3.66 (1H, m)	4.42 (1H, s)
7b	3.52 (1H, m)	3.49 (1H, dd, 9.4, 11.9)	3.45 (1H, dd, 8.6, 12.3)	3.81 (1H, m)	3.90 (1H, dd, 8.8, 12.7)	3.80 (1H, m)	4.44 (1H, m)
11a	2.09 (2H, m)	2.09 (2H, m)	2.10 (2H, m)	2.12 (2H, m)	2.14 (2H, m)	2.22 (1H, dd, 4.9, 17.5)	2.23 (1H, m)
11b						2.46 (1H, m)	2.33 (1H, m)
12a	1.76 (1H, m)	1.78 (2H, m)	1.80 (2H, m)	1.82 (2H, m)	1.85 (2H, m)	1.58 (1H, m)	1.66 (1H, m)
12b	1.91 (1H, m)					1.97 (1H, m)	2.01 (1H, m)
13a	2.38 (1H, dd, 8.8, 14.9)	2.37 (1H, dd, 8.7, 14.9)	2.44 (1H, m)	2.40 (1H, dd, 8.7, 14.8)	2.47 (1H, m)	2.36 (1H, dd, 9.6, 15.3)	2.19 (1H, m)
13b	2.99 (1H, dd, 4.7, 14.6)	3.05 (1H, dd, 4.7, 14.9)	3.01 (1H, dd, 4.8, 14.9)	3.03 (1H, dd, 4.5, 15.0)	3.03 (1H, dd, 4.2, 14.9)	2.77 (1H, dd, 3.2, 15.3)	2.75 (1H, dd, 3.4, 15.3)
14	2.85 (1H, m)	2.85 (1H, m)	2.85 (1H, m)	2.86 (1H, m)	2.88 (1H, m)	3.01 (dt, 3.1, 10.2)	3.00 (1H, dt, 3.4, 6.2)
15	3.42 (1H, m)	3.45 (1H, m)	3.44 (1H, m)	3.44 (1H, m)	3.44 (1H, m)	3.85 (1H, m)	3.60 (1H, m)
16a	1.97 (1H, m)	1.93 (1H, m)	1.95 (1H, m)	1.94 (1H, m)	1.96 (1H, m)	1.83 (1H, m)	1.34 (1H, m)
16b	1.32 (1H, m)	1.33 (1H, m)	1.34 (1H, m)	1.32 (1H, m)	1.37 (1H, m)	1.29 (1H, m)	1.93 (1H, m)
17a	2.67 (1H, m)	2.63 (1H, m)	2.66 (1H, m)	2.64 (1H, m)	2.66 (1H, m)	2.42 (1H, m)	2.43 (1H, m)
17b	2.44 (1H, m)	2.43 (1H, m)	2.43 (1H, m)	2.43 (1H, m)	2.57 (1H, m)	2.73 (1H, m)	2.50 (1H, m)
18	2.69 (1H, m)	2.51 (1H, m)	2.52 (1H, m)	2.66 (1H, m)	2.67 (1H, m)	3.11 (1H, m)	2.92 (1H, m)
19a	3.24 (1H, dd, 6.8, 13.9)	3.58 (1H, dd, 6.1, 13.9)	3.59 (1H, dd, 6.3, 13.9)	3.75 (1H, dd, 6.1, 14.4)	3.80 (1H, dd, 6.4, 14.2)	4.09 (1H, t, 11.7)	4.04 (1H, m)
19b	3.07 (1H, dd, 7.7, 13.8)	3.18 (1H, dd, 3.9, 13.8)	3.16 (1H, dd, 5.3, 13.9)	3.51 (1H, dd, 3.9, 13.8)	3.56 (1H, dd, 5.2, 14.2)	2.88 (1H, dd, 6.5, 12.2)	4.20 (1H, t, 11.9)
20	1.19 (3H, d, 6.9)	1.36 (3H, d, 7.1)	1.34 (3H, d, 7.1)	1.34 (3H, d, 7.1)	1.33 (3H, d, 7.1)	1.20 (3H, d, 7.3)	1.09 (3H, d, 6.9)
21	3.81 (1H, d, 11.4)	3.80 (1H, d, 11.2)	4.56 (1H, d, 11.5)	3.82 (1H, d, 11.2)	4.43 (1H, d, 11.6)	4.41 (1H, d, 11.9)	4.02 (1H, m)
	4.00 (1H, d, 11.4)	3.94 (1H, d, 11.2)	4.36 (1H, d, 11.5)	4.00 (1H, d, 11.1)	4.59 (1H, d, 11.6)	4.44 (1H, d, 12.0)	4.46 (1H, m)
23	3.65 (3H, s)	3.65 (3H, s)	3.66 (3H, s)	3.65 (3H, s)	3.67 (3H, s)	3.68 (3H, s)	3.70 (3H, s)
25			2.14 (3H, s)		2.14 (3H, s)	2.06 (3H, s)	2.07 (3H, s)

1373, and 1237 cm^{-1}; ^1H and ^{13}C NMR data (Tables 1 and 2, respectively); FABMS *m/z* 444 $(M+H)^+$; HRFABMS *m/z* 444.2373 (M+H; calcd for $C_{25}H_{34}NO_6$, 444.2386).

5.3.6. Daphniglaucin J (6). Colorless solid; $[\alpha]_D^{24}=-17°$ (*c* 0.4, CH_3OH); IR (neat) ν_{max} 3400, 2950, 1730, 1690, 1240, 1200, 1175, 1130, and 755 cm^{-1}; ^1H and ^{13}C NMR data (Tables 1 and 2, respectively); FABMS *m/z* 430 $(M+H)^+$; HRFABMS *m/z* 430.2610 (M+H; calcd for $C_{25}H_{36}NO_5$, 430.2593).

5.3.7. Daphniglaucin K (7). Colorless solid; $[\alpha]_D^{24}=-13°$ (*c* 0.7, CH_3OH); IR (neat) ν_{max} 2950, 1730, 1685, 1435, 1240, 1200, 1175, 1130, and 755 cm^{-1}; ^1H and ^{13}C NMR data (Tables 1 and 2, respectively); FABMS *m/z* 430 $(M+H)^+$; HRFABMS *m/z* 430.2610 (M+H; calcd for $C_{25}H_{36}NO_5$, 430.2594).

5.4. Computational methods

Conformational searching for daphniglaucin D (**1**) was carried out using Pseudo Monte Carlo simulation in Macromodel program (v6.0).[17] Each conformer was finally minimized by molecular mechanics calculation of MMFF force field.[18] Three thousand Monte Carlo steps were performed, yielding 77 unique conformations in the energy region of 0–10 kcal/mol and the lowest energy conformers belonging to two separate clusters were represented as **A** (90.22 kcal/mol) and **B** (98.21 kcal/mol) (Fig. 2), whose direction of nitrogen lone pair was different from each other.

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Rapid syntheses of oligo(*p*-phenyleneethynylene)s via iterative convergent approach

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Abstract—A general and controlled bidirectional growth strategy enable a very rapid and efficient construction of oligo(phenyleneethynylene)s possessing functional groups such as methylthio and thioacetate groups at both ends. The strategy employs only one reaction type with good to moderate yields to grow the conjugated chains. The synthesis is efficient and can give 23 benzene rings and 22 carbon–carbon triple bonds in the conjugated chains. The compounds are fully characterized by ^{1}H and ^{13}C NMR and UV/vis and fluorescence spectroscopy.

1. Introduction

Recently, conjugated oligomers of precise length have drawn much attention due to their interesting optical, electrical, optoelectronic properties, and their applications in optoelectronic devices such as molecular wires, molecular-scale electronic devices, solar cells, light-emitting diodes, and field-effect transistors.[1–13] Furthermore, since the oligomers of the repeating unit of a polymer are often useful in understanding the properties of a polymer system, this is due to the close analogy of their physical properties, as well as the ease of characterization of the oligomeric system. These compounds can be served as models for analogous polymers and they can also be used for the construction of nanoarchitectures such as molecular wires in molecular scale electronic devices.[1] The precise length and well-defined conjugated oligomers can play an important role because their precise chemical structure and conjugation length may lead to define functionality and facilitate control over their supramolecular structures in the preparation of organic thin films.[14] As to our knowledge, Tour and his co-workers have reported the synthesis of the longest OPE containing 16 benzene rings and 16 carbon–carbon triple bonds so far.[15] Recently, we have reported a very rapid and efficient construction of oligo(*p*-phenylenevinylene)s (OPV) compounds with precise length and possessing functional groups such as aldehyde and mercapto groups at both ends.[16] That strategy employed only one reaction type with high yields and stereoselectivities to grow the conjugated chains. In this paper, we report the similar rapid synthesis of oligo(*p*-phenyleneethynylene)s (OPE) derivatives with thiomethyl (SMe) or thioacetyl (SAc) end groups from the repeating one building block molecule with three benzene rings and four carbon–carbon triple bonds and a series of Sonogashira and desilylation reactions to build one OPE with 23 benzene rings and 22 triple bonds in its conjugation system. Similar oligomer with 23 aromatic rings and 22 carbon–carbon triple bonds in its conjugation system has been reported by Tour and his co-worker.[17]

2. Results and discussion

Our strategy in synthesizing the OPEs was shown in Scheme 1. The key to the overall strategy is the synthesis of building block molecule **1** with three benzene rings and three carbon–carbon triple bonds. In order to control the growth of the OPE chain, it is necessary to effectively block one terminus of the growing OPE chain which was successfully accomplished with monomer **1**. Thus, monomer **1** possesses an iodo group at one end and a trimethylsilylacetylenyl group at the other end. The iodo terminus of monomer **1** can couple with the terminal acetylenes under the Sonogashira reaction condition while the other terminal trimethylsilylacetylenyl group of monomer **1** can be tolerated under this reaction condition. Therefore, 2 equiv. of monomer **1** can couple with 1 equiv. of compound **2** under the Sonogashira reaction conditions and give oligomer **3** in 59% yield. The following desilylation under basic condition afford oligomer **4** in

Keywords: Oligo(phenyleneethynylene)s; OPEs; Sonogashira reaction; Desilylation.
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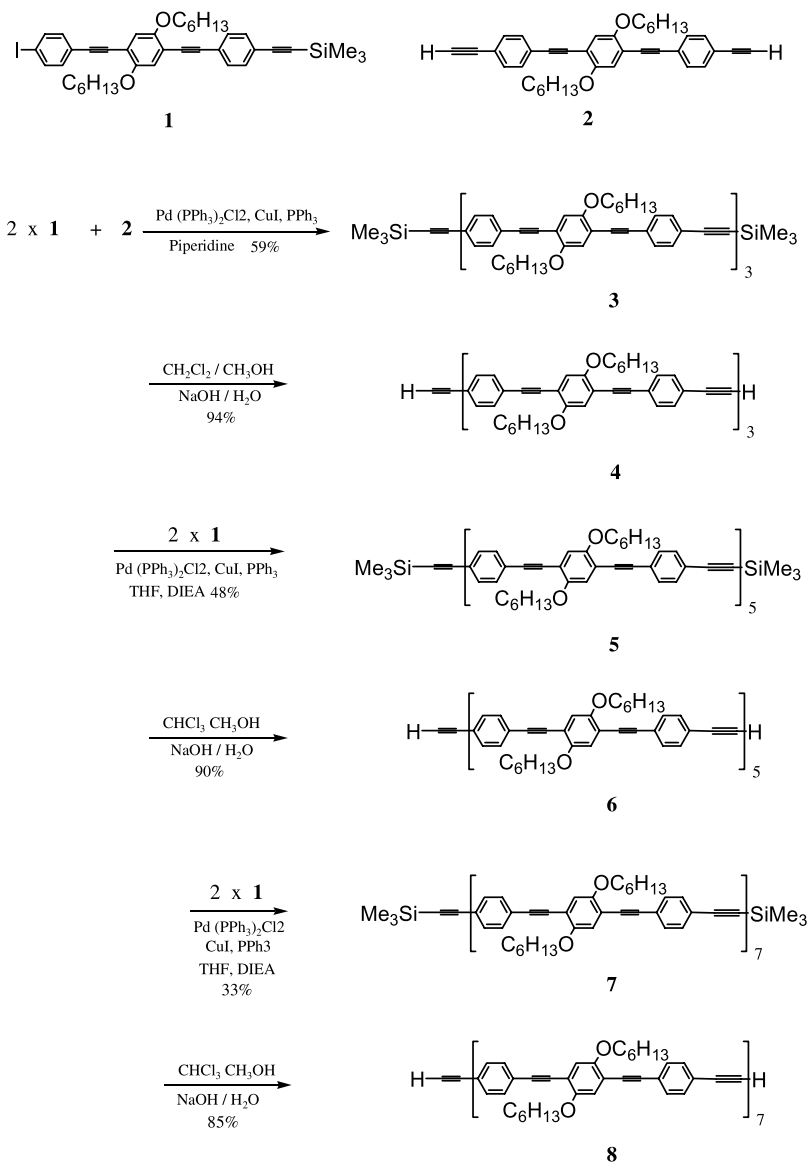
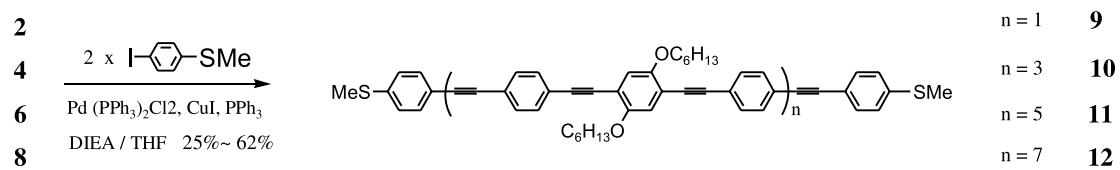


Scheme 1. Iterative coupling reaction for the synthesis of OPEs.

94% yield. Similar coupling of 1 equiv. of oligomer **4** with 3 equiv. of monomer **1** under Sonogashira reaction conditions and followed by basic desilylation successfully afford oligomer **5** and **6**, in 48 and 90% yields, respectively. Iterative coupling of 1 equiv. of oligomer **6** with 2 equiv. of monomer **1** under Sonogashira reaction conditions and followed by basic desilylation can give oligomer **7** and **8**, in 33 and 85% yields, respectively. Accordingly, the growth of OPE chain commences with compound **2** and thereafter monomer **1** is added in a repetitive stepwise fashion to add six benzene rings and six carbon–carbon triple bonds at one time. The process could be repeated to quickly build up longer OPE molecules possessing terminal acetylene groups as the functionalized termini. Oligomers **2**, **4**, **6**, and **8** with two terminal acetylene groups at the termini can further undergo Sonogashira reaction with 2 equiv. of 1-iodo-4-methylthiobenzene to form **9**–**12** in 62, 52, 31, and 24% yields, respectively (Scheme 2). It is needed to know that the introduction of masked thiol (mercapto) end-groups at the terminal positions of the oligomers can serve as an anchor groups for attachment to the gold electrode surface.[18,19] The single crystal X-ray analysis of oligomer **9** shows that the distance between the two sulfur atoms is 33.635 Å (Fig. 1).[20] In addition, when oligomers **2** and **4** were treated with 2 equiv. of *p*-iodophenylthioacetate under the Sonogashira reaction conditions, oligomers **13** and **14**



Scheme 2. Preparation of OPEs with methylsulfide as the terminal groups.

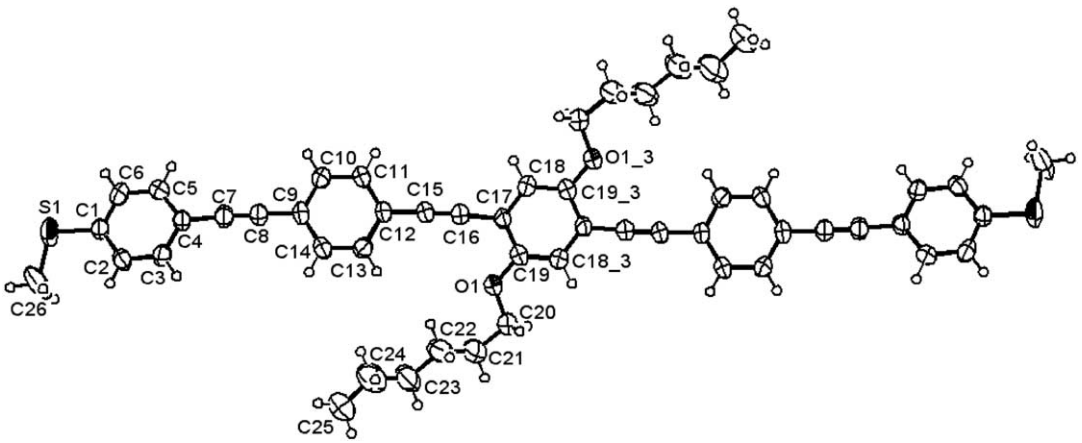
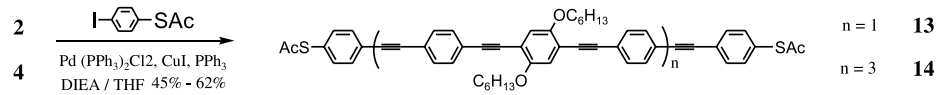
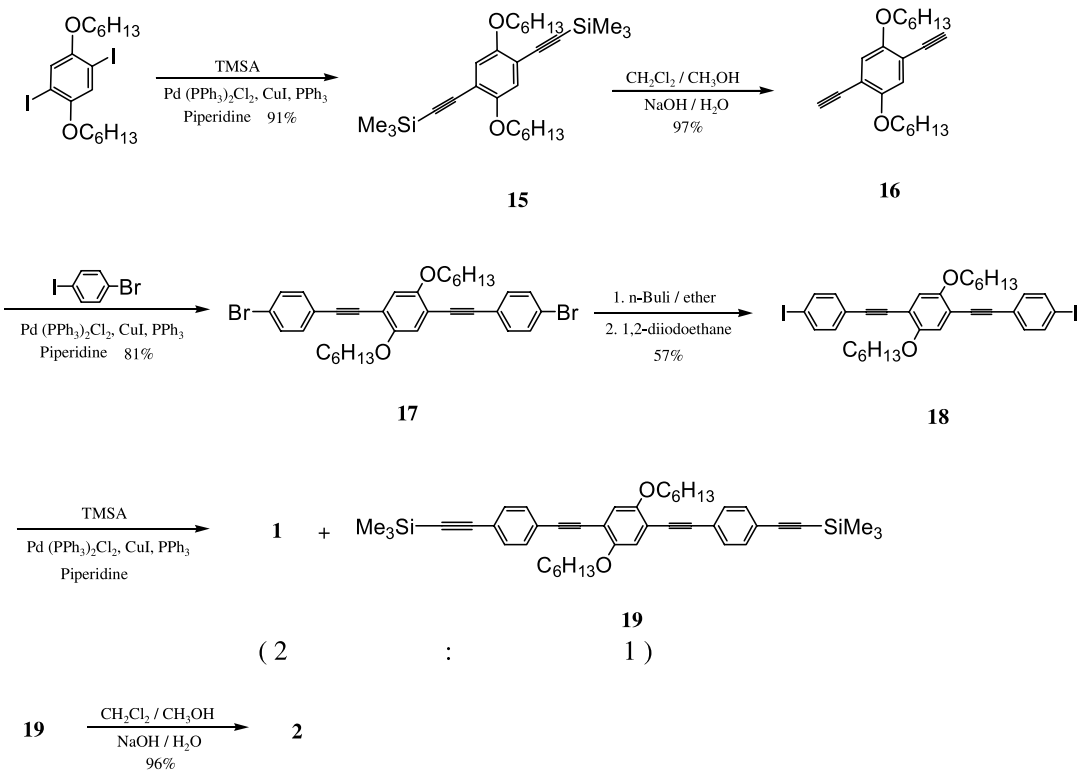


Figure 1. X-ray of compound **9**.

could be isolated in 52 and 45% yields, respectively (Scheme 3). The lower yields for the preparation of longer OPEs may due to their lower solubilities under the reaction conditions and some unknown by-products with lower R_f values on thin layer chromatography analysis using a mixture of hexane and chloroform as the mobile phase. The transformation of the terminal methylsulfide groups on **9** to the two terminal mercapto groups in good yield (>90% yield) can be done by treating **9** with 5 equiv. of sodium 2-methyl-2-propanethiolate in very dry DMF.[21] Reduced solubility of the longer oligomers poses a problem in the purification of these compounds, but analytically pure samples could be obtained through careful flash column chromatography using mixtures of chloroform and hexane as the mobile phase. Yields for each of the steps are fair to moderate with decreased solubility of the longer OPEs limiting the yields somewhat. Presently, we have succeeded in the synthesis and purification of oligomer **12**, which has 23 benzene rings and 22 triple bonds in its conjugation pathway, and a molecular weight of 3775.2238. Our success



Scheme 3. Preparation of OPEs with thioacetate as the terminal groups.



Scheme 4. Synthesis of building block molecules **1** and **2**.

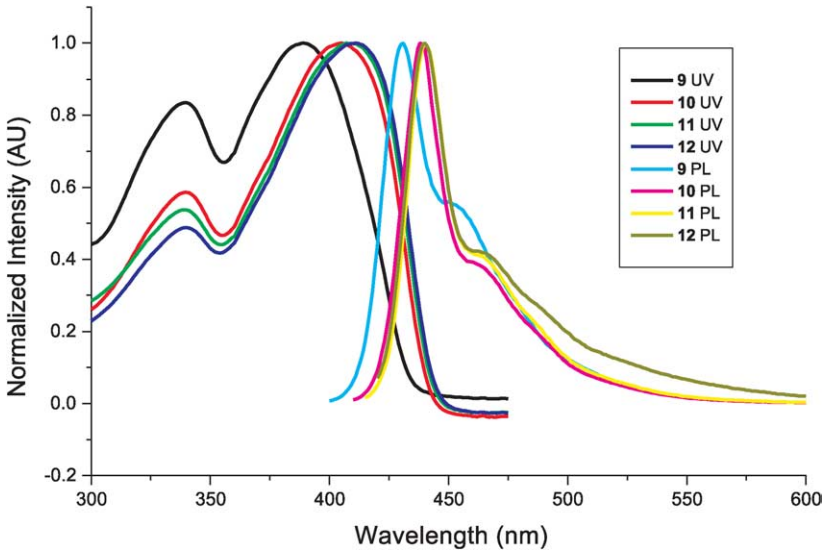


Figure 2. UV and Em of OPE oligomers **9** (5.32×10^{-6} M), **10** (4.06×10^{-6} M), **11** (3.33×10^{-6} M), and **12** (2.04×10^{-6} M) in $CHCl_3$ at 25 °C.

of preparing such a longer OPE may be due to its better solubility in the reaction solvents than most reported OPEs in their reaction solvents. The presence of the 2,5-alkoxyl groups in every three benzene rings of these OPEs may also increase their solubilities in the reaction solvents.[16] Synthesis of longer oligomers is still in progress. All of the spectroscopic studies and elemental analysis results are consistent with the proposed molecular structures.

The strategy in synthesizing the building block molecules for OPEs was shown in Scheme 4. Thus, 1,4-diiodo-2,5-dihexyloxybenzene[22] was reacted with 2 equiv. of trimethylsilylacetylene under Sonogashira reaction conditions could afford compound **15** (91% yield), which was desilylated under basic reaction conditions to give compound **16** in 97% yield. Dibromo compound **17** was prepared in 81% yield by Sonogashira coupling reaction from 1 equiv. of compound **16** and 2 equiv. of 4-bromo-1-iodobenzene in highly regioselective manner. Lithium-halogen exchange reaction followed by iodination with 1,2-diiodoethane could give diiodo compound **18** in 57% yield. Sonogashira reaction of 1 equiv. of diiodo compound **18** with 1 equiv. of trimethylsilylacetylene could afford compound **1** and compound **19** in 52 and 24% yields, respectively. The two products could be separated from the reaction mixture by flash column chromatography using a mixture of hexane and ethyl acetate as the mobile phase. An alternative approach and high yield (>93%) to the rapid synthesis of OPE molecule **19** is to react 2.2 equiv. of trimethylsilylethynyl with 1 equiv. of diiodo compound **18** under the Sonogashira reaction conditions.

The absorption and emission spectra for the series of OPEs that possess the methylthio end groups are shown in Figure 2. All of the oligomers show strong and broad absorption in the visible region. Elongation of the conjugation length from oligomer **9** to oligomer **10** results in a red shift of 16 nm (Table 1). However, only little red shift is noticed after the conjugation length reaches 11 benzene rings and 10 triple bonds. The saturation in λ_{max} has been observed previously and arises because of the limitations to electron delocalization in the longer oligomers.[23] Thus, the effective conjugation length in this series of oligomers is reached at oligomer **10**. All the four OPEs **9**–**12** showed a shorter absorption wavelength maximum at 340 nm. Elongation of the conjugation length from **9** to **12** results in a red shift of 9 nm in the emission spectra, while a red shift of 7 nm from **9** to **10** and a red shift of 2 nm from **10** to **11** and the same λ_{max} for **11** and **12** in the emission spectra. The extinction coefficients based on the oligomer molecules OPEs **9**–**12** are 1.00×10^5, 1.91×10^5, 3.07×10^5, and 4.88×10^5, respectively. It indicates that increasing the conjugation length of OPE may also increase the transition probability of electrons from their ground states to the excited states. There is a major band with a shoulder to the red of moderate intensity in the emission spectrum of OPEs **9**–**12**. It is noteworthy that the half bandwidths of the emission spectra of OPEs **9**–**12** are much narrow as compared with that of OPVs.[16] At present, it is not clear why this should be the case. No change in any of the emission spectra was observed when fluorescence measurements were made over a wide range of concentrations ($2\times10^{-5}-5\times10^{-8}$ M), suggesting that excimer formation does not occur. The fluorescence quantum yields of the OPEs **9** to **12** in dichloromethane are 80, 77, 77, and 63%, respectively (Table 1). It is interesting to note that the quantum yields are decreased as the conjugation length increases.

Table 1. The absorption λ_{max} (in $CHCl_3$), extinction co-efficiency, emission λ_{max} (in $CHCl_3$), and fluorescent quantum yield of OPEs

Oligomer	UV λ_{max} (nm)	$\varepsilon\times10^{-5}$	Em λ_{max} (nm)	Φ_F[a]
9	389	1.00	431	0.80
10	405	1.91	438	0.77
11	407	3.07	440	0.77
12	411	4.88	440	0.63

[a] Use *p*-distyrylbenzene ($\Phi_F\cong0.9$) to compare with in dichloromethane.[24]

It should be pointed out that various syntheses of different OPEs have been reported in the past.[25–28] Tour et al. have reported the improved and new synthesis of OPE molecules with nitro groups and with nitrile group as the alligator clip to a metal surface as the potential molecular electronic

devices.[25] Their rapid bi-directional synthesis of OPEs containing with or without thienyl rings or the solid phase synthesis of OPEs are also noteworthy.[1,26] Godt et al. have applied the iterative convergent/divergent strategy based on the bromine–iodine selectivity of the palladium-catalyzed alkyne-aryl coupling reactions to form OPEs with 9 mer.[27] Meier et al. have investigated the non-linear optics of monodisperse OPEs with up to 6 mer.[28] The work presented in this paper is distinct from others in that our approach is open ended and very versatile, and it enables us to synthesize longer oligomers that more closely resemble organic polymeric conducting materials. Due to the fact that the Sonogashira reaction tolerates a wide variety of functional groups,[18,19] it should be possible to synthesize many different OPE molecules of various lengths and structures. This is useful for fine-tuning the band gap in emissive organic materials. Also noteworthy is the use of only one reaction type to construct the whole molecules. The use of building blocks with three benzene rings allows for efficient and fast construction of the OPE chain. After desilylation steps, two terminal acetylene functional groups are left for further chemical manipulation which may include either continued elongation or reaction with an end-functionalized polymer to form novel diblock copolymers or with an end-capped monomer to form longer oligomers. Controlled bidirectional growth is also possible, enabling a very rapid construction of OPEs possessing various functional groups at both ends. Thus, we can use the iterative coherent approach to effectively and rapidly synthesize longer OPEs.

In summary, our general and controlled bidirectional growth strategy enables a very rapid and efficient construction of OPEs possessing functional groups at both ends. So far, we can prepare oligomer **12**, which has 23 benzene rings and 22 triple bonds in its conjugation system. The strategy employs only one reaction type to grow the conjugated chains. We intend to use these molecules in the production of novel molecular wires.

3. Experimental

3.1. General

All reactions were carried out under an atmosphere of nitrogen. Tetrahydrofuran (THF) was dealt with dried NaH and then distilled over sodium/benzophenone ketyl whenever needed. All organic extracts were dried over anhydrous magnesium sulfate. TLC was done on aluminum sheets with precoated silica gel 60 F_{254} (40×80 mm) from Merck. Purification by column chromatography was carried out with neutral silica gel 60 (70–230 mesh ASTM). The purity of each compound was judged to be >95% by ^{1}H NMR or ^{13}C NMR spectral analyses. Melting points (Mps) were taken on a MEL-TEMP capillary tube apparatus and are uncorrected. IR spectra were recorded as either Nujol mulls or in the solution form as denoted. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on either a 300, 400 or 500 MHz instrument using TMS (0 ppm) and $CDCl_3$ (77.0 ppm) as internal standards. HRMS spectra were collected on an Autospec orthogonal acceleration-time of flight mass spectrometer with a resolution of 6000 (5% valley definition), and fitted with a magnet bypass flight tube. MALDI-MS spectra were collected on spectrometer equipped with a nitrogen laser (337 nm) and operated in the delayed extraction reflector mode. MS spectra were determined on a Shimadzu QP-1000 spectrometer or Fisons MD800 GC/MS or VG 70-250S spectrometer. UV and fluorescent spectra were recorded in $CHCl_3$ solution unless otherwise stated.

3.1.1. 1,4-Bis-hexyloxy-2,5-bis-trimethylsilylethynylbenzene 15. To a dried round-bottomed flask were added 1,4-bis-hexyloxy-2,5-diiodobenzene[22] (10.0 g, 18.87 mmol), bis(triphenylphosphine)palladium dichloride (0.52 g, 0.74 mmol), copper(I) iodide (0.28 g, 1.47 mmol), triphenylphosphine (0.77 g, 2.94 mmol). The system was evacuated and flushed with nitrogen (3×) and the dry piperidine (50 mL) was degassed with nitrogen and then added. Under stirring, trimethylsilylacetylene (3.71 g, 37.85 mmol) was added to solution. The mixture was stirred at rt for 6 h. The solvent was evaporated, and chloroform was added. The organic phase was washed with saturated solution of NH_4Cl (3×50 mL), solution of NaCl (3×50 mL), and dried over anhydrous $MgSO_4$. The solvent was removed in vacuum, and residue was purified by column chromatography (silica gel, hexane/chloroform, 10:0.5) to give the compound **15** as white solid (8.09 g, 91% yield). Mp 75–76 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.25 (s, 18H), 0.90 (t, J=7 Hz, 6H), 1.30–1.35 (m, 8H), 1.47–1.52 (m, 4H), 1.75–1.80 (m, 4H), 3.94 (t, J=7 Hz, 4H), 6.88 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.03, 14.17, 22.72, 25.77, 29.37, 31.69, 69.49, 100.15, 101.13, 113.98, 117.23, 154.07 ppm; IR ($CHCl_3$) ν 2137, 1269, 1015 cm^{-1}; MS (m/z) 470.2 (M^+); HRMS calcd for $C_{28}H_{46}O_2Si_2$ 470.3036, found 470.3032.

3.1.2. 1,4-Diethynyl-2,5-bis-hexyloxybenzene 16. Compound **15** (8.0 g, 16.98 mmol) was dissolved in $CHCl_3$ (50 mL), CH_3OH (10 mL) and solution of NaOH (2.7 g, 67.5 mol) in 10 mL of water were added. The mixture was stirred at rt for 12 h, and then washed with saturated solution of NaCl (3×50 mL), and dried over anhydrous $MgSO_4$. The solvent was removed in vacuum, and residue was recrystallized from $CHCl_3$/hexane to provide pure compound **16** as white solid (5.32 g, 97% yield). Mp 70–71 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J=7 Hz, 6H), 1.33–1.35 (m, 8H), 1.42–1.47 (m, 4H), 1.75–1.84 (m, 4H), 3.34 (s, 2H), 3.97 (t, J=7 Hz, 4H), 6.95 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.93, 22.50, 25.50, 29.00, 31.44, 69.52, 79.70, 82.37, 113.16, 117.60, 153.89 ppm; IR ($CHCl_3$) ν 2106, 1269, 1015 cm^{-1}. MS (m/z) 326.3 (M^+); HRMS calcd for $C_{22}H_{30}O_2$ 326.2246, found 326.2254.

3.1.3. 1,4-Bis-(4-bromo-phenylethynyl)-2,5-bis-hexyloxybenzene 17. To a dried round-bottomed flask were added compound **16** (5.0 g, 15.31 mmol), 1-bromo-4-iodobenzene (8.67 g, 30.64 mmol), bis(triphenylphosphine)-palladium dichloride (0.43 g, 0.61 mmol), copper(I) iodide (0.23 g, 1.21 mmol), triphenylphosphine (0.63 g, 2.40 mmol). The system was evacuated and flushed with nitrogen (3×), the dry piperidine (60 mL) was degassed with nitrogen and then added into the reaction mixture. The mixture was stirred at rt for 8 h. The solvent was evaporated, and chloroform was added. The organic phase was washed

with saturated solution of NH_4Cl (3×50 mL), solution of NaCl (3×50 mL), and dried over anhydrous $MgSO_4$. The solvent was removed in vacuum, and residue was purified by column chromatography (silica gel, hexane/chloroform, 10:0.5) to give compound **17** as faint yellow solid (7.89 g, 81% yield). Mp 112–113 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J=7 Hz, 6H), 1.33–1.37 (m, 8H), 1.51–1.56 (m, 4H), 1.79–1.86 (m, 4H), 4.02 (t, J=7 Hz, 4H), 6.70 (s, 2H), 7.39 (d, J=8 Hz, 4H), 7.49 (d, J=8 Hz, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.02, 22.62, 25.70, 29.24, 31.56, 69.54, 87.05, 93.82, 113.78, 116.72, 122.35, 122.49, 131.57, 132.92, 153.60 ppm; IR ($CHCl_3$) ν 2209, 1274, 1186, 1067 cm^{-1}; MS (m/z) 634 (M^+); HRMS calcd for $C_{34}H_{36}O_2Br_2$ 634.1082, found 634.1096.

3.1.4. 1,4-Bis-hexyloxy-2,5-bis(4-iodo-phenylethynyl)-benzene 18. To a dried two-neck round-bottomed flask was added compound **17** (10 g, 15.72 mmol), the system was evacuated and flushed with nitrogen. Dry ether (200 mL) was added, and solution of *n*-BuLi (2.5 M, 12.6 mL) in ether (100 mL) was then added dropwise at 0 °C. After stirring at 0 °C for 3 h, the solution of 1,2-diiodoethane (8.90 g, 31.56 mmol) in 20 mL of ether was added, the reaction mixture was stirred at rt for 12 h. The solution was then washed with saturated solution of $Na_2S_2O_3$ (2×50 mL), solution of NaCl (3×50 mL), and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum, the crude product was purified by column chromatography (silica gel, hexane/$CHCl_3$=5:0.5) to give compound **18** as a light yellow solid (6.5 g, 57% yield). Mp 110–111 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J=7 Hz, 6H), 1.29–1.36 (m, 8H), 1.47–1.54 (m, 4H), 1.78–1.97 (m, 4H), 4.01 (t, J=7 Hz, 4H), 6.98 (s, 2H), 7.24 (d, J=8 Hz, 4H), 7.67 (d, J=8 Hz, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.05, 22.63, 25.72, 29.25, 31.57, 69.56, 87.35, 94.00, 94.16, 113.80, 116.74, 122.92, 133.01, 137.49, 153.61 ppm; IR ($CHCl_3$) ν 2199, 1274, 1212, 1051 cm^{-1}; MS (m/z) 730 (M^+); HRMS calcd for $C_{34}H_{36}O_2I_2$ 730.0805, found 730.0811.

3.1.5. {4-[2,5-Bis-hexyloxy-4-(4-iodo-phenylethynyl)-phenylethynyl]phenylethynyl}-tri-methylsilane 1 and 1,4-bis-hexyloxy-2,5-bis(4-trimethylsilanylethynyl-phenyl-ethynyl)benzene 19. To a dried round-bottomed flask were added compound **18** (5.0 g, 6.85 mmol), bis(triphenylphosphine)palladium dichloride (0.11 g, 0.16 mmol), copper(I) iodide (0.06 g, 0.32 mmol), triphenylphosphine (0.16 g, 0.61 mmol). The system was evacuated and flushed with nitrogen (3×), the dry piperidine (30 mL) was degassed with nitrogen and then added into the reaction mixture. Under stirring, trimethylsilylacetylene (0.68 g, 6.94 mmol) was added to the solution. The mixture was stirred at rt for 3 h. The solvent was evaporated, and chloroform was added. The organic phase was washed with saturated solution of NH_4Cl (3×50 mL), solution of NaCl (3×50 mL), and dried over anhydrous $MgSO_4$. The solvent was removed in vacuum, and residue was separated by column chromatography (silica gel, hexane/chloroform, 10:0.5–1) to give the unreacted compound **18** (1.2 g), compound **1** (2.51 g), and compound **19** (1.1 g).

Compound **1**. Yellow solid (2.51 g, 52% yield). Mp 98–99 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.26 (s, 9H), 0.90 (t, J=7 Hz, 6H), 1.30–1.35 (m, 8H), 1.51–1.56 (m, 4H), 1.79–1.86 (m, 4H), 4.02 (t, J=7 Hz, 4H), 6.99 (s, 2H), 7.24 (d, J=8 Hz, 4H), 7.45 (s, 4H), 7.68 (d, J=8 Hz, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 0.10, 14.03, 22.62, 25.71, 29.25, 31.56, 69.55, 69.58, 87.38, 87.88, 93.97, 94.12, 94.61, 96.31, 104.65, 113.75, 113.93, 116.76, 122.87, 122.94, 123.45, 131.31, 131.85, 133.00, 137.48, 153.62 ppm; IR ($CHCl_3$) ν 2147, 1274, 1248, 1191 cm^{-1}; MS (m/z) 700 (M^+); HRMS calcd for $C_{39}H_{45}O_2SiI$ 700.2234, found 700.2227.

Compound **19**. Yellow solid (1.10 g, 24% yield). Mp 156–157 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.26 (s, 18H), 0.90 (t, J=7 Hz, 6H), 1.34–1.38 (m, 8H), 1.52–1.54 (m, 4H), 1.82–1.87 (m, 4H), 4.02 (t, J=7 Hz, 4H), 7.00 (s, 2H), 7.45 (s, 8H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.10, 14.03, 22.63, 25.73, 29.26, 31.58, 59.57, 87.91, 94.60, 96.29, 104.66, 113.87, 116.77, 122.85, 123.47, 131.31, 131.85, 153.63 ppm; IR ($CHCl_3$) ν 2147, 1409, 1378, 1020 cm^{-1}; MS (m/z) 670.4 (M^+); HRMS calcd for $C_{44}H_{54}O_2Si_2$ 670.3662, found 670.3652.

The compound **19** can also be obtained in 96% yield by reaction of compound **18** and 2.0 equiv. of trimethylsilylacetylene.

3.1.6. 1,4-Bis-(4-ethynyl-phenylethynyl)-2,5-bis-hexyl-oxy-benzene 2. Compound **19** (2.0 g, 2.98 mmol) was dissolved in $CHCl_3$ (50 mL), CH_3OH (10 mL) and solution of NaOH (0.96 g, 24.0 mol) in 10 mL of water were added. The mixture was stirred at rt for 12 h, and then washed with saturated solution of NaCl (3×50 mL), and dried over anhydrous $MgSO_4$. The solvent was removed in vacuum, and residue was recrystallized from $CHCl_3$/hexane to provide pure compound **2** as yellow solid (1.50 g, 96% yield). Mp 112–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J=7 Hz, 6H), 1.31–1.36 (m, 8H), 1.50–1.58 (m, 4H), 1.80–1.87 (m, 4H), 3.18 (s, 2H), 4.03 (t, J=7 Hz, 4H), 7.01 (s, 2H), 7.47 (s, 8H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.01, 22.62, 25.72, 29.25, 31.57, 69.55, 78.93, 83.28, 87.97, 94.39, 113.84, 116.76, 121.83, 123.89, 131.38, 132.01, 153.65 ppm; IR ($CHCl_3$) ν 2099, 1284, 1017 cm^{-1}; MS (m/z) 526 (M^+); HRMS calcd for $C_{38}H_{38}O_2$ 526.2872, found 526.2866.

Oligomer **3**. To a dried round-bottomed flask were added compound **1** (1.73 g, 2.47 mmol), compound **2** (0.65 g, 1.23 mmol), bis(triphenylphosphine)palladium dichloride (0.04 g, 0.06 mmol), copper(I) iodide (0.02 g, 0.11 mmol), triphenylphosphine (0.06 g, 0.23 mmol). The system was evacuated and flushed with nitrogen (3×), the dry piperidine (50 mL) was degassed with nitrogen and then added. The mixture was stirred at rt for 12 h. The solvent was evaporated, and chloroform was added. The organic phase was washed with saturated solution of NH_4Cl (3×50 mL), solution of NaCl (3×50 mL), and dried over anhydrous $MgSO_4$. The solvent was removed in vacuum, and residue was purified by column chromatography (silica gel, hexane/chloroform, 10:6) to give the oligomer **3** as yellow solid (1.22 g, 59% yield). Mp 146–147 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.26 (s, 18H), 0.85–0.92 (t, J=7 Hz, 18H), 1.30–1.37 (m, 24H), 1.55–1.58 (m, 12H), 1.83–1.87 (m, 12H), 4.03 (t, J=7 Hz, 12H), 7.02 (s, 6H), 7.45 (s, 8H), 7.52 (s,

16H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ −0.09, 14.04, 22.64, 25.75, 29.29, 31.60, 69.61, 87.92, 88.06, 91.08, 94.67, 96.31, 104.68, 113.93, 116.81, 122.82, 123.48, 131.33, 131.52, 131.87, 132.41, 153.67 ppm; IR ($CHCl_3$) ν 2135, 1277, 1019 cm^{-1}; MS (*m*/*z*) 1670.5 (M^+); HRMS calcd for $C_{116}H_{126}O_6Si_2$ 1670.9093, found 1670.9072.

Oligomer **4**. Oligomer **3** (1.0 g, 0.60 mmol) was dissolved in $CHCl_3$ (60 mL), CH_3OH (10 mL) and solution of NaOH (0.3 g, 7.5 mol) in 10 mL of water were added. The mixture was stirred at 50 °C for 15 h, and then washed with saturated solution of NaCl (3×50 mL), and dried over anhydrous $MgSO_4$. The solvent was removed in vacuum, and residue was recrystallized from $CHCl_3$/hexane to provide pure oligomer **4** as yellow solid (0.86 g, 94% yield). Mp 117–119 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86–0.93 (m, 18H), 1.30–1.37 (m, 24H), 1.52–1.55 (m, 12H), 1.84–1.88 (m, 12H), 3.18 (s, 2H), 4.04 (m, 12H), 7.02 (s, 6H), 7.47 (s, 8H), 7.52 (s, 16H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.05, 22.65, 25.75, 29.30, 31.60, 69.62, 78.92, 83.32, 88.06, 91.09, 94.42, 94.70, 113.97, 116.86, 121.85, 122.83, 123.48, 123.93, 131.41, 131.53, 132.05, 153.69 ppm; IR ($CHCl_3$) ν 2099, 1280, 1015 cm^{-1}; MS (*m*/*z*) 1527.1 (M^+); HRMS calcd for $C_{110}H_{110}O_6$ 1526.8302, found 1526.8350.

Oligomer **5**. To a dried round-bottomed flask were added compound **1** (0.80 g, 1.14 mmol), bis(triphenylphosphine)-palladium dichloride (0.04 g, 0.06 mmol), copper(I) iodide (0.02 g, 0.11 mmol), triphenylphosphine (0.06 g, 0.23 mmol). The system was evacuated and flushed with nitrogen (3×), THF (20 mL) and DIEA (20 mL) were degassed with nitrogen and then added. Compound **4** (0.95 g, 0.57 mmol) was evacuated and flushed with nitrogen (3×) in another dried round-bottomed flask, and dissolved in degassed THF (25 mL), and then added above system. The mixture was stirred at rt for 12 h and then at 50 °C for 8 h. The solvent was evaporated, and chloroform was added. The organic phase was washed with saturated solution of NH_4Cl (3×50 mL), solution of NaCl (3×50 mL), and dried over anhydrous $MgSO_4$. The solvent was removed in vacuum, and residue was purified by column chromatography (silica gel, hexane/chloroform, 10:6) to give the oligomer **5** as yellow solid (0.73 g, 48% yield). Mp 188–189 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.26 (s, 18H), 0.89–0.94 (m, 30H), 1.35–1.39 (m, 40H), 1.53–1.56 (m, 20H), 1.84–1.89 (m, 20H), 4.01–4.07 (m, 20H), 7.01–7.02 (m, 10H), 7.45 (s, 8H), 7.52 (s, 32H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ −0.10, 14.05, 22.65, 25.75, 29.29, 31.60, 69.61, 87.93, 88.07, 91.08, 94.68, 96.31, 104.67, 113.93, 116.80, 122.82, 123.48, 131.32, 131.52, 131.86, 153.68 ppm; IR ($CHCl_3$) ν 2145, 1279, 1020 cm^{-1}; MS (*m*/*z*) 2671.8 (M^+); HRMS calcd for $C_{188}H_{198}O_{10}Si_2$ 2671.4524, found 2671.4532.

Oligomer **6**. Oligomer **5** (0.80 g, 0.30 mmol) was dissolved in $CHCl_3$ (70 mL), CH_3OH (10 mL) and solution of NaOH (0.3 g, 7.5 mol) in 10 mL of water were added. The mixture was stirred at 75 °C for 24 h, and then washed with saturated solution of NaCl (3×50 mL), dried over anhydrous $MgSO_4$. The solvent was removed in vacuum, and residue was recrystallized from $CHCl_3$/hexane to provide pure oligomer **6** as yellow solid (0.68 g, 90% yield). Mp 146–147 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83–0.97 (m, 30H), 1.35–1.42 (m, 40H), 1.53–1.57 (m, 20H), 1.84–1.91 (m, 20H), 3.18 (s, 2H), 4.02–4.07 (m, 20H), 7.02 (s, 10H), 7.47 (s, 8H), 7.52 (s, 32H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.16, 22.76, 25.87, 29.42, 31.72, 69.76, 79.02, 83.43, 88.20, 91.21, 94.53, 94.81, 114.08, 116.97, 121.97, 122.95, 123.61, 124.06, 131.53, 131.64, 132.16, 153.82 ppm; IR ($CHCl_3$) ν 2101, 1282, 1017 cm^{-1}; MS (*m*/*z*) 2527.5 (M^+); HRMS calcd for $C_{182}H_{182}O_{10}$ 2527.3733, found 2527.3742.

Oligomer **7**. To a dried round-bottomed flask were added compound **1** (0.36 g, 0.51 mmol), bis(triphenylphosphine)-palladium dichloride (0.02 g, 0.03 mmol), copper(I) iodide (0.01 g, 0.05 mmol), triphenylphosphine (0.03 g, 0.11 mmol). The system was evacuated and flushed with nitrogen (3×), THF (20 mL) and DIEA (20 mL) were degassed with nitrogen and then added. Compound **6** (0.65 g, 0.26 mmol) was evacuated and flushed with nitrogen (3×) in another dried round-bottomed flask, and dissolved in degassed THF (35 mL), and then added above system. The mixture was stirred at 50 °C for 24 h. The solvent was evaporated, and chloroform was added. The organic phase was washed with saturated solution of NH_4Cl (3×50 mL), solution of NaCl (3×50 mL), and dried over anhydrous $MgSO_4$. The solvent was removed in vacuum, and residue was purified by column chromatography (silica gel, hexane/chloroform, 10:6) to give the oligomer **7** as yellow solid (0.31 g, 33% yield). Mp 176–177 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.26 (s, 18H), 0.83–0.97 (m, 42H), 1.35–1.43 (m, 56H), 1.53–1.58 (m, 28H), 1.84–1.91 (m, 28H), 4.03–4.07 (m, 28H), 7.02 (s, 14H), 7.45 (s, 8H), 7.52 (s, 48H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ −0.10, 14.05, 22.65, 25.75, 29.29, 31.60, 69.60, 88.06, 91.08, 94.68, 96.30, 104.65, 113.91, 116.79, 122.81, 123.47, 131.32, 131.51, 131.86, 153.67 ppm; IR ($CHCl_3$) ν 2145, 1278, 1019 cm^{-1}; MS (*m*/*z*) 3671.5 (M^+); HRMS calcd for $C_{260}H_{270}O_{14}Si_2$ 3671.9954, found 3671.9962.

Oligomer **8**. Oligomer **7** (0.60 g, 0.16 mmol) was dissolved in $CHCl_3$ (80 mL), CH_3OH (10 mL) and solution of NaOH (0.15 g, 3.75 mol) in 10 mL of water were added. The mixture was stirred at 75 °C for 35 h, and then washed with saturated solution of NaCl (3×50 mL), dried over anhydrous $MgSO_4$. The solvent was removed in vacuum, and residue was recrystallized from $CHCl_3$/hexane to provide pure oligomer **8** as yellow solid (0.49 g, 85% yield). Mp 155–156 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89–0.93 (m, 42H), 1.35–1.43 (m, 56H), 1.54–1.59 (m, 28H), 1.82–1.91 (m, 28H), 3.18 (s, 2H), 4.03–4.07 (m, 28H), 7.02 (s, 14H), 7.47 (s, 8H), 7.52 (s, 48H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.16, 22.76, 25.87, 29.42, 31.72, 69.75, 79.01, 83.42, 88.19, 91.21, 94.53, 94.81, 114.06, 116.96, 121.96, 122.94, 123.61, 124.05, 131.52, 131.64, 132.16, 153.81 ppm; IR ($CHCl_3$) ν 2101, 1280, 1015 cm^{-1}; MS (*m*/*z*) 3527.7 (M^+); HRMS calcd for $C_{254}H_{254}O_{14}$ 3527.9164, found 3527.9172.

3.1.7. 1,4-Bis-hexyloxy-2,5-bis-[4-(4-methylsulfanyl-phenylethynyl)-phenylethynyl]-benzene 9. To a dried round-bottomed flask were added compound **2** (0.50 g, 0.95 mmol), 1-iodo-4-methylsulfanyl-benzene (0.48 g, 1.92 mmol), bis(triphenylphosphine)-palladium dichloride (0.03 g, 0.04 mmol), copper(I) iodide (0.02 g, 0.11 mmol), triphenylphosphine (0.06 g, 0.23 mmol). The system was evacuated and flushed with nitrogen (3×), the dry piperidine

(30 mL) was degassed with nitrogen and then added. The mixture was stirred at rt for 10 h. The solvent was evaporated, and chloroform was added. The organic phase was washed with saturated solution of NH_4Cl (3×50 mL), solution of NaCl (3×50 mL), and dried over anhydrous $MgSO_4$. The solvent was removed in vacuum, and residue was purified by column chromatography (silica gel, hexane/chloroform, 10:4) to give the oligomer **9** as yellow solid (0.45 g, 62% yield). This oligomer **9** can be further purified by recrystallization from $CHCl_3$ to give crystals for X-ray analysis. Mp 187–188 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J=7 Hz, 6H), 1.35–1.39 (m, 8H), 1.53–1.58 (m, 4H), 1.84–1.88 (m, 4H), 2.51 (s, 6H), 4.04 (t, J=7 Hz, 4H), 7.02 (s, 2H), 7.22 (d, J=8 Hz, 4H), 7.45 (d, J=8 Hz, 4H), 7.50 (s, 8H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.05, 15.32, 22.65, 25.75, 29.29, 31.60, 69.60, 87.88, 89.27, 91.17, 94.73, 113.91, 116.80, 119.24, 123.11, 123.15, 125.81, 131.42, 131.48, 131.87, 139.64, 153.65 ppm; IR ($CHCl_3$) ν 2212, 1275, 1089, 1011 cm^{-1}; MS (*m*/*z*): 770 (M^+); HRMS calcd for $C_{52}H_{50}O_2S_2$ 770.3252, found 770.3251.

Oligomer **10**. To a dried round-bottomed flask were added 1-iodo-4-methylsulfanyl-benzene (0.13 g, 0.52 mmol), bis(triphenyl-phosphine)palladium dichloride (0.02 g, 0.03 mmol), copper(I) iodide (0.01 g, 0.05 mmol), triphenylphosphine (0.03 g, 0.11 mmol). The system was evacuated and flushed with nitrogen (3×), THF (10 mL) and DIEA (15 mL) were degassed with nitrogen and then added. Compound **4** (0.40 g, 0.26 mmol) was evacuated and flushed with nitrogen (3×) in another dried round-bottomed flask, and dissolved in degassed THF (20 mL), and then added above system. The mixture was stirred at rt 8 h and at 50 °C for 6 h. The solvent was evaporated, and chloroform was added. The organic phase was washed with saturated solution of NH_4Cl (3×50 mL), solution of NaCl (3×50 mL), and dried over anhydrous $MgSO_4$. The solvent was removed in vacuum, and residue was purified by column chromatography (silica gel, hexane/chloroform, 10:6) to give the oligomer **10** as yellow solid (0.24 g, 52% yield). Mp 179–180 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J=7 Hz, 18H), 1.26–1.38 (m, 24H), 1.51–1.63 (m, 12H), 1.82–1.91 (m, 12H), 2.51 (s, 6H), 4.05 (t, J=7 Hz, 12H), 7.02 (s, 6H), 7.22 (d, J=8 Hz, 4H), 7.44 (d, J=8 Hz, 4H), 7.50 (s, 8H), 7.52 (s, 16H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.05, 15.32, 22.65, 25.75, 29.29, 31.60, 69.61, 87.88, 88.07, 89.27, 91.09, 91.18, 94.67, 94.77, 113.86, 113.92, 113.98, 116.81, 119.24, 122.82, 123.14, 123.48, 125.82, 131.42, 131.48, 131.52, 131.87, 139.65, 153.68 ppm; IR ($CHCl_3$) ν 2210, 1276, 1088, 1011 cm^{-1}; MS (*m*/*z*) 1771 (M^+); HRMS calcd for $C_{124}H_{122}O_6S_2$1770.8682, found 1770.8695.

Oligomer **11**. To a dried round-bottomed flask were added 1-iodo-4-methylsulfanyl-benzene (0.10 g, 0.40 mmol), bis(triphenylphosphine)palladium dichloride (0.02 g, 0.03 mmol), copper(I) iodide (0.01 g, 0.05 mmol), triphenylphosphine (0.03 g, 0.11 mmol). The system was evacuated and flushed with nitrogen (3×), THF (10 mL) and DIEA (15 mL) were degassed with nitrogen and then added. Compound **6** (0.50 g, 0.20 mmol) was evacuated and flushed with nitrogen (3×) in another dried round-bottomed flask, and dissolved in degassed THF (20 mL), and then added above system. The mixture was stirred at rt for 8 h and at 50 °C for another 6 h. The solvent was evaporated, and chloroform was added. The organic phase was washed with saturated solution of NH_4Cl (3×50 mL), solution of NaCl (3×50 mL), and dried over anhydrous $MgSO_4$. The solvent was removed in vacuum, and residue was purified by column chromatography (silica gel, hexane/chloroform, 10:8) to give the oligomer **11** as yellow solid (0.17 g, 31% yield). Mp 167–168 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83–0.95 (m, 30H), 1.32–1.38 (m, 40H), 1.51–1.58 (m, 20H), 1.82–1.91 (m, 20H), 2.51 (s, 6H), 4.05 (t, J=7 Hz, 20H), 7.02 (s, 10H), 7.22 (d, J=8 Hz, 4H), 7.44 (d, J=8 Hz, 4H), 7.50 (s, 8H), 7.52 (s, 32H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.03, 15.31, 22.63, 25.73, 29.28, 31.58, 69.60, 87.86, 88.05, 89.25, 91.07, 94.67, 113.90, 116.78, 119.23, 122.80, 123.12, 123.46, 125.80, 131.40, 131.50, 131.85, 139.63, 153.66 ppm; IR ($CHCl_3$) ν 2210, 1276, 1089, 1010 cm^{-1}; MS (*m*/*z*) 2771.7 (M^+); HRMS calcd for $C_{196}H_{194}O_{10}S_2$ 2771.4113, found 2771.4122.

Oligomer **12**. To a dried round-bottomed flask were added 1-iodo-4-methylsulfanyl-benzene (0.05 g, 0.20 mmol), bis(triphenyl-phosphine)palladium dichloride (0.02 g, 0.03 mmol), copper(I) iodide (0.01 g, 0.05 mmol), triphenylphosphine (0.03 g, 0.11 mmol). The system was evacuated and flushed with nitrogen (3×), THF (10 mL) and DIEA (15 mL) were degassed with nitrogen and then added. Compound **8** (0.35 g, 0.10 mmol) was evacuated and flushed with nitrogen (3×) in another dried round-bottomed flask, and dissolved in degassed THF (20 mL), and then added above system. The mixture was stirred at 50 °C for 30 h. The solvent was evaporated, and chloroform was added. The organic phase was washed with saturated solution of NH_4Cl (3×50 mL), solution of NaCl (3×50 mL), and dried over anhydrous $MgSO_4$. The solvent was removed in vacuum, and residue was purified by column chromatography (silica gel, hexane/chloroform, 10:6) to give the oligomer **12** as yellow solid (0.09 g, 24% yield). Mp 175–176 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83–0.95 (m, 42H), 1.32–1.38 (m, 56H), 1.51–1.58 (m, 28H), 1.82–1.91 (m, 28H), 2.51 (s, 6H), 4.05 (t, J=7 Hz, 28H), 7.02 (s, 14H), 7.22 (d, J=8 Hz, 4H), 7.44 (d, J=8 Hz, 4H), 7.50 (s, 8H), 7.52 (s, 48H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.04, 15.31, 22.64, 25.74, 29.28, 31.59, 69.59, 88.05, 91.07, 94.67, 113.90, 116.79, 122.80, 123.11, 123.46, 125.80, 131.51, 131.85, 139.63, 153.66 ppm; IR ($CHCl_3$) ν 2210, 1082, 1012 cm^{-1}; MS (*m*/*z*) 3772 (M^+); HRMS calcd for $C_{268}H_{266}O_{14}S_2$ 3771.9544, found 3771.9552.

3.1.8. Thioacetic acid *S*-[4-(4-{4-[4-(4-acetylsulfanyl-phenylethynyl)-phenylethynyl]-2,5-bis-hexyloxyl-phenylethynyl}phenylethynyl)phenyl]ester 13. To a dried round-bottomed flask were added 1-(4-iodo-phenylthio)ethan-1-one (0.42 g, 1.51 mmol), bis(triphenyl-phosphine)palladium dichloride (0.05 g, 0.07 mmol), copper(I) iodide (0.03 g, 0.16 mmol), triphenylphosphine (0.08 g, 0.31 mmol). The system was evacuated and flushed with nitrogen (3×), THF (10 mL) and DIEA (10 mL) were degassed with nitrogen and then added. Compound **2** (0.40 g, 0.76 mmol) was evacuated and flushed with nitrogen (3×) in another dried round-bottomed flask, and dissolved in degassed THF (10 mL), and then added above system. The mixture was stirred at rt for 12 h. The solvent was evaporated, and chloroform was added. The organic

phase was washed with saturated solution of NH_4Cl (3×50 mL), solution of NaCl (3×50 mL), and dried over anhydrous $MgSO_4$. The solvent was removed in vacuum, and residue was purified by column chromatography (silica gel, hexane/chloroform, 10:4) to give the oligomer **13** as yellow solid (0.33 g, 52% yield). Mp 165–166 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J=7 Hz, 6H), 1.35–1.40 (m, 8H), 1.53–1.56 (m, 4H), 1.81–1.88 (m, 4H), 2.44 (s, 6H), 4.04 (t, J=7 Hz, 4H), 7.02 (s, 2H), 7.40 (d, J=8 Hz, 4H), 7.51 (s, 8H), 7.55 (d, J=8 Hz, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.04, 22.64, 25.74, 29.29, 30.27, 31.59, 69.62, 88.09, 90.49, 90.79, 94.66, 113.94, 116.83, 122.67, 123.58, 124.28, 128.28, 131.50, 131.58, 132.16, 134.22, 153.69, 193.38 ppm; IR ($CHCl_3$) ν 2201, 1701, 1213, 1120, 1016 cm^{-1}; MS (*m*/*z*) 826 (M^+); HRMS calcd for $C_{54}H_{50}O_4S_2$ 826.3151, found 826.3157.

Oligomer **14**. To a dried round-bottomed flask were added 1-(4-iodophenylthio)-ethan-1-one (0.21 g, 0.76 mmol), bis(triphenylphosphine)palladium dichloride (0.03 g, 0.04 mmol), copper(I) iodide (0.02 g, 0.11 mmol), triphenylphosphine (0.08 g, 0.15 mmol). The system was evacuated and flushed with nitrogen (3×), THF (10 mL) and DIEA (15 mL) were degassed with nitrogen and then added. Compound **4** (0.58 g, 0.38 mmol) was evacuated and flushed with nitrogen (3×) in another dried round-bottomed flask, and dissolved in degassed THF (20 mL), and then added above system. The mixture was stirred at rt for 12 h. The solvent was evaporated, and chloroform was added. The organic phase was washed with saturated solution of NH_4Cl (3×50 mL), solution of NaCl (3×50 mL), and dried over anhydrous $MgSO_4$. The solvent was removed in vacuum, and residue was purified by column chromatography (silica gel, hexane/chloroform, 10:4) to give the oligomer **14** as yellow solid (0.31 g, 45% yield). Mp 167–168 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88–0.93 (m, 18H), 1.32–1.38 (m, 24H), 1.54–1.56 (m, 12H), 1.82–1.91 (m, 12H), 2.44 (s, 6H), 4.05 (m, 12H), 7.02 (s, 6H), 7.41 (d, J=8 Hz, 4H), 7.52 (s, 24H), 7.56 (d, J=8 Hz, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.05, 22.65, 25.75, 29.29, 30.29, 31.60, 69.61, 88.07, 90.48, 90.79, 91.08, 94.69, 113.92, 116.80, 122.67, 122.82, 123.47, 123.57, 124.28, 128.26, 131.52, 131.59, 132.17, 134.24, 153.68, 193.46 ppm; IR ($CHCl_3$) ν 2201, 1705, 1212, 1016 cm^{-1}; MS (*m*/*z*) 1827 (M^+); HRMS calcd for $C_{126}H_{122}O_8S_2$ 1826.8581, found 1826.8589.

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$SnCl_4$-mediated oxidative biaryl coupling reaction of 1-naphthol and subsequent ring closure of 2,2′-binaphthol to the dinaphthofuran framework

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Abstract—A simple method for the direct synthesis of 2,2′-binaphthols **2** and dinaphtho[1,2-*b*;2′,1′-*d*]furans **3** under mild conditions was developed, utilizing a biaryl coupling reaction via electron donor–acceptor complexes of 1-naphthols with $SnCl_4$. Heating of the complex in a sealed tube for (18–24 h) afforded the corresponding *o*–*o* coupled product **2** in excellent yield. Prolonged reaction (56–65 h) under the same conditions afforded **3** in high yield in one step. We also found that in the case of α-naphthol without substituents other than a hydroxyl group at the C-1 position, regioselective *o*–*o* coupling reaction proceeded. The products **2a**, **2b** and **2g** should be useful as synthetic intermediates for naturally occurring 3,3′-bijuglone, 3,3′-biplumbagin and elliptinone.

1. Introduction

Since the construction of the biaryl substructure is of importance for the synthesis of a variety of natural products, including binaphthoquinones, lignans, alkaloids, flavonoids, and coumarins,[1] and binaphthols are useful as chirality inducers,[2] we have been focused on the oxidative biaryl coupling of hydroxyarenes. Nature makes extensive use of this coupling reaction for the selective construction of complex compounds from simple starting materials such as naphthols and phenols.[3]

Although coupling reactions of 1-naphthols (NPOH) for preparation of 2,2′-binaphthols (BNPOH) by utilizing metal salts,[4] Lewis acids,[5] electrolytic methods,[6] thermal disproportionation[7] and aerobic oxidation[8] have been studied extensively, poor selectivity and low yield of the desired products, accompanied with side reactions, have often been reported, so that the reactions are difficult to control. Synthesis of the dinaphthofuran (DNF) framework requires generally two steps, namely, the biaryl coupling of NPOH and subsequent ring closure of the resulting BNPOH. Although a number of authors have obtained the DNF framework in two steps,[9] only one example of such synthesis in one step has been recorded.[7] However, this method required elevated temperature (350–400 °C) and a long reaction time.

On the other hand, stannic chloride or tin tetrachloride ($SnCl_4$; SC) is used extensively in organic synthesis as a Lewis acid for enhancing a variety of organic reactions. For example, it is used to promote electrophilic aromatic substitutions including Friedel–Craft alkylation,[11a] nucleophilic additions such as the Evans aldol[11b] reaction and the Mukaiyama–Michael[11c] reaction, and pericyclic reactions such as the Diels–Alder reaction[11d] and ene reaction.[11e] SC is classified as hard Lewis acid according to hard and soft acids and bases (HSAB) theory, and therefore interacts preferentially with hard oxygen (*O*-donor) and nitrogen bases (*N*-donor). Since it is known that SC as an inorganic acceptor forms σ-type[12] or π-type[13] electron donor–acceptor (EDA) complexes with aryl donors (naphthol, etc.), charge transfer (CT) interactions might play an important role in these electron-transfer reactions. In addition, many studies on thermal and photochemical reactions via EDA complexes have been reported.[14] In contrast, there have been only a few reports to date on oxidative reactions with SC (applications of $SnCl_4$).[15]

In preliminary communications,[16] we reported the direct synthesis of BNPOH and the DNF framework utilizing oxidative coupling reaction via the EDA complex of NPOH with SC. We now provide greater detail and experimental procedures, and also describe some ancillary studies.

Keywords: Naphthol; Coupling reactions; Tin tetrachloride; Biaryls.
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2. Results and discussion

We investigated the oxidative biaryl coupling reaction of NPOHs **1a**–**1h**[17] (including precursors for the synthesis of natural products) and the naphthol ethers **1i**–**j** with several Lewis acids under various conditions. To determine the optimum conditions for the coupling reaction, detailed preliminary experiments were done with NPOH **1a** as a model substrate[17]. Several Lewis acids ($SnCl_4$, $TiCl_4$, $AlCl_3$, etc.) as an electron acceptors and various solvents (CH_2Cl_2, $MeNO_2$, THF, benzene, DMF, etc.) were investigated, and the results are summarized in Table 1 and Scheme 1.

The efficiency of this reaction is highly dependent upon the nature of the solvent, with solvents having a low donor number,[18] such as CH_2Cl_2 and $MeNO_2$, being particularly favorable. The conversion of **1a** to **2a** was completely inhibited in DMF and THF. The best result was obtained with $SnCl_4$ (1.3 equiv.) in CH_2Cl_2 as a solvent at 100 °C in a sealed tube. That is, the reaction of **1a** using $SnCl_4$ in CH_2Cl_2 afforded only the *o*–*o* coupled product (**2a**; BNPOH) in an almost quantitative yield (Table 1, entry 4). A similar result was obtained in the dark. The addition of $SnCl_4$ dissolved in the solvent to the solution of **1a** immediately afforded a yellow-green solution. This observation suggests the formation of the EDA complex of $SnCl_4$ with 1-naphthol **1a**. New (charge transfer) absorption band was observed at 486 nm in the absorption spectra of the $SnCl_4$ complex with **1a** in CH_2Cl_2.[12] The biaryl coupling reaction of **1a** using $SnCl_4$ in CH_2Cl_2 did not proceed at 23 °C (room temperature), but the mixture changed into a deep-red colored solution with heating at 100 °C, and the biaryl coupling reactions proceeded.

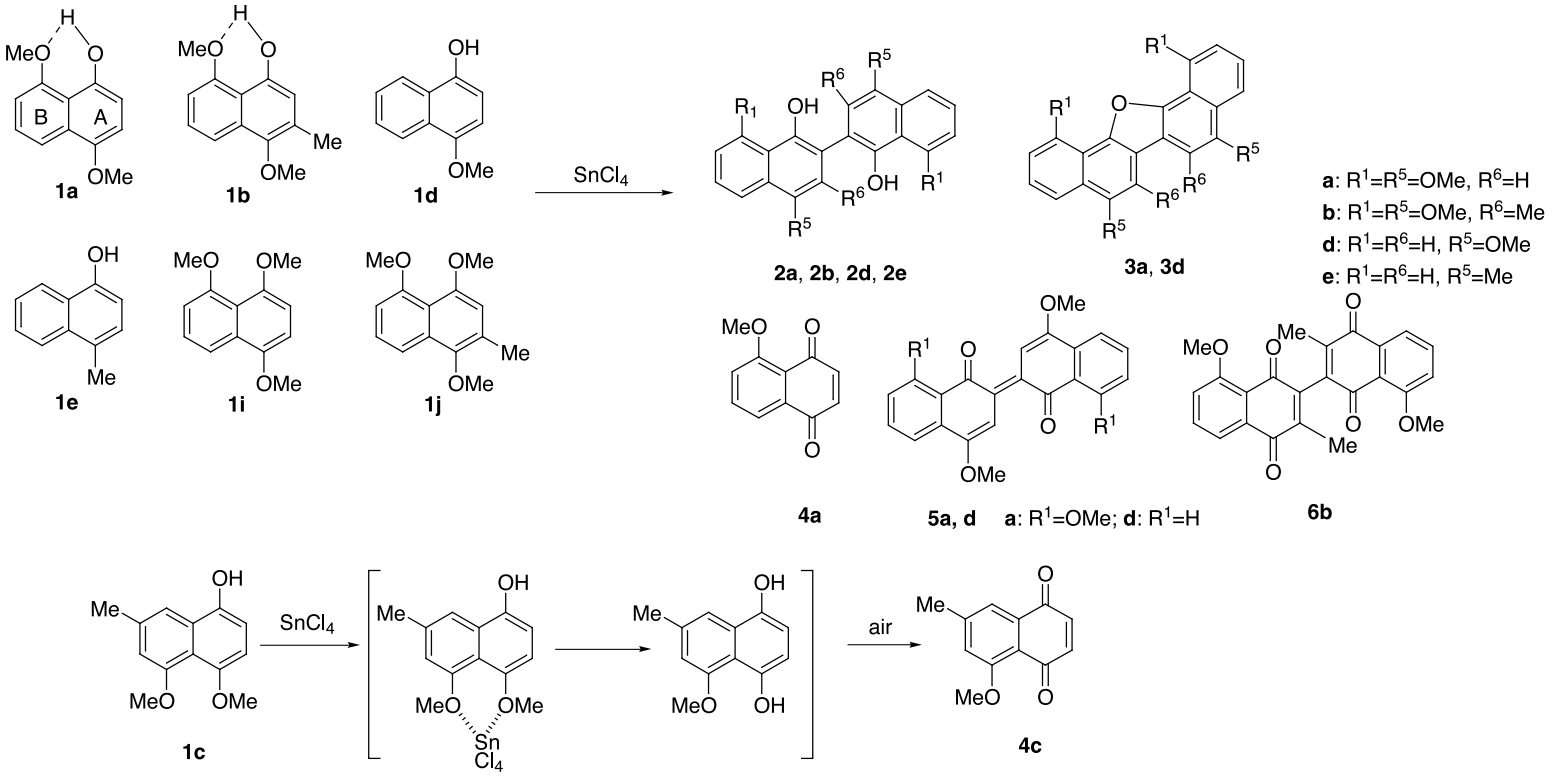
We found that the nature of the major product changed drastically with the reaction time. In contrast to the above reaction for 24 h, prolonged reaction (56 h) under the same conditions selectively afforded DNF **3a** in 92% yield in one step from **1a** (entry 6). In addition, we found also that the coupling reaction proceeds in the presence of a catalytic amount of SC. For example, the reaction **1a** with SC (0.25 equiv.) in CH_2Cl_2 or $MeNO_2$ gave the results shown in entries 11 and 13. In addition, the transformations of **1a** to **3a** proceeded stoichiometrically overall, as discussed below (refer to Table 3, entry 2).

The optimized protocol was subsequently extended to a

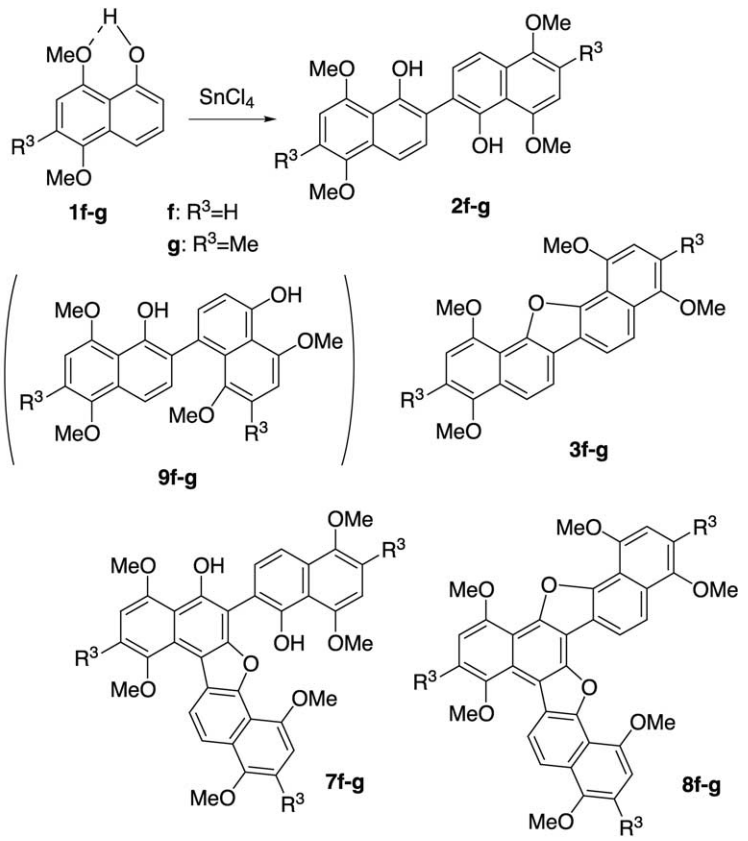
Table 1. Biaryl coupling reactions via the EDA complex of 1-naphthols **1** with acceptor[a]

Entry	Substrate	Acceptor (1.3 equiv.)	Solvent	Temperature (°C)	Time (h)	Product (isolated yield, %)					Recovered
						2	**3**	**4**	**5**	**6**	**1** (%)
1	**1a**	—	CH_2Cl_2	100	24						100
2	**1a**	—	$MeNO_2$	80	7						100
3	**1a**	$SnCl_4$	$MeNO_2$	23	12						100
4	**1a**	$SnCl_4$	CH_2Cl_2	100	24	97	Trace				—
5	**1a**	$SnCl_4$	CH_2Cl_2	100	48	84	13				—
6	**1a**	$SnCl_4$	CH_2Cl_2	100	56		92				—
7	**1a**	$SnCl_4$	$MeNO_2$	100	0.8		60				—
8	**1a**	$SnCl_4$	$MeNO_2$	80	1.5	82					—
9	**1a**	$SnCl_4$	$MeNO_2$	80	70	Trace	57				—
10[b]	**1a**	$SnCl_4$	CH_2Cl_2	100	76	86	4				9
11[c]	**1a**	$SnCl_4$	CH_2Cl_2	100	96	59	14				12
12[b]	**1a**	$SnCl_4$	$MeNO_2$	80	3.5	86					—
13[c]	**1a**	$SnCl_4$	$MeNO_2$	80	21	66	23				7
14	**1b**	$SnCl_4$	$MeNO_2$	100	6	98					—
15	**1c**	$SnCl_4$	CH_2Cl_2	23	3			32			—
16	**1d**	$SnCl_4$	CH_2Cl_2	100	18	98					—
17	**1d**	$SnCl_4$	CH_2Cl_2	100	65		84				—
18	**1e**	$SnCl_4$	CH_2Cl_2	100	48	52					38
19	**1i**	$SnCl_4$	CH_2Cl_2	100	24						84
20	**1i**	$SnCl_4$	CH_2Cl_2	100	48		4				77
21	**1j**	$SnCl_4$	CH_2Cl_2	100	48						93
22	**1a**	$SnCl_4$	Benzene	100	24	48	4				—
23	**1a**	$SnCl_4$	DMF	100	24						100
24	**1a**	$SnCl_4$	THF	100	24						100
25[d]	**1a**	$TiCl_4$	CH_2Cl_2	100	24	10					88
26[d]	**1a**	$TiCl_4$	$MeNO_2$	100	0.5		69				—
27[e]	**1a**	$AlCl_3$	CH_2Cl_2	100	24						83
28[e]	**1a**	$AlCl_3$	$MeNO_2$	100	24	38	17				—
29[f]	**1a**	Ag_2O	$CHCl_3$	23	1	86		Trace	7		—
30[f]	**1b**	Ag_2O	$CHCl_3$	23	0.5	35				30	—
31[f]	**1d**	Ag_2O	$CHCl_3$	23	1	20			75		—
32[f]	**1e**	Ag_2O	$CHCl_3$	23	1	12					—

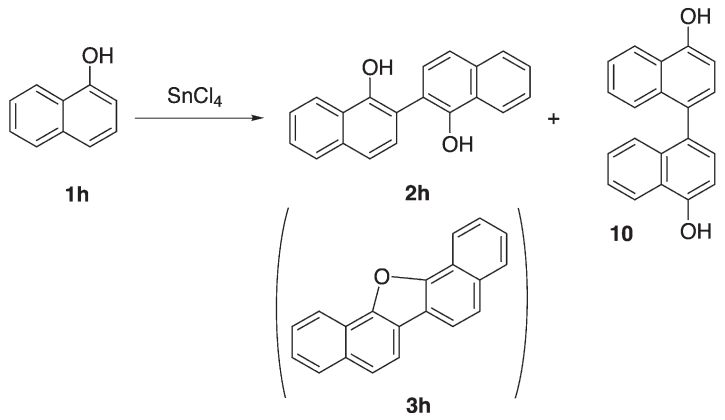
[a] The reactions of naphthols (1 mmol) with $SnCl_4$ (1.3 equiv.) were carried out using an argon-saturated solvent in a sealed tube with stirring under normal laboratory light. Similar results were obtained in the dark.
[b] With $SnCl_4$ (0.5 equiv.).
[c] With $SnCl_4$ (0.25 equiv.).
[d] This reaction was carried out with $TiCl_4$ (1.3 equiv.) in place of $SnCl_4$ under the same conditions as above.
[e] This reaction was carried out with $AlCl_3$ (1.3 equiv.) under the same conditions as above.
[f] With Ag_2O (1.5 equiv.) in $CHCl_3$ under air.


1a
1b
1d
1e
1i
1j
SnCl4
2a, 2b, 2d, 2e
3a, 3d
a: R1=R5=OMe, R6=H
b: R1=R5=OMe, R6=Me
d: R1=R6=H, R5=OMe
e: R1=R6=H, R5=Me
4a
5a, d
a: R1=OMe; d: R1=H
6b
1c
air
4c

Scheme 1.



Scheme 2.



Scheme 3.

Table 2. Reactions of the naphthols with acceptor[a]

Entry	Substrate	Acceptor	Solvent	Temperature (°C)	Time (h)	Product (isolated yield, %)[b]						Recovered
						2	**3**	**7**	**8**	**9**	**10**	**1** (%)
1	**1f**	$SnCl_4$	CH_2Cl_2	100	121	1		2	1			58
2	**1f**	$SnCl_4$	$MeNO_2$	100	4.3	16	8					24
3	**1f**	$SnCl_4$	$MeNO_2$	100	15		Trace		9			—[c]
4	**1g**	$SnCl_4$	CH_2Cl_2	100	121	5		18	12			58
5	**1h**	$SnCl_4$	CH_2Cl_2	100	121	30					4	52
6[b]	**1f**	Ag_2O	$CHCl_3$	23	1	25				30		—[c]
7[b]	**1h**	Ag_2O	$CHCl_3$	23	3	6						—[c]

[a] The reactions of naphthols (1 mmol) with $SnCl_4$ (1.3 equiv.) were carried out using an argon-saturated solvent in a sealed tube with stirring under normal laboratory light. Similar results were obtained in the dark.
[b] With Ag_2O (1.5 equiv.) under air.
[c] Along with a complex mixture including polymers.

range of substrates (Table 1). For NPOHs **1b** and **1d** substituted with a methoxyl group at the R^5 position on ring A, the biaryl coupling took place smoothly to afford the corresponding BNPOH **2** in excellent yields (entries 14 and 16). However, in the case of NPOH **1c**, the coupling reaction did not occur to yield *p*-naphthoquinone **4c** (entry 15).[12m] In the case of NPOH **1e** substituted with alkyl (methyl) in place of the R^5 methoxyl group, **2e** was obtained in CH_2Cl_2, but the yield was lower (52%) (entry 18). Alternatively, in the case of the naphthol-ethers **1i** and **1j** corresponding to **1a** and **1b**, the coupled products were hardly obtained under similar conditions, and entry 20 shows that prolonged reaction gave **3a** in only 4% yield. These results show that the hydroxyl group in NPOHs, including **1a**,**b**,**d**,**e**, is important for the coupling reaction, in contrast with the previous report on the Scholl reaction.[19] Next, the oxidation of **1a**,**b**,**d**,**e** using the well-known Ag_2O as a coupling reagent were conducted in $CHCl_3$ at 23 °C. In all cases, the yield and selectivity of coupling products in the reactions with Ag_2O were lower, in comparison with the cases using SC (entries 29–32).

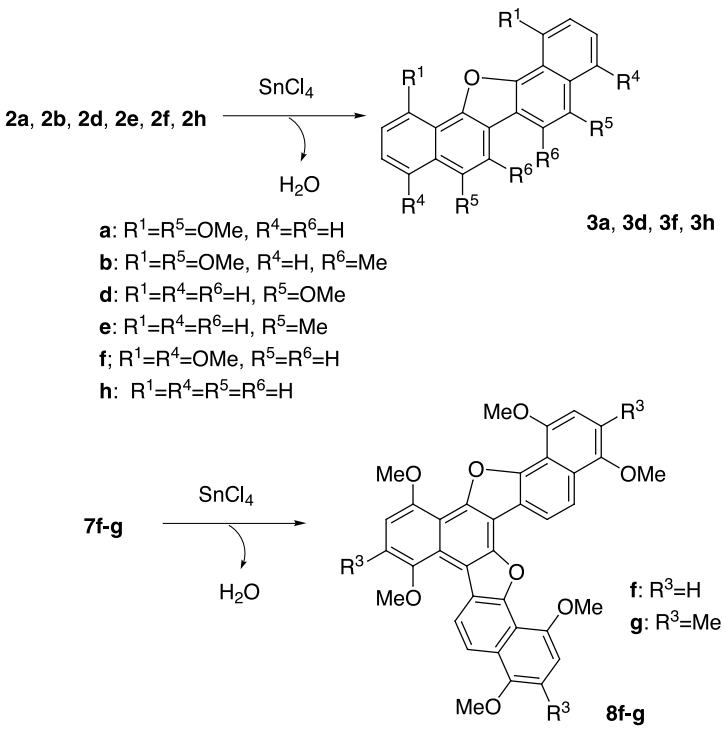
Next, the reactions of **1f**, **1g** and **1h**, which lack the methoxyl group on ring A, were carried out (Schemes 2 and 3 and Table 2). These coupling reactions were very sluggish in CH_2Cl_2. A longer period of reaction of **1f**–**g** (121 h) afforded BNPOH **2f**–**g** and the naphthol trimers **7f**–**g** and **8f**–**g** in very low yields (Table 2, entries 1 and 4). In contrast with these results, the reaction of **1f** for 4.3 h in $MeNO_2$ in place of CH_2Cl_2 gave **2f** (16%) and **3f** (8%) (entry 2), and similar reaction for 15 h afforded **8**, with the disappearance of **1f** (entry 3). However, polymeric compounds were formed in both cases. In the cases of **1f** using Ag_2O, the *o*–*o* coupled product **2f** (25%) and the *o*–*p* coupled product **9f** (30%) were obtained (entry 6).

Table 3. Reactions of the naphthols **2** and **7** with $SnCl_4$ at 100 °C[a]

Entry	NPOH	Solvent	Time (h)	Product (%)[b]		Recovered
				3	**8**	**2** (%)
1	**2a**	CH_2Cl_2	2	98		—
2[c]	**2a**	CH_2Cl_2	2.5	21		72
3	**2b**	$MeNO_2$	8	—[d]		30
4	**2d**	CH_2Cl_2	63	91		—
5	**2e**	CH_2Cl_2	23	—[d]		68
6	**2f**	$MeNO_2$	7	29		14
7	**2h**	CH_2Cl_2	118	11		58
8[d]	**7f**	$MeNO_2$	1.5	—	82	—
9	**7g**	$MeNO_2$	1	—	80	—

[a] The reaction mixture was vigorously stirred with $SnCl_4$ (1.3 equiv.) using an argon-saturated solvent at 100 °C under normal laboratory light in a sealed tube. Similar results were obtained in the dark.
[b] Isolated yield.
[c] With $SnCl_4$ (0.25 equiv.).
[d] Along with a complex mixture including polymers.

It is known that in the case of 2-substituted naphthalenes such as 2-naphthol, the regioselective coupling reaction proceed comparatively easily to afford the corresponding 1,1′-binaphthol.[4i,8a,b] However, regioselective *ortho*/*ortho*-coupling is more difficult to control in the reaction of 1-substituted naphthalenes such as 1-naphthol. There are many reports on the oxidative coupling reaction of α-naphthol **1h**.[4] In general, the coupling reaction by means of chemicals, such as $FeCl_3$,[4f,i] MnO_2,[4g] benzoyl peroxide[4a] and electrolysis[6a] is known to produce a preponderance of the *p*–*p* coupled product **10** over the *o*–*o* coupled product **2h**. The formation process of **2h** is generally believed to involve the naphthoxy radical. Poutsma et al. reported only that thermolysis of **1h** at 400 °C afforded predominantly the *o*–*o* coupled products,



Scheme 4.

2h (27%) and **3h** (33%), and **10** (3.8%), together with by-products.[7] We examined the reaction of **1h** with SC in CH_2Cl_2. Interestingly, the *ortho*/*ortho* coupling reaction proceeded regioselectively to afford **2h**[6a] in 30% yield, along with **10** (4%)[24h] and the recovered **1h** (52%) (Table 2, entry 5). This result provides some clues to the reaction mechanism via EDA complex formation of NPOH **1** with SC. The reason for this regioselectivity is discussed below.

In order to confirm the formation process of DNF **3** from NPOH **1** via BNPOH **2**, the ring closure of **2** with $SnCl_4$ (1.3 equiv.) was carried out as shown in Scheme 4 and Table 3. Both **2a** and **2d** gave the corresponding **3a** and **3d** in high yields. In the cases of **2f** and **2h**, the yields of the corresponding DNF **3** were poor. However, the reactions of **2b** and **2e** did not afford the corresponding furans **3** (entries 3 and 5). When a catalytic amount (0.25 equiv.) of SC was used, non-reacted **2a** (72%) was recovered with the formation of **3a** (21%) in the reaction of **2a** (entry 2). This result indicated that the conversion of **2** to **3** proceeded stoichiometrically. Furthermore, the naphthol trimers **7f**–**g** could be easily converted to the corresponding furans **8f**–**g** by the reaction with SC (Scheme 4).

The noteworthy features of the present reactions with SC are as follows (Scheme 5).

(1) BNPOH **2a**, **2b** and **2d** were obtained in a comparatively short time (18–24 h) in satisfactory to excellent yield by the reactions of the corresponding NPOH **1a**, **1b** and **1d** with SC (1.3 equiv.), while prolonged reaction (56–65 h) of **1a** and **1d** under the same conditions gave DNF **3a** and **3d** in high yield. These reactions can be conveniently performed with electron-rich NAP having a methoxyl group at the R^5 position on ring A.

(2) However, there is an exception in the case of **1c** as a substrate; the coupling reaction to **2c** did not take place. The reason for this may be that **1c** is much more oxidizable than the other compounds because it has the lowest oxidation potential (0.82 V vs Ag/AgCl), as described below.

(3) The reaction of **1h** without a substituent other than the hydroxyl group regioselectively afforded **2h** as a major product.

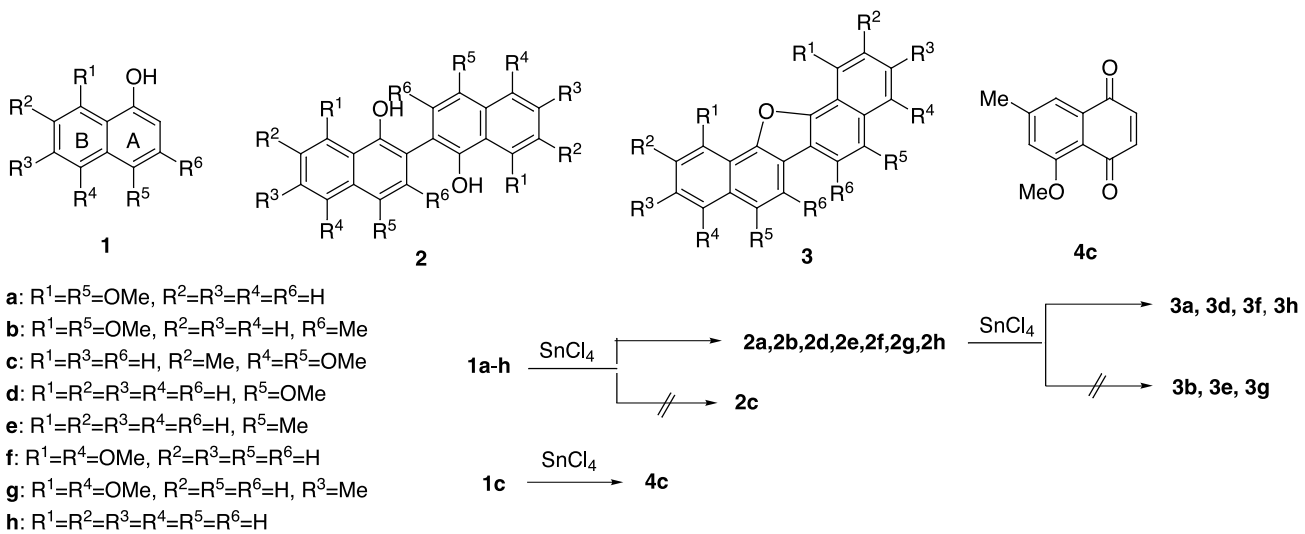
(4) BNPOHs **2b**, **2e** and **2g** having a methyl group on ring A or B could not be converted to the corresponding DNFs **3b**, **3e** and **3g**. The reason for this is considered as follows: in the case of **2b**, it is due to the steric hindrance of a methyl group at the R^6 position; in the cases of **2e** and **2g**, it is owing to side-chain oxidation, including C–H bond cleavage[20] of the methyl group, which is preferred to hydroxyl group deprotonation on ring A.

(5) The different yields of **2** or **3**, the formation of different products, and the different reaction times in the present reactions with SC are a consequence of the structural differences. In particular, the methoxyl group at R^5 on ring A plays an important role in the oxidation of NPOH. That is, the methoxyl group is considered not only to activate the NPOH ring for the formation of the EDA complex with SC, but also to inhibit the production of polymeric compounds, including **8**, via reaction at the substituted position (R^5 position). This consideration is also supported by the electrochemical studies described below.

2.1. Electrochemistry of naphthol derivatives 1, 2 and 7

In general, electron-donating or electron-accepting ability is reflected in the oxidation or reduction potential one of compounds.[21] Therefore, the oxidation potentials (the half-wave potential ($E_{1/2}$), V vs Ag/AgCl) of the first one-electron transfer from **1**, **2** or **7** in argon-saturated CH_2Cl_2 and $MeNO_2$ were measured by cyclic voltammetry (CV). In all cases, irreversible waves were observed. The results are summarized in Table 4. On the other hand, the first half-wave reduction potential of SC in CH_2Cl_2 was also measured by CV. The irreversible wave was observed, but it was not clear.

The oxidation potentials of **1**, **2** and **7** in $MeNO_2$ showed lower values than those in CH_2Cl_2, i.e. a solvent effect of $MeNO_2$ was observed. In fact, the oxidations with SC in



Scheme 5.

Table 4. Oxidation potentials in the first wave of the naphthol derivatives **1**, **2** and **7** in CH_2Cl_2 or $MeNO_2$[a]

Entry	Naphthol	CH_2Cl_2 $+E^{ox}_{1/2}$	$MeNO_2$ $+E^{ox}_{1/2}$
1	**1a**	0.95	0.77
2	**1b**	1.02	0.87
3	**1c**	0.82	0.64
4	**1d**	0.95	0.70
5	**1e**	1.10	0.93
6	**1f**	1.09	0.89
7	**1g**	1.14	0.93
8	**1h**	1.16	1.06
9	**1i**	0.97	0.78
10	**1j**	1.08	0.88
11	**2a**	0.84	0.65
12	**2b**	1.02	0.87
13	**2d**	—[b]	0.58
14	**2e**	0.83	0.78
15	**2f**	1.09	0.83
16	**2g**	1.04	0.72
17	**2h**	1.01	0.88
18	**7f**	0.75	0.68
19	**7g**	0.75	0.65

[a] Potentials (V) are vs Ag/AgCl; all substrates were measured in the range of about 0.0–2.0 V. The oxidation potentials of anodic current (E) were obtained by cyclic voltammetry of 0.1 mM solutions of the substrates in an argon-saturated solvent (CH_2Cl_2 or $MeNO_2$) containing 0.1 M *n*-Bu_4NClO_4 as a supporting electrolyte at a Pt (platinum)-electrode. The voltage scan rate in cyclic voltammetry was 100 mV s^{-1} at 23 °C. $E^{ox}_{1/2}$=the first half-wave oxidation potential.

[b] Oxidation potential of **2d** could exactly not be measured since **2d** is poorly soluble in CH_2Cl_2.

$MeNO_2$ proceeded more rapidly than those in CH_2Cl_2 in all cases. However, complex mixtures including polymeric compounds were observed in almost all cases. The oxidation potential of **2d** could not be measured exactly, because of the poor solubility of **2d** in CH_2Cl_2.

The oxidation potentials of NPOH **1**, except for **1i** (+0.97 V) and **1j** (+1.08 V), in CH_2Cl_2 increased in the order of **1c** (+0.82 V)<**1a**=**1d** (+0.95 V)<**1b** (+1.02 V)<**1f** (+1.09 V)<**1e** (+1.10 V)<**1g** (1.14 V)<**1h** (+1.16 V) (Table 4). NPOH **1c** having two methoxyl groups showed the lowest oxidation potential, whereas **1h**, which lacks a methoxyl group, showed the highest oxidation potential among NPOHs **1**. The oxidation potentials of BNPOH **2** are slightly lower than or almost equal to those of the corresponding monomers **1** (entries 11–17). The trimeric furans **7f**–**g** have the lowest oxidation potential of all the compounds (entries 18–19).

A comparison of the oxidation potentials of NPOH **1** indicated that a methoxyl (–OMe) or a methyl (–Me) group has a different substituent effect depending on the substituted position as follows: (i) –OMe at the R^5 or R^4 position, and –Me at R^5 decreased the oxidation potential due to their electron-donating effect (compare the oxidation potential of **1h** with that of **1d**, **1e** or **1f**); (ii) in contrast, –Me at R^3 or R^6 slightly increased the oxidation potential (compare **1a** with **1b** or **1f** with **1g**); (iii) –OMe at R^1 has no influence on the oxidation potential, presumably due to hydrogen-bond formation (compare **1a** with **1d**)[25]; (iv) the effect of the hydroxyl group on ring A is similar to that of –OMe at the same position (compare **1a** with **1i** or **1b** with **1j**). Among these substituents, –OMe at R^5 showed the strongest substituent effect, namely, electron-donating effect, and in fact the oxidation potential of **1d** (+0.95 V) is greatly shifted towards lower potential at 0.21 V as compared with that of **1h** (+1.16 V).

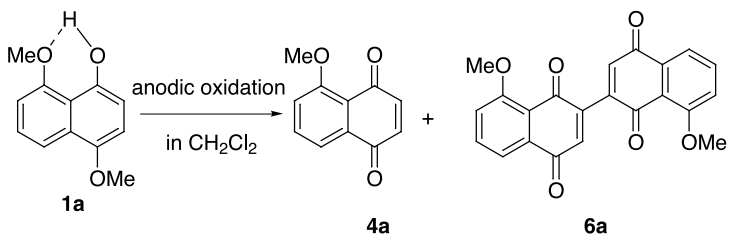
Furthermore, we examined the electrochemical reaction of **1a** in argon-saturated CH_2Cl_2 under constant potential conditions in an undivided cell (Scheme 6). Since the first wave onset oxidation potential and the half-wave oxidation potential of **1a** are 0.75 and 0.95 V (vs Ag/AgCl), anodic oxidation was conducted at the corresponding potentials. The reaction at 0.80 or 0.95 V gave **4a** in a yield of 60 or 34% and **6b** in a yield of 23 or 11%, respectively (Scheme 6). These results are clearly different from those of the reaction with SC.

The electrochemical studies suggested that NPOH **1a**–**d** having –OMe at the R^5 position (oxidation potentials range from 0.82 to 1.02 V) are stronger donors than **1e**–**h**. In addition, they interact strongly with SC, and one-electron transfer to SC takes place more easily to form the corresponding radical cation species.

2.2. Proposed mechanism for the SC-mediated oxidative reaction of NPOH

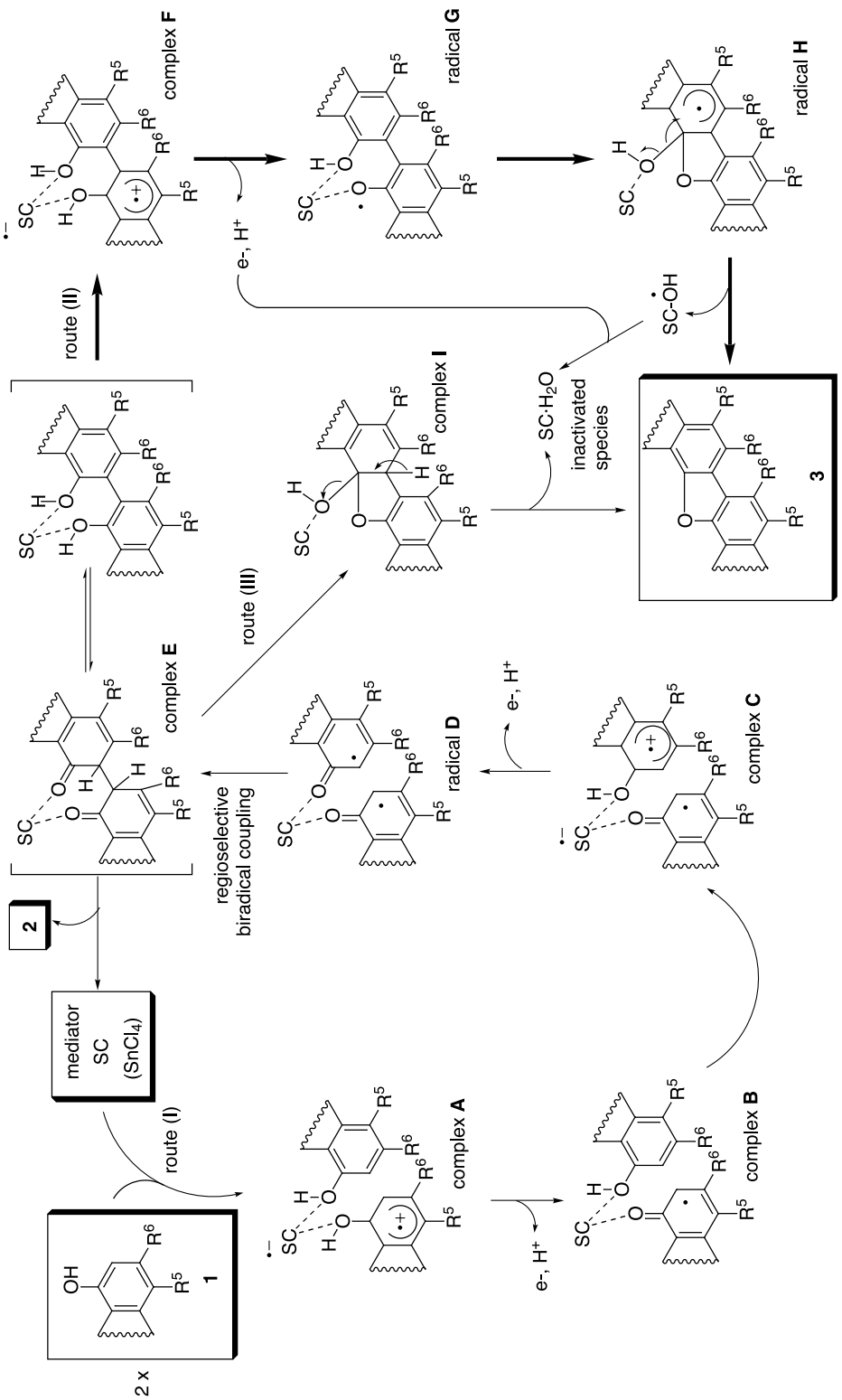
The proposed mechanism for the SC-mediated oxidative reaction of **1** to **2** or **3** is illustrated in Scheme 7. This is slightly revised from the mechanism proposed in our previous report, on the basis of further experiments and novel information described below. The additional experiments showed that the oxidative coupling of **1** proceeded with a catalytic cycle of SC, while the transformations of **2** to **3** proceeded stoichiometrically. In addition, the reaction of 1-naphthol **1h** without any substituent gave regioselectively the *o*–*o* coupled product **2h** as described above. In particular, this result provides a clue for analysis of the mode of coordination in the EDA complex formed by NPOH **1** with SC.

It is known that SC forms six coordination complexes, as a σ-type EDA complex, with hydroxyarenes[12k] and aromatic aldehydes[12c,h,l] as an *O*-donor, etc., or with pyridine[12i] and



1a **4a** **6a**

Scheme 6.


2 x
1
route (I)
mediator
SC
(SnCl4)
2
complex A
complex B
complex C
radical D
complex E
regioselective
biradical coupling
route (II)
complex F
radical G
radical H
route (III)
complex I
e-, H+
SC·H2O
inactivated
species
SC-OH
3

Scheme 7.

2,2′-bipyridine[12j] as an *N*-donor, etc. There are two limiting modes of complexation of NPOH **1** with SC: the 2:1 complex or the 1:1 complex (**1** to $SnCl_4$). Yamamoto and co-workers reported that the σ-type EDA complex is formed between SC and two hydroxyl moieties as *O*-donors in 1,1′-binaphthol.[12a] In addition, Denmark et al.[12c,d] showed by ^{13}C NMR and ^{119}Sn NMR spectral studies that an octahedral 2:1 complex (aldehyde or HMPA to $SnCl_4$) is the coordinated species present upon combination of 4-*tert*-butylbenzaldehyde or HMPA (hexamethylphosphorus triamide) with SC. From the regioselective formation of **2h** and the above information, we believe that an octahedral 2:1 complexes can form rather than the 1:1 complexes proposed previously by us, in the coordination of **1** with SC as shown in Scheme 7. This reaction is initiated by the formation of the EDA complex **A** of two NPOH **1** with SC. Solvents such as CH_2Cl_2 and $MeNO_2$ receive one-electron transfer from the anion radical species ($SC^{-\cdot}$) and subsequent one-proton transfer from the NPOH site to reform SC. The regioselective *ortho*/*ortho* coupling for the formation of **2** proceeds via radical **D**, which is the σ-type complex involving SC and two carbonyl moieties.

The formation mechanism of **3** from **1** can be rationalized in terms of biaryl coupling within radical **D** and subsequent ring closure to form the DNF ring, based on the results listed in Table 3, entries 1, 2, 4 and 6. Although the exact mode of ring closure is not clear, we believe that it may proceed via radical pathways[22] involving the formation of H_2O (the naphthoxy radical-induced reaction) as shown by the bold arrows, rather than nonradical pathways[8b] (the Lewis acid-promoted dehydration pathway) because of the formation of polymeric compounds (including **8**) as described above (Table 2, entries 1–3 and Table 3, entry 6). In this step, SC is inactivated by the resulting H_2O. In the present oxidation, SC plays an important role. That is, it acts not only as a characteristic Lewis acid catalyst, but also as a mediator for electron transfer. Alternatively, CH_2Cl_2 and $MeNO_2$ used as

Table 5. ^{13}C and ^{1}H NMR spectral data (δ/ppm) for compounds **2f**,[a] **3f**,[a] **7f**[b] and **7g**[b]

Carbon	**2f**		**3f**		**7f**		**7g**	
No.	^{13}C	^{1}H[c]	^{13}C	^{1}H[c]	^{13}C	^{1}H[c]	^{13}C	^{1}H[c]
1	151.2		149.3		150.5		150.3	
2	121.3		105.8	6.85 d (8.5)	105.1	7.14 d (8.6)	109.9	6.85s
3	112.6	7.49 d (8.5)	104.0	6.96 d (8.5)	106.7	7.20 d (8.6)	125.1	
4	130.3	7.79 d (8.5)	150.0		150.1		146.8	
4a	127.9		125.8		121.5		126.3	
5	150.5		117.5	8.26 d (8.8)	115.8	8.06 d (9.2)	116.1	7.99 d (9.2)
6	103.6	6.67 d (8.5)	118.2	8.11 d (8.8)	123.48	8.71 d (9.2)	123.67	8.80 d (9.2)
6a			120.9		122.1		120.4	
6b			120.9		123.52		106.4	
6c					114.9		123.69	
7	103.1	6.70 d (8.5)	118.2	8.11 d (8.8)	148.3		147.8	
8	150.4		117.5	8.26 d (8.8)	107.5	6.89 d (8.5)	128.0	
8a	115.8		125.8					
9			150.0		104.2	6.87 d (8.5)	108.0	7.12s
10			104.0	6.96 d (8.5)	149.1		152.6	
10a					113.7		112.3	
11			105.8	6.85 d (8.5)	152.0		151.4	
12			149.3		108.2		107.2	
12a			115.0		154.1		154.5	
12b			151.0					
13a			151.0					
13b			115.0					
1′	151.2				151.8		152.1	
2′	121.3				107.4		113.7	
3′	112.6	7.49 d (8.5)			130.3	7.59 d (8.6)	131.0	7.66 d (8.5)
4′	130.3	7.79 d (8.5)			111.0	7.74 d (8.6)	111.9	7.63 d (8.5)
4a′	127.9				127.2		129.8	
5′	150.5				149.3		147.1	
6′	103.6	6.67 d (8.5)			104.15[d]	6.92 d (8.6)	125.4	
7′	103.1	6.70 d (8.5)			104.17[d]	6.96 d (8.6)	107.3	6.93s
8′	150.4				149.7		151.8	
8a′	115.8				115.1		114.1	
Others[e,f]								

Assignment based on $^{1}H-^{1}H$ COSY, $^{1}H-^{13}C$ COSY and HMBC spectra.

[a] Data recorded in $CDCl_3$ at 500 MHz (^{1}H NMR) and 125 MHz (^{13}C NMR).

[b] Data recorded in CD_3SOCD_3 at 500 MHz (^{1}H NMR) and 125 MHz (^{13}C NMR).

[c] Coupling constants (*J* in Hz) are given in parentheses.

[d] Interchangeable.

[e] ^{13}C NMR; **2f**: 55.9 (5- and 5′-OMe), 56.4 (8- and 8′-OMe). **3f**: 56.8 (1 and 12-OMe), 55.9 (4- and 9-OMe). **7f**: 57.0 (1-OMe), 55.3 (4-OMe), 56.28 (7-OMe), 55.7 (10-OMe), 55.6 (5′-OMe), 56.31 (8′-OMe). **7g**: 15.6 (3-Me), 15.9 (8-Me), 15.5 (6′-Me), 55.9 (1-OMe), 60.5 (4-OMe), 60.2 (7-OMe or 5′-OMe), 56.8 (10-OMe), 60.3 (7-OMe or 5′-OMe), 56.2 (8′-OMe).

[f] ^{1}H NMR; **2f**: 3.96 (s, 5- and 5′-OMe), 3.99 (s, 8- and 8′-OMe), 9.86 (s, 1- and 1′-OH). **3f**: 4.23 (s, 1- and 12-OMe), 4.03 (s, 4- and 9-OMe). **7f**: 4.10 (s, 1-OMe), 4.16 (s, 4-OMe), 3.53 (s, 7-OMe), 3.96 (s, 10-OMe), 3.99 (s, 5′-OMe), 4.01 (s, 8′-OMe), 10.63 (s, 11-OH), 9.94 (s, 1′-OH). **7g**: 2.45 (s, 3-Me), 2.62 (s, 8-Me), 2.49 (s, 6′-Me), 3.64 (s, 1-OMe), 3.90 (s, 4-OMe), 3.71 (s, 7-OMe), 4.17 (s, 10-OMe), 3.91 (s, 5′-OMe), 4.08 (s, 8′-OMe), 10.35 (s, 11-OH), 9.73 (s, 1′-OH).

solvents may also act as one-electron and one-proton acceptors[23] from the anion radical species (SC−·) and NPOH, playing the same role as that of O_2 reported previously by us.[16b] The difference of reactivities in CH_2Cl_2 or $MeNO_2$ may be based on the difference of one-electron accepting ability from the anion radical species (SC−·).

2.3. Structure of the novel trimeric furan 7f

The structure of **7f** was elucidated by means of detailed analyses of the ^1H and ^{13}C NMR spectra with the aid of various 2D NMR experiments, and also by chemical transformation to **8f** as shown in Scheme 4.

All ^1H and ^{13}C NMR signal assignments, except for those of the carbons C6′ and C7′, were confirmed by means of H–H COSY, C–H COSY and HMBC spectral analyses and by comparison of the spectra with those of the reference compounds **2f** and **3f** (which were synthesized by us) (refer to Table 5 and Figures 1 and 2).

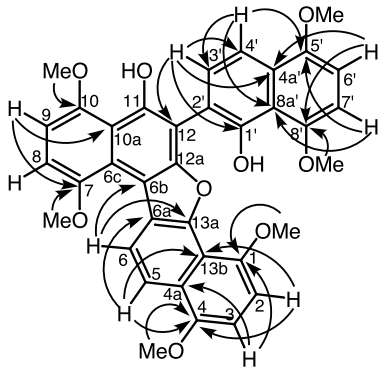


Figure 1. Long range $^1H-^{13}C$ correlations of **7f** in the HMBC spectrum.

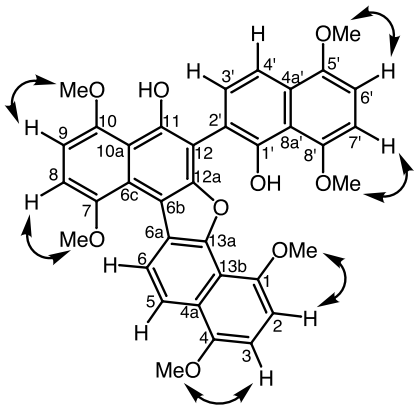


Figure 2. NOE interactions observed in the NOESY spectrum of **7f**.

The ^1H NMR spectrum of **7f** showed the following features: (i) two pairs of *ortho*-coupled aromatic protons at δ 8.06 (d, J=9.2 Hz) and δ 8.71 (d, J=9.2 Hz) assignable to protons at C1 and C6, and aromatic protons at δ 7.59 (d, J=8.6 Hz) and δ 7.74 (d, J=8.6 Hz) assignable to the protons at C3′ and C4′; (ii) a singlet (δ 3.53) of C(7)-OMe, presumably due to the shielding effect of the dinaphthofuran ring, was observed at higher field as compared with the other singlet signals of Ar-OMe at δ 3.96, 3.99, 4.01, 4.10 and 4.16. The ^{13}C NMR spectrum of **7f** displayed signals for all 36 carbons in the molecule: six aromatic methoxyls, and 30 aromatic carbons, ten of which were protonated, ten quaternary, and ten bearing oxygen (Table 5). The reaction of **7f** with SC gave the trimer **8f** in 82% yield (refer to Scheme 4). Accordingly, the above data proved that **7f** has a naphthol trimer structure with a dinaphthofuran unit and a naphthol unit. The structure of **7g** was also elucidated by similar analysis.

3. Conclusion

In conclusion, SC-mediated oxidation of NPOHs **1** made it possible to control the synthesis in the direction of either BNPOH or the DNF framework. For example, the reaction of **1a**, **1b**, or **1d** with SC for a short time (18–24 h) afforded the corresponding BNPOH **2a**, **2b** or **2d** in excellent yield, while prolonged reaction (56–65 h) of **1a** or **1d** under the same conditions gave DNF **3a** or **3d** in high yield. For the formation of BNPOH and DNF frameworks through the present oxidation, NPOHs such as **1a**, **1b**, **1d** substituted with –OMe at the R^5 position in the range of oxidation potential from 0.95 to 1.02 V in CH_2Cl_2, are concluded to be the best substrates. The resulting products **2a**, **2b** and **2g** would be useful synthetic intermediates for naturally occurring 2,2′-bijuglone, 3,3′-biplumpugin and elliptinone. We will report the syntheses of these natural products in the following article.

4. Experimental

4.1. General

All melting points are uncorrected. IR and UV spectra were recorded on a JASCO IR-700 and a JASCO Ubest-55 spectrometer. ^1H and ^{13}C NMR spectra were recorded on JEOL JNM-AL300 and JNM-alpha 500 spectrometers, with tetramethylsilane as an internal standard ($CDCl_3$, CD_3COCD_3 and CD_3SOCD_3 solution). Mass spectra were recorded on a JEOL JMS-D300 or a Shimadzu QP-5000 spectrometer. Elemental analyses were done using a Yanaco CHN-MT-3 apparatus. Merck Kieselgel 60 (230–400 mesh), Wako silica gel C-200 (200 mesh) and Merck Kieselgel 60 F_{254} were used for flash column chromatography, column chromatography and thin-layer chromatography (TLC), respectively. Each organic extract was dried over $MgSO_4$ or Na_2SO_4. Oxidation and reduction potentials were measured on a Yanaco P-1100 voltammetric analyzer by cyclic voltammetry. Storage and handling of $SnCl_4$: $SnCl_4$ should be stored in container with silica gel, blue, middle granule to minimize exposure to moisture. The container should be flushed with N_2 or Ar and tightly sealed. Perform all manipulations under N_2 or argon. All reactions were carried out in the anhydrous state.

4.2. The oxidation potentials of 1a–h, 2a–b, 2d–h and 7f–g, the reduction potential of $SnCl_4$, and the charge-transfer absorptions of the EDA complex of 1a with $SnCl_4$

The oxidation potentials shown in Table 4, and the reduction potential of $SnCl_4$ were measured by cyclic voltammetry

using an Ag/AgCl reference electrode at a platinum electrode with 0.1 M tetrabutylammonium perchlorate as a supporting electrolyte in an argon-saturated solvent (CH_2Cl_2 or $MeNO_2$). The charge-transfer absorption described in the text were measured soon after mixing **1a** (7.65×10^{-5} M) with $SnCl_4$ (7.98×10^{-5} M) in argon-saturated CH_2Cl_2.

4.3. Synthesis of 1-naphthols 1a–j

1-Naphthols **1a**,[17a,b] **1b**,[17c] **1c**,[17d–f] **1f**,[17g] and **1g**[17h] were synthesized according to the protocol reported previously, and **1d** and **1h** are commercially available (Tokyo Kasei Chemical Industries, Ltd., Japan).

4.3.1. 4-Methyl-l-naphthol (1e). A solution of 4-methy1-1-naphthalenecarboxaldehyde (100 mg, 0.59 mmol) and *m*-chloroperbenzoic acid (303 mg, 1.76 mmol, purity;80%) in CH_2C1_2 (10 ml) was rapidly stirred for 19 h. Aqueous sodium thiosulfate (4 ml, 10% solution) was introduced, and after being stirred for 30 min the mixture was poured into an additional 8 ml of aqueous thiosulfate and vigorously shaken. The phases were separated, the aqueous phase was extracted with CH_2Cl_2, and the organic phase was washed successively with aqueous thiosulfate and brine, dried, and evaporated to give 6.87 g (29.7 mmol, 99%) of crude formate. The crude formate was dissolved in acetone (10 ml) and cooled in an ice bath, ice-cold 10% aqueous HCl (3 ml) was added, and the whole was refluxed for 4 h. The reaction mixture was poured into ice-water and extracted with CH_2C1_2. The organic phase was washed sequentially with water and brine, then dried, and evaporated. The residue was subjected to flash chromatography (AcOEt–hexane=1:10) to yield **1e** (81 mg, 87%), as colorless needles (petroleum ether), mp 81–81.5 °C (lit.[24g] 80–81 °C). IR (KBr) cm^{-1}: 3434, 3374, 1589, 1513. ^1H NMR ($CDCl_3$) δ: 2.61 (3H, s, 4-Me), 5.08 (1H, s, 1-OH), 6.72 (1H, d, J=7.5 Hz, 2-H), 7.13 (1H, dd, J=0.9, 7.5 Hz, 3-H), 7.47–7.57 (2H, m, 6 and 7-H), 7.92–7.95 (1H, m, 5-H), 8.19–8.22 (1H, m, 8-H). LR-MS *m/z*: 158 (M^+). HR-MS calcd for $C_{11}H_{10}O$: 158.0729. Found: 158.0771.

4.3.2. 1,4,5-Trimethoxynaphthalene (1i). A solution of $SnCl_2{\cdot}2H_2O$ (2.9 g) in conc. HCl (2.9 ml) was added to a solution of 5-methoxy-1,4-naphthoquinone (667 mg, 3.5 mmol) in 95% EtOH (28 ml) under a nitrogen atmosphere at 0 °C, and the mixture was stirred at ambient temperature for 30 min. To the reaction mixture was added Me_2SO_4 (4.79 ml), followed by 25% KOH solution (44.8 ml), and the whole was stirred for 15 min. The reaction mixture was poured into ice water and acidified with dilute HCl, and the whole was extracted with ether. The organic layer was washed with H_2O, then dried with Na_2SO_4, and concentrated. The residue was subjected to flash chromatography (AcOEt–hexane=1:8) to yield **1i** (549 mg, 72%), as a light blue amorphous powder (MeOH), mp 117–118 °C (lit.[24e] 116–117.5 °C). IR (KBr) cm^{-1}: 2944, 2908, 2832, 1595. ^1H NMR ($CDCl_3$) δ: 3.92 (3H, s, OMe), 3.94 (3H, s, OMe), 3.97 (3H, s, OMe), 6.73 (1H, d, J=8.5 Hz, Ar-H), 6.79 (1H, d, J=8.5 Hz, Ar-H), 6.91 (1H, d, J=7.8 Hz, Ar-H), 7.83 (1H, dd, J=7.8, 8.5 Hz, Ar-H), 7.86 (1H, d, J=8.5 Hz, Ar-H). ^{13}C NMR ($CDCl_3$) δ: 55.8, 56.4, 57.4, 104.2, 106.7, 107.1, 114.6, 118.4, 125.9, 128.8, 149.6, 150.8, 156.7. MS *m/z*: 218 (M^+). HR-MS calcd for $C_{13}H_{14}O_3$: 218.0943. Found: 218.0956.

4.3.3. 1,4,5-Trimethoxy-2-methylnaphthalene (1j). A solution of $SnCl_2{\cdot}2H_2O$ (2.9 g) in conc. HCl (2.9 ml) was added to a solution of 5-methoxy-2-methyl-1,4-naphthoquinone[17] (667 mg, 3.5 mmol) in 95% EtOH (28 ml) under a nitrogen atmosphere at 0 °C, and the mixture was stirred at ambient temperature for 30 min. To the reaction mixture was added Me_2SO_4 (4.79 ml), followed by 25% KOH solution (44.8 ml), and the whole was stirred for 15 min. The reaction mixture was poured into ice water and acidified with dilute HCl, and the whole was extracted with ether. The organic layer was washed with H_2O, then dried with Na_2SO_4, and concentrated. The residue was subjected to flash chromatography (AcOEt–hexane=1:8) to yield (549 mg, 72%), as light yellow crystals (hexane), mp 68.5–69 °C (lit.[24f] 69–70 °C). IR (KBr) cm^{-1}: 2930, 2840, 1601. ^1H NMR ($CDCl_3$) δ: 2.41 (3H, s, Me), 3.81 (3H, s, OMe), 3.91 (3H, s, OMe), 3.94 (3H, s, OMe), 6.63 (1H, s, C3-H), 6.79 (1H, d, J=7.5 Hz, C6-H), 7.37 (1H, dd, J=7.5, 8.2 Hz, C7-H), 7.66 (1H, dd, J=0.9, 8.3 Hz, C8-H). ^{13}C NMR ($CDCl_3$) δ: 16.1, 56.3, 56.8, 60.9, 105.7, 109.4, 114.4, 117.0, 126.4, 126.5, 131.4, 147.1, 153.0, 157.3. MS *m/z*: 232 (M^+). HR-MS calcd for $C_{14}H_{16}O_3$: 232.1100. Found: 232.1075.

4.4. General procedure for oxidative reaction of naphthols 1, 2 and 7 with various acceptors such as $SnCl_4$, $TiCl_4$ and $AlCl_3$ in CH_2Cl_2 or $MeNO_2$ as a solvent

The acceptor (1.3, 0.5 or 0.25 equiv.) was added to a solution of the naphthol (1 mmol) in the solvent listed above (20 ml) and the mixture was stirred for 20 min at room temperature under normal laboratory light in an argon atmosphere. Then, the reaction mixture was heated in a sealed tube with stirring until disappearance of the naphthol, except in the cases where the starting material was recovered. The reaction mixture was poured into ice water, 10% HCl was added, and the whole was extracted with $CHCl_3$. The organic layer was washed with H_2O, then dried and concentrated. The residue was subjected to flash column chromatography on silica gel with the designated solvents as follows: AcOEt–hexane (1:6; for **2a** and **3a** in Table 1); CH_2Cl_2–hexane (2:1; for **2f**, **7f** and **8f** in Table 2); CH_2Cl_2–hexane (2:1; for **2f**, **3f** and **8f** in Table 2); CH_2Cl_2–hexane (2:1; for **2g**, **7g** and **8g** in Table 2); CH_2Cl_2–hexane (2:1; for **2h** and **10** in Table 2). Yields for **2a–b**, **2d**, **2e–h**, **3a**, **3d**, **3f–g**, **6d**, **5c**, **5d**, **7f–g**, **8f–g**, **10** are listed in Tables 1–3. Similar results were obtained when the reactions were carried out in the dark.

4.4.1. 4,4′,8,8′-Tetramethoxy-2,2′-di-1,1′-naphthol (2a). Colorless needles ($CHCl_3$–hexane), mp 207–209 °C. IR (KBr) cm^{-1}: 3348, 1646, 1606, 1584. ^1H NMR ($CDCl_3$) δ: 3.95 (6H, s, 4 and 4′-OMe), 4.03 (6H, s, 8 and 8′-OMe), 6.87 (2H, d, J=8.6 Hz, 7 and 7′-H), 6.92 (2H, s, 3 and 3′-H), 7.35 (2H, t, J=8.6 Hz, 6 and 6′-H), 7.89 (2H, d, J=8.6 Hz, 5 and 5′-H), 9.87 (2H, s, 1 and 1′-OH). ^{13}C NMR ($CDCl_3$) δ: 56.0 (C4 and C4′-O*Me*), 56.1 (C8 and C8′-O*Me*), 105.2 (C7 and C7′), 109.4 (C3 and C3′), 115.7 (C8a and C8a′), 116.0 (C5 and C5′), 119.4 (C2 and C2′), 125.0 (C6 and C6′), 127.6 (C4a and C4a′), 144.7 (C1 and C1′), 147.6 (C4 and C4′),

156.2 (C8 and C8′). LR-MS *m*/*z*: 406 (M^+). HR-MS calcd for $C_{24}H_{22}O_6$: 406.1416. Found: 406.1433. Anal. calcd for $C_{24}H_{22}O_6$: C, 70.92; H, 5.46. Found: C, 70.82; H, 5.43.

4.4.2. 1,5,8,12-Tetramethoxydinaphtho[1,2-*b*:1′,2′-*d*]-furan (3a). Colorless needles ($CHCl_3$–hexane), mp 300–303 °C. IR (KBr) cm^{-1}: 1692, 1589. ^1H NMR ($CDCl_3$) δ: 4.15 (6H, s, 5 and 8-OMe), 4.27 (6H, s, 1 and 12-OMe), 7.09 (2H, d, *J*=7.9 Hz, 2 and 11-H), 7.34 (2H, s, 6 and 7-H), 7.47 (2H, t, *J*=7.9, 8.2 Hz, 3 and 7-H), 8.01 (2H, d, *J*=8.2 Hz, 4 and 9-H). ^{13}C NMR ($CDCl_3$) δ: 56.0 (C5- and C8-O*Me*), 56.3 (C1 and C12-O*Me*), 96.2 (C6 and C7), 106.6 (C2 and C11), 114.7 (C12a and C13b), 115.3 (C4 and C9), 119.7 (C6a and C6b), 125.2 (C3 and C10), 126.7 (C4a and C8a), 145.8 (C12b and C13a), 151.7 (C5 and C8), 155.0 (C1 and C12). LR-MS *m*/*z*: 388 (M^+). HR-MS calcd for $C_{24}H_{20}O_5$: 388.1311. Found: 388.1334. Anal. calcd for $C_{24}H_{20}O_5$: C, 74.21; H, 5.19. Found: C, 74.19; H, 5.18.

4.4.3. 4,4′,8,8′-Tetramethoxy-3,3′-dimethyl[2,2′]di-1,1′-naphthol (2b). Colorless needles ($CHCl_3$–MeOH), mp 251–252 °C. IR (KBr) cm^{-1}: 3372, 1606. ^1H NMR ($CDCl_3$) δ: 2.10 (6H, s, 3 and 3′-Me), 3.87 (6H, s, 4 and 4′-OMe), 3.99 (3H, s, 8 and 8′-OMe), 6.77 (2H, d, *J*=7.7 Hz, 7 and 7′-H), 7.35 (2H, dd, *J*=7.7, 7.9 Hz, 6 and 6′-H), 7.74 (2H, d, *J*=7.9 Hz, 5- and 5′-H), 9.38 (2H, s, 1 and 1′-OH). ^{13}C NMR ($CDCl_3$) δ: 13.2 (C3 and C3′-Me), 56.0 (C8 and C8′-O*Me*), 61.2 (C4 and C4′-O*Me*), 103.6 (C7 and C7′), 114.1 (C8a and C8a′), 115.8 (C5 and C5′), 120.2 (C2 and C2′), 125.5 (C6 and C6′), 128.7 (C4a and C4a′), 130.0 (C3 and C3′), 146.2 (C1 and C1′), 147.1 (C4 and C4′), 156.5 (C8 and C8′). LR-MS *m*/*z*: 434 (M^+). HR-MS calcd for $C_{26}H_{26}O_6$: 434.1730. Found: 434.1766. Anal. calcd for $C_{26}H_{26}O_6$: C, 71.87; H, 6.03. Found: C, C, 71.67; H, 6.00.

4.4.4. 4,4′-Dimethoxy[2,2′]binaphthalenyl-1,1′-diol (2d). Colorless needles (benzene), mp 223–224 °C (lit.[24a] 206–207 °C). IR (KBr) cm^{-1}: 3434, 1596. ^1H NMR ($CDCl_3$) δ: 3.99 (6H, s, 4 and 4′-OMe), 5.44 (2H, s, 1 and 1′-OH), 6.73 (2H, s, 3 and 3′-H), 7.58–7.61 (4H, m, Ar-H), 8.28–8.30 (4H, m, Ar-H). LR-MS *m*/*z*: 346 (M^+). HR-MS calcd for $C_{22}H_{18}O_4$: 346.1200. Found: 346.1222. Anal. calcd for $C_{22}H_{18}O_4$: C, 76.29; H, 5.24. Found: C, C, 76.19; H, 5.22.

4.4.5. 5,8-Dimethoxydinaphtho[1,2-*b*;2′,1′-*d*]furan (3d). Light blue needles (benzene), mp 215.5–216.5 °C (lit.[24b] 216–217 °C). IR (KBr) cm^{-1}: 1598, 1583. ^1H NMR ($CDCl_3$) δ: 4.12 (6H, s, 5 and 8-OMe), 7.23 (2H, s, 6 and 7-H), 7.54 (2H, ddd, *J*=1.3, 7.0, 8.4 Hz, 2 and 11-H, or 3 and 10-H), 7.67 (2H, ddd, *J*=1.3, 7.0, 8.4 Hz, 2 and 11-H, or 3 and 10-H), 8.37 (2H, broad d, *J*=8.5 Hz, 1 and 12-H, or 4 and 9-H), 8.47 (2H, broad d, *J*=7.7 Hz, 1 and 12-H, or 4 and 9-H). LR-MS *m*/*z*: 328 (M^+). HR-MS calcd for $C_{22}H_{16}O_3$: 328.1095. Found: 328.1146. Anal. calcd for $C_{22}H_{16}O_3$: C, 80.47; H, 4.91. Found: 80.37; H, 4.93.

4.4.6. 4,4′-Dimethyl[2,2′]binaphthalenyl-1,1′-diol (2e). Colorless amorphous powder ($CHCl_3$–hexane), mp 219–220 °C. IR (KBr) cm^{-1}: 3054, 2938, 1603, 1573, 1504. ^1H NMR ($CDCl_3$) δ: 2.67 (6H, d, *J*=0.7 Hz, 4 and 4′-Me), 5.59 (2H, s, 1 and 1′-OH), 7.23 (2H, d, *J*=0.7 Hz, 3 and 3′-H), 7.55–7.65 (4H, m, 6, 6′, 7 and 7′-H), 8.00 (2H, dd, *J*=1.5, 7.5 Hz, 5 and 5′-H), 8.36 (2H, dd, *J*=1.5, 7.5 Hz, 8 and 8′-H). ^{13}C NMR ($CDCl_3$) δ: 18.81 (C4 and C4′-*Me*), 115.13 (C2 and C2′), 122.95 (C8 and C8′), 124.15 (C5 and C5′), 124.73 (C8a and C8a′), 125.61 (C6 and C6′, or C7 and C7′), 126.80 (C6 and C6′, or C7 and C7′), 127.41 (C4 and C4′), 128.07 (C3 and C3′), 133.54 (C4a and C4a′), 147.46 (C1 and C1′). LR-MS *m*/*z*: 314 (M^+). HR-MS calcd for $C_{22}H_{18}O_2$: 314.1302. Found: 314.1292. Anal. calcd for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77. Found: C, 84.00; H, 5.79.

4.4.7. 1-Methoxy-7-methyl-1,4-naphthoquinone (4c). Yellow needles ($CHCl_3$–hexane), mp 169.5–170 °C (lit.[24c] 166.5–167.5 °C). IR (KBr) cm^{-1}: 1651, 1599. ^1H NMR ($CDCl_3$) δ: 2.48 (3H, s, 7-Me), 4.00 (3H, s, 5-OMe), 6.84 (2H, s, 2 and 3-H), 7.11 (1H, s, 6-H), 7.55 (1H, s, 8-H). LR-MS *m*/*z*: 202 (M^+). HR-MS calcd for $C_{12}H_{10}O_3$: 202.0627. Found: 202.0614. Anal. calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.98. Found: C, C, 71.30; H, 4.95.

4.4.8. 5,5′,8,8′-Tetramethoxy[2,2′]di-1,1′-naphthol (2f). Colorless needles (hexane–AcOEt), mp 257–260.5 °C. IR (KBr) cm^{-1}: 3358. ^1H NMR ($CDCl_3$) δ: 3.96 (6H, s, 5 and 5′-OMe), 3.99 (6H, s, 8 and 8′-OMe), 6.67 (2H, d, *J*=8.5 Hz, 6 and 6′-H), 6.70 (2H, d, *J*=8.5 Hz, 7 and 7′-H), 7.49 (2H, d, *J*=8.5 Hz, 3 and 3′-H), 7.79 (2H, d, *J*=8.5 Hz, 4 and 4′-H), 9.86 (2H, s, 1 and 1′-OH). ^{13}C NMR ($CDCl_3$) δ: 55.9 (5 and 5′-O*Me*), 56.4 (8 and 8′-O*Me*), 103.1 (C7 and C7′), 103.6 (C6 and C6′), 112.6 (C3 and C3′), 115.8 (C8a and C8a′), 121.3 (C2 and C2′), 127.9 (C4a and C4a′), 130.3 (C4 and C4′), 150.39 (C8 and C8′), 150.46 (C5 and C5′), 151.2 (C1 and C1′). LR-MS *m*/*z*: 406 (M^+). HR-MS calcd for $C_{24}H_{22}O_6$: 406.1416. Found: 406.1433. Anal. calcd for $C_{24}H_{22}O_6$: C, 70.92; H, 5.46. Found: C, 71.10; H, 5.44. Anal. calcd for $C_{24}H_{22}O_6$: C, 70.92; H, 5.46. Found: 70.62; H, 5.48.

4.4.9. 1,4,9,12-Tetramethoxydinaphtho[1,2-*b*;2′,1′-*d*]-furan (3f). Pale yellow amorphous powder (ether–hexane), mp 202–203.5 °C. IR (KBr) cm^{-1}: 2922, 1578, 1456. ^1H NMR ($CDCl_3$) δ: 4.03 (6H, s, 4 and 9-OMe), 4.23 (6H, s, 1 and 12-OMe), 6.85 (2H, d, *J*=8.5 Hz, 3 and 10-H), 6.96 (2H, d, *J*=8.5 Hz, 2 and 11-H), 8.11 (2H, d, *J*=8.8 Hz, 6 and 7-H), 8.26 (2H, d, *J*=8.8 Hz, 5 and 8-H). ^{13}C NMR ($CDCl_3$) δ: 55.9 (4 and 9-O*Me*), 56.8 (1 and 12-O*Me*), 104.0 (C3 and C10), 105.8 (C2 and C11), 115.0 (C12a and C13b), 117.5 (C5 and C8), 118.2 (C6 and C7), 120.9 (C6a and C6b), 125.8 (C4a and C8a), 149.3 (C1 and C12), 150.0 (C4 and C9), 151.0 (C12b and C13a). LR-MS *m*/*z*: 388 (M^+). HR-MS calcd for $C_{24}H_{26}O_5$: 388.1305. Found: 388.1341. Anal. calcd for $C_{24}H_{20}O_5$: C, 74.21; H, 5.19. Found: C, 74.31; H, 5.17.

4.4.10. 12-(1′-Hydroxy-5′,8′-dimethoxynaphthalen-2′-yl)-1,4,7,10-tetramethoxy-13-oxa-dibenzo[*a*,*g*]fluoren-11-ol (7f). Light brown amorphous powder ($CHCl_3$–MeOH), mp 263–265 °C. IR (KBr) cm^{-1}: 3346, 1612, 1449. ^1H NMR (CD_3SOCD_3) δ: 3.53 (3H, s, 7-OMe), 3.96 (3H, s, 10-OMe), 3.99 (3H, s, 5′-OMe), 4.01 (3H, s, 8′-OMe), 4.10 (6H, each s, 1- and 4-OMe), 6.87 (1H, d, *J*=8.5 Hz, 9-H), 6.89 (1H, d, *J*=8.5 Hz, 8-H), 6.92 (1H, d, *J*=8.6 Hz, 6′-H), 6.96 (1H, d, *J*=8.6 Hz, 7′-H), 7.14 (1H, d, *J*=8.6 Hz, 2-H), 7.20 (1H, d, *J*=8.6 Hz, 3-H), 7.59 (1H, d, *J*=8.6 Hz, 3′-H), 7.74 (1H, d, *J*=8.6 Hz, 4′-H), 8.06 (1H, d, *J*=9.2 Hz, 5-H), 8.71 (1H, d, *J*=9.2 Hz, 6-H), 9.94 (1H, s,

1′-OH), 10.63 (1H, s, 11-OH). ^{13}C NMR (CD_3SOCD_3) δ: 55.34 (4-O*Me*), 55.64 (5′-O*Me*), 55.66 (10-O*Me*), 56.28 (7-O*Me*), 56.31 (8′-O*Me*), 57.00 (1-O*Me*), 104.15 (C6′ or C7′), 104.17 (C6′ or C7′), 104.19 (C9), 105.12 (C2), 106.74 (C3), 107.39 (C2′), 107.53 (C8), 108.23 (C12), 111.03 (C4′), 113.48 (C13b), 113.73 (C10a), 114.93 (C6c), 115.09 (C8a′), 115.78 (C5), 121.46 (C4a), 122.09 (C6a), 123.48 (C6), 123.52 (C6b), 127.19 (C4a′), 130.29 (C3′), 148.28 (C7), 149.05 (C10), 149.27 (C5′), 149.31 (C13a), 149.73 (C8′), 150.09 (C4), 150.54 (C1), 151.20 (C11), 151.75 (C1′), 154.08 (C12a). LR-MS *m/z*: 606 (M^+). HR-MS calcd for $C_{36}H_{30}O_9$: 606.1881. Found: 606.1887. Anal. calcd for $C_{36}H_{30}O_9$: C, 71.28; H, 4.98. Found: C, 70.98; H, 5.05.

4.4.11. 1,4,8,11,13,16-Heptamethoxydinaphtho[2,1-*d*;2′,1′-*d*′]naphtho[1,2-*b*;3,4-*b*′]difuran (8f). Pale brown needles ($CHCl_3$–MeOH), mp 221–223 °C. IR (KBr) cm^{-1}: 1582, 1459. ^{1}H NMR ($CDCl_3$) δ: 4.05 (3H, s, OMe), 4.06 (3H, s, OMe), 4.20 (3H, s, OMe), 4.26 (3H, s, OMe), 4.29 (3H, s, OMe), 4.29 (3H, s, OMe), 6.84 (1H, d, *J*=8.6 Hz, Ar-H), 6.88 (1H, d, *J*=8.6 Hz, Ar-H), 6.977 (1H, d, *J*=8.5 Hz, Ar-H), 6.984 (1H, d, *J*=8.5 Hz, Ar-H), 7.06 (1H, d, *J*=8.6 Hz, Ar-H), 7.10 (1H, d, *J*=8.6 Hz, Ar-H), 8.23 (1H, d, *J*=9.3 Hz, Ar-H), 8.42 (1H, d, *J*=8.7 Hz, Ar-H), 8.66 (1H, d, *J*=8.7 Hz, Ar-H), 8.89 (1H, d, *J*=9.3 Hz, Ar-H). ^{13}C NMR ($CDCl_3$) δ: 55.6 (Ar-O*Me*), 55.9 (Ar-O*Me*), 56.7 (Ar-O*Me*), 56.9 (Ar-O*Me*), 57.0 (Ar-O*Me*), 103.7, 104.1, 105.4, 105.6, 105.7, 106.7, 109.6, 112.6, 113.2, 114.5, 114.7, 116.7, 118.1, 119.1, 119.9, 121.1, 123.1, 124.5, 124.9, 125.7, 149.19, 149.23, 149.4, 149.7, 149.9, 150.5, 150.9, 151.2, 151.5. LR-MS *m/z*: 588 (M^+). HR-MS calcd for $C_{36}H_{28}O_8$: 588.1776. Found: 588.1807. Anal. calcd for $C_{36}H_{28}O_8$: C, 73.46; H, 4.79. Found: C, 73.56; H, 4.77.

4.4.12. 5,5′,8,8′-Trimethoxy-6,6′-dimethyl[2,2′]di-1,1′-naphthol (2g). Colorless needles (ether–hexane), mp 229–232 °C. IR (KBr) cm^{-1}: 3378, 1618. ^{1}H NMR ($CDCl_3$) δ: 2.43 (6H, s, 6 and 6′-Me), 3.87 (6H, s, 5 and 5′-OMe), 3.88 (6H, s, 8 and 8′-OMe), 6.00 (2H, s, 7 and 7′-H), 7.51 (2H, d, *J*=8.5 Hz, 3 and 3′-H), 7.62 (2H, d, *J*=8.5 Hz, 4 and 4′-H), 9.77 (2H, s, 1 and 1′-OH). ^{13}C NMR ($CDCl_3$) δ: 16.2 (6 and 6′-*Me*), 56.3 (8 and 8′-O*Me*), 61.0 (5 and 5′-O*Me*), 107.1 (C7 and C7′), 112.4 (C3 and C3′), 114.8 (C8a and C8a′), 119.8 (C2 and C2′), 125.5 (C4a and C4a′), 130.4 (C6 and C6′), 130.9 (C4 and C4′), 148.0 (C8 and C8′), 151.5 (C5 and C5′), 152.3 (C1 and C1′). LR-MS *m/z*: 434 (M^+). HR-MS calcd for $C_{26}H_{26}O_6$: 434.1730. Found: 434.1746. Anal. calcd for $C_{26}H_{26}O_6$: C, 71.87; H, 6.03. Found: C, 71.52; H, 6.01.

4.4.13. 12-(1-Hydroxy-5,8-dimethoxy-6-methylnaphthalen-2-yl)-1,4,7,10-tetramethoxy-3,8-dimethyl-13-oxadibenzo[*a,g*]fluoren-11-ol (7g). Pale green amorphous powder ($CHCl_3$–hexane), mp 249–251 °C. IR (KBr) cm^{-1}: 3372, 1619, 1581. ^{1}H NMR (CD_3SOCD_3) δ: 2.45 (3H, s, 3-Me), 2.49 (3H, s, 6′-Me), 2.62 (3H, s, 8-Me), 3.64 (3H, s, 1-OMe), 3.71 (3H, s, 7-OMe), 3.90 (3H, s, 4-OMe), 3.91 (3H, s, 5′-OMe), 4.08 (3H, s, 8′-OMe), 4.17 (3H, s, 10-OMe), 6.85 (1H, s, 2-H), 6.93 (1H, s, 7′-H), 7.12 (1H, s, 9-H), 7.63 (1H, d, *J*=8.5 Hz, 4′-H), 7.66 (1H, d, *J*=8.5 Hz, 3′-H), 7.99 (1H, d, *J*=9.2 Hz, 5-H), 8.80 (1H, d, *J*=9.2 Hz, 6-H), 9.73 (1H, s, 1′-OH), 10.35 (1H, s, 11-OH). ^{13}C NMR (CD_3SOCD_3) δ: 15.50 (C6′-*Me*), 15.59 (C3-*Me*), 15.88 (C8-*Me*), 55.88 (C1-O*Me*), 56.21 (C8′-O*Me*), 56.82 (C10-O*Me*), 60.21 (C7 or C5′-O*Me*), 60.25 (C7 or C5′-O*Me*), 60.48 (C4-O*Me*), 106.43 (C6b), 107.21 (C12), 107.31 (C7′), 107.97 (C9), 109.92 (C2), 110.87 (C4′), 112.28 (C10a), 112.45 (C13b), 113.67 (C2′), 114.10 (C8a′), 116.07 (C5), 120.36 (C6a), 123.67 (C6), 123.69 (C6c), 125.05 (C3), 125.43 (C6′), 126.30 (C4a), 127.96 (C8), 129.77 (C4a′), 131.03 (C3′), 146.84 (C4), 147.14 (C5′), 147.81 (C7), 149.82 (C13a), 150.29 (C1), 151.41 (C11), 151.75 (C8′), 152.10 (C1′), 152.59 (C10), 154.48 (C12a). LR-MS *m/z*: 648 (M^+). HR-MS calcd for $C_{39}H_{36}O_9$: 648.2349. Found: 648.2386. Anal. calcd for $C_{39}H_{36}O_9$: C, 72.21; H, 5.59. Found: C, 72.41; H, 5.60. Anal. calcd for $C_{39}H_{36}O_9$: C, 72.21; H, 5.59. Found: C, C, 72.15; H, 5.61.

4.4.14. 1,4,8,11,13,16-Heptamethoxy-2,9,15-trimethyldinaphtho[2,1-*d*:2′,1′-*d*′]naphtho[1,2-*b*:3,4-*b*′]difuran (8g). Red amorphous powder (hexane–AcOEt), mp 147–148 °C. IR (KBr) cm^{-1}: 2926, 1620, 1586, 1452. ^{1}H NMR ($CDCl_3$) δ: 2.56 (3H, s, Me), 2.56 (3H, s, Me), 2.68 (3H, s, Me), 3.73 (3H, s, OMe), 3.985 (3H, s, OMe), 3.988 (3H, s, OMe), 4.27 (3H, s, OMe), 4.31 (3H, s, OMe), 4.33 (3H, s, OMe), 6.885 (1H, s, Ar-H), 6.888 (1H, s, Ar-H), 7.00 (1H, s, Ar-H), 8.05 (1H, d, *J*=9.2 Hz, Ar-H), 8.22 (1H, d, *J*=8.6 Hz, Ar-H), 8.66 (1H, d, *J*=8.6 Hz, Ar-H), 9.02 (1H, d, *J*=9.2 Hz, Ar-H). LR-MS *m/z*: 630 (M^+). HR-MS calcd for $C_{39}H_{34}O_8$: 630.2244. Found: 630.2261. Anal. calcd for $C_{39}H_{34}O_8$: C, 74.27; H, 5.43. Found: C, 74.17; H, 5.40.

4.4.15. 2,2′-Binaphthalenyl-1,1′-diol (2h). Colorless powder (benzene–hexane), mp 222–223 °C (lit.[10] 221–223 °C). IR (KBr) cm^{-1}: 3051, 1599, 1568. ^{1}H NMR ($CDCl_3$) δ: 5.66 (2H, s, Ar-OH), 7.39 (2H, d, *J*=8.27 Hz, Ar-H), 7.55–7.60 (6H, m, Ar-H), 7.86–7.89 (2H, m, Ar-H), 8.32–8.35 (2H, m, Ar-H). LR-MS *m/z*: 286 (M^+). Anal. calcd for $C_{20}H_{14}O_2$: C, 83.90; H, 4.93. Found: C, 83.98; H, 4.90.

4.4.16. Dinaphtho[1,2-*b*;2′,1′-*d*]furan (3h). Colorless needles (ethanol), mp 179–180 °C (lit.[7] 178–180 °C). IR (KBr) cm^{-1}: 2935, 1570. ^{1}H NMR ($CDCl_3$) δ: 7.50–7.59 (4H, m, 2, 2′-H and 3, 3′-H), 7.69 (2H, d, *J*=8.25 Hz, 5,5′-H or 6,6′-H), 7.80 (2H, d, *J*=8.25 Hz, 5,5′-H or 6,6′-H), 7.88–7.91 (2H, m, 1,1′-H or 4,4′-H), 8.19–8.22 (2H, m, 1,1′-H or 4,4′-H). LR-MS *m/z*: 268 (M^+).

4.4.17. 1,1′-Binaphthalenyl-4,4′-diol (10). Colorless powder (benzene), mp 293–294 °C (lit.[6a] 296–298 °C). IR (KBr) cm^{-1}: 3385, 1593. ^{1}H NMR (CD_3COCD_3) δ: 7.04 (2H, d, *J*=7.53 Hz, 2, 2′-H), 7.27 (2H, d, *J*=7.53 Hz, 3, 3′-H), 7.28–7.29 (4H, m, Ar-H), 7.42–7.47 (2H, m, Ar-H), 8.35 (2H, broad d, J=8.27 Hz, Ar-H), 9.15 (2H, s, Ar-OH). LR-MS *m/z*: 286 (M^+). Anal. calcd for $C_{20}H_{14}O_2$: C, 83.90; H, 4.93. Found: C, 84.01; H, 4.95.

4.5. General procedure for oxidation of 1-naphthols with Ag_2O

A mixture of selected 1-naphthols **1** (2.3 mmol) in $CHCl_3$ (10 ml) containing 1.5 equiv. of Ag_2O (80 mg, 0.344 mmol) was stirred at 23 °C in an air atmosphere. The solvent was removed and the residue was subjected to flash column

chromatography on silica gel with the designated solvents as follows: AcOEt–hexane (1:6; for **2a**, **1a** and **5a** in Table 1); AcOEt–hexane (1:5; for **2b** and **4b** in Table 1); AcOEt–hexane (1:5; for **2d** and **6d** in Table 1); CH_2Cl_2–hexane (2:1; for **2f** and **9f** in Table 2). Yields for **2a**, **5a**, **2b**, **6b**, **2d**, **5d**, **2e**, **2h** and **9f** are listed in Tables 1 and 2.

4.5.1. 5-Methoxy-1,4-naphthoquinone (4a). Yellow needles (ether–hexane), mp 187–189 °C (lit.[17a] 180–185 °C). IR (KBr) cm^{-1}: 1655, 1581. ^1H NMR ($CDCl_3$) δ: 4.02 (3H, s, O*Me*), 6.88 (2H, s, Ar-H), 7.32 (1H, dd, *J*=1.8, 7.8 Hz, Ar-H), 7.67–7.76 (2H, m, Ar-H). ^{13}C NMR ($CDCl_3$) δ: 56.5 (C5-O*Me*), 118.0, 119.2, 119.7, 134.1, 135.0, 136.2, 140.9, 159.6, 184.4 (C1 or C4), 185.2 (C1 or C4). HR-MS calcd for $C_{11}H_8O_3$: 188.0471. Found: 188.0486. Anal. calcd for $C_{11}H_8O_3$: C, 70.21; H, 4.29. Found: $C_{24}H_{18}O_6$: C, 70.41; H, 4.31.

4.5.2. 4,8,4′,8′-Tetramethoxy[2,2′]binaphthalenylidene-1,1′-dione (5a). Deep purple needles ($CHCl_3$–hexane), mp 261–262 °C. IR (KBr) cm^{-1}: 1613, 1581, 1564. ^1H NMR ($CDCl_3$) δ: 3.99 (6H, s, 8 and 8′-OMe), 4.01 (6H, s, 4 and 4′-OMe), 7.00 (2H, d, *J*=8.2 Hz, 7 and 7′-H), 7.41 (2H, dd, *J*=0.9, 7.5 Hz, 5 and 5′-H), 7.52 (2H, t, *J*=8.2 Hz, 6 and 6′-H), 7.92 (2H, s, 3 and 3′-H). ^{13}C NMR ($CDCl_3$) δ: 55.90 (4 and 4′-O*Me*), 56.32 (8 and 8′-O*Me*), 102.28 (C3 and C3′), 112.46 (C7 and C7′), 114.61 (C5 and C5′), 120.63 (C8a and C8a′), 133.35 (C4a and C4a′), 133.83 (C6 and C6′), 134.49 (C2 and C2′), 155.42 (C4 and C4′), 159.90 (C8 and C8′), 189.49 (C1 and C1′). LR-MS *m/z*: 404 (M^+). HR-MS calcd for $C_{24}H_{20}O_6$: 404.1254. Found: 404.1267. Anal. calcd for $C_{24}H_{20}O_6$: C, 71.28; H, 4.98. Found: C, 71.08; H, 4.95.

4.5.3. 4,4′-Dimethoxy[2,2′]binaphthalenylidene-1,1′-dione (5d). Deep blue needles (benzene), mp 257–258 °C (lit.[24a] 257–258 °C). IR (KBr) cm^{-1}: 1606, 1584, 1561. ^1H NMR ($CDCl_3$) δ: 4.08 (6H, s, 4 and 4′-OMe), 7.48 (2H, broad t, *J*=7.7 Hz, 7 and 7′-H), 7.61 (2H, broad t, *J*=7.7 Hz, 6 and 6′-H), 7.79 (2H, broad d, *J*=7.7 Hz, 8 and 8′-H), 8.17 (2H, broad d, *J*=7.7 Hz, 5 and 5′-H), 8.42 (2H, s, 3 and 3′-H). LR-MS *m/z*: 344 (M^+). HR-MS calcd for $C_{22}H_{16}O_4$: 344.1044. Found: 344.1029. Anal. calcd for $C_{22}H_{16}O_4$: C, 76.73; H, 4.68. Found: C, 76.93; H, 4.69.

4.5.4. 5,5′-Dimethoxy-2,2′-dimethyl[3,3′]binaphthoquinone (6b). Yellow needles ($CHCl_3$–hexane), mp 261–263 °C. IR (KBr) cm^{-1}: 1659, 1588. ^1H NMR ($CDCl_3$) δ: 2.00 (6H, s, 2 and 2′-Me), 3.95 (3H, s, 5 and 5′-OMe), 7.28 (2H, dd, *J*=0.9, 8.2 Hz, 6 and 6′-H), 7.69 (2H, dd, *J*=7.7 Hz, 7 and 7′-H), 7.81 (2H, dd, *J*=1.1, 7.5 Hz, 8 and 8′-H). ^{13}C NMR ($CDCl_3$) δ: 13.8 (C2 and C2′-Me), 56.3 (C8 and C8′-O*Me*), 117.7 (C6 and C6′), 119.3 (C8 and C8′), 119.7 (C5a and C5a′), 134.2 (C8a and C8a′), 134.9 (C7 and C7′), 142.8 (C2 and C2′, or C3 and C3′), 142.9 (C2 and C2′, or C3 and C3′), 159.7 (C5 and C5′), 182.0 (C4 and C4′), 184.8 (C1 and C1′). LR-MS *m/z*: 402 (M^+). HR-MS calcd for $C_{24}H_{18}O_6$: 402.1103. Found: 402.1131. Anal. calcd for $C_{24}H_{18}O_6$: C, 71.64; H, 4.51. Found: $C_{24}H_{18}O_6$: C, 71.54; H, 4.52.

4.5.5. 5,5′,8,8′-Tetramethoxy-2,4′-di-1,1′-naphthol (9f). Colorless needles, mp 221–223 °C. IR (KBr) cm^{-1}: 3336, 1612 1392, 1250, 1051. ^1H NMR ($CDCl_3$) δ: 3.32 (3H, s, OMe), 3.96 (3H, s, OMe), 3.98 (3H, s, OMe), 4.05 (3H, s, OMe), 6.63 (1H, d, *J*=8.4 Hz, Ar-H), 6.66 (1H, d, *J*=8.3 Hz, Ar-H), 6.68 (1H, d, *J*=8.3 Hz, Ar-H), 6.74 (1H, d, *J*=8.6 Hz, Ar-H), 6.97 (1H, d, *J*=8.1 Hz, Ar-H), 7.24 (1H, d, *J*=8.1 Hz, Ar-H), 7.35 (1H, d, *J*=8.4 Hz, Ar-H), 7.71 (1H, d, *J*=8.6 Hz, Ar-H), 9.59 (1H, s, OH), 9.83 (1H, s, OH). MS *m/z*: 406 (M^+). HR-MS calcd for $C_{24}H_{22}O_6$: 406.1416. Found: 406.1440. Anal. calcd for $C_{24}H_{22}O_6$: C, 70.92; H, 5.46. Found: C, 70.68; H, 5.47.

4.5.6. 5,5′,8,8′-Trimethoxy-6,6′-dimethyl-2,4′-di-1,1′-naphthol (9g). Colorless needles, mp 246–247 °C (ether–hexane). IR (KBr) cm^{-1}: 3336, 1612. ^1H NMR ($CDCl_3$) δ: 2.34 (3H, s, Me), 2.43 (3H, s, Me), 3.00 (3H, s, OMe), 3.89 (3H, s, OMe), 3.96 (3H, s, OMe), 4.06 (3H, s, OMe), 6.56 (1H, s, Ar-H), 6.64 (1H, s, Ar-H), 6.91 (1H, d, *J*=8.1 Hz, Ar-H), 7.25 (1H, d, *J*=8.1 Hz, Ar-H), 7.43 (1H, d, *J*=8.5 Hz, Ar-H), 7.55 (1H, d, *J*=8.5 Hz, Ar-H), 9.50 (1H, s, OH), 9.74 (1H, s, OH). ^{13}C NMR ($CDCl_3$) δ: 16.1, 16.7, 56.1, 56.4, 60.4, 61.0, 106.7, 107.5, 110.1, 111.1, 114.0, 115.4, 124.7, 124.8, 126.3, 126.8, 129.4, 129.8, 130.6, 132.3, 147.9, 149.2, 150.9, 152.3, 154.5. MS *m/z*: 434 (M^+). HR-MS calcd for $C_{26}H_{26}O_6$: 434.1730. Found: 434.1758. Anal. calcd for $C_{26}H_{26}O_6$: C, 71.87; H, 6.03. Found: C, 71.97; H, 6.01.

4.6. Anodic oxidation of NPOH 1a

A solution of **1a** (58 mg, 0.142 mmol) in CH_2Cl_2 (30 ml) was oxidized at 0.80 or 0.95 V (vs Ag-AgCl) under an argon atmosphere for 1 h in the presence of *n*-$Bu_4N{\cdot}ClO_4$ (1.02 g) as a supporting salt using platinum mesh as an anode and a cathode, and an Ag-AgCl reference electrode, in a divided cell (H-shaped glass cell) through glass filters. Based on CV curves, the oxidation potential of **1a** was 0.78 or 0.95 V vs Ag-AgCl (the first onset oxidation potential or the first half-wave oxidation potential in CV). The solvent was evaporated and the residue was purified by flash column chromatography on silica gel using hexane–AcOEt (2:1) as an eluent to give **4a** (60 or 34%) and **6a** (23 or 11%), respectively. **6a**: yellow needles ($CHCl_3$–hexane), mp 202–204 °C. IR (KBr) cm^{-1}: 1644, 1604, 1570. ^1H NMR ($CDCl_3$) δ: 3.99 (6H, s, 5 and 5′-OMe), 6.95 (2H, s, 2 and 2′-H), 7.33 (2H, d, *J*=8.2 Hz, 6 and 6′-H), 7.71 (2H, t, *J*=7.9, 8.2 Hz, 7 and 7′-H), 7.76 (2H, d, *J*=7.9 Hz, 8 and 8′-H). ^{13}C NMR ($CDCl_3$) δ: 56.5 (C5 and C5′-O*Me*), 118.2 (C6 and C6′), 119.1 (C8 and C8′), 119.8 (C5a and C5′a), 134.2 (C8a and C8a′), 134.8 (C2 and C2′), 135.2 (C7 and C7′), 146.8 (C3 and C3′), 160.1 (C5 and C5′), 182.1 (C4 and C4′), 184.4 (C1 and C1′). LR-MS *m/z*: 374 (M^+). HR-MS calcd for $C_{22}H_{14}O_6$: 374.0790. Found: 374.0762. Anal. calcd for $C_{22}H_{14}O_6$: C, 70.59; H, 3.77. Found: C, 70.49; H, 3.78.

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25. In the ^{1}H NMR spectra of NPOH **1a** and **1d**, the signal (δ 10.50 ppm) of a hydroxyl proton at the C1-position in **1a** was observed at lower field than the corresponding signals (δ 5.66 ppm) in **1d**.

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Asymmetric nucleophilic substitution of α-bromo amides via dynamic kinetic resolution for the preparation of dipeptide analogues

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Abstract—Asymmetric nucleophilic substitution reactions of α-bromo α-aryl acetamides derived from L-amino acids are described. The simple and practical syntheses of dipeptide analogues have been developed with dibenzylamine, TBAI and a base to provide **2a**–**2n** and **4** in 50–98% yields with diastereomeric ratios from 74:26 to >99:1. Mechanistic investigations suggest that α-bromo acetamides are configurationally labile under the reaction condition and the primary pathway of the asymmetric induction is a dynamic kinetic resolution. The semiempirical calculations of two epimeric transition states of **1b** found that (α*S*)-epimer is the faster reacting epimer with the formation of an intermolecular hydrogen bond that facilitates delivery of the amine nucleophile.

1. Introduction

Chiral auxiliary mediated dynamic resolution of α-halo carboxylic acid derivatives has been recently recognized as an effective synthetic method for asymmetric syntheses of α-amino acids, α-mercapto acids, and α-hydroxy acids.[1] Since α-haloacyl compounds are easily obtained in racemic form and configurational lability of them is readily induced, dynamic resolution in nucleophilic substitutions at α-halo carbon center can allow easy access to a wide range of enantioenriched α-heteroatom substituted carboxylic acid derivatives. Additionally, extension of this methodology to stereoselective modification of peptides is of obvious synthetic utility, in which chiral information of the adjacent amino acids is transferred to new bond formation at α-halo carbon center. The direct modification of peptide chain seems to be an attractive synthetic strategy for peptidomimetics since numerous peptide analogues can be efficiently prepared using easily accessible and relatively inexpensive amino acid precursor.[2] We have recently reported our preliminary results on dynamic resolution of α-bromo acetamides in nucleophilic substitution for asymmetric syntheses of di- and tripeptide analogues.[3] The chiral information of an amino acid precursor is efficiently transferred to the new C–N bond formation at α-halo carbon center, which can build an unnatural amino acid onto the amino acid precursor with remarkable stereoselectivity. Herein we describe our recent progress to extend the scope of the methodology and to provide the mechanistic and stereochemical rationale.

2. Results and discussion

We previously reported that L-proline and L-leucine are efficient precursors for asymmetric syntheses of dipeptide analogues via dynamic resolution of the corresponding α-bromo acetamides **1a** and **1b** as shown in Table 1, entries 1 and 2. When the two diastereomeric mixture (ca. 50:50) of *N*-(α-bromo-α-phenylacetyl)-(L)-proline methyl ester **1a** was treated with dibenzylamine (Bn_2NH), tetrabutylammonium iodide (TBAI) and triethylamine (Et_3N) in CH_2Cl_2 at room temperature, the dipeptide analogues **2a** was obtained in 93% yield with >99:1 diastereomeric ratio (dr, α*R*:α*S*). Also, the reactions of leucine methyl ester **1b** under the same condition gave the dipeptide analogue **2b** in 83% yield with 89:11 dr (α*R*:α*S*). In this paper, the scope of the observed dynamic resolution has been examined with 12 different L-amino acid precursors. The substitution reactions of α-bromo-α-phenyl acetamides **1c**–**1n** derived from the corresponding L-amino acid methyl esters and racemic α-bromo-α-phenyl acetic acid were investigated as

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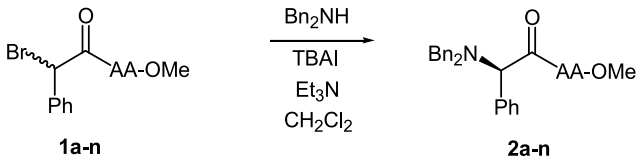
Table 1. Reactions of α-bromo acetamides **1a**–**1n**



1a-n **2a-n**

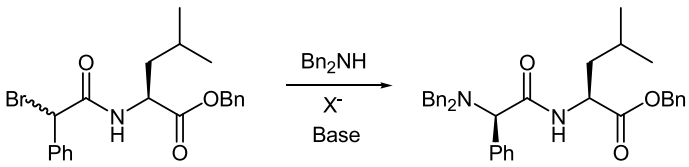
Entry[a]	S.M.[b]	L-AA[b]	Product	%Yield[c]	dr[d] (α*R*:α*S*)
1	**1a**	Pro	**2a**	93	>99:1
2	**1b**	Leu	**2b**	83	89:11
3	**1c**	Ala	**2c**	96	90:10
4	**1d**	Val	**2d**	81	95:5
5	**1e**	Ile	**2e**	95	93:7
6	**1f**	Phe	**2f**	91	90:10
7	**1g**	Trp	**2g**	98	90:10
8	**1h**	Phg	**2h**	52	84:16
9	**1i**	Tyr	**2i**	77	90:10
10	**1j**	Asp (*O*-Me)	**2j**	86	74:26
11	**1k**	Glu (*O*-Me)	**2k**	50	88:12
12	**1l**	Lys (*N*-Cbz)	**2l**	91	90:10
13	**1m**	Ser (*O*-Bn)	**2m**	50	91:9
14	**1n**	Cys (*S*-Bn)	**2n**	57	87:13

[a] All reactions were carried out in CH_2Cl_2 for 24 h at rt.
[b] Initial drs of **1a**–**1n** are approximately 50:50.
[c] Isolated yields.
[d] The drs are determined by ^1H NMR of reaction mixture using the authentic products prepared from racemic phenylglycine as a standard.

shown in Table 1. Treatment of alanine methyl ester **1c** with Bn_2NH (1.2 equiv.), TBAI (1.0 equiv.) and Et_3N (1.0 equiv.) in CH_2Cl_2 for 24 h at room temperature gave **2c** in 96% yield with 90:10 dr (entry 3). Higher level of selectivities were observed with L-valine ester and L-isoleucine ester which have more sterically demanding secondary alkyl side chain (entries 4 and 5). The reactions of α-bromo acetamides **1f**, **1g** and **1i** derived from amino acids with aromatic side chain showed almost same drs as leucine methyl ester **1b**. Mild drops in stereoselectivity andyield were seen with α-bromo acetamide **1h** derived from L-phenylglycine (entry 8). α-Bromo acetamides **1j**–**1n** derived from L-aspartic acid, L-glutamic acid, L-lysine, L-serine, and L-cysteine were also examined with the protection of side chain functionality as shown in Table 1, entries 10–14. Considerable loss of stereoselectivity (74:26 dr) was observed with α-bromo acetamide **1j** derived from L-aspartic acid. Glutamic acid dimethyl ester **1k** and *N*-Cbz protected lysine methyl ester **1l** gave the dipeptide analogues **2k** and **2l** with 88:12 dr and 90:10 dr, respectively (entries 11 and 12). Similar stereoselectivities were observed in the reactions of *O*-benzyl protected serine derivative **1m** and *S*-benzyl protected cysteine derivative **1n** with moderate yields (entries 13 and 14). As can be seen in Table 1, the survey of various amino acid precursors indicates that highest stereoselectivity (>99:1) was observed with α-bromo acetamide **1a** derived from L-proline and other α-bromo acetamides **1b**–**1n** provided the dipeptide analogues **2b**–**2n** with good stereoselectivities, ranging from 74:26 dr to 95:5 dr.

In an effort to improve the stereoselectivity of the nucleophilic substitution of α-bromo acetamides **1b**–**1n** with dibenzylamine nucleophile, various reaction conditions have been examined as shown in Table 2 with leucine benzyl ester **3**. Of the solvents explored, CH_2Cl_2 consistently gave the best results (entry 1). The dipeptide analogue **4** was obtained from **3** with 87:13 dr in *n*-hexane, 85:15 dr in ether, 90:10 dr in CH_3CN, 89:11 dr in NMP, 92:8 dr in DMF, and 86:14 dr in *p*-dioxane (entries 2–7). We also examined the substitutions at 0 and 50 °C (entries 8 and 9).

Table 2. Effects of substitution conditions on the stereoselectivities



3 **4**

Entry[a]	Solvent	Base	X^-	Temperature	Yield[b]	dr[c] (α*R*:αS)
1	CH_2Cl_2	Et_3N	TBAI	rt	95	93:7
2	*n*-Hexane	Et_3N	TBAI	rt	55	87:13
3	Ether	Et_3N	TBAI	rt	73	85:15
4	CH_3CN	Et_3N	TBAI	rt	91	90:10
5	NMP	Et_3N	TBAI	rt	48	89:11
6	DMF	Et_3N	TBAI	rt	68	92:8
7	*p*-Dioxane	Et_3N	TBAI	rt	68	86:14
8	CH_2Cl_2	Et_3N	TBAI	0 °C	77	92:8
9	CH_2Cl_2	Et_3N	TBAI	50 °C	85	93:7
10	CH_2Cl_2	None	None	rt	43	66:34
11	CH_2Cl_2	Et_3N	None	rt	51	71:29
12	CH_2Cl_2	None	TBAI	rt	90	89:11
13	CH_2Cl_2	Et_3N	TBAI (0.1 equiv.)	rt	88	88:12
14	CH_2Cl_2	Et_3N	TBAB	rt	85	88:12
15	CH_3CN	Et_3N	KI	rt	73	92:8
16	CH_2Cl_2	DBN	TBAI	rt	10	90:10
17	CH_2Cl_2	DBU	TBAI	rt	46	86:14
18	CH_2Cl_2	DIEA	TBAI	rt	97	94:6

[a] All reactions were carried out for 24 h with **3** (1.0 equiv., ca. 50:50 dr), dibenzylamine (1.2 equiv.), X^- (1.0 equiv.) and a base (1.2 equiv.).
[b] Isolated yields.
[c] The drs of **4** are determined by ^1H NMR of reaction mixture using the authentic products prepared from racemic phenylglycine as a standard.

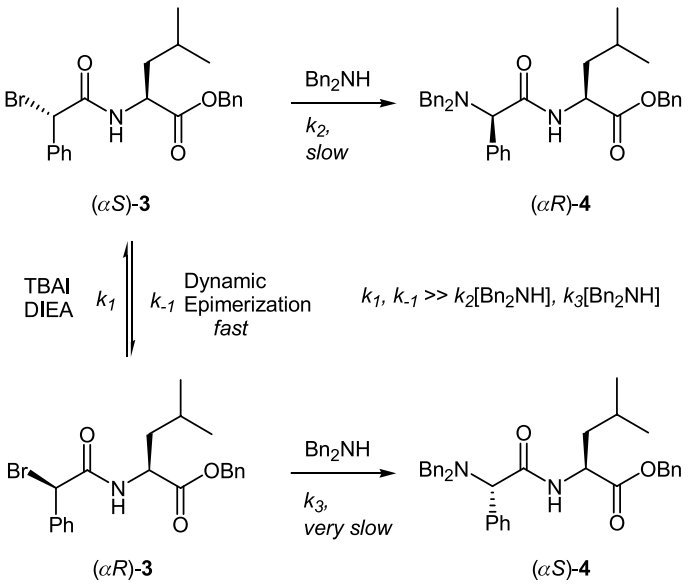
Temperature appeared to have little influence on the selectivity. The results in entries 10–12 pointed to the importance of the presence of TBAI for rate acceleration and high stereoselectivity. The reaction in the absence of both TBAI and Et_3N for 24 h gave the product with slower rate and much lower stereoselectivity (66:34 dr). The lack of stereoselectivity in the absence of TBAI may be explained by the slow epimerization of **3** with respect to the substitution with the amine nucleophile.[4] Use of catalytic amount of TBAI eroded the selectivity, probably due to less efficient epimerization process (entry 13). When KI was used as an epimerizing agent, the reaction gave almost same selectivity (92:8 dr) as the reaction with TBAI, which was better than the reaction with bromide epimerizing agent, TBAB (entries 14–15). Slightly diminished stereoselectivity with poor yield was observed by changing the base from Et_3N to DBU or DBN (entries 16 and 17). The addition of diisopropylethylamine (DIEA) afforded the dipeptide analogue **4** with highest stereoselctivity (94:6 dr) in 97% yield (entry 18). We were pleased to observe that DIEA promoted reactions of most α-bromo acetamides gave the improved stereoselectivities, compared to the stereoselectivities of the reactions with Et_3N shown in Table 1. The reactions of **1b**, **1e**, **1g**, **1h**, and **1i** with DIEA and TBAI provided the products with 93:7 dr, 97:3 dr, 93:7 dr, 87:13 dr and 93:7 dr, respectively.

The *R*-configuration at α-position of major product **4** was assigned by comparison to the ^1H NMR of authentic epimers individually prepared from the coupling of L-leucine derivative and (*S*)- or (*R*)-phenylglycine derivative, and also confirmed by comparison of chiral-HPLC retention time with authentic epimers using racemic material as a standard. The configurational stability of the dipeptide analogue **4** was examined by the treatment with Bn_2NH (1.2 equiv.), TBAI (1.0 equiv.) and DIEA (1.0 equiv.) in CH_2Cl_2 for 24 h. No epimerization at two stereogenic centers of **4** was detected by ^1H NMR and Chiral-HPLC, ruling out the possibility of epimerization after the replacement of Br with dibenzylamine. Thus, the observed asymmetric induction is the results of dynamic resolution in nucleophilic substitution of two epimeric mixture of α-bromo acetamide **3**.

There are two limiting pathways which could account for the observed dynamic resolution in nucleophilic substitution of α-bromo acetamide **3**. In one limiting pathway, α-bromo stereogenic center undergoes rapid epimerization between (α*S*)-**3** and (α*R*)-**3** and one of two epimers reacts preferentially under the reaction condition. This is a case of dynamic kinetic resolution, in which the stereoselectivity is determined by the difference in the epimeric transition state energies for the reaction with dibenzylamine. In a different limiting pathway, the stereoselectivity of the reaction is determined by the ratio of (α*S*)-**3** and (α*R*)-**3** that is established before the substitution. This is termed dynamic thermodynamic resolution because the ratio of two epimers is thermodynamically controlled and the stereoselectivity of the reaction is not determined by the difference in the rates of substitutions with dibenzylamine.

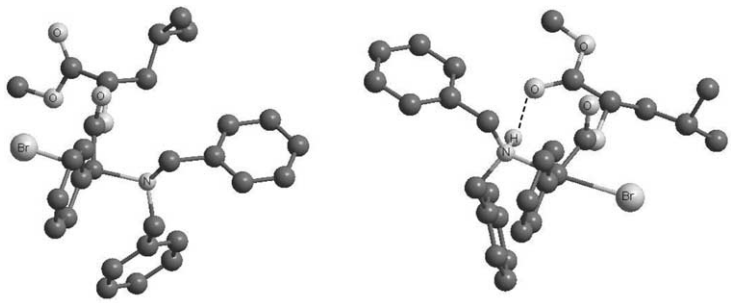
A series of reactions as shown in Table 3 has been carried

Table 3. Dynamic kinetic resolution of α-bromo acetamide **3**



Entry	S.M.	Condition	Product (α*R*:α*S*)	Yield (%)
1	**3** (57:43)	TBAI, DIEA, rt	**3** (52:48)	75
2	**3** (78:22)	TBAI, DIEA, rt	**3** (52:48)	78
3	**3** (72:28)	TBAI, DIEA, Bn_2NH, rt	**4** (94:6)	96
4	**3** (30:70)	TBAI, DIEA, Bn_2NH, rt	**4** (95:5)	98

All reactions were carried out for 24 h at rt. The drs of **3** and **4** were determined by ^1H NMR of reaction mixture using the authentic products prepared from racemic α-bromo phenyl acetic acid and phenylglycine, respectively, as standards.



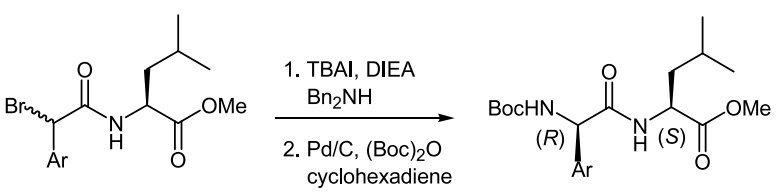
(αR)-**1b-TS;** ΔH = 109.04 kcal/mol (αS)-**1b-TS;** ΔH = 106.04 kcal/mol

Figure 1. Transition states for the reactions of slower reacting (α*R*)-**1b** and faster reacting (α*S*)-**1b** with dibenzylamine. Hydrogens have been removed for clarity.

out to differentiate the two possible pathways of asymmetric induction in nucleophilic substitution reactions of α-bromo amides. When the mixture of two epimers was allowed to reach thermodynamic equilibrium in the presence of TBAI and DIEA, the epimeric ratio of recovered **3** was analyzed by ^{1}H NMR, determined to be 52:48 in both cases with **3** of 57:43 dr and 78:22 dr, respectively (entries 1 and 2). These results indicate that α-bromo amide **3** is configurationally labile under the reaction condition and the thermodynamic stabilities of two epimers are almost same, ruling out dynamic thermodynamic resolution as a primary pathway. When **3** with 72:28 dr was treated with dibenzylamine in the presence of both TBAI and DIEA, the reaction gave the product **4** with 94:6 dr as shown in entry 3. In addition, almost same dr of product **4** was observed in the reaction of **3** with reversed diastereomeric enrichment of 30:70 dr. Thus, the diastereomeric ratio of product **4** is independent of the starting ratio of two epimers of **3** and would depend solely on the difference in the epimeric transition state energies. These results could be taken to suggest that the epimerization of **3** promoted by TBAI and DIEA is sufficiently fast with respect to the rate of substitution (k_1, $k_{-1} \gg k_2$[dibenzylamine], k_3[dibenzylamine]) and the primary pathway of the asymmetric induction is a dynamic kinetic resolution.

In order to gain further understanding of the dynamic kinetic resolution, we proceed to calculate the transition states of both leucine methyl esters (α*R*)-**1b** and (α*S*)-**1b** using semi-empirical methods.[5] The main results of the calculations after full optimizations at HF/6-31G(d) level are shown in Figure 1. The only constraint was the distance between the two reaction centers during the transition state search. Starting from the sufficiently long distance, this distance constraint has been reduced systematically by monitoring the energy of the corresponding conformation. At this level of theory, only one transition state was found for each epimer, with the transition state (α*S*)-**1b**–**TS** having the lower enthalpy value. The energy difference of about 3.0 kcal/mol between the transition state structures (α*R*)-**1b**–**TS** and (α*S*)-**1b**–**TS** is fully consonant with the highly stereoselective character of the dynamic kinetic resolution process. Based on the results of the calculations, we conclude that the (α*S*)-**1b** is the faster reacting diastereomer and this is due to formation of an intermolecular hydrogen bond that facilitates delivery of the amine nucleophile. The model proposed here, by relying on hydrogen bonding, is consistent with the poor stereoselectivities of the reactions with thiol nucleophiles and metalated nucleophiles, relatively poor hydrogen bond donor nucleophiles.[6]

For further *N*-terminal functionalization of the dipeptide analogues, the *N*,*N*-dibenzyl protecting group is removed and converted to the Boc group with Pd/C, cyclohexadiene, and $(Boc)_2O$ as shown in Scheme 1.[7] *N*-Boc-D-phenylglycyl-L-leucine methyl ester **6** was obtained in 47% overall yield with 93:7 dr from α-phenylacetyl leucine methyl ester **1b**. The diastereomerically pure *N*-Boc dipeptide analogues **7** was obtained in 30% overall yield after silica gel column chromatography from α-(*p*-fluorophenyl)acetyl leucine methyl ester **5**. The isolated yields of **6** and **7** generally were not high, but the procedure was performed at a relatively small scale and no further attempts were made to optimize the yields for the deprotection. This methodology provides the unique possibility to synthesize a wide range of D-arylglycine dipeptide analogues with various L-amino acids. It is well known that D-phenylglycine dipeptides have interesting properties and can be applied, for example, as tumor and tissue-dissolving compounds of low toxicity and as resolving agents.[8]



Scheme 1.

3. Conclusion

We have shown that dynamic resolution of α-bromo amides can be successfully applied towards the preparation of enantioenriched dipeptide analogues. The methodology has been particularly successful for α-bromo α-aryl acetamides, affording a generalized and practical method for the asymmetric syntheses of D-arylglycine dipeptide analogues.[9] Mechanistic investigations along with semi-empirical calculations suggest that α-bromo α-aryl acetamides are configurationally labile under the reaction condition and the primary pathway of the asymmetric induction is a dynamic kinetic resolution. The methodology of the present work should also be applicable to stereo-selective syntheses and mechanistic analysis of a number of related systems.

4. Experimental

4.1. General procedure for the preparation of 1a–1n, 3, and 5

L-Amino acid methyl (or benzyl) ester (1.0 equiv.), racemic α-bromo phenylacetic acid (1.0 equiv.), DCC (1.0 equiv.), Et_3N (1.1 equiv.) and DMAP (0.2 equiv.) were dissolved in CH_2Cl_2 and stirred at room temperature for 3 h. The precipitate was filtered off and the organic phase was washed with water. The organic phase was dried over $MgSO_4$, filtered and concentrated to provide the crude product that was purified by column chromatography on silica gel.

4.1.1. (*S*)-*N*-(α-Bromo-α-phenylacetyl) proline methyl ester (1a). A colorless oil was obtained in 36% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.52–7.32 (m, 5H), 5.64, 5.41 (s, 1H), 4.54, 4.45 (m, 1H), 3.72, 3.65 (s, 3H), 3.33 (m, 1H), 2.15–1.84 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.5, 166.3, 136.0, 129.3, 128.9, 128.5, 60.0, 59.8, 52.6, 47.5, 29.2, 25.3. HRMS calcd for $C_{14}H_{16}BrNO_3$: 325.0314. Found: 325.0326.

4.1.2. (*S*)-*N*-(α-Bromo-α-phenylacetyl) leucine methyl ester (1b). A colorless oil was obtained in 34% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.50–7.07 (m, 6H), 5.46, 5.44 (s, 1H), 4.60 (m, 1H), 3.73, 3.72 (s, 3H), 1.63 (m, 3H), 0.92 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.1, 167.5, 137.6, 129.4, 128.9, 128.3, 52.7, 51.0, 41.5, 25.2, 23.1, 22.3. Anal. calcd for $C_{15}H_{20}BrNO_3$: C, 52.64; H, 5.89; N, 4.09. Found: C, 52.66; H, 5.92; N, 3.91.

4.1.3. (*S*)-*N*-(α-Bromo-α-phenylacetyl) alanine methyl ester (1c). A colorless oil was obtained in 53% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.28–7.49 (m, 6H), 5.45, 5.38 (s, 1H), 4.55 (m, 1H), 3.71, 3.70 (s, 3H), 1.41 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.1, 167.4, 137.5, 129.5, 128.8, 128.3, 52.9, 50.8, 49.3, 18.2. Anal. calcd for $C_{12}H_{14}BrNO_3$: C, 48.02; H, 4.70; N, 4.67. Found: C, 48.02; H, 4.82; N, 4.43.

4.1.4. (*S*)-*N*-(α-Bromo-α-phenylacetyl) valine methyl ester (1d). A colorless oil was obtained in 53% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.49–7.15 (m, 5H), 7.15, 7.08 (d, *J*=8.0, 8.2 Hz, 1H), 5.48, 5.45 (s, 1H), 4.55 (m, 1H), 3.74 (s 3H), 2.23 (m, 1H), 0.93 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.2, 167.5, 137.6, 129.5, 129.3, 128.8, 58.3, 52.7, 51.6, 31.8, 19.3, 18.1. Anal. calcd for $C_{14}H_{13}BrNO_3$: C, 51.23; H, 5.53; N, 4.27. Found: C, 51.42; H, 5.44; N, 3.95.

4.1.5. (*S*)-*N*-(α-Bromo-α-phenylacetyl) isoleucine methyl ester (1e). A colorless oil was obtained in 13% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.49–7.29 (m, 5H), 7.19, 7.12 (d, *J*=8.0, 8.0 Hz, 1H), 5.47, 5.44 (s, 1H), 4.59 (d, *J*=4.6 Hz, 1H), 3.74 (s, 3H), 1.97 (m, 1H), 1.44 (m, 1H), 1.19 (m, 1H), 0.91 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.1, 167.3, 137.6, 129.5, 128.3, 128.7, 57.6, 52.6, 51.7, 38.3, 25.6, 15.9, 11.9. Anal. calcd for $C_{15}H_{20}BrNO_3$: C, 52.64; H, 5.89; N, 4.09. Found: C, 52.66; H, 5.94; N, 4.15.

4.1.6. (*S*)-*N*-(α-Bromo-α-phenylacetyl) phenylalanine methyl ester (1f). A colorless oil was obtained in 30% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.26–7.00 (m, 11H), 5.37, 5.31 (s, 1H), 4.85 (m, 1H), 3.68, 3.66 (m, 3H), 3.10 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.8, 167.3, 137.5, 135.8, 129.7, 129.3, 129.0, 128.8, 128.3, 127.6, 54.3, 52.9, 51.1, 37.9. Anal. calcd for $C_{13}H_{13}BrNO_3$: C, 57.46; H, 4.82; N, 3.72. Found: C, 57.35; H, 4.76; N, 3.44.

4.1.7. (*S*)-*N*-(α-Bromo-α-phenylacetyl) tryptophan methyl ester (1g). A colorless oil was obtained in 40% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 8.3 (br, 1H), 7.54–7.06 (m, 10H), 6.82 (m, 1H), 5.32, 5.30 (s, 1H), 4.89 (m, 1H), 3.66, 3.64 (s, 3H), 3.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.2, 167.5, 137.5, 136.6, 129.5, 129.3, 128.9, 127.7, 123.6, 122.6, 120.1, 118.9, 111.8, 109.7, 54.1, 53.0, 51.2, 27.8. Anal. calcd for $C_{20}H_{19}BrN_2O_3$: C, 57.84; H, 4.61; N, 6.75. Found: C, 57.80 H, 4.65; N, 6.48.

4.1.8. (*S*)-*N*-(α-Bromo-α-phenylacetyl) phenylglycine methyl ester (1h). A colorless oil was obtained in 33% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.72–7.21 (m, 11H), 5.53 (m, 1H), 5.44, 5.41 (s, 1H), 3.68, 3.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.2, 167.1, 137.5, 136.3, 129.5, 129.3, 129.2, 128.9, 128.4, 127.7, 57.6, 53.3, 51.0. Anal. calcd for $C_{17}H_{16}BrNO_3$: C, 56.37; H, 4.45; N, 3.87. Found: C, 56.66; H, 4.30; N, 3.62.

4.1.9. (*S*)-*N*-(α-Bromo-α-phenylacetyl) tyrosine methyl ester (1i). A colorless oil was obtained in 39% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.42–6.54 (m, 11H), 5.39, 5,38 (s, 1H), 4.83 (m, 1H), 3.76, 3.74 (s, 3H), 3.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.0, 167.6, 156.0, 137.3, 130.7, 129.6, 129.4, 128.7, 126.9, 116.1, 54.4, 53.0, 51.3, 37.3. Anal. calcd for $C_{18}H_{18}BrNO_4$: C, 55.12; H, 4.63; N, 3.57. Found: C, 55.14; H, 4.45; N, 3.41.

4.1.10. (*S*)-*N*-(α-Bromo-α-phenylacetyl) aspartic acid dimethyl ester (1j). A colorless oil was obtained in 20% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.68–7.26 (m, 6H), 5.44, 5.40 (s, 1H), 4.60 (m, 1H), 3.77, 3.69 (s, 3H), 3.07, 2.89 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.7, 170.9, 167.4, 137.5, 129.3, 128.7, 128.3, 53.4, 52.5, 51.1, 49.8, 36.0. Anal. calcd for $C_{14}H_{16}BrNO_5$:

C, 46.95; H, 4.50; N, 3.91. Found: C, 46.95; H, 4.65; N, 3.97.

4.1.11. (*S*)-*N*-(α-Bromo-α-phenylacetyl) glutamic acid dimethyl ester (1k). A colorless oil was obtained in 26% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.49–7.32 (m, 6H), 5.46, 5.45 (s, 1H), 4,61 (m, 1H), 3.72 (s, 3H), 3.65 (s, 3H), 2.38 (m, 2H), 2.25 (m, 1H), 2,05 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.4, 172.0, 167.8, 137.2, 129.5, 128.8, 128.3, 61.3, 52.8, 52.3, 50.8, 30.3, 27.3. Anal. calcd for $C_{15}H_{18}BrNO_5$: C, 48.40; H, 4.87; N, 3.76. Found: C, 48.38; H, 4.72; N, 3.61.

4.1.12. (*S*)-*N*-(α-Bromo-α-phenylacetyl) lysine(*N*-benzyloxycarbonyl) methyl ester (1l). A colorless oil was obtained in 44% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.47–7.27 (m, 11H), 5.44, 5.43 (s, 1H), 5.07 (s, 2H), 5.02 (m, 1H), 4.56 (m, 1H), 3.71, 3.70 (s, 3H), 1.86 (m, 1H), 1.72 (m, 1H), 1.46 (m, 2H), 1.31 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.6, 167.5, 157.0, 137.5, 137.0, 129.5, 129.2, 128.9, 128.5, 128.3, 128.1, 67.0, 53.1, 52.9, 51.0, 40.9, 32.0, 29.6, 22.7. Anal. calcd for $C_{23}H_{27}BrN_2O_3$: C, 56.22; H, 5.54; N, 5.70. Found: C, 56.19; H, 5.65; N, 5.58.

4.1.13. (*S*)-*N*-(α-Bromo-α-phenylacetyl) serine(*O*-benzyl) methyl ester (1m). A colorless oil was obtained in 22% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.50–7.24 (m, 11H), 5.44, 5.43 (s, 1H), 4.72 (m, 1H), 4.51 (m, 2H), 3.89 (m, 1H), 3.75 (m, 3H), 3.71 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 170.5, 167.3, 137.8, 129.5, 129.3, 128.9, 128.4, 128.3, 128.2, 128.0, 73.6, 69.4, 53.8, 53.1, 51.3. Anal. calcd for $C_{19}H_{20}BrNO_3$: C, 56.17 H, 4.96; N, 3.45. Found: C, 56.20; H, 4.97; N, 3.34.

4.1.14. (*S*)-*N*-(α-Bromo-α-phenylacetyl) cysteine(*S*-benzyl) methyl ester (1n). A colorless oil was obtained in 40% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.51–7.25 (m, 11H), 5.44, 5.43 (s, 1H), 4.78 (m, 1H), 3.74 (s, 3H), 3.68 (m,2H), 2.95 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.0, 167.3, 137.8, 129.4, 129.6, 129.4, 129.3, 129.0, 128.3, 127.7, 53.2, 52.8, 51.2, 37.0, 33.5. Anal. calcd for $C_{19}H_{20}BrNO_3S$: C, 54.03; H, 4.77; N, 3.32. Found: C, 54.25; H, 4.77; N, 3.15.

4.1.15. (*S*)-*N*-(α-Bromo-α-phenylacetyl) leucine benzyl ester (3). A colorless oil was obtained in 70% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.45–7.29 (m, 10H), 7.01 (m, 1H), 5.45, 5.42 (s, 1H), 5.17 (m, 2H), 4.66 (m, 1H), 1.66 (m, 3H), 0.89 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.5, 167.3, 137.6, 135.6, 129.5, 129.3, 129.0, 128.8, 128.7, 128.6, 67.6, 52.2, 51.5, 41.7, 25.3, 23.2, 22.3. Anal. calcd for $C_{21}H_{24}BrNO_3$: C, 60.29; H, 5.78; N, 3.35. Found: C, 60.54; H, 5.82; N, 3.12.

4.1.16. (*S*)-*N*-[α-Bromo-α-(*p*-fluorophenyl)acetyl] leucine methyl ester (5). A colorless oil was obtained in 47% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.50–7.43 (m, 2H), 7.06–7.01 (m, 3H), 5.45, 5.42 (s, 1H), 4.61 (m, 1H), 3.75, 3.74 (s, 3H), 1.64 (m, 3H), 0.94 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.2, 167.1, 164.5, 133.4, 130.8, 116.5, 52.8, 52.0, 50.0, 25.3, 23.2, 22.3. Anal. calcd for $C_{15}H_{19}BrFNO_3$: C, 50.01; H, 5.32; N, 3.89. Found: C, 50.09; H, 5.23; N, 3.74.

4.2. General procedure for asymmetric preparation of dipeptide analogues 2a–2n, and 4

To a solution of (α*RS*)-α-bromo acetamides in dry CH_2Cl_2 (ca. 0.1 M) at room temperature was added dibenzylamine (1.2 equiv.), TBAI (1.0 equiv.) and Et_3N (or DIEA, 1.2 equiv.). The resulting reaction mixture was stirred at room temperature for 24 h. The solvent in mixture was evaporated and the crude product was purified by column chromatography on silica gel.

4.2.1. (*S*)-*N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl] proline methyl ester (2a). A colorless oil was obtained in 93% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.43–7.20 (m, 16H), 4.61 (m, 2H), 3.94–3.80 (m, 4H), 3.85 (s, 3H), 3.03 (m, 1H), 2.82 (m, 1H), 2.11 (m, 1H), 1.90 (m, 2H), 1.68 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.3, 171.9, 141.1, 137.2, 129.6, 129.3, 129.0, 128.8, 128.2, 127.1, 64.1, 59.0, 54.6, 52.7, 46.8, 29.5, 25.2. Anal. calcd for $C_{23}H_{30}N_2O_3$: C, 75.99; H, 6.83; N, 6.33. Found: C, 75.98; H, 6.86; N, 6.20.

4.2.2. (*S*)-*N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl] leucine methyl ester (2b). A colorless oil was obtained in 83% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.78 (d, *J*=8.8 Hz, 1H), 7.47–7.18 (m, 15H), 4.72 (m, 1H), 4.45 (s, 1H), 3.91 (d, *J*=13.6 Hz, 2H), 3.73 (s, 3H), 3.28 (d, *J*=13.6 Hz, 2H), 1.63 (m, 3H), 0.94 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.8, 171.8, 139.0, 133.8, 131.0, 129.2, 129.0, 128.5, 128.3, 127.8, 67.5, 54.9, 52.6, 51.0, 42.1, 25.4, 23.3, 22.3. Anal. calcd for $C_{29}H_{34}N_2O_3$: C, 75.95; H, 7.47; N, 6.11. Found: C, 75.91; H, 7.46; N, 6.10.

4.2.3. (*S*)-*N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl] alanine methyl ester (2c). A colorless oil was obtained in 96% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.81 (d, *J*=8.8 Hz, 1H), 7.40–7.23 (m, 15H), 4.65 (m, 1H), 4.43 (s, 1H), 3.89 (d, *J*=13.7 Hz, 2H), 3.76 (s, 3H), 3.28 (d, *J*=13.7 Hz, 2H), 1.42 (d, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.8, 171.6, 139.0, 134.1, 130.9, 129.3, 129.0, 128.5, 128.3, 127.7, 67.8, 54.9, 52.9, 48.4, 18.8. Anal. calcd for $C_{26}H_{28}N_2O_3$: C, 74.97; H, 6.78; N, 6.73. Found: C, 74.80; H, 6.91; N, 6.65.

4.2.4. (*S*)-*N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl] valine methyl ester (2d). A colorless oil was obtained in 81% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.95 (d, *J*=9.2 Hz, 1H), 7.45–7.23 (m 15H), 4.66 (m, 1H), 4.47 (s, 1H), 3.91 (d, *J*=13.6 Hz, 2H), 3.73 (s, 3H), 3.25 (d, *J*=13.6 Hz, 2H), 2.26 (m, 1H), 0.96 (d, *J*=7.2 Hz, 3H), 0.92 (d, *J*=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.8, 171.9, 138.9, 133.6, 131.1, 129.3, 129.0, 128.6, 128.3, 127.8, 67.5, 57.4, 54.8, 52.5, 31.8, 19.5, 18.1. Anal. calcd for $C_{28}H_{32}N_2O_3$: C, 75.65; H, 7.26; N, 6.30. Found: C, 75.73; H, 7.44; N, 6.21.

4.2.5. (*S*)-*N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl] isoleucine methyl ester (2e). A colorless oil was obtained in 95% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.97 (d, *J*=9.2 Hz, 1H), 7.42–7.21 (m, 15H), 4.70 (m, 1H), 4.46 (s, 1H), 3.91 (d, *J*=13.6 Hz, 2H), 3.73 (s, 3H), 3.21 (d, *J*=13.6 Hz, 2H), 1.97 (m, 1H), 1.47 (m, 1H), 1.20 (m, 1H), 0.89 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.7, 171.7, 139.0, 133.6, 131.1, 129.3, 129.0, 128.5, 128.3, 127.8, 67.5, 56.8, 54.9, 52.4, 38.2, 25.7, 16.1, 12.1. Anal. calcd for

$C_{29}H_{34}N_2O_3$: C, 75.95; H, 7.47; N, 6.11. Found: C, 75.99; H, 7.60; N, 5.92.

4.2.6. (*S*)-*N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl] phenylalanine methyl ester (2f). A colorless oil was obtained in 91% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.80 (d, *J*=8.4 Hz, 1H), 7.36–7.07 (m, 20H), 5.03 (m, 1H), 4.39 (s, 1H), 3.84 (m, 2H), 3.69 (s, 3H), 3.17 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.4, 171.8, 138.8, 136.3, 133.1, 131.2, 129.7, 129.2, 129.1, 129.0, 128.9, 128.4, 128.2, 127.6, 67.4, 54.7, 53.2, 52.6, 38.1. Anal. calcd for $C_{32}H_{32}N_2O_3$: C, 78.02; H, 6.55; N, 5.69. Found: C, 78.06; H, 6.65; N, 5.65.

4.2.7. (*S*)-*N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl] tryptophan methyl ester (2g). A colorless oil was obtained in 98% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 8.2 (br, 1H), 7.84 (d, *J*=8.0 Hz, 1H), 7.56–7.07 (m, 20H), 6.81 (s, 1H), 5.04 (m,1H), 4.38 (s, 1H), 3.82 (d, *J*=13.6 Hz, 2H), 3.64 (s, 3H), 3.39 (m, 2H), 3.13 (d, *J*=13.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.0, 172.0, 138.9, 136.7, 133.5, 131.2, 129.2, 128.8, 128.4, 128.2, 127.8, 127.6, 123.3, 122.7, 120.1, 119.0, 111.7, 110.2, 67.6, 54.8, 52.9, 52.7, 27.9. Anal. calcd for $C_{34}H_{33}N_3O_3$: C, 76.81; H, 6.26; N, 7.90. Found: C, 76.79; H, 6.19; N, 7.69.

4.2.8. (*S*)-*N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl] phenylglycine methyl ester (2h). A colorless oil was obtained in 52% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 8.33 (m, 1H), 7.45–7.22 (m, 20H), 5.62 (m, 1H), 4.44 (s, 1H), 3.94 (d, *J*=13.6 Hz, 2H), 3.74 (m, 3H), 3.27 (d, *J*=13.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.7, 171.5, 139.0, 137.3, 133.7, 131.0, 129.3, 129.2, 129.1, 129.0, 128.9, 128.6, 128.3, 127.7, 67.6, 57.0, 55.0, 53.2. Anal. calcd for $C_{31}H_{30}N_2O_3$: C, 77.80; H, 6.32; N, 5.85. Found: C, 77.71; H, 6.39; N, 5.73.

4.2.9. (*S*)-*N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl] tyrosine methyl ester (2i). A colorless oil was obtained in 77% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.84 (d, *J*=8.4 Hz, 1H), 7.38–7.20 (m, 15H), 6.95 (d, *J*=8.2 Hz, 2H), 6.73 (d, *J*=8.2 Hz, 2H), 5.72 (br, 1H), 4.95 (m, 1H), 3.84 (d, *J*=13.6 Hz, 2H), 3.69 (s, 3H), 3.09 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.5, 172.1, 155.6, 138.7, 133.0, 131.2, 130.8, 129.2, 128.9, 128.4, 128.3, 127.8, 127.7, 116.1, 67.5, 54.7, 53.3, 52.7, 37.3. Anal. calcd for $C_{32}H_{32}N_2O_4$: C, 75.57; H, 6.34; N, 5.51. Found: C, 75.53; H, 6.42; N, 5.40.

4.2.10. (*S*)-*N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl] aspartic acid dimethyl ester (2j). A colorless oil was obtained in 86% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 8.51 (d, *J*=8.8 Hz, 1H), 7.44–7.24 (m, 15H), 4.99 (m, 1H), 4.42 (s, 1H), 3.92 (d, *J*=13.6 Hz, 2H), 3.74 (s, 3H), 3.69 (s, 3H), 3.28 (d, *J*=13.6 Hz, 2H), 3.11 (m, 1H), 2.82 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.1, 171.8, 156.8, 139.0, 137.0, 133.8, 130.9, 129.3, 129.0, 128.9, 128.5, 128.4, 128.3, 127.8, 67.6, 67.9, 54.9, 52.8, 52.2, 32.4. Anal. calcd for $C_{28}H_{30}N_2O_5$: C, 70.87; H, 6.37; N, 5.90. Found: C, 70.81; H, 6.40; N, 5.71.

4.2.11. (*S*)-*N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl] glutamic acid dimethyl ester (2k). A colorless oil was obtained in 50% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.93 (d, *J*=8.4 Hz, 1H), 7.49–7.24 (m, 15H), 4.72 (m, 1H), 4.44 (s, 1H), 3.94 (d, *J*=13.6 Hz, 2H), 3.75 (s, 3H), 3,64 (s, 3H), 3.27 (d, *J*=13.6 Hz), 2.28 (m, 3H), 2.05 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.3, 172.6, 172.0, 138.9, 133.7, 131.0, 129.3, 129.1, 128.9, 128.5, 127.8, 67.6, 54.9, 52.1, 51.8, 30.3, 27.7. Anal. calcd for $C_{29}H_{31}N_2O_5$: C, 70.72; H, 6.57; N, 5.89. Found: C, 70.89; H, 6.75; N, 5.67.

4.2.12. (*S*)-*N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl] lysine(*N*-carbonyloxybenzyl) methyl ester (2l). A colorless oil was obtained in 91% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.88 (d, *J*=8.4 Hz, 1H), 7.40–7.22 (m, 20H), 5.04 (s, 2H), 4.68 (m, 1H), 4.44 (s, 1H), 3.88 (d, *J*=13.6 Hz, 2H), 3.74 (s, 3H), 3.27 (d, *J*=13.6 Hz, 2H), 3.08 (m, 2H), 1.91 (m, 1H), 1.70 (m, 1H), 1.46 (m, 2H), 1.24 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.1, 171.8, 156.8, 139.0, 137.0, 133.9, 130.9, 129.3, 129.0, 128.9, 128.5, 128.4, 128.3, 127.8, 67.6, 66.9, 54.9, 52.8, 52.2, 41.1, 32.4, 29.7, 22.8. Anal. calcd for $C_{37}H_{41}N_2O_5$: C, 73.12; H, 6.80; N, 6.91. Found: C, 73.11; H, 6.67; N, 7.02.

4.2.13. (*S*)-*N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl] serine(*O*-benzyl) methyl ester (2m). A colorless oil was obtained in 50% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 8.35 (d, *J*=8.4 Hz, 1H), 7.39–7.19 (m, 20H), 4.84 (m, 1H), 4.58 (s, 2H), 4.45 (s, 1H), 4.03 (m, 1H), 3.95 (d, *J*=13.6 Hz, 2H), 3.72 (m, 4H), 3.22 (d, *J*=13.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.0, 171.2, 139.0, 137.9, 133.6, 131.2, 129.4, 128.9, 128.8, 128.5, 128.4, 128.3, 128.1, 127.7, 73.9, 70.2, 67.6, 54.9, 52.9. Anal. calcd for $C_{33}H_{34}N_2O_3$: C, 75.84; H, 6.56; N, 5.36. Found: C, 75.91; H, 6.62; N, 5.34.

4.2.14. (*S*)-*N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl] cysteine(*S*-benzyl) methyl ester (2n). A colorless oil was obtained in 57% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 8.32 (d, *J*=7.2 Hz, 1H), 7.68–7.22 (m, 20H), 4.92 (m, 1H), 4.46 (s, 1H), 3.90 (d, *J*=13.6 Hz, 2H), 3.69 (m, 5H), 3.26 (d, *J*=13.6 Hz, 2H), 2.91 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.9, 171.7, 138.9, 137.9, 131.6, 131.1, 129.4, 129.2, 129.0, 128.9, 128.6, 128.3, 128.0, 127.7, 67.6, 55.0, 53.0, 51.6, 36.9, 33.8. Anal. calcd for $C_{33}H_{34}N_2O_3S$: C, 73.58; H, 6.36; N, 5.20. Found: C, 73.35; H, 6.34; N, 5.06.

4.2.15. (*S*)-*N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl] leucine benzyl ester (4). A colorless oil was obtained in 97% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.79 (d, *J*=8.4 Hz, 1H), 7.38–7.22 (m, 20H), 5.18 (m, 2H), 4.73 (m, 1H), 4.43 (s, 1H), 3.87 (d, *J*=13.6 Hz, 2H), 3.21 (d, *J*=13.6 Hz, 2H), 1.74 (m, 1H), 1.61 (m, 2H), 0.92 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.1, 171.8, 139.0, 135.8, 133.7, 131.0, 129.2, 129.0, 128.8, 128.6, 128.5, 128.2, 127.7, 67.5, 54.9, 51.2, 41.9, 25.4, 23.3, 22.2. Anal. calcd for $C_{35}H_{38}N_2O_3$: C, 78.62; H, 7.16; N, 5.24. Found: C, 78.83; H, 7.26; N, 4.90. The absolute configurations of two epimers of **4** were confirmed by comparison of Chiral-HPLC retention time with authentic material individually prepared from the coupling of L-leucine derivative and (*S*)- or (*R*)-phenylglycine derivative using racemic material as a standard. [Chiralcel OD column; 5% 2-propanol in hexane; 0.5 mL/min; (α*R*)-epimer had a retention time of 14.8 min, (α*S*)-epimer had a retention time of 14.1 min].

4.3. General procedure for deprotection of *N*,*N*-dibenzyl group

To a solution of dibenzyl ester (1 equiv.) and $(Boc)_2O$ (2 equiv.) in absolute ethanol under an N_2 gas atmosphere was added 10% Pd–C followed by 1,4-cyclohexadiene (20 equiv.); 7 days later, the mixture was filtered through Celite and concentrated to provide the product after column chromatography on silica gel.

4.3.1. (*S*)-*N*-[(*R*)-α-Phenyl-*N*-(*tert*-butoxycarbonyl)-glycinyl] leucine methyl ester (6). A colorless oil was obtained in 57% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.38–7.27 (m, 5H), 6.42 (d, J=8.2 Hz, 1H), 5,80 (br, 1H), 5.20 (br, 1H), 4.58 (m, 1H), 3.72 (s, 3H), 1.20–1.65 (m, 3H), 1.40 (s, 9H), 0.76 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.6, 170.3, 155.3, 138.8, 129.3, 128.7, 127.6, 80.5, 52.7, 51.2, 41.5, 28.6, 25.1, 23.0, 21.9. The spectral data of **6** were identical to those of the authentic material reported previously.[10]

4.3.2. (*S*)-*N*-[(*R*)-α-(*p*-Fluorophenyl)-*N*-(*tert*-butoxycarbonyl)glycinyl] leucine methyl ester (7). A colorless oil was obtained in 32% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.35 (m, 2H), 7.03 (m, 2H), 6.14 (d, J=8.4 Hz, 1H), 5.68 (br, 1H), 5.12 (br, 1H), 4.61 (m, 1H), 3.73 (s, 3H), 1.60–1.32 (m, 3H), 1.41 (s, 9H), 0.81 (d, J=6.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.4, 169.9, 155.3, 135.0, 129.5, 116.5, 116.2, 78.0, 52.8, 51.2, 41.6, 28.6, 25.0, 23.0, 22.0. $[\alpha]_D$=−76.4 (c=0.021, $CHCl_3$). HRMS calcd for $C_{20}H_{29}FN_2O_5$: 396.2061. Found: 396.2045. The absolute configuration of dipeptide analogue **7** is provisionally assigned to α*R* by analogy to the formation of (α*R*)-**6**.

Acknowledgements

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4. The low selectivities in the absence of TBAI observed in entries 10 and 11, Table 2 suggest the possibility that the leaving group in the nucleophilic substitution in the presence of TBAI is iodide rather than bromide. Further mechanistic investigation for details of the process is underway.
5. Calculations are performed with a semiempirical approximation using AM1. The software used was Spartan 5.1, wavefunction, Inc.
6. When nucleophiles such as benzylthiol, tritylthiol, sodium malonate, sodium azide, potassium acetate, potassium thioacetate and potassium phthalate were used for the reaction with **1b**, the corresponding substitution products were obtained in 17–88% yields with diastereomeric ratios from 51:49 to 55:45.
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Pictet Spengler-type reactions in 3-arylmethylpiperazine-2,5-diones. Synthesis of pyrazinotetrahydroisoquinolines

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Abstract—The behavior of aldehydes and acetals as *N*-alkylating agents of 1-acetyl-3-arylmethylpiperazine-2,5-diones and the subsequent cyclization of the *N*-alkylated products was studied. Use of paraformaldehyde in different reaction conditions gave 6-unsubstituted 3,6,11,11a-tetrahydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4-diones and, in some cases, benzo[*f*]pyrazino[1,2-*c*]1,3-oxazepine-1,4-diones. Succesful reactions with benzaldehyde required a first activation of the lactam function and a catalyzed *N*-alkylation with the aldehyde dimethyl acetal. The isolated *O*,*N*-amidoacetals thus obtained were submitted to a diastereoselective Pictet Spengler-type reaction that worked with arenes at several degrees of ring activation and with thiophene to give 6-phenylpyrazinoisoquinolinediones and the corresponding thieno analog.

1. Introduction

Many tetrahydroisoquinoline antitumor antibiotics, such as saframycins and ecteinascidin 743 (ET-743, Yondelis™) are potent cytotoxic agents (Fig. 1).[1,2] Their natural scarcity and the complexity of synthetic methods so far described have limited their development as antitumor drugs, which is headed by ET-743.[3–7] Structure–activity correlations are also relatively unexplored, because most synthetic approaches have focused to their total synthesis.[8–14] The work carried out so far in this direction has revealed the importance of the *N*-methyl substituent and the side chain at the isoquinoline C(1)-position.[15,16] It is also known that the antitumor activity of ET-743 may be maintained in simpler analogues such as phtalascidin.[17,18]

We proposed that the *A*-*E*-pentacyclic skeleton of these compounds, exemplified by saframycin **A**, could be approached from 6-substituted 2-acetyl-3,6,11,11a-tetrahydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4-diones (**IV**) according to Scheme 1. The R^3-substituent in compounds **I** that seems to be crucial for the antitumor activity, usually a cyano or a hydroxy group, will be introduced by interchange of the lactam-carbonyl group in compounds **II**, that are accessible by Pictet Spengler-type cyclization of compounds **III** previous reduction of the C(1)-carbonyl group.[19] Because our aim was to develop a flexible strategy that

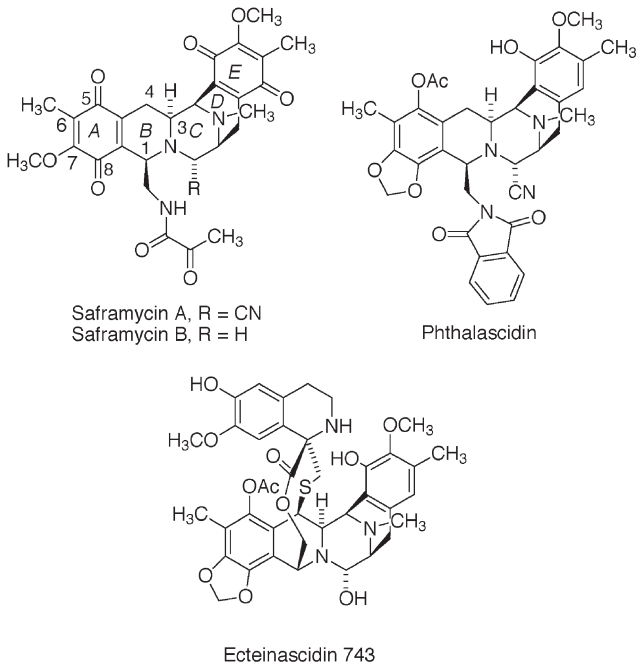

Figure 1. Some bioactive pyrazinoisoquinoline compounds.

permit variations of substituents in rings *A*, *B* and *E*, synthesis of compounds **III** was outlined by condensation of compounds **IV** with aromatic aldehydes, followed by catalytic hydrogenation. A first Pictet Spengler-type reaction between 1-acetyl-3-arylmethyl-2,5-piperazine-diones **1**

Keywords: Annulations; Acetals; Electrophilic aromatic substitution; Acyliminium cations.
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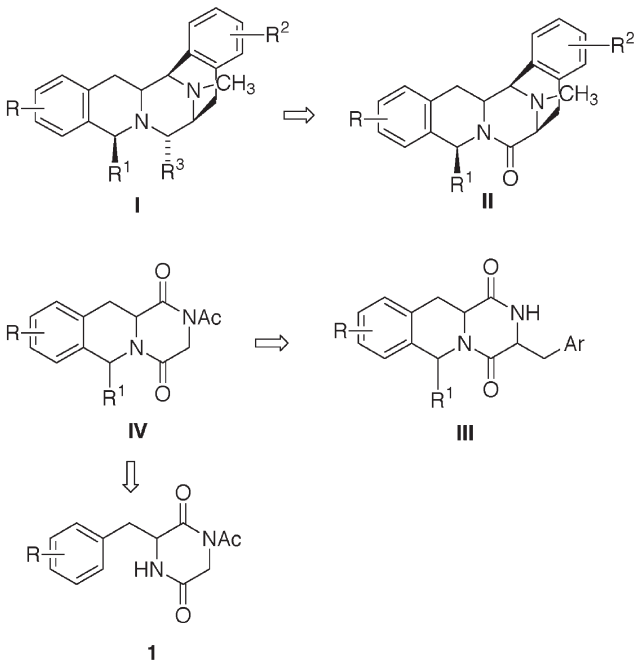


Scheme 1.

and aldehydes or their equivalents will give pyrazinotetrahydroisoquinolines **IV**.

We expect the feasible oxidative *O*-demethylation of compounds **I** or **II** containing methoxy groups at the *ortho*-positions of rings *A* and *E* into saframycin analogs. Fukuyama[20] and Kubo[21,22] have previously used compounds **1** as starting materials for the synthesis of (±)-saframycins, but in their strategies, formation of the pyridine *B*-ring was accomplished in a rather elaborated system already containing rings *C*–*E*. Here, we describe efficient approaches to compounds **IV** (R=H, 9-OMe, 7,8,10-$(OMe)_3$, 9-Me-7,8,10-$(OMe)_3$; R^1=H, Ph) and an analog where ring *A* is thiophene.

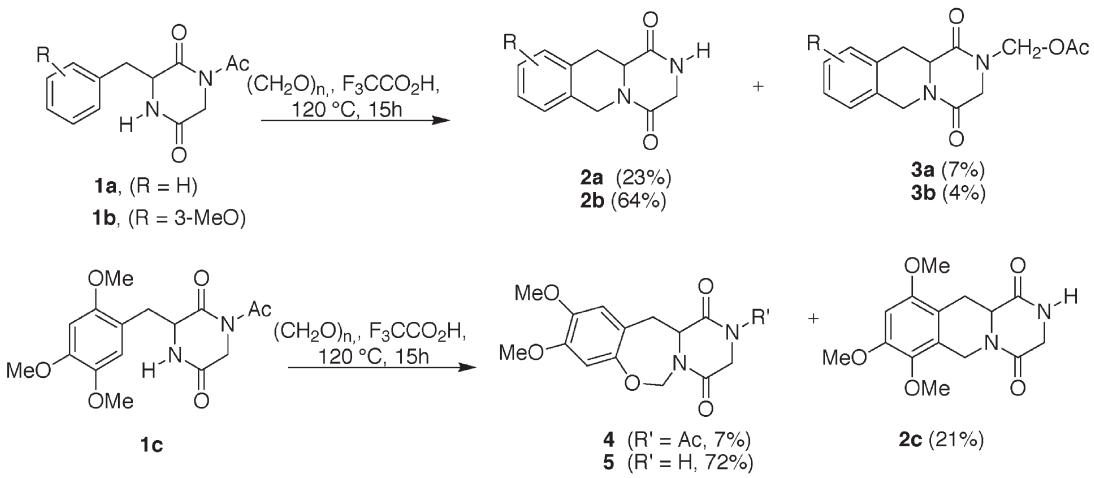
The high reactivity of acyliminium salts derived from one-pot reactions between *N*-acyl- or *N*-sulfonyl-2-arylethylamines and aldehydes or their equivalents allows 6-*endo*-*trig* cyclizations giving *N*-acyl(sulfonyl)-1,2,3,4-tetrahydroisoquinolines. This strategy has been widely applied to obtain a high number of tetrahydro-isoquinolines.[23–27] However, literature precedents for similar cyclizations in 3-arylmethyl-2,5-piperazinediones were disappointing.[28] The cyclization of adequate *N*-alkoxyalkyl secondary amides (*O*,*N*-acetals) was first reported by Kubo in 1987.[29]

Cyclic amides may be *N*-alkoxymethylated with formaldehyde acetals and different Lewis acids,[30] and these products generate *N*-acyliminium ions, by the intermediacy of Lewis acids such as $TiCl_4$, BF_3OEt_2, $InCl_3$, TMSOTf or $NbCl_5$, that react with nucleophiles.[31]

In a previous communication, we reported an efficient trimethylsilyl triflate catalyzed aldol-type reaction[32] between the *O*-trimethylsilyllactim of 1-acetyl-2,5-dimethoxyphenylmethyl-2,5-piperazinedione and acetaldehyde dimethylacetal, as well as the subsequent transformation of the *N*-methoxyethyl derivative thus obtained into compound **IV** (R=7,10-$(MeO)_2$; R^1=Me).[33] Here, we study *N*-alkylations with formaldehyde, benzaldehyde and benzaldehyde dimethylacetal of differently substituted compounds **1** and the cyclization of these products. An optimized straithforward synthesis of compounds **1**, that starts from 1,4-diacetylpiperazine-2,5-dione and the corresponding aromatic aldehyde has been reported.[34]

2. Results and discussion

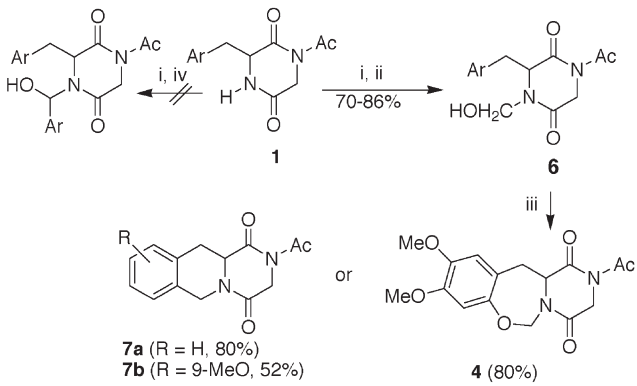
First attempts to obtain the 6-unsubstituted tricyclic system in one-pot procedure were performed by treatment of **1** with paraformaldehyde under different acid and temperature conditions. The best results so far obtained in the conversion of compounds **1a**, **1b** and **1c** into compounds **IV** (R^1=H), without isolation of their *N*-hydroxymethyl intermediates, are shown in Scheme 2. A disadvantage of this method was the loss of the *N*-acetyl substituent, which is necessary to give anchimerical assistance in the proposed conversion of compounds **IV** into compounds **III**.[35] In fact, we obtained variable yields of *N*-deacetyl-pyrazino[1,2-*b*]isoquinolines (**2a**–**2c**) and traces of the *N*-acetoxymethyl analogs (**3a**, **3b**). The later compounds are probably formed by addition of formaldehyde to compounds **2** and subsequent



Scheme 2.

O-acetylation. In the case of **1c**, the main reaction took place onto the *ortho*-methoxy group to give 1,3-benzoxazepine derivatives (**4** and **5**). It is remarkable the scarcity of literature references concerning the synthesis of 1,3-oxazepine-fused rings, although some related precedents of *N*-acyliminium trapping have been reported.[36]

The above results prompted us to use milder conditions and a two-steps procedure, with isolation of the *N*-hydroxymethyl intermediates **6** (Scheme 3). Thus, previous activation with chlorotrimethylsilane of the cyclic amide function of compounds **1** to give the corresponding *O*-trimethylsilyllactims,[37] and subsequent treatment with paraformaldehyde and $BF_3{\cdot}Et_2O$ as an acid catalyst, we got **6**. These isolated products were treated with *p*-toluenesulfonic acid to give the *N*-acetyl compounds **7** in moderate to good yields. As it was expected, the 2,4,5- trimethoxy derivative **1c** gave the oxazepine **4**. However, all efforts to extend this method to the less reactive benzaldehyde failed. Then, we turned our attention towards aldol-type condensations of compounds **1** with benzaldehyde dimethylacetal.



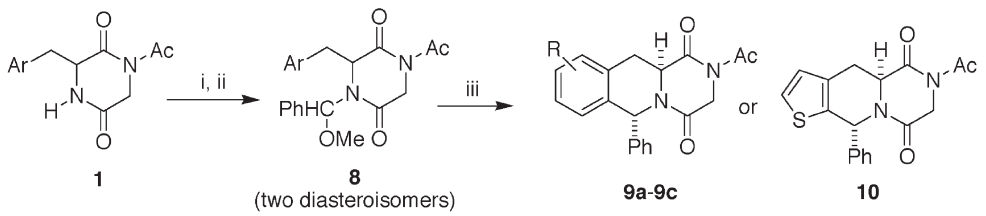
i: TMSCl, Et_3N, CH_2Cl_2, rt. ii: $(CH_2O)_n$, $BF_3.Et_2O$, 4d. iii: *p*TsOH (10%), CH_2Cl_2, 80 °C, 20-48 h. iv: C_6H_5CHO , $BF_3.Et_2O$, 4d.

Scheme 3.

The trimethylsilyl triflate catalyzed aldol-type reaction[33] worked with *O*-silyllactims derived from compounds **1a**–**1e** and benzaldehyde dimethylacetal, giving in a one-pot reaction good yields of the *N*-methoxybenzyl derivatives **8a**–**8e** as a nearly equimolecular mixture of diastereoisomers (Scheme 4). With the exception of **8d**, these compounds gave in *p*-toluenesulfonic acid the desired 6-*endo-trig* cyclizations, affording good yields of compounds **9** as the only reaction products. It is noticeable that the mild reaction conditions used in the full process are compatible with the *N*-acetyl substituent, and that the trimethoxy derivative **8c** gave **9c** without traces of any fused 1,3-oxazepine. When the cyclization of **8d** was performed in conc. H_2SO_4, *N*-deacetyl-**9d** was obtained after 30 min at room temperature in 80% yield. Its conversion to **9d** by treatment with acetic anhydride was quantitative.

The *trans*-relationship between the H(6) and H(11a)-protons which was previously observed in the above mentioned 6-methyl analog,[33] was confirmed in all compounds **9** by NMR experiments. This geometry is the expected for these acyliminium cation-mediated cyclizations, since the *O*,*N*-acetals have to adopt an *E*-configuration in order to minimize the steric interactions between the phenyl substituent and the vicinal piperazinedione C(4)═O group. Since this relative configuration is opposite to that of ring *B* in the natural cytotoxic antibiotics, we studied the synthesis of the *cis*-isomers by starting from the 3-arylmethylen-piperazinedione **11**,[34] and expecting a final diastereoselective hydrogenation of the putative unsaturated tricyclic system **13**.

However, although the same *N*-alkylation conditions permitted the synthesis of the unsaturated *N*-methoxybenzyl derivative **12**, all attempts to cyclize this compound in acid media failed (Scheme 5). Fortunately, we have developed a two-step procedure to transform the *trans*-isomers of compounds **IV** into their *cis*-isomers. It takes place by a regioselective radical bromination followed by espontaneous elimination of HBr. The 11,11a-didehydroderivatives,

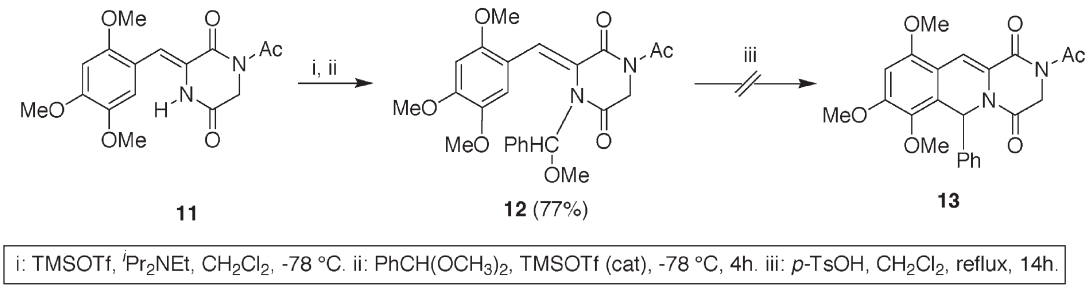


Ar	Comp.	Yield (%)
Phenyl	**8a**	80
3-Methoxyphenyl	**8b**	91
2,4,5-Trimethoxyphenyl	**8c**	87
3-Methyl-2,4,5-trimethoxyphenyl	**8d**	95
3-Thienyl	**8e**	78

Comp.	Yield (%)
9a	78
9b	79
9c	80
9d	20[a]
10	80

i: TMSOTf, $^{i}Pr_2NEt$, CH_2Cl_2, -78 °C. ii: $PhCH(OCH_3)_2$, TMSOTf (cat), -78 °C, 4h. iii: *p*-TsOH, CH_2Cl_2, 80°C, 14h. [a] Conc· H_2SO_4, r. t., 30 min. yielded 80% of *N*-deacetyl-**9d** (see text).

Scheme 4.



Scheme 5.

which are analogs of **13**, thus obtained gave the *cis*-isomers by catalytic hydrogenation.[33,38]

We conclude that the trimethysilyl triflate catalyzed *N*-methoxybenzylation of compounds **1**, followed by acid treatment, is a simple procedure to obtain 2-acetyl-6-phenyl derivatives of 3,6,11,11a-tetrahydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4-diones and 3,6,10,10a-tetrahydro-2*H*-thieno[3′,2′-4,5]pyrido[1,2-*a*]pyrazine-1,4-dione, and that this cyclization works with arenes at several degrees of ring activation. Additionally, the unsaturated precursors, such as **11**, are unsuitable starting materials. Finally, we have shown that novel tricyclic systems containing a fused 1,3-oxazepine ring can be obtained in one-pot reactions of certain compounds **1** with formaldehyde.

3. Experimental

All reagents were of commercial quality (Aldrich, Fluka, SDS, Probus) and were used as received. Solvents (SDS, Scharlau) were dried and purified using standard techniques. Reactions were monitored by thin layer chromatography, on aluminium plates coated with silica gel or aluminium oxide with fluorescent indicator (Merck 60 F_{254}). Separations by flash chromatography were performed on silica gel (Merck 60, 230–400 mesh) or aluminium oxide (Merck 90, 70–230 mesh). Melting points were uncorrected and were determined either using recrystallized samples or samples which crystallized during concentration of the chromatography eluents. Infrared spectra were recorded with solid compounds compressed into KBr pellets or as films over NaCl in the case of oils. NMR spectra were obtained in $CDCl_3$ at 250 MHz for ^1H and at 63 MHz for ^{13}C (Servicio de Resonancia Magnética Nuclear, Universidad Complutense). When necessary, assignments were aided by DEPT, COSY and ^{13}C–^1H correlation experiments. Elemental analyses were determined by the Servicio de Microanálisis Elemental, Universidad Complutense. The starting 3-arylmethylene (**11**) and 3-arylmethyl-2,5-piperazinediones (**1**) were obtained as reported in Ref. 30.

3.1. One pot reaction of compounds 1 with paraformaldehyde and AcOH/trifluoroacetic acid. General procedure

Compounds **1** (10 mmol) and paraformaldehyde (20 mmol) were added to a 8:2 mixture of AcOH/trifluoroacetic acid (10 mL). After 13 h of reflux, the reaction mixture was allowed to cool ar r.t. A 20% aqueous $NaHCO_3$ solution (200 mL) was then added and the mixture was extracted with EtOAc (3×50 mL). The extracts were washed with 20% aqueous $NaHCO_3$ solution (2×50 mL) and H_2O (2×50 mL) and finally dried over Na_2SO_4. The solvent was removed and the residue was chromatographed in silica gel using first ethyl acetate/hexane (1:1) and then pure ethyl acetate as eluents to give compounds **2** and **3** or **4** and **5**.

3.1.1. 3,6,11,11a-Tetrahydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione (2a). White solid, yield: 23%. Mp 171–172 °C; IR (KBr, cm^{-1}) 3057, 2360, 1679, 1648; ^1H NMR (250 MHz) δ 7.25–7.15 (m, 4H), 7.03 (s, 1H), 5.28 (d, 1H, J=17.2 Hz), 4.36 (d, 1H, J=17.2 Hz), 4.23 (dd, 1H, J=12.2, 3.8 Hz), 4.12 (s, 2H), 3.41 (dd, 1H, J=16.0, 3.8 Hz), 3.06 (dd, 1H, J=16.0, 12.2 Hz); ^{13}C NMR (63 MHz) δ 167.9, 162.6, 132.6, 131.7, 129.1, 127.7, 127.6, 127.5, 126.7, 55.7, 45.2, 44.6, 33.6. Anal. calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.61; H, 5.86; N, 13.00.

3.1.2. 9-Methoxy-3,6,11,11a-tetrahydro-2*H*-pyrazino-[1,2-*b*]-isoquinoline-1,4-dione (2b). White solid, yield: 64%. Mp 129–130 °C; IR (KBr, cm^{-1}) 3257, 2935, 1660; ^1H NMR (250 MHz) δ 7.18 (ws, 1H), 7.07 (d, 1H, J= 8.4 Hz), 6.79 (dd, 1H, J=8.4, 2.3 Hz), 6.70 (d, 1H, J= 2.3 Hz), 5.18 (d, 1H, J=16.8 Hz), 4.30 (d, 1H, J=16.8 Hz), 4.19 (m, 1H), 4.09 (s, 2H), 3.78 (s, 3H), 3.35 (dd, 1H, J=15.6, 3.9 Hz), 3.02 (dd, 1H, J=15.6, 12.1 Hz); ^{13}C NMR (63 MHz) δ 168.1, 162.8, 158.9, 133.8, 127.8, 123.8, 120.9, 113.7, 55.7, 45.2, 44.1, 33.7. Anal. calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.16; H, 5.56; N, 11.12.

3.1.3. 7,8,10-Trimethoxy-3,6,11,11a-tetrahydro-2*H*-pyrazino-[1,2-*b*]-isoquinoline-1,4-dione (2c). White solid, yield: 21%. Mp 174–175 °C; IR (KBr, cm^{-1}) 2927, 1668, 1652; ^1H NMR (250 MHz) δ 6.82 (ws, 1H), 6.41 (s, 1H), 5.49 (d, 1H, J=17.9 Hz), 4.20 (d, 1H, J=17.9 Hz), 4.12 (dd, 1H, J=13.0, 3.8 Hz), 4.10 (s, 2H), 3.88 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.48 (dd, 1H, J=16.7, 3.8 Hz), 2.65 (dd, 1H, J=16.7, 13.0 Hz); ^{13}C NMR (63 MHz) δ 168.0, 162.4, 153.7, 151.7, 139.3, 126.7, 113.5, 95.8, 60.9, 56.5, 56.1, 55.7, 45.2, 40.9, 28.0. Anal. calcd for $C_{15}H_{18}N_2O_5$: C, 58.82; H, 5.92; N, 9.15. Found: C, 58.67; H, 5.73; N, 9.04.

3.1.4. 2-Acetoxymethyl-3,6,11,11a-tetrahydro-2*H*-pyrazino-[1,2-*b*]isoquinoline-1,4-dione (3a). Pale yellow oil, yield: 7%.; IR (NaCl, cm^{-1}) 2925, 1745, 1667; ^1H NMR (250 MHz) δ 7.28–7.15 (m, 4H), 5.48 (d, 1H, J=18.1 Hz), 5.44 (d, 1H, J=18.1 Hz), 5.18 (d, 1H, J=16.9 Hz), 4.43 (d, 1H, J=16.9 Hz), 4.24 (dd, 1H, J=12.0, 3.9 Hz), 4.21 (s, 2H), 3.43 (dd, 1H, J=16.0, 3.9 Hz), 3.07 (dd, 1H, J=16.0,

12.0 Hz), 2.05 (s, 3H); ^{13}C NMR (63 MHz) δ 171.0, 166.9, 162.8, 132.7, 131.7, 129.0, 127.6, 126.7, 69.5, 56.0, 50.6, 44.4, 33.3, 21.1. Anal. calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.13; H, 5.57; N, 9.53.

3.1.5. 2-Acetoxymethyl-9-methoxy-3,6,11,11a-tetrahydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione (3b). White solid, yield: 4%. Mp 40–41 °C; IR (KBr, cm^{-1}) 2927, 1743, 1670; ^{1}H NMR (250 MHz) δ 7.08 (d, 1H, *J*=8.5 Hz), 6.81 (dd, 1H, *J*=8.5, 2.5 Hz), 6.73 (d, 1H, *J*=2.5 Hz), 5.50 (d, 1H, *J*=10.2 Hz), 5.42 (d, 1H, *J*=10.2 Hz), 5.09 (d, 1H, *J*=16.6 Hz), 4.39 (d, 1H, *J*=16.6 Hz), 4.22 (dd, 1H, *J*=12.0, 4.0 Hz), 4.20 (s, 2H), 3.38 (dd, 1H, *J*=16.0, 4.0 Hz), 3.04 (dd, 1H, *J*=16.0, 12.0 Hz), 2.12 (s, 3H); ^{13}C NMR (63 MHz) δ 170.6, 166.5, 162.4, 158.6, 133.6, 127.4, 123.4, 113.4, 69.2, 55.5, 49.6, 40.7, 33.1, 20.7. Anal. calcd for $C_{16}H_{19}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.15; H, 5.59; N, 8.47.

3.1.6. 2-Acetyl-9,10-dimethoxy-2,3,12,12a-tetrahydro-6*H*-benzo[*f*]pyrazino[1,2-*c*]1,3-oxazepine-1,4-dione (4). White solid, yield: 7%. Mp 262 °C (dec.); see below other analytical data.

3.1.7. 9,10-Dimethoxy-2,3,12,12a-tetrahydro-6*H*-benzo-[*f*]-pyrazino[1,2-*c*]1,3-oxazepine-1,4-dione (5). White solid, yield: 72%. Mp 115–116 °C; IR (KBr, cm^{-1}) 2940, 1672; ^{1}H NMR (250 MHz) δ 5.59 (s, 1H), 5.29 (s, 1H), 4.54 (dd, 1H, *J*=9.2, 7.7 Hz), 4.11 (d, 1H, *J*=16.8 Hz), 3.90 (d, 1H, *J*=16.8 Hz), 3.76 (d, 2H, *J*=19.6 Hz), 3.74 (s, 3H), 3.59 (s, 3H), 2.56 (dd, 1H, *J*=13.6, 7.7 Hz), 2.39 (dd, 1H, *J*=13.6, 9.2 Hz; ^{13}C NMR (63 MHz) δ 182.1, 176.3, 171.5, 169.5, 163.7, 150.4, 114.0, 102.1, 58.7, 56.9, 55.6, 54.8, 47.5, 46.3, 40.8. Anal. calcd for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.58. Found: C, 57.38; H, 5.53; N, 9.40.

3.2. *N*-Hydroxymethylation of compounds 1. General procedure

To a suspension of **1** (0.92 mmol) in dry CH_2Cl_2 (60 mL) was added trimethylsilyl chloride (0.92 mmol) and Et_3N (0.92 mmol) and the suspension was vigorously stirred under argon atmosphere at room temperature for 2.5 h. Then a solution of paraformaldehyde (1.1 mmol) and $BF_3{\cdot}Et_2O$ (0.46 mmol) in dry CH_2Cl_2 (10 mL) was added and the reaction was stirred for additional 4 days at room temperature, washed with aqueous $NaHCO_3$ (5 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The evaporation of the solvent gave a residue which was purified by chromatography in silica gel by eluting with DCM/EtOAc (8:2) to give compounds **6**.

3.2.1. 1-Acetyl-3-benzyl-4-hydroxymethylpiperazine-2,5-dione (6a). Colorless oil, yield: 70%; IR (NaCl, cm^{-1}) 3409, 2957, 1713, 1683; ^{1}H NMR (250 MHz) δ 7.29–7.25 (m, 3H), 7.12 (m, 2H), 5.27 (d, 1H, *J*=9.4 Hz), 4.73 (d, 1H, *J*=9.4 Hz), 4.57 (t, 1H, *J*=4.7 Hz), 4.27 (d, 1H, *J*=18.1 Hz), 3.26 (d, 2H, *J*=4.7 Hz), 2.53 (s, 3H), 2.39 (d, 1H, *J*=18.1 Hz); ^{13}C NMR (63 MHz) δ (63 MHz) δ 171.8, 169.0, 164.5, 134.7, 130.3, 130.1, 129.5, 128.5, 68.2, 61.9, 45.5, 38.8, 27.6. Anal. calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.57; H, 5.53; N, 10.07.

3.2.2. 1-Acetyl-4-hydroxymethyl-3(3-methoxybenzyl)-piperazine-2,5-dione (6b). White solid; yield: 71%. Mp 86–87 °C; IR (KBr, cm^{-1}) 3401, 2940, 2838, 1708, 1674; ^{1}H NMR (250 MHz) δ 7.18 (dd, 1H, *J*=8.1, 5.1 Hz), 6.83 (dd, 1H, *J*=8.5, 1.4 Hz), 6.75–6.72 (m, 2H), 5.01 (d, 1H, *J*=10.8 Hz), 4.79 (d, 1H, *J*=10.8 Hz), 4.52 (t, 1H, *J*=4.5 Hz), 4.26 (d, 1H, *J*=18.2 Hz), 3.72 (s, 3H), 3.29 (d, 1H, *J*=18.2 Hz), 2.44 (d, 1H, *J*=18.2 Hz), 2.54 (s, 3H); ^{13}C NMR (63 MHz) δ (63 MHz) δ 171.8, 168.8, 166.1, 160.3, 135.8, 130.5, 122.4, 116.1, 113.8, 71.0, 64.2, 55.6, 45.5, 39.6, 27.6. Anal. calcd for $C_{15}H_{18}N_2O_5$: C, 58.82; H, 5.92; N, 9.15. Found: C, 58.54; H, 5.89; N, 8.93.

3.2.3. 1-Acetyl-4-hydroxymethyl-3(2,4,5-trimethoxybenzyl)-piperazine-2,5-dione (6c). White solid; yield: 86%. Mp 142–143 °C; IR (KBr, cm^{-1}) 3390, 2941, 2840, 1705, 1669; ^{1}H NMR (250 MHz) δ 6.64 (s, 1H), 6.42 (s, 1H), 5.02 (d, 1H, *J*=10.8 Hz), 4.58 (d, 1H, *J*=10.8 Hz), 4.46 (d, 1H, *J*=5.0 Hz), 4.39 (d, 1H, *J*=18.0 Hz), 3.85 (s, 3H), 3.72 (s, 6H), 3.21 (d, 1H, *J*=5.0 Hz), 3.20 (d, 1H, *J*=5.0 Hz), 2.93 (d, 1H, *J*=18.0 Hz), 2.52 (s, 3H); ^{13}C NMR (63 MHz) δ (63 MHz, $CDCl_3$) δ 171.3, 168.1, 164.9, 151.8, 149.4, 142.7, 114.8, 112.9, 96.4, 68.8, 61.9, 56.4, 55.8, 55.6, 45.2, 32.2, 26.9. Anal. calcd for $C_{17}H_{22}N_2O_7$: C, 55.73; H, 6.05; N, 7.65. Found: C, 55.35; H, 6.01; N, 7.51.

3.3. Cyclization reactions of compounds 6 with *p*-toluenesulfonic acid

Compounds **6** (0.66 mmol) were stirred and refluxed in dry dichloromethane (20 mL) with a catalytic amount of *p*-toluenesulfonic acid (0.066 mmol) for 2 days. The solution was cooled to r.t., poured into saturated $NaHCO_3$ aqueous solution and extracted by DCM (30 mL×3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 filtered and evaporated. The residue was purified by chromatography in silica gel by eluting with EtOAc/hexane (8:2).

3.3.1. 2-Acetyl-3,6,11,11a-tetrahydro-2*H*-pyrazino[1,2-*b*]-isoquinoline-1,4-dione (7a). White solid; yield: 80%. Mp 92–93 °C; IR (KBr, cm^{-1}) 2933, 1713, 1668; ^{1}H NMR (250 MHz) δ 7.28–7.22 (m, 4H), 4.90 (d, 1H, *J*=16.3 Hz), 4.73 (d, 1H, *J*=17.6 Hz), 4.64 (d, 1H, *J*=16.3 Hz), 4.30 (dd, 1H, *J*=10.9, 4.5 Hz), 4.18 (d, 1H, *J*=17.6 Hz), 3.38 (dd, 1H, *J*=15.6, 4.5 Hz), 3.16 (dd, 1H, *J*=15.6, 10.9 Hz), 2.61 (s, 3H); ^{13}C NMR (63 MHz) δ 171.5, 168.0, 163.6, 132.5, 132.1, 128.3, 127.6, 127.5, 126.4, 56.7, 45.8, 43.6, 32.6, 27.2. Anal. calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 64.93; H, 5.48; N, 10.41.

3.3.2. 2-Acetyl-9-methoxy-3,6,11,11a-tetrahydro-2*H*-pyrazino-[1,2-*b*]isoquinoline-1,4-dione (7b). White solid, yield: 52%. Mp 52–53 °C; IR (KBr, cm^{-1}) 2936, 1713, 1673; ^{1}H NMR (250 MHz) δ 7.11 (d, 1H, *J*=8.2 Hz), 6.82 (dd, 1H, *J*=8.2, 2.5 Hz), 6.78 (s, 1H), 4.79 (d, 1H, *J*=16.0 Hz), 4.72 (d, 1H, *J*=17.7 Hz), 4.57 (d, 1H, *J*=16.0 Hz), 4.26 (dd, 1H, *J*=10.8, 4.5 Hz), 4.14 (d, 1H, *J*=17.7 Hz), 3.31 (dd, 1H, *J*=15.6, 4.5 Hz), 3.12 (dd, 1H, *J*=15.6, 10.8 Hz), 2.60 (s, 3H); ^{13}C NMR (63 MHz) δ 171.8, 168.5, 164.0, 159.3, 134.2, 127.8, 124.6, 113.7, 113.5, 57.0, 55.7, 46.2, 43.5, 32.1, 27.6. Anal. calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.21; H, 5.59; N, 9.45.

3.3.3. 2-Acetyl-9,10-dimethoxy-2,3,12,12a-tetrahydro-6*H*-benzo[*f*]pyrazino[1,2-*c*]1,3-oxazepine-1,4-dione (4). Yield: 80%. Mp 262 °C (dec.); IR (KBr, cm^{-1}) 1662, 1602; ^1H NMR (250 MHz) δ 5.84 (s, 1H), 5.36 (s, 1H), 5.02 (d, 1H, J=16.7 Hz), 4.51 (dd, 1H, J=8.7, 6.4 Hz), 4.06 (d, 1H, J=12.1 Hz), 3.91 (d, 1H, J=16.7 Hz), 3.64 (s, 3H), 3.61 (s, 3H), 3.45 (d, 1H, J=12.1 Hz), 2.91 (dd, 1H, J=13.7, 6.4 Hz), 2.39 (dd, 1H, J=13.7, 8.7 Hz), 2.56 (s, 3H); ^{13}C NMR (63 MHz) δ 181.7, 175.2, 171.5, 169.2, 163.3, 151.2, 111.7, 102.5, 60.3, 56.7, 55.7, 54.7, 47.5, 46.8, 39.6, 27.5. Anal. calcd for $C_{16}H_{18}N_2O_6$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.34; H, 5.48; N, 7.89.

3.3.4. *N*-Alkoxybenzylation of compounds 1 and 11. General procedure. To a solution of **1** or **11** (1.63 mmol) in dry CH_2Cl_2 (25 mL), under an Ar atmosphere and at −78 °C was added with stirring $^iPr_2NEt$ (0.31 mL, 1.79 mmol) and TMSOTf (0.35 mL, 1.96 mmol). After 4 h at the same temperature, benzaldehyde dimethyl acetal (1.96 mmol) and TMSOTf (0.01 mL) were added, and the reaction was kept for additional 4 h. This mixture was poured onto a saturated NH_4Cl aqueous solution and extracted with CH_2Cl_2 (30 mL×3). The combined extracts were washed with H_20 and brine, dried over anhydrous Na_2SO_4, filtered and concentrated.

3.3.5. 1-Acetyl-3-benzyl-4-(1-methoxybenzyl)-2,5-piperazine-dione (8a). Chromatographic separation (EtOAc/hexane 1:1, silica gel) gave **8a** as two diastereomers (1:1); yield: 80%. Diastereomer **A**: Mp 89–90 °C; IR (KBr, cm^{-1}) 3032, 2937, 1712, 1678; ^1H NMR (250 MHz) δ 7.67 (dd, 2H, J=7.6, 1.4 Hz), 7.49 (m, 2H), 7.42 (m, 2H), 7.20 (m, 2H), 6.78 (s, 1H), 6.74 (dd, 2H, J=7.6, 1.6 Hz), 4.54 (dd, 1H, J=6.7, 3.9 Hz), 4.49 (d, 1H, J=18.1 Hz), 3.37 (s, 3H), 2.62 (dd, 1H, J=13.9, 3.9 Hz), 2.54 (d, 1H, J=18.1 Hz), 2.53 (s, 3H), 2.09 (dd, 1H, J=13.9, 6.7 Hz); ^{13}C NMR (63 MHz) δ 171.7, 168.8, 166.3, 137.6, 134.8, 130.2, 129.7, 129.4, 129.3, 128.3, 127.0, 126.8, 83.2, 57.4, 56.5, 46.0, 38.9, 27.6. Anal. calcd for: $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 68.47; H, 6.07; N, 7.42.

Diastereomer **B**: Mp 98–99 °C; IR (KBr, cm^{-1}) 2938, 2837, 1709, 1679; ^1H NMR (250 MHz) δ 7.44–7.37 (m, 5H), 7.31–7.26 (m, 3H), 7.20 (m, 2H), 6.71 (s, 1H), 4.41 (d, 1H, J=18.3 Hz), 4.06 (dd, 1H, J=5.7, 4.1 Hz), 3.69 (s, 3H), 3.34 (dd, 1H, J=12.7, 5.7 Hz), 3.24 (dd, 1H, J=12.7, 4.1 Hz), 2.52 (d, 1H, J=18.3 Hz), 2.45 (s, 3H); ^{13}C NMR (63 MHz) δ 171.2, 168.2, 165.7, 135.5, 134.7, 129.7, 129.1, 129.0, 128.9, 127.9, 126.3, 85.3, 59.0, 57.8, 45.2, 40.0, 27.1. Anal. calcd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 68.56; H, 5.98; N, 7.39.

3.3.6. 1-Acetyl-3-(3-methoxybenzyl)-4-(1-methoxybenzyl)-2,5-piperazinedione (8b). Chromatographic separation (EtOAc/hexane 1:1, silica gel) gave **8b** as two diastereomers (1:1); yield: 91%. Diastereomer **A**: Colorless oil; IR (NaCl, cm^{-1}) 2940, 2837, 1711, 1680; ^1H NMR (250 MHz) δ 7.45–7.34 (m, 5H), 7.16 (dd, 1H, J=8.0, 7.6 Hz), 6.86 (m, 2H), 6.75 (d, 1H, J=7.6 Hz), 6.70 (s, 1H), 4.84 (dd, 1H, J=5.6, 4.0 Hz), 4.42 (d, 1H, J=18.2 Hz), 3.74 (s, 3H), 3.68 (s, 3H), 3.26 (dd, 1H, J=13.5, 5.6 Hz), 3.18 (dd, 1H, J=13.5, 4.0 Hz), 2.58 (d, 1H, J=18.2 Hz), 2.44 (s, 3H); ^{13}C NMR (63 MHz) δ (63 MHz, $CDCl_3$) δ 171.2, 168.3, 165.7, 159.7, 136.1, 135.4, 129.9, 129.1, 129.0, 126.4, 121.7, 115.3, 113.5, 85.4, 59.0, 57.8, 55.1, 45.3, 39.9, 27.1. Anal. calcd for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.24; H, 6.15; N, 6.85.

Diastereomer **B**: Colorless oil; IR (NaCl, cm^{-1}) 2939, 2834, 1711, 1676; ^1H NMR (250 MHz, $CDCl_3$) δ 7.67 (dd, 2H, J=7.8, 1.5 Hz), 7.5 (dd, 1H, J=8.5, 1.5 Hz), 7.43 (dd, 2H, J=5.6, 1.5 Hz), 7.09 (t, 1H, J=8.0 Hz), 6.77 (s, 1H), 6.75 (dd, 1H, J=7.6, 2.1 Hz), 6.35 (d, 1H, J=7.6 Hz), 6.23 (d, 1H, J=2.1 Hz), 4.54 (dd, 1H, J=6.0, 3.8 Hz), 4.52 (d, 1H, J=18.1 Hz), 3.70 (s, 3H), 3.37 (s, 3H), 2.61 (d, 1H, J=18.1 Hz), 2.60 (dd, 1H, J=14.0, 3.8 Hz), 2.53 (s, 3H), 2.06 (dd, 1H, J=14.0, 6.0 Hz); ^{13}C NMR (63 MHz) δ 171.3, 168.4, 165.9, 159.7, 137.3, 135.8, 129.8, 129.3, 128.9, 126.3, 121.4, 114.8, 113.4, 83.6, 57.3, 56.0, 55.1, 45.6, 38.5, 27.2. Anal. calcd for: $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.39; H, 5.98; N, 6.96.3.

3.3.7. 1-Acetyl-3-(2,4,5-trimethoxybenzyl)-4-(1-methoxy-benzyl)-2,5-piperazinedione (8c). Chromatographic separation (EtOAc/hexane 1:1, silica gel) gave **8c** as two diastereomers (1:1); yield: 87%. Diastereomer **A**: Mp 51–52 °C; IR (KBr, cm^{-1}) 2939, 2836, 1711, 1679; ^1H NMR (250 MHz) δ 7.42 (m, 5H), 6.75 (s, 1H), 6.70 (s, 2H), 6.41 (s, 1H), 4.75 (d, 1H, J=18.0 Hz), 3.95 (dd, 1H, J=8.9, 4.9 Hz), 3.86 (s, 3H), 3.81 (s, 3H), 3.66 (s, 3H), 3.64 (s, 3H), 3.60 (d, 1H, J=18 Hz), 3.31 (dd, 1H, J=13.5, 4.9 Hz), 3.11 (dd, 1H, J=13.5, 8.9 Hz), 2.41 (s, 3H); ^{13}C NMR (63 MHz) δ (63 MHz) δ 171.6, 167.4, 166.2, 151.7, 149.2, 142.8, 135.9, 129.0, 128.9, 128.6, 126.3, 115.2, 113.8, 96.5, 85.1, 58.7, 57.4, 56.5, 56.0, 55.7, 46.0, 33.5, 26.9. Anal. calcd for $C_{24}H_{28}N_2O_7$: C, 63.15; H, 6.18; N, 6.18. Found: C, 63.24; H, 5.98; N, 6.03.

Diastereomer **B**: Mp 91–92 °C; IR (KBr, cm^{-1}) 2935, 2831, 1711, 1679; ^1H NMR (250 MHz) δ 7.63 (dd, 2H, J=7.7, 0.9 Hz), 7.45 (m, 3H), 6.72 (s, 1H), 6.34 (s, 1H), 5.98 (s, 1H), 4.73 (d, 1H, J=17.9 Hz), 4.30 (dd, 1H, J=9.5, 4.5 Hz), 3.83 (d, 1H, J=13.2 Hz), 3.82 (s, 3H), 3.73 (s, 3H), 3.61 (s, 3H), 3.59 (d, 1H, J=17.9 Hz), 3.36 (s, 3H), 2.42 (s, 3H), 2.19 (dd, 1H, J=13.2, 4.5 Hz); ^{13}C NMR (63 MHz) δ 171.3, 167.4, 165.9, 151.3, 148.8, 142.6, 128.9, 127.4, 126.3, 114.1, 112.9, 96.2, 82.9, 57.0, 56.8, 56.3, 55.8, 55.5, 46.1, 31.7, 26.8. Anal. calcd for $C_{24}H_{28}N_2O_7$: C, 63.15; H, 6.18; N, 6.14. Found: C, 62.88; H, 5.85; N, 5.93.

3.3.8. 1-Acetyl-3-(3-methyl-2,4,5-trimethoxybenzyl)-4-(1-methoxybenzyl)-2,5-piperazinedione (8d). Chromatographic separation (EtOAc/hexane 1:1, silica gel) gave **8d** as two diastereomers (1:1); yield: 86%. Diastereomer **A**: colorless oil; IR (NaCl, cm^{-1}) 2941, 2838, 1715, 1694; ^1H NMR (250 MHz) δ 7.62 (m, 2H), 7.40 (m, 3H), 6.69 (s, 1H), 5.81 (s, 1H), 4.59 (d, 1H, J=18.2 Hz), 4.30 (dd, 1H, J=8.4, 4.2 Hz), 3.68 (s, 3H), 3.60 (dd, 1H, J=17.8, 8.4 Hz), 3.16 (d, 1H, J=18.2 Hz), 2.44 (s, 3H), 2.26(dd, 1H, J=17.8, 4.2 Hz), 2.01 (s, 3H), ^{13}C NMR (63 MHz) δ (63 MHz) δ 171.4, 166.8, 165.7, 150.7, 148.8, 147.4, 137.2, 128.9, 128.8, 128.4, 126.2, 125.3, 121.8, 111.2, 82.8, 60.4, 60.3, 60.1, 55.7, 53.3, 46.2, 32.6, 26.4, 9.2. Anal. calcd for $C_{25}H_{30}N_2O_7$: C, 63.82; H, 6.43; N, 5.95. Found: C, 64.14; H, 6.78; N, 6.03.

Diastereomer **B**: colorless oil; IR (NaCl, cm^{-1}) 2937, 2838, 1710, 1682; ^1H NMR (250 MHz) δ 7.50–7.30 (m, 5H), 6.69 (s, 1H), 6.68 (s, 1H), 4.61 (d, 1H, J=18.4 Hz), 3.95 (dd, 1H, J=8.1, 4.3 Hz), 3.80 (s, 3H), 3.77 (s, 3H), 3.65 (s, 3H), 3.57 (s, 3H), 3.31 (dd, 1H, J=13.4, 4.4 Hz), 3.24 (d, 1H, J=18.3 Hz), 3.07 (dd, 1H, J=13.4, 8.1 Hz), 2.41 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (63 MHz) δ 171.7, 167.0, 166.0, 151.2, 149.1, 147.7, 135.7, 129.1, 129.0, 128.7, 126.3, 125.7, 122.3, 112.2, 85.3, 60.6, 60.4, 59.0, 57.5, 55.9, 46.1, 34.3, 26.7, 9.5. $C_{25}H_{30}N_2O_7$: C, 63.82; H, 6.43; N, 5.95. Found: C, 63.74; H, 6.98; N, 6.15.

3.3.9. 1-Acetyl-4-(1-methoxy-1-phenylmethyl)-3-(3-thienyl-methyl)-2,5-piperazinedione (8e). Chromatographic separation (DCM, silica gel) gave **8e** as two diastereomers (1:1); 78%. Diastereomer **A**: Mp 102–103 °C; IR (KBr, cm^{-1}) 2938, 1709, 1678; ^1H NMR (250 MHz) δ 7.47–7.37 (m, 5H), 7.29 (dd, 1H, J=4.9, 2.9 Hz), 7.13 (dd, 1H, J=2.9, 1.3 Hz), 6.90 (dd, 1H, J=4.9, 1.3 Hz), 6.70 (s, 1H), 4.20 (d, 1H, J=18.0 Hz), 4.02 (dd, 1H, J=5.1, 3.6 Hz), 3.72 (s, 3H), 3.41 (dd, 1H, J=14.1, 5.1 Hz), 3.23 (dd, 1H, J=14.1, 3.6 Hz), 2.49 (d, 1H, J=18.0 Hz), 2.46 (s, 3H); ^{13}C NMR (63 MHz) δ (63 MHz, $CDCl_3$) δ 171.3, 168.7, 165.8, 135.3, 134.7, 129.2, 129.1, 128.7, 126.8, 126.5, 124.6, 85.8, 59.1, 58.3, 45.5, 34.9, 27.6. Anal. calcd for $C_{19}H_{20}N_2O_4S$: C, 61.27; H, 5.41; N, 7.52. Found: C, 61.13; H, 5.57; N, 7.34.

Diastereomer **B**: Mp 111–112 °C; IR (KBr, cm^{-1}) 2934, 2835, 1713, 1674; ^1H NMR (250 MHz) δ 7.65 (d, 1H, J=7.8 Hz), 7.50–7.40 (m, 3H), 7.19 (dd, 1H, J=4.5, 2.9 Hz), 6.77 (s, 1H), 6.65 (dd, 1H, J=2.9, 0.7 Hz), 6.55 (dd, 1H, J=4.5, 1.1 Hz), 4.54 (dd, 1H, J=5.8, 3.5 Hz), 4.50 (d, 1H, J=18.0 Hz), 3.38 (s, 3H), 2.71 (dd, 1H, J=14.4, 3.5 Hz), 2.54 (s, 3H), 2.47 (d, 1H, J=18.0 Hz), 2.08 (dd, 1H, J=14.4, 5.8 Hz); ^{13}C NMR (63 MHz) δ 171.3, 168.8, 165.8, 137.4, 134.4, 129.2, 129.1, 128.1, 126.7, 126.2, 124.0, 83.6, 56.4, 56.1, 45.4, 32.9, 27.2. Anal. calcd for $C_{19}H_{20}N_2O_4S$: C, 61.27; H, 5.41; N, 7.52. Found: C, 61.08; H, 5.36; N, 7.46.

3.3.10. 1-Acetyl-4-(1-methoxybenzyl)-3-(2,4,5-trimethoxy)-benzylidene-2,5-piperazinedione (12). Chromatographic separation (DCM/EtOAc 9:1, silica gel) gave **12**; white solid, yield: 77%. Mp 131 °C; IR (KBr, cm^{-1}) 2938, 1705; ^1H NMR (250 MHz) 7.07 (s, 1H), 7.02 (m, 3H), 6.88 (m, 2H), 6.74 (s, 1H), 6.19 (s, 1H), 5.83 (s, 1H), 4.49 (d, 1H, J=15.7 Hz), 4.10 (d, 1H, J=15.7 Hz), 3.73 (s, 3H), 3.65 (s, 3H), 3.59 (s, 3H), 3.05 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (63 MHz) δ 171.1, 167.1, 165.6, 152.9, 151.4, 142.2, 136.1, 128.5, 128.1, 127.9, 127.5, 126.6, 126.5, 90.4, 57.2, 56.4, 56.0, 55.9, 45.9, 26.2. Anal. calcd for $C_{24}H_{26}N_2O_7$: C, 63.43; H, 5.77; N, 6.16. Found: C, 63.02; H, 5.61; N, 5.93.

3.4. Cyclization reactions of compounds 8 with *p*-toluenesulfonic acid. Synthesis of compounds 9 and 10

Compounds **8** were cyclized in the same conditions that compounds **6** (see above).

3.4.1. 2-Acetyl-6-phenyl-3,6,11,11a-tetrahydro-2*H*-pyrazino-[1,2-*b*]isoquinoline-1,4-dione (9a). Chromatographic separation (hexane/EtOAc 9:1, silica gel) gave **9a** as a white solid; yield: 78%. Mp 72–73 °C; IR (KBr, cm^{-1}) 2924, 1709, 1668; ^1H NMR (250 MHz) δ 7.27–7.04 (m, 9H), 6.88 (s, 1H), 4.49 (d, 1H, J=18.1 Hz), 4.38 (m, 1H), 4.30 (d, 1H, J=18.1 Hz), 3.22 (m, 2H), 2.49 (s, 3H); ^{13}C NMR (63 MHz) δ 171.7, 167.7, 162.3, 140.1, 133.5, 132.2, 129.1, 128.7, 128.6, 128.2, 127.8, 127.2, 55.2, 53.7, 45.8, 32.2, 27.3. Anal. calcd for $C_{20}H_{19}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.65; H, 5.38; N, 8.15.

3.4.2. 2-Acetyl-9-methoxy-6-phenyl-3,6,11,11a-tetrahydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione (9b). Chromatographic separation (EtOAc/hexane 1:1, silica gel) gave **9b** as a white solid; yield: 79%. Mp 48–49 °C; IR (KBr, cm^{-1}) 2936, 2836, 1710, 1668; ^1H NMR (250 MHz) δ 7.33–7.27 (m, 3H), 7.19 (m, 2H), 7.03 (d, 1H, J=8.4 Hz), 6.91 (s, 1H), 6.82 (dd, 1H, J=8.4, 2.7 Hz), 6.78 (d, 1H, J=2.7 Hz), 4.68 (d, 1H, J=18.1 Hz), 4.55 (dd, 1H, J=9.7, 6.1 Hz), 4.50 (d, 1H, J=18.1 Hz), 3.97 (s, 3H), 3.36 (m, 2H), 2.68 (3H); ^{13}C NMR (63 MHz) δ 171.7, 167.7, 162.2, 158.8, 140.3, 133.4, 129.6, 128.6, 128.5, 128.1, 125.7, 113.4, 55.3, 54.8, 53.5, 45.8, 32.4, 27.2. Anal. calcd for $C_{21}H_{20}N_2O_4$: C, 69.22; H, 5.53; N, 7.69. Found: C, 69.15; H, 5.25; N, 7.31.

3.4.3. 2-Acetyl-7,8,10-trimethoxy-6-phenyl-3,6,11,11a-tetrahydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione (9c). Chromatographic separation (EtOAc/hexane 1:1, silica gel) gave **9c** as a white solid; yield: 80%. Mp 63–64 °C; IR (KBr, cm^{-1}) 2939, 1709, 1666; ^1H NMR (250 MHz) δ 7.31–7.26 (m, 3H), 7.22–7.19 (m, 2H), 7.10 (s, 1H), 6.51 (s, 1H), 4.61 (d, 1H, J=18.3 Hz), 4.33 (dd, 1H, J=11.6, 5.1 Hz), 4.23 (d, 1H, J=18.3 Hz), 3.87 (s, 3H), 3.86 (s, 3H), 3.44 (s, 3H), 3.30 (dd, 1H, J=16.8, 5.1 Hz), 2.87 (dd, 1H, J=16.8, 11.6 Hz), 2.56 (s, 3H); ^{13}C NMR (63 MHz) δ 172.3, 168.5, 162.2, 153.3, 152.0, 140.1, 139.7, 129.0, 128.9, 128.7, 128.4, 113.3, 60.6, 56.5, 56.1, 53.3, 51.8, 46.2, 27.7, 27.3. Anal. calcd for $C_{23}H_{24}N_2O_6$: C, 65.08; H, 5.70; N, 6.60. Found: C, 64.96; H, 5.53; N, 6.21.

3.4.4. 2-Acetyl-9-methyl-7,8,10-trimethoxy-6-phenyl-3,6,11,11a-tetrahydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione (9d). Chromatographic separation (EtOAc/hexane 1:1, silica gel) gave **9d** as a yellow oil; yield: 20%; IR (NaCl, cm^{-1}) 2941, 1769, 1714, 1668; ^1H NMR (250 MHz) δ 7.40–7.10 (m, 4H), 7.08 (s, 1H), 6.89 (s, 1H), 4.59 (d, 1H, J=18.3 Hz), 4.37 (dd, 1H, J=10.6, 5.2 Hz), 4.35 (d, 1H, J=18.2 Hz), 3.77 (s, 3H), 3.75 (s, 3H), 3.46 (s, 3H), 3.33 (dd, 1H, J=16.4, 5.2 Hz), 3.04 (dd, 1H, J=16.4, 11.4 Hz), 2.56 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (63 MHz) δ 171.8, 167.8, 162.4, 152.1, 150.7, 146.2, 139.8, 128.7, 128.1, 125.6, 125.4, 121.0, 83.9, 60.3, 60.0, 59.8, 53.1, 51.4, 45.8, 27.3, 26.9. 9.5. Anal. calcd for $C_{24}H_{26}N_2O_6$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.96; H, 5.73; N, 6.24.

3.4.5. 2-Acetyl-6-phenyl-3,6,10,10a-tetrahydro-2*H*-thieno[2′,3′-5,4]pyrido[1,2-*a*]pyrazine-1,4-dione (10). Chromatographic separation (hexane/EtOAc 7:3, silica gel) gave **10** as a white solid; yield: 80%. Mp 134–135 °C; IR (KBr, cm^{-1}) 1700, 1663; ^1H NMR (250 MHz) δ 7.28 (m, 5H), 7.26 (d, 1H, J=5.1 Hz), 7.04 (s, 1H), 6.83 (d, 1H, J=5.1 Hz), 4.65 (d, 1H, J=18.5 Hz), 4.31 (dd, 1H, J=12.2, 4.3 Hz), 4.05 (d, 1H, J=18.5 Hz), 3.03 (dd, 1H, J=15.9, 4.3 Hz), 2.90 (dd, 1H, J=15.9, 12.2 Hz); ^{13}C NMR (63 MHz) δ 171.8, 167.6, 161.6, 139.3, 133.0, 132.6, 128.8, 128.7, 128.5, 126.2, 125.5, 53.3, 53.1, 45.7, 30.9, 27.3.

Anal. calcd for $C_{18}H_{16}N_2O_3S$: C, 63.51; H, 4.74; N, 8.23. Found: C, 63.28; H, 4.76; N, 8.10.

3.4.6. Cyclization reaction of compunds 8d with sulfuric acid. Synthesis of compounds *N*-deacetyl-9d. Compound **8d** (0.42 mmol) was stirred in sulfuric acid (6 mL) for 30 min. at r.t. The solution was poured into ice-water and the aqueous solution was extracted with ethyl acetate (100 mL×2). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 filtered and evaporated to give an oil that was recrystallized in DCM/hexane (1:5) to give *N*-deacetyl-**9d**. White solid, yield: 80%. Mp 178 °C; IR (KBr, cm^{-1}) 3241, 2940, 1689, 1661; ^1H NMR (250 MHz) δ 7.30–7.20 (m, 5H), 7.11 (s, 1H), 4.20 (dd, 1H, J=12.3, 4.5 Hz), 4.10 (s, 2H), 3.74 (s, 3H), 3.73 (s, 3H), 3.48 (dd, 1H, J=16.9, 4.6 Hz), 3.39 (s, 3H), 2.87 (dd, 1H, J=16.8, 12.4 Hz), 2.23 (s, 3H); ^{13}C NMR (63 MHz) δ 168.0, 161.0, 152.1, 150.5, 146.1, 140.5, 128.5, 128.3, 128.0, 125.4, 125.1, 121.5, 60.1, 59.9, 59.5, 51.4, 50.7, 44.7, 28.1, 9.4. Anal. calcd for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.60; H, 6.11; N, 7.02.

3.5. *N*-Acetylation of *N*-deacetyl-9d. Synthesis of 9d

Compound *N*-deacetyl-**9d** (33 mmol) was refluxed in acetic anhydride (10 mL) for 4 h. After cooling to r.t. the solvent was removed in vacuo to give **9d** as a yellow oil in quantitative yield.

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38. This unsaturated tricyclic system may be derived to the corresponding unsaturated pentacyclic core of the natural antibiotics (unpublished results).

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Conformationally regulated fluorescent sensors. Study of the selectivity in Zn^{2+} versus Cd^{2+} sensing☆

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Abstract—The Zn^{2+} and Cd^{2+} complexing properties of four ligands containing a 4,4′-substituted biphenyl moiety are described. Ligands **1** and **3**, containing only one 1-aza-18-crown-6 cavity, lead to selective complexation of Cd^{2+} versus Zn^{2+}. Ligand **4**, with two crown cavities linked to a tetramethylbenzidine unit, is able to form 1:1 complexes with Zn^{2+} and Cd^{2+}, showing a higher complexing constant with Zn^{2+} than with Cd^{2+}, probably due to enthalpic factors. Several complementary experiments suggest that the 1:1 complexes formed by ligand **4** involve both crown cavities acting together to give rise to clamp structures. The formation of this type of zinc complex gives rise to red shifted emission bands and distinct quenching of the fluorescence. A similar situation is observed with cadmium but the change is then less pronounced. When mixtures of both salts are used, ligand **4** selectively responds to zinc. Finally, ligand **2**, which also has two crown cavities but contains nitro rather than amino groups in the biphenyl moiety, shows no propensity to form clamp complexes and, for this reason, it complexes cadmium much more strongly than zinc and binds the former selectively when mixtures of both salts are used in complexing experiments.

1. Introduction

The design and preparation of sensors for cations, anions or neutral molecules is one of the most developed fields within supramolecular chemistry. These sensors are usually comprised of two well-defined subunits: a suitable binding site and a unit able to transmit to the macroscopic world information about the complexing process occurring on the molecular scale. According to the character of this transducer unit, sensors may be, for example, redox, or photoactive. There are many examples in the literature which make use of aromatic systems as photoactive groups.[1] These are often derived from anthracene, naphthalene or other fused-ring aromatic compounds but there are few references related to biphenyl derivatives. However, the redox and photophysical properties of tetramethylbenzidine (TMB) have been widely studied and the results obtained suggest that this system could be satisfactorily used as a transducer in sensor molecules.[2a] For most of the photoactive units studied until now, the fluorescence behaviour is modified through electronic effects (for example, when a lone pair on a nitrogen atom, which quenches the emission of a fluorophore via photoinduced electron transfer, is involved in complexation, the fluorescence is restored),[2b] whilst only a small number of examples have been reported in which a photoactive response is achieved through conformational change.[3]

With this in mind, our research group has been working on the synthesis and complexing studies of different ligands containing the tetramethylbenzidine moiety. These studies have been aimed at assessing the influence of complexation on the dihedral angle between the aromatic rings in TMB and thus on their redox and fluorescent properties. The prepared ligands contained a crown ether bound to the 2 and 2′ positions of the TMB unit. The fluorescence and the redox behaviour of these macrocyclic compounds have been studied and some of them have shown interesting properties as sensors for transition metal cations.[4]

In this contribution, we report on the preparation and sensing properties of two new ligands and their comparison with other two compounds previously prepared in our group.[5] Two of the studied ligands contain the TMB unit as the fluorophore, linked to either one or two complexing units (Chart 1). This type of compound can be related to

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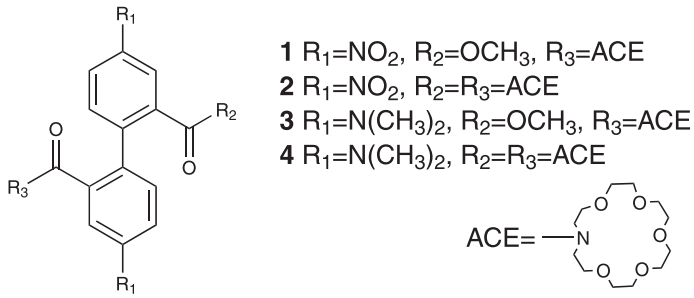
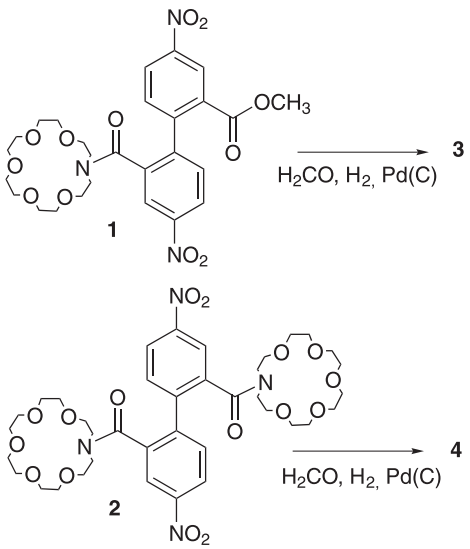


Chart 1.

those previously synthesised by our group[4] but the new ligands show more freedom because the rotation between the two aromatic rings of the biphenyl system is not precluded. Compounds with two crown cavities have shown to allow different modes of complexation of cations, with different stoichiometry, according to their ionic radii.[6] Additionally, the formation of 'clamp' complexes (in which the metal ion is bound simultaneously to the two crown units within the same molecule) could induce strong changes in conformation of the photoactive subunits and thus lead to large perturbations in the fluorescent properties of these ligands. One additional advantage of these ligands is that they can be synthesised readily from commercially available materials and synthons whose preparation is already well-established.

2. Synthesis and results

The synthesis of compounds **1** and **2** has been recently described.[5] Catalytic reduction of compounds **1** and **2** in the presence of formaldehyde gave rise to compounds **3** and **4** in high yield (Scheme 1).[7]



Scheme 1.

2.1. Complexing experiments

Our prime interest was directed toward the study of Zn^{2+} and Cd^{2+} complexation for two reasons: (a) the chemical properties of Cd^{2+} compounds are similar to those of the corresponding Zn^{2+} compounds, so that their discrimination is an important challenge[8] and (b) the biological activity of Cd^{2+} is in striking contrast to the activity of Zn^{2+}. The latter is crucial in a number of important biological processes, whereas Cd^{2+} is one of the most toxic metals.[9] For all these reasons, several systems have been developed to complex these cations and to be able to act as sensors.[10]

Complexing studies of $Cd(NO_3)_2$ and $Zn(NO_3)_2$ using ligands **1**–**4** were carried out by titration experiments monitored by ^1H NMR and fluorescence spectroscopies.

(a) NMR Studies in acetonitrile

Although, the effect of complexation could be often observed in the whole spectra we have focused our study on ^1H NMR aromatic signals where changes can be more clearly monitorised. Thus, complexation of $Cd(NO_3)_2$ by ligand **1**, in acetonitrile, gives rise to a clear broadening and modifications in the shifts of the aromatic signals in the proton NMR spectrum. According to the mole ratio method,[11] the change of the slope at $M/L=1$ in the plot of the ^1H NMR of the signal initially centred at $\delta=7.66$ ppm clearly evidences the formation of a 1:1 complex. Additionally, by using the Benesi–Hildebrand[12] equation a complexing constant of log $K=2.09$ was determined (Table 1). By contrast, the lack of any shift or shape change in the signals upon addition of $Zn(NO_3)_2$ indicates that significant complexation is not achieved under this conditions.

Studies carried out with ligand **3** showed that this ligand is able to complex both salts, $Cd(NO_3)_2$ and $Zn(NO_3)_2$. Following the procedure described above (using the signal initially centred at $\delta=6.97$ ppm in the case of Zn^{2+} and at $\delta=7.23$ ppm for Cd^{2+}, as these signals suffer less broadening and bigger displacement when complexing those metals) a 1:1 stoichiometry for the complexes was determined. The stability constants determined in this case (log $K=0.80$ for $Zn(NO_3)_2$ and log $K=2.27$ for $Cd(NO_3)_2$) demonstrated that this

Table 1. Complexing constants (log K) for **1**–**4** in CD_3CN at 295 K

Ligand	$Zn(NO_3)_2$	$Cd(NO_3)_2$
1	—	2.09±0.02
2	—	2.473±0.005
3	0.80±0.07	2.27±0.01
4	2.50±0.07	1.98±0.01

ligand, too, forms stronger complexes with Cd(II) than with Zn(II). As it was expected, when a mixture of both salts was added, the ^{1}HNMR registered spectra was clearly similar to that obtained when only Cd(II) was present in the medium.

When ligand **2** was treated with $Cd(NO_3)_2$, a broadening of signal at δ=7.75 ppm and shift of all aromatic proton NMR signals is observed. Analysis of the titration data (using signal originally centred at δ=8.33 ppm) entirely fit to a 1:1 stoichiometry model. In addition formation of a 1:1 complex (LM) was clearly detected by electrospray ionization mass spectrometry (ESI-MS) showing a signal at m/z=468, both when 1:1 and 2:1 metal-to-ligand ratio solutions were introduced. In any case, no signal at m/z=261 corresponding to a 2:1 (LM_2) complex was observed in the spectra, indicating that its amount is negligible under these conditions. Its association constant value is similar to that determined above for **1**·$Cd(NO_3)_2$ (log K=2.473 for ligand **2** and 2.09 for ligand **1**). When $Zn(NO_3)_2$ was used as a salt, changes in the shape of the ^{1}H NMR signals are completely different to those with $Cd(NO_3)_2$, unfortunately association constants could not be calculated using NMR titration experiments because of insufficient changes in the chemical shifts of sharp signals (δ=7.74 ppm) for a quantitative study, and the strong broadening and merging observed for the remaining aromatic signals (δ=8.33 and 8.29 ppm), which prohibits accurate chemical shift determination. Additionally, the lack of change in the UV spectra titration (neither with Zn^{2+} nor Cd^{2+}) prevented the use of absorption spectroscopy as an alternative method. However, formation of a LM complex was observed by ESI-MS (m/z=443). No LM_2 complex signal was observed in the ESI-MS spectrum (m/z=238), even when a 2:1 metal-to-ligand ratio solution was injected. When ligand **2** was titrated versus a mixture of both salts, the obtained proton NMR spectra match those obtained when titration was done with $Cd(NO_3)_2$ alone.

When similar experiments were carried out with compound **4**, more interesting results were observed. ^{1}H NMR titration experiments with $Zn(NO_3)_2$ show an upfield shift of the signal at δ=7.14 ppm whereas a new set of signals appears at δ=6.85 and 6.76 accompanied by a decrease of the intensity of the ligand signals at δ=6.74 and 6.61 ppm (Fig. 1). Two different methods were used to determine the complex stoichiometry. Thus, according to the mole ratio method,[11] the abrupt change of the slope at M/L=1 in the plot of the ^{1}H NMR chemical shift of the signal

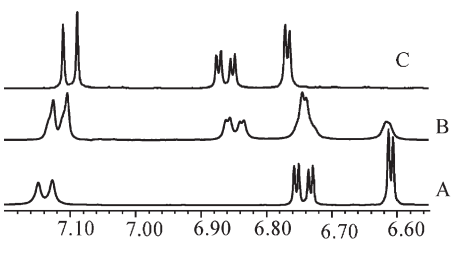


Figure 1. Titration of ligand **4** with Zn^{2+} in CD_3CN. (A) Ligand **4**; (B) **4**+1 equiv. Zn^{2+}; (C) **4**+3.5 equiv. Zn^{2+}.

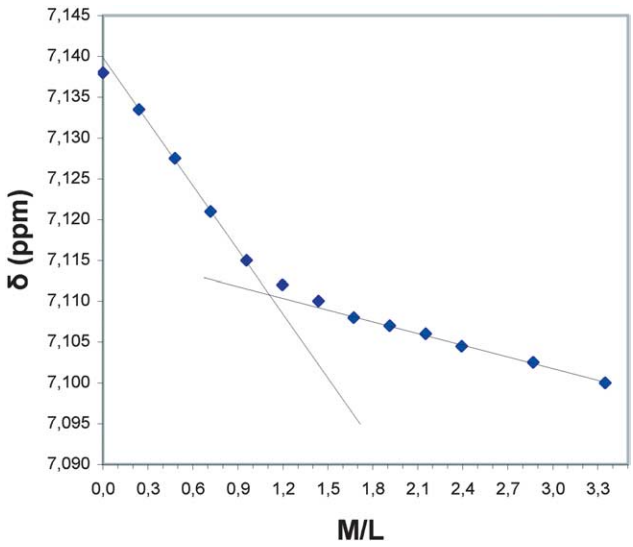


Figure 2. Variation of ^{1}H NMR signal of **4** centred at 7.14 ppm (2.72×10^{-2} M in CD_3CN) upon addition of increasing concentrations of $Zn(Tf)_2$ (0.25–3.3 equiv. versus L).

initially centred at δ=7.14 ppm (Fig. 2) unequivocally suggests the formation of a 1:1 complex with a high stability. No changes of slope are observed at further M/L ratios. From the analysis of the changes in the intensities of the new signals, the same conclusion as above can be drawn. Thus, after addition of 1 equiv. of metal, signals at δ=6.74 and 6.61 ppm disappear and no further significant increase in the intensity of the new ones can be observed upon further addition of metal up to 3.5 equiv. and no evidence of LM_2 was found. The LM stoichiometry was further supported by a signal at m/z=442 in the ESI-MS spectra, with no trace of signals due to LM_2. A stability constant of log K=2.50 was determined by using the Benesi–Hildebrand equation (Table 1). $Cd(NO_3)_2$ interacts with **4** in a similar way to $Zn(NO_3)_2$ (Fig. 3). Also in this case, a new set of signals appears in the aromatic area in proton NMR spectra upon the addition of increasing amounts of the salt. The main difference as regards Zn (II) case, is now a splitting experienced by signal at δ=7.14 ppm instead of its mere upfield shift, and the fact that signals corresponding to the free ligand can still be observed even after addition of 10 equiv. of cation. NMR data fit the Benesi–Hildebrand model for a 1:1 stoichiometry, that was supported by a signal at m/z=466 for **4**-Cd(II) in the corresponding ESI-MS spectra. The stability constant thus calculated was log K=1.98. Somewhat surprisingly, although the Zn^{2+} and Cd^{2+} complexing constants with **4** are not very different (Table 1), when

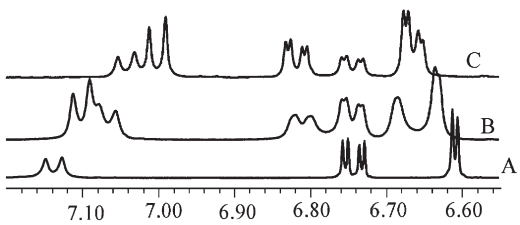


Figure 3. Titration of ligand **4** with Cd^{2+} in CD_3CN. (A) Ligand **4**; (B) **4**+1 equiv. Cd^{2+}; (C) **4**+3.5 equiv. Cd^{2+}.

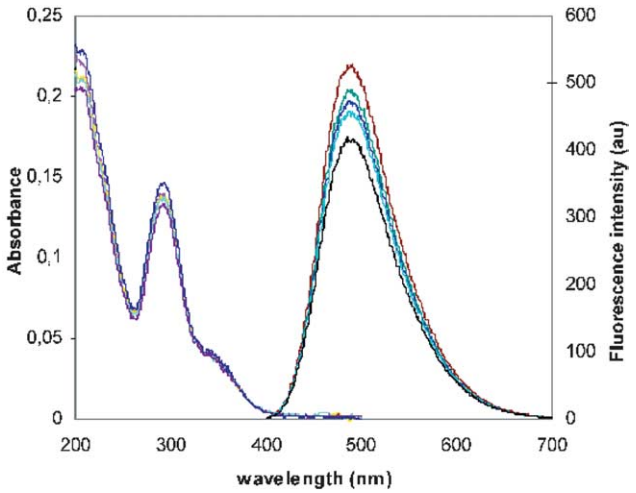


Figure 4. UV–visible absorbance (from 200 to 400 nm) and fluorescence emission (λ_{exc}=340 nm) spectra (from 400 to 700 nm) of **3** (5.53×10^{-6} M in acetonitrile) and upon addition of increasing concentrations of $Cd(Tf)_2$ (1–10 equiv.), in the presence of Bu_4NClO_4 (1.41×10^{-4} M).

both salts are present, in competition experiments, a bigger interaction of **4** with Zn^{2+} when compared to Cd^{2+} is observed. In fact, identical ^1H NMR spectra are obtained either on titration with Zn^{2+} or with a 1:1 solution of Zn^{2+} and Cd^{2+} salts.

(b) Fluorescence studies in acetonitrile

Ligands **3** and **4** are strongly fluorescent and even though the stability constants for the complexes are not too high, they have been investigated as potential fluorescent sensors for Cd(II) and Zn(II). The UV–visible absorbance spectrum of ligand **3**, in acetonitrile, shows a strong absorbance in the UV region, centred at 293 nm (ε=24,600), with a pronounced shoulder at longer wavelength, centred at 353 nm (ε=5895). Upon excitation at 340 nm, compound **3** gave an intense fluorescence emission band centred at 488 nm, with a quantum yield of 0.15 (see Fig. 4). Ligand **4** gave very similar absorbance and emission spectra: λ_{max} in UV-absorption was 295 nm (ε=29,600), with a shoulder at 333 nm (ε=5680) and, in emission, λ_{max}=474 nm, ϕ=0.08 (see Figs. 5 or 6). These values compare with a measured quantum yield of 0.04 for

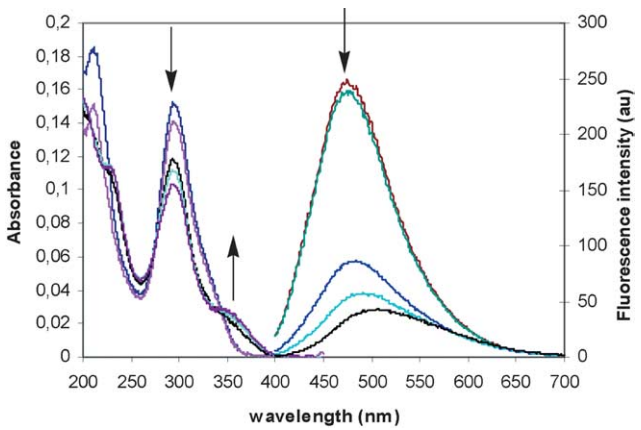


Figure 5. UV–visible absorbance (from 200 to 400 nm) and fluorescence emission (λ_{exc}=340 nm) spectra (from 400 to 700 nm) of **4** (4.51×10^{-6} M in acetonitrile) and upon addition of increasing concentrations of $Zn(Tf)_2$ (1–10 equiv.), in the presence of Bu_4NClO_4 (1.41×10^{-4} M).

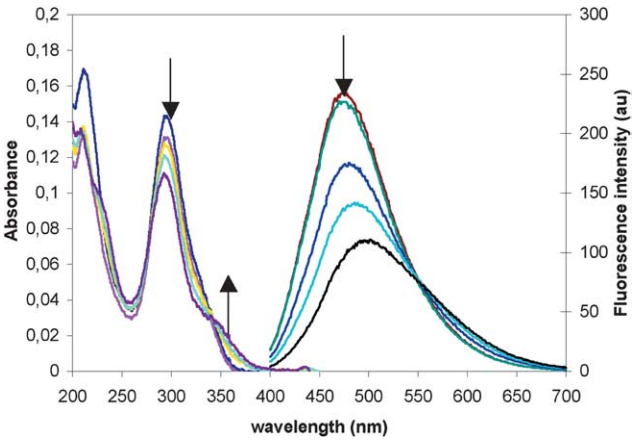


Figure 6. UV–visible absorbance (from 200 to 400 nm) and fluorescence emission (λ_{exc}=340 nm) spectra (from 400 to 700 nm) of **4** (4.76×10^{-6} M in acetonitrile) and upon addition of increasing concentrations of $Cd(Tf)_2$ (1–10 equiv.), in the presence of Bu_4NClO_4 (1.41×10^{-4} M).

tetramethylbenzidine itself under the same conditions, indicating a significant enhancement of the fluorescence upon introduction of the substituents.

Upon titration of ligand **3** with increasing amounts of $Zn(Tf)_2$ or $Cd(Tf)_2$ (Fig. 4) in acetonitrile, no significant changes in the absorption spectra were recorded. Similarly, the emission spectrum was scarcely affected, with any change in the spectral profile or wavelength of maximum emission, and only a very small reduction (ca. 10%) in the intensity, after addition of two or more equivalents of the metal.

Completely different behaviour was observed with ligand **4**. As noted above, the absorbance and emission spectra of **4** itself are very similar to those of **3**. However, titration of ligand **4** against the same salts led to a much more pronounced and red-shifted shoulder in the UV spectra (a 17 nm shift for $Zn(Tf)_2$ and a 9 nm shift for $Cd(Tf)_2$), and a well-defined isosbestic point at 340 nm. The addition of Zn^{2+} or Cd^{2+} (as triflate salts) to acetonitrile solutions of ligand **4** gave rise to a red shift in the emission spectrum (e.g., the emission maximum shifted by 17 nm after the addition of 2 equiv. of Zn^{2+} and by 12 nm in the case of Cd^{2+}; λ_{exc}=340 nm). Use of the corresponding nitrate salts in acetonitrile gave similar results. Additionally, both cations induced a partial quenching of the fluorescence, with Zn^{2+} displaying a larger effect (76% quenching after 2 equiv. of metal) (Fig. 5) than Cd^{2+} (38% quenching under the same conditions) (Fig. 6).

3. Discussion of results

Ligands **1** and **3** give rise to 1:1 complexes as expected because they only have a crown cavity available to complex cations. Ligand **1** complexes Cd^{2+} but complexation with Zn^{2+} is too weak to be observed. Ligand **3**, on the other hand, complexes both Zn^{2+} and Cd^{2+}, but the complex with the latter is stronger. One reason for this behaviour can be found in the different ionic radii of the two cations (0.74 Å for Zn^{2+} and 0.97 Å for Cd^{2+}) that allow Cd^{2+} to fit better into the coronand cavity. Geometry optimisation by molecular mechanics methods (MM+)[13] predicts a mean

cavity size (4.23 Å—2rOcovalent) rather larger than what is found (3.91 Å—2rOcovalent) for similar systems which are already known to exhibit slightly higher complexing constants for Cd^{2+} versus Zn^{2+}.[14] The titration experiments only showed shifts in the NMR resonances, as opposed to a new set of signals, demonstrating that the interchange, of Zn^{2+} or Cd^{2+} with only one crown cavity, is fast on the ^1H NMR time scale. As expected, given the presence of deactivating nitro groups, ligand **1** is scarcely emissive under ambient conditions (Φ value less than 5.10^{-4} at λ_{exc}=340 nm). Fluorescence is therefore not a viable tool for investigating the complexing chemistry of this ligand. By contrast, ligand **3** was found to be highly fluorescent (Φ=0.15). Triflate metallic salts were chosen to perform the titrations on the fluorescent studies due to their well established photochemical inertia. However, the same tests repeated under the same conditions using nitrate salts instead of triflates raised similar results, showing that the counteranion has no influence on the fluorescent response.

The experiments carried out with **3**, which will be used as mono-crown reference compound in the forward discussion, allow us to establish that complexation into the cavity has no influence on the photoactive group, neither in UV absorbance nor in fluorescence emission. Probably, complexation in the cavity only involves the oxygen atoms, affecting neither the amido group nor the electronic density of the biphenyl unit. Although the participation of the amide oxygen atoms, in the case of complexation of cadmium, could be invoked in accounting for the observed selectivity, comparison of IR spectroscopic data for ligands and the corresponding Zn^{2+} and Cd^{2+} complexes, shows that changes in the stretching frequency of the amide carbonyl group are not significant. In addition, this ligand only has one site suitable for binding, so that complexation in the cavity should have little or no influence on the dihedral angle between the aromatic rings on the TMB unit.

The ^1H NMR studies carried out with ligand **2** showed the formation of the corresponding complexes with $Cd(NO_3)_2$ and $Zn(NO_3)_2$. Both complexes have a 1:1 stoichiometry and the number of signals observed in the proton spectrum agrees with a symmetrical structure. The symmetry of the complex can be due to: (a) a fast interchange which makes both cavities equivalent on the NMR time scale or (b) the formation of a clamp complex involving both crown cavities. However, the latter possibility can be disregarded due to the results of UV spectra titrations. Thus, addition to **2** of either Zn^{2+} or Cd^{2+}, provoked absolutely no change neither in the intensity nor in the wavelength of the maximum, pointing out that no modification in the dihedral angle in the TMB unit is produced. As a consequence of this, the former premise is much more acceptable and the different values obtained for the corresponding stability constants agree with the proposal, put forward above, concerning the influence of the ionic radii in leading to a good size-match between the Cd^{2+} cation and the cavity of the crown. Finally, as in **1**, emission of fluorescence in ligand **2** is negligible for the same reason. Thus, this technique cannot give any information about the nature of the complex. Regarding these facts, the behaviour of **2** resembles to that of **1**.

A 1:1 stoichiometry is also observed in the complexes of ligand **4** with both cations even in the presence of large amounts of salts. But the rest of results obtained for ligand **4** are clearly different. The appearance of a new set of different well-resolved signals in the aromatic region belonging to a new species (the corresponding complex) coupled with the decrease of ligand signals strongly implies that, contrary to what happened in the case of **2**, the kinetics of exchange between the ligand and complex are now far slower when compared to the NMR-time scale. It may also be noted that, only three signals are observed for the aromatic protons in both the ligand and the complex species, clearly indicating a symmetrical structure for both. All these observations led us to propose a clamp structure for the complexes formed with ligand **4**. The alternative fast interchange of metal between the two cavities, as for **2**, through the free ligand can be dismissed, owing to the demonstration of slow kinetics of exchange between complex and free ligand described above. On the other hand, comparison in the UV and fluorescent behaviour between the results obtained with ligand **4** and those observed with ligand **3** clearly suggests that the new band that appears in the UV spectrum corresponds to the clamp complex formed that induces changes in the structure strong enough to modify absorption. Formation of a simple 1:1 complex with the cation hosted in just one of the two cavities would be expected, on the contrary, to lead to similar, unresponsive behaviour to that observed with ligand **3**. The significant changes in the fluorescence spectrum of ligand **4** upon complexation of Zn^{2+} or Cd^{2+} are indicative of a profound interaction and effect on the conformation. These results are consistent with the information obtained from NMR spectroscopy and help to confirm the proposition that a clamp complex is produced, the formation of which is accompanied by substantial modification of the value in dihedral angle between both aromatic rings. Such a change will be responsible for the observed perturbations in the absorption and emission bands. The greater extent of quenching observed with zinc compared to cadmium is consistent with the larger equilibrium constant associated with formation of the clamp-type complex for zinc, as revealed by the NMR data and titration discussed above. When competitive experiments were carried out, ligand **4**, selectively responds toward Zn^{2+} in the presence of Cd^{2+}. The higher affinity of this ligand for zinc over cadmium seems to be related to energetic factors: although the formation of the clamp compound certainly results in a loss of entropy, it is, on the other hand, accompanied by a gain in the enthalpy due to a higher number of oxygen–metal interactions. Thus, for both metal complexes, the enthalpic factor must outweigh the entropic one when the clamp complex is formed. Zn^{2+} is a significantly harder metal ion than Cd^{2+} due to its smaller size and, for this reason, a higher increase in the enthalpy is expected when it forms a clamp complex compared to Cd^{2+}, as a result of better 'hard-to-hard' interaction with oxygen.

Even though, ligands **2** and **4** have similar disposed crowns, the obtaining results demonstrate that substituents at the 4,4′ positions in the biphenyl system have strong influence in the type of complex formed. Thus, the dymethylamino groups give rise to clamp complexes (strong modifications in the UV spectra) whereas the nitro groups only allow the cation

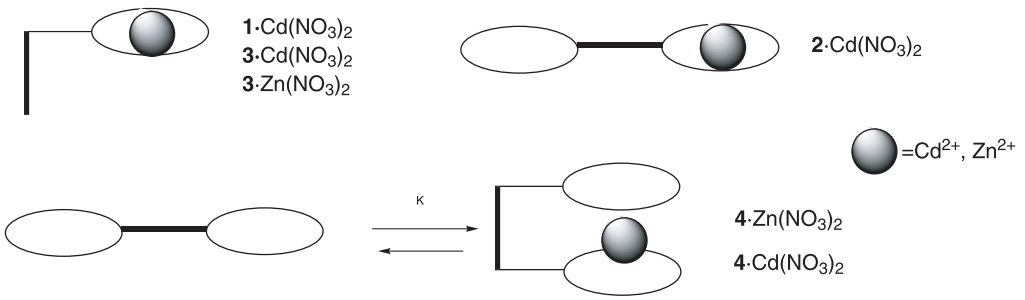


Chart 2. Types of complexes proposed.

interaction with one crown cavity (no modification was observed in the UV spectra). The complexing behaviour of the four ligands in the presence of $Cd(NO_3)_2$ and $Zn(NO_3)_2$ is schematically reflected in Chart 2.

4. Conclusions

Two new ligands containing a 4,4′-substituted biphenyl moiety have been prepared and their complexating properties have been studied. Similar studies have been carried out with the previously reported ligands **1** and **2**. Ligands containing only one crown cavity (**1** and **3**) complex cadmium with log *K* values of the order of 2, whilst the zinc complexes are much weaker. This behaviour is probably related to the cation size that allows cadmium (larger than zinc) to fit better into the cavity. When mixtures of both cations are added to any of these ligands, cadmium is selectively complexed over zinc.

Results obtained with ligand **4**, which offers two crown cavities in its structure for potential metal binding, and dimethylamino groups in the biphenyl moiety, are more interesting. This ligand is able to form clamp complexes which are far more stable than those with the metal ion interacting with only one cavity, probably for enthalpic reasons. The zinc ion, although too small to fit into a single cavity is, in contrast, bound efficiently by both cavities in the clamp complex.

The formation of this type of zinc complex gives rise to red shifted emission bands and distinct quenching of the fluorescence. A similar situation is observed with cadmium but the change is then less pronounced, attributable to its lower constant of complexation. Of particular significance is the observation that, when mixtures of both salts are used, ligand **4** selectively responds to zinc through a clamp complex.

Finally, ligand **2**, which contains nitro rather than amino groups in the biphenyl moiety, shows no propensity to form clamp complexes and, for this reason, it complexes cadmium much more strongly than zinc and binds the former selectively when mixtures of both salts are used in complexing experiments.

5. Experimental

5.1. General methods

All commercially available reagents were used without further purification. Benzene was dried over sodium. Water sensitive reactions were performed under argon. Column chromatographies were carried out on SDS activated neutral aluminium oxide (0.05–0.2 mm; activity degree 1).

Melting points were measured with a Cambridge Instrument and are uncorrected. IR spectra were recorded on a Perkin–Elmer 1750 FT-IR and a Bruker Equinox 55 FT-IR. NMR spectra were recorded with Bruker Avance 300/500 and Varian Unity-300/400 spectrometers. Chemical shifts are reported in parts per million downfield from TMS. Spectra were referenced to residual undeuterated solvent. High resolution mass spectra were taken with a Fisons VG-AUTOSPEC and those using the electrospray ionizing technique were recorded on an HPLC-MS with ion trap Bruker 3000-Esquire Plus. UV spectra were run at 20 °C (thermostated) on a Shimadzu UV-2102 PC or on a Biotech Instruments XL spectrometer. Steady-state fluorescence measurements were carried out using an Instruments SA (Jobin-Yvon) Fluoromax-2, equipped with a red sensitive Hamamatsu R928 photomultiplier tube, and a Varian Cary Eclipse Fluorimeter.

5.1.1. Synthesis of 3. A heterogeneous mixture of **1** (0.312 g, 0.527 mmol), formaldehyde (0.2 ml, 37% solution in H_2O) and 10% Pd–C (0.1 g) in absolute ethanol (30 ml) was stirred under H_2 atmosphere at room temperature for 24 h. The reaction mixture was filtered, the ethanolic filtrate concentrated and the crude reaction product purified by column chromatography through neutral alumina with CH_2Cl_2:AcOEt (7:3) as eluents, leading to **3** as a green oil (0.145 g, 0.246 mmol) (47% yield). IR ν_{max} (KBr) 1720 (–OC=O), 1680 (–NC=O), 1607, 1434 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (1H, d, J=8.5 Hz, Ar-H), 7.11 (1H, d, J=2.8 Hz, Ar-H), 6.97 (1H, d, J=8.5 Hz, Ar-H), 6.78 (1H, dd, J_1=8.5 Hz, J_2=2.6 Hz, Ar-H), 6.69 (1H, dd, J_1=8.5 Hz, J_2=2.8 Hz, Ar-H), 6.64 (1H, d, J=2.6 Hz, Ar-H), 3.67 (3H, s, $-COOCH_3$), 3.61–3.43 (24H, m, $-CH_2-$ linked to O and N); 2.97 (6H, s, $-N(CH_3)_2$); 2.96 (6H, s, $-N(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.50 (s, –CON), 169.95 (s, CO_2Me), 149.61 (s), 149.45 (s), 136.95 (s), 132.95 (s), 131.76 (d), 131.36 (d), 128.35 (s), 125.77 (s), 115.18 (d), 113.66 (d), 112.90 (d), 110.77 (d), 71.11 (t), 70.99 (t), 70.94 (t), 70.79 (t), 70.75 (t), 70.61 (t), 69.34 (t), 52.28 (q), 48.96 (t), 45.65 (t), 40.86 (q), 40.84 (q); HRMS (EI): M^+ found 587.3185. $C_{31}H_{45}N_3O_8$ requires 587.3206; UV (CH_3CN): ε=24,600, λ_{max}=293 nm; ε=5895, λ_{max}=353 nm (shoulder).

5.1.2. Synthesis of 4. A heterogeneous mixture of **2**

(0.300 g, 0.364 mmol), formaldehyde (0.2 ml, 37% solution in H_2O) and 10% Pd–C (0.1 g) in absolute ethanol (30 ml) was stirred under H_2 atmosphere at room temperature for 24 h. The reaction mixture was filtered, the ethanolic solution concentrated and the crude reaction product purified by column chromatography through neutral alumina with AcOEt:MeOH (9:1) as eluents, leading to **4** as a green oil (0.150 g, 0.183 mmol) (50% yield) that eventually solidified. 49–54 °C. IR ν_{max} (KBr): 2901, 2874, 1626 (C═O), 1605 (C═C), 1468, 1352, 1112 (C–O), 948 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.17 (2H, d, J_1=8.5 Hz, Ar-H), 6.64 (2H, dd, J_1=8.5 Hz, J_2=2.6 Hz, Ar-H), 6.59 (2H, d, J_2=2.6 Hz, Ar-H), 3.8–3.4 (48H, m broad band, $-CH_2-$ linked to O and N), 2.93 (12H, s, $-N(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.44 (s), 149.17 (s), 137.11 (s), 130.82 (d), 125.02 (s), 112.74 (d), 111.07 (d), 71.06 (t), 70.87 (t), 70.70 (t), 70.60 (t), 70.43 (t), 68.94 (t), 49.48 (t), 45.35 (t), 40.57 (q); HRMS (EI): Found (M^+) 818.4690; $C_{42}H_{66}N_4O_{12}$ requires: 818.4677. Found (M^++1): 819.4779; $C_{42}H_{67}N_4O_{12}$ requires: 819.4755; UV (CH_3CN): ε=29,600, λ_{max}=295 nm; ε=5680, λ_{max}=333 nm (shoulder).

5.2. General procedure for complex generation

To the corresponding ligand (4×10^{-5} mol) dissolved in the minimum amount of acetonitrile (ca. 1.5 ml), the stated salt (4×10^{-5} mol) in the same solvent (ca. 1.5 ml) was added and the mixture stirred for 4 h at room temperature. Then, the solvent was removed in vacuum.

5.2.1. 1·Cd(NO$_3$)$_2$. Yellow wax. IR ν_{max} (KBr): 3569 (C–H), 1723 (C═$OOCH_3$), 1626 (C═O–$N(CH_2)_2$), 1523 (NO_2), 1351 (NO_2), 1095 (C–O) cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ: 8.75 (1H, s, Ar-H), 8.45 (1H, dd, J_1=8.5 Hz, J_2=2.4 Hz, Ar-H), 8.31 (2H, m, Ar-H) 7.64 (1H, d, J=8 Hz, Ar-H), 3.73–3.50 (27H, m, $-COOCH_3$ and broad band, $-CH_2-$ linked to O and N); ^{13}C NMR (100 MHz, CD_3CN) (: 167.97 (s), 165.14 (s), 147.97 (s), 147.57 (s), 144.26 (s), 136.83 (s), 132.57 (d), 131.00 (d), 125.86 (s), 125.29 (s), 124.71 (d), 123.14 (d), 122.00 (d), 71.60 (t), 70.27 (t), 69.32 (t), 68.89 (t), 68.65 (t), 52.58 (q), 48.94 (t), 45.39 (t).

5.2.2. 2·Cd(NO$_3$)$_2$. Yellow wax. IR ν_{max} (KBr): 2873, 1635 (C═O), 1524 (N═O, asym.), 1456, 1351 (N═O, sym.), 1250, 1176 (C–O), 1096, 1047, 1032, 742, 639 (C–O) cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ: 8.41 (2H, m, Ar-H), 8.31 (2H, dd, J_1=8.4 Hz, J_2=2 Hz, Ar-H), Ar-H), 7.62 (2H, Ar-H), 4.10–3.50 (48H, m, broad band, $-CH_2-$ linked to O and N); ^{13}C NMR (75 MHz, CH_3CN) δ: 169.96 (s), 149.35 (s), 142.66 (bs), 139.19 (bs), 132.63 (bs), 124.74 (d), 124.56 (d), 73.02 (bs), 71.68 (t), 71.56 (t), 71.22 (t), 70.99 (t), 70.89 (t), 70.77 (t), 70.53 (t), 70.21 (t), 67.19 (t), 50.91 (bs), 47.42 (t)

5.2.3. 2·Zn(NO$_3$)$_2$. Yellow wax. IR ν_{max} (KBr): 2874, 1653, 1635 (C═O), 1525 (N═O, asym.), 1351 (N═O, sym.), 1260 (C–O), 1159, 1112, 1097, 1047, 1032, 640 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ: 8.34 (2H, s broad, Ar-H), 8.31 (2H, dd, J_1=8.4 Hz, J_2=2 Hz, Ar-H), 7.73 (2H, d, J=8.4 Hz, Ar-H), 3.80–3.40 (48H, m, broad band, $-CH_2-$ linked to O and N); ^{13}C NMR (75 MHz, CH_3CN) δ: 149.13 (s), 132.07 (bs), 127.21 (d), 124.56 (d), 71.79 (t), 71.67 (t), 71.62 (t), 71.52 (t), 71.47 (t), 71.41 (t), 71.37 (t), 71.22 (t), 70.99 (t), 69.16 (bs), 49.44 (t), 48.30 (t), 47.37 (t).

5.2.4. 3·Cd(NO$_3$)$_2$. Amorphous yellow crystals, mp: 129–131 °C. IR ν_{max} (KBr): 3560 (C–H), 1715 (C═$OOCH_3$), 1607 (C═O–$N(CH_2)_2$), 1433 ($N(CH_3)_2$), 1093 (C–O) cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ: 7.18 (2H, m, Ar-H), 7.04 (1H, d, J_1=8.4 Hz, Ar-H), 6.93 (2H, dd, J_1=8.4 Hz, J_2=2.4 Hz, Ar-H), 6.85 (1H, d, J=2.4 Hz, Ar-H), 3.68–3.51 (27H, m, $-COOCH_3$ and broad band, $-CH_2-$ linked to O and N), 3.03 (6H, s, $-N(CH_3)_2$); ^{13}C NMR (100 MHz, CD_3CN) (: 173.21 (s), 170.71 (s), 150.88 (s), 138.07 (s), 133.61 (s), 132.32 (s), 128.64 (d), 127.01 (d), 126.39 (s), 116.05 (s), 114.56 (d), 114.44 (d), 114.25 (d), 112.00 (d), 74.79 (t), 72.65 (t), 71.53 (t), 70.87 (t), 70.51 (t), 52.91 (q), 50.04 (t), 45.81 (t), 41.24 (q), 41.10 (q).

5.2.5. 3·Zn(NO$_3$)$_2$. Yellow wax. IR ν_{max} (KBr): 3500 (C–H), 1716 (C═$OOCH_3$), 1607 (C═O–$N(CH_2)_2$), 1112 (C–O) cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ: 7.20 (1H, d, J=8.4 Hz, 2Ar-H), 7.11 (1H, s, Ar-H), 6.99 (1H, d, J=8.4 Hz, 2Ar-H), 6.88 (1H, d, J=8.4 Hz, Ar-H), 6.80 (1H, s, Ar-H), 6.66 (1H, d, J=2.8 Hz, Ar-H), 3.65 (3H, s, $-COOCH_3$), 3.53–3.43 (24H, m, broad band, $-CH_2-$ linked to O and N), 3.00 (6H, s, $-N(CH_3)_2$), 2.98 (6H, s, $-N(CH_3)_2$); ^{13}C NMR (100 MHz, CD_3CN) (: 172.43 (s), 170.28 (s), 149.75 (s), 138.26 (s), 132.84 (s), 132.27 (s), 129.32 (d), 126.08 (d), 125.89 (s), 116.24 (s), 115.52 (d), 113.99 (d), 113.26 (d), 111.85 (d), 75.23 (t), 72.70 (t), 71.03 (t), 70.65 (t), 70.38 (t), 53.05 (q), 49.28 (t), 46.54 (t), 41.56 (q), 41.68 (q).

5.2.6. 4·Cd(NO$_3$)$_2$. Yellow wax. IR ν_{max} (KBr): 2903, 2872, 1653 (C═O), 1603 (C═C), 1472, 1352, 1252, 1178, 1112 (C–O), 1031, 945, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.00 (2H, d, J_1=8.4 Hz, Ar-H), 6.82 (2H, dd, J_1=8.6 Hz, J_2=2.4 Hz, Ar-H), 6.67 (2H, d, J_2=2.4 Hz, Ar-H), 4.0–3.4 (48H, m broad band, $-CH_2-$ linked to O and N)), 2.97 (12H, s, $-N(CH_3)_2$); ^{13}C NMR (75 MHz, CH_3CN) δ: 175.88 (s), 151.06 (s), 136.06 (s), 132.00 (d), 125.85 (s), 115.00 (d), 111.49 (d), 73.68 (t), 72.95 (t), 72.82 (t), 72.66 (t), 71.92 (t), 70.90 (t), 70.84 (t), 70.69 (t), 70.58 (t), 70.45 (t), 70.24 (t), 69.91 (t), 52.14 (t), 47.02 (t), 41.12 (q). MS (Electrospray): m/z 465.9 (466.2 calcd for $C_{42}H_{66}N_4O_{12}Cd$); ^{13}C NMR (75 MHz, CH_3CN) δ: 175.88 (s), 151.06 (s), 136.06 (s), 132.00 (d), 125.85 (s), 115.00 (d), 111.49 (d), 73.68 (t), 72.95 (t), 72.82 (t), 72.66 (t), 71.92 (t), 70.90 (t), 70.84 (t), 70.69 (t), 70.58 (t), 70.45 (t), 70.24 (t), 69.91 (t), 52.14 (t), 47.02 (t), 41.12 (q).

5.2.7. 4·Zn(NO$_3$)$_2$. Amorphous yellow crystals, mp: 156–160 °C. IR ν_{max} (KBr): 2903, 2872, 1653 (C═O), 1607 (C═C), 1473, 1352, 1251, 1112 (C–O), 945 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.10 (2H, d, J_1=8.6 Hz, Ar-H), 6.86 (2H, dd, J_1=8.6 Hz, J_2=2.4 Hz, Ar-H), 6.77 (2H, d, J_2=2.4 Hz, Ar-H), 3.95–3.40 (48H, m broad band, $-CH_2-$ linked to O and N), 2.99 (12H, s, $-N(CH_3)_2$); ^{13}C NMR (75 MHz, CH_3CN) δ: 176.39 (s), 151.00 (s), 135.16 (s), 132.22 (d), 125.46 (s), 115.45 (d), 111.47 (d), 71.74 (t), 71.71 (t), 71.61 (t), 71.48 (t), 71.45 (t), 69.59 (t), 68.96 (t), 52.93 (t), 47.47 (t), 41.10 (q). MS (Electrospray): m/z 441.1 (441.2 calcd for $C_{42}H_{66}N_4O_{12}Zn$).

5.3. General procedure for NMR titrations

NMR titrations were carried out by placing, in an NMR tube, the ligand (2×10^{-4} mol) in CD_3CN (0.7 ml) and recording its ^1H NMR spectrum. After addition of the corresponding salt (4.5×10^{-6} mol), or mixture of salts in competition experiments (4.5×10^{-6} mol each), and evaporation of some of the solvent, in order to keep a constant volume, the resulting ^1H NMR spectrum was recorded. The previous process was repeated until the total amount of salt (stated in each case) was added. From the analysis of the spectral assembly, stoichiometries of the complexes were determined using, when possible, the mole ratio method.[11] Complexing constants were determined, regarding LM_2, LM and L_2M possible stoichiometries, by fitting the data to the Benesi–Hildebrand Equation[12] or by running the Clinp 2.1 program.[15] Stoichiometries which best fits experimental data to the model were utilized to calculate values of constants given in Table 1.

5.4. General procedure for UV and fluorimetric titrations

UV and fluorimetric titrations were carried out in 1 cm pathlength quartz fluorescence cells at 20 °C (thermostated). The concentration of **2**, **3** and **4** was ca. 5×10^{-6} M in acetonitrile (spectroscopic grade). An approximately constant ionic strength was maintained by addition of ca. 30 mol of the inert salt $N(Bu)_4ClO_4$ per mol of ligand. The measurements were recorded in the presence of Zn (II) and Cd (II) triflates metal-to-ligand ratio 1:1, 2:1, 12:1. Zn (II) and Cd (II) nitrates were used instead of triflates in the case of **2**. For competition experiments a 1:1 Zn (II) and Cd (II) triflates solution was used. When necessary, ε were calculated after deconvolution of spectra using CONVOL program.[16] Quantum yields were measured using quinine sulphate monohydrate in H_2SO_4 (1 M, aq.) as the standard (Φ=0.546).[17]

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Synthesis and antitrypanosomal activity of 2-aminomethyl-1-(2-oxyphenyl)naphthalenes☆

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Dedicated to Professor Dr. Helmut Quast on the occasion of his 70th birthday

Abstract—A broad variety of enantiopure axially chiral 2-aminomethyl-1-(2-oxyphenyl)naphthalenes were prepared via short and efficient synthetic pathways by using the 'lactone method' for the regio- and stereoselective construction of the biaryl axis. Their in vitro activity against *Trypanosoma cruzi*, the causative agent of Chagas' disease, was evaluated. In particular, the *M*-configured atropisomers, with the 2-oxy function equipped with an *O*-triflate group, were found to exhibit good antitrypanosomal activities (down to IC_{50}=1.6 μg/mL), combined with low levels of cytotoxicity.

1. Introduction

Chagas' disease (American trypanosomiasis), caused by the parasitic protozoa *Trypanosoma cruzi*, is a serious threat to people living in Central and South America, where it is endemic in 21 countries.[1] According to the World Health Organization (WHO), a total of 16–18 million people are infected, causing ca. 50.000 casualties a year, and 100 million, that is, one fourth of the population of these countries, are at risk.[1] Current treatments of Chagas' disease are based on nifurtimox (**1**)[2,3] or benznidazol (**2**)[4–6] (Fig. 1). These two compounds show poor clinical efficiency and cause numerous unfavorable side effects, like nausea, skin rashes, peripheral neuritis, bone-marrow depression, weight loss, and sleeping disorders.[7] All this emphasizes the necessity to develop new drugs for the treatment of Chagas' disease.

We have recently discovered a new class of natural products with, in part, high antitrypanosomal activities, the naphthylisoquinoline alkaloids like, for example,

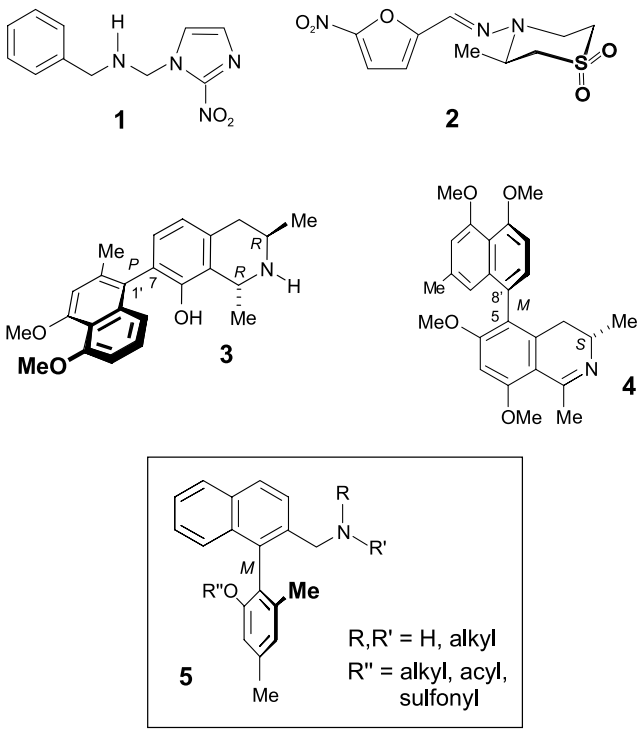

Figure 1. Nifurtimox (**1**) and benznidazol (**2**), drugs currently used for the treatment of Chagas' disease, the likewise antitrypanosomal naphthylisoquinoline alkaloids dioncophylline A (**3**) and ancistrotanzanine B (**4**), and general structure of the simplified target structures **5**.

☆ Part 109 in the series 'Novel Concepts in Directed Biaryl Synthesis', for part 108, see Ref. 20.

Keywords: Axially chiral biaryls; Atropisomerism; Asymmetric synthesis; Antitrypanosomal activity; Chagas' disease.
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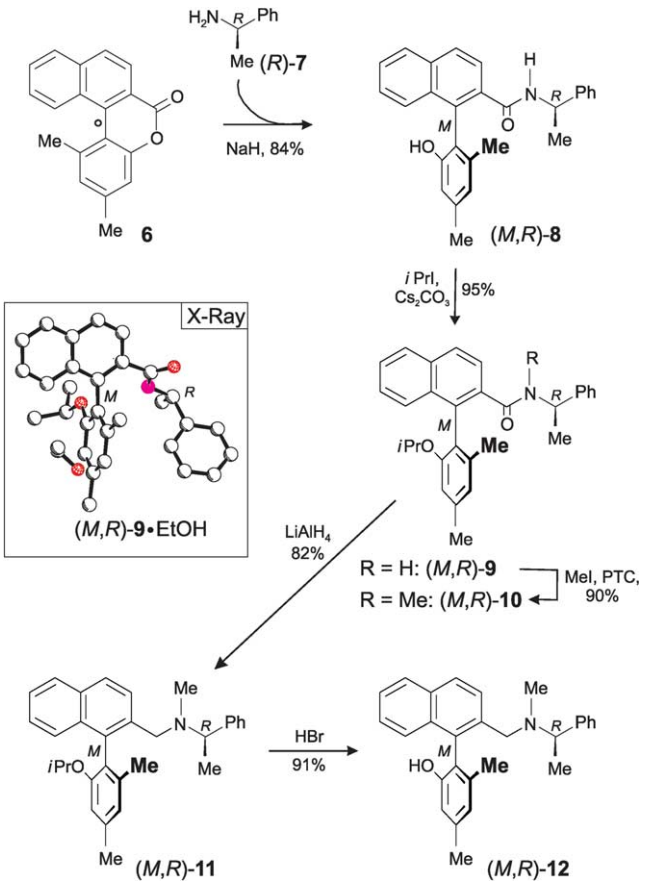
dioncophylline A (**3**) and ancistrotanzanine B (**4**), which show low IC_{50} values against *T. cruzi* of 0.70 and 1.5 μg/mL, respectively. Although total synthetic pathways have been developed, thus making these and other naphthylisoquinolines accessible,[8] there is urgent demand for the search of even more active analogs with simpler and thus easier-to-access structures. This prompted us to synthesize a variety of closely related biaryls in order to establish structure–activity relationships. In this paper, we report on a group of related, still axially chiral, but simplified 2-aminomethyl-1-(2-oxyphenyl)naphthalenes of type **5**, some of which exhibit excellent antitrypanosomal activities, in particular their *O*-triflate derivatives.

2. Results and discussion

2.1. Chemistry

All biaryls were synthesized in a stereochemically homogeneous form, by using the 'lactone method'.[8] The stereochemical key step of this procedure is the atropo-enantioselective ring cleavage of configurationally unstable biaryl lactones like **6** (Scheme 1), here with the sodium salt of (1*R*)-phenylethylamine [(*R*)-**7**], yielding the dia- and enantiomerically pure biaryl amide (*M*,*R*)-**8** in 84% yield.[9] *O*-Isopropylation of the phenolic hydroxy function of (*M*,*R*)-**8** delivered the protected amide (*M*,*R*)-**9**; its anticipated structure and absolute configuration were confirmed by X-ray diffraction analysis. *N*-Methylation of (*M*,*R*)-**9**, reduction of the amide function, and deprotection of the phenolic OH group delivered the biaryl amide (*M*,*R*)-**12**.



Scheme 1. Synthesis of the enantiopure biaryl aminophenol (*M*,*R*)-**12** and molecular structure of (*M*,*R*)-**9**·EtOH (hydrogen atoms omitted for reasons of clarity).

The secondary biaryl amines (*M*,*R*)-**16** and (*M*,*S*)-**16** were prepared by amination of the enantiopure *O*-benzylated bromide (*M*)-**14**[10] with (*R*)- or (*S*)-phenylethylamine [(*R*)-**7** or (*S*)-**7**] and subsequent deprotection of the phenolic oxygen function with BCl_3 (Scheme 2). The derivative (*M*)-**13**, with the biaryl axis as the only element of chirality, was synthesized by treatment of (*M*)-**14** with benzylamine.

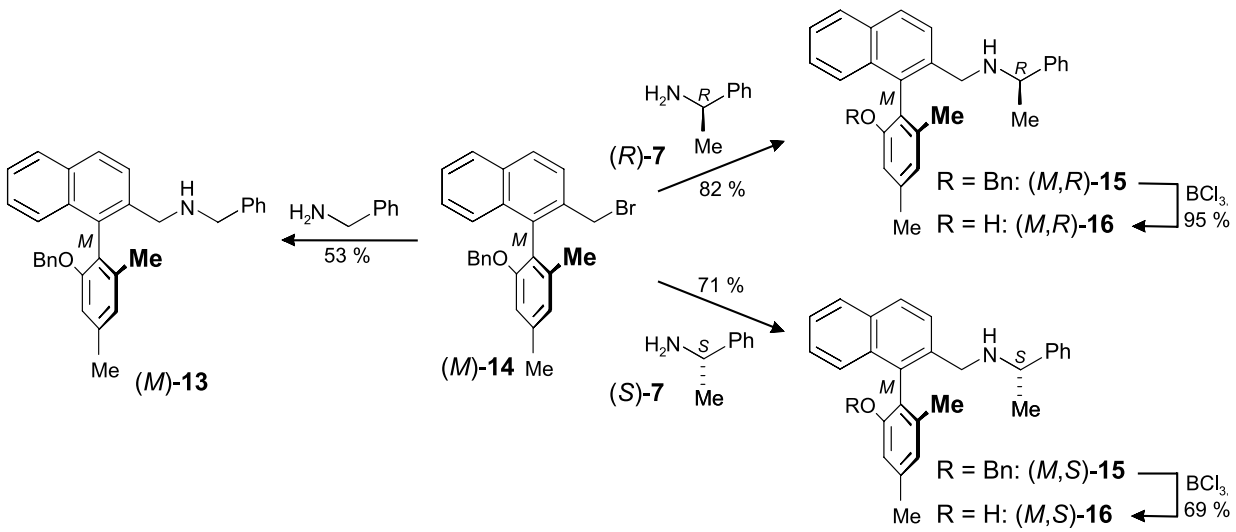
Starting from (*M*,*R*)-**12** and (*M*,*R*)-**16**, a series of differently *O*-functionalized biaryl amines were synthesized, using established standard procedures (Scheme 3). *O*-Sulfonylation of the tertiary biaryl amine (*M*,*R*)-**12** provided (*M*,*R*)-**17**, (*M*,*R*)-**18**, and (*M*,*R*)-**19** (for its molecular structure, see Fig. 2), and acylation with Mosher acid gave (*M*,*R*)-**20**. The MOM ether (*M*,*R*)-**21** and the acetate (*M*,*R*)-**22** were prepared from the secondary amine (*M*,*R*)-**16**.

Since the initial screening against *T. cruzi* had provided the aminotriflate (*M*,*R*)-**19** as the most active compound (see Table 1, Section 2.2), we synthesized several structurally related biarylic triflates. For an investigation of the influence of the two elements of chirality, the biaryl axis and the benzylic stereocenter, we prepared, exemplarily for **19**, all of its four stereoisomers, (*M*,*R*)-**19** (also accessible from (*M*,*R*)-**12**, see Scheme 3), (*M*,*S*)-**19**, (*P*,*S*)-**19**, and (*P*,*R*)-**19**, from the *O*-methylated bromides (*M*)-**23** and (*P*)-**23**[11] by amination and subsequent *O*-deprotection and *O*-triflation (Scheme 4). In order to investigate whether the stereocenter in the *N*-containing side chain is necessary, we analogously

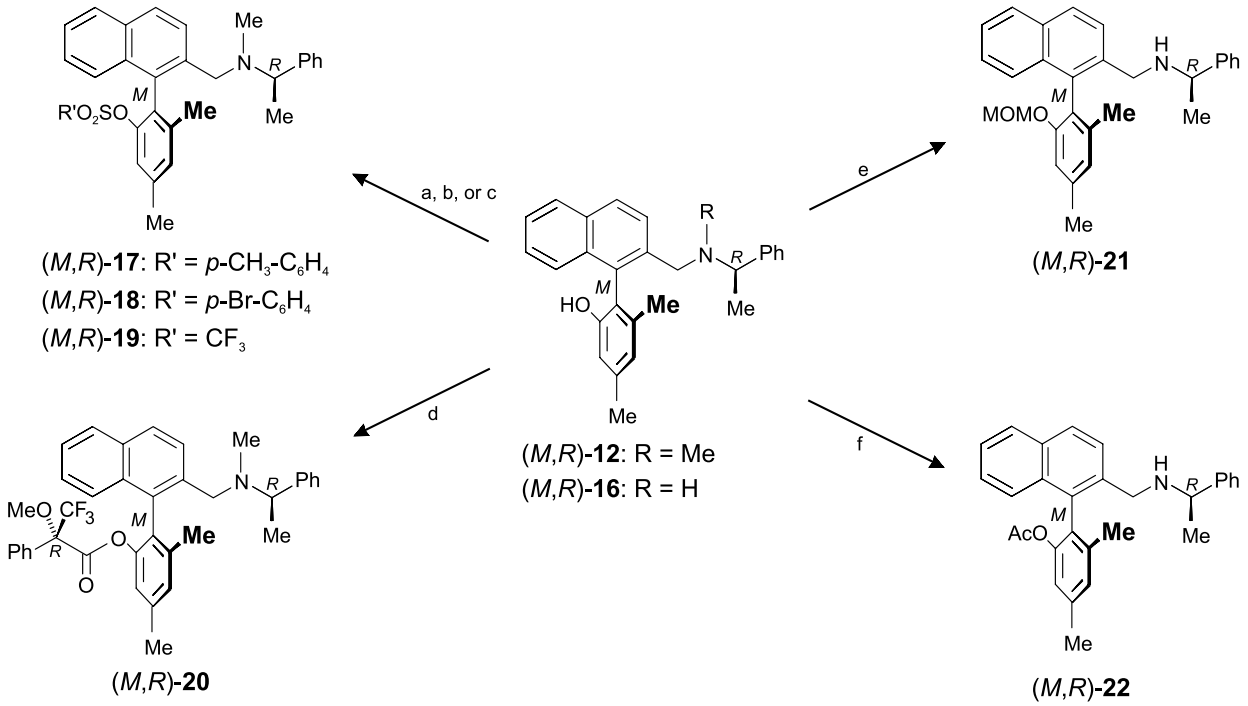
Table 1. Antitrypanosomal activities and cytotoxicities

Compound	IC_{50} [μg/mL] *T. cruzi*	IC_{50}/MIC [μg/mL] cytotoxicity (L6)
Standard	0.4[a]	0.005[b]
(*M*,*R*)-**9**	5.8	92
(*M*)-**13**	5.6	7.2
(*M*,*R*)-**15**	42.9	>90
(*M*,*S*)-**15**	4.6	>90
(*M*,*S*)-**16**	1.8	10
(*M*,*R*)-**17**	14.5	>90
(*M*,*R*)-**18**	37.8	n.e.[c]
(*M*,*R*)-**19**	2.5	>90
(*M*,*S*)-**19**	⇒1.6	⇒>90
(*P*,*R*)-**19**	11.3	>90
(*P*,*S*)-**19**	49.5	n.e.[c]
(*M*,*R*)-**20**	10.9	>90
(*M*,*R*)-**21**	2.1	11.7
(*M*,*R*)-**22**	1.4	2.8
(*M*,*R*)-**24**	2.4	14.1
(*M*,*S*)-**24**	5.3	n.e.[c]
(*P*,*R*)-**24**	1.4	5.5
(*P*,*S*)-**24**	3.4	n.e.[c]
(*M*)-**25**	8.5	n.e.[c]
(*P*)-**25**	2.9	n.e.[c]
(*M*)-**26**	4.6	67
(*P*)-**26**	9.0	>90

[a] Benznidazole (**2**).
[b] Podophyllotoxin.
[c] N.e.=not evaluated.



Scheme 2. Synthesis of the secondary biaryl amines (*M*)-**13**, (*M*,*R*)-**16**, and (*M*,*S*)-**16**.



Scheme 3. Synthesis of (*M*,*R*)-**17**–**22**. (a) *p*-Toluenesulfonic acid, NEt_3; (b) *p*-bromophenylsulfonic acid, NEt_3; (c) Tf_2O, DABCO; (d) (*R*)-Mosher acid, DCC, DMAP; (e) MOMCl, NaH; (f) AcCl, pyridine.

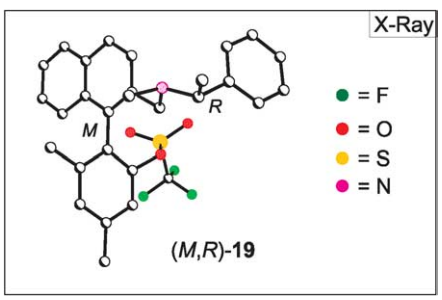
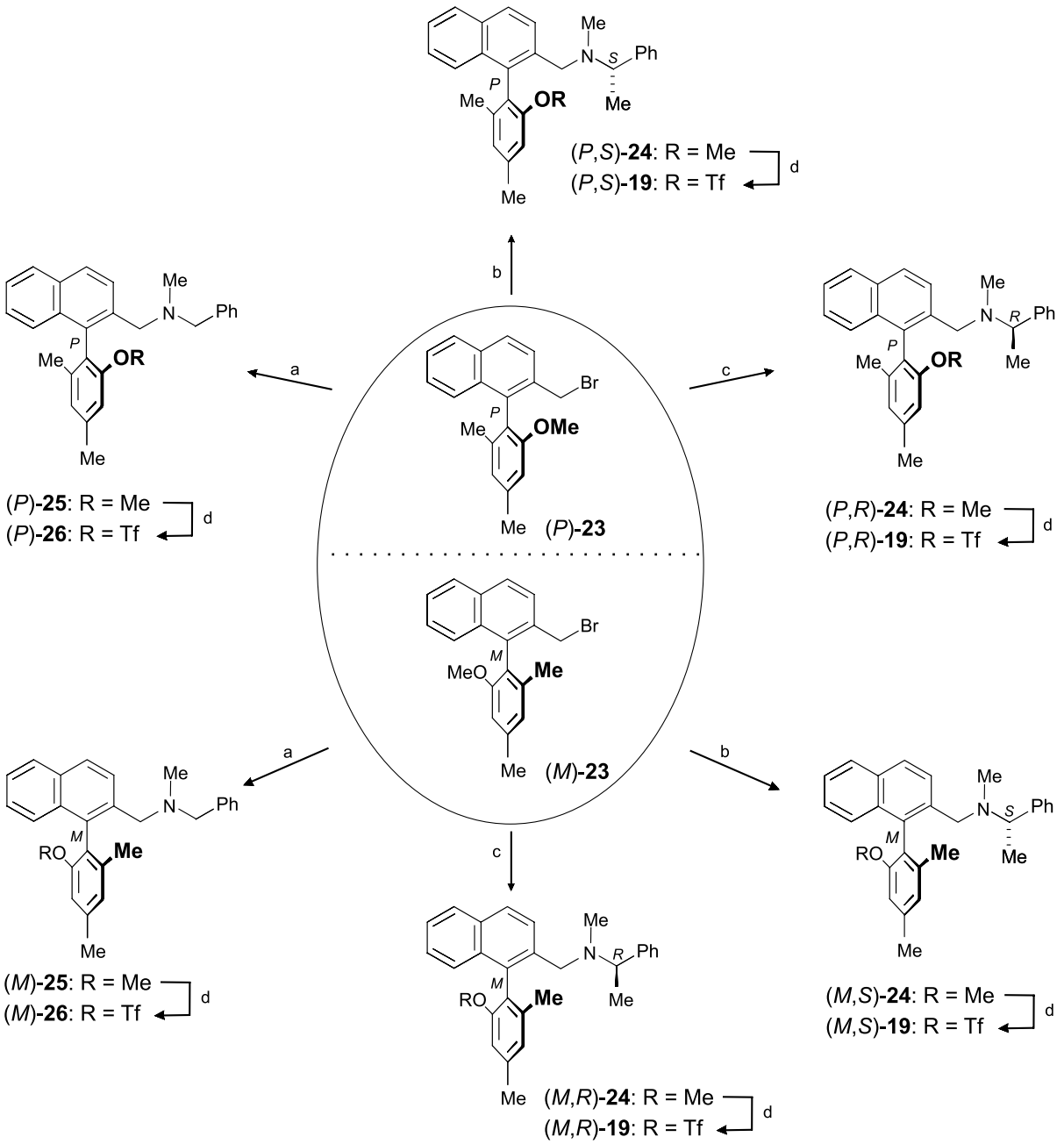


Figure 2. Molecular structure of (*M*,*R*)-**19** in the crystal (hydrogen atoms omitted for reasons of clarity).

synthesized the exclusively axially chiral amines (*M*)-**26** and (*P*)-**26**.

2.2. Antitrypanosomal activity

The 2-aminomethyl-1(2-oxyphenyl)naphthalene derivatives thus synthetically available were evaluated against *T. cruzi* using rat skeletal myoblasts (L-6 cells) in vitro. The results are summarized in Table 1. Good antitrypanosomal activities with IC_{50} values <3 μg/mL were found for the biaryls (*M*,*S*)-**16**, (*M*,*R*)-**19**, (*M*,*S*)-**19**, (*M*,*R*)-**21**, (*M*,*R*)-**22**, (*M*,*R*)-**24**, (*P*,*R*)-**24**, and (*P*)-**25**. Since these compounds possess different substituents on the phenolic oxygen (Me, MOM, Ac, Tf), the substitution pattern at this site does not



Scheme 4. Synthesis of the enantio- and diastereomerically pure triflates **19** and **26**. (a) *N*-methylbenzylamine; (b) (*S*)-*N*-methyl-1-phenylethylamine; (c) (*R*)-*N*-methyl-1-phenylethylamine; (d) 1. HBr; 2. Tf_2O, DABCO.

seem to be essential for attaining high antitrypanosomal activities. The levels of cytotoxicity of these biaryls, by contrast, are significantly influenced by the nature of this substituent: Only the *O*-triflate derivatives (*M*,*R*)-**19** and (*M*,*S*)-**19** were virtually non-toxic (IC_{50}/MIC>90 μg/mL) and exhibited quite promising activity-to-cytotoxicity ratios of more than 35 and 55, respectively. The stereochemical orientation at the biaryl axis plays an important role, too: In the case of the *O*-triflate derivatives **19** and **26**, the *M*-configured biaryls were always more active than their *P*-atropisomers, for example, (*M*,*S*)-**19**: IC_{50}=1.6 μg/mL vs. (*P*,*S*)-**19**: IC_{50}=49.5 μg/mL, while for the *O*-alkyl substituted compounds **24** and **25**, the opposite behavior was observed. No such trend is obvious for the stereogenic center in the *N*-alkyl side chain. Nevertheless, the increased steric demand of the *N*-1-phenylethyl group compared to that of the *N*-benzyl moiety seems to be advantageous, as deduced from their higher activities, for example, (*M*,*S*)-**19** (IC_{50}=1.6 μg/mL) and (*M*,*R*)-**19** (IC_{50}=2.5 μg/mL) vs. (*M*)-**26** (IC_{50}=4.6 μg/mL). Thus, the most promising derivative found within these investigations is the very active and virtually nontoxic, axially chiral and, simultaneously, centrochiral biaryl (*M*,*S*)-**19** (IC_{50}=1.6 μg/mL) possessing an *O*-triflate substituent and the *N*−1-phenylethyl side chain.

3. Conclusion

Axially chiral 2-aminomethyl-1-(2-oxyphenyl)naphthalene

derivatives have proven to be easily prepared in short, directed synthetic sequences, leading to enantio- and diastereomerically pure material. Several representatives of this class of compounds possess significant activities against the protozoan parasite *T. cruzi*, without any notable cytotoxicities. The as yet most promising compound is the *O*-triflated aminophenol (*M*,*S*)-**19**, which provides a good antitrypanosomal activity of IC_{50}=1.6 μg/mL combined with a low level of cytotoxicity (IC_{50}/MIC>90 μg/mL), now making in vivo experiments a rewarding goal. This work is under investigation.

4. Experimental

4.1. General

Melting points were determined with a Kofler melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer polarimeter. IR spectra were scanned from KBr pellets or neat using a Perkin–Elmer spectrophotometer model 1420. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC 250 (250 MHz) or a Bruker Avance 400 (400 MHz) instrument using the deuterated solvent as an internal reference; *J* values are given in Hertz. Elemental analyses were performed in the Institute of Inorganic Chemistry of the University of Würzburg. Mass spectra were measured on a Finnigan MAT 2000 mass spectrometer at 70 eV. All reactions with moisture and/or air sensitive materials were carried out with flame-dried glassware using the Schlenk tube technique under inert argon atmosphere. The enantiopure biaryls (*M*,*R*)-**8**[9] and (*M*)-**14**[10] were synthesized according to literature procedures. The melting points and elemental analyses of some of the amines were measured using their hydrochlorides or hydrobromides, which were prepared by treatment of an ethereal solution of the free amine with gaseous HCl or aqueous HBr.

4.1.1. (*M*,*R*)-1-(2-Isopropoxy-4,6-dimethylphenyl)-*N*-(1-phenylethyl)naphthalene-2-carboxamide [(*M*,*R*)-9]. A suspension of (*M*,*R*)-**8** (1.16 g, 2.94 mmol), isopropyl iodide (1.18 mL, 11.8 mmol), and Cs_2CO_3 (1.92 g, 5.88 mmol) in acetone (120 mL) was stirred for 2 d at room temperature. The inorganic salts were removed by filtration and the residue was chromatographed on silica gel (petroleum ether/diethyl ether=10:1→1:1) yielding (*M*,*R*)-**9** (1.22 g, 2.79 mmol, 95%) as colorless crystals; mp 143 °C. $[\alpha]_D^{20}$=−16.4 (*c* 1.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.92–7.85 (m, 3H), 7.60–7.21 (m, 6H), 6.91–6.84 (m, 4H), 6.60 (d, *J*=6.0 Hz, 1H), 5.12 (sept., *J*=6.1 Hz, 1H), 4.37 (qui., *J*=6.1 Hz, 1H), 2.49 (s, 3H), 1.76 (s, 3H), 1.45 (d, *J*=6.9 Hz, 3H), 1.10 (d, *J*=6.1 Hz, 3H), 0.92 (d, *J*=6.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 168.6, 155.0, 143.1, 139.2, 138.8, 134.1, 134.0, 132.9, 132.1, 128.1, 127.9, 127.6, 126.7, 126.5, 126.3, 126.2, 126.0, 125.6, 124.8, 123.9, 112.1, 70.3, 49.1, 22.4, 21.7, 21.7, 21.5, 19.7. IR (KBr): ν 3447, 2928, 1649, 1519, 1102, 805 cm^{-1}. MS: *m*/*z* 437 (M^+, 26), 274 (100), 259 (9), 120 (22). Anal. calcd for $C_{30}H_{31}NO_2$: C, 82.34; H, 7.14; N, 3.20; found C, 81.82; H, 7.24; N, 2.94.

4.1.2. (*M*,*R*)-1-(2-Isopropoxy-4,6-dimethylphenyl)-*N*-methyl-*N*-(1-phenylethyl)naphthalene-2-carboxamide [(*M*,*R*)-10]. A suspension of the amide (*M*,*R*)-**9** (1.32 g, 2.94 mmol), MeI (19.8 mL, 835 mg, 5.88 mmol), NaOH (2.41 g, 60.3 mmol), NBu_4I (109 mg, 294 μmol), and K_2CO_3 (4.90 g, 1.23 mmol) in benzene (80 mL) was refluxed for 3 d. Aqueous NH_3 (2 N, 30 mL) was added at room temperature. After 30 min of stirring, the solvent was removed in vacuo, the residue was taken up in diethyl ether (30 mL) and filtered through a plug of celite. The crude product was purified by column chromatography (petroleum ether/diethyl ether=5:1) yielding (*M*,*R*)-**10** as white crystals; mp 156–158 °C. $[\alpha]_D^{20}$=+237.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz): 5:1-mixture of interconverting rotational isomers with respect to the N–C=O–bond; major isomer: δ 7.91–7.86 (m, 2H), 7.51–7.29 (m, 4H), 7.19–7.16 (m, 3H), 6.83 (br., 3H), 6.62 (s, 1H), 6.02 (q, *J*=7.0 Hz, 1H), 4.25 (sept., *J*=6.1 Hz, 1H), 2.49 (s, 6H), 2.05 (s, 3H), 1.55 (d, *J*=7.0 Hz, 3H), 0.77 (d, *J*=6.1 Hz, 3H), 0.71 (d, *J*=6.1 Hz, 3H); minor isomer: δ 7.81–7.74 (m, 2H), 6.67 (s, 1H), 5.16 (q, *J*=7.0 Hz, 1H), 4.40 (sept., *J*=6.1 Hz, 1H), 2.41 (s, 6H), 2.07 (s, 3H), 0.98 (d, *J*=6.1 Hz, 3H), 0.86 (d, *J*=6.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 63 MHz): major isomer: δ 171.2, 155.6, 141.6, 140.3, 138.4, 138.2, 133.1, 132.9, 132.4, 128.5, 127.8, 127.4, 127.0, 126.4, 126.2, 126.0, 125.9, 124.3, 123.5, 123.0, 110.6, 69.3, 49.4, 30.9, 21.9, 21.7, 21.5, 20.4, 15.4; minor isomer: δ 171.9, 140.6, 140.2, 134.5, 133.1, 132.6, 127.9, 127.1, 126.7, 126.6, 124.0, 123.5, 111.3, 69.9, 55.6, 27.8, 22.8, 22.0, 21.5, 19.3. IR (KBr): ν 3025, 2973, 2922, 1635, 1618, 1449, 1312, 1117, 1083, 817, 758, 703, 597 cm^{-1}. MS: *m*/*z* 451 (M^+, 73), 408 (8), 392 (4), 274 (100). Anal. calcd for $C_{31}H_{33}NO_2$: C, 82.45; H, 7.36; N, 3.10; found C, 81.69; H, 7.06; N, 2.99.

4.1.3. (*M*,*R*)-1-(2-Isopropoxy-4,6-dimethylphenyl)-2-[*N*-methyl-*N*-(1-phenylethyl)aminomethyl]naphthalene [(*M*,*R*)-11]. To a solution of (*M*,*R*)-**10** (1.36 g, 2.94 mmol) in THF (80 mL), LAH (1.12 g, 29.4 mmol) was added and the reaction was stirred for 3 h. After hydrolysis with 0.1 N HCl (20 mL), the aqueous phase was extracted with diethyl ether (100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by chromatography on silica gel (petroleum ether/diethyl ether=3:1→diethyl ether) afforded (*M*,*R*)-**11** (1.23 g, 2.65 mmol, 90%) as a colorless oil; $[\alpha]_D^{20}$=+23.8 (*c* 1.25, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.86–7.80 (m, 3H), 7.40–7.10 (m, 8H), 6.76 (s, 1H), 6.64 (s, 1H), 4.21 (sept., *J*=6.1 Hz, 1H), 3.49 (q, *J*=6.7 Hz, 3H, NC*H*CH_3), 3.38 (d, *J*=14 Hz, 1H), 3.31 (d, *J*=14 Hz, 1H), 2.42 (s, 3H), 2.02 (s, 3H), 1.77 (s, 3H), 1.24 (d, *J*=6.7 Hz, 3H), 0.85 (d, *J*=6.1 Hz, 3H), 0.76 (d, *J*=6.1 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 155.7, 145.4, 138.6, 137.7, 136.2, 134.3, 132.6, 128.0, 127.7, 127.5, 126.9, 126.7, 126.5, 125.9, 125.3, 125.1, 124.7, 122.7, 111.8, 69.5, 63.2, 56.3, 38.8, 30.9, 21.8, 21.7, 20.0, 18.1. IR (neat): ν 3050, 2970, 1605, 1450, 1308, 1114, 1069, 817, 760, 698 cm^{-1}. MS: *m*/*z* 437 (70, M^+), 422 (73), 332 (34), 303 (95), 259 (100), 43 (3). MS (EI) exact mass calcd for: $C_{31}H_{35}NO$: 437.2719; found 437.2711.

4.1.4. (*M*,*R*)-1-(2-Hydroxy-4,6-dimethylphenyl)-2-[*N*-methyl-*N*-(1-phenylethyl)aminomethyl]naphthalene [(*M*,*R*)-12]. (*M*,*R*)-**11** (524 mg, 1.20 mmol) was dissolved in HBr (20 mL, 48% in HOAc) and heated to reflux

overnight. The solvent was removed under reduced pressure, and the residue was dissolved in MeOH (20 mL) and filtered through a plug of basic alumina (activity 3). Purification by column chromatography (silica gel, petroleum ether/ethyl acetate=1:1) gave (*M*,*R*)-**12** (430 mg, 1.09 mmol, 91%) as a yellow oil; $[\alpha]_D^{20}=-25.8$ (*c* 1.2, $CHCl_3$). ^1H NMR (400 MHz, acetone-d_6): δ 8.12 (s, br., 1H), 7.91–7.88 (m, 2H), 7.78 (d, *J*=12.8 Hz, 1H), 7.44–7.19 (m, 8H), 6.61 (s, 2H), 3.59 (q., *J*=6.8 Hz, 1H), 3.56 (d, *J*=12.1 Hz, 1H), 3.35 (d, *J*=12.1 Hz, 1H), 2.36 (s, 3H), 2.07 (s, 3H), 1.71 (s, 3H), 1.26 (d, *J*=6.8 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 156.0, 144.5, 139.0, 138.7, 136.9, 135.3, 134.1, 133.9, 128.9, 128.8, 128.7, 128.0, 127.7, 126.7, 126.4, 126.1, 123.9, 123.2, 116.0, 64.2, 57.4, 38.8, 21.4, 20.2, 18.3. IR (neat): ν 3057, 2971, 2913, 2846, 1614, 1565, 1494, 1312, 1154, 1048, 838, 809, 762, 702 cm^{-1}. MS: *m*/*z* 395 (M^+, 11), 380 (10), 291 (34), 303 (95), 259 (100). MS (EI) exact mass calcd for: $C_{28}H_{29}NO$ 395.2256; found 395.2257.

4.2. General procedure for the preparation of the arylsulfonic esters (*M*,*R*)-17 and (*M*,*R*)-18

The aminoalcohol (*M*,*R*)-**12** (1.0 equiv.) was treated at 0 °C in dry dichloromethane [5 mL/mmol (*M*,*R*)-**12**] with triethylamine (1.5 equiv.) and *p*-toluenesulfonic acid or *p*-bromophenylsulfonic acid (1.1 equiv.). The reaction mixture was stirred overnight and the solvent was removed in vacuo. The crude product was chromatographed on silica gel (petroleum ether/diethyl ether=5:1) to give (*M*,*R*)-**17** or (*M*,*R*)-**18**.

4.2.1. (*M*,*R*)-2-[*N*-Methyl-*N*-(1-phenylethyl)aminomethyl]-1-(2-(4-methylbenzenesulfonyloxy)-4,6-dimethylphenyl)]naphthalene [(*M*,*R*)-17]. Yield: 53%. $[\alpha]_D^{20}=+17.1$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, acetone-d_6): δ 7.89 (s, 1H), 7.87 (s, 1H), 7.78 (d, *J*=8.2 Hz, 1H), 7.44 (t, *J*=7.1 Hz, 1H), 7.31–7.23 (m, 8H), 7.01 (d, *J*=8.4 Hz, 1H), 6.88–6.83 (m, 4H), 1.19 (d, *J*=6.1 Hz, 3H), 3.41 (q, *J*=6.1 Hz, 1H), 3.35 (s, 2H), 2.49 (s, 3H), 2.27 (s, 3H), 1.94 (s, 3H), 1.81 (s, 3H). ^{13}C NMR (400 MHz, acetone-d_6): δ 148.8, 145.6, 145.4, 140.5, 139.7, 137.4, 134.1, 133.6, 133.0, 132.5, 130.7, 130.1, 129.9, 128.9, 128.7, 128.5, 128.2, 127.8, 127.7, 127.5, 126.8, 126.3, 125.9, 120.7, 64.4, 57.5, 38.9, 21.5, 21.2, 20.2, 18.8. IR (neat): ν 3058, 3029, 2973, 2924, 2844, 2782, 1618, 1598, 1493, 1451, 1370, 1284, 1191, 1178, 1155, 1093, 1027, 946, 855, 815, 777, 701, 669 cm^{-1}. MS: *m*/*z* 549 (M^+, 19), 534 (41), 272 (7), 260 (100). MS (EI) exact mass calcd for $C_{35}H_{35}NO_3S$: 549.2338; found 549.2338.

4.2.2. (*M*,*R*)-1-(2-(4-Bromobenzene sulfonyloxy-4,6-dimethylphenyl)-2-[*N*-methyl-*N*-(1-phenylethyl)aminomethyl]naphthalene [(*M*,*R*)-18]. Yield: 40%. $[\alpha]_D^{20}=+29.6$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.78–7.68 (m, 3H), 7.40 (t, *J*=7.08 Hz, 1H), 7.32–7.26 (m, 5H), 7.24–7.19 (m, 2H), 7.12 (s, 1H), 6.98 (d, *J*=8.5 Hz, 1H), 6.90 (d, *J*=8.7 Hz, 2H), 6.65 (d, *J*=8.6 Hz, 2H), 3.41 (q, *J*=6.7 Hz, 1H), 3.33 (d, *J*=13.9 Hz, 1H), 3.24 (d, *J*=13.9 Hz, 1H), 2.48 (s, 3H), 1.91 (s, 3H), 1.78 (s, 3H), 1.20 (d, *J*=6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 144.7, 139.7, 138.9, 136.7, 134.8, 132.4, 132.1, 131.3, 131.2, 129.4, 128.2, 128.1, 127.9, 127.8, 127.6, 127.5, 127.0, 126.7, 126.1, 125.5, 125.2, 120.7, 63.5, 56.7, 38.4, 21.3, 20.0, 18.2. IR (neat): ν 3060, 2970, 2925, 2846, 2782, 1641, 1620, 1576, 1453, 1374, 1281, 1190, 1092, 1068, 1027, 947, 788 cm^{-1}. MS: *m*/*z*: 615/613 (9/9, M^+), 600/598 (25/23), 510/508 (7/7), 260 (100), 105 (39). MS (EI) exact mass calcd for $C_{34}H_{32}BrNO_3S$: 613.12862; found 613.12755.

4.2.3. (*M*,*R*)-1-[2-(3,3,3-Trifluoro-2-methoxy-2-phenylpropanoyloxy)-4,6-dimethylphenyl]-2-[*N*-methyl-*N*-(1-phenylethyl)aminomethyl]naphthalene [(*M*,*R*)-20]. A solution of (*M*,*R*)-**12** (50.0 mg, 126 μmol), (*R*)-Mosher acid (32.1 mg, 138 μmol), 29.0 mg DCC (138 μmol), and a catalytic amount of DMAP in dry dichloromethane (2 mL) was stirred for 12 h. The precipitate was filtered off, the mixture concentrated in vacuo and the crude product purified by column chromatography (silica gel, diethyl ether) to give (*M*,*R*)-**20** (65.1 mg, 106 μmol, 84%) as a yellow oil; $[\alpha]_D^{20}=+4.0$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.79–7.85 (m, 3H), 7.18–7.43 (m, 9H), 7.12 (s, 1H), 7.03 (t, *J*=7.8 Hz), 6.87 (s, 1H), 6.81 (d, *J*=7.8 Hz), 3.40 (q, *J*=6.6 Hz, 1H), 3.29 (d, *J*=13.9 Hz, 1H), 3.24 (d, *J*=13.9 Hz, 1H), 2.77 (s, 3H), 2.46 (s, 3H), 1.91 (s, 3H), 1.86 (s, 3H), 1.11 (d, *J*=6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.7, 165.0, 148.4, 144.7, 139.5, 138.6, 136.7, 132.7, 132.3, 131.8, 131.5, 129.7, 129.2, 129.0, 128.7, 128.1, 128.0, 127.8, 127.7, 127.5, 127.2, 126.9, 126.6, 126.2, 125.7, 125.4, 124.3, 119.7, 63.4, 56.4, 54.6, 38.6, 29.7, 29.0, 21.3, 19.8, 17.8. IR (neat): ν 3060, 2930, 2854, 1763, 1741, 1712, 1652, 1620, 1508, 1495, 1451, 1360, 1346, 1267, 1228, 1185, 1120, 1080, 1032, 1002, 891, 864, 817, 764, 746, 727, 700 cm^{-1}. MS: *m*/*z* 611 (1, M^+), 189 (17), 83 (100). MS (EI) exact mass calcd for $C_{38}H_{36}F_3NO_3$: 611.2647; found 611.2647.

4.2.4. (*M*)-2-Bromomethyl-1-(2-methoxy-4,6-dimethylphenyl)naphthalene [(*M*)-23]. A suspension of (*M*)-2-hydroxymethyl-1-(2-hydroxy-4,6-dimethylphenyl)naphthalene[12] (320 mg, 1.15 mmol), methyl iodide (220 μL, 490 mg, 3.45 mmol), and Cs_2CO_3 (318 mg, 2.30 mmol) in acetone (20 mL) was stirred for 12 h at room temperature. The solvent was removed in vacuo and the residue purified by column chromatography (silica gel, petroleum ether/ ethyl ether=10:1→1:1) to give a colorless oil, which was dissolved in dichloromethane (10 mL). PPh_3 (520 mg, 1.98 mmol) and $(CBrCl_2)_2$ (646 mg, 1.98 mmol) were added. After 1 h of stirring, the solvent was removed in vacuo and the resulting oil was filtered through a plug of silica gel. Crystallization from dichloromethane/petroleum ether delivered (*M*)-**23** (350 mg, 986 μmol, 99%) as pale yellow needles; mp 148–149 °C. $[\alpha]_D^{20}=+35.1$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.87–7.84 (m, 2H), 7.64 (d, *J*=8.4 Hz, 1H), 7.47–7.43 (m, 1H), 7.34–7.30 (m, 2H), 6.82 (s, 1H), 6.71 (s, 1H), 4.41 (d, *J*=9.8 Hz, 1H), 4.37 (d, *J*=9.8 Hz, 1H), 3.60 (s, 3H), 1.83 (s, 3H), 1.49 (s, 3H). ^{13}C NMR (100 MHz, CDCl3): δ 157.2, 138.9, 138.6, 135.2, 133.3, 133.1, 132.5, 128.1, 127.5, 126.4, 126.2, 126.1, 123.4, 122.5, 109.3, 55.6, 33.1, 21.8, 19.9. IR (KBr): ν 3050, 3025, 2912, 1610, 1575, 1460, 1313, 1238, 830, 761 cm^{-1}. MS: *m*/*z* 356/354 (22/23, M^+), 275 (100), 260 (47), 245 (26), 229 (21). Anal. calcd for $C_{20}H_{19}BrO$: C, 67.61; H, 5.39; found C, 68.05; H, 5.67.

4.2.5. (*P*)-2-Bromomethyl-1-(2-methoxy-4,6-dimethylphenyl)naphthalene [(*P*)-23]. In an analogous way, (*P*)-**23** was prepared from (*P*)-2-hydroxymethyl-1-(2-hydroxy-4,6-dimethylphenyl)naphthalene[12] according to procedure 4.9. $[\alpha]_D^{20}=-35.4$ (*c* 1.0, $CHCl_3$). All other spectroscopic and physical data were identical to those of (*M*)-**23**.

4.3. General procedure for the preparation of different amines from the bromides (*M*)-14, (*M*)-23, and (*P*)-23

To a solution of (*M*)-**14**, (*M*)-**23**, or (*P*)-**23** in dichloromethane (2–4 mL/mmol bromide) the respective amine (2.0 equiv.) was added. The reaction mixture was stirred until complete conversion was detected by TLC (deactivated silica gel, petroleum ether/diethyl ether=5:1). The solution was made alkaline with 2 N NaOH and was exhaustively extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/diethyl ether=10:1) gave the desired amine.

4.3.1. (*M*)-1-(2-Benzyloxy-4,6-dimethylphenyl)-2-(*N*-benzylaminomethyl)naphthalene [(*M*)-13]. Yield: 53%. Characterized as the hydrobromide (*M*)-**13**·HBr. Mp 174 °C (dichloromethane/petroleum ether). $[\alpha]_D^{20}=+39.4$ (*c* 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, actone-d_6): δ 7.92–7.90 (m, 2H), 7.81 (d, *J*=8.6 Hz, 1H), 7.45–7.41 (m_c, 1H), 7.36–7.29 (m, 2H), 7.24–7.16 (m, 5H), 7.11–7.05 (m, 3H), 6.91–6.86 (m, 4H), 4.93 (d, *J*=12.4 Hz, 1H), 4.88 (d, *J*=12.4 Hz, 1H), 3.66–3.64 (m, 4H), 2.40 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 156.2, 139.6, 138.4, 137.1, 135.2, 134.3, 133.0, 132.7, 128.2, 128.1, 128.0, 127.4, 127.3, 126.8, 126.4, 125.9, 125.7, 125.3, 124.6, 124.0, 111.7, 70.1, 53.2, 51.6, 21.7, 19.7. IR (neat): ν 3057, 3031, 2920, 2852, 1607, 1569, 1449, 1313, 1163, 1091, 817, 694 cm^{-1}. MS: *m*/*z* 457 (M^+, 15), 366 (54), 350 (26), 246 (7), 91 (100). Anal. calcd for $C_{33}H_{31}NO$·HBr: C, 73.60; H, 5.99; N, 2.60; found C, 74.31; H, 6.04; N, 2.80.

4.3.2. (*M*,*R*)-1-(2-Benzyloxy-4,6-dimethylphenyl)-2-[*N*-(1-phenylethyl)amino-methyl]naphthalene [(*M*,*R*)-15]. Yield: 82%. $[\alpha]_D^{20}=+59.3$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88–7.83 (m, 2H), 7.57 (d, *J*=8.3 Hz, 1H), 7.44–7.41 (m_c, 1H), 7.39–7.32 (m, 1H), 7.29–7.04 (m, 7H), 6.81–6.72 (m, 4H), 4.78 (s, 2H), 3.60 (q, *J*=6.5 Hz, 1H), 3.51 (d, *J*=12.6 Hz, 1H), 3.47 (d, *J*=12.6 Hz, 1H), 2.43 (s, 3H), 1.79 (s, 3H), 1.13 (d, *J*=6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4, 145.8, 138.32, 138.26, 137.2, 136.3, 134.2, 132.9, 132.8, 128.2, 128.1, 127.9, 127.18, 127.16, 126.6, 126.3, 125.7, 125.1, 124.7, 123.8, 111.4, 69.8, 57.5, 50.4, 24.3, 21.7, 19.7. IR (neat): ν 3057, 2960, 2920, 1610, 1573, 1493, 1452, 1375, 1315, 1165, 1095, 820, 736 cm^{-1}. MS: *m*/*z*: 471 (M^+, 31) [M^+], 456 (13), 380 (27), 350 (35), 259 (88), 91 (100). Anal. calcd for $C_{34}H_{33}NO$: C, 86.59; H, 7.05; N, 2.97; found C, 87.40; H, 7.15; N, 2.85.

4.3.3. (*M*,*S*)-1-(2-Benzyloxy-4,6-dimethylphenyl)-2-[*N*-(1-phenylethyl)aminomethyl]naphthalene [(*M*,*S*)-15]. Yield: 71%. Characterized as the hydrobromide (*M*,*S*)-**15**·HBr. Mp 156 °C (dichloromethane/petroleum ether). $[\alpha]_D^{20}=+31.4$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.92–7.88 (m, 2H), 7.70 (d, *J*=8.3 Hz, 1H), 7.45–7.41 (m_c, 1H), 7.36–7.08 (m, 10H), 6.91–6.86 (m, 4H), 4.87 (s, 2H), 3.65 (q, *J*=6.5 Hz, 1H), 3.49 (d, *J*=12.4 Hz, 1H), 3.42 (d, *J*=12.4 Hz, 1H), 2.41 (s, 3H), 1.78 (s, 3H), 1.16 (d, *J*=6.5 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ=157.2, 147.0, 139.1, 138.5, 137.7, 133.9, 133.5, 129.0, 128.9, 128.5, 128.1, 127.9, 127.4, 127.33, 127.28, 126.6, 126.3, 126.0, 125.4, 124.4, 111.2, 70.4, 59.0, 51.0, 25.2, 21.7, 20.0. IR (neat): ν 3400, 3012, 2999, 2915, 2895, 1592, 1577, 1478, 1300, 1258, 1082, 1019, 811, 692 cm^{-1}. MS: *m*/*z* 471 (M^+, 43), 456 (23), 380 (29), 350 (43), 259 (100), 91 (84). Anal. calcd for $C_{34}H_{33}NO$·HBr: C, 73.91; H, 6.20; N, 2.53; found C, 73.96; H, 6.48; N, 2.69.

4.3.4. (*M*,*R*)-1-(2-Methoxy-4,6-dimethylphenyl)-2-[*N*-methyl-*N*-(1-phenylethyl)aminomethyl]naphthalene [(*M*,*R*)-24]. Yield: 84%. Characterized as the hydrochloride (*M*,*R*)-**24**·HCl. Mp 141 °C (dichloromethane/petroleum ether). $[\alpha]_D^{20}=-21.7$ (*c* 0.95, $CHCl_3$). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.89–7.87 (m, 3H), 7.43–7.39 (m_c, 1H), 7.35–7.23 (m, 5H), 7.20–7.17 (m, 2H), 6.84 (s, 1H), 6.81 (s, 1H), 3.48 (s, 3H), 3.37 (d, *J*=13.6 Hz, 1H), 3.31 (d, *J*=13.6 Hz, 1H), 2.42 (s, 3H), 2.02 (s, 3H), 1.75 (s, 3H), 1.21 (d, *J*=6.6 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 158.2, 146.0, 139.1, 138.8, 137.0, 135.0, 133.8, 133.5, 128.9, 128.2, 127.9, 127.7, 127.4, 126.5, 126.2, 125.8, 124.6, 123.8, 110.0, 64.0, 57.1, 55.5, 39.1, 21.7, 20.0, 18.4. IR (neat): ν 2929, 2853, 1612, 1573, 1451, 1314, 1239, 1165, 1097, 1028, 941, 830, 814, 763, 701 cm^{-1}. MS: *m*/*z* 409 (M^+, 40), 394 (45), 332 (7), 304 (19), 290 (17), 275 (100), 260 (38), 245 (18), 105 (25). Anal. calcd for $C_{29}H_{31}NO$·HCl: C, 78.09; H, 7.23; N, 3.14; found C, 78.64; H, 7.32; N, 3.18.

4.3.5. (*P*,*S*)-1-(2-Methoxy-4,6-dimethylphenyl)-2-[*N*-methyl-*N*-(1-phenylethyl)aminomethyl]naphthalene [(*P*,*S*)-24]. Characterized as the hydrochloride (*P*,*S*)-**24**·HCl. $[\alpha]_D^{20}=+18.9$ (*c* 0.5, $CHCl_3$). All other spectroscopic and physical data were identical to those of (*M*,*R*)-**24**·HCl.

4.3.6. (*M*,*S*)-1-(2-Methoxy-4,6-dimethylphenyl)-2-[*N*-methyl-*N*-(1-phenylethyl)aminomethyl]naphthalene [(*M*,*S*)-24]. Yield: 75%. Characterized as the hydrochloride (*M*,*S*)-**24**·HCl. Mp 129 °C (dichloromethane/petroleum ether). $[\alpha]_D^{20}=-103.8$ (*c* 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J*=8.1 Hz, 1H), 7.82 (d, *J*=8.6 Hz, 1H), 7.81 (d, *J*=8.1 Hz, 1H), 7.38–7.33 (m, 3H), 7.28–7.25 (m, 4H), 7.20–7.15 (m, 1H), 6.77 (s, 1H), 6.66 (s, 1H), 3.52 (s, 3H), 3.44 (q, *J*=6.7 Hz, 1H), 3.39 (d, *J*=13.6 Hz, 1H), 3.20 (d, *J*=13.6 Hz, 1H), 2.43 (s, 3H), 2.04 (s, 3H), 1.60 (s, 3H), 1.26 (d, *J*=6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2, 145.2, 138.5, 138.0, 136.2, 133.9, 132.7, 132.5, 128.1, 127.9, 127.5, 127.0, 126.5, 125.6, 125.5, 124.9, 123.9, 123.0, 109.0, 63.7, 56.4, 55.2, 38.5, 21.7, 19.7, 18.6. IR (KBr): ν 3056, 3027, 2970, 2932, 1610, 1575, 1452, 1315, 1097, 909, 702 cm^{-1}. MS: *m*/*z* 409 (M^+, 41) [M^+], 394 (41), 275 (100). Anal. calcd for $C_{29}H_{31}NO$·HCl: C, 78.09; H, 7.23; N, 3.14; found C, 77.92; H, 7.33; N, 3.23.

4.3.7. (*M*,*S*)-1-(2-Methoxy-4,6-dimethylphenyl)-2-[*N*-methyl-*N*-(1-phenylethyl)aminomethyl]naphthalene [(*M*,*S*)-24]. Characterized as the hydrochloride (*M*,*S*)-**24**·HCl. $[\alpha]_D^{20}=+99.2$ (*c* 1.0 in $CHCl_3$). All other

spectroscopic and physical data were identical to those of (*P*,*R*)-**24**·HCl.

4.3.8. (*M*)-2-(*N*-Benzyl-*N*-methylaminomethyl)-1-(2-methoxy-4,6-dimethylphenyl)naphthalene [(*M*)-25]. Yield: 94%. Characterized as the hydrochloride (*M*)-**25**·HCl. Mp 126 °C (dichloromethane/petroleum ether). $[\alpha]_D^{20}=-29.1$ (*c* 0.7, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J*=8.2 Hz, 1H), 7.87–7.83 (m, 2H), 7.42–7.37 (m_c, 1H), 7.33–7.27 (m, 6H), 7.22 (d, *J*=6.7 Hz, 1H), 6.81 (s, 1H), 6.69 (s, 1H), 3.55 (s, 3H), 3.49–3.30 (m, 4H), 2.46 (s, 3H), 2.08 (s, 3H), 1.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2, 139.9, 138.4, 138.1, 135.6, 134.0, 132.7, 132.5, 128.8, 128.1, 127.9, 127.2, 126.8, 126.7, 125.0, 123.9, 123.0, 109.1, 62.2, 59.3, 55.3, 42.4, 21.8, 19.7. IR (KBr): ν 3056, 3020, 2945, 2919, 1619, 1575, 1494, 1461, 1097, 789, 735 cm^{-1}. MS: *m*/*z* 395 (M^+, 68), 364 (8), 304 (40), 275 (37), 274 (100), 91 (51). Anal. calcd for $C_{28}H_{29}NO$·HCl: C, 77.85; H, 7.00; N, 3.24; found: C, 77.84; H, 7.21; N, 3.18.

4.3.9. (*P*)-2-(*N*-Benzyl-*N*-methylaminomethyl)-1-(2-methoxy-4,6-dimethylphenyl)naphthalene [(*P*)-25]. $[\alpha]_D^{20}=+27.6$ (*c* 1.0, $CHCl_3$). All other spectroscopic and physical data were identical to those of (*M*)-**25**.

4.4. General procedure for the debenzylation of the amines (*M*)-15

To a solution of the amine (*M*)-**15** in dichloromethane [10 mL/mmol (*M*)-**15**], a 1.0 M solution of BCl_3 in *n*-hexane (2.0 equiv.) was added at 0 °C. After 40 min of stirring, the reaction mixture was cautiously hydrolyzed with water [15 mL/mmol (*M*)-**15**], made alkaline with K_2CO_3, and exhaustively extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. The resulting oily product (*M*)-**16** was purified by chromatography (petroleum ether/diethyl ether=1:1).

4.4.1. (*M*,*R*)-1-(2-Hydroxy-4,6-dimethylphenyl)-2-[*N*-(1-phenylethyl)amino-methyl]naphthalene [(*M*,*R*)-16]. Yield: 95%. Mp 132 °C (dichloromethane/petroleum ether). $[\alpha]_D^{20}=+13.2$ (*c* 1.2, $CHCl_3$). All other spectroscopic and physical data were identical to those reported in ref.[10]

4.4.2. (*M*,*S*)-1-(2-Hydroxy-4,6-dimethylphenyl)-2-[*N*-(1-phenylethyl)amino-methyl]naphthalene [(*M*,*S*)-16]. Yield: 69%. Mp 127 °C (dichloromethane/petroleum ether). $[\alpha]_D^{20}=+35.0$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J*=7.9 Hz, 1H), 7.82 (d, *J*=8.2 Hz, 1H), 7.48–7.39 (m_c, 1H), 7.38–7.23 (m_c, 8H), 6.90 (s, 1H), 6.79 (s, 1H), 3.74 (q, *J*=6.7 Hz, 1H), 3.58 (s, 2H), 2.42 (s, 3H), 1.71 (s, 3H), 1.35 (d, *J*=6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.4, 144.2, 138.6, 138.0, 135.0, 133.4, 133.1, 128.8, 128.3, 127.9, 127.4, 126.8, 126.5, 126.3, 126.2, 125.8, 124.7, 123.3, 118.1, 58.7, 51.4, 22.5, 21.3, 20.1. IR (KBr): ν 3500–2200, 3230, 3030, 2930, 2890, 2830, 1595, 1435, 1295, 1085, 1035, 805, 695. MS: *m*/*z*: 381 (M^+, 54) [M^+], 366 (40), 276 (39), 261 (100), 260 (75), 259 (69), 120 (22), 105 (32). Anal. calcd for $C_{27}H_{27}NO$: C, 85.00; H, 7.13; N, 3.67; found C, 85.39; H, 7.37; N, 3.65.

4.4.3. (*M*,*R*)-1-(2-Methoxymethoxy-4,6-dimethylphenyl)-2-[*N*-(1-phenylethyl)aminomethyl]naphthalene [(*M*,*R*)-21]. NaH (9.11 mg, 368 μmol) was added to a solution of (*M*,*R*)-**16** (70.4 mg, 184 μmol) in diethyl ether (10 mL). MOMCl (32 μL, 368 μmol) was added after 30 min and stirring was continued for 16 h. The solvent was removed in vacuo and the residue purified by column chromatography (petroleum ether/diethyl ether=2:1) to give (*M*,*R*)-**21** (62 mg, 146 μmol, 79%) as a yellowish oil; $[\alpha]_D^{20}=+79.5$ (*c* 0.8, $CHCl_3$). ^1H NMR (400 MHz, acetone-d_6): δ 7.91–7.88 (m, 2H), 7.74 (d, *J*=8.6 Hz, 1H), 7.44–7.40 (m_c, 1H), 7.34–7.14 (m, 7H), 6.96 (s, 1H), 6.85 (s, 1H), 4.87 (d, *J*=6.7 Hz, 1H), 4.80 (d, *J*=6.7 Hz, 1H), 3.68 (q, *J*=6.5 Hz, 1H), 3.45 (s, 2H), 2.93 (s, 3H), 2.41 (s, 3H), 1.72 (s, 3H), 1.22 (d, *J*=6.5 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 156.0, 147.1, 139.1, 138.7, 137.7, 134.7, 133.8, 133.5, 129.1, 128.8, 128.3, 127.9, 127.3, 126.6, 126.2, 126.0, 125.7, 125.0, 113.9, 94.9, 58.8, 55.8, 50.6, 25.0, 21.7, 19.9. IR (neat): ν 3054, 2958, 2922, 2855, 1613, 1574, 1491, 1450, 1310, 1209, 1150, 1100, 1049, 991, 820, 757 cm^{-1}. MS: *m*/*z* 425 (M^+, 48), 410 (26), 380 (49), 320 (42), 259 (100), 105 (70). Anal. calcd for $C_{29}H_{31}NO_2$·HCl: C, 75.39; H, 6.98; N, 3.03; found C, 75.17; H, 6.65; N, 2.87.

4.4.4. (*M*,*R*)-1-(2-Acetoxy-4,6-dimethylphenyl)-2-[*N*-methyl-*N*-(1-phenylethyl)aminomethyl]naphthalene [(*M*,*R*)-22]. A solution of (*M*,*R*)-**16** (90.1 mg, 236 μmol), pyridine (38 μL, 472 μmol), and acetyl chloride (34 μL, 472 μmol) in dichloromethane (5 mL) was stirred at room temperature for 16 h, followed by hydrolysis with water (5 mL). After extraction with diethyl ether (20 mL), the combined organic layers were dried over $MgSO_4$, filtered, and evaporated in vacuo. The crude product was purified by column chromatography, affording (*M*,*R*)-**22** (41.3 mg, 97.6 μmol, 41%) as a colorless oil; $[\alpha]_D^{20}=+47.0$ (*c* 0.9, $CHCl_3$). ^1H NMR (400 MHz, acetone-d_6): δ 7.92–7.88 (m, 2H), 7.76 (d, *J*=8.6 Hz, 1H), 7.45–7.41 (m_c, 1H), 7.33–7.16 (m, 7H), 7.07 (s, 1H), 6.94 (s, 1H), 3.71 (q, *J*=6.6 Hz, 1H), 3.47 (d, *J*=12.9 Hz, 1H), 3.42 (d, *J*=12.9 Hz, 1H), 2.42 (s, 3H), 1.79 (s, 3H), 1.51 (s, 3H), 1.24 (d, *J*=6.6 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 169.0, 150.1, 147.0, 139.3, 139.1, 137.9, 133.5, 133.0, 132.8, 129.6, 129.0, 128.9, 128.7, 128.4, 128.1, 127.3, 126.6, 126.5, 126.1, 121.8, 58.7, 50.0, 21.1, 20.2, 19.9. IR (neat): ν 3330, 3057, 2964, 2922, 2857, 1703, 1620. 1453, 1368, 1620, 1453, 1368, 1317, 1246, 1205, 1151, 1107, 1045, 871, 820, 758, 702 cm^{-1}. MS: *m*/*z* 423 (M^+, 20), 408 (30), 318 (100), 259 (37), 105 (37). MS (EI) exact mass calcd for $C_{29}H_{29}NO_2$: 423.2198; found 423.2194.

4.5. General procedure for the preparation of the aminotriflates 19 and 26

A solution of **24** or **25** in 48% aqueous HBr (5 mL/mmol amine) was refluxed for 6 h. The solvent was removed in vacuo, the residue dissolved in MeOH (5 mL/mmol amine) and passed through a plug of celite. The solvent was evaporated under reduced pressure and the residue was dissolved in dry dichloromethane (5 mL/mmol amine) under nitrogen at room temperature. DABCO (2.0 equiv.) and triflic anhydride (2.0 equiv.) were added. The reaction mixture was stirred at room temperature for 16 h, the solvent was removed in vacuo and the product was purified

by column chromatography (petroleum ether/diethyl ether=5:1).

4.5.1. (*M*,*R*)-1-(2-Trifluoromethanesulfonyloxy-4,6-dimethylphenyl)-2-[*N*-methyl-*N*-(1-phenylethyl)aminomethyl]naphthalene [(*M*,*R*)-19]. Yield: 71%. Mp 37 °C (diethyl ether/petroleum ether). $[\alpha]_D^{20}=-14.7$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, acetone-d_6): δ 8.00–7.93 (m, 2H), 7.85 (d, *J*=8.6 Hz, 1H), 7.45 (m_c, 1H), 7.41–7.36 (m, 2H), 7.29–7.28 (m, 4H), 7.26–7.18 (m, 3H), 3.46 (q, *J*=6.8 Hz, 1H), 3.39 (d, *J*=11.8 Hz, 1H), 3.35 (d, *J*=11.8 Hz, 1H), 2.52, (s, 3H), 2.01 (s, 3H), 1.90 (s, 3H), 1.21 (d, *J*=6.8 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 148.7, 145.2, 141.7, 140.9, 137.5, 133.8, 133.0, 131.6, 131.2, 129.4, 129.3, 129.2 (q, J_{C-F}=324 Hz), 128.9, 128.3, 128.1, 127.6, 127.1, 126.4, 125.9, 119.7, 64.9, 57.6, 39.1, 21.1, 20.1, 19.1. IR (neat): ν 3005, 2912, 1592, 1395, 1202, 1120, 805 cm^{-1}. MS: *m*/*z* 527 (M^+, 16), 512 (38), 422 (7), 259 (100). Anal. calcd for $C_{29}H_{28}F_3NO_3S$: C, 66.02; H, 5.35; N, 2.65; S, 6.08; found C, 65.87; H, 5.48; N, 2.60; S, 5.94.

O-Triflation of the phenol (*M*,*R*)-**12** according to the general procedure 4.15 delivered (*M*,*R*)-**19** in 89% yield.

4.5.2. (*P*,*S*)-1-(2-Trifluoromethanesulfonyloxy-4,6-dimethylphenyl)-2-[*N*-methyl-*N*-(1-phenylethyl)aminomethyl]naphthalene [(*P*,*S*)-19]. $[\alpha]_D^{20}=+15.2$ (*c* 1.0, $CHCl_3$). All other spectroscopic and physical data were identical to those of (*M*,*R*)-**19**.

4.5.3. (*M*,*S*)-1-(2-Trifluoromethanesulfonyloxy-4,6-dimethylphenyl)-2-[*N*-methyl-*N*-(1-phenylethyl)aminomethyl]naphthalene [(*M*,*S*)-19]. Yield: 76%. $[\alpha]_D^{20}=+22.6$ (*c* 0.8, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.90–7.82 (m, 3H), 7.41 (m_c, 1H), 7.33–7.27 (m, 4H), 7.25–7.24 (m, 1H), 7.20–7.16 (m, 3H), 7.10 (s, 1H), 3.45 (q, *J*=6.5 Hz, 3H), 3.35 (d, *J*=13.9 Hz, 1H), 3.28 (d, *J*=13.9 Hz, 1H), 2.46 (s, 3H), 2.01 (s, 3H), 1.80 (s, 3H), 1.22 (t, *J*=6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 144.6, 140.6, 139.4, 136.6, 132.8, 132.7, 132.1, 130.4, 130.1, 128.7, 128.6, 128.5, 128.0, 127.6, 127.5, 127.2, 127.0, 126.7, 126.4, 126.3, 126.1, 125.4, 125.3, 125.1, 119.0, 118.0, 63.6, 56.5, 38.5, 21.2, 19.8, 18.0. IR (neat): ν 3061, 3029, 2967, 2017, 1631, 1451, 1213, 938, 822 cm^{-1}. MS: *m*/*z* 527 (M^+, 41), 512 (100), 422 (17), 259 (74), 244 (65). Anal. calcd for $C_{29}H_{28}F_3NO_3S$: C, 66.02; H, 5.35; N, 2.65; S, 6.08; found C, 65.95; H, 5.49; N, 2.60; S, 5.94.

4.5.4. (*P*,*R*)-1-(2-Trifluoromethanesulfonyloxy-4,6-dimethylphenyl)-2-[*N*-methyl-*N*-(1-phenylethyl)aminomethyl]naphthalene [(*P*,*R*)-19]. $[\alpha]_D^{20}=-23.5$ (*c* 0.9, $CHCl_3$). All other spectroscopic and physical data were identical to those of (*M*,*S*)-**19**.

4.5.5. (*M*)-1-(2-Trifluoromethanesulfonyloxy-4,6-dimethylphenyl)-2-(*N*-benzyl-*N*-methylaminomethyl)naphthalene [(*M*)-26]. Yield: 82%. Mp 52 °C (diethyl ether/petroleum ether). $[\alpha]_D^{20}=-53.8$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J*=8.6 Hz, 1H), 7.98 (s, 1H), 7.95 (d, *J*=7.4 Hz, 1H), 7.48 (dt, *J*=7.0, 1.3 Hz, 1H), 7.39 (dt, *J*=7.0, 1.4 Hz, 2H), 7.32–7.30 (m, 7H), 3.46–3.39 (m, 3H), 3.36 (d, *J*=13.7 Hz, 1H), 2.53 (s, 3H), 2.07 (s, 3H), 1.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.6, 141.4, 141.0, 140.3, 137.1, 133.9, 133.0, 131.7, 131.2, 129.6, 129.5, 129.2, 129.0, 127.7, 127.2, 126.5, 126.0, 120.5, 119.9, 119.3 (q, J_{C-F}=319 Hz), 63.2, 60.3, 42.5, 21.2, 20.0. IR (neat): ν 3058, 3033, 2924, 2839, 1621, 1556, 1511, 1496, 1225, 945, 822 cm^{-1}. MS: *m*/*z* 513 (M^+, 29), 422 (24), 259 (100), 91 (49). Anal. calcd for $C_{28}H_{26}F_3NO_3S$: C, 65.48; H, 5.10; N, 2.73; S, 6.24; found C, 65.73; H, 5.40; N, 2.59; S, 5.91.

4.5.6. (*P*)-1-(2-Trifluoromethanesulfonyloxy-4,6-dimethylphenyl)-2-(*N*-benzyl-*N*-methylaminomethyl)naphthalene [(*P*)-26]. $[\alpha]_D^{20}=+48.5$ (*c* 0.8, $CHCl_3$). All other spectroscopic and physical data were identical to those of (*M*)-**26**.

4.6. Biological testing

4.6.1. *Trypanosoma cruzi*. Rat skeletal myoblasts (L-6 cells) were seeded in 96-well microtiter plates at 2000 cells/well/100 μL in RPMI 1640 medium with 10% FBS and 2mM L-glutamine. After 24 h of incubation at 37 °C in 5% CO_2 in air, 50 μL of a trypanosome suspension containing 5000 trypomastigote *T. cruzi* [Tulahuen C2C4 strain, containing the β-galactosidase (Lac Z) gene] from culture were added to the wells. 48 h later the medium was removed from the wells and replaced by 100 μL fresh medium with or without a serial drug dilution. Seven 3-fold dilutions were used covering a range from 90 μg/mL to 0.123 μg/mL. Each drug was tested in duplicate. Active compounds were tested twice for confirmation. After 96 h of incubation the plates were inspected under an inverted microscope to assure growth of the controls and sterility. Then the substrate CPRG/Nonidet (50 μL) was added to all wells. The color reaction that developed during the following 2–4 h was read photometrically at 540 nm. Data were transferred into a graphic program (e.g., EXCEL), sigmoidal inhibition curves determined and IC_{50} values calculated.[13]

4.6.2. Cytotoxicity. Cytotoxicity was assessed in the same assay using noninfected L-6 cells and the same serial drug dilution. The MIC was determined microscopically after 4 d.

4.7. Crystallographic part

4.7.1. Crystal structure of (*M*,*R*)-9·EtOH. Crystals of (*M*,*R*)-**9**·EtOH suited for an X-ray structure analysis were obtained from EtOH. The data were collected on a Bruker AXS P4-diffractometer using a graphite monochromated Mo K_α radiation (λ=0.71073 Å) at room temperature. The structure was solved by direct methods and refined by full-matrix anisotropic least square calculations with the aid of the programs SHELXS[14] and SHELXL,[14] respectively.

4.7.2. Crystal structure of (*M*,*R*)-19. Crystal data for compound (*M*,*R*)-**19** were collected from a shock cooled crystal on a BRUKER SMART-APEX diffractometer with a D8-goniometer (graphite Mo K_α radiation, λ=0.71073 Å) equipped with a low temperature device[15] in ω-scan mode at 100(2) K. The data were integrated with SAINT[16] and an empirical adsorption correction was applied (SADABS).[17] The structure was solved by direct methods (SHELXS97)[18]

and refined by full matrix least square calculations against F^2 (SHELXL97).[19] All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were assigned ideal positions using a riding model with U_{iso} constrained to 1.2 (and 1.5) times U_{eq} value of the parent atom.

Crystallographic data (excluding structure factors) reported in this publication have been deposited with Cambridge Crystallographic Data Center as supplementary publication no. CCDC-226172. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: (internat.) +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk].

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Synthesis and antitumor activities of glucan derivatives

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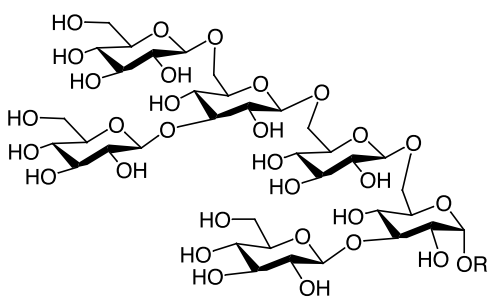
Abstract—A highly efficient and practical method for the preparation of β-D-Glc-(1→6)-[β-D-Glc-(1→3)]-β-D-Glc-(1→6)-β-D-Glc-(1→6)-[β-D-Glc-(1→3)]-D-Glc-OMe was described. A dendritic nonasaccharide was also synthesized. The antitumor activities of hexasaccharide, the dendrimer, their sulfated derivatives, together with the natural glucan–protein and the corresponding polysaccharide isolated from barmy mycelium of *Grifola frondosa*, were preliminarily investigated based on Sarcoma-180 studies in mice tests. Our results suggest that the sulfated branching oligosaccharide and natural glycoprotein have better antitumor activities comparing to the parent sugar residue (oligosaccharide or polysaccharide).

1. Introduction

A family of glucans containing a main chain of β-D-(1→3)-glucopyranosyl units, and a short β-D-glucopyranosyl side chains at O-6 have received considerable attention because of their antitumor activities (immunomodulating action).[1] Schizophyllan,[2] scleroglucan,[3] epiglucan[4] and lentinan[5] are the most well-known members of this group of polysaccharides. It is known that the immunopharmacological activities of soluble (1→3)-β-D-glucans are closely related to the organization of the (1→3)-β-linked backbone into a triple helix, the frequency and the complexity of side-branching, and their molecular weight.[6] However, Tsuzuki and co-workers[7] have also found that the conformation of β-glucans, either single or triple helix, is independent on the hematopoietic response. To investigate the structure–activity relationship, we have synthesized a series of β-D-glucosyl oligosaccharides to mimic the repeating units of natural β-glucan chains.[8] The mice tests revealed that our previously synthesized β-D-glucopyranosyl oligosaccharides showing weaker antitumor activities compared to the reported natural polysaccharides. A literature survey suggested that sulfation of the oligosaccharides could result an increasing anti-tumor and anti-HIV activities.[9] Here, we would like to report the synthesis of sulfated methyl β-D-glucopyranosyl-(1→6)-[β-D-glucopyranosyl-(1→3)]-β-D-gluco pyranosyl-(1→6)-β-D-glucopyranosyl-(1→6)-[β-D-glucopyranosyl-(1→3)]-α-D-glucopyranoside and a sulfated cluster compound containing three β-D-glucopyranosyl-(1→6)-[β-D-glucopyranosyl-(1→3)]-α-D-glucopyranoside components. Interestingly, the hexa-β-D-glucoside, β-D-Glc-(1→6)-[β-D-Glc-(1→3)]-β-D-Glc-(1→6)-β-D-Glc-(1→6)-[β-D-Glc-(1→3)]-D-Glc, has been well characterized as an elicitor of plant phytoalexin accumulation.[10] Our research revealed that the sulfated hexa-β-D-glucoside may also be a potent antitumor agent based on Sarcoma-180 model studies of mice tests.

2. Results and discussion

Hexa-β-D-glucopyranosides (compounds **1** and **2**, Fig. 1) have been previously prepared by Takahashi[11] and Ogawa.[12] We here modified the synthesis based on our findings of highly efficient and practical synthesis of 3,6-branched oligosaccharides.[13] Thus, phenyl 2,4-di-*O*-acetyl-



1 R = Me
2 R = CH_2=CH-CH_2-

Figure 1. Structures of hexa-β-D-glucopyranosides **1** and **2**.

Keywords: Carbohydrates; Glycosylations; Antitumor agents; Glycodendrimers; Oligosaccharides.
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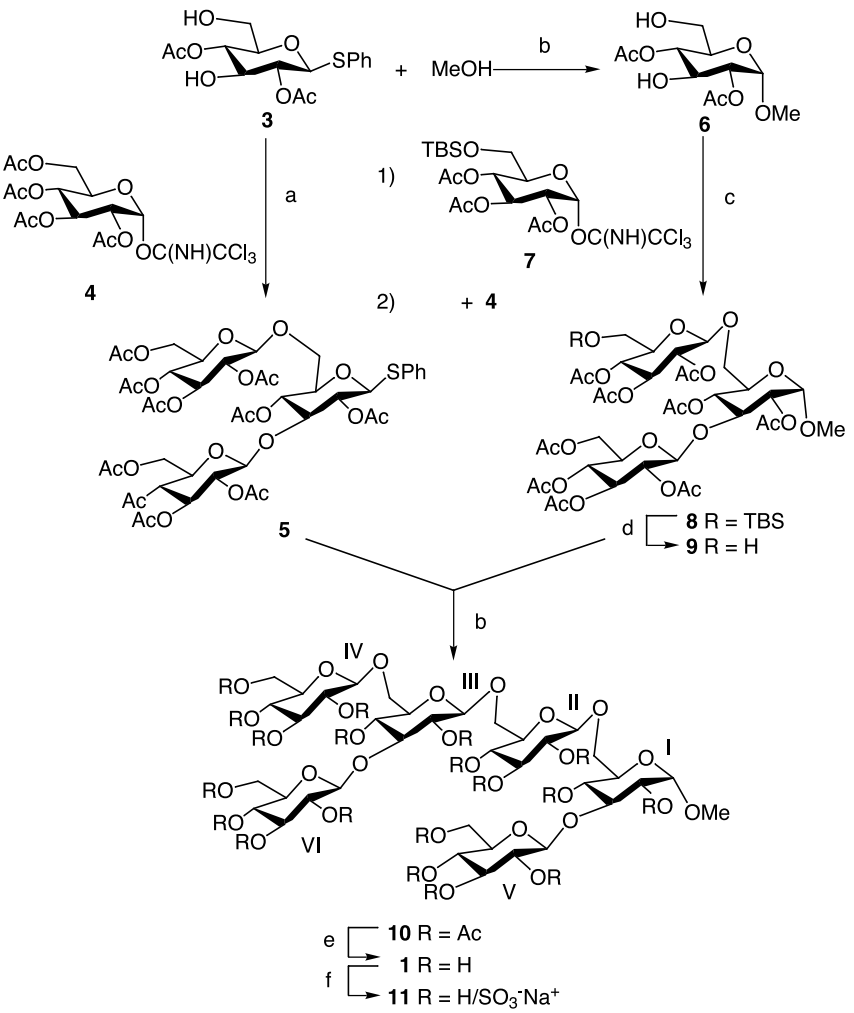
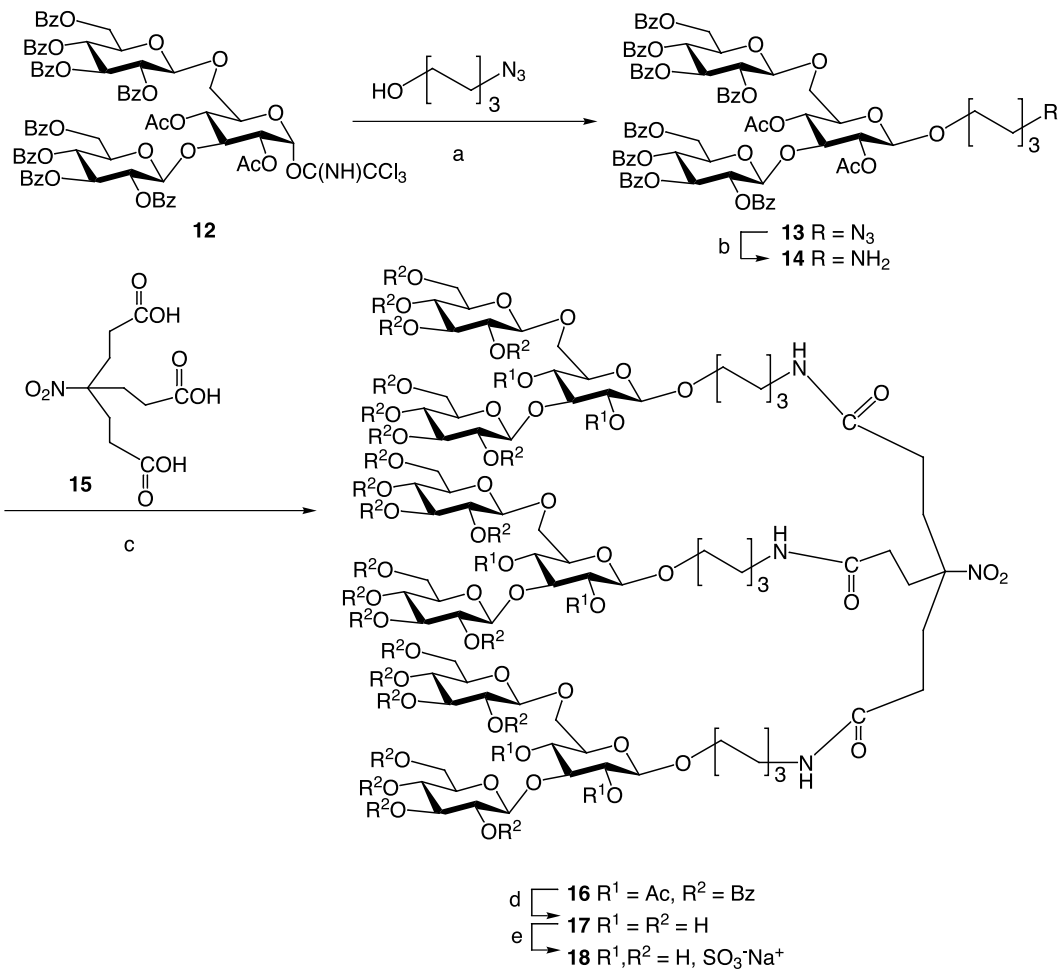


Scheme 1. Synthesis of hexa-β-D-glucopyranoside **1**. Reaction conditions: (a) TMSOTf, CH_2Cl_2, 0 °C, 82%; (b) NIS, TMSOTf, 63% for **6**; 86% for **10** (from **8**); (c) TMSOTf, CH_2Cl_2, −42 °C; then TMSOTf, 0 °C, 76% (two steps); (d) 95% TFA; (e) NaOMe, MeOH, 93%; (f) SO_3·Pyr, DMF.

1-thio-β-D-glucopyranoside (**3**)[13a] was condensed with glycosyl donor 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate (**4**)[14] in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) in CH_2Cl_2 to give trisaccharide **5** in one pot with 82% isolated yield. Three doublets at δ 4.43 ppm (J=7.9 Hz), 4.52 ppm (J=8.0 Hz) and 4.54 ppm (J=10.0 Hz) in ^{1}H NMR spectra of **5** clearly indicated all three β-configuration in this trisaccharide. Thioglycoside **5** was used as a latent glycosyl donor in the final assembly of the target hexasaccahride. Attempt to transfer the partially protected donor **3** into its methyl glycoside derivative using *N*-iodosuccinimide (NIS) and TMSOTf as catalysts resulted in however **6** as a major product (63%). The formation of α isomer can be rationalized by a S_N2 reaction of methanol with 1,6-anhydrosugar intermediate formed from intermolecular ring closure of **3** (Scheme 1).[15]

With 3,6-diol **6** in hand, we next applied a one-pot sequential glycosylation to the synthesis of trisaccharide acceptor **9**. To this end, 6-*O*-silylated trichloroacetimidate **7**[16] (1.1 equiv.) was regioselectively coupled with diol **6** using catalytic amount of TMSOTf (0.07 equiv.) at −42 °C in anhydrous methylene chloride. The second donor **4** (1.5 equiv.) was added into the above mixture at 0 °C 2 h later, affording trisaccharide **8** in 76% yield within another 2 h. It is noteworthy that an extra amount of TMSOTf (0.01 equiv.) was needed to complete the reaction after the addition of **4**. The treatment of **8** with 95% trifluoroacetic acid (TFA) for 1 h gave trisaccharide acceptor **9**. The resulting crude product was co-evaporated with toluene three times and then directly used for the next step without further purification. Coupling of **5** and **9** in CH_2Cl_2 at 0 °C under promotion of NIS and TMSOTf gave hexasaccharide **10** in 86% yield over two steps. ^{1}H−^{1}H COSY, TOCSY, HMBC and HMQC spectra analyses clearly indicated 6 H-1s [δ_H 4.29 (H-1^{III}), 4.49 (H-1^{II}), 4.51 (H-1^{IV}), 4.58 (H-1^{VI}), 4.61 (H-1^{V}), 4.77 (H-1^{I}) ppm] and 6 C-1s [δ_C 96.4 (C-1^{I}), 100.6 (C-1^{III}, C-1^{V}), 100.8 (C-1^{VI}, C-1^{IV}), 100.9 (C-1^{II}) ppm], confirming the correct linkages of **10**. Standard Zemplén deacetylation[17] of **10** furnished hexa-β-D-glucopyranoside **1** as an amorphous solid. Sulfation of **1** with SO_3·Pyr (10 equiv.) at 50 °C in *N*,*N*-dimethylformamide (DMF) for 3 days, followed by conversion to the sodium salt, removal of pyridine and purification on a Sephadex LH-20 column, furnished a mixture of sulfated **11**. The microanalysis for **11** was C 16.22%, H 1.73% and S 19.90%. This highly sulfated mixture was thus obtained in 5 steps at 38% overall yield starting from **3**, and was directly used for the following bioassay.



Scheme 2. Synthesis of nonasaccharide dendritic compound **17**. Reaction conditions: (a) TMSOTf, CH_2Cl_2, 0 °C, 84.7%; (b) $Pd(OH)_2$/C, H_2, EtOAc–EtOH, 93.4%; (c) HOBt, DCC, DMF, rt, 57.2%; (d) NaOMe, MeOH, 91.5%; (e) SO_3·Pyr, DMF.

Glycodendrimers have been prepared to give rise of new kinds of glycoconjugate derivatives and polysaccharide mimics.[18] Some of them have shown highly improved bioactivities compared to the monomers.[19] Encouraged by these results, we prepared a carbohydrate dendrimer based on a combination of 3,6-branched trisaccharides as dendritic components and noncarbohydrate units as trivalent cores (Scheme 2). Thus, the coupling of trisaccharide imidate **12**[8c] and 6-azido-1-hexanol under standard glycosylation conditions gave 6-azidohexyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→6)- [2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→3)]-2,4-di-*O*-acetyl-β-D-glucopyranoside (**13**), a key component for our target synthesis, in high yield. $Pd(OH)_2$ catalyzed hydrogenation of **13** gave amine derivative **14**, which was further condensed with triacid **15**[20] in the presence of HOBt and DCC in DMF to give fully protected trimer **16** in 57.2% yield. The newly formed amide bond was characterized by CON*H* peaks appearing at δ 6.04 ppm (3H, J=5.5 Hz) in ^{1}H NMR spectrum, and further confirmed with a mass of 4804 $(M+Na)^+$ of MALDITOF-MS spectrum. Deacylation of **16** with 1 N NaOMe afforded free nonasaccharide dendritic compound **17**. Further sulfation of **17** with SO_3·Pyr (10 equiv.) in DMF as described in the preparation of **11**, furnished the desired dendrimer **18**. Sodium salt of **18**, after purification on LH-20 column, was directly used for the next bioassay.

Working for the same project to investigate possible antitumor β-glucan, we have also extracted and isolated a glucan protein (**19**) from barmy mycelium of *Grifola frondosa* (Maitake) with a molecular weight of 95 K. After removal of the protein (accounts for 24% of total molecular weight), a pure polysaccharide (**20**) was obtained. The structure of this polysaccharide is determined as a β-D-glucan with the following basic repeating unit (Fig. 2) by a $NaIO_4$ oxidation, methylation, acetolysis and 2D NMR spectra analysis.[21]

The antitumor activities of compounds **1**, **11**, **17**, **18**, **19** and **20** were preliminarily studied according to the method described by Sasaki and co-workers.[5b] ICR mice weighing about 20 g were used for the bioassay. Seven-day-old Sarcoma-180 ascites (0.2 mL, about 5×10^6 cells) were transplanted into the right groins of mice. The test samples, dissolved in distilled water, were injected daily for 10 days starting 24 h after tumor implantation. At the end of the 12th day, the mice were killed, and the tumors were extirpated and weighted. The results (Table 1), compared to lentinan and cyclophosphamide (CTX) in the parallel test, suggest that compound **11** and **19** may be potent antitumor agents. Low tumor inhibition rates of **17** and **18** indicate that structurally highly branched oligosaccharides may not be helpful to their bioactivities. A main chain with β-(1→6)[22]

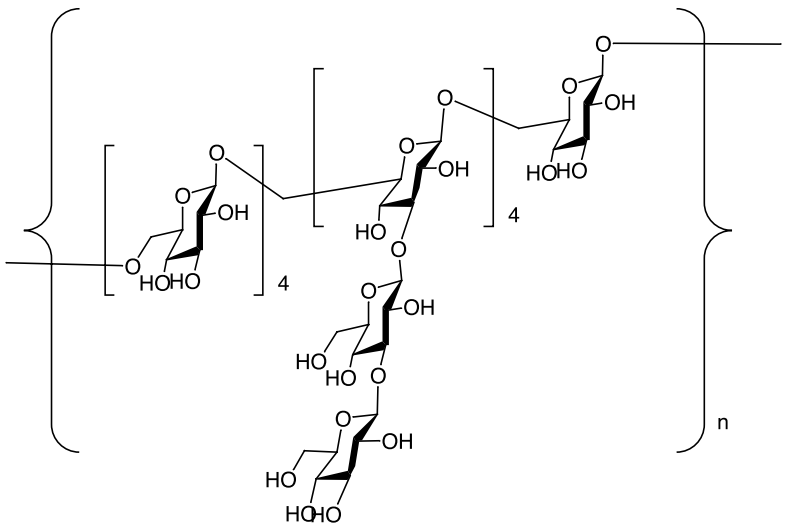


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Figure 2. Proposed structure of β-D-glucan isolated from barmy mycelium of *Grifola frondosa* (Maitake).

Table 1. Preliminary studies on antitumor activities of compounds **1**, **11** and **17**–**20**

Sample	Dose (mg/Kg)	ΔBody weight (g)	Weight of tumor (g)	Inhibition rate (%)
Control	0	10.4±2.3	1.42±0.45	0
CTX	30	8.7±1.5	0.35±0.09***	75
Lentinan	2.0	12.9±2.0	0.95±0.56**	33
1	5.0	9.6±1.8	1.15±0.41**	19
11	2.5	12.6±3.2	0.88±0.46*	38
11	5.0	11.0±1.1	0.74±0.23**	48
11	10.0	10.8±1.9	0.58±0.15***	59
17	2.0	6.9±1.3	1.11±0.60*	22
18	2.0	9.6±1.6	1.09±0.63*	23
19	1.0	12.7±1.8	0.44±0.13***	69
20	1.0	10.8±1.3	0.80±0.22**	43

t-test: *$p<0.05$; **$p<0.01$; ***$p<0.001$.

or β-(1→3)[8b,9b] linkage can be important. More details about the action mechanism for **11** and **19** are currently under investigation by our collaborators.

3. Conclusions

A highly efficient and practical method was described for the preparation of 3,6-branched hexa-β-D-glucopyranosyl derivatives. A dendritic nonasaccharide was also synthesized. The antitumor activities of oligosaccharide **1**, dendrimer **17**, their sulfated derivatives **11** and **18**, together with a natural glucan–protein **19** and the corresponding glucan **20**, isolated from barmy mycelium of *Grifola frondosa* (Maitake), were preliminarily investigated in vivo based on Sarcoma-180 model studies. Our current research suggests that the sulfated branching oligosaccharide and natural glycoprotein have better antitumor activities comparing to the parent sugar residue alone (oligosaccharide or polysaccharide). Beside on this result, some structural closely related glycopeptides and BSA attached glycoconjugates are now under preparation in our lab.

4. Experimental

4.1. General methods

Optical rotations were determined at 25 °C with a Perkin–Elmer Model 241-Mc automatic polarimeter. ^{1}H NMR, ^{13}C NMR and ^{1}H–^{1}H COSY, NOESY and ^{1}H–^{13}C COSY spectra were recorded with Bruker ARX 400 or 500 spectrometers in $CDCl_3$, CD_3OD or D_2O. Chemical shifts are given in ppm downfield from internal Me_4Si. Mass spectra were measured using MALDITOF-MS with CCA as matrix or recorded with a VG PLATFORM mass spectrometer using the ESI technique to introduce the sample. Thin-layer chromatography (TLC) was performed on silica gel HF_{254} with detection by charring with 30% (v/v) H_2SO_4 in MeOH or in some cases by a UV detector. General column chromatography was conducted by elution of a column (8×200 mm, 15×300 mm, 35×400 mm) of silica gel (100–200 mesh) with EtOAc–petroleum ether (60–90 °C) as the eluent, while the sulfated products were purified on Sephadex LH-20 column using water as eluent. Solutions were concentrated at <60 °C under reduced pressure.

4.1.1. Methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-(1→6)-[2,3,4,6-tetra-*O*- acetyl-β-D-glucopyranosyl-(1→3)]-2,4-di-*O*-acetyl-α-D-glucopyranoside (5). To a cooled solution (0 °C) of **3** (1.1 g, 3.1 mmol) and **4** (3.2 g, 6.5 mmol) in anhydrous CH_2Cl_2 (20 mL) was added TMSOTf (50 μL, 0.28 mmol). The mixture was stirred at these conditions for 4 h and quenched with Et_3N. The solvents were evaporated in vacuo and the residue was purified on a silica gel column (petroleum ether–EtOAc, 1:1) to give latent trisaccharide donor **5** as a syrup (2.54 g, 82%); $[\alpha]_D^{25}=-11$ (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.96, 1.97, 2.00, 2.01, 2.02, 2.03, 2.10, 2.17, 2.21, 2.23 (10 s, 10×3H, $COCH_3$), 3.57 (ddd, 1H, *J*=5.5, 11.9, 8.8 Hz), 3.60–3.66 (m, 3H), 3.78 (t, 1H, *J*=8.8 Hz), 4.02 (dd, 1H, *J*=5.5, 11.9 Hz), 4.11–4.17 (m, 2H), 4.43 (d, 1H, *J*=7.9 Hz, H-1^{II}), 4.52 (d, 1H, *J*=8.0 Hz, H-1^{III}), 4.54 (d, 1H, *J*=10.0 Hz, H-1^{I}), 4.57 (dd, 1H, *J*=2.0, 11.9 Hz), 4.62

(dd, 1H, *J*=3.3, 12.5 Hz), 4.72 (dd, 1H, *J*=3.3, 12.6 Hz), 4.96 (dd, 1H, *J*=10.0, 10.8 Hz, H-2^{I}), 5.00–5.05 (m, 2H), 5.11–5.21 (m, 4H), 7.25–7.50 (m, 4H, Ph). Anal. Calcd for $C_{44}H_{56}O_{25}S$: C, 51.97; H, 5.55. Found: C, 52.20; H, 5.48.

4.1.2. Methyl 6-*O*-*tert*-butyldimethylsilyl-2,3,4-tri-*O*-acetyl-β-D-glucopyranosyl- (1→6)-[2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-(1→3)]-2,4-di-*O*-acetyl-α-D-glucopyranoside (8). To a cold solution (−42 °C) of **6** (1.37 g, 4.91 mmol) and **7** (2.78 g, 4.93 mmol) in anhydrous CH_2Cl_2 (20 mL) was added TMSOTf (60 μL, 0.33 mmol). The mixture was stirred at this temperature (usually 2 h) until all starting materials were consumed according to TLC (petroleum ether/EtOAc 1/1), and then warmed to 0 °C. Compound **4** (2.42 g, 4.93 mmol) in dry CH_2Cl_2 (5 mL) was added into the above mixture dropwise at 0 °C, followed by the addition of extra TMSOTf (10 μL, 0.05 mmol), and the mixture was kept at these conditions for 2 h, then quenched with Et_3N. The solvents were evaporated in vacuo and the residue was purified by silica gel column chromatography (petroleum ether–EtOAc, 1:1) to give trisaccharide **8** as a syrup (3.77 g, 76%); $[\alpha]_D^{25}$=+41° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03, 0.04 (2 s, 6H, $(CH_3)_2Si$), 0.88 (s, 9H, *t*-Bu), 1.97, 1.98, 1.99, 2.01, 2.02, 2.03, 2.07, 2.18 (8 s, 27H, 9 CH_3CO), 3.38 (s, 3H, OCH_3), 3.45 (dd, 1H, *J*=6.8, 10.7 Hz, H-6a^{III}), 3.52 (ddd, 1H, *J*=2.9, 4.7, 9.9 Hz, H-5^{I}), 3.64 (ddd, 1H, *J*=2.2, 9.4, 4.6 Hz, H-5^{II}), 3.66–3.75 (m, 2H, H-6^{I}), 3.88 (ddd, 1H, *J*=1.8, 6.8, 9.5 Hz, H-5^{III}), 3.93 (dd, 1H, *J*=1.8, 10.7 Hz, H-6b^{III}), 4.04 (dd, 1H, *J*=2.2, 12.4 Hz, H-6a^{II}), 4.11 (t, 1H, *J*=9.3 Hz, H-3^{I}), 4.34 (dd, 1H, *J*=4.6, 12.4 Hz, H-6b^{II}), 4.49 (d, 1H, *J*=8.0 Hz, H-1^{III}), 4.65 (d, 1H, *J*=8.1 Hz, H-1^{II}), 4.80 (dd, 1H, *J*=9.3, 9.9 Hz, H-4^{I}), 4.81 (d, 1H, *J*=3.7 Hz, H-1^{I}), 4.83 (dd, 1H, *J*=3, 7, 9.3 Hz, H-2^{I}), 4.88 (dd, 1H, *J*=8.1, 9.3 Hz, H-2^{II}), 4.97 (dd, 1H, *J*=8.0, 9.5 Hz, H-2^{III}), 5.01 (t, 1H, *J*=9.5 Hz, H-4^{III}), 5.04 (t, 1H, *J*=9.4 Hz, H-4^{II}), 5.11 (t, 1H, *J*=9.4 Hz, H-3^{II}), 5.20 (t, 1H, *J*=9.5 Hz, H-3^{III}). MALDITOF-MS calcd for $C_{43}H_{66}O_{25}Si$: 1010 $[M]^+$. Found 1033 $[M+Na]^+$. Anal. Calcd for $C_{43}H_{66}O_{25}Si$: C, 51.08; H, 6.58. Found: C, 51.27; H, 6.52.

4.1.3. Methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-(1→6)-[2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-(1→3)]-2,4-di-*O*-acetyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-acetyl-β-D-glucopyranosyl-(1→6)-[2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-(1→3)]-2,4-di-*O*-acetyl-α-D-glucopyranoside (10). Compound **8** (4.55 g, 4.5 mmol) was stirred in 95% TFA (30 mL) at rt for 1 h and then evaporated with toluene (3×50 mL) for 3 times to give the dried crude **9**. To a cooled solution (0 °C) of **5** (4.576 g, 4.5 mmol) and crude **9** (4.03 g, 4.5 mmol) in anhydrous CH_2Cl_2 (50 mL) was added TMSOTf (60 μL, 0.33 mmol). The mixture was stirred at this temperature for 2 h, and then quenched with Et_3N. The solvents were evaporated in vacuo and the residue was purified by silica gel column chromatography (petroleum ether–EtOAc, 1.5:1) to give hexasaccharide **10** as a syrup (6.98 g, 86%); $[\alpha]_D^{25}$=−3 (*c* 4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.93, 1.94, 1.95, 1.96, 1.97, 1.98, 1.99, 2.00, 2.01, 2.03, 2.05, 2.06, 2.13, 2.15 (14 s, 57H, 19 CH_3CO), 3.35 (s, 3H, OCH_3), 3.42–3.48 (m, 2H, H-5^{I}, H-6a^{I}), 3.50 (dd, 1H, *J*=7.0, 10.5 Hz, H-6a^{II}), 3.54–3.60 (m, 2H, H-5^{II}, H-5^{III}), 3.62–3.70 (m, 3H, H-5^{IV}, H-5^{V}, H-5^{VI}), 3.79–3.88 (m, 4H, H-3^{III}, H-6b^{I}, H-6a^{III}, H-6b^{III}), 3.91 (dd, 1H, *J*=2.5, 10.5 Hz, H-6b^{II}), 4.01 (dd, 1H, *J*=2.5, 7.5 Hz, H-6a^{VI}), 4.03 (dd, 1H, *J*=2.0, 7.5 Hz, H-6a^{V}), 4.06–4.12 (m, 2H, H-6b^{V}, H-3^{I}), 4.24 (dd, 1H, *J*=4.5, 12.0 Hz, H-6a^{IV}), 4.29 (d, 1H, *J*=8.0 Hz, H-1^{III}), 4.30 (dd, 1H, *J*=3.0, 7.5 Hz, H-6b^{VI}), 4.34 (dd, 1H, *J*=4.0, 12.0 Hz, H-6b^{IV}), 4.49 (d, 1H, *J*=8.0 Hz, H-1^{II}), 4.51 (d, 1H, *J*=8.0 Hz, H-1^{IV}), 4.58 (d, 1H, *J*=8.0 Hz, H-1^{VI}), 4.61 (d, 1H, *J*=8.0 Hz, H-1^{V}), 4.71 (t, 1H, *J*=9.5 Hz, H-4^{III}), 4.77 (d, 1H, *J*=3.5 Hz, H-1^{I}), 4.78–4.93 (m, 7H), 4.94 (dd, 1H, *J*=8.0, 9.5 Hz, H-2^{IV}), 5.01 (t, 1H, *J*=9.0 Hz, H-4^{VI}), 5.02 (t, 1H, *J*=9.5 Hz, H-4^{V}), 5.03 (t, 1H, *J*=9.5 Hz, H-4^{IV}), 5.08 (t, 1H, *J*=9.5 Hz, H-3^{VI}), 5.10 (t, 1H, *J*=9.0 Hz, H-3^{V}), 5.15 (t, 1H, *J*=9.5 Hz, H-3^{II}), 5.18 (t, 1H, *J*=9.5 Hz, H-3^{IV}). δ_C (125 MHz, $CDCl_3$) 20.3, 20.5, 20.6, 20.7, 20.9, 61.7, 61.8, 67.4, 68.0, 68.1, 68.3, 68.4, 68.5, 68.6, 68.7, 68.9, 71.0, 71.1, 71.2, 71.6, 71.7, 71.9, 72.5, 72.6, 72.7, 73.0, 73.2, 76.0, 78.7, 96.4 (C-1^{I}), 100.6 (C-1^{III}, C-1^{V}), 100.8 (C-1^{VI}, C-1^{IV}), 100.9 (C-1^{II}), 168.9, 169.0, 169.3, 169.4, 169.6, 169.7, 169.8, 170.1, 170.3, 170.4, 170.5, 170.6. MALDITOF-MS calcd for $C_{75}H_{102}O_{50}$: 1802 $[M]^+$. Found 1825 $[M+Na]^+$. Anal. Calcd for $C_{75}H_{102}O_{50}$: C, 49.95; H, 5.70. Found: C, 50.21; H, 5.77.H-4H

4.1.4. Methyl β-D-glucopyranosyl-(1→6)-[β-D-glucopyranosyl-(1→3)]-β-D- glucopyranosyl-(1→6)-β-D-glucopyranosyl-(1→6)-[β-D-glucopyranosyl-(1→3)]-α-D-glucopyranoside (1). A solution of **10** (2.6 g, 1.44 mmol) in ammonia–saturated MeOH (300 mL) was stirred at rt for 7 days. The solvents were evaporated, and the residue was purified on a Sephadex LH-20 column with water as the eluent to give **1** as an amorphous solid after lyophilization (1.3 g, 90%); $[\alpha]_D^{25}$=+7 (*c* 1, H_2O); ^{1}H NMR (500 MHz, D_2O) δ 3.28 (t, 1H, *J*=9.1 Hz,), 3.30 (t, 1H, *J*=9.1 Hz), 3.34 (t, 1H, *J*=9.30 Hz), 3.37 (t, 1H, *J*=9.5 Hz), 3.38–3.48 (m, 13H), 3.51 (t, 2H, *J*=9.5 Hz), 3.58–3.93 (m 18H), 4.15–4.23 (m, 2H, H-3^{I}, H-3^{III}), 4.50 (d, 2H, *J*=7.9 Hz), 4.55 (d, 1H, *J*=8.0 Hz), 4.69 (d, 1H, *J*=8.0 Hz), 4.73 (d, 1H, *J*=8.0 Hz), 4.80 (d, 1H, *J*=3.7 Hz). δ_C (125 MHz, $CDCl_3$) 55.0, 60.5, 67.6, 67.7, 68.4, 68.6, 69.2, 69.3, 69.4, 70.2, 70.5, 72.6, 72.9, 73.2, 74.4, 74.6, 75.3, 75.4, 75.7, 75.8, 82.0, 84.0, 99.0, 102.5, 102.6, 102.7 (3C). ESI-MS calcd for $C_{37}H_{64}O_{31}$: 1004 $[M]^+$, found 1003 $[M-H]^+$.

4.1.5. 6-Azidohexyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-[2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→3)]-2,4-di-*O*-acetyl-β-D-glucopyranoside (13). To a solution of 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-[2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→3)]-2,4-di-*O*-acetyl-β-D-glucopyranosyl trichloroacetimidate (**12**, 586 mg, 0.4 mmol) and 6-azido-1-hexanol (52 mg, 0.4 mmol) in anhydrous dichloromethane (3 mL) was added TMSOTf (10 μL, 0.06 mmol) at 0 °C under N_2 protection. The reaction mixture was stirred for 2 h, at the end of which time TLC indicated the completion of the reaction. The mixture was neutralized with Et_3N, concentrated and purified by flash chromatography using 2:1 petroleum ether–EtOAc as the eluent to give syrupy **13** (476 mg, 84.7%); $[\alpha]_D^{20}$=−101 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 Hz, $CDCl_3$) δ 1.06–1.15 (m, 4H, $-CH_2CH_2-$), 1.19–1.26 (m, 2H, $-CH_2CH_2-$), 1.45–1.52 (m, 2H, $-CH_2CH_2-$), 1.86 (s, 3H, CH_3CO), 1.91 (s, 3H, CH_3CO), 2.95 (m, 1H, OCH_2), 3.21 (t, 2H, CH_2N_3), 3.34–3.38 (m, 1H, OCH_2), 3.49–3.51 (m, 1H, H-5^{I}), 3.62 (dd, 1H, $J_{6a,6b}$=11.2 Hz,

$J_{6a,5}$=5.7 Hz, H-6a^{I}), 3.78–4.92 (m, 2H, H-3^{I}, H-6b^{I}), 4.04–4.16 (m, 3H, H-1^{I}, H-5^{II}, H-5^{III}), 4.41–4.50 (m, 2H, 2H-6), 4.58–4.66 (m, 2H, 2H-6), 4.69–4.81 (m, 2H, H-2^{I} and H-4^{I}), 4.89 (d, 1H, $J_{1,2}$=7.6 Hz, H-1), 4.91 (d, 1H, $J_{1,2}$=7.8 Hz, H-1), 5.36 (dd, 1H, $J_{2,3}$=9.6 Hz, $J_{1,2}$=7.8 Hz, H-2), 5.49 (dd, 1H, $J_{2,3}$=9.6 Hz, $J_{1,2}$=7.6 Hz, H-2), 5.60–5.68 (m, 2H, H-4^{II} and H-4^{III}), 5.83–5.90 (m, 2H, H-3^{II} and H-3^{III}), 7.28–8.04 (m, 40H, *Ph*). MALDITOF-MS calcd for $C_{84}H_{79}N_3O_{26}$: 1545 $[M]^+$, found 1568 $[M+Na]^+$. Anal. Calcd for $C_{84}H_{79}N_3O_{26}$: C, 65.24; H, 5.15. Found: C, 65.05; H, 5.07.

4.1.6. 6-Aminohexyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-[2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→3)]-2,4-di-*O*-acetyl-β-D-glucopyranoside (14). Compound **13** (431 mg, 0.278 mmol) was dissolved in EtOAc–EtOH (1:1, 10 mL) containing $Pd(OH)_2$/C (20%, 40 mg) at rt. H_2 was bubbled into the mixture at the flow rate of 100 mL/min while stirring at atmospheric pressure for 4 h. The mixture was then filtered over Celite and the filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography (CH_2Cl_2/MeOH: 5/1) afforded **14** (394 mg, 93.4%) as a syrup; $[\alpha]_D^{20}=-4$ (*c* 1, $CHCl_3$); ^{1}H NMR (400 Hz, $CDCl_3$) δ 1.03–1.14 (m, 4H, $-CH_2CH_2-$), 1.17–1.24 (m, 2H, $-CH_2CH_2-$), 1.61–1.68 (m, 2H, $-CH_2CH_2-$), 1.88 (s, 3H, CH_3CO), 1.89 (s, 3H, CH_3CO), 2.86–2.95 (m, 3H, CH_2N_3 and one proton of OCH_2), 3.34–3.37 (m, 1H, OCH_2), 3.48–3.51 (m, 1H, H-5^{I}), 3.59 (dd, 1H, $J_{6a,6b}$=11.6 Hz, $J_{6a,5}$=5.7 Hz, H-6a^{I}), 3.85–4.92 (m, 2H, H-3^{I}, H-6b^{I}), 4.06 (d, 1H, $J_{1,2}$=7.8 Hz, H-1^{I}), 4.07–4.16 (m, 2H, H-5^{II} and H-5^{III}), 4.44–4.48 (m, 2H, H-6), 4.58–4.65 (m, 2H, H-6), 4.71–4.76 (m, 2H, H-2^{I} and H-4^{I}), 4.91 (d, 1H, $J_{1,2}$=7.8 Hz, H-1), 4.92 (d, 1H, $J_{1,2}$=7.6 Hz, H-1), 5.36 (dd, 1H, $J_{2,3}$=9.6 Hz, $J_{1,2}$=7.8 Hz, H-2), 5.50 (dd, 1H, $J_{2,3}$=9.6 Hz, $J_{1,2}$=7.6 Hz, H-2), 5.62–5.69 (m, 2H, H-4^{II} and H-4^{III}), 5.85–5.91 (m, 2H, H-3^{II} and H-3^{III}), 7.25–8.02 (m, 40H, *Ph*). MALDITOF-MS calcd for $C_{84}H_{81}NO_{26}$: 1519 $[M]^+$, found 1542 $[M+Na]^+$. Anal. Calcd for $C_{84}H_{81}NO_{26}$: C, 66.35; H, 5.37. Found: C, 66.21; H, 5.45.

4.1.7. Fully protected dendrimer 16. A mixture of compound **14** (375 mg, 0.2 mmol), the triacid **15** (22 mg, 0.08 mmol) and HOBT (33 mg, 0.2 mmol) in dry DMF (3 mL) was stirred at 0 °C for 0.5 h. Then DCC (51 mg, 0.248 mmol) was added and the reaction mixture was stirred at 0 °C for 0.5 h, then at rt for 30 h. The mixture was filtered and the filtrate was concentrated. The resulting crude product was diluted in EtOAc (30 mL) and subsequently washed successively with 5% HCl, saturated aqueous $NaHCO_3$ and water. The organic phase was concentrated and purified by flash chromatography (petroleum ether–EtOAc, 1:5) to complete **16** (219 mg, 57.2%) as a syrup; $[\alpha]_D^{20}=-6$ (*c* 1, $CHCl_3$); ^{1}H NMR (400 Hz, $CDCl_3$) δ 1.04–1.18 (m, 3×4H, $-CH_2CH_2-$), 1.29–1.38 (m, 3×2H, $-CH_2CH_2-$), 1.58–1.72 (m, 3×2H, $-CH_2CH_2-$), 1.86 (s, 3×3H, CH_3CO), 1.89 (s, 3×3H, CH_3CO), 2.04–2.08 (m, 3×2H, CH_2), 2.18–2.23 (m, 3×2H, CH_2), 2.91–2.98 (m, 3×1H, OCH_2), 3.06–3.13 (m, 3×2H, CH_2NHCO), 3.34–3.39 (m, 3×1H, OCH_2), 3.47–3.51 (m, 3×1H, H-5^{I}), 3.63 (dd, 3×1H, $J_{6a,6b}$=11.7 Hz, $J_{6a,5}$=6.8 Hz, H-6a^{I}), 3.81–4.90 (m, 3×2H, H-3^{I} and H-6b^{I}), 4.05–4.15 (m, 3×3H, H-1^{I}, H-5^{II} and H-5^{III}), 4.42–4.49 (m, 3×2H, H-6), 4.59–4.65 (m, 3×2H, H-6), 4.70–4.79 (m, 3×2H, H-2^{I} and H-4^{I}), 4.90 (d, 3×1H, $J_{1,2}$=7.8 Hz, H-1), 4.92 (d, 3×1H, $J_{1,2}$=7.6 Hz, H-1), 5.36 (dd, 3×1H, $J_{2,3}$=9.6 Hz, $J_{1,2}$=7.8 Hz, H-2), 5.50 (dd, 3×1H, $J_{2,3}$=9.6 Hz, $J_{1,2}$=7.6 Hz, H-2), 5.60–5.68 (m, 3×2H, H-4^{II} and H-4^{III}), 5.84–5.91 (m, 3×2H, H-3^{II} and H-3^{III}), 6.04 (br t, 3×1H, *J*=5.5 Hz, N*H*), 7.25–8.02 (m, 3×40H, *Ph*). MALDITOF-MS calcd for $C_{262}H_{252}N_4O_{83}$: 4781 $[M]^+$, found: 4804 $[M+Na]^+$.

4.1.8. Free dendrimer 17. To a solution of **16** (196 mg, 0.04 mmol) in MeOH (5 mL) was added NaOMe until the pH reached 10. The mixture was stirred at rt for 2 days, neutralized with Amberlite IR-120 (H^+). The solvents were filtered, and the filtrate was concentrated to dryness under reduced pressure. The residue was subjected to chromatography on a Sephadex LH-20 column with MeOH as the eluent to give **17** as a white solid (76 mg, 91.5%); $[\alpha]_D^{20}=-5$ (*c* 1, CH_3OH); ^{1}H NMR (400 Hz, CD_3OD) δ 1.19–1.36 (m, 3×4H, $-CH_2CH_2-$), 1.48–1.56 (m, 3×2H, $-CH_2CH_2-$), 1.58–1.66 (m, 3×2H, $-CH_2CH_2-$), 2.06–2.18 (m, 3×4H, $-CH_2CH_2-$), 3.07 (t, 3×2H, CH_2NHCO), 3.12 (dd, 3×1H, $J_{2,3}$=9.6 Hz, $J_{3,4}$=10.2 Hz, H-3^{I}), 3.14–3.60 (m, 3×16H), 3.71 (dd, 3×1H, $J_{6a,6b}$=11.5 Hz, $J_{6a,5}$=5.5 Hz, H-6), 3.76–3.83 (m, 3×2H), 4.04–4.09 (m, 3×1H), 4.23 (d, 3×1H, $J_{1,2}$=7.8 Hz, H-1), 4.31 (d, 3×1H, $J_{1,2}$=7.6 Hz, H-1), 4.47 (d, 3×1H, $J_{1,2}$=7.6 Hz, H-1); δ_C (100 Hz, CD_3OD) 26.7, 30.2, 30.6, 31.2, 40.5 (CH_2NHCO), 62.6, 62.8, 69.8, 70.0, 71.0, 71.60, 74.4, 75.1, 75.5, 76.8, 77.8, 78.0, 78.2, 94.4 (CNO_2), 103.9 (*C*-1), 105.0 (*C*-1), 105.2 (*C*-1), 174.0 (NH*C*O). MALDITOF-MS Calcd for $C_{82}H_{144}N_4O_{53}$: 2032 $[M]^+$, found: 2055 $[M+Na]^+$; 2071 $[M+K]^+$.

4.1.9. General procedure for sulfation of compounds 1 and 17. A mixture of oligosaccharide (**1** or **17**) and SO_3·Pyr (10 equiv.) in DMF was stirred at 50 °C for 3 days. Before 3 N NaOH was added, pyridine was removed in vacuo, and the residue was purified on a Sephadex LH-20 column using water as eluent furnished a mixture of sulfated compound **11** or **18** which were used for the next bioassay after freeze-drying. Microanalysis data for compound **11**: C 16.22%, H 1.73%, S 19.90%. Microanalysis for compound **18**: C 21.01%, H 2.54%, S 17.79%.

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First functionalization by metallation of the pyridine moiety of 4-methoxypyridopyrimidines. Diazines: Part 38

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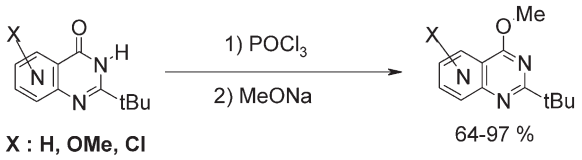
Abstract—Starting from pyridopyrimidin-4(3*H*)-ones, a general synthetic route leading to 4-methoxypyridopyrimidines is described. The first lithiation and functionalization of the pyridine moiety has been studied. According to various structural parameters, the regioselectivity of the metallation is discussed. The functionalization of the 4-methoxypyridopyrimidines via the metallation reaction, provides an efficient process to access new substituted pyridopyrimidines.

Among the three classes of pyridodiazines, the pyridopyrimidines are by far the most explored because of their biological activities as isosteres of quinazolines and pteridines. Various pyridopyrimidines have been claimed to have medicinal applications such as antibacterials,[1] antiallergics,[2] CNS stimulants[3] and inhibitors of enzyme adenosine kinase[4] (AK) or dihydrofolate reductase[5] (DHFR). Non-medicinal uses claimed for pyridopyrimidines include uses as growth promoters, herbicides, agricultural fungicides and UV absorbants.[6]

For the reasons given above, the synthesis of pyridopyrimidine derivatives provides an interesting challenge. Construction of pyridopyrimidines involves fusion of the pyridine ring onto the preformed pyrimidine ring or on the contrary by cyclization of appropriately substituted pyrimidines or pyridines whose syntheses are not always easy. The relative position of the nitrogen atom in the pyridine ring leads to four 4-methoxypyridopyrimidine systems (Scheme 1).



Scheme 1.

The functionalization via metallation of the pyridine moiety of these compounds could provide a consistent strategy for the synthesis of new pyridopyrimidines. In previous papers, we have presented the lithiation of the benzene moiety of benzodiazines: cinnolines,[7] quinazolines,[8,9] quinoxalines and phthalazines[9] and more recently the lithiation of the pyridine ring of various pyridopyrimidin-4(3*H*)-ones.[10] As a continuation of our studies on metallation of *ortho*-condensed diazines, we report here the synthesis, the direct lithiation and the functionalization of 4-methoxypyridopyrimidines.

A general synthetic route could be one starting from pyridopyrimidin-4(3*H*)-ones previously described.[10] The 4-oxo compounds have been converted to their 4-chloro derivatives using phosphorus oxychloride which in turn reacted with sodium methoxide to give the expected 4-methoxypyridopyrimidines (Scheme 1).

According to this general synthetic method, seven new 4-methoxypyridopyrimidines **1**–**7** have been obtained in moderate to good yield (Scheme 2). We have now examined the direct lithiation and functionalization of these methoxypyridopyrimidines.

During the lithiation of the benzene moiety of various benzodiazines,[7–9] an exceptional regioselective metallation at the C_8 position, *peri* to the ring nitrogen atom N_1 was highlighted.

In the case of 4-methoxypyridopyrimidines, several parameters may be taken into account to direct the regioselectivity of the metallation (Scheme 3): the *peri* nitrogen atom N_1 of the pyrimidine moiety, the nitrogen atom N_x of the

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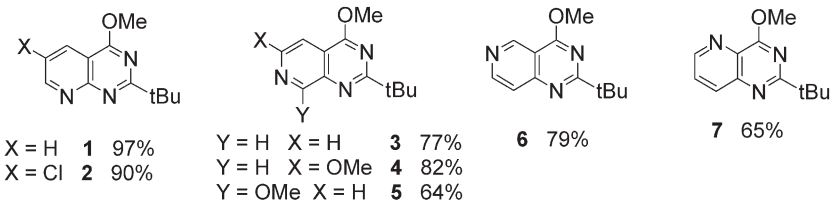
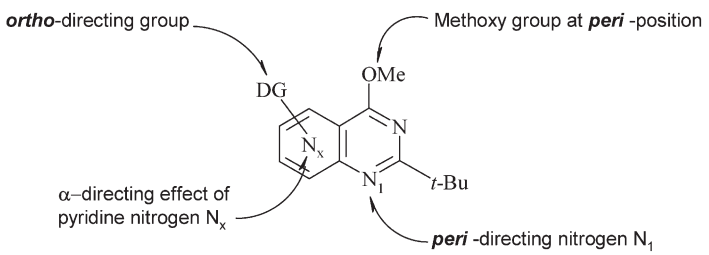


Scheme 2.



Scheme 3.

pyridine moiety and the presence of a substituent such as a chlorine atom or a methoxy group inducing *ortho*-metallation with compounds **2** and **4**. For all these compounds except for **7**, the influence of the methoxy group at the *peri* position may also be important, since during the metallation of 1-methoxynaphthalene, it has been observed that a methoxy group at such a position can induce a highly selective metallation at the peri C_8 position.[11]

It must be noted that the *tert*-butyl group at the C_2 position has been chosen to avoid lithiation or nucleophilic addition of the metallating agent at this position.[11–13] Moreover, the quaternary carbon of the *tert*-butyl group eliminates the possibility of a deprotonation on the C_α carbon of the lateral chain.[14–16]

1. Results

Reaction of **1** and **7** in anhydrous THF with *n*-butyllithium as metallating agent at −78 °C for 1 h followed by reaction with acetaldehyde or diphenyl disulfide as electrophile gave only addition products resulting from a nucleophilic attack of *n*-butyllithium at the α position of the pyridine nitrogen. To avoid this competitive nucleophilic addition, the metallation was achieved by using lithium alkylamides which are known to be less nucleophilic than alkyllithiums.[17]

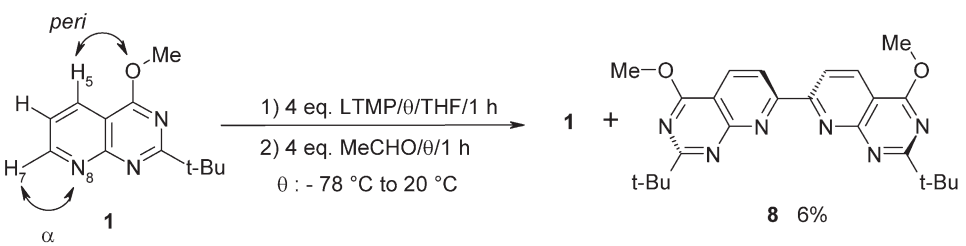
With the aim of determining the relative influence of structural parameters on the lithiation, we have first studied the metallation of compounds **1**, **5** and **7** which present only two effects. For compounds **1** and **5** these competitive effects are the *peri* effect of the methoxy group and the α effect of the pyridine nitrogen N_8 or N_7, whereas for **7**, they are between the two ring nitrogen atoms namely, N_1 of the pyrimidine moiety and N_5 of the pyridine ring.

The lithiation of **1** was attempted with an excess of lithium 2,2,6,6-tetramethylpiperidide (LTMP) (4 equiv.) from −78 to 20 °C for 1 h followed by reaction with acetaldehyde as electrophile. Under these conditions, starting material was recovered together with small amount of dimer **8**, whose formation can be explained either by a radical mechanism or by an addition–elimination reaction (Scheme 4).

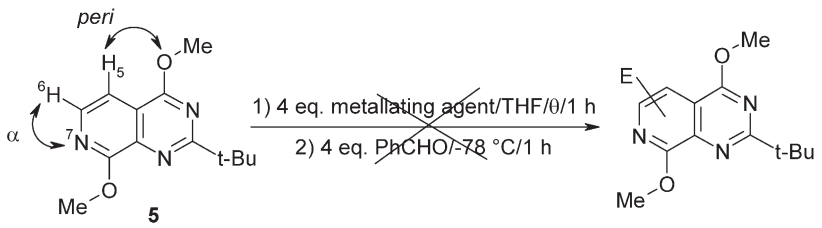
Treatment of **5** with 4 equiv. of LTMP at −78 or at 25 °C in THF for 1 h followed by addition of benzaldehyde gave only starting material. Attempts using *n*-butyllithium as metalling agent were also unsuccessful, 75% of the starting material being recovered (Scheme 5).

The lack of metallation for compounds **1** and **5** reveals that the two single independent effects (the *peri* effect of the methoxy group at C_4 and the α effect of the pyridine nitrogen atom N_x) when they are isolated, are insufficient to allow lithiation.

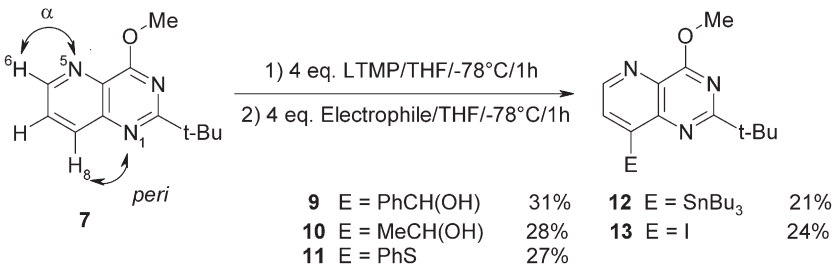
Treatment of **7** under the same experimental conditions followed by reaction with various electrophiles led to 8-substituted compounds with moderate yields, highlighting



Scheme 4.



Scheme 5.



Scheme 6.

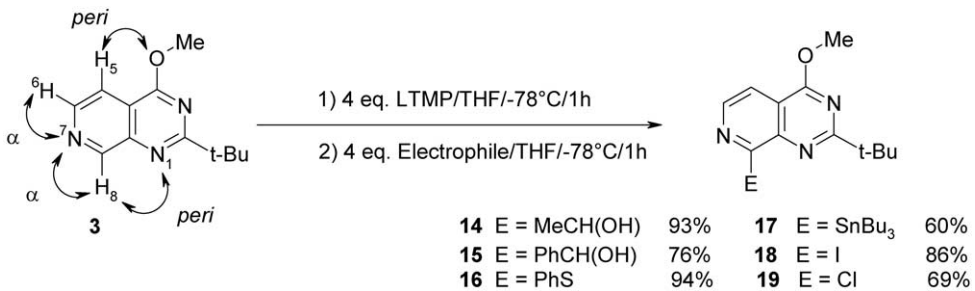
regioselective metallation at position C_8 *peri* to the ring nitrogen N_1 (Scheme 6).

For compound **7**, there is a competitive effect between the α effect of the pyridine nitrogen N_5 and the *peri* effect of the nitrogen atom N_1. The complete regioselectivity observed at C_8 highlights a greater capacity for this last parameter to induce metallation. This result allows us to rank the two relative effects: *peri* effect pyrimidine N_1>α effect pyridine N_x.

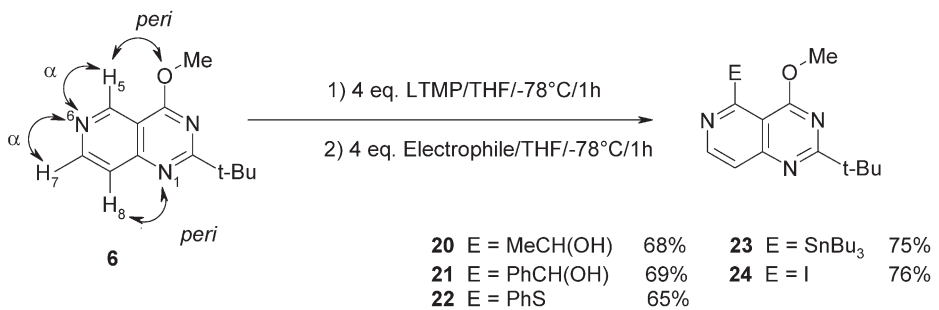
Metallation of compounds **3** and **6** devoid of an *ortho*-directing group on the pyridine moiety was then studied. For each compound, three different effects could influence the regioselectivity of the lithiation: the *peri* effects of the methoxy group and of the ring nitrogen N_1, and the α effect of the pyridine ring nitrogen N_x. It may be noted that for compound **3**, the hydrogen atom H_8 is submitted simultaneously to two effects (Scheme 7), such a situation also being observed for H_5 of compound **6** (Scheme 8).

Treatment of **3** using the experimental conditions previously used, followed by reaction with various electrophiles, afforded exclusively 8-substituted compounds **14**–**19** in good yields (Scheme 7).

It may thus be concluded as previously that: *peri* effect



Scheme 7.



Scheme 8.

pyrimidine N_1>α effect pyridine N_x and that: *peri* effect pyrimidine N_1>*peri* effect of OMe group.

For metallation of compound **6**, under same experimental conditions, a regioselective functionalization at the C_5 position was observed leading to compounds **20**–**24** (Scheme 8).

For compound **6**, there is a competition between the single effect of the *peri* nitrogen atom N_1 at the C_8 position and the influence of the α effect of the pyridine nitrogen atom N_6 which is either solely at the C_7 position or associated with the *peri* effect of the methoxy group at the C_5 position. This last position was regioselectively lithiated, and such a result highlights that two weak effects acting simultaneously such as the α effect of the pyridine nitrogen N_x and the *peri* effect of the methoxy group could be more important that a single stronger effect such as that of *peri* nitrogen N_1. (α effect pyridine N_x+*peri* effect of OMe group)>*peri* effect N_1.

We then carried out the metallation of compounds **2** and **4** which have a substituent on the pyridine moiety. It appeared interesting to examine if the presence of an *ortho*-directing group, such as a methoxy group *ortho* to a free position of the pyridine moiety, could allow functionalization of the ring. With this aim, we examined the lithiation of compound **4**.

For compound **4**, the presence of a methoxy group at C_6 leaves two positions which can be metallated (C_5 and C_8) allowing the competitive effects towards the metallation to be compared (Scheme 9). The C_5 position is influenced simultaneously by two methoxy groups, one as *ortho*-directing group at C_6 and the other group at the *peri* position C_4, whereas the C_8 position is under the influence of the *peri* effect of the ring nitrogen N_1 associated with the α effect of the pyridine nitrogen N_7.

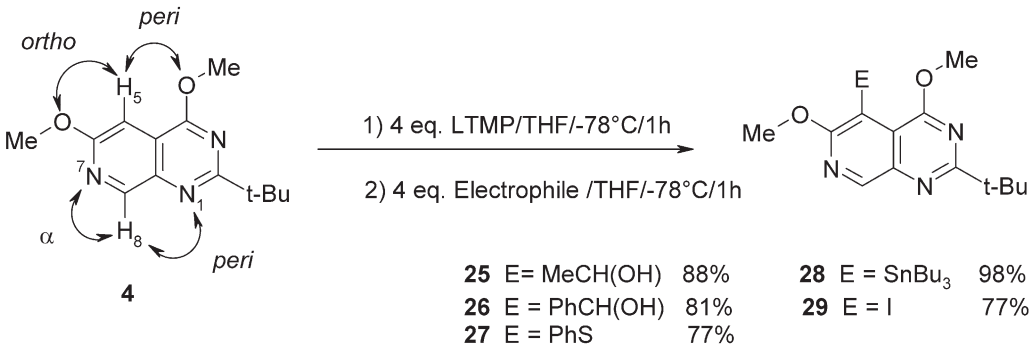
Metallation of **4** under the experimental conditions previously used followed by reaction with various electrophiles led to 5-substituted compounds **25**–**29** thus implying a total regioselective metallation at this position (Scheme 9).

In the case of compound **4**, the combined *peri* effect of the C_4 methoxy group and the *ortho*-directing effect of the C_6 methoxy group is more efficient than the combined effects of the *peri* nitrogen atom N_1 and the pyridine nitrogen N_7 (Scheme 9). (*ortho* effect of OMe group+*peri* effect of OMe group)>(*peri* effect pyrimidine N_1+α effect pyridine N_x).

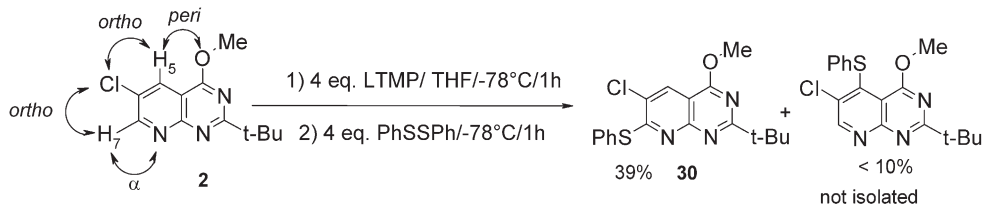
For compound **2**, the presence of the chlorine atom at the C_6 position produces a regioselectivity problem since it influences at once the two *ortho* positions C_5 and C_7. Each of these positions is also influenced by a second effect, the *peri* effect of the methoxy group for C_5 and the α effect of the pyridine nitrogen N_8 for the C_7 position (Scheme 10). Metallation of **2** was performed with 4 equiv. of LTMP at −78 °C in THF for 1 h, with diphenyl disulfide as electrophile. Under these conditions, we observed the formation of two functionalized compounds, together with starting material (25%). The main compound **30** substituted at the C_7 position was obtained in 39% yield while a small amount (<10%) of a 5-substituted compound was identified by NMR (Scheme 10).

The results obtained with compound **2** reveal that the *ortho*-directing effect of the chlorine atom associated with the α effect of the pyridine nitrogen N_8 is more efficient that when it is associated with the *peri* effect of the methoxy group. These results suggest that the pyridine nitrogen effect N_x is slightly stronger than the *peri* effect of the methoxy group. α effect pyridine N_x>*peri* effect of OMe group.

Though it is not possible to compare the sole effect of the *ortho*-directing methoxy group with the other structural effects, the latter results suggest that this effect could be very



Scheme 9.



Scheme 10.

strong. Indeed, when it is associated with the weak *peri* effect of the methoxy group, the global effect is superior to two combined stronger effects (*peri* effect of nitrogen N_1 and the α effect of pyridine nitrogen N_x).

The previous results thus allow classification of the directing effects as following: *ortho* effect of OMe group> *peri* effect pyrimidine N_1>α effect pyridine N_x>*peri* effect of OMe group.

2. Conclusion

Direct lithiation of the pyridine moiety of various 4-methoxypyridopyrimidines has been performed and studied. We have analyzed and appreciated the relative influence of different structural parameters on the regioselectivity of the metallation. In most cases, the highly regioselective metallation of these compounds provides an efficient method to access a wide range of new substituted pyridopyrimidines.

3. Experimental

Melting points were determined on a Kofler hot-stage. The ^1H and ^{13}C NMR spectra were recorded in deuteriochloroform on Bruker instruments (Avance 300). Microanalyses were performed on a Carlo Erba CHNOS 1160 apparatus. The IR spectra were obtained as potassium bromide pellets with a Perkin–Elmer FTIR 1650 spectrophotometer.

3.1. General procedure for the synthesis of various 4-methoxypyridopyrimidines via 4-chloropyridopyrimidines

The various pyridopyrimidin-4(3*H*)-ones used as starting material were synthesized according to the literature.[10]

A mixture of dry pyridopyrimidin-4(3*H*)-one and phosphorous oxychloride (15–30 mL) was refluxed for 3 h. The solvent was removed under reduced pressure, the oily residue was poured on ice and treated with sodium carbonate. The cold aqueous solution was extracted with ethyl acetate (3×20 mL), the combined organic extracts were dried over magnesium sulfate and evaporated under reduced pressure to give crude 4-chloropyridopyrimidine which was not isolated.

The crude chloro derivative was introduced into a solution of sodium methoxide (5 equiv.) in methanol (50 mL) and refluxed for 12–24 h. After cooling, the solvent was removed under reduced pressure. The residue was hydrolyzed with 20 mL of water and extracted with dichloromethane or ethyl acetate (3×20 mL). The organic layer was dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography on silica gel.

3.1.1. 2-*tert*-Butyl-4-methoxypyrido[2,3-*d*]pyrimidine (1). Reaction of 2-*tert*-butylpyrido[2,3-*d*]-pyrimidin-4(3*H*)-one (1 g, 5 mmol) with phosphorous oxychloride (20 mL) according to the general procedure, followed by reaction with sodium methoxide (5 equiv., 1.33 g) gave after purification by column chromatography (silica, eluent: ethyl acetate/diethyl ether (3/7)) 1.04 g (97%) of **1** as an oïl; ^1H NMR ($CDCl_3$): δ 1.42 (s, 9H, *tert*-butyl); 4.12 (s, 3H, OMe); 7.36 (dd, J_{H6-H7}=8.2 Hz, J_{H5-H6}=4.5 Hz, 1H, H_6); 8.38 (dd, J_{H6-H7}=8.2 Hz, J_{H5-H7}=2.3 Hz, 1H, H_7); 8.38 (dd, J_{H5-H6}=4.52 Hz, J_{H5-H7}=2.3 Hz, 1H, H_5); ^{13}C NMR ($CDCl_3$): δ 29.6 ($3Me_{tert\text{-}butyl}$); 40.3 (CMe_3); 54.7 (OMe); 109.6 (C_{py}); 122.0 (CH_{py}); 133.2 (CH_{py}); 156.8 (CH_{py}); 160.3 (C_{py}); 167.7 (C_{py}); 177.2 (C_{py}). Anal. calcd for $C_{12}H_{15}N_3O$ (217.27): C, 66.34; H, 6.96; N, 19.34. Found: C, 65.98; H, 6.84; N, 19.41.

3.1.2. 2-*tert*-Butyl-6-chloro-4-methoxypyrido[2,3-*d*]pyrimidine (2). Reaction of 2-*tert*-butyl-6-chloropyrido[2,3-*d*]-pyrimidin-4(3*H*)-one (0.5 g, 2.1 mmol) with phosphorous oxychloride (20 mL) according to the general procedure, followed by reaction with sodium methoxide (5 equiv., 0.57 g) gave after purification by column chromatography (silica, eluent: dichloromethane) 0.48 g (90%) of **2** as a white solid, mp=56–57 °C; ^1H NMR ($CDCl_3$): δ 1.38 (s, 9H, *tert*-butyl); 4.10 (s, 3H, OMe); 8.29 (d, J_{H5-H7}=2.4 Hz, 1H, H_5); 8.88 (d, J_{H7-H5}=2.4 Hz, 1H, H_7); ^{13}C NMR ($CDCl_3$): δ 28.1 ($3Me_{tert\text{-}butyl}$); 38.9 (CMe_3); 53.6 (OMe); 108.3 (C_{py}); 127.7 (C_{py}); 130.2 (CH_{py}); 154.6 (CH_{py}); 156.9 (C_{py}); 165.6 (C_{py}); 176.0 (C_{py}). Anal. calcd for $C_{12}H_{14}N_3ClO$ (251.72): C, 57.26; H, 5.61; N, 16.69. Found: C, 57.11; H, 5.65; N, 16.62.

3.1.3. 2-*tert*-Butyl-4-methoxypyrido[3,4-*d*]pyrimidine (3). Reaction of 2-*tert*-butylpyrido[3,4-*d*]-pyrimidin-4(3*H*)-one (1 g, 5 mmol) with phosphorous oxychloride (30 mL) according to the general procedure, followed by reaction with sodium methoxide (5 equiv., 1.33 g) gave after purification by column chromatography (silica, eluent: diethyl ether) 0.87 g (77%) of **3** as a white solid, mp=121–122 °C; ^1H NMR ($CDCl_3$): δ 1.39 (s, 9H, *tert*-butyl); 4.11 (s, 3H, OMe); 7.78 (dd, J_{H5-H6}=5.65 Hz, J_{H5-H8}=1.1 Hz, 1H, H_5); 8.56 (d, J_{H6-H5}=5.65 Hz, 1H, H_6); 9.26 (d, J_{H8-H6}=1.1 Hz, 1H, H_8); ^{13}C NMR ($CDCl_3$): δ 29.6 ($3Me_{tert\text{-}butyl}$); 40.2 (CMe_3); 54.5 (OMe); 111.5 (CH_{py}); 118.7 (C_{py}); 144.6 (CH_{py}); 146.3 (C_{py}); 152.8 (CH_{py}); 166.3 (C_{py}); 175.0 (C_{py}). Anal. calcd for $C_{12}H_{15}N_3O$ (217.27): C, 66.34; H, 6.96; N, 19.34. Found: C, 66.19; H, 7.05; N, 18.91.

3.1.4. 2-*tert*-Butyl-4,6-dimethoxypyrido[3,4-*d*]pyrimidine (4). Reaction of 2-*tert*-butyl-6-methoxypyrido[3,4-*d*]-pyrimidin-4(3*H*)-one (0.5 g, 2.1 mmol) with phosphorous oxychloride (15 mL) according to the general procedure, followed by reaction with sodium methoxide (5 equiv., 0.58 g) gave after purification by column chromatography (silica, eluent: diethyl ether/petroleum ether (5/5)) 0.43 g (82%) of **4** as a white solid, mp=78–79 °C; ^1H NMR ($CDCl_3$): δ 1.33 (s, 9H, *tert*-butyl); 3.91 (s, 3H, OMe); 4.03 (s, 3H, OMe); 7.04 (s, 1H, H_5); 8.86 (s, 1H, H_8); ^{13}C NMR ($CDCl_3$): δ 28.1 ($3Me_{tert\text{-}butyl}$); 38.4 (CMe_3); 52.9 (OMe); 53.3 (OMe); 96.8 (CH_{py}); 120.7 (C_{py}); 140.5 (C_{py}); 148.8 (CH_{py}); 160.2 (C_{py}); 164.3 (C_{py}); 170.1 (C_{py}). Anal. calcd for $C_{13}H_{17}N_3O_2$ (247.29): C, 63.14; H, 6.93; N, 16.99. Found: C, 63.21; H, 6.95; N, 17.07.

3.1.5. 2-*tert*-Butyl-4,8-dimethoxypyrido[3,4-*d*]pyrimidine (5). Reaction of 2-*tert*-butyl-8-methoxypyrido[3,4-*d*]-pyrimidin-4(3*H*)-one (0.5 g, 2.1 mmol) with phosphorous

oxychloride (15 mL) according to the general procedure, followed by reaction with sodium methoxide (5 equiv., 0.58 g) gave after purification by column chromatography (silica, eluent: diethyl ether/petroleum ether (5/5)) 0.34 g (64%) of **5** as a white solid, mp=185–186 °C; ^{1}H NMR ($CDCl_3$): δ 1.40 (s, 9H, *tert*-butyl); 4.08 (s, 3H, OMe); 4.09 (s, 3H, OMe); 7.34 (d, J=5.65 Hz, 1H, H_5); 8.00 (d, J=5.65 Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$): δ 28.3 ($3Me_{tert\text{-}butyl}$); 38.9 (CMe_3); 53.0 (OMe); 53.3 (OMe); 107.8 (CH_{py}); 118.6 (C_{py}); 136.9 (C_{py}); 139.5 (CH_{py}); 158.9 (C_{py}); 164.8 (C_{py}); 172.9 (C_{py}). Anal. calcd for $C_{13}H_{17}N_3O_2$ (247.29): C, 63.14; H, 6.93; N, 16.99. Found: C, 62.87; H, 6.84; N, 16.56.

3.1.6. 2-*tert*-Butyl-4-methoxypyrido[4,3-*d*]pyrimidine (6). Reaction of 2-*tert*-butylpyrido[4,3-*d*]-pyrimidin-4(3*H*)-one (1 g, 5 mmol) with phosphorous oxychloride (20 mL) according to the general procedure, followed by reaction with sodium methoxide (5 equiv., 1.33 g) gave after purification by column chromatography (silica, eluent: ethyl acetate/petroleum ether (5/5)) 0.84 g (79%) of **6** as a white solid, mp=55–56 °C; ^{1}H NMR ($CDCl_3$): δ 1.36 (s, 9H, *tert*-butyl); 4.11 (s, 3H, OMe); 7.59 (dd, J_{H8-H7}=5.8 Hz, J_{H8-H5}=0.75 Hz, 1H, H_8); 8.70 (d, J_{H7-H8}=5.8 Hz, 1H, H_7); 9.35 (s, 1H, H_5); ^{13}C NMR ($CDCl_3$): δ 29.5 ($3Me_{tert\text{-}butyl}$); 40.4 (CMe_3); 54.4 (OMe); 111.1 (C_{py}); 121.0 (CH_{py}); 148.9 (CH_{py}); 151.1 (CH_{py}); 155.0 (C_{py}); 167.3 (C_{py}); 177.9 (C_{py}). Anal. calcd for $C_{12}H_{15}N_3O$ (217.27): C, 66.34; H, 6.96; N, 19.34. Found: C, 66.32; H, 6.84; N, 19.43.

3.1.7. 2-*tert*-Butyl-4-methoxypyrido[3,2-*d*]pyrimidine (7). Reaction of 2-*tert*-butylpyrido[3,2-*d*]-pyrimidin-4(3*H*)-one (1 g, 5 mmol) with phosphorous oxychloride (30 mL) according to the general procedure, followed by reaction with sodium methoxide (5 equiv., 1.33 g) gave after purification by column chromatography (silica, eluent: ethyl acetate/dichloromethane (5/5)) 0.69 g (65%) of **7** as an ochre solid, mp<50 °C; ^{1}H NMR ($CDCl_3$): δ 1.37 (s, 9H, *tert*-butyl); 4.16 (s, 3H, OMe); 7.59 (dd, J_{H7-H6}=8.7 Hz, J_{H7-H8}=4.15 Hz, 1H, H_7); 8.11 (dd, J_{H6-H7}=8.7 Hz, J_{H6-H8}=1.5 Hz, 1H, H_6); 8.79 (dd, J_{H8-H7}=4.15 Hz, J_{H8-H6}=1.5 Hz, 1H, H_8); ^{13}C NMR ($CDCl_3$): δ 29.7 ($3Me_{tert\text{-}butyl}$); 40.0 (CMe_3); 54.8 (OMe); 127. 9 (CH_{py}); 131.7 (C_{py}); 136.3 (CH_{py}); 147.1 (C_{py}); 150.0 (CH_{py}); 166.1 (C_{py}); 173.8 (C_{py}). Anal. calcd for $C_{12}H_{15}N_3O$ (217.27): C, 66.34; H, 6.96; N, 19.34. Found: C, 66.51; H, 6.98; N, 19.31.

3.2. General procedure for metallation of 2-*tert*-butyl-4-methoxypyridopyrimidines by lithium 2,2,6,6-tetramethylpiperidide

Procedure A. A solution of *n*-butyllithium (1.6 or 2.5 M in hexane) was added to cold (−78 °C), stirred and anhydrous mixture of THF (15 mL) and 2,2,6,6-tetramethylpiperidine (TMPH) under an atmosphere of dry nitrogen. The mixture was warmed to 0 °C. After 30 min, the mixture temperature was cooled to −78 °C and added to a cold (−78 °C) solution of the 2-*tert*-butyl-4-methoxypyridopyrimidine dissolved in THF (10 mL). The mixture was then stirred for 5 min and heated to T (°C). After 1 h of stirring at T (°C), the temperature was decreased to −78 °C and the electrophile introduced and stirring was continued for t hour(s) at this temperature. Hydrolysis was then carried out at −78 °C using a solution of water and ethanol (5/5). When the electrophile was iodine, the solution was decolorized with sodium thiosulfate. At room temperature, water (10 mL) was added to the mixture and THF was removed under reduced pressure. The aqueous layer was extracted with dichloromethane or ethyl acetate (3×20 mL), the combined organic extracts were then dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography on silica gel.

Procedure B. The workup of the procedures A and B is similar but differs only by the order of introduction of the electrophile. For procedure B, the lithiated product was introduced onto the solution of iodine in THF.

3.2.1. Metallation of 2-*tert*-butyl-4-methoxypyrido[2,3-*d*]-pyrimidine (1)

3.2.1.1. 7,7′-bis-(2-*tert*-Butyl-4-methoxypyrido[2,3-*d*]-pyrimidine) (8). Metallation of **1** (100 mg, 0.46 mmol) according to the procedure A with *n*-BuLi 1.6 M (4 equiv., 1.15 mL), TMPH (4 equiv., 0.32 mL), T=0 °C, followed by reaction with acetaldehyde (1 mL excess), t=1 h, gave after purification by column chromatography (silica, eluent: ethyl acetate/dichloromethane (5/5)) 11 mg (6%) of **8** as a white solid, mp>250 °C; ^{1}H NMR ($CDCl_3$): δ 1.46 (s, 9H, *tert*-butyl), 4.16 (s, 3H, OMe), 8.57 (d, J=8.3 Hz, 1H, H_5), 8.98 (d, J=8.3 Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$): δ 29.7 ($3Me_{tert\text{-}butyl}$), 40.5 (CMe_3), 54.8 (OMe), 110.3 (C_{py}), 121.5 (CH_{py}), 134.2 (CH_{py}), 160.0 (C_{py}), 161.4 (C_{py}), 167.8 (C_{py}), 177.8 (C_{py}). Anal. calcd for $C_{24}H_{28}N_6O_2$ (432.526): C, 66.65; H, 6.53; N, 19.43. Found: C, 66.38; H, 6.56; N, 19.31.

3.2.1.2. 2-*tert*-Butyl-8-(hydroxyphenylmethyl)-4-methoxypyrido[3,2-*d*]pyrimidine (9). Metallation of **7** (50 mg, 0.23 mmol) according to the procedure A with *n*-BuLi 1.6 M (4 equiv., 0.58 mL), TMPH (4 equiv., 0.16 mL), T=−78 °C, followed by reaction with benzaldehyde (5 equiv., 0.10 mL), t=1 h, gave after purification by column chromatography (silica, eluent: ethyl ether) 23 mg (31%) of **9** as a white solid, mp=134–135 °C; ^{1}H NMR ($CDCl_3$): δ 1.40 (s, 9H, *tert*-butyl); 4.18 (s, 3H, OMe); 6.23 (m, 1H, C*H*OH); 6.73 (m, 1H, OH); 7.25 (m, 3H, Ph); 7.35 (d, J=4.5 Hz, 1H, H_7); 7.42 (m, 2H, Ph); 8.73 (d, J=4.5 Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$): δ 29.6 ($3Me_{tert\text{-}butyl}$); 40.2 (CMe_3); 55.1 (OMe); 75.9 (CHOH); 125.7 (CH_{py}); 127.0 ($2CH_{Ph}$); 128.1 (CH_{Ph}); 128.8 ($2CH_{Ph}$); 131.6 (C_{Ph}); 142.3 (C_{py}); 145.4 (C_{py}); 148.4 (C_{py}); 150.1 (CH_{py}); 166.9 (C_{py}); 173.0 (C_{py}). Anal. calcd for $C_{19}H_{21}N_3O_2$ (323.39): C, 70.57; H, 6.55; N, 12.99. Found: C, 70.76; H, 6.79; N, 12.49.

3.2.1.3. 2-*tert*-Butyl-8-(1-hydroxyethyl)-4-methoxypyrido[3,2-*d*]pyrimidine (10). Metallation of **7** (50 mg, 0.23 mmol) according to the procedure A with *n*-BuLi 1.6 M (4 equiv., 0.58 mL), TMPH (4 equiv., 0.16 mL), T=−78 °C, followed by reaction with acetaldehyde (5 equiv., 0.07 mL), t=1 h, gave after purification by column chromatography (silica, eluent: dichloromethane/ethyl acetate (5/5)) 17 mg (28%) of **10** as a glassy solid, mp=121–122 °C; ^{1}H NMR ($CDCl_3$): δ 1.40 (s, 9H, *tert*-butyl); 1.62 (d, J=6.4 Hz, 3H, Me); 4.19 (s, 3H, OMe); 5.25 (m, 1H, C*H*OH); 6.01 (m, 1H, OH); 7.46 (d, J=4.5 Hz, 1H, H_7); 8.76 (d, J=4.5 Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$): δ 24.1 (Me); 29.6 ($3Me_{tert\text{-}butyl}$); 40.1 (CMe_3); 55.1 (OMe); 69.8 (CHOH); 124.3 (CH_{py}); 131.5 (C_{py}); 145.5 (C_{py}); 150.0 (C_{py}); 150.2 (CH_{py}); 166.9 (C_{py}); 172.7 (C_{py}). Anal. calcd

for $C_{14}H_{19}N_3O_2$ (261.32): C, 64.35; H, 7.33; N, 16.08. Found: C, 64.43; H, 7.42; N, 15.84.

3.2.1.4. 2-*tert*-Butyl-4-methoxy-8-phenylthiopyrido-[3,2-*d*]pyrimidine (11). Metallation of **7** (50 mg, 0.23 mmol) according to the procedure A with *n*-BuLi 1.6 M (4 equiv., 0.58 mL), TMPH (4 equiv., 0.16 mL), $T=-78$ °C, followed by reaction with diphenyl disulfide (4 equiv., 201 mg) in solution with anhydrous THF (5 mL), $t=1$ h, gave after purification by column chromatography (silica, eluent: dichloromethane) 20 mg (27%) of **11** as an oil; ^{1}H NMR ($CDCl_3$): δ 1.43 (s, 9H, *tert*-butyl); 4.17 (s, 3H, OMe); 6.73 (d, $J=4.9$ Hz, 1H, H_7); 7.45 (m, 3H, Ph); 7.58 (m, 2H, Ph); 8.38 (d, $J=4.9$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$): δ 29.7 ($3Me_{tert\text{-butyl}}$); 40.3 (CMe_3); 55.0 (OMe); 121.8 (CH_{py}); 129.5 (C_{py}); 130.1 (C_{Ph}); 130.4 (CH_{Ph}); 130.6 ($2CH_{Ph}$); 136.4 ($2CH_{Ph}$); 143.9 (C_{py}); 149.2 (CH_{py}); 152.5 (C_{py}); 166.2 (C_{py}); 172.9 (C_{py}). Anal. calcd for $C_{18}H_{19}N_3OS$ (325.43): C, 66.43; H, 5.88; N, 12.91; S, 9.85. Found: C, 66.73; H, 5.95; N, 13.09; S, 9.73.

3.2.1.5. 2-*tert*-Butyl-8-(tri-*n*-butylstannyl)-4-methoxy-pyrido[3,2-*d*]pyrimidine (12). Metallation of **7** (50 mg, 0.23 mmol) according to the procedure A with *n*-BuLi 1.6 M (4 equiv., 0.58 mL), TMPH (4 equiv., 0.16 mL), $T=-78$ °C, followed by reaction with tri-*n*-butylstannyl chloride (5 equiv., 0.32 mL), $t=1$ h, gave after purification by column chromatography (silica, eluent: dichloromethane) 25 mg (21%) of **12** as an oil; ^{1}H NMR ($CDCl_3$): δ 0.77 (t, 9H, Me); 1.18 (m, 12H, CH_2); 1.39 (s, 9H, *tert*-butyl); 1.44 (m, 6H, $SnCH_2$); 4.16 (s, 3H, OMe); 7.78 (td, $J=4.15$ Hz, $J_{H7-Sn}=19.2$ Hz, 1H, H_7); 8.68 (q, $J=4.15$ Hz, $J_{H6-Sn}=9.4$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$): δ 10.9 (CH_2); 14.0 (Me); 27.7 (CH_2); 29.5 (CH_2); 29.9 ($3Me_{tert\text{-butyl}}$); 40.0 (CMe_3); 54.8 (OMe); 130.0 (C_{py}); 136.5 (CH_{py}); 148.8 (CH_{py}); 152.5 (C_{py}); 157.5 (C_{py}); 166.7 (C_{py}); 172.4 (C_{py}). Anal. calcd for $C_{24}H_{41}N_3OSn$ (506.30): C, 56.93; H, 8.16; N, 8.30. Found: C, 57.08; H, 8.32; N, 8.38.

3.2.1.6. 2-*tert*-Butyl-8-iodo-4-methoxypyrido[3,2-*d*]-pyrimidine (13). Metallation of **7** (50 mg, 0.23 mmol) according to the procedure B with *n*-BuLi 1.6 M (4 equiv., 0.58 mL), TMPH (4 equiv., 0.16 mL), $T=-78$ °C, followed by reaction with iodine (5 equiv., 292 mg) in solution with anhydrous THF (5 mL), $t=1$ h, gave after purification by column chromatography (silica, eluent: dichloromethane) 19 mg (24%) of **13** as an yellow oil; ^{1}H NMR ($CDCl_3$): δ 1.42 (s, 9H, *tert*-butyl); 4.19 (s, 3H, OMe); 8.20 (d, $J=4.5$ Hz, 1H, H_7); 8.35 (d, $J=4.5$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$): δ 29.7 ($3Me_{tert\text{-butyl}}$); 41.0 (CMe_3); 55.4 (OMe); 115.1 (C_{py}); 131.4 (C_{py}); 138.6 (CH_{py}); 147.3 (C_{py}); 149.7 (CH_{py}); 166.6 (C_{py}); 174.6 (C_{py}). Anal. calcd for $C_{12}H_{14}IN_3O$ (343.16): C, 42.00; H, 4.11; N, 12.24. Found: C, 41.73; H, 4.60; N, 12.60.

3.2.2. Metallation of 2-*tert*-butyl-4-methoxypyrido[3,4-*d*]-pyrimidine (3)

3.2.2.1. 2-*tert*-Butyl-8-(1-hydroxyethyl)-4-methoxy-pyrido[3,4-*d*]pyrimidine (14). Metallation of **3** (50 mg, 0.23 mmol) according to the procedure A with *n*-BuLi 1.6 M (4 equiv., 0.58 mL), TMPH (4 equiv., 0.16 mL), $T=-78$ °C, followed by reaction with acetaldehyde (5 equiv., 0.07 mL), $t=1$ h, gave after purification by column chromatography (silica, eluent: dichloromethane/ethyl acetate (5/5)) 56 mg (93%) of **14** as an ochre solid, mp=90–91 °C; ^{1}H NMR ($CDCl_3$): δ 1.37 (s, 9H, *tert*-butyl); 1.61 (d, $J=6.40$ Hz, 3H, Me); 4.11 (s, 3H, OMe); 5.47 (m, 1H, C*H*OH); 5.54 (d, $J=7.5$ Hz, 1H, OH); 7.69 (d, $J=5.6$ Hz, 1H, H_5); 8.45 (d, $J=5.66$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$): δ 24.1 (Me); 29.5 ($3Me_{tert\text{-butyl}}$); 40.3 (CMe_3); 54.7 (OMe); 70.2 (CHOH); 114.8 (CH_{py}); 118.8 (C_{py}); 142.7 (CH_{py}); 143.5 (C_{py}); 163.0 (C_{py}); 166.8 (C_{py}); 173.7 (C_{py}). Anal. calcd for $C_{14}H_{19}N_3O_2$ (261.32): C, 64.35; H, 7.33; N, 16.08. Found: C, 64.62; H, 7.49; N, 16.13.

3.2.2.2. 2-*tert*-Butyl-8-(hydroxyphenylmethyl)-4-methoxypyrido[3,4-*d*]pyrimidine (15). Metallation of **3** (100 mg, 0.46 mmol) according to the procedure A with *n*-BuLi 1.6 M (4 equiv., 1.15 mL), TMPH (4 equiv., 0.31 mL), $T=-78$ °C, followed by reaction with benzaldehyde (4 equiv., 0.20 mL), $t=1$ h, gave after purification by column chromatography (silica, eluent: (1) petroleum ether/diethyl ether (7/3), (2) dichloromethane/ethyl acetate (5/5)) 113 mg (76%) of **15** as a white solid, mp=130 °C; ^{1}H NMR ($CDCl_3$): δ 1.36 (s, 9H, *tert*-butyl); 4.05 (s, 3H, OMe); 6.35 (d, $J=8.4$ Hz, 1H, C*H*OH); 6.47 (d, $J=8.4$ Hz, 1H, OH); 7.12 (m, 3H, H_{Ph}); 7.52 (d, $J=7.3$ Hz, 2H, H_{Ph}); 7.68 (d, $J=5.5$ Hz, 1H, H_5); 8.48 (d, $J=5.5$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$): δ 29.6 ($3Me_{tert\text{-butyl}}$); 40.4 (CMe_3); 54.7 (OMe); 75.5 (CHOH); 115.2 (CH_{py}); 119.2 (C_{Ph}); 127.1 ($2CH_{Ph}$); 127.5 (CH_{Ph}); 128.4 ($2CH_{Ph}$); 142.9 (CH_{py}); 143.4 (C_{py}); 143.6 (C_{py}); 161.0 (C_{py}); 166.8 (C_{py}); 173.9 (C_{py}). Anal. calcd for $C_{19}H_{21}N_3O_2$ (323.39): C, 70.57; H, 6.55; N, 12.99. Found: C, 70.87; H, 6.88; N, 12.84.

3.2.2.3. 2-*tert*-Butyl-4-methoxy-8-phenylthiopyrido-[3,4-*d*]pyrimidine (16). Metallation of **3** (100 mg, 0.46 mmol) according to the procedure A with *n*-BuLi 1.6 M (4 equiv., 1.15 mL), TMPH (4 equiv., 0.31 mL), $T=-78$ °C, followed by reaction with diphenyl disulfide (4 equiv., 402 mg) in solution with anhydrous THF (5 mL), $t=1$ h, gave after purification by column chromatography (silica, eluent: (1) petroleum ether/dichloromethane (7/3), (2) petroleum ether/dichloromethane (8/2)) 140 mg (94%) of **16** as a glassy solid, mp=89–90 °C; ^{1}H NMR ($CDCl_3$): δ 1.42 (s, 9H, *tert*-butyl); 4.08 (s, 3H, OMe); 7.37 (m, 3H, H_{Ph}); 7.40 (d, $J=5.5$ Hz, 1H, H_5); 7.58 (m, 2H, H_{Ph}); 8.16 (d, $J=5.5$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$): δ 29.7 ($3Me_{tert\text{-butyl}}$); 40.4 (CMe_3); 54.7 (OMe); 111.6 (CH_{py}); 117.5 (C_{py}); 129.3 (CH_{Ph}); 129.5 ($2CH_{Ph}$); 130.2 (C_{Ph}); 136.1 ($2CH_{Ph}$); 143.7 (C_{py}); 144.1 (CH_{py}); 162.2 (C_{py}); 166.4 (C_{py}); 174.2 (C_{py}). Anal. calcd for $C_{18}H_{19}N_3OS$ (325.43): C, 66.43; H, 5.88; N, 12.91; S, 9.85. Found: C, 66.61; H, 5.97; N, 12.82; S, 9.71.

3.2.2.4. 2-*tert*-Butyl-8-(tri-*n*-butylstannyl)-4-methoxy-pyrido[3,4-*d*]pyrimidine (17). Metallation of **3** (100 mg, 0.46 mmol) according to the procedure A with *n*-BuLi 1.6 M (4 equiv., 1.15 mL), TMPH (4 equiv., 0.31 mL), $T=-78$ °C, followed by reaction with tri-*n*-butylstannyl chloride (4 equiv., 0.51 mL), t=1 h, gave after purification by column chromatography (silica, eluent: dichloromethane) 139 mg (60%) of **17** as an oil; ^{1}H NMR ($CDCl_3$): δ 0.71 (t, $J=7.3$ Hz, 9H, 3Me); 1.16 (m, 12H, $4CH_2$); 1.34 (s, 9H, *tert*-butyl); 1.42 (m, 6H, $3CH_2$); 4.03 (s, 3H, OMe); 7.55 (q, $J_{H5-H6}=5.5$ Hz, $J_{H5-Sn}=0.74$ Hz, 1H, H_5); 8.65 (d, $J=5.5$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$): δ 11.1 ($SnCH_{2Bu3Sn}$); 14.0 (Me_{Bu3Sn}); 27.7 ($SnCH_2CH_2$); 29.6 (CH_2Me); 29.6 ($3Me_{tert\text{-butyl}}$); 40.2 (CMe_3); 54.4 (OMe); 113.3 (CH_{py}); 115.8 (C_{py}); 145.7 (CH_{py}); 151.2 (C_{py}); 167.0 (C_{py}); 173.5 (C_{py}); 182.8 (C_{py}). Anal. calcd for

$C_{24}H_{41}N_3OSn$ (506.30): C, 56.93; H, 8.16; N, 8.30. Found: C, 56.82; H, 8.21; N, 8.35.

3.2.2.5. 2-*tert*-Butyl-8-iodo-4-methoxypyrido[3,4-*d*]-pyrimidine (18). Metallation of **3** (100 mg, 0.46 mmol) according to the procedure B with *n*-BuLi 1.6 M (4 equiv., 1.15 mL), TMPH (4 equiv., 0.31 mL), $T=-78$ °C, followed by reaction with iodine (4 equiv., 468 mg) in solution with anhydrous THF (5 mL), $t=1$ h, gave after purification by column chromatography (silica, eluent: dichloromethane) 136 mg (86%) of **18** as a white solid, mp=123–124 °C; ^{1}H NMR ($CDCl_3$): δ 1.40 (s, 9H, *tert*-butyl); 4.12 (s, 3H, OMe); 7.68 (d, $J=5.5$ Hz, 1H, H_5); 8.29 (d, $J=5.5$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$): δ 29.6 ($3Me_{tert\text{-butyl}}$); 40.5 (CMe_3); 55.1 (OMe); 115.7 (CH_{py}); 118.5 (C_{py}); 129.8 (C_{py}); 145.2 (CH_{py}); 147.2 (C_{py}); 166.8 (C_{py}); 175.9 (C_{py}). Anal. calcd for $C_{12}H_{14}IN_3O$ (343.16): C, 42.00; H, 4.11; N, 12.24. Found: C, 41.89; H, 4.28; N, 12.29.

3.2.2.6. 2-*tert*-Butyl-8-chloro-4-methoxypyrido[3,4-*d*]-pyrimidine (19). Metallation of **3** (23 mg, 0.11 mmol) according to the procedure B with *n*-BuLi 1.6 M (4 equiv., 0.26 mL), TMPH (4 equiv., 0.07 mL), $T=-78$ °C, followed by reaction with hexachloroethane (4 equiv., 100 mg) in solution with anhydrous THF (5 mL), $t=1$ h, gave after purification by column chromatography (silica, eluent: dichloromethane) 18 mg (69%) of **19** as a white solid, mp=126–127 °C; ^{1}H NMR ($CDCl_3$): δ 1.40 (s, 9H, *tert*-butyl); 4.12 (s, 3H, OMe); 7.74 (d, $J=5.3$ Hz, 1H, H_5); 8.29 (d, $J=5.3$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$): δ 29.5 ($3Me_{tert\text{-butyl}}$); 40.5 (CMe_3); 54.9 (OMe); 115.6 (CH_{py}); 120.5 (C_{py}); 142.9 (CH_{py}); 144.1 (C_{py}); 152.5 (C_{py}); 166.6 (C_{py}); 175.8 (C_{py}). Anal. calcd for $C_{12}H_{14}ClN_3O$ (251.72): C, 57.26; H, 5.61; N, 16.69. Found: C, 57.32; H, 5.63; N, 16.16.

3.2.3. Metallation of 2-*tert*-butyl-4-methoxypyrido[4,3-*d*]-pyrimidine (6)

3.2.3.1. 2-*tert*-Butyl-5-(1-hydroxyethyl)-4-methoxy-pyrido[4,3-*d*]pyrimidine (20). Metallation of **6** (50 mg, 0.23 mmol) according to the procedure A with *n*-BuLi 1.6 M (4 equiv., 0.58 mL), TMPH (4 equiv., 0.16 mL), $T=-78$ °C, followed by reaction with acetaldehyde (5 equiv., 0.07 mL), $t=1$ h, gave after purification by column chromatography (silica, eluent: dichloromethane/ethyl acetate (7/3)) 41 mg (68%) of **20** as an oil; ^{1}H NMR ($CDCl_3$): δ 1.38 (s, 9H, *tert*-butyl); 1.40 (d, $J=6.4$ Hz, 3H, Me); 4.14 (s, 3H, OMe); 5.18 (m, 1H, C*H*OH); 5.63 (m, 1H, OH); 7.56 (d, $J=5.8$ Hz, 1H, H_8); 8.59 (d, $J=5.8$ Hz, 1H, H_7); ^{13}C NMR ($CDCl_3$): δ 25.7 (Me); 29.5 ($3Me_{tert\text{-butyl}}$); 40.2 (CMe_3); 54.6 (OMe); 68.8 (CHOH); 108.0 (C_{py}); 120.8 (CH_{py}); 148.1 (CH_{py}); 157.4 (C_{py}); 164.3 (C_{py}); 166.8 (C_{py}); 177.4 (C_{py}). Anal. calcd for $C_{14}H_{19}N_3O_2$ (261.32): C, 64.35; H, 7.33; N, 16.08. Found: C, 64.42; H, 7.37; N, 16.36.

3.2.3.2. 2-*tert*-Butyl-5-(hydroxyphenylmethyl)-4-methoxypyrido[4,3-*d*]pyrimidine (21). Metallation of **6** (50 mg, 0.23 mmol) according to the procedure A with *n*-BuLi 1.6 M (4 equiv., 0.58 mL), TMPH (4 equiv., 0.16 mL), $T=-78$ °C, followed by reaction with benzaldehyde (5 equiv., 0.10 mL), $t=1$ h, gave after purification by column chromatography (silica, eluent: dichloromethane/ethyl acetate (7/3)) 51 mg (69%) of **21** as a white solid, mp=115–116 °C; ^{1}H NMR ($CDCl_3$): δ 1.32 (s, 9H, *tert*-butyl); 3.97 (s, 3H, OMe); 5.96 (d, $J=7.5$ Hz, 1H, C*H*OH); 6.52 (d, $J=7.5$ Hz, 1H, OH); 7.16 (m, 5H, Ph); 7.62 (d, $J=5.65$ Hz, 1H, H_8); 8.70 (d, $J=5.65$ Hz, 1H, H_7); ^{13}C NMR ($CDCl_3$): δ 29.5 ($3Me_{tert\text{-butyl}}$); 40.2 (CMe_3); 54.1 (OMe); 74.5 (CHOH); 108.8 (C_{py}); 121.4 (CH_{py}); 127.8 (CH_{Ph}); 128.0 ($2CH_{Ph}$); 128.7 ($2CH_{Ph}$); 143.8 (C_{Ph}); 147.8 (CH_{py}); 157.5 (C_{py}); 161.0 (C_{py}); 166.6 (C_{py}); 177.7 (C_{py}). Anal. calcd for $C_{19}H_{21}N_3O_2$ (323.39): C, 70.57; H, 6.55; N, 12.99. Found: C, 70.63; H, 6.45; N, 12.67.

3.2.3.3. 2-*tert*-Butyl-4-methoxy-5-phenylthiopyrido-[4,3-*d*]pyrimidine (22). Metallation of **6** (50 mg, 0.23 mmol) according to the procedure A with *n*-BuLi 1.6 M (4 equiv., 0.58 mL), TMPH (4 equiv., 0.16 mL), $T=-78$ °C, followed by reaction with diphenyl disulfide (4 equiv., 201 mg) in solution with anhydrous THF (5 mL), $t=1$ h, gave after purification by column chromatography (silica, eluent: dichloromethane) 48 mg (65%) of **22** as an ochre solid, mp=101–102 °C; ^{1}H NMR ($CDCl_3$): δ 1.36 (s, 9H, *tert*-butyl); 4.19 (s, 3H, OMe); 7.23 (d, $J=5.65$ Hz, 1H, H_8); 7.37 (m, 3H, Ph); 7.50 (m, 2H, Ph); 8.24 (d, $J=5.65$ Hz, 1H, H_7); ^{13}C NMR ($CDCl_3$): δ 29.5 ($3Me_{tert\text{-butyl}}$); 40.1 (CMe_3); 54.5 (OMe); 109.3 (C_{py}); 117.4 (CH_{py}); 129.4 ($2CH_{Ph}$); 129.5 (CH_{Ph}); 130.7 (C_{Ph}); 136.2 ($2CH_{Ph}$); 149.6 (CH_{py}); 157.4 (C_{py}); 161.1 (C_{py}); 166.9 (C_{py}); 177.2 (C_{py}). Anal. calcd for $C_{18}H_{19}N_3OS$ (325.43): C, 66.43; H, 5.88; N, 12.91; S, 9.85. Found: C, 66.51; H, 5.85; N, 12.72; S, 9.71.

3.2.3.4. 2-*tert*-Butyl-5-(tri-*n*-butylstannyl)-4-methoxy-pyrido[4,3-*d*]pyrimidine (23). Metallation of **6** (50 mg, 0.23 mmol) according to the procedure A with *n*-BuLi 1.6 M (4 equiv., 0.58 mL), TMPH (4 equiv., 0.16 mL), $T=-78$ °C, followed by reaction with tri-*n*-butylstannyl chloride (5 equiv., 0.32 mL), $t=1$ h, gave without purification (degradation on column chromatography) 174 mg (75%) of **23** as an oil; ^{1}H NMR ($CDCl_3$): δ 0.76–1.59 (3m, 27H, $SnBu_3$); 1.38 (s, 9H, *tert*-butyl); 4.11 (s, 3H, OMe); 7.45 (q, $J=5.65$ Hz, $J_{H8-Sn}=0.72$ Hz, 1H, H_8); 8.83 (d, $J=5.65$ Hz, 1H, H_7); ^{13}C NMR ($CDCl_3$): δ 10.3 (CH_2); 12.6 (Me); 26.3 (CH_2); 28.1 (CH_2); 28.2 ($3Me_{tert\text{-butyl}}$); 38.8 (CMe_3); 52.7 (OMe); 115.8 (C_{py}); 117.6 (CH_{py}); 149.4 (CH_{py}); 152.6 (C_{py}); 166.2 (C_{py}); 175.1 (C_{py}); 177.1 (C_{py}). $C_{24}H_{41}N_3OSn$ (HRMS: 506.30).

3.2.3.5. 2-*tert*-Butyl-5-iodo-4-methoxypyrido[4,3-*d*]-pyrimidine (24). Metallation of **6** (50 mg, 0.23 mmol) according to the procedure B with *n*-BuLi 1.6 M (4 equiv., 0.58 mL), TMPH (4 equiv., 0.16 mL), $T=-78$ °C, followed by reaction with iodine (5 equiv., 292 mg) in solution with anhydrous THF (5 mL), $t=1$ h, gave after purification by column chromatography (silica, eluent: dichloromethane/ethyl acetate (9/1)) 60 mg (76%) of **24** as an yellow solid, mp=102–103 °C; ^{1}H NMR ($CDCl_3$): δ 1.35 (s, 9H, *tert*-butyl); 4.12 (s, 3H, OMe); 7.53 (d, $J=5.65$ Hz, 1H, H_8); 8.35 (d, $J=5.65$ Hz, 1H, H_7); ^{13}C NMR ($CDCl_3$): δ 29.4 ($3Me_{tert\text{-butyl}}$); 40.3 (CMe_3); 54.2 (OMe); 114.7 (C_{py}); 115.0 (C_{py}); 121.6 (CH_{py}); 150.3 (CH_{py}); 156.4 (C_{py}); 165.0 (C_{py}); 177.2 (C_{py}). Anal. calcd for $C_{12}H_{14}IN_3O$ (343.16): C, 42.00; H, 4.11; N, 12.24. Found: C, 41.87; H, 4.43; N, 12.18.

3.2.4. Metallation of 2-*tert*-butyl-4,6-dimethoxypyrido-[3,4-*d*]pyrimidine (4)

3.2.4.1. 2-*tert*-Butyl-5-(1-hydroxyethyl)-4,6-dimethoxy-pyrido[3,4-*d*]pyrimidine (25). Metallation of **4** (50 mg, 0.20 mmol) according to the procedure A with *n*-BuLi 1.6 M (4 equiv., 0.51 mL), TMPH (4 equiv., 0.14 mL), $T=-78$ °C, followed by reaction with acetaldehyde (5 equiv., 0.05 mL), $t=1$ h, gave after purification by

column chromatography (silica, eluent: petroleum ether/diethyl ether (5/5)) 51 mg (88%) of **25** as a glassy solid, mp<50 °C; ^{1}H NMR ($CDCl_3$): δ 1.36 (s, 9H, *tert*-butyl); 1.54 (d, J=6.8 Hz, 3H, *Me*CH); 4.05 (s, 3H, OMe); 4.09 (s, 3H, OMe); 4.19 (d, J=12.1 Hz, 1H, OH); 5.99 (m, 1H, C*H*OH); 8.83 (s, 1H, H_8); ^{13}C NMR ($CDCl_3$): δ 23.5 (Me); 29.5 ($3Me_{tert\text{-butyl}}$); 39.5 (CMe_3); 54.6 (2OMe); 66.3 (CHOH); 119.0 (C_{py}); 119.4 (C_{py}); 143.2 (C_{py}); 148.6 (CH_{py}); 158.5 (C_{py}); 166.0 (C_{py}); 171.1 (C_{py}). Anal. calcd for $C_{15}H_{21}N_3O_3$ (291.35): C, 61.84; H, 7.27; N, 14.42. Found: C, 61.91; H, 7.36; N, 14.15.

3.2.4.2. 2-*tert*-Butyl-5-(hydroxyphenylmethyl)-4,6-dimethoxypyrido[3,4-*d*]pyrimidine (26). Metallation of **4** (50 mg, 0.20 mmol) according to the procedure A with *n*-BuLi 1.6 M (4 equiv., 0.51 mL), TMPH (4 equiv., 0.14 mL), T=−78 °C, followed by reaction with benzaldehyde (4 equiv., 0.09 mL), t=1 h, gave after purification by column chromatography (silica, eluent: petroleum ether/diethyl ether (7/3)) 58 mg (81%) of **26** as a glassy solid, mp<50 °C; ^{1}H NMR ($CDCl_3$): δ 1.36 (s, 9H, *tert*-butyl); 3.93 (s, 6H, 2OMe); 4.44 (d, J=12.4 Hz, 1H, OH); 7.02 (d, J=12.4 Hz, 1H, C*H*OH); 7.18 (m, 5H, Ph); 8.92 (s, 1H, H_8); ^{13}C NMR ($CDCl_3$): δ 29.5 ($3Me_{tert\text{-butyl}}$); 39.6 (CMe_3); 54.4 (OMe); 54.8 (OMe); 70.2 (CHOH); 117.1 (C_{Ph}); 119.7 (C_{py}); 125.8 ($2CH_{Ph}$); 127.1 (CH_{Ph}); 128.4 ($2CH_{Ph}$); 143.4 (C_{py}); 144.2 (C_{py}); 149.8 (CH_{py}); 159.1 (C_{py}); 165.6 (C_{py}); 171.3 (C_{py}). Anal. calcd for $C_{21}H_{23}N_3O_3$ (353.42): C, 67.97; H, 6.56; N, 11.89. Found: C, 68.11; H, 6.85; N, 12.04.

3.2.4.3. 2-*tert*-Butyl-4,6-dimethoxy-5-phenylthiopyrido-[3,4-*d*]pyrimidine (27). Metallation of **4** (50 mg, 0.20 mmol) according to the procedure A with *n*-BuLi 1.6 M (4 equiv., 0.51 mL), TMPH (4 equiv., 0.14 mL), T=−78 °C, followed by reaction with diphenyl disulfide (4 equiv., 176 mg) in solution with anhydrous THF (5 mL), t=1 h, gave after purification by column chromatography (silica, eluent: dichloromethane) 55 mg (77%) of **27** as a glassy solid, mp=71–72 °C; ^{1}H NMR ($CDCl_3$): δ 1.35 (s, 9H, *tert*-butyl); 3.87 (s, 3H, OMe); 3.92 (s, 3H, OMe); 7.02 (m, 3H, Ph); 7.10 (m, 2H, Ph); 8.91 (s, 1H, H_8); ^{13}C NMR ($CDCl_3$): δ 29.5 ($3Me_{tert\text{-butyl}}$); 39.6 (CMe_3); 54.3 (OMe); 55.2 (OMe); 107.6 (C_{py}); 123.4 (C_{Ph}); 125.9 (CH_{Ph}); 127.8 ($2CH_{Ph}$); 129.0 ($2CH_{Ph}$); 138.4 (C_{py}); 143.7 (C_{py}); 150.5 (CH_{py}); 161.6 (C_{py}); 165.9 (C_{py}); 171.7 (C_{py}). Anal. calcd for $C_{19}H_{21}N_3O_2S$ (355.46): C, 64.20; H, 5.95; N, 11.82; S, 9.02. Found: C, 64.11; H, 6.09; N, 11.73; S, 8.96.

3.2.4.4. 2-*tert*-Butyl-5-(tri-*n*-butylstannyl)-4,6-dimethoxypyrido[3,4-*d*]pyrimidine (28). Metallation of **4** (50 mg, 0.20 mmol) according to the procedure A with *n*-BuLi 1.6 M (4 equiv., 0.51 mL), TMPH (4 equiv., 0.14 mL), T=−78 °C, followed by reaction with tri-*n*-butylstannyl chloride (4 equiv., 0.23 mL), t=1 h, gave after purification by column chromatography (silica, eluent: petroleum ether/diethyl ether (9/1)) 107 mg (98%) of **28** as an oil; ^{1}H NMR ($CDCl_3$): δ 0.78 (t, J=7.2 Hz, 9H, 3Me); 1.03 (m, 6H, $3CH_{2SnBu3}$); 1.24 (m, 6H, $3CH_{2SnBu3}$); 1.37 (s, 9H, *tert*-butyl); 1.40 (m, 6H, $3CH_{2SnBu3}$); 3.89 (s, 3H, OMe); 4.04 (s, 3H, OMe); 8.83 (t, J_{H8-Sn}=2.9 Hz, 1H, H_8); ^{13}C NMR ($CDCl_3$): δ 12.0 (Me); 12.7 ($SnCH_2$); 26.43 ($SnCH_2CH_2$); 28.15 (CH_2Me); 28.2 ($3Me_{tert\text{-butyl}}$); 38.2 (CMe_3); 52.6 (OMe); 52.9 (OMe); 112.5 (C_{py}); 127.1 (C_{py}); 141.6 (C_{py}); 148.9 (CH_{py}); 164.9 (C_{py}); 165.0 (C_{py}); 168.9 (C_{py}). Anal. calcd for $C_{25}H_{43}N_3O_2Sn$ (536.33): C, 55.99; H, 8.08; N, 7.83. Found: C, 55.91; H, 7.95; N, 7.97.

3.2.4.5. 2-*tert*-Butyl-5-iodo-4,6-dimethoxypyrido[3,4-*d*]-pyrimidine (29). Metallation of **4** (50 mg, 0.20 mmol) according to the procedure B with *n*-BuLi 1.6 M (4 equiv., 0.51 mL), TMPH (4 equiv., 0.14 mL), T=−78 °C, followed by reaction with iodine (4 equiv., 205 mg) in solution with anhydrous THF (5 mL), t=1 h, gave after purification by column chromatography (silica, eluent: dichloromethane) 58 mg (77%) of **29** as a white solid, mp=87–88 °C; ^{1}H NMR ($CDCl_3$): δ 1.35 (s, 9H, *tert*-butyl); 4.01 (s, 3H, OMe); 4.08 (s, 3H, OMe); 8.77 (s, 1H, H_8); ^{13}C NMR ($CDCl_3$): δ 29.5 ($3Me_{tert\text{-butyl}}$); 39.7 (CMe_3); 53.8 (OMe); 56.0 (OMe); 124.5 (C_{py}); 126.2 (C_{py}); 143.4 (C_{py}); 149.8 (CH_{py}); 160.6 (C_{py}); 164.2 (C_{py}); 171.2 (C_{py}). Anal. calcd for $C_{13}H_{16}N_3O_2I$ (343.16): C, 41.84; H, 4.32; N, 11.26. Found: C, 41.98; H, 4.57; N, 11.67.

3.2.5. Metallation of 2-*tert*-butyl-6-chloro-4-methoxypyrido[2,3-*d*]pyrimidine (2)

3.2.5.1. 2-*tert*-Butyl-6-chloro-4-methoxy-7-phenylthiopyrido[2,3-*d*]pyrimidine (30). Metallation of **2** (50 mg, 0.20 mmol) according to the procedure A with *n*-BuLi 1.6 M (4 equiv., 0.49 mL), TMPH (4 equiv., 0.14 mL), T=−78 °C, followed by reaction with diphenyl disulfide (4 equiv., 173 mg) in solution with anhydrous THF (5 mL), t=1 h, gave after purification by column chromatography (silica, eluent: (1) dichloromethane, (2) petroleum ether/diethyl ether (5/5)) 27 mg (39%) of **30** as a white solid, mp=204–205 °C; ^{1}H NMR ($CDCl_3$): δ 1.30 (s, 9H, *tert*-butyl); 4.07 (s, 3H, OMe); 7.41 (m, 3H, Ph); 7.58 (m, 2H, Ph); 8.18 (s, 1H, H_5); ^{13}C NMR ($CDCl_3$): δ 29.5 ($3Me_{tert\text{-butyl}}$); 40.4 (CMe_3); 54.8 (OMe); 107.3 (C_{py}); 126.6 (C_{py}); 128.6 (C_{Ph}); 129.8 ($2CH_{Ph}$); 130.0 (CH_{Ph}); 131.4 (CH_{py}); 135.9 ($2CH_{Ph}$); 158.2 (C_{py}); 166.5 (C_{py}); 166.9 (C_{py}); 177.6 (C_{py}). Anal. calcd for $C_{18}H_{18}ClN_3OS$ (359.88): C, 60.08; H, 5.04; N, 11.68; S, 8.91. Found: C, 60.11; H, 5.18; N, 11.56; S, 8.44.

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Syntheses and electronic properties of the nickel and palladium complexes of the octaethylporphyrin(M1)–(dihexylbithiophene)$_n$–octaethylporphyrin(M2) system [OEP(M1)–(DHBTh)$_n$–OEP(M2)] connected with the diacetylene linkage. A methodology for molecular design of the particular electronic structure

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Abstract—The palladium complexes of highly extended π-electronic conjugation system, octaethylporphyrin(Pd)–(dihexylbithiophene)$_n$–octaethylporphyrin(Pd) [OEP(Pd)–(DHBTh)$_n$–OEP(Pd), n=1–6], were synthesized, in which all the chromophores are connected with diacetylene linkage. The unsymmetrical derivatives of OEP(Ni)–DHBTh–OEP(Pd) were also successfully synthesized. Electronic properties of these symmetrical and unsymmetrical complexes were conclusively described, as compared with those of OEP(Ni)–(DHBTh)$_n$–OEP(Ni). Based on the structure elements, a methodical guiding principle for molecular design of the particular electronic structure will be proposed.

1. Introduction

In recent years, a great deal of effort has been paid for the construction of the oligomers and arrays on the basis of heterocyclic aromatic nuclei such as porphyrin[1] and thiophene,[2] by virtue of their high susceptibilities to the light and electronic stimulations, for enhancement of the particular properties as the material functions. On the other hand, a variety of technological researches of the material functions has been intensively demonstrated to control and tune their function mobilities and efficiencies purposively.[3] The optoelectronic devices well organized from the results based on such enhancement and control methodologies would be most promising as the practical materials to support the everyday life in the present photonics society. Especially in the latter researches, the fundamental intention is to establish the methodical guiding principle for the development of new organic materials together with the molecular design.

Previously, we studied the structural properties of the oligo(3-hexylthiophene) derivatives [oligo(HTh)$_m$, m=1–8] from the viewpoint of the molecular planarity for π-electronic conjugation and showed that the internal bithiophene unit (IBU) of oligo(HTh)m plays an important role in construction of the principal electronic structure.[4] When two HTh rings are coupled at 2(5)-position, the three orientationally isomeric dihexylbithiophenes (DHBTh) with head-to-head (HH), head-to-tail (HT) and tail-to-tail (TT) orientations are produced as the fundamental IBU. One of the structure elements for deformation from the π-electronic conjugation planarity of the DHBTh derivative is substantially caused by the orientation modes of DHBTh, mainly due to the steric repulsion between the hexyl substituent and the sulfur atom on the neighboring HTh moiety.[5] In fact, the MM2 calculation indicates that the π-electronic conjugation planarities of the fundamental DHBTh units increase in order of the orientation modes; HH<HT<TT,[6] which brings about the respective molecular peculiarities not only

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in their electrostatic properties but also in their chemical reactivities and processes as a consequence.[7] In particular, from the studies of the donor–acceptor DHBTh derivatives was exhibited experimentally a structure–property relationship of the higher third-order nonlinear optical (NLO) behavior with the more conjugation planarities, though qualitatively.[8]

Very recently, in connection with a wide-ranging utility of the least-bulky, rigid and straight linkage of acetylene,[9] an extended π-electronic conjugation system of the DHBTh derivatives **1** and **3** combined with the nickel (Ni) complex of octaethylporphyrin [OEP(Ni)] has been synthesized to figure out the feature as a function unit for optoelectronic devices,[10] in which all the chromophores are connected with 1,3-butadiyne (diacetylene) (Chart 1). In the OEP(Ni)–DHBTh–OEP(Ni) system, these DHBTh isomers including the HT isomer **2** were also found to afford the characteristic absorption spectra of the OEP nuclei in a region of 400–500 nm, but to split their Soret bands regularly into two main bands in response to the respective orientations of DHBTh.[11] Yet, the electrochemical experiment clearly showed that the electron-releasing abilities of **1**–**3** change regularly in order of the π-electronic conjugation planarities of DHBTh.

These preliminary investigations of the DHBTh derivatives evidently show that the molecular peculiarities are closely related with the orientation of DHBTh, though the theoretical interpretation of the orientation effect of DHBTh on their electronic properties remains unsolved. Furthermore, since the orientational effect of DHBTh can be expanded to those of all the dialkylbithiophenes (DABTh), the particular fundamental DABTh unit could define the particular π-electronic conjugation planarity and thus the particular electronic property. In other words, the particular electronic property could be constructed by introducing the adequate DABTh constituent into the particular π-electronic conjugation system purposively. Therefore, the studies along this line would provide a new tool for molecular design of the particular electronic structures of the DABTh derivatives.

In this study, the palladium (Pd) complexes **4** and **5**, described as OEP(Pd)–DHBTh–OEP(Pd), have been newly synthesized, in which the central DHBTh constituent possesses HH and TT orientation modes (Chart 1). Since the behavior of the HT isomer **2** can be deduced to be intermediate between those of **1** and **3**,[11] the present studies are focused on the orientational DHBTh isomers with the lowest and highest π-electronic conjugation planarities. Furthermore, in the synthesis of **4** and **5**, the more extended DHBTh compounds describable as OEP(Pd)–$(DHBTh)_n$–OEP(Pd) (n=2–6; **16**–**20** for **4** and **21**–**25** for **5**) were

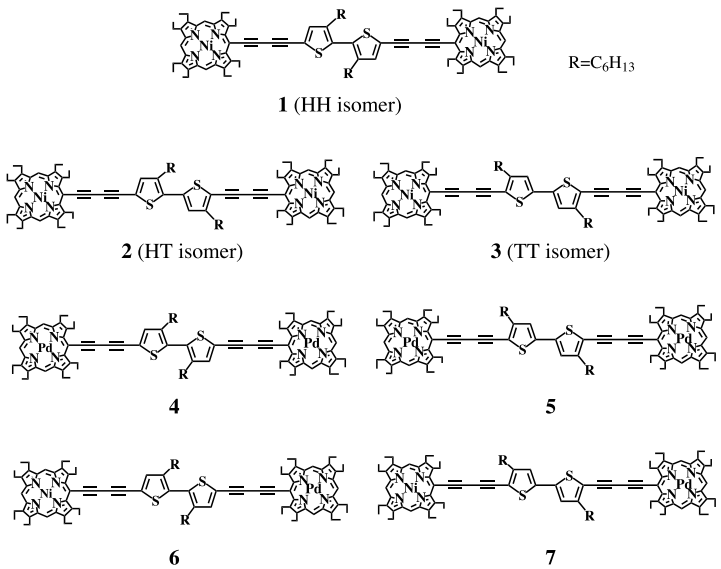
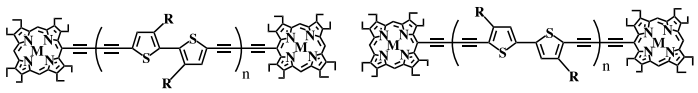


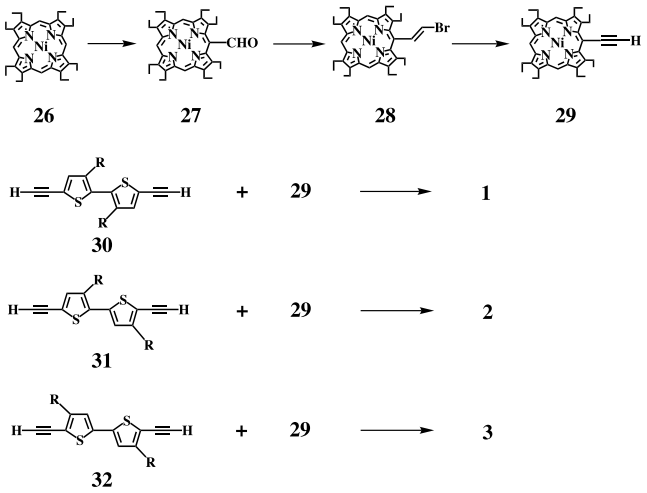
Chart 1.



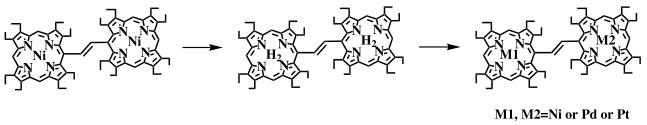
M=Ni	M=Pd
8: n=2	**16:** n=2
9: n=3	**17:** n=3
10: n=4	**18:** n=4
11: n=5	**19:** n=5
	20: n=6

M=Ni	M=Pd
12: n=2	**21:** n=2
13: n=3	**22:** n=3
14: n=4	**23:** n=4
15: n=5	**24:** n=5
	25: n=6

Chart 2.



Scheme 1.



Scheme 2.

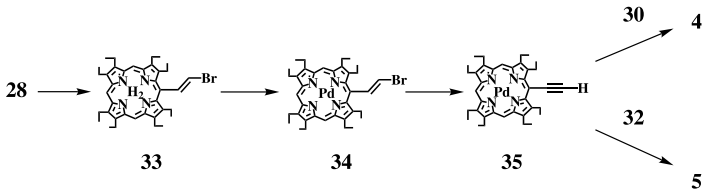
simultaneously obtained, similar to the corresponding Ni complexes (Chart 2). In connection with an intensive research on the optoelectronic molecular devices,[1–3] as a next stage toward our applicative purposes, we also planned to introduce the unsymmetrical element electronically into the symmetrical OEP(M)–DHBTh–OEP(M) system in order to seek for the anisotropic energy- and/or electron-transfer functionality. Among several methodologies for unsymmetrization of the molecule, we originally designed the OEP(Ni)–DHBTh–OEP(Pd) derivative, and were successful in the synthesis of **6** and **7** (Chart 1).[12]

Here, we wish to report the syntheses of the title compounds and to describe their structural and electronic properties conclusively. Then, we wish to discuss about the properties of the OEP(Ni)–DHBTh–OEP(Pd) system to figure out its hybridism appearance as a function unit for optoelectronic molecular devices, as compared with those of the symmetrical OEP(Ni/Pd)–DHBTh–OEP(Ni/Pd) ones. Finally, in relation to the molecular design for the electronic device, a methodical guiding principle for the particular electronic structure in the OEP(M1)–$(DHBTh)_n$–OEP(M2) system will be introduced, based on the structure elements such as orientation and number of DHBTh, incorporated metals and symmetry of molecule.

2. Results and discussion

2.1. Synthesis of OEP(M1)–$(DHBTh)_n$–OEP(M2)

As reported previously,[10,11] the OEP(Ni)–DHBTh–OEP(Ni) derivatives **1**–**3** were synthesized by cross-coupling reactions between the OEP(Ni) ethynyl compound **29** and the corresponding DHBTh diethynyl compounds **30**–**32**, as shown in Scheme 1. Thus, the synthesis of the compounds **4**–**7** were originally planned by incorporation of the respective metal ions into the free-bases from **1** and **3**, according to our conventional procedures for the synthesis of the OEP(M1)–OEP(M2) complexes connected with the vinylene linkage (Scheme 2).[13] Denickelation of **1** and **3** to the corresponding free-bases, however, was entirely unsuccessful under the ordinary reaction conditions,[14] producing hardly soluble materials which possess no OEP framework. This result is probably attributed to an inherent property of the diacetylene linkage, which is unstable under the severely acidic conditions. On one hand, the ethynyl OEP(Pd) **35** was successfully derived from the bromovinyl OEP(Ni) **28**. As shown in Scheme 3, the free-base **33**[15] obtained by treatment of **28** with conc. sulfuric acid was fairly unstable and thus without purification was provided for subsequent metalation with palladium(II) acetate [$Pd(OAc)_2$] to the bromovinyl OEP(Pd) **34**. Dehydrobromination of **34** with sodium hydride–dimethylsulfoxide (NaH–DMSO) in dimethoxyethane readily occurred to



Scheme 3.

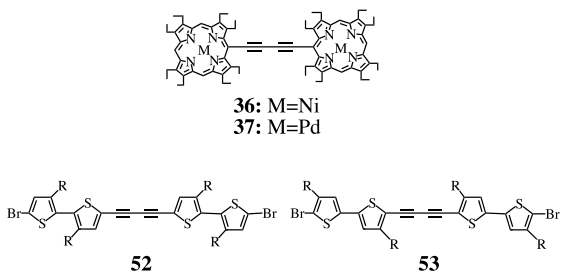
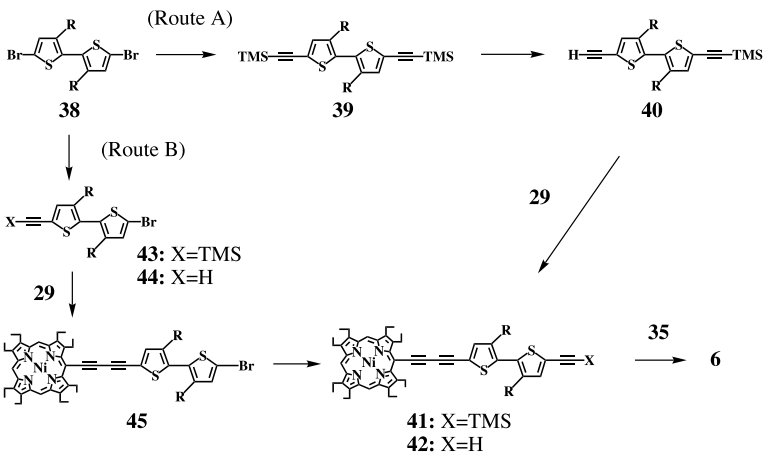


Chart 3.

afford **35** in 60% yield. Then, in case of the symmetrical OEP(Pd)–DHBTh–OEP(Pd) derivatives, similarly for **1**,[10] cross-coupling reaction of **35** with the HH(DHBTh) ethynyl compound **30** under the Eglinton conditions[16] afforded the product **4** in 9% yield as reddish purple microcrystals (Scheme 3). In this reaction, the more extended OEP(Pd)–$HH(DHBTh)_n$–OEP(Pd) derivatives **16**–**20** also formed in respective yields of 6–8%, reflecting the higher reactivity of the terminal acetylene in **30** than that in **35**. In the same way, the reaction of **35** with the TT(DHBTh) ethynyl compound **32** afforded the products of OEP(Pd)–$TT(DHBTh)_n$–OEP(Pd); **5** (14%) and **21**–**25** (2–14%). In both coupling

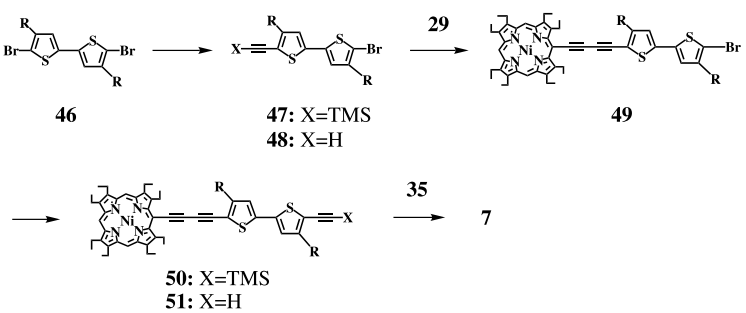


Scheme 4.

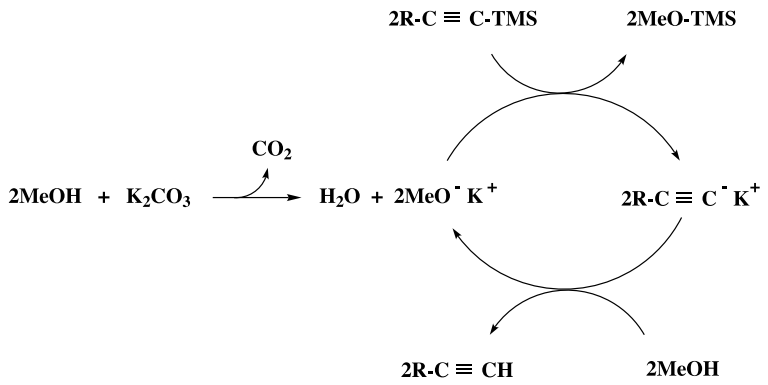
reactions, the diacetylene-group connected OEP(Pd) dimer **37** simultaneously formed in quantity as by-product (Chart 3). Even though these reaction mixtures seemed to be complicated, all the products could be separated in pure forms by column chromatography on silica gel (SiO_2) with hexane–$CHCl_3$ (7:3), being eluted from the respective fractions in order of the larger molecular weights.

Since the denickelation from **1** and **3** to the corresponding free-bases met without success, the synthetic route for the unsymmetrical derivatives **6** and **7** was newly developed, in which the introduction of the terminal acetylene function into the synthetic intermediate was a key step. As summarized in Schemes 4 and 5, the synthetic principle is to employ the coupling reaction of the OEP(Pd) acetylene **35** with the counterpart OEP(Ni)–DHBTh acetylene **42** or **51**. As to the synthetic route for HH isomer **6**, the two possibilities (Routes A and B) for the key compound **41** were first examined. One is the reaction of the OEP(Ni) acetylene **29** with the HH(DHBTh) terminal acetylene **40**. The compound **40** in which an additional acetylenic function is protected with trimethylsilyl (TMS) group should be led by partial hydrolysis from the DHBTh bis(TMS-ethynyl) compound **39**.[17] However, it is generally hard to terminate the hydrolysis of oligo(TMS-ethynyl) compounds at a particular stage. In fact, under the conditions for hydrolysis of **39** with 1 M amount of K_2CO_3 in methanol (MeOH), only isolated product was the compound **30** completely hydrolyzed. After several examinations, the compound **40** was barely obtained under the very limited conditions; one-tenth molar amount of K_2CO_3, high-dilution in hexane–MeOH (4:1) and short-time reaction at room temperature. When the terminal acetylene **40** thus obtained was coupled with **29** in the presence of copper(II) acetate [$Cu(OAc)_2$] in a mixture of MeOH–pyridine (Py) (1:5),[10] to be surprised, the products were mostly the OEP(Ni)–$(DHBTh)_n$–OEP(Ni) derivatives (n=0–3), together with some amount recovery of **29**. This result also indicates that the TMS-protecting group removes very fast from **40** even under the employed Eglinton conditions, similar to alkaline hydrolysis of **39**, through a plausible mechanism that removal of the TMS group accelerates in a methoxide anion-mediated cycle, as depicted in Scheme 6. However, MS and ^1H NMR spectral measurements for a small amount of the residue clearly indicated an existence of the desired compound **41** (MW=1068.23). Taking the above expectations into consideration, the coupling reaction between **29** and **40** in the presence of $Cu(OAc)_2$ in a sole solvent of Py was carried out, successfully affording **41**. Nevertheless, the yield of **41** in this reaction was very low to be only 7%. It might also be concluded to give evidence of removal of the TMS group in the course of the reaction somehow, from the fact that the rest products were accompanied by a fairly large quantity of the extended OEP(Ni)–$(DHBTh)_n$–OEP(Ni) derivatives. In this respect, it should be noted that Py is basic enough to attack the TMS group on the ethynyl function, though not so strong as methoxide anion. In addition, the isolated yield of the DHBTh terminal acetylene **40** by the partial hydrolysis of **39** was 20% at best and the hydrolysis itself was very poor in reproducibility.

Then, in consequence of the preliminary investigations, some disadvantages in Route A for **41** were cleared up by



Scheme 5.

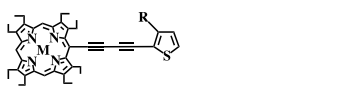


Scheme 6.

taking another synthetic Route B via the OEP(Ni)–DHBTh bromide **45**. Thus, the HH(DHBTh) dibromide **38**[7b] was transformed into the mono(TMS-ethynyl) bromide **43** in a moderate yield, which was readily hydrolyzed to afford the terminal acetylene **44**. The cross-coupling reaction between **29** and **44** in a molar ratio of 1:5 afforded **45** in 48% yield, together with the diacetylene-group connected HH(DHBTh) dimer **52** (Chart 3). Successively, the bromo compound **45** was treated with TMS-acetylene (TMSA) to give the desired TMS-ethynyl compound **41** in 63% yield, which was hydrolyzed quantitatively to afford the OEP(Ni)–DHBTh terminal acetylene **42**. Finally, the terminal acetylene **42** was nimbly provided for coupling with an excessive molar amount of **35**, affording the HH isomeric derivative **6** in 35% yield, together with the respective OEP(M) dimers **8** (8%) and **37** (10%). Similarly, as shown in Scheme 5, the TT(DHBTh) terminal acetylene **51** was smoothly obtained, through a series of reactions via the OEP(Ni)–TT(DHBTh) bromide **49** starting from the corresponding dibromide **46**.[7b] Then, the TT isomer **7** could be led by an oxidative coupling of the terminal acetylenes **35** and **51**. Compounds **6** and **7**, the first example of the unsymmetrical OEP(M1)–DHBTh–OEP(M2) system, could readily be separated by column chromatography on silica gel with hexane–$CHCl_3$ (7:3), both of which are fairly stable and are recrystallized from $CHCl_3$–MeOH to form dark bluish green microcrystallines.[12]

Furthermore, in order to verify the fundamental constituents responsible for the respective electronic structures peculiar to the OEP(M)–$(DHBTh)_n$–OEP(M) system, the diacetylene-group connected OEP(M) derivatives **55**, **56** and **57** were synthesized by the similar ways (see Chart 4).

In view of our applicative purposes, the synthetic success of the OEP(Ni)–DHBTh terminal acetylenes **42** and **51** stimulates us strongly to investigate the new triad systems. In practice, the present synthetic methodology could introduce a variety of the π-electronic component (π-EC) as the function moiety purposively to construct the OEP(M)–DHBTh–(π-EC) derivatives (Chart 5).[18] Also, it is worthy of note that not only all the chromophores are well-defined and thus the structure–property relationships



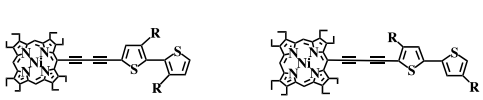


Chart 4.

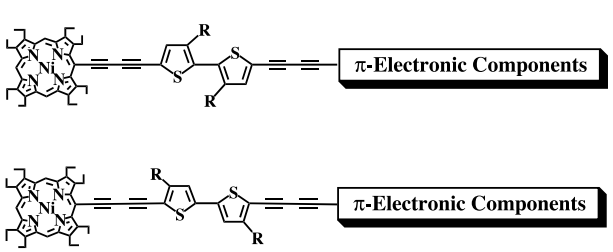
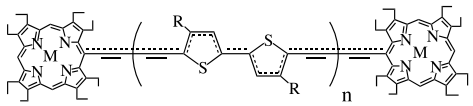


Chart 5.



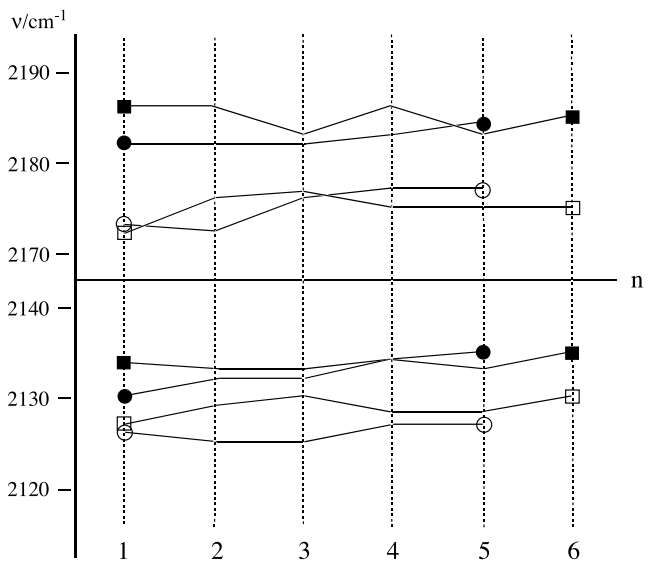


Figure 1. Plots of wave-numbers for the OEP(M)–$(DHBTh)_n$–OEP(M) derivatives in a region between 2120 and 2190 cm^{-1} against the number of DHBTh. Filled circle for a series of the Ni complexes with HH orientation. Open circle for a series of the Ni complexes with TT orientation. Filled square for a series of the Pd complexes with HH orientation. Open square for a series of the Pd complexes with TT orientation.

of the functionalities are precisely analyzable (vide infra), but also further sophisticated optoelectronic cooperations are likely to arise from the interactions of such versatile π-EC with OEP(M) through the DHBTh constituents.

2.2. Structural properties of the OEP(M1)–$(DHBTh)_n$–OEP(M2) system

Molecular structures of the title compounds were determined mainly by MS, IR and ^{1}H NMR spectral measurements as well as elemental analysis. MS spectra of the products obtained in the present work were taken by either EI, FAB or ESI-FT-ICR MS technical method, exhibiting fairly simple and regular fragmentation patterns.[11] However, the symmetrical and unsymmetrical derivatives neither showed particular differences in fragmentation process, except for the fragmentation groups (FG) due to the nature of incorporated metals M1 and M2, nor did the corresponding isomers with HH and TT orientation modes. IR spectra of **1**–**7** were also relatively simple and similar to each other. Their spectral patterns were scarcely affected by the symmetry element, but a characteristic feature of these structures in stretching vibrations due to the diacetylene linkage reflected the orientation of DHBTh. The OEP(M1)–$(DHBTh)_n$–OEP(M2) derivatives including **8**–**25** afforded the two medium peaks at around ν=2130 and 2180 cm^{-1} (Fig. 1). The TT series exhibited a fairly low wave-number shift, as compared with the HH series, reaching a maximum difference of 14 cm^{-1} between **6** and **7**. This result clearly indicates that the TT series induce a cumulated character into the diacetylene linkage preferably (vide infra).

^{1}H NMR spectra for HH isomeric series of **1**, **4** and **6** are shown in Figure 2 and the chemical shifts for selected protons of **1**–**25** are summarized in Table 1. Similar to the Ni complexes **1** and **3**, the OEP(Pd)–DHBTh–OEP(Pd) derivatives **4** and **5** exhibit the spectra composed of two singlet peaks due to *meso*-protons (*meso*-H) and one singlet peak due to Th-protons (Th-H). Spectra also clearly show that one of four sets for methylene-H belonging to the OEP ring resonates at the lower field separately due to the ring current effect of the diacetylene linkage, supporting their symmetrical and rigid frameworks. But, this spectral simplicity leads to a useful probe for the structural analysis; the chemical shift of *meso*-H is regarded as a measure of the diamagnetic ring current effect of OEP(M) and the chemical shift of Th-H as a measure of the anisotropic effect from OEP(M).[19] It is apparent that the ring current effects of OEP(M) weaken in consequence of the reformed conjugation system with the diacetylene linkage more or less, shifting *meso*-H to the high field by ca. 0.35 ppm for the diacetylene-group connected OEP(Ni) dimer **36** based on OEP(Ni) and by 0.1–0.15 ppm for the corresponding OEP(Pd) dimer **37** based on OEP(Pd), respectively

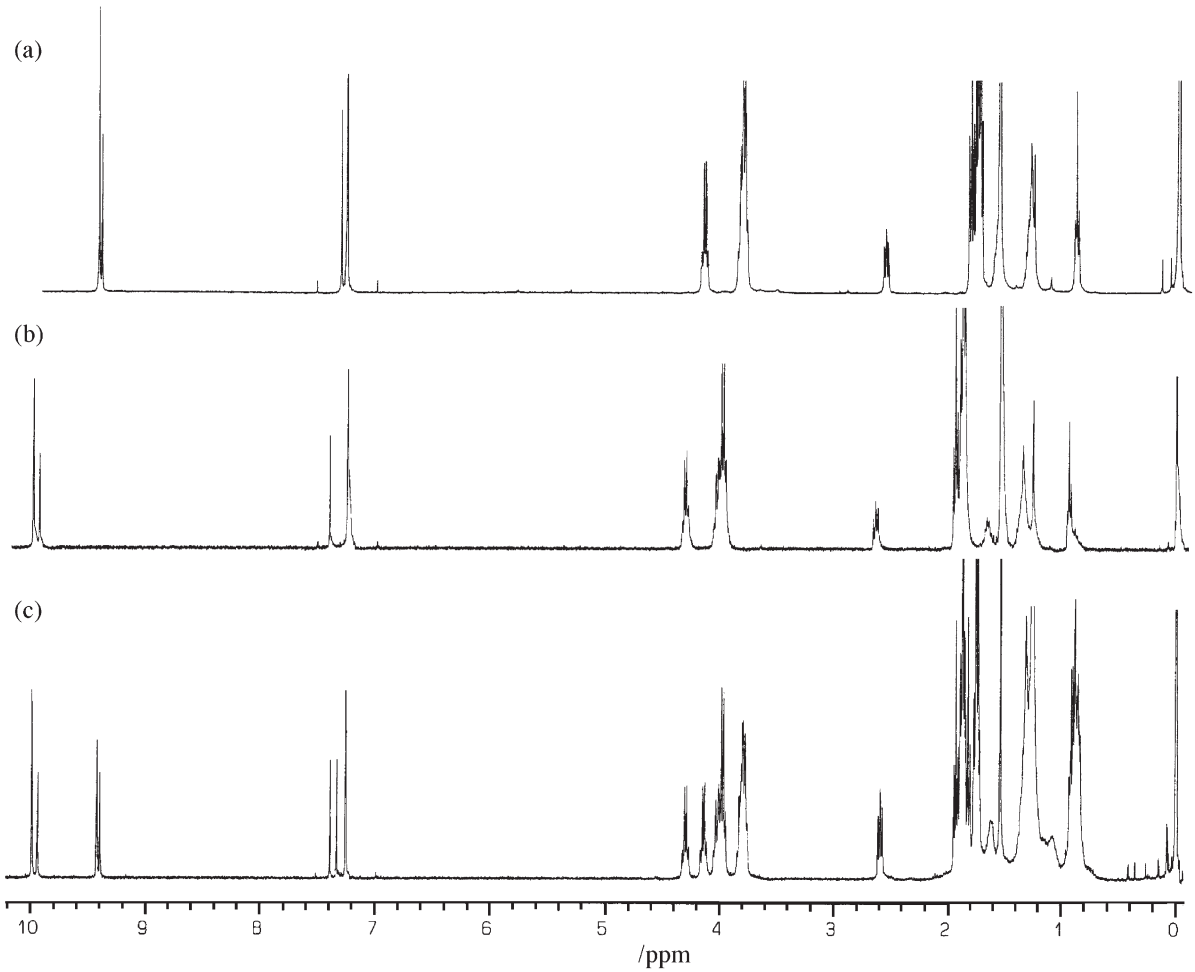


Figure 2. ^{1}H NMR spectra of (a) **1**, (b) **4** and (c) **6** (400 MHz, $CDCl_3$).

Table 1. Chemical shifts (δ/ppm) of the selected protons in **1**–**25** (400 MHz, $CDCl_3$)

Compounds	*meso*-H	Th-H	Compounds	*meso*-H	Th-H	Compounds	*meso*-H	Th-H
1	9.42	7.33	**8**	9.42	7.29, 7.23	**16**	10.00	7.37, 7.25
	9.40			9.39			9.95	
3	9.41	7.00	**9**	9.42	7.28–7.21	**17**	9.98	7.37–7.22
	9.39			9.39			9.93	
4	10.00	7.41	**10**	9.42	7.28–7.21	**18**	9.98	7.37–7.21
	9.95			9.39			9.93	
5	10.02	7.11	**11**	9.42	7.28–7.21	**19**	9.99	7.37–7.21
	9.96			9.39			9.94	
6	9.98	7.38	**12**	9.41	6.95, 6.93	**20**	10.00	7.05, 7.02
	9.93	7.33		9.38			9.95	
	9.42		**13**	9.42	6.98–6.94	**21**	9.99	7.05–6.97
	9.39			9.39			9.94	
7	10.02	7.07	**14**	9.42	6.96–6.94	**22**	10.01	7.04–6.96
	9.95	7.06		9.39			9.96	
	9.42		**15**	9.42	7.00–6.94	**23**	9.99	7.05–6.96
	9.39			9.39			9.94	
						24	10.00	7.05–6.96
							9.95	
						25	10.00	7.05–6.96
							9.96	

(Chart 6). In contrast with the diacetylene linkage, when the DHBTh constituent is incorporated into **36** and **37** to form **1** and **4**, *meso*-H for both **1** and **4** are found almost unchanged from those of **36** and **37**, appearing at δ=9.42 and 9.40 for **1** and δ=10.00 and 9.95 for **4**. This result indicates that the ring current effect of OEP(M) is reduced by the diacetylene linkage intensively, but not by the DHBTh constituents substantially. Yet, Th-H for the HH derivatives **1** and **4** appeared at the lower field in common by ca. 0.3 ppm than the corresponding ones for the TT isomers **3** and **5**, due to the greater anisotropic effects of the diacetylene linkage as well as the OEP(M) ring on Th-H of the former group. Except for one finding where the anisotropic effect of OEP(Pd) is more intensive than that of OEP(Ni) to affect Th-H of the present system absolutely by ca. 0.1 ppm due to its greater ring current, these results conclude that the tendency in chemical shift changes is the same in the present system, regardless of the orientation of DHBTh and the incorporated metals, in a quantitative sense as well.

On the other hand, the unsymmetrical OEP(Ni)–DHBTh–OEP(Pd) derivative **6** exhibited the characteristic spectrum of both structural features of **1** and **4**, simply affording pairs of the corresponding peaks for almost all the protons including alkyl substituent ones. It is interesting to realize that *meso*-H in **6** appear at the very similar positions to the corresponding *meso*-H in **1** and **4**, though Th-H in **6** take a middle position between those of **1** and **4** (vide infra). Similarly to the conclusion from **1** and **4**, this result indicates that the compound **6** is not perturbed enough to reform to a certain hybridized structure between **1** and **4** by unsymmetrization of this type, but possesses a simply combined structure between them. This spectral appearance is also the same for the TT isomer **7** which is formally regarded as a hybrid between **3** and **5**. In the strict sense, the HT(DHBTh) derivative **2** would also be regarded as an unsymmetrical compound, though its terminal chromophores are both OEP(Ni) (Chart 6). The compound **2** also possesses the same OEP(Ni) ring currents and shows the spectrum reflecting an in-between structural property of **1** and **3**.[11] Therefore, all the derivatives **1**–**7** in the present system can be concluded to possess the fairly simple skeletal features, regardless of the symmetry of molecule, with the respective ring currents of OEP(M) in **36** and **37** remaining to a great extent. However, it should be noted that a remarkable difference in the electronic properties appears in such a simple skeletal system reflecting those structural elements (vide infra).

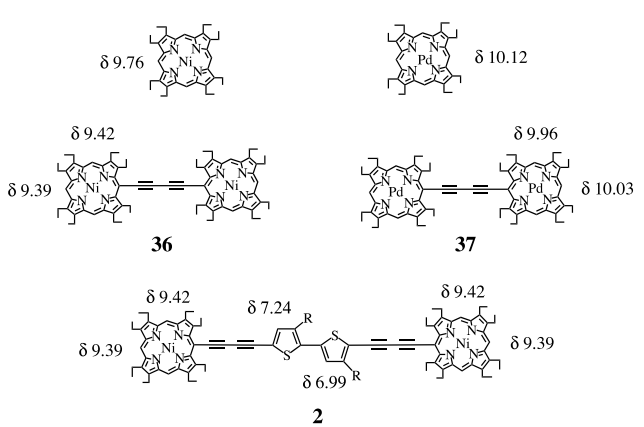


Chart 6.

One dimensionally extended OEP(M)–$(DHBTh)_n$–OEP(M) derivatives (**8**–**25**) also bring about some finding for the present peculiar system. As derived from the previous study,[11] it is further confirmed that the Pd complexes as well as the Ni ones show the unique spectral features with simple regularity. Thus, it is shown that all the compounds **8**–**25** in both HH and TT series possess the ring currents of OEP(M) almost the same as those for **36** and **37**, regardless of the number of DHBTh, exhibiting *meso*-H at around 9.4 ppm for the Ni complexes and 9.9–10 ppm for the Pd complexes (Table 1). This result exactly indicates that all the DHBTh constituents in **8**–**25** have no abilities to perturb the ring current of OEP(M), similarly to the case for **1**–**7**. Such a structural property indicates that the area of influence from the anisotropic effect of OEP(M) could be estimated accurately by the chemical shift analysis of Th-H,

because all the DHBTh constituent are fixed both independently and regularly with a rigid diacetylene linkage in one direction. The chemical shift differences of Th-H in the present system are not so large, but all the peaks can be unmistakably assigned to the respective ones. Chemical shifts of Th-H in the Ni complex **11** (n=5) and the Pd complex **20** (n=6), for example, are plotted in Figure 3. Although ring current models for prediction of the chemical shifts has been proposed,[20] it is clearly shown that the anisotropic effect from the OEP(M) ring current in the present system decreases exponentially in distance along the rod direction, in accordance with Johnson–Bovey correlation. Taking molecular model examinations into consideration, the anisotropic effect of the OEP(Ni) ring terminated at the third Th-H (Hc) which is estimated to lie at 25 Å from the nearer OEP(Ni) ring. On the other hand, the anisotropic effect of the OEP(Pd) ring proves to extend up to the fourth Hd due to its greater ring current, which is placed ca. 30 Å apart from the nearer OEP(Pd) ring.

These results conclude that the OEP(M)–$(DHBTh)_n$–OEP(M) system behaves in the unique skeletal features where both OEP(M) and DHBTh constituents are simply combined with the rigid diacetylene linkage and thus all the Th-H respond regularly to the magnetical stimulation, regardless of the orientation of DHBTh. Accordingly, as one of the potential utilities, the present system could be shown to be a molecular scale for quantitative estimation of the particular properties such as ^{1}H NMR and electronic absorption spectral behaviors.

2.3. Electronic properties of the OEP(M1)–$(DHBTh)_n$–OEP(M2) system

Electronic absorption spectral measurements were performed at 25 °C in $CHCl_3$. The spectra for HH series of the complexes **1**, **4** and **6** and those for TT series of the corresponding complexes **3**, **5** and **7** are shown in Figures 4 and 5, respectively. As contrasted with high similarity in the skeletal features between **1**–**7**, absorption spectra were characteristic of each series. In both series, the absorption bands of the Pd complexes proved to shift to the shorter wavelengths and to be slightly sharper, as compared with those of the corresponding Ni complexes, with a tendency that the longer wavelength bands, Q bands, are much sensitive to the incorporated metal.

In case of the symmetrical OEP(M)–DHBTh–OEP(M) system, the spectra exhibited the characteristic features reflecting the orientation of DHBTh, to afford a simple conclusion that the HH isomers afford almost one broad Soret bands, while the TT isomers exhibit the two splitting Soret bands with clear maxima (λ_1 and λ_2).[10] On the other hand, based on the result from the ^{1}H NMR spectral study, the unsymmetrical OEP(Ni)–DHBTh–OEP(Pd) system **6** and **7** were expected to show in-between spectra of the symmetrical Ni and Pd complexes. In fact, in terms of molecular skeleton, another unsymmetrical HT isomer **2** clearly exhibited the mean spectrum between **1** and **3**.[11] Also, compounds **6** and **7** possess similar absorptions over the spectral regions of the symmetrical ones **1/4** and **3/5**, respectively, with the characteristic features due to the orientation element remaining more or less. However, the vibrational structures and maxima of Soret and Q bands in the respective spectra were found rather to exhibit the feature of the OEP(Pd) constituent in both **6** and **7**, which is much eminent in the TT isomer **7**. These results might be attributed to the stability of the respective OEP(M) rings due to the greater back-donation interaction of the heavier M(II) ion with the OEP ring system, which induces OEP(Pd) to be isolated much intensively from an extension of the π-electronic conjugation,[21] as has been also observed in the vinylene-group connected OEP(M) oligomers.[13,22] Conversely, it indicates that the OEP(Ni) ring is much mobile to

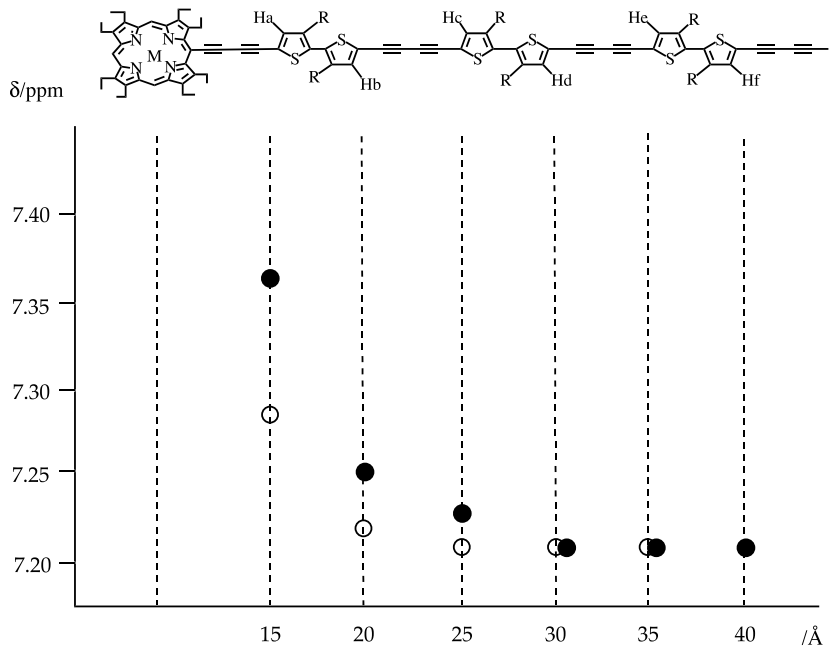


Figure 3. Chemical shift plots of Th-H for **11** (○) and **20** (●) against the distance from the center of the terminal OEP(M) ring of OEP(M)–$(DHBTh)_n$–OEP(M).

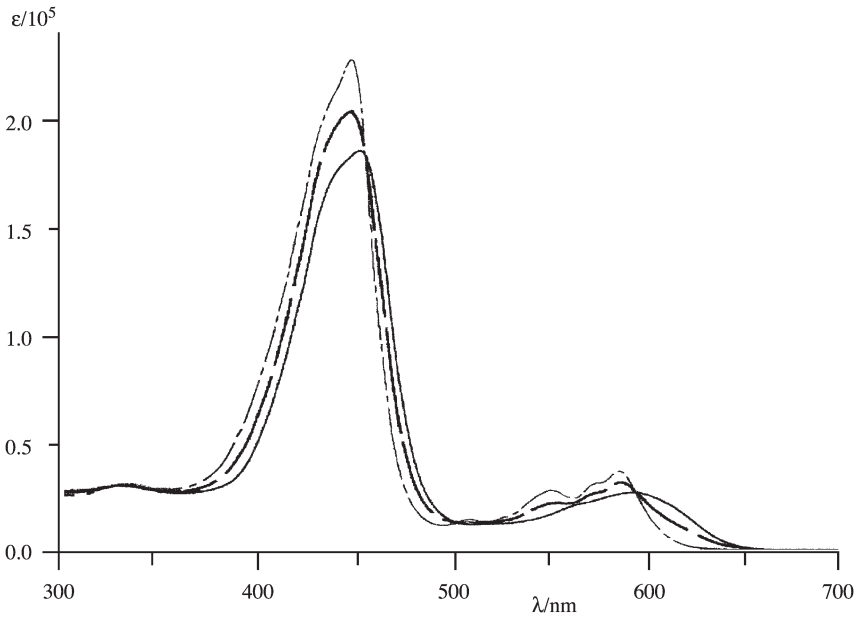


Figure 4. Electronic absorption spectra of **1** (—), **4** (···) and **6** (– – –) ($CHCl_3$, 25 °C).

participate in the π-electronic conjugation system through the diacetylene linkage preferably. Therefore, spectra of **6** and **7** might be regarded as combined ones between an extended π-electronic conjugation system of OEP(Ni) and diacetylene linkage and a fairly independent OEP(Pd) system. Particularly in the isomer **7**, the former π-electronic conjugation system would further interact with the TT(DHBTh) constituent to lose the electronic nature of OEP(Ni) itself, resulting in more clear-cut spectral feature of OEP(Pd). To clarify the combined electronic structures of **6** and **7** quantitatively, further investigations are under way.

As observed in the previous study of the extended OEP(Ni)–$(DHBTh)_n$–OEP(Ni) system,[11] the corresponding Pd complexes also exhibited an n-dependent spectral behavior with regularity, which is very important for development of the electronic devices.[3] To sum up, with increases of *n*, the Ni complexes gradually change Soret band into the very broad band at around 450 nm for HH series or fuse the split Soret bands into the longer wavelength band at around 480 nm for TT series. In case of the Pd complexes, Soret bands of HH series gradually became much broad on going from n=1 (**4**) to n=6 (**20**) to show the loosely depressed absorption bands at around 440 nm, with the respective maxima shifting slightly to the shorter wavelengths (Fig. 6a). On the other hand, the TT series also exhibited a different behavior from the HH series, in which the two λ_1 and λ_2 maxima of Soret band at 435 and 477 nm for **5** (n=1) seem to gather and gradually to fuse into the λ_2 band at around 475 nm for **25** (n=6) (Fig. 6b). It is also emphasized that in both complexes Soret bands increased their intensities with increases of *n*, while Q bands regularly decreased with the electronic structures remaining. It is worthy of note that one of the requirements for tuning the function efficiencies of the electronic devices is to possess the specific absorption band in the molecule, of which its intensity is regularly variable.

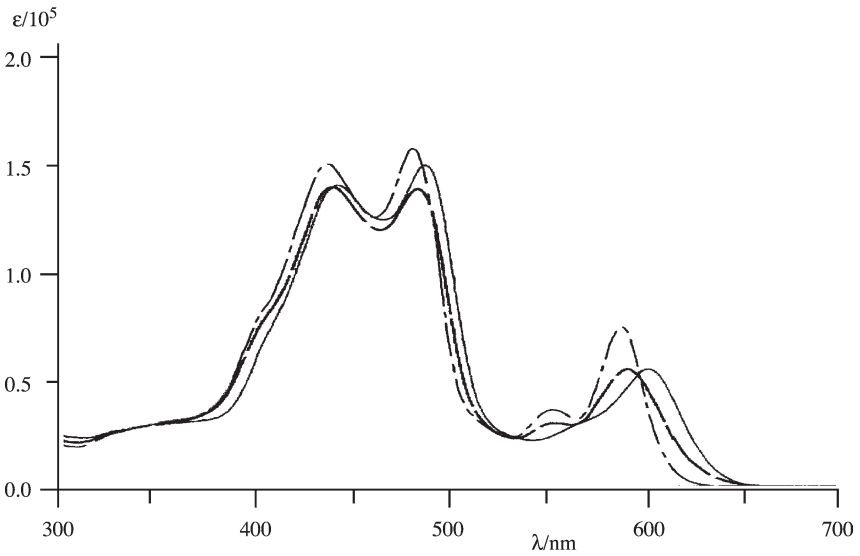


Figure 5. Electronic absorption spectra of **3** (—), **5** (···) and **7** (– – –) ($CHCl_3$, 25 °C).

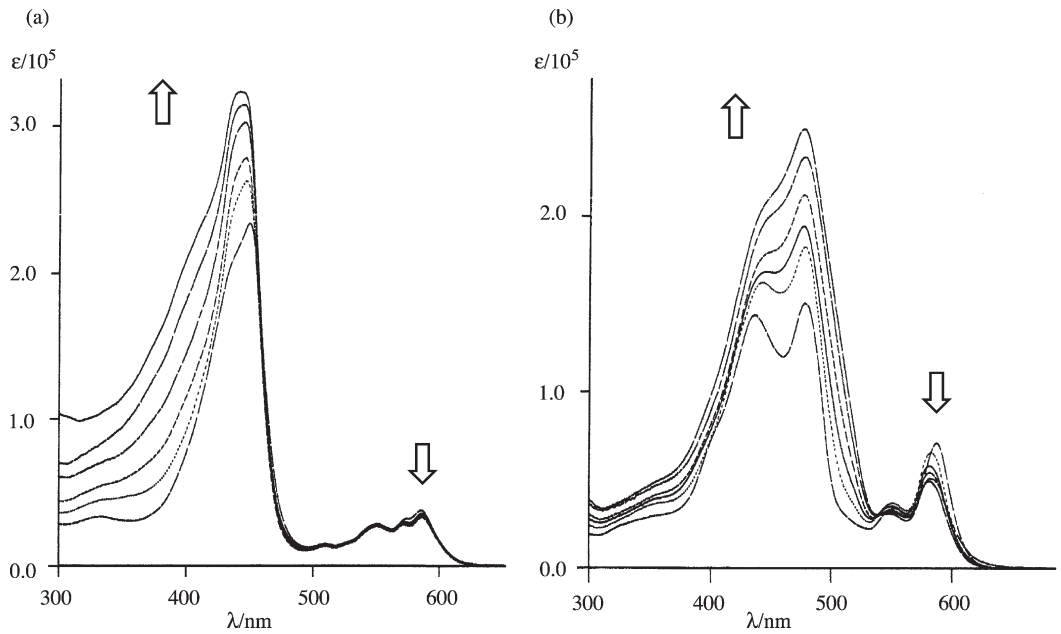


Figure 6. Electronic absorption spectra of the OEP(Pd)–$(DHBTh)_n$–OEP(Pd): (a) the HH series (**4** and **16**–**20**) and (b) the TT series (**5** and **21**–**25**) ($CHCl_3$, 25 °C). Arrows show the spectral behaviors changed with increases of *n*.

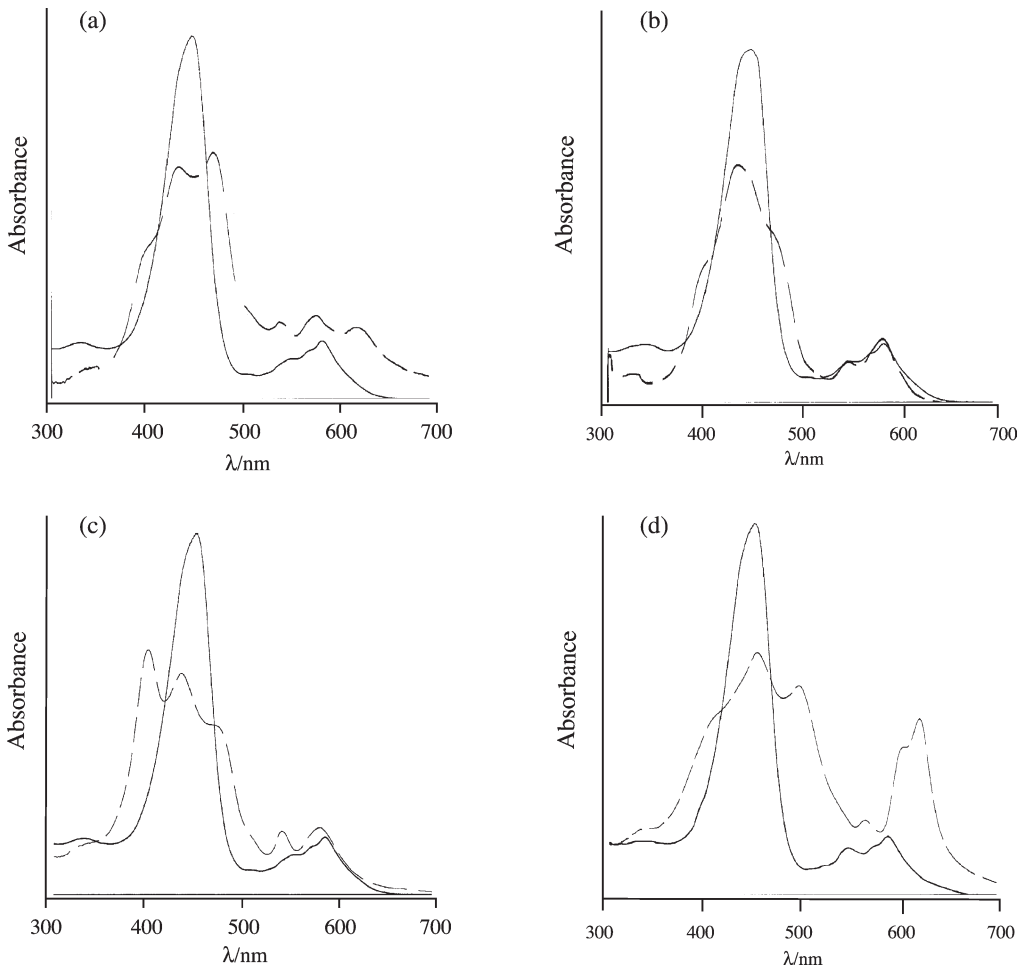


Figure 7. Electronic absorption spectra of the OEP(Ni)–DHBTh–OEP(Pd) derivatives **6** and **7**: (a) in hexane, (b) in acetone and (c) in DMF. Electronic absorption spectra of **4** and **5** in hexane are given in (d). Spectra of HH isomers (**4** and **6**) were recorded by solid line and the corresponding spectra of TT isomers (**5** and **7**) by broken line.

2.4. Solvent effect on the electronic absorption spectra

It would be deduced from the investigations mentioned so far that other external stimulations would bring out some different properties into this system reflecting the structural elements such as the orientation of DHBTh and the incorporated metals. In addition, the unsymmetrical feature was also found to appear in a solvent effect on their absorption spectra. Spectra of **6** and **7** were further taken in hexane, acetone and *N*,*N*-dimethylformamide (DMF), relatively good solvents for these derivatives, and were compared with those in $CHCl_3$ (Figs. 4, 5 and 7). The HH isomer **6** afforded nearly the same spectra in all the solvents as that in $CHCl_3$, though slight batho- and hypsochromic shifts of the respective bands were observed in accordance with ε and π^* values of the solvent polarities.[4b,7a,8] On the other hand, to be surprised, the TT isomer **7** did afford much different spectra from that in $CHCl_3$ to exhibit the new band at around λ_{max}=640 nm with long absorption tail in hexane (Fig. 7a)[12] or to deform the absorption curves of Soret band in acetone (Fig. 7b) and in DMF (Fig. 7c). Such a new Q band in hexane did not clearly appear in acetone and DMF, but the absorption curve of Soret band in hexane was almost the same as that in $CHCl_3$. In order to make a closer inspection of these results, spectral behaviors of the related compounds were preliminarily examined. The spectral features in the solvent-dependent experiments are summarized in Table 2. The symmetrical Ni complexes **1** and **3** did scarcely exhibit such a solvent effect on their spectra, nor did another unsymmetrical HT isomer **2**. The Pd complexes **4** and **5**, however, apparently showed the similar behavior to that for **6** and **7**, revealing that the only TT isomer **5** intensified the new absorption band (λ_{max}=635 nm) and deformed Soret band much further in hexane (Fig. 7d).

Table 2. Solvent dependent spectral changes of Soret and Q bands

Compounds	Soret bands			Q bands		
	Hexane	Acetone	DMF	Hexane	Acetone	DMF
1	*	*	*	*	*	*
3	*	*	*	*	*	*
4	*	X	—	*	X	—
5	XX	X	—	XXX	XX	—
6	*	*	*	*	*	*
7	X	XX	XXX	XX	*	XX

Differences between the spectra in the tested solvents and that in $CHCI_3$ are defined as XXX for the large and X for the small changes (see Fig. 7). The asterisk marks little spectral changes between them. The compounds **4** and **5** are insoluble in DMF.

Although several induction factors for these phenomena such as molecular association[11] and electronic structure reformation would be pointed out, the interaction origin of the solvents with OEP(M) nuclei in the present system remains unsolved. These phenomena are primarily deducible to arise from the perturbation to non- and π-bonding MO levels of the more planar molecules **5** and **7** somehow, in consequence of further freedom from the degenerated states of both Soret and Q bands through the solvent polarizabilities. A conclusive interpretation for these solvent-dependent spectral behaviors, however, should wait for further studies.

Based on these results, at this stage it might be derived that the OEP(Pd)–TT(DHBTh) constituent is essential in the present system for such an intensive solvent effect on the absorption spectra. And yet, the present study suggests that an electronic communication between the two terminal OEP(M) rings takes place, especially in the unsymmetrical system of the TT isomer **7** efficiently, to give rise to a polarization action at the ground state.

2.5. Cyclic voltammetry of the OEP(M1)–$(DHBTh)_n$–OEP(M2) system

The porphyrin derivatives are known to possess the high susceptibility to the electrochemical stimulation,[23] based on which a variety of researches for the optoelectronic devices[1–3] and the electron- and energy-transfer assemblies[24] aiming at the artificial photosynthesis reaction center have been vastly demonstrated. The redox reactions of **1**–**7** by means of cyclic voltammetry (CV) were all reversibly observed and analyzed to proceed via three steps of one-, one- and two-electron transfer processes for the dinucleic OEP compounds and via two steps of one- and one-electron transfer processes for the mononucleic OEP ones.[11] Their half-wave oxidation potentials together with those of the reference compounds are summarized (Table 3), among which the first oxidation potential (E_1) is regarded as a measure of electron-releasing ability of the molecule. Table shows that distinct from the vinylene linkage,[13,22] the diacetylene linkage is less effective not only for electronic conjugation with the 18 π-electron system of OEP(M) at the neutral state but also for stabilization of the first oxidation product, radical cation, via delocalization throughout the molecule. Nevertheless, as compared with E_1 values of OEP(M), the OEP(M) dimers (**36** and **37**) bring in nearly the same to smaller values, proving that the diacetylene linkage enhances the electron-releasing ability of the OEP(Pd) complex much preferably. On the other hand, in case of the compounds in which one of the OEP(M) rings in **36** and **37** is replaced with HTh or DHBTh constituent, their electron-releasing abilities apparently decrease (**54**–**57**). This result should be attributed to the energy state differences between OEP(Ni) and those constituents. Among other things, it is worthy of note that **57** possesses the E_1 value relatively

Table 3. Half wave oxidation potentials ($E_{1/2}$/mV) of the OEP(M1)–DHBTh–OEP(M2) and reference OEP(M) derivatives

Compounds	$E^1_{1/2}$(1e)	$E^2_{1/2}$(1e)	$E^3_{1/2}$(2e)
1	880	960	1330
3	820	960	1390
4	890	1130	1640
5	870	1110	1680
6	880	1040	1340
7	820	1030	1320
OEP(Ni)	860	1320	
OEP(Pd)	1040	1780	
36	860	1010	1350
37	910	1060	1650
54	900	1260	
55	960	1290	
56	910	1280	
57	870	1240	

CV was performed at 25 °C in CH_2Cl_2 containing *n*-Bu_4NClO_4GC (working *E*), Pt (counter *E*), and SCE (reference *E*).[11] Scan rate; 120 mV s^{-1}.

closer to that of **36**, while **54** and **56** possess the similar values to each other.

Although the E_1 values for the OEP(M1)–DHBTh–OEP(M2) derivatives are in such a narrow region between 820 and 890 mV, several findings can be clearly pointed out. All the Pd complexes show the higher E_1 values than the corresponding Ni complexes, indicating the greater back-donative ability of Pd(II) ion contributes to the lowering of HOMO level of the molecule preferably. In case of the symmetrical OEP(M)–DHBTh–OEP(M) system (**1**, **3**, **4** and **5**), the E_1 values reflect the orientation of DHBTh, resulting in the higher electron-releasing abilities for the TT isomers. The unsymmetrical OEP(Ni)–DHBTh–OEP(Pd) derivatives **6** and **7** were expected to be oxidized via the four-step process, but in fact exhibited the three-step oxidation process with the same tendency as the symmetrical ones at a scan rate of 120 mV s^{-1}, to show the higher electron-releasing ability for the TT isomer **7** with a difference of ΔE_1=60 mV between them. The difference ΔE_1 values between HH and TT isomers are greater in the Ni complexes than in the Pd complexes. Yet, it is noted that not only E_1 but also ΔE_1 values are eventually the same between symmetrical OEP(Ni)–DHBTh–OEP(Ni) and unsymmetrical OEP(Ni)–DHBTh–OEP(Pd) systems. These results indicate that the interaction between OEP(Ni) and DHBTh through the diacetylene linkage is much intensive to elevate the HOMO level, as compared with that between OEP(Pd) and DHBTh, predominantly bringing about an electrochemical appearance of the OEP(Ni) constituent in the molecule.

In case of the further extended OEP(M)–$(DHBTh)_n$–OEP(M) system, no inclusive consequence could be obtained more than that from the Ni complexes,[11] especially because of the poorer solubilities of the Pd complexes in ordinary solvents with the higher n. However, taking the result from the OEP(M)–DHBTh–OEP(M) derivatives into consideration, it may be also given as a conclusion that the OEP(Ni) complex participates in the π-electronic conjugation with the $TT(DHBTh)_n$ constituents much efficiently even through the rigid linkage of diacetylene to elevate the HOMO levels of the molecules, which is consistent with a finding from the absorption spectral study.

2.6. Main electronic structure for the OEP(M1)–$(DHBTh)_n$–OEP(M2) system

It is apparent that all the characteristic spectral behaviors of **1**–**25** substantially come from the structure elements; the orientation of DHBTh, the incorporated metals, the numbers of DHBTh and the symmetry of molecule in this system. So far, a variety of the DHBTh derivatives have been demonstrated from the viewpoint of the structure–property relationship, regarding the orientation effect of DHBTh on the conformational planarity of the molecule as a controller tool for the material function.[4,7,8,10,11] In short, the HH(DHBTh) constituent interrupts the π-electronic conjugation by increasing the dihedral angle (DA)[6] between the two HTh rings of DHBTh, in contrast with the TT(DHBTh) constituent with a fairly planar conformation convenient for transmission of the π-electronic conjugation throughout the molecule. Thus, in case of the HH series, it may be as well to explain that the electronic structures gradually separate into the two main characteristic features with increases of n; one arises from the OEP(M)–HTh component like **54** and **55**, another arises from the remaining HTh-HH$(DHBTh)_{n-2}$–HTh component, resulting in their combined broad spectra (Fig. 6a). On the other hand, the TT series seems to extend their π-electronic conjugation systems between two terminal OEP(M) rings through the $TT(DHBTh)_n$ constituents, which would result in some reduction of the HOMO–LUMO energy difference of OEP(M). However, if any, an extension of the π-electronic conjugation of this type simultaneously would weaken the interaction between two terminal OEP(M) rings, because the two OEP(M) rings move in the opposite direction and exist apart from each other by ca. 13 Å every one increment of n. Accordingly, it is likely that such a regular extension of the molecular length induces the TT series gradually to recover the electronically degenerated structure of the particular chromophore (Fig. 6b). This is practically related with a regular change that their Soret bands increase the intensities with increases of *n*, while Q bands decrease reversely. As deduced in the previous report,[11] one possible understanding on these results would be made by presuming an existence of π-electronic interaction between the two terminal OEP(M) rings. This is originally based on the electronic structures observed for **36**[15] and **37** (*n*=0), in which those Soret bands appear as the three split bands at around 420, 450 and 485 nm (Fig. 8), in contrast with one broad Soret band at around 445 nm for **54** and **55**. Alternatively, it is also likely that a particular π-electronic reorganization between the three chromophores in this system; OEP(M), diacetylene and DHBTh, produces an entirely new electronic system sensitive to the orientation of DHBTh. If a substituent is attractive enough to interact with the electronic system of OEP(M), even a mono-substituted OEP(M) derivative could lose a highly degenerated D_{4h} electronic structure of OEP(M) to generate the new electronic transition.[25] As a consequence, it is confidently verified that the two main characteristic features of the OEP(M)–TT(DHBTh) component like **57** and the remaining $TT(DHBTh)_{n-2}$ component are the candidates for the

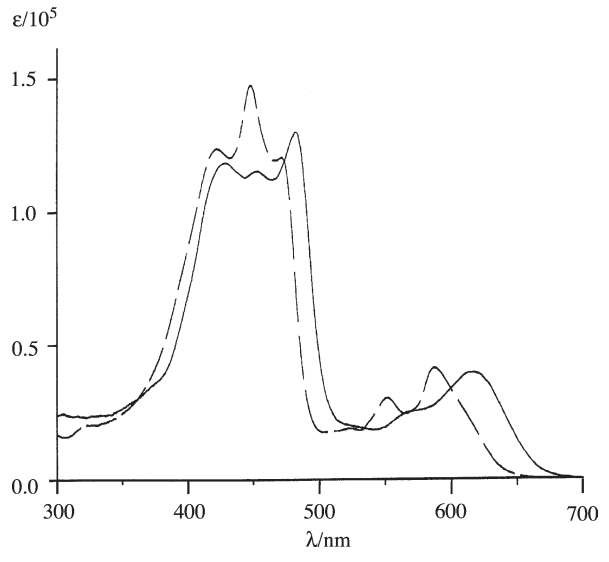


Figure 8. Electronic absorption spectra of **36** (–) and **37** (– – –) ($CHCl_3$, 25 °C).

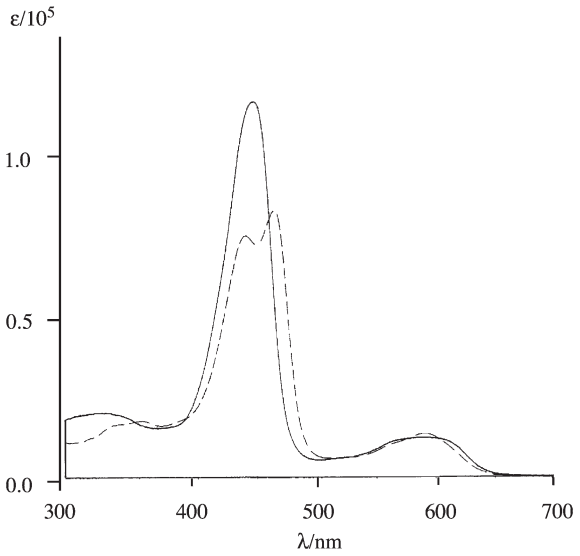


Figure 9. Electronic absorption spectra of **56** (–) and **57** (– – –) ($CHCl_3$, 25 °C).

principal electronic structures of the TT series. In practice, the spectrum of the OEP(Ni)–HH(DHBTh) derivative **56** exhibited one broad Soret band at the maximum of 446 nm eventually the same as that for **54**, while the spectrum of the TT isomer **57** apparently exhibited a split Soret band with two maxima of 440 and 463 nm, respectively (Fig. 9). This result evidently indicates that the π-electronic interaction between the two terminal OEP(M) rings is not necessary for the splitting of Soret band of the present π-electronic system. It also proves that the terminal HTh ring of DHBTh in **56** behaves just as a sterical substituent without any electronic affection on the system, while the one in **57** behaves as an cooperative chromophore sensitive enough to generate a new electronic transition. The same interpretation could also be led from the electrochemical behaviors of **56** and **57**, compatible with a fact that the electron-releasing ability of the HH isomer **56** is almost comparable to that of **54** (vide ante). In conclusion, as an essential framework for the main electronic structure, the HH series comes from the OEP(M)–HTh constituent, while the TT series from the one of OEP(M)–TT(DHBTh). In such a mechanistic aspect as described above, these main chromophores in the respective series interact to each other through the remaining HTh-HH(DHBTh)$_{n-2}$–HTh or TT(DHBTh)$_{n-2}$ constituents, to bring out the respective spectral feature of the present system depending on both the orientation and number of DHBTh and the incorporated metals (Fig. 10).

3. Conclusion

The synthetic methods for both symmetrical and unsymmetrical complexes of the OEP(M)–DHBTh–OEP(M) system have been conclusively described. Particularly, it is notable that the synthetic success of the terminal acetylenes **42** and **51** would lead to a general synthetic method for a variety of the OEP(M)–DHBTh–(π-EC) derivatives and would impel the present research onto the further application stage. ^{1}H NMR spectral study makes it confirmed that all the OEP(M)–(DHBTh)$_n$–OEP(M) derivatives possess the fairly simple skeletal features, regardless of the symmetry of molecule, with the respective ring currents of OEP(M) in **36** and **37** remaining to a great extent. And thus, the deshielded area from anisotropic effect of OEP(M) has proven to expand up to 25 Å for the Ni complexes and 30 Å for the Pd complexes, reflecting the magnitudes of their ring currents (Fig. 3). From the IR spectral measurements, it is derived that the diacetylene linkage for the TT series exhibits a greater contribution to an extension of the resonance structure with the OEP and DHBTh nuclei, regardless of the number of DHBTh. As contrasted with such a simple regularity in a rigid and straight molecular skeleton, the present π-electronic conjugation system possess characteristic absorption spectral features, reflecting several structure elements. The appearances of Soret and Q bands are peculiar to the present one-dimensionally extended π-electronic conjugation system, which exactly reflect the orientation of DHBTh. Absorption spectra for the HH, HT and TT isomers **1**–**3** show the respective Soret bands to split into two main $\pi \rightarrow \pi^*$ transitions regularly, among which all the shorter wavelength λ_1 bands appear at around 440 nm. The longer wavelength λ_2 bands, however, appear at the longer wavelength region separately over a range of 45 nm. In both HH and TT series, the spectra of the Pd complexes **4** and **5** exhibit slight hypsochromic shift and sharpened, as compared with those for the corresponding Ni complexes **1** and **3**. It is also proved that the introduction of (DHBTh)$_n$ into **36** and **37** to form OEP(M)–(DHBTh)$_n$–OEP(M) (**8**–**25**) induces the gradual reformation between the two main electronic structures, reflecting both the orientation and n of DHBTh. With increases of n, the HH series the combined electronic system between OEP(M)–HTh and HTh–HH(DHBTh)$_{n-2}$–HTh, while the TT series does the conjugation system between OEP(M)–TT(DHBTh) and TT(DHBTh)$_{n-2}$ (Fig. 10). The solvent-dependent spectra of the OEP(Ni)–TT(DHBTh)–OEP(Pd) derivative **7** have been remarkably observed, though the transition origins of the sensitive bands to the solvent polarity must be further

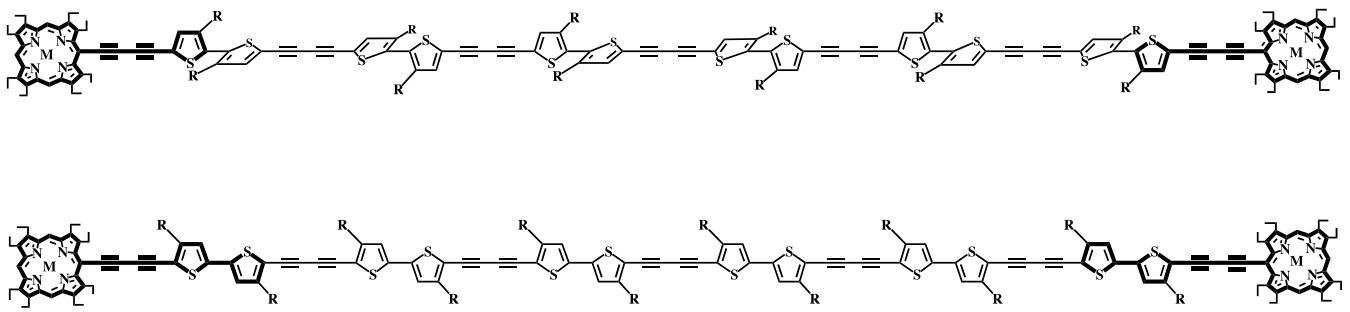


Figure 10. Characteristic feature of the main electronic structures for HH (upper) and TT (lower) series of the OEP(M)–(DHBTh)$_n$–OEP(M) system.

clarified. Concurrently with the orientation of DHBTh, the unsymmetrization by introducing the different OEP(M) rings into the present system is also potentially effective to conduct the electron transfer functionality from one side to the other.

In consequence, the electronic absorption spectra of the OEP(M1)–$(DHBTh)_n$–OEP(M2) system could be affected substantially by the following structure elements. Putting those structure elements together from the material viewpoint, the orientation of DHBTh could be regarded as a function selector to construct the main electronic structure of the system, the incorporated metal ions M as a modulation tool for adjustment of the transition energy for each function band and the number of DHBTh as a fine tuner to select the susceptibility to the external electronic stimulations. Therefore, a particular electronic structure of OEP(M1)–$(DHBTh)_n$–OEP(M2) corresponding to the particular electronic property would be constructed by choosing these three structure elements purposively. Since the structure elements could be generalized to expand into the orientations of DABTh, many other metal ions and the greater numbers of *n*, respectively, the present study would provide a methodology for construction of the particular electronic structures of various DABTh derivatives at the stage of molecular design.

4. Experimental

4.1. General

The melting points were determined on a hot-stage apparatus and are uncorrected. IR spectra were measured on a Jasco FT/IR 7300 spectrophotometer as KBr disk or neat sample; only significant absorptions are reported. EI and FAB mass spectra were recorded with JEOL JMS-700 and/or AX-505 spectrometers. In case of the hard ionization by the above techniques, ESI-FT-ICR mass spectra were performed with a Bruker BioAPEX 70e spectrometer equipped with a 7T superconducting magnet, using a sample in a solution of $CHCl_3$:MeOH (3:2). ^{1}H NMR spectra were measured in $CDCl_3$ solutions at 25 °C on JEOL MAC-FX (90 MHz) and/or JEOL α-400 (400 MHz) spectrometers and were recorded in δ values (/ppm) with TMS as an internal standard. The coupling constants (*J*) are given in Hz. Electronic absorption spectra were measured in $CHCl_3$ solution on a Shimadzu UV-2200A spectrophotometer (sh=shoulder), unless otherwise stated. CV was performed on a BAS CV-27 potentiometer in CH_2Cl_2 in the presence of *n*-Bu_4NClO_4 at a scan rate of 120 mV/s^{-1}.[11] SiO_2 (Fujisilysia BW 820MH or BW 127ZH) and aluminum oxide (Al_2O_3, CAMAG 504-C-1) were used for column chromatography. THF was distilled over calcium hydride and then over sodium diphenylketyl under argon (Ar) before use. The reactions were followed by TLC aluminum sheets precoated with Merck SiO_2 F_{254} or with Merck Al_2O_3 GF_{254}. Organic extracts were dried over anhydrous sodium sulfate or magnesium sulfate prior to removal of the solvents. OEP(H_2) was prepared from methyl 3-oxopentanoate, according to the literature.[26]

4.1.1. 5-(2-Bromovinyl)-2,3,7,8,12,13,17,18-octaethylporphyrinatopalladium(II) (34). To a solution of **28**[15] (300 mg, 0.43 mmol) in $CHCl_3$ (20 cm^3) was added conc. sulfuric acid (10 cm^3). The mixture was stirred at an ambient temperature for 3 h. Poured into iced water, the reaction mixture was neutralized with sat. sodium bicarbonate ($NaHCO_3$) and extracted with $CHCl_3$. The extracts were washed with brine and then dried. The residue obtained after removal of the solvent was chromatographed on SiO_2 (3.2×3 cm) with $CHCl_3$ to afford **33**, which was used for the next step without further purification. **33**[15]: ^{1}H NMR (90 MHz) δ=10.11 (2H, s, *meso*-H), 9.94 (1H, s, *meso*-H), 9.62 (1H, d, *J*=14 Hz, C*H*=CHBr), 6.44 (1H, d, *J*=14 Hz, CH=C*H*Br), 4.21–3.87 (16H, m, CH_2), 1.98–1.58 (24H, m, CH_3), −3.27 (2H, br s, NH). A mixture of all the crude product **33** and $Pd(OAc)_2$ (145 mg, 0.65 mmol) in $CHCl_3$–MeOH (120 cm^3, 5:1) was stirred at an ambient temperature overnight. Poured into water, the mixture was extracted with $CHCl_3$. The extracts were washed with brine and then dried. The residue obtained after removal of the solvent was chromatographed on SiO_2 (4.2×15 cm) with hexane–$CHCl_3$ (1:1) to afford **34** (230 mg, 72% based on **28**): Bright reddish fine needles ($CHCl_3$–MeOH); mp >260 °C (gradual dec); Mass (FAB) *m*/*z* 745 and 747 (M^++1 and M^++3) for $C_{38}H_{45}N_4BrPd$, MW=744.1; IR (KBr) 2962, 2929 and 2869 (CH) cm^{-1}; ^{1}H NMR (400 MHz) δ=10.05 (2H, s, *meso*-H), 10.01 (1H, s, *meso*-H), 9.64 (1H, d, *J*=14 Hz, C*H*=CHBr), 6.11 (1H, d, *J*=14 Hz, CH=C*H*Br), 4.06–3.96 (16H, m, CH_2), 1.91–1.70 (24H, m, CH_3); UV–VIS ($CHCl_3$) λ_{max}=402 (ε 126300), 518 (9900) and 553 nm (18400). Found: C, 61.05; H, 6.33; N, 7.26%. Calcd for $C_{38}H_{45}N_4BrPd$: C, 61.34; H, 6.10; N, 7.53%.

4.1.2. 5-Ethynyl-2,3,7,8,12,13,17,18-octaethylporphyrinatopalladium(II) (35). To a solution of DMSO (0.8 cm^3) in 1,2-dimethoxyethane (70 cm^3) was added NaH (60% in oil, 108 mg, 2.69 mmol) under Ar atmosphere. After 15 min, **34** (200 mg, 0.27 mmol) was added to the resulting solution and the mixture was stirred under reflux for 5 h. After addition of a small crashed ice, the reaction mixture was extracted with $CHCl_3$. The extracts were washed with brine and then dried. The residue obtained after removal of the solvent was chromatographed on SiO_2 (3.2×11 cm) with hexane–$CHCl_3$ (7:3) to afford **35** (107 mg, 60%): Reddish purple needles ($CHCl_3$–MeOH); mp >250 °C (gradual dec); Mass (FAB) *m*/*z* 664 (M^++1) for $C_{38}H_{44}N_4Pd$, MW=663.2; IR (KBr) 3318 (C≡CH), 2962, 2929, 2869 (CH) and 2098 cm^{-1} (C≡C); ^{1}H NMR (400 MHz) δ=10.01 (2H, s, *meso*-H), 9.97 (1H, s, *meso*-H), 4.49 (1H, s, C≡CH), 4.35 (4H, q, *J*=7 Hz, 3,7-*CH*$_2$CH$_3$), 4.06–3.96 (12H, m, *CH*$_2$CH$_3$), 1.90–1.72 (24H, m, CH$_2$*CH*$_3$); UV–VIS λ_{max}=412 (ε 149500), 533 (9300), 558 (7500) and 572 nm (15900). Found: C, 68.28; H, 7.18; N, 8.33%. Calcd for $C_{38}H_{44}N_4Pd$: C, 68.82; H, 6.69; N, 8.45%. The 2-methoxyvinyl OEP(Pd) derivative (15 mg, 8%) corresponding to **34** was also obtained from the later fractions with hexane–$CHCl_3$ (1:1): Reddish needles ($CHCl_3$–MeOH); mp 225–230 °C (dec); Mass (FAB) *m*/*z* 696 (M^++1) for $C_{39}H_{48}N_4OPd$, MW=695.2; IR (KBr) 2963, 2929 and 2869 cm^{-1} (CH); ^{1}H NMR (400 MHz) δ=10.01 (2H, s, *meso*-H), 9.96 (1H, s, *meso*-H), 8.37 (1H, d, *J*=13 Hz, *CH*=CHOCH$_3$), 5.94 (1H, d, *J*=13 Hz, CH=*CH*OCH$_3$), 4.02 (3H, s, OCH$_3$), 4.06–3.98 (16H, m,

CH_2CH_3), 1.90–1.72 (24H, m, CH_2CH_3); UV–VIS λ_{max}=403 (ε 150000), 519 (12500) and 553 nm (21700). Found: C, 67.30; H, 7.22; N, 7.90%. Calcd for $C_{39}H_{48}N_4OPd$: C, 67.37; H, 6.96; N, 8.06%.

4.1.3. 5,5′-Bis{4-[2,3,7,8,12,13,17,18-octaethylporphyrinatopalladium(II)-5′-yl]-1,3-butadiynyl}-3,3′-dihexyl-2,2′-bithiophene (4) and its further extended HH(DHBTh)$_n$ derivatives (16–20). A solution of **30**[17] (50 mg, 0.13 mmol) and **35** (190 mg, 0.29 mmol) in Py–MeOH (160 cm^3, 5:1) was added to the solution of $Cu(OAc)_2$ (793 mg, 4.37 mmol) in Py–MeOH (30 cm^3, 5:1) at 40 °C dropwise over 1 d. Stirred for additional 5 h, the reaction mixture was poured into water, shaken with dil. HCl to be slightly acidic and extracted with $CHCl_3$. The extracts were washed with sat. $NaHCO_3$ thoroughly and with brine successively. The residue obtained after removal of the solvent was chromatographed on SiO_2 (3×75 cm) with hexane–$CHCl_3$ (7:3) to afford the OEP(Pd)–HH(DHBTh)$_n$–OEP(Pd) derivatives; **20** (n=6; 5 mg, 6% based on **30**), **19** (n=5; 7 mg, 8% based on **30**), **18** (n=4; 7 mg, 8% based on **30**), **17** (n=3; 8 mg, 7% based on **30**), **16** (n=2; 10 mg, 7% based on **30**), **4** (n=1; 20 mg, 9% based on **30**) and **37** (n=0, 56 mg, 30% based on **35**) in order. **4**: Reddish purple microcrystals ($CHCl_3$–MeOH); mp 264–268 °C (dec); Mass (ESI-FT-ICR) m/z 568.58112 (M^{3+}) for $C_{100}H_{114}N_8S_2Pd_2$, MW=1704.9; IR (KBr) 2962, 2928, 2869 (CH), 2186 and 2134 cm^{-1} (C≡C); ^{1}H NMR (400 MHz) δ=10.00 (4H, s, *meso*-H), 9.95 (2H, s, *meso*-H), 7.41 (2H, s, Th-H), 4.31 (8H, q, J=7 Hz, 3,7-CH_2CH_3), 4.06-3.96 (24H, m, CH_2CH_3), 2.63 (4H, t, J=7 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.96–1.86 (48H, m, CH_2CH_3), 1.34–1.25 (16H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.94 (6H, t, J=7 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$); UV–VIS λ_{max}=435 (ε 175000, sh), 449 (235000), 511 (15400), 551 (29200), 575 (32600) and 586 nm (38500). Found: C, 70.10; H, 7.01; N, 6.23%. Calcd for $C_{100}H_{114}N_8S_2Pd_2$: C, 70.44; H, 6.74; N, 6.57%. **16**: Reddish purple microcrystals ($CHCl_3$–MeOH); mp >270 °C (gradual dec); Mass (ESI-FT-ICR) m/z 417.13692 (M^{5+}) for $C_{124}H_{142}N_8S_4Pd_2$, MW=2085.5; IR (KBr) 2961, 2927, 2869 (CH), 2186 and 2133 cm^{-1} (C≡C); ^{1}H NMR (400 MHz) δ=10.00 (4H, s, *meso*-H), 9.95 (2H, s, *meso*-H), 7.37 (2H, s, Th-H), 7.25 (2H, s, Th-H), 4.30 (8H, q, J=7 Hz, 3,7-CH_2CH_3), 4.01–3.96 (24H, m, CH_2CH_3), 2.57 (8H, t, J=7 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.94–1.85 (48H, m, CH_2CH_3), 1.35–1.25 (32H, br m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.93–0.89 (12H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$); UV–VIS λ_{max}=446 (ε 264000), 511 (14400), 551 (27800), 573 (29400) and 586 nm (34400). Found: C, 71.18; H, 7.11; N, 5.12%. Calcd for $C_{124}H_{142}N_8S_4Pd_2$: C, 71.41; H, 6.87; N, 5.38%. **17**: Reddish purple microcrystals ($CHCl_3$–MeOH); mp >270 °C (gradual dec); Mass (ESI-FT-ICR) m/z 493.39105 (M5+) for $C_{148}H_{170}N_8S_6Pd_2$, MW=2466.1; IR (KBr) 2961, 2926, 2854 (CH), 2183 and 2133 cm^{-1} (C≡C); ^{1}H NMR (400 MHz) δ=9.98 (4H, s, *meso*-H), 9.93 (2H, s, *meso*-H), 7.37 (2H, s, Th-H), 7.25 (2H, s, Th-H), 7.22 (2H, s, Th-H), 4.28 (8H, q, J=7 Hz, 3,7-CH_2CH_3), 4.03–3.93 (24H, m, CH_2CH_3), 2.57–2.47 (12H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.93–1.84 (48H, m, CH_2CH_3), 1.34–1.25 (48H, br m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.92–0.86 (18H, br m, $CH_2CH_2CH_2CH_2CH_2CH_3$); UV–VIS λ_{max}=446 (ε 279000), 511 (13800), 551 (27400), 572 (28600) and 587 nm (33700). Found: C, 72.00; H, 7.21; N, 4.35%. Calcd for $C_{148}H_{170}N_8S_6Pd_2$: C, 72.08; H, 6.95; N, 4.55%. **18**: Reddish purple microcrystals ($CHCl_3$–MeOH); mp 270–275 °C (dec); Mass (ESI-FT-ICR) m/z 711.81722 (M^{4+}) for $C_{172}H_{198}N_8S_8Pd_2$, MW=2846.6; IR (KBr) 2960, 2925, 2855 (CH), 2186 and 2134 cm^{-1} (C≡C); ^{1}H NMR (400 MHz) δ=9.98 (4H, s, *meso*-H), 9.93 (2H, s, *meso*-H), 7.37 (2H, s, Th-H), 7.25 (2H, s, Th-H), 7.22 (2H, s, Th-H), 7.21 (2H, s, Th-H), 4.29 (8H, q, J=7 Hz, 3,7-CH_2CH_3), 4.04–3.94 (24H, m, CH_2CH_3), 2.57–2.47 (16H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.94–1.84 (48H, m, CH_2CH_3), 1.29–1.25 (64H, br m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.92–0.86 (24H, br m, $CH_2CH_2CH_2CH_2CH_2CH_3$); UV–VIS λ_{max}=445 (ε 303000), 510 (14400), 550 (28200), 573 (29900) and 586 nm (35600). Found: C, 72.48; H, 7.30; N, 3.66%. Calcd for $C_{172}H_{198}N_8S_8Pd_2$: C, 72.57; H, 7.02; N, 3.94%. **19**: Reddish purple microcrystals ($CHCl_3$–MeOH); mp 270–274 °C (dec); Mass (ESI-FT-ICR) m/z 1075.96174 (M^{3+}) for $C_{196}H_{226}N_8S_{10}Pd_2$, MW=3227.2; IR (KBr) 2959, 2925, 2854 (CH), 2183 and 2133 cm^{-1} (C≡C); ^{1}H NMR (400 MHz) δ=9.99 (4H, s, *meso*-H), 9.94 (2H, s, *meso*-H), 7.37 (2H, s, Th-H), 7.25 (2H, s, Th-H), 7.22 (2H, s, Th-H), 7.21 (4H, br s, Th-H), 4.29 (8H, q, J=7 Hz, 3,7-CH_2CH_3), 4.05–3.95 (24H, m, CH_2CH_3), 2.57–2.47 (20H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.94–1.84 (48H, m, CH_2CH_3), 1.29–1.25 (80H, br m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.90–0.86 (30H, br m, $CH_2CH_2CH_2CH_2CH_2CH_3$); UV–VIS λ_{max}=444 (ε 316000), 510 (16000), 551 (29000), 572 (31000) and 587 nm (36000). Found: C,72.63; H,7.33; N, 3.20%. Calcd for $C_{196}H_{226}N_8S_{10}Pd_2$: C, 72.94; H, 7.06; N, 3.48%. **20**: Reddish purple microcrystals ($CHCl_3$–MeOH); mp 275–280 °C (dec); Mass (ESI-FT-ICR) m/z 1202.90751 (M^{3+}) for $C_{220}H_{254}N_8S_{12}Pd_2$, MW=3607.8; IR (KBr) 2959, 2925, 2854 (CH), 2185 and 2135 cm^{-1} (C≡C); ^{1}H NMR (400 MHz) δ=10.00 (4H, s, *meso*-H), 9.95 (2H, s, *meso*-H), 7.37 (2H, s, Th-H), 7.25 (2H, s, Th-H), 7.22 (2H, s, Th-H), 7.21 (6H, br s, Th-H), 4.29 (8H, q, J=7 Hz, 3,7-CH_2CH_3), 4.05–3.95 (24H, m, CH_2CH_3), 2.57–2.47 (24H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.94–1.84 (48H, m, CH_2CH_3), 1.29–1.25 (96H, br m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.90–0.86 (36H, br m, $CH_2CH_2CH_2CH_2CH_2CH_3$); UV–VIS λ_{max}=441 (ε 325000), 509 (15000), 551 (29000), 573 (31000) and 587 nm (36000). Found: C,73.18; H,7.28; N, 2.95%. Calcd for $C_{220}H_{254}N_8S_{12}Pd_2$: C, 73.24; H, 7.10; N, 3.11%. **37**: Reddish purple microcrystals ($CHCl_3$–MeOH); mp >270 °C (gradual dec); Mass (ESI-FT-ICR) m/z 441.56183 (M^{3+}) for $C_{76}H_{86}N_8Pd_2$, MW=1324.3; IR (KBr) 2963, 2929, 2870 (CH) and 2125 cm^{-1} (C≡C); ^{1}H NMR (400 MHz) δ=10.03 (4H, s, *meso*-H), 9.96 (2H, s, *meso*-H), 4.55 (8H, q, J=8 Hz, 3,7-CH_2CH_3), 4.11–3.98 (24H, m, CH_2CH_3), 2.10 (12H, t, J=7 Hz, CH_2CH_3), 1.90 (36H, t, J=7 Hz, CH_2CH_3); UV–VIS λ_{max}=422 (ε 124000), 447 (148000), 471 (121000), 552 (30700) and 587 nm (41900). Found: C, 68.77; H, 6.81; N, 8.19%. Calcd for $C_{76}H_{86}N_8Pd_2$: C, 68.93; H, 6.55; N, 8.47%.

4.1.4. 5,5′-Bis{4-[2,3,7,8,12,13,17,18-octaethylporphyrinatopalladium(II)-5′-yl]-1,3-butadiynyl}-4,4′-dihexyl-2,2′-bithiophene (5) and its further extended TT(DHBTh)$_n$ derivatives (21–25). A solution of **32**[17] (58 mg, 0.15 mmol) and **35** (220 mg, 0.33 mmol) in Py–MeOH (180 cm^3, 5:1) was added to the mixture of Cu(OAc)2 (921 mg, 5.07 mmol) in Py–MeOH (36 cm^3,

5:1) at 40 °C dropwise over 1 d. Stirred at 40 °C for additional 5 h, the reaction mixture was poured into water, shaken with dil. HCl to be slightly acidic and extracted with $CHCl_3$. The extracts were washed with sat. $NaHCO_3$ thoroughly and with brine successively. The residue obtained after removal of the solvent was chromatographed on SiO_2 (3×90 cm) with hexane–$CHCl_3$ (7:3) to afford the OEP(Pd)–TT(DHBTh)$_n$–OEP(Pd) derivatives: **25** (n=6; 2 mg, 2% based on **32**), **24** (n=5; 4 mg, 4% based on **32**), **23** (n=4; 8 mg, 7% based on **32**), **22** (n=3; 15 mg, 12% based on **32**), **21** (n=2; 22 mg, 14% based on **32**), **5** (n=1; 35 mg, 14% based on **32**) and **37** (88 mg, 40% based on **35**) in order. **5**: Deep green microcrystals ($CHCl_3$–MeOH); mp >280 °C (gradual dec); Mass (ESI-FT-ICR) m/z 568.58167 (M^{3+}) for $C_{100}H_{114}N_8S_2Pd_2$, MW=1704.9; IR (KBr) 2962, 2928, 2869 (CH), 2172 and 2127 cm^{-1} (C≡C); ^1H NMR (400 MHz) δ=10.02 (4H, s, *meso*-H), 9.96 (2H, s, *meso*-H), 7.12 (2H, s, Th-H), 4.33 (8H, q, J=7 Hz, 3,7-CH_2CH_3), 4.07–3.97 (24H, m, CH_2CH_3), 2.90 (4H, t, J=8 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.97–1.86 (48H, m, CH_2CH_3), 1.44–1.42 (16H, br m, $CH_2CH_2CH_2CH_2CH_2$-CH_3), 0.96 (6H, t, J=7 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$); UV–VIS λ_{max}=435 (ε 144000), 477 (151000), 552 (34800) and 587 nm (71500). Found: C, 70.22; H, 7.00; N, 6.29%. Calcd for $C_{100}H_{114}N_8S_2Pd_2$: C, 70.44; H, 6.74; N, 6.57%. **21**: Reddish purple microcrystals ($CHCl_3$–MeOH); mp 272–275 °C (dec); Mass (ESI-FT-ICR) m/z 417.13773 (M^{5+}) for $C_{124}H_{142}N_8S_4Pd_2$, MW=2085.5; IR (KBr) 2962, 2929, 2869 (CH), 2176 and 2129 cm^{-1} (C≡C); ^1H NMR (400 MHz) δ=9.99 (4H, s, *meso*-H), 9.94 (2H, s, *meso*-H), 7.05 (2H, s, Th-H), 7.02 (2H, s, Th-H), 4.31 (8H, q, J=8 Hz, 3,7-CH_2CH_3), 4.06–3.95 (24H, m, CH_2CH_3), 2.86 (4H, t, J=8 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 2.75 (4H, t, J=8 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.95–1.85 (48H, m, CH_2CH_3), 1.41–1.38 (32H, br m, $CH_2CH_2CH_2CH_2CH_2$-CH_3), 0.96–0.93 (12H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$); UV–VIS λ_{max}=441 (ε 163000), 478 (183000), 551 (37600) and 583 nm (66200). Found: C, 71.08; H,6.99; N, 5.16%. Calcd for $C_{124}H_{142}N_8S_4Pd_2$: C, 71.41; H, 6.87; N, 5.38%. **22**: Reddish purple microcrystals ($CHCl_3$–MeOH); mp 265–270 °C (dec); Mass (ESI-FT-ICR) m/z 493.39126 (M^{5+}) for $C_{148}H_{170}N_8S_6Pd_2$, MW=2466.1; IR (KBr) 2962, 2928, 2869 (CH), 2177 and 2130 cm^{-1} (C≡C); ^1H NMR (400 MHz) δ=10.01 (4H, s, *meso*-H), 9.96 (2H, s, *meso*-H), 7.05 (2H, s, Th-H), 7.02 (2H, s, Th-H), 6.97 (2H, s, Th-H), 4.31 (8H, q, J=8 Hz, 3,7-CH_2CH_3), 4.06–3.96 (24H, m, CH_2CH_3), 2.88–2.70 (12H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.95–1.85 (48H, m, CH_2CH_3), 1.36–1.34 (48H, br m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.96–0.88 (18H, br m, CH_2-$CH_2CH_2CH_2CH_2CH_3$); UV–VIS λ_{max}=445 (ε 169000), 476 (195000), 551 (35900) and 581 nm (58700). Found: C, 71.78; H, 7.18; N, 4.28%. Calcd for $C_{148}H_{170}N_8S_6Pd_2$: C, 72.08; H, 6.95; N, 4.55%. **23**: Reddish purple microcrystals ($CHCl_3$–MeOH); mp >275 °C (gradual dec); Mass (ESI-FT-ICR m/z 711.80986 (M^{4+}) for $C_{172}H_{198}N_8S_8Pd_2$, MW=2846.6; IR (KBr) 2961, 2927, 2856 (CH), 2175 and 2128 cm^{-1} (C≡C); ^1H NMR (400 MHz) δ=9.99 (4H, s, *meso*-H), 9.94 (2H, s, *meso*-H), 7.04 (2H, s, Th-H), 7.01 (2H, s, Th-H), 6.96 (4H, br s, Th-H), 4.30 (8H, q, J=7 Hz, 3,7-CH_2CH_3), 4.05–3.95 (24H, m, CH_2CH_3), 2.87–2.71 (16H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.95–1.86 (48H, m, CH_2CH_3), 1.35–1.25 (64H, br m, $CH_2CH_2CH_2CH_2CH_2$-CH_3), 0.96–0.92 (24H, br m, $CH_2CH_2CH_2CH_2CH_2CH_3$); UV–VIS λ_{max}=447 (ε 180000), 477 (213000), 550 (33700) and 581 nm (54900). Found: C, 72.22; H, 7.30; N, 3.77%. Calcd for $C_{172}H_{198}N_8S_8Pd_2$: C, 72.57; H, 7.02; N, 3.94%. **24**: Reddish purple microcrystals ($CHCl_3$–MeOH); mp >275 °C (gradual dec); Mass (ESI-FT-ICR) m/z 1075.96228 (M^{3+}) for $C_{196}H_{226}N_8S_{10}Pd_2$, MW=3227.2; IR (KBr) 2960, 2926, 2856 (CH), 2175 and 2128 cm^{-1} (C≡C); ^1H NMR (400 MHz) δ=10.00 (4H, s, *meso*-H), 9.95 (2H, s, *meso*-H), 7.05 (2H, s, Th-H), 7.02 (2H, s, Th-H), 6.97 (4H, br s, Th-H), 6.96 (2H, br s, Th-H), 4.31 (8H, q, J=7, 3,7-CH_2CH_3), 4.06–3.96 (24H, m, CH_2CH_3), 2.88–2.69 (20H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.95–1.85 (48H, m, CH_2CH_3), 1.35–1.25 (80H, br m, $CH_2CH_2CH_2CH_2$-CH_2CH_3), 0.96–0.88 (30H, br m, $CH_2CH_2CH_2CH_2CH_2$-CH_3); UV–VIS λ_{max}=448 (ε 201000), 477 (234000), 550 (32600) and 581 nm (51600). Found: C, 72.81; H, 7.28; N, 3.19%. Calcd for $C_{196}H_{226}N_8S_{10}Pd_2$: C, 72.94; H, 7.06; N, 3.48%. **25**: Reddish purple microcrystals ($CHCl_3$–MeOH); mp >275 °C (gradual dec); Mass (ESI-FT-ICR) m/z 1202.91876 (M^{3+}) for $C_{220}H_{254}N_8S_{12}Pd_2$, MW=3607.8; IR (KBr) 2959, 2925, 2854 (CH), 2175 and 2130 cm^{-1} (C≡C); ^1H NMR (400 MHz) δ=10.00 (4H, s, *meso*-H), 9.96 (2H, s, *meso*-H), 7.05 (2H, s, Th-H), 7.02 (2H, s, Th-H), 6.97 (4H, br s, Th-H), 6.96 (4H, br s, Th-H), 4.31 (8H, q, J=7 Hz, 3,7-CH_2CH_3), 4.04–3.96 (24H, m, CH_2CH_3), 2.88–2.69 (24H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.95–1.85 (48H, m, CH_2CH_3), 1.29–1.25 (96H, br m, CH_2CH_2-$CH_2CH_2CH_2CH_3$), 0.90–0.86 (36H, br m, $CH_2CH_2CH_2$-$CH_2CH_2CH_3$); UV–VIS λ_{max}=449 (ε 213000), 476 (250000), 548 (31700) and 581 nm (50000). Found: C, 73.11; H, 7.33; N, 3.01%. Calcd for $C_{220}H_{254}N_8S_{12}Pd_2$: C, 73.24; H, 7.10; N, 3.11%.

4.1.5. 5-Ethynyl-5′-(trimethylsilylethynyl)-3,3′-dihexyl-2,2′-bithiophene (40). A solution of **39**[17] (800 mg, 1.52 mmol) and K_2CO_3 (20 mg, 0.14 mmol) in hexane–MeOH (300 cm^3, 4:1) was stirred under Ar atmosphere at an ambient temperature for 2 h. Poured into water, the organic layer was shaken with brine and dried. The residue obtained after removal of the solvent was chromatographed on Al_2O_3 (3.2×20 cm) with hexane to afford **40** (135 mg, 20%) and **30**[17] (297 mg) successively, together with recovery of **39** (27 mg). **40**: Yellow oil; Mass (EI) m/z 456 (M^++1) for $C_{27}H_{38}S_2Si$, MW=454.8; ^1H NMR (400 MHz) δ=7.12 (1H, s, Th-H), 7.10 (1H, s, Th-H), 3.38 (1H, s, C≡CH), 2.45 (4H, br t, J=8 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.6–1.1 (8H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.9–0.7 (6H, br t, J=6 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.25 (9H, s, $Si(CH_3)_3$). Found: C, 71.02; H, 8.33%. Calcd for $C_{27}H_{38}S_2Si$: C, 71.30; H, 8.43%.

4.1.6. 5-(Trimethylsilylethynyl)-5′-{4-[2,3,7,8,12,13,17,18-octaethylporphyrinatonickel(II)-5-yl]-1,3-butadiynyl}-3,3′-dihexyl-2,2′-bithiophene (41) (Route A). To a solution of $Cu(OAc)_2$ (1.0 g, 5.5 mmol) in Py (36 cm^3) was added the solution of **29** (83 mg, 0.13 mmol) and **40** (258 mg, 0.57 mmol) in Py (200 cm^3) at 40 °C for 1 d. Stirred for additional 5 h, the reaction mixture was poured into water and extracted with $CHCl_3$. The extracts were washed with dil. HCl, sat. $NaHCO_3$, brine successively, and then dried. The residue obtained after removal of the solvent was chromatographed on SiO_2 (3.2×20 cm) with hexane–$CHCl_3$ (7:3) to afford **41** (10 mg, 7%, see below), together

with a mixture (80 mg) of OEP(Ni)–$(DHBTh)_n$–OEP(Ni) (n=2–4)[11] by means of ^{1}H NMR and MS spectral measurements.

4.1.7. 5-Bromo-5′-ethynyl-3,3′-dihexyl-2,2′-bithiophene (44). To a mixture of **38**[7b] (1.06 g, 2.15 mmol), dichlorobis(triphenylphosphine)palladium(II) [$(Ph_3P)_2PdCl_2$] (75 mg, 0.11 mmol) and copper(I) iodide (CuI) (10.2 mg, 0.05 mmol) in diisopropylamine (DIA) (20 cm^3) was added TMS-acetylene (0.26 cm^3, 1.89 mmol). The mixture was stirred at an ambient temperature for 1 h. The reaction mixture was poured into water and extracted with hexane. The extracts were washed with brine and then dried. The residue obtained after removal of the solvent was chromatographed on SiO_2 (4.7×60 cm) with hexane to afford **43** (730 mg, 76%) and **39**[17] (100 mg) successively. **43**: Pale yellow oil; Mass (EI) *m*/*z* 511 and 513 (M^++1 and M^++3) for $C_{25}H_{37}S_2BrSi$, MW=509.7; ^{1}H NMR (400 MHz) δ=7.08 (1H, s, Th-H), 6.90 (1H, s, Th-H), 2.44 (4H, t, J=8 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.48–1.22 (16H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.86 (6H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.24 (9H, s, $Si(CH_3)_3$). Found: C, 58.87; H, 7.55%. Calcd for $C_{25}H_{37}S_2BrSi$: C, 58.91; H, 7.32%. Under Ar atmosphere, a mixture of **43** (720 mg, 1.41 mmol) and K_2CO_3 (20 mg, 0.14 mmol) in hexane–MeOH (10 cm^3, 1:1) was stirred at an ambient temperature for 3 h. Poured into water, the reaction mixture was extracted with hexane, washed with brine and then dried. The residue obtained after removal of the solvent was chromatographed on Al_2O_3 (3.2×3 cm) to afford **44** (580 mg, 94%) as pale yellow oil. **44**: Mass (EI) *m*/*z* 438 and 440 (M^++1 and M^++3) for $C_{22}H_{29}S_2Br$, MW=437.5; ^{1}H NMR (400 MHz) δ=7.13 (1H, s, Th-H), 6.92 (1H, s, Th-H), 3.37 (1H, s, C≡CH), 2.44 (4H, J=8 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.53–1.23 (16H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.87 (6H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$). Found: C, 60.51; H, 6.83%. Calcd for $C_{22}H_{29}S_2Br$: C, 60.40; H, 6.69%.

4.1.8. 5-Bromo-5′-{4-[2,3,7,8,12,13,17,18-octaethylporphyrinatonickel(II)-5-yl]-1,3-butadiynyl}-3,3′-dihexyl-2,2′-bithiophene (45). To a solution of $Cu(OAc)_2$ (1.51 g, 8.32 mmol) in Py–MeOH (60 cm3, 5:1) was added the solution of **29** (328 mg, 0.53 mmol) and **44** (228 mg, 0.52 mmol) in Py–MeOH (300 cm^3, 5:1) at 40 °C for 1 d. Poured into water, the reaction mixture was extracted with $CHCl_3$. The extracts were washed with dil. HCl, sat. $NaHCO_3$, brine successively, and then dried. The residue obtained after removal of the solvent was chromatographed on SiO_2 (3.2×20 cm) with hexane–$CHCl_3$ (7:3) to afford **45** (260 mg, 48%) as deep bluish green microcrystals ($CHCl_3$–hexane). **45**: mp >270 °C (gradual dec); Mass (FAB) *m*/*z* 1052 and 1054 (M^++1 and M^++3) for $C_{60}H_{71}N_4S_2BrNi$, MW=1050.9; IR (KBr) 2962, 2929, 2869 (CH), 2181 and 2130 cm^{-1} (C≡C); ^{1}H NMR (400 MHz) δ=9.42 (2H, s, *meso*-H), 9.39 (1H, s, *meso*-H), 7.27 (2H, s, Th-H), 6.94 (2H, s, Th-H), 4.12 (4H, q, J=7 Hz, 3,7-CH_2CH_3), 3.81–3.76 (12H, m, CH_2CH_3), 2.50 (4H, t m, J=8 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.81–1.70 (24H, m, CH_2CH_3), 1.55–1.24 (16H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.88 (6H, t m, J=7 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$); UV–VIS λ_{max}=446 (ε 129500) and 588 nm (12000). Found: C, 68.44; H, 7.02; N, 5.55%. Calcd for $C_{60}H_{71}N_4S_2BrNi$: C, 68.57; H, 6.81; N, 5.34%. **36**[15] (69 mg) and the dimer of **44** (**52**, 52 mg) were also obtained. **52**: Semi-solid; Mass (EI) *m*/*z* 873, 875 and 877 (M^+, M^++2 and M^++4) for $C_{44}H_{56}S_4Br_2$, MW=872.9; IR (neat) 2955, 2926, 2856 (CH), 2139 cm^{-1} (C≡C); ^{1}H NMR (400 MHz) δ=7.19 (2H, s, Th-H), 6.93 (1H, s, Th-H), 2.47 (4H, J=7.2 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 2.44 (J=7.2 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.50–1.23 (32H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.86 (12H, t m, $CH_2CH_2CH_2CH_2CH_2CH_3$); λ_{max}=245 (relative intensity; 0.854), 365 (1.00) and 386 nm (0.845, sh). Found: C, 60.18; H, 6.75%. Calcd for $C_{44}H_{56}S_4Br_2$: C, 60.54; H, 6.47%. Further trial for satisfactory elemental analysis of **52** was given up.

4.1.9. 5-Ethynyl-5′-{4-[2,3,7,8,12,13,17,18-octaethylporphyrinatonickel(II)-5-yl]-1,3-butadiynyl}-3,3′-dihexyl-2,2′-bithiophene (42) (Route B for 41). To a solution of **45** (200 mg, 0.19 mmol), $(Ph_3P)_2PdCl_2$ (666 mg, 0.95 mmol) and CuI (10.2 mg, 0.05 mmol) in DIA (15 cm^3) was added TMS-acetylene (3 cm^3, 22 mmol). The mixture was stirred at an ambient temperature for 10 h. The reaction mixture was poured into water and extracted with $CHCl_3$. The extracts were washed with brine and then dried. The residue obtained after removal of the solvent was chromatographed on SiO_2 (4.7×10 cm) with hexane–$CHCl_3$ (9:1) to afford **41** (129 mg, 63%) as black purple microcrystals ($CHCl_3$–MeOH). **41**: mp >270 °C (gradual dec); Mass (FAB) *m*/*z* 1069 (M^++1) for $C_{65}H_{80}N_4S_2NiSi$, MW=1068.3; IR (KBr) 2963, 2929, 2870 (CH), 2144 cm^{-1} (C≡C); ^{1}H NMR (400 MHz) δ=9.42 (2H, s, *meso*-H), 9.39 (1H, s, *meso*-H), 7.27 (1H, s, Th-H), 7.12 (1H, s, Th-H), 4.12 (4H, q, J=7 Hz, 3,7-CH_2CH_3), 3.83–3.75 (12H, m, CH_2CH_3), 2.50 (4H, t m, J=8 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.81–1.70 (24H, m, CH_2CH_3), 1.42–1.25 (16H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.89 (6H, t m, J=7 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.26 (9H, s, $Si(CH_3)_3$); UV–VIS λ_{max}=446 (ε 151000) and 591 nm (16200). Found: C, 72.95; H, 7.80; N, 5.24%. Calcd for $C_{65}H_{80}N_4S_2NiSi$: C, 73.08; H, 7.55; N, 5.25%. A solution of **41** (100 mg, 0.09 mmol) and K_2CO_3 (13 mg, 0.09 mmol) in $CHCl_3$–MeOH (10 cm^3, 4:1) was stirred at an ambient temperature under Ar atmosphere for 10 h. Poured into water, the reaction mixture was extracted with $CHCl_3$. The extracts were washed with brine and then dried. The residue obtained after removal of the solvent was chromatographed on Al_2O_3 (3.2×3 cm) with $CHCl_3$ to afford **42** (94 mg, 99%). **42**: Dark bluish green microcrystals ($CHCl_3$–MeOH); mp 255–260 °C (dec); Mass (FAB) *m*/*z* 997 (M^++1) for $C_{62}H_{72}N_4S_2Ni$, MW=996.0; IR (KBr) 3310 (C≡CH), 2963, 2929, 2870 (CH), 2145 cm^{-1} (C≡C); ^{1}H NMR (400 MHz) δ=9.42 (2H, s, *meso*-H), 9.39 (1H, s, *meso*-H), 7.28 (1H, s, Th-H), 7.16 (1H, s, Th-H), 4.13 (4H, q, J=7 Hz, 3,7-CH_2CH_3), 3.81–3.77 (12H, m, CH_2CH_3), 3.39 (1H, s, C≡CH), 2.49 (4H, t m, J=8 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.81–1.71 (24H, m, CH_2CH_3), 1.25 (16H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.87 (6H, t m, J=7 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$); UV–VIS λ_{max}=445 (relative intensity, 1.00) and 590 nm (0.107). Found: C, 74.38; H, 7.63; N,5.46%. Calcd for $C_{62}H_{72}N_4S_2Ni$: C, 74.77; H, 7.29; N, 5.63%. Further trial for satisfactory elemental analysis of **42** was given up.

4.1.10. 5-Bromo-5′-ethynyl-4,4′-dihexyl-2,2′-bithiophene (48). To a mixture of **46**[7b] (1.0 g, 2.03 mmol), $(Ph_3P)_2PdCl_2$

(71 mg, 0.10 mmol) and CuI (10 mg, 0.05 mmol) in DIA (15 cm^3) was added TMS-acetylene (0.23 cm^3, 1.66 mmol). The mixture was stirred at an ambient temperature for 1 h. The reaction mixture was poured into water and extracted with hexane. The extracts were washed with brine and then dried. The residue obtained after removal of the solvent was chromatographed on SiO_2 (3.2×20 cm) with hexane to afford **47** (420 mg, 50%) and the bis(TMS-ethynyl) derivative[17] (60 mg) successively, together with recovery of **46** (430 mg). **47**: Pale yellow oil; Mass (EI) *m/z* 511 and 513 (M^++1 and M^++3) for $C_{25}H_{37}S_2BrSi$, MW=509.7; ^{1}H NMR (400 MHz) δ=6.82 (1H, s, Th-H), 6.80 (1H, s, Th-H), 2.60–2.40 (4H, t m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.51–1.31 (16H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.90–087 (6H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.24 (9H, s, $Si(CH_3)_3$). Found: C, 58.77; H, 7.55%. Calcd for $C_{25}H_{37}S_2BrSi$: C, 58.91; H, 7.32%. Under Ar atmosphere, a mixture of **47** (380 mg, 0.75 mmol) and K_2CO_3 (10 mg, 0.072 mmol) in hexane–MeOH (12 cm^3, 1:1) was stirred at an ambient temperature for 3 h. Poured into water, the reaction mixture was extracted with hexane, washed with brine and then dried. The residue obtained after removal of the solvent was chromatographed on Al_2O_3 (3.2×3 cm) to afford **48** (300 mg, 92%) as pale yellow oil. **48**: Mass (EI) *m/z* 438 and 440 (M^++1 and M^++3) for $C_{22}H_{29}S_2Br$, MW=437.5; ^{1}H NMR (400 MHz) δ=6.83 (1H, s, Th-H), 6.80 (1H, s, Th-H), 3.48 (1H, s, C≡CH), 2.66–2.49 (4H, t m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.64–1.20 (16H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.90–0.87 (6H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$). Found: C, 60.48; H, 6.83%. Calcd for $C_{22}H_{29}S_2Br$: C, 60.40; H, 6.69%.

4.1.11. 5-Bromo-5′-{4-[2,3,7,8,12,13,17,18-octaethylporphyrinatonickel(II)-5-yl]-1,3-butadiynyl}-4,4′-dihexyl-2,2′-bithiophene (49). To a solution of $Cu(OAc)_2$ (1.28 g, 7.05 mmol) in Py–MeOH (42 cm^3, 5:1) was added the solution of **29** (180 mg, 0.29 mmol) and **48** (256 mg, 0.59 mmol) in Py–MeOH (240 cm^3, 5:1) at 40 °C for 1 d. Poured into water, the reaction mixture was extracted with $CHCl_3$. The extracts were washed with dil. HCl, sat. $NaHCO_3$, brine successively, and then dried. The residue obtained after removal of the solvent was chromatographed on SiO_2 (3.2×20 cm) with hexane–$CHCl_3$ (7:3) to afford **49** (133 mg, 43%) as deep bluish green microcrystals ($CHCl_3$–hexane). **49**: mp >260 °C (gradual dec); Mass (FAB) *m/z* 1052 and 1054 (M^++1 and M^++3) for $C_{60}H_{71}N_4S_2BrNi$, MW=1050.9; IR (KBr) 2962, 2929, 2869 (CH), 2173 and 2126 cm^{-1} (C≡C); ^{1}H NMR (400 MHz) δ=9.42 (2H, s, *meso*-H), 9.39 (1H, s, *meso*-H), 6.88 (2H, s, Th-H), 4.13 (4H, q, *J*=7 Hz, 3,7-CH_2CH_3), 3.83–3.77 (12H, m, CH_2CH_3), 2.77 (2H, t, *J*=7 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 2.54 (2H, t, *J*=7 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.81–1.68 (24H, m, CH_2CH_3), 1.61–1.31 (16H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.90 (6H, t m, *J*=6, $CH_2CH_2CH_2CH_2CH_2CH_3$); UV–VIS λ_{max}=440 (ε 85490), 464 (95620) and 592 nm (16120). Found: C, 68.38; H, 6.98; N, 5.46%. Calcd for $C_{60}H_{71}N_4S_2BrNi$: C, 68.57; H, 6.81; N, 5.34%. **36**[15] (38 mg) and the dimer of **48** (**53**, 72 mg) were also obtained. **53**: Semi-solid; Mass (EI) *m/z* 872, 874 and 876 (M^+, M^++2 and M^++4) for $C_{44}H_{56}S_4Br_2$, MW=872.9; IR (neat) 2953, 2925, 2855 cm^{-1} (CH), 2134 (C≡C); ^{1}H NMR (400 MHz) δ=6.87 (2H, s, Th-H), 6.85 (1H, s, Th-H), 2.68 (4H, *J*=7.3 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 2.52 (*J*=7.3 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.63–1.25 (32H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.90 (12H, t m, $CH_2CH_2CH_2CH_2CH_2CH_3$); UV λ_{max}=263 (relative intensity; 0.373), 406 (1.00) and 445 nm (0.519, sh). Found: C, 60.42; H, 6.77%. Calcd for $C_{44}H_{56}S_4Br_2$: C, 60.54; H, 6.47%.

4.1.12. 5-Ethynyl-5′-{4-[2,3,7,8,12,13,17,18-octaethylporphyrinatonickel(II)-5-yl]-1,3-butadiynyl}-4,4′-dihexyl-2,2′-bithiophene (51). To a solution of **49** (230 mg, 0.22 mmol), $(Ph_3P)_2PdCl_2$ (750 mg, 1.07 mmol) and CuI (102 mg, 0.54 mmol) in DIA (20 cm^3) was added TMS-acetylene (2.8 cm^3, 20.2 mmol). The mixture was stirred at an ambient temperature for 16 h. The reaction mixture was poured into water and extracted with $CHCl_3$. The extracts were washed with brine and then dried. The residue obtained after removal of the solvent was chromatographed on SiO_2 (3.2×10 cm) with hexane–$CHCl_3$ (7:3) to afford **50** (200 mg, 86%) as dark bluish green microcrystals ($CHCl_3$–MeOH). **50**: mp >270 °C (gradual dec); Mass (FAB) *m/z* 1069 (M^++1) for $C_{65}H_{80}N_4S_2NiSi$, MW=1068.3; IR (KBr) 2963, 2929, 2870 (CH), 2137 cm^{-1} (C≡C); ^{1}H NMR (400 MHz) δ=9.42 (2H, s, *meso*-H), 9.39 (1H, s, *meso*-H), 6.96 (1H, s, Th-H), 6.94 (1H, s, Th-H), 4.13 (4H, q, *J*=7 Hz, 3,7-CH_2CH_3), 3.84–3.76 (12H, m, CH_2CH_3), 2.77 (2H, t, *J*=7 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 2.65 (2H, t m, *J*=7 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.81–1.68 (24H, m, CH_2CH_3), 1.42–1.33 (16H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.89 (6H, t m, *J*=7 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.26 (9H, s, $Si(CH_3)_3$); UV–VIS λ_{max}=442 (ε 79000), 470 (87500), 522 (12300), 570 (15500, sh) and 594 nm (16400). Found: C, 74.66; H, 7.55; N, 5.83%. Calcd for $C_{65}H_{80}N_4S_2NiSi$: C, 74.77; H, 7.29; N, 5.63%. A solution of **50** (80 mg, 0.07 mmol) and K_2CO_3 (10 mg, 0.07 mmol) in $CHCl_3$–MeOH (8 cm^3, 1:1) was stirred at an ambient temperature under Ar atmosphere for 12 h. Poured into water, the reaction mixture was extracted with $CHCl_3$. The extracts were washed with brine and then dried. The residue obtained after removal of the solvent was chromatographed on Al_2O_3 (3.2×3 cm) with $CHCl_3$ to afford **51** (72 mg, 97%). **51**: Dark bluish green microcrystals ($CHCl_3$–MeOH); mp 275–280 °C (dec); Mass (FAB) *m/z* 997 (M^++1) for $C_{62}H_{72}N_4S_2Ni$, MW=996.0; IR (KBr) 3300 (C≡CH), 2963, 2929, 2870 (CH), 2140 cm^{-1} (C≡C); ^{1}H NMR (400 MHz) δ=9.42 (2H, s, *meso*-H), 9.39 (1H, s, *meso*-H), 6.97 (1H, s, Th-H), 6.96 (1H, s, Th-H), 4.13 (4H, q, *J*=7 Hz, 3,7-CH_2CH_3), 3.82–3.77 (12H, m, CH_2CH_3), 3.53 (1H, s, C≡CH), 2.77 (2H, t, *J*=7 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 2.67 (2H, t, *J*=7 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.81–1.72 (24H, m, CH_2CH_3), 1.66–1.25 (16H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.90 (6H, t m, *J*=7 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$); UV–VIS λ_{max}=443 (relative intensity, 0.861) 468 (1.00), 558 (0.115, sh) and 594 nm (0.174). Found: C, 74.63; H, 7.44; N, 5.58%. Calcd for $C_{62}H_{72}N_4S_2Ni$: C, 74.77; H, 7.29; N, 5.63%.

4.1.13. 5-{4-[2,3,7,8,12,13,17,18-Octaethylporphyrinatonickel(II)-5-yl]-1,3-butadiynyl}-5′-{4-[2,3,7,8,12,13,17,18-octaethylporphyrinatopalladium(II)-5-yl]-1,3-butadiynyl}-3,3′-dihexyl-2,2′-bithiophene (6). To a solution of $Cu(OAc)_2$ (168 mg, 0.92 mmol) in Py–MeOH (10 cm^3, 5:1) was added a solution of **35** (60 mg, 0.09 mmol) and **42** (26 mg, 0.026 mmol) in Py–MeOH

(30 cm^3, 5:1) at 40 °C over 2 h. Stirred for additional 10 h, the reaction mixture was poured into water and extracted with $CHCl_3$. The extracts were washed with dil. HCl, sat. $NaHCO_3$, brine successively, and then dried. The residue obtained after removal of the solvent was chromatographed on SiO_2 (3.2×20 cm) with hexane–$CHCl_3$ (7:3) to afford **6** (15 mg, 35%). **6**: Dark bluish green microcrystals ($CHCl_3$–MeOH); mp >270 °C (gradual dec); Mass (FAB) *m/z* 1658 (M^++1) for $C_{100}H_{114}N_8S_2NiPd$, MW=1657.2; IR (KBr) 2962, 2927, 2869 (CH), 2185 and 2131 cm^{-1} (C≡C); ^1H NMR (400 MHz) δ=9.98 (2H, s, *meso*-H), 9.93 (1H, s, *meso*-H), 9.42 (2H, s, *meso*-H), 9.39 (1H, s, *meso*-H), 7.38 (1H, s, Th-H), 7.33 (1H, s, Th-H), 4.30 (4H, q, *J*=7 Hz, 3,7-CH_2CH_3), 4.15 (4H, q, *J*=7 Hz, 3,7-CH_2CH_3), 4.03–3.94 (12H, m, CH_2CH_3), 3.82–3.77 (12H, m, CH_2CH_3), 2.59 (4H, t m, *J*=8 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.94–1.71 (48H, m, CH_2CH_3), 1.25 (16H, m, $CH_2CH_2CH_2CH_2CH_2$-CH_3), 0.88 (6H, t m, *J*=7 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$); UV–VIS λ_{max}=449 (ε 210000), 554 (23280), 575 (29800, sh) and 586 nm (33160). Found: C, 72.48; H, 7.21; N, 6.68%. Calcd for $C_{100}H_{114}N_8S_2NiPd$: C, 72.48; H, 6.94; N, 6.77%. From the other fractions, **8**[11] (10 mg) and **37** (13 mg) were also obtained.

4.1.14. 5-{4-[2,3,7,8,12,13,17,18-Octaethylporphyrinatonickel(II)-5-yl]-1,3-butadiynyl}-5′-{4-[2,3,7,8,12,13,17,18-octaethylporphyrinatopalladium(II)-5-yl]-1,3-butadiynyl}-4,4′-dihexyl-2,2′-bithiophene (7). To a solution of $Cu(OAc)_2$ (630 mg, 3.47 mmol) in Py–MeOH (24 cm^3, 5:1) was added the solution of **35** (200 mg, 0.30 mmol) and **51** (134 mg, 0.135 mmol) in Py–MeOH (120 cm^3, 5:1) at 40 °C over 2 h. Stirred for additional 15 h, the reaction mixture was poured into water and extracted with $CHCl_3$. The extracts were washed with dil. HCl, sat. $NaHCO_3$, brine successively, and then dried. The residue obtained after removal of the solvent was chromatographed on SiO_2 (3.2×25 cm) with hexane–$CHCl_3$ (7:3) to afford **7** (80 mg, 36%). **7**: Dark green microcrystals ($CHCl_3$–MeOH); mp >265 °C (gradual dec); Mass (FAB) *m/z* 1658 (M^++1) for $C_{100}H_{114}N_8S_2NiPd$, MW=1657.2; IR (KBr) 2962, 2929, 2869 (CH), 2179 and 2125 cm^{-1} (C≡C); ^1H NMR (400 MHz) δ=10.02 (2H, s, *meso*-H), 9.95 (1H, s, *meso*-H), 9.42 (2H, s, *meso*-H), 9.39 (1H, s, *meso*-H), 7.07 (1H, s, Th-H), 7.06 (1H, s, Th-H), 4.30 (4H, q, *J*=7 Hz, 3,7-CH_2CH_3), 4.14 (4H, q, *J*=7 Hz, 3,7-CH_2CH_3), 4.01–3.97 (12H, m, CH_2CH_3), 3.81–3.78 (12H, m, CH_2CH_3), 2.80 (4H, t m, *J*=8 Hz, $CH_2CH_2CH_2$-$CH_2CH_2CH_3$), 1.95–1.74 (48H, m, CH_2CH_3), 1.38 (16H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.94 (6H, t m, *J*=7 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$); UV–VIS λ_{max}=438 (ε 134000), 480 (133000), 553 (29000) and 590 nm (52700). Found: C, 72.31; H, 7.17; N, 6.91%. Calcd for $C_{100}H_{114}$-N_8S_2NiPd: C, 72.48; H, 6.94; N, 6.77%. From the other fractions, **12**[11] (20 mg) and **37** (25 mg) were also obtained.

4.1.15. 5-[4-(3-Hexyl-2-thienyl)-1,3-butadiynyl]-2,3,7,8,12,13,17,18-octaethylporphyrinatopalladium(II) (55). A solution of **35** (140 mg, 0.16 mmol) and 2-ethynyl-3-hexylthiophene[17] (384 mg, 2.0 mmol) in Py–MeOH (240 cm^3, 5:1) was added to the solution of $Cu(OAc)_2$ (3.35 g, 18.5 mmol) in Py–MeOH (120 cm^3, 5:1) at 40 °C dropwise over 12 h. After stirred at 40 °C for additional 5 h, the reaction mixture was poured into water, shaken with dil. HCl to be slightly acidic and extracted with $CHCl_3$. The extracts were washed with sat. $NaHCO_3$ thoroughly and brine successively, and then dried. The residue obtained after removal of the solvent was chromatographed on SiO_2 (3.2×20 cm) with hexane–$CHCl_3$ (7:3) to afford **55** (88 mg, 49%), together with the diacetylene-group connected HTh dimer[17] (370 mg) and a trace amount recovery of **35**. **55**: Reddish purple microcrystals ($CHCl_3$–hexane); mp 255–258 °C (dec); Mass (FAB) *m/z* 854 (M^++1) for $C_{50}H_{58}N_4SPd$, MW=853.5; IR (KBr) 2963, 2929, 2869 (CH), 2187 and 2132 cm^{-1} (C≡C); ^1H NMR (400 MHz) δ=9.99 (2H, s, *meso*-H), 9.94 (1H, s, *meso*-H), 7.28 (1H, d, *J*=5.2 Hz, Th-H), 6.96 (1H, d, *J*=5.2 Hz, Th-H), 4.30 (4H, q, *J*=7.2 Hz, 3,7-CH_2CH_3), 4.05–3.95 (12H, m, CH_2CH_3), 2.90 (2H, t, *J*=7.6 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.92–1.78 (24H, m, CH_2CH_3), 1.26 (8H, br m, $CH_2CH_2CH_2CH_2$-CH_2CH_3), 0.88–0.83 (3H, t, *J*=7.2 Hz, $CH_2CH_2CH_2CH_2$-CH_2CH_3); UV–VIS λ_{max}=438 (ε 136000), 508 (6800), 549 (16000), 570 (13400) and 586 nm (20600). Found: C, 70.09; H, 6.98; N, 6.28%. Calcd for $C_{50}H_{58}N_4SPd$: C, 70.37; H, 6.85; N, 6.57%.

4.1.16. 5-[4-(3,3′-Dihexyl-2,2′-bithiophen-5-yl)-1,3-butadiynyl]-2,3,7,8,12,13,17,18-octaethylporphyrinatonickel(II) (56). A solution of **29** (145 mg, 0.24 mmol) and 5-ethynyl-3,3′-dihexyl-2,2′-bithiophene[17] (430 mg, 1.20 mmol) in Py–MeOH (400 cm^3, 5:1) was added to the solution of $Cu(OAc)_2$ (2.1 g, 11.6 mmol) in Py–MeOH (75 cm^3, 5:1) at 40 °C dropwise over 1 d. After stirred at 40 °C for additional 5 h, the reaction mixture was poured into water, shaken with dil. HCl to be slightly acidic and extracted with $CHCl_3$. The extracts were washed with sat. $NaHCO_3$ thoroughly and brine successively, and then dried. The residue obtained after removal of the solvent was chromatographed on SiO_2 (4.2×30 cm) with hexane–$CHCl_3$ (7:3) to afford **56** (70 mg, 31%) and the diacetylene-group connected HH(DHBTh) dimer[17] (270 mg), together with a trace amount recovery of **29**. **56**: Brownish green microcrystals ($CHCl_3$–MeOH); mp >280 °C (gradual dec); Mass (FAB) *m/z* 973 (M^++1) for $C_{60}H_{72}N_4S_2Ni$, MW=972.0; IR (KBr) 2962, 2928, 2869 (CH), 2182 and 2130 cm^{-1} (C≡C); ^1H NMR (400 MHz) δ=9.42 (2H, s, *meso*-H), 9.39 (1H, s, *meso*-H), 7.32 (1H, d, *J*=5.6 Hz, Th-H), 7.29 (1H, s, Th-H), 6.98 (1H, d, *J*=5.6 Hz, Th-H), 4.12 (4H, q, *J*=7 Hz, 3,7-CH_2CH_3), 3.84–3.76 (12H, m, CH_2CH_3), 2.55 (2H, t, *J*=7.6 Hz, $CH_2CH_2CH_2CH_2CH_2$-CH_3), 2.49 (2H, t, *J*=7.6 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.82–1.71 (24H, m, CH_2CH_3), 1.26 (16H, br m, CH_2CH_2-$CH_2CH_2CH_2CH_3$), 0.88–0.83 (6H, m, $CH_2CH_2CH_2CH_2$-CH_2CH_3); UV–VIS λ_{max}=446 (ε 112900), 562 (11100, sh), 589 (12100) and 615 nm (11300, sh). Found: C, 74.01; H, 7.58; N, 5.51%. Calcd for $C_{60}H_{72}N_4S_2Ni$: C, 74.14; H, 7.47; N, 5.77%.

4.1.17. 5-[4-(4,4′-Dihexyl-2,2′-bithiophen-5-yl)-1,3-butadiynyl]-2,3,7,8,12,13,17,18-octaethylporphyrinatonickel(II) (57). A solution of **29** (70 mg, 0.11 mmol) and 5-ethynyl-4,4′-dihexyl-2,2′-bithiophene[17] (430 mg, 1.20 mmol) in Py–MeOH (240 cm^3, 5:1) was added to the solution of $Cu(OAc)_2$ (1.74 g, 9.6 mmol) in Py–MeOH (60 cm^3, 5:1) at 40 °C dropwise over 1 d. After stirred at 40 °C for additional 5 h, the reaction mixture was poured into water, shaken with dil. HCl to be slightly acidic and

extracted with $CHCl_3$. The extracts were washed with sat. $NaHCO_3$ thoroughly and brine successively, and then dried. The residue obtained after removal of the solvent was chromatographed on SiO_2 (3.3×35 cm) with hexane–$CHCl_3$ (1:1) to afford **57** (64 mg, 58%) and the diacetylene-group connected TT(DHBTh) dimer (180 mg),[17] together with a trace amount recovery of **29**. **57**: Greenish purple microcrystals ($CHCl_3$–MeOH); mp >280 °C (gradual dec); Mass (FAB) *m/z* 973 (M^++1) for $C_{60}H_{72}N_4S_2Ni$, MW=972.0; IR (KBr) 2961, 2928, 2869 (CH), 2180 and 2129 cm^{-1} (C≡C); ^1H NMR (400 MHz) δ=9.42 (2H, s, *meso*-H), 9.39 (1H, s, *meso*-H), 7.05 (1H, d, *J*=1.2 Hz, Th-H), 6.96 (1H, s, Th-H), 6.84 (1H, d, *J*=1.2 Hz, Th-H), 4.13 (4H, q, *J*=7 Hz, 3, 7-CH_2CH_3), 3.84–3.75 (12H, m, CH_2CH_3), 2.77 (2H, t, *J*=7.6 Hz, $CH_2CH_2CH_2CH_2CH_2$-CH_3), 2.59 (2H, t, *J*=7.6 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.82–1.71 (24H, m, CH_2CH_3), 1.36–1.32 (16H, m, CH_2-$CH_2CH_2CH_2CH_2CH_3$), 0.90 (6H, br t, *J*=6.8 Hz, CH_2CH_2-$CH_2CH_2CH_2CH_3$); UV–VIS λ_{max}=439 (ε 74000), 463 (81700), 558 (10800, sh), 594 (13200) and 618 nm (9700, sh). Found: C, 74.00; H, 7.68; N, 5.66%. Calcd for $C_{60}H_{72}N_4S_2Ni$: C, 74.14; H, 7.47; N, 5.77%.

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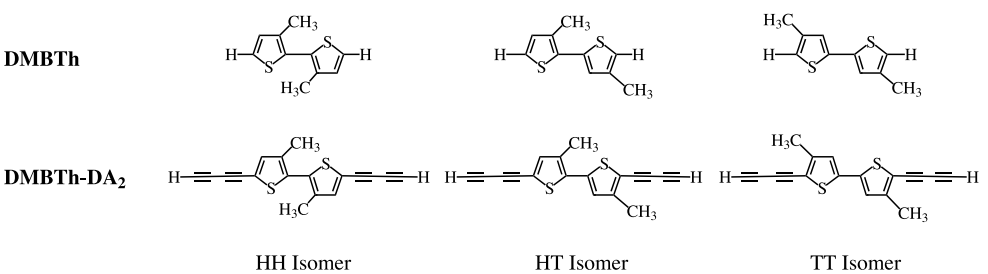

Chart 7.

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The CA.M lattice revisited. Gel formation from a linear bis-isocyanuric acid and 2-amino-4,6-bis-(4-*tert*-butylphenylamino)-1,3,5-triazine

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Abstract—Five bis(isocyanuric) acid dimers have been prepared and characterised. The introduction of flexible alkyl chains was necessary to aid solubility. On mixing with *N*,*N*-bis(4-*tert*-butyphenyl)melamine in THF followed by slow evaporation, a viscous gel can form which is interpreted as evidence for the assembly of an infinite 2-D hydrogen bonded network.

1. Introduction

The cyanuric acid–melamine lattice (CA.M)[1,2] has been a source of inspiration[3,4] for the study of hydrogen bonded aggregates. By mixing melamine derivatives and isocyanuric acid or dialkylbarbituric acid derivatives, hydrogen bonding is restricted to give discrete aggregates which can be studied in solution and in some cases crystallised.[4,5] The crystallisation of diethylbarbituric acid with *N*,*N*-bis(4-substituted phenyl)melamines gives either linear tape, crinkled tape or a rosette motif depending upon the substituents on the aryl rings.[5] If 4-*tert*-butyl substituted aryl rings are used as substituents then the rosette motif (Fig. 1) crystallises. The steric bulk of the *tert*-butyl groups disfavours linear or crinkled tapes. This structure prepared by us is very similar to the original rosette crystallised by the group of Whitesides.[5] The motif is not quite planar in contrast to the cyclic motif observed in the crystal structure of the CA.M lattice[2] suggesting that the deviation from planarity is a consequence of crystal packing forces since there are no steric interactions between the substituents.

In the structure of components **1** and **2**, rosette motifs form sheets that extend in $\{1\bar{1}\bar{1}\}$ planes. These sheets are packed in parallel fashion. Adjacent sheets within the stack are related by inversion symmetry. In two of the three independent molecules of **1**, the alkyl chains adopt an all-*trans* conformation resulting in an essentially planar $H_3C(CH_2)_3C(CH_2)_3CH_3$ unit. The mean plane of this unit is approximately perpendicular to that of the ring. In the third independent molecule of **1**, both alkyl chains are in end-*gauche* conformation

Our approach to preparing new networked materials was to attempt to 'expand' the CA.M lattice by introducing a linear spacer between pairs of cyanuric acids. The anticipated 2-D hydrogen bonded network is shown in Figure 2. It would consist of sheets with hexagonal cavities which are lined by six *N*,*N*-bis(4-*tert*-butyphenyl) groups of the melamines. This example would represent a macrocyclic architecture formed by supramolecular chemistry that can bind to a multiple number of six exchangeable melamine derivatives with convergent functionality that forms a cavity.

2. Results and discussion

Initially we prepared the linear bis-isocyanuric acids **11** and **15** (Schemes 1 and 2). Biuret **3** was nitrated to give nitrobiuret **4**[5] then reacted with 4-iodoaniline or 2-chloro-4-iodoaniline to give compounds **5** and **6**, respectively. Cyclisation was achieved by heating with NaOEt in EtOH with $(EtO)_2C{=}O$.[3] To our surprise, compound **7** underwent Sonogashira coupling with trimethylsilylacetylene despite possessing the acidic functionality of the isocyanuric acid group. Building block **10** was formed by removing the trimethylsilyl group with KOH/MeOH. Coupling of compound **7** with **10** gave the first isocyanuric acid dimer **11**.

Keywords: 2-Amino-4,6-bis-(4-*tert*-butylphenylamino)-1,3,5-triazine; Cyanuric acid; Hydrogen bonding; Rosette motif.
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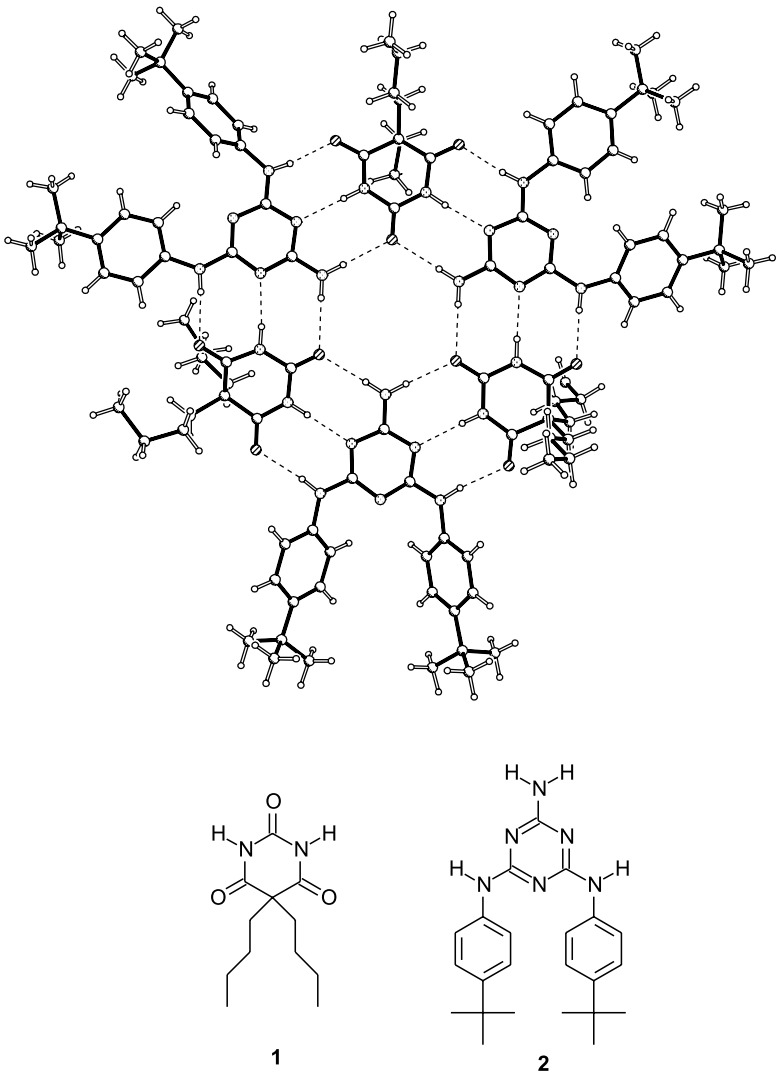


Figure 1. Crystal structure of a rosette formed from components **1** and **2**.

Dimer **15** was prepared by palladium catalysed coupling of diethnylbenzene **14**[6] with 4-iodophenylisocyanuric acid **7**.

Both dimers **11** and **15** are poorly soluble but were of interest because they might have packed well in a crystal lattice. They dissolved in DMSO allowing good proton and carbon spectra to be obtained but were too involatile to provide mass spectral molecular ions. Ideally for rosette formation, solubility in $CHCl_3$ is desired because in this relatively non-polar solvent strong hydrogen bonding between components can occur. In contrast, in polar solvents such as DMSO and THF, hydrogen bonding between components is much weaker and rosette aggregates break up. However, we anticipated that for a concentrated solution in a polar solvent, 2-D network formation may still occur because of cooperative stabilisation owing to the infinite network. A 2-D network should be more stable than 1-D chains which should be more stable than discrete aggregates. However, all attempts made to form a network from dimers **11** and **15** with *N*,*N*-bis(4-*tert*-butylphenyl)-melamine in THF and DMSO were unsuccessful. In all cases, slow evaporation of solvent gave a powder which could not be characterised.

Given that $CHCl_3$ is a more desirable solvent for these studies a further series of dimers **29**–**31** were prepared which contained solubilising alkyl chains in the centre (Scheme 3). The synthesis of diethnyl precursors **26**–**28**[7,8] follows standard methods and indeed all of the intermediates have been previously reported.[7–11] Palladium coupling of compounds **27**–**28** with 4-iodophenylisocyanuric acid **7** gave the extended dimers **29** and **31**, respectively. Palladium coupling of precursor **26** was less successful. The purification was aided by the flexible alkyl chains, which enhance solubility and give the compounds surfactant-like properties. Excess iodophenylisocyanuric acid is easily removed by extraction of the crude solid with aqeous NaOH. The sodium salt of this is water soluble while the sodium salt, mono or bis, of the dimer is still insoluble in acid or base. The dimer is then treated with acid to ensure reprotonation. The dimers are much more soluble than the unsubstituted dimers **11** and **15** and can be dissolved in THF. The molecular ion in the MALDI mass spectrum showed the same peak intensity pattern as that calculated theoretically which aided characterisation. However, although good proton and carbon spectra were obtained, the MALDI spectra showed evidence of oligomers of compounds **26**–**28** coupled terminally with isocyanuric

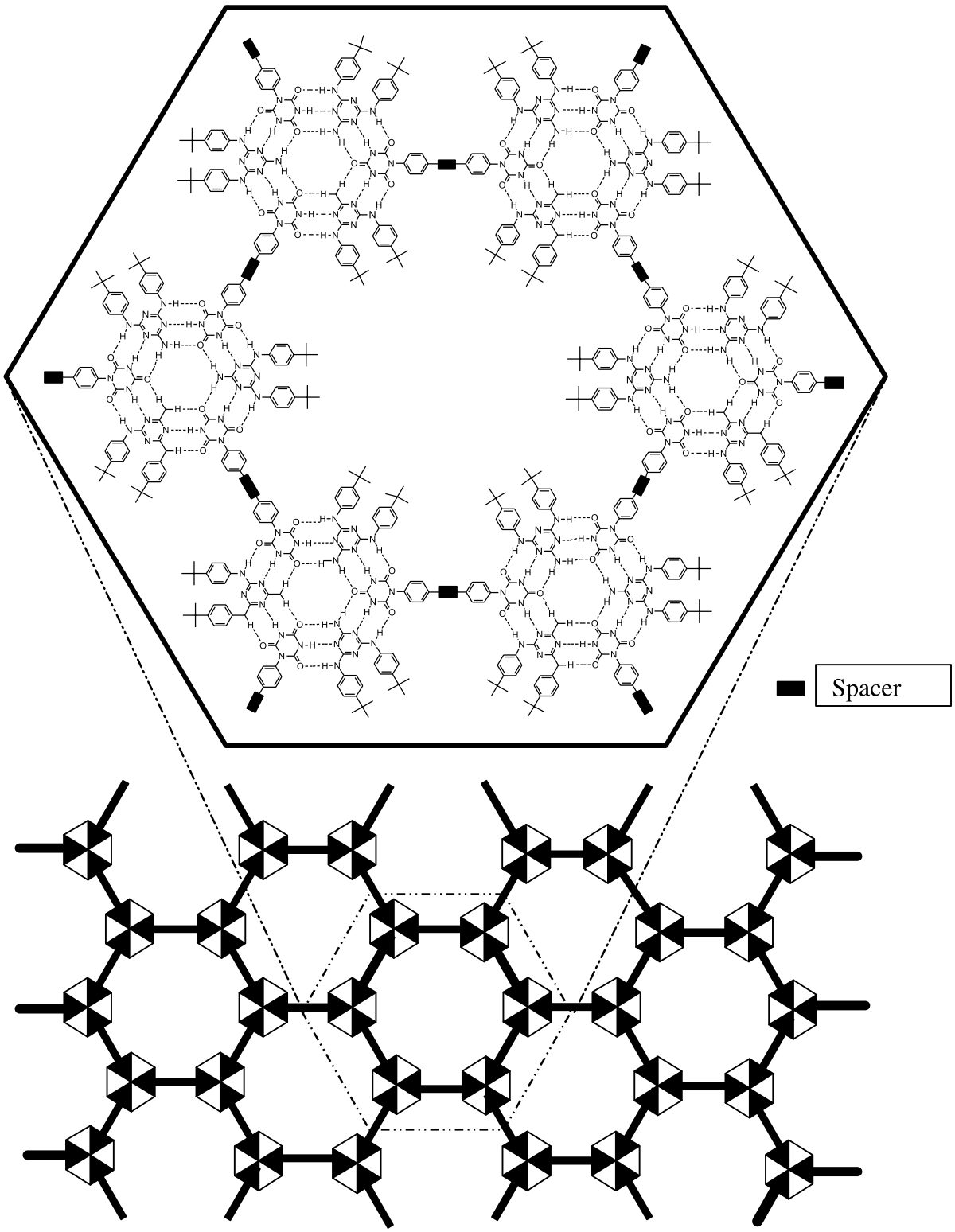
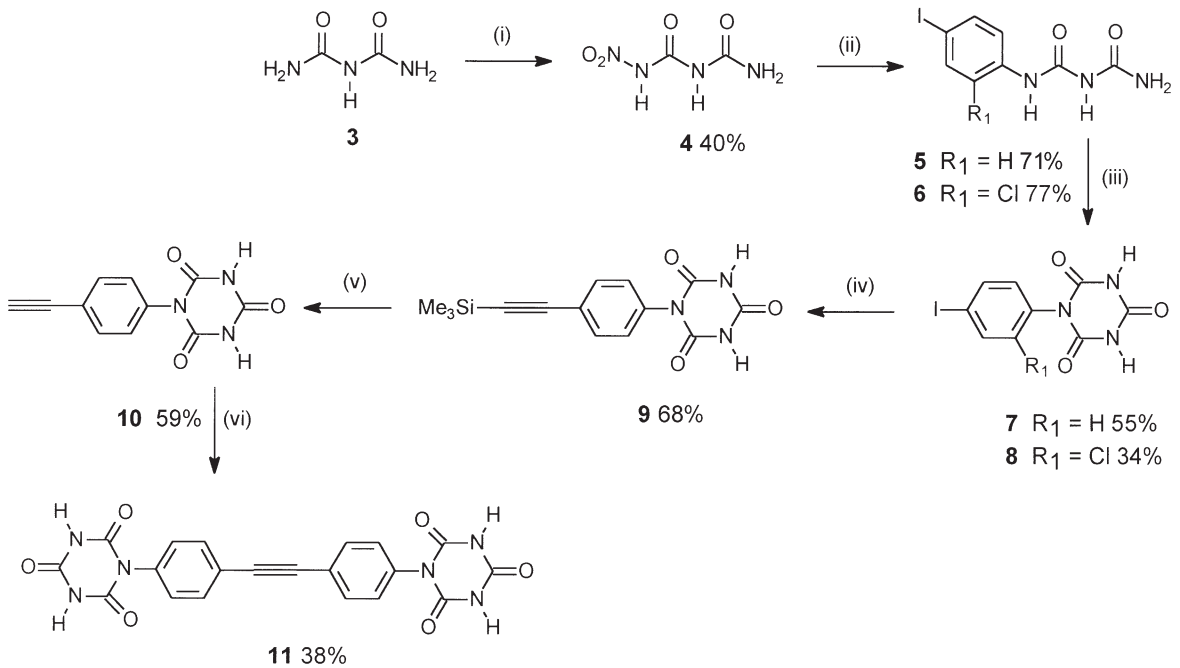


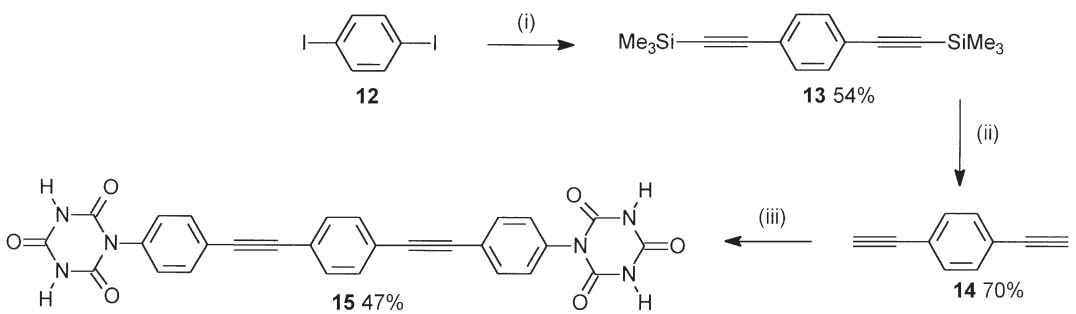
Figure 2. Drawing of the proposed 2-D structural motif formed between compounds **29** and **2**.

acids. For this reason an alternative route to prepare **29** was used which involved coupling *N*-(4-ethynylphenyl)isocyanuric acid **10** with 1,4-didecyloxy-2,5-diiodobenzene **21**. This route avoids the formation of similar polymeric oligomers and gives a product of greater purity (Scheme 4). Unfortunately dimers **29** and **31**, which possesses a longer side chain, are not soluble in $CHCl_3$. To enhance solubility in $CHCl_3$, dimer **30** was prepared which has a chlorine substituent adjacent to each isocyanuric acid. This should cause some molecular twisting and reduce the symmetry and so enhance solubility. Compound **30** has a slight solubility in $CHCl_3$ because a suspension of **30** in $CHCl_3$ turns yellow in colour although the solubility is not enough to obtain NMR data in $CHCl_3$.

2-D network formation was studied in concentrated THF



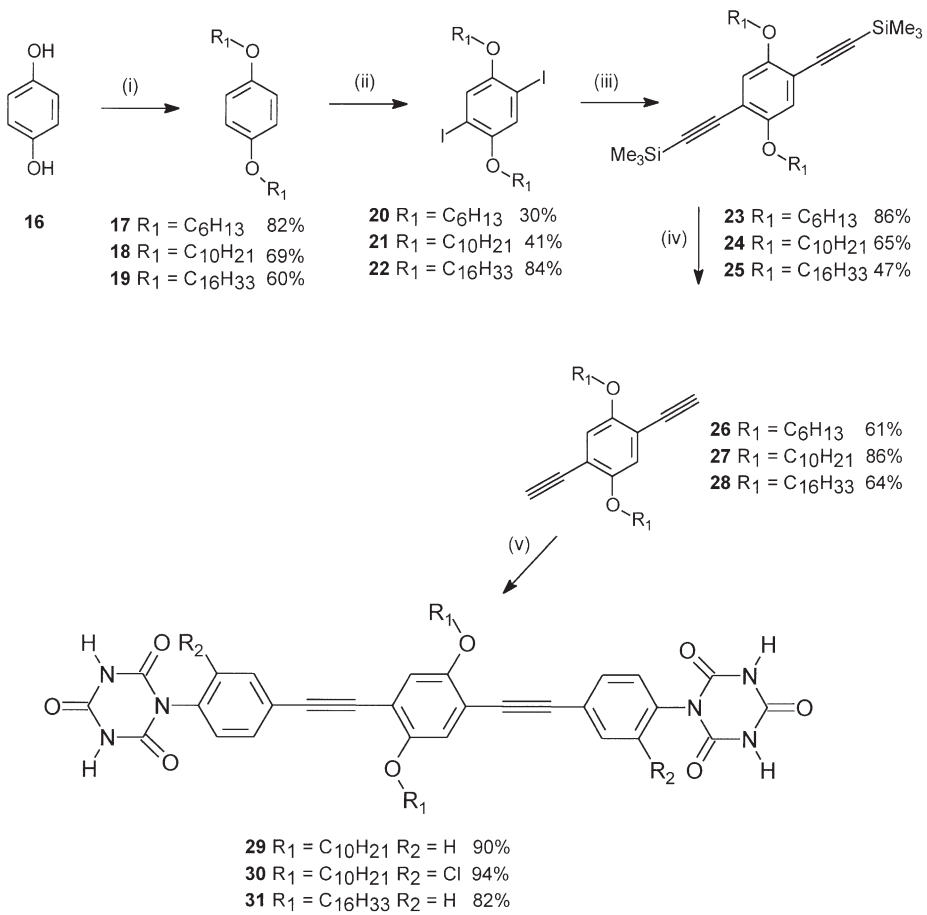
Scheme 1. Reagents and conditions: (i) HNO_3/H_2SO_4 (40%); (ii) 4-iodoaniline or 2-chloro-4-iodoaniline/H_2O/△; (iii) diethyl carbonate/Na/EtOH/△; (iv) **7**/TMS–C_2H/$(PPh_3)_2PdCl_2$/CuI/Et_3N/RT/THF/1–3 days; (v) KOH/MeOH/rt/15; (vi) **7**/$(PPh_3)_2PdCl_2$/CuI/Et_3N.



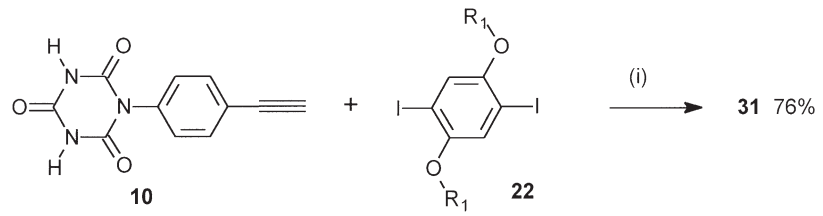
Scheme 2. Reagents and conditions: (i) TMS–C_2H/$(PPh_3)_2PPCl_2$/CuI/Et_3N/rt/THF; (ii) KOH/MeOH/rt/15 min; (iii) **7**/$(PPh_3)_2PdCl_2$/CuI/Et_3N/rt.

solution. An interesting result was obtained from mixing THF solutions of dimer **29** with *N*,*N*-bis(4-*tert*-butyphenyl)-melamine **1**. A solution of the dimer in THF was mixed with a solution of compound **1** and allowed to slowly evaporate in a sample vial. In one case this was done over a few months in an NMR tube. As the solvent slowly evaporates the solutions become thick and viscous with gel like properties. A skin could form on the surface which redissolved on mixing and heating. The gel would not pour from the vessel. If desolvation was continued the sample eventually reverted to a dry flaky powder. In contrast if the dimer **29** alone or the melamine **1** alone is slowly concentrated in THF no gel like phase is observed but a powder eventually forms. Also concentration of a solution of the dimer with *N*,*N*-bis(phenyl)melamine does not give a viscous gel like phase but forms a powder as the components precipitate from solution. The viscous gel phase is interesting evidence for the formation of extended 2-D sheets depicted in diagram 2 which are still in solution. On slow solvent evaporation an extended network of hydrogen bonds could form, stabilised by the infinite network. A concentrated solution is necessary because of the polar solvent THF which would normally break up rosettes. *N*,*N*-bis(4-*tert*-butyphenyl)melamine **1** favours rosette formation over other structural motifs, so the motif depicted in Figure 2 is our proposal. Dimers **30** and **31** did not form gels with melamine **1** from THF showing that the gel formation is sensitive to the dimer structure. The precipitated material may still consist of extended networks but it is difficult to characterise. Evidently a dimer soluble in $CHCl_3$ is desired because the network formation could be studied in a less concentrated solution and may be easier to crystallise. Furthermore the methodology to produce compounds with this type of spacer structure that are soluble in water is known[12] so isocyanuric acid dimers with these spacers might allow assembly in water to be studied.

In conclusion, linear bis(isocyanuric) acid dimers have been prepared and characterised. On mixing one with *N*,*N*-bis(4-*tert*-butyphenyl)melamine in THF followed by slow evaporation, a gel forms which is interpreted as evidence for the assembly of an infinite and soluble 2-D hydrogen bonded network The network is predicted to have hexagonal like cavities each of which binds six exchangeable melamines on the inside with the *tert*-butylphenyl groups pointing inwards forming a cavity.[13]



Scheme 3. Reagents and conditions: (i) hexylbromide, decylbromide or hexadecylbromide/K_2CO_3/acetone/△; (ii) $I_2/KIO_3/H_2SO_4$/HOAc/H_2O; (iii) TMS–$C_2H/(PPh_3)_2PdCl_2$/CuI/Et_3N/rt/THF; (iv) KOH/MeOH/THF/2 h; (v) **7** or **8**/$(PPh_3)_2PdCl_2$/CuI/Et_3N/△.



Scheme 4. Reagents and conditions: (i) $(PPh_3)_2PdCl_2$/CuI/Et_3N/Δ.

3. Experimental

3.1. General

Melting points were carried out using a Kofler hot-stage microscope and are uncorrected. Butterworth Laboratories, using a PE.2400 CHN analyser, conducted elemental analysis. Ultraviolet spectra were recorded on a Perkin–Elmer Lambda 15 UV–VIS spectrometer using DCM, THF and DMSO as the solvents. Infrared spectra were recorded on an ATI Mattson FTIR spectrometer. ^1H and ^{13}C NMR spectra were obtained at 250 and 62.9 MHz, respectively, on a Brucker AC 250 spectrometer and at 400 and 100.5 MHz, respectively on a Varian 400 spectrometer. Chemical shifts (δ) are given in ppm relative to the residual solvent. Coupling constants, (J) are given in Hz. All compounds were prepared to a high standard of purity, greater than 95% as determined by ^1H NMR spectra. Low-resolution mass spectra were obtained using electrospray ionization on a Finnigan Navigator Mass Spectrometer and accurate mass at the University of Wales. Swansea using fast atom bombardment methods and MALDI. For dimers **29**, **30** and **31** the theoretical peak pattern for the MALDI spectrum is listed. Aldrich, Lancaster Synthesis, Avocado and BDH supplied starting materials. Et_3N was dried by distillation from CaH_2, EtOH was dried by distillation from magnesium, toluene from sodium, and THF from potassium using benzophenone as the indicator. All dried solvents were transferred from the stills to the reaction vessels using oven dried glass syringes under nitrogen. Reactions requiring anhydrous conditions were carried out in three-necked r.b. flasks, which were flame dried while under vacuum and then purged three times with either argon or nitrogen.

3.1.1. 1-Nitrobiuret 4.[3] Biuret **3** (51.5 g, 0.5 mol) was added in 1 g portions to a mixture of sulphuric acid (125 mL, ~97%) and nitric acid (30 mL, ~69%), chilled in an ice bath, over 30 min. After the mixture had been stirred for 2 h, all the solid had dissolved, and the solution was poured onto ice (1 kg). The ice was allowed to melt and the precipitate was filtered. The precipitate was suspended in water (1 L), chilled in an ice bath, and sodium hydroxide (400 mL, 1 M) was added to bring the pH to ~8.5. The solution was filtered cold and the product precipitated with concentrated HCl to pH~2, filtered, washed with water and dried under vacuum to give the title compound (30 g, 40%) as a white powder; δ_H (250 MHz; DMSO-d_6) 4.95 (2H, s, br, NH_2), 7.07–7.39 (1H, d, NH) and 9.42 (1H, s); δ_C (62.9 MHz; DMSO-d_6)148.8 and 153.2; *m/z* (ES) 147.0 (M^++Na, 100%).

3.1.2. 1-(4-Iodophenyl)biuret 5. *General procedure*. A mixture of 1-nitrobiuret **4** (4.78 g, 32 mmol) and 4-iodoaniline (5.14 g, 25 mmol) in water (50 mL) was heated at reflux for 2 h. The precipitated product was filtered hot, washed with water and MeOH to give the title compound (5.4 g, 71%) as a grey powder, mp >230 °C. (Found: C, 31.7; H, 2.6; N, 13.8. $C_8H_8IN_3O_2$ requires C, 31.5; H, 2.6; N, 13.8%); ν_{max} (KBr)/cm^{-1} 3386vs, 3311m, 3241m, 3207m, 3151m, 3050m, 2979m, 2923m, 1729vs, 1689vs, 1581vs, 1533vs, 1508vs, 1481s, 1429vs, 1384vs, 1299vs, 1213vs, 1118s, 1078m, 991w, 879w, 815s, 732m, 682w and 651; δ_H (250 MHz; DMSO-d_6) 6.90 (2H, vbs, NH_2), 7.29 (2H, d, *J*=8.6 Hz), 7.61 (2H, d, *J*=8.6 Hz), 8.93 (1H, s) and 10.05 (1H, s); δ_C (62.9 MHz; DMSO-d_6) 86.3, 121.3, 137.5, 138.1, 151.9 and 155.5; *m/z* 305.9741 (M^++H. $C_8H_9IN_3O_2$ requires 305.9739).

3.1.3. 1-(2-Chloro-4-iodophenyl)biuret 6. 3.1 g, 77%. Grey powder, mp >230 °C (decomp. from water) ν_{max}(KBr)/cm^{-1} 3441m, 3256m, 3194m, 1704s, 1621m, 1590s, 1578s, 1505s, 1370m, 1351m, 1297m, 1272m, 1257s, 1232s and 818m; δ_H (250 MHz; [$^2H_6$]DMSO) 6.9 (2H, br s, NH_2), 7.64 (1H, d, *J*=8.9 Hz, Ar), 7.83 (1H, s, Ar), 8.03 (1H, d, *J*=8.6 Hz, Ar), 9.34 (1H, s, NH) and 10.9 (1H, s, NH); δ_C(62.9 MHz; DMSO-d_6) 61.2, 86.3, 122.6, 123.1 135.2, 136.5, 151.6 and 155.8; *m/z* (EI) 357.0 (M^++NH_4, 100%) and 340.0 (M^++H, 31), *m/z* (EI) 339.9351 (M^++H, 100. $C_8H_7ClIN_3O_2$ requires 339.9344).

3.1.4. *N*-(4-Iodophenyl)isocyanuric acid 7. *General procedure*. Sodium ethoxide was prepared by dissolving sodium (0.49 g, 21 mmol) in dry ethanol (60 mL) under an argon atmosphere. Biuret **5** (1.83 g, 6 mmol) and diethyl carbonate (1.42 g, 12 mmol) were added to this solution. The mixture was heated at reflux for 24 h, allowed to cool and toluene was added. The sodium salt was filtered, washed with toluene and dried. The solid was dissolved in water, filtered and dilute HCl was added and the precipitate was filtered, washed with water and dried under vacuum to give the title compound (1.1 g, 55%) as a white powder, mp >200 °C. (Found: C, 32.1; H, 1.8; N, 12.3. $C_9H_6IN_3O_3$ requires C, 32.6; H, 1.8; N, 12.7%); ν_{max} (KBr)/cm^{-1} 3212s, 3064s, 2831m, 1799vs, 1762vs, 1693vs, 1479vs, 1402vs, 1211m, 1114w, 1068w, 1010w, 881w, 823m and 744vs; δ_H (250 MHz; DMSO-d_6) 7.16 (2H, d, *J*=8.5 Hz), 7.82 (2H, d, *J*=8.5 Hz), and 11.58 (2H, bs); δ_C (62.9 MHz; DMSO-d_6) 94.9, 131.6, 134.2, 137.7, 148.9 and 149.6; *m/z* 331.1 (M^+, 100%).

3.1.5. *N*-(2-Chloro-4-iodophenyl)isocyanuric acid 8. 0.54 g, 34%. White powder, mp >260 °C (from water). ν_{max}(KBr)/cm^{-1} 3420br, 3208br, 3082br, 2847w, 1751s, 1704s, 1574m, 1476s, 1419s, 1408s, 1375m, 830m, 789m, 761m, 603m, 555m and 533m; δ_H (250 MHz; DMSO-d_6) 7.33 (1H, d, *J*=8.2 Hz, Ar), 7.81 (1H, d, *J*=7.9 Hz, Ar), 8.05 (1H, s, Ar) and 11.9 (2H, br s, NH); δ_C (62.9 MHz; DMSO-d_6) 96.3, 131.6, 133.1, 133.6, 137.1, 137.2, 148.7 and 148.8; *m/z* (ES^-) 364.3 (M−H, 100%); *m/z* (ES^-) 363.8987 (M−H, 100% $C_9H_5ClIN_3O_3$ requires 363.8991).

3.1.6. *N*-(4-Trimethylsilylethynylphenyl)isocyanuric acid 9. A mixture of isocyanuric acid **7** (0.4 g, 1 mmol), trimethylsilylacetylene (0.23 g, 2 mmol), $Pd(PPh_3)_2Cl_2$ (20 mg, 28 μmol), CuI (4 mg, 21 μmol) in THF (25 mL) and Et_3N (4 mL) under an argon atmosphere was stirred, at rt, for 8 h. The solvent was removed under reduced pressure and the residue, dissolved in DCM, filtered through silica to elute impurities followed by elution with ethyl acetate. The solvent was removed under reduced pressure and the residue washed with light petroleum to give the title compound (0.25 g, 68%) as an off white solid, mp >250 °C. (Found: C, 55.0; H, 5.0; N, 12.9. $C_{11}H_{10}N_3O_3$ requires C, 55.8; H, 5.0; N, 13.9%); ν_{max} (KBr)/cm^{-1} 2969vs, 2939vs 2759vs, 2678vs, 2474m, 1463vs, 1413s, 1359m, 1162s, 1064w, 1029vs, 842w and 798m; δ_H (250 MHz; DMSO-d_6) 0.24 (9H, s, Si–Me), 7.34 (2H, d, *J*=8.2 Hz), 7.53 (2H, d, *J*=8.2 Hz) and 11.58 (2H, bs); δ_C (62.9 MHz; DMSO-d_6) −0.1, 95.1, 104.5, 122.3, 129.7, 132.0, 134.7, 148.9 and 149.6; *m/z* (ES) 301 (M^++Na, 100%); *m/z* (ES) 319.1224 (M+NH_4, 100% $C_{14}H_{15}N_3SiO_3$ requires 319.1221).

3.1.7. *N*-(4-Ethynylphenyl)isocyanuric acid 10. Isocyanuric acid **9** (0.71 g, 2.3 mmol) was suspended in ethanol (40 mL). Aqueous sodium hydroxide (40 mL, 1 M) was added and the solution stirred. After 1 h the solvent was reduced to 50 mL and concentrated HCl was added to adjust the pH to 7. The precipitate was filtered and the residue was washed with water to give the title compound (0.32 g, 59%) as off white solid, mp >200 °C (from water). (Found: C, 57.1; H, 3.2; N, 17.3. $C_{11}H_{10}N_3O_3$ requires C, 57.6; H, 3.1; N, 18.3%); ν_{max} (KBr)/cm^{-1} 3484w, 3413m, 3303m, 3226vs, 3201vs, 3097vs, 3054vs, 2875s, 2420m, 2358vs, 2329vs, 1984m, 1810vs, 1675vs, 1612m, 1502vs, 1380vs, 1267w, 1211m, 1095m, 908w, 840m, 809w, 754vs, 725vs, 632vs, 547s, 474w and 428s; δ_H (250 MHz; DMSO-d_6) 4.27 (1H, s, CCH), 7.36 (2H, d, *J*=8.3 Hz), 7.56 (2H, d, *J*=8.3 Hz), and 11.59 (2H, s); δ_C (62.9 MHz; DMSO-d_6) 81.6, 82.9, 122.0, 129.7, 132.2, 134.7, 148.9 and 149.6; *m/z* 228.1 (M^+−H, 100%) *m/z* 247.0827 (M^++NH_4, 100% $C_{11}H_7N_3O_3$ requires 247.0827).

3.1.8. Bis-1,2-ethynyl-(4-phenylisocyanuric acid) 11. A stirred solution of 1-(4-ethynylphenyl)isocyanuric acid **10** (250 mg, 1.09 mmol),1-(4-iodophenyl)isocyanuric acid **7** (360 g, 1.09 mmol) and CuI and $(PPh_3)_2PdCl_2$ in catalytic amounts dissolved in degassed anhydrous THF (40 mL) was treated with Et_3N (3 mL). The mixture was refluxed for 24 h, then another aliquot of 1-(*p*-iodophenyl)isocyanuric

acid (200 g) was added. The organic solvent was removed under reduced pressure before the remaining solid was partially dissolved up in 10% sodium hydroxide (40 mL). The insoluble material was collected by filtration then stirred as a suspension in THF (60 mL) and water (60 mL) whilst conc. hydrochloric acid (15 mL) was added dropwise. The acidic mixture was allowed to stir for 2 h, followed by removal of the organic solvent under reduced pressure, addition of water (30 mL), filtration and a final wash with fresh water (20 mL) to give the title compound (180 mg, 38%) as a brown powder, mp >250 °C (from tetrahydrofuran) ν_{max}(KBr)/cm^{-1} 3454br, 3216m, 3070m, 2833m, 1791s, 1762s, 1522s, 1444s, 1408s, 1214w, 840m, 756m, 744m, 734m, 721m, and 549m; δ_H(250 MHz; DMSO-d_6) 7.41 (4H, d, J=7.6 Hz, Ar), 7.65 (4H, d, J=7.3 Hz, Ar) and 11.64 (4H, s, NH); δ_C(250 MHz; DMSO-d_6) 89.4, 122.3, 129.8, 131.9, 134.6, 148.9 and 149.8.

3.1.9. 1,4-Bis(trimethylsilylethynyl)benzene 13.[6] Trimethylsilylacetylene (3.57 g, 0.036 mol) was added to a stirred solution of 1,4-diiodobenzene (4.0 g, 0.012 mol), CuI and $(PPh_3)_2PdCl_2$ in catalytic amounts dissolved in degassed anhydrous Et_3N (60 mL). The reaction mixture was refluxed for 8 h under a nitrogen atmosphere then the solvent was removed under reduced pressure. The residue was taken up in DCM and filtered through a silica plug. Afterwards the solvent was removed under reduced pressure. The residue was dissolved in (1:1) methanol/ethylacetate (40 mL) and cooled in an ice water bath for 3 h. The product readily crystallised and was collected by filtration to yield the title compound (1.75 g, 54%) as clear crystalline material, mp 121–123 °C (from methanol/ethylacetate 1:1) (lit. 122 °C) δ_H(250 MHz; $CDCl_3$) 0.24 (18H, s, Si(CH_3)$_3$) and 7.38 (4H, s, Ar); δ_C(62.9 MHz; $CDCl_3$) −0.06, 96.3, 104.6, 123.2 and 131.8.

3.1.10. 1,4-Diethynylbenzene 14.[6] To a stirred solution of 1,4-bis(trimethylsilylethynyl)benzene **13** (1.5 g, 5.55 mmol) in DCM (25 mL) and methanol (25 mL), was added dropwise potassium hydroxide (1 M, 10 mL). The mixture was left to stir for 3 h, then the organic solvent was removed under reduced pressure. Water (30 mL) was added and the mixture was extracted with ether (3×30 mL), dried with $MgSO_4$ and treated with decolourising charcoal. The solvent was removed under reduced pressure to yield the title compound (0.48 g, 70%) as a white solid, mp 94–95 °C (from diethyl ether) (lit 95–96 °C) δ_H(250 MHz; $CDCl_3$) 3.2 (2H, s, acetylenic H) and 7.45 (4H, s, Ar); δ_C(62.9 MHz; $CDCl_3$) 79.1, 83.1, 122.6 and 132.0.

3.1.11. 1,4-Phenylethynyl-(4-phenylisocyanuric acid) 15. A stirred solution of 1,4-diethynylbenzene 14 (200 mg, 3.17 mmol), 1-(4-iodophenyl)isocyanuric acid 7 (2.1 g, 12.7 mmol) and CuI and $(PPh_3)_2PdCl_2$ in catalytic amounts dissolved in degassed anhydrous THF (60 mL) was treated with Et_3N (5 mL). The mixture was refluxed for 12 h, then the organic solvent was removed under reduced pressure, redissolved in a large volume of THF and filtred through a silica plug. After concentration, the remaining solid was partially dissolved up in 10% sodium hydroxide (40 mL). The insoluble material was collected by vacuum filtration then stirred as a suspension in THF (60 mL) and water (60 mL) whilst conc. hydrochloric acid (15 mL) was added dropwise. The acidic mixture was allowed to stir for 2 h, followed by removal of the organic solvent under reduced pressure, addition of water (30 mL), filtration and a final wash with fresh water (20 mL) to give the title compound (393 mg, 47%) as a pale yellow powder, mp >250 °C (from water). (Found C: 62.6, H, 3.6. $C_{28}H_{16}N_6O_6$ requires C, 63.2; H, 3.0%); λ_{max}(DMSO)/nm 325 (log ε 4.6); ν_{max}(KBr)/cm^{-1} 3783w, 3258s, 3098s, 3063s, 1796s, 1754vs, 1692vs, 1488vs, 1460s, 1418s, 1390m, 838w and 787vs; δ_H(250 MHz; DMSO-d_6) 7.41 (4H, d, J=8.2 Hz, Ar), 7.63 (4H, s, Ar), 7.66 (4H, d, J=8.6 Hz, Ar) and 11.64 (4H, s, NH); δ_C(62.9 MHz; DMSO-d_6) 89.6, 90.8, 122.2, 122.4, 129.7, 131.8, 132.0, 134.7, 148.9 and 149.7.

3.1.12. 1,4-Dihexyloxybenzene 17.[9] *General procedure*. A solution of hydroquinone (18.2 g, 0.110 mol), bromohexane (40.4 g, 0.242 mol) and K_2CO_3 (15.2 g) in acetone (400 mL), was refluxed under a nitrogen atmosphere for 3 days. Toluene (300 mL) was added, then the solution was filtered hot, and the filtrate was concentrated to a brown solid which was redissolved in DCM. Washed twice with dilute sodium dithionate and dilute sodium hydroxide, dried over $MgSO_4$, and reduced to 10 mL appearing as an orange solution. This was then passed through a silca plug and concentrated to give the title compound (25.1 g, 82%), as a crystalline solid, mp 44–45 °C (from acetone). ν_{max}(KBr)/cm^{-1} 2924vs, 2871vs, 1509s, 1476m, 1396m, 1286m, 1237vs, 1115m, 1033s, 996m, 828s, 773m and 730w; δ_H(250 MHz; $CDCl_3$) 0.90 (6H, t, J=6.5 Hz, Me), 1.34 (12H, m, CH_2), 1.75 (4H, m, CH_2), 3.89 (4H, t, J=6.6 Hz, OCH_2) and 6.81 (4H, s, Ph); δ_C(62.9 MHz; $CDCl_3$) 14.1, 22.7, 25.8, 29.4, 31.7, 68.7, 115.4 and 153.2; m/z (EI) 278.2245 (M^+, $C_{18}H_{30}O_2$ requires 278.2240), m/z (ES) 279.1 (M^++Na, 100%).

3.1.13. 1,4-Didecyloxybenzene 18.[10] 18.3 g, 69%. White powder, mp 67–68 °C (from ethanol/dichloromethane 1:1); ν_{max}(KBr)/cm^{-1} 2961s, 2936s, 2857s, 1509s, 1476m, 1396m, 1380w, 1287m, 1244vs, 1115m, 1032s, 828s, 772m and 659m; δ_H(250 MHz; $CDCl_3$) 0.88 (6H, t, J=6.6 Hz, Me), 1.26 (28H, m, CH_2), 1.77 (4H, m, OCH$_2$CH_2), 3.89 (4H, t, J=6.5 Hz, OCH_2) and 6.81 (4H, s, Ph); δ_C(62.9 MHz; $CDCl_3$)14.2, 22.7, 22.9, 29.2, 29.3, 29.4, 29.6, 31.9, 68.7, 115.4 and 153.2 (one resonance is missing); m/z (EI) 290.4 (M^+, 100%).

3.1.14. 1,4-Dihexadecyloxybenzene 19.[7] 15.2 g, 60%. White solid, mp 82–84 °C (from ethanol); ν_{max}(KBr)/cm^{-1}; δ_H(250 MHz; $CDCl_3$) 0.84 (6H, br t, Me), 1.25 (52H, m, $C_{13}H_{23}$), 1.73 (4H, m, OCH$_2$CH_2), 3.88 (4H, t, J=6.7 Hz, OCH_2) and 6.8 (4H, s, Ph); δ_C(62.9 MHz; $CDCl_3$) 14.2, 22.7, 26.1, 29.4, 29.6, 29.7, 32.0, 69.7, 115.4 and 153.2 (8 missing resonances).

3.1.15. 1,4-Dihexyloxy-2,5-diiodobenzene 20.[11] *General procedure*. A solution of 1,4-dihexyloxy **17** benzene (1.0 g, 3.6 mmol), KIO_3 (0.92 g, 1.8 mmol) and iodine (0.23 g, 4.3 mmol) in acetic acid (50 mL), sulphuric acid (1 mL) and water (5 mL), was refluxed for 4 h. To the reaction was added iodine (0.2 g, 1.58 mmol) and KIO_3 (0.5 g, 2.34 mmol), and reflux continued for another 7 h. A solution of sodium thionite (2.0 g in water 20 mL) was added and a

colour change from orange to yellow was observed. The precipate was filtered to give the title compound (0.58 g, 30%) as yellow/white crystalline blocks mp 58–59 °C (from ethanol) ν_{max}(KBr)/cm^{-1} 3493m, 3424m, 2943s, 2851m, 1451s, 1347m, 1209vs, 1061m, 993m and 937m; δ_H(250 MHz; $CDCl_3$) 0.90 (6H, t, J=6.9 Hz, Me), 1.33 (12H, m, CH_2), 1.79 (4H, m, CH_2), 3.92 (4H, t, J=6.4 Hz, CH_2) and 7.16 (2H, s, Ph); δ_C(62.9 MHz; $CDCl_3$) 14.1, 22.6, 25.8, 29.2, 31.5, 70.4, 86.3, 122.8 and 152.9; *m/z* (ES) 530.1 (M^+, 100%).

3.1.16. 1,4-Didecyloxy-2,5-diiodobenzene 21.[8] 2.7 g, 41%. White powder, mp 62–63 °C (from ethanol). (Found: C, 48.2; H, 6.7. $C_{26}H_{44}I_2O_2$ requires C, 48.6; H, 6.9%); ν_{max}(KBr)/cm^{-1} 2940s, 2925vs, 2846s, 1487m, 1447m, 1388m, 1354m, 1264w, 1216s, 1071m, 1053m and 847m; δ_H(250 MHz; $CDCl_3$) 0.87 (6H, t, J=6.6 Hz, Me), 1.27 (28H, m, CH_2)1.8 (4H, m, OCH_2CH_2), 3.9 (4H, t, J=6.4 Hz, OCH_2) and 7.2 (2H, s, Ph); δ_C(62.9 MHz; $CDCl_3$) 14.2, 22.7, 26.1, 29.2, 29.3, 29.4, 29.6, 32.0, 70.4, 86.4, 122.8 and 152.9 (one missing resonance); *m/z* (EI) 660 (M^++NH_4, 100%) and 642.3 (M^+, 75).

3.1.17. 1,4-Dihexadecyloxy-2,5-diiodobenzene 22.[7] 6.07 g, 84%. White powder, mp 77–79 °C (from ethanol/dichloromethane 1:1) δ_H(250 MHz; $CDCl_3$) 0.87 (6H, br t, CH_3), 1.25 (52H, m, CH_2), 1.78 (4H, br t, OCH_2CH_2), 3.91 (4H, br t, OCH_2) and 7.16 (2H, s, Ar); δ_C(62.9 MHz; $CDCl_3$) 14.2, 22.7, 26.1, 29.2, 29.3, 29.4, 29.6, 29.7, 29.9, 32.0, 70.4, 86.3, 122.8 and 152.9 (6 resonances are overlapping).

3.1.18. 1,4-Bis(trimethylsilylethynyl)-2,5-dihexyloxybenzene 23.[7] *General procedure*. A stirred solution of 1,4-dihexyloxy-2,5-diiodobenzene **20** (1.24 g, 0.92 mmol) trimethylsilylacetylene (0.92 g, 9.35 mmol), $(PPh_3)_2PdCl_2$ (60 mg, 0.086 mmol) and of CuI (40 mg, 0.21 mmol) in anhydrous THF (20 mL) was treated with Et_3N (2 mL, 0.014 mol) under nitrogen at room temperature. The reaction was stirred for 24 h after which the solvent was removed in vacuo. The solid was dissolved in CH_2Cl_2 (10 mL), filtered through a 4 cm silica plug and eluted with dichloromethane to give the title compound (0.48 g, 86%) as a grey crystalline solid, mp 91–92 °C (from methanol) λ_{max}(CH_2Cl_2)/nm 237 (log ε 5.2), 270 (5.3), 285 (5.7) and 344 (5.0); ν_{max}(KBr)/cm^{-1} 2960s, 2939s, 2868m, 2156m, 1500m, 1469m, 1408m, 1386s, 1249s, 1225s, 1203s, 1032s, 894s, 867vs, 758m, 730m, 693m, 664m and 625m; δ_H(250 MHz; $CDCl_3$) 0.24 (18H, s, $SiMe_3$), 0.89 (6H, br t, Me), 1.3 (8H, m, C_2H_4), 1.55 (4H, m, CH_2), 1.75 (4H, m, CH_2), 3.93 (4H, t, J=6.3 Hz, OCH_2) and 6.88 (2H, s, Ph); δ_C(62.9 MHz; $CDCl_3$) −0.03, 14.0, 22.7, 25.7, 29.3, 31.6, 69.4, 100.1, 101.1, 113.9, 117.2 and 154.0; *m/z* (ES) 471.3104 (M^++H, 100%) $C_{28}H_{47}Si_2O_2$ requires 471.3109), *m/z* (ES) 470.2 (M, 87%), 431.3 (35), 359.2 (53), 293.1 (40) and 279.1 (100).

3.1.19. 1,4-Bis(trimethylsilylethynyl)-2,5-didecyloxybenzene 24.[8] 2.17 g, 65%. Grey crystalline solid, mp 72–73 °C (from methanol) λ_{max}(CH_2Cl_2)/nm 237 (log ε 4.2), 270 (4.2), 285 (4.5) and 345 (3.9); ν_{max}(KBr)/cm^{-1} 2943s, 2851m, 2157m, 1500m, 1471m, 1388m, 1225s, 1204m, 1032m, 893s, 855s and 759m; δ_H(250 MHz; $CDCl_3$) 0.24 (18H, s, $SiMe_3$), 0.89 (6H, m, Me), 1.23 (24H, m, C_6H_{12}), 1.45 (4H, m, CH_2), 1.75 (4H, m, CH_2), 3.93 (4H, t, J=6.3 Hz, OCH_2) and 6.85 (2H, s, Ph); δ_C(62.9 MHz; $CDCl_3$) −0.04, 8.8, 14.1, 22.7, 26.0, 29.3, 29.4, 29.6, 29.65, 31.9, 46.5, 69.4, 100.1, 101.0, 113.9, 117.1 and 154.0; *m/z* (EI) 583.5 (M^++H, 100%).

3.1.20. 1,4-Bis(trimethylsilylethynyl)-2,5-dihexadecyloxybenzene 25.[7] 0.87 g, 47%. Off-white solid, mp 65–66 °C (from dichloromethane) δ_H(250 MHz; $CDCl_3$) 0.24 (18H, s, $Si(CH_3)_3$), 0.87 (6H, br t, CH_3), 1.25 (52H, m, $C_{14}H_{28}$), 3.93 (4H, t, J=6.3 Hz, OCH_2) and 6.88 (2H, s, Ar); δ_C(62.9 MHz; $CDCl_3$) 0.0, 14.2, 22.7, 26.1, 29.4, 29.5, 29.7, 32.0, 69.5, 100.1, 101.1, 113.9, 117.2 and 154.0 (8 resonances are overlapping).

3.1.21. 1,4-Diethynyl-2,5-dihexyloxybenzene 26.[7] *General procedure*. A stirred solution of 1,4-bis-trimethylsilylethynyl-2,5-dihexyloxybenzene **23** (250 mg, 0.53 mmol) in anhydrous THF (20 mL) and methanol (20 mL) was treated with (4 mL) 20% KOH, and continued to stir for another 3 h. The reaction mixture was reduced to the aqueous slurry, where more water (30 mL) was added and extracted with dichloromethane (3×50 mL). The combined extracts were dried and evaporated under reduced pressure to give the title compound (100 mg, 61%) as a yellow crystalline solid, mp 69–71 °C (from methanol) λ_{max}(CH_2Cl_2)/nm 233 (log ε 4.0) and 271 (4.3); ν_{max}(KBr)/cm^{-1} 3266s, 2959s, 2939s, 2917s, 2852s, 1499s, 1468s, 1385s, 1218vs, 1197s, 1029s, 997m, 862m and 652m; δ_H(250 MHz; $CDCl_3$) 0.89 (6H, m, 2×CH_3), 1.33 (12H, m, 2×C_3H_6), 1.76 (4H, m, 2×OCH_2CH_2), 3.35 (2H, s, 2×C_2H), 3.96 (4H, t, J=6.4 Hz, 2×OCH_2) and 6.94 (2H, s, Ph); δ_C(62.9 MHz; $CDCl_3$) 14.1, 22.6, 25.6, 28.1, 31.5, 69.6, 79.2, 83.0, 113.3, 117.7 and 154.8; *m/z* (ES) 470.2 (M^+, 87%), 431.3 (35), 359.2 (53), 293.1 (40) and 279.1 (100).

3.1.22. 1,4-Diethynyl-2,5-didecyloxybenzene 27.[8] 1.06 g, 86%. Yellow powder, mp 70–72 °C (from methanol) λ_{max}(CH_2Cl_2)/nm 232 (log ε 4.0), 262 (4.3), 271 (4.5), 337 (3.9); ν_{max}(KBr)/cm^{-1} 3285s, 2927vs, 2850s, 1502m, 1471m, 1384s, 1270m, 1215s, 1048m, 1028m, 992m, 867m, 667m and 646m; δ_H(250 MHz; $CDCl_3$) 0.86 (6H, m, Me), 1.25 (28H, m, C_7H_{14}), 1.77 (4H, m, OCH_2CH_2), 3.3 (2H, s, C*H*), 3.95 (4H, t, J=6.6 Hz, OCH_2) and 6.93 (2H, s, Ph); δ_C(62.9 MHz; $CDCl_3$) 14.2, 22.7, 25.9, 29.1, 29.4, 29.6, 31.9, 69.6, 79.8, 82.4, 113.2, 117.7 and 154.0 (2 missing resonances); *m/z* (ES) 456.3836 (M^++NH_4) $C_{30}H_{46}O_2$ requires 456.3836); *m/z* (EI) 456.6 (M^++NH_4, 83%) and 439.5 (M^++H, 100).

3.1.23. 1,4-Diethynyl-2,5-dihexadecyloxybenzene 28.[7] 0.51 g, 64%. Yellow solid, mp 87–88 °C (lit. 89–90 °C) (from methanol) δ_H(250 MHz; $CDCl_3$) 0.87 (6H, br t, CH_3), 1.25 (52H, m, $C_{13}H_{26}$), 1.75 (4H, br t, OCH_2CH_2), 3.32 (2H, s, CCH), 3.95 (4H, t, J=6.3 Hz, OCH_2) and 6.94 (2H, s, Ar); δ_C(62.9 MHz; $CDCl_3$) 14.1, 22.7, 25.9, 29.2, 29.4, 29.6, 29.7, 32.0, 69.7, 79.8, 82.4, 113.3, 117.7 and 154.0 (7 resonances are missing).

3.1.24. 1,4-Bis[4-(isocyanuric acid)phenylethynyl)-2,5-didecyloxybenzene 29. *General procedure Method 1*. To a stirred solution of *N*-(4-iodophenyl)isocyanuric acid **7**

(0.5 g, 1.14 mmol), 1,4-diethynyl-2,5-dihexyloxybenzene **26** (1.13 g, 3.42 mmol), copper(I) iodide (40 mg, 0.21 mmol), bis(triphenylphosphine)palladium(II) chloride (40 mg, 0.0567 mmol) in anhydrous THF (30 mL) degassed for 20 min, was added freshly distilled anhydrous triethylamine (5 mL). This was left to stir for 24 h, then concentrated and redissolved in fresh tetrahydrofuran and purified by flash column chromatography on silica using initally dichloromethane to elute an orange impurity, followed by tetrahydrofuran. Concentration gave a brown solid which was sonicated first with 10% sodium hydroxide and filtered, then sonicated with 10% hydrochloric acid and filtered to give the title compound (0.87 g, 90%) as a yellow powder, mp >280 °C (from tetrahydrofuran) λ_{max}(THF)/nm 270 (log ε 5.0) and 396 (4.3); ν_{max}(KBr)/cm^{-1} 2952m, 2924m, 2851m, 1754s, 1719vs, 1513w, 1493w, 1441m, 1408w, 1275w, 1217m, 1025w, 870w and 660w; δ_H(400 MHz; THF-d_8) 0.56 (6H, br t, CH_3), 0.98 (24H, m, CH_2), 1.27 (4H, m, CH_2CH$_2$CH$_2$O), 1.53 (4H, m, CH_2CH$_2$O), 3.74 (4H, t, J=6.1 Hz, OCH$_2$), 6.78 (2H, s, Ar), 6.97 (4H, d, J=8.6 Hz, Ar), 7.23 (4H, d, J=8.6 Hz, Ar) and 10.34 (4H, br s, NH); δ_C(100.5 MHz; THF-d_8) 15.5, 24.6, 28.1, 31.2, 31.3, 31.4, 31.6, 31.7, 33.9, 71.2, 88.8, 95.7, 116.0, 118.6, 125.7, 131.1, 133.4, 150.2, 151.1 and 155.9; *m/z* (MALDI) 2154.2 (8%), 1717.9 (27) and 1280.6 (94), 847.4 (4), 846.3 (18), 845.3 (56), 844.3 (100) $C_{48}H_{56}N_6Cl_2O_8$ requires 847.4 (3%), 846.4 (17), 845.4 (57), 844.4 (100).

3.1.25. 1,4-Bis[4-(isocyanuric acid)-3-chlorophenylethynyl)-2,5-didecyloxybenzene 30. 0.50 g, 94%. Yellow powder, mp 265 and 289 °C by DSC (from tetrahydrofuran) λ_{max}(THF)/nm 243 (log ε 4.7), 309 (4.7) and 376 (4.6); ν_{max}(KBr)/cm^{-1} 3221w, 3087m, 2923s, 2852m, 2213w, 1792m, 1725vs, 1594m, 1506m, 1490m, 1421s, 1277w, 1216m, 1079m, 759m, 595m and 531m; δ_H(400 MHz; THF-d_8) 0.77 (6H, br t, CH_3), 1.29 (28H, m, C_7H_{14}), 1.75 (4H, m, OCH$_2$CH_2), 3.95 (4H, br t, OCH$_2$), 7.05 (2H, s, Ar), 7.30 (2H, br d, Ar), 7.40 (2H, br d, Ar), 7.55 (2H, s, Ar) and 11.75 (4H, s, NH); δ_C(100.5 MHz; THF-d_8)14.0, 23.1, 26.6, 29.8, 29.9, 30.1, 30.2, 32.4, 69.7, 88.7, 92.9, 114.2, 117.0, 126.4, 130.7, 131.8, 132.5, 132.6, 134.0, 148.6, 148.8 and 154.5 (1 resonance is missing); *m/z* (MALDI) 1348.9 (16%) 918.5 (3), 917.5 (8), 916.5 (15), 915.5 (40), 914.5 (78), 913.5 (58) and 912.5 (100) $C_{48}H_{54}N_6Cl_2O_8$ requires 918.3 (2%), 917.3 (8), 916.3 (15), 915.3 (40), 914.3 (80), 913.3 (57) and 912.3 (100).

3.1.26. 1,4-Bis[4-(isocyanuric acid)phenylethynyl)-2,5-dihexadecyloxybenzene 31. 0.44 g, 82%. Pale yellow powder, mp 142–175 °C (from tetrahydrofuran) λ_{max}(THF)/nm 229 (log ε 4.7), 279 (4.8) and 357 (4.5); ν_{max}(KBr)/cm^{-1} 3221br, 3087br, 2921s, 2852m, 1752m, 1716s, 1515m, 1496m, 1442m, 1220m, 760 and 550; δ_H(250 MHz; THF-d_8) 0.90 (6H, br d, CH_3), 1.25 (48H, m, $C_{12}H_{24}$), 1.50 (4H, m, CH_2), 1.75 (4H, m, OCH$_2$CH_2), 3.95 (4H, br t, OCH_2), 7.00 (2H, s, Ar), 7.20 (4H, br d, Ar), 7.45 (4H, br d, Ar) and 10.70 (4H, s, NH); δ_C(62.9 MHz; THF-d_8) 14.0, 23.1, 29.4, 29.5, 29.6, 29.7, 29.9, 30.2, 32.4, 69.7, 87.3, 94.2, 114.4, 117.2, 124.2, 129.6, 131.8, 134.7, 148.7, 149.6 and 154.4; *m/z* (MALDI) 1012.5 (53%), 819.6 (100) 1016.6 (2), 1015.7 (6), 1014.5 (20), 1013.5 (55) and 1012.5 (100) $C_{60}H_{80}N_6O_8$ requires 1016.6 (2%), 1015.6 (7), 1014.6 (25), 1013.6 (70) and 1012.6 (100).

Method 2. To a stirred solution of *N*-(4-ethynylphenyl)isocyanuric acid **10** (250 mg, 1.09 mmol), 1,4-dihexadecyloxy-2,5-diiodobenzene **21** (0.49 g, 0.606 mmol), copper(I) iodide (15 mg, 0.79 mmol), bis(triphenylphosphine)-palladium(II) chloride (20 mg, 0.029 mmol) in anhydrous THF (40 mL) degassed for 20 min, was added freshly distilled anhydrous Et_3N (2 mL). This was left to reflux for 48 h then concentrated and redissolved in fresh THF to dry load onto a column, and purified by flash column chromatography on silica initially using dichloromethane to elute an orange impurity, followed by tetrahydrofuran. Concentration gave a brown solid which was sonicated first with 10% sodium hydroxide and filtered, then sonicated with 10% hydrochloric acid and filtered to give the title compound (0.44 g, 82%) identical to that reported previously.

3.2. Crystal structure determination[14]

Intensity data were recorded at 150 K, using a Nonius Kappa CCD area-detector diffractometer mounted at the window of a rotating anode FR591 generator with a molybdenum anode (λ=0.71073 Å). ϕ and ω scans were carried out to fill the Ewald sphere. An empirical absorption correction was applied using SORTAV. The structure was solved by direct methods and refined on F^2 by full-matrix least-squares refinements. Crystallographic data: Formula $C_{105}H_{150}N_{24}O_9$; M=1892.49, triclinic space group $P\bar{1}$, unit cell dimensions a=14.0756(11) Å, b=18.494(2) Å, c=22.732(3) Å, α=84.478(8)° β=86.697(9)° γ=69.622(4)°, U=5519.6(10) Å^3, Z=2, D_c=1.139 Mg/m^3, μ(Mo Kα)=0.075 mm^{-1}. Colourless plate, crystal size 0.10×0.02×0.02 mm^3. θ range for data collection 2.3–25.1°; 27,949 collected reflections of which 17,899 are independent [R_{int}=0.142]. Structure refinement with 17,899 data for 1253 parameters, GOF=1.13, final R indices for data with [$F2>2\sigma(F2)$] $R1$=0.1331, $wR2$=0.1690; R indices for all data $R1$=0.2819, $wR2$=0.2008. CCDC 225189.

References and notes

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13. We have named this proposed network 'The Garden of Eden' owing to its aesthetic symmetry and its anticipated potential, with mixtures of modified melamines, to mimic a process by which life might have originated on earth. The Garden of Eden described in the Bible is not ascribed hexagonal symmetry though. The painting by Masaccio 'Adam and Eve Banished from Paradise' (1424–1428), Brancacci Chapel, Florence, Italy, depicts the descent of Adam and Eve, hence 'life' from The Garden of Eden.
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