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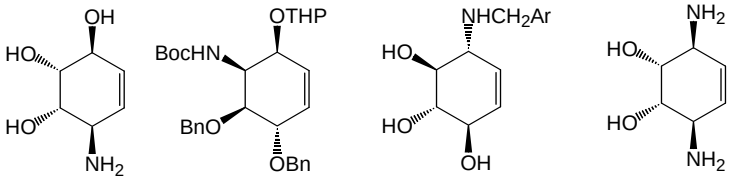
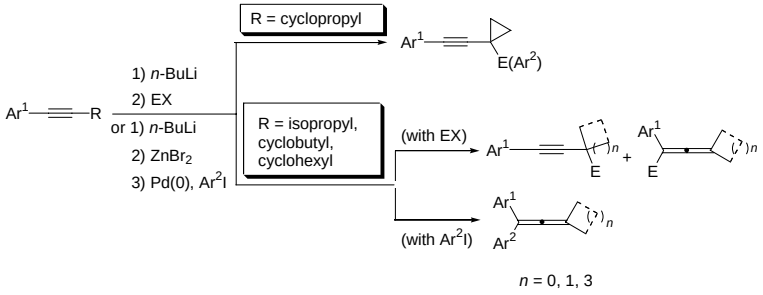
Contents

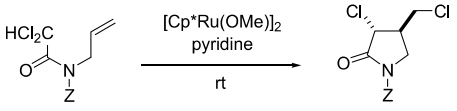
REPORT

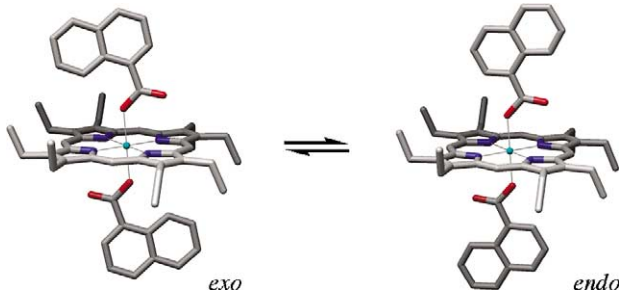


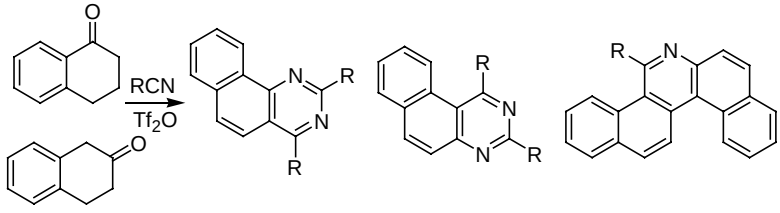
The synthetic approaches to the title compounds are summarized together with their activities as glycosidase inhibitors.

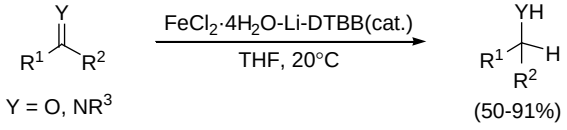
ARTICLES

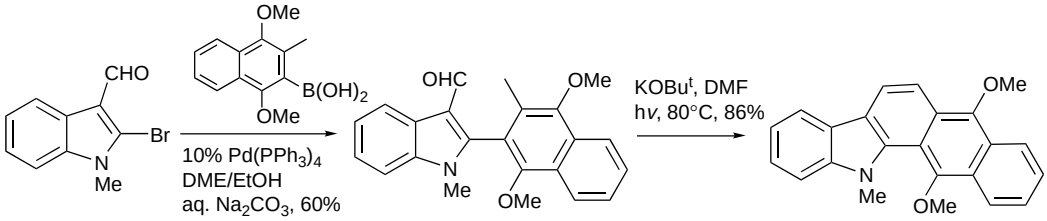


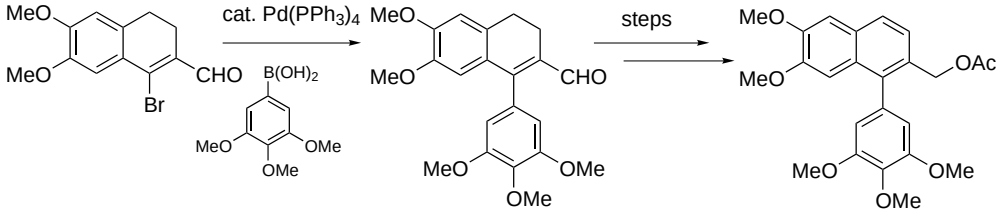


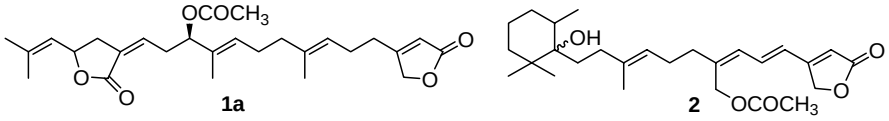


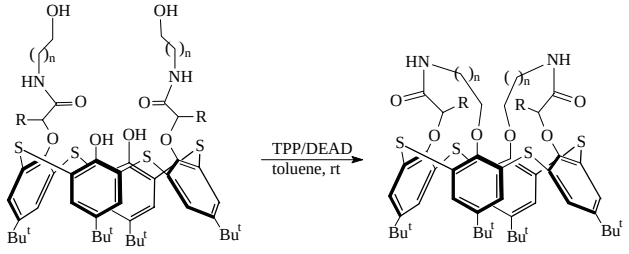




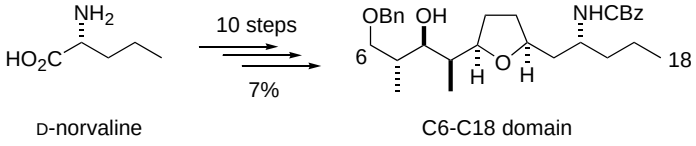




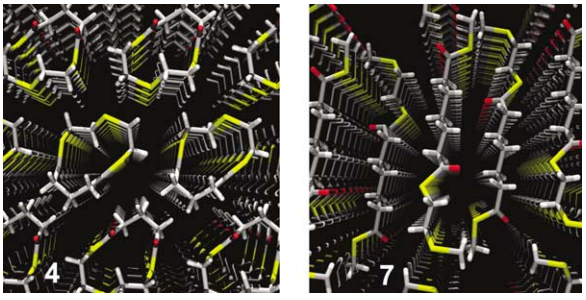


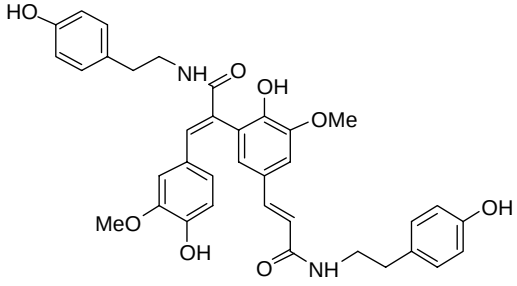


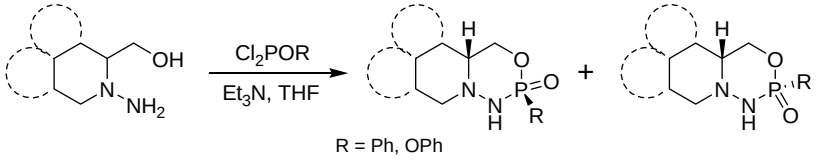
R = H, Me, Ph; n = 1, 2, 4

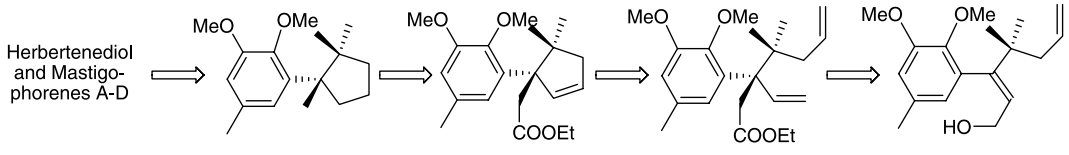


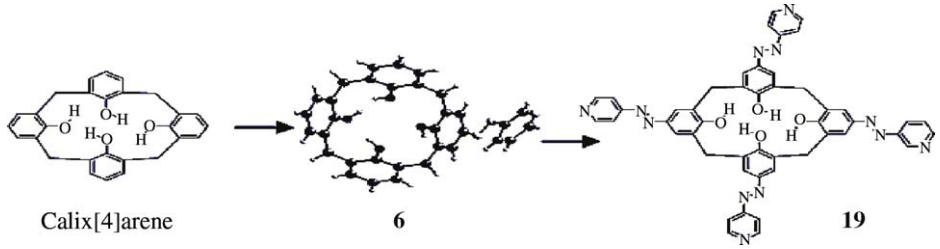
D-norvaline C6-C18 domain

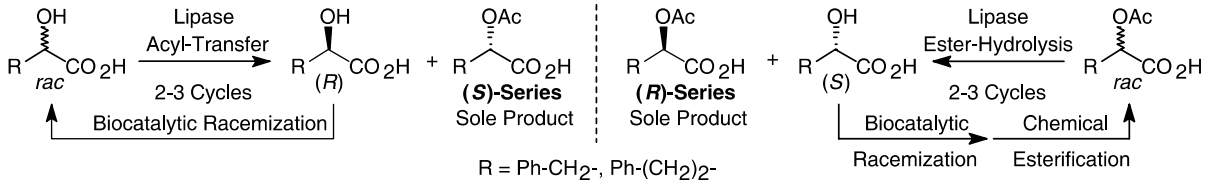


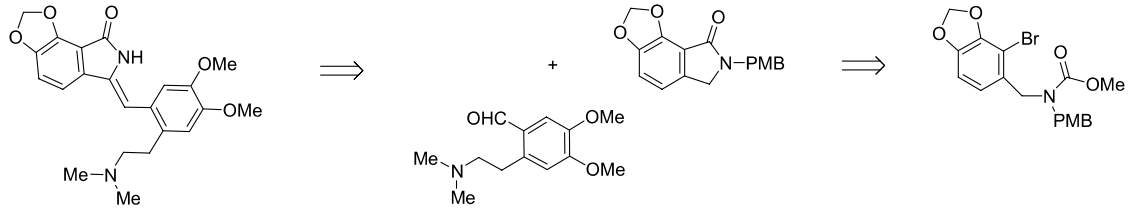


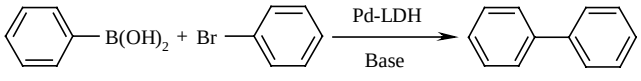


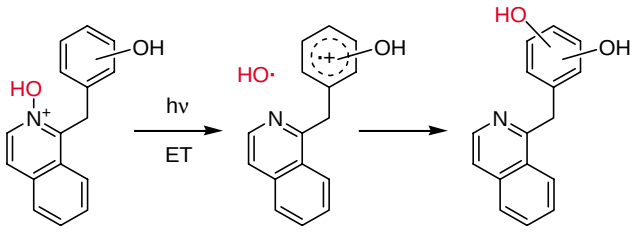












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Synthesis of amino- and diaminoconduritols and their applications

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Contents

Keywords: Conduritols; Conduramines; Diaminoconduritols; Asymmetric synthesis.

Abbreviations: Ac, acetyl; aq, aqueous; AIBN, 2,2′-azobis(isobutyronitrile); Bn, benzyl; Boc, *tert*-butyloxycarbonyl; *n*-Bu, *n*-butyl; *s*-Bu, *sec*-butyl; *t*-Bu, *tert*-butyl; Bz, benzoyl; CAN, ceric ammonium nitrate; Cbz, benzyloxycarbonyl; CC, column chromatography; *m*-CPBA, 3-chloroperbenzoic acid; CSA, camphorsulfonic acid; dba, dibenzylideneacetone; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DEAD, diethyl azodicarboxylate; △, solvent heated under reflux; DHP, dihydropyran; DIPEA, diisopropylethylamine; DMAP, 4-(*N*,*N*-dimethylamino)pyridine; DME, 1,2-dimethoxyethane; DMF, *N*,*N*-dimethylformamide; DMP, 1,3-dimethoxypropane; DMSO, dimethylsulfoxide; dppe, 1,2-(diphenylphosphino)ethane; Et, ethyl; FC, flash chromatography; FVT, flash vacuum thermolysis; HMPA, hexamethylphosphoric triamide; Imd, imidazole; $LiAlH_4$, lithium aluminium hydride; LHMDS, lithium hexamethyldisilazane; Me, methyl; MOM, methoxymethyl; MPM, *p*-methoxybenzyl; Ms, methanesulfonyl (mesyl); NBS, *N*-bromosuccinimide; NMO, *N*-methylmorpholine *N*-oxide; Phth, phthaloyl; PPL, porcine pancreatic lipase; PPTS, pyridinium *p*-toluenesulfonate; Py, pyridine; rt, room temperature; Red-Al, sodium bis(2-methoxyethoxy)aluminium hydride; TBAF, *tetra*-butylammonium fluoride; TBME (*t*-BME), *tert*-butyl methyl ether; TBSOTf, *tert*-butyldimethylsilyl triflate; TBS (TBDMS), *tert*-butyldimethylsilyl; TEA, triethylamine; TES, triethylsilyl; TESOTf, triethylsilyl triflate; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TMEDA, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; TMS, trimethylsilyl; TMSOTf, trimethylsilyl triflate; Troc, 2,2,2-trichloroethoxycarbonyl; Ts, tosyl=*para*-toluenesulfonyl; *p*-TsOH, *para*-toluenesulfonic acid; $Cu(acac)_2$, copper(II) acetylacetonate.

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1. Introduction

Conduritols **1**–**6** (cyclohex-5-ene-1,2,3,4-tetrols) are a class of polyols valuable as starting materials for the synthesis of biologically active compounds.[1] The ten possible stereoisomers, two *meso*-forms (conduritols A and D) and four couples of enantiomers (conduritols B, C, E and F), have been obtained in enantiomerically pure forms[1] (Fig. 1).

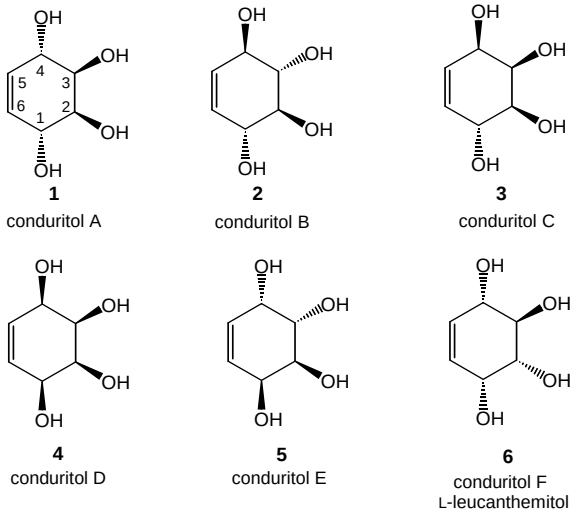


Figure 1.

In nature, the occurrence of only two conduritols A and F, has been established.[1]

Conduramines are purely synthetic aminocyclohexenetriols,[1a,b,h] formally derived from conduritols, in which one of the OH groups is exchanged for an amino moiety (Fig. 2). Conduramines and their analogues are important intermediates in the synthesis of amino- and diaminocyclitols.[2] Some aminoconduritols have shown interesting inhibitory activities towards glycosidases.[3] The syntheses of aminoconduritols have been partially reviewed.[1a,b,g,h,4] Conduramines have also been used as intermediates in the preparation of azasugars,[5] aminosugars,[6] sphingosines,[7] lactams,[8] and narcissus alkaloids.[9]

Aminoconduritols are also structural elements of many naturally occurring biological active compounds. A number of *Amaryllidaceae* alkaloids, for example, compounds **7** and **8**, having a [1,3]-dioxolophenanthridone skeleton, contain the conduramine A structure and show interesting inhibitory activity towards some glycosidases.[10] Most of these alkaloids contain the hydroxylated aminoconduritol A-1 subunit, for example, compounds **9** and **10** (Fig. 3).

In this review, we survey the general synthetic strategies applied to the preparation of amino- and diaminoconduritols and their analogues. We also give a short summary of the activities found for conduramines and diaminoconduritols as glycosidase inhibitors.

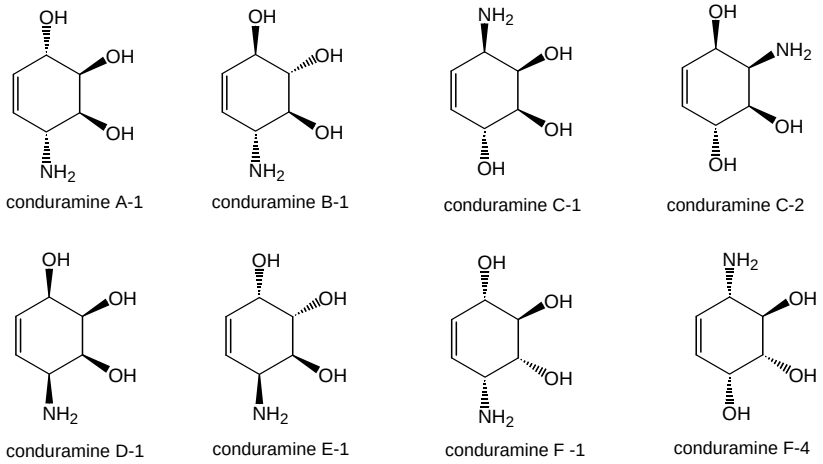


Figure 2.

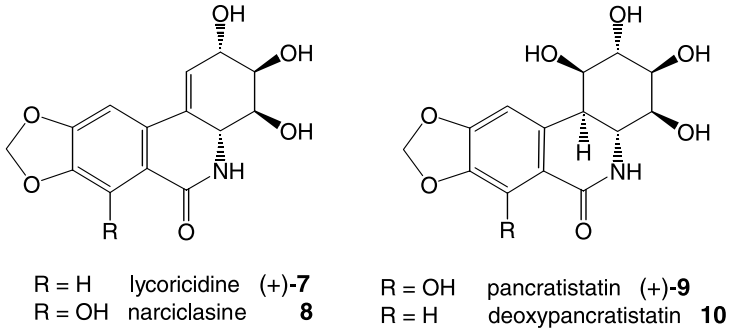


Figure 3.

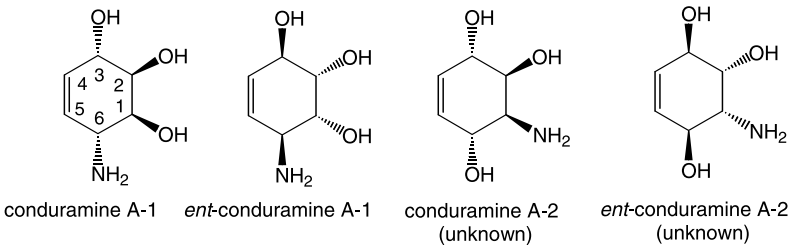


Figure 4.

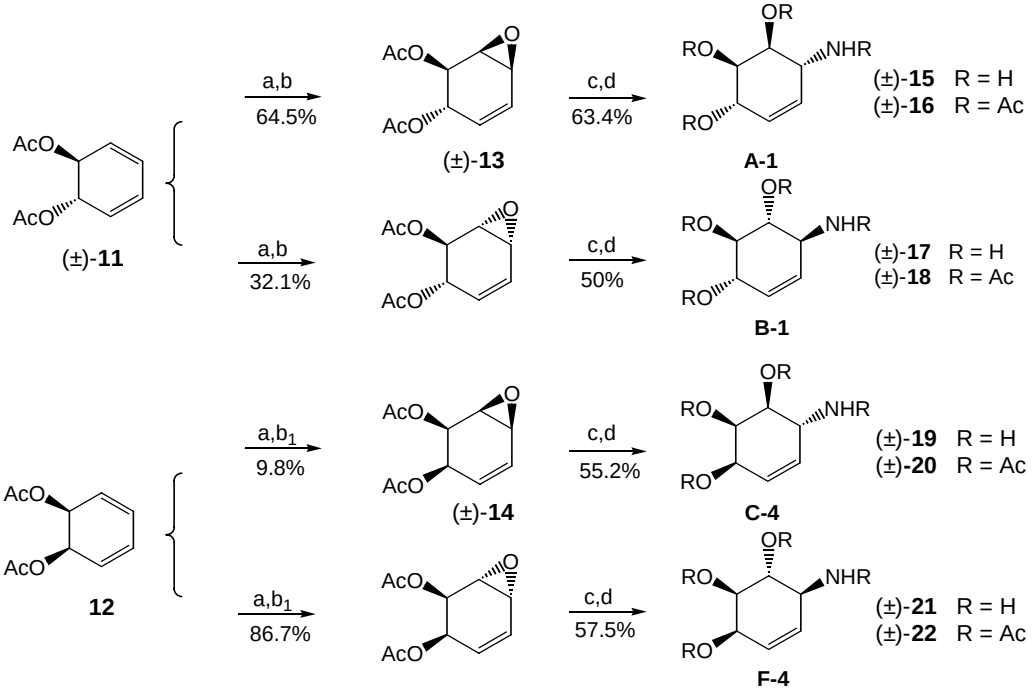
2. Aminoconduritols

2.1. Synthesis of aminoconduritols A

There are two types of conduramines A, conduramine A-1 and its enantiomer (*ent*-A-1), and conduramine A-2 and its enantiomer (*ent*-A-2) (Fig. 4). The two latter compounds have not yet been described. In this review, we will use numbering for conduramines according to the IUPAC recommendations.[11] The trivial nomenclature of conduramines arises from their correlation with naturally occurring conduritols, for example, conduritols A and F. Thus, if the trivial numbering of conduritols is used, replacement of the hydroxy group at C(1) of conduritol A with an amino moiety produces conduramine A-1. Similarly, replacement of HO–C(4) in conduritol F produces conduramine F-4. Moreover, if the corresponding conduritol is naturally occurring, its conduramine analogue is described as 'pseudo-natural', for example, conduramines A-1 and F-1. The corresponding conduramine enantiomers which virtually do not have natural conduritol analogues are referred to as *ent*.

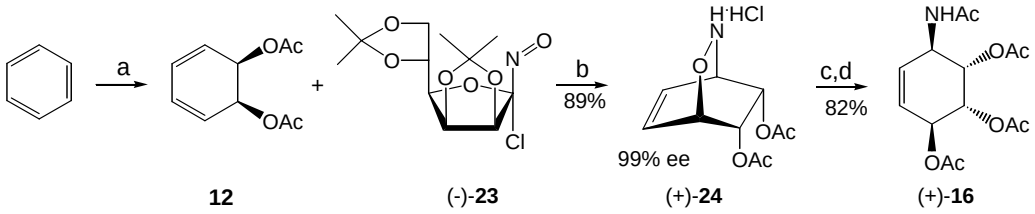
2.1.1. Synthesis of aminoconduritol A-1 and analogues. The first successful synthesis of racemic conduramines A-1, B-1, C-4 and F-4 was achieved by Nakajiama et al.[12] in 1962. Their syntheses involved the epoxidation of racemic *trans*-**11** or *cis*-cyclohexa-3,5-diene-1,2-yl diacetate **12** that were derived from tetrachlorocyclohexane. The reaction gave a mixture of two isomers, one of which [(±)-**13** or (±)-**14**] could be separated by crystallization. *Anti*-openings of the corresponding epoxides were carried out in NH_3/MeOH, giving four aminoconduritols, (±)-**15**, (±)-**17**, (±)-**19** and (±)-**21**, that were characterized as the corresponding crystalline tetraacetates, (±)-**16**, (±)-**18**, (±)-**20** and (±)-**22**. Other regioisomers were not formed, because ammonia attacks the epoxide ring selectively in the allylic positions (Scheme 1).

The hetero-Diels–Alder addition of *cis*-cyclohexa-3,5-diene-1,2-yl diacetate **12** with the nitroso compound (−)-**23** derived from D-mannose allowed the preparation of the corresponding dihydrooxazine (+)-**24** with very high optical purity (99% ee).[13] Selective reduction of the N–O bond of (+)-**24** (Zn/HCl) provided the enantiomerically



Reagents and conditions: a) $PhCO_3H$, $CHCl_3$, rt, 3 d; b: separation of (±)-**13** by crystallization; b_1: separation of (±)-**14** by crystallization; c) MeOH, NH_3; d) Ac_2O, Py.

Scheme 1.

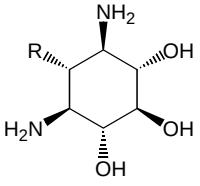


Reagents and conditions: a) (i) microbial dioxygenase oxidation; (ii) Ac_2O/Py, 4 h, rt (96%); b) $CHCl_3$/EtOH, -70 °C, then 4 d at - 40 °C; c) Zn/HCl-H_2O, 5 °C, 7 h; d) Ac_2O/Py.

Scheme 2.

enriched conduramine A-1 tetraacetate (+)-**16** in 82% yield (Scheme 2).

The majority of aminoglycoside antibiotics contain 2-deoxystreptamine (2-DOS) **25** and streptamine **26** as aminocyclitol subunits (Fig. 5).[14] Isomers of aminocyclitols



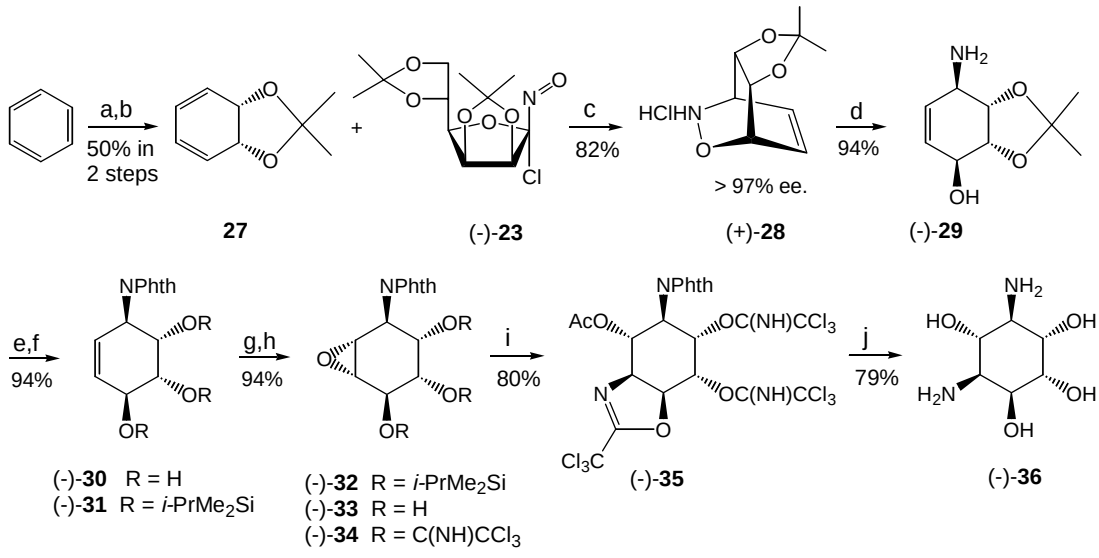
25 R = H
26 R = OH

Figure 5.

25 and **26** in which the configuration of the amino groups is not changed are attractive targets for stereoselective synthesis. They have found several applications including the generation of new antibiotics able to combat mutagenesis of bacteria,[15] and as ligands in the construction of cytostatic platinum complexes.[16]

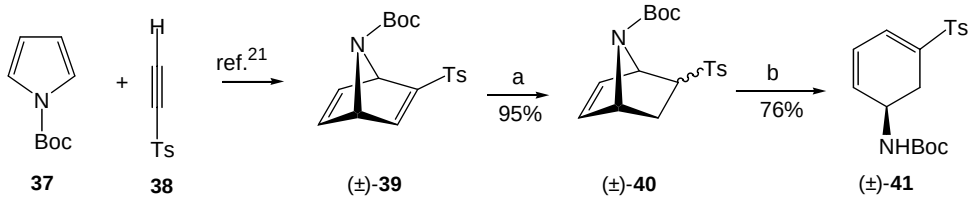
Piepersberg and co-workers[17] presented a stereoselective route to optically pure *cis*-1,3-diamino-1,3-dideoxycyclitol (−)-**36** based on the hetero-Diels–Alder reaction of nitroso dienophile (−)-**23** with protected *cis*-cyclohexa-3,5-diene-1,2-diol **27** (Scheme 3).

The starting diol,[18] which was obtained from benzene by microbial oxidation, was protected as its stable 1,2-*O*-isopropylidene derivative **27**.[19] The *meso*-diene **27** was subjected to a hetero-Diels–Alder reaction with (−)-furanosyl chloride **23** and gave the dihydrooxazine (+)-**28**



Reagents and conditions: a) *Pseudomonas putida*; b) *p*-TsOH, Me_2CO, 0-5 °C, 3 h; c) Et_2O-EtOH, -30 °C, 7 d; d) Al/Hg, aq. THF (20:1), 0 °C, 2 d; e) *N*-ethoxycarbonylphthalimide, Na_2CO_3, Me_2CO, $CaSO_4$, 30 °C, 1 d; f) (i) 80% AcOH, 65 °C, 2 h; (ii) *i*-$PrMe_2SiCl$, Imd, CH_2Cl_2, rt, 12 h; g) (i) *p*-$O_2NC_6H_4CO_3H$; (ii) 75% AcOH, rt, 2 d; h) Cl_3CCN, DBU, CH_2Cl_2, -30 °C, 3 d; i) (i) Et_3Al, DME, 0 °C, 3 h; (ii) EtOH, 30 min; (iii) Ac_2O/Py, rt, 12 h; j) (i) 1 mol dm^{-3} HCl, rt, 3 h; (ii) N_2H_4, EtOH-$CHCl_3$, 80 °C, 12 h.

Scheme 3.



Reagents and conditions: a) $NaBH_4$, MeOH, 0 °C; b) LHMDS, THF, -78 °C to rt.

Scheme 4.

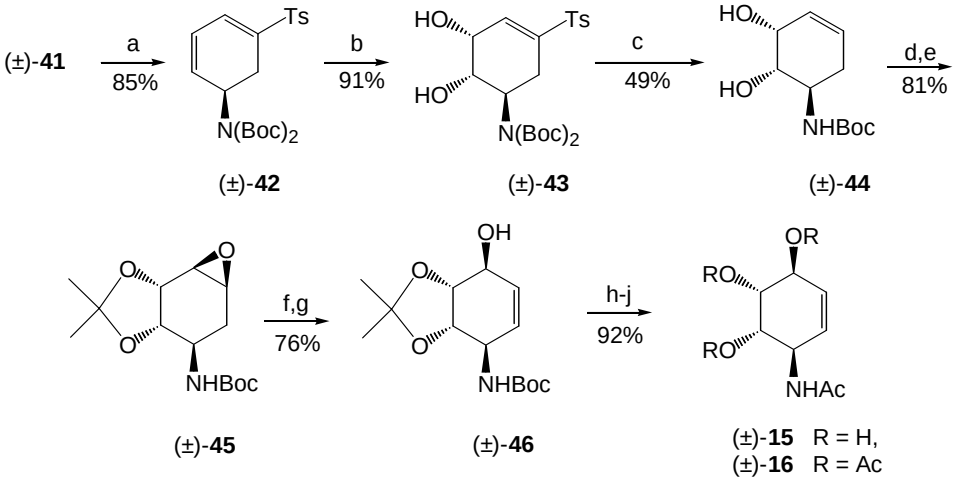
(>97% ee). After reduction (Al/Hg, aq THF) of the N–O bond, aminocyclohexenol (−)-**29** was obtained in 94% yield. Amine (−)-**29** was protected by phthaloylation[20] to give the corresponding phthalimide that was then hydrolyzed into the triol (−)-**30**. Epoxidation of the corresponding silyl diether (−)-**31** with *p*-nitroperbenzoic acid led to the *trans*-epoxide (−)-**32** exclusively (Scheme 3).

The silyl protective groups in (−)-**32** were removed by acidic hydrolysis ((−)-**33**) and were replaced by trichloroacetimidato functions to give derivative (−)-**34**. The second nitrogen function was introduced by stereoselective epoxide ring opening by the vicinal trichloroacetimidato residue in the presence of Et_3Al. 3,4-Dihydro-1,3-oxazole (−)-**35** was obtained in 80% yield. Hydrolytic cleavage of the oxazine ring (aq HCl) preceded the complete, simultaneous removal of all protective groups, yielding (−)-**36** (Scheme 3).

Starting from the Diels–Alder adduct (±)-**39** of the acetylene **38** and *N*-*t*-butoxycarbonylpyrrole (**37**) (Scheme 4), a compound described first by Altenbach et al.,[21] Muchowski and co-workers[22] have developed a synthetic pathway for (±)-conduramine A-1 [(±)-**15**] (Scheme 5), (±)-conduramine C-1 tetraacetate, (±)-conduramine D-1 and (±)-conduramine F-1. Reduction of (±)-**39** with $NaBH_4$ gave 7-azanorbornene (±)-**40**, which was then converted into the racemic diene **41** on treatment with a strong base [$(Me_3Si)_2NLi$].

From (±)-**41** and applying a chemo- and face-selective dihydroxylation of the di-Boc- protected amine (±)-**42**, diol (±)-**43** was obtained in good yield (Scheme 5). The same reaction applied to (±)-**41** gave a 1:1 mixture of two diastereomeric diols.

Reduction of the sulfone moiety of (±)-**43** with Na/Hg afforded (±)-**44**. After protection of its diol unit as an acetonide and face-selective epoxidation of its alkene moiety, epoxide (±)-**45** was isolated in 81% yield. Regioselective ring opening of epoxide (±)-**45** was possible with PhSeLi, which attacked (S_N2) the less sterically hindered center. The selenide obtained was not isolated, but directly oxidized with H_2O_2, which led to the regioselective formation of the allylic alcohol (±)-**46**. After deprotection, (±)-conduramine A-1 [(±)-**15**] was obtained and characterized as its peracetate acetamido derivative [(±)-**16**].

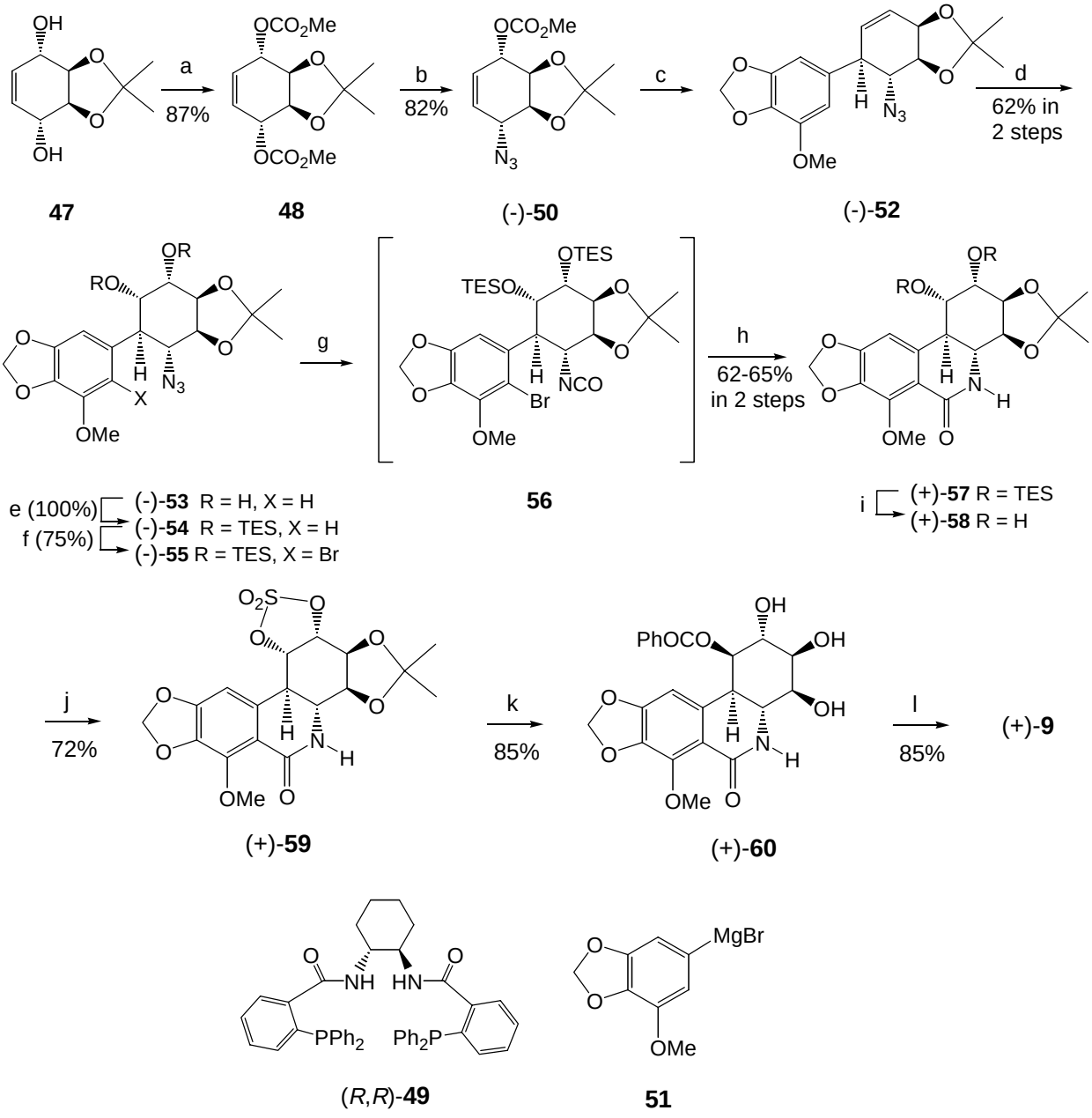


Reagents and conditions: a) $(Boc)_2O$, DMAP, MeCN; b) OsO_4-NMO, $NaHCO_3$, *t*-BuOH, H_2O, THF, rt; c) 6% Na/Hg, Na_2HPO_4, MeOH-THF, -12 °C; d) $Me_2C(OMe)_2$, Me_2CO, *p*-TsOH, rt; e) *m*-CPBA, $NaHCO_3$, CH_2Cl_2; f) $(PhSe)_2$, *n*-BuLi, THF; g) (i) H_2O_2, DIPEA, CH_2Cl_2, 0 °C; (ii) THF, reflux; h) TFA, H_2O/CH_2Cl_2; i) NH_3/ MeOH; j) Ac_2O/Py, DMAP.

Scheme 5.

As already mentioned, pancratistatin **9** which contains a hydroxylated conduramine structure is a member of the *Amaryllidacene* group of alkaloids. It has been used in folk medicine since ancient Greek times[23] and was isolated by Pettit and co-workers from the root the Hawaiian plant *Pancratium littorale*.[24]

Trost and Pulley[25] have described a synthetic strategy for (+)-pancratistatin, where they have used the conduramine A-1 analogue (−)-**50** and Grignard reagent **51** for the coupling reaction as the key step (Scheme 6). The synthesis started from the readily available diol **47**, which was converted into the dicarbonate **48**. The desymmetrization



Reagents and conditions: a) (i) *n*-BuLi, THF, 0 ^{o}C; (ii) $ClCO_2Me$; b) 0.5 mol% $(\pi\text{-}C_3H_7PdCl)_2$, 0.75 mol% (*R*,*R*)-**49**, $TMSN_3$, CH_2Cl_2, rt; c) **51**, CuCN, THF-Et_2O, 0 ^{o}C; d) cat. OsO_4, $NMO{\cdot}H_2O$, CH_2Cl_2, rt; e) TESOTf, 2,6-lutidine, CH_2Cl_2; f) NBS, DMF; g) (i) Me_3P, THF, H_2O; (ii) $COCl_2$, THF, Et_3N; h) *t*-BuLi, Et_2O, -78 ^{o}C; i) TBAF, THF, -78 to 0 ^{o}C; j) (i) $SOCl_2$, Et_3N; (ii) cat. $RuCl_3{\cdot}H_2O$, $NaIO_4$, CCl_4, MeCN, H_2O, rt; k) $PhCO_2Cs$, DMF, then work up with THF, H_2O, cat. H_2SO_4; l) (i) MeOH, K_2CO_3, rt; (ii) LiI, DMF, 80 ^{o}C .

Scheme 6.

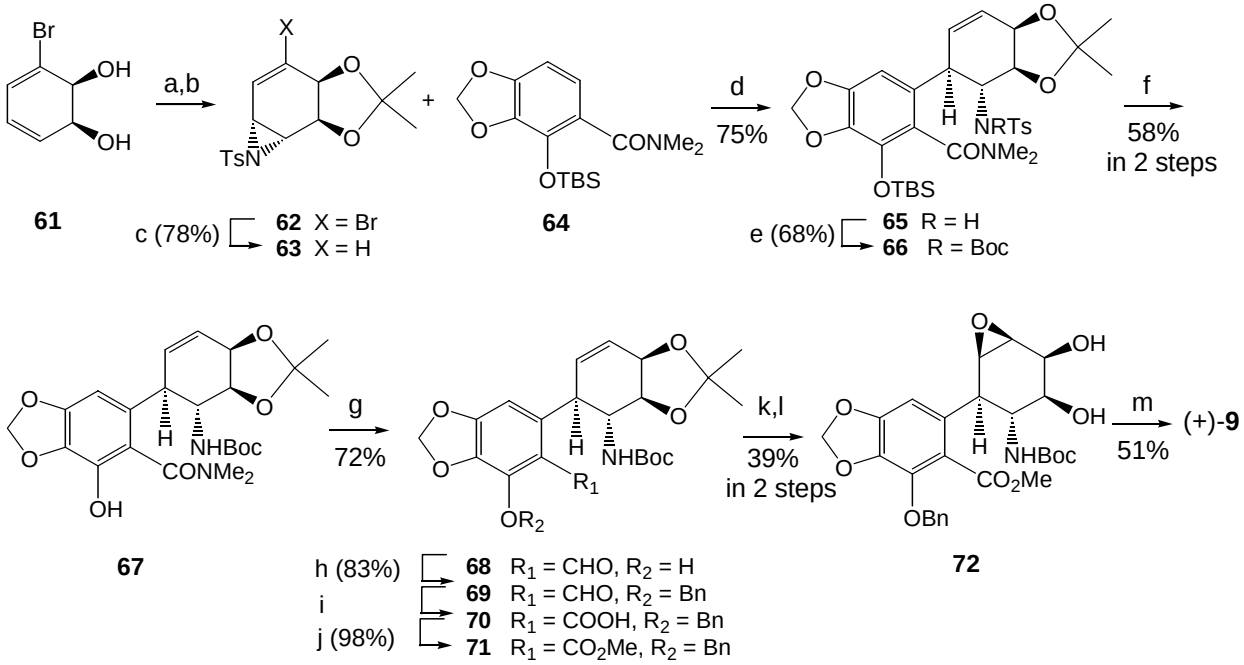
which utilizes a Pd complex derived from (*R*,*R*)-ligand **49** and π-allylpalladium chloride gave azide (−)-**50** in 82% yield with >95% ee. Addition of the Grignard reagent **51** to the mixture of azide (−)-**50** and CuCN led to the desired adduct (−)-**52**. Cis-dihydroxylation ($NMO \cdot H_2O$, cat. OsO_4, CH_2Cl_2) gave diol (−)-**53** which was transformed into (−)-**55** in two steps via (−)-**54**. The isocyanate **56** was formed by reacting (−)-**55** with $Me_3P/THF/H_2O$ and $COCl_2$. Treatment of **56** with *t*-BuLi led to metal/halogen exchange, the latter reaction being faster than addition to the isocyanate. The resultant aryllithium underwent spontaneous addition to form lactam (+)-**57**. Deprotection (TBAF, THF, −78 °C) of the silyl ether (+)-**57**→(+)-**58**, followed by trans-diaxial ring opening of the cyclic sulfate (+)-**59** in which the acetonide cleaves simultaneously with hydrolysis of the alkyl sulfate, provided derivative (+)-**60**. Simple removal of the benzoyl and methyl ether groups in (+)-**60** completes the synthesis of (+)-pancratistatin [(+)-**9**] (Scheme 6).

Independently, Hudlicky and co-workers[26] have developed an alternative enantioselective total synthesis of (+)-pancratistatin **9**. The key step in their synthesis was the coupling reaction of tosylaziridine **63** with amide **64** via *ortho*-metallation of the latter compound (Scheme 7).

The commercially available diol **61** was converted into conduramine A-1 precursor **62**, which was subsequently reduced (Bu_3SnH/AIBN, THF) into **63** in 78% yield. Amide **64** was subjected to *ortho*-metallation below −90 °C and converted in situ into the corresponding lithium cyanocuprate species $[Ar_2Cu(CN)Li_2]$, the addition of which to **63** produced tosylamide **65**. Amide **65** was converted into the Boc derivative **66** and, subsequently, reductive detosylation (Na/anthracene, DME) gave phenol **67**. Reduction of the dimethylamide **67** with Red-Al into aldehyde **68** and protection of the phenol moiety afforded **69**. The latter compound was oxidized into acid **70** and converted into the methyl ester **71** in 98% yield. Deprotection and $VO(acac)_2$-catalyzed epoxidation with *t*-BuO_2H, afforded the β-epoxide **72** selectively (lateral control by the free hydroxyl group). Near-neutral conditions (H_2O, cat. BzONa, 100 °C, 6d) transformed epoxide into (+)-pancratistatin [(+)-**9**] in 51% yield (Scheme 7).

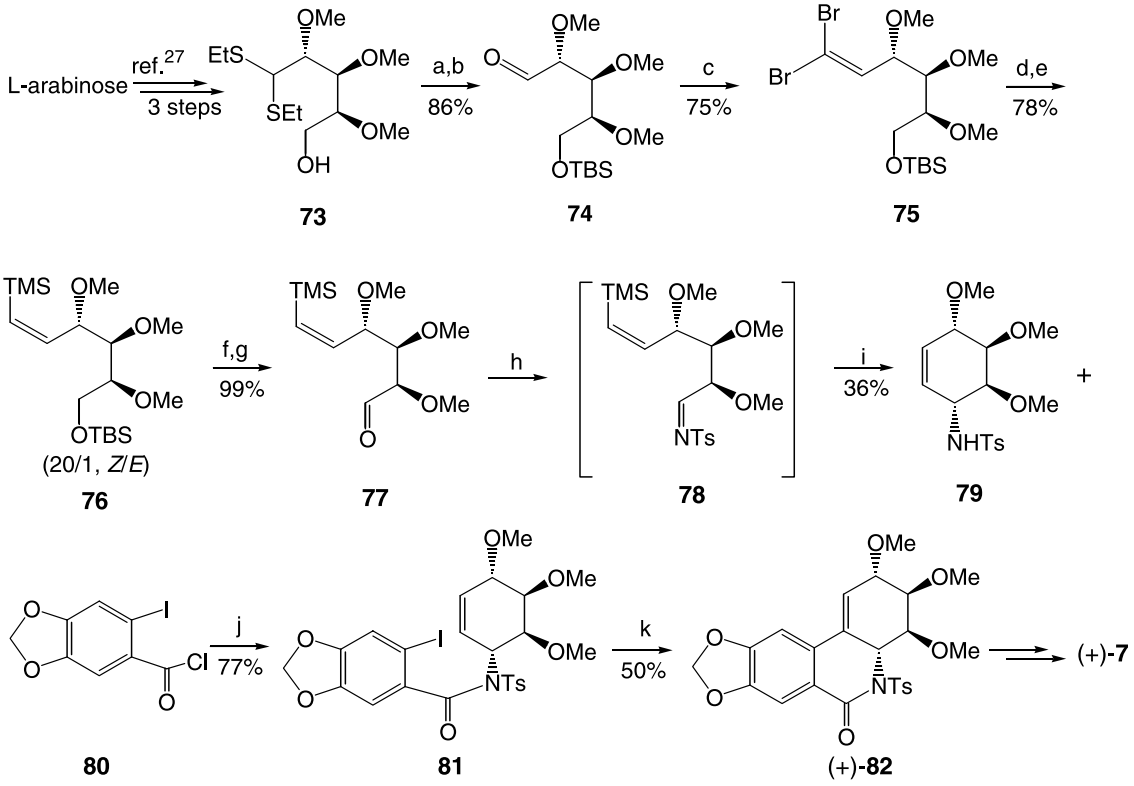
A convergent synthesis of a protected version of (+)-lycoricidine [(+)-**7**] has been accomplished by McIntosh and Weinreb.[10] In their synthesis, conduramine A-1 derivative **79** was an important synthetic intermediate (Scheme 8).

The synthesis starts from L-arabinose, which was converted in three steps into dithioacetal **73**.[27] The primary OH function of **73** was protected as a silyl ether. Subsequent hydrolysis of the dithioacetal gave aldehyde **74** in 86%



Reagents and conditions: a) DMP, *p*-TsOH, CH_2Cl_2; b) PhI=NTs, $Cu(acac)_2$, MeCN; c) Bu_3SnH, AIBN, THF; d) (i) *s*-BuLi, TMEDA, THF, -90 °C, 1.5 h; (ii) CuCN, -90 to -20 °C; (iii) **64**, -78 °C, $BF_3 \cdot Et_2O$, then to rt over 8 h; e) (i) *s*-BuLi, THF, 0 °C, 15 min; (ii) $(Boc)_2O$, reflux, 4 d; f) (i) Na/anthracene, DME, -78 °C, 15 min; (ii) TBAF, THF, 0 °C, 1.5 h; g) Red-Al, morpholine, THF, -45 °C, 31 h; h) BnBr, K_2CO_3, DMF, rt, 4 h; i) 2-methyl-2- butene, $NaClO_2$, KH_2PO_4, *t*-BuOH, H_2O, rt, overnight; j) CH_2N_2; k) AcOH, aq. THF, 75 °C, 3 h; l) *t*-BuO_2H; $VO(acac)_2$, PhH, 60 °C, 2 h; m) H_2O, BzONa (cat.), 100 °C, 6 d.

Scheme 7.



Reagents and conditions: a) TBSCl, DMAP, Imd, DMF, rt, 16 h; b) HgO, $HgCl_2$, Me_2O-H_2O (9:1), 50 °C, 1 h; c) PPh_3, CBr_4, CH_2Cl_2, Et_3N, -78 °C, 5 min; d) (i) *n*-BuLi, THF, TMEDA, -78 °C; (ii) TMSCl, -78 °C, 3 h, then 3 h at rt; e) H_2/5% Pd/$BaSO_4$ (2 mol %), Py, rt, 20 h; f) AcOH/H_2O (2:1), rt, 12 h; g) Swern oxidation; h) TsNCO (2 eq.), $(CH_2)_2Cl_2$, 80 °C, 24 h; i) $BF_3{\cdot}Et_2O$, 0 °C to rt; j) Et_3N, DMAP, CH_2Cl_2, rt, 36 h; k) Pd(dppe)$_2$ (20 mol %), TlOAc, DMF, 68 °C, 36 h.

Scheme 8.

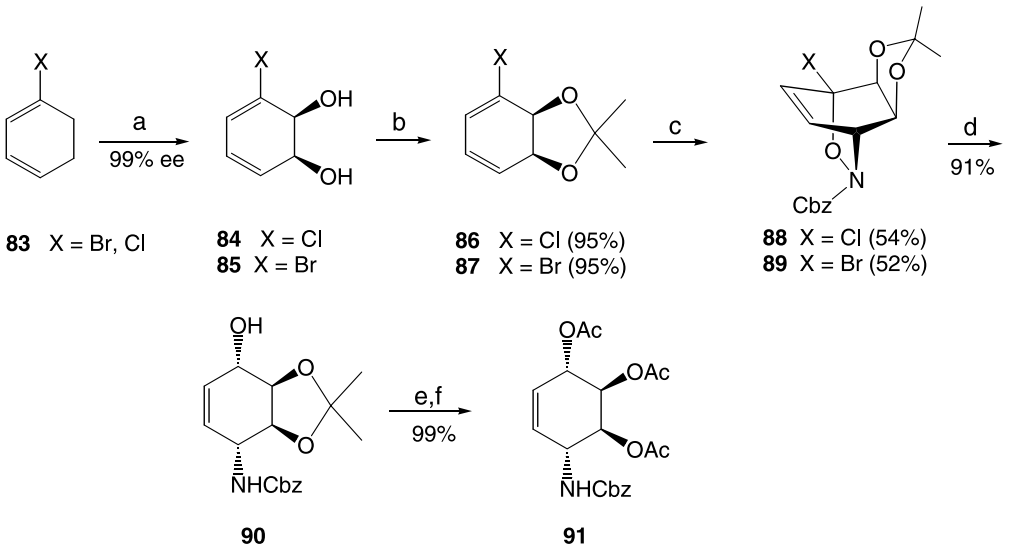
yield. In the next step, the Corey–Fuchs procedure was applied [PPh_3 (2 equiv)/CBr_4, Et_3N, −78 °C, 5 min] for one-carbon homologation and under these conditions, olefin **75** was obtained in 75% yield. Compound **75** was then transformed into the corresponding acetylene. Subsequent catalytic hydrogenation of the ethynylsilane using H_2/Pd/$BaSO_4$ gave the vinylsilane **76** with good *Z*/*E* stereoselectivity (20:1). The silyl ether **76** (inseparable mixture of *Z*/*E* isomers) was cleaved under mild conditions and the alcohol obtained was oxidized to give **77** in very good yield. Vinylsilane aldehyde **77** was converted into *N*-sulfonylimine **78** under neutral conditions. The imine **78** was treated in situ with $BF_3{\cdot}Et_2O$ in order to induce electrophilic ring cyclization into the conduramine A-1 derivative **79** (Scheme 8). Coupling of 6-iodopiperonyl chloride **80** and conduramine **79** afforded the *N*-acylsulfonamide **81**. Cyclization of **81** using a variation of the Ogawa procedure [Pd(dppe)$_2$, TlOAc, DMF] afforded the desired protected (+)-lycoricidine [(+)-**82**].

Hudlicky and co-workers[28–30] have devised a very effective synthetic strategy to produce either (+)- or (−)-conduramine A-1 derivatives from a single, optically pure, chloro- (**84**) or 1-bromodiol (**85**). Diols **84** and **85** were obtained form the corresponding inexpensive halobenzenes **83** by fermentation with a *Pseudomonas putida* strain, Pp 39D (Scheme 9). Protection of diols **84** and **85** as the acetonides **86** and **87**, respectively, and their subsequent hetero-Diels–Alder addition with CbzN=O[31] gave the corresponding oxazolidines **88** and **89**.

Reduction of bromide **89** and subsequent cleavage of the N–O bond were accomplished with Al/Hg and this afforded **90**. Acidic treatment of **90** and subsequent acetylation of the free hydroxyl groups led to the fully protected conduramine A-1 derivative **91** (Scheme 9).

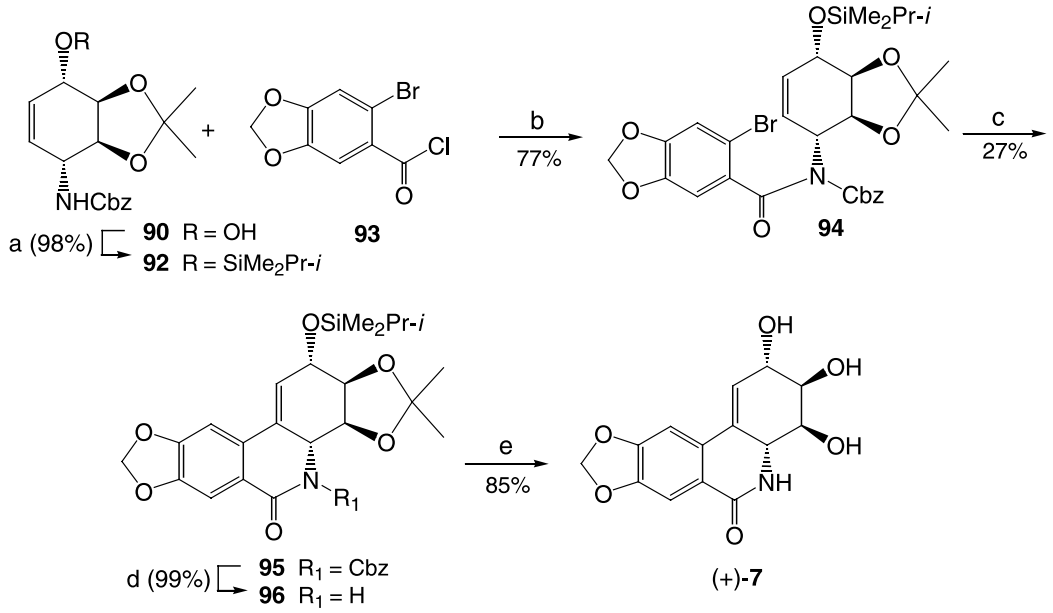
The same synthetic scheme has been used by Hudlicky and Olivo[28] in their total synthesis of (+)-lycoricidine [(+)-**7**] (Scheme 10). The starting alcohol **90** (Scheme 9) was silylated with *i*-PrMe_2SiCl to afford **92** in 98% yield. Reaction of **92** with **93** gave the amide **94**. The ring closure of **94** into **95** was accomplished in 27% yield by means of a modified Heck cyclization [Pd(OAc)$_2$, TlOAc, dppe, anisole]. Amide **95** was then deprotected with Pd/C to yield the derivative **96**. Treatment of **96** with CF_3CO_2H at 0 °C afforded optically pure (+)-lycoricidine [(+)-**7**].

More recently, Hudlicky and Akgün[30] have applied a similar synthetic methodology, leading to the first total synthesis of *ent*-7-deoxypancratistatin via a protected form of *ent*-conduramine A-1 [(+)-**101**] and diol **98**. The latter



Reagents and conditions: a) *Pseudomonas putida*, Pp 39D; b) DMP, Me_2CO, *p*-TsOH; c) Bu_4NIO_4 and CbzNHOH; d) Al/Hg, THF-H_2O; e) AcOH-THF-H_2O; f) Ac_2O/Py.

Scheme 9.

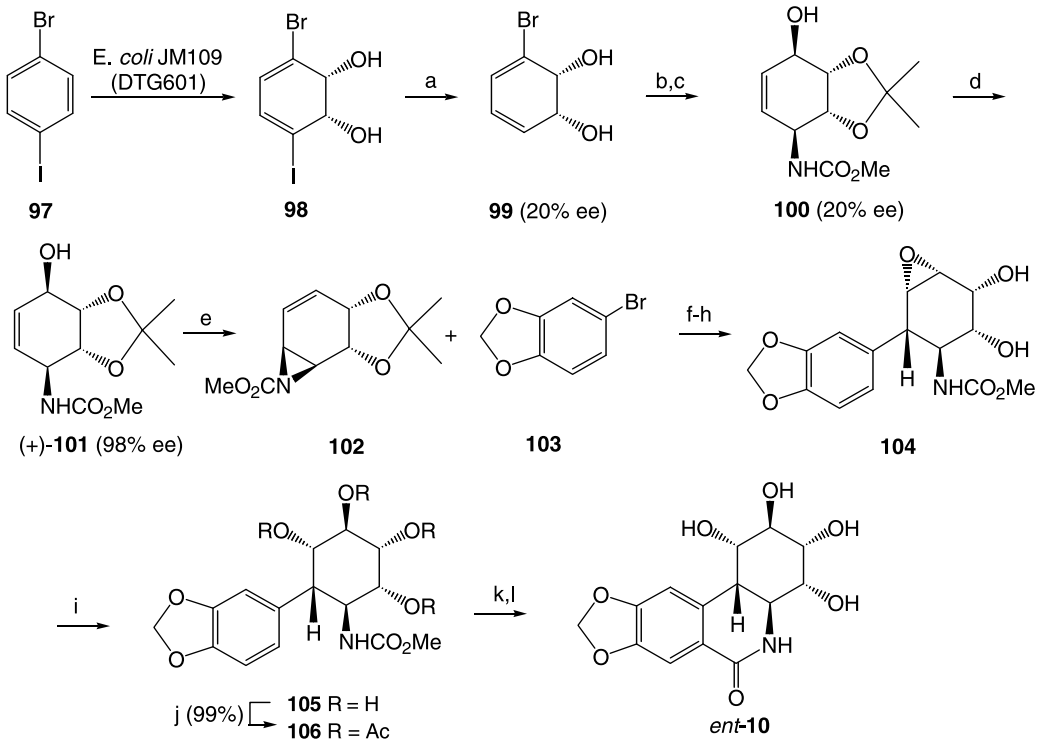


Reagents and conditions: a) $ClSiMe_2Pr$-*i*, Imd, CH_2Cl_2; b) (i) *n*-BuLi, THF, -78 °C; c) $Pd(OAc)_2$, TlOAc, dppe, anisole; d) Pd(C), cyclohexene-EtOH; e) TFA, 0 °C.

Scheme 10.

compound was generated by an improved chemoenzymatic means (Scheme 11). Oxidation of *p*-bromoiodobenzene **97** gave the diol **98**, which was subjected to Bu_3SnH reduction. The *ent*-diol **99** was isolated with 20% ee only. The Diels–Alder reaction of **99** with $MeCO_2NHOH$ proceeded with excellent regio- and stereospecifity to afford the bromooxazine, which was then transformed into the intermediate **100**.

Enantiomerically enriched compound (+)-**101** (>98% ee) was subjected to a Mitsunobu reaction[32] to give aziridine **102** (Scheme 11). Regioselective addition of the cuprate derived from **103** (*n*-BuLi, Cu) provided, after deprotection (95%), a diol, which was then subjected to vanadium oxide-catalyzed epoxidation, giving **104**. Acidic hydrolysis of the epoxide **104** provided the tetrol **105** that was then acetylated into **106**. Exposure of **106** to modified Bischler–Napieralski



Reagents and conditions: a) Bu_3SnH, AIBN, THF; b) (i) DMP, Me_2CO, *p*-TsOH; (ii) $HONHCO_2Me$, $NaIO_4$, H_2O, MeOH; c) Al/Hg, THF-H_2O; d) PPL, pH 7; e) PPh_3, DEAD, THF; f) *n*-BuLi, Cu, $BF_3{\cdot}Et_2O$, -78 °C; g) Dowex-50W, MeOH; h) $VO(acac)_2$, *t*-BuOH, PhH, 70 °C; i) BzONa, H_2O, 100 °C; j) Ac_2O/Py; k) Tf_2O, DMAP, CH_2Cl_2, 0 °C; l) K_2CO_3, MeOH.

Scheme 11.

conditions[33] and subsequent deprotection furnished the alkaloid, *ent*-7-deoxypancratistatin (*ent*-**10**).

Protected forms of the enantiomer of conduramine A-1 have been obtained by Johnson and co-workers.[9c] The Diels–Alder addition of diene **27** with PhCON═O (formed in situ by oxidation of benzohydroxamic acid with Et_4NIO_4) provided (±)-**107**. Reduction of the N–O bond of (±)-**107** gave (±)-**108**. Treatment of (±)-**108** with *Pseudomonas cepacia* (Amano P-30) lipase in isopropenyl acetate gave a 1:1 mixture of the acetate (+)-**110** and alcohol (−)-**109** that were readily separated by column chromatography. Acetate (+)-**110** was treated with NH_3 in MeOH to give (+)-**111**. Treatment of (+)-**111** and (−)-**109** under acidic conditions led to both enantiomers of *N*-benzoyl conduramine A-1, (+)-**112** and (−)-**112**, respectively (Scheme 12).

Fortamine (**113**) and 2-deoxyfortamine (**114**) are the aminocyclitol portions of the broad- spectrum antibiotics, fortimicin A (**115**) and istamycin A (**116**), respectively (Fig. 6).[34]

The syntheses of racemic fortamine [(±)-**113**] and 2-deoxyfortamine [(±)-**114**] have been reported by Knapp and co-workers in 1983.[35] Monoepoxidation of cyclohexa-1,3-diene (**117**) gave epoxide (±)-**118**, the reaction of which with $MeNH_2$ was highly regioselective and furnished (±)-**119** (Scheme 13).

N-Acylation and *O*-methylation of (±)-**119** led to (±)-**120**, which was then bromocyclized into (±)-**121**. This established the protected *cis*-4,5-methylaminoalcohol and E_2 elimination (DBU) gave an alkene that was epoxidized into a 9:1 (to 23:1) mixture of oxiranes. The major epoxide (±)-**122** was converted into the conduramine A-2 analogue (±)-**123** by a selenophenolate addition/selenoxide elimination sequence. Epoxidation of (±)-**123** gave (±)-**124** as a single isomer. This epoxide reacted with NaN_3 to give an azide, the reduction of which led to (±)-**125**. Acidic treatment of (±)-**125** and neutralization gave racemic fortamine (±)-**113**.

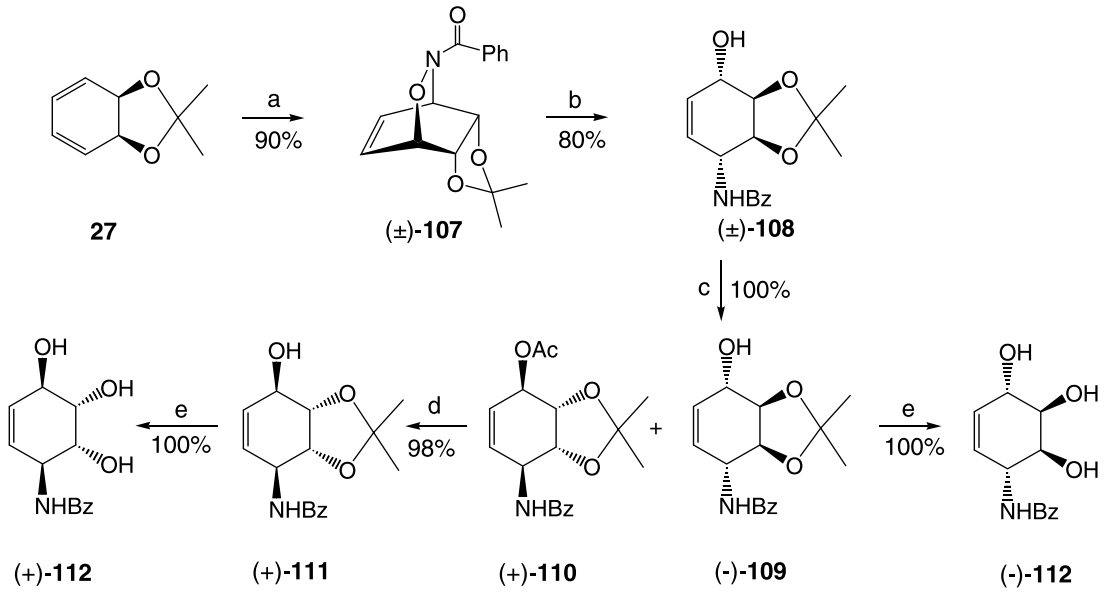
In 1986, the same team[36] described a synthesis of (−)-fortamine [(−)-**113**] and (+)-deoxyfortamine [(+)-**114**].

2.2. Synthesis of aminoconduritols B

There are two types of conduramines B, conduramine B-1 and its enantiomer (*ent*-B-1), and conduramine B-2 and its enantiomer (*ent*-B-2) (Fig. 7). Both conduramine B-2 and *ent*-B-2 are unknown compounds.

2.2.1. Synthesis of aminoconduritol B-1 and analogues. The first synthesis of racemic conduramine B-1 peracetate [(±)-**18**] has been reported by Nakajima et al.[12] (Scheme 1).

A protected form of enantiomerically pure (−)-conduramine B-1 has been obtained through dynamic kinetic



Scheme 12.

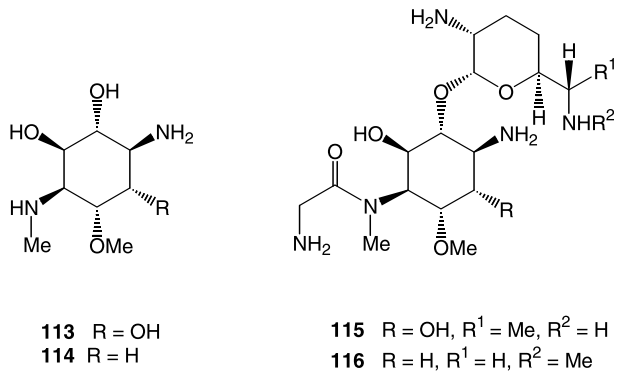
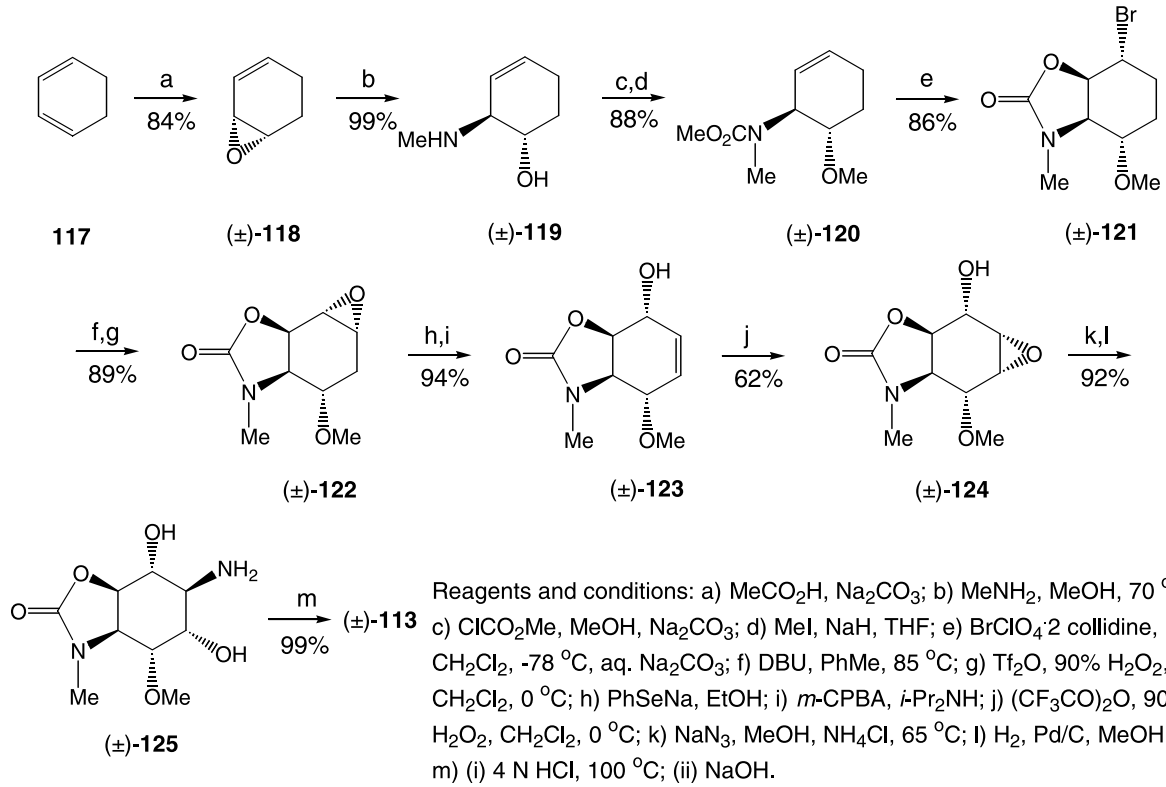


Figure 6.

asymmetric transformation (DYKAT) of the fully protected (±)-conduritol B (±)-**126** by Trost and co-workers.[37] This racemic conduritol tetraacetate (±)-**126** was prepared in three steps from benzoquinone by a simple modification of Guo's method.[38] Tetratrichloroethyl carbonate (±)-**127** was derived from (±)-**126** by a two-step, one-pot procedure. Phthalimidation of (±)-**127** in the presence of 2.5 mol% of $(dba)_3Pd_2\cdot CHCl_3$ and the chiral ligand (*R*,*R*)-**49** gave the protected conduramine B-1 derivative (−)-**128a** in 37% yield and 97% ee (Scheme 14). When the catalyst loading was increased to 5 mol%, the reaction proceeded to give a 61% yield (95% ee) in a process that is, at least in part, a DYKAT. When dibenzylamine was used, a DYKAT was observed, since complete conversion into (−)-**128b** in 89% yield (95% ee) could be achieved.

Unprotected conduramine B-1 hydrochloride [(−)-**135**·HCl] was first prepared by Stick and co-workers (Scheme 15).[39] Methyl α-D-glucopyranoside **129** was transformed into enone **130**[40] and then into the allylic alcohol **131** under Luche's conditions ($NaBH_4$, $CeCl_3\cdot 7H_2O$, MeOH).[41] The alcohol **131** was converted into the amide (−)-**133** through an Overman rearrangement[42] of the trichloroacetamidate (+)-**132** and hydrolysis of (−)-**133** gave the amine (−)-**134**. Debenzylation of (−)-**134** (Na/NH_3/THF) followed by treatment with 1 N HCl gave conduramine B-1 hydrochloride [(−)-**135**·HCl], which was characterized as the amide (−)-**18**.

(−)-Conduramine B-1 [(−)-**17**] has been prepared recently by Vogel and co-workers.[43] Aminoconduritol (−)-**17** has been derived from (+)-7-oxabicyclo[2.2.1]hept-5-en-2-one[44] [(+)-**136** (Scheme 16), a naked sugar of the first generation[45]], applying chemistry reported for the synthesis of (−)-conduritol F.[46] Dibenzyl acetal (+)-**137** was obtained from ketone (+)-**136** in two steps. Treatment of (+)-**137** with strong acid (HSO_3F) led to the partially protected *trans*-diol, which, after Pd-catalyzed hydrogenolysis, gave (+)-**138** (92%, two steps) and ketone (−)-**139** was obtained in two more steps. Reduction of cyclohexenone (−)-**139**[41] with $NaBH_4/CeCl_3\cdot 7H_2O$ in MeOH (0 °C, 3 h) gave a 2.5:1 mixture of conduritol F and conduritol B derivatives, (−)-**140** and (−)-**141**, respectively, in 98% yield. Treatment of this mixture with phthalimide, diethyl azodicarboxylate (DEAD) and triphenylphosphine (all in 1.25 equiv)[32,47] in dry toluene (0 °C, 12 h) provided a 3.8:1 mixture of *N*-substituted phthalimides, (−)-**142** and (−)-**143** (87%), that were separated by FC on silica gel. Under acidic conditions (1% *p*-TsOH in MeOH, 65 °C, 45 min), (−)-**142** was converted into triol (−)-**144** in 95% yield. Transaminolysis of (−)-**144** with $MeNH_2$ (41% in H_2O, 20 °C) and purification on a Dowex-50W-X2 (H^+ form) column provided pure (−)-conduramine B-1 [(−)-**17**] in 95% yield (Scheme 16).



Scheme 13.

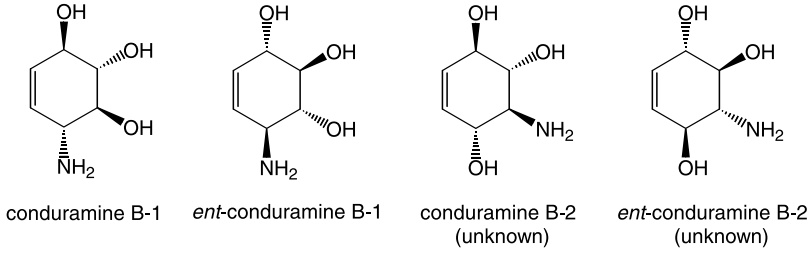
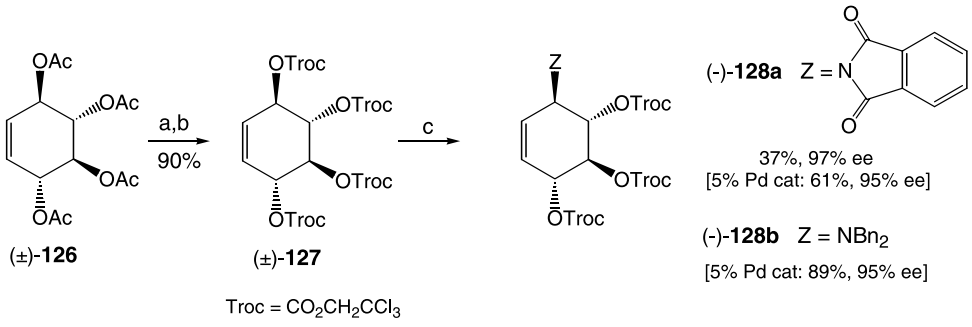
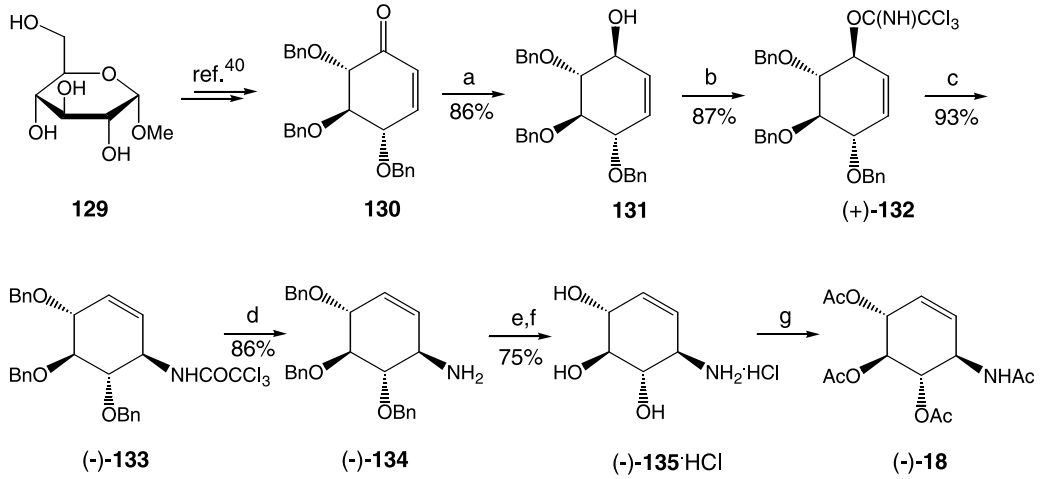


Figure 7.

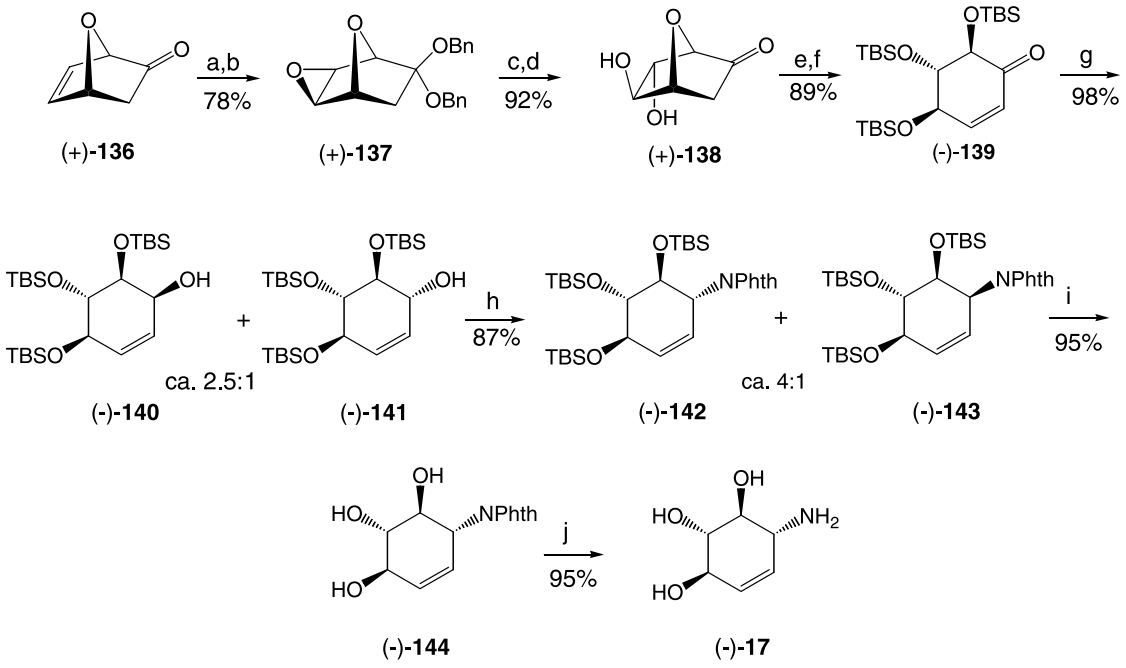


Scheme 14.



Reagents and conditions: a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C; b) Cl_3CCN, NaH, CH_2Cl_2, rt, 1 h; c) xylene, Δ, 9 h; d) 6 N NaOH, EtOH, rt, overnight; e) Na/NH_3, THF,-78 °C, 1 h; f) 1 N HCl; g) Ac_2O/Py, DMAP, rt.

Scheme 15.



Reagents and conditions: a) BnOTMS, TMSOTf, CH_2Cl_2 4 °C, 4 h; b) *m*-CPBA, $CHCl_3$, rt, 6 h; c) BnOH, CH_2Cl_2, HSO_3F, -15 °C to rt, overnight; d) H_2, 10% Pd/C, EtOH:H_2O (9:1 v/v), 4 d; e) TBSCl, Imd, DMF, rt, 6 h; f) TBSOTf, Et_3N, PhH, 6 h; g) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C; h) PPh_3, phthalimide, DEAD, PhMe, 0 °C, 12 h, separation by CC, i) 1% *p*-TsOH in MeOH, reflux, 45 min; j) 40% $MeNH_2$ in H_2O, rt, 1 h, filtration on Dowex-50W-X2 (H^+ form)/2 N NH_4OH.

Scheme 16.

The same method starting from (−)-**136** allowed the synthesis of (+)-*ent*-conduramine B-1 [(+)-**17**] for the first time.[43]

2.3. Synthesis of aminoconduritols C

There are four types of conduramines C, conduramine C-1 and its enantiomer (*ent*-C-1), conduramine C-2 and *ent*-C-2, conduramine C-3 and *ent*-C-3, and conduramine C-4 and *ent*-C-4 (Fig. 8). Conduramines C-2, C-3 and C-4 in both enantiomeric forms are unknown compounds.

2.3.1. Synthesis of aminoconduritol C-1 and analogues. In 1992, Johnson and co-workers[9c] reported the first

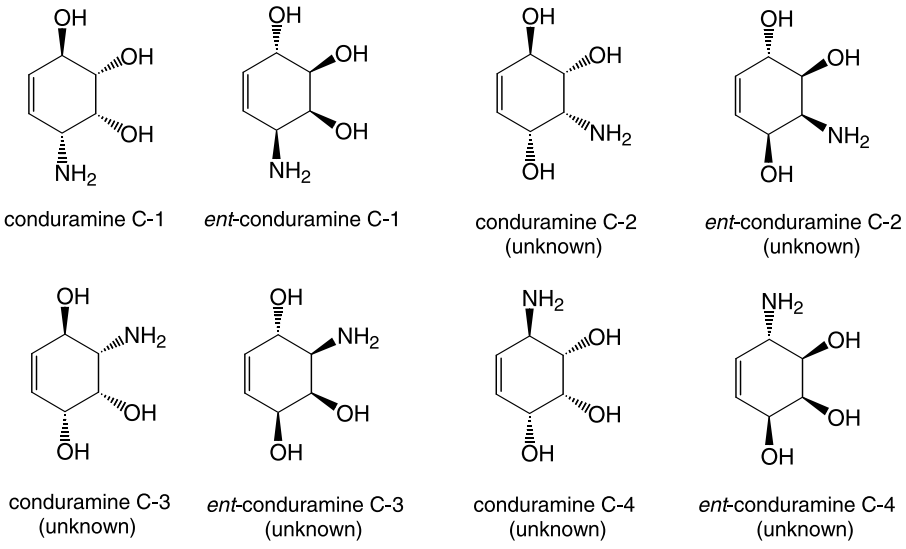
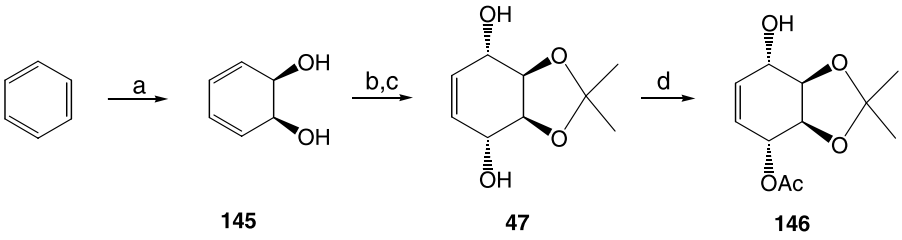


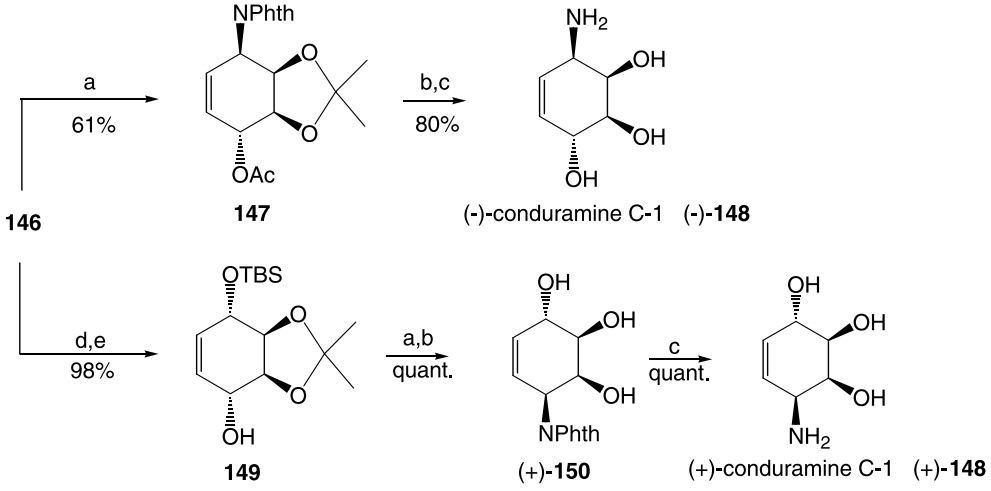
Figure 8.



Reagents and conditions: a) *Pseudomonas putida*; b) 2,2-dimethoxypropane, *p*-TsOH; c) O_2 then $(NH_2)_2CS$; d) *Pseudomonas cepacia* lipase (Amano P-30), isopropenyl acetate, 55 °C.

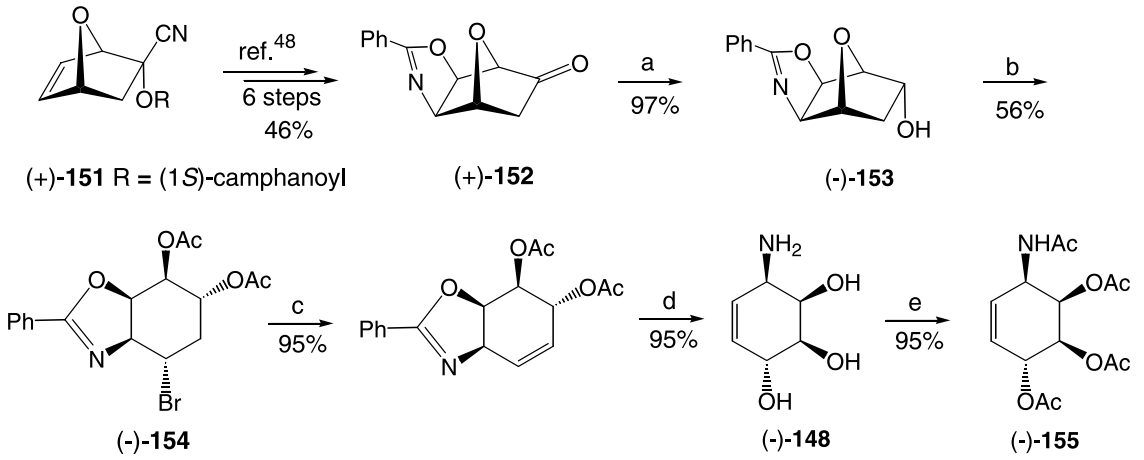
Scheme 17.

syntheses of (−)- and (+)-conduramine C-1, (−)-**148** and (+)-**148** (Schemes 17 and 18). Microbial oxidation of benzene into cyclohexa-3,5-diene-1,2-diol (**145**), followed by treatment with $(MeO)_2CMe_2$ under acidic conditions, produced *meso*-2,3-*O*-isopropylideneconduritol A (**47**). Its desymmetrization to **146** was realized by *Pseudomonas cepacia* lipase-catalyzed monoacetylation in pure isopropenyl acetate (Scheme 17).



Reagents and conditions: a) PPh_3, phthalimide, DEAD, PhMe, 0 °C, 1 h, b) *p*-TsOH, MeOH, reflux; c) 40% aq. $MeNH_2$; d) TBSCl, Imd, DMF; e) K_2CO_3, MeOH.

Scheme 18.



Reagents and conditions: a) $NaBH_3CN$, MeOH, 0 °C, then 5.5 h, rt; b) 33% HBr in AcOH, 60° C, 3 d; c) DBU, PhMe, Δ, 2 h; d) (i) 5 N HCl, Δ 2 h; (ii) Dowex (500 x 4); e) Ac_2O/Py.

Scheme 19.

Treatment of **146** with phthalimide applying the Mitsunobu protocol[32] gave the fully protected conduramine C-1 derivative **147** which, under acidic conditions followed by treatment with 40% aq $MeNH_2$, gave (−)-conduramine C-1 [(−)-**148**]. Silylation/deacetylation of **146** gave alcohol **149**. Deprotection (*p*-TsOH in MeOH) afforded triol (+)-**150** which, upon aminolysis, gave (+)-conduramine C-1 [(+)-**148**] (Scheme 18).

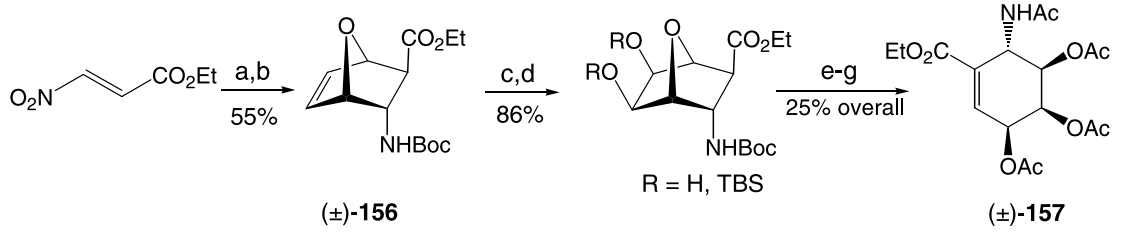
An alternative approach to the asymmetric synthesis of (−)-conduramine C-1 was developed by Allemann and Vogel,[2j] who used the naked sugar (+)-**151** as the starting material. The tricyclic ketone (+)-**152**[48] was obtained in six steps with an overall yield of 46%. Ketone (+)-**152** was reduced to the corresponding *endo*-alcohol (−)-**153**, the treatment of which with boiling HBr/AcOH provided the diacetate (−)-**154**. Regioselective *anti*-eliminaton of HBr with DBU and acidic hydrolysis furnished (−)-conduramine C-1 [(−)-**148**], which was also characterized as its peracetate (−)-**155** (Scheme 19).

A substituted racemic conduramine C-1 derivative that is, in fact, a β-amino acid derivative [(±)-**157**] was described by Masesane and Steel.[49] Their synthesis started with the oxanorbornene derivative (±)-**156**, obtained by Diels–Alder addition of ethyl (*E*)-nitroacrylate and furan. The selective *exo*-dihydroxylation of the alkene moiety of (±)-**156**, followed by base-induced fragmentation (LiHMDS, THF, −50 °C) of the oxanorbornane skeleton (E_1cb elimination), provided the desired conduramine derivative (±)-**157** (Scheme 20).

An approach to racemic conduramine C-1[21] is presented in Scheme 21 in which an initial OsO_4-catalyzed hydroxylation of (±)-**39** and subsequent protection gave acetonide (±)-**158**. Reduction of (±)-**158** ($NaBH_4$, MeOH) give a mixture (ca. 5.5:1) of the *exo* and *endo* isomers of (±)-**159**. Reaction of this mixture with LHMDS led to derivative (±)-**160**. Reductive desulfonylation gave compound (±)-**161** that was converted into the conduramine C-1 derivative (±)-**162** by a three-step process. After deprotection and acetylation of (±)-**162**, racemic conduramine C-1 tetraacetate [(±)-**155**] was obtained.

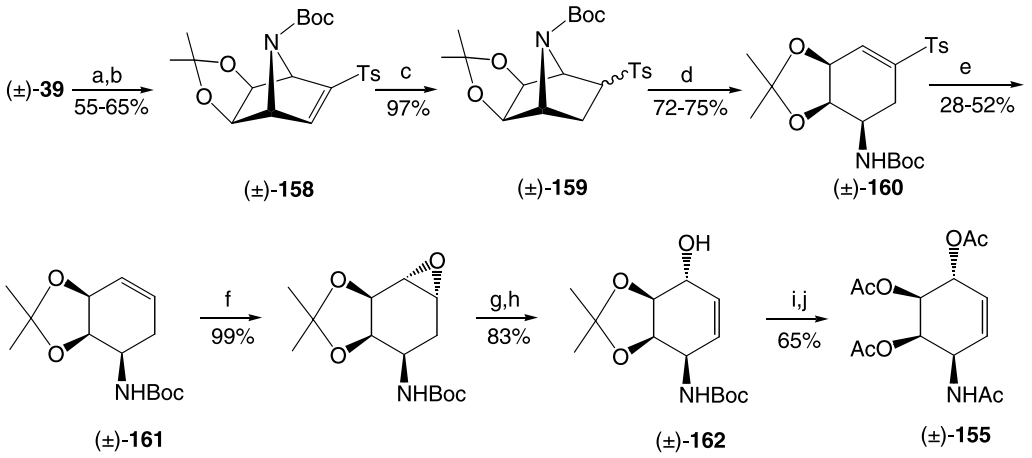
2.3.2. Synthesis of aminoconduritol C-2 analogues. Hygromycin A **163** is an antibiotic produced by cultures of several types of *Streptomyces*[50] and is widely used against Gram-positive and Gram-negative bacteria.[50a,b] It contains the unique aminocyclitol structure **164** (Fig. 9).

In 1989 Ogawa and co-workers[51] reported the total synthesis of this antibiotic from D-glucose. The key aminocyclitol (−)-**164** was obtained from the conduramine C-2 derivative **169** (Scheme 22).[51a] The known 5-enopyranoside **165** was



Reagents and conditions: a) furan, $CHCl_3$, -20 °C; b) (i) Zn/HCl, EtOH; (ii) Boc_2O, TEA; c) cat. OsO_4, $Me_3NO{\cdot}H_2O$, Me_2CO; d) TBSCl, Imd, CH_2Cl_2; e) LiHMDS, THF, -50 °C to 25 °C; f) TBAF, THF; g) Ac_2O/Py.

Scheme 20.



Reagents and conditions: a) cat. OsO_4, NMO, $NaHCO_3$, *t*-BuOH, H_2O, THF; b) $Me_2C(OMe)_2$-Me_2CO, *p*-TsOH; c) $NaBH_4$, MeOH; d) LHMDS, THF, -78 °C to rt; e) SmI_2/THF-HMPA, -23 °C; f) *m*-CPBA, $NaHCO_3$, CH_2Cl_2; g) $(PhSe)_2$, *n*-BuLi, THF; h) H_2O_2, CH_2Cl_2 then *i*-Pr_2NEt, THF, Δ; i) TFA, H_2O/CH_2Cl_2; j) NH_3/MeOH; j) Ac_2O/Py, DMAP.

Scheme 21.

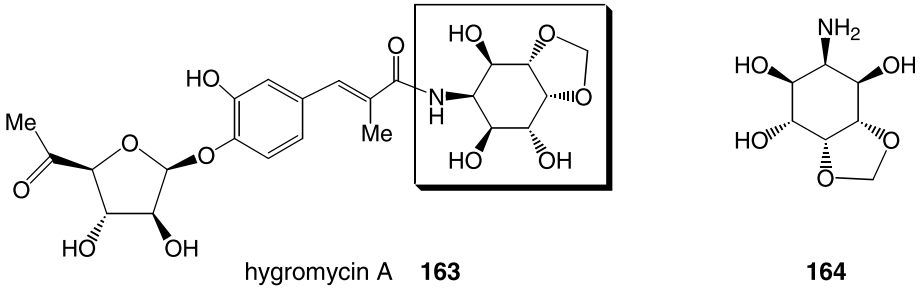
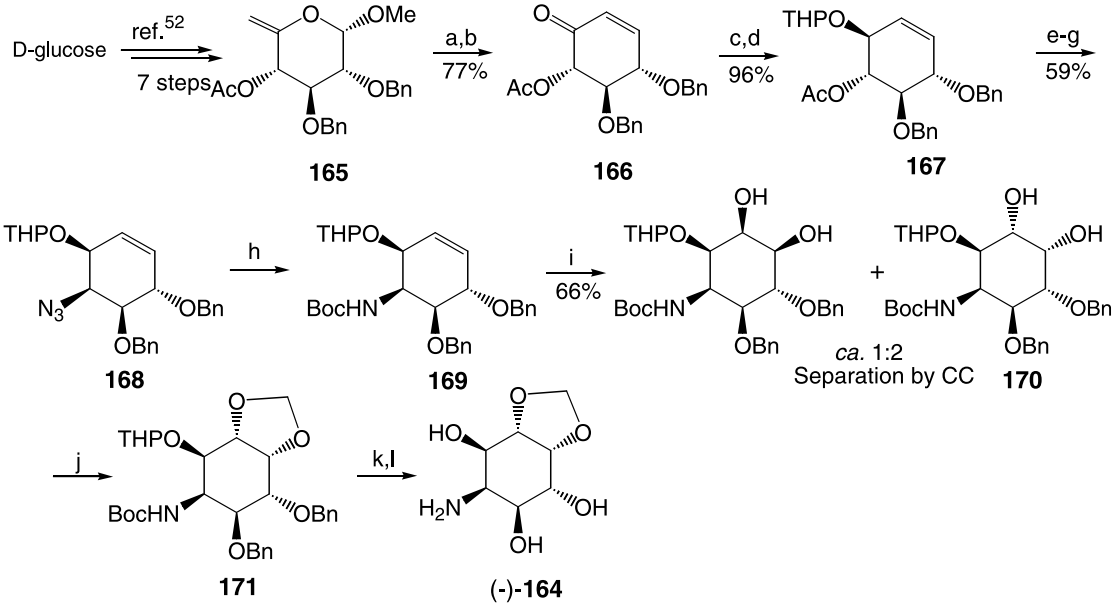
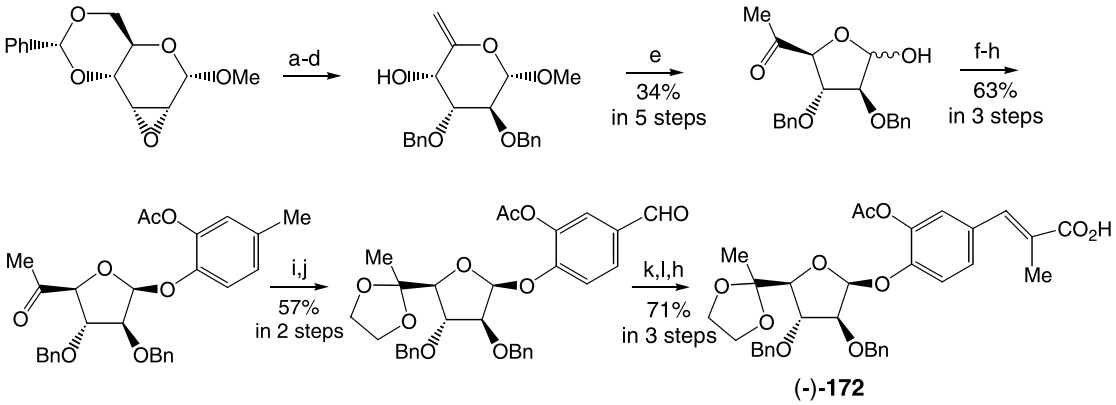


Figure 9.



Reagents and conditions: a) $HgCl_2$, Me_2O-H_2O (1:2), Δ; b) MsCl, Et_3N, CH_2Cl_2; c) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C; d) DHP, PPTS, CH_2Cl_2; e) MeONa, MeOH; f) MsCl, Py, 50 °C; g) NaN_3, HMPA, 100 °C; h) (i) $LiAlH_4$, Et_2O, 0 °C, (ii) $(Boc)_2O$, Et_3N, CH_2Cl_2; i) cat. OsO_4, NMO, DMF-H_2O (4:1), 75 °C; j) NaH, CH_2Br_2, DMF, 0 °C to rt; k) $H_2/Pd(OH)_2$, EtOH; l) TFA, $CHCl_3$, rt.

Scheme 22.



Reagents and conditions: a) (i) NaOH, H_2O, Δ, 48 h; (ii) BnCl, DMSO, rt, 4 h; b) 80% AcOH, 80 °C, 30 min; c) MeI, PPh_3, DEAD, THF, rt, 19 h; d) DBU, PhMe, 80 °C, 23 h; e) IR-120B resin (H^+ form), THF-H_2O (5:2), rt, 22 h; f) 3-benzyloxy-4-hydroxybenzaldehyde, PPh_3, DEAD, THF, rt, 2.5 h; g) H_2, $Pd(OH)_2$, AcOEt, rt, 30 min; h) Ac_2O/Py, rt, 30 min; i) $(CH_2OMe_3Si)_2$, TMSOTf, CH_2Cl_2, -5 °C, 8 h; j) CAN, MeCN-H_2O (1:2), 5 °C; k) $Ph_3P{=}C(Me)CO_2Et$, CH_2Cl_2, rt, 14 h; l) 1M NaOH, MeOH, 50 °C, overnight.

Scheme 23.

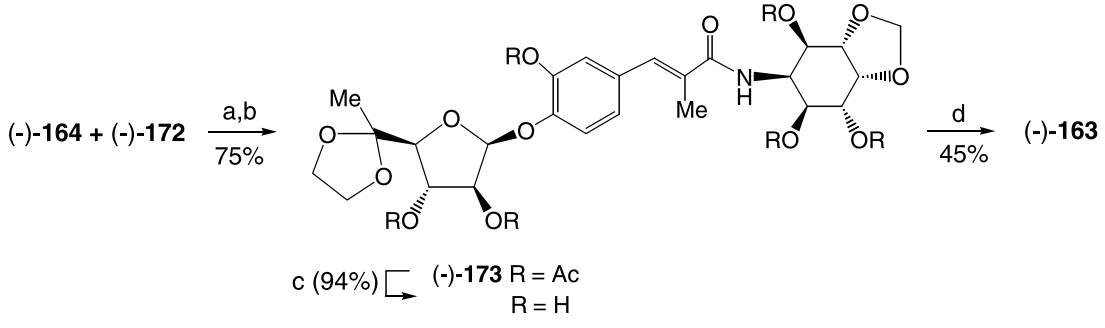
prepared from D-glucose in seven steps.[52] Ferrier reaction of **165**, followed by dehydration, afforded the cyclohexene derivative **166** (77%). Reduction of the carbonyl group of **166** ($NaBH_4/CeCl_3\cdot 7H_2O$) proceeded stereoselectively to give a single alcohol, which was isolated as the THP ether **167**, as a mixture of two diastereoisomers (96%). *O*-Deacetylation of **167** followed by treatment with MsCl gave the mesylate and subsequent treatment with NaN_3 in HMPA gave the azide **168** (59%). Azide **168** was reduced with $LiAlH_4$ and the amine obtained was converted into its Boc-derivative **169**. Dihydroxylation of **169** (OsO_4) gave a 1:2 mixture of two compounds in 66% yield. From this mixture, the *neo*-inosamine-2 derivative **170** was isolated by column chromatography. Further transformations (three steps) via **171** gave aminocyclitol (−)-**164** (Scheme 22).

The second fragment of (−)-hygromycin A containing 2-methylcaffeic acid [(−)-**172**] was prepared as outlined in Scheme 23.

The coupling reaction of the optically active aminocyclitol (−)-**164** and sugar fragment (−)-**172** was conducted under Shioiri's protocol[53] [$(EtO)_2P(O)CN$, Et_3N, DMF] and the condensate was obtained as the acetate (−)-**173**, *O*-deacetylation and acid hydrolysis giving (−)-hygromycin A [(−)-**163**] (Scheme 24).

In 1995, Plumet and co-workers[54] applied a highly diastereoselective dihydroxylation of an amino-deoxy-conduritol C-2 analogue, easily accessible from a 7-oxanorbornenic derivative, in the synthesis of the aminocyclitol moiety of hygromycin A.

2.3.3. Synthesis of aminoconduritol C-4 analogues. The synthesis of (±)-conduramine C-4 was reported for the first time by Nakajima et al.,[12] starting from *cis*-benzene diacetate **12**. Epoxidation of **12** followed by opening of the epoxide [(±)-**14**] with NH_3 in MeOH provided the (±)-aminoconduritols C-4 [(±)-**19**] (Scheme 1).

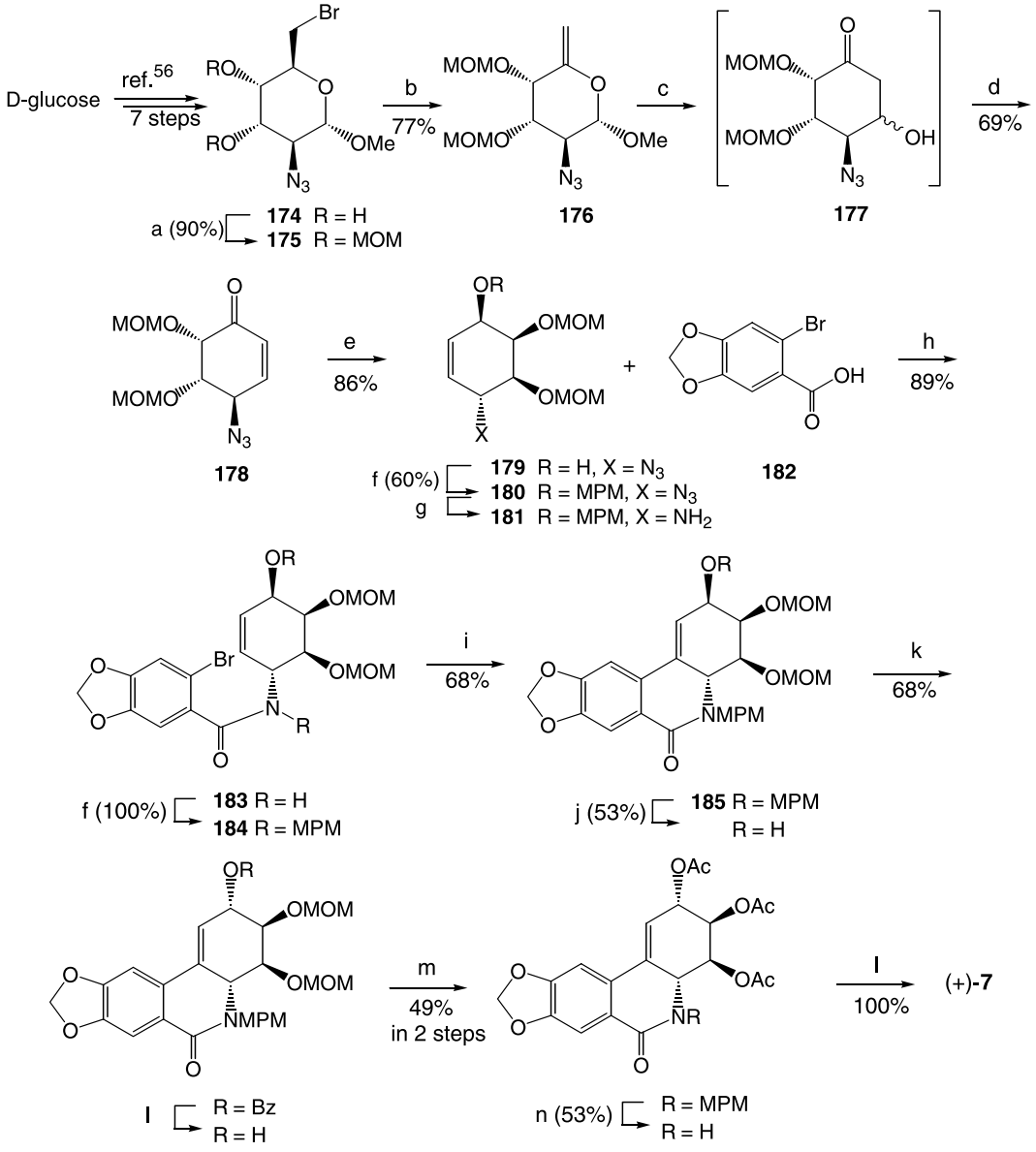


Reagents and conditions: a) $(EtO)_2P(O)CN$, Et_3N, DMF, 0 °C, 2.5 h; b) Ac_2O/Py, rt, 2 h; c) MeONa, MeOH, 0 °C, 30 min; d) TFA-H_2O (3:2), rt, 1 h.

Scheme 24.

Ogawa and co-workers[55] designed an elegant synthesis for optically active (+)-lycorcidine (+)-**7** starting from D-glucose. The key step in their synthesis is the Ferrier rearrangement used to construct the optically active cyclohexenone **178** which was then converted into the conduramine C-4 derivative **181** (Scheme 25).

The hydroxyl groups in **174**, obtained in seven steps from D-glucose,[56] were protected as the methoxymethyl diether **175**. This latter compound was then treated with DBU to afford **176** in good yield. The catalytic Ferrier rearrangement of **176** induced by $(CF_3CO_2)_2Hg$ provided the cyclohexanone derivative **177**, which was dehydrated in situ (MsCl, Et_3N) to give enone **178**. Reduction of the carbonyl group of **178** ($NaBH_4$, $CeCl_3\cdot 7H_2O$, MeOH) proceeded with good stereoselectivity, and alcohol **179** was obtained as a single product and was protected as a *p*-methoxybenzyl ether **180**. Reduction of the azido function of **180** gave the corresponding amine **181**, which was reacted with carboxylic acid **182** to give amide **183** (89% overall yield, based on **180**). Protection of the amide nitrogen (*p*-$MeOC_6H_4CH_2Cl$, NaH) led to compound **184**. Treatment of the fully protected amide **184** under modified Heck conditions (see Scheme 10) afforded a product **185** (68% yield) possessing the phenanthridone skeleton. This compound was subsequently converted into the final product [(+)-**7**] in six additional steps, as outlined in Scheme 25.



Reagents and conditions: a) MOMCl, DIPEA, CH_2Cl_2; b) DBU, PhMe, Δ; c) $(CF_3CO_2)_2Hg$ (1 mol %), Me_2CO-H_2O (2:1), rt; d) MsCl, Et_3N, CH_2Cl_2; e) $NaBH_4$, $CeCl_3\cdot 7H_2O$, MeOH; f) NaH, MPMCl, DMF; g) $LiAlH_4$, Et_2O; h) $(EtO)_2P(O)CN$, Et_3N, DMF; i) $Pd(OAc)_2$ (20 mol %), dppe (40 mol %), TlOAc, DMF, 140 °C; j) DDQ, CH_2Cl_2/H_2O (19:1); k) Ph_3P, DEAD, $PhCO_2H$, THF; l) MeONa, MeOH, rt; m) (i) 1M HCl aq./THF (1:1), 50 °C; (ii) Ac_2O/Py; n) TFA/$CHCl_3$ (1:1), rt, 2 h.

Scheme 25.

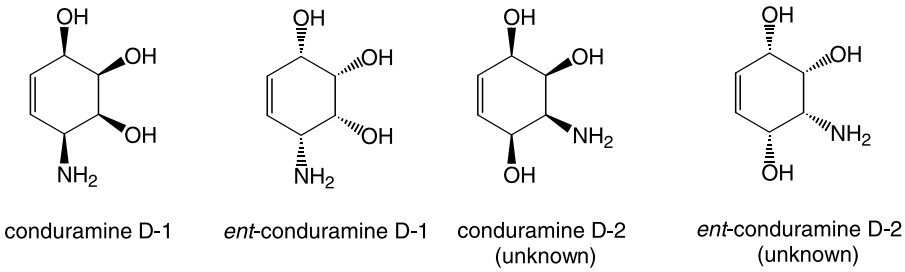


Figure 10.

2.4. Synthesis of aminoconduritols D

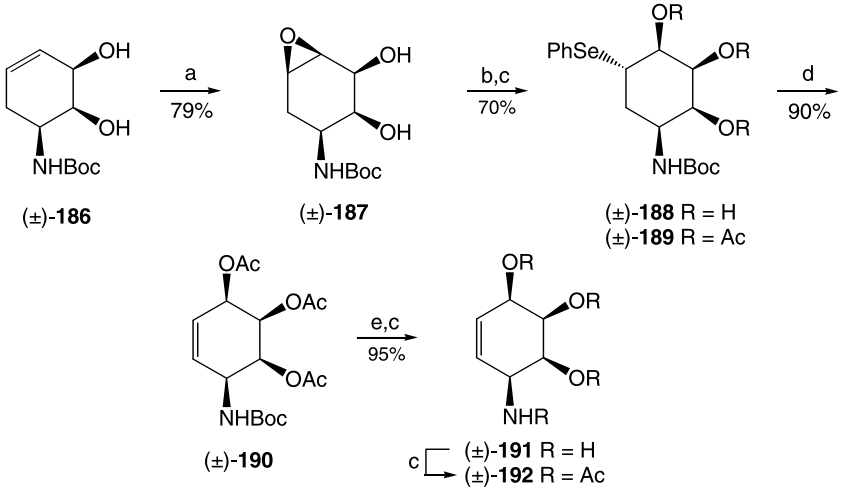
There are two types of conduramines D, conduramine D-1 and its enantiomer (*ent*-D-1), and conduramine D-2 and its enantiomer (*ent*-D-2) (Fig. 10). The two latter compounds have not yet been described.

2.4.1. Synthesis of aminoconduritol D-1 analogues. Conduramine D-1 [(±)-**191**] was first prepared by Muchowski and co-workers[21] as the racemic form using *cis*-diol (±)-**186** as the starting material. Oxidation of (±)-**186** with *m*-CPBA gave epoxide (±)-**187** with five contiguous cis substituents exclusively. The transformation of (±)-**187** into conduramine D-1 (±)-**191** and its crystalline peracetate derivative (±)-**192** (Scheme 26) was then effected by a methodology similar to that used for the generation of several other conduramines (Schemes 5, 21 and 34) and which implies the regioselective epoxide ring opening (±)-**187**→(±)-**188**, subsequent esterification of (±)-**188** into (±)-**189** and oxidative *syn*-elimination of the selenide to give alkene intermediate (±)-**190**. Final deacetylation of (±)-**190** produced the unprotected (±)-aminoconduritol D-1 [(±)-**191**], which was characterized as its peracetate (±)-**192**.

2.5. Synthesis of aminoconduritols E

There are two types of conduramines E, conduramine E-1 and its enantiomer (*ent*-E-1) and conduramine E-2 and its enantiomer (*ent*-E-2) (Fig. 11). The two latter compounds are unknown.

2.5.1. Synthesis of aminoconduritol E-1 and analogues. In 1995, Trost and Pulley[57] described an efficient



Reagents and conditions: a) *m*-CPBA, $NaHCO_3$, CH_2Cl_2; b) $(PhSe)_2$, *n*-BuLi, THF; c) Ac_2O/Py, DMAP; d) H_2O_2, DIPEA, CH_2Cl_2, 0 °C, then THF, Δ; e) 5 N HCl/Δ.

Scheme 26.

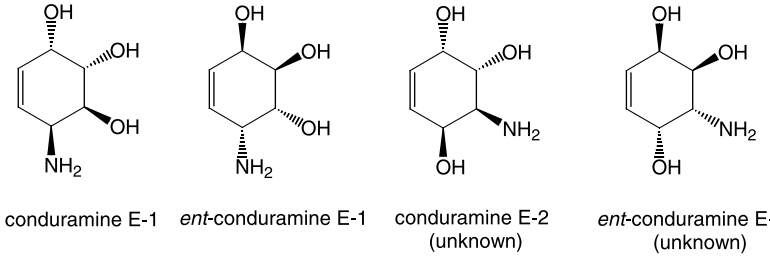
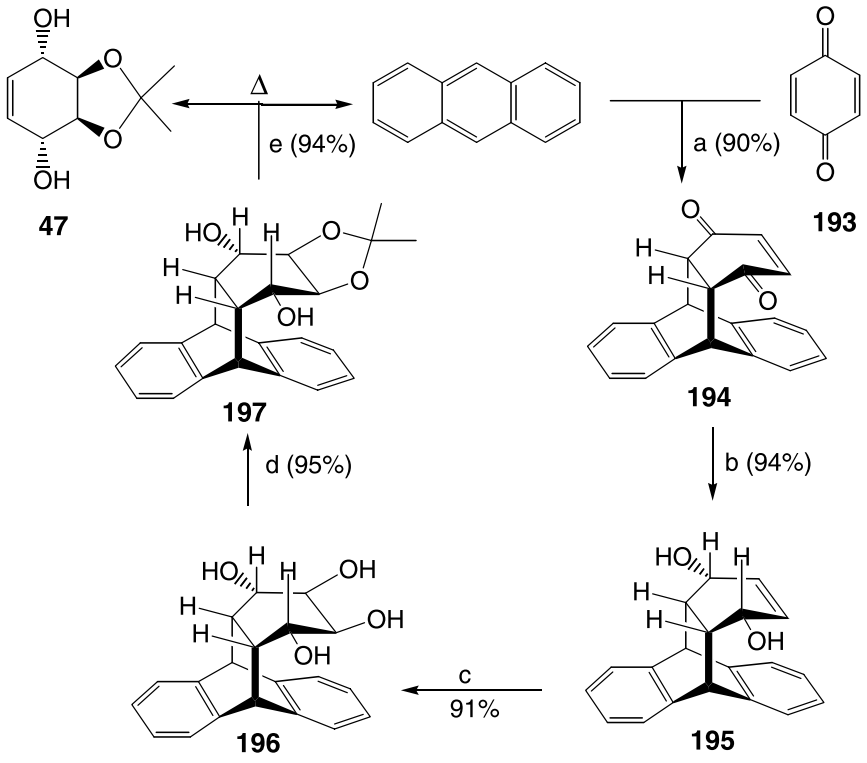


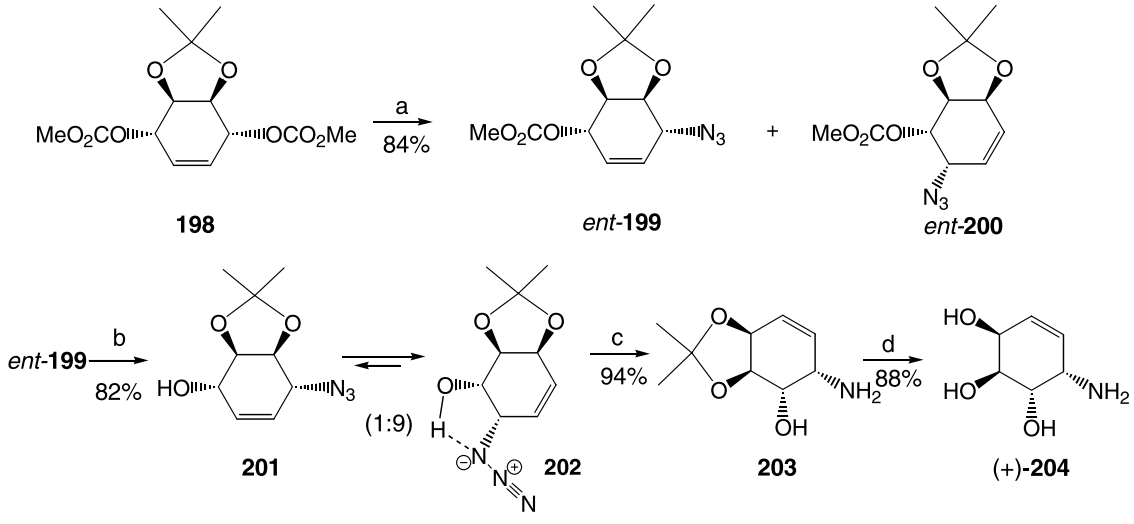
Figure 11.



Reagents and conditions: a) xylene, Δ; b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, CH_2Cl_2; c) cat. OsO_4, $NMO{\cdot}2H_2O$, Py, *t*-BuOH, H_2O, D; d) Me_2CO, $Me_2C(OMe)_2$, *p*-TsOH; e) FVT, 500 °C.

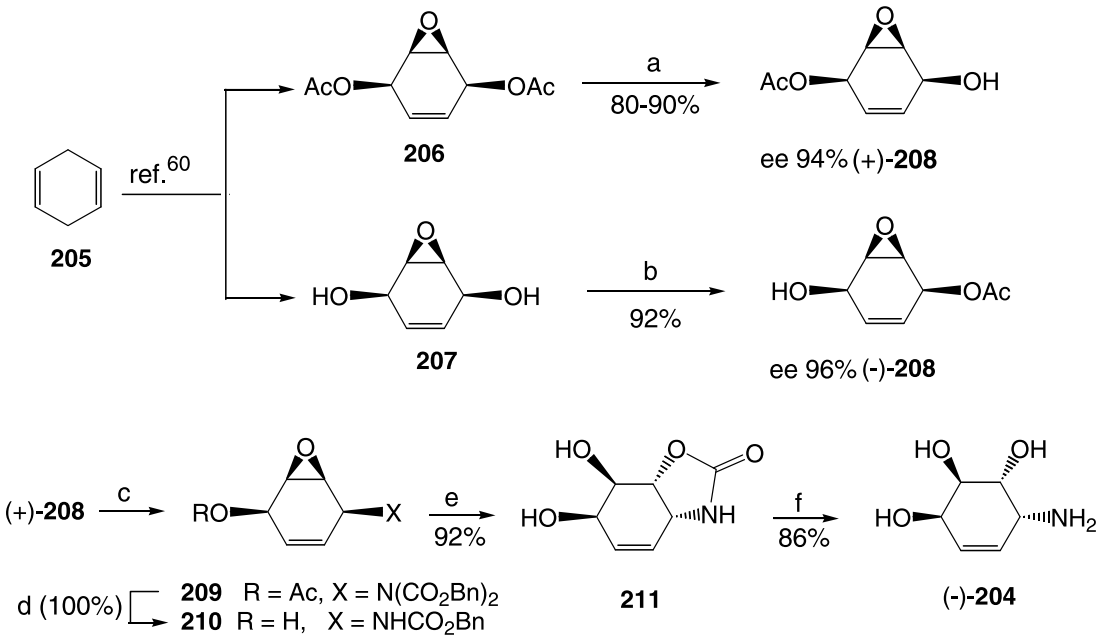
Scheme 27.

preparation of (+)-conduramine E-1 [(+)-**204**]. Conduritol A acetonide **47** was prepared as shown in Scheme 27 using a modification of the method of Cambie et al.[58] *p*-Benzoquinone (**193**) added to anthracene giving adduct **194**. Reduction of the dione under Luche's conditions provided **195** with high stereoselectivity (steric factor). Dihydroxylation of the cyclohexene moiety **195** gave tetrol **196** that was converted into its monoacetonide **197** (Scheme 27). Flash high vacuum pyrolysis furnished diol **47**, which was then converted into the dimethyl carbonate **198** (Scheme 28).



Reagents and conditions: a) 1.5% (*R,R*)-**49**, 0.5% $[\eta^3\text{-}C_3H_5PdCl]_2$, $TMSN_3$, CH_2Cl_2, 0 °C, 2 h; b) K_2CO_3, MeOH, 50 °C; c) Me_3P, THF, H_2O; d) 2 N HCl, H_2O, THF.

Scheme 28.



Reagents and conditions: a) *n*-hexane, 0.2 N pH 7 phosphate buffer, SP 523 (4% w/w), rt; b) TBME-vinyl acetate, Lipozyme IM (5% w/w), rt; c) nucleophile [$HN(CO_2Bn)_2$], PPh_3, DEAD, THF, rt; d) NH_3/MeOH, rt; e) AcOH, H_2O, 110 °C; f) $Ba(OH)_2$, 50 °C.

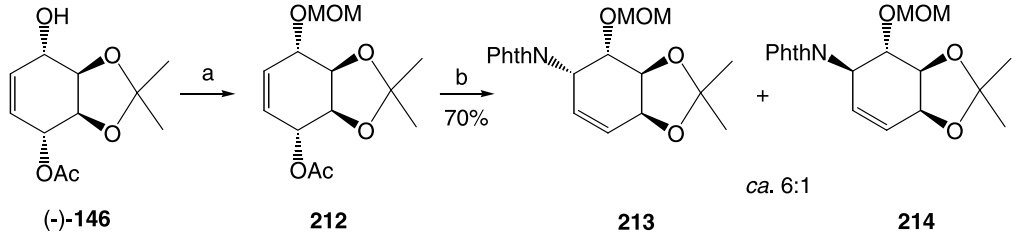
Scheme 29.

Using $[\eta^3\text{-}C_3H_5PdCl]_2$ as the palladium(0) source and the homochiral diphosphine (*R*,*R*)-**49** (see Scheme 6) compound **198** was converted into a mixture of two allylic azides, *ent*-**199** and *ent*-**200**, with high enantioselectivity. Subjecting *ent*-**199** to hydrolysis (K_2CO_3, MeOH), a 1:9 mixture of alcohols **201** and **202** was obtained. Compound **202** was isolated in 82% yield. A simple Staudinger-type reduction of **202** to amine **203**, followed by acidic hydrolysis, led to (+)-conduramine E-1 [(+)-**204**, ee >95%] (Scheme 28).

Recently, Prinzbach and co-workers[59] have reported a synthesis of (−)-conduramine E-1, starting from 1,4-cyclohexadiene (**205**). The epoxy-diacetate **206** and diol **207**, prepared according to a procedure that they had already disclosed in 1972,[60] were submitted to enantioselective lipase-catalyzed hydrolysis, giving either allylic alcohol (+)-**208** or its enantiomer (−)-**208**, depending upon the type of enzymes used (Scheme 29). Mitsunobu substitution of (+)-**208** with $HN(CO_2Bn)_2$ provided **209**. Selective removal of one of the two benzyl carbamate moieties gave **210** quantitatively. Treatment of **210** under acidic conditions provided a regioselective ring opening of the epoxide under assistance by the neighbouring carbamate group. This generated isoxazolone **211**, the hydrolysis of which under basic conditions produced (−)-conduramine E-1 [(−)-**204**].

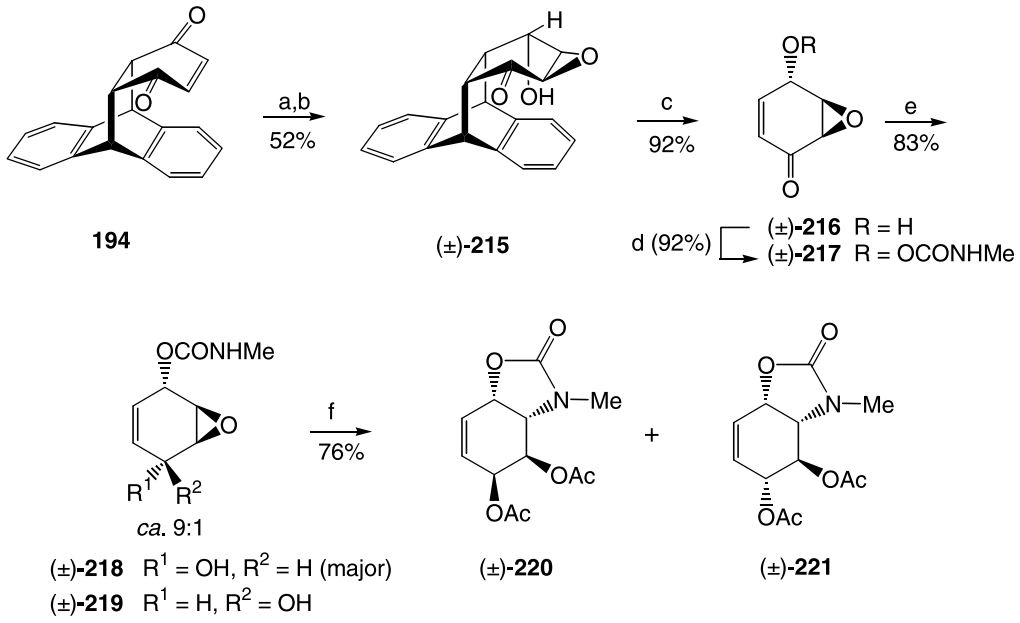
Fully protected conduramine E-1 derivative **213** and conduramine F-4 derivative **214** have been obtained by Johnson and co-workers.[9c] Treatment of **212** (derived from (−)-**146** by treatment with MOMCl, DIPEA) under the conditions shown in Scheme 30, gave two protected aminoconduritols **213** and **214** in a ratio of ca. 6:1.

The racemic forms of conduramine E-2 derivative (±)-**220** and conduramine F-2 derivative (±)-**221** have been obtained applying the method used by Combie and



Reagents and conditions: a) MOMCl, DIPEA; b) $Pd(PPh_3)_4$, DMF, dppe, 50 °C, potassium phthalimide.

Scheme 30.



Reagents and conditions: a) 27% aq. H_2O_2, K_2CO_3, CH_2Cl_2/MeOH (1:1), 40 min; b) $NaBH_4$, $ZnCl_2$, THF, 1 h; c) pyrolysis, 460 °C, 0.2 mmHg, 30 min; d) MeNCO, cat. Me_2SnCl_2 (2 mol %), CH_2Cl_2, rt, 3 h; e) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0 °C, 10 min; f) (i) *t*-BuOK, THF, 2 h, rt; (ii) Ac_2O/Py, rt.

Scheme 31.

co-workers[61] in their synthesis of 3-*O*-demethylfortamine. The Diels–Alder adduct **194** of anthracene and 1,4-benzoquinone was converted into a mixture of (±)-**220** and (±)-**221** in five steps and 33% overall yield. Epoxidation of the enedione moiety of **194** and subsequent stereoselective reduction of one of the two ketone groups gave the alcohol (±)-**215**. Flash vacuum pyrolysis of (±)-**215** liberated (±)-**216** and anthracene. Reaction of (±)-**216** with methyl isocyanate furnished the corresponding methyl carbamate (±)-**217**. Reduction of the carbonyl group of (±)-**217** under Luche′s conditions led to an inseparable mixture of two diastereomeric allylic alcohols (±)-**218** and (±)-**219**. Treatment of this mixture with *t*-BuOK promoted the intramolecular ring opening of the epoxides and formation of the corresponding oxazolinone-diols that were acetylated into a 1:2 mixture of (±)-**220** and (±)-**221** (Scheme 31).

2.6. Synthesis of aminoconduritols F

There are four types of conduramines F, conduramine F-1 and its enantiomer (*ent*-F-1), conduramine F-2 and *ent*-F-2, conduramine F-3 and *ent*-F-3 and conduramine F-4 and *ent*-F-4 (Fig. 12). Conduramines F-2 and F-3 in both enantiomeric forms are unknown.

2.6.1. Synthesis of aminoconduritol F-1. The first examples of optically pure conduramines and derivatives were presented by Paulsen and co-workers,[62] who obtained

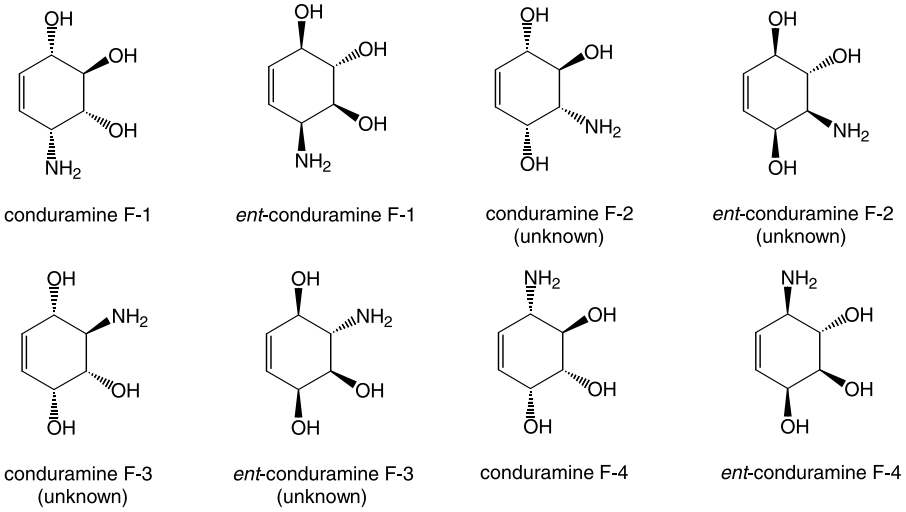
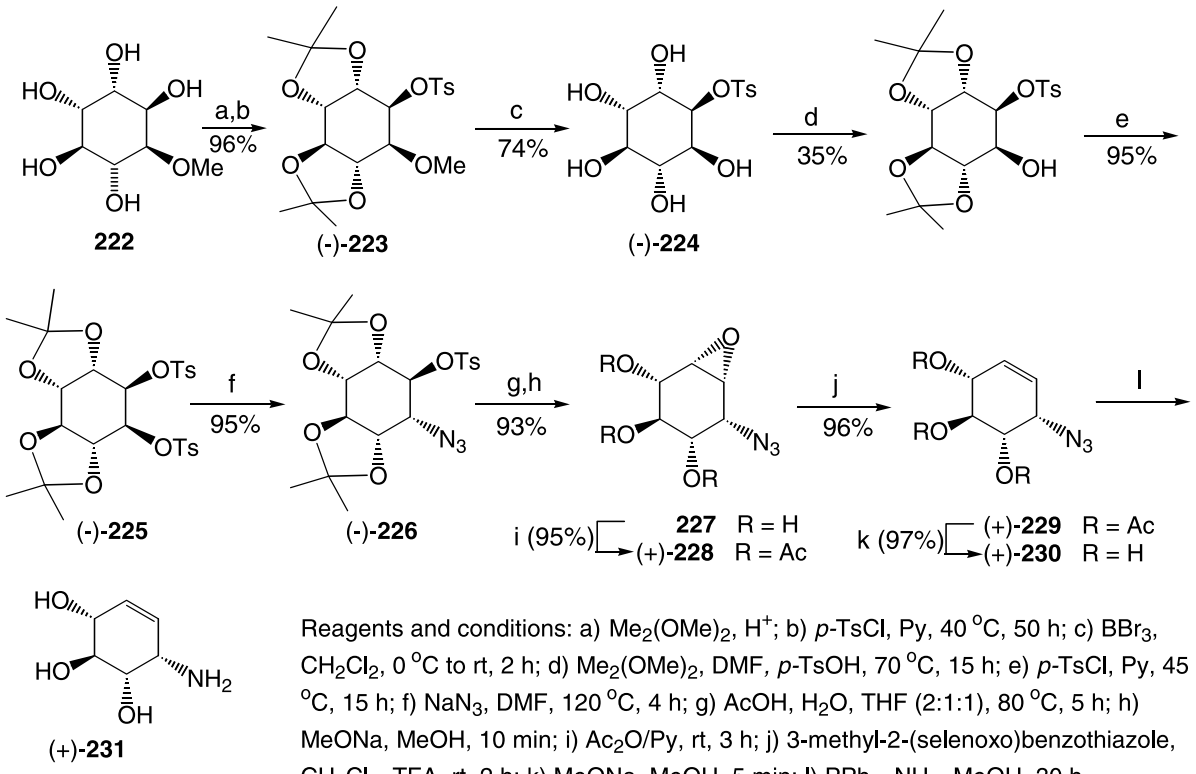


Figure 12.



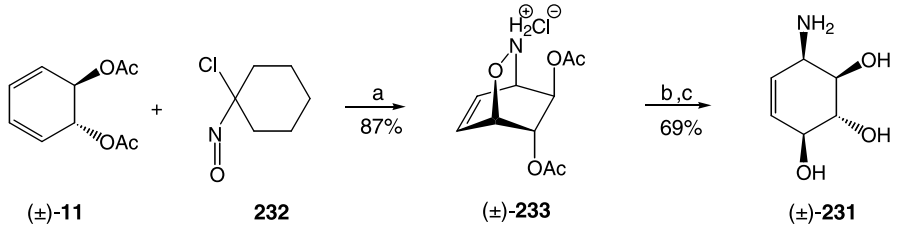
Scheme 32.

(+)-conduramine F-1 [(+)-**231**] (Scheme 32) from natural quebrachitol (2-*O*-methyl-L-*chiro*-inositol) **222**.

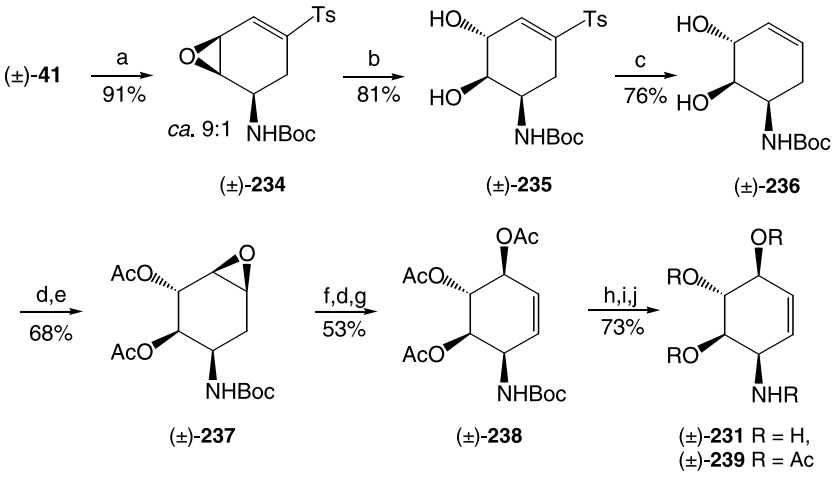
Treatment of **222** with 2,2-dimethoxypropane under acidic conditions followed by classical tosylation afforded di-*O*-isopropylidene-tosylate (−)-**223**. Compound (−)-**223** reacted with BBr_3 in CH_2Cl_2 to give after aqueous work-up 1-*O*-tosylate (−)-**224** which was converted into the ditosylate (−)-**225** in two steps. Selective displacement of the equatorial tosyloxy group of (−)-**225** by NaN_3 gave (−)-**226**. Acidic hydrolysis of the diacetonide and subsequent treatment under basic conditions led to the formation of the azido-epoxide **227**, which, after acetylation, gave triol (+)-**228**. Deoxygenation of the epoxide (+)-**228** provided the cyclohexene derivative (+)-**229**. Zemplen's methanolysis gave triol (+)-**230** which was converted into (+)-conduramine F-1 [(+)-**231**] (Scheme 32).[62]

Kresze and Dittel[63] have developed a short, elegant, four-step route to racemic conduramine F-1 [(±)-**231**]. The adduct (±)-**233** obtained by hetero-Diels–Alder addition of 1-chloro-1-nitrosocyclohexane **232** and *trans*-1,3-cyclohexadiene-5,6-diyl diacetate (±)-**11** in EtOH solution was treated with NH_3/MeOH. Subsequent reduction of the N–O bond produced (±)-**231** in good yield (Scheme 33).

More recently, Muchowski and co-workers[21] have synthesized (±)-conduramine F-1 [(±)-**231**] starting from diene (±)-**41** (for details, see Scheme 4). Peracid oxidation of (±)-**41** gave a 9:1 mixture of the corresponding epoxides. The major compound (±)-**234** underwent acid-promoted epoxide hydrolysis. The reaction is highly stereoselective due to the allylic activation and gave the *trans*-diol (±)-**235** in 81% yield. After reductive desulfonylation of (±)-**235**, giving enediol (±)-**236**, acetylation of the diol and epoxidation of the cyclohexene



Scheme 33.



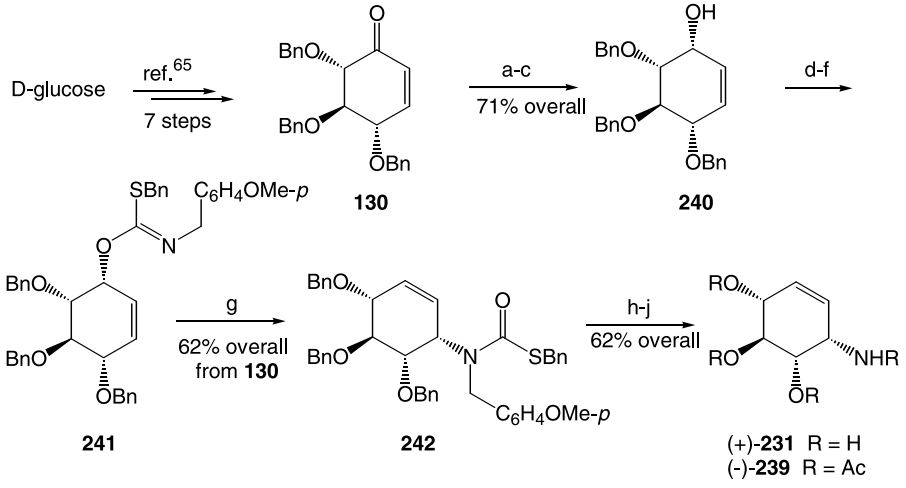
Reagents and conditions: a) *m*-CPBA, CH_2Cl_2; b) H_2O, H_2SO_4, THF, 70 °C; c) 6% Na/Hg, Na_2HPO_4, MeOH, THF, -23 °C; d) Ac_2O/Py; e) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 45 °C; f) $(PhSe)_2$, *n*-BuLi, THF; g) H_2O_2, *i*-Pr_2NEt, CH_2Cl_2, THF, 50 °C; h) 10% HCl, THF, Δ; i) NH_3/MeOH; j) Ac_2O/Py, DMAP.

Scheme 34.

moiety provided (±)-**237**. Five more steps converted (±)-**237** into (±)-conduramine F-1 [(±)-**231**]. The steps involved epoxide ring opening with PhSeLi and subsequent oxidative *syn*-elimination of the intermediate selenide. This generated the fully protected (±)-conduramine F-1 derivative (±)-**238**. Deprotection of (±)-**238** gave (±)-**231** that was characterized as its peracetylated derivative (±)-**239** (Scheme 34).

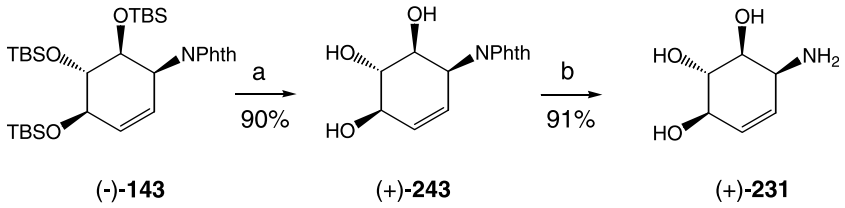
A new route to optically active conduramine F-1 was developed by Knapp and co-workers,[64] based on the [3,3]sigmatropic rearrangements of carbonimidothioate **241** derived from the allylic alcohol **240**, which was prepared from enone **130**[65] (see Scheme 15). Reduction of ketone **130** under Luche's conditions provided **131**, which was inverted into **240** by a Mitsunobu displacement reaction and alkaline methanolysis. Condensation of the sodium alcoholate of **240** with *p*-methoxybenzyl isocyanate, followed by quenching with benzyl bromide, led to carboimidothionate **241**. This latter compound underwent rearrangement in refluxing toluene to give the thiocarbamate **242** (44% overall from **240**). Removal of the *N*-(*p*-methoxybenzyl) group, followed by exhaustive debenzylation (Na/NH_3, THF), provided (+)-7-*nor*-valienamine [(+)-**231**], which was isolated as its peracetate (+)-**239** (Scheme 35).

(+)-*ent*-Conduramine F-1 [(+)-**231**] has been prepared recently by Łysek et al.[66] Under acidic conditions (1% *p*-TsOH in MeOH), compound (−)-**143** was converted into triol (+)-**243** in 90% yield. Transaminolysis of (+)-**243**



Reagents and conditions: a) $NaBH_4$, aq. $CeCl_3$, MeOH; b) $PhCO_2H$, DEAD, Ph_3P; c) aq. KOH, MeOH, 60 °C; d) NaH, THF; e) *p*-(MeO)$C_6H_4CH_2NCS$; f) BnBr; g) PhMe, Δ, 48 h; h) TFA, 2 h; i) Na/NH_3, THF, -55° C, 3 min; j) Ac_2O/Py, DMAP, 12 h, rt.

Scheme 35.



Reagents and conditions: a) 1% *p*-TsOH in MeOH, reflux, 40 min; j) 40% $MeNH_2$ in H_2O, rt, 1 h, filtration on Dowex-50W-X2 (H^+ form)/2 N NH_4OH.

Scheme 36.

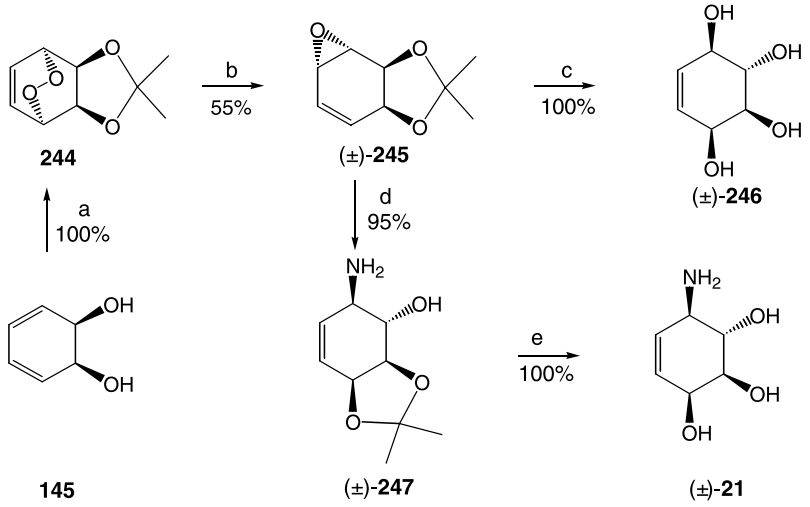
(41% $MeNH_2/H_2O$) and purification on a Dowex-50W-X2 (H^+ form) column gave pure (+)-conduramine F-1 [(+)-**231**] in 91% yield (Scheme 36).

2.6.2. Synthesis of aminoconduritol F-4 and analogues. As shown in Scheme 1, racemic conduramine F-4 was prepared for the first time by Nakajima et al.[12] *cis*-Benzene diacetate **12** was converted in two steps into (±)-aminoconduritol F-4 [(±)-**21**], which was characterized as its tetraacetate (±)-**22**.

The stereospecific synthesis of racemic conduramine F-4 [(±)-**21**] has also been achieved by Balci and co-workers.[67] The cyclohexadiene diol **145**, available from benzene by microbial oxidation using *Pseudomonas putida* (see Scheme 17), was protected as an acetonide and was then submitted to photosensitized oxidation of its diene moiety. The hetero-Diels–Alder reaction of singlet oxygen was highly face-selective for steric reasons and provided the *endo*-peroxide **244**, treatment of which with $POEt_3$ gave the allylic epoxide (±)-**245**, which can be hydrolyzed into (±)-conduritol F [(±)-**246**][68] or ammonolyzed with ammonia in methanol, giving the semiprotected (±)-conduramine F-4 derivative (±)-**247**. Acidic hydrolysis of the acetonide (±)-**247** provided (±)-**21** (Scheme 37).

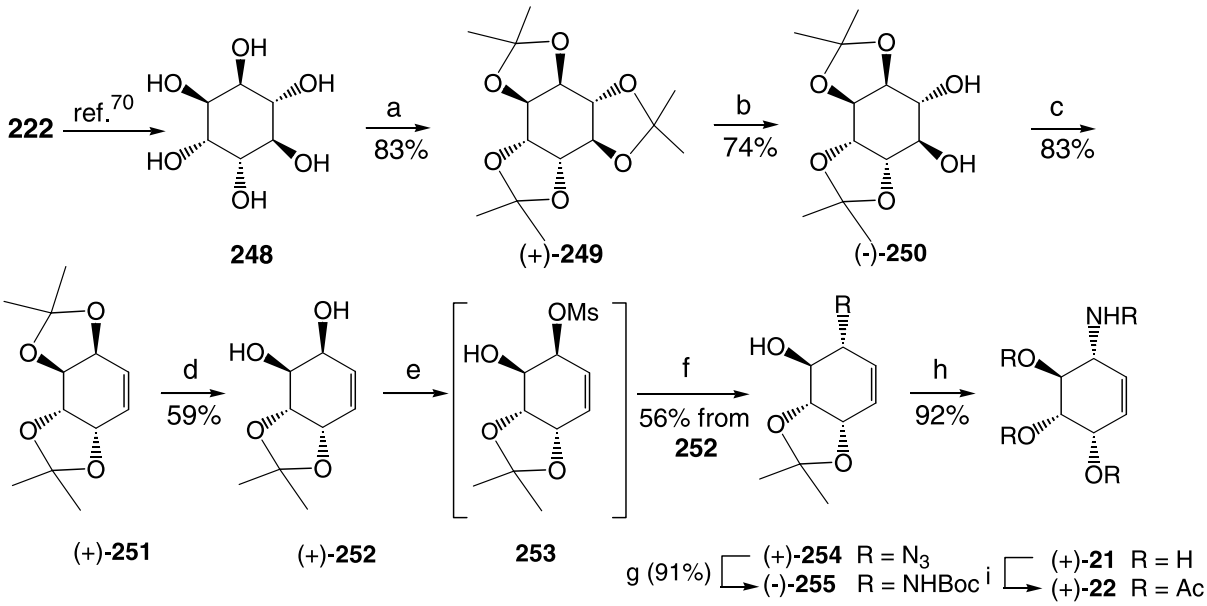
Later, (+)-conduramine F-4 [(+)-**21**] was obtained by Chida et al.,[69] who used this amine in their total synthesis of the novel cerebrosides, acanthacerebroside A and astrocerebroside A, isolated from starfish. L-*chiro*-Inositol **248** was prepared from L-quebrachitol **222** by a known procedure.[70] Treatment of **248** with 2,2-dimethoxypropane afforded the tris-acetonide (+)-**249** and its *trans*-*O*-isopropylidene group (ring strain relief) was removed selectively under acidic conditions to give the known diol (−)-**250** in 74% yield (Scheme 38).

The reaction of (−)-**250** with PPh_3, imidazole and I_2 in toluene cleanly generated the protected conduritol E derivative (+)-**251**. Treatment of (+)-**251** with an acidic resin afforded the mono-*O*-isopropylidene derivative (+)-**252**. The reaction of (+)-**252** with MsCl at −45 °C gave the allylic mesylate **253**, which was reacted with NaN_3 in situ to provide the single allylic azide (+)-**254** in 56% yield. It should be pointed out that it is well known that allylic azides exist as equilibrating mixtures of two isomers.[71] The reduction of azide (+)-**254**, followed by carbamate formation, gave (−)-**255**. Removal of the protecting groups in (−)-**255** afforded (+)-**21**, which was identified as the known conduramine F-4 tetraacetate (+)-**22** (Scheme 38).



Reagents and conditions: a) (i) $(MeO)_2CMe_2$, *p*-TsOH; (ii) O_2, tetraphenylporphyrin, hν, CCl_4, 4 h; b) $CHCl_3$, $POEt_3$, 0 °C to rt, 1 h; c) 1 N H_2SO_4, rt, 1 h; (ii) $BaCO_3$, 10 min; d) NH_3/MeOH, rt, 24 h; e) (i) 1 N H_2SO_4, rt, 3 h; (ii) $BaCO_3$, 10 min.

Scheme 37.



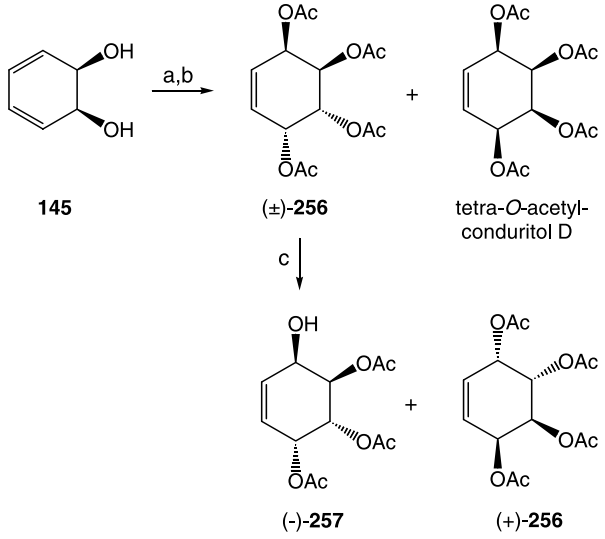
Reagents and conditions: a) 2,2-dimethoxypropane, DMF, *p*-TsOH, 70 °C, 42 h; b) CSA, THF, MeOH, 0 °C, 9 h; c) PPh_3, I_2, Imd, PhMe, D, 1 h; d) Amberlite IR-120B (H^+ form), THF, MeOH, rt, 12 h; e) MsCl, Py, CH_2Cl_2, -45 °C, 2 h; f) NaN_3, DMF, rt, 13 h; g) (i) $LiAlH_4$, THF, 0 °C to rt, 3 h; (ii) Boc_2O, rt, 4 h; h) (i) TFA, CH_2Cl_2, 0 °C to rt, 1 h; (ii) H_2O, 0 °C to rt, 3 h; i) Ac_2O/Py, rt, 4 h (90%).

Scheme 38.

In 1997, Nicolosi and co-workers[72] developed an efficient enzymatic preparation of (+)- and (−)-conduritol E. The triacetyl derivative of conduritol E (−)-**257** has been used in the synthesis of (−)-conduramine F-4 [(−)-**21**] (see Scheme 40). Compound (±)-**256** was prepared according to the Carless procedure[73] from **145**. Dihydroxylation of **145** with NMO in the presence of OsO_4 followed by acetylation led to (±)-**256** (63% yield). Minor amounts of protected conduritol D were also isolated (27% yield) (Scheme 39).

The ester (±)-**256** was subjected to alcoholysis with *n*-BuOH in *tert*-butyl methyl ether using lipase from *Mucor miehei* (Lipozyme® IM) (conv. 22%, 5 h) as catalyst. GC analysis of the reaction mixture showed the presence of unreacted ester (+)-**256** and a single product (−)-**257** (ee >95%).

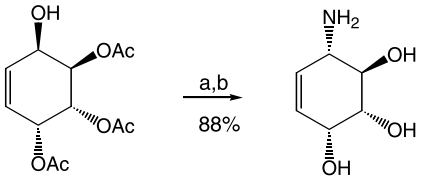
The free hydroxyl group of (−)-**257** makes this compound suitable for the synthesis of cyclitols and conduramines.



Reagents and conditions: a) cat. OsO_4, NMO, CH_2Cl_2, 4 °C, 24 h; b) Ac_2O/Py; c) Lipozyme(R) IM, *n*-BuOH, *t*-BEM, 45 °C, 300 rpm, 5 h, (conv. 22%, ee > 95%).

Scheme 39.

Amination of (−)-**257** (Mitsunobu conditions[32]) yielded the corresponding phthalimide derivative which, on treatment with 40% aq $MeNH_2$, gave (−)-conduramine F-4 [(−)-**21**] (Scheme 40).



(-)-**257** (-)-**21**

Reagents and conditons: a) phthalimide, PPh_3, DEAD, rt, 3 h; b) 40% aq. $MeNH_2$, rt, 15 min.

Scheme 40.

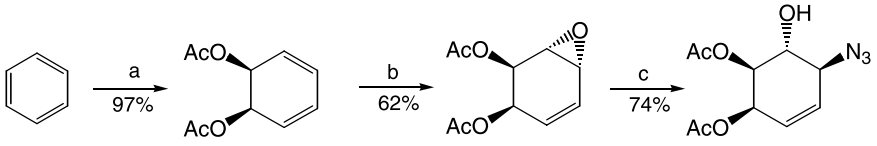
The racemic precursor of conduramine F-4 (**259**) was described by Lehmann and Moritz.[74] Diacetate **12** derived from benzene underwent selective *anti*-epoxidation, giving (±)-**258**. Subsequent ring opening of the oxirane with NaN_3 in AcOH gave the azide (±)-**252** (74%) (Scheme 41).

3. Diaminoconduritols

Diaminoconduritols are important intermediates in the synthesis of diaminoinositols and antibiotics.[75] They have also been used as ligands in antitumor platinum complexes.[76]

Glycosylation of conduramines generates unusual pseudodisaccharides and disaccharides of biological interest. Diazide (+)-**265** was obtained by the β-D-galactosylation of (±)-**263** and *o*-niphegal **264** (Scheme 42). It is a competitive inhibitor of β-D-galactosidase from *Escherichia coli*.[77] In the first two steps, the benzophenone **193** was converted into the diol (±)-**261**. Treatment of (±)-**261** with KOH, followed by ring opening of the dioxirane (±)-**262**[78] and subsequent glycosidation, gave (+)-**265**. Diazide (±)-**263** can be easily converted into the respective diaminoconduritol via Paulsen's method.[62]

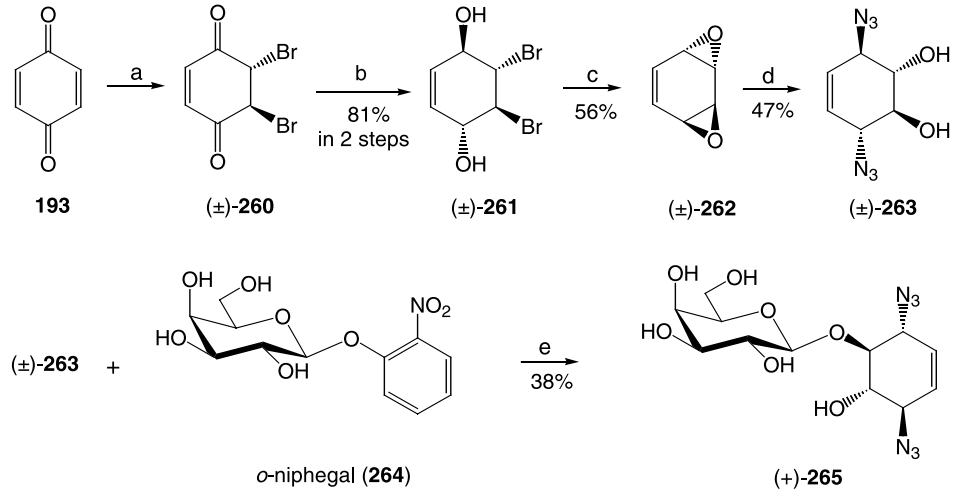
In 1979, Vogel and co-workers[79] described the synthesis of *meso*-diaminoconduritol **268**. Reaction of *syn*-benzene dioxide **266** with NaN_3 ($MeOH$, $MgCl_2$) led to regioselective (allylic activation) ring opening of the two oxirane rings to form the diazide **267**. Reduction was effected by



12 (±)-**258** (±)-**259**

Reagents and conditions: a) (i) chemical oxidation; (ii) Ac_2O/Py (1:2), rt; b) *m*-CPBA, CH_2Cl_2, Na_2CO_3, rt, 1 d; c) 70% AcOH, NaN_3, 60 °C.

Scheme 41.

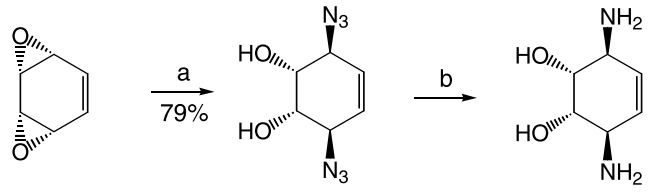


193 (±)-**260** (±)-**261** (±)-**262** (±)-**263**

o-niphegal (**264**) (+)-**265**

Reagents and conditions: a) Br_2, CCl_4, 0 °C; b) $NaBH_4$, H_2O, Et_2O, rt; c) KOH, $MgSO_4$, Et_2O, 0 °C; d) NaN_3, $ZnSO_4{\cdot}H_2O$, MeOH, Δ, 90 min; e) Na-K-phosphate buffer, β-D-galactosidase from *E. coli*, 6 h, rt, then 95 °C, 5 min.

Scheme 42.

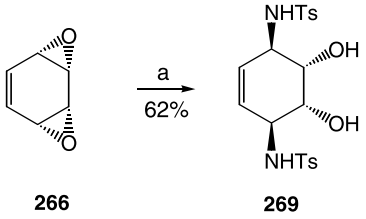


Reagents and conditions: a) NaN_3, $MgCl_2$, MeOH; b) PPh_3, MeOH/NH_3, Py.

Scheme 43.

PPh_3/MeOH/NH_3 and gave meso-diaminoconduritol **268** (Scheme 43).

Prinzbach and co-workers[80] have used a similar procedure to that outlined in Scheme 43 for the synthesis of meso-diaminoconduritol derivative **269** (Scheme 44). Nucleophilic opening of the two epoxides in **266** gave the diol **269** in 62% yield.



Reagents and conditions: a) chloramine T, $ZnSO_4$, MeOH, rt, 18 h.

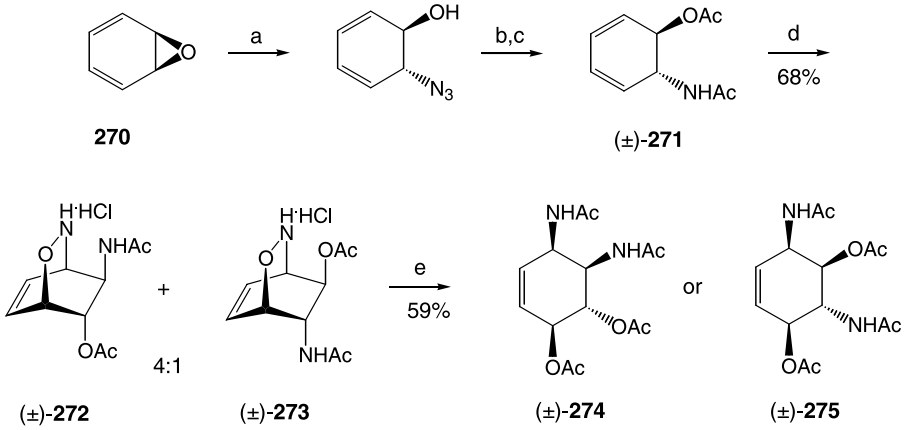
Scheme 44.

Kresze and co-workers[81] have applied the hetero-Diels–Alder reaction of racemic cyclohexadiene derivative (±)-**271**, derived from benzene epoxide **270**. The cycloaddition of (±)-**271** with 1-chloro-1-nitrosocyclohexane **232** gave a 4:1 mixture of adducts (±)-**272** and (±)-**273**. The major isomer (±)-**272** was treated with Zn in aqueous HCl to reduce the N–O bond. After work-up with acetic anhydride, the peracetylated diaminoconduramine derivative (±)-**274** was obtained (Scheme 45). The minor isomer (±)-**273** can also be converted into derivative (±)-**275** using the same method.

A very simple approach to 1,4-diaminoconduritols has been proposed by Kozlov et al.[82] As shown in Scheme 46, treatment of *anti*-benzene dioxide (±)-**262** with 2 equiv of piperidine gave the *trans*-3,6-dipiperidin-1-yl-cyclohex-4-ene-1,2-diol (±)-**276** in 34% yield. Analogous reactions with an excess of primary or secondary amines ($EtNH_2$, $PhNH_2$, $BnNH_2$, cyclohexyloamine, pyrrolidine, morpholine, Me_2NH, Et_2NH) led to the *N*-substituted diaminoconduritol derivatives (±)-**276** in 51–94% yield.

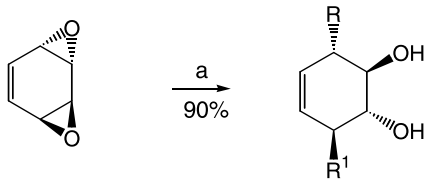
The synthesis of racemic fortamine, the aglycone of antibiotics such as fortimicins A and B, was described by Kuo et al.[83] Hetero-Diels–Alder addition of dimethyl azodicarboxylate to *trans*-1,3-cyclohexadiene-5,6-diol diacetate [(±)-**11**] gave (±)-**277** that can be converted into the 1,4-diaminoconduramine derivative (±)-**278** by reductive cleavage of the N–N bond (Scheme 47).

A few diaminoconduritol derivatives of the type **294** (see Scheme 49) were obtained as optically pure intermediates during the enantioselective synthesis of (−)-fortamine described by Ohno et al.[84] These authors used pig liver esterase (PLE) to convert racemic diester (±)-**279** into



Reagents and conditions: a) NaN_3, H_2O; b) $LiAlH_4$; c) Ac_2O/Py, DMAP, Et_2O, 0 °C (65%); d) **232**, EtOH:hexane (2:1), -22 °C; d) EtOH:hexane (2:1), -22 °C, 6 w; e) (i) Zn/HCl, H_2O, 0 °C, 7 h, (ii) Ac_2O/Py, rt, 20 h.

Scheme 45.



(±)-**262** (±)-**276**

R = R^1 = piperidino, EtNH, PhNH, BnNH, cyclohexylamino, pyrrolidino, morpholino, Me_2N, Et_2N

Reagents and conditions: a) piperidine or amines in excess.

Scheme 46.

optically active monoester **280** (>96% ee), which was then converted into all of the stereoisomers of the β-amino esters **281**–**284**, in a stereoselective manner (Scheme 48).

One of the nitrogen functions was introduced by Curtius rearrangement[84a] and the second by stereoselective ring opening of the epoxide by an azide [(−)-**289**→(−)-**290**]. The crucial step of this synthesis was the conversion of the acid (−)-**293** into the alkene (+)-**294** via a reaction first described by Barton and co-workers[85] (Scheme 49) and that implies radical intermediates. The key intermediate (−)-**289** was derived from **284**. After acidic hydrolysis of the *tert*-butyl ester with CF_3CO_2H, iodolactonization and treatment with DBU provided lactone (−)-**285**. *N*-metylation of (−)-**285** gave (−)-**286**, which was then methanolyzed into the methyl ester (+)-**287**. Esterification of alcohol (+)-**287** with methanesulfonyl chloride and Et_3N gave (−)-**288**, the epoxydation of which with MCPBA was highly face selective producing epoxide (−)-**289**. Treatment of epoxide (−)-**289** with Me_3SiN_3, followed acidic work-up and catalytic hydrogenation provided (−)-**291** that was silylated into the (+)-**292**. Saponification of (+)-**292** furnished carboxylic acid (−)-**293**.

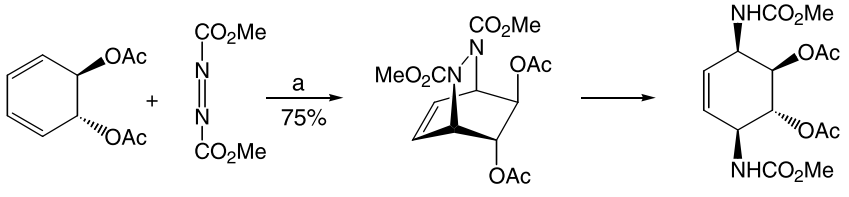
The first example of a 2,3-diaminoconduritol has been reported by Cerè and co-workers in 1998.[86] Starting with the thiepane derivative (−)-**295**, derived from D-mannitol,[87] they reacted this with NaN_3 and the azido derivative (−)-**296** obtained was oxidized to the corresponding sulfone (−)-**297**. Olefination applying the Ramberg-Bäcklung conditions gave the diazido compound (−)-**298**. Reduction of the azido functions led to the *O*-protected diaminoconduritol derivative (−)-**299** (Scheme 50).

More recently, the same authors[88] have published the synthesis of enantiomerically pure deprotected diaminoconduritol **300** (Scheme 51) using a similar methodology.

4. Biological importance of aminoconduritols and aminocyclitols

It has been shown that a conduramine F-4 derivative plays an important role in the synthesis of 1,5-lactams, which act as therapeutic agents for viral infections, particularly HIV infections.[8]

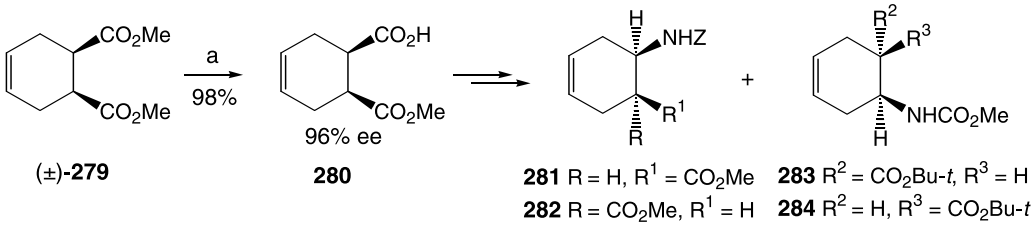
Aminocyclitols and diaminocyclitols, derived from conduramines and their analogues, comprise parts of aminoglycoside antibiotics, which are among the oldest and best known antibiotics.[2,89] It has been shown that antibiotics[90] such as kanamycin B, tobramycin B and their analogues[91]



(±)-**11** (±)-**277** (±)-**278**

Reagents and conditions: a) cyclohexane, hν, 46-50 °C, 24 h.

Scheme 47.

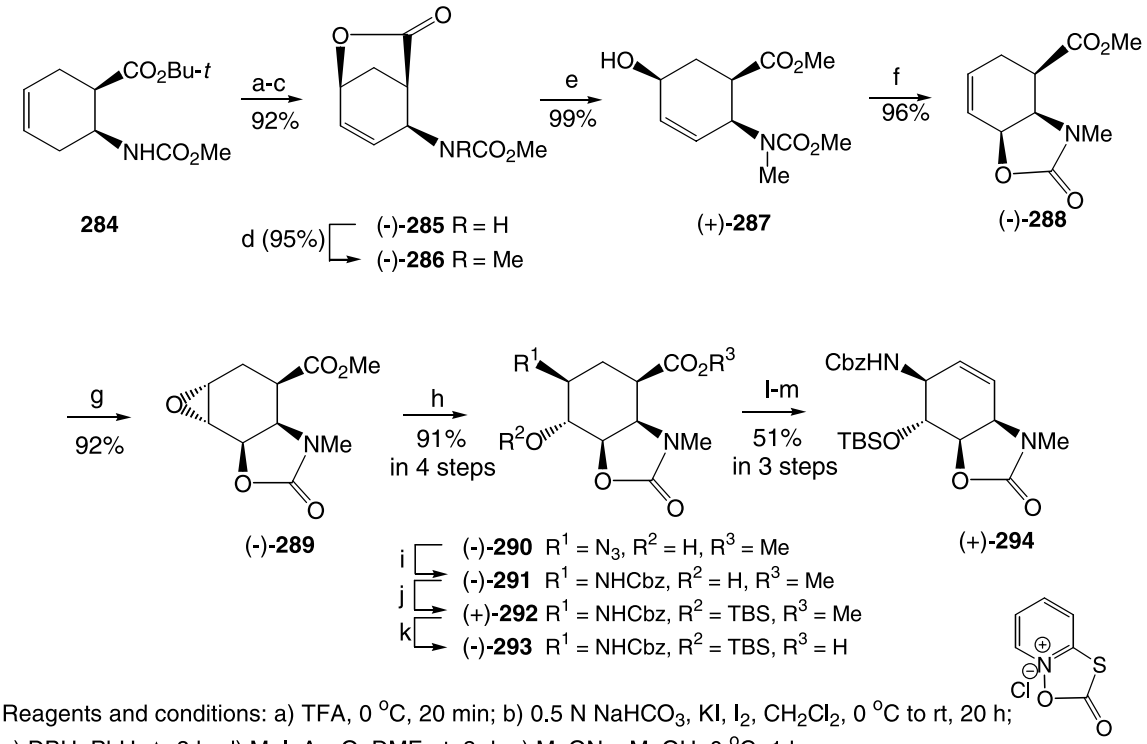


(±)-**279** **280**

281 R = H, R^1 = CO_2Me **283** R^2 = CO_2Bu-*t*, R^3 = H
282 R = CO_2Me, R^1 = H **284** R^2 = H, R^3 = CO_2Bu-*t*

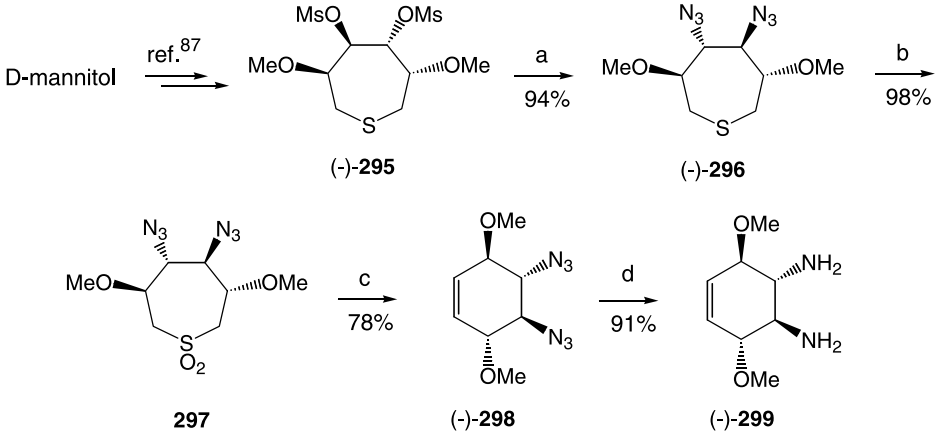
Reagents and conditions: a) pig liver esterase (PLE).

Scheme 48.



Reagents and conditions: a) TFA, 0 °C, 20 min; b) 0.5 N $NaHCO_3$, KI, I_2, CH_2Cl_2, 0 °C to rt, 20 h; c) DBU, PhH, Δ, 3 h; d) MeI, Ag_2O, DMF, rt, 2 d; e) MeONa, MeOH, 0 °C, 1 h; f) (i) MsCl, Et_3N, CH_2Cl_2, 2 h, 0 °C; (ii) Δ, 1 h; g) *m*-CPBA, CH_2Cl_2, 0 °C to rt, 2 d; h) (i) $TMSN_3$, $ZnCl_2$, $ClCH_2CH_2Cl$, Δ, 1.5 h; (ii) HCl/MeOH, rt; i) (i) H_2, Pd/C, MeOH, rt; (ii) benzyl chloroformate, dioxane, 0.5 N $NaHCO_3$, 0 °C to rt, 1 h; j) TBSCl, Imd, DMF, rt, 12 h; k) 1 N NaOH, MeOH, rt, 12 h; l) (i) Barton's reagent, DMAP, PhH, phosgene dimer, 0 °C to rt, 12 h (ii) $CBrCl_3$, Δ, 10 h; (ii) DBU, PhMe, Δ, 12 h.

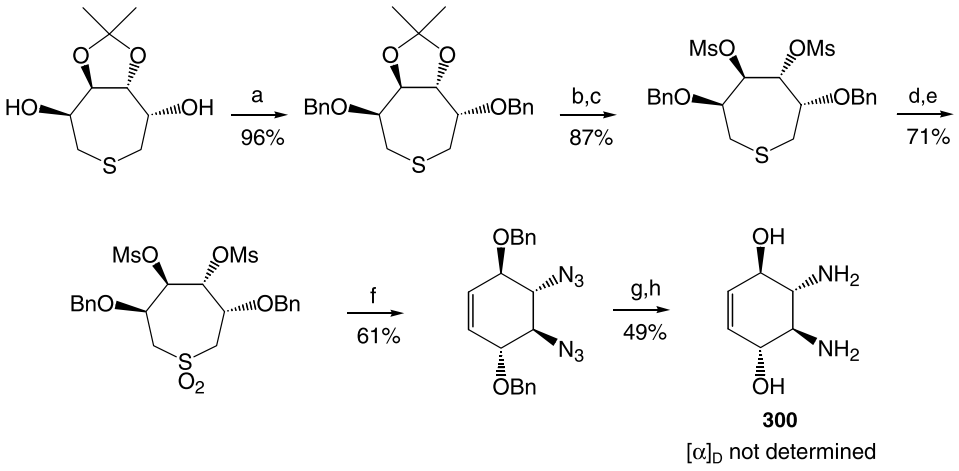
Scheme 49.



Reagents and conditions: a) NaN_3, DMSO, 120 °C, 20 h; b) *m*-CPBA, CH_2Cl_2, 3 h, rt; c) CCl_4, BuOH, H_2O, KOH, 3 h, rt; d) $LiAlH_4$, THF, 5 h, Δ.

Scheme 50.

interact with a number of RNA sequences including two important HIV regulatory domains, RRE[92] and TAR.[93] The binding between RNA and aminoglycosides reveals the interplay between the hydroxyl and their neighboring ammonium groups.[94] These discoveries demonstrate that compounds that possess arrays of hydroxyl and amino groups are potentially interesting systems, as they can target pivotal RNA sites, and are thus candidates for drug



Reagents and conditions: a) NaH, BnBr, KI, THF, rt, 19 h; b) TFA, H_2O (1:10), MeCN, 24 h, 95 °C; c) MsCl, Py, 5 h, 15 °C; d) NaN_3, DMSO, 2 h, 120 °C; e) *m*-CPBA, CH_2Cl_2, rt, 4 h; f) CCl_4, *t*-BuOH, H_2O, KOH, 7 h, rt; g) Et_3N, $HS(CH_2)_3SH$, MeOH, 48 h, rt; h) BCl_3, CH_2Cl_2, -78 °C, 2 h then 0 °C, 12 h.

Scheme 51.

discovery.[95] Aminocyclitols and their analogues can also be glycosidase inhibitors and thus be potential anticancer or antiviral agents.[96]

The fermentation-derived aminocyclitol, valienamine (**301**)[97] (Fig. 13), and several analogues[98] exhibit α-glucosidase inhibitory activity by virtue of a protonated amino group aptly positioned where a protonated interpyranosidic oxygen might bind in the enzyme active site.[99] Valienamine-based *pseudo*-oligosaccharides such as acarbose (**302**),[100] adiposin-1 (**303**),[101] and trestatin A[102] show enhanced α-glucosidase inhibition, presumably because two or more *pseudo*-sugar units bind more strongly than a single monosaccharide mimetic.[103] Even simple alkyl substitution (e.g., 2-phenethyl or β-hydroxyphenethyl) on the nitrogen of valienamine enhances inhibition of porcine maltase and sucrase.[104] In Table 1, we have summarized the inhibitory data reported for conduramine and diaminoconduritol derivatives **300** and **304–314**.

Recently, we reported that (−)-conduramine B-1 [(−)-**17**, Scheme 16] does not inhibit β-glucosidases and β-xylosidases, although this compound mimics β-glycopyranosides and β-xylopyranosides. We found, however, that *N*-benzyl derivatives of (−)-**17** are good competitive inhibitors of these enzymes. The most potent β-glucosidase inhibitor, **308** (−)-*N*-(*p*-phenylbenzyl)-conduramine B-1 [(−)-*N*-[(1,1′-biphenyl)-4-ylmethyl]-conduramine B-1], was also the most selective inhibitor in assays involving α-glucosidases from rice and yeast, amyloglucosidase from *Aspergillus niger* and *Rhizopus* mold, β-glucosidases from almonds and *Caldocellum saccharolyticum* and β-xylosidase form *Aspergillus niger*.[43a] Thus, *N*-benzyl

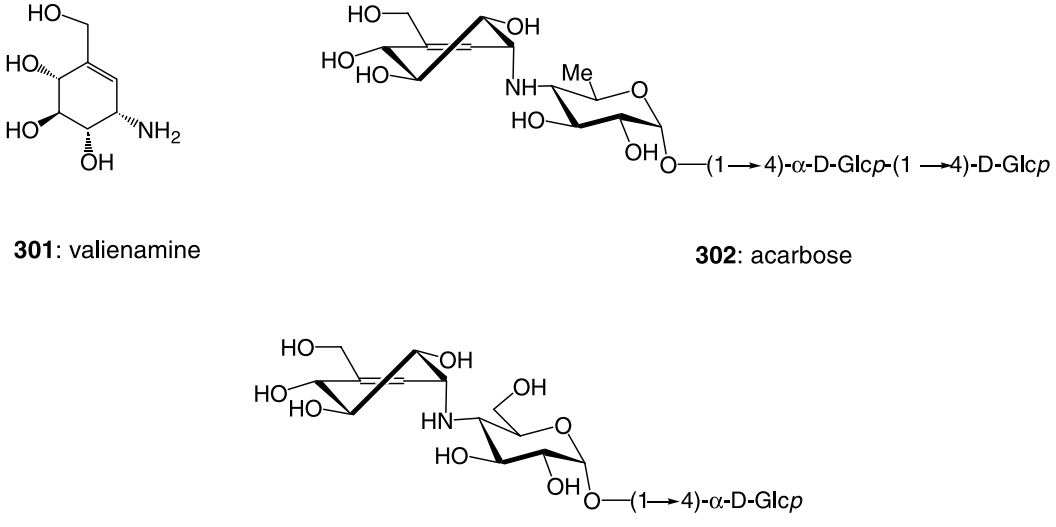
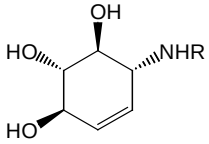
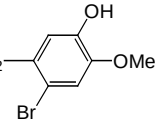
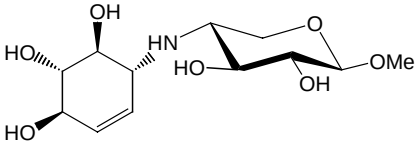
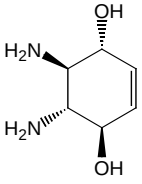
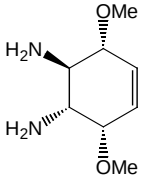
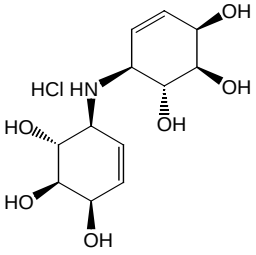
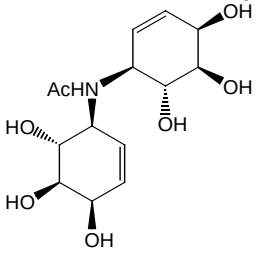


Figure 13.

Table 1. Glycosidase inhibitory activities for amino- and diaminoconduritols (IC_{50}, K_i in μM)

β-Glucosidase inhibitors	α-Mannosidase inhibitors
	
304 [43a], R = Bn, IC_{50} = 32; K_i = 10 (almonds)	**304** [43b], R = Bn, IC_{50} = 171 (jack beans), IC_{50} = 225 (almonds)
305 [43a], R = $CH_2C_6H_4OH$-*p*, IC_{50} = 72 (almonds)	**305** [43b], R = $CH_2C_6H_4OH$-*p*, IC_{50} = 100 (jack beans), IC_{50} = 183 (almonds)
306 [43a], R = $CH_2C_6H_4OMe$-*p*, IC_{50} = 52; K_i = 25 (almonds)	**306** [43b], R = $CH_2C_6H_4OMe$-*p*, IC_{50} = 91 (jack beans), IC_{50} = 86 (almonds)
307 [43a], R = $CH_2C_6H_4Cl$-*p*, IC_{50} = 35 (almonds), IC_{50} = 185 (*Caldocellum saccharolyticum*)	**307** [43b], R = $CH_2C_6H_4Cl$-*p*, IC_{50} = 91 (jack beans), IC_{50} = 77 (almonds)
308 [43a], R = $CH_2C_6H_4Ph_4$-*p*, IC_{50} = 32; K_i = 8 (almonds), IC_{50} = 35 (*Caldocellum saccharolyticum*)	**308** [43b], R = $CH_2C_6H_4Ph$-*p*, IC_{50} = 29; K_i = 4.8 (jack beans), IC_{50} = 32; K_i = 16 (almonds)
309 [43a], R = $CH_2C_6H_4OPh$-*p*, IC_{50} = 43; K_i = 13 (almonds), IC_{50} = 52 (*Caldocellum saccharolyticum*)	**309** [43b], R = $CH_2C_6H_4OPh$-*p*, IC_{50} = 40; K_i = 14 (jack beans), IC_{50} = 63 (almonds)
	310 [43b], R = A **310** [43b], R = 
	IC_{50} = 154 (jack beans)
β-Xylosidase inhibitors	
	
311 [39], K_i = 40 (*Thermoanaerobacterium saccharolyticum*)	
α-Glucoside inhibitors	
	
300 [88], K_i = 190 (baker's yeast)	**312** [88], K_i = 700 (baker's yeast)
	
313 [3], IC_{50} = 1400	**314** [3], IC_{50} = 1350
β-Galactosidase inhibitors	
313 [3], IC_{50} = 620	**314** [3], IC_{50} = 100

derivatives of (−)-conduramine B-1 should be tested for their ability to act as chemical chaperones and for their therapeutic potential against Gaucher's disease.[105] With a structure having one hydroxymethyl group less than that in β-valienamine derivatives,[106] which have been shown to act as chemical chaperones[107] to accelerate transport and maturation of F2/3I mutant β-glucosidase,[106] the *N*-benzyl derivatives of (−)-conduramine B-1 are expected to be more hydrophobic than the corresponding valienamine derivatives and thus to have a better chance to become orally active drugs in the treatment of Gaucher's disease.

Recently, Ogawa and co-workers[108] reported that β-valienamine, as (−)-conduramine B [(−)-**17**] does not inhibit β-glucosidase from almonds, but is a weak inhibitor (IC_{50} = 190 μM) of α-mannosidase from jack beans. Similarly, (−)-conduramine B-1 has been found to inhibit α-mannosidases from jack beans and from almonds, whereas it does not inhibit any of the other glycosidases (α-L-fucosidase, α-galactosidases, β-galactosidases, α-glucosidases, amyloglucosidases, β-glucosidases, β-mannosidase, β-xylosidase, α-*N*-acetylgalacto-saminidases, or β-*N*-acetyl glucosaminidases). As for the inhibition of β-glucosidases from almonds and from *Saccharomyces*

cerevisiae, **308** presented the highest inhibitory activity toward α-mannosidases. Expectedly, (+)-conduramine B-1 and its *N*-substituted derivatives did not inhibit these enzymes at 1 mM concentration.[43b]

5. Conclusions

In recent years, a number of highly efficient and enantioselective syntheses of conduramines (aminoconduritols) and diaminoconduritols have been developed. The methods rely on pure chemical processes or on combinations of the latter with enzymatic or microbiological pathways. Because of their alkene moieties, conduramines and diaminoconduritols can be seen as synthetic intermediates for the aminocyclitols and more complicated polyfunctional compounds of biological interest. The fact that these systems display arrays of amines and polyols will make them partners of sublibraries for the combinatorial preparation of biopolymer ligands by analogy with the known information for aminoglycoside antibiotics that recognize specific structural elements of RNA. Conduramines have interesting inhibitory activities toward various glycosidases. In the case of (−)-conduramine B-1, *N*-benzylation generates good inhibitors of β-D-glucosidases and of α-D-mannosidases with K_i values in the low micromolecular range.

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Biographical sketch

R. Łysek was born in Miechów (Poland). He received his Ph.D. degree (2000) from the Institute of Organic Chemistry of the PAS (Warsaw) under the guidance of Prof. Marek Chmielewski. His thesis work focused on the [2+2]cycloaddition of chlorosulfonyl isocyanate to chiral *C*-silylated vinyl ethers and alkoxyallenes. In 1997–1999 he visited the University of Tübingen (Germany) three times working on the field of the synthesis of heterocyclic compounds (Prof. W. Voelter). In 2001 he received a fellowship of the Foundation for Polish Science (FNP) and the joint SIGMA-ALDRICH-Poland. Co./Polish Chemical Society prize for the best Ph.D. thesis in organic chemistry in 2000. In 2002 he spent a few months in Institute of Biochemistry and Biophysics of the PAS (Warsaw) working on isolation and transformation of natural products (Prof. T. Chojnacki). From the January 2003 till now Dr. Łysek is working as a post-doctoral fellow with Prof. P. Vogel (EPFL, Lausanne). He is co-author of 28 publications. His research intrests include synthetic methodology, heterocyclic chemistry, asymmetric synthesis and medicinal chemistry in drug discovery.

Pierre Vogel. After his Ph.D. studies at the University of Lausanne, Switzerland (1969, Prof. Horst Prinzbach), he spent 2 years at Yale University with Prof. Martin Saunders. He then joined the research laboratory of Syntex in Mexico City and worked with Prof. Pierre Crabbé. He returned to the University of Lausanne where he was promoted to full professor in 1977. He has been associate professor at the Ecole Normale Supérieure in Paris, at the University of Paris VI, and at the University of Montpellier, France. He also taught at the Universities of Rouen and Caen in Normandy and at the Ecole Polytechnique in Paliseau near Paris. He obtained the Novartis lectureship for 2003 and was elected Boehringer-Ingelheim Distinguished Lecture for 2005. Since 2001, Prof. P. Vogel chairs the Laboratory of Glycochemistry and Asymmetric Synthesis of the Ecole Polytechnique Fédérale de Lausanne (EPFL), Switzerland. He has published three books and has co-authored more than 400 publications in the fields of physical organic chemistry, organic and organometallic synthesis, catalysis, glycochemistry and bioorganic chemistry.

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The cyclopropyl effect on the regioselectivity of coupling reactions involving the lithiation of 1-cyclopropyl-2-arylacetylenes

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Abstract—The cyclopropyl effect controlled the regioselectivity of the cross coupling reactions of propargylic/allenylic metallic species with electrophiles affording alkynic cyclopropanes. It was proposed that the strain in cyclopropyl ring, which makes the formation of vinylidenecyclopropanes unfavorable, determined the regioselectivity. Control experiment of *i*-propyl, cyclobutyl, and cyclohexyl-phenylacetylenes were conducted to support the above speculation.

1. Introduction

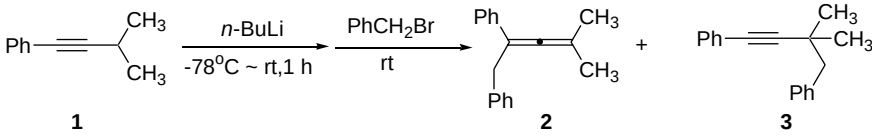
Selectivity control in a reaction is a very important issue in organic synthesis and remains to be a challenge to chemists.[1] Recently, tremendous attention has been paid to the selective synthesis of alkynes or allenes from propargylic/allenylic metallic species due to the presence of equilibrium mixture of propargylic and allenylic metallic derivatives.[2] Recently, we observed that the regioselectivity of Pd-catalyzed cross coupling reactions involving propargylic/allenylic species can be tuned by the steric, electronic, and ligand effects.[3] Herein, we report a cyclopropyl effect in the regioselectivity control in the lithiation of 1-aryl-1-alkynes and the subsequent cross coupling with electrophiles.

2. Results and discussion

First, it was observed that lithiation reaction of 1-phenyl-3-methyl-1-butyne **1**, a secondary alkyl substituted 1-aryl-1-alkyne, and the subsequent reaction with benzyl bromide afforded a mixture of 1,2-diphenyl-4-methyl-2,3-pentadiene **2** and 1,4-diphenyl-3,3-dimethylbut-1-yne **3** with a ratio of 70:30, a regioselectivity different from that of 1°-alkyl-substitute d 1-aryl-1-alkynes[3a,3b] (Scheme 1).

Furthermore, it was interesting to observe that the same reaction of 1-phenyl-2-cyclopropylacetylene **4a** afforded alkyne **5a** as the only product (entry 1, Table 1). The lithiation reaction of **4a** and the subsequent reaction with different electrophiles afforded alkynic products **5** highly selectively (Table 1), which is in accordance with the reported data.[4]

When a four-membered ring or six-membered ring was applied instead of the cyclopropyl ring, mixtures of alkynes and allenes were formed again (compare Table 1 with Scheme 2), indicating the strain in the three-membered ring may be the key factor determining the regioselectivity. With this observation, it was reasoned that the corresponding lithiation, transmetallation and subsequent Pd(0)-catalyzed cross coupling reaction with organic halides may also lead



1 2 3

Scheme 1. >99% (**2**:**3**=70:30). The yield and ratio are determined by 300 MHz ^{1}H NMR spectra analysis with CH_2Br_2 as the internal standard.

Keywords: Lithiation; Coupling; Palladium; Regioselectivity; Alkynes; Organic halides.
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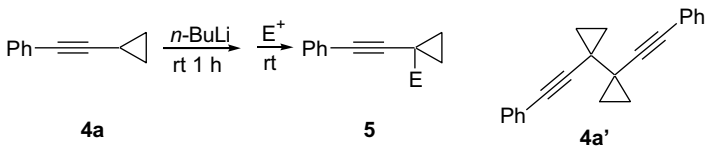
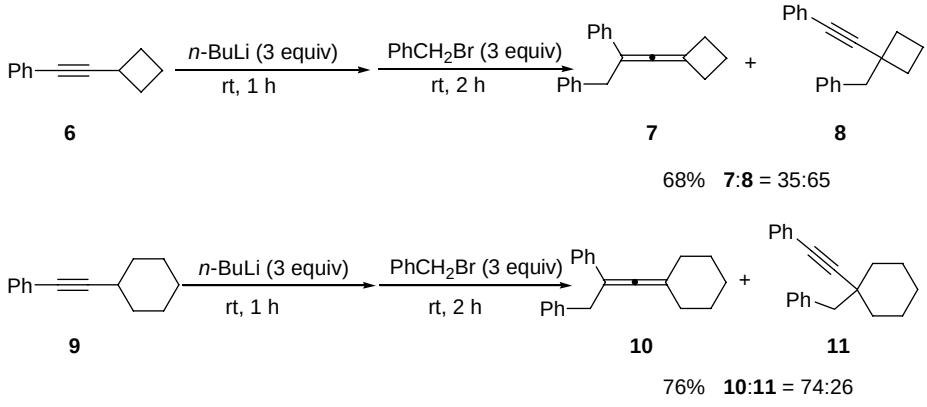
Table 1. The lithiation of 1-cyclopropyl-2-phenylacetylene **4a** and the subsequent reactions with electrophiles



4a **5** **4a'**

Entry	E^+	Yield of **5** (%)
1	$PhCH_2Br$	78 (**5a**)
2	$CH_2{=}CHCH_2Br$	77 (**5b**)[a]
3	n-C_4H_9Br	43 (**5c**)
4	PhCH=NTs	50 (**5d**)[b]
5	CH_3I	76 (**5e**)

[a] n-BuLi (2 equiv) and allyl bromide (4 equiv) were used. Compound **4a'** (2%) was also formed.
[b] The reaction was carried out at 0 °C.



Scheme 2.

to the highly selective formation of alkynes, instead of the usual products, allenes.

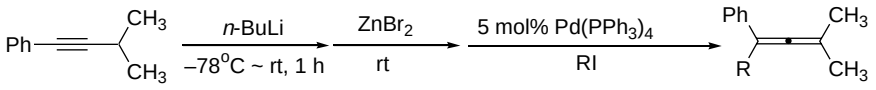
In fact, the lithiation of 1-phenyl-3-methyl-1-butyne **1**, transmetallation and the Pd(0)-catalyzed cross coupling[5] with aryl halides afforded allenes **12** as the only product as expected (Table 2).

However, in contrast to the results shown in Table 2, when 1-cyclopropyl-2-arylacetylene **4** was used in the same sequential reaction, substituted cyclopropyl alkynes **13** were afforded as the only products. The results listed in Table 3 indicated that: (1) the reactions gave alkynes exclusively; (2) the yields are very sensitive to the substituents of aryl halides. The more sterically hindered aryl halides afforded the products in lower yields (entries 2 and 3, Table 3); (3) the aryl halides with an electron-withdrawing substituent showed better results than those with an electron-donating group (compare entries 4 and 5 with entry 6 in Table 3).

When 1,4-diiodobenzene was used, the reaction produced 57% yield of the mono-cross coupling product **13l** and 18% yield of the double cross coupling product **13l'** (Scheme 3).

In order to clarify the cyclopropyl effect, the same sequential reaction of 1-cyclobutyl-2-phenylacetylene **6** and 1-cyclohexyl-2-phenylacetylene **9** were studied (Scheme 4). Here, again allenes were formed exclusively (compare Scheme 4 with Table 2).

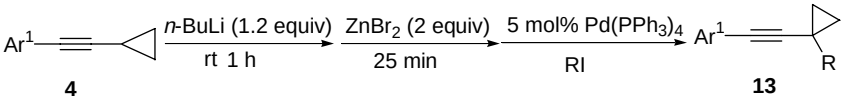
Table 2. The lithiation of 1-phenyl-3-methyl-1-butyne, transmetallation, and Negishi-type cross coupling with aryl halides



1 **12**

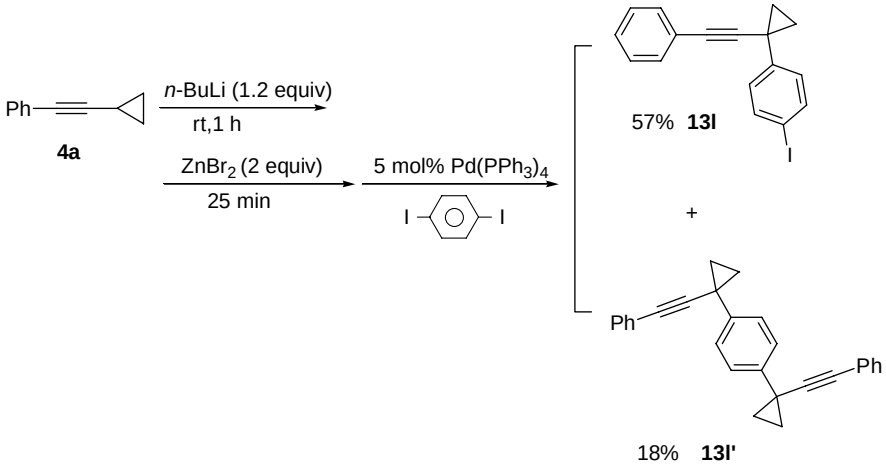
Entry	R	Yield of **12** (%)
1	Ph	47 (**12a**)
2	α-$C_{10}H_8$	25 (**12b**)
3	p-$MeOC_6H_4$	71 (**12c**)
4	p-$MeO_2CC_6H_4$	91 (**12d**)
5	o-$CH_3C_6H_4$	40 (**12e**)
6	(*E*)-CH=$CHCO_2CH_3$	37 (**12f**)

Table 3. The lithiation of 1-cyclopropyl-2-arylacetylenes, transmetallation, and Negishi-type cross coupling with aryl halides

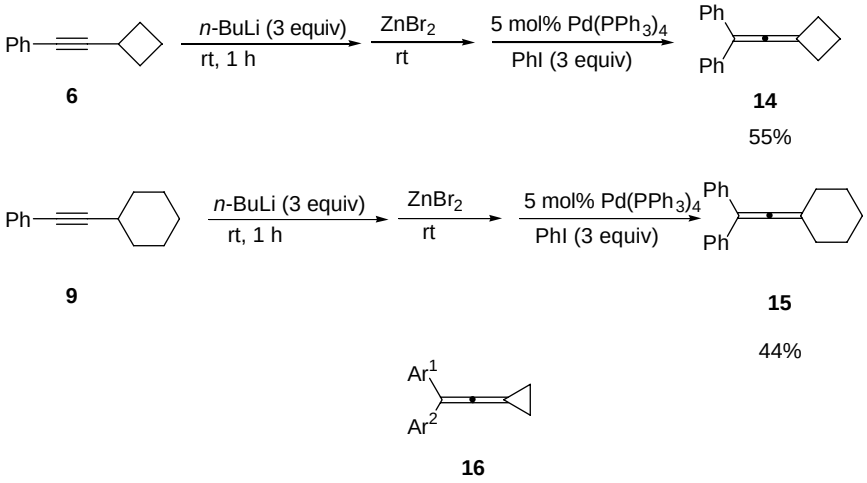


4 **13**

Entry	Ar^1	R	Yield of **13** (%)
1	Ph (**4a**)	Ph	72 (**13a**)
2	Ph (**4a**)	α-$C_{10}H_8$	27 (**13b**)
3	Ph (**4a**)	*o*-MeC_6H_4	25 (**13c**)
4	Ph (**4a**)	*p*-$MeO_2CC_6H_4$	98 (**13d**)
5	Ph (**4a**)	*p*-NCC_6H_4	88 (**13e**)
6	Ph (**4a**)	*p*-$MeOC_6H_4$	33 (**13f**)
7	Ph (**4a**)	(*E*)-CH=$CHCO_2Me$	34 (**13g**)
8	Ph (**4a**)	*p*-BrC_6H_4	64 (**13h**)
9	Ph (**4a**)	*p*-ClC_6H_4	55 (**13i**)
10	*p*-PhC_6H_4 (**4b**)	*p*-NCC_6H_4	70 (**13j**)
11	*p*-PhC_6H_4 (**4b**)	*p*-$MeO_2CC_6H_4$	51 (**13k**)



Scheme 3.



Scheme 4.

Based on these facts, it was quite clear that it was the enhanced ring strain in vinylidenecyclopropanes **16** caused by the direct connection of the carbon–carbon double bond with the cyclopropyl ring that led to the highly selective formation of alkynic cyclopopanes **5** and **13**.

In conclusion, the cyclopropyl effect tuned the selectivity in the reactions described above: the coupling reaction of cyclopropyl substituted 1-aryl-1-alkynes afforded alkynic cyclopropanes while that of other 1-aryl-1-(2°-alkyl)-substituted alkynes yielded a mixture of alkynes and allenes

or allenes exclusively. Further studies in this area are currently underway in our laboratory.

3. Experimental

3.1. Preparation of the starting materials 1, 4a, 4b, 6, and 9

3.1.1. Synthesis of 1-phenyl-3-methyl-1-butyne 1.[6] To 100 mL of anhydrous liquid ammonia was added lithium belt (0.47 g, 60 mmol) in portion and the mixture was stirred under −40 °C for 1 h. After evaporation of NH_3, phenylacetylene (5.5 mL, 50 mmol) and 20 mL of 1,4-dioxane were added. Then the mixture was kept under reflux for 20 min. After that, it was transferred into a glassware, which was put in an autoclave and *i*-propyl bromide (9.4 mL, 100 mmol) was added subsequently. The mixture was heated at 150 °C in the closed autoclave for 16 h. After the reaction was complete, the mixture was cooled down, poured into cold water and extracted with ether. Drying over anhydrous $MgSO_4$, rotary evaporation, and distillation afforded **1** as a liquid (1.418 g, 20%, bp 67 °C/5 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.38–7.22 (m, 2H), 7.20–7.15 (m, 3H), 2.69 (heptet, J=6.7 Hz, 1H), 1.18 (d, J=6.7 Hz, 6H).

3.1.2. Synthesis of 1-cyclopropyl-2-phenylacetylene 4a.[7] $Pd(PPh_3)_4$ (500 mg, 0.5 mol%), CuI (270 mg, 1 mol%), and PhI (8.8 mL, 78.5 mmol) were dissolved in 250 mL of $(i\text{-Pr})_2NH$. A solution of cyclopropylacetylene (8 mL, 94 mmol) in 100 mL of $(i\text{-Pr})_2NH$ was added dropwise into the mixture under N_2 and stirred at rt. When the reaction was complete as monitored by TLC (eluent: petroleum ether (60–90 °C)), a brown precipitate appeared. Filtration, rotary evaporation, and flash chromatography on silica gel (petroleum ether) afforded **4a** (11.544 g, ~99%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.40–7.35 (m, 2H), 7.28–7.23 (m, 3H), 1.48–1.42 (m, 1H), 0.91–0.78 (m, 4H).

3.1.3. Synthesis of 1-cyclopropyl-2-(*p*-phenylphenyl)-acetylene 4b. The reaction of *p*-phenylphenyl bromide (1.165 g, 5 mmol), cyclopropylacetylene (0.85 mL, 10 mmol), and $Pd(PPh_3)_4$ (58 mg, 1 mol%) afforded **4b** as a solid (700 mg, 64%) according to the procedure for the synthesis of **4a**. Compound **4b**: mp 67–68 °C (petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.60–7.30 (m, 9H), 1.57–1.40 (m, 1H), 0.93–0.78 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ=140.4, 140.1, 132.0, 128.8, 127.4, 126.9, 126.8, 122.8, 94.1, 75.6, 8.6, 0.2; MS (70 eV): *m*/*z* (%): 218 (M^+, 100.00); IR (neat): 2231, 1486 cm^{-1}. Anal. Calcd for $C_{17}H_{14}$: C, 93.54; H, 6.46; found C, 93.54; H, 6.54.

3.1.4. Synthesis of cyclobutylacetylene.[8] *n*-BuLi (21 mL, 0.034 mol, 1.6 M in hexanes) was added to a solution of 6-chloro-1-hexyne (1.855 g, 0.016 mol) in THF dropwise at −78 °C. After being stirred for 20 min at −78 °C, it was allowed to warm up naturally to rt and stirred overnight. When the reaction was complete, it was quenched with saturated aqueous solution of NH_4Cl and extracted with ether. Drying over anhydrous $MgSO_4$ and removing ether by distillation afforded a solution of the product in THF, which was submitted to next step directly.

3.1.5. Synthesis of 1-cyclobutyl-2-phenylacetylene 6.[7] The solution of cyclobutylacetylene in THF from above was added dropwise to a mixture of phenyl iodide (0.9 mL, 0.008 mol), CuI (15 mg, 1 mol%), $Pd(PPh_3)_4$ (46 mg, 0.5 mol%) and 3 mL $(i\text{-Pr})_2NH$ under N_2 and stirred at rt. When the reaction was complete as monitored by TLC (eluent: petroleum ether (60–90 °C)), a brown precipitate appeared. Filtration, rotary evaporation, and flash chromatography on silica gel (petroleum ether) afforded **6** as a liquid (0.373 g, 30%). ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.42–7.37 (m, 2H), 7.30–7.25 (m, 3H), 3.30–3.20 (m, 1H), 2.40–2.19 (m, 4H), 2.05–1.91 (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ=131.5, 128.1, 127.5, 123.9, 93.9, 81.1, 30.0, 25.5, 19.2.

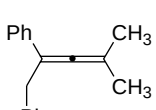
3.1.6. Synthesis of 1-cyclohexyl-2-phenylacetylene 9.[9] A suspension of zinc dust (2.24 g, 0.040 mol) in 20 mL of THF were added one drop each of 1,2-dibromoethane and TMSCl. After being stirred at rt for 20 min, cyclohexyl iodide (4.20 g, 20 mmol) was added and stirred overnight at 40–50 °C. After the excessive zinc dust was filtered under N_2, $CuCN\cdot 2LiCl$ (175 mg, 5 mol%) and phenylethynyl iodide (2.0 mL, 15 mmol) were added and stirred at rt. When the reaction was complete as monitored by TLC (eluent: petroleum ether (60–90 °C)), saturated aqueous solution of $FeSO_4$ was added and the mixture was extracted with ether. Drying over anhydrous $MgSO_4$, rotary evaporation and flash chromatography on silica gel (petroleum ether) afforded **9** (0.268 g, 9%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.42–7.37 (m, 2H), 7.30–7.24 (m, 3H), 2.62–2.54 (m, 1H), 1.91–1.85 (m, 2H), 1.81–1.72 (m, 2H), 1.60–1.48 (m, 3H), 1.42–1.31 (m, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ=131.5, 128.1, 127.4, 124.1, 94.4, 80.4, 32.7, 29.6, 25.9, 24.9.

3.2. Typical procedure for the coupling reactions with or without Pd(0) catalyst

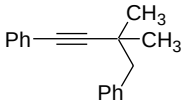
3.2.1. Synthesis of 1-(phenylethynyl)-1-benzylcyclopropane 5a. To a solution of 1-cyclopropyl-2-phenylacetylene (56 mg, 0.39 mmol) in THF (3 mL) in a dry Schlenk tube was added *n*-BuLi (0.30 mL, 1.6 M in hexanes, 0.47 mmol) at −78 °C under N_2. After being warmed up naturally and stirred 1 h at rt, benzyl bromide (0.056 mL, 0.47 mmol) was added. When the reaction was complete as monitored by TLC (eluent: petroleum ether (60–90 °C)), it was quenched with saturated aqueous solution of NH_4Cl and extracted with ether. Drying over anhydrous $MgSO_4$, rotary evaporation, and flash chromatography on silica gel (petroleum ether) afforded **5a** (71 mg, 78%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.37–7.18 (m, 10H), 2.77 (s, 2H), 1.04 (dd, J_1=6.6 Hz, J_2=4.2 Hz, 2H), 0.82 (dd, J_1=6.6 Hz, J_2=4.2 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ=139.3, 131.5, 129.2, 128.1, 127.4, 126.3, 123.8, 94.9, 77.6, 43.4, 15.3, 13.4; MS (70 eV): *m*/*z* (%): 232 (M^+, 39.70), 115 (100.00); IR (neat) 2226, 1597, 1494 cm^{-1}; HRMS calcd for $C_{18}H_{16}Na$ [M^++Na]: 255.1150, found 255.1171.

The following compounds were prepared according to the procedure described in this section.

3.2.1.1. Synthesis of 1,2-diphenyl-4-methyl-2,3-pentadiene (2) and 1,4-diphenyl-3,3-dimethyl-1-butyne (3).



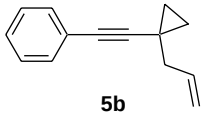
2



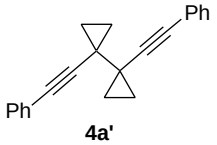
3

The reaction of 1-phenyl-3-methyl-1-butyne **1** (124 mg, 0.86 mmol), *n*-BuLi (0.54 mL, 1.6 M in hexanes, 1.0 mmol), and benzyl bromide (0.13 mL, 1.1 mmol) afforded a mixture of compounds **2** and **3**. The combined yield of **2** and **3** is >99% (**2**:**3**=70:30), which was determined by 300 MHz ^{1}H NMR spectra with CH_2Br_2 as the internal standard. Pure samples for the analysis were obtained by repeated chromatography on silica gel. Compound **2**: liquid, ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.48–7.44 (m, 2H), 7.36–7.31 (m, 6H), 7.27–7.21 (m, 2H), 3.83 (s, 2H), 1.78 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 203.4, 140.1, 137.7, 128.7, 128.2, 128.1, 126.1, 125.9, 102.7, 98.5, 37.3, 20.1; MS (70 eV): *m*/*z* (%): 234 (M^+, 52.99), 143 (100.00); IR (neat): 1952, 1598, 1493 cm^{-1}; HRMS calcd for $C_{18}H_{18}$ [M^+]: 234.1409, found: 234.1410. Compound **3**: liquid, ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.40–7.20 (m, 10H), 2.77 (s, 2H), 1.27 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ=138.3, 131.4, 130.6, 128.1, 127.6, 127.5, 126.3, 124.0, 96.9, 81.6, 49.1, 32.8, 29.1; MS (70 eV): *m*/*z* (%): 234 (M^+, 17.72), 143 (100.00); IR (neat): 2230, 1598, 1491 cm^{-1}; HRMS calcd for $C_{18}H_{18}$ [M^+]: 234.14089, found: 234.1406.

3.2.1.2. Synthesis of 1-(2′-phenylethynyl)-1-allylcyclopropane (5b) and 1,1′-diphenylethynylbicyclopropyl (4a′).



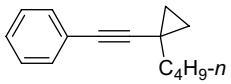
5b



4a'

The reaction of 1-cyclopropyl-2-phenylacetylene **4a** (56 mg, 0.39 mmol), *n*-BuLi (0.49 mL, 0.79 mmol, 1.6 M in hexanes), and allyl bromide (0.14 mL, 1.58 mmol) afforded **5b** (55 mg, 77%) and **4a′** (2 mg, 2%). Compound **5b**: liquid, ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.42–7.37 (m, 2H), 7.32–7.25 (m, 3H), 6.09–5.95 (m, 1H), 5.22–5.11 (m, 2H), 2.24 (d, J=6.6 Hz, 2H), 1.04 (dd, J_1=6.9 Hz, J_2= 4.5 Hz, 2H), 0.76 (dd, J_1=6.9 Hz, J_2=4.5 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ=135.5, 131.6, 128.1, 127.4, 123.9, 116.5, 94.7, 77.02, 42.0, 15.0, 12.1; MS (70 eV): *m*/*z* (%): 182 (M^+, 30.29), 115 (100.00); IR (neat) 2226, 1642, 1598, 1494 cm^{-1}; HRMS calcd for $C_{14}H_{14}Na$ [M^++Na]: 205.0993, found: 205.1001. Compound **4a′**: solid, mp 82–83 °C (petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.40–7.33 (m, 4H), 7.28–7.23 (m, 6H), 1.19 (dd, J_1= 7.5 Hz, J_2=4.8 Hz, 4H), 1.06 (dd, J_1=7.5 Hz, J_2=4.8 Hz, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ=131.6, 128.1, 127.6, 123.6, 92.4, 77.8, 15.8, 14.6; MS (70 eV): *m*/*z* (%): 282 (M^+, 100.00); IR (neat) 2223, 1597, 1488 cm^{-1}; Anal. Calcd for $C_{22}H_{18}$: C, 93.58; H, 6.42; found: C, 93.61; H, 6.47.

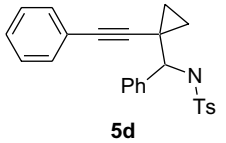
3.2.1.3. Synthesis of 1-(2′-phenylethynyl)-1-*n*-butylcyclopropane (5c).



5c

The reaction of 1-cyclopropyl-2-phenylacetylene **4a** (55 mg, 0.39 mmol), *n*-BuLi (0.29 mL, 0.46 mmol, 1.6 M in hexanes), and *n*-butyl bromide (0.059 mL, 0.55 mmol) afforded **5c** (33 mg, 43%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.40–7.35 (m, 2H), 7.28–7.20 (m, 3H), 1.63–1.52 (m, 2H), 1.44–1.30 (m, 4H), 0.97 (dd, J_1=6.6 Hz, J_2= 3.9 Hz, 2H), 0.92 (t, J=7.2 Hz, 3H), 0.65 (dd, J_1=6.6 Hz, J_2=3.9 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ=131.6, 128.1, 127.3, 124.0, 95.3, 76.6, 38.0, 30.1, 22.6, 15.6, 14.1, 12.4; MS (70 eV): *m*/*z* (%): 198 (M^+, 18.38), 141 (100.00); IR (neat) 2220, 1598, 1491 cm^{-1}; HRMS calcd for $C_{15}H_{19}$ [M^++H]: 199.1487, found: 199.1507.

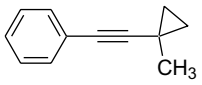
3.2.1.4. Synthesis of *N*-[phenyl-(1-(2′-phenylethynyl)-cyclopropyl)methyl]*p*-toluenesulfonamide (5d).



5d

The reaction of 1-cyclopropyl-2-phenylacetylene **4a** (58 mg, 0.41 mmol), *n*-BuLi (0.31 mL, 0.49 mmol, 1.6 M in hexanes), and *N*-benzylidene-*p*-toluenesulfonamide (127 mg, 0.49 mmol) afforded **5d** (82 mg, 50%) as a solid, mp 100–102 °C (petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.62 (d, J=8.4 Hz, 2H), 7.31–7.20 (m, 10H), 7.11 (d, J=8.4 Hz, 2H), 5.63 (d, J= 7.8 Hz, 1H), 3.87 (d, J=7.8 Hz, 1H), 2.34 (s, 3H), 1.04–0.86 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ=143.0, 138.8, 137.7, 131.6, 129.2, 128.1, 128.0, 127.96, 127.6, 127.2, 127.0, 122.9, 90.4, 80.2, 63.3, 21.4, 19.1, 16.3, 14.7; MS (70 eV): *m*/*z* (%): 401 (M^+, 0.73), 260 (100.00); IR (neat) 3253, 2229, 1600 cm^{-1}. Anal. Calcd for $C_{25}H_{23}NO_2S$: C, 74.78; H, 5.77; N, 3.49; found: C, 75.08; H, 5.93; N, 3.42.

3.2.1.5. Synthesis of 1-(2′-phenylethynyl)-1-methylcyclopropane (5e).[10]

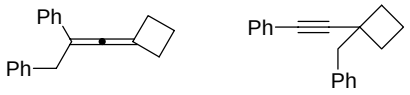


5e

The reaction of 1-cyclopropyl-2-phenylacetylene **4a** (59 mg, 0.42 mmol), *n*-BuLi (0.31 mL, 0.50 mmol, 1.6 M in hexanes), and CH_3I (0.052 mL, 0.83 mmol) afforded **5e** (50 mg, 76%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.40–7.33 (m, 2H), 7.26–7.21 (m, 3H), 1.35 (s, 3H), 0.99

(dd, $J_1=6.6$ Hz, $J_2=4.2$ Hz, 2H), 0.66 (dd, $J_1=6.6$ Hz, $J_2=4.2$ Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) $\delta=131.6$, 128.1, 127.4, 123.9, 96.1, 75.7, 24.2, 16.6, 7.2; IR (neat) 2219, 1597, 1495 cm^{-1}.

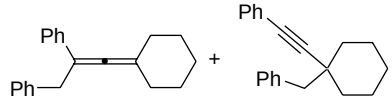
3.2.1.6. Synthesis of 2,3-diphenylpropenylidenecyclobutane (7) and 1-(phenylethynyl)-1-benzylcyclobutane (8).



7 **8**

The reaction of 1-cyclobutyl-2-phenylacetylene **6** (32 mg, 0.20 mmol), *n*-BuLi (0.38 mL, 0.60 mmol, 1.6 M in hexanes), and benzyl bromide (72 μL, 0.60 mmol) afforded **7** (12 mg, 24%) and **8** (22 mg, 44%). Compound **7**: liquid, ^{1}H NMR (300 MHz, $CDCl_3$) $\delta=7.42$–7.39 (m, 2H), 7.32–7.12 (m, 8H), 3.78 (s, 2H), 3.02–2.90 (m, 2H), 2.82–2.70 (m, 2H), 2.02–1.80 (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) $\delta=196.9$, 139.9, 137.5, 128.8, 128.2, 128.1, 126.4, 126.2, 125.9, 107.0, 104.1, 37.6, 29.8, 17.4; MS (70 eV): *m*/*z* (%): 246 (M^+, 2.26), 91 (100.00); IR (neat): 1945, 1602, 1495 cm^{-1}; HRMS calcd for $C_{19}H_{18}$ [M^+]: 246.1409, found: 246.1381. Compound **8**: liquid, ^{1}H NMR (300 MHz, $CDCl_3$) $\delta=7.42$–7.21 (m, 10H), 3.0 (s, 2H), 2.40–1.90 (m, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) $\delta=138.5$, 131.4, 130.0, 128.1, 127.8, 127.4, 126.3, 124.0, 96.5, 82.8, 45.8, 37.9, 34.1, 16.3; MS (70 eV): *m*/*z* (%): 246 (M^+, 16.02), 84 (100.00); IR (neat): 1598, 1492 cm^{-1}; HRMS calcd for $C_{19}H_{18}$ [M^+]: 246.1409, found: 246.1430.

3.2.1.7. Synthesis of 2,3-diphenylpropenylidenecyclohexane (10) and 1-(phenylethynyl)-1-benzylcyclohexane (11).



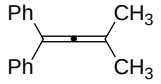
10 **11**

The reaction of 1-cyclohexyl-2-phenylacetylene **9** (37 mg, 0.20 mmol), *n*-BuLi (0.38 mL, 0.60 mmol, 1.6 M in hexanes), and benzyl bromide (72 μL, 0.60 mmol) afforded **10** and **11** as a mixture (42 mg, 76%) with a ratio of **10**:**11**=74:26, which was determined by 300 MHz ^{1}H NMR spectra. The mixture is a solid. Compound **10**: ^{1}H NMR (300 MHz, $CDCl_3$) $\delta=7.42$–7.14 (m, 10H), 3.73 (s, 2H), 2.20–2.00 (m, 2H), 1.80–1.20 (m, 8H), (a signal at 2.8 (s, 2H) was observed for **11**); MS (70 eV): *m*/*z* (%): 274 (M^+, 28.76), 91 (100.00); IR (neat): 1946 cm^{-1}. Anal. Calcd for $C_{21}H_{22}$: C, 91.92; H, 8.08; found: C, 92.02; H, 8.14.

3.2.2. Synthesis of 1-(phenylethynyl)-1-phenylcyclopropane 13a. To a solution of 1-cyclopropyl-2-phenylacetylene (56 mg, 0.39 mmol) in THF (3 mL) in a dry Schlenk tube was added *n*-BuLi (0.30 mL, 1.6 M in hexanes, 0.47 mmol) at −78 °C under N_2. After being warmed up naturally and stirred 1 h at rt, a solution of dry $ZnBr_2$ (178 mg, 0.79 mmol) in THF (4 mL) was added. After being stirred for 25 min at this temperature, $Pd(PPh_3)_4$ (15 mg, 5 mol%) and iodobenzene (29 μL, 0.26 mmol) were added subsequently at rt with stirring. After the reaction was complete as monitored by TLC (eluent: petroleum ether (60–90 °C)), it was quenched with saturated aqueous solution of NH_4Cl and extracted with ether. Drying over anhydrous $MgSO_4$, rotary evaporation, and flash chromatography on silica gel (petroleum ether) afforded **13a** (41 mg, 72%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta=7.50$–7.15 (m, 10H), 1.54 (dd, $J_1=6.9$ Hz, $J_2=4.5$ Hz, 2H), 1.33 (dd, $J_1=6.9$ Hz, $J_2=4.5$ Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) $\delta=141.9$, 131.7, 128.3, 128.2, 127.7, 126.0, 125.5, 123.7, 93.7, 78.3, 20.5, 16.2; MS (70 eV): *m*/*z* (%): 218 (M^+, 100.00); IR (neat) 2235, 1598, 1491 cm^{-1}; HRMS calcd for $C_{17}H_{14}$ [M^+]: 218.1096, found 218.1088.

The following compounds were prepared according to the procedure described in this section

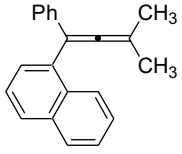
3.2.2.1. Synthesis of 1,1-diphenyl-3-methylbuta-1,2-diene (12a).[11]



12a

The reaction of 1-phenyl-3-methyl-1-butyne **1** (58 mg, 0.40 mmol), *n*-BuLi (0.30 mL, 0.48 mmol, 1.6 M in hexanes), $ZnBr_2$ (180 mg, 0.80 mmol), $Pd(PPh_3)_4$ (16 mg, 5 mol%), and iodobenzene (30 μL, 0.27 mmol) afforded **12a** (28 mg, 47%) as a solid, mp 54–55 °C (hexane). ^{1}H NMR (300 MHz, $CDCl_3$) $\delta=7.34$–7.20 (m, 10H), 1.88 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) $\delta=203.7$, 138.0, 128.5, 128.2, 126.7, 107.7, 98.3, 20.4; MS (70 eV): *m*/*z* (%): 220 (M^+, 58.75), 205 (100.00); IR (neat): 1948, 1595, 1489 cm^{-1}.

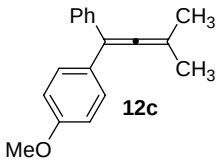
3.2.2.2. Synthesis of 1-phenyl-1-(1′-naphthyl)-3-methylbuta-1,2-diene (12b).



12b

The reaction of 1-phenyl-3-methyl-1-butyne **1** (57 mg, 0.40 mmol), *n*-BuLi (0.30 mL, 0.48 mmol, 1.6 M in hexanes), $ZnBr_2$ (180 mg, 0.80 mmol), $Pd(PPh_3)_4$ (16 mg, 5 mol%), 1-naphthyl iodide (40 μL, 0.27 mmol) afforded **12b** (18 mg, 25%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta=7.97$–7.80 (m, 3H), 7.52–7.35 (m, 4H), 7.26–7.14 (m, 5H), 1.88 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) $\delta=203.1$, 138.6, 135.5, 133.8, 132.1, 128.25, 128.22, 127.70, 127.66, 126.8, 126.31, 126.27, 125.8, 125.7, 125.6, 104.6, 98.2, 20.3; MS (70 eV): *m*/*z* (%): 270 (M^+, 27.72), 255 (100.00); IR (neat): 1948, 1596, 1490 cm^{-1}; HRMS calcd for $C_{21}H_{18}$ [M^+]: 270.1409, found: 270.1434.

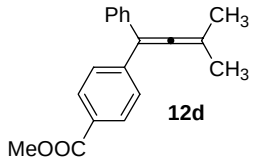
3.2.2.3. Synthesis of 1-phenyl-1-(4′-methoxyphenyl)-3-methylbuta-1,2-diene (12c).



12c

The reaction of 1-phenyl-3-methyl-1-butyne **1** (58 mg, 0.40 mmol), *n*-BuLi (0.30 mL, 0.48 mmol, 1.6 M in hexanes), $ZnBr_2$ (180 mg, 0.80 mmol), $Pd(PPh_3)_4$ (16 mg, 5 mol%), and 4-iodoanisole (63 mg, 0.27 mmol) afforded **12c** (48 mg, 71%) as a solid, mp 45–46 °C (hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.44–7.22 (m, 7H), 6.86 (d, J=8.7 Hz, 2H), 3.80 (s, 3H), 1.87 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ=203.3, 158.6, 138.4, 130.4, 129.6, 128.4, 128.2, 126.7, 113.7, 107.1, 98.2, 55.3, 20.6; MS (70 eV): *m*/*z* (%): 250 (M^+, 80.10), 235 (100.00); IR (neat): 1948, 1605, 1508 cm^{-1}. Anal. Calcd for $C_{18}H_{18}O$: C, 86.36; H, 7.25; found: C, 86.30; H, 6.98.

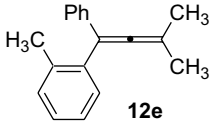
3.2.2.4. Synthesis of 1-phenyl-1-(4′-methoxycarbonylphenyl)-3-methylbuta-1,2-diene (12d).



12d

The reaction of 1-phenyl-3-methyl-1-butyne **1** (58 mg, 0.40 mmol), *n*-BuLi (0.30 mL, 0.48 mmol, 1.6 M in hexanes), $ZnBr_2$ (180 mg, 0.80 mmol), $Pd(PPh_3)_4$ (8 mg, 5 mol%), and methyl 4-iodobenzoate (35 mg, 0.13 mmol) afforded **12d** (33 mg, 91%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.91 (d, J=8.4 Hz, 2H), 7.33–7.17 (m, 7H), 3.83 (s, 3H), 1.82 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ=204.5, 167.0, 143.1, 137.4, 129.5, 128.5, 128.3, 128.24, 128.19, 127.0, 107.3, 99.1, 52.0, 20.3; MS (70 eV): *m*/*z* (%): 278 (M^+, 91.82), 263 (100.00); IR (neat): 1946, 1720, 1606, 1491 cm^{-1}; HRMS calcd for $C_{19}H_{19}O_2$ [M^++H]: 279.1385, found: 279.1382.

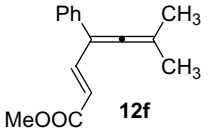
3.2.2.5. Synthesis of 1-phenyl-1-(2′-methylphenyl)-3-methylbuta-1,2-diene (12e).



12e

The reaction of 1-phenyl-3-methyl-1-butyne **1** (57 mg, 0.40 mmol), *n*-BuLi (0.30 mL, 0.48 mmol, 1.6 M in hexanes), $ZnBr_2$ (180 mg, 0.80 mmol), $Pd(PPh_3)_4$ (16 mg, 5 mol%), and 2-methylphenyl iodide (34 μL, 0.27 mmol) afforded **12e** (25 mg, 40%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.32–7.16 (m, 9H), 2.24 (s, 3H), 1.87 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ=202.2, 138.3, 137.2, 136.8, 130.4, 130.2, 128.2, 127.3, 126.7, 126.2, 125.8, 105.4, 97.9, 20.3, 20.2; MS (70 eV): *m*/*z* (%): 234 (M^+, 25.04), 219 (100.00); IR (neat): 1951, 1598, 1489 cm^{-1}; HRMS calcd for $C_{18}H_{18}$ [M^+]: 234.1409, found: 234.1435.

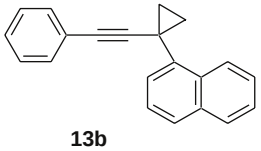
3.2.2.6. Synthesis of 1-phenyl-1-(*E*-methoxycarbonylethenyl)-3-methylbuta-1,2-diene (12f).



12f

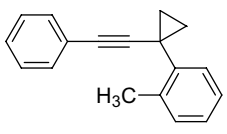
The reaction of 1-phenyl-3-methyl-1-butyne **1** (58 mg, 0.40 mmol), *n*-BuLi (0.30 mL, 0.48 mmol, 1.6 M in hexanes), $ZnBr_2$ (180 mg, 0.80 mmol), $Pd(PPh_3)_4$ (16 mg, 5 mol%), and methyl (*E*)-3-iodopropenoate[3] (57 mg, 0.27 mmol) afforded **12f** (23 mg, 37%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.50 (d, J=15.9 Hz, 1H), 7.40–7.20 (m, 5H), 5.93 (d, J=15.9 Hz, 1H), 3.75 (s, 3H), 1.84 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ=207.8, 167.5, 143.9, 135.7, 128.5, 127.9, 127.3, 119.0, 104.8, 98.5, 51.5, 19.9; MS (70 eV): *m*/*z* (%): 228 (M^+, 100.00); IR (neat): 1942, 1720, 1622 cm^{-1}; HRMS calcd for $C_{15}H_{16}O_2$ [M^+]: 228.1150, found: 228.1171.

3.2.2.7. Synthesis of 1-(phenylethynyl)-1-(1′-naphthyl)cyclopropane (13b).


13b

The reaction of 1-cyclopropyl-2-phenylacetylene **4a** (56 mg, 0.39 mmol), *n*-BuLi (0.30 mL, 0.47 mmol, 1.6 M in hexanes), $ZnBr_2$ (180 mg, 0.80 mmol), $Pd(PPh_3)_4$ (15 mg, 5 mol%), and 1-naphthyl iodide (38 μL, 0.26 mmol) afforded **13b** (19 mg, 27%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ=8.66 (d, J=9.0 Hz, 1H), 7.89 (d, J=8.1 Hz, 1H), 7.86 (d, J=8.1 Hz, 1H), 7.80–7.15 (m, 9H), 1.62 (dd, J_1=6.9 Hz, J_2=4.5 Hz, 2H), 1.33 (dd, J_1=6.9 Hz, J_2=4.5 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ=138.2, 134.2, 132.8, 131.9, 128.7, 128.3, 128.2, 127.7, 126.5, 126.2, 126.0, 125.7, 125.6, 123.9, 95.3, 76.7, 17.5, 15.7; MS (70 eV): *m*/*z* (%): 268 (M^+, 1.63), 84 (100.00); IR (neat) 2227, 1596, 1491 cm^{-1}; HRMS calcd for $C_{21}H_{17}$ [M^++H]: 269.1330, found: 269.1332.

3.2.2.8. Synthesis of 1-(phenylethynyl)-1-(2′-methylphenyl)cyclopropane (13c).

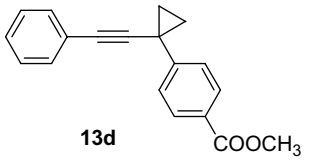


13c

The reaction of 1-cyclopropyl-2-phenylacetylene **4a** (56 mg, 0.39 mmol), *n*-BuLi (0.30 mL, 0.47 mmol, 1.6 M in hexanes), $ZnBr_2$ (180 mg, 0.80 mmol), $Pd(PPh_3)_4$ (15 mg, 5 mol%), and 2-iodotoluene (33 μL, 0.26 mmol) afforded **13c** (15 mg, 25%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.38–7.30 (m, 3H), 7.25–7.11 (m, 6H), 2.60 (s, 3H), 1.44 (dd, J_1=6.9 Hz, J_2=4.5 Hz, 2H), 1.19 (dd, J_1=6.9 Hz,

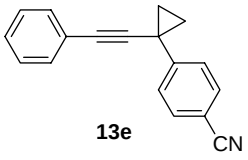
J_2=4.5 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ=139.8, 139.0, 131.6, 130.3, 128.9, 128.0, 127.4, 127.2, 125.8, 123.8, 94.3, 76.0, 19.6, 17.1, 16.1; MS (70 eV): *m/z* (%): 232 (M^+, 34.12), 202 (100.00); IR (neat) 2232, 1597, 1488 cm^{-1}; HRMS calcd for $C_{18}H_{16}$ [M^+]: 232.1252, found: 232.1266.

3.2.2.9. Synthesis of 1-(phenylethynyl)-1-(4′-methoxycarbonylphenyl)cyclopropane (13d).



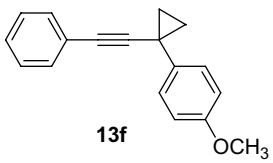
The reaction of 1-cyclopropyl-2-phenylacetylene **4a** (56 mg, 0.39 mmol), *n*-BuLi (0.30 mL, 0.47 mmol, 1.6 M in hexanes), $ZnBr_2$ (178 mg, 0.79 mmol), $Pd(PPh_3)_4$ (8 mg, 5 mol%), and methyl 4-iodobenzoate (34 mg, 0.13 mmol) afforded **13d** (35 mg, 98%) as a solid, mp 79–81 °C (petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.98 (d, J=9.0 Hz, 2H), 7.49–7.40 (m, 4H), 7.33–7.29 (m, 3H), 3.90 (s, 3H), 1.64 (dd, J_1=7.2 Hz, J_2=4.2 Hz, 2H), 1.40 (dd, J_1=7.2 Hz, J_2=4.2 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ=166.9, 147.5, 131.7, 129.6, 128.2, 127.9, 127.7, 125.0, 123.3, 92.5, 79.1, 52.0, 21.7, 16.5; MS (70 eV): *m/z* (%): 276 (M^+, 70.56), 217 (100.00); IR (neat) 2230, 1717, 1282 cm^{-1}. Anal. Calcd for $C_{19}H_{16}O_2$ C, 82.58; H, 5.84; found: C, 82.31; H, 5.60.

3.2.2.10. Synthesis of 1-(phenylethynyl)-1-(4′-cyanophenyl)cyclopropane (13e).



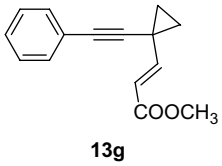
The reaction of 1-cyclopropyl-2-phenylacetylene **4a** (56 mg, 0.39 mmol), *n*-BuLi (0.30 mL, 0.47 mmol, 1.6 M in hexanes), $ZnBr_2$ (180 mg, 0.80 mmol), $Pd(PPh_3)_4$ (8 mg, 5 mol%), and 4-iodobenzonitrile (31 mg, 0.13 mmol) afforded **13e** (29 mg, 88%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.57 (d, J=9.0 Hz, 2H), 7.46–7.40 (m, 4H), 7.31–7.22 (m, 3H), 1.66 (dd, J_1=7.8 Hz, J_2=4.5 Hz, 2H), 1.38 (dd, J_1=7.8 Hz, J_2=4.5 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ=147.8, 132.1, 131.7, 128.3, 128.1, 125.8, 123.0, 119.0, 109.5, 91.7, 79.6, 22.0, 16.6; MS (70 eV): *m/z* (%): 243 (M^+, 100.00); IR (neat) 2227, 1609, 1507 cm^{-1}; HRMS calcd for $C_{18}H_{14}N$ [M^++H]: 244.1126, found: 244.1136.

3.2.2.11. Synthesis of 1-(phenylethynyl)-1-(4′-methoxylphenyl)cyclopropane (13f).



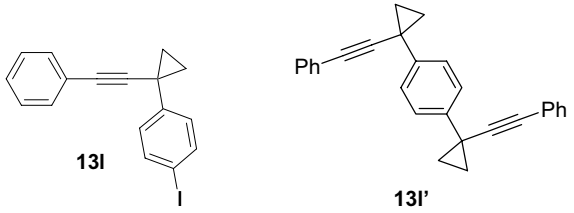
The reaction of 1-cyclopropyl-2-phenylacetylene **4a** (57 mg, 0.40 mmol), *n*-BuLi (0.30 mL, 0.48 mmol, 1.6 M in hexanes), $ZnBr_2$ (180 mg, 0.80 mmol), $Pd(PPh_3)_4$ (15 mg, 5 mol%), and 4-iodoanisole (63 mg, 0.27 mmol) afforded **13f** (22 mg, 33%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.45–7.40 (m, 2H), 7.35–7.23 (m, 5H), 6.85 (d, J=9.0 Hz, 2H), 3.79 (s, 3H), 1.48 (dd, J_1=6.9 Hz, J_2=4.5 Hz, 2H), 1.26 (dd, J_1=6.9 Hz, J_2=4.5 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ=158.0, 134.0, 131.7, 128.2, 127.6, 127.0, 123.7, 113.7, 94.3, 77.8, 55.3, 19.7, 15.6; MS (70 eV): *m/z* (%): 248 (M^+, 100.00); IR (neat) 2232, 1248 cm^{-1}; HRMS calcd for $C_{18}H_{16}O$ [M^+]: 248.1201, found: 248.1216.

3.2.2.12. Synthesis of 1-(phenylethynyl)-1-(*E*-methoxycarbonylethenyl)cyclopropane (13g).



The reaction of 1-cyclopropyl-2-phenylacetylene **4a** (56 mg, 0.39 mmol), *n*-BuLi (0.30 mL, 0.47 mmol, 1.6 M in hexanes), $ZnBr_2$ (178 mg, 0.79 mmol), $Pd(PPh_3)_4$ (15 mg, 5 mol%), and methyl (*E*)-3-iodopropenate[12] (55 mg, 0.26 mmol) afforded **13g** (20 mg, 34%) as a solid, mp 80–81 °C (petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.44–7.38 (m, 2H), 7.32–7.24 (m, 3H), 6.38 (d, J=15.0 Hz, 1H), 6.31 (d, J=15.0 Hz, 1H), 3.74 (s, 3H), 1.53 (dd, J_1=7.2 Hz, J_2=4.2 Hz, 2H), 1.25 (dd, J_1=7.2 Hz, J_2=4.2 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ=167.1, 151.9, 131.7, 128.2, 128.0, 123.0, 119.2, 89.3, 80.8, 51.5, 19.9, 15.7; MS (70 eV): *m/z* (%): 226 (M^+, 41.01), 165 (100.00); IR (neat) 2230, 1716, 1645, 1201, 1165 cm^{-1}. Anal. Calcd for $C_{15}H_{14}O_2$ C, 79.62; H, 6.24; found: C, 79.63; H, 6.27.

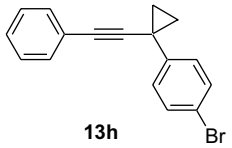
3.2.2.13. Synthesis of 1-(phenylethynyl)-1-(4′-iodophenyl)cyclopropane (13l) and 1,4-bis(1′-phenylethynyl-1′-cyclopropyl)benzene (13l′).



The reaction of 1-cyclopropyl-2-phenylacetylene **4a** (64 mg, 0.45 mmol), *n*-BuLi (0.34 mL, 0.54 mmol, 1.6 M in hexanes), $ZnBr_2$ (203 mg, 0.90 mmol), $Pd(PPh_3)_4$ (26 mg, 5 mol%), and 1,4-diiodobenzene (74 mg, 0.23 mmol) afforded **13l** (45 mg, 57%) and **13l′** (15 mg, 18%). Compound **13l**: liquid, ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.61 (d, J=8.7 Hz, 2H), 7.45–7.38 (m, 2H), 7.31–7.23 (m, 3H), 7.13 (d, J=8.7 Hz, 2H), 1.55 (dd, J_1=7.5 Hz, J_2=4.8 Hz, 2H), 1.29 (dd, J_1=7.5 Hz, J_2=4.8 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ=141.8, 137.3, 131.7, 128.2, 127.8, 127.6, 123.4, 92.9, 91.0, 78.7, 20.7, 16.0; MS (70 eV): *m/z* (%): 344 (M^+, 46.09), 202 (100.00); IR (neat) 2232, 1598, 1486 cm^{-1}; HRMS calcd for $C_{17}H_{13}I$

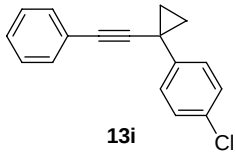
[M^+]: 344.0062, found: 344.0086. Compound **13l′**: solid, mp 97–100 °C (petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.50–7.40 (m, 4H), 7.35 (s, 4H), 7.31–7.24 (m, 6H), 1.53 (dd, J_1=7.5 Hz, J_2=4.8 Hz, 4H), 1.32 (dd, J_1=7.5 Hz, J_2=4.8 Hz, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ=139.7, 131.7, 128.2, 127.6, 125.6, 123.7, 93.8, 78.2, 20.3, 15.9; MS (70 eV): *m/z* (%): 358 (M^+, 20.6), 217 (100.00); IR (neat) 2231, 1597, 1491 cm^{-1}; HRMS calcd for $C_{28}H_{23}$ [M^++1]: 359.1800, found: 359.1809.

3.2.2.14. Synthesis of 1-(phenylethynyl)-1-(4′-bromophenyl)cyclopropane (13h).



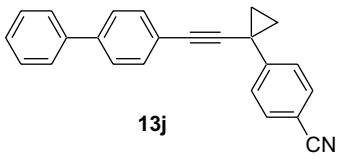
The reaction of 1-cyclopropyl-2-phenylacetylene **4a** (66 mg, 0.46 mmol), *n*-BuLi (0.35 mL, 0.56 mmol, 1.6 M in hexanes), $ZnBr_2$ (203 mg, 0.90 mmol), $Pd(PPh_3)_4$ (18 mg, 5 mol%), and 1-bromo-4-iodobenzene (87 mg, 0.31 mmol) afforded **13h** (59 mg, 64%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.48–7.41 (m, 4H), 7.33–7.24 (m, 5H), 1.57 (dd, J_1=7.5 Hz, J_2=4.8 Hz, 2H), 1.32 (dd, J_1=7.5 Hz, J_2=4.8 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ=141.1, 131.7, 131.3, 128.2, 127.8, 127.3, 123.4, 119.8, 93.0, 78.7, 20.6, 16.0; MS (70 eV): *m/z* (%):298 (M^+(^{81}Br), 296 (M^+(^{79}Br), 20.79), 17.88), 217 (79.30), 215 (100.00); IR (neat) 2233, 1598, 1488 cm^{-1}; HRMS calcd for $C_{17}H_{13}^{79}Br$ [M^+]: 296.0201, found: 296.0193.

3.2.2.15. Synthesis of 1-(phenylethynyl)-1-(4′-chlorophenyl)cyclopropane (13i).



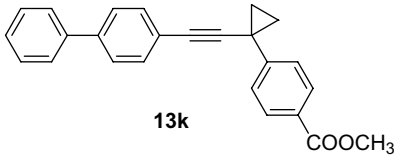
The reaction of 1-cyclopropyl-2-phenylacetylene **4a** (65 mg, 0.46 mmol), *n*-BuLi (0.34 mL, 0.55 mmol, 1.6 M in hexanes), $ZnBr_2$ (203 mg, 0.90 mmol), $Pd(PPh_3)_4$ (18 mg, 5 mol%), and 1-chloro-4-iodobenzene (73 mg, 0.31 mmol) afforded **13i** (43 mg, 55%) as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.50–7.42 (m, 2H), 7.36–7.24 (m, 7H), 1.57 (dd, J_1=7.5 Hz, J_2=4.8 Hz, 2H), 1.32 (dd, J_1=7.5 Hz, J_2=4.8 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ=140.5, 131.75, 131.67, 128.4, 128.2, 127.8, 126.9, 123.4, 93.1, 78.6, 20.6, 15.9; MS (70 eV): *m/z* (%): 254 (M^+(^{37}Cl), 14.06), 252 (M^+(^{35}Cl), 42.85), 217 (100.00); IR (neat) 2233, 1598, 1492 cm^{-1}; HRMS calcd for $C_{17}H_{13}^{35}Cl$ [M^+]: 252.0706, found: 252.0725.

3.2.2.16. Synthesis of 1-(*p*-phenylphenyl)ethynyl-1-(4′-cyanophenyl)cyclopropane (13j).



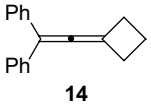
The reaction of 1-cyclopropyl-2-(*p*-phenylphenyl)acetylene **4b** (87 mg, 0.40 mmol), *n*-BuLi (0.30 mL, 0.48 mmol, 1.6 M in hexanes), $ZnBr_2$ (180 mg, 0.80 mmol), $Pd(PPh_3)_4$ (12 mg, 5 mol%), and 4-iodobenzonitrile (46 mg, 0.20 mmol) afforded **13j** (45 mg, 70%) as a solid, mp 118–119 °C (petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.62–7.35 (m, 13H), 1.70 (dd, J_1=7.5 Hz, J_2=4.5 Hz, 2H), 1.42 (dd, J_1=7.5 Hz, J_2=4.5 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ=147.8, 140.8, 140.3, 132.2, 132.1, 128.8, 127.6, 127.0, 125.8, 121.9, 119.0, 109.6, 92.4, 79.5, 22.1, 16.7; MS (70 eV): *m/z* (%): 319 (M^+, 100.00); IR (neat) 2227, 1606, 1486 cm^{-1}. Anal. Calcd for $C_{24}H_{17}N$: C, 90.25; H, 5.36; N, 4.39; found: C, 90.06; H, 5.20; N, 4.19.

3.2.2.17. Synthesis of 1-(*p*-phenylphenyl)ethynyl-1-(4′-methoxycarbonylphenyl)cyclopropane (13k).



The reaction of 1-cyclopropyl-2-(*p*-phenylphenyl)acetylene **4b** (87 mg, 0.40 mmol), *n*-BuLi (0.30 mL, 0.48 mmol, 1.6 M in hexanes), $ZnBr_2$ (180 mg, 0.80 mmol), $Pd(PPh_3)_4$ (8 mg, 5 mol%), and methyl 4-iodobenzoate (38 mg, 0.13 mmol) afforded **13k** (26 mg, 51%) as a solid, mp 156 °C (petroleum ether–Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ=8.00 (d, J=8.7 Hz, 2H), 7.62–7.24 (m, 11H), 3.91 (s, 3H), 1.67 (dd, J_1=7.5 Hz, J_2=4.5 Hz, 2H), 1.43 (dd, J_1=7.5 Hz, J_2=4.5 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ=166.9, 147.5, 140.6, 140.3, 132.1, 129.7, 128.8, 127.8, 127.6, 127.0, 126.9, 125.1, 122.3, 93.3, 79.0, 52.0, 21.8, 16.6; MS (70 eV): *m/z* (%): 352 (M^+, 100.00); IR (neat) 2215, 1714, 1282 cm^{-1}. Anal. Calcd for $C_{25}H_{20}O_2$: C, 85.20; H, 5.72; found: C, 85.01; H, 5.71.

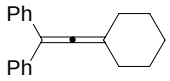
3.2.2.18. Synthesis of 2,2-diphenyl vinylidenecyclobutane (14).



The reaction of 1-cyclobutyl-2-phenylacetylene **6** (79 mg, 0.50 mmol), *n*-BuLi (0.94 mL, 1.51 mmol, 1.6 M in hexanes), $ZnBr_2$ (340 mg, 1.51 mmol), $Pd(PPh_3)_4$ (29 mg, 5 mol%), and iodobenzene (169 μL, 1.51 mmol) afforded **14** (64 mg, 55%) as a solid, mp 54–55 °C (petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.40–7.20 (m, 10H), 3.05 (t, J=8.1 Hz, 4H), 2.03 (pentet, J=7.8 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ=197.2, 138.0, 128.5, 128.2, 127.0, 111.6, 103.6, 30.1, 17.5; MS (70 eV): *m/z* (%): 232

(M^+, 18.60), 204 (100.00); IR (neat): 1940, 1596, 1491 cm^{-1}. Anal. Calcd for $C_{18}H_{16}$: C, 93.06; H, 6.94; found: C, 92.92; H, 7.05.

3.2.2.19. Synthesis of 2,2-diphenyl vinylidenecyclohexane (15).



15

The reaction of 1-cyclohexyl-2-phenylacetylene **9** (94 mg, 0.51 mmol), *n*-BuLi (0.95 mL, 1.52 mmol, 1.6 M in hexanes), $ZnBr_2$ (343 mg, 1.52 mmol), $Pd(PPh_3)_4$ (29 mg, 5 mol%), and iodobenzene (171 μL, 1.52 mmol) afforded **15** (59 mg, 44%) as a solid, mp 97–98 °C (petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ=7.40–7.20 (m, 10H), 2.32–2.28 (m, 4H), 1.73–1.65 (m, 4H), 1.61–1.55 (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ=200.4, 138.2, 128.4, 128.2, 126.6, 107.4, 105.6, 31.4, 27.6, 26.1; MS (70 eV): *m/z* (%): 260 (M^+, 90.62), 217 (100.00); IR (neat): 1945, 1597, 1488 cm^{-1}. Anal. Calcd for $C_{20}H_{20}$: C, 92.26; H, 7.74; found: C, 92.24; H, 7.86.

Acknowledgements

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A coordinatively unsaturated ruthenium methoxide as a highly effective catalyst for the halogen atom-transfer radical cyclization of *N*-allyl dichloroacetamides and related reactions

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Abstract—Atom-transfer radical cyclization (ATRC) catalyzed by coordinatively unsaturated ruthenium alkoxides **4**, $[(\eta^5\text{-}C_5Me_5)\text{-}Ru(OR)]_2$, is investigated, and ruthenium methoxide **4a** (R = Me) is found to exhibit excellent catalytic activity for the cyclization of *N*-allyl-α,α-dichloroacetamides at ambient temperature. Addition of some amounts of two-electron donor ligands such as pyridine and triphenylphosphine improves the catalyst efficiency to afford the corresponding γ-lactams in high yields. The high catalytic activity of this catalyst system enables to control the diastereoselectivity of this 5-*exo* cyclization kinetically. The present **4a**/pyridine system is also effective for the 4-*exo* cyclization of *N*-vinylacetamides to afford the corresponding β-lactams in quantitative yields. The **4a**/pyridine system is also active towards the ATRP of methyl methacrylate (MMA) at room temperature to afford the poly(MMA) with narrow molecular weight distributions ($M_w/M_n = 1.2$) at the initial stage.

1. Introduction

Atom-transfer radical reaction (ATRR) has now become one of the most important carbon–carbon bond-forming reactions, being utilized for synthetic organic chemistry and polymer synthesis.[1–3] In particular, our discovery of copper-catalyzed cyclizations of allyl α,α,α-trichloroacetates[4a] and *N*-allyl-α,α,α-trichloroacetamides[4b] offered a research field of transition metal-catalyzed atom-transfer radical cyclization (ATRC), which has afforded powerful synthetic methods for carbo- and heterocycles including macrolide and alkaloid skeletons.[5] From the synthetic point-of-view, it should be noted that requirement of high reaction temperatures is a general disadvantage of ATRR, especially in the reactions involving activation of less reactive carbon–halogen bonds. In our earliest report on the cyclization of α-halogenated *N*-allylacetamides, either $RuCl_2(PPh_3)_3$ or CuCl catalyst was effective at 140 °C.[4b] Later elaboration to improve the reaction conditions revealed that the reaction was facilitated by increasing the halogen atom at the α-position and/or introduction of electron-withdrawing group on the nitrogen atom.[4e,f] This is presumably due to the fact that these substituents lower the LUMO of α-halogenated acetyl moiety and facilitate abstraction of a halogen atom by transition metal catalysts. On the other hand, several reactive catalyst systems, which can promote the reaction at low temperature, were developed; in particular, catalyst systems composed of CuCl and bidentate diamines[4c] and isolable coordinatively unsaturated ruthenium amidinates **1**–**3** were found to be one of the most effective catalysts for ATRR (Fig. 1).[6c,7] Thus, combination of the selection of appropriate substrates, which have suitable electronic structures for ATRR, with powerful catalyst systems realized the cyclization of *N*-allyl-α,α,α-trichloroacetamides below room temperature within a few hours. However, the cyclization of less reactive substrates such as *N*-allyl-α,α-dichloroacetamides is slow even using CuCl/bipyridine and ruthenium amidinates as the catalyst and it is necessary to apply high reaction temperatures (>80 °C) to obtain the product in good yield.[4e,7,8] This indicates the requirement to seek for catalysts more powerful enough to activate a carbon–chlorine bond of *N*-allyl dichloroacetamides with ease to afford the corresponding γ-lactams.

For the development of highly reactive new catalysts, we have been interested in use of coordinatively unsaturated transition metal complexes. ATRC is generally explained by the catalytic cycle shown in Scheme 1. The atom-transfer

Keywords: Coordinatively unsaturated complex; Polymerization; Radical cyclization; Ruthenium.
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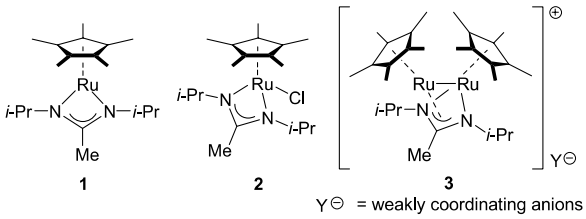
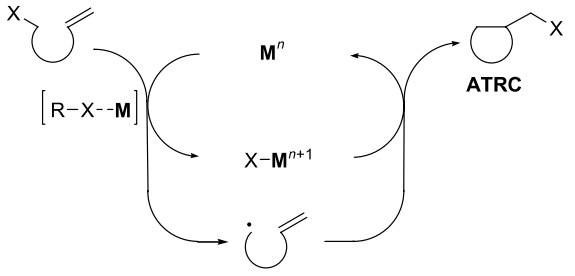


Figure 1. Ruthenium amidinate complexes **1**–**3**.



Scheme 1. Atom-transfer reaction with transition metal complex.

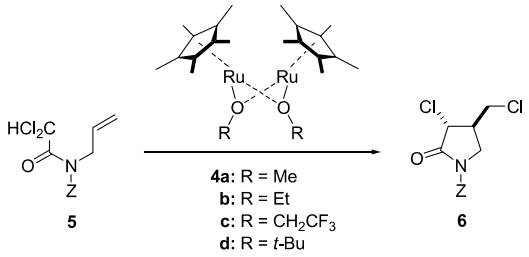
reaction of organic halides (R–X) with transition metals (M) proceeds via the redox mechanism involving a [R–X···M] complex as an intermediary species, and the formal oxidation state of the metal species is increased by one, and M–X is formed by the halogen abstraction.[9] In the [R–X···M] complex, M has to be coordinatively unsaturated, and thus, use of isolated coordinatively unsaturated complexes as the catalyst could facilitate the production of [R–X···M], which subsequently undergoes atom-transfer process to produce the radical species ($R^{\cdot}$) to initiate the reaction. If M has appropriate redox potentials, the catalytic cycle illustrated in Scheme 1 could be successfully operated.

In fact, ruthenium amidinate complexes **1**–**3** showed a coordinatively unsaturated nature, and actually behaved as efficient catalysts for ATRR as described in our previous papers.[6c,7] For further studies in this line, we were interested in isolable ruthenium alkoxides $[(\eta^5\text{-}C_5Me_5)Ru(OR)]_2$ **4**, which exist in solution as coordinatively unsaturated dimers having 32 valence electrons and reversibly forms monomers in contact with appropriate ligands.[10] The formed monomer, which was stabilized by the ligand, is still coordinatively unsaturated (16 valence electrons), being able to accept the coordination of R–X for its activation.[10c,11] In this paper, we wish to report that coordinatively unsaturated ruthenium alkoxides actually behave as the catalyst for the cyclization of *N*-allyl-α,α-dichloroacetamides **5** and related reactions. The scope of these ruthenium alkoxides as catalysts for ATRC is described in relation to the low-temperature activation of organic halides and stereochemical outcomes of the reactions, and their performance is compared with that for atom-transfer radical polymerization (ATRP) (Scheme 2).

2. Results and discussion

2.1. Atom-transfer radical cyclization

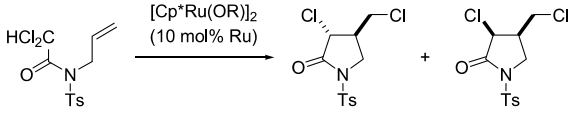
As we expected, $[Cp^*Ru(OMe)]_2$ **4a** was effective for the activation of a C–Cl bond at ambient temperature.



Scheme 2. ATRC of *N*-allyl-α,α-dichloroacetamides **5**.

Treatment of α,α-dichloroacetamide **5a** (0.2 mmol) with **4a** (10 mol% of Ru) in dichloromethane for 4 h under an argon atmosphere afforded the cyclic product **6a** in 50% isolated yield with a trans/cis ratio of 86:14 (Table 1, entry 1). The alkoxy group on the ruthenium apparently affected the catalytic activity; the ethoxy complex **4b** gave **6a** in 34% yield (entry 2), whereas no product was obtained by the use of trifluoroethyl and *t*-butyl derivatives (**4c** and **4d**) as catalysts (entries 3 and 4). It is noteworthy that ruthenium halide complexes such as $[Cp^*Ru^{II}Cl]_4$ and $[Cp^*Ru^{III}Cl_2]_2$ are not effective for this cyclization at ambient temperature (<5% yields). These results showed that the sterically less-hindered alkoxide ligand plays a crucial role in enhancing the reactivity of the ruthenium complexes towards organic halides via the one-electron redox process, which may be related to the π-donation by alkoxide lone pairs. Among the solvents examined, dichloromethane proved to be the most effective for both chemical yield and trans/cis ratio of the product (entries 5–8).

Table 1. Radical cyclization of **5a** with $[Cp^*Ru(OR)]_2$ **4a**–**d**[a]



Entry	Cat.	Solvent	Time (h)	Yield (%)	trans/cis[b]
1	**4a**	CH_2Cl_2	4	50	86:14
2	**4b**	CH_2Cl_2	4	34	85:15
3	**4c**	CH_2Cl_2	4	0	—
4	**4d**	CH_2Cl_2	4	0	—
5	**4a**	CH_2Cl_2	16	64	86:14
6	**4a**	Benzene	16	33	83:17
7	**4a**	MeCN	16	32	82:18
8[c]	**4a**	Et_2O	16	<10	78:22

[a] All reactions were carried out using 0.2 mmol of **5a**, 0.01 mmol of **4** in 1.5 mL of solvent at room temperature.
[b] Determined by ^{1}H NMR analysis.
[c] 0.03 mmol (30 mol% Ru) was used.

Despite the high catalytic activity for the cyclization of dichloroacetamide **5a**, a disadvantage of **4a** is its short lifetime as shown in the reaction profiles (Fig. 2, left; a); the reaction was terminated after some of the starting materials were consumed (~80%, TON≤8). Although the catalytic activity (initial reaction rate) was slightly decreased, addition of pyridine to the reaction mixture depresses inactivation of the catalyst (Fig. 2, left; b). The effects of pyridine and other ligands, which affect the catalytic efficiency in the reaction of **5a** with **4a** in dichloromethane at ambient temperature, are summarized in Table 2.

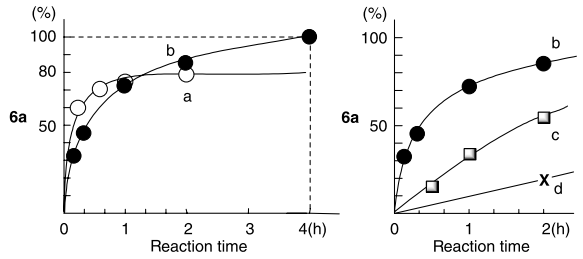


Figure 2. The plots of formed **6a** (%) versus time (h): (a) catalyzed by **4a** (○); (b) catalyzed by **4a**/pyridine (●); (c) catalyzed by **3** (□); (d) catalyzed by CuCl/bipyridine (×).

Table 2. Additive effects in the reaction of **5a** with **4a**[a]

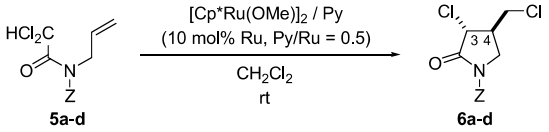
Entry	Additive	Additive/Ru	Yield (%)	Trans/cis[b]
1	—	—	50	86:14
2	PPh_3	0.5	95	87:13
3	DMAP	0.5	91	89:11
4	Pyridine	0.5	>99	87:13
5	Pyridine	1.0	>99	87:13
6	Pyridine	2.0	>99	87:13
7	Pyridine	3.0	89	87:13
8	Pyridine	0.25	>99	87:13

[a] All reactions were carried out using 0.2 mmol of **2**, 0.01 mmol of **4a** and additive in 1.5 mL of CH_2Cl_2 at room temperature for 4 h.
[b] Determined by ^{1}H NMR analysis.

Remarkable improvement in the catalytic efficiency was achieved by the addition of donor ligands (0.5 equiv for Ru), and pyridine proved to be the most effective for this catalyst system (entries 1 vs 2–4). We also found that the addition of 0.25–2.0 equiv of pyridine for Ru resulted in satisfactory yields within 4 h (entries 4–8). It is noteworthy that both the catalytic activity and efficiency of the present $[Cp^*Ru(OMe)]_2$/pyridine system exceeds those of either the CuCl/bipyridine or the cationic diruthenium amidinate systems; the conventional Cu-catalyzed cyclization of dichloroacetamide is very slow at that temperature (2 h, 20% yield). The reaction catalyzed by the ruthenium complex **3**, which is the most effective catalyst for this type of cyclization, was faster than that with the CuCl/bypridine system but slower than that with **4a**, but terminated before reaching completion (3 h, 88% yield) (Fig. 2, right).

Table 3 summarizes the results obtained for the reaction of various *N*-allyl-α,α-dichloroacetamides **5a–e** catalyzed by 5 mol% of $[Cp^*Ru(OMe)]_2$ **4a** (i.e., 10 mol% Ru) and 5 mol% of pyridine (Ru/pyridine = 0.5) in dichloromethane (1.5 mL). In all reactions, the product was formed in high yields, except in the case of the N–H congener **5e** (entry 6). High catalytic activity of the present catalyst system was also demonstrated in the cyclization of *N*-benzyl and *N*-phenyl derivatives **5c** and **5d**, which are both known as less reactive substrates than **5a** and **5b**.[4f,12] Although the reaction of **5c** with this catalyst system was not so fast at room temperature (20 h; 76% yield), the reaction at 40 °C for 7 h gave the product **6c** in quantitative yield (entries 3 and 4). In the reaction of **5d**, the cyclic product **6d** was obtained in 90% isolated yield by the use of 30 mol% Ru at room temperature for 17 h (entry 5). In all cases, the trans/cis ratio of the product was controlled as ca. 4:1. The relative stereochemistry of the major isomer of **6d** was determined to be 3,4-*trans* by X-ray diffraction (Fig. 3, left). The 3,4-*trans* stereochemistry of major products **6a–c** was assigned by the similarity seen in the ^{1}H NMR spectra to those reported by Slough[8a] and Gelfi.[8b]

Table 3. Radical cyclization of various *N*-allyldichloroacetamides **5a–d**[a]



Entry	Substrate	Time (h)	Yield (%)	Trans/cis[b]
1	**5a** (Z=Ts)	4	92	87:13
2	**5b** (Z=Allyl)	5	95	80:20
3	**5c** (Z=Bn)	20	76	81:19
4[c]	**5c**	7	>99	82:18
5[d]	**5d** (Z=Ph)	17	90	83:17
6	**5e** (Z=H)	4	<1	—

[a] All reactions were carried out using 0.2 mmol of **5**, 0.01 mmol of **4a** and 0.01 mmol of pyridine in 1.5 mL of CH_2Cl_2 at room temperature.
[b] Determined by ^{1}H NMR analysis.
[c] In dichloroethane at 40 °C.
[d] 0.03 mmol of **4a** (30 mol% Ru) and 0.03 mmol of pyridine were used.

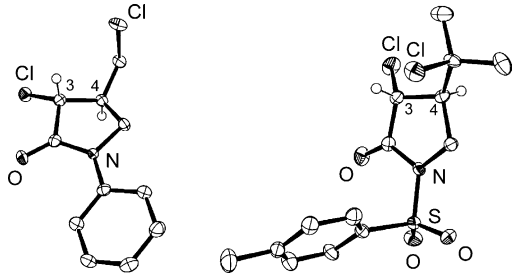
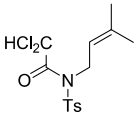
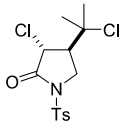
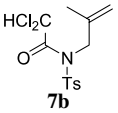
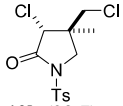
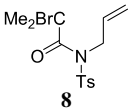
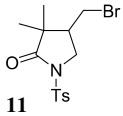
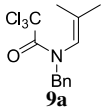
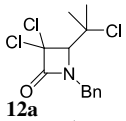
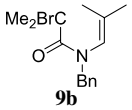
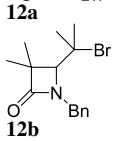


Figure 3. The ORTEP drawings of 3,4-*trans*-**6d** (left) and 3,4-*trans*-**10a** (right). For clarify, only H atoms at the C3 and C4 positions are shown.

The efficiency of $[Cp^*Ru(OMe)]_2$/pyridine system eventually led to three important aspects in the ATRC. First, the reaction of *N*-tosyl-α,α-dichloroacetamides **7a** and **7b** bearing substituted allyl groups such as prenyl and methallyl moieties, which are less reactive substrates than the *N*-allyl homologue **5a**,[8e] proceeded even at ambient temperature to afford the corresponding γ-lactams **10a** and **10b** in good yields (Table 4, entries 1 and 2). The relative stereochemistry of the major product **10a** was determined to be 3,4-*trans* by X-ray diffraction (Fig. 3, right). It is noteworthy that the diastereoselectivity of the reaction of methallyl derivative **7b** reaches to 93:7. The 3,4-*trans* configuration of the major product **10b** was determined by difference NOE experiments; no NOEs were obtained between the methine proton (H^3) at the 3-position and the methyl protons at the 4-position (4-Me) for the major isomer, whereas 6.7% NOE to 4-Me by irradiation of H^3 and 10.7% NOE to H^3 by irradiation of 4-Me for the minor isomer. This catalyst system was also effective for the cyclization of α-monobromoacetamide **8** and the corresponding brominated γ-lactam **11** was obtained in 98% yield (entry 3). Application of this catalyst system to β-lactam synthesis is also possible; 4-*exo* cyclization predominantly proceeded by the reaction of *N*-vinylacetamides **9a** and **9b** to give the corresponding β-lactams **12a** and **12b** in quantitative yields as the sole products (entries 4 and 5).

Table 4. Radical cyclization of various acetamides **9–11**[a]

Entry	Substrate	Time (h)	Product (trans/cis)[b]	Yield (%)
1[c]	 **7a**	4	 **10a** (80:20)	80
2	 **7b**	16	 **10b** (93:7)	70
3[d]	 **8**	4	 **11**	98
4	 **9a**	4	 **12a**	>99
5	 **9b**	4	 **12b**	>99

[a] All reactions were carried out using 0.02 mmol of substrate, 0.03 mmol of **4a** and 0.03 mmol of pyridine in 1.5 mL of CH_2Cl_2 at room temperature.
[b] Determined by ^{1}H NMR analysis.
[c] 0.02 mmol of **4a** (20 mol% Ru) and 0.02 mmol of pyridine were used.
[d] 0.01 mmol of **4a** (10 mol% Ru) and 0.01 mmol of pyridine were used.

The advantage of the coordinatively unsaturated $[Cp^*Ru(OMe)]_2$ complex **4a** is its easy preparation by the literature method[10b–d] and the redox properties suitable for the ATRC of *N*-allyl dichloroacetamides. It is known that there are some relations between the redox properties and the efficiency of the catalyst in the conventional CuCl/bipyridine catalyst system and the coordinatively unsaturated diruthenium amidinate **3** active for ATRC.[7b] The redox potentials for CuCl/bipyridine in THF is $E_{pa}=+0.03$ V, $E_{pc}=-0.13$ V [Cu^I/Cu^{II}], whereas that of **3** is $E_{pa}=-0.002$ V, $E_{pc}=-0.05$ V [Ru^{II}/Ru^{III}]. In contrast, cyclic voltammogram of **4a** (R=Me) in THF shows a quasi-reversible one-electron oxidation wave ($E_{pa}=-0.13$ V, $E_{pc}=-0.20$ V versus Ag/Ag^+ at the scan rate of 0.1 V/s) due to the Ru^{II}/Ru^{III} oxidation process. These data showed that the ruthenium methoxide **4a** is a stronger electron donor than the CuCl/bipyridine and the diruthenium amidinate **3**, and reasonably explain facile activation of a C–Cl bond in *N*-allyl dichloroacetamides, less reactive substrates than *N*-allyl trichloroacetamides.

An interesting feature of the **4a**-catalyzed cyclization of *N*-allyl dichloroacetamides is its stereoselectivity. It is known that equilibrium between the *trans*- and *cis*-isomers of the γ-lactams **6** formed from α,α-dichloroacetamides **5** took place easily in the presence of transition metal complexes over 80 °C.[13] For example, the thermodynamically controlled ratio of *trans*-**6a** to *cis*-**6a** reached ca. 4:1; this is in accord with that the ab initio study predicts energy difference between two isomers to be ca. 3 kcal/mol.[14] The diastereomer ratio of **6a** obtained by the present catalyst system is ca. 6.7:1, and no equilibrium between the two isomers is observed in the presence of the catalyst at room temperature. These results suggest that the reaction of α,α-dichloroacetamides **5** by the **4a**/pyridine catalyst is controlled kinetically, which is similar to the cationic diruthenium amidinate **3** reported previously.[7] Interestingly, MO calculations indicate that there is no substantial energy difference (<0.1 kcal/mol)[14] between *trans*-**10b** and *cis*-**10b** in the case of the reaction of **7b**. Furthermore, activation energies of both pathways via the free radical mechanism are almost the same (ca. 5 kcal/mol).[15] Nevertheless, higher trans-selectivity of the cyclization of **7b** (*N*-methallyl:trans/cis=ca. 13.3:1) was observed than that of **5a** (*N*-allyl:trans/cis=ca. 6.7:1). This may be explained by the Ru-coordinated transition states (Fig. 4). Both 3,4-*cis*-**6a** and 3,4-*cis*-**10b** are obtained via the transition states **A** and **B**. In the transition state **B**, the steric repulsion between the methyl substituent of **7b** and bulky η^5-C_5Me_5 ligand on the Ru is expected to be more important than that between H and η^5-C_5Me_5 ligand in **A**. Therefore, the cyclization of **7b** proceeds through the transition state **C**, which affords the 3,4-*trans* isomer.

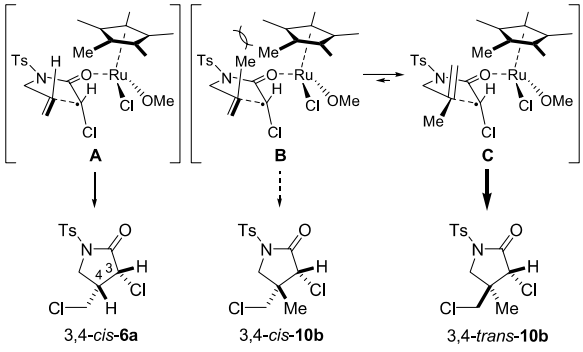
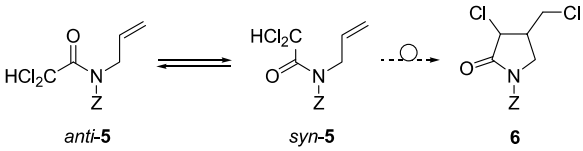


Figure 4. Proposed transition states.

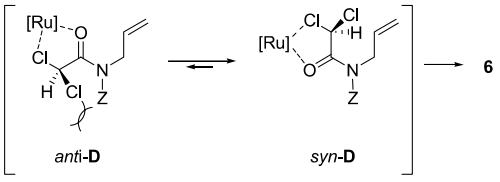
It is well known that radical cyclization of ω-olefinic haloamides at low temperatures has a problem of low yields of the product due to high rotational barrier (16–22 kcal/mol) of the $C_{carbonyl}$–N.[4f,12] As shown in Scheme 3, there are two possible rotamers, *anti*-**5** and *syn*-**5**, and *anti*-**5** is the rotamer unfavorable for the cyclization. From the ^{1}H NMR spectra of amides **5a** (Z=Ts) and **5d** (Z=Ph), single set of signals is observed. However, the spectrum of **5c** (Z=Bn) shows two sets of signals (ca. 1:1) due to the rotational isomers around the $C_{carbonyl}$–N bond. Preliminary DFT caluculations[14] suggest that there is no substantial energy difference between two rotamers of **5a**



5a: *anti* ≈ *syn* (< 0.3 kcal/mol))
5b: *anti* = *syn*
5c: *anti* < *syn* (0.7 kcal/mol)
5d: *anti* > *syn* (4.3 kcal/mol)

Scheme 3. The conformation of **5a–d** in solution.

(<0.3 kcal/mol) and **5c** (0.7 kcal/mol), whereas *anti*-**5d** (4.3 kcal/mol) is the stable conformer for the other one. We have previously reported that the rotation barrier of the *N*-tosylated acetamides was much lower than that of the *N*-benzyl derivatives; *syn–anti* interconversion of the tosyl-protected amides was first in the NMR time scale, leading to the appearance of a single set of sharp signals.[4f,12d] Two apparent reasons of higher reactivity of **5a** than that of **5c** and **5d** are the introduction of the electron-withdrawing substituent on the N atom, which lowers the LUMO of the α-C–Cl bond described above, and facile formation of the rotamer favorable for the cyclization by the amide rotation. While in the case of **5c** and **5d**, high population of the undesired rotamer makes the reaction slower, but the reactivity of the catalyst is high enough to provide the product under milder conditions (<40 °C) than the cyclization catalyzed by the conventional CuCl/bipyridine catalyst. Such high reactivity may be explained by the oxophilic nature of the coordinatively unsaturated ruthenium methoxide, which could provide its interaction with the oxygen atom of amide **5**. As shown in Scheme 4, the coordination makes *syn*-**D** a more favorable conformation than *anti*-**D** because of the steric repulsion between the Cl atom at the α-position and the substituent (Z) on the N atom.

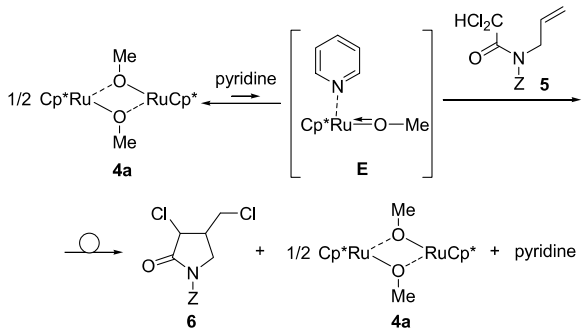


Scheme 4. The conformation of Cp*Ru(OMe)/**5** in the cyclization.

One of the most interesting questions in this cyclization is what is a net catalyst species in solution. As noted above, the ruthenium alkoxides **4** exist as a dimer in crystal structures,[10c,d] whereas they are possibly dissociated to the corresponding monomer in contact with appropriate ligand. In fact, the several coordinatively unsaturated Cp*Ru(OR)L were isolated and characterized by Caulton and coworkers.[10g] Since the addition of auxiliary ligands is important for efficient catalytic reactions, a probable answer is the reaction proceeding through a monomeric active species. Although clear evidence for the complexation between $[Cp^*Ru(OMe)]_2$ **4a** and pyridine was not visible on the ^1H NMR spectrum of a mixture of **4a** and pyridine, in which only dimeric **4a** and free pyridine were observed, we consider at present stage that the coordination can take place reversibly, and a small amount of active catalyst stabilized by pyridine promote the cyclization. In other words, the success of **4a**/pyridine system for the ATRC is provided by the stabilization of the coordinatively unsaturated, unstable monomeric Cp*Ru(OMe) species with pyridine (Scheme 5, **E**). The ATRC of **5** proceeds via the complex **E** to afford the product **6**. Then the stable dimer **4a** and free pyridine are regenerated, as shown in Scheme 5.

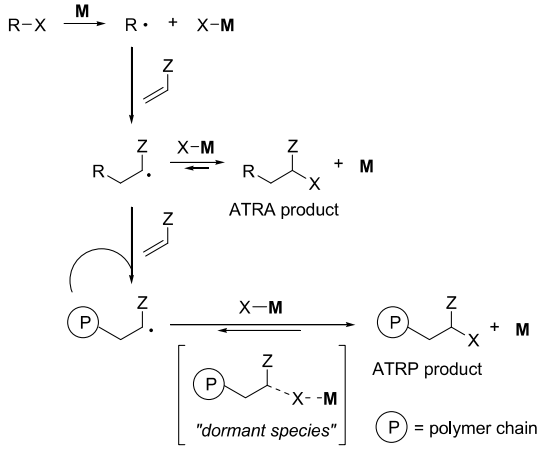
2.2. Atom-transfer radical polymerization

In the above sections, we have demonstrated high catalytic reactivity of the coordinatively unsaturated $[Cp^*Ru(OMe)]_2$



Scheme 5. Proposed reaction mechanisms for ATRC catalyzed by **4a**/pyridine system.

4a having appropriate redox potentials for ATRC in the presence of pyridine. The success of these studies prompted us to extend catalysis of the coordinatively unsaturated ruthenium methoxide to ATRP. As described in our previous paper,[7b] coordinatively unsaturated species facilitates the initial step of ATRC, cleavage of a C–X bond of the substrate, which is the most important point for the catalytic cycle as shown in Scheme 1. In contrast, the catalyst for ATRP has to play important roles not only for the activation of the organic halide initiators to start the polymerization but also the reactivation of a C–X bond at the terminal of the intermediate polymer (the dormant species) as shown in Scheme 6. The coordinatively unsaturated species should be advantageous to take part in the facile activation of the organic halide initiators and the dormant species. In contrast, a possible drawback deduced from our results of ATRC is instability of the coordinatively unsaturated species, which makes the reactivation of dormant species ineffective in the time running. The deactivation of the catalyst should affect the polymerization behavior. Sawamoto and coworker reported a coordinatively unsaturated ruthenium complex, $Ru(Cp^*)Cl(PCy_3)$, catalyzes rapid but 'ill-controlled' polymerization of methyl methacrylate (MMA) to give poly(MMA) with quite broad molecular weight distributions ($M_w/M_n=2.8$–6.2).[16] In sharp contrast, we found that the coordinatively unsaturated ruthenium amidinate **3** can effectively activate a C–X bond of organic halides resulting in the formation of poly(MMA) having a halogen atom end group with narrow molecular weight distributions ($M_w/M_n \leq 1.3$), but the polymerization is terminated before complete conversion of monomers.[7b]



Scheme 6. Proposed mechanisms for ATRP.

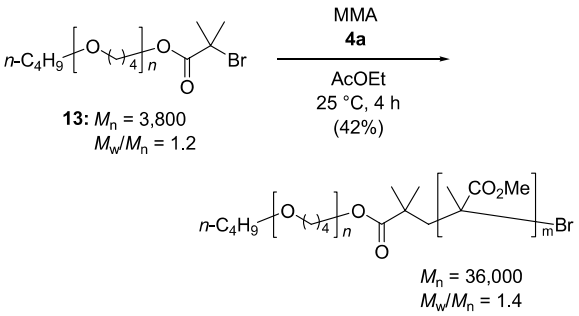
Table 5. Radical polymerization of MMA with **4a**[a]

Entry	Initiator	Additive[b]	Yield (%)[c]	M_n[d]	M_w/M_n[d]
1	CCl_4	—	16	3900	1.3
2	CCl_4	Pyridine	20	3100	1.2
3	Cl_3CCO_2Me	—	21	5500	1.4
4	Cl_3CCO_2Me	Pyridine	20	4000	1.2
5	Cl_2HCCO_2Et	—	17	9600	1.6
6	Cl_2HCCO_2Et	Pyridine	18	7000	1.3

[a] All reactions were carried out using 9.5 μmol of **4a**, 9.5 mmol of MMA, and 38 μmol of initiator in 2 mL of ethyl acetate at 60 °C for 12 h.
[b] 0.5 equiv for Ru was used.
[c] Determined by ^{1}H NMR analysis.
[d] Determined by GPC analysis of the crude product.

A mixture of $[Cp^*Ru(OMe)]_2$ **4a** (9.5 μmol), MMA (1 mL, 9.5 mmol), and initiator (38 μmol) was stirred at 60 °C for 12 h (Table 5). The reaction using carbon tetrachloride as an initiator produced poly(MMA) with $M_n=3900$; $M_w/M_n=1.3$ in 16% yield as shown in entry 1. The molecular weight distribution of formed polymer was slightly improved ($M_w/M_n=1.2$) by the addition of pyridine (0.5 equiv for Ru), but the averaged molecular weight (M_n) decreased (entries 1 vs 2). The polymerization was also achieved by the use of α,α,α-trichloro- and α,α-dichloroacetates as initiators (entries 3–6). In all cases, the present polymerization was terminated within 3 h, showing that **4a** is reactive; but has a short lifetime.[17]

We also examined the activation of a carbon–halogen bond of macroinitiators, which is known to be less reactive than that of commonly used organic initiators. Matyjaszewski reported the polymerization of MMA with CuBr/dNbipy [dNbipy=4,4′-di(5-nonyl)-2,2′-bipyridine] using poly(THF)-derived bromopropionate as the initiator, in which a temperature over 90 °C (24 h, >97% conversion) was required for the reaction.[18a] The ruthenium methoxide **4a** catalyzed the polymerization of MMA using the macroinitiator **13**[18,19] derived from polybutylene oxides, [poly(THF)], bearing a 2-bromoisobutyl group at the polymer terminal ($M_n=3800$; $M_w/M_n=1.2$)[7b] at 25 °C for 4 h to form the polymer of $M_n=35{,}000$ and $M_w/M_n=1.4$; the ^{1}H NMR spectrum of the obtained copolymer revealed that the product contains both poly(THF) and poly(MMA) segments (Scheme 7).[20] In the conversion of this particular polymerization, the chain growth was terminated after 47% of MMA was consumed (42% isolated yield). These results clearly showed that **4a** acts as an efficient catalyst for the activation of a C–Br bond of less reactive macromolecule initiator at low temperature, but the catalyst system is not stable enough to achieve the complete conversion of the monomers.



Scheme 7. Polymerization of MMA using macroinitiator **13**.

3. Conclusion

In our examinations for the coordinatively unsaturated ruthenium alkoxide, $[(\eta^5\text{-}C_5Me_5)Ru(OMe)]_2$ **4a**, as the ATRC and ATRP catalyst, we found that **4a** can effectively activate a C–X bond of organic or macromolecular halides at low temperature (room temperature).[21] In the cyclization reaction, the **4a**/pyridine system is useful for the synthesis of both β- and γ-lactams under mild conditions. The catalytic activity of the present system is even higher than the conventional CuCl/bipyridine catalyst and the diruthenium amidinate complex **3**. This clearly shows an advantage of coordinatively unsaturated complexes in catalyst efficiency for the halogen abstraction at the initial stage of the catalytic cycle, which especially contributes to rapid ATRC and controlling the relative stereochemistry of newly formed stereocenters. This catalyst system is also active towards polymerization of methacrylate using poly(THF)-derived macroinitiator, giving poly(THF)–poly(MMA) block copolymer with narrow molecular weight distributions; however, the polymerization is often accompanied by the catalyst deactivation leading to low conversion of the monomer. In other words, the present coordinatively unsaturated polymerization catalyst has a strong point in the efficiency but not in the durability. Consequently, the results presented in this paper demonstrate that the use of coordinatively unsaturated species is a reasonable strategy for the development of good catalysts for ATRC. For their application to ATRP, the polymerization is well-controlled at the initial stage, however, durability has somehow to be added to the catalyst to achieve high conversion of the monomer. These findings provide important aspects in catalyst search for atom-transfer radical reactions.

4. Experimental

4.1. General methods

All reactions were carried out under a nitrogen or argon atmosphere. Solvents were distilled under an inert gas atmosphere from CaH_2 (dichloromethane, acetonitrile and dichloroethane) or sodium/benzophenone (benzene and ether) prior to use. Carbon tetrachloride was purchased from Wako Pure Chemical Ind., Ltd. Methyl trichloroacetate and ethyl dichloroacetate were purchased from Tokyo Chemical Industry Co., Ltd. ^{1}H and ^{13}C NMR spectra were measured on JEOL ECA 400 (400 MHz) and ECA 600 (600 MHz) spectrometers. Chemical shifts for ^{1}H NMR are described in parts per million downfield from tetramethylsilane as an internal standard ($\delta=0$) in $CDCl_3$, unless otherwise noted. Chemical shifts for ^{13}C NMR are expressed in parts per million in $CDCl_3$ as an internal standard ($\delta=77.1$), unless otherwise noted. IR spectra were measured on a JASCO FT/IR-550 spectrometer. Column chromatography was performed with silica gel (Merck, Art 7734). Elemental analysis was performed by the Elemental Analysis Center, Faculty of Science, Kyushu University. HRMS analysis was performed by the Analytical Center in Institute for Materials Chemistry

and Engineering, Kyushu University. Analytical thin-layer chromatography (TLC) was performed on glass plates and aluminum sheets precoated with silica gel (Merck, Kieselgel 60 F_{254}, layer thickness 0.25 and 0.2 mm, respectively). Visualization was accomplished by UV light (254 nm), anisaldehyde, and phosphomolybdic acid. GPC analyses of the polymers were performed with a JASCO DG-1580-83 degasser, PU-980 HPLC pump, UV-970 UV/vis detector, RI-930 RI detector, and CO-2065-plus column oven (at 40 °C) using a Shodex GPC-KF-804L connected with a GPC KF-805L in THF. Calibration was carried out on the basis of retention time of a standard sample of poly(methyl methacrylate) (Shodex Standard M-75) 7 samples (M_w/M_n=1.02–1.09), of which the M_n range is 1.84×10^3–1.99×10^6. [(η^5-C_5Me_5)Ru(OR)]$_2$ complexes **4a–d**[10b–d] were prepared by the literature methods. Acetamide derivatives **5**, **7–9** were prepared according to the literature methods.[4,8] Macroinitiator **13** was prepared by our method.[7b,19a]

4.2. General procedure for the atom-transfer radical cyclization of *N*-allyl-α-halogenated acetamies catalyzed by [(η^5-C_5Me_5)Ru(OMe)]$_2$/bipyridine system

In a typical example, [(η^5-C_5Me_5)Ru(OMe)]$_2$ (**4a**, 5.3 mg, 0.01 mmol, 10 mol% Ru) was measured into a flask, then freshly distilled, carefully degassed dichloromethane (1.5 mL) and pyridine (0.8 μL, 0.5 equiv for Ru) were added. This catalyst solution was transferred to the reaction flask in which contains *N*-allyl-*N*-tosyl-2,2-dichloroacetamide (**5a**, 64.4 mg, 0.2 mmol). After the resulting solution was stirred at ambient temperature for 4 h, the reaction mixture was filtered through a pad of Celite and Florisil, and then the filtrate was concentrated under reduced pressure. Purification by silica gel chromatography (1:1 hexane/ether) gave the product (**6a**) in 92% yield (59.3 mg): the cis/trans ratio was determined by ^{1}H NMR analysis.

4.2.1. 3-Chloro-4-chloromethyl-1-(*p*-toluenesulfonyl)-pyrrolidin-2-one (6a).[8a] *trans-Isomer*. ^{1}H NMR (600 MHz, $CDCl_3$): δ=2.46 (s, 3H), 2.82 (m, 1H), 3.68–3.78 (m, 3H), 4.11 (dd, J=10.2, 8.1 Hz, 1H), 4.34 (d, J=9.3 Hz, 1H), 7.34 (d, J=8.3 Hz, 2H), 7.94 (d, J=8.3 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=21.8, 42.3, 44.2, 47.0, 56.1, 128.3, 130.0, 134.3, 146.1, 166.7.

cis-Isomer. ^{1}H NMR (600 MHz, $CDCl_3$): δ=2.46 (s, 3H), 2.95 (ddddd, J=8.3, 7.6, 7.3, 6.8, 6.1 Hz, 1H), 3.53 (dd, J=11.5, 7.6 Hz, 1H), 3.66 (dd, J=10.3, 8.3 Hz, 1H), 3.71 (dd, J=11.5, 6.8 Hz, 1H), 4.13 (dd, J=10.3, 7.3 Hz, 1H), 4.44 (d, J=6.1 Hz, 1H), 7.37 (d, J=8.3 Hz, 2H), 7.92 (d, J=8.3 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=21.8, 40.4, 41.0, 47.9, 57.6, 128.2, 130.0, 134.0, 146.0, 166.8.

4.2.2. 3-Chloro-4-chloromethyl-1-allyl-pyrrolidin-2-one (6b). IR (neat): ν=1705 cm^{-1}; HRMS. Calcd for $C_8H_{11}Cl_2NO$: [M]=207.0218. Found: [M]=207.0211; *trans-Isomer*. ^{1}H NMR (600 MHz, $CDCl_3$): δ=2.87 (ttd, J=8.2, 6.6, 4.4 Hz, 1H), 3.28 (dd, J=9.9, 6.6 Hz, 1H), 3.53 (dd, J=9.9, 8.2 Hz, 1H), 3.72 (dd, J=11.5, 6.6 Hz, 1H), 3.76 (dd, J=11.5, 4.4 Hz, 1H), 3.91 (dd, J=14.8, 6.0 Hz, 1H), 3.97 (dd, J=14.8, 6.0 Hz, 1H), 4.37 (d, J=8.2 Hz, 1H), 5.24 (d, J=17.0 Hz, 1H), 5.26 (d, J=10.4 Hz, 1H), 5.72 (ddt, J=17.0, 10.4, 6.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=43.5, 44.8, 45.9, 47.0, 56.6, 119.2, 131.1, 168.3.

cis-Isomer. ^{1}H NMR (600 MHz, $CDCl_3$): δ=2.92 (tdt, J=8.2, 7.1, 6.6 Hz, 1H), 3.28 (dd, J=9.9, 8.2 Hz, 1H), 3.47 (dd, J=9.9, 7.1 Hz, 1H), 3.62 (dd, J=11.0, 8.2 Hz, 1H), 3.80 (dd, J=11.0, 6.6 Hz, 1H), 3.88–4.00 (m, 2H), 4.46 (d, J=6.0 Hz, 1H), 5.20–5.27 (m, 2H), 5.72 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=40.7, 42.0, 45.5, 48.1, 57.6, 118.9, 131.1, 169.0.

4.2.3. 3-Chloro-4-chloromethyl-1-benzyl-pyrrolidin-2-one (6c).[4e,8b] Diastereomer ratio was determined by capillary GLC analysis: TC-17 (30 M), column temperature 240 °C, ditection FID, t_R=20.3 min (trans), 21.2 min (cis). *trans-Isomer*. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.82 (ddddd, J=9.0, 8.1, 7.1, 6.1, 4.9 Hz, 1H), 3.17 (dd, J=10.0, 7.1 Hz, 1H), 3.43 (dd, J=10.0, 8.1 Hz, 1H), 3.66 (dd, J=11.7, 6.1 Hz, 1H), 3.70 (dd, J=11.7, 4.9 Hz, 1H), 4.40 (d, J=9.0 Hz, 1H), 4.43 (d, J=14.6 Hz, 1H), 4.58 (d, J=14.6 Hz, 1H), 7.19–7.41 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=43.5, 44.9, 47.0, 47.5, 56.8, 128.2, 128.3, 129.0, 135.2, 168.6.

cis-Isomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.87 (ddddd, J=8.1, 7.8, 7.1, 6.8, 6.3 Hz, 1H), 3.16 (dd, J=10.0, 8.1 Hz, 1H), 3.36 (dd, J=10.0, 7.1 Hz, 1H), 3.57 (dd, J=11.2, 7.8 Hz, 1H), 3.77 (dd, J=11.2, 6.8 Hz, 1H), 4.43 (d, J=14.6 Hz, 1H), 4.51 (d, J=6.3 Hz, 1H), 4.57 (d, J=14.6 Hz, 1H), 7.19–7.41 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=40.8, 42.0, 47.1, 48.0, 57.7, 128.1, 128.2, 129.0, 135.3, 169.4.

4.2.4. 3-Chloro-4-chloromethyl-1-phenyl-pyrrolidin-2-one (6d). *trans-Isomer*. White solid; mp 113–114 °C; elemental Anal. Calcd (%) for $C_{11}H_{11}Cl_2NO$: C, 54.12; H, 4.54; N, 5.74. Found: C, 53.79; H, 4.57; N, 5.70; ^{1}H NMR (600 MHz, $CDCl_3$): δ=2.99 (ddddd, J=8.8, 8.2, 7.7, 6.6, 3.8 Hz, 1H), 3.82 (dd, J=11.5, 6.6 Hz, 1H), 3.83 (dd, J=9.9, 7.7 Hz, 1H), 3.87 (dd, J=11.5, 3.8 Hz, 1H), 4.00 (dd, J=9.9, 8.2 Hz, 1H), 4.54 (d, J=8.8 Hz, 1H), 7.22 (t, J=7.1 Hz, 1H), 7.41 (dd, J=8.2, 7.1 Hz, 2H), 7.63 (d, J=8.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=43.1, 44.4, 48.6, 57.4, 120.0, 125.6, 129.1, 138.4, 167.4.

cis-Isomer. ^{1}H NMR (600 MHz, $CDCl_3$): δ=3.08 (m, 1H), 3.73 (dd, J=11.5, 8.2 Hz, 1H), 3.80–3.91 (m, 3H), 4.63 (d, J=6.0 Hz, 1H), 7.22 (m, 1H), 7.41 (m, 2H), 7.63 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=40.3, 41.9, 49.8, 58.7, 120.2, 125.7, 129.1, 138.4, 167.4.

4.2.5. 3-Chloro-4-chloroisopropyl-1-(*p*-toluenesulfonyl)-pyrrolidin-2-one (10a). *trans-Isomer*. Elemental Anal. Calcd (%) for $C_{14}H_{17}Cl_2NO_3S$: C, 48.01; H, 4.89; N, 4.00. Found: C, 47.96; H, 4.90; N, 4.00; ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.60 (s, 3H), 1.72 (s, 3H), 2.45 (s, 3H), 2.67 (ddd, J=8.8, 8.2, 7.7 Hz, 1H), 3.85 (dd, J=10.4, 7.7 Hz, 1H), 4.10 (dd, J=10.4, 8.8 Hz, 1H), 4.51 (d, J=8.2 Hz, 1H), 7.36 (d, J=8.8 Hz, 2H), 7.95 (d, J=8.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=21.7, 31.1, 31.4, 46.4, 52.9, 56.0, 69.6, 128.4, 129.9, 134.2, 146.0, 167.2.

cis-Isomer. ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.53 (s, 3H), 1.62 (s, 3H), 2.42 (s, 3H), 2.91 (ddd, J=9.9, 6.6, 5.0 Hz,

1H), 3.92 (dd, J=10.4, 9.9 Hz, 1H), 4.20 (dd, J=10.4, 6.6 Hz, 1H), 4.34 (d, J=5.0 Hz, 1H), 7.30 (d, J=8.7 Hz, 2H), 7.74 (d, J=8.7 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=25.5, 30.6, 31.7, 41.0, 50.1, 57.0, 67.0, 127.1, 128.1, 134.0, 143.3, 166.7.

4.2.6. 3-Chloro-4-chloromethyl-4-methyl-1-(*p*-toluenesulfonyl)-pyrrolidin-2-one (10b). Elemental Anal. Calcd (%) for $C_{13}H_{15}Cl_2NO_3S$: C, 46.44; H, 4.50; N, 4.17. Found: C, 46.69; H, 4.58; N, 4.13. *Major isomer*. ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.13 (s, 3H), 2.46 (s, 3H), 3.52 (d, J=11.5 Hz, 1H), 3.56 (d, J=11.5 Hz, 1H), 3.72 (d, J=10.4 Hz, 1H), 3.88 (d, J=10.4 Hz, 1H), 4.52 (s, 1H), 7.36 (d, J=8.8 Hz, 2H), 7.93 (d, J=8.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=18.5, 21.7, 43.9, 47.7, 52.8, 61.0, 128.1, 129.92, 134.2, 145.91, 166.4.

Minor isomer. ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.31 (s, 3H), 2.46 (s, 3H), 3.37 (d, J=11.5 Hz, 1H), 3.54 (d, J=11.5 Hz, 1H), 3.63 (d, J=10.4 Hz, 1H), 4.00 (d, J=10.4 Hz, 1H), 4.18 (s, 1H), 7.36 (d, J=8.8 Hz, 2H), 7.93 (d, J=8.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=20.7, 21.7, 42.9, 47.3, 53.2, 63.3, 128.1, 129.86, 134.1, 145.89, 166.6.

4.2.7. 3,3-Dimethyl-4-bromomethyl-1-(*p*-toluenesulfonyl)-pyrrolidin-2-one (11).[8c] ^{1}H NMR (600 MHz, $CDCl_3$): δ=0.89 (s, 3H), 1.16 (s, 3H), 2.44 (s, 3H), 2.45 (dddd, J=9.9, 8.8, 7.7, 4.4 Hz, 1H), 3.20 (t, J=9.9 Hz, 1H), 3.43 (dd, J=9.9, 4.4 Hz, 1H), 3.46 (dd, J=10.4, 8.8 Hz, 1H), 4.15 (dd, J=10.4, 7.7 Hz, 1H), 7.34 (d, J=8.2 Hz, 2H), 7.91 (d, J=8.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=17.8, 21.7, 23.4, 29.7, 45.0, 45.4, 48.8, 128.0, 129.7, 134.8, 145.3, 176.8.

4.2.8. 3,3-Dichloro-4-(1-chloroisopropyl)-1-benzyl-azetidin-2-one (12a).[23] ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.74 (s, 3H), 1.81 (s, 3H), 4.23 (s, 1H), 4.33 (d, J=14.9 Hz, 1H), 4.98 (d, J=14.9 Hz, 1H), 7.20–7.43 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=26.2, 29.0, 46.2, 68.5, 77.8, 81.2, 128.3, 128.5, 128.9, 133.9, 161.7.

4.2.9. 3,3-Dimethyl-4-(1-bromoisopropyl)-1-benzyl-azetidin-2-one (12b).[24] ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.27 (s, 3H), 1.39 (s, 3H), 1.80 (s, 3H), 1.81 (s, 3H), 3.60 (s, 1H), 4.23 (d, J=15.4 Hz, 1H), 4.92 (d, J=15.4 Hz, 1H), 7.27–7.36 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=17.9, 24.0, 31.3, 32.6, 45.0, 55.3, 65.1, 72.8, 127.6, 128.5, 128.6, 136.1, 174.7. HRMS. Calcd for $C_{15}H_{20}BrNO$: [M]=309.0728. Found: [M]=309.0725.

4.3. Polymerization of MMA using macroinitiator 13

A mixture of $[Cp^*Ru(OMe)]_2$ **4a** (5 mg, 9 μmol), MMA (1 mL, 9.5 mmol), and macroinitiator **13** [M_n=3800, M_w/M_n=1.2] (68 mg, 18 μmol) was placed in a glass tube. The mixture was degassed three times, and sealed in vacuo. After it was stirred at 25 °C for 4 h, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in THF and was purified by precipitation by adding methanol gave the block copolymer in 42% yield. The GPC analysis showed M_n=36,000, M_w/M_n=1.4.

4.4. Electrochemical measurements

Cyclic voltammetric studies were carried out using a BAS 50B/W electrochemical analyzer in a globe box filled with purified nitrogen. The measurement was performed at room temperature using a ruthenium or copper complex (0.0015 mmol) in THF (5 mL) containing Bu_4NPF_6 (0.1 M) as a supporting electrolyte. A three-electrode cell was used, which was equipped with a platinum disk working electrode, a platinum wire counter electrode, and a silver reference electrode comprised of a silver wire in count with $AgNO_3$ (0.01 M) and Bu_4NPF_6 (0.2 M) in acetonitrile.

4.5. X-ray structure determination and details of refinement

X-ray-quality crystals of **5a**, **6d** and **10a** were grown from a mixture of CH_2Cl_2 and hexane, and mounted in a glass capillary. All measurements were made on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Cu Kα radiation; λ=1.54187 Å for **5a**, and on a Rigaku Saturn CCD area detector with graphite monochromated Mo Kα radiation; λ=0.71070 Å. The crystal-to-detector distance was 127.40 mm for **5a**, 45.09 mm for **6d**, and 45.07 mm for **10a**. The data were collected at 123(1) K to a maximum 2θ value of 136.5° for **5a**, and of 55.0° for **6d** and **10a**. The structures were solved by direct methods,[25] and expanded using Fourier techniques.[26] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement on F^2 was based on 2393 observed reflections and 185 variable parameters for **5a**, on 2502 observed reflections and 148 variable parameters for **6d**, and on 3461 observed reflections and 207 variable parameters for **10a**. Neutral atom scattering factors were taken from Cromer and Waber.[27] All calculations were performed using the CrystalStructure[28,29] crystallographic software package. The numbering schemes employed are shown in Figure 3 (3,4-*trans*-**6a** and 3,4-*trans*-**10a**) and Supporting information (**5a**), which were drawn with ORTEP at 50% probability elipsoids. Crystallographic data (excluding structure factors) for the structure has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-290147 for **5a**, CCDC-290148 for 3,4-*trans*-**6d**, and CCDC-290149 for 3,4-*trans*-**10a**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.01.011. Tables of crystal structure parameters and details of data correction, bond angles and distances, and atomic positional and thermal parameters of **5a**, 3,4-*trans*-**6d** and 3,4-*trans*-**10a**.

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17. An interesting difference between the ruthenium alkoxide **4a** and the diruthenium amidinate **3** as the polymerization catalyst is observed in the end group of the formed polymer. ATRP by **3** afforded the polymer having halogen atom at the end group, which undergoes reactivation by **3** to regenerate the active radical species at the polymer end. In contrast, post-polymerization of MMA from poly(MMA) (M_n=4000; M_w/M_n=1.2), which was obtained by the reaction shown in Table 5, entry 4 proceeded even at 25 °C to afford the poly(MMA) of M_n=40,000, but some of the starting macroinitiator remained. ^{1}H NMR spectra of polymers formed by **4a** showed two broad signals at δ 6.15 and 5.42 ppm, which are assignable to the vinylic protons at the polymer end. These results suggest that the poly(MMA) formed by the present catalyst system contained both the terminal chloride (**F**) and the *exo*-methylene moiety (**G**). This may be attributed to the fact that **3** has a cationic species, which act as a Lewis acid, whereas **4d** is a metal alkoxide, which can behave as a base.

F G

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20. The reason why the polymerization of MMA proceeded at low temperature using poly(THF)-derived initiator **13** is not clear at present. We assumed that the polyether moiety of both the initiator **13** and the dormant chain might effectively stabilize the highly reactive ruthenium alkoxide **4a** with an oxophilic nature.
21. For the metal-catalyzed atom-transfer reactions, the redox mechanisms shown in Scheme 1 are often proposed. Although possible involvement of free radical chain processes cannot be completely excluded in the ATRC and ATRP reactions presented in this paper, the following points strongly support the redox mechanism. First, the same coordinatively unsaturated complex catalyzes the both ATRC and ATRP; this suggests that these reactions proceed through similar mechanisms. Second, free radical polymerization generally provides polymers with wide molecular weight distributions, and termination process is disproportionation (Ref. 22). In contrast, the ATRP presented in this paper achieves the production of polymers having a halogen atom end group with narrow M_w/M_ns; this strongly suggests interaction of the radical species at the polymer end with the metallic species leading to abstraction of the halogen atom from the M–X species by the polymer radical. As a consequence of the first and the second points, ATRC should also be promoted by the redox mechanism not involving the free radical chain process.
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Structure elucidation of dicarboxylate complex of Sn^{IV} porphyrin with a ring current effect model

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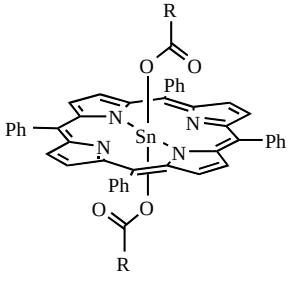
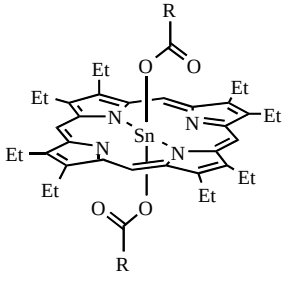
Abstract—A new simple model of porphyrin ring current effect was proposed based on a line current approximation. It can reproduce the porphyrin-induced shifts for several Sn(IV)(tpp) and Sn(IV)(oep) dicarboxylate complexes quite satisfactorily. Perpendicular arrangement of the aromatic rings in the diaromatic-carboxylate complexes of Sn(IV)(tpp) and Sn(IV)(oep) was clarified with this porphyrin ring current effect model. There are two structures, *exo* and *endo*, in solution in dinaphthalene-1- and 2- carboxylate complexes of Sn(IV)(tpp) and Sn(IV)(oep). The *exo* conformer is in dynamic equilibrium with the *endo* form in solution. Thermodynamic data of these conformational equilibria are given.

1. Introduction

Determination of significantly populated conformers in extremely flexible molecules is a matter of long-standing interest. Although the X-ray crystallographic analysis is one of the most promising methods to know the precise structure, it provides only a limited number of structures in the solid state. On the other hand, NMR spectroscopy affords much useful information for not only the structures in solution but also the dynamic equilibrium between them. Freezing the conformational equilibrium, the common method for analysis, is often not experimentally attained in highly flexible molecules. It is well known that NMR chemical shifts reflect molecular structure. Hence, variation in the local environment affects chemical shieldings, and the change in chemical shifts of nuclei caused by adjacent substituents provides valuable information about the relative arrangement of the nuclei with respect to these nearby substituents.[1] From this point of view, we have developed an efficient method for conformational analysis by using chemical shift simulation method.[2] The chemical shift changes caused by secondary induced magnetic fields due to aromatic ring current have proven effective for this purpose.[3]



1 : R = Ph
3 : R = 1-Adamantyl
5 : R = 1-Naphthyl
7 : R = 2-Naphthyl



2 : R = Ph
4 : R = 1-Adamantyl
6 : R = 1-Naphthyl
8 : R = 2-Naphthyl

We have developed a new simple model of porphyrin ring current effect[4] and have succeeded for the conformational analysis of dinaphthalene-1-carboxylate complex of Sn^{IV} (tetraphenylporphyrin).[5] In this paper, we report a full account of the conformational analysis of several dicarboxylate complexes of Sn^{IV}(porphyrin), including the construction of the model of porphyrin ring current effect.

2. Results and discussion

To construct a model of porphyrin ring current effect, the established geometries of the compounds having the known induced shift values caused from porphyrin ring current effect are necessary. We utilized several dicarboxylate

Keywords: Conformation analysis; Density functional calculation; Porphyrin ring current; Structure elucidation.
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complexes of Sn^{IV}(tetraphenylporphyrin), [Sn^{IV}(tpp)][6] and Sn^{IV}(octaethylporphyrin), [Sn^{IV}(oep)]. The structure of dibenzoate complex of Sn^{IV}(tpp) in the crystalline state has been reported,[7] however, that of adamantyl-1-carboxylate complex is not known. Moreover, since it is known that the structure obtained by an X-ray crystallographic analysis has lesser positional accuracy of protons than that of heavier elements, density functional theory (DFT) calculations (at the B3LYP/LANL2DZ level of theory) were carried out to have precise geometries of these compounds.[8] The structures of dicarboxylate complexes of Sn^{IV}(tpp) thus obtained have common characteristic features; (1) the orientation of the carboxylate plane (O–C═O), with respect to the porphyrin ring, (2) small tilting of Sn–O bond from the vertical axis of the porphyrin plane, (3) upward bending of one of the four peripheral phenyl rings from the porphyrin plane to have a close proximity to the carbonyl oxygen of a ligand.

2.1. Structure of dibenzoate complex of Sn^{IV}(porphyrin)

In the crystalline state, the carboxylate plane (O–C═O) of **1** is roughly perpendicular to the porphyrin ring and has eclipsed arrangement with respect to the line connecting the two diagonal *meso* carbon atoms on the porphyrin ring. The eclipsed arrangement is common in several dicarboxylate complexes of Sn^{IV}(tpp) in the crystalline state.[7,9] The benzene ring of **1** is not perpendicular to the porphyrin plane and leans ca. 25° from the normal of the plane. Similar angle of bending of the benzene ring from the porphyrin plane was observed in *m*-hydroxy benzoate complex.[7]

By contrast, the benzene ring of the calculated structure of **1** is perpendicular to the porphyrin plane (Fig. 1). The carboxylate plane, which is almost identical to that of the benzene is roughly eclipsed with respect to the line connecting the two *meso* carbons on the porphyrin ring. The Sn–O bond is not completely perpendicular to the porphyrin plane, as indicated by small deviations from right angle; N–Sn–O angles (92.4, 92.0, 87.6, 88.0°). Since the C–C bond connecting the phenyl and carboxylate groups is not parallel to the Sn–O bond, the two *ortho* aromatic protons of the benzoate are not equidistant from the porphyrin plane. One peripheral phenyl ring on the porphyrin, which is the closest to the carbonyl oxygen of the benzoate, bends upward to a detectable extent. A similar upward bending of the phenyl ring closest to the carbonyl oxygen was found in dicarboxylate complexes of Sn^{IV}(tpp) in their crystalline state.[7,9] The upward bending of the phenyl ring should be a result of an attractive interaction between the electronegative carbonyl oxygen and the *ortho* proton of the phenyl ring.[10] The diagonal phenyl ring on the porphyrin bends downward to have close proximity to the corresponding carbonyl oxygen of the *trans* benzoate. By contrast, two proximal phenyl rings bend neither upward or downward at all. Further supports of the attractive interaction can be found in the dihedral angles between the peripheral phenyl and porphyrin rings. While the two proximal phenyl rings rotate from the perpendicular position by 20°, the upward bent ring has smaller rotation angle (10°) to have a small distance from the carbonyl oxygen to the *ortho* proton of the phenyl ring.

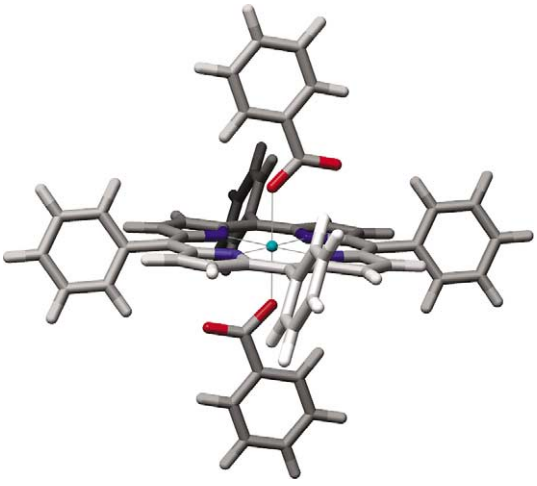

Figure 1. Molecular structure of **1** obtained from DFT calculations.

In the octaethyl porphyrin, orientation of a methyl group of each ethyl moiety can be up (*u*) or down (*d*) from the porphyrin ring. Inspection of the Cambridge crystal data base[11] suggested that an arrangement of the ethyl groups in *uuuudddd* fashion is the most frequently found one. From this reason, we employed this arrangement for the calculation of the structure of the complexes. The structural characteristics found in **1** except the upward bending of a peripheral substituent are also seen in the calculated structure of the dibenzoate complex of Sn^{IV}(oep) **2** (Fig. 2). A similar perpendicular arrangement of the benzene plane with respect to the porphyrin ring was obtained. The carboxylate plane, which is nearly identical to that of the benzene, is again roughly eclipsed with respect to the line connecting the two *meso* carbons on the porphyrin ring.

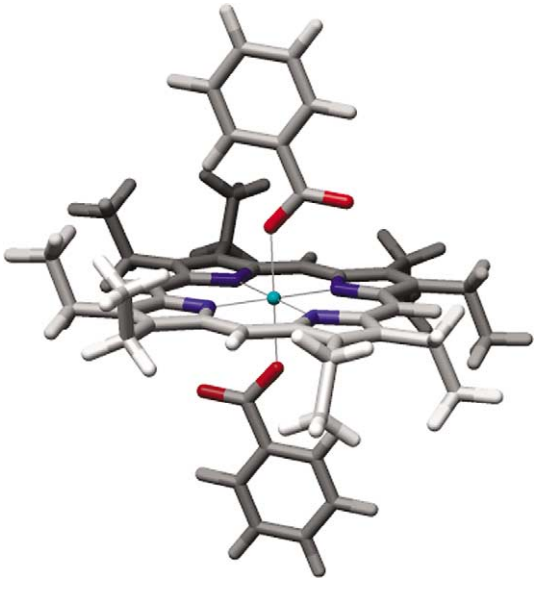

Figure 2. Molecular structure of **2** obtained from DFT calculations.

2.2. Structure of diadamantyl-1-carboxylate complex of Sn^{IV}(porphyrin)

The structural characteristics found in **1** are also found in the calculated structure of diadamantyl-1-carboxylate complex

of Sn^{IV}(tpp) **3** (Fig. 3). Small tilting of Sn–O bond from the vertical axis of the porphyrin plane was observed, as indicated by N–Sn–O angles (92.1, 91.8, 87.9, 88.2°). The carboxylate plane has roughly eclipsed arrangement with respect to the line connecting the two *meso* carbons on the porphyrin ring. The upward bending of the phenyl ring closest to the carboxylate is also observed. The dihedral angles between the peripheral phenyl and porphyrin rings indicate more clearly the attractive interaction. While the two proximal phenyl rings rotate from the perpendicular orientation by 20°, the upward bent ring has almost perpendicular arrangement; the rotation angle is only 2°.

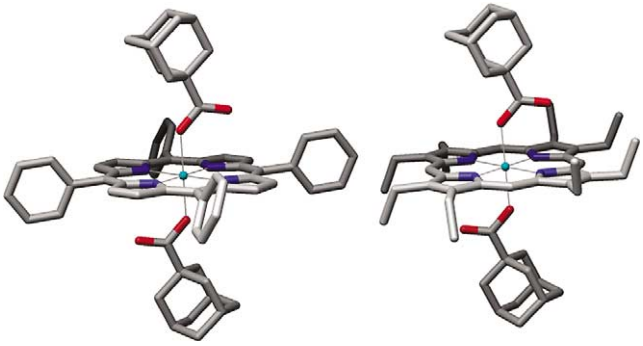

Figure 3. Molecular structures of **3** (left) and **4** (right) obtained from DFT calculations.

The tilting of Sn–O bond from the vertical axis of the porphyrin plane is conspicuous in the calculated structure of diadamantyl-1-carboxylate complex of Sn^{IV}(oep) **4**, as can be seen in N–Sn–O angles (95.3, 93.7, 85.0, 86.0°) (Fig. 3). The eclipsed arrangement of the carboxylate plane with respect to the line connecting the two *meso* carbons on the porphyrin ring was also observed in this structure.

2.3. Construction of a model of porphyrin ring current effect

Many models of porphyrin ring current effect have been reported since the first report of the NMR spectra of porphyrins by Becker and Bradley.[12] Our new model is based on a classical line current approximation as discussed originally by Salem.[13] In this simple model, the secondary magnetic field at a given proton is calculated on the assumption that the line current flows exactly through the C–C and C–N bonds of porphyrin ring. The field (H') due to the current flowing in a polygon is a sum of contributions from the edges. The magnitude of the contribution of a particular edge AB at a point P is

$$H'_{AB} = J(\sin\theta_2 - \sin\theta_1)/cR$$

where J is the line current and c is the velocity of light (Fig. 4).

In order to have induced shifts caused by the porphyrin ring current effect, estimation of the magnitude of the line current has to be given correctly. To construct the model of porphyrin ring current effect, the established geometries of the compounds having the known induced shift values caused from porphyrin ring current effect are necessary.

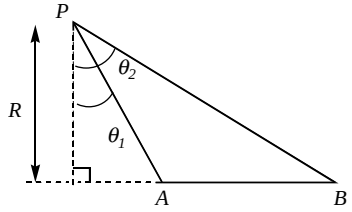

Figure 4. Calculation of magnetic field at P due to current in AB.

The chemical shift differences between the free carboxylic acid and its Sn(IV) porphyrin complex are mainly caused from two factors; complexation shift and ring current effect. It is known that the complexation shifts are negligibly small at points other than close to the site of complexation in saturated ligands.[12g] In **3** and **4**, the protons closest to the site of complexation are five bonds apart from the metal atom. Hence, the effect of the complexation shift on all the protons should be negligibly small. Similar treatment was applied to the case of the aromatic ligands, although an aromatic ligand has significant effect of the complexation shift.[12g]

Our current loop model is similar to that of Abraham's one.[12b] In this model, a current running along the two C–C bonds passing through a *meso* position separates into two (i_1, i_2) at an α-position of a pyrrole ring (Fig. 5). We employed the Abraham's ratio ($i_1/i_2=2.146$) of the two currents. We can estimate the magnitude of the line current of outer and inner arcs of the pyrrole ring ($i_1=0.87i_B$, $i_2=0.41i_B$, where i_B is the line current of benzene ring[2a]) to reproduce the ring current shift values of **1**, **2**, **3**, and **4**. Table 1 gives the observed and calculated ring current shifts in **1**, **2**, **3**, and **4**. The root mean square (rms) error is satisfactorily small (0.069 ppm). Excellent correlation of these data is obtained in a linear regression analysis [14 data (range of the observed shift, 0.81–3.53 ppm) $\Delta\delta_{obs} = a\cdot\Delta\delta_{calcd}$; $a=1.005$, $R^2=0.995$].

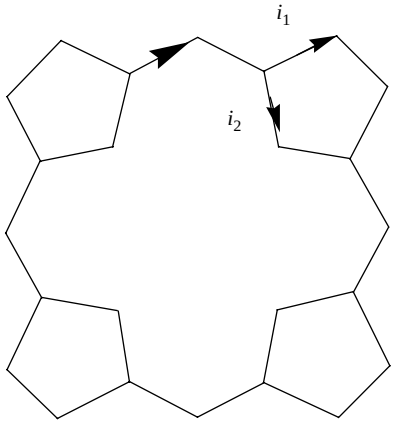

Figure 5. Current loop model for porphyrin ring.

Successful reproduction of the ring current induced shifts of the aromatic ligands in **1** and **2** with the same line current to the one, which reproduced the ring current shifts of the saturated ligands quite satisfactorily suggested clearly that our assumption of the negligible contribution of the complexation shift on the aromatic ligand is valid in these

Table 1. Observed and calculated ring-current shifts in **1**, **2**, **3**, and **4** (ppm)

Nucleus	Shifts	
	Obsd	Calcd
H_o(**1**)	3.19[a]	3.12_7
H_m(**1**)	1.15[a]	1.15_2
H_p(**1**)	0.95[a]	0.89_6
H_o(**2**)	3.53	3.42_6
H_m(**2**)	1.29	1.27_4
H_p(**2**)	1.07	0.98_4
H_2(**3**)	2.96[a]	2.90_6
H_3(**3**)	1.10[a]	1.15_6
H_{4eq}(**3**)	1.17[a]	1.22_2
H_{4ax}(**3**)	0.81[a]	0.88_6
H_2(**4**)	3.22	3.24_1
H_3(**4**)	1.22	1.28_6
H_{4eq}(**4**)	1.26	1.38_3
H_{4ax}(**4**)	0.92	0.99_8

[a] From Ref. 6.

complexes. The contour maps of the induced shift values caused from the porphyrin ring current effect are given in Figure 6 together with those of tetraphenylporphyrin. The latter is a simple sum of the shift values caused from the porphyrin ring current effect and those from the four peripheral benzene rings.

2.4. Structures of dinaphthoic-1-carboxylate complex of Sn^{IV}(tpp) 5

In order to know the structure of **5** in the crystalline state, an X-ray crystallographic analysis of **5** was carried out.[14] As can be clearly seen in Figure 7, the naphthalene ring of **5** is perpendicular to the porphyrin ring. The carboxylate plane of **5** is also perpendicular to the porphyrin ring and has roughly eclipsed arrangement with respect to the line connecting the two *meso* carbons. However, the naphthalene plane has roughly eclipsed with respect to the line connecting the two diagonal porphyrin nitrogen atoms. The small tilting of Sn–O bond from the vertical axis of the porphyrin plane was also found in this structure (N–Sn–O angles: 95.9, 92.2, 84.1, 87.8°). Also seen in this structure is the upward bending (11.2°) of one of the peripheral phenyl rings from the porphyrin plane, which is closest to the carbonyl oxygen of the ligand.

The DFT structure is slightly different from that in the crystalline state. Although, the orientations of the carboxylate planes of the two structures are quite similar with each other, those of the naphthalenes with respect to the carboxylate plane are different. The DFT structure has a smaller dihedral angle of the two planes (15.6°) than that in the crystalline state (35.7°). The common characteristic features of the Sn^{IV}(tpp) complexes are also seen in the calculated structure. The small tilting of Sn–O bond from the vertical axis of the porphyrin plane (N–Sn–O angles: 93.2, 92.2, 87.1, 87.6°) and the upward bending of one of the peripheral phenyl rings (4.4°) were found.

Since the aromatic ring of naphthalene-1-carboxylic acid is not symmetrical with respect to the arene carbonyl C–C pinched bond, two orientation of the naphthalene ring is possible. One is the orientation found in the crystal and the other is that obtained by 180° rotation around the C–C bond. The DFT calculation showed that the latter is also the energy minimum on the potential energy surface. The naphthalene ring of the latter conformer is perpendicular to the porphyrin ring. The carboxylate plane is also perpendicular and has roughly eclipsed arrangement with respect to the line connecting the two *meso* carbons. In this conformer, the dihedral angle between the naphthalene and the carboxylate planes (2.3°) is smaller than the former conformer. The small tilting of Sn–O bond from the vertical axis of the porphyrin plane was also found in this structure (N–Sn–O angles: 93.2, 93.0, 87.2, 87.6°). Small but prominent upward bending of one of the peripheral phenyl rings from the porphyrin ring (3.1°) was also found in this conformer.

2.5. Conformational analysis of 5 in solution

Two conformations, 'vertical' and 'horizontal', were proposed for the structure of aromatic carboxylate complex of Sn^{IV}(tpp).[6] In order to elucidate the structure of **5** in solution, NMR measurements of **5** at various temperatures were carried out. At room temperature two prominent signals were found at 5.29 and 4.47 ppm. These are assigned to H_2 and H_8, respectively, and are both significantly upfield shifted from the corresponding proton of the naphthalene carboxylic acid. When lower the temperature the former shifted to the lower and the latter to the higher magnetic fields (Fig. 8). This suggested that at least two conformers are in equilibrium in solution, however, it is difficult to identify how many conformers are contributing to the equilibrium because neither signal separation nor extensive signal broadening was detected down to −60 °C.

The DFT calculation disclosed that two conformers (*exo*, *endo*) are possible for **5** (Fig. 9). In order to determine the relative ratio of the two conformers in solution, the chemical shift changes caused by the porphyrin ring current was found to be very informative. Before determining the relative ratio of the two, the theoretical induced shifts of the naphthalene protons of the two DFT structures were estimated by the calculation of the porphyrin ring current effect, and they are shown in Table 2.

Excellent agreement of the calculated induced shifts with those of the observed was given when both of the conformers are present in the solution in a 64:36 (*exo*:*endo*) ratio at 25 °C. Table 3 gives the observed and calculated ring current shifts in **5**. The root mean square (rms) error is again satisfactorily small (0.076 ppm). Excellent correlation of these data is obtained in a linear regression analysis [7 data (range of the observed shift, 0.61–4.60 ppm) $\Delta\delta_{obs} = a \cdot \Delta\delta_{calcd}$; $a = 1.0124$, $R^2 = 0.997$].

The relative ratio of the two conformers is temperature dependent and the temperature variation of the relative ratio is shown in Table 4.

From this analysis, it is found that the two conformers are in dynamic equilibrium in solution; the free energy difference between the two conformers at a given temperature was obtained. Thermodynamic parameters of the equilibrium of the two conformers ($\Delta H_{endo-exo} = 1.08$ kcal/mol, $\Delta S_{endo-exo} = 2.5$ cal/mol deg) were obtained by van't Hoff plot analysis.

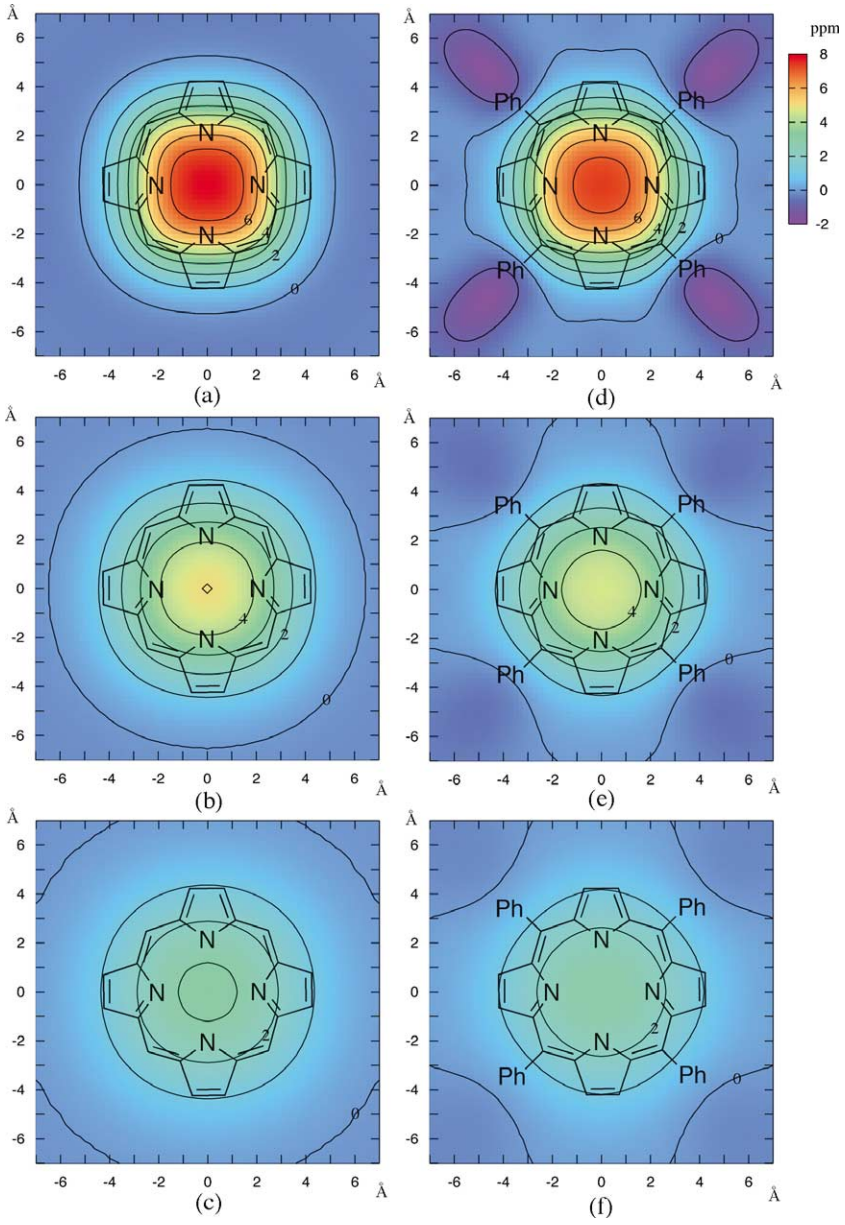

Figure 6. Contour maps of the induced shift values caused from porphyrin ring current (a) vertical section at 3.0 Å, (b) 4.0 Å, and (c) 5.0 Å. Contour maps of tetraphenylporphyrin, in which the peripheral phenyl rings have perpendicular arrangement (d) 3.0 Å, (e) 4.0 Å, and (f) 5.0 Å (ppm).

2.6. Structure and conformational analysis of dinaphthoic-1-carboxylate complexes of Sn^{IV}(oep) 6

DFT calculations of dinaphthoic-1-carboxylate complex of Sn^{IV}(oep) **6** were carried out for both the *exo* and *endo* conformations (Fig. 10). The general structural characteristics found in **5** are also seen in the calculated structures. The perpendicular arrangement of the naphthalene plane with respect to the porphyrin ring was obtained. The carboxylate plane is again perpendicular to the porphyrin and roughly eclipsed with respect to the line connecting the two *meso* carbons on the porphyrin ring. While the naphthalene plane in the *endo* structure is almost identical to the carboxylate plane that of the *exo* structure has rotated from the carboxylate plane by 14.8°. The small tilting of Sn–O bond from the vertical axis of the porphyrin plane was also found in these structures (N–Sn–O angles, *exo*: 93.1, 92.9, 86.9, 87.1°, *endo*: 92.9, 92.9, 87.1, 87.1°).

As in the case of **5**, the ^{1}H NMR spectra of **6** are temperature dependent. At room temperature two prominent signals were found at 4.42 and 4.74 ppm. These are assigned to H_2 and H_8, respectively, and are both significantly up-field shifted from the corresponding proton of the naphthalene carboxylic acid.

Excellent agreement of the calculated induced shifts with those of the observed was given when both of the conformers are present in the solution in a 48:52 (*exo*:*endo*) ratio at room temperature. The theoretical induced shifts of *exo* and *endo* conformers are given in Table 5. Table 6 gives the observed and calculated ring current shifts in **6**. The root mean square (rms) error is again satisfactorily small (0.096 ppm). Excellent correlation of these data is obtained in a linear regression analysis [7 data (range of the observed shift, 0.61–4.33 ppm) $\Delta\delta_{obs} = a \cdot \Delta\delta_{calcd}$; $a = 1.033$, $R^2 = 0.998$].

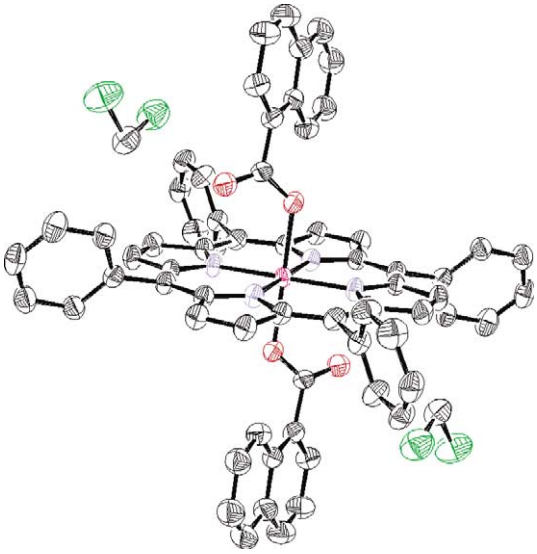

Figure 7. ORTEP drawing of **5**.

When lower the temperature H_2 peak shifted slightly and H_8 prominently to the higher magnetic field. The chemical shift differences from room temperature to −60 °C are 0.03, −0.04, −0.07, −0.06, −0.08, −0.06, and 0.23 for H_2, H_3, H_4, H_5, H_6, H_7, and H_8, respectively, (+ denotes up-field shift). The temperature dependent changes of the relative ratio of the two conformers were obtained by the chemical shift changes of these proton signals at several temperatures. Thermodynamic parameters of the equilibrium of the two conformers ($\Delta H_{endo-exo}=0.21$ kcal/mol, $\Delta S_{endo-exo}=0.9$ cal/mol deg) were obtained by van't Hoff plot analysis.

2.7. Structures and conformational analysis of dinaphthoic-2-carboxylate complexes of Sn^{IV}(tpp) 7

DFT calculation of dinaphthoic-2-carboxylate complex of Sn^{IV}(tpp) **7** was carried out for the *exo* and *endo* conformers (Fig. 11). The structural characteristics in dicarboxylate complex of Sn^{IV}(tpp) are found both in *exo* and *endo* structures. The perpendicular arrangement of the naphthoic-2-carboxylate plane to the porphyrin ring was observed with the eclipsed arrangement with respect to the line connecting the two *meso* carbons of the porphyrin ring. Upward bending of one of the peripheral benzene rings (5.5°, both of the structures) was again observed in the calculated structures. The small tilting of Sn–O bond from the vertical axis of the porphyrin plane was also found in these structures (N–Sn–O angles, *exo*: 92.4, 91.7, 87.6, 88.3°, *endo*: 92.3, 91.9, 87.7, 88.1°).

The theoretical induced shifts of the naphthalene protons of the two DFT structures were estimated by the calculation of the porphyrin ring current effect and are shown in Table 7.

Excellent agreement of the calculated induced shifts with those of the observed was given when both of the conformers are present in the solution in a 61:39 (*exo*:*endo*) ratio at 25 °C. Table 8 gives the observed and calculated ring current shifts in **7**. The root mean square (rms) error is again satisfactorily small (0.061 ppm). Excellent correlation of these data is obtained in a linear regression analysis [7 data (range of the observed shift, 0.44–3.46 ppm) $\Delta\delta_{obs}=a\cdot\Delta\delta_{calcd}$; $a=1.009$, $R^2=0.998$].

Contrary to the case of **5**, the ^{1}H NMR spectra of **7** in $CDCl_3$ did not show sizable temperature dependence down to −60 °C. The maximum shift difference (−0.05 ppm) from room temperature to −60 °C is found on H_4, H_5, and H_7; hence, the temperature variation of the ratio of the two conformers is negligibly small in this case.

2.8. Structure and conformational analysis of dinaphthoic-2-carboxylate complexes of Sn^{IV}(oep) 8

DFT calculations of dinaphthoic-2-carboxylate complex of Sn^{IV}(oep) **8** were carried out for both the *exo* and *endo* conformations (Fig. 12). In these structures, naphthalene-2-carboxylates are planar and have perpendicular arrangement to the porphyrin ring. The naphthoic-2-carboxylate planes in these conformers are eclipsed with respect to the line connecting the two *meso* carbons on the porphyrin ring.

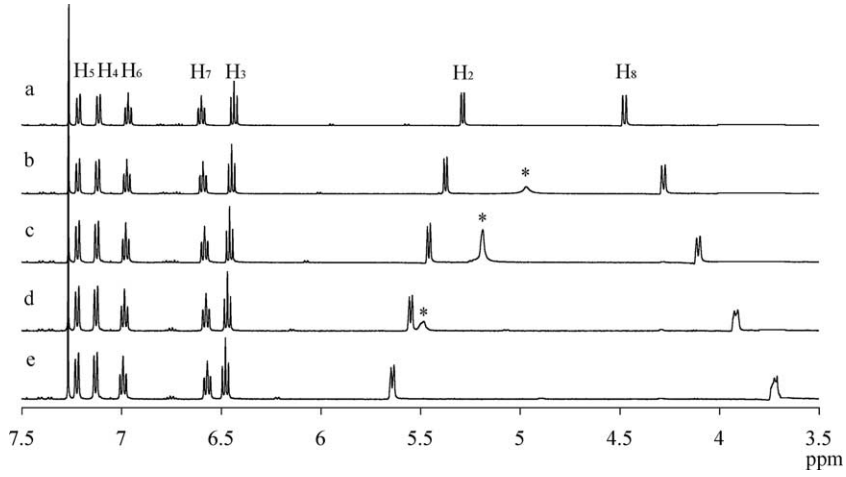

Figure 8. A part of proton NMR spectra of **5** in $CDCl_3$ at various temperatures, (a) 25 °C, (b) 0 °C, (c) −20 °C, (d) −40 °C and (e) −60 °C. * Symbols indicate signals of water.

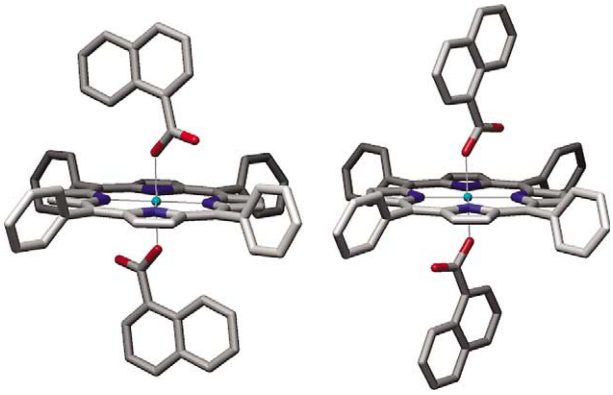

Figure 9. Molecular structures (*exo*(left), *endo*(right)) of **5** obtained from DFT calculations.

Table 2. Calculated ring-current shifts of *exo* and *endo* conformers of **5**

Nucleus	Shifts	
	exo	*endo*
H_2	2.084	4.774
H_3	0.983	1.359
H_4	0.852	0.903
H_5	0.739	0.675
H_6	0.588	0.519
H_7	1.069	0.638
H_8	6.105	1.926

Table 3. Observed (25 °C) and calculated ring-current shifts of **5** (ppm)

Nucleus	Shifts	
	Obsd	Calcd
H_2	3.10	3.05_7
H_3	1.12	1.11_9
H_4	0.98	0.87_1
H_5	0.71	0.71_6
H_6	0.61	0.56_3
H_7	1.07	0.91_3
H_8	4.60	4.59_3

Table 4. Relative ratio (%) of two conformers of **1** in $CDCl_3$

Temperature (°C)	*exo*	*endo*
25	63.8	36.2
0	67.5	32.5
−20	71.0	29.0
−40	74.5	25.5
−60	78.5	21.5

The theoretical induced shifts of the naphthalene protons of the two DFT structures were estimated by the calculation of the porphyrin ring current effect and are shown in Table 9.

Excellent agreement of the calculated induced shifts with those of the observed was given when both of the conformers are present in the solution in a 58:42 (*exo*:*endo*) ratio at 25 °C. Table 10 gives the observed and calculated ring current shifts of **8**. The root mean square (rms) error is again satisfactorily small (0.078 ppm). Excellent correlation of these data is obtained in a linear regression analysis

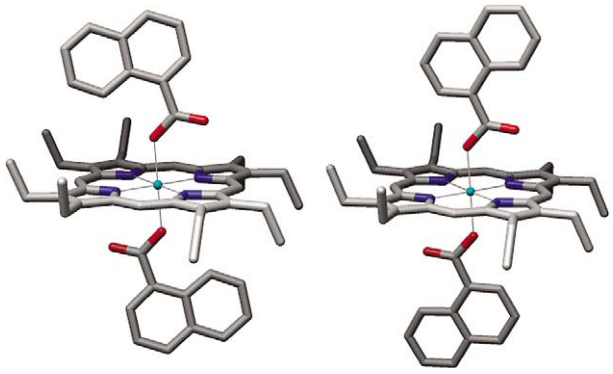

Figure 10. Molecular structures (*exo*(left), *endo*(right)) of **6** obtained from DFT calculations.

Table 5. Calculated ring-current shifts of *exo* and *endo* conformers of **6**

Nucleus	Shifts	
	exo	*endo*
H_1	2.321	5.104
H_3	1.092	1.486
H_4	0.949	0.985
H_5	0.834	0.757
H_6	0.677	0.611
H_7	1.207	0.792
H_8	6.401	2.212

Table 6. Observed (25 °C) and calculated ring-current shifts of **6** (ppm)

Nucleus	Shifts	
	Obsd	Calcd
H_2	3.97	3.77_6
H_3	1.26	1.29_8
H_4	1.02	0.96_7
H_5	0.72	0.79_4
H_6	0.61	0.64_2
H_7	1.04	0.99_0
H_8	4.33	4.21_1

[7 data (range of the observed shift, 0.49–3.76 ppm) $\Delta\delta_{obs} = a \cdot \Delta\delta_{calcd}$; $a = 1.024$, $R^2 = 0.998$].

As in the case of **7**, the ^1H NMR spectra of **8** in $CDCl_3$ does not show sizable temperature dependence down to −60 °C. The maximum shift difference from room temperature to

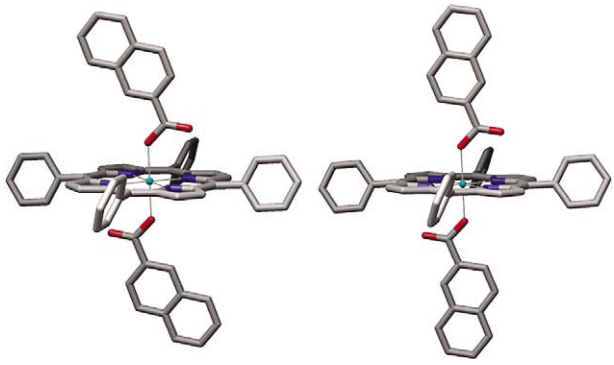

Figure 11. Molecular structures (*exo*(left), *endo*(right)) of **7** obtained from DFT calculations.

Table 7. Calculated ring-current shifts of *exo* and *endo* conformers of **7**

Nucleus	Shifts	
	exo	*endo*
H_1	4.353	1.926
H_3	2.056	4.327
H_4	1.034	1.328
H_5	0.677	0.686
H_6	0.456	0.452
H_7	0.401	0.461
H_8	1.176	0.778

Table 8. Observed (25 °C) and calculated ring-current shifts of **7** (ppm)

Nucleus	Shifts	
	Obsd	Calcd
H_1	3.46	3.39_8
H_3	3.01	2.95_0
H_4	1.11	1.15_0
H_5	0.57	0.68_1
H_6	0.44	0.45_4
H_7	0.46	0.42_5
H_8	0.96	1.01_9

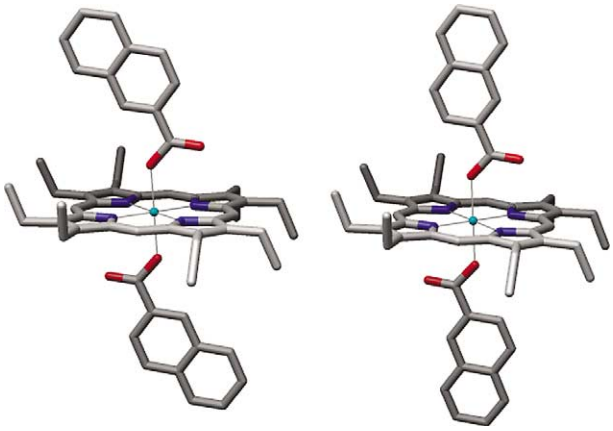

Figure 12. Molecular structures (*exo*(left), *endo*(right)) of **8** obtained from DFT calculations.

−60 °C (−0.07 ppm) is found on H_4; hence, the temperature variation of the ratio of the two conformers is negligibly small in this case.

2.9. Solvent effect

The dynamic equilibrium of the *exo* and *endo* conformers is observed in both the dinaphthoic-1- and 2-carboxylate complexes of Sn^{IV}(porphyrin). In the case of **5**, the relative ratio of the two conformers showed extensive temperature dependence in $CDCl_3$. In order to have information about the effect of the solvent on the dynamic equilibrium, the similar conformational analyses in different solvents were carried out (Table 11).

Table 9. Calculated ring-current shifts of *exo* and *endo* conformers of **8**

Nucleus	Shifts	
	exo	*endo*
H_1	4.656	2.207
H_3	2.194	4.699
H_4	1.113	1.438
H_5	0.710	0.732
H_6	0.498	0.501
H_7	0.527	0.536
H_8	1.249	0.914

Table 10. Observed (25 °C) and calculated ring-current shifts of **8** (ppm)

Nucleus	Shifts	
	Obsd	Calcd
H_1	3.76	3.63_5
H_3	3.35	3.23_8
H_4	1.25	1.24_8
H_5	0.64	0.71_9
H_6	0.50	0.49_9
H_7	0.49	0.53_1
H_8	1.03	1.10_9

Table 11. Relative ratio (%) of two conformers of **5**

Temperature (°C)	CD_2Cl_2		THF-d_8	
	exo	*endo*	*exo*	*endo*
25	58	42	57	43
0	62	38	59	41
−20	66	34	62	38
−40	69	31	65	35
−60	73	27	68	32
−90	80	20	74	26

Thermodynamic parameters of the equilibrium of the two conformers were obtained by van't Hoff plot analysis: in CD_2Cl_2, $\Delta H_{endo-exo}=0.99$ kcal/mol, $\Delta S_{endo-exo}=2.7$ cal/mol deg, in THF-d_8, $\Delta H_{endo-exo}=0.73$ kcal/mol, $\Delta S_{endo-exo}=1.9$ cal/mol deg. These thermodynamic parameters are not significantly different to those in $CDCl_3$ ($\Delta H_{endo-exo}=1.08$ kcal/mol, $\Delta S_{endo-exo}=2.5$ cal/mol deg). The enthalpy difference varies from 1.08 to 0.73 kcal/mol. The entropy differences in these solvents are all positive and do not show extensive variation regardless of the solvent, suggesting that the solvent does not play an important role in the dynamic equilibrium between *exo* and *endo* conformers in solution. The DFT vibration analysis of the two conformers in vapor phase supports this conclusion and gave a small positive entropy difference (6.2 cal/mol deg).

3. Conclusion

A new simple model of porphyrin ring current effect was given based on a classical line current approximation. It can succeed to reproduce the porphyrin-induced shifts caused from the ring current effect for several Sn^{IV}(porphyrin) dicarboxylate complexes. The successful reproduction of the porphyrin-induced shifts by using the same ring current effect for both aromatic and aliphatic ligands clarified that the complexation shift has negligible contribution to the induced shifts of the aromatic ligands. Thus, the porphyrin-induced shifts are caused from the ring current effect of the porphyrin ring. The porphyrin-induced shift values for the ligands in Sn^{IV}(tpp) dicarboxylate complexes are a simple sum of the shift values caused from the porphyrin ring current effect and those from the four perpendicular benzene rings. By contrast, those for the ligands in Sn^{IV}(oep)

dicarboxylate complexes are just from the porphyrin ring current effect, suggesting that ethyl groups on the porphyrin ring give no effect on the ring current effect.

In the DFT structure of dibenzoate complex of Sn^{IV}(porphyrin), the C–C bond connecting the phenyl and carboxylate groups is not perpendicular to the porphyrin, giving two discrete calculated induced shift values for the two *ortho* aromatic protons. Since the observed induced shift value of the *ortho* proton can be reproduced nicely with the simple average of the two calculated values, the rotation around the C–C bond connecting the phenyl and carboxylate groups is fast enough on the NMR time scale. Similar fast rotation was observed in every dicarboxylate complexes of Sn^{IV}(porphyrin). In the case of Sn^{IV}(porphyrin) complexes of asymmetric aromatic carboxylate such as 1-napathoic acid, DFT calculations gave two conformers by the rotation of the C–C bond connecting the naphtyl and carboxylate groups. The relative ratio of the two conformers was estimated by their calculated chemical induced shifts. The ratio is dependent on the temperature. The thermodynamic parameters of the conformational equilibrium were obtained by analyses of variable temperature ^{1}H NMR experiments. Thus, we have found that the ring current induced chemical shift changes of ligands are useful for the structure elucidation and conformational analysis of metalloporphyrin complexes in solution, and that the ring current induced shift values give highly reliable knowledge about the structure.

4. Experimental

4.1. General procedures

The ^{1}H and ^{13}C NMR spectra were recorded with a JEOL-ECA 600 and JEOL-Lambda 500 NMR spectrometer at 600 and 500 MHz (^{1}H NMR) and 150 and 125.65 MHz (^{13}C NMR). All NMR experiments were obtained using the standard pulse programs and sequences. The mass spectra were taken with a Simadzu MALDI-TOFMS AXIMA-CFR plus at the Instrument center for Chemical Analysis, Hiroshima University.

4.1.1. Dihydroxo(5,10,15,20-tetraphenylporphyrinato)-tin(IV). This compound was prepared by using the reported proccedure.[15]

4.1.2. Dihydroxo(2,3,7,8,12,13,17,18-octaethylporphyrinato)-tin(IV). 2,3,7,8,12,13,17,18-Octaethylporphyrin (64.7 mg, 0.12 mmol) was dissolved in pyridine (10 ml) and tin(II) chloride dihydorate (254.4 mg, 1.22 mmol) was added and the mixture heated to reflux for 9 h. Excess water was added to precipitate the product which was the filtered, washed with water. Potassium carbonate (200 mg, 1.45 mmol) and the product were dissolved in a mixture of tetrahydrofuran (40 ml) and water (10 ml) and heated to reflux for 6 h. The organic solvent was removed and the aqueous layer was extracted with dichloromethane. The organic layer was washed with water and then dried over anhydrous sodium sulfate, filtered and then the solvent was removed to give the crude product, which was recrystallized (hexane/dichloromethane 1:1) to give dihydroxo(2,3,7,8,12,13,17,18-octaethylporphyrinato)-tin(IV) (40.2 mg, 0.059 mmol, 48%) as metallic purple crystalline solids that were suitable for X-ray analysis (CCDC 274126). ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.48 (s, 4H), 4.20 (q, J= 7.8 Hz, 8H), 2.03 (t, J=7.8 Hz, t). ^{13}C NMR (125.65 MHz, $CDCl_3$) δ 143.9, 143.3, 97.3, 19.9, 18.5. MALDI-TOF m/z 669.265 [$(M-OH)^+$ requires 669.262].

4.2. General method of NMR experiment

Tin porphyrin (0.003 mmol) was added to a solution of carboxylic acid (0.01 mmol) in $CDCl_3$ (1.0 ml). The mixture was sonicated at room temperature for 1 h. After 24 h, chemical shifts of dicarboxylate complex of Sn^{IV}porphyrin were measured.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.01.020.

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14. The crystal data for $\mathbf{5}\cdot 2CH_2Cl_2$ are as follows; $\mathbf{5}\cdot 2CH_2Cl_2$: $C_{66}H_{42}N_4O_4Sn\cdot 2CH_2Cl_2$, $F_W=1240.62$, triclinic, space group $P-1$ with $a=8.6600(5)$ Å, $b=12.1150(8)$ Å, $c=15.0710(7)$ Å, $\alpha=104.541(4)$, $\beta=104.088(4)$, $\gamma=104.171(2)°$, $V=1403.48(14)$ Å^3, and $Z=1$. Data were collected at 298 K on a Mac Science DIP2030 imaging plate equipped with graphite-monochromated Mo Kα radiation ($\lambda=0.71073$ Å). Unit cell parameters were determined by auto-indexing several images in each data set separately with the program DENZO. For each data set, rotation images were collected in 3° increments with a total rotation of 180° about ϕ. Data were processed by using SCALEPACK. (The programs DENZO and SCALEPACK are available from Mac Science Co., Z. Otwinowski, University of Texas, Southwestern Medical Center.) Of 5813 total unique reflections, 5010 were considered observed at the level of $|Fo|>4.0\sigma|Fo|$. On WinGX (Farrugia, L. J., *J. Appl. Crystallogr.* **1999**, *32*, pp 837–838), the structures were solved by the direct method (SIR-97, Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G. Polidori, G.; Spagna, R., *J. Appl. Crystallogr.* **1999**, *32*, pp 115–119) and refined by full-matrix least squares refinements on F^2 (Sheldrick, G. M. *SHELXL-97*: Program for the Refinement of Crystal Structures, University of Göttingen: Göttingen, Germany, 1997). All non-hydrogen atoms were refined anisotropically, and all hydrogen atoms were placed using AFIX instructions. The structure converged with $R=0.1029$, $wR=0.2311$. Crystallographic results have been deposited with the Cambridge Crystallographic Data Centre, UK as supplementary publication number CCDC No. 256448. Copy of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033 or e-mail: data_request@ccdc.cam.ac.uk.
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The reaction of tetralones with nitriles: a simple approach to the synthesis of new substituted benzo[*h*]quinazolines, benzo[*f*]quinazolines and dibenzo[*a*,*i*]phenanthridines

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Abstract—The one-pot reaction of 1-tetralone with nitriles in the presence of triflic anhydride affords in good yields 2,4-disubstituted 5,6-dihydrobenzo[*h*]quinazolines, which oxidation with DDQ leads to the corresponding benzo[*h*]quinazolines. 2-Tetralone undergoes identical process forming 1,3-disubstituted 5,6-dihydrobenzo[*f*]quinazolines. However, when the reaction of 2-tetralone is carried out with methylthiocyanate as nitrile, 5-methylthiotetrahydrodibenzo[*a*,*i*]phenanthridines are isolated in good yields. Easy transformations of the methylthio group offer possible access to a variety of substituted dibenzo[*a*,*i*]phenanthridines.

1. Introduction

Among the pyrimidine derivatives, one of the prominent compounds are the benzoquinazolines. They constitute the core of naturally ocurring products such as the cytotoxic alkaloid samoquasine A.[1] The benzoquinazoline skeleton is commonly found in substances exhibiting a wide range of biological properties. 1,3-Diaminobenzoquinazolines were evaluted many years ago as antifolate and antimalarial agents.[2] Other benzoquinazoline derivatives are used as substitutes for thymine in nucleic acid complexes,[3] while anilinoquinazolines are potent and selective inhibitors of erbB2 receptor tyrosine kinase.[4] Quinazolinones present inhibitory activity of thymidate synthase.[5–8] Recently, 4-(dimethylamino)quinazolines are described as antagonist for the melanin-concentrating hormone receptor 1[9] and pyrazoloquinazolines are reported as novel Gly/NMDA receptor antagonist.[10]

Phenanthro fused heterocycles are also of interest in many aspects. Natural products such as tylophorine, antofine and cryptoleurine posess the phenanthro fused heterocycle skeleton.[11] Phenanthridine derivatives exhibit interesting pharmacological properties related to the planarity of the system. Consequently, these compounds present a DNA-chain intercalating ability[12] and benzophenanthridines are reported as compounds with topoisomerase I-targeting activity and cytotoxicity.[13] Moreover, this heterocyclic system posesses important photoconducting, opto-electrical switching and photovoltaic properties[14] with many applications in the field of dye-lasers and electroluminiscence.[15]

The construction of the quinazoline moiety involves cyclization of appropriate substituted benzenes whose preparations are not always easy. Other approaches are based on the reaction of 1,3-dicarbonyl compounds with a suitable N–C–N fragment.[16,17] Modern methods employ either catalyst- and solvent free conditions [18] or supercritical carbon dioxide[19] to prepare quinazoline derivatives. The preparation of the phenanthridine ring also requires the selection of suitable precursors that are not easy to synthesize. Some methods make use of appropriately substituted isoquinolines.[20] Other methods employing simple starting compounds are limited by numerous steps and poor yields. The four-step preparation of benzo[*c*]phenanthridine from formaldehyde and 2-methylbenzonitrile has a 6% yield overall.[21] Many methods to prepare quinazolines and phenanthridines are reported in the

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literature. In spite of their importance, only very few of them involve less than a few steps.[22]

Herein, we wish to report that the one-pot reaction of 1- and 2-tetralone with nitriles in the presence of triflic anhydride (Tf_2O) affords substituted dihydrobenzo[*h*]quinazolines (**1**), dihydrobenzo[*f*]quinazolines (**2**) and tetrahydro[*a*,*i*]dibenzophenanthridines (**3**) (Fig. 1) in good yields, which can be easily oxidized to their aromatic counterparts.

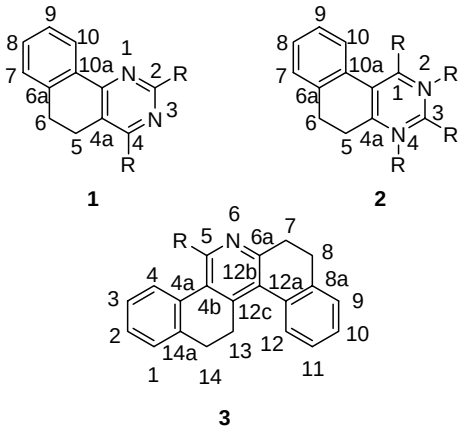
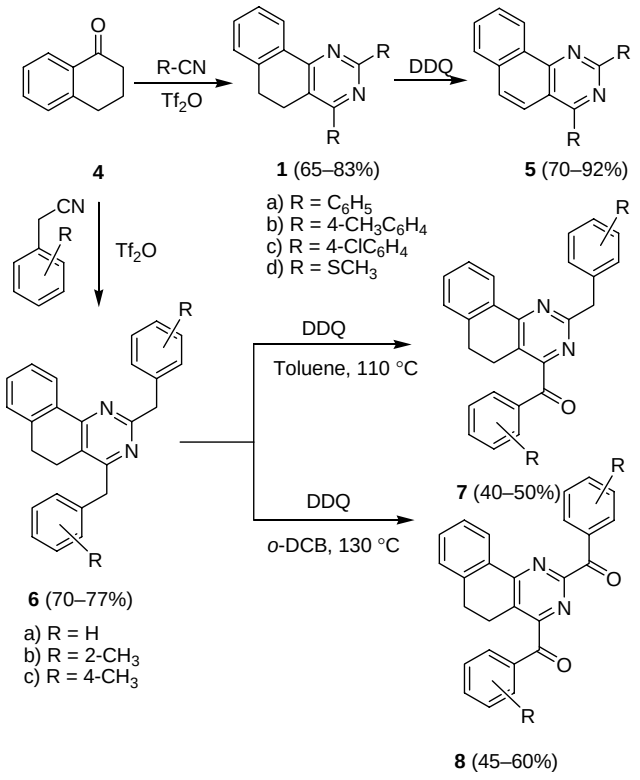


Figure 1. General structure of prepared compounds.

2. Results and discussion

In previous papers we have reported the synthesis of a variety of heterocyclic systems based on the reaction of carbonyl compounds with nitriles in the presence of triflic anhydride.[23–27] The reaction of 1-tetralone (**4**) with various nitriles and Tf_2O under mild conditions (see Section 3) affords 2,4-disubstituted 5,6-dihydrobenzo[*h*]benzoquinazolines (**1**) in good yield (Scheme 1). The well-known mechanism involves the formation of a trifliloxycarbenium ion, which is trapped by the nitrile forming a nitrilium ion. A second molecule of nitrile reacts with the intermediate to give the corresponding quinazoline after elimination of TfOH and loss of a proton.[23] Minor amounts of the vinyl triflate from 1-tetralone (3,4-dihydronaphthalen-1-yl triflate) were detected as side product of the reaction (see Section 3). Its formation is a consequence of a competitive reaction involving the trifliloxycarbenium ion intermediate, which eliminates a proton before it undergoes nucleophilic attack by the nitrile. The oxidation of compounds **1** by means of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in *o*-DCB at 130 °C affords benzoquinazolines **5**. Employing toluene as solvent and hence a lower reaction temperature produces an undesirable mixture of compounds that reduces the yield of this reaction. The use of benzyl nitriles in the reaction with 1-tetralone allows the preparation of 2,4-dibenzyl substituted dihydrobenzoquinazolines **6**. The oxidation of these benzyl derivatives with DDQ can be controlled by the temperature and hence by the choice of the reaction solvent. Thus, when the reaction is carried out in boiling toluene only the methylene group attached at the C4 position reacts to form monocarbonyl compounds **7**. If the reaction is carried out in *o*-DCB at 130 °C both methylene groups are oxidized affording the dicarbonyl compounds **8**.

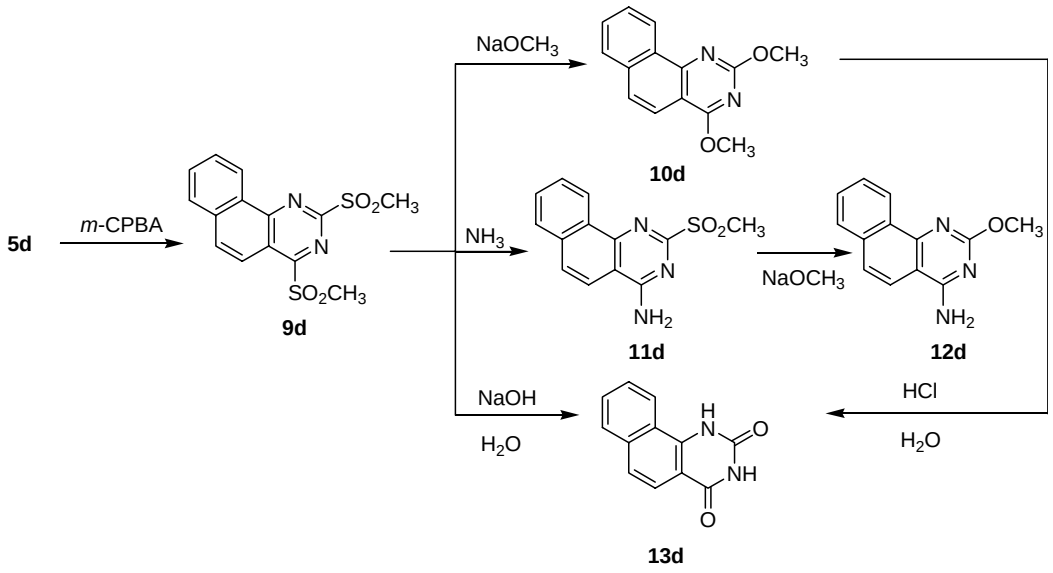
The reaction can be checked using ^{13}C NMR. Compound **6a** exhibits two methylene carbon signals at 41.36 and 45.84 ppm corresponding to both benzyl groups. Using 1D and 2D techniques, the signal at 45.84 ppm was unequivocally assigned to the CH_2 group attached at the C2 position. The reaction of **6a** in boiling toluene affords **7a** whose ^{13}C NMR spectra reveals a new signal at 193.64 ppm representing a new carbonyl group and only one methylene group at 45.79 ppm representing the unreacted benzyl group at the C2 position. In contrast, when the reaction is carried out in *o*-DCB at 130 °C two new carbonyl signals appear at 191.03 and 192.95 ppm, respectively, and both signals of the CH_2 dissapear.



Scheme 1.

The reaction of 1-tetralone (**4**) with methylthiocyanate affords the 2,4-bis(thiomethyl)-5,6-dihydrobenzo[*h*]quinazoline **1d**, which reacts with DDQ to form **5d**.

The easy conversion of the thiomethyl group via nucleophilic displacements into other interesting groups opens a new synthetic route to other quinazoline derivatives otherwise not easy to prepare. Thus, the reaction of **5d** with *m*-CPBA produces the corresponding 2,4-bis(methylsulfonyl) derivative **9d** (Scheme 2). The nucleophilic substitution of the methylsulfonyl group using sodium methoxide affords the dimethoxy derivative **10d**. The reaction of **9d** with ammonia at room temperature permits only the substitution of the methylsulfonyl group at C4 (**11d**) and the subsequent reaction with sodium methoxide leads to the formation of the aminomethoxy derivative **12d**. The hydrolysis of **9d** carried out with boiling aqueous sodium hydroxide forms the uracil **13d**. This compound is also available from the acid hydrolysis of **10d**.



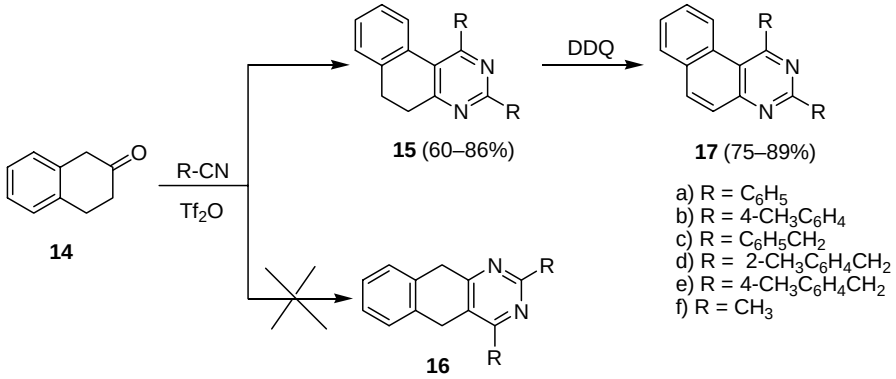
Scheme 2.

The reaction of 2-tetralone (**14**) with nitriles in the presence of triflic anhydride leads to the formation of 1,3-disubstituted 5,6-dihydrobenzo[*f*]quinazolines (**15**), which can be oxidized using DDQ to form the corresponding benzo[*f*]quinazolines (**17**) (Scheme 3).

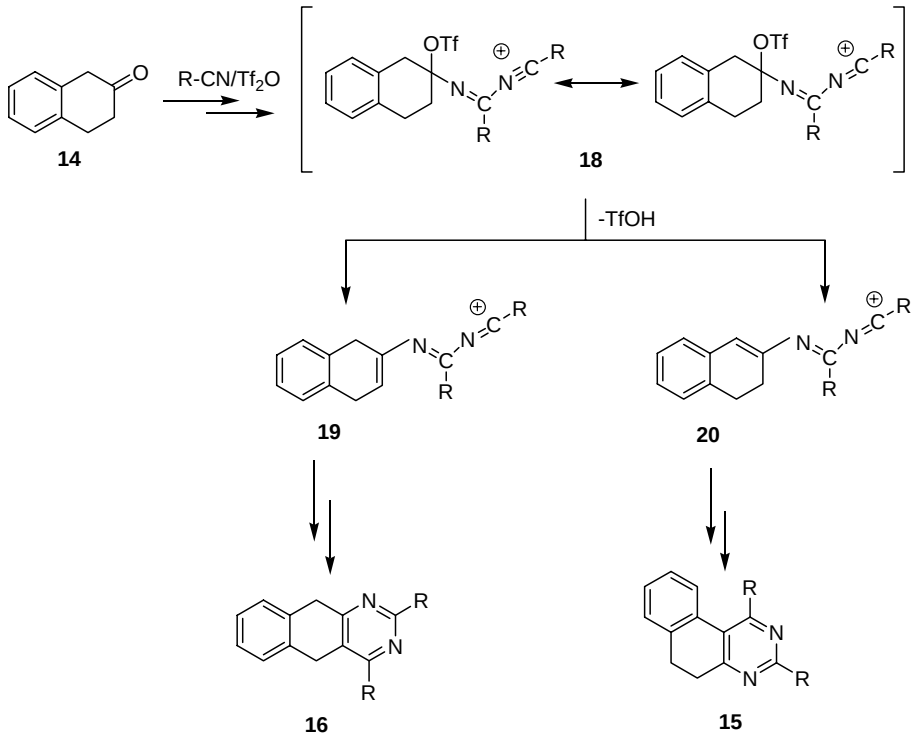
With two different positions alpha to the carbonyl group on 2-tetralone (**14**), one can envisage the formation of two possible products, the isomeric dihydrobenzo[*f*]quinazolines (**15**) and dihydrobenzo[*g*]quinazolines (**16**). In fact, the exclusive formation of quinazolines **15** raises the question of the regioselective advantage of the hydrogen atoms alpha both to the carbonyl and phenyl group. The reaction of linear aliphatic ketones with nitriles was investigated by us[28] demonstrated that the regioselectivity of this process is controlled by the relative stabilities of the cationic intermediates. The general proposed mechanism[24] involves the formation of an imonium intermediate (**18**), which easily eliminates triflic acid (Scheme 4). Trace amounts of 3,4-dihydronaphthalen-2-yl triflate are also formed (see Section 3).

The TfOH elimination leads to the formation of olefins **19** and **20**. Theoretical calculations by means of molecular mechanics (PM3 and AM1) within Hyperchem v6.03 program show that intermediate **20** is more stable than **19**. For example, intermediate **20** is 11.38 kJ mol^{-1} (PM3) more stable than the corresponding isomer **19** when R = C_6H_5. This energy difference explains the formation of quinazolines **15**. To confirm the proposed structure of the dihydrobenzo[*f*]quinazoline we used NOE experiments, which were carried out on compound **15f**. The irradiation of the signal at 2.70 corresponding to the CH_3 on C1 causes a signal enhancement of the aromatic proton H10 (7.60 ppm). In contrast, a hypothetical dihydrobenzo[*g*]quinazoline **16a** should exhibit, under the same irradiation, only a NOE effect in the aliphatic region (Scheme 5).

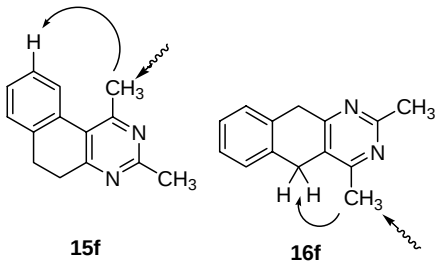
When 2-tetralone (**14**) reacts with benzyl nitriles, 1,3-disubstituted dihydrobenzo[*f*]quinazolines **15c–e** are obtained (Scheme 3). However, if the benzyl nitrile bears electron withdrawing groups, significant amounts of pyrimidines **22** was also obtained in addition to the expected quinazolines **21** (Scheme 6). The amounts of pyrimidines **22** increases at higher temperatures. Surprisingly, benzonitrile also affords a pyrimidine type product **23** when the reaction is carried out at 120 °C. Thus, the reaction of 2-tetralone and benzonitrile was investigated under various temperature conditions. The results show that when this reaction is carried out at room temperature exclusively the quinazoline



Scheme 3.



Scheme 4.



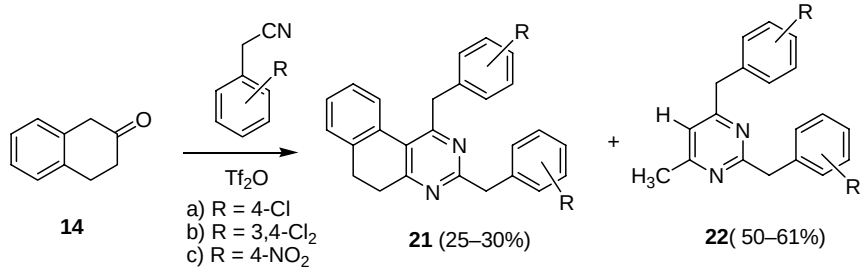
Scheme 5.

15a is exclusively formed while pyrimidine **23** is the main reaction product when the temperature is raised to 120 °C (Scheme 7).

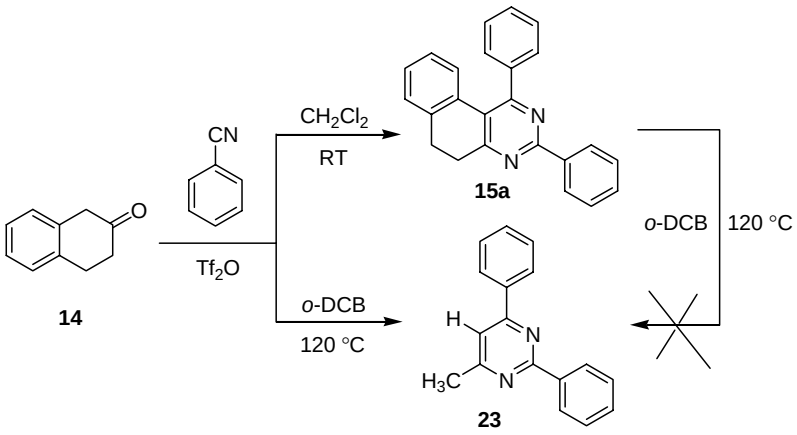
The formation of pyrimidine **23** could not be explained by a fragmentation process promoted by temperature. Heating **15a** in *o*-DCB at 120 °C for several hours, even in the presence of Tf_2O and/or TfOH, does not afford pyrimidine **23**. NOE experiments with compound **22c** were performed to confirm the pyrimidine structure and to achieve the complete assignments of the ^1H NMR signals. Irradiations and signals enhancement are summarized in Scheme 8. The observed results confirm the proposed structure (Scheme 8). Experiments are in progress to determine the exact mechanism of the pyrimidine formation.

The reaction of 2-tetralone (**14**) with methylthiocyanate (Scheme 9) leads to a mixture of the expected dihydrobenzoquinazoline **24** and a new compound, which was identified as tetrahydrodibenzo[*a*,*i*]phenanthridine **25**. The pentacyclic structure of **25** cannot be explained by the general mechanism for the reaction between ketones and nitriles.[23] Moreover, the presence of only one nitrogen atom in the structure of **25** indicates that the cyclodimerisation process of the nitrile does not take place. In contrast to the general mechanism, only one molecule of the nitrile and two molecules of the starting ketone participate in the reaction.

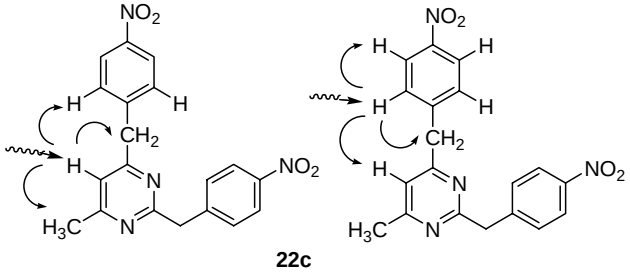
We have proposed a mechanism to explain these results. The first step involves the aldol condensation of the tetralone **14** induced by traces of triflic acid to form the



Scheme 6.



Scheme 7.



Scheme 8.

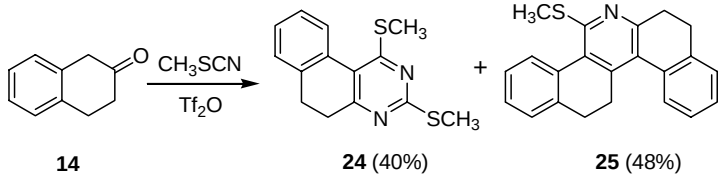
hydroxyketone **26**. The last step of this condensation involves the elimination of a water molecule and affords the two isomeric binaphthalenones **27** and **28** (Scheme 10). The reaction of the enone **27** with methylthiocyanate followed by loss of TfOH and cyclization affords the tetrahydrodibenzo[*a*,*i*]phenanthridine **24**. In contrast, if the enone **28** undergoes the same process, the isomeric tetrahydrodibenzo[*a*,*j*]phenanthridine **30** should be formed. A similar mechanism has been reported that involves an aldol condensation of cyclobutanone and subsequent reaction with only one nitrile molecule has been reported.[29]

In order to distinguish between phenanthridines **25** and **30**, we used NOE experiments. Because the chemical shift of the thiomethyl group (2.69 ppm) is close to the signals of the methylene protons, it is very difficult to irradiate the CH_3S signal without perturbation of other nuclei. To avoid this problem, we prepared several derivatives of **25** based on the reactions shown in Scheme 3. The oxidation of **25** with *m*-CPBA in dichloromethane affords the sulfone **32**, which reacts with a methanolic solution of sodium methoxide leading to the methoxyphenanthridine **33** (Scheme 11).

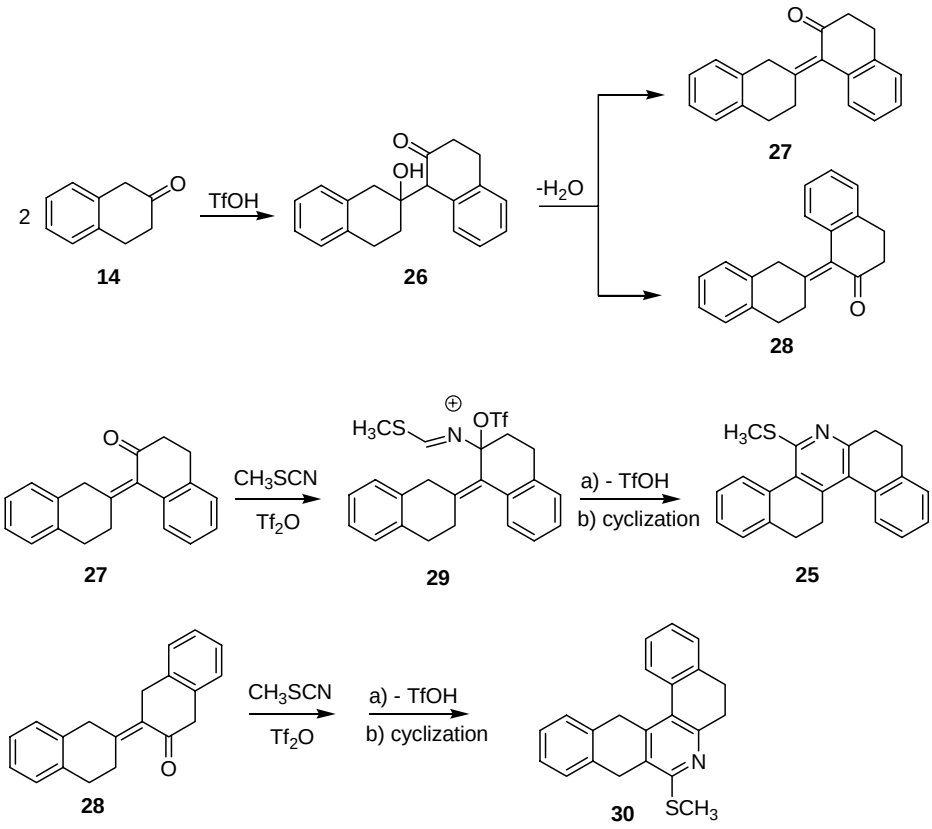
The ^{1}H NMR spectra of **33** shows a singlet at 4.09 ppm corresponding to the CH_3O group, which does not overlap with the signals of H13 and H14. Moreover, H7 and H8 appear as a singlet at 2.29 ppm. Irradiation of the CH_3O signal produces a significant enhancement of the signal at 8.28 ppm corresponding to H4. Another small signal enhancement is observed at 2.29 ppm, which corresponds to H7 and H8 (Scheme 12 and Fig. 2). The structure of the isomeric phenanthridine **34** could be discarded because an irradiation on the methoxy signal could not produce a signal enhancement in the aromatic region.

The reaction of **25** with DDQ affords the totally aromatic phenanthridine **31**. Unfortunately, this compound is unreactive towards nucleophiles and the thiomethyl group cannot be replaced in this polyaromatic system.

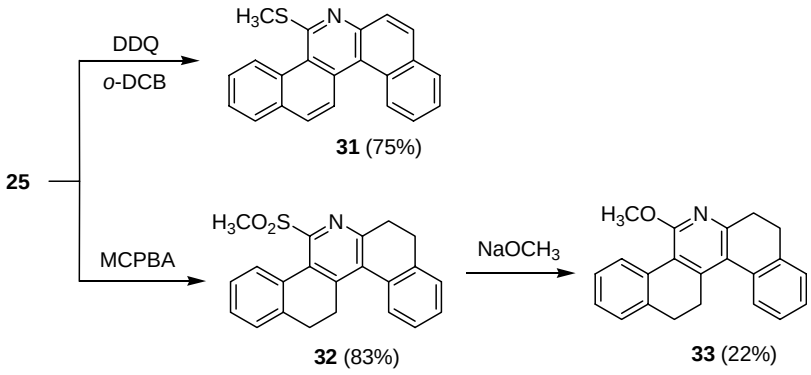
In summary, we report that the one-pot reaction of 1- and 2-tetralone with nitriles affords 2,4-disubstituted dihydrobenzo[*h*]quinazolines and 1,3-disubstituted dihydrobenzo[*f*]quinazolines, respectively. These compounds can be easily converted into their corresponding benzoquinazolines via DDQ oxidation. The reaction of 2-tetralone with nitriles is a regiospecific process and is proposed a mechanism to explain the results. Benzoquinazolines bearing thiomethyl groups can be used as starting materials for the synthesis of several variously substituted quinazolines. On the other hand, the reaction of 2-tetralone with methylthiocyanate is a one-step procedure to obtain substituted dibenzophenanthridines. A mechanism for this reaction is postulated.



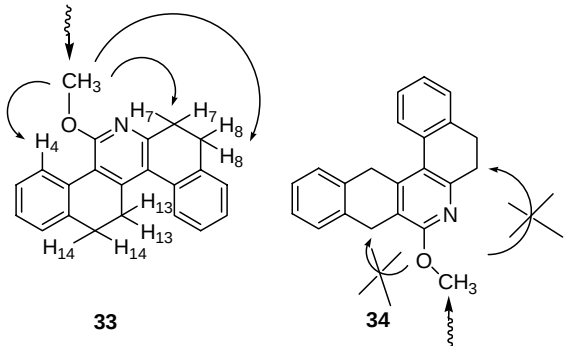
Scheme 9.



Scheme 10.



Scheme 11.



Scheme 12.

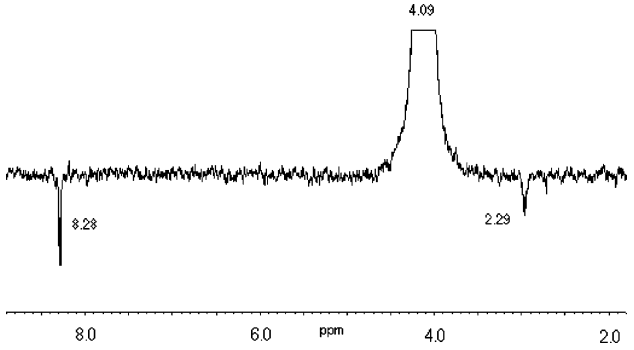


Figure 2.

3. Experimental

3.1. General

All reagents were commercial grade and were used as received unless otherwise indicated. Triflic anhydride was prepared from TfOH and redistilled twice prior to use.[30,31] Solvents were distilled from an appropriate drying agent before use. Reactions were monitored by thin-layer chromatography (TLC) using silica gel plates having $60F_{250}$. Column chromatography was performed using silica gel 60 (70–230 mesh). Melting points were determined on a Gallenkamp apparatus in open capillary tubes and are uncorrected. The IR spectra were measured with a Shimadzu FTIR 8300 instrument and samples pellets were produced with potassium bromide spectroscopic grade. NMR spectra were recorded on a Bruker DPX 300 and Bruker Avance AV 500 at 300 MHz for ^{1}H and 75.47 MHz for ^{13}C and 500 MHz for ^{1}H and 125.72 MHz for ^{13}C, respectively. Chemical shifts are given in δ units (ppm) to residuals $CHCl_3$ (7.26 and 77.0, respectively) and DMSO (2.50 and 39.5, respectively). J values are in Hz. Mass spectra were carried out on a HP 5989A quadrupole instrument at 70 eV with a source temperature of 200 °C. Elemental analysis was carried out with a Perkin-Elmer 2400 CHN apparatus.

3.2. Preparation of 2,4-disubstituted dehydrogenize[*h*]-quinazolines 1a–d: general procedure

A mixture of 1-tetralone (**4**) (0.5 g, 4.3 mmol) and 9 mmol of the corresponding nitrile dissolved in 30 mL of CH_2Cl_2 was cooled at 0 °C. Triflic anhydride (1.3 g, 4.5 mmol) in 15 mL of CH_2Cl_2 was added dropwise. The reaction mixture was allowed to stand to room temperature and stirred at this temperature for 24 h. The reaction can be monitored by TLC. The reaction mixture was hydrolyzed by careful addition of saturated aqueous solution of sodium hydrogen carbonate until was basic. The organic layer was separated, washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue purified by flash chromatography using hexane/ethyl acetate 9:1 as eluent. The crude product was distilled or recrystallized.

3.2.1. 2,4-Diphenyl-5,6-dihydrobenzo[*h*]quinazoline 1a. Purification of crude product by column chromatography afforded 0.93 g (65%), mp 170–171 °C (EtOH); ν (KBr) 1610, 1540, 1400, 770, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.91 (m, 2H, CH_2), 3.10 (m, 2H, CH_2), 7.45 (m, 2H), 7.28 (m, 2H), 7.46 (m, 6H), 7.70 (m, 2H), 8.58 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ: 24.78 (CH_2), 27.82 (CH_2), 123.44, 126.04, 127.26, 127.72, 128.15, 128.29, 128.36, 129.21, 130.80, 133.38, 138.22, 139.00, 160.10, 162.14, 164.28 (arom.) ppm; *m*/*z* (EI, 70 eV): 334 ($M^{+\cdot}$, 63), 333 (100), 127 (20), 77 ($C_6H_5^+$, 59). Anal. Calcd for $C_{24}H_{18}N_2$: C 86.20, H 5.43, N 8.38%, found C 86.04, H 5.39, N 8.29.

3.2.2. 2,4-Bis(4-methylphenyl)-5,6-dihydrobenzo[*h*]-quinazoline 1b. Purification of crude product by column chromatography afforded 1.08 g (70%), mp 169–170 °C ($CHCl_3$/MeOH); ν (KBr) 1615, 1540, 1400, 810, 770 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.44 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 2.90 (m, 2H, CH_2), 3.10 (m, 2H, CH_2), 7.30 (m, 1H), 7.40 (m, 1H), 7.50 (m, 2H), 7.70 (m, 2H), 8.60 (m, 1H), 8.66 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ: 21.43 (CH_3), 21.53 (CH_3), 24.78 (CH_2), 27.82 (CH_2), 123.44, 126.04, 127.26, 127.72, 128.15, 128.29, 128.36, 129.21, 130.80, 133.38, 138.22, 139.00, 160.10, 162.14, 164.28 (arom.) ppm; *m*/*z* (EI, 70 eV): 362 ($M^{+\cdot}$, 85), 361 (100), 127 (20), 91 ($C_7H_7^+$, 59). Anal. Calcd for $C_{26}H_{22}N_2$: C 86.15, H 6.12, N 7.73%, found C 87.97, H 6.08, N 7.66.

3.2.3. 2,4-Bis(4-chlorophenyl)-5,6-dihydrobenzo[*h*]quinazoline 1c. Purification of crude product by column chromatography gave 1.42 g (83%), mp 118–119 °C ($CHCl_3$/MeOH); ν (KBr) 1600, 1540, 1400, 850, 770 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.92 (m, 2H, CH_2), 3.06 (m, 2H, CH_2), 7.30 (m, 1H), 7.49 (m, 6H), 7.64 (m, 2H), 8.60 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ: 24.77 (CH_2), 27.69 (CH_2), 123.58, 126.04, 127.35, 127.80, 128.60, 129.47, 130.59, 131.07, 133.04, 135.51, 136.48, 1136.53, 136.55, 139.07, 160.41, 161.24, 163.14 (arom.) ppm; *m*/*z* (EI, 70 eV): 402 ($M^{+\cdot}$, 63), 401 (100). Anal. Calcd for $C_{24}H_{16}Cl_2N_2$: C 71.47, H 4.00, Cl 17.58, N 6.95%, found C 71.39, H 3.69, Cl 17.44, N 6.79.

3.2.4. 2,4-Bis(methylthio)-5,6-dihydrobenzo[*h*]quinazoline 1d. Purification of crude product by column chromatography afforded 0.82 g (70%), mp 110–111 °C (EtOH); ν (KBr) 1530, 1440, 1360 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.61 (s, 3H, SCH_3), 2.65 (s, 3H, SCH_3), 2.80 (t, 2H, J=7.2 Hz, CH_2), 2.96 (t, 2H, J=7.2 Hz, CH_2) 7.23 (m, 1H), 7.35 (m, 2H), 8.33 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 12.73 (CH_3S), 14.31 (CH_3S), 22.92 (CH_2), 27.11 (CH_2), 125.94, 127.10, 127.85, 130.66, 132.19, 138.76, 155.78, 167.85, 168.88 (arom.) ppm; *m*/*z* (EI, 70 eV): 274 ($M^{+\cdot}$, 100), 259 (M−CH_3, 27), 241 (M−SH, 65). Anal. Calcd for $C_{14}H_{14}N_2S_2$: C 72.70, H 4.07, N 7.06, S 16.17%, found C 72.72, H 3.90, N 6.90, S 16.05.

3.2.5. 2,4-Dibenzyl-5,6-dihydrobenzo[*h*]quinazoline 6a. Purification of crude product by column chromatography gave 1.08 g (70%), mp 71–72 °C (EtOH); ν (KBr) 1555, 1491, 1390, 740, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.84 (m, 4H, CH_2), 4.21 (s, 2H, CH_2), 4.36 (s, 2H, CH_2), 7.28 (m, 11H), 7.50 (m, 2H), 8.37 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 22.91 (CH_2), 27.31 (CH_2), 41.36 (CH_2), 45.84 (CH_2), 123.68, 125.89, 126.20, 126.42, 127.17, 127.67, 128.25, 128.52, 129.29, 130.64, 132.90, 137.87, 138.80, 139.13, 159.32, 165.68, 167.17 (arom.) ppm; *m*/*z* (EI, 70 eV): 362 ($M^{+\cdot}$, 65), 361 (100). Anal. Calcd for $C_{26}H_{22}N_2$: C 86.15, H 6.12, N 7.73%, found C 87.99, H 6.05, N 7.60.

3.2.6. 2,4-Bis(2-methylbenzyl)-5,6-dihydrobenzo[*h*]quinazoline 6b. Purification of crude product by column chromatography afforded 1.25 g (75%), mp 103–104 °C (EtOH); ν (KBr) 1554, 1384, 742 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.33 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 2.84 (m, 4H, AA′BB′ system CH_2), 4.15 (s, 2H, CH_2), 4.34 (s, 2H, CH_2), 6.88 (d, 1H, J=7 Hz), 7.15 (m, 7H), 7.38 (m, 3H), 8.35 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 19.98 (CH_3), 20.09 (CH_3), 22.92 (CH_2), 27.40 (CH_2), 38.88 (CH_2), 43.34 (CH_2), 123.84, 125.78, 125.89, 125.98, 126.39, 126.50, 127.22, 127.72, 128.42, 130.09, 130.23, 130.64, 133.01, 136.62, 137.06, 137.72, 138.84, 159.07, 165.73, 167.35 (arom.) ppm; *m*/*z* (EI, 70 eV): 390 ($M^{+\cdot}$, 87), 389 (100),

375 ($M-CH_3$, 10). Anal. Calcd for $C_{28}H_{26}N_2$: C 86.12, H 6.71, N 7.17%, found C 86.00, H 6.66, N 7.09.

3.2.7. 2,4-Bis(4-methylbenzyl)-5,6-dihydrobenzo[*h*]-quinazoline 6c. Purification of crude product by column chromatography afforded 1.30 g (77%), mp 108–109 °C (EtOH); ν (KBr) 1556, 1388, 808, 744 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.30 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.81 (m, 4H, AA′BB′ system CH_2), 4.16 (s, 2H, CH_2), 4.30 (s, 2H, CH_2), 7.12 (m, 7H), 7.39 (m, 4H), 8.35 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 20.99 (CH_3), 21.06 (CH_3), 22.88 (CH_2), 27.30 (CH_2), 40.95 (CH_2), 45.36 (CH_2), 123.65, 125.89, 127.14, 127.64, 128.51, 128.96, 128.13, 129.20, 130.60, 132.91, 134.72, 135.65, 136.03, 138.81, 159.31, 165.82, 167.28 (arom.) ppm; *m/z* (EI, 70 eV): 390 ($M^{+\cdot}$, 100), 389 (100). Anal. Calcd for $C_{28}H_{26}N_2$: C 86.12, H 6.71, N 7.17%, found C 85.99, H 6.61, N 7.15.

3.2.8. 3,4-Dihydronaphthalen-1-yl triflate. This product was isolated from the reaction mixtures in 3–6% yield, bp=50 °C (0.5 Torr, kugelrohr); IR (film)=1420, 1247, 1142 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.52 (m, 2H, CH_2), 2.88 (m, 2H, CH_2), 6.03 (t, 1H, J=5.0 Hz, =CH), 7.29 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$) δ: 22.30 (C3), 26.82 (C4), 117.69 (C=), 118.64 (q, CF_3, J=318 Hz), 121.22, 126.91, 127.73, 128.67, 129.16, 136.23 (arom.), 146.38 (=C) ppm; *m/z* (EI, 70 eV): 278 ($M^{+\cdot}$, 20), 145 (M−Tf, 100), 129 (M−OTf, 21).

3.3. Preparation of benzo[*h*]quinazolines 5: general procedure

A mixture of 0.9 mmol of the corresponding dihydrobenzoquinazoline **1** and DDQ (0.4 g, 1.8 mmol) in 10 mL of *o*-DCB was heated at 120 °C during 3 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography using hexane/ethyl acetate 9:1 as eluent.

3.3.1. 1,3-Diphenylbenzo[*h*]quinazoline 5a. Purification of crude product by column chromatography afforded 0.24 g (80%), mp 152–153 °C (EtOH); ν (KBr) 1566, 1490, 804, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.72 (m, 13H), 8.86 (m, 2H), 9.55 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 119.26, 122.82, 125.34, 127.32, 127.82, 128.51, 128.70, 129.65, 130.04, 130.31, 130.48, 135.09, 138.07, 138.47, 151.92, 162.13, 166.76 (arom.) ppm; *m/z* (EI, 70 eV): 332 ($M^{+\cdot}$, 63), 331 (100), 253 (11). Anal. Calcd for $C_{24}H_{16}N_2$: C 86.72, H 4.85, N 8.43%, found C 86.59, H 4.88, N 8.38.

3.3.2. 2,4-Bis(4-methlphenyl)benzo[*h*]quinazoline 5b. Purification of crude product by column chromatography afforded 0.25 g (86%), mp 151–152 °C (EtOH); ν (KBr) 1560, 1439, 1095, 761 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.47 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 7.35 (m, 4H), 7.85 (m, 7H), 8.75 (d, 2H, J=8 Hz) 9.54 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 21.47 (CH_3), 21.56 (CH_3), 119.09, 122.99, 125.34, 127.16, 127.37, 127.68, 128.66, 129.25, 129.88, 130.30 130.82, 135.07, 135.34, 135.88, 139.75, 140.59, 151.85, 160.23, 166.66 (arom.) ppm; *m/z* (EI, 70 eV): 360 ($M^{+\cdot}$, 85), 359 (100), 345 ($M-CH_3$, 20). Anal. Calcd for $C_{26}H_{20}N_2$: C 86.64, H 5.59, N 7.77, found C 86.50, H 5.44, N 7.69.

3.3.3. 2,4-Bis(methylthio)benzo[*h*]quinazoline 5d. Purification of crude product by column chromatography gave 0.23 g (93%), mp 103–104 °C (EtOH); ν (KBr) 1560, 1490, 800, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.71 (s, 3H, CH_3), 2.77 (s, 3H, CH_3), 7.77 (m, 5H), 9.16 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 12.74 (CH_3), 14.44 (CH_3), 118.18, 120.06, 125.28, 126.29, 127.08, 127.75, 129.55, 129.64, 135.41, 148.15, 167.26, 169.81 (arom.) ppm; *m/z* (EI, 70 eV): 272 ($M^{+\cdot}$, 100), 257 ($M-CH_3$, 38), 239 (M−SH, 51), 225 ($M-SCH_3$, 13). Anal. Calcd for $C_{14}H_{12}N_2S_2$: C 61.73, H 4.44, N 10.28, S 23.54%, found C 61.66, H 4.40, N 10.11, S 23.44.

3.4. Preparation of monobenzoyldihydrobenzo[*h*]quinazolines 7: general procedure

A mixture of 0.55 mmol of the corresponding dihydroquinazoline **6** and DDQ (0.25 g, 1.1 mmol) in 20 mL of toluene was heated at 100 °C during 3 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography using hexane/ethyl acetate 9:1 as eluent.

3.4.1. 4-Benzoyl-2-benzyl-5,6-dihydrobenzo[*h*]quinazoline 7a. Purification of crude product by column chromatography afforded 0.1 g (50%) of an undistillable oil; ν (film) 1676 (C=O), 1569, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.9 (m, 4H, CH_2), 4.35 (s, 2H, CH_2), 7.35 (m, 11H), 7.90 (m, 2H), 8.42 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 22.85 (CH_2), 27.16 (CH_2), 45.79 (CH_2), 123.42, 125.99, 126.41, 127.36, 128.01, 128.36, 128.58, 129.32, 130.62, 131.41, 132.33, 134.06, 135.25, 138.63, 139.37, 160.83, 161.16. 167.21 (arom.), 193.64 (CO) ppm; *m/z* (EI, 70 eV): 376 ($M^{+\cdot}$, 100), 375 (38), 271 ($M-C_6H_5CO$, 25). Anal. Calcd for $C_{26}H_{20}N_2O$: C 82.95, H 5.35, N 7.44%, found C 82.92, H 5.29, N 7.32.

3.4.2. 4-(4-Methylbenzoyl)-2-(4-methylbenzyl)-5,6-dihydrobenzo[*h*]quinazoline 7c. Purification of crude product by column chromatography afforded 0.09 g (40%), mp 113–114 °C (hexane); ν (KBr) 1672 (C=O), 1604, 1555, 777 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.32 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 2.87 (m, 4H, CH_2), 4.30 (s, 2H, CH_2), 7.11 (m, 2H), 7.24 (m, 4H), 7.38 (m, 3H), 7.80 (m, 2H), 8.40 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 21.05 (CH_3), 21.85 (CH_3), 22.87 (CH_2), 27.19 (CH_2), 45.38 (CH_2), 123.14, 125.98, 127.31, 129.96, 129.04, 129.16, 129.33, 130.72, 131.31, 132.42, 132.82, 135.63, 135.85, 139.35, 145.21, 161.01, 161.18, 167.41 (arom.), 193.37 (CO) ppm; *m/z* (EI, 70 eV): 404 ($M^{+\cdot}$, 100), 403 (54). Anal. Calcd for $C_{28}H_{24}N_2O$: C 83.14, H 5.98, N 6.93%, found C 83.01, H 5.87, N 6.82.

3.5. Preparation of dibenzoyldihydrobenzo[*h*]quinazolines 8: general procedure

A mixture of 0.70 mmol of the corresponding dihydroquinazoline **6** and DDQ (0.31 g, 1.65 mmol) in 20 mL of *o*-DCB was heated at 150 °C during 3 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography using hexane/ethyl acetate 9:1 as eluent.

3.5.1. 2,4-Bis(benzoyl)-5,6-dihydrobenzo[*h*]quinazoline 8a. Purification of crude product by column

chromatography afforded 0.12 g (45%), mp 157–158 °C (EtOH); ν (KBr) 1679 (C═O), 1593, 1452, 740, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.02 (m, 4H, CH_2), 7.47 (m, 9H), 8.02 (m, 4H), 8.42 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 23.38 (CH_2), 26.85 (CH_2), 126.50, 127.35, 128.15, 128.32, 128.78, 130.55, 131.00, 131.57, 132.17, 133.58, 134.42, 134.94, 135.23, 160.44, 161.01, 161.47 (arom.), 191.03, 192.95 (CO) ppm; *m/z* (EI, 70 eV): 390 ($M^{+\cdot}$, 158), 389 (15), 284 (M−C_6H_5CO, 43), 77 ($C_6H_5^+$, 100). Anal. Calcd for $C_{26}H_{18}N_2O_2$: C 79.98, H 4.65, N 7.17%, found C 79.87, H 4.61, N 7.00.

3.5.2. 2,4-Bis(4-methylbenzoyl)-5,6-dihydrobenzoquinazoline 8c. Purification of crude product by column chromatography afforded 0.18 g (60%), mp 143–144 °C (hexane); ν (KBr) 1678 (C═O), 1668 (CO), 1604, 1550, 950 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.42 (s, 6H, CH_3), 2.94 (s, 2H, CH_2), 7.33 (m, 7H), 7.94 (m, 2H), 8.42 (m, 2H), 9.32 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 21.80 (CH_3), 21.86 (CH_3), 23.36 (CH_2), 26.87 (CH_2), 126.48, 126.99, 127.58, 128.12, 129.08, 129.52, 130.66, 131.16, 131.66, 132.05, 132.52, 132.70, 139.37, 144.61, 145.66, 160.75, 161.28, 161.33 (arom.), 190.77, 192.67 (CO) ppm; *m/z* (EI, 70 eV): 418 ($M^{+\cdot}$, 100), 417 (20), 298 (90). Anal. Calcd for $C_{28}H_{22}N_2O_2$: C 80.36, H 5.30, N 6.69%, found C 80.25, H 5.28, N 6.59.

3.5.3. 2,4-Bis(methylsulfonyl)benzo[*h*]quinazoline 9d. To a stirred solution of 2,4-bis(methylthio)benzo[*h*]quinazoline **5d** containing 0.5 g (1.83 mmol) in 20 mL of anhydrous dichloromethane was added slowly a solution of 1.27 g (7.32 mmol) of *m*-CPBA in 20 mL of dichloromethane. The mixture was stirred at room temperature for 4 h. An aqueous solution of $Na_2S_2O_3$ (5%) was then added and the layers shaked and separated. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers washed with $NaHCO_3$ aqueous solution, brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by recrystallization to give 0.52 g (85%) of **9d**, mp 191–192 °C (EtOH); ν (KBr): 1388, 1303 (SO_2), 1143, 947, 785 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.54 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 7.99 (m, 5H), 9.20 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 39.67 (CH_3), 42.39 (CH_3), 115.17, 118.09, 125.38, 128.53, 128.87, 129.06, 131.91, 132.65, 135.98 (arom.) ppm; *m/z* (EI, 70 eV): 336 ($M^{+\cdot}$, 20), 272 (M−SO_2, 100), 195 (67). Anal. Calcd for $C_{14}H_{12}N_2O_4S_2$: C 49.99, H 3.60, N 8.33, S 19.06%, found C 49.87, H 3.55, N 8.21, S 18.98.

3.5.4. 2,4-Dimethoxybenzo[*h*]quinazoline 10d. A solution containing 0.2 g (0.59 mmol) of **9d** and sodium methoxide (0.15 g, 2.36 mmol) in 20 mL of dry methanol was refluxed for 2 h. After addition of water and extraction with dichloromethane, the organic layers were washed with brine. Elimination of solvent affords a residue, which was purified by recrystallization giving 0.13 g (90%) of **10d**, mp 101–102 °C (EtOH); ν (KBr): 1267, 1195, 765 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.18 (s, 3H, CH_3), 4.21 (s, 3H, CH_3), 7.67 (m, 5H), 7.90 (m, 5H), 9.06 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 54.49 (CH_3), 54.78 (CH_3), 109.38, 119.53, 124.52, 124.93, 126.53, 127.75, 129.30, 135.74, 152.09, 162.37, 169.06 (arom.) ppm; *m/z* (EI, 70 eV): 240 ($M^{+\cdot}$, 47), 239 (100), 225 (M−CH_3, 8). Anal. Calcd for $C_{14}H_{12}N_2O_2$: C 69.99, H 5.03, N 11.66%, found C 69.85, H 4.91, N 11.59.

3.5.5. 4-Amino-2-(methylsulfonyl)benzo[*h*]quinazoline 11d. A continuous stream of ammonia gas was bubbled through a solution of 0.2 g (0.59 mmol) of **9d** in 20 mL of dichloromethane at room temperature. After 2 h, the solvent was eliminated, the residue washed gently with water and purified by recrystallization giving 0.12 g (74%) of **11d**, mp 275 °C (EtOH, decomp.); ν (KBr): 3490, 3298 (NH_2), 1637, 1488, 1313 (SO_2), 777 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.44 (s, 3H, CH_3), 7.77 (m, 2H), 8.05 (m, 3H), 8.53 (br s, 2H, NH_2), 8.93 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 38.39 (CH_3), 110.66, 119.32, 124.25, 127.56, 127.95, 128.08, 128.95, 129.88, 134.81, 147.74, 162.04, 162.60 (arom.) ppm; *m/z* (EI, 70 eV): 273 ($M^{+\cdot}$, 45), 258 (M−CH_3, 15), 194 (M−CH_3SO_2, 100). Anal. Calcd for $C_{13}H_{11}N_3O_2S$: C 57.13, H 4.06, N 15.37, S 11.73%, found C 57.03, H 3.96, N 15.25, S 11.69.

3.5.6. 4-Amino-2-(methoxy)benzo[*h*]quinazoline 12d. A solution containing 0.2 g (0.59 mmol) of **11d** and sodium methoxide (0.15 g, 2.36 mmol) in 20 mL of dry methanol was refluxed for 2 h. After addition of water and extraction with dichloromethane, the organic layers were washed with brine. Elimination of solvent affords a residue, which was purified by recrystallization giving 0.14 g (85%) of **12d**, mp 274–275 °C (EtOH); ν (KBr): 3450, 3233 (NH_2), 1355, 1078, 796 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.08 (s, 3H, CH_3), 7.59 (m, 4H), 7.78 (m, 1H), 8.80 (br s, 2H, NH_2) 8.98 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 54.25 (CH_3), 106.96, 118.49, 123.85, 124.90, 126.51, 127.54, 129.13, 129.63, 135.48, 151.21, 162.42, 163.33 (arom.) ppm; *m/z* (EI, 70 eV): 225 ($M^{+\cdot}$, 100), 224 (57), 195 (48). Anal. Calcd for $C_{13}H_{11}N_3O$: C 69.32, H 4.92, N 18.66%, found C 69.20, H 4.80, N 18.55.

3.5.7. Benzo[*h*]quinazoline-2,4-(1*H*,3*H*)-dione 13d. Compound **11d** (0.2 g, 0.59 mmol) was suspended in 20 mL of aqueous NaOH 10% and refluxed 2 h. The reaction mixture was acidified with HCl 10% until pH 2 and the solid was collected by filtration and washed gently with cold water. Recrystallization in hot water gave 0.1 g (80%) of **13d**. If the hydrolysis was carried out by reluxing **11d** in aqueous hydrochloric acid 1:1, compound **13** was obtained in 53% yield, mp decomposition; ν (KBr): 3278 (NH), 1664, 1598 (CO), 790, 756 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 7.10 (d, 1H, J=9.6 Hz), 7.40 (t, 1H, J=9.6 Hz), 7.50 (t, 1H, J=9.6 Hz), 8.78 (d, 1H, J=9.6 Hz) 10.05 (br s, 2H, NH_2) ppm; ^{13}C NMR (DMSO-d_6) δ:109.70, 116.44, 123.25, 124.52, 125.76, 127.37, 128.02, 129.04, 136.54, 153.75 (arom.), 158.64, 165.93 (CO) ppm; *m/z* (EI, 70 eV): 212 ($M^{+\cdot}$, 10), 78 (100). Anal. Calcd for $C_{12}H_8N_2O_2$: C 67.92, H 3.80, N 13.20%, found C 67.79, H 3.71, N 13.13.

3.6. Preparation of 1,3-disubstituted 5,6-dihydrobenzo[*f*]-quinazolines 15a–f: general procedure

A mixture of 2-tetralone (**14**) (0.5 g, 4.3 mmol) and 9 mmol of the corresponding nitrile dissolved in 30 mL of CH_2Cl_2 was cooled at 0 °C. Triflic anhydride (1.3 g, 4.5 mmol) in 15 mL of CH_2Cl_2 was added dropwise. The reaction mixture was allowed to stand to room temperature and stirred at this

temperature for 24 h. The reaction can be monitored by TLC. The reaction mixture was hydrolyzed by careful addition of saturated aqueous solution of sodium hydrogen carbonate until was basic. The organic layer was separated, washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue purified by flash chromatography using hexane/ethylacetate 9:1 as eluent. The crude product was distilled or recrystallized.

3.6.1. 1,3-Diphenyl-5,6-dihydrobenzo[*f*]quinazoline 15a. Purification of crude product by column chromatography afforded 1.01 g (86%), mp 121–122 °C (hexane); ν (KBr) 1603, 1537, 1421, 762, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.09 (m, 4H, CH_2), 6.95 (m, 2H), 7.17 (m, 1H), 7.28 (m, 1H), 7.46 (m, 6H), 7.70 (m, 2H), 8.60 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ: 28.45 (CH_2), 32.14 (CH_2), 123.99, 126.01, 127.83, 127.88, 128.23, 128.46, 128.50, 128.84, 129.40, 129.65, 130.43, 131.14, 137.64, 138.17, 139.54, 161.54, 161.98, 168.96 (arom.) ppm; *m/z* (EI, 70 eV): 334 ($M^{+\cdot}$, 63), 333 (100). Anal. Calcd for $C_{24}H_{18}N_2$: C 86.20, H 5.43, N 8.38%, found C 86.09, H 5.33, N 8.26.

3.6.2. 1,3-Bis(4-methylphenyl)-5,6-dihydrobenzo[*f*]quinazoline 15b. Purification of crude product by column chromatography afforded 0.99 g (80%), mp 180–181 °C (EtOH); ν (KBr) 1539, 1423, 802 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.43 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.07 (m, 4H, CH_2), 6.94 (m, 8H), 7.61, 8.48 ($AA'XX'$system, 4H) ppm; ^{13}C NMR ($CDCl_3$) δ: 21.47 (CH_3), 21.54 (CH_3), 28.50 (CH_2), 32.17 (CH_2), 123.54, 125.97, 127.68, 127.77, 128.20, 128.74, 129.19, 129.21, 129.62, 131.45, 135.02, 136.74, 138.09, 139.44, 140.55, 161.56, 161.91, 168.76 (arom.) ppm; *m/z* (EI, 70 eV): 362 ($M^{+\cdot}$, 77), 361 (100). Anal. Calcd for $C_{26}H_{22}N_2$: C 86.15, H 6.12, N 7.73%, found C 85.98, H 6.09, N 7.65.

3.6.3. 1,3-Dibenzyl-5,6-dihydrobenzo[*f*]quinazoline 15c. Purification of crude product by column chromatography afforded 0.93 g (60%), mp 80–81 °C (EtOH); ν (KBr) 1541, 1494, 1398 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.92 (m, 4H, CH_2), 4.28 (s, 2H, CH_2), 4.37 (s, 2H, CH_2), 7.33 (m, 14H) ppm; ^{13}C NMR ($CDCl_3$) δ: 28.31 (CH_2), 32.18 (CH_2), 41.73 (CH_2), 45.55 (CH_2), 125.47, 126.35, 126.63, 127.65, 127.91, 128.18, 128.32, 128.54, 128.90, 129.27, 130.97, 138.58, 162.67, 166.30, 168.46 (arom.) ppm; *m/z* (EI, 70 eV): 362 ($M^{+\cdot}$, 52), 361 (100). Anal. Calcd for $C_{26}H_{22}N_2$: C 86.15, H 6.12, N 7.73%, found C 85.98, H 5.98, N 7.69.

3.6.4. 1,3-Bis(2-methylbenzyl)-5,6-dihydrobenzo[*f*]quinazoline 15d. Purification of crude product by column chromatography afforded 0.84 g (50%), mp 110–111 °C (EtOH); ν (KBr) 1541, 1394, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.22 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.97 (m, 4H, CH_2), 4.29 (s, 2H, CH_2), 4.31 (s, 2H, CH_2), 6.98 (m, 1H), 7.26 (m, 11H) ppm; ^{13}C NMR ($CDCl_3$) δ: 19.77 (CH_3), 20.01 (CH_3), 28.39 (CH_2), 32.23 (CH_2), 39.76 (CH_2), 43.08 (CH_2), 125.38, 125.79, 126.00, 126.46, 126.77, 127.36, 127.97, 128.16, 128.87, 130.01, 130.14, 130.16, 131.08, 136.60, 137.15, 137.23, 137.52, 138.65, 162.85, 166.54, 168.23 (arom.) ppm; *m/z* (EI, 70 eV): 390 ($M^{+\cdot}$, 100), 389 (26), 375 ($M-CH_3$, 62). Anal. Calcd for $C_{28}H_{26}N_2$: C 86.12, H 6.71, N 7.17%, found C 85.99, H 6.60, N 7.09.

3.6.5. 1,3-Bis(4-methylbenzyl)-5,6-dihydrobenzo[*f*]quinazoline 15e. Purification of crude product by column chromatography afforded 1.25 g (75%), mp 101–102 °C (EtOH); ν (KBr) 1550, 1394, 792 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.34 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.91 (m, 4H, CH_2), 4.23 (s, 2H, CH_2), 4.32 (s, 2H, CH_2), 7.17 (m, 11H), 7.46 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 21.06 (CH_3), 28.31 (CH_3), 32.20 (CH_2), 41.34 (CH_2), 45.17 (CH_2), 125.35, 126.60, 127.68, 127.85, 128.08, 128.73, 129.01, 129.12, 129.21, 131.06, 136.65, 135.79, 138.55, 162.86, 166.49, 168.38 (arom.) ppm; *m/z* (EI, 70 eV): 390 ($M^{+\cdot}$, 57), 389 (100). Anal. Calcd for $C_{28}H_{26}N_2$: C 86.12, H 6.71, N 7.17%, found C 85.89, H 6.61, N 7.08.

3.6.6. 1,3-Dimethyl-5,6-dihydrobenzo[*f*]quinazoline 15f. Purification of crude product by column chromatography afforded 0.54 g (60%), mp 87–88 °C (EtOH); ν (KBr) 1552, 1375, 788 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.62 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 2.82 (m, 4H, CH_2), 7.23 (m, 3H), 7.50 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 24.65 (CH_3), 25.53 (CH_3), 28.23 (CH_2), 31.86 (CH_2), 124.33, 126.43, 127.51, 127.86, 131.17, 138.41, 161.38, 164.36, 167.24 (arom.) ppm; *m/z* (EI, 70 eV): 210 ($M^{+\cdot}$, 100), 209 (40). Anal. Calcd for $C_{14}H_{14}N_2$: C 79.97, H 6.71, N 13.32%, found C 79.86, H 6.66, N 13.29.

3.7. Synthesis of dibenzyldihydroquinazolines 21 and dibenzylpyrimidines 22

According to the general procedure in Section 3.6, the reaction of 2-tetralone and 4-chlorobenzylnitrile afforded a reaction mixture, which was chromatographied giving 0.56 (30%) of **21a** and 0.90 g (61%) of **22a**.

3.7.1. 1,3-Bis(4-chlorobenzyl)-5,6-dihydrobenzo[*f*]quinazoline 21a. Mp 97–98 °C; ν (KBr) 1541, 1394, 752 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.91 (m, 4H, CH_2), 4.19 (s, 2H, CH_2), 4.31 (s, 2H, CH_2), 7.21 (m, 11H), 7.41 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 28.23 (CH_2), 32.12 (CH_2), 41.05 (CH_2), 44.76 (CH_2), 125.48, 126.68, 127.51, 128.05, 128.39, 128.59, 130.32, 130.60, 132.28, 136.93, 137.16, 138.63, 162.26, 165.87, 168.63 (arom.) ppm; *m/z* (EI, 70 eV): 430 ($M^{+\cdot}$, 59), 429 (100). Anal. Calcd for $C_{26}H_{20}Cl_2N_2$: C 72.39, H 4.67, Cl 16.44, N 6.49%, found C 72.25, H 4.59, Cl 16.38, N 6.36.

3.7.2. 2,4-Bis(4-chlorobenzyl)-6-methylpyrimidine 22a. Undistillable oil; ν (film) 1587, 1545, 1373 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.40 (s, 3H, CH_3), 3.97 (s, 2H, CH_2), 4.18 (s, 2H, CH_2), 6.71 (s, 1H), 7.21 (m, 8H) ppm ^{13}C NMR ($CDCl_3$) δ: 24.13 (CH_3), 43.23 (CH_2), 41.12 (CH_2), 117.08, 128.39, 128.78, 130.50, 130.59, 132.22, 132.71, 136.17, 167.60, 168.68, 168.70 ppm (arom.); *m/z* (EI, 70 eV): 342 ($M^{+\cdot}$, 94), 321 (100). Anal. Calcd for $C_{19}H_{16}Cl_2N_2$: C 66.48, H 4.70, Cl 20.66, N 8.16%, found C 66.31, H 4.65, Cl 20.58, N 8.11.

Using the general procedure in Section 3.6, the reaction of 2-tetralone and 3,4-dichlorobenzylnitrile afforded a reaction mixture, which was chromatographied giving 0.53 (25%) of **21b** and 0.88 g (50%) of **22b**.

3.7.3. 1,3-Bis(3,4-dichlorobenzyl)-5,6-dihydrobenzo[*f*]-quinazoline 21b. Undistillable oil; ν (film) 1541, 1471, 1394 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.92 (m, 4H, CH_2), 4.16 (s, 2H, CH_2), 4.29 (s, 2H, CH_2), 7.04 (m, 1H), 7.30 (m, 9H) ppm ^{13}C NMR ($CDCl_3$) δ: 28.17 (CH_2), 32.06 (CH_2), 40.72 (CH_2), 44.42 (CH_2), 125.67, 126.76, 127.44, 128.16, 128.48, 128.58, 128.71, 130.23, 130.43, 130.55, 130.63, 130.94, 131.12, 132.20, 132.48, 138.45, 138.70, 161.66, 165.31, 168.86 (arom.) ppm; *m/z* (EI, 70 eV): 498 ($M^{+\cdot}$, 48), 497 (100). Anal. Calcd for $C_{26}H_{18}Cl_4N_2$: C 62.42, H 3.63, Cl 28.35, H 5.60%, found C 62.29, H 3.59, Cl 28.22. N 5.55.

3.7.4. 2,4-Bis(3,4-dichlorobenzyl)-6-methylpyrimidine 22b. Mp 83–84 °C (EtOH); ν (film) 1583, 1472, 1363 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.43 (s, 3H, CH_3), 3.95 (s, 2H, CH_2), 4.15 (s, 2H, CH_2), 6.77 (s, 1H), 7.06 (m, 1H), 7.18 (m, 1H), 7.38 (m, 4H) ppm ^{13}C NMR ($CDCl_3$) δ: 24.12 (CH_3), 42.87 (CH_2), 44.78 (CH_2), 117.29, 128.60, 128.65, 130.17, 130.55, 131.09, 132.16, 132.60, 137.79, 138.55, 167.94, 168.26 (arom.) ppm; *m/z* (EI, 70 eV): 410 ($M^{+\cdot}$, 100), 409 (92). Anal. Calcd for $C_{19}H_{14}Cl_4N_2$: C 55.37, H 3.42, Cl 34.41, N 6.80%, found C 55.27, H 3.39, Cl 34.43, N 6.70.

Using the general procedure in Section 3.6, the reaction of 2-tetralone and 4-nitrobenzylnitrile afforded a reaction mixture, which was chromatographied giving 0.58 (30%) of **21c** and 0.78 g (50%) of **22c**.

3.7.5. 1,3-Bis(4-nitrobenzyl)-5,6-dihydrobenzo[*f*]quinazoline 21c. Mp 144–145 °C (MeOH); ν (film) 1543, 1346 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.93 (m, 4H), 4.30 (s, 2H, CH_2), 4.46 (s, 2H, CH_2), 7.36 (m, 8H), 8.14 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$) δ: 28.15 (CH_2), 32.09 (CH_2), 41.62 (CH_2), 45.13 (CH_2), 123.51, 123.63, 125.88, 126.80, 127.30, 128.30, 128.76, 129.89, 130.10, 130.25, 138.75, 145.83, 146.17, 146.78, 161.34, 164.98, 169.14 (arom.) ppm; *m/z* (EI, 70 eV): 452 ($M^{+\cdot}$, 51), 451 (100), 422 (M−NO, 23). Anal. Calcd for $C_{26}H_{20}N_4O_4$: C 69.02, H 4.46, N 12.38%, found C 68.88, H 4.39, N 12.29.

3.7.6. 5-Methyl-2,4-bis(2-nitrobenzyl)pyrimidine 22c. Mp 142–143 (EtOH); ν (film) 1546, 1342 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.93 (s, 3H, CH_3), 4.04 (s, 2H, CH_2), 4.23 (s, 2H, CH_2), 6.75 (s, 1H), 7.38 (m, 4H), 8.08 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$) δ: 24.55 (CH_3), 43.94 (CH_2), 45.91 (CH_2), 117.99, 123.94, 124.27, 130.45, 130.48, 145.52, 146.32, 167.91, 168.39, 168.61 (arom.) ppm; *m/z* (EI, 70 eV): 364 ($M^{+\cdot}$, 100), 363 (97), 334 (M−NO, 23), 317 (M−NO_2H, 20). Anal. Calcd for $C_{19}H_{16}N_4O_4$: C 62.63, H 4.43, N 15.38% found C 62.55, H 4.30, N 15.22.

3.7.7. 3,4-Dihydronaphthalen-2-yl triflate. This product was isolated from the reaction mixtures in 4–7% yield, bp= 50 °C (0.5 Torr, kugelrohr); IR (film)=1420, 1247, 1142 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.72 (t, 2H, J=8.3 Hz, CH_2), 3.08 (t, 2H, J=8.3 Hz, CH_2), 6.51 (s, 1H, =CH), 7.15 (m, 4H) ppm; *m/z* (EI, 70 eV): 278 ($M^{+\cdot}$, 30), 145 (M−Tf, 22), 129 (M−OTf, 100).

3.8. Preparation of benzo[*f*]quinazolines 17: general procedure

A mixture of 0.9 mmol of the corresponding dihydrobenzoquinazoline **15** and DDQ (0.4 g, 1.8 mmol) in 10 mL of *o*-DCB was heated at 120 °C during 3 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography using hexane/ethyl acetate 9:1 as eluent.

3.8.1. 1,3-Diphenylbenzo[*f*]quinazoline 17a. Purification of crude product afforded 0.23 g (80%), mp 149–150 °C (EtOH); ν (KBr) 1603, 1531, 1429, 775, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.25 (m, 1H), 7.53 (m, 7H), 7.80 (m, 4H), 8.05 (2H, AB system, J=9.1 Hz), 8.71 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ: 119.34, 126.42, 127.08, 127.33, 127.75, 128.54, 128.63, 128.75, 129.04, 129.14, 130.55, 132.77, 135.59, 137.73, 141.91, 154.35, 159.79, 166.22 (arom.) ppm; *m/z* (EI, 70 eV): 332 ($M^{+\cdot}$, 70), 331 (100). Anal. Calcd for $C_{24}H_{16}N_2$: C 86.72, H 4.85, N 8.43%, found C 86.66, H 4.73, N 8.31.

3.8.2. 1,3-Bis(4-methylphenyl)benzo[*f*]quinazoline 17b. Purification of crude product afforded 0.28 g (86%), mp 174–175 °C (EtOH); ν (KBr) 1604, 1471, 831, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.45 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 7.29 (m, 5H), 7.50 (m, 1H), 7.63 (d, 2H, J=9.0 Hz), 7.88 (m, 2H), 8.05 (2H, AB system, J=9.56 Hz), 8.59 (d, 2H, J=9.0 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ: 21.53 (CH_3), 21.55 (CH_3), 119.16, 126.28, 128.67, 127.34, 127.71, 128.57, 128.66, 129.15, 129.26, 129.68, 132.65, 135.07, 135.50, 139.12, 139.61, 140.68, 154.34, 159.84, 166.14 (arom.) ppm; *m/z* (EI, 70 eV): 360 ($M^{+\cdot}$, 73), 359 (100). Anal. Calcd for $C_{26}H_{20}N_2$: C 86.64, H 5.59, N 7.77%, found C 86.54, H 5.44, N 7.71.

3.8.3. Reaction of 2-tetralone (14) with benzonitrile in *o*-DCB as solvent. The reaction was carried out following the general procedure in Section 3.6 heating at 120 °C for 24 h. Purification of crude product afforded 0.63 g (60%) of 4-methyl-2,6-diphenylpyrimidine **23**. (Lit.[32]), mp 101–102 °C (EtOH); ν (KBr) 1600, 1570, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.65 (s, 3H, CH_3), 7.47 (s, 1H), 7.53 (m, 6H), 8.22 (m, 2H), 8.60 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ: 24.61 (CH_3), 113.96, 127.20, 128.37, 128.44, 128.85, 130.47, 130.66, 137.29, 163.69, 164.33, 167.76 (arom.) ppm; *m/z* (EI, 70 eV): 246 ($M^{+\cdot}$, 100), 143 (M−C_6H_5CN, 26). Anal. Calcd for $C_{17}H_{14}N_2$: C 82.90, H 5.73, N 11.37%, found C 82.82, H 5.62, N 11.31.

3.9. The reaction of 2-tetralone with methylthiocyanate: general procedure

A mixture of 2-tetralone (**14**) (0.3 g, 2.05 mmol) and 0.62 g (8.56 mmol) of methylthiocyanate dissolved in 10 mL of *o*-DCB was cooled at 0 °C. Triflic anhydride (0.70 g, 2.46 mmol) in 15 mL of *o*-DCB was added dropwise. The reaction mixture was allowed to stand to room temperature and stirred at this temperature for 24 h and then at 120 °C for 3 h. The reaction can be monitored by TLC. The reaction mixture was hydrolyzed by careful addition of saturated aqueous solution of sodium hydrogen carbonate until was basic. The organic layer was separated, washed with brine

and dried over $MgSO_4$. The solvent was removed in vacuo and the residue purified by flash chromatography using hexane/ethylacetate 9:1 as eluent. The crude product afforded 0.22 g (40%) of **24** and 0.31 g (48%) of **25**.

3.9.1. 1,3-Bis(methylthio)-5,6-dihydrobenzoquinazoline 24. Mp 89–90 °C (hexane); ν (KBr) 1523, 1421, 1344 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.61 (s, 3H, SCH_3), 2.63 (s, 3H, SCH_3), 2.85 (m, 4H, CH_2), 7.29 (m, 3H), 8.11 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 13.90 (CH_3S), 14.15 (CH_3S), 28.10 (CH_2), 31.72 (CH_2), 121.86, 126.24, 126.59, 127.85, 127.96, 130.47, 137.89, 165.31, 165.53, 168.02, (arom.) ppm; *m/z* (EI, 70 eV): 274 ($M^{+\cdot}$, 100), 273 (80), 259 (M−CH_3, 18), 241 (M−SH, 19). Anal. Calcd for $C_{14}H_{14}N_2S_2$: C 61.28, H 5.14, N 10.21, S 32.37%, found C 61.17, H 5.09, N 10.11, S 32.22.

3.9.2. 5-(Methylthio)-7,8,13,14-tetrahydrodibenzo[*a*,*i*]-phenanthridine 25. Mp 149–150 °C (EtOH); ν (KBr) 1544, 1427, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.66 (m, 2H, CH_2), 2.69 (s, 3H, SCH_3), 3.03 (m, 6H, CH_2), 7.36 (m, 7H), 8.23 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 14.60 (CH_3S), 28.88 (CH_2), 29.48 (CH_2), 32.95 (CH_2), 124.76, 125.91, 126.12, 127.03, 127.26, 127.68, 127.70, 127.84, 128.56, 129.08, 132.40, 133.18, 138.97, 139.05, 144.70, 153.34, 157.39 (arom.) ppm; *m/z* (EI, 70 eV): 329 ($M^{+\cdot}$, 94), 328 (100), 314 (M−CH_3, 19), 296 (M−SH, 22). Anal. Calcd for $C_{22}H_{19}NS$: C 80.20, H 5.81, N 4.25, S 9.73%, found C 80.10, H 5.77, N 4.11, S 9.65.

3.9.3. 5-(Methylsulfonyl)-7,8,13,14-tetrahydrodibenzo[*a*,*i*]phenanthridine 32. To a stirred solution of 5-(methylthio)-7,8,13,14-tetrahydrodibenzo[*a*,*i*]phenanthridine **25** containing 0.5 g (1.52 mmol) in 20 mL of anhydrous dichloromethane was added slowly a solution of 1.1 g (6.54 mmol) of *m*-CPBA in 20 mL of dichloromethane. The mixture was stirred at room temperature for 4 h. An aqueous solution of $Na_2S_2O_3$ (5%) was then added and the layers shaked and separated. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers washed with $NaHCO_3$ aqueous solution, brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by recrystallization to give 0.45 g (83%) of **28**, mp 234–235 °C (EtOH); ν (KBr): 1402, 1261 (SO_2), 1124, 764 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.71 (t, 2H, J=8.5 Hz, CH_2), 3.01 (m, 4H, 2H), 3.14 (d, 2H, J=8.5 Hz, CH_2), 3.44 (s, 3H, CH_3), 7.35 (m, 6H), 7.50 (m, 1H), 8.27 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 29.15 (CH_2), 29.43 (CH_2), 32.60 (CH_2), 41.78 (CH_3), 126.38, 126.44, 126.62, 128.18, 128.92, 128.95, 129.63, 130.19, 130.96, 131.79, 138.04, 139.67, 148.12, 151.91, 156.62 (arom.) ppm; *m/z* (EI, 70 eV): 361 ($M^{+\cdot}$, 100), 360 (60), 296 (M−SO_2H, 17), 282 (M−CH_3SO_2, 72). Anal. Calcd for $C_{22}H_{19}NO_2S$: C 73.10, H 5.30, N 3.88, S 8.87%, found C 72.95, H 5.25, N 3.76, S 8.77.

3.9.4. 5-Methoxy-7,8,13,14-tetrahydrodibenzo[*a*,*i*]phenanthridine 33. A solution containing 0.3 g (0.59 mmol) of **32** and sodium methoxide (0.15 g, 2.36 mmol) in 20 mL of dry methanol was refluxed for 2 h. After addition of water and extraction with dichloromethane, the organic layers were washed with brine. Elimination of solvent affords a residue, which was purified by recrystallization giving 0.04 g (22%) of **33**, mp 141–142 °C (EtOH); ν (KBr): 1296, 1066, 796 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.69 (m, 2H, CH_2), 2.93 (s, 4H, CH_2), 3.11 (m, 2H, CH_2), 4.09 (s, 3H, CH_3), 7.27 (m, 7H), 8.27 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 28.45 (CH_2), 29.38 (CH_2), 29.40 (CH_2), 32.68 (CH_2), 53.37 (CH_3), 116.58, 122.79, 125.97, 126.26, 126.60, 126.87, 126.91, 127.65, 128.02, 128.20, 131.57, 133.41, 137.98, 138.64, 146.59, 155.95, 158.82 (arom.) ppm; *m/z* (EI, 70 eV): 313 ($M^{+\cdot}$, 100), 312 (89), 296 (M−CH_3, 10). Anal. Calcd for $C_{22}H_{19}NO$: C 84.31, H 6.11, N 4.47%, found C 84.23, H 6.05, N 4.38.

3.9.5. 5-(Methylthio)dibenzo[*a*,*i*]phenanthridine 31. A mixture of 0.9 mmol of **25** and DDQ (0.83 g, 3.6 mmol) in 10 mL of *o*-DCB was heated at 120 °C during 3 h. The solvent was removed under reduced pressure and the residue is purified by flash chromatography using hexane/ethyl acetate 9:1 as eluent. The crude product afforded 0.22 g (75%) of **31**, mp 133–134 °C (EtOH); ν (KBr) 1261, 1020, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.93 (s, 3H, CH_3), 7.72 (m, 4H), 8.07 (m, 5H), 8.93 (m, 2H), 9.55 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 29.68 (CH_3), 124.26, 125.22, 125.98, 126.53, 126.75, 126.88, 127.54, 127.79, 128.22, 128.83, 129.49, 130.34, 130.69, 132.48, 132.77, 134.83, 172.28 (arom.) ppm; *m/z* (EI, 70 eV): 325 ($M^{+\cdot}$, 61), 324 (100), 310 (M−CH_3, 19), 278 (M−SCH_3, 24). Anal. Calcd for $C_{22}H_{15}NS$: C 81.20, H 4.65, N 4.30, S 9.85%, found C 81.11, H 4.50, N 4.26, S 9.77.

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New active-iron based reducing system for carbonyl compounds and imines. Stereoselective reduction of cyclic ketones

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Abstract—The reaction of different carbonyl compounds and imines with a mixture of iron(II) chloride tetrahydrate, an excess of lithium powder, and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB, 5 mol%) in THF at room temperature, led to the formation of the corresponding alcohols and amines, respectively. The process was also applied to the transformation of α,β-unsaturated carbonyl compounds into the corresponding saturated alcohols. The new reducing system exhibited good to excellent diastereoselectivity toward the reduction of different monocyclic and polycyclic ketones.

1. Introduction

From the fundamental point of view, reduction reactions of unsaturated organic substrates represent one of the most widely used and valuable functional group transformations in synthetic organic chemistry. Metal-mediated reductions of unsaturated organic substrates by hydrogen- or electron-transfer, are currently considered as interesting alternatives to the widely used catalytic hydrogenation, because of their both considerable practical and fundamental importance. Their practical meaning arise from the fact that such reactions are convenient both in large- or lab-scale synthesis, since there is no need to employ a high hydrogen pressure or to use hazardous reducing agents.

Among the various reducible substrates, aldehydes, ketones, α,β-unsaturated carbonyl compounds and imines, are of great relevance in order to obtain the corresponding alcohols and amines, respectively. Different valuable methods have been reported to perform these reactions, from which four important general procedures can be highlighted involving the use of (a) metal hydrides; (b) dissolving metals; (c) catalytic hydrogenation, mainly under heterogeneous reaction conditions and (d) transfer hydrogenation.[1] Some other methods, such as electrochemical or enzymatic methods are of less general application.

On the other hand, the stereoselective reduction of cyclic ketones is an extremely important reaction in organic synthesis. Most of the published results in this area consist in using metal hydrides or complex reducing agents, for which correlations of the stereochemical outcome have been proposed by numerous investigators.[2] In general, bulky reducing agents favour the approach to the carbonyl group via an equatorial trajectory, giving the thermodynamically less stable axial alcohol. Among the known methods to achieve this transformation, those involving the Selectride reagents developed by Brown are the most notable,[3] although many other interesting methods have been reported.[4] Concerning the synthesis of the more stable equatorial alcohols from cyclic ketones, although several valuable methods have been devised,[5] generally acceptable reagents for this transformation are not as well developed.

In recent years, we have worked with new reducing systems based on the use of activated transition metals, mainly active nickel, generated from the system $NiCl_2 \cdot 2H_2O$–Li–arene (cat.), which demonstrated to be very efficient in the reduction of a wide variety of organic functionalities.[6] More recently, and taking into account the periodic table proximity and the little work published regarding copper-mediated reduction reactions, we focused on the copper-based $CuCl_2 \cdot 2H_2O$–Li–arene (cat.) combination, which

Keywords: Reduction; Ketones; Aldehydes; Imines; Stereoselectivity; Arene catalysis; Active iron.
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was found to be very efficient in the reduction of carbonyl compounds and imines,[7] as well as in the hydrodehalogenation[8a] of aryl and alkyl halides.[8b]

The results obtained thereof together with our ongoing interest in the field above described, encouraged us to explore new metal alternatives to these active-metal based reducing systems, now focusing on iron, as a possible candidate to be used in the reduction or carbonyl compounds and imines. Iron salts are cheap when compared with other transition metal salts. Other main advantages are, however, the fact that its environmental impact is virtually nil and that there is no exposure limit to humans, as stated by the OSHA (United States Occupational Safety and Health Administration).

In this sense, most of the literature revised deals with the reduction of α,β-unsaturated carbonyl compounds. Conjugate reduction can be accomplished either by using hydridoiron complexes, prepared in situ from iron pentacarbonyl $Fe(CO)_5$ and a small amount of NaOH in methanol,[9] or by the binuclear cluster hydride $NaHFe_2(CO)_2$ with both excellent yields and mild reaction conditions.[10] On the other hand, the *cis*-hydride η^2-dihydrogen iron complex, $[P(CH_2CH_2PPh_2)_3Fe(H)(H_2)]BPh_4$, has been used as homogeneous catalyst in the hydrogen transfer reduction of α,β-unsaturated ketones to give either the saturated ketones, or the saturated or unsaturated alcohols, depending on the substrate, with fairly good results.[11] In another case, the iron(II) or (III) chloride–sodium hydride system has demonstrated to be an effective reducing agent for the reduction of ketones and aldehydes to the corresponding alcohols but with long reaction times.[12]

Finally, to the best of our knowledge, no published results appear in the literature regarding the iron-mediated stereoselective reduction of cyclic ketones (a fundamental subject in the synthesis of organic biomolecules) or the reduction of imines.

In this paper, we want to present a simple and effective methodolgy to accomplish the reduction of carbonyl compounds and imines under very mild reaction conditions, based on the use of active iron, generated from commercially available iron(II) chloride tetrahydrate, lithium and a catalytic amount of DTBB (4,4′-di-*tert*-butylbiphenyl) as electron carrier.[13] The results obtained are encouraging since aldehydes, ketones (including saturated, cyclic, and α,β-unsaturated substrates) and imines are reduced to the corresponding alcohols and amines in good yields, the reduction of cyclic ketones showing good to excellent diastereoselectivity.

2. Results and discussion

2.1. Reduction of carbonyl compounds

The reaction of different ketones and aldehydes with a mixture of iron(II) chloride tetrahydrate (1.0–2.5 mmol), an excess of lithium powder (1/8 molar ratio, referred to the iron salt), and a catalytic amount of DTBB (0.1 mmol/mmol of iron salt, 5 mol%) in tetrahydrofuran at room temperature, led to the corresponding secondary and primary alcohols, respectively, in good yields (Table 1).

Two blank experiments with nonan-5-one demonstrated the necessity of using the hydrated iron salt: either without the mentioned salt or using the corresponding anhydrous one, the starting material was recovered accompanied by traces of the pinacol coupling products after stirring overnight at room temperature.

The reducing system found application in the reduction of linear acyclic (Table 1, entry 1), dicycloalkyl (Table 1, entry 2), polycyclic (Table 1, entry 3), and aromatic ketones (Table 1, entries 4 and 5). For instance, the reduction of 2-adamantan-2-one (Table 1, entry 3) using 2 equiv of the reducing system rendered the corresponding 2-adamantan-2-ol in excellent yield. Lower conversion of the highly hindered ketone dicyclohexylketone (Table 1, entry 2), was, however, obtained and proved to be difficult to improve even with long reaction times, higher reaction temperature, or using an excess of the reducing system. More intriguing was the mediocre conversion achieved with acetophenone (Table 1, entry 4), above all taking into account that the related compound benzophenone (Table 1, entry 5) gave the corresponding alcohol in good yield after a reasonable reaction time.

On the other hand, the mentioned reducing system showed a remarkable behaviour in the reduction of cyclic ketones prone to yield diastereomeric alcohol products (Table 1, entries 6–10). In general, good to excellent diastereoselectivity was obtained, which was, however, difficult to rationalise in terms of a general mechanism, due to the different factors affecting the reduction pathway of cyclic ketones, namely: the nature of the metal, the structure of the ketone, the size of the reducing agent, the solvent, and the possibility of conformational equilibrium and of electrophilic assistance. Nonetheless, some comparison can be established on the basis of the examples available in the literature and of the steric approach control and product development control applied by Dauben and co-workers,[14] and redefined later by Brown and Deck[15] as steric strain control and product stability control, for the reduction of relatively hindered or unhindered cyclic ketones, respectively.

In the case of 4-*tert*-butylcyclohexanone (Table 1, entry 6), in which the bulky *tert*-butyl group is far from the carbonyl group, the resulting product was the thermodynamically more stable equatorial alcohol (eq/ax 99:1), *trans*-4-*tert*-butylcyclohexanol, the reduction seemingly being product stability controlled. Taking into account that the ratio of the alcohols formed remained constant after complete disappearance of the starting material, and considering that in an equilibrium mixture the more stable equatorial alcohol predominates by only 2.4:1, we discarded any isomerizing process.[2e] On one hand, the result obtained resembles those with the most common metal hydrides ($LiAlH_4$, $NaBH_4$, or $LiBH_4$, up to eq/ax 94:6)[16] or the complex reducing agents of Caubère's group (up to eq/ax 90:10).[17] In both cases, it was demonstrated that a maximum selectivity towards the axial attack was achieved by the addition of alkaline salts (like the LiCl in situ generated in our reaction). On the other

Table 1. Reduction of carbonyl compounds

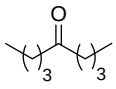
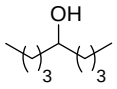
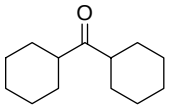
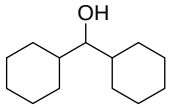
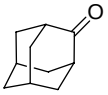
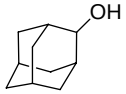
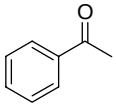
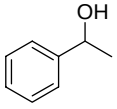
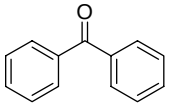
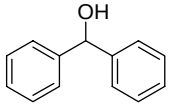
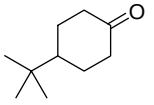
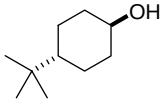
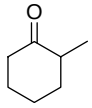
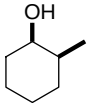
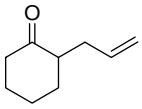
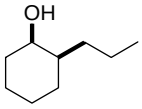
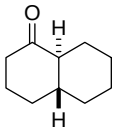
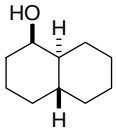
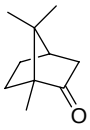
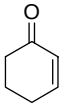
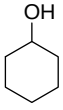
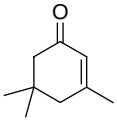
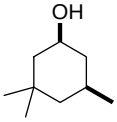
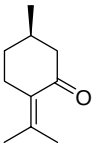
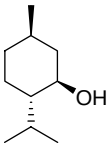
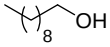
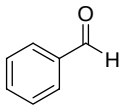
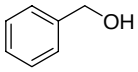
Entry	Carbonyl compound	Reaction conditions		Product[a]	
		$FeCl_2 \cdot 4H_2O$ (equiv)	t (h)	Structure	Yield (%)[b]
1		1.0	4		85
2		2.0	24		53[c]
3		2.0	3		90
4		2.0	24		50[d]
5		2.0	5		77
6		1.0	4		70[e]
7		1.5	3		82[f]
8		2.0	12		74[g]
9		1.5	3		91[h]
10		2.0	24		62[i]
11		2.5	4		82[j]
12		2.5	5		78[k]
13		2.5	5		75[l]
14		1.0	6		82

Table 1 (*continued*)

Entry	Carbonyl compound	Reaction conditions		Product[a]	
		$FeCl_2 \cdot 4H_2O$ (equiv)	*t* (h)	Structure	Yield (%)[b]
15		1.0	8		60[m]

[a] All isolated products were >95% pure (GLC).
[b] Isolated yield after column chromatography (silica gel, hexane/EtOAc) based on the starting material, unless otherwise stated.
[c] 60% Conversion; 40% recovered starting material.
[d] 55% Conversion; 45% recovered starting material.
[e] Diastereoisomeric ratio: trans/cis 99:1.
[f] Diastereoisomeric ratio: cis/trans 95:5.
[g] Diastereoisomeric ratio: cis/trans 95:5.
[h] Diastereoisomeric ratio: cis/trans 99:1.
[i] Diastereoisomeric ratio: *endo*/*exo* 90:10.
[j] GLC yield based on the starting material (cyclohexanol as external standard).
[k] 86% Conversion; diastereoisomeric ratio: cis/trans 99:1.
[l] Diastereoisomeric ratio: menthol/neoisomenthol/neomenthol 75:6:19.
[m] 70% Conversion; 25% recovered starting material.

hand, lithium in liquid ammonia afforded only the trans isomer, although in moderate yield (57%) and accompanied with unreacted ketone (25%) and the corresponding pinacol (18%).[18]

In the reduction of more hindered ketones (Table 1, entries 7–9), the reaction apparently proceeded through the approach of the reducing species from the less hindered side of the substrate, rendering the less stable axial alcohol, the reduction apparently being steric strain controlled. In particular, the diastereoselectivity observed in the reduction of 2-methylcyclohexanone (Table 1, entry 7, ax/eq 95:5) was comparable to that obtained with the more hindered lithium and potassium Selectrides (up to ax/eq 99:1) or with dicyclohexylborane (ax/eq 94:6)[19] in contrast with the major equatorial alcohol obtained with other common reducing systems such as $LiAlH_4$, $NaBH_4$, 9-BBN,[19] $BH_3 \cdot THF$[20] or with Li/NH_3.[21] The reduction of *trans*-decalone was highly effective (Table 1, entry 9), providing both high yield (91%) and diastereoselectivity (ax/eq 99:1), therefore being much superior to that reported with $NaBH_4$/MeOH (ax/eq ~35:65).[22]

Interestingly, the reduction of (±)-camphor (Table 1, entry 10) leading to the more stable of the two possible isomers, *endo*-borneol (*endo*/*exo* 90:10), required long reaction times (24 h) and an excess of the reducing system for a 70% conversion of the starting material. In this case, the stereochemistry of the alcohol product obtained was more consistent with a dissolving metal-type mechanism.[23] Thus, *endo*-borneol was the major product (*endo*/*exo* 82:18) in the reduction of (±)-camphor by alkali-metal/NH_3,[24] whereas M/NH_3 in the presence of MBr (M=Li, K) reduced (+)-camphor in a 53:47–80:20 *endo*/*exo* ratio of the corresponding alcohols.[25] According to Huffman and Charles,[21] for a hindered ketone, or one reacting sluggishly at the carbonyl carbon atom, the principal pathway for the reduction using dissolving metals would be that through the corresponding dianion, leading to a near-equilibrium distribution of product alcohols, which is quite consistent with our experimental observations.

When the above described methodology was applied to α,β-unsaturated carbonyl compounds (Table 1, entries 11–13), the use of an equimolecular amount of the metal salt afforded different mixtures of both possible partially reduced products (saturated ketones and α,β-unsaturated alcohols) together with the unreacted starting material. Unfortunately, all our efforts to drive the reaction pathway towards only one of these semireduction products were unsuccessful, even at low temperature (−10 to −78 °C) or at shorter reaction times. By using a 1:2.5 ketone to iron salt molar ratio, the process afforded the corresponding saturated alcohols in good yields. Regarding the stereochemistry of the reaction products, isophorone (Table 1, entry 12) was reduced to the more stable 1,5-diequatorial 3,3,5-trimethylcyclohexanol with excellent diastereoselectivity (see Table 1, footnote k). On the other hand, the reduction of (+)-pulegone also rendered the most stable of the four possible diastereomers, (−)-menthol, as the major product accompanied by minor amounts of neomenthol and neoisomenthol (see Table 1, footnote 1). Similar selectivity towards the axial attack on the carbonyl group of (+)-pulegone was also reported with $NaBH_4$–MeOH[26] or with lithium pyrrolidinoborohydride.[5d] On the other hand, the dissolving-metal reduction (both in the presence or absence of proton donors) of 3,3,5-trimethylcyclohexanone[21] and menthone[27] afforded high ratios of equatorial to axial alcohols, whereas the reduction of the former by either $LiAlH_4$ or $NaBH_4$ gave the axial alcohol as the major product.[28]

Finally, the reducing system described herein also found application in the reduction of aldehydes to the corresponding primary alcohols (Table 1, entries 14 and 15). Decanal was transformed into decan-1-ol in good yield (Table 1, entry 14), whereas benzaldehyde could not be completely reduced, exhibiting a similar behaviour to that of acetophenone (Table 1, entry 4).

Some additional experiments were carried out in order to disclose the main reaction mechanism operating in the above reactions. For instance, when 2-methylcyclohexanone was subjected to reduction with anhydrous $FeCl_2$–Li–DTBB (cat.)

under a molecular hydrogen atmosphere for 24 h, 2-methylcyclohexanol was obtained in 23% yield but with opposite diastereoselectivity to that shown in Table 1 (entry 7). The 75:25 trans/cis ratio obtained for 2-methylcyclohexanol might discard a catalytic hydrogenation-type reaction, in which iron would catalyse the addition to the carbonyl group of the molecular hydrogen resulting from the reaction of the excess of lithium with the hydration water of the iron salt. Despite the platinum-catalysed hydrogenation of 2-methylcyclohexanone in protic solvents furnished mainly the cis product, it is well known that several factors such as the structure of the substrate, the catalyst, the solvent, the reaction temperature, the pressure of hydrogen and other reaction conditions, can vary the stereochemistry of the catalytic hydrogenation of cyclic ketones.[29]

A preliminary mechanistic proposal can be made according to all the data showed above. A metal-dissolving reaction mechanism could be very plausible, which would directly explain the formation of the most stable *trans*-4-*tert*-butylcyclohexanol (Table 1, entry 6) and *endo*-borneol (Table 1, entry 10) by protonation of the most stable carbanion intermediate.[23b] In these two cases, a fast equilibrium between the two epimeric carbanions, followed by a slow protonation step through the lower axial and exo protonation transition states, respectively, would account for the formation of the thermodynamically more stable products. In contrast, due to the presence of acidic protons in the reaction medium, a kinetically controlled protonation of the intermediate carbanion can take place prior to equilibration,[23a] to furnish the less thermodynamically stable axial alcohols in the case of the structurally related 2-methylcyclohexanone, 2-allylcyclohexanone, and *trans*-decalone (Table 1, entries 7–9).

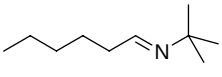
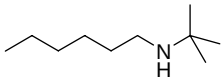
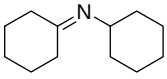
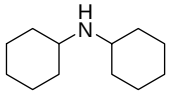
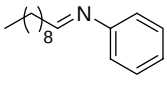
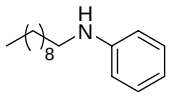
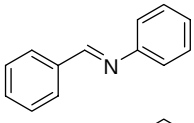
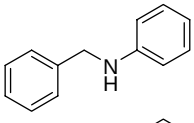
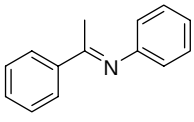
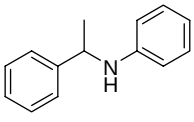
The reduction of α,β-unsaturated cyclic ketones (Table 1, entries 11–13) could be also explained in terms of a dissolving-metal mechanism. Assuming that two steps are involved in this process, reduction of the carbon–carbon double bond and reduction of the carbonyl group, enolate formation in the first step may lead to equilibration before reduction of the carbonyl group in (+)-pulegone, leaving the isopropyl group mainly trans to the methyl group (94:6). The high ratios in favour of the equatorial alcohols could be also explained by an equilibration pathway in the second step and are in agreement with those reported in the literature.[21,27]

Nonetheless, even with the assumption that a dissolving-metal mechanism is operating in the reduction of cyclic ketones, it must be pointed out the controversy arisen about whether these reductions are kinetically or thermodynamically controlled. As stated by Huffman, the different explanations proposed to account for the stereoselectivity of these reductions are of dubious predictive value.[30]

2.2. Reduction of imines

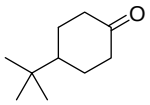
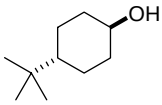
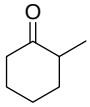
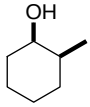
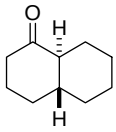
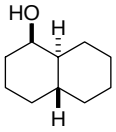
Table 2 lists the results obtained in the reduction of a series of aldimines and ketimines by applying the same above mentioned protocol for the reduction of carbonyl compounds. The corresponding secondary amines were obtained in good yields using a 1:2.0–2.5 imine to iron salt molar ratio. The lower yield observed in the case of the aldimine derived from benzaldehyde and aniline can be attributed to an overreduction, to some extent, at the benzylic position (Table 2, entry 4). On the contrary, this side reaction was not observed in the reduction of the ketimine derived from acetophenone and benzylamine, probably due to the shorter reaction time required (Table 2, entry 5).

Table 2. Reduction of imines

Entry	Imine	Reaction conditions		Product[a]	
		$FeCl_2 \cdot 4H_2O$	*t* (h)	Structure	Yield (%)[b]
1		2.0	8		78
2		2.0	12		74
3		2.5	14		82
4		2.5	14		65
5		2.5	8		77

[a] All isolated products were >95% pure (GLC).
[b] Isolated yield after column chromatography (silica gel, hexane/EtOAc) based on the starting material.

Table 3. Comparative stereoselective reduction of ketones with different metal salts

Entry	Ketone	Product[a]			
		Structure[b]	$NiCl_2 \cdot 2H_2O$[c]	$CuCl_2 \cdot 2H_2O$[c]	$FeCl_2 \cdot 4H_2O$[c]
1			95:5 (73)	95:5 (70)	99:1 (70)
2			90:10 (85)	85:15 (73)	95:5 (82)
3			99:1 (88)	99:1 (84)	99:1 (91)
4			80:20 (65)	85:15 (55)	90:10 (62)

[a] The reducing system was composed of the hydrated metal salt (1–2 mmol), an excess of lithium powder (1/8 molar ratio, referred to the metal salt), and a catalytic amount of DTBB (0.1 mmol/mmol of metal salt) in THF at room temperature.
[b] The structure of the major diastereoisomer is shown.
[c] Diastereomeric ratio determined by GLC/MS; isolated yields after column chromatography (silica gel, hexane/EtOAc) in parentheses.

Taking into account the previous reduction studies on carbonyl compounds and imines carried out with other transition-metal salts, we also want to compare herein the reactivity and selectivity of the present reducing system with those of the closely related nickel and copper salts, $NiCl_2 \cdot 2H_2O$[31] and $CuCl_2 \cdot 2H_2O$,[7] respectively. Concerning the reactivity, in general, similar results were obtained both in the reduction of carbonyl compounds and imines irrespective of the reducing system used, in all cases with moderate to good yields.[7,31] As regards the selectivity, however, the $NiCl_2 \cdot 2H_2O$-based system showed to be more selective in the reduction of α,β-unsaturated ketones, several examples of which could be transformed into the corresponding saturated ketones or saturated alcohols depending on the amount of salt used. In order to compare the stereoselectivity, 4-*tert*-butylcyclohexanone, 2-methylcyclohexanone, *trans*-decalone, and (±)-camphor were used as substrates and subjected to reduction with $NiCl_2 \cdot 2H_2O$, $CuCl_2 \cdot 2H_2O$, and $FeCl_2 \cdot 4H_2O$, under the same reaction conditions (Table 3). Comparable isolated yields of the products were obtained for any of the substrates studied. It is worthy of note that the highest diastereoselectivities were reached with the present reducing system, $FeCl_2 \cdot 4H_2O$. Despite in most of the cases the values are relatively high and not very different, it can be concluded that the efficiency in diastereoselectivity follows the trend: $FeCl_2 \cdot 4H_2O > NiCl_2 \cdot 2H_2O \approx CuCl_2 \cdot 2H_2O$, which is the same order found for the atomic radii of the corresponding metals. The importance of the structure of the starting ketone in the final result is exemplified by the reduction of *trans*-decalone, which is reduced with equal diastereoselectivity by any of the reducing systems (Table 3, entry 3). The fact that the selectivities observed work in the same direction for any of the metal salts tested, indicate that a similar type of reaction mechanism may be operating in all these reductions (see above).

3. Conclusion

In conclusion, we have described herein a new procedure to reduce carbonyl compounds and imines to the corresponding alcohols and secondary amines, respectively, under very mild reaction conditions, using the active iron-based reducing combination $FeCl_2 \cdot 4H_2O$–Li–DTBB (cat.). The most prominent feature of this system is the high diastereoselectivity achieved in the reduction of cyclic ketones, higher than that achieved with the $NiCl_2 \cdot 2H_2O$ and $CuCl_2 \cdot 2H_2O$ salts. In addition, the simplicity, together with the commercial availability ($NiCl_2 \cdot 2H_2O$ is not commercially available) and low toxicity of the iron salt (much lower than the analogous nickel or copper salts previously studied), makes this new system a very attractive alternative to other reducing agents. We are actively exploring new applications of this reagent to the reduction of other organic functional groups.

4. Experimental

4.1. General

All moisture sensitive reactions were carried out under a nitrogen atmosphere. Anhydrous tetrahydrofuran was freshly distilled from sodium/benzophenone ketyl. Other solvents used were treated prior to use by standard methods.[32] Iron(II) chloride tetrahydrate was commercially available (Aldrich). Column chromatography was performed with Merck silica gel 60 (0.040–0.063 μm, 240–400 mesh). Thin-layer chromatography (TLC) was performed on precoated silica gel plates (Merck 60, F254, 0.25 mm). Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker ARX-300 spectrophotometer using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal

reference. Mass spectra (EI) were obtained at 70 eV on a Hewlett Packard HP-5890 GC/MS instrument equipped with a HP-5972 selective mass detector. Infrared (FT-IR) spectra were obtained on a Nicolet-Nexus spectrophotometer. The purity of volatile compounds and the chromatographic analyses (GC) were determined with a Shimadzu GC-9A instrument equipped with a flame-ionization detector and a 2 m column (1.5% OV17 9_A SUS Chrom 103 80/1000), using nitrogen as carrier gas.

All starting carbonyl compounds (Table 1) were commercially available (Merck, Aldrich, Fluka) of the best grade and were used without further purification. Imines showed in entries 1,[33] 2,[34] 3,[33] 4,[35] and 5[33] (Table 2) were prepared according to the corresponding literature procedures. In all cases, except for benzylideneaniline, the crude imine was used for the reduction step without further purification.

4.2. Reduction of carbonyl compounds and imines using the $FeCl_2 \cdot 4H_2O$–Li–DTBB (cat.) combination. General procedure

A solution of the corresponding carbonyl compound (1.0 mmol) in THF (10 mL) was added to a mixture of iron(II) chloride tetrahydrate (198 mg, 1.0 mmol), lithium powder (56 mg, 8.0 mmol) and DTBB (27 mg, 0.1 mmol), at room temperature under a nitrogen atmosphere. The reaction mixture, which was initially dark green, changed to black, indicating that iron(0) was formed. The reaction time was monitored by GLC. After a total conversion of the starting material, the resulting suspension was diluted with ether (10 mL) and carefully hydrolysed with water (15 mL, for imines), or with 10% hydrochloric acid solution (15 mL, for carbonyl compounds). The organic layer was dried over anhydrous magnesium sulfate and evaporated (15 Torr) to give a residue, which after purification by column chromatography (silica gel, hexane/EtOAc) yielded the corresponding pure compound. For volatile products, the dried organic layer was analysed by GLC using octan-1-ol as an internal standard. Nonan-5-ol, dicyclohexylmethanol, adamantan-2-ol, *sec*-phenethyl alcohol, diphenylmethanol, *cis*- and *trans*-4-*tert*-butylcyclohexanol, *cis*-2-methylcyclohexanol, *endo*-borneol, cyclohexanol, (−)-menthol, *n*-decanol, and benzyl alcohol, as well as *N*-dicyclohexylamine and phenylbenzylamine, were characterised by comparison of their chromatographic and spectral data with those of the corresponding commercially available pure samples. ($1R^*$,$4aR^*$,$8aS^*$)-decahydronaphthalen-1-ol,[36] *cis*-2-propylcyclohexanol,[37] *cis*-3,3,5-trimethylcyclohexanol,[38] *N*-*tert*-butylhexylamine,[31,39] *N*-decylaniline,[40] and *N*-benzyl-1-phenethylamine,[31,41] were characterised by comparison of their chromatographic and spectral data with those described in the literature.

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A concise synthesis of novel naphtho[*a*]carbazoles and benzo[*c*]carbazoles

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Abstract—Starting from simple indole precursors the synthesis of naphtho[*a*]carbazoles and benzo[*c*]carbazoles is described. Key steps include the use of the Suzuki–Miyaura reaction to afford 2- or 3-aryl substituted indoles, as well as a potassium *t*-butoxide and light assisted aromatic ring-forming reaction.

1. Introduction

Indolocarbazoles such as rebeccamycin **1** and staurosporine **2** display a range of biological activities that make them attractive compounds to synthetic and medicinal chemists.[1–4] As a result, the synthesis of many analogues, for example, **3** and **4** and the benzo- and naphtho-fused carbazoles such as **5** and **6** (Fig. 1), have been described. Compound **3** has been found to be a potent tyrosine kinase inhibitor of vascular endothelial growth factor R2,[5] while isogranulatimide **4** has been described as an G2 checkpoint inhibitor.[5a] The naphtho- and benzo-fused carbazoles (although rarely found in Nature) are of interest owing to their potential as antitumour agents.

For example, the synthetic naphtho[*a*]carbazole[6] **5** is a potential candidate for cancer treatment as a result of DNA intercalative binding properties[7] and the well-known indole/naphthalene bioisotery,[8] while benzo[*c*]carbazole **6**[9] shows promising profiles for intra-cyclin dependent kinase selectivity. In general it has been found that modification of the indolo[2,3-*a*]carbazole framework can lead to products with very different useful pharmacological properties and biological activities.[5]

In these laboratories, we have developed novel methodology for the synthesis of benzo[*a*]carbazoles and pyrido[2,3-*a*]-carbazoles[10,11] by means of a novel light- and base-assisted cyclization reaction to form a centrally-positioned aromatic

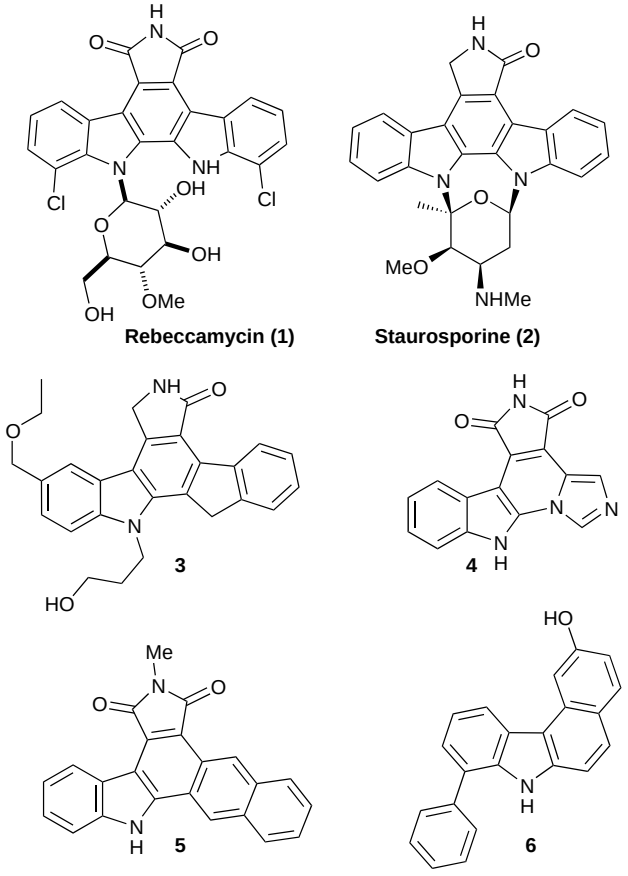

Figure 1. Representative biologically active indolocarbazoles and naphtho- and benzo-fused carbazoles.

Keywords: Suzuki–Miyaura reaction; Carbazoles; Antitumour; Potassium *t*-butoxide.
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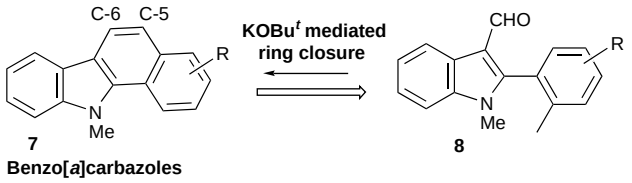


Figure 2. Retrosynthesis of benzo[*c*]carbazoles.

ring (Fig. 2). For benzo[*a*]carbazoles **7**, for example, the last step entails the construction of the C-5/C-6 bond (i.e., **8**→**7**) by our novel ring-forming reaction.[11]

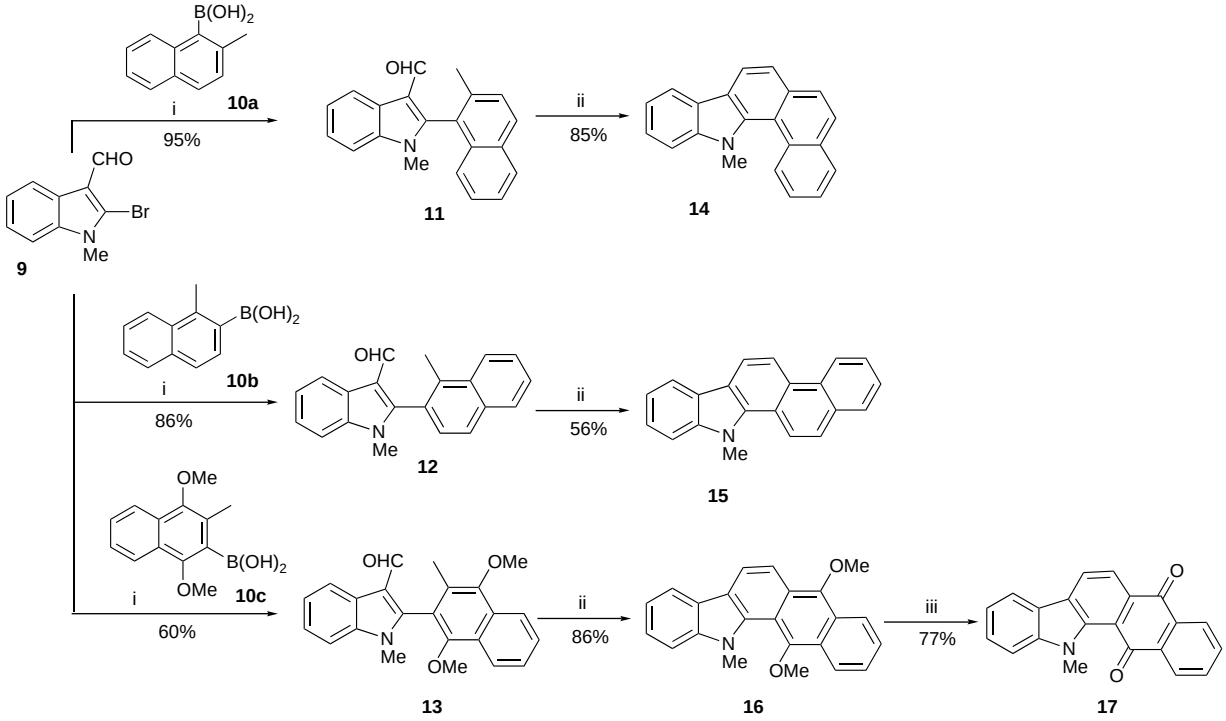
2. Results and discussion

As part of our ongoing programme we wished to extend the methodology developed for the synthesis of benzo[*a*]carbazoles to the synthesis of naphtho[*a*]-fused carbazoles and carbazoles containing rings fused onto the *c*-face. These extensions are described in this paper.[12]

As a starting point for this work we believed that treatment of the readily available *N*-methyl-2-bromoindole-3-carbaldehyde **9**[11] with a number of naphthaleneboronic acids, as we had done previously for benzeneboronic acids would provide easy access to naphtho[*a*]carbazoles. However, since the desired naphthaleneboronic acids were not commercially available, the initial task was to synthesize them. Boronic acid **10a** was prepared by treating 1-bromo-2-methylnaphthalene[13] with *n*-BuLi followed by the addition of trimethyl borate and then hydrochloric acid. The more challenging synthesis of boronic acid **10b** involved treatment of 1-methylindene with KOBu^t and $CHBr_3$ to give 2-bromo-1-methylnaphthalene,[14] which was treated in the same manner as 1-bromo-2-methylnaphthalene to afford 1-methyl-2-naphthylboronic acid **10b**. Boronic acid **10c** was synthesised as described previously.[15] Treatment of **10a–c** with **9** under aqueous Suzuki–Miyaura coupling reaction conditions afforded the desired biaryl compounds **11**, **12** and **13** in good yields (Scheme 1). It was clear from the spectroscopic data that the desired products had been formed. In particular, the presence of the aromatic methyl protons in the range of δ 2.2–2.5 in the ^{1}H NMR spectra were a good indication that the reaction had proceeded. Exposure of each of these substrates (**11**, **12** and **13**) to reaction conditions (KOBu^t, DMF, hν) that we have developed for forming new aromatic rings gave the desired naphtho-fused carbazoles **14**, **15** and **16** in fair to good yields (56–86%).[11,15] Naphthocarbazole **16** could also be oxidised with ceric ammonium nitrate to afford quinone **17**.[16]

As depicted in the retrosynthesis in Figure 3, we planned to extend this synthesis to benzo[*c*]carbazoles such as **18** from indoles such as **19** or **20** containing a substituted aromatic ring at the 3-position. Examination of the retrosynthesis shows that a carbonyl-containing substituent is required *ortho* to the biaryl linkage, either on the benzene ring or the indole nucleus. In addition, either the benzene ring or the indole nucleus must possess a methyl substituent at the 2-position. The biaryl linkage for both possible retrosynthesis could be formed, as before, using Suzuki–Miyaura coupling methodology.

As the first option we choose to attempt the synthesis using the disconnection leading to the placement of the carbonyl on the 2-position of the indole nucelus (i.e., **19**, Fig. 4). We believed that further disconnection would lead to a 3-bromoindole derivative such as **21**. The synthesis of **21a**



Scheme 1. Reagents and conditions: (i) 10 mol% $Pd(PPh_3)_4$, DME/EtOH, 2 M aq Na_2CO_3, reflux 48 h; (ii) KOBu^t, DMF, hν, 80 °C, 10 min; (iii) CAN, THF, rt.

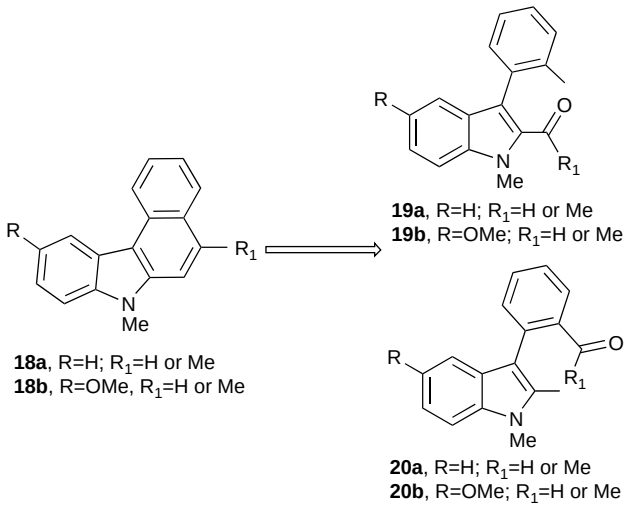


Figure 3. Retrosynthesis of benzo[*c*]carbazoles.

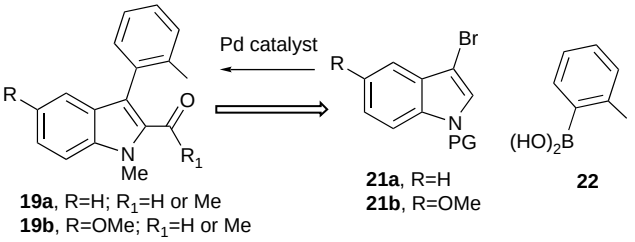


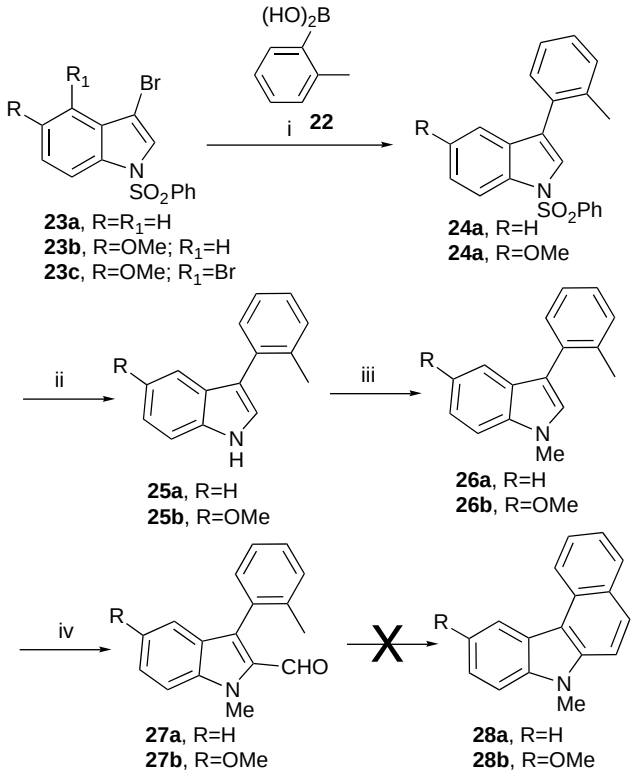
Figure 4. Retrosynthesis of **19**.

($PG{=}SO_2Ph$) has been described in the literature[17] and the toluene boronic acid **22** is commercially available and has been made and used many times in our laboratories. We thought that the carbonyl containing substituent at C-2 of the indole nucleus could be introduced once the aromatic ring had been placed at C-3 of the indole by means of a Suzuki–Miyaura coupling reaction.

The synthesis commenced with the preparation of the known compound **23a**[17] as well as its 5-methoxy analogue **23b**. The analogue **23b** was prepared by bromination of 5-methoxyindole followed by protection of the resulting 3-bromo-5-methoxyindole with phenylsulfonyl chloride to afford **23b** in 65% over two steps. If the steps were reversed and 5-methoxy-1-(phenylsulfonyl)-1*H*-indole was treated with bromine significant amounts of **23c** were isolated unless the reaction was done very carefully.

Treatment of both **23a** and **23b** under Suzuki–Miyaura reaction conditions with toluene boronic acid **22** provided the desired 3-aryl substituted indoles **24a** and **24b** in good yield (Scheme 2). In order to introduce the aldehyde substituent at the 2-position of the indole nucleus the phenylsulfonyl group on the indole nitrogen was removed and replaced by a methyl in a two-step procedure.

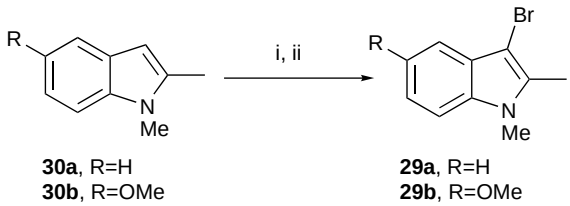
The first step was accomplished with K_2CO_3 in MeOH to give **25a** and **25b** and the second by exposure of the free indole nitrogen to $(MeO)_2SO_2$ and NaH to afford **26a** and **26b**. Attachment of the formyl group at C-2 was achieved by treatment of **26a** and **26b** under classical



Scheme 2. Reagents and conditions: (i) 10 mol% $Pd(PPh_3)_4$, DME, aq K_2CO_3, reflux, 18 h, **24a**, 100%; **24b**, 99%; (ii) MeOH, K_2CO_3, reflux, **25a**, 93%; **25b**, 96%; (iii) $(MeO)_2SO_2$, THF, NaH, rt, **26a**, 99%; **26b**, 99%; (iv) $POCl_3$, DMF, reflux, **27a**, 60%; **27b**, 27%; (v) $KOBu^t$, DMF, hν, 80 °C, 10 min, no reaction.

Vilsmeier–Haack reaction conditions to provide **27a** and **27b** in mediocre to poor yields of 60 and 27%, respectively. We were now in a position to attempt the base mediated ring closure reaction to hopefully yield the desired products **28a** and **28b**. To our surprise all attempts at this reaction failed to produce the desired products and the only detectable products from this reaction were the result of deformylation yielding **26a** and **26b**.[18] Hence the alternative retrosynthesis outlined in Figure 3 giving intermediates **20a** and **20b** was pursued in which the positions of the carbonyl and methyl substiuent were interchanged.

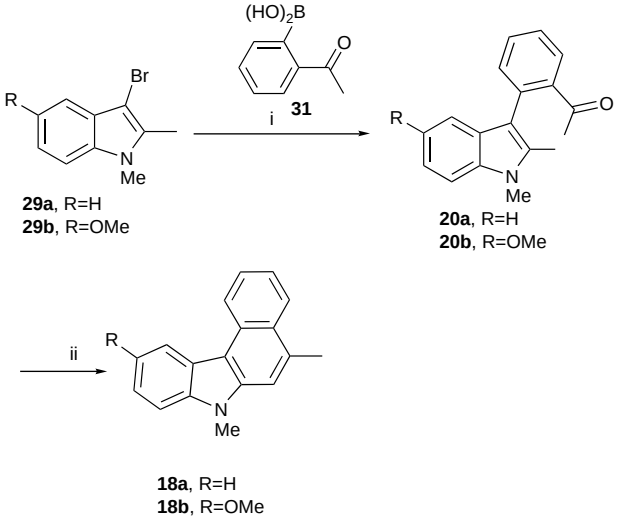
In order to achieve the synthesis of **20a–b**, suitable 2-brominated indole precursors **29a** and **29b** were prepared (Scheme 3). Exposure of 2-methylindole **30a** to molecular bromine followed by protection of the indole nitrogen by *N*-methylation afforded **29a** in good yield. The synthesis of methoxyindole **29b** was accomplished from **30b**, but in this case the bromination of **30b** was accomplished with



Scheme 3. Reagents and conditions: **30a**→**29a** (i) Br_2, DMF, rt, 99%; (ii) $(MeO)_2SO_2$, NaH, THF, 18 h, 99%. **30b**→**29b** (i) NBS, CH_2Cl_2, cat. SiO_2, 30 min, 99%; (ii) $(MeO)_2SO_2$, NaH, THF, 48 h, 94%.

N-bromosuccinimide (NBS), as the use of molecular bromine resulted in simultaneous bromination of the electron-rich aromatic ring. Both **29a** and **29b** were unstable and had to be used immediately in subsequent steps.

Treatment of both **29a** and **29b** under non-aqueous Suzuki–Miyaura coupling conditions with the commercially available boronic acid **31** resulted in the formation of the desired biaryl compounds **20a** and **20b** in good yields (Scheme 4). Exposure of **20a** and **20b** to potassium *t*-butoxide in the presence of light gave the desired benzo[*c*]carbazoles **18a** and **18b** in good yield. Clear evidence for the formation of the products was provided by spectroscopy. For example, in the ^{1}H NMR spectrum of **18a** an aromatic methyl at δ 2.79 was present and it was noted that both the acetyl methyl and the methyl at the 2-position of the indole nucleus of the starting material **20a** were no longer observed.



Scheme 4. Reagents and conditions: (i) 20 mol% $Pd(PPh_3)_4$, DMF, K_3PO_4, 100 °C, 65 h, **20a**, 83%; **20b**, 80%; (ii) $KOBu^t$, DMF, hν, 80 °C, 10 min, **18a**, 71%; **18b**, 70%.

In conclusion, we have been able to show that both [*a*]-fused naphtho- and [*c*]-fused benzocarbazoles can be synthesised from simple indole precursors using our well developed aromatic ring-forming reaction.

3. Experimental

3.1. General

^{1}H and ^{13}C NMR spectra were recorded either on a Bruker ADVANCE 300 (300.132 MHz for ^{1}H, 75.473 for ^{13}C), a Bruker DRX-400 (400.132 MHz for ^{1}H, 100.625 for ^{13}C) or a Bruker AC-200 (200.13 MHz for ^{1}H, 50.32 for ^{13}C) spectrometer at the frequency indicated. *J*-values are given in Hz. Infra-red spectra were recorded on either a Bruker IFS 25 Fourier Transform spectrometer, or on a Bruker Vector 22 Fourier Transform spectrometer. Mass spectra were recorded on a Kratos MS 9/50, VG 70E MS or a VG 70 SEQ mass spectrometer. Macherey-Nagel Kieselgel 60 (particle size 0.063–0.200 mm) was used for conventional silica gel chromatography, and Macherey-Nagel Kieselgel 60 (particle size 0.040–0.063 mm) was used for preparative flash chromatography. All solvents used for reactions and chromatography were distilled prior to use. THF and Et_2O were freshly distilled from sodium benzophenone ketyl under nitrogen.

3.1.1. 1-Bromo-2-methylnaphthalene. A solution of Br_2 (0.40 mL, 7.8 mmol) in acetic acid (2 mL) was added dropwise to a solution of 2-methylnaphthalene (1.01 g, 7.10 mmol) and anhydrous KOAc (0.75 g, 7.8 mmol) in AcOH (2 mL). After the mixture had been stirred for 15 min it was added to CH_2Cl_2 (20 mL) and the solution was washed with saturated aq $NaHCO_3$ (30 mL) and H_2O (20 mL). The residue obtained upon evaporation was purified by column chromatography (20% EtOAc–hexane) to obtain the product, 1-bromo-2-methylnaphthalene (1.43 g, 92%) as a clear oil. The spectral data agreed with that described in the literature.[13]

3.1.2. 2-Bromo-1-methylnaphthalene. $KOBu^t$ (2.10 g, 18.6 mmol) was stirred in 25 mL anhydrous Et_2O under N_2 atmosphere. Redistilled 1-methylindene (2.01 g, 15.5 mmol) was added dropwise to yield an orange slurry. Freshly distilled $CHBr_3$ (4.85 g, 19.6 mmol) was then added dropwise over a period of 35 min. The slurry became pink, then red and finally a deep red-violet with precipitation of solid material. The reaction mixture was periodically cooled to 20 °C while it was stirred for 2.5 h. The mixture was then quenched with water (50 mL) and extracted with Et_2O (3×50 mL) followed by brine. The mixture was filtered and dried with $MgSO_4$ to give brown oil. The oil was slurred in 37.5 mL of absolute EtOH and 0.50 g of KOH and heated at reflux for 30 min. Hexane (50 mL) was added and the mixture was heated for 30 min and filtered. The mixture was then rinsed with hexane (3×50 mL) and the solution was finally evaporated on a rotary evaporator. The crude material was then purified by column chromatography (5–20% EtOAc–hexane) to give the product, 2-bromo-1-methylnaphthalene (3.8 g, 38%) as a yellow oil. The ^{1}H and ^{13}C NMR spectral data agreed with that described in the literature.[14]

3.1.3. 2-Methyl-1-naphthylboronic acid 10a. *n*-BuLi (1.2 M, 3.9 mL, 4.7 mmol) was added dropwise to a solution of 1-bromo-2-methylnaphthalene (1.01 g, 4.57 mmol) in THF (30 mL) at −78 °C. The reaction mixture was stirred for 30 min at −78 °C, then $B(OMe)_3$ (1.39 g, 1.50 mL, 13.4 mmol) was added. The resulting mixture was stirred at −78 °C for a further 30 min and then allowed to warm to rt. The reaction mixture was acidified with aq 10% HCl solution and extracted with Et_2O (3×30 mL). The organic layer was then dried with $MgSO_4$ and concentrated under vacuum to afford an off-white crystalline material, 2-methyl-1-naphthylboronic acid **10a** (0.74 g, 87%), which was used without further purification or characterization.

3.1.4. 1-Methyl-2-naphthylboronic acid 10b. *n*-BuLi (1.4 M, 2.1 mL, 2.9 mmol) was added dropwise to a solution of 2-bromo-1-methylnaphthalene (0.50 g, 2.3 mmol) in THF (15 mL) at −78 °C. The reaction mixture was then treated as described above and $B(OMe)_3$

(0.70 g, 0.75 mL, 6.7 mmol) was added. An off-white crystalline material, 1-methyl-2-naphthylboronic acid **10b** (0.39 g, 93%) was produced, which was used without further purification or characterization.

3.1.5. 1,4-Dimethoxy-3-methyl-2-naphthylboronic acid 10c. 2-Bromo-1,4-dimethoxy-3-methylnaphthalene was prepared according to Ref. 19. This was then treated as described above to afford the desired boronic acid **10c**.[15]

3.2. Representative procedure for the Suzuki coupling reactions

3.2.1. 1-Methyl-2-(2-methyl-1-naphthyl)-1*H*-indole-3-carbaldehyde 11. A solution of 2-bromo-1-methyl-1*H*-indole-3-carbaldehyde **9** (0.100 g, 0.420 mmol) in DME (2 mL) was deoxygenated by passing N_2 through the mixture for 5 min. The deoxygenated mixture was added to $Pd(PPh_3)_4$ (10 mol%, 0.048 g, 0.040 mmol) and stirred under N_2 for 10 min at rt. A solution of 2-methyl-1-naphthylboronic acid **10a** (0.110 g, 0.591 mmol) in EtOH (1.5 mL) was deoxygenated and added to the reaction mixture. The mixture was stirred for a further 10 min. A deoxygenated 2 M aq Na_2CO_3 solution (3.0 mL, 6.0 mmol) was added and the reaction mixture was stirred at rt for 5 min before being heated at reflux for 2 days. The mixture was cooled to rt and quenched with H_2O (20 mL). The organic material was extracted with CH_2Cl_2 (3×30 mL) and the solvent was evaporated under reduced pressure. The crude product was subjected to column chromatography (2–10% EtOAc–hexane) to afford 1-methyl-2-(2-methyl-1-naphthyl)-1*H*-indole-3-carbaldehyde **11** as an off-white solid (0.120 g, 95%). Mp 146–147 °C; ν_{max}/cm^{-1} 1655 (C=O), 1579 (ArC=C), 1501, 1466, 1444 and 1421; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.28 (3H, s, $ArCH_3$), 3.42 (3H, s, NCH_3), 7.23 (1H, m, Ar-H), 7.35–7.51 (6H, m, 6×Ar-H), 7.91 (1H, d, J=8.0 Hz, Ar-H), 7.96 (1H, d, J=8.5 Hz, Ar-H), 8.48 (1H, m, Ar-H) and 9.45 (1H, s, CHO); δ_C (75 MHz; $CDCl_3$) 20.5 ($ArCH_3$), 30.2 (NCH_3), 109.8 (Ar-CH), 116.4 (Ar-C), 122.3 (Ar-CH), 123.3 (Ar-CH), 123.8 (Ar-CH), 124.4 (Ar-C), 125.0 (Ar-CH), 125.3 (Ar-C), 125.7 (Ar-CH), 127.4 (Ar-CH), 128.1 (2×Ar-CH), 130.2 (Ar-CH), 131.7 (Ar-C), 133.6 (Ar-C), 137.3 (Ar-C), 137.6 (Ar-C) and 149.4 (Ar-C), 186.0 (CHO); MS m/z 299 (M^+, 100%), 284 (38), 282 (55), 254 (19) and 127 (14); HRMS calcd for $C_{21}H_{17}NO$: 299.1310, found: 299.1307.

The following compounds were prepared in a similar manner.

3.2.2. 1-Methyl-2-(1-methyl-2-naphthyl)-1*H*-indole-3-carbaldehyde 12. The product **12** was isolated as an off-white solid (0.162 g, 86%) from **9** (0.150 g, 0.630 mmol) and **10b** (0.164 g, 0.882 mmol). Mp 184–186 °C; IR ν_{max}/cm^{-1} 1652 (C=O), 1610, 1579 and 1528 (ArC=C); δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.52 (3H, s, $ArCH_3$), 3.53 (3H, s, NCH_3), 7.35–7.43 (4H, m, 4×Ar-H), 7.61–7.67 (2H, m, 2×Ar-H), 7.83 (1H, d, J=8.4 Hz, Ar-H), 7.93–7.96 (1H, m, Ar-H), 8.11–8.14 (1H, m, Ar-H), 8.43–8.46 (1H, m, Ar-H), 9.61 (1H, s, CHO); δ_C (75 MHz; $CDCl_3$) 17.0 ($ArCH_3$), 31.0 (NCH_3), 110.2 (Ar-CH), 116.6 (Ar-C), 122.6 (Ar-CH), 123.7 (Ar-CH), 124.3 (Ar-CH), 125.0 (Ar-CH), 125.6 (Ar-C), 125.9 (Ar-C), 126.9 (Ar-CH), 127.5 (2×Ar-CH), 128.1 (Ar-CH), 129.2 (Ar-CH), 132.9 (Ar-C), 134.3 (Ar-C), 135.9 (Ar-C), 137.8 (Ar-C), 152.2 (Ar-C), 186.6 (CHO); MS m/z 299 (M^+, 78%), 284 (100), 282 (74), 254 (24); HRMS calcd for $C_{21}H_{17}NO$: 299.1310, found: 299.1309.

3.2.3. 1-Methyl-2-(1,4-dimethoxy-2-methyl-3-naphthyl)-1*H*-indole-3-carbaldehyde 13. The product **13** was isolated as a yellow solid (0.224 g, 60%) from **9** (0.247 g, 1.04 mmol) and **10c** (0.359 g, 1.46 mmol). Mp 147–148 °C; IR ν_{max}/cm^{-1} 1655 (C=O) and 1593 (ArC=C); δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.16 (3H, s, $ArCH_3$), 3.55 and 3.60 (each 3H, s, 2×OCH_3), 3.95 (3H, s, NCH_3), 7.37–7.47 (3H, m, 3×Ar-H), 7.57–7.67 (2H, m, 2×Ar-H), 8.13–8.20 (2H, m, 2×Ar-H), 8.42–8.45 (1H, m, Ar-H), 9.73 (1H, s, CHO); δ_C (75 MHz; $CDCl_3$), 13.8 ($ArCH_3$), 30.4 (NCH_3), 61.5 and 62.0 (2×OCH_3), 109.9 (Ar-CH), 115.8 (Ar-C), 119.4 (Ar-C), 122.0 (Ar-CH), 122.4 (Ar-CH), 122.9 (Ar-CH), 123.0 (Ar-CH), 123.7 (Ar-CH), 125.2 (Ar-C), 126.3 (Ar-CH), 126.3 (Ar-C), 127.1 (Ar-C), 127.7 (Ar-CH), 129.9 (Ar-C), 137.6 (Ar-C), 147.2 (Ar-C), 150.4 (Ar-C), 152.2 (Ar-C), 185.6 (CHO); MS m/z 360 (M^++1, 25%) 359 (M^+, 100), 344 (23), 329 (20), 328 (68) and 285 (17); HRMS calcd for $C_{23}H_{21}NO_3$: 359.1521, found: 259.1535.

3.3. Representative procedure for the ring-forming reactions

3.3.1. 13-Methyl-13*H*-naphtho[1,2-*a*]carbazole 14. $KOBu^t$ (0.06 g, 0.53 mmol) was added to 1-methyl-2-(2-methyl-1-naphthyl)-1*H*-indole-3-carbaldehyde **11** (0.045 g, 0.15 mmol) dissolved in dry DMF (6 cm^3) and was heated under N_2 atmosphere at 80 °C while being irradiated with a high pressure mercury lamp through a quartz filter for 10 min. The reaction mixture was quenched with H_2O (50 mL) and extracted with Et_2O (3×50 mL). The organic layer was dried with $MgSO_4$ and filtered. It was then evaporated and subjected to column chromatography (10–20% EtOAc–hexane) to afford the product **14** (0.034 g, 85%) as an off-white solid. Mp 113–115 °C; IR ν_{max}/cm^{-1} 1616 (ArC=C), 1559 and 1527; δ_H (300 MHz; $CDCl_3$; Me_4Si) 3.78 (3H, s, NCH_3), 7.31–7.34 (1H, m, Ar-H), 7.49–7.61 (4H, m, 4×Ar-H), 7.70 (1H, d, J=8.1 Hz, Ar-H), 7.74 (1H, d, J=8.7 Hz, Ar-H), 7.86 (1H, d, J=8.7 Hz, Ar-H), 7.93 (1H, d, J=7.9 Hz, Ar-H), 8.15 (1H, d, J=7.7 Hz, Ar-H), 8.22 (1H, d, J=8.1 Hz, Ar-H) and 8.66 (1H, d, J=8.1 Hz, Ar-H); δ_C (75 MHz; $CDCl_3$) 37.6 (NCH_3), 111.2 (Ar-CH), 118.2 (Ar-C), 119.3 (Ar-CH), 120.0 (Ar-CH), 120.6 (Ar-CH), 121.3 (Ar-CH), 123.9 (Ar-C), 124.8 (Ar-C), 125.1 (Ar-CH), 125.7 (2×Ar-CH), 125.9 (Ar-CH), 127.7 (2×Ar-CH), 127.9 (Ar-CH), 128.5 (Ar-C), 132.1 (Ar-C), 132.4 (Ar-C), 140.0 (Ar-C) and 145.9 (Ar-C); MS m/z 281 (M^+, 100%), 266 (18), 265 (19) and 141 (9); HRMS calcd for $C_{21}H_{12}N$: 281.1204, found: 281.1203.

The following compounds were prepared in a similar manner.

3.3.2. 11-Methyl-11*H*-naphtho[2,1-*a*]carbazole 15. The product **15** was isolated as an off-white solid (0.045 g, 56%) from **12** (0.085 g, 0.28 mmol). Mp 213–216 °C; IR ν_{max} ($CHCl_3$)/cm^{-1} 1617 and 1572 (ArC=C), 1466, 1437 and 1407; δ_H (300 MHz; $CDCl_3$; Me_4Si) 4.43 (3H, s, NCH_3), 7.30–7.35 (1H, m, Ar-H), 7.50–7.71 (4H, m, 4×Ar-H), 7.86

(1H, d, J=9.2 Hz, Ar-H), 7.94 (1H, d, J=7.6 Hz, Ar-H), 8.20 (1H, d, J=7.8 Hz, Ar-H), 8.35 (1H, d, J=8.7 Hz, Ar-H), 8.60 (1H, d, J=8.7 Hz, Ar-H), 8.71 (1H, d, J=9.2 Hz, Ar-H) and 8.82 (1H, d, J=8.3 Hz, Ar-H); δ_C (75 MHz; $CDCl_3$) 34.4 (NCH_3), 109.0 (Ar-CH), 114.8 (Ar-CH), 119.2 (Ar-CH), 119.5 (Ar-CH), 119.8 (Ar-CH), 120.7 (Ar-C), 121.0 (Ar-CH), 122.8 (Ar-C), 123.5 (Ar-CH), 125.3 (Ar-CH), 125.8 (Ar-CH), 126.1 (Ar-CH), 126.7 (Ar-CH), 128.4 (Ar-CH), 129.7 (Ar-C), 131.1 (Ar-C), 131.2 (Ar-C), 137.0 (Ar-C) and 141.6 (Ar-C), (one quaternary C not observed); MS m/z 281 (M+, 100%), 266 (22), 252 (3) and 140 (2); HRMS calcd for $C_{21}H_{15}N$: 281.1204, found: 281.1209.

3.3.3. 5,13-Dimethoxy-12-methyl-12*H*-naptho[2,3-*a*]-carbazole 16. The product **16** was isolated as a pale yellow solid (0.050 g, 81%) from **13** (0.065 g, 0.18 mmol). Mp 133–135 °C; IR ν_{max} /cm^{-1} 1605 (ArC=C); δ_H (300 MHz; $CDCl_3$; Me_4Si) 3.81 (3H, s, NCH_3), 4.17 and 4.25 (each 3H, s, 2×OCH_3), 7.33–7.38 (1H, m, Ar-H), 7.49–7.58 (3H, m, 3×Ar-H), 7.63 (1H, d, J=8.2 Hz, Ar-H), 8.09 (2H, s, 2×Ar-H), 8.14 (1H, d, J=7.8 Hz, Ar-H), 8.33–8.37 (1H, m, Ar-H) and 8.42–8.45 (1H, m, Ar-H); δ_C (75 MHz; $CDCl_3$) 37.2 (NCH_3), 62.0 and 63.0 (2×OCH_3), 110.7 (Ar-CH), 115.0 (Ar-CH), 115.4 (Ar-C), 119.1 (Ar-C), 119.3 (Ar-CH), 119.4 (Ar-CH), 120.3 (Ar-CH), 122.4 (Ar-CH), 122.7 (Ar-CH), 124.0 (Ar-C), 124.7 (Ar-CH), 124.8 (Ar-C), 125.4 (Ar-CH), 125.5 (Ar-CH), 125.6 (Ar-C), 125.7 (Ar-C), 137.9 (Ar-C), 143.3 (Ar-C), 147.1 (Ar-C) and 148.7 (Ar-C); MS m/z 342 (M^++1, 34%), 341 (M^+, 80), 327 (20), 326 (100), 312 (16), 311 (42), 310 (44), 282 (8), 170 (14), 163 (10), 155 (14), 149 (18) and 69 (13); HRMS calcd for $C_{23}H_{19}NO_2$: 341.1416, found: 341.1411.

3.3.4. 12-Methyl-5*H*-naphtho[2,3-*a*]carbazole-5,13-(12*H*)-dione 17. Carbazole **16** (10 mg, 0.0029 mmol) in THF was stirred together with cerium(IV) ammonium nitrate (7 mg, 0.013 mmol) at rt for 30 min. Water was added to the reaction mixture and the organic material was extracted into Et_2O (3×20 mL). The combined organic layers were dried with $MgSO_4$ and filtered. The organic solvent was then evaporated and subjected to column chromatography (20–40% EtOAc–hexane) to afford the product **17** as an orange solid (7 mg, 77%). mp193–195 °C; IR ν_{max}/cm^{-1} 1644 (C=O), 1621 and 1594 (ArC=C); δ_H (300 MHz; $CDCl_3$; Me_4Si) 4.03 (3H, s, NCH_3), 7.32–7.37 (1H, m, Ar-H), 7.54–7.63 (2H, m, 2×Ar-H), 7.74–7.83 (2H, m, 2×Ar-H), 8.13 (1H, d, J=7.8 Hz, Ar-H), 8.24–8.30 (3H, m, 3×Ar-H) and 8.40 (1H, d, J=8.0 Hz, Ar-H); δ_C (75 MHz; $CDCl_3$) 36.0 (NCH_3), 110.5 (Ar-CH), 119.0 (Ar-CH), 120.8 (Ar-CH), 120.9 (Ar-CH), 121.9 (Ar-C), 125.2 (Ar-CH), 126.7 (Ar-CH), 126.8 (Ar-CH), 128.3 (Ar-CH), 131.1 (Ar-C), 132.6 (Ar-C), 133.2 (Ar-C), 133.4 (Ar-CH), 133.9 (Ar-CH), 135.4 (Ar-C), 140.0 (Ar-C), 143.2 (Ar-C), 145.5 (Ar-C), 183.7 (C=O) and 191.8 (C=O); MS m/z 312 (M^+, 22%), 311 (92), 310 (100), 297 (33), 282 (8), 254 (11), 155 (5) and 127 (7); HRMS calcd for $C_{21}H_{13}O_2N$: 311.0946, found: 311.0946.

3.3.5. 3-Bromo-1-(phenylsulfonyl)-1*H*-indole 23a. 1-(Phenylsulfonyl)-1*H*-indole (2.00 g, 7.77 mmol) was dissolved in CH_2Cl_2 (60 mL). To the resulting solution, Br_2 (1.37 g, 0.440 mL, 8.55 mmol) was added dropwise. The red reaction mixture was then stirred at rt for 4.5 h, and then poured into a saturated solution of aq $NaHCO_3$ (80 mL). The resulting two layers were separated, and the organic layer successively washed with aq $Na_2S_2O_3$ (60 mL), H_2O (60 mL), brine (60 mL) and then dried with $MgSO_4$ mixed with charcoal. The solvent was removed under reduced pressure and the crude residue was purified by chromatography (20% EtOAc–hexane) to afford the product **23a** (2.58 g, 99%) as light orange crystals. Mp 125–126 °C, lit. (125–127 °C);[17] δ_H (400 MHz; $CDCl_3$; $MeSi_4$) 7.29–7.57 (6H, m, 6×Ar-H), 7.63 (1H, s, 2-H), 7.87–7.91 (2H, m, 2×Ar-H) and 7.99 (1H, d, J=8.3 Hz, Ar-H); δ_C (50 MHz; $CDCl_3$) 99.8 (Ar-C), 113.6 (Ar-CH), 120.0 (Ar-CH), 124.0 (Ar-CH), 124.7 (Ar-CH), 125.8 (Ar-CH), 126.8 (2×Ar-CH), 129.3 (Ar-C), 129.4 (2×Ar-CH), 134.1 (Ar-CH), 134.2 (Ar-C) and 137.8 (Ar-C).[17]

3.3.6. 3-Bromo-5-methoxy-1-(phenylsulfonyl)-1*H*-indole 23b. 5-Methoxyindole (200 mg, 1.36 mmol) was dissolved in DMF (5 mL). To the resulting solution Br_2 (219 mg, 0.070 mL, 1.37 mmol) dissolved in DMF (5 mL) was added dropwise within a few minutes at rt while stirring. The end point of the reaction was easily detectable by the appearance of the halogen colour (light brown). The reaction mixture was then poured onto ice and H_2O (50 mL) containing 0.5% NH_3 and 0.1% sodium metabisulphite. The white precipitate formed was then filtered, washed with cold H_2O and dried. Recrystallization was carried out from EtOH/H_2O to give fluffy white crystals (256 mg, 83%) of 3-bromo-5-methoxy-1*H*-indole. To an ice-cold mixture of powdered NaOH (55 mg, 1.37 mmol) and tetrabutylammonium bromide (3.7 mg, 0.015 mmol) in dry CH_2Cl_2 (3 mL) under N_2 was added solid 3-bromo-5-methoxy-1*H*-indole (100 mg, 0.442 mmol) followed by the addition of phenylsulfonyl chloride (94 mg, 0.068 mL, 0.53 mmol). The reaction mixture was then stirred vigorously at rt for 2 h. The white precipitate that formed was filtered off and the solid was purified by silica gel column chromatography (20% EtOAc–hexane) to afford the product **23b** (126 mg, 78%) as a white solid. Mp 131–133 °C; IR ν_{max} ($CHCl_3$)/cm^{-1} 1615 and 1583 (ArC=C), 1475, 1447, 1435 and 1375; δ_H (300 MHz; $CDCl_3$; Me_4Si) 3.84 (3H, s, OMe), 6.89 (1H, d, J=1.2 Hz, 4-H), 6.98 (1H, dd, J=6.8, 1.2 Hz, 6-H), 7.42–7.46 (2H, m, 2×Ar-H), 7.53–7.58 (1H, m, 2×Ar-H), 7.58 (1H, s, 2-H), 7.84–7.86 (2H, m, Ar-H) and 7.89 (1H, d, J=6.8 Hz, 7-H); δ_C (75 MHz; $CDCl_3$) 55.7 (OMe), 99.8 (3-C), 101.9 (Ar-CH), 114.7 (Ar-CH), 115.4 (Ar-CH), 125.4 (Ar-CH), 126.8 (2×Ar-CH), 128.8 (Ar-C), 129.3 (2×Ar-CH), 130.8 (Ar-C), 134.0 (Ar-CH), 137.8 (Ar-C) and 157.1 (5-C); MS m/z 367 (M+, 64%), 365 (64), 226 (98), 224 (100), 211 (14), 209 (14), 183 (21), 181 (16), 178 (25), 124 (21), 102 (16), 81 (15), 77 (51) and 69 (36); HRMS calcd for $C_{15}H_{12}Br^{79}NO_3S$: 364.9721, found: 364.9722.

3.3.7. 3,4-Dibromo-5-methoxy-1-(phenylsulfonyl)-1*H*-indole 23c. 5-Methoxy-1-(phenylsulfonyl)-1*H*-indole (2.00 g, 6.97 mmol) was dissolved in CCl_4 (60 mL). To the resulting solution, Br_2 (1.22 g, 0.40 mL, 7.67 mmol) was added dropwise. The red reaction mixture was then stirred at rt for 4.5 h, and then poured into saturated solution of aq $NaHCO_3$ (80 mL). The resulting two layers were separated, and the organic layer successively washed with aq $Na_2S_2O_3$ (60 mL), water (60 mL), brine (60 mL) and then dried with $MgSO_4$ mixed with charcoal. The solvent was removed

under reduced pressure and the crude residue was purified by chromatography (10% EtOAc–hexane) to afford the product **23c** (2.53 g, 82%) as orange crystals. Mp 129 °C; IR ν_{max}/cm^{-1} 1600, 1582, 1561 (ArC=C), 1462, 1449, 1415 and 1375; δ_H (400 MHz; $CDCl_3$; Me_4Si) 3.91 (3H, s, OCH_3), 6.98 (1H, d, $J=9.1$ Hz, 6-H), 7.44–7.49 (2H, m, 2×Ar-H), 7.56–7.60 (1H, m, Ar-H), 7.67 (1H, s, 2-H), 7.83–7.87 (2H, m, 2×Ar-H) and 7.94 (1H, d, $J=9.1$ Hz, 7-H); δ_C (100 MHz; $CDCl_3$) 57.7 (OCH_3), 98.9 (3-C)[a], 103.9 (4-C)[a], 111.6 (Ar-CH), 113.5 (Ar-CH), 127.2 (2× Ar-CH), 127.5 (Ar-C), 128.5 (Ar-CH), 129.8 (Ar-C), 129.9 (2×Ar-CH), 134.7 (Ar-CH), 137.8 (Ar-C) and 153.6 (5-C); MS *m/z* 347 (M^+, 100%), 445, (68), 443 (36), 415 (15), 306 (46), 304 (100), 302 (51), 289 (26), 265 (21), 261 (24), 256 (35), 214 (26), 132 (22), 130 (22), 97 (21), 85 (17), 83 (30), 81 (38), 77 (53), 73 (40), 71 (29), 69 (82), 67 (27), 60 (32), 57 (53), 56 (20), 55 (74), 51 (20), 43 (80), 41 (86) and 39 (19); HRMS calcd for $C_{15}H_{11}^{79}Br_2NO_3S$ 442.8826, found: 442.8944. The position of the bromine atom was determined by NOE spectroscopy.

3.3.8. 2-Methylphenylboronic acid 22. 1-Bromo-2-methylbenzene (5.00 g, 3.50 mL, 29.3 mmol) was dissolved in THF (30 mL) and cooled to −78 °C. *n*-Butyllithium (25.1 mL, 32.2 mmol) was added dropwise and the resulting white suspension was stirred at −78 °C under an atmosphere of nitrogen for 30 min. After this time trimethyl borate (9.11 g, 9.8 mL, 37.7 mmol) was added dropwise and the reaction mixture stirred for a further 30 min at −78 °C. The reaction mixture was then gradually warmed to rt and acidified with 10% aq HCl and extracted with CH_2Cl_2 (3× 60 mL) and the combined organic extracts were dried with $MgSO_4$. The inorganic solids were filtered off and the solvent removed under reduced pressure to afford white crystalline material **23** in quantitative yield. The product was then used without any further purification or characterisation.[20]

3.3.9. 3-(2-Methylphenyl)-1-(phenylsulfonyl)-1*H*-indole 24a. A solution of 3-bromo-1-(phenylsulfonyl)-1*H*-indole **23a** (0.25 g, 0.74 mmol) in DME (6 mL) was deoxygenated by passing through it a fast stream of N_2 for 5 min. This deoxygenated solution was added to $Pd(PPh_3)_4$ (10%, 86 mg, 0.074 mmol) and stirred under an atmosphere of N_2 at rt for 10 min. A solution of 2-bromophenylboronic acid **22** (0.15 g, 1.1 mmol) in 96% EtOH (2 mL) was also deoxygenated and added to mixture. The mixture was stirred for another 10 min followed by the addition of a deoxygenated aq Na_2CO_3 solution (3.2 mL, 6.3 mmol). The resulting mixture was further stirred at rt under N_2 for 10 min. The mixture was then heated at reflux for 18 h under N_2. The mixture was cooled to rt and quenched with H_2O (20 mL). The organic material was extracted into CH_2Cl_2 (3×30 mL), the combined organic extracts dried with $MgSO_4$ and the solvent evaporated under reduced pressure. The crude residue was purified with column chromatography (20% EtOAc–hexane) to afford the product **24a** (0.26 g, 100%) as a light orange oil. IR ν_{max}/cm^{-1} 1523 (ArC=C), 1425 and 1374; δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.19 (3H, s, $ArCH_3$), 7.19–7.41 (7H, m, 7×Ar-H), 7.41–7.46 (2H, m, 2×Ar-H), 7.51–7.54 (2H, m, 2×Ar-H), 7.90–7.93 (2H, m, 2×Ar-H) and 8.05–8.08 (1H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 20.3 ($ArCH_3$), 113.8 (Ar-CH), 120.7 (Ar-CH), 123.5 (Ar-CH), 123.7 (Ar-C), 124.0 (Ar-CH), 124.9 (Ar-CH), 125.8 (Ar-CH), 126.7 (2×Ar-CH), 127.9 (Ar-CH), 129.2 (2×Ar-CH), 130.4 (Ar-CH), 130.5 (Ar-CH), 130.7 (Ar-C), 131.8 (Ar-C), 133.8 (Ar-CH), 135.0 (Ar-C), 136.8 (Ar-C) and 138.1 (Ar-C); MS *m/z* 348 (M^+ + 1, 15%), 347 (M^+, 61), 207 (18), 206 (100), 204 (18), 178 (31), 103 (4) and 77 (10); HRMS calcd for $C_{21}H_{17}NO_2S$ 347.0980, found: 347.0980.

3.3.10. 5-Methoxy-3-(2-methylphenyl)-1-(phenylsulfonyl)-1*H*-indole 24b. A solution of 3-bromo-5-methoxy-1-(phenylsulfonyl)-1*H*-indole **23b** (2.21 g, 6.04 mmol) in DME (48 mL) was deoxygenated by passing through it a fast stream of N_2 for 5 min. This deoxygenated solution was added to $Pd(PPh_3)_4$ (10%, 0.70 g, 0.60 mmol) and stirred under an atmosphere of N_2 at rt for 10 min. A solution of 2-bromophenylboronic acid **22** (1.23 g, 9.07 mmol) in 96% ethanol (16 mL) was also deoxygenated and added to mixture. The mixture was stirred for another 10 min followed by the addition of deoxygenated aq 2 M Na_2CO_3 (26 mL, 51.3 mmol) solution. The resulting mixture was further stirred at rt under N_2 for 10 min. The mixture was then heated at reflux for 18 h under N_2. The mixture was cooled to rt and quenched with H_2O (80 mL). The organic material was extracted into CH_2Cl_2 (3×80 mL), the combined organic extracts dried with $MgSO_4$ and the solvent evaporated under reduced pressure. The crude residue was purified with column chromatography (20% EtOAc–hexane) to afford the product **24b** (2.25 g, 99%) as white crystals. Mp 127–128 °C (MeOH); IR ν_{max}/cm^{-1} 1616, 1558 (ArC=C), 1540, 1521, 1506, 1458 and 1365; δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.18 (3H, s, $ArCH_3$), 3.73 (3H, s, OCH_3), 6.72 (1H, d, $J=2.5$ Hz, 4-H), 6.96 (1H, dd, $J=8.7$, 2.5 Hz, 6-H), 7.26–7.32 (4H, m, 4×Ar-H), 7.41–7.47 (3H, m, 3×Ar-H), 7.51–7.53 (1H, m, Ar-H), 7.86–7.90 (2H, m, 2×Ar-H) and 7.94–7.97 (1H, dd, $J=9.0$, 0.4 Hz, Ar-H); δ_C (50 MHz; $CDCl_3$) 20.3 ($ArCH_3$), 55.7 (OCH_3), 102.9 (Ar-CH), 114.0 (Ar-CH), 114.8 (Ar-CH), 124.0 (Ar-C), 124.9 (Ar-CH), 125.8 (Ar-CH), 126.7 (2×Ar-CH), 128.0 (Ar-CH), 129.2 (2×Ar-CH), 129.7 (Ar-C), 130.4 (Ar-CH), 130.5 (Ar-CH), 131.8 (Ar-C), 131.9 (Ar-C), 133.7 (Ar-CH), 136.9 (Ar-C), 138.1 (Ar-C) and 156.8 (5-C); MS *m/z* 378 (M^+ + 1, 25%), 377 (M^+, 100), 237 (15), 236 (80), 205 (14), 204 (19), 192 (9), 165 (10) and 77 (10); HRMS calcd for $C_{22}H_{19}NO_3S$ 377.1086, found: M^+ 377.1078.

3.3.11. 3-(2-Methylphenyl)-1*H*-indole 25a. 3-(2-Methylphenyl)-1-(phenylsulfonyl)-1*H*-indole **24a** (0.028 g, 0.080 mmol) was dissolved in MeOH (20 mL) at rt under N_2. K_2CO_3 (1.78 g, 12.9 mmol) was added to the solution and the reaction mixture heated to reflux under an atmosphere of N_2 for 18 h. The mixture was allowed to cool to rt, filtered and the filtrate concentrated under reduced pressure. H_2O (15 mL) was added to the crude material and slowly acidified to pH 2–4 with aq 10% HCl. The aq portion was saturated with solid NaCl and the organic material extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were washed with H_2O (2×20 mL), brine (2× 20 mL), dried with $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to column chromatography (20% EtOAc–hexane) to afford product **25a** (0.16 g, 93%) as a light yellow oil. IR ν_{max}/cm^{-1} 3487 (NH) and 1523 (ArC=C); δ_H (200 MHz; $CDCl_3$; $MeSi_4$) 2.31

(3H, s, $ArCH_3$), 7.09–7.33 (6H, m, 6×Ar-H), 7.37–7.44 (2H, m, 2×Ar-H), 7.52 (1H, dd, $J=7.9$, 1.1 Hz, Ar-H) and 8.09 (1H, br s, N-H); δ_C (100 MHz; $CDCl_3$) 20.7 ($ArCH_3$), 111.2 (Ar-CH), 117.4 (Ar-C), 119.9 (Ar-CH), 120.1 (Ar-CH), 122.1 (Ar-CH), 122.7 (Ar-CH), 125.6 (Ar-CH), 126.7 (Ar-CH), 127.1 (Ar-C), 130.3 (Ar-CH), 130.9 (Ar-CH), 134.4 (Ar-C), 135.8 (Ar-C) and 136.8 (Ar-C); MS *m/z* 208 ($M^+ +1$, 16%), 207 (M^+, 100), 206 (63), 204 (16), 178 (15) and 102 (10); HRMS calcd for $C_{15}H_{13}N$ 207.1048, found: 207.1050.

3.3.12. 5-Methoxy-3-(2-methylphenyl)-1*H*-indole 25b. 5-Methoxy-3-(2-methylphenyl)-1-(phenylsulfonyl)-1*H*-indole **24b** (0.30 mg, 0.80 mmol) was dissolved in MeOH (30 mL) at rt under N_2. K_2CO_3 (1.76 g, 12.7 mmol) was added to the solution and the reaction mixture heated to reflux under an atmosphere of N_2 for 18 h. The mixture was allowed to cool to rt, filtered and the filtrate concentrated under reduced pressure. H_2O (30 mL) was added to the crude material and slowly acidified to pH 2–4 with 10% HCl. The aq portion was saturated with solid NaCl and extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were washed with H_2O (2×30 mL), brine (2×30 mL), dried with $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to column chromatography (20% EtOAc–hexane) to afford product **25b** (0.18 g, 96%) as a light yellow oil. IR ν_{max}/cm^{-1} 3417 br (NH) 1624 and 1603 (ArC=C), 1582, 1545, 1481, 1455 and 1439; δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.32 (3H, s, $ArCH_3$), 3.78 (3H, s, OCH_3), 6.89 (1H, dd, $J=8.7$, 2.5 Hz, 6-H), 6.93 (1H, d, $J=2.5$ Hz, Ar-H), 7.11 (1H, d, $J=2.5$ Hz, Ar-H), 7.25–7.34 (4H, m, 4×Ar-H), 7.40–7.42 (1H, m, ArH) and 8.09 (1H, br s, N-H); δ_C (100 MHz; $CDCl_3$) 20.7 ($ArCH_3$), 55.9 (OCH_3), 101.6 (Ar-CH), 111.9 (Ar-CH), 112.6 (Ar-CH), 117.3 (Ar-C), 123.5 (Ar-CH), 125.6 (Ar-CH), 126.7 (Ar-CH), 127.5 (Ar-C), 130.3 (Ar-CH), 130.8 (Ar-CH), 131.0 (Ar-C), 134.6 (Ar-C), 136.9 (Ar-C) and 154.4 (5-C); MS *m/z* 238 ($M^+ +1$, 17%), 237 (M^+, 100), 222 (51), 206 (12), 194 (17) and 165 (11); HRMS calcd for $C_{16}H_{15}NO$ 237.1155, found: 237.1164.

3.3.13. 1-Methyl-3-(2-methylphenyl)-1*H*-indole 26a. To a solution of 3-(2-methylphenyl)-1*H*-indole **25a** (0.45 g, 2.2 mmol) in THF (10 mL) was added dimethyl sulfate (1.8 mol equiv, 0.50 g, 0.37 mL, 3.9 mmol) followed by NaH (50% in oil, 0.12 g, 5.2 mmol). The resulting mixture was stirred at rt under a constant flow of N_2 for 18 h. The reaction was quenched with H_2O (20 mL), extracted with Et_2O (3×50 mL), combined organic layers dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (20% EtOAc–hexane) to afford **26a** (481 mg, 99%); IR ν_{max}/cm^{-1} 1653, 1634 and 1616 (ArC=C); δ_H (200 MHz; $CDCl_3$; $MeSi_4$) 2.32 (3H, s, $ArCH_3$), 3.78 (3H, s, NCH_3), 7.00 (1H, s, 2-H), 7.07–7.26 (1H, m, Ar-H), 7.28–7.41 (6H, m, 6×Ar-H) and 7.49–7.54 (1H, m, Ar-H); δ_C (50 MHz; $CDCl_3$) 20.8 ($ArCH_3$), 32.7 (NCH_3), 109.3 (Ar-CH), 115.9 (Ar-C), 119.4 (Ar-CH), 120.2 (Ar-CH), 121.7 (Ar-CH), 125.6 (Ar-CH), 126.5 (Ar-CH), 127.5 (Ar-CH), 130.3 (Ar-CH), 130.8 (Ar-CH), 132.2 (Ar-C), 134.5 (Ar-C) and 136.7 (Ar-C), (one quaternary C not observed); MS *m/z* 221 (M^+, 100%), 220 (57), 204 (13) and 178 (9); HRMS calcd for $C_{16}H_{15}N$ 221.1204, found: 221.1199.

3.3.14. 5-Methoxy-1-methyl-3-(2-methylphenyl)-1*H*-indole 26b. To a solution of 5-methoxy-3-(2-methylphenyl)-1*H*-indole **25b** (175 mg, 0.737 mmol) in THF (10 mL) was added dimethyl sulfate (0.14 g, 0.10 mL, 1.1 mmol) followed by NaH (50% in oil, 0.043 g, 1.8 mmol). The resulting mixture was stirred at rt under a constant flow of N_2 for 18 h. The reaction was quenched with H_2O (15 mL), extracted with Et_2O (3×30 mL), combined organic layers dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (20% EtOAc–hexane) to afford **26b** (183 mg, 99%); IR ν_{max}/cm^{-1} 1618 and 1603 (ArC=C), 1576, 1559 and 1542; δ_H (400 MHz; $CDCl_3$; $MeSi_4$) 2.33 (3H, s, $ArCH_3$), 3.78 (3H, s, NCH_3)[a], 3.79 (3H, s, OCH_3)[a], 6.90–6.94 (2H, m, 2×Ar-H), 6.99 (1H, s, 2-H), 7.22–7.25 (3H, m, 3×Ar-H), 7.30–7.32 (1H, m, Ar-H) and 7.39–7.41 (1H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 20.7 ($ArCH_3$), 32.9 (NCH_3), 55.9 (OCH_3), 101.7 (Ar-CH), 110.1 (Ar-CH), 112.1 (Ar-CH), 115.5 (Ar-C), 125.6 (Ar-CH), 126.5 (Ar-CH), 127.8 (Ar-C), 128.1 (Ar-CH), 130.4 (Ar-CH), 130.7 (Ar-CH), 132.1 (Ar-C), 134.6 (Ar-C), 136.7 (Ar-C) and 154.3 (5-C); MS *m/z* 252 ($M^+ +1$, 27%), 251 (M^+, 100%) 236 (54), 218 (15), 208 (9) and 165 (8); HRMS calcd for $C_{17}H_{17}NO$ 251.1310, found: 251.1296.

3.3.15. 1-Methyl-3-(2-methylphenyl)-1*H*-indole-2-carbaldehyde 27a. DMF (0.30 g, 0.30 mL, 4.1 mmol) was added to $POCl_3$ (0.42 g, 0.25 mL, 2.71 mmol) at 0 °C under an atmosphere of N_2. The resulting salt was treated with a solution of 1-methyl-3-(2-methylphenyl)-1*H*-indole **26a** (300 mg, 1.36 mmol) in toluene (6 mL). The resulting reaction mixture was heated at reflux for 42 h under N_2 atmosphere. The reaction mixture was then cooled to rt, quenched with water and the excess $POCl_3$ neutralised with Na_2CO_3. The crude product was extracted with CH_2Cl_2 (3×50 mL), the combined organic extracts dried with $MgSO_4$, and evaporated under reduced pressure. The crude material was purified by column chromatography (20% EtOAc–hexane) to afford product **27a** (202 mg, 60%) as a light brown oil. IR ν_{max}/cm^{-1} 1709 (C=O) and 1608 (ArC=C); δ_H (200 MHz; $CDCl_3$; $MeSi_4$) 2.18 (3H, s, $ArCH_3$), 4.16 (3H, s, NCH_3), 7.11–7.15 (1H, m, Ar-H), 7.23–7.44 (7H, m, 7×Ar-H) and 9.66 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 20.9 ($ArCH_3$), 32.2 (NCH_3), 110.8 (Ar-CH), 121.3 (Ar-CH), 122.9 (Ar-CH), 125.9 (Ar-CH), 126.7 (Ar-C), 127.7 (Ar-CH), 128.7 (Ar-CH), 130.7 (Ar-CH), 131.7 (Ar-C), 131.8 (Ar-C), 131.9 (Ar-C), 132.5 (Ar-CH), 138.2 (Ar-C), 140.0 (Ar-C) and 184.2 (CHO); MS *m/z* 250 ($M^+ +1$, 18%), 249 (M^+, 100), 234 (32), 232 (69), 220 (18), 217 (24) and 204 (18); HRMS calcd for $C_{17}H_{15}NO$ 249.1154, found: 249.1158.

3.3.16. 5-Methoxy-1-methyl-3-(2-methylphenyl)-1*H*-indole-2-carbaldehyde 27b. DMF (0.124 g, 0.13 mL, 1.70 mmol) was added to $POCl_3$ (0.17 g, 0.10 mL, 1.1 mmol) at 0 °C under an atmosphere of N_2. The resulting salt was treated with a solution of 5-methoxy-1-methyl-3-(2-methylphenyl)-1*H*-indole **26b** (140 mg, 0.557 mmol) in toluene (4 mL). The reaction mixture was then heated to reflux for 42 h under N_2 atmosphere. The reaction mixture was then cooled to rt, quenched with water and excess $POCl_3$ neutralised with Na_2CO_3. The crude product was extracted into CH_2Cl_2 (3×30 mL), the combined organic

extracts dried with $MgSO_4$, and evaporated under reduced pressure. The crude material was purified by column chromatography (20% EtOAc–hexane) to afford product **27b** (156 mg, 27%) as a brown oil. IR ν_{max}/cm^{-1} 1716 (C=O), 1654 and 1617 (ArC=C); δ_H (400 MHz; $CDCl_3$, $MeSi_4$) 2.23 (3H, s, $ArCH_3$), 3.78 (3H, s, NCH_3), 4.17 (3H, s, OCH_3), 6.75 (1H, d, $J=2.3$ Hz, 4-H) and 7.15 (1H, dd, $J=9.1$, 2.3 Hz, 6-H), 7.28–7.41 (5H, m, 5×Ar-H) and 9.63 (1H, s, CHO); δ_C (50 MHz; $CDCl_3$) 20.6 ($ArCH_3$), 33.1 (NCH_3), 56.0 (OCH_3), 100.6 (Ar-CH), 109.9 (Ar-CH), 116.1 (Ar-C), 120.9 (Ar-C), 125.8 (Ar-CH), 127.0 (Ar-CH), 130.5 (Ar-CH), 130.6 (Ar-CH), 131.6 (Ar-C), 132.7 (Ar-CH), 133.0 (Ar-C), 133.8 (Ar-C), 136.8 (Ar-C), 156.5 (5-C) and 190.4 (CHO); MS *m/z* 280 ($M^+ +1$, 30%), 279 (M^+, 100), 264 (19), 262 (38), 247 (16), 218 (9), 206 (10), 204 (9), 192 (6), 165 (9) and 152 (6); HRMS calcd for $C_{18}H_{17}NO_2$ 279.1259, found: 279.1253.

3.3.17. 1-[2-(1,2-Dimethyl-1*H*-indol-3-yl)phenyl]-ethanone 20a. (a) 2-Methyl-1*H*-indole (1.00 g, 7.62 mmol) was dissolved in DMF (7.5 mL). A solution of Br_2 (1.22 g, 0.390 mL, 7.62 mmol) in DMF (7.5 mL) was added to the reaction mixture and the resulting solution was stirred at rt under N_2 atmosphere for 4 h. After this time the reaction mixture was poured into an ice-cold mixture of H_2O (10 mL), a 25% aq NH_3 solution (10 mL) and an aq solution of $NaHSO_3$ (10 mL). The resulting precipitate was then dissolved in CH_2Cl_2 (20 mL). The organic layer was sequentially washed with H_2O (20 mL), aq NaCl (20 mL), dried with $MgSO_4$ and concentrated in vacuo. The residue was then loaded on a silica gel column and eluted with 20% EtOAc–hexane to afford the desired product 3-bromo-2-methyl-1*H*-indole (1.61 g, 100%) as an off-white solid. δ_H (200 MHz; $CDCl_3$; $MeSi_4$) 2.40 (3H, s, 2-CH_3), 7.13–7.23 (3H, m, 3×Ar-H), 7.45–7.47 (1H, m, 7-H) and 8.0 (1H, br s, NH); δ_C (50 MHz; $CDCl_3$) 12.2 (2-CH_3), 100.3 (3-C), 112.0 (7-C), 121.5 (Ar-CH), 121.9 (Ar-CH), 122.3 (Ar-CH), 128.2 (Ar-C), 130.3 (Ar-C) and 136.7 (Ar-C).[21]

(b) To the intermediate 3-bromo-2-methyl-1*H*-indole (1.60 g, 7.60 mmol) in THF (50 mL) was added dimethyl sulfate (1.44 g, 1.08 mL, 11.4 mmol) followed by sodium hydride (50% in oil, 0.44 g, 18 mmol). The resulting mixture was stirred at rt under a constant flow of N_2 for 18 h. The reaction was quenched with H_2O (35 mL), extracted with Et_2O (3×40 mL), the combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (20% EtOAc–hexane) to afford **30a**[22] (1.68 g, 99%) which was used immediately in the next reaction. δ_H (200 MHz; $CDCl_3$; $MeSi_4$) 2.36 (3H, s, 2-CH_3), 3.59 (3H, s, NCH_3), 7.12–7.20 (3H, m, 3×Ar-H) and 7.45–7.49 (1H, m, Ar-H); δ_C (50 MHz; $CDCl_3$) 12.4 (2-CH_3), 33.5 (NCH_3), 102.4 (3-C), 112.9 (Ar-CH), 121.9 (Ar-CH), 122.3 (Ar-CH), 123.2 (Ar-CH), 128.7 (Ar-C), 130.8 (Ar-C) and 137.2 (Ar-C).

(c) Boronic acid **31** (0.29 g, 1.7 mmol) was dissolved in DMF (1.5 mL) and O_2 removed from the solution by three freeze-thaw cycles. 3-Bromo-1,2-dimethyl-1*H*-indole **30a** (0.20 g, 0.89 mmol), K_3PO_4 (0.57 g, 2.7 mmol) and $Pd(PPh_3)_4$ (20 mol%, 0.21 g, 0.18 mmol) were added sequentially under an Ar atmosphere. The reaction flask was sealed tightly and heated at 100 °C for 65 h. After this time the reaction mixture was cooled and followed by the addition of saturated solution of brine (10 mL). The reaction mixture was extracted with Et_2O (4×15 mL), and the organic extracts were combined and concentrated under reduced pressure. Purification of the residue by column chromatography (20% EtOAc–hexane) afforded the biaryl compound **20a** as a yellow-brown oil (0.19 g, 83%); IR ν_{max}/cm^{-1} 1683 (C=O) and 1614 and 1596 (ArC=C), 1558, 1541 and 1472; δ_H (400 MHz; $CDCl_3$; $MeSi_4$) 1.88 (3H, s, 2-CH_3), 2.26 (3H, s, CH_3CO), 3.74 (3H, s, NCH_3), 7.32 (1H, d, $J=8.2$ Hz, Ar-H), 7.18–7.24 (1H, m, Ar-H), 7.25–7.31 (1H, m, Ar-H), 7.37–7.44 (3H, m, 3×Ar-H) and 7.50–7.55 (1H, m, Ar-H), 7.63 (1H, d, $J=7.7$ Hz, Ar-H); δ_C (100 MHz; $CDCl_3$) 10.9 (2-CH_3), 29.3 (NCH_3), 29.8 (CH_3CO), 108.8 (Ar-CH), 112.9 (Ar-C), 118.6 (Ar-CH), 120.0 (Ar-CH), 121.5 (Ar-CH), 126.8 (Ar-CH), 127.4 (Ar-C), 128.0 (Ar-CH), 130.8 (Ar-CH), 132.1 (Ar-CH), 133.8 (Ar-C), 134.6 (Ar-C), 136.7 (Ar-C), 142.2 (Ar-C) and 205.0 (CH_3CO); MS *m/z* 264 ($M^+ +1$, 20%), 263 (M^+, 100), 262 (11), 249 (14), 248 (68), 245 (16), 234 (10), 233 (21), 218 (14), 204 (16) and 144 (10); HRMS calcd for $C_{18}H_{17}NO$: 263.1310, found: M^+263.1312.

3.3.18. 1-[2-(5-Methoxy-1,2-dimethyl-1*H*-indol-3yl)-phenyl]ethanone 20b. (a) 5-Methoxy-2-methyl-1*H*-indole (600 mg, 3.72 mmol) was dissolved in CH_2Cl_2 (4 mL). To the resulting solution was added a small amount (ca. 100 mg) of silica gel followed by *N*-bromosuccinimide (660 mg, 3.72 mmol). The resulting mixture was stirred at rt for 30 min under an atmosphere of N_2. The reaction was quenched with H_2O (30 mL), extracted with CH_2Cl_2 (3×50 mL), the combined organic extracts were dried with $MgSO_4$ and then concentrated under reduced pressure. The residue was purified by column chromatography (20% EtOAc–hexane) to afford 3-bromo-5-methoxy-2-methyl-1*H*-indole (870 mg, 99%). δ_H (400 MHz; $CDCl_3$; $MeSi_4$) 2.38 (3H, s, 2-CH_3), 3.87 (3H, s, OCH_3), 6.80 (1H, dd, $J=8.7$, 2.1 Hz, 6-H), 6.91 (1H, d, $J=1.5$ Hz, 4-H), 7.12 (1H, d, $J=8.7$ Hz, 7-H) and 7.89 (1H, br s, NH); δ_C (100 MHz; $CDCl_3$) 12.4 (2-CH_3), 55.8 (OCH_3), 90.0 (3-C), 100.0 (6-C), 111.5 (Ar-CH), 112.3 (Ar-CH), 128.1 (Ar-C), 129.6 (Ar-C), 133.1 (Ar-C) and 154.7 (5-C).

(b) To a solution of 3-bromo-5-methoxy-2-methyl-1*H*-indole (350 mg, 1.46 mmol) in THF (10 mL) was added dimethyl sulfate (0.28 g, 0.21 mL, 2.2 mmol) followed by NaH (50% in oil, 0.084 g, 2.2 mmol). The resulting mixture was stirred at rt under a constant flow of N_2 for 18 h. The reaction was quenched with H_2O (20 mL), extracted with Et_2O (3×20 mL), and the combined organic layers dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (20% EtOAc–hexane) to afford **30b** (350 mg, 94%) which was used as soon as possible in the next reaction. δ_H (400 MHz; $CDCl_3$; $MeSi_4$) 2.38 (3H, s, 2-CH_3), 3.71 (3H, s, NCH_3), 3.87 (3H, s, OCH_3), 6.82 (1H, dd, $J=8.8$, 2.4 Hz, 6-H), 6.91 (1H, d, $J=2.2$ Hz, 4-H) and 7.13 (1H, d, $J=8.8$ Hz, 7-H); δ_C (100 MHz; $CDCl_3$) 11.5 (2-CH_3), 30.3 (NCH_3), 55.8 (OCH_3), 88.5 (3-C), 99.9 (4-C), 109.8 (Ar-CH), 111.9 (Ar-CH), 127.1 (Ar-CH), 131.2 (Ar-C), 134.5 (Ar-C) and 154.5 (5-C).

(c) Boronic acid **31** (260 mg, 1.59 mmol) was dissolved in DMF (2 mL) and O_2 removed from the solution by three freeze-thaw cycles. 3-Bromo-5-methoxy-1,2-dimethyl-1*H*-indole **30b** (200 mg, 0.79 mmol), K_3PO_4 (0.50 g, 2.4 mmol) and $Pd(PPh_3)_4$ (20 mol%, 0.18 g, 0.16 mmol) were added sequentially under an Ar atmosphere. The reaction flask was sealed tightly and heated at 100 °C, for 65 h. After this time the reaction mixture was cooled and followed by the addition of saturated solution of brine (15 mL). The reaction mixture was extracted with Et_2O (4×20 mL), the organic extracts were combined and concentrated under reduced pressure. Purification of the residue by column chromatography (20% EtOAc–hexane) afforded the biaryl compound **20b** as a yellow-brown oil (0.19 g, 80%); IR ν_{max}/cm^{-1} 1684 (C=O), 1597 and 1617 (C=C), 1489 and 1456; δ_H (300 MHz; $CDCl_3$; $MeSi_4$) 1.89 (3H, s, 2-CH_3), 2.24 (3H, s, CH_3CO), 3.71 (3H, s, NCH_3)[a], 3.78 (3H, s, OCH_3)[a], 6.85–6.88 (2H, m, 2×Ar-H), 7.20 (1H, d, J=9.5 Hz, Ar-H), 7.25–7.48 (2H, m, 2×Ar-H) and 7.52–7.57 (1H, m, Ar-H), 7.62–7.65 (1H, m, Ar-H); δ_C (75 MHz; $CDCl_3$) 10.9 (2-CH_3), 29.7 (CH_3CO), 29.8 (NCH_3), 55.8 (OCH_3), 100.4 (Ar-CH), 109.5 (Ar-CH), 111.4 (Ar-CH), 112.6 (Ar-C), 126.6 (Ar-CH), 127.6 (Ar-C), 128.0 (Ar-CH), 130.8 (Ar-CH), 131.9 (Ar-CH), 133.8 (Ar-C), 135.0 (Ar-C), 142.1 (Ar-C), 154.6 (Ar-C) and 205.1 (CH_3CO), (one quaternary not observed, assignments with same superscript may be interchanged); MS *m/z* 294 (M^++1, 21%), 293 (M^+, 100), 279 (7), 278 (35), 263 (8), 250 (6), 247 (5), 234 (5), 207 (6), 206 (8) and 165 (5); HRMS calcd for $C_{19}H_{19}NO_2$: 293.1416, found: M^+293.1407.

3.3.19. 5,7-Dimethyl-7*H*-benzo[*c*]carbazole 18a. 1-[2-(1,2-Dimethyl-1*H*-indol-3-yl)phenyl]ethanone **20a** (96 mg, 0.36 mmol) was dissolved in DMF (4 mL) at 80 °C. To the resulting solution was added ^{t}BuOK (0.164 mg, 1.46 mmol). The resulting reaction mixture was stirred at 80 °C and irradiated with a high pressure mercury lamp through a quartz filter for 10 min. After this time, the reaction was quenched with H_2O (15 mL), extracted with Et_2O (3×20 mL) before the organic fractions were combined. The fractions were dried with $MgSO_4$, concentrated under reduced pressure and the residue purified by column chromatography (20% EtOAc–hexane) to afford **18a** as yellow crystals (63 mg, 71%). Mp 112 °C; IR ν_{max}/cm^{-1} 1617 and 1591 (ArC=C), 1523, 1465, 1416, 1378; δ_H (400 MHz; $CDCl_3$; $MeSi_4$) 2.79 (3H, d, J=0.9 Hz, $ArCH_3$), 3.79 (3H, s, NCH_3), 7.31–7.38 (2H, m, 2×Ar-H), 7.41–7.48 (3H, m, 3×Ar-H), 7.65–7.69 (1H, m, Ar-H), 8.08 (1H, d, J=8.4 Hz, Ar-H), 8.50 (1H, d, J=8.0 Hz, Ar-H) and 8.77 (1H, d, J=8.2 Hz, Ar-H); δ_C (100 MHz; $CDCl_3$) 20.6 ($ArCH_3$), 29.0 (NCH_3), 108.9 (Ar-CH), 111.2 (Ar-CH), 113.4 (Ar-C), 119.6 (Ar-CH), 121.6 (Ar-CH), 122.5 (Ar-CH), 123.5 (Ar-CH), 123.6 (Ar-CH), 125.2 (Ar-CH), 125.5 (Ar-CH), 126.5 (Ar-CH), 128.2 (Ar-C), 130.2 (Ar-C), 133.4 (Ar-C), 138.2 (Ar-C) and 139.6 (Ar-C); MS *m/z* (M^++1, 21%) 245 (M^+, 100), 244 (26), 230 (7), 229 (6), 228 (5), 202 (5) and 122 (9); HRMS calcd for $C_{18}H_{15}N$: 245.1205, found: M^+245.1198.[23]

3.3.20. 10-Methoxy-5,7-dimethyl-7*H*-benzo[*c*]carbazole 18b. 1-[2-(5-Methoxy-1,2-dimethyl-1*H*-indol-3-yl)phenyl]-ethanone **20b** (114 mg, 0.389 mmol) was dissolved in DMF (4 mL) at 80 °C. To the resulting solution was added ^{t}BuOK (0.21 g, 1.9 mmol). The resulting reaction mixture was stirred at 80 °C and irradiated with a high pressure mercury lamp through a quartz filter for 10 min. The reaction was quenched with H_2O (15 mL), extracted with Et_2O (3×20 mL) and the organic fractions were combined. The organic fractions were dried with $MgSO_4$, concentrated under reduced pressure and the residue purified by column chromatography (20% EtOAc–hexane) to afford **18b** as yellow crystals (92 mg, 70%). Mp 120 °C; IR ν_{max}/cm^{-1} 1671, 1608 (ArC=C), 1566, 1532 and 1428; δ_H (400 MHz; $CDCl_3$; $MeSi_4$) 2.84 (3H, s, $ArCH_3$), 3.88 (3H, s, NCH_3)[a], 4.01 (3H, s, OCH_3)[a], 7.11 (1H, dd, J=8.8, 2.2 Hz, 9-H), 7.37–7.51 (3H, m, 3×Ar-H), 7.68–7.72 (1H, m, Ar-H), 8.00 (1H, d, J=2.2 Hz, 11-H), 8.12 (1H, d, J=8.3 Hz, Ar-H) and 8.71 (1H, d, J=8.2 Hz, Ar-H); δ_C (100 MHz; $CDCl_3$) 20.7 ($ArCH_3$), 28.9 (NCH_3), 56.3 (OCH_3), 105.1 (Ar-CH), 109.4 (Ar-CH), 111.4 (Ar-CH), 112.5 (Ar-CH), 113.1 (Ar-C), 122.4 (Ar-CH), 123.3 (Ar-CH), 123.7 (Ar-C), 125.3 (Ar-CH), 126.5 (Ar-CH), 128.1 (Ar-C), 130.2 (Ar-C), 133.4 (Ar-C), 134.9 (Ar-C), 138.8 (Ar-C) and 154.1 (10-C), (assignments with same superscript may be interchanged); MS *m/z* (M^++1, 24%) 275 (M^+, 100), 261 (10), 260 (39), 233 (6), 232 (30), 217 (9), 216 (6), 137 (12), 116 (8) and 115 (7); HRMS calcd for $C_{19}H_{17}NO$: 275.1310, found: M^+275.1308.

Acknowledgements

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Methodology for the synthesis of 1,2-disubstituted arylnaphthalenes from α-tetralones

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Abstract—α-Tetralones were initially converted into 1-bromo-dihydronaphthalene-2-carbaldehydes and 1-bromo-naphthalene-2-carbaldehydes. These precursors were then subjected to Suzuki coupling reactions to afford 1,2-disubstituted aryldihydronaphthalenes and 1,2-disubstituted arylnaphthalenes, respectively. The former products were oxidized with DDQ to give 1,2-disubstituted arylnaphthalenes.

1. Introduction

The synthesis of aromatic compounds containing biaryl axes continues to be important as a result of the biological activities associated with the biaryl natural products[1] as well as their use as ligands in transition metal catalysed reactions.

For example, the naturally occurring compound (*S*)-gossypol **1** (Fig. 1) contains a biaryl axis. Restricted rotation about this axis imparts chirality to the molecule. Pharmacologically it is known to be an oral antifertility agent, and it shows potential for the treatment of HIV infections, diabetic complications and cancer.[2] Recent work has also shown that the phenyl-naphthalene core is effective in thyromimetics[3a] and shows high ceramide-mediated proapoptotic activity on human breast cancer cells.[3b]

Apart from their interesting biological activity, biaryl naphthalene compounds also find application as chiral catalysts. The first and most frequently used chiral phosphine ligand is BINAP **2** (Fig. 1). This is illustrated by the work of Noyori who has shown that the ruthenium complexes of **2** are capable of effecting asymmetric hydrogenations and have even found industrial applications.[4,5]

The atropisomers of (1,1′-binaphthyl)-2,2′-diol **3** and its derivatives (Fig. 1) are widely used in asymmetric synthesis, either as ligands or as chiral auxiliaries. For example, the binaphthol derivative **4** has been used as a chiral ligand in the copper-catalysed Michael addition of dialkylzinc reagents to cyclic α,β-unsaturated ketones.[6] In addition, an important contribution using binaphthols in organic synthesis has come from the group of Shibasaki[7,8] in that it has been shown that a number of characterised heterobimetallic asymmetric binaphthols are capable of catalyzing a variety of reactions.

General methods for the synthesis of biaryl compounds include the use of oxidative coupling methods.[9] Otherwise, traditional methods for the assembly of the biaryl axis such as the Suzuki–Miyaura[10,11] and Stille reactions are used.[12] For the synthesis of suitably substituted biaryl compounds

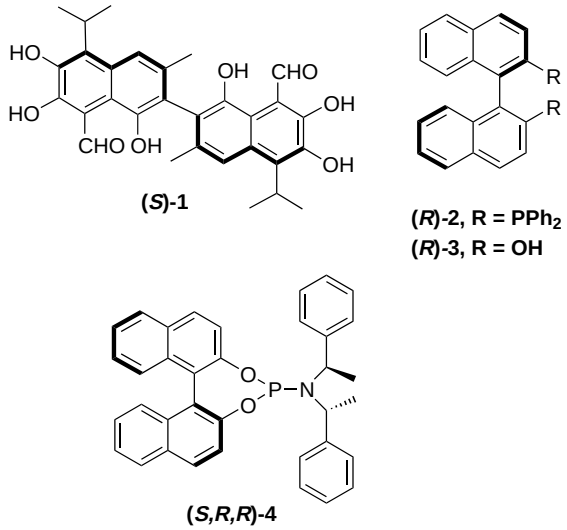

Figure 1.

Keywords: Suzuki-Miyaura coupling reactions; Aromatization; Arylnaphthalenes; α-Tetralone.
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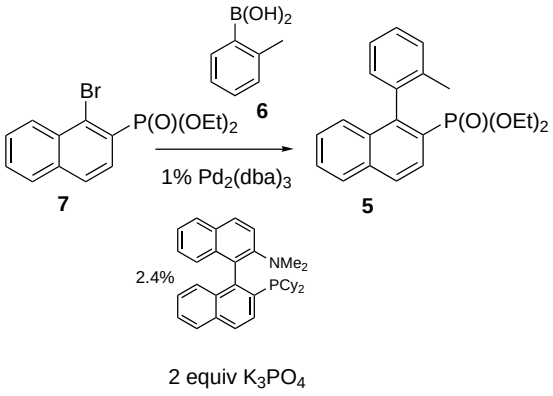
both of these methods depend on the synthesis of suitably substituted aromatic compounds and in the case of arylnaphthalenes the synthesis depends on the availability of suitably substituted naphthalenes.[13] For example, the arylnaphthalene **5** has been made by the coupling of tolylboronic acid **6** and **7** (Scheme 1).[14]



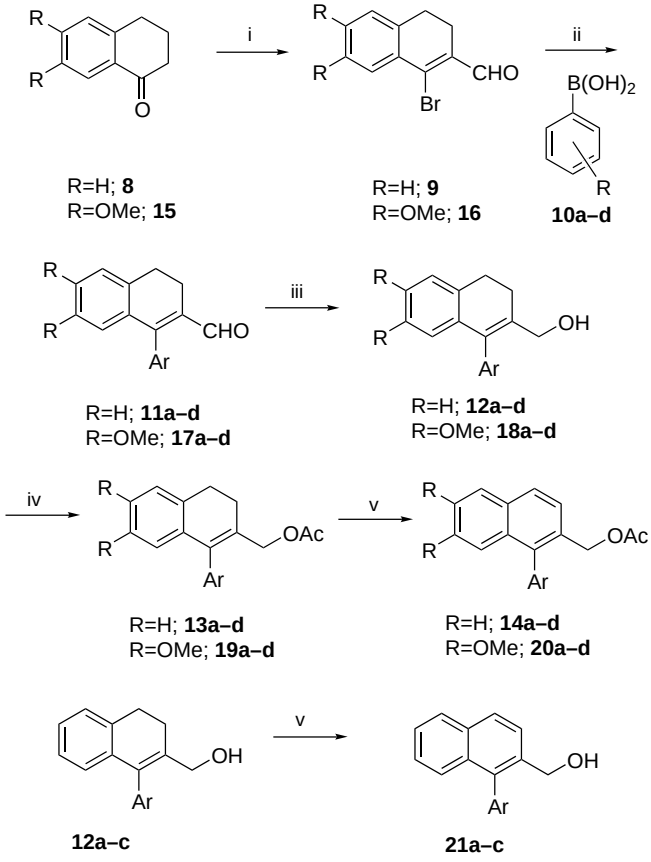
Scheme 1.

Our research group has been involved in the synthesis of biaryl compounds and naphthalenes[15] and in this paper we report on the use of α-tetralones as suitable commercially available substrates for the synthesis of simple arylnaphthalenes. We show that α-tetralones can be used as 'substitutes' for naphthalenes as these are readily converted into the naphthalene portion of the arylnaphthalene. Related results on the use of tetralones for building substituted naphthalenes have been reported by two other research group.[3,16]

2. Results and discussion

Following literature protocol, readily available α-tetralone **8** was converted into the known dihydronaphthalene **9** in good yield as shown in Scheme 2.[17,18] Using our well-developed Suzuki–Miyaura reaction conditions we then attempted to produce a number of aryldihydronaphthalenes. Reaction of **9** with catalytic $Pd(PPh_3)_4$ in the presence of boronic acids **10a–d** and aqueous Na_2CO_3 and DME afforded the desired Suzuki coupling products **11a–d** in good to excellent yields.[19] Subsequently the products were then reduced to alcohols **12a–d** using sodium borohydride in ethanol. The resultant alcohols **12a–d** were protected as their esters using acetic anhydride and pyridine to give **13a–d**. Finally, all that was required was the oxidation of dihydronaphthalenes **13a–d** to afford the desired biaryl naphthalenes. The use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in CH_2Cl_2 afforded good yields of the desired arylnaphthalenes **14a–d** from **13a–d** demonstrating that tetralones can be used as substitutes for naphthalenes.

Dimethoxybromodihydronaphthalene-2-carbaldehyde **16** was synthesized from a different tetralone substrate, 6,7-dimethoxytetralone **15**, using DMF and potassium tribromide in CH_2Cl_2 in a similar manner to that described for tetralone **8**. As shown in Scheme 2 the exposure of **16** to boronic acids **10a–d** under aqueous Suzuki coupling reaction conditions in the presence of $[Pd(PPh_3)_4]$ gave



Scheme 2. Reagents and Conditions: (i) DMF, PBr_3, CH_2Cl_2, reflux, R = H, 70%; R = OMe, 63%; (ii) cat. $Pd(PPh_3)_4$, aqueous Na_2CO_3, boronic acid **10**, DME/EtOH, reflux; (iii) $NaBH_4$, EtOH, rt; (iv) Ac_2O, pyridine, reflux; (v) DDQ, CH_2Cl_2, reflux; for yields see Table 1.

aryl 6,7-dimethoxycarbaldehydes **17a–d** in good yields. Reduction of the carbaldehydes **17a–d** using sodium borohydride in ethanol gave dimethoxydihydronaphthalene alcohols **18a–d** in very good yields. As in the previous series, the resultant alcohols were then protected as their esters to give **19a–d**. The subsequent dimethoxydihydronaphthalene esters were then dehydrogenated as before to the envisaged substituted biaryl dimethoxynaphthalenes **20a–d** using DDQ in CH_2Cl_2 and the products were obtained in satisfactory yields (Table 1).

It has to be mentioned that an attempt was made to aromatize some of the dihydronaphthalene carbaldehydes **11a–d** using DDQ as reagent in CH_2Cl_2, as was done with the dihydronaphthalene esters. Unfortunately, in all cases only the starting material was obtained or uncharacterizable products were obtained.

In order to try and decrease the number of steps required to obtain the desired biaryl naphthalenes, the aromatization reaction was attempted on the related alcohols **12a–c**. (Scheme 2). Three of the dihydronaphthalene alcohols **12a–c** were aromatized using this methodology to afford **21a–c** in good yields.

As an alternative to produce the same arylnaphthalene alcohols we decided to investigate aromatization of the initial dihydronaphthalenes with alternative reagents. After

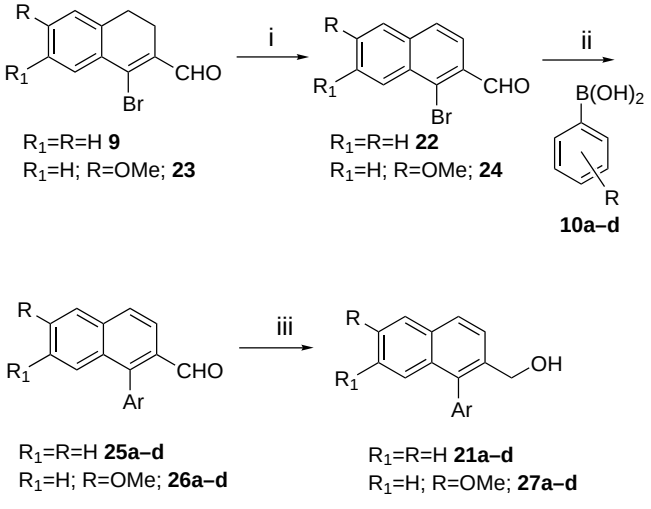
Table 1. Yields for Scheme 2

Entry	Ar	%		%	Entry	%	Entry	%	Entry	%
9→11a	3,4,5-(MeO)C_6H_2	83	**11a→12a**	100	**12a→13a**	98	**13a→14a**	78	**12a→21a**	82
9→11b	Naphthyl	93	**11b→12b**	94	**12b→13b**	94	**13b→14b**	95	**12b→21b**	79
9→11c	Ph	100	**11c→12c**	94	**12c→13c**	82	**13c→14d**	93	**12c→21c**	77
9→11d	2-MePh	78	**11d→12d**	94	**12d→13d**	94	**13d→14d**	100		
16→17a	3,4,5-(MeO)C_6H_2	88	**17a→18a**	87	**18a→19a**	80	**19a→20a**	74		
16→17b	Naphthyl	87	**17b→18b**	100	**18b→19b**	89	**19b→20b**	78		
16→17c	Ph	83	**17c→18c**	100	**18c→19c**	88	**19c→20c**	100		
16→17d	2-MePh	98	**17d→18d**	87	**18d→19d**	88	**19d→20d**	78		

extensive experimentation with **9** it was found that careful treatment of the substrate with selenium powder in a small amount of DMSO for 5 min at 170 °C resulted in acceptable yields of the desired product **22**. The related monomethoxydihydronaphthalene **23** also gave the desired naphthalene **24** in good yield (72%). The remaining steps for the production of a variety of 1-arylnaphthalenes were straightforward. Treatment of both **22** and **24** with the boronic acids **10a–d** gave the desired naphthalenes **25a–d** and **26a–d** with an aldehyde substituent in the 2-position. All the aldehydes were then reduced with $NaBH_4$ to give alcohols **21a–d** as well as the monomethoxynaphthalenes **27a–d** (Table 2, Scheme 3).

Table 2. Yields for Scheme 3

Entry	Ar	%	Entry	%
22→25a	3,4,5-(MeO)C_6H_2	94	**25a→21a**	82
22→25b	Naphthyl	89	**25b→21b**	93
22→25c	Ph	87	**25c→21c**	91
22→25d	2-MePh	94	**25d→21d**	95
24→26a	3,4,5-(MeO)C_6H_2	80	**26a→27a**	89
24→26b	Naphthyl	74	**26b→27b**	95
24→26c	Ph	90	**26c→27c**	100
24→26d	2-MePh	71	**26d→27d**	93

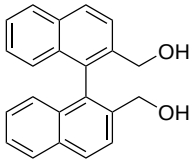


Scheme 3. Reagents and Conditions: (i) Se powder, DMSO, 170 °C, R=H, 69%; R=OMe, 72%; (ii) cat. $Pd(PPh_3)_4$, aqueous Na_2CO_3, boronic acid **10**, DME/EtOH, reflux; (iii) $NaBH_4$, EtOH, rt; for yields see Table 2.

In conclusion, we have developed a new straight-forward method for the synthesis of arylnaphthalenes where the regiochemistry of the product is defined unambiguously from the tetralone. This eliminates the difficulties of preparing 1-bromonaphthalenes by direct bromination of naphthalenes, as these reactions generally afford mixtures of products, particularly if the naphthalene is substituted. For example, bromination of 6,7-dimethoxy-2-naphthaldehyde would not afford **24**.

Specifically, we have been able to develop a two step procedure for the synthesis of aryldihydronaphthalenes **11a–d** and **17a–d** from tetralones **8** and **15**, which can be converted into the corresponding arylnaphthalenes. In addition, a two step procedure for the synthesis of 1-bromo-2-formylnaphthalenes (**22** and **24**) has been developed. These products can be utilized in Suzuki–Miyaura reactions to afford biaryl compounds.

Future work will entail the introduction of an oxygen substituent in the *ortho* position of the boronic acid. This will provide arylnaphthalenes such as **28** with two oxygen containing substituents *ortho* to the biaryl axis. These will be potential ligands for metal catalyzed reactions.



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3. Experimental

3.1. General

All reagents used were Analytical Grade Reagents from Fluka and Aldrich. *n*-BuLi was obtained from Aldrich and used as supplied. THF was dried by distillation from sodium wire/benzophenone, DMF by distillation from CaH_2. All other solvents were BDH/HP high purity grade and distilled before use. Thin-layer chromatography was carried out on Macherey-Nagel Alugram Sil G/UV_{254} Plates, pre-coated with 0.25 mm silica gel 60. Detection was done under ultra violet light at 254 nm. For column chromatography, Macherey-Nagel silica gel (32–63 μm) was used, with gel mass 30 times that of sample, eluting with the stated solvent mixtures. Melting points were determined on a Reichert hot-stage microscope. Infrared spectra were run on the Bruker Vector 22 Fourier Transform spectrometer. Absorption maxima are reported in wavenumbers (cm^{-1}), with s=strong, m=medium and w=weak. NMR spectroscopic analysis was done on an Ultrashield 300 MHz/54 Bohr magnet. The frequency at which ^1H NMR spectra were reported was 300.131 MHz (rounded to 300 MHz) using

tetramethylsilane at 0.000 ppm as a standard. These spectra are reported as parts per million (ppm), with s=singlet, d=doublet, dd=doublet of a doublet, t=triplet, dt=doublet of a triplet, m=multiplet. The ^{13}C NMR spectra were reported at a frequency of 75.475 MHz (rounded to 75 MHz) using $CDCl_3$ at 77.00 ppm as a standard.

3.1.1. Bromo-3,4-dihydronaphthalene-2-carbaldehyde 9. Dry DMF (8.02 mL, 103.2 mmol) in dry CH_2Cl_2 (50 mL) was cooled to 0 °C and phosphorus tribromide (8.00 mL, 89.5 mmol) was added drop-wise. The mixture was stirred at 0 °C for 1 h during which time a pale yellow suspension was formed. A solution of α-tetralone **8** (4.58 mL, 5.03 g, 34.4 mmol) in dry CH_2Cl_2 (90 mL) was added and the mixture was heated under reflux for 1 h. After cooling to 0 °C, aqueous $NaHCO_3$ was added slowly until the effervescence had subsided. Extraction of the organic material into CH_2Cl_2 (3×100 mL) was followed by drying the organic layer ($MgSO_4$). The solution was filtered through a Celite plug and evaporation of the excess solvent resulted into brown oil. Column chromatography eluting with 30% ethyl acetate/hexane gave the product **9** as a brown solid (5.71 g, 70%) with identical spectroscopic data to that described in the literature.[17,18]

3.1.2. 1-Bromo-6,7-dimethoxy-3,4-dihydronaphthalene-2-carbaldehyde 16. Dry DMF (0.56 mL, 7.27 mmol) in dry CH_2Cl_2 (20 mL) was cooled to 0 °C and phosphorus tribromide (0.60 mL, 6.30 mmol) was added drop-wise. The mixture was stirred at 0 °C for 2 h and a pale yellow suspension was formed. A solution of 6,7-dimethoxy-α-tetralone **15** (0.50 g, 2.42 mmol) in dry CH_2Cl_2 (30 mL) was added and the mixture was stirred at reflux for 12 h. After cooling to 0 °C, aqueous $NaHCO_3$ was added slowly until the effervescence had subsided. Extraction of the organic material into CH_2Cl_2 (3×100 mL) was followed by drying of the organic layer ($MgSO_4$), filtration through a Celite plug and evaporation of the excess solvent, which resulted into a yellow oil. Column chromatography (30% ethyl acetate/hexane) gave **16** as a yellow crystalline solid (0.45 g, 63%). This decomposed on standing and was therefore used immediately. IR ν_{max} (cm^{-1}) 1659 (s, C=O stretch), 1601, 1589, 1549 (s, C=C stretch); ^1H NMR δ/ppm 10.19 (1H, s, CHO), 7.42 (1H, s, Ar-H), 6.71 (1H, s, Ar-H), 3.95 (3H, s, OMe), 3.94 (3H, s, OMe), 2.80–2.75 (2H, m, CH_2), 2.64–2.58 (2H, m, CH_2); ^{13}C NMR δ/ppm 23.0 (CH_2), 27.1 (CH_2), 56.1 (OCH_3), 56.2 (OCH_3), 110.5 (CH), 112.1 (CH), 125.6 (C), 132.4 (C), 133.0 (C), 139.2 (C), 147.7 (C), 151.5 (C), 192.9 (CHO); MS (EI) *m/z* (%): 298 ($M^{+81}Br$, 94), 296 ($M^{+79}Br$, 100), 286 (17), 206 (50), 265 (22), 189 (53), 188 (43), 178 (24), 174 (19), 150 (42), 145 (35), 115 (39), 102 (22), 63 (18); HRMS calculated for $C_{13}H_{13}O_3{}^{79}Br$ M^+ 296.0048, found 296.0019.

3.1.3. 3,4,5-Trimethoxyphenylboronic acid 10a. To a stirred solution of 1-bromo-3,4,5-trimethoxybenzene (0.50 g, 2.02 mmol) in THF (30 mL) at −78 °C under nitrogen was added *n*-BuLi (1.56 mL, 2.22 mmol) drop-wise. The reaction mixture was stirred at −78 °C for 30 min before trimethylborate (0.68 mL, 6.07 mmol) was added and the mixture stirred for another 30 min at −78 °C. The subsequent mixture was then allowed to warm to room temperature before being acidified with aqueous 10% HCl. Extraction of the organic material into CH_2Cl_2 (3×100 mL) was followed by drying the organic layer ($MgSO_4$) before being concentrated under reduced pressure to give a cream white semi-solid **10a** (0.43 g, 100%) that was not purified further.

3.1.4. 1-Naphthylboronic acid 10b. In a similar manner to that described above bromonaphthalene (0.50 g, 2.41 mmol) in THF (40 mL) was converted into boronic acid **10b** (0.26 g, 63%) using *n*-BuLi (1.90 mL, 12.66 mmol) and $B(OMe)_3$ (0.81 mL, 7.24 mmol).

3.1.5. Phenylboronic acid 10c. Boronic acid **10c**, a cream white semi-solid (1.47 g, 89%) was synthesized from bromobenzene (1.43 mL, 13.58 mmol), *n*-BuLi (1.87 mL, 14.9 mmol) and $B(OMe)_3$ (1.96 mL, 4.07 mmol) in a similar way as described above.

3.1.6. *o*-Tolylboronic acid 10d. Using the same procedure as described above 2-bromotoluene (1.40 mL, 11.63 mmol) was converted to boronic acid **10d**, a white solid (1.34 g, 85%).

3.1.7. 1-(3,4,5-Trimethoxyphenyl)-3,4-dihydronaphthalene-2-carbaldehyde 11a. To $[Pd(PPh_3)_4]$ (0.22 g, 0.19 mmol) was added a deoxygenated solution of **9** (0.46 g, 1.940 mmol) in DME (10 mL). This was followed by a deoxygenated solution of boronic acid **10a** (0.62 g, 2.91 mmol) in ethanol (5 mL), and then a deoxygenated solution of aqueous sodium carbonate (1.77 g, 16.5 mmol in 8.2 mL water). The resultant mixture was heated under reflux under nitrogen for 46 h over which time the solution turned deep red. After allowing the mixture to cool to room temperature, it was quenched with water (50 mL) and the organic material was then extracted with CH_2Cl_2 (3×100 mL). The resultant organic extracts were combined, dried ($MgSO_4$), filtered through a Celite plug and the excess solvent removed using a rotary evaporator. The subsequent oil was purified by column chromatography (30% ethyl acetate/hexane) to afford the desired product **11a** as a brown solid (4.80 g, 83%). Mp=112–114 °C; IR ν_{max} (cm^{-1}) 1659 (s, C=O stretch), 1575, 1564 (s, C=C stretch); ^1H NMR δ/ppm 9.65 (1H, s, CHO), 7.26–7.31 (2H, m, 2×ArH), 7.19–7.16 (1H, m, ArH), 6.99–6.96 (1H, m, ArH), 6.51 (2H, s, 2×ArH), 3.93 (3H, s, OCH_3), 3.84 (6H, s, 2×OCH_3), 2.94–2.89 (2H, m, CH_2), 2.71–2.65 (2H, m, CH_2); ^{13}C NMR δ/ppm 20.2 (CH_2), 27.5 (CH_2), 56.2 (2×OCH_3), 60.9 (OCH_3), 107.7 (2×ArCH), 126.7 (CH), 127.8 (CH), 128.3 (CH), 130.2 (CH), 130.7 (C), 134.2 (C), 134.8 (C), 138.0 (C), 138.5 (C), 153.1 (2×C), 154.2 (C), 193.4 (CHO); MS (EI) *m/z* (%): 325 (M+1, 22), 324 (M^+, 100), 293 (22), 281 (52), 265 (18), 168 (31), 153 (25), 51 (11); HRMS calculated for $C_{20}H_{20}O_4$ M^+ 324.1362, found 324.1362.

3.1.8. 1-(1-Naphthyl)-3,4-dihydronaphthalene-2-carbaldehyde 11b. Using the same procedure as outlined above **11b**, a light brown oil (0.55 g, 93%) was obtained from a mixture of $[Pd(PPh_3)_4]$ (0.25 g, 0.21 mmol), dihydronaphthalene **9** (0.50 g, 2.11 mmol), boronic acid **10b** (0.54 g, 3.16 mmol, in ethanol 5 mL) and aqueous sodium carbonate (1.90 g, 17.9 mmol in 8.9 mL of water). IR ν_{max} (cm^{-1}) 1660 (s, C=O stretch), 1607, 1561 (m, C=C stretch); ^1H NMR δ/ppm 9.40 (1H, s, CHO), 7.92 (2H, t,

J=8.8 Hz, 2×ArH), 7.59–7.34 (5H, m, 5×ArH), 7.31–7.24 (2H, m, 2×ArH), 6.95 (1H, t, J=7.7 Hz, ArH), 6.64 (1H, d, J=7.7 Hz, ArH), 3.02–3.08 (2H, m, CH_2), 2.84–2.94 (1H, m, CH), 2.66–2.77 (1H, m, CH); ^{13}C NMR δ/ppm 20.1 (CH_2), 27.7 (CH_2), 125.1 (CH), 125.9 (CH), 126.3 (CH), 126.8 (CH), 126.9 (CH), 127.9 (CH), 128.1 (CH), 128.4 (CH), 128.4 (CH), 128.9 (CH), 130.2 (CH), 132.6 (C), 132.9 (C), 133.5 (C), 135.0 (C), 135.8 (C), 138.1 (C), 153.0 (C), 193.0 (CHO); MS (EI) m/z (%): 285 (M+1, 62), 284 (M^+, 100), 283 (89), 268 (27), 265 (39), 256 (62), 255 (89), 254 (33), 253 (68), 252 (73), 250 (27), 241 (27), 240 (43), 239 (67), 228 (33), 226 (22), 165 (21), 129 (22), 128 (73), 127 (39), 126 (42), 119 (22), 113 (20); HRMS calculated for $C_{21}H_{16}O$ M^+ 284.1201, found 284.1202.

3.1.9. 1-Phenyl-3,4-dihydronaphthalene-2-carbaldehyde 11c. In a similar manner as described above a mixture of [$Pd(PPh_3)_4$] (0.25 g, 0.21 mmol), dihydronaphthalene **9** (0.50 g, 2.11 mmol), boronic acid **10c** (0.39 g, 3.16 mmol, in ethanol 7 mL) and aqueous sodium carbonate (1.90 g, 17.9 mmol in 8.9 mL of water) was used to synthesize **11c** as a light brown crystalline solid (0.49 g, 100%). Mp=68–71 °C; IR ν_{max} (cm^{-1}) 1658 (s, C=O stretch), 1607, 1596 (m, C=C stretch); ^{1}H NMR δ/ppm 9.63 (1H, s, CHO), 7.50–7.47 (3H, m, 3×ArH), 7.35–7.30 (4H, m, 4×ArH), 7.18–7.12 (1H, dt, J=7.8, 1.9 Hz, ArH), 6.90 (1H, d, J=7.7 Hz, ArH), 2.97–2.92 (2H, m, CH_2), 2.76–2.71 (2H, m, CH_2); ^{13}C NMR δ/ppm 20.2 (CH_2), 27.5 (CH_2) 126.6 (CH), 127.8 (CH), 128.2 (2×CH), 128.4 (2×CH), 130.2 (C), 130.4 (2×C), 134.3 (C), 135.0 (C), 135.2 (ArC), 138.6 (C), 154.4 (ArC), 193.4 (CHO); MS (EI) m/z (%): 234 (M^+, 100), 233 (52), 205 (73), 202 (66), 189 (26), 178 (35), 165 (26), 128 (49), 127 (27), 78 (25), 29 (31); HRMS calculated for $C_{17}H_{14}O$ M^+ 234.1045, found 234.1045.[19]

3.1.10. 1-(*o*-Tolyl)-3,4-dihydronaphthalene-2-carbaldehyde 11d. Similarly [$Pd(PPh_3)_4$] (0.24 g, 0.210 mmol), a solution of dihydronaphthalene **9** (0.50 g, 2.11 mmol) in DME (10 mL), a solution of boronic acid **10d** (0.43 g, 3.16 mmol) in ethanol (5 mL), and a solution of aqueous sodium carbonate (1.90 g, 17.9 mmol in 8.9 mL of water) was used to synthesize carbaldehyde **11d** as a yellow crystalline solid (0.41 g, 78%). Mp=59–61 °C; IR ν_{max} (cm^{-1}) 1660 (s, C=O stretch), 1606, 1599 (m, C=C stretch); ^{1}H NMR δ/ppm 9.48 (1H, s, CHO), 7.35–7.25 (5H, m, 5×ArH), 7.16 (1H, d, J=6.9 Hz, ArH), 7.10 (1H, dt, J=7.8, 2.4 Hz, ArH), 6.73 (1H, d, J=7.8 Hz, ArH), 2.94 (2H, t, J=8.0 Hz, CH_2), 2.83–2.73 (1H, m, CH), 2.66–2.55 (1H, CH), 2.08 (3H, s, CH_3); ^{13}C NMR δ/ppm 19.6 (CH_3), 19.8 (CH_2), 27.5 (CH_2), 125.7 (CH), 126.7 (CH), 127.5 (CH), 127.9 (CH), 128.5 (CH), 130.2 (CH), 130.2 (CH), 130.5 (CH), 134.3 (C), 134.4 (C), 134.8 (C), 136.7 (C), 138.4 (C), 154.2 (C), 193.1 (CHO); MS (EI) m/z (%): 249 (M+1, 23), 248 (M^+, 74), 247 (35), 233 (100), 229 (28), 215 (51), 203 (51), 202 (53); HRMS calculated for $C_{18}H_{16}O$ M^+ 248.1201, found 248.1198.

3.1.11. 6,7-Dimethoxy-1-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalene-2-carbaldehyde 17a. To [$Pd(PPh_3)_4$] (0.19 g, 0.16 mmol) was added a deoxygenated solution of dihydronaphthalene **16** (0.48 g, 1.62 mmol) in DME (10 mL). This was followed by a deoxygenated solution of boronic acid **10a** (0.51 g, 2.42 mmol) in ethanol (5 mL), and then a deoxygenated solution of aqueous sodium carbonate (1.45 g, 13.7 mmol in 6.9 mL water). The resultant mixture was refluxed under nitrogen for 64 h during which time the mixture turned deep red. After allowing it to cool down to room temperature, the mixture was quenched with water (50 mL) and the organic material extracted with CH_2Cl_2 (3×100 mL). The resultant organic extracts were combined, dried ($MgSO_4$), and then filtered through a Celite plug and the excess solvent removed using a rotary evaporator. The subsequent oil was purified by column chromatography using 30% ethyl acetate/hexane as eluent to afford carbaldehyde **17a** as a yellow crystalline solid (0.55 g, 88%). Mp=139–141 °C; IR ν_{max} (cm^{-1}) 1652 (s, C=O stretch), 1603, 1581, 1556 (m, C=C stretch); ^{1}H NMR δ/ppm 9.59 (1H, s, CHO), 6.79 (1H, s, ArH), 6.52 (2H, s, 2×ArH), 6.49 (1H, s, ArH), 3.94 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 3.85 (6H, s, 2×OCH_3), 3.65 (3H, s, OCH_3), 2.88–2.82 (2H, m, CH_2), 2.70–2.64 (2H, m, CH_2); ^{13}C NMR δ/ppm 20.9 (CH_2), 27.8 (CH_2), 56.3 (OCH_3), 56.4 (OCH_3), 56.6 (2×OCH_3), 61.3 (OCH_3), 108.1 (2×CH), 111.4 (CH), 112.4 (CH), 127.6 (C), 131.3 (C), 132.8 (C), 133.1 (C), 138.4 (C), 147.8 (C), 151.2 (C), 153.4 (2×C), 154.9 (C), 193.5 (CHO); MS (EI) m/z (%): 385 (M+1, 27), 384 (M^+, 100), 372 (52), 371 (31), 370 (45), 369 (31), 368 (93), 366 (24), 353 (30), 343 (39), 337 (32), 195 (20), 181 (20), 28 (70); HRMS calculated for $C_{22}H_{24}O_6$ M^+ 384.1573, found 384.1573.

3.1.12. 6,7-Dimethoxy-1-(1-naphthyl)-3,4-dihydronaphthalene-2-carbaldehyde 17b. Using the same procedure as outlined above, a mixture of [$Pd(PPh_3)_4$] (0.12 g, 0.10 mmol), dihydronaphthalene **16** (0.30 g, 1.01 mmol), boronic acid **10b** (0.26 g, 1.51 mmol, in ethanol 5 mL) and aqueous sodium carbonate (0.91 g, 8.58 mmol in 4.5 mL of water) was used to synthesize carbaldehyde **17b** as a light brown oil (0.28 g, 87%). IR ν_{max} (cm^{-1}) 1652 (s, C=O stretch), 1604, 1557 (s, C=C stretch); ^{1}H NMR δ/ppm 9.44 (1H, s, CHO), 7.84 (2H, t, J=9.0 Hz, 2×ArH), 7.51–7.27 (5H, m, 5×ArH), 6.74 (1H, s, ArH), 6.07 (1H, s, ArH), 3.84 (3H, s, OCH_3), 3.26 (3H, s, OCH_3), 2.94–2.76 (3H, m, CH_2+CH), 2.67–2.56 (1H, m, CH); ^{13}C NMR δ/ppm 20.7 (CH_2), 27.5 (CH_2), 55.8 (OCH_3), 55.9 (OCH_3), 110.9 (CH), 111.6 (CH), 124.9 (CH), 125.9 (CH), 126.3 (CH), 126.7 (CH), 127.6 (C), 128.3 (CH), 128.3 (CH), 128.8 (CH), 132.2 (C), 132.5 (C), 133.0 (C), 133.4 (C), 133.9 (C), 147.4 (C), 150.7 (C), 153.2 (C), 192.7 (CHO); MS (EI) m/z (%): 345 (M+1, 63), 344 (M^+, 100), 315 (49), 313 (22), 262 (50), 239 (27), 232 (24), 226 (21), 205 (31), 189 (23), 128 (79), 119 (29), 115 (24), 85 (35), 83 (52); HRMS calculated for $C_{23}H_{20}O_3$ M^+ 344.1412, found 344.1412.

3.1.13. 6,7-Dimethoxy-1-phenyl-3,4-dihydronaphthalene-2-carbaldehyde 17c. In a similar manner as described above [$Pd(PPh_3)_4$] (0.12 g, 0.10 mmol), dihydronaphthalene **16** (0.30 g, 1.01 mmol), boronic acid **10c** (0.18 g, 1.51 mmol, in ethanol 5 mL) and aqueous sodium carbonate (0.91 g, 8.58 mmol in 4.3 mL of water) afforded **17c** as a yellow solid (0.22 g, 83%). Mp=114–117 °C; IR ν_{max} (cm^{-1}) 1650 (s, C=O stretch), 1605, 1557 (s, C=C stretch); ^{1}H NMR δ/ppm 9.53 (1H, s, CHO), 7.48–7.45 (3H, m, 3×ArH), 7.32–7.29 (2H, m, 2×ArH), 6.81 (1H, s, ArH), 6.39 (1H, s, ArH), 3.95 (3H, s, OCH_3), 3.61 (3H, s, OCH_3), 2.90–2.85 (2H, m, CH_2), 2.72–2.68 (2H, m, CH_2); ^{13}C NMR

δ/ppm 20.4 (CH_2), 27.4 (CH_2), 55.9 (2×OCH_3), 110.9 (CH), 111.9 (CH), 127.1 (C), 128.4 (2×CH), 128.6 (CH), 130.4 (2×CH), 132.4 (C), 132.6 (C), 135.4 (C), 147.2 (C), 150.6 (C), 154.6 (C), 192.9 (CHO); MS (EI) *m/z* (%): 295 (M+1, 26), 294 (M^+, 100), 293 (21), 265 (22), 189 (15), 178 (19); HRMS calculated for $C_{19}H_{18}O_3$ M^+ 294.1256, found 294.1256.

3.1.14. 6,7-Dimethoxy-1-(*o*-tolyl)-3,4-dihydronaphthalene-2-carbaldehyde 17d. Similarly [$Pd(PPh_3)_4$] (0.20 g, 0.11 mmol), dihydronaphthalene **16** (0.50 g, 1.68 mmol) in DME (10 mL), boronic acid **10d** (0.36 g, 2.52 mmol, in ethanol 10 mL) and aqueous sodium carbonate (1.56 g, 14.30 mmol in 7.4 mL of water) afforded carbaldehyde **17d** as a light brown oil (0.51 g, 98%). IR ν_{max} (cm^{-1}) 1656 (s, C=O stretch), 1606 (m, C=C stretch); ^{1}H NMR δ/ppm 9.41 (1H, s, CHO), 7.35–7.25 (3H, m, 3×ArH), 7.16 (1H, d, *J*=7.4 Hz, ArH), 6.79 (1H, s, ArH), 6.24 (1H, s, ArH), 3.93 (3H, s, OCH_3), 3.57 (3H, s, OCH_3), 2.90–2.83 (2H, m, CH_2), 2.78–2.73 (1H, m, CH), 2.64–2.55 (1H, m, CH), 2.08 (3H, s, CH_3); ^{13}C NMR δ/ppm 19.6 (CH_3), 19.9 (CH_2), 27.4 (CH_2), 55.9 (2×OCH_3), 110.9 (CH), 111.0 (CH), 125.7 (CH), 126.9 (C), 128.5 (CH), 130.2 (CH), 130.4 (CH), 132.4 (C), 132.5 (C), 134.9 (C), 136.6 (C), 147.6 (C), 150.7 (C), 154.5 (C), 192.8 (CHO); MS (EI) *m/z* (%): 308 (M^+, 100), 249 (16), 108 (31), 58 (20); HRMS calculated for $C_{20}H_{20}O_3$ M^+ 308.1412, found 308.1396.

3.1.15. [1-(3,4,5-Trimethoxyphenyl)-3,4-dihydronaphthalen-2-yl]methanol 12a. To a solution of carbaldehyde **11a** (0.51 g, 1.57 mmol) in ethanol (30 mL) was added $NaBH_4$ (0.07 g, 1.96 mmol). The reaction mixture was stirred at room temperature for 2 h after which time it turned cream white. The mixture was then extracted with CH_2Cl_2 (3×100 mL). The organic extracts were combined, dried ($MgSO_4$), and then filtered through a Celite plug and concentrated in vacuo. The subsequent colourless oil was purified by column chromatography using 30% ethyl acetate/hexane as eluent to afford **12a** as a white crystalline solid (0.51 g, 100%). Mp=115–116 °C; IR ν_{max} (cm^{-1}) 3421 (m, broad, OH stretch), 1583, 1507 (s, C=C stretch); ^{1}H NMR δ/ppm 7.17–7.02 (3H, m, 3×ArH), 6.72 (1H, dd, *J*=7.3, 1.0 Hz, ArH), 6.39 (2H, s, 2×ArH), 4.12 (2H, s, CH_2OH), 3.89 (3H, s, OCH_3), 3.80 (6H, s, 2×OCH_3), 2.90 (2H, dd, *J*=8.4, 7.6 Hz, CH_2), 2.54 (2H, dd, *J*=8.4, 7.5 Hz, CH_2), 1.85 (1H, s, CH_2OH); ^{13}C NMR δ/ppm 25.1 (CH_2), 28.1 (CH_2), 55.9 (2×OCH_3), 60.8 (OCH_3), 63.5 (CH_2OH), 106.9 (2×CH), 126.1 (CH), 126.2 (CH), 126.8 (CH), 127.1 (CH), 133.9 (C), 135.4 (C), 135.8 (C), 135.9 (C), 136.8 (C), 153.0 (2×C), (one quaternary carbon missing); MS (EI) *m/z* (%): 327 (M+1, 22), 326 (M^+, 100), 297 (25), 295 (27) 181 (10), 168 (24), 165 (14), 129 (21); HRMS calculated for $C_{20}H_{22}O_4$ M^+ 326.1518, found 326.1519.

3.1.16. [1-(1-Naphthyl)-3,4-dihydronaphthalen-2-yl]methanol 12b. Similarly using $NaBH_4$ (0.05 g, 1.32 mmol) in EtOH (10 mL) carbaldehyde **11b** (0.30 g, 1.06 mmol) was reduced to alcohol **12b**, a cream white semi-solid (0.29 g, 94%). IR ν_{max} (cm^{-1}) 3384 (s, broad, OH stretch), 1648, 1588, 1576 (m, C=C stretch); ^{1}H NMR δ/ppm 7.87 (2H, t, *J*=7.3 Hz, 2×ArH), 7.68 (1H, d, *J*=8.5 Hz, ArH), 7.54–7.43 (2H, m, 2×ArH), 7.38–7.29 (2H, m, 2×ArH), 7.24–7.20 (1H, m, ArH), 7.07–7.12 (1H, m, ArH), 6.90 (1H, t, *J*=7.5 Hz, ArH), 6.41 (1H, d, *J*=7.7 Hz, ArH), 3.92 (2H, s, CH_2OH), 3.08–3.02 (2H, m, CH_2), 2.73–2.65 (2H, m, CH_2); ^{13}C NMR δ/ppm 25.2 (CH_2), 28.4 (CH_2), 63.8 (CH_2OH), 125.5 (CH), 125.7 (CH), 125.9 (CH), 126.1 (CH), 126.3 (CH), 126.4 (CH), 126.9 (CH), 127.2 (CH), 127.5 (CH), 127.7 (CH), 128.3 (CH), 132.6 (C), 133.7 (C), 133.9 (C), 135.3 (C), 135.9 (C), 137.7 (C), (one quaternary carbon missing); MS (EI) *m/z* (%): 286 (M^+, 21), 268 (32), 267 (45), 255 (41), 253 (62), 251 (77), 249 (19), 239 (24), 238 (64), 229 (19), 228 (24), 225 (31), 215 (29), 165 (28), 152 (21), 141 (36), 129 (50), 128 (100), 127 (52), 115 (55), 77 (21), 31 (42); HRMS calculated for $C_{21}H_{18}O$ M^+ 286.1358, found 286.1356.

3.1.17. (1-Phenyl-3,4-dihydronaphthalen-2-yl)methanol 12c. Using the same procedure as outlined above, $NaBH_4$ (0.03 g, 0.19 mmol) in EtOH (10 mL) carbaldehyde **11c** (0.17 g, 0.72 mmol) afforded alcohol **12c** as a yellow oil (0.16 g, 94%). IR ν_{max} (cm^{-1}) 3386 (s, broad, OH stretch), 1654, 1598 (m, C=C stretch); ^{1}H NMR δ/ppm 7.37–7.29 (3H, m, 3×ArH), 7.13–7.11 (3H, m, 3×ArH), 7.08–7.06 (1H, dd, *J*=7.3, 1.1 Hz, ArH), 6.99 (1H, t, *J*=7.2 Hz, ArH), 6.60 (1H, d, *J*=7.6 Hz, ArH), 4.02 (2H, s, CH_2OH), 2.86 (2H, dd, *J*=8.4, 7.5 Hz, CH_2), 2.51 (2H, dd, *J*=8.4, 7.5 Hz, CH_2); ^{13}C NMR δ/ppm 25.0 (CH_2), 28.1 (CH_2), 63.3 (CH_2OH), 126.0 (CH), 126.1 (CH), 126.7 (CH), 126.9 (CH), 127.0 (CH), 128.2 (2×CH), 129.8 (2×CH), 135.5 (C), 135.8 (C), 135.9 (C), 136.1 (C), 138.3 (C); MS (EI) *m/z* (%): 237 (M+1, 20), 236 (M^+, 100), 235 (20), 234 (62), 233 (33), 224 (24), 218 (38), 217 (36), 215 (24), 208 (36), 205 (77), 204 (25), 203 (46), 202 (52), 189 (21), 179 (26), 178 (36), 165 (23), 159 (21), 130 (23), 129 (34), 128 (20), 127 (22), 115 (35), 105 (23), 101 (23), 91 (76), 77 (26); HRMS calculated for $C_{17}H_{16}O$ M^+ 236.1201, found 236.1201.

3.1.18. [1-(*o*-Tolyl)-3,4-dihydronaphthalen-2-yl]methanol 12d. Similarly using $NaBH_4$ (0.05 g, 1.41 mmol) in EtOH (10 mL) carbaldehyde **11d** (0.32 g, 1.13 mmol) was reduced to alcohol **12d**, a white semi-solid (0.30 g, 94%). IR ν_{max} (cm^{-1}) 3416 (s, broad, OH stretch), 1629 (m, C=C); ^{1}H NMR δ/ppm 7.26–6.99 (7H, m, 7×ArH), 6.50 (1H, d, *J*=7.6 Hz, ArH), 3.98 (2H, s, CH_2OH), 2.93 (2H, dd, *J*=8.3, 7.7 Hz, CH_2), 2.56 (2H, dd, *J*=8.5, 7.5 Hz, CH_2), 2.06 (3H, s, $ArCH_3$); ^{13}C NMR δ/ppm 19.4 (CH_2), 24.9 (CH_2), 28.3 (CH_3), 63.6 (CH_2OH), 125.5 (CH), 125.8 (CH), 126.4 (CH), 126.8 (CH), 127.2 (CH), 127.4 (CH), 129.9 (CH), 130.1 (CH), 135.1 (C), 135.4 (C), 135.5 (C), 135.7 (C), 136.8 (C), 137.7 (C); MS (EI) *m/z* (%): 251 (M+1, 40), 250 (M^+, 100), 235 (66), 232 (26), 219 (59), 218 (27), 217 (74), 216 (20), 215 (44), 204 (38), 203 (47), 202 (53), 179 (23), 178 (27), 159 (30), 129 (36), 128 (25), 119 (34), 115 (29), 105 (52), 101 (20), 91 (43), 43 (39); HRMS calculated for $C_{18}H_{18}O$ M^+ 250.1358, found 250.1358.

3.1.19. [6,7-Dimethoxy-1-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-2-yl]methanol 18a. In a similar manner as described above, $NaBH_4$ (0.06 g, 1.72 mmol) in EtOH (10 mL) was used to reduce carbaldehyde **17a** (0.53 g, 1.34 mmol) to alcohol **18a**, a white semi-solid (0.46 g, 87%). IR ν_{max} (cm^{-1}) 3517 (s, broad, OH stretch), 1651 (m, C=C stretch); ^{1}H NMR δ/ppm 6.66 (1H, s, ArH), 6.33 (2H, s, 2′ and 6′-H), 6.24 (1H, s, ArH), 4.04 (2H, s, CH_2OH), 3.83 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.75

(6H, s, 2×OCH_3), 3.54 (3H, s, OCH_3), 2.78 (2H, dd, J= 8.4, 7.6 Hz, CH_2), 2.46 (2H, dd, J=8.5, 7.6 Hz, CH_2); ^{13}C NMR δ/ppm 25.5 (CH_2), 27.9 (CH_2), 55.9 (OCH_3), 56.1 (3×OCH_3), 60.9 (OCH_3), 63.8 (CH_2OH), 106.9 (2′ and 6′-C), 110.7 (CH), 110.9 (CH), 128.5 (C), 128.6 (C), 133.6 (C), 133.9 (C), 135.8 (C), 136.9 (C), 146.9 (C), 147.9 (C), 153.4 (2×C); MS (EI) m/z (%): 387 (M+1, 63), 386 (M^+, 100), 357 (22), 355 (44), 189 (21), 164 (18), 152 (16), 31 (12); HRMS calculated for $C_{22}H_{24}O_6$ M^+ 386.1729, found 386.1729.

3.1.20. [6,7-Dimethoxy-1-(1-naphthyl)-3,4-dihydronaphthalen-2-yl]methanol 18b. Similarly $NaBH_4$ (0.03 g, 0.19 mmol) in EtOH (10 mL), reduced carbaldehyde **17b** (0.25 g, 0.73 mmol) to alcohol **18b**, obtained as a light brown oil (0.25 g, 100%). IR ν_{max} (cm^{-1}) 3481 (m, broad, OH stretch), 1604 (m, C=C stretch); ^{1}H NMR δ/ppm 7.76 (2H, t, J=7.3 Hz, 2×ArH), 7.58 (1H, d, J=8.4 Hz, ArH), 7.42–7.31 (2H, m, 2×ArH), 7.27–7.19 (2H, m, 2×ArH), 6.67 (1H, s, ArH), 5.89 (1H, s, ArH), 3.78 (2H, s, CH_2OH), 3.77 (3H, s, OCH_3), 3.23 (3H, s, OCH_3), 2.91–2.84 (2H, m, CH_2), 2.59–2.54 (2H, m, CH_2); ^{13}C NMR δ/ppm 25.3 (CH_2), 28.1 (CH_2), 55.8 (OCH_3), 55.9 (OCH_3), 63.7 (CH_2OH), 110.5 (CH), 110.9 (CH), 125.4 (CH), 125.7 (CH), 125.8 (CH), 126.1 (CH), 127.3 (CH), 127.6 (CH), 128.2 (CH), 128.8 (C), 132.5 (C), 133.4 (C), 133.6 (C), 135.5 (2×C), 135.9 (C), 146.9 (C), 147.9 (C); MS (EI) m/z (%): 347 (M+1, 43), 346 (M^+, 100), 345 (21), 344 (53), 330 (25), 315 (34), 239 (24), 226 (18), 215 (19); HRMS calculated for $C_{23}H_{22}O_3$ M^+ 346.1569, found 346.1569.

3.1.21. (6,7-Dimethoxy-1-phenyl-3,4-dihydronaphthalen-2-yl)methanol 18c. Using the same procedure as described above, $NaBH_4$ (0.03 g, 0.81 mmol) in EtOH (10 mL) reduced aldehyde **17c** (0.17 g, 0.65 mmol) to alcohol **18c** obtained as a light yellow oil (0.20 g, 100%). IR ν_{max} (cm^{-1}) 3449 (m, broad, OH stretch), 1573, (m, C=C stretch); ^{1}H NMR δ/ppm 7.41–7.30 (3H, m, 3×ArH), 7.18–7.15 (2H, m, 2×ArH), 6.72 (1H, s, ArH), 6.19 (1H, s, ArH), 4.06 (2H, s, CH_2OH), 3.88 (3H, s, OCH_3) 3.56 (3H, s, OCH_3), 2.85 (2H, t, J=8.1 Hz, CH_2), 2.54 (2H, t, J= 8.1 Hz, CH_2); ^{13}C NMR δ/ppm 25.5 (CH_2), 28.0 (CH_2), 55.8 (OCH_3), 55.9 (OCH_3), 63.7 (CH_2OH), 110.8 (CH), 110.9 (CH), 127.1 (CH), 128.2 (2×CH), 128.5 (C), 128.8 (C), 129.9 (2×CH), 133.8 (C), 135.8 (C), 138.4 (C), 146.9 (C), 147.9 (C); MS (EI) m/z (%): 296 (M^+, 12), 263 (14), 219 (69), 154 (43), 131 (22), 87 (23), 57 (100), 41 (23); HRMS calculated for $C_{19}H_{20}O_3$ M^+ 296.1412, found 296.1403.

3.1.22. [6,7-Dimethoxy-1-(*o*-tolyl)-3,4-dihydronaphthalen-2-yl]methanol 18d. Similarly $NaBH_4$ (0.05 g, 1.29 mmol) in EtOH (10 mL) was used to reduce aldehyde **17d** (0.32 g, 1.04 mmol) to alcohol **18d** obtained as a yellow semi-solid (0.28 g, 87%). IR ν_{max} (cm^{-1}) 3508 (m, broad, OH stretch), 1605, 1573 (m, C=C stretch); ^{1}H NMR δ/ppm 7.27–7.19 (3H, m, 3×ArH), 7.06 (1H, d, J=6.7 Hz, ArH), 6.74 (1H, s, ArH), 6.06 (1H, s, ArH), 3.97 (2H, s, CH_2OH), 3.87 (3H, s, OCH_3), 3.54 (3H, s, OCH_3), 2.89–2.84 (2H, m, CH_2), 2.57–2.52 (2H, m, CH_2), 2.06 (3H, s, $ArCH_3$); ^{13}C NMR δ/ppm 19.5 (CH_3), 25.2 (CH_2), 28.1 (CH_2), 55.9 (OCH_3), 56.0 (OCH_3), 63.8 (CH_2OH), 110.0 (CH), 111.1 (CH), 125.8 (CH), 127.5 (CH), 128.2 (C), 128.4 (C), 130.0 (2×C), 133.5 (C), 135.0 (C), 136.7 (C), 137.8 (C), 147.2 (C), 147.9 (C); MS (EI) m/z (%): 311 (M+1, 19), 310 (M^+, 80), 309 (23), 308 (75), 294 (33), 293 (35), 279 (56), 191 (26), 189 (26), 166 (40), 148 (100), 83 (30), 57 (38), 43 (27), 41 (22); HRMS calculated for $C_{20}H_{22}O_3$ M^+ 310.1569, found 310.1569.

3.1.23. [1-(3,4,5-Trimethoxyphenyl)-3,4-dihydronaphthalen-2-yl]methyl acetate 13a. A mixture of alcohol **12a** (0.38 g, 1.16 mmol), pyridine (5 mL) and acetic anhydride (5 mL) was refluxed under nitrogen for 16 h during which time the mixture turned black. After cooling to room temperature, excess solvent was removed under reduced pressure and the resultant oil purified by column chromatography using 30% ethyl acetate/hexane as eluent to afford the acetate **13a** as yellow crystalline solid (0.42 g, 98%). Mp=81–83 °C; IR ν_{max} (cm^{-1}) 1734 (s, C=O stretch), 1584 (s, C=C stretch); ^{1}H NMR δ/ppm 7.16–7.07 (3H, m, 3×ArH), 6.74 (1H, d, J=7.3 Hz, ArH), 6.41 (2H, s, 2′ and 6′-H), 4.61 (2H, s, CH_2OAc), 3.90 (3H, s, OCH_3), 3.82 (6H, s, 2×OCH_3), 2.92 (2H, dd, J=8.4, 7.7 Hz, CH_2), 2.46 (2H, dd, J=8.4, 7.7 Hz, CH_2), 2.07 (3H, s, OAc); ^{13}C NMR δ/ppm 20.9 (CH_2), 25.4 (OAc), 27.9 (CH_2), 56.0 (2× OCH_3), 60.8 (OCH_3), 65.6 (CH_2OAc), 106.8 (2′ and 6′-C), 126.3 (CH), 126.3 (CH), 127.1 (CH), 127.2 (CH), 131.0 (C), 133.4 (C), 135.4 (C), 135.6 (C), 137.0 (C), 138.3 (C), 153.1 (2×C), 170.9 ($OCOCH_3$); MS (EI) m/z (%): 369 (M+1, 11), 368 (M^+, 51), 309 (12), 308 (18), 293 (22), 278 (33), 277 (100), 246 (17); HRMS calculated for $C_{22}H_{24}O_5$ M^+ 368.1624, found 368.1620.

3.1.24. [1-(1-Naphthyl)-3,4-dihydronaphthalen-2-yl]methyl acetate 13b. In a similar manner as described above alcohol **12b** (0.25 g, 0.87 mmol) gave **13b** as a yellow oil (0.27 g, 94%). IR ν_{max} (cm^{-1}) 1734 (s, C=O stretch), 1593 (m, C=C stretch); ^{1}H NMR δ/ppm 7.86–7.82 (2H, m, 2×ArH), 7.65 (1H, d, J=8.5 Hz, ArH), 7.52–7.42 (2H, m, 2×ArH), 7.39–7.29 (2H, m, 2×ArH), 7.18 (1H, d, J=7.3 Hz, ArH), 7.08 (1H, t, J=7.4 Hz, ArH), 6.87 (1H, t, J=7.5 Hz, ArH), 6.41 (1H, d, J=7.7 Hz, ArH), 4.42 (2H, s, CH_2OAc), 3.02 (2H, m, CH_2), 2.60–2.54 (2H, m, CH_2), 1.92 (3H, s, OAc); ^{13}C NMR δ/ppm 20.8 (CH_2), 25.5 (OAc), 28.2 (CH_2), 65.6 (CH_2OAc), 125.6 (CH), 125.9 (CH), 126.0 (CH), 126.1 (CH), 126.2 (CH), 126.3 (CH), 127.3 (2×CH), 127.6 (CH), 128.0 (CH), 128.4 (CH), 132.5 (C), 133.0 (C), 133.8 (C), 135.3 (C), 135.6 (C), 135.8 (C), 136.3 (C), 171.0 ($OCOCH_3$); MS (EI) m/z (%): 329 (M+1, 25), 328 (M^+, 77), 270 (29), 269 (100), 268 (53), 267 (56), 266 (58), 265 (74), 263 (21), 255 (41), 254 (52), 253 (99), 252 (97), 249 (22), 241 (25), 240 (31), 239 (67), 228 (25), 226 (23), 165 (23), 141 (60), 133 (20), 129 (32), 128 (29), 127 (25), 126 (51), 117 (26), 115 (28), 91 (30), 43 (63); HRMS calculated for $C_{23}H_{20}O_2$ M^+ 328.1463, found 328.1463.

3.1.25. (1-Phenyl-3,4-dihydronaphthalen-2-yl)methyl acetate 13c. Similarly alcohol **12c** (0.25 g, 1.06 mmol afforded acetate **13c** as a yellow oil (0.24 g, 82%). IR ν_{max} (cm^{-1}) 1735 (s, C=O stretch), 1656, 1598 (m, C=C stretch); ^{1}H NMR δ/ppm 7.39–7.33 (3H, m, 3×ArH), 7.18–7.09 (5H, m, 5×ArH), 7.02 (1H, t, J=7.3 Hz, ArH), 6.63 (1H, d, J=7.6 Hz, ArH), 4.56 (2H, s, CH_2OAc), 2.92 (2H, dd, J=8.3, 7.7 Hz, CH_2), 2.46 (2H, dd, J=8.3, 7.7 Hz, CH_2), 2.04 (3H, s, OAc); ^{13}C NMR δ/ppm) 20.9 (CH_2), 25.7 (OAc), 27.6 (CH_2), 65.5 (CH_2OAc), 126.2 (CH), 126.4

(CH), 127.2 (CH), 127.2 (CH), 127.3 (CH), 128.3 (2×CH), 129.9 (2×CH), 131.1 (C), 135.6 (C), 135.8 (C), 137.9 (C), 138.3 (C), 170.9 ($OCOCH_3$); MS (EI) *m/z* (%): 278 (M^+, 55), 266 (20), 234 (22), 220 (29), 219 (100), 218 (62), 217 (62), 216 (75), 215 (76), 205 (42), 204 (55), 203 (95), 202 (92), 191 (40), 189 (41), 179 (23), 178 (51), 165 (33), 141 (26), 129 (37), 128 (31), 127 (21), 115 (44), 101 (23), 91 (89), 77 (22), 43 (73); HRMS calculated for $C_{19}H_{18}O_2$ M^+ 278.1307, found 278.1307.

3.1.26. [1-(*o*-Tolyl)-3,4-dihydronaphthalen-2-yl]methyl acetate 13d. Similarly alcohol **12d** (0.20 g, 0.80 mmol) gave acetate **13d** as a light brown oil (0.22 g, 94%). IR ν_{max} (cm^{-1}) 1725 (s, C=O stretch), 1605, 1575 (m, C=C stretch); ^1H NMR δ/ppm 7.27–7.01 (7H, m, 7×ArH), 6.52 (1H, d, J=7.6 Hz, ArH), 4.50 (1H, d, J=14.4 Hz, one of CH_2OAc), 4.43 (1H, d, J=14.4 Hz, one of CH_2OAc), 2.93 (2H, dd, J=8.4, 7.7 Hz, CH_2), 2.47 (2H, dd, J=8.4, 7.5 Hz, CH_2), 2.06 (3H, s, $ArCH_3$)[a], 2.03 (3H, s, $OCOCH_3$)[a], assignments with the same superscript may be interchanged; ^{13}C NMR δ/ppm 19.4 ($ArCH_3$), 20.9 (CH_2), 25.1 (OAc), 28.1 (CH_2), 65.4 (CH_2OAc), 125.6 (CH), 125.8 (CH), 126.4 (CH), 127.1 (CH), 127.2 (CH), 127.7 (CH), 130.0 (2×CH), 131.0 (C), 135.0 (C), 135.4 (C), 136.7 (C), 137.2 (C), 137.4 (C), 170.9 ($OCOCH_3$); MS (EI) *m/z* (%): 292 (M^+, 10), 232 (24), 217 (100), 105 (6), 91 (5), 43 (9); HRMS calculated for $C_{20}H_{20}O_2$ M^+ 292.1463, found 292.1425.

3.1.27. [6,7-Dimethoxy-1-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-2-yl]methyl acetate 19a. Using the same procedure as outlined above alcohol **18a** (0.37 g, 0.96 mmol) afforded acetate **19a** as light yellow oil (0.33 g, 80%). IR ν_{max} (cm^{-1}) 1731 (s, C=O stretch), 1583 (s, C=C stretch); ^1H NMR δ/ppm 6.73 (1H, s, ArH), 6.42 (2H, s, 2′ and 6′-H), 6.32 (1H, s, ArH), 4.60 (2H, s, CH_2OAc), 3.90 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.82 (6H, s, 2×OCH_3), 3.62 (3H, s, OCH_3), 2.85 (2H, dd, J=8.4, 7.6 Hz, CH_2), 2.44 (2H, dd, J=8.4, 7.8 Hz, CH_2), 2.07 (3H, s, OAc); ^{13}C NMR δ/ppm 20.9 (CH_2), 25.8 (OAc), 27.7 (CH_2), 55.8 (OCH_3), 55.9 (OCH_3), 56.1 (2×OCH_3), 60.9 (OCH_3), 65.8 (CH_2OAc), 106.9 (2′ and 6′-C), 110.8 (CH), 110.9 (CH), 128.2 (C), 128.5 (C), 128.7 (C), 133.5 (C), 137.0 (C), 138.1 (C), 147.0 (C), 148.2 (C), 153.1 (2×C), 171.0 ($OCOCH_3$); MS (EI) *m/z* (%): 352 (M^+, 54), 188 (28), 87 (14), 57 (77), 43 (100); HRMS calculated for $C_{22}H_{24}O_4$ M^+ 352.1675, found 352.1743.

3.1.28. [6,7-Dimethoxy-1-(1-naphthyl)-3,4-dihydronaphthalen-2-yl]methyl acetate 19b. Similarly alcohol **18b** (0.17 g, 0.49 mmol) afforded acetate **19b** as yellow semi-solid (0.17 g, 89%). IR ν_{max} (cm^{-1}) 1730 (s, C=O stretch), 1605 (m, C=C stretch); ^1H NMR δ/ppm 7.88–7.84 (2H, m, 2×ArH), 7.65 (1H, d, J=8.4 Hz, ArH), 7.54–7.42 (2H, m, 2×ArH), 7.37–7.31 (2H, m, 2×ArH), 6.77 (1H, s, ArH), 5.99 (1H, s, ArH), 4.43 (1H, d, J=12.2 Hz, one of CH_2OAc), 4.38 (1H, d, J=12.2 Hz, one of CH_2OAc), 3.87 (3H, s, OCH_3), 3.33 (3H, s, OCH_3), 2.97–2.89 (2H, m, CH_2), 2.59–2.53 (2H, m, CH_2), 1.95 (3H, s, OAc); ^{13}C NMR δ/ppm 20.8 (CH_2), 25.7 (OAc), 27.9 (CH_2), 55.8 (OCH_3), 55.9 (OCH_3), 65.6 (CH_2OAc), 110.6 (CH), 110.9 (CH), 125.4 (CH), 125.8 (2×CH), 126.0 (CH), 127.4 (CH), 127.9 (CH), 128.1 (C), 128.2 (CH), 128.5 (C), 130.5 (C), 132.3 (C), 133.6 (C), 135.5 (C), 135.9 (C), 147.0 (C), 148.1 (C), 170.9 ($OCOCH_3$); MS (EI) *m/z* (%): 389 (M+1, 29), 388 (M^+, 100), 329 (32), 328 (71), 327 (23), 298 (25), 297 (54), 239 (24), 141 (19); HRMS calculated for $C_{25}H_{24}O_4$ M^+ 388.1675, found 388.1675.

3.1.29. (6,7-Dimethoxy-1-phenyl-3,4-dihydronaphthalen-2-yl)methyl acetate 19c. Similarly alcohol **18c** (0.15 g, 0.58 mmol) gave acetate **19c** as a yellow solid (0.17 g, 88%). Mp=106 °C; IR ν_{max} (cm^{-1}); 1732 (s, C=O stretch), 1605, 1573 (m, C=C stretch); ^1H NMR δ/ppm 7.43–7.34 (3H, m, 3×ArH), 7.19–7.16 (2H, m, 2×ArH), 6.72 (1H, s, ArH), 6.20 (1H, s, ArH), 4.54 (2H, s, CH_2OAc), 3.89 (3H, s, OCH_3) 3.56 (3H, s, OCH_3), 2.85 (2H, dd, J=8.5, 7.6 Hz, CH_2), 2.44 (2H, dd, J=8.4, 7.7 Hz, CH_2), 2.04 (3H, s, OAc); ^{13}C NMR δ/ppm 20.9 (CH_2), 25.7 (CH_2), 27.7 (CH_3), 55.8 (OCH_3), 55.9 (OCH_3), 65.6 (CH_2OH), 110.8 (CH), 110.9 (CH), 127.3 (CH), 128.2 (2×CH), 128.5 (C), 128.8 (C), 129.8 (2×CH), 137.9 (C), 138.1 (C), 146.9 (C), 148.0 (2×C), 171.1 ($OCOCH_3$), (one quaternary carbon missing); MS (EI) *m/z* (%): 339 (M+1, 31), 338 (M^+, 100), 336 (36), 279 (71), 278 (95), 277 (53), 248 (41), 247 (64), 245 (32), 203 (27), 189 (24), 165 (21), 91 (21), 43 (66); HRMS calculated for $C_{21}H_{22}O_4$ M^+ 338.1518, found 338.1519.

3.1.30. [6,7-Dimethoxy-1-(*o*-tolyl)-3,4-dihydronaphthalen-2-yl]methyl acetate 19d. In a similar manner as described above alcohol **18d** (0.28 g, 0.90 mmol) afforded acetate **19d** as cream white semi-solid (0.28 g, 88%). IR ν_{max} (cm^{-1}); 1731 (s, C=O stretch), 1605, 1510 (s, C=C stretch); ^1H NMR δ/ppm 7.26–7.21 (3H, m, 3×ArH), 7.07 (1H, d, J=6.6 Hz, ArH), 6.73 (1H, s, ArH), 6.08 (1H, s, ArH), 4.48 (1H, d, J=12.1 Hz, one of CH_2OAc), 4.42 (1H, d, J=12.1 Hz, one of CH_2OAc), 3.88 (3H, s, OCH_3), 3.54 (3H, s, OCH_3), 2.90–2.84 (2H, m, CH_2), 2.45 (2H, dd, J=8.7, 7.4 Hz, CH_2), 2.06 (3H, s, OAc)[a], 2.03 (3H, s, $ArCH_3$)[a], assignments with the same superscript may be interchanged; ^{13}C NMR δ/ppm 19.3 ($ArCH_3$), 20.9 (CH_2), 25.4 (OAc), 27.8 (CH_2), 55.9 (2×OCH_3), 65.5 (CH_2OAc), 109.9 (CH), 110.9 (CH), 125.8 (CH), 127.6 (CH), 127.9 (C), 128.4 (C), 128.7 (C), 129.9 (CH), 130.0 (CH), 136.6 (C), 137.1 (C), 137.3 (C), 147.2 (C), 148.1 (C), 171.1 ($OCOCH_3$); ^{13}C NMR δ/ppm 20.1 (CH_2), 27.7 (CH_2), 125.1 (CH), 125.9 (CH), 126.3 (CH), 126.76 (CH), 126.79 (CH), 127.9 (CH), 128.1 (CH), 128.39 (CH), 128.4 (CH), 128.9 (CH), 130.2 (CH), 132.6 (C), 132.9 (C), 133.5 (C), 135.0 (C), 135.8 (C), 138.1 (C), 153.0 (C), 193.0 (CHO); MS (EI) *m/z* (%): 353 (M+1, 24), 352 (M^+, 40), 351 (10), 292 (53), 277 (100), 245 (33), 201 (27), 115 (27), 43 (44); HRMS calculated for $C_{22}H_{24}O_4$ M^+ 352.1675, found 352.1766.

3.1.31. [1-(3,4,5-Trimethoxyphenyl)naphthalen-2-yl]-methyl acetate 14a. To a solution of acetate **13a** (0.50 g, 1.46 mmol) in dry CH_2Cl_2 (30 mL) was added DDQ (0.85 g, 1.98 mmol) and the mixture immediately turned green. The reaction mixture was then refluxed under nitrogen for 16 h over which time it turned pale green. After allowing to cool to room temperature, the mixture was poured into an aqueous solution of 5% $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3×100 mL). The organic extracts were combined, washed with brine (20 mL), dried ($MgSO_4$), filtered through Celite plug and the excess solvent removed in vacuo. The resultant oil was purified by column

chromatography using 30% ethyl acetate as eluent to obtain the substituted naphthalene **14a** as an orange solid (0.39 g, 78%). Mp = 85–87 °C; IR ν_{max} (cm^{-1}) 1734 (s, C=O stretch), 1582 (s, C=C stretch); ^{1}H NMR δ/ppm 7.89–7.85 (2H, m, 2×ArH), 7.60–7.54 (2H, m, 2×ArH), 7.51–7.38 (2H, m, 2×ArH), 6.55 (2H, s, 2′ and 6′-H), 5.07 (2H, s, CH_2OAc), 3.96 (3H, s, OCH_3), 3.82 (6H, s, 2×OCH_3), 2.07 (3H, s, OAc); ^{13}C NMR δ/ppm 20.9 (OAc), 56.0 (2×OCH_3), 60.9 (OCH_3), 64.7 (CH_2OAc), 107.3 (2′ and 6′-C), 126.0 (2×CH), 126.2 (CH), 126.7 (CH), 127.7 (CH), 127.9 (CH), 130.8 (C), 132.6 (C), 133.0 (C), 133.2 (C), 137.3 (C), 139.3 (C), 153.0 (2×C), 170.6 ($OCOCH_3$); MS (EI) *m/z* (%): 367 (M+1, 66), 366 (M^+, 100), 320 (39), 305 (48), 291 (33), 277 (29), 276 (28), 275 (24), 189 (23), 43 (29); HRMS calculated for $C_{22}H_{22}O_5$ M^+ 366.1467, found 366.1468.

3.1.32. [1-(1-Naphthyl)naphthalen-2-yl]methyl acetate 14b. In a similar manner as described above DDQ (0.21 g, 0.91 mmol) was used to convert acetate **13b** (0.20 g, 0.61 mmol) into **14b**, obtained as a light yellow oil (0.19 g, 95%). IR ν_{max} (cm^{-1}) 1738 (s, C=O stretch), 1593, 1587 (m, C=C stretch); ^{1}H NMR δ/ppm 7.98–7.89 (4H, m, 4×ArH), 7.67–7.58 (2H, m, 2×ArH), 7.47–7.39 (3H, m, 3×ArH), 7.24–7.16 (4H, m, 4×ArH), 4.93 (1H, d, J=12.5 Hz, one of CH_2OAc), 4.84 (1H, d, J=12.5 Hz, one of CH_2OAc), 1.84 (3H, s, OAc); ^{13}C NMR δ/ppm 20.6 (OAc), 64.7 (CH_2OAc), 125.4 (CH), 125.9 (CH), 126.1 (2×CH), 126.2 (CH), 126.3 (CH), 126.4 (CH), 126.8 (CH), 127.8 (CH), 127.9 (CH), 128.1 (CH), 128.2 (CH), 128.2 (CH), 132.0 (C), 132.8 (C), 133.1 (C), 133.2 (C), 133.6 (C), 135.4 (C), 137.4 (C), 171.0 ($OCOCH_3$); MS (EI) *m/z* (%): 327 (M+1, 51), 326 (M^+, 97), 284 (21), 268 (20), 267 (60), 266 (85), 265 (100), 263 (27), 262 (43), 253 (40), 251 (64), 249 (21), 238 (23), 43 (19); HRMS calculated for $C_{23}H_{18}O_2$ M^+ 326.1307, found 326.1307.

3.1.33. (1-Phenylnaphthalen-2-yl)methyl acetate 14c. Similarly acetate **13c** (0.14 g, 0.50 mmol) afforded the arylnaphthalene **14c** as light yellow oil (0.13 g, 93%) using DDQ (0.17 g, 0.75 mmol) in CH_2Cl_2 (15 mL). IR ν_{max} (cm^{-1}) 1738 (s, C=O stretch), 1597 (m, C=C stretch); ^{1}H NMR δ/ppm 7.88–7.83 (2H, m, 2×ArH), 7.57 (1H, d, J=8.5 Hz, ArH), 7.47–7.43 (5H, m, 5×ArH), 7.30–7.15 (3H, m, 3×ArH), 5.00 (2H, s, CH_2OAc), 2.02 (3H, s, OAc); ^{13}C NMR δ/ppm) 20.9 (CH_3), 64.7 (CH_2OH), 125.9 (CH), 126.1 (CH), 126.2 (CH), 126.7 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 128.2 (2×CH), 130.2 (2×CH), 130.8 (C), 132.7 (C), 133.1 (C), 137.8 (C), 139.5 (C), 170.6 ($OCOCH_3$); MS (EI) *m/z* (%): 277 (M+1, 24), 276 (M^+, 100), 234 (23), 215 (78), 202 (34); HRMS calculated for $C_{19}H_{16}O_2$ M^+ 276.1150, found 276.1113.

3.1.34. [1-(*o*-Tolyl)naphthalen-2-yl]methyl acetate 14d. Similarly using DDQ (0.46 g, 1.53 mmol) in CH_2Cl_2 (30 mL) acetate **13d** (0.20 g, 0.51 mmol) afforded the substituted naphthalene **14d** as a light brown crystalline solid (0.20 g, 100%). Mp = 86–90 °C; IR ν_{max} (cm^{-1}) 1736 (s, C=O stretch); ^{1}H NMR δ/ppm 7.88–7.83 (2H, m, 2×ArH), 7.58 (1H, d, J=8.5 Hz, ArH), 7.46–7.41 (1H, m, ArH), 7.35–7.27 (5H, m, 5×ArH), 7.13 (1H, d, J=7.5 Hz, ArH), 4.97 (1H, d, J=12.4 Hz, one of CH_2OAc), 4.95 (1H, d, J=12.4 Hz, one of CH_2OAc), 2.00 (3H, s, $ArCH_3$)[a], 1.91 (3H, s, OAc)[a]; ^{13}C NMR δ/ppm 19.9 ($ArCH_3$)[a], 20.7 ($OCOCH_3$)[a], 64.7 (CH_2OAc), 125.8 (CH), 126.0 (CH), 126.1 (CH), 126.1 (CH), 126.3 (CH), 127.7 (CH), 127.8 (CH), 127.9 (CH), 129.9 (CH), 130.0 (CH), 130.7 (C), 132.2 (C), 133.1 (C), 136.9 (C), 137.1 (C), 138.7 (C), 170.9 ($OCOCH_3$), assignments with the same superscript may be interchanged; MS (EI) *m/z* (%): 291 (M+1, 30), 290 (M^+, 85), 231 (80), 229 (89), 216 (75), 215 (100), 202 (50), 189 (22), 149 (31), 43 (71); HRMS calculated for $C_{20}H_{18}O_2$ M^+ 290.1307, found 290.1307.

3.1.35. [6,7-Dimethoxy-1-(3,4,5-trimethoxyphenyl)-naphthalen-2-yl]methyl acetate 20a. Using DDQ (0.48 g, 2.10 mmol) in CH_2Cl_2 (30 mL) according to the same procedure as outlined above acetate **19a** (0.30 g, 0.70 mmol) gave the naphthalene **20a** as yellow crystalline solid (0.22 g, 74%). Mp = 150–152 °C; IR ν_{max} (cm^{-1}) 1736 (s, C=O stretch), 1625, 1583 (s, C=C stretch); ^{1}H NMR δ/ppm 7.64 (1H, d, J=8.4 Hz, ArH), 7.36 (1H, d, J=8.4 Hz, ArH), 7.08 (1H, s, ArH), 6.76 (1H, s, ArH), 6.48 (2H, s, 2′ and 6′-H), 4.94 (2H, s, CH_2OH), 3.93 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.76 (6H, s, 2×OCH_3), 3.67 (3H, s, OCH_3), 1.98 (3H, s, OAc); ^{13}C NMR δ/ppm 20.9 (OAc), 55.7 (OCH_3), 55.8 (OCH_3), 56.1 (2×OCH_3), 60.9 (OCH_3), 64.9 (CH_2OAc), 105.4 (CH), 106.2 (CH), 107.2 (2×CH), 124.8 (CH), 126.2 (CH), 128.2 (C), 129.1 (C), 129.2 (C), 133.6 (C), 137.2 (C), 138.1 (C), 149.5 (C), 149.6 (C), 153.1 (2×C), 170.6 ($OCOCH_3$); MS (EI) *m/z* (%): 427 (M+1, 19), 426 (M^+, 70), 81 (18), 69 (41), 57 (29), 55 (23), 43 (27), 41 (21), 31 (23), 28 (100); HRMS calculated for $C_{24}H_{26}O_7$ M^+ 426.1679, found 426.1678.

3.1.36. [6,7-Dimethoxy-1-(1-naphthyl)naphthalen-2-yl]methyl acetate 20b. Similarly acetate **19b** (0.22 g, 0.57 mmol) gave the substituted arylnaphthalene **20b**, as a yellow solid (0.17 g, 78%) using DDQ (0.13 g, 0.57 mmol) in CH_2Cl_2 (15 mL). Mp = 110–114 °C; IR ν_{max} (cm^{-1}) 1736 (s, C=O stretch), 1624 (m, C=C stretch); ^{1}H NMR δ/ppm 7.85 (2H, t, J=7.8 Hz, 2×ArH), 7.72 (1H, d, J=8.4 Hz, ArH), 7.53–7.32 (4H, m, 4×ArH), 7.18–7.14 (2H, m, 2×ArH), 7.11 (1H, s, ArH), 6.35 (1H, s, ArH), 4.82 (1H, d, J=12.3 Hz, one of CH_2OAc), 4.69 (1H, d, J=12.3 Hz, one of CH_2OAc), 3.91 (3H, s, OCH_3), 3.36 (3H, s, OCH_3), 1.72 (3H, s, OAc); ^{13}C NMR δ/ppm 20.6 (OAc), 55.4 (OCH_3), 55.8 (OCH_3), 64.9 (CH_2OAc), 105.5 (CH), 106.2 (CH), 124.9 (CH), 125.4 (CH), 125.9 (CH), 126.0 (2×CH), 126.4 (CH), 127.8 (CH), 128.2 (CH), 128.2 (CH), 128.8 (C), 129.2 (C), 130.3 (C), 132.6 (C), 133.6 (C), 135.7 (C), 136.1 (C), 149.6 (C), 149.7 (C), 170.5 ($OCOCH_3$); MS (EI) *m/z* (%): 387 (M+1, 25), 386 (M^+, 100), 385 (26), 384 (90), 372 (32), 371 (22), 370 (27), 368 (19), 344 (20), 343 (27), 149 (25); HRMS calculated for $C_{25}H_{22}O_4$ M^+ 386.1518, found 386.1519.

3.1.37. (6,7-Dimethoxy-1-phenylnaphthalen-2-yl)methyl acetate 20c. Similarly dihydronaphthalene **19c** (0.17 g, 0.56 mmol) gave the substituted naphthalene **20c** as a yellow crystalline solid (0.17 g, 100%) using DDQ (0.38 g, 1.66 mmol) in CH_2Cl_2 (20 mL). Mp = 75–78 °C; IR ν_{max} (cm^{-1}) 1736 (s, C=O stretch), 1624 (m, C=C stretch); ^{1}H NMR δ/ppm 7.62 (1H, d, J=8.4 Hz, ArH), 7.36–7.33 (4H, m, 4×ArH), 7.23–7.19 (2H, m, 2×ArH), 7.06 (1H, s, ArH), 6.63 (1H, s, ArH), 4.87 (2H, s, CH_2OAc), 3.90 (3H, s,

OCH_3) 3.59 (3H, s, OCH_3), 1.93 (3H, s, OAc); ^{13}C NMR δ/ppm 20.9 (OAc), 55.4 (OCH_3), 55.8 (OCH_3), 64.9 (CH_2OAc), 105.4 (CH), 106.1 (CH), 124.9 (CH), 126.1 (CH), 127.5 (CH), 128.3 (2×CH), 129.1 (C), 129.1 (C), 129.9 (2×CH), 138.1 (C), 138.3 (C), 149.4 (C), 149.5 (C), 170.6 ($OCOCH_3$), (one quaternary carbon missing); MS (EI) *m/z* (%): 337 (M+1, 59), 336 (M^+, 100), 265 (19), 246 (37), 245 (56), 215 (24), 203 (26), 202 (33), 191 (22), 189 (40), 43 (42); HRMS calculated for $C_{21}H_{20}O_4$ M^+ 336.1362, found 336.1362.

3.1.38. [6,7-Dimethoxy-1-(*o*-tolyl)naphthalen-2-yl]-methyl acetate 20d. In a similar manner as described above dihydronaphthalene **19d** (0.31 g, 0.88 mmol) was converted into naphthalene **20d**, which was obtained as a yellow solid (0.24 g, 78%) using DDQ (0.20 g, 0.88 mmol) in CH_2Cl_2 (20 mL). Mp=91–93 °C; IR ν_{max} (cm^{-1}) 1736 (s, C=O stretch), 1624 (m, C=C stretch); ^1H NMR δ/ppm 7.73 (1H, d, J=8.4 Hz, ArH), 7.45 (1H, d, J=8.4 Hz, ArH), 7.36–7.25 (3H, m, 3×ArH), 7.16 (1H, s, ArH), 7.16–7.14 (1H, s, ArH), 6.53 (1H, s, ArH), 4.93 (1H, d, J=12.2 Hz, one of CH_2OAc), 4.87 (1H, d, J=12.2 Hz, one of CH_2OAc), 4.00 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 2.00 (3H, s, $ArCH_3$), 1.94 (3H, s, $OCOCH_3$); ^{13}C NMR δ/ppm 19.5 ($ArCH_3$), 20.8 ($OCOCH_3$), 55.5 (OCH_3), 55.8 (OCH_3), 64.9 (CH_2OAc), 104.8 (CH), 106.3 (CH), 124.9 (CH), 125.9 (CH), 126.0 (CH), 127.9 (CH), 129.0 (C), 129.1 (C), 129.9 (2×CH), 136.8 (C), 137.5 (C), 137.6 (C), 149.6 (C), 149.7 (C), 170.7 ($OCOCH_3$), (one quaternary carbon missing); MS (EI) *m/z* (%): 351 (M+1, 44), 350 (M^+, 100), 291 (26), 290 (28), 276 (15), 275 (19), 260 (17), 259 (46), 202 (17), 189 (16), 43 (18); HRMS calculated for $C_{22}H_{22}O_4$ M^+ 350.1518, found 350.1517.

3.1.39. [1-(3,4,5-Trimethoxyphenyl)naphthalen-2-yl]-methanol 21a. To a solution of dihydronaphthalenylmethanol **12a** (0.11 g, 0.34 mmol) in CH_2Cl_2 (15 mL) was added DDQ and a green solution resulted. The resultant mixture was refluxed for 16 h after which time it turned dark brown. The mixture was then allowed to cool to room temperature before being neutralized with 5% $NaHCO_3$ (10 mL) and being extracted with CH_2Cl_2 (3×50 mL). The organic extracts were combined, washed with brine and concentrated under reduced pressure to give a brown oil. The oil was purified by column chromatography using 30% ethylacetate/hexane as an eluent to give **21a** as a yellow solid (0.09 g, 82%). Mp=90–91 °C; IR ν_{max} (cm^{-1}) 3488 (s, broad, OH stretch), 1582 (s, C=C stretch); ^1H NMR δ/ppm 7.90 (1H, d, J=8.4 Hz, ArH), 7.87 (1H, d, J=8.5 Hz, ArH), 7.69 (1H, d, J=8.5 Hz, ArH), 7.54 (1H, d, J=8.3 Hz, ArH), 7.49–7.37 (2H, m, 2×ArH), 6.53 (2H, s, 2′ and 6′-H), 4.61 (2H, s, CH_2OH), 3.95 (3H, s, OCH_3), 3.81 (6H, s, 2×OCH_3); ^{13}C NMR δ/ppm 56.1 (2×OCH_3), 60.9 (OCH_3), 63.4 (CH_2OH), 107.2 (2×CH), 125.7 (2×CH), 126.1 (CH), 126.6 (CH), 127.8 (CH), 128.0 (CH), 132.6 (C), 132.8 (C), 133.6 (C), 135.6 (C), 137.1 (C), 137.9 (C), 153.0 (2×C); MS (EI) *m/z* (%): 325 (M+1, 10), 324 (M^+, 100), 219 (9), 165 (7), 18 (7); HRMS calculated for $C_{20}H_{20}O_4$ M^+ 324.1361, found 324.1351.

3.1.40. [1-(1-Naphthylnaphthalen-2-yl]methanol 21b. In a similar manner to that described above DDQ (0.48 g, 2.09 mmol) was used to convert dihydronaphthalene **12b** (0.40 g, 1.39 mmol) into **21b**, a brown crystalline solid (0.31 g, 79%). Mp=116–119 °C; IR ν_{max} (cm^{-1}) 3386 (s, broad, OH stretch), 1592, 1568 (m, C=C stretch); ^1H NMR δ/ppm 7.89–7.79 (4H, m, 4×ArH), 7.67 (1H, d, J=8.5 Hz, ArH), 7.51–7.46 (1H, m, ArH), 7.38–7.28 (3H, m, 3×ArH), 7.17–7.06 (4H, m, 4×ArH), 4.32 (1H, d, J=13.0 Hz, one of CH_2OH), 4.27 (1H, d, J=13.0 Hz, one of CH_2OH); ^{13}C NMR δ/ppm 63.3 (CH_2OH), 125.4 (CH), 125.7 (2×CH), 125.8 (CH), 126.0 (CH), 126.1 (CH), 126.4 (CH), 126.9 (CH), 127.8 (CH), 127.9 (CH), 128.1 (CH), 128.3 (2×CH), 132.7 (C), 132.8 (C), 133.0 (C), 133.6 (C), 135.5 (C), 135.7 (C), 136.7 (C); MS (EI) *m/z* (%): 285 (M+1, 23), 284 (M^+, 100), 265 (32), 128 (18); HRMS calculated for $C_{21}H_{16}O$ M^+ 284.1201, found 284.1202.

3.1.41. (1-Phenylnaphthalen-2-yl)methanol 21c. Similarly dihydronaphthyl alcohol **12c** (0.26 g, 1.10 mmol) afforded naphthalene **21c** as a light yellow oil (0.20 g, 78%) using DDQ (0.25 g, 1.10 mmol) in CH_2Cl_2 (25 mL). IR ν_{max} (cm^{-1}) 3420 (m, broad, OH stretch), 1596 (s, C=C stretch); ^1H NMR δ/ppm 7.89 (1H, d, J=8.4 Hz, ArH), 7.87 (1H, d, J=8.4 Hz, ArH), 7.68 (1H, d, J=8.5 Hz, ArH), 7.49–7.41 (5H, m, 5×ArH), 7.37–7.34 (3H, m, 3×ArH), 4.56 (2H, s, CH_2OH); ^{13}C NMR δ/ppm 63.3 (CH_2OH), 125.6 (CH), 125.7 (CH), 125.9 (CH), 126.5 (CH), 127.4 (CH), 127.7 (CH), 127.9 (CH), 128.3 (2×CH), 130.0 (2×CH), 132.6 (C), 132.8 (C), 135.5 (C), 137.8 (C), 138.1 (C); MS (EI) *m/z* (%): 235 (M+1, 28), 234 (M^+, 100), 215 (50), 205 (46), 202 (35), 157 (14), 129 (22), 108 (16); HRMS calculated for $C_{17}H_{14}O$ M^+ 234.1045, found 234.1046.

3.1.42. 1-Bromonaphthalene-2-carbaldehyde 22. 1-Bromo-3,4-dihydronaphthalene-2-carbaldehyde (0.45 g, 1.898 mmol), selenium powder (0.30 g, 5.694 mmol) and dimethyl sulfoxide (0.5 mL) were slowly heated to 170 °C. The reaction mixture was heated at the same temperature for 5 min where sputtering took place. After sputtering had ceased, the mixture was allowed to cool to room temperature before being filtered and washed with an excess amount of CH_2Cl_2. The excess solvent was removed on a rotary evaporator to obtain a black oil that was purified by column chromatography using 5% ethyl acetate/hexane as eluant to give the desired product **22** as a bright yellow solid (0.31 g, 69%). Mp=106–108 °C; IR ν_{max} (cm^{-1}) 1687 (s, C=O stretch), 1619, 1597 (s, C=C stretch); ^1H NMR δ/ppm 10.67 (1H, s, CHO), 8.53–8.50 (1H, m, ArH), 7.95–7.84 (3H, m, 3×ArH), 7.72–7.67 (2H, m, 2×ArH); ^{13}C NMR δ/ppm 124.1 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.5 (C), 129.7 (CH), 131.1 (C), 132.1 (C), 137.2 (C), 192.8 (CHO); MS (EI) *m/z* (%): 235 ($M^{+81}Br$, 99), 233 ($M^{+79}Br$, 100), 206 (28), 127 (35), 126 (89), 63 (15); HRMS calculated for $C_{11}H_7O^{79}Br$ M^+ 233.9680, found 233.9708.

3.1.43. 6-Methoxy-1-bromo-3,4-dihydronaphthalene-2-carbaldehyde 23. Dry DMF (8.0 mL, 102.1 mmol) in dry CH_2Cl_2 (60.0 mL) was cooled to 0 °C and phosphorus tribromide (8.4 mL, 88.52 mmol) was added drop-wise. The mixture was stirred at 0 °C for 1 h and a cream white suspension formed. A solution of 6,7-dimethoxy-α-tetralone (6.00 g, 34.05 mmol) in dry CH_2Cl_2 (50 mL) was added and the mixture was heated under reflux for 16 h. After cooling to 0 °C, aqueous $NaHCO_3$ was added slowly until the

effervescence had subsided. Extraction of the organic material into CH_2Cl_2 (3×100 mL) was followed by drying the organic layer ($MgSO_4$). The solution was filtered through a Celite plug and evaporation of the excess solvent resulted into brown oil. Column chromatography eluting with 30% ethyl acetate/hexane gave the product **23** as a yellow solid (7.79 g, 86%). Mp=61–62 °C; IR ν_{max} (cm^{-1}) 1659 (s, C=O stretch), 1606, 1586, 1552 (s, C=C stretch); ^{1}H NMR δ/ppm 10.20 (1H, s, CHO), 7.83 (1H, d, J=8.7 Hz, 8-H), 6.82 (1H, dd, J=8.7, 2.6 Hz, 7-H), 6.72 (1H, d, J=2.5 Hz, 5-H), 3.86 (3H, s, OMe), 2.80 (2H, dd, J=8.4, 7.2 Hz, CH_2), 2.60 (2H, dd, J=8.7, 6.0 Hz, CH_2); ^{13}C NMR δ/ppm 22.7 (CH_2), 27.7 (CH_2), 55.4 (OCH_3), 112.1 (CH), 113.3 (CH), 125.9 (C), 130.7 (CH), 132.1 (C), 139.0 (C), 141.2 (C), 162.0 (C), 192.9 (CHO); MS (EI) m/z (%): 267 (M^{+81}Br, 80), 265 (M^{+79}Br, 83), 236 (28), 187 (46), 159 (97), 158 (100), 144 (59), 128 (41), 115 (81); HRMS calculated for $C_{12}H_{11}O_2^{79}Br$ M^+ 265.9942, found 265.9936.

3.1.44. 6-Methoxy-1-bromonaphthalene-2-carbaldehyde 24. Using the same procedure as described above, 6-methoxy-1-bromo-3,4-dihydronaphthalene-2-carbaldehyde **23** (3.98 g, 14.90 mmol) was converted into 7-methoxy-1-bromonaphthalene-2-carbaldehyde **24** in the presence of selenium powder (2.30 g, 29.80 mmol) and dimethyl sulfoxide (2 mL). The product was obtained as a light brown solid (2.85 g, 72%). Mp=123–126 °C; IR ν_{max} (cm^{-1}) 1682 (s, C=O stretch), 1620 (s, C=C stretch); ^{1}H NMR δ/ppm 10.58 (1H, s, CHO), 8.36 (1H, d, J=9.4 Hz, 8-H), 7.87 (1H, d, J=8.7 Hz, 3- or 4-H), 7.68 (1H, d, J=8.7 Hz, 3- or 4-H), 7.28 (1H, dd, J=9.4, 2.5 Hz, 7-H), 7.11 (1H, d, J=2.5 Hz, 5-H), 3.96 (3H, s, OMe); ^{13}C NMR δ/ppm 55.6 (OCH_3), 106.4 (CH), 120.7 (CH), 124.7 (CH), 126.9 (CH) 127.2 (C), 129.4 (C), 129.8 (CH), 130.4 (C), 139.0 (C), 160.6 (C), 192.5 (CHO); MS (EI) m/z (%): 265 (M^{+81}Br, 47), 263 (M^{+79}Br, 46), 261 (100), 202 (17), 156 (16), 113 (22), 73 (17); HRMS calculated for $C_{12}H_9O_2^{79}Br$ M^+ 263.9786, found 263.9750.

3.1.45. 1-(3,4,5-Trimethoxyphenyl)-naphthalene-2-carbaldehyde 25a. To [$Pd(PPh_3)_4$] (0.14 g, 0.127 mmol) was added deoxygenated solutions of **22** (0.30 g, 1.276 mmol) in DME (10 mL) and 3,4,5-trimethoxy-1-phenylboronic acid **10a** (0.38 g, 1.914 mmol) in ethanol (5 mL). This was followed by a deoxygenated solution of aqueous sodium carbonate (1.06 g, 10.85 mmol in 5.0 mL water). The resultant mixture was refluxed under nitrogen for 46 h over which time it turned deep red. After allowing to cool to room temperature, the mixture was quenched with water (10 mL) and the organic material extracted with CH_2Cl_2 (3×25 mL). The resultant organic extracts were combined, dried ($MgSO_4$), filtered through a Celite plug and the excess solvent removed using a rotary evaporator. The subsequent oil was purified by column chromatography using 30% ethyl acetate/hexane as the eluent to afford the desired product **25a** as a yellow solid (0.40 g, 94%). Mp=89–92 °C; IR ν_{max} (cm^{-1}) 1694 (s, C=O stretch), 1626, 1597 (s, C=C stretch); ^{1}H NMR δ/ppm 9.96 (1H, s, CHO), 8.05 (1H, d, J=8.6 Hz, ArH), 7.93 (2H, d, J=8.4 Hz, 2×ArH), 7.76 (1H, d, J=8.2 Hz, ArH), 7.65–7.61 (1H, m, ArH), 7.52–7.48 (1H, m, ArH), 6.63 (2H, s, 2′ and 6′-H), 3.85 (9H, s, 3×OCH_3); ^{13}C NMR δ/ppm 56.2 (2×OCH_3), 60.8 (OCH_3), 108.2 (2×CH), 121.9 (CH), 123.5 (C), 126.9 (CH), 127.6 (CH), 128.1 (CH), 128.3 (CH), 128.7 (CH), 130.6 (C), 131.1 (C), 132.4 (C), 136.0 (C), 146.3 (C), 152.9 (2×C), 192.7 (CHO); MS (EI) m/z (%): 323 (M+1, 22), 322 (M^+, 100), 279 (63), 219 (15), 165 (24); HRMS calculated for $C_{20}H_{18}O_4$ M^+ 322.1205, found 322.1186.

3.1.46. 1-(1-Naphthyl)-naphthalene-2-carbaldehyde 25b. Using the same procedure as described above, **22** (0.30 g, 1.276 mmol) was reacted with 1-naphthylboronic acid **10b** (0.31 g, 1.914 mmol) under Suzuki coupling conditions to give **25b** as a yellow crystalline solid (0.32 g, 89%). Mp=112–114 °C; IR ν_{max} (cm^{-1}) 1687 (s, C=O stretch), 1619 and 1593 (m, C=C stretch); ^{1}H NMR δ/ppm 9.68 (1H, s, CHO), 8.15 (1H, d, J=8.6 Hz, ArH), 8.02–7.92 (4H, m, 4×ArH), 7.62–7.54 (2H, m, 2×ArH), 7.49–7.44 (2H, m, 2×ArH), 7.36 (1H, d, J=8.1 Hz, ArH), 7.31–7.25 (2H, m, 2×ArH), 7.20 (1H, d, J=8.4 Hz, ArH); ^{13}C NMR δ/ppm 122.1 (CH), 125.0 (CH), 126.2 (CH), 126.3 (CH), 126.8 (CH), 126.9 (CH), 127.7 (CH), 128.2 (CH), 128.3 (CH), 128.6 (CH), 128.8 (CH), 128.9 (CH), 129.1 (CH), 132.1 (C), 132.9 (C), 133.0 (C), 133.3 (C), 133.5 (C), 136.1 (C), 144.8 (C), 192.4 (CHO); MS (EI) m/z (%): 283 (M+1, 23), 282 (M^+, 100), 281 (81), 265 (26), 253 (86), 252 (97), 126 (35), 113 (15); HRMS calculated for $C_{21}H_{14}O$ M^+ 282.1045, found 282.1035.

3.1.47. 1-Phenylnaphthalene-2-carbaldehyde 25c. Substituted naphthalene **25c** was obtained as a light yellow oil (0.26 g, 87%) from the Suzuki coupling of bromonaphthalene carbaldehyde **22** (0.30 g, 1.276 mmol) and 1-phenylboronic acid (0.22 g, 1.914 mmol) using the same procedure as outlined above. ^{1}H NMR δ/ppm 9.89 (1H, s, CHO), 8.06 (1H, d, J=8.6 Hz, ArH), 7.92 (2H, d, J=9.7 Hz, 2×ArH) 7.67–7.58 (2H, m, 2×ArH), 7.52–7.51 (3H, m, 3×ArH), 7.47–7.31 (3H, m, 3×ArH); ^{13}C NMR δ/ppm 122.1 (CH), 126.8 (CH), 127.7 (CH), 128.2 (CH), 128.2 (2×CH), 128.3 (CH), 128.4 (CH), 128.7 (CH), 130.9 (2×CH), 131.2 (C), 132.4 (C), 135.2 (C), 136.1 (C), 146.5 (C), 192.6 (CHO); MS (EI) m/z (%): 233 (M+1, 18), 232 (M^+, 100), 202 (64), 101 (18); HRMS calculated for $C_{17}H_{12}O$ M^+ 232.0888, found 232.0865.

3.1.48. 1-(*o*-Tolyl)naphthalene-2-carbaldehyde 25d. Using the same procedure as outlined above, tolylnaphthalene carbaldehyde **25d** was synthesized as a yellow crystalline solid (0.29 g, 94%) from the Suzuki coupling of carbaldehyde **22** (0.30 g, 1.276 mmol) and *o*-tolylboronic acid **10d**. Mp=60–61 °C; IR ν_{max} (cm^{-1}) 1687 (s, C=O stretch), 1626, 1618, 1596 (s, C=C stretch); ^{1}H NMR δ/ppm 9.82 (1H, s, CHO), 8.07 (1H, d, J=8.6 Hz, ArH), 7.93 (2H, d, J=9.1 Hz, 2×ArH), 7.64–7.59 (1H, m, ArH), 7.48–7.31 (5H, m, 5×ArH), 7.24 (1H, d, J=6.6 Hz, ArH), 1.96 (3H, s, $ArCH_3$); ^{13}C NMR δ/ppm 20.0 ($ArCH_3$), 122.0 (CH), 125.7 (CH), 126.9 (CH), 127.2 (CH), 128.3 (CH), 128.4 (CH), 128.6 (CH), 128.8 (CH) 130.1 (CH), 130.9 (CH), 131.0 (C), 132.1 (C), 134.8 (C), 136.2 (C), 137.3 (C), 146.3 (C), 192.6 (CHO); MS (EI) m/z (%): 246 (M^+, 100), 231 (38), 218 (88), 202 (43), 130 (39), 99 (10), 68 (74); HRMS calculated for $C_{18}H_{14}O$ M^+ 246.1045, found 246.1049.

3.1.49. 1-(3,4,5-Trimethoxyphenyl)-6-methoxynaphthalene-2-carbaldehyde 26a. In the same way as outlined above, 7-methoxy-1-bromonaphthalene **24** (0.30 g, 1.132 mmol) and 3,4,5-trimethoxy-1-phenylboronic acid **10a** (0.36 g, 1.697 mmol) were subjected to Suzuki coupling reaction conditions to give the desired product **26a**, as a light yellow crystalline solid (0.32 g, 80%). Mp = 132–134 °C; IR ν_{max} (cm^{-1}) 1690 (s, C=O stretch), 1623, 1599 (s, C=C stretch); ^{1}H NMR δ/ppm 9.89 (1H, s, CHO), 8.02 (1H, d, J=8.6 Hz, 4-H), 7.80 (1H, d, J=8.6 Hz, 3-H), 7.65 (1H, d, J=9.2 Hz, 8-H), 7.21 (1H, d, J=2.5 Hz, 5-H), 7.13 (1H, dd, J=9.2, 2.5 Hz, 7-H), 6.61 (2H, s, 2′ and 6′-H), 3.96 (6H, s, 2×OCH_3), 3.84 (6H, s, 2×OCH_3); ^{13}C NMR δ/ppm 55.4 (OCH_3), 56.2 (2×OCH_3), 61.0 (OCH_3), 106.3 (CH), 108.2 (2×CH), 119.5 (CH), 122.7 (CH), 127.0 (CH), 127.4 (C), 129.3 (CH), 129.5 (C), 130.8 (C), 137.7 (C), 137.9 (C), 146.4 (C), 152.9 (2×C), 159.9 (C), 192.4 (CHO); MS (EI) m/z (%): 352 (M^+, 57), 309 (23), 304 (25), 246 (100), 231 (36), 215 (37), 202 (35), 185 (30), 115 (19); HRMS calculated for $C_{21}H_{20}O_5$ M^+ 352.1311, found 352.1341.

3.1.50. 6-Methoxy-1-(1-naphthyl)naphthalene-2-carbaldehyde 26b. Using the same procedure as described above, bromonaphthalene carbaldehyde **24** (0.30 g, 1.132 mmol) and 1-naphthylboronic acid **10b** (0.29 g, 1.697 mmol) were coupled to give biaryl **26b**, as a yellow solid (0.26 g, 74%). Mp = 181–184 °C; IR ν_{max} (cm^{-1}) 1676 (s, C=O stretch), 1619 (m, C=C stretch); ^{1}H NMR δ/ppm 9.61 (1H, s, CHO), 8.12 (1H, d, J=8.6 Hz, ArH), 8.01 (1H, d, J=8.3 Hz, ArH), 7.96 (1H, d, J=8.3 Hz, ArH), 7.89 (1H, d, J=8.7 Hz, ArH), 7.63–7.58 (1H, m, ArH), 7.50–7.46 (2H, m, 2×ArH), 7.32–7.19 (4H, m, 4×ArH), 6.96 (1H, dd, J=9.2, 2.6 Hz, 7-H), 3.93 (3H, s, OCH_3); ^{13}C NMR δ/ppm 55.4 (OCH_3), 106.3 (CH), 119.5 (CH), 122.8 (CH), 124.9 (CH), 126.1 (CH), 126.2 (CH), 126.7 (CH), 127.3 (CH), 128.1 (C), 128.2 (CH), 128.8 (CH), 129.0 (CH), 129.4 (CH), 130.4 (C), 133.0 (C), 133.2 (C), 133.4 (C), 138.0 (C), 144.9 (C), 159.9 (C), 192.2 (CHO); MS (EI) m/z (%): 313 (M+1, 23), 312 (M^+, 100), 239 (33), 218 (43), 144 (13), 130 (19), 68 (33); HRMS calculated for $C_{22}H_{16}O_2$ M^+ 312.1150, found 312.1174.

3.1.51. 6-Methoxy-1-phenylnaphthalene-2-carbaldehyde 26c. In the same manner as detailed above, carbaldehyde **26c** was synthesized as a thick yellow oil (0.27 g, 90%) from the Suzuki coupling of carbaldehyde **24** (0.30 g, 1.132 mmol) and phenylboronic **10c** (0.20 g, 1.697 mmol). IR ν_{max} (cm^{-1}) 1681 (s, C=O stretch), 1616, 1573 (s, C=C stretch); ^{1}H NMR δ/ppm 9.81 (1H, s, CHO), 8.04 (1H, d, J=8.7 Hz, 4-H), 7.79 (1H, d, J=8.7 Hz, 3-H) 7.51–7.49 (4H, m, 4×ArH), 7.38–7.35 (2H, m, 2×ArH), 7.21–7.19 (1H, m, ArH), 7.08 (1H, dd, J=9.3, 2.6 Hz, 7-H), 6.92–6.83 (1H, m, ArH), 3.93 (3H, s, OCH_3); ^{13}C NMR δ/ppm 55.4 (OCH_3), 106.3 (CH), 119.3 (CH), 120.3 (C), 122.8 (CH), 127.0 (CH), 127.4 (C), 128.1 (2×CH) 129.3 (CH), 129.5 (CH), 130.8 (2×CH), 135.2 (C), 137.9 (C), 146.7 (C), 159.9 (C), 192.5 (CHO); MS (EI) m/z (%): 263 (M+1, 33), 262 (M^+, 40), 218 (100), 130 (61), 99 (11), 68 (82); HRMS calculated for $C_{18}H_{14}O_2$ M^+ 262.0993, found 262.0991.

3.1.52. 6-Methoxy-1-(*o*-tolyl)naphthalene-2-carbaldehyde 26d. 1-Bromo-7-methoxynaphthalene-2-carbaldehyde **24** (0.30 g, 1.132 mmol) and *o*-tolylboronic **10d** (0.22 g, 1.697 mmol) were coupled in the same manner as described above to give the desired product **26d**, as a light yellow oil (0.22 g, 71%). IR ν_{max} (cm^{-1}) 1674 (s, C=O stretch), 1618 (s, C=C stretch); ^{1}H NMR δ/ppm 9.74 (1H, s, CHO), 8.04 (1H, d, J=8.6 Hz, 4-H), 7.80 (1H, d, J=8.6 Hz, 3-H), 7.44–7.29 (4H, m, 4×ArH), 7.25–7.21 (2H, m, 2×ArH), 7.07 (1H, dd, J=9.2, 2.5 Hz, 7-H), 3.95 (3H, s, OCH_3), 1.96 (3H, s, $ArCH_3$); ^{13}C NMR δ/ppm 19.9 ($ArCH_3$), 55.4 (OCH_3), 106.4 (CH), 119.4 (CH), 122.8 (CH), 125.6 (CH), 126.9 (CH), 128.5 (CH), 128.9 (CH) 129.3 (C), 130.0 (CH), 130.7 (CH), 130.9 (C), 134.9 (C), 137.2 (C), 138.0 (C), 146.3 (C), 160.0 (C), 192.3 (CHO); MS (EI) m/z (%): 277 (M+1, 21), 276 (M^+, 100), 261 (32), 245 (16), 215 (22), 202 (24); HRMS calculated for $C_{19}H_{16}O_2$ M^+ 276.1150, found 276.1156.

3.1.53. [1-(3,4,5-Trimethoxyphenyl)naphthalen-2-yl]-methanol 21a. To a solution of carbaldehyde **25a** (0.17 g, 0.527 mmol) in ethanol (5 mL) was added $NaBH_4$ (0.03 g, 0.659 mmol). The reaction mixture was stirred at room temperature for 5 min after which time it turned cream white. The mixture was quenched with water (5 mL) before being extracted with CH_2Cl_2 (3×15 mL). The organic extracts were combined, dried ($MgSO_4$), and then filtered through a Celite plug and concentrated in vacuo. The subsequent colourless oil was purified by column chromatography using 30% ethyl acetate/hexane as eluent to afford **21a** as light yellow crystalline solid (0.14 g, 82%) with identical spectroscopic data to that described previously.

3.1.54. [1-(1-Naphthyl)naphthalen-2-yl]methanol 21b. In the same manner as outlined above, carbaldehyde **25b** (0.30 g, 1.062 mmol) was converted to a biaryl alcohol **21b**, as a brown solid (0.28 g, 93%) using sodium borohydride (0.05 g, 1.328 mmol) with identical spectroscopic data to that described previously.

3.1.55. (1-Phenylnaphthalen-2-yl)methanol 21c. Using sodium borohydride (0.05 g, 1.238 mmol) in the manner as outlined above, phenylnaphthyl carbaldehyde **25c** (0.23 g, 0.990 mmol) was converted into alcohol **21c**, as a yellow sticky oil (0.21 g, 91%) with identical spectroscopic data to that described previously.

3.1.56. [1-(*o*-Tolyl)naphthalen-2-yl]methanol 21d. The desired product **21d**, was synthesized as a thick yellow oil (0.19 g, 95%) from carbaldehyde **25d** (0.20 g, 0.812 mmol) using sodium borohydride (0.04 g, 1.015 mmol) in the same way as described above. IR ν_{max} (cm^{-1}) 3408 (s, broad, OH stretch), 1621, 1596, 1572 (s, C=C stretch); ^{1}H NMR δ/ppm 7.90 (1H, d, J=8.4 Hz, ArH), 7.87 (1H, d, J=7.5 Hz, ArH), 7.70 (1H, d, J=8.4 Hz, ArH), 7.48–7.43 (1H, m, ArH), 7.35–7.24 (5H, m, 5×ArH), 7.14 (1H, d, J=7.3 Hz, ArH), 4.48 (2H, s, CH_2OH), 1.91 (3H, s, $ArCH_3$); ^{13}C NMR δ/ppm 19.7 ($ArCH_3$), 63.4 (CH_2OH), 125.7 (2×CH), 125.9 (CH), 126.0 (CH), 126.1 (CH), 127.9 (2×CH), 128.0 (CH), 130.0 (CH), 130.1 (CH), 132.2 (C), 132.9 (C), 135.4 (C), 136.9 (C), 137.1 (C), 137.6 (C); MS (EI) m/z (%): 248 (M^+, 60), 230 (100), 218 (20), 215 (69), 202 (34), 82 (19);

HRMS calculated for $C_{18}H_{16}O$ M^+ 248.1201, found 248.1248.

3.1.57. [6-Methoxy-1-(3,4,5-trimethoxyphenyl)naphthalen-2-yl]methanol 27a. Using the same procedure as described above, carbaldehyde **26a** (0.18 g, 0.511 mmol) in ethanol (5 mL) was converted into the alcohol **27a** produced as white flakes (0.16 g, 89%) using sodium borohydride (0.02 g, 0.638 mmol). Mp=163–164 °C; IR ν_{max} (cm^{-1}), 1690 (s, C=O stretch), 1623 (s, C=C stretch); ^1H NMR δ/ppm 7.79 (1H, d, J=8.5 Hz, 4-H), 7.63 (1H, d, J=8.5 Hz, 3-H), 7.44 (1H, d, J=9.2 Hz, 8-H), 7.17 (1H, d, J=2.5 Hz, 5-H), 7.06 (1H, dd, J=9.2, 2.6 Hz, 7-H), 6.52 (2H, s, 2′ and 6′-H), 4.58 (2H, s, CH_2OH), 3.95 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 3.82 (6H, s, 2×OCH_3); ^{13}C NMR δ/ppm 55.3 (OCH_3), 56.1 (2×OCH_3), 60.9 (OCH_3), 63.4 (CH_2OH), 105.7 (CH), 107.1 (2×CH), 118.7 (CH), 126.5 (CH), 126.8 (CH), 128.0 (C), 128.2 (CH), 133.3 (C), 133.7 (C), 134.1 (C), 137.1 (C), 138.0 (C), 153.1 (2×C), 157.5 (C); MS (EI) m/z (%): 354 (M^+, 42), 304 (100), 264 (23), 213 (35), 175 (21), 152 (11); HRMS calculated for $C_{21}H_{22}O5$ M^+ 354.1467, found 354.1448.

3.1.58. [6-Methoxy-1-(1-naphthyl)naphthalen-2-yl]-methanol 27b. Sodium borohydride (0.03 g, 0.880 mmol) was used as explained above to convert carbaldehyde **26b** (0.22 g, 0.704 mmol) in ethanol (8 mL) into the alcohol **27b**, as a light brown solid (0.21 g, 95%). Mp=142–143 °C; IR ν_{max} (cm^{-1}) 3366 (s, broad, OH stretch), 1625, 1598, 1579 (m, C=C stretch); ^1H NMR δ/ppm 7.96–7.92 (2H, m, 2×ArH), 7.87 (1H, d, J=8.5 Hz, ArH), 7.73 (1H, d, J=8.5 Hz, ArH), 7.59 (1H, d, J=7.1 Hz, ArH), 7.57 (1H, d, J=8.2 Hz, ArH), 7.48–7.43 (1H, m, ArH), 7.39 (1H, d, J=7.0 Hz, ArH), 7.28–7.18 (3H, m, 3×ArH), 7.07 (1H, d, J=9.2 Hz, 8-H), 6.90 (1H, dd, J=9.2, 2.5 Hz, 7-H), 4.37 (2H, s, CH_2OH), 3.91 (3H, s, OCH_3); ^{13}C NMR δ/ppm 55.3 (OCH_3), 63.4 (CH_2OH), 105.8 (CH), 118.7 (CH), 125.4 (CH) 125.8 (CH), 126.0 (CH), 126.4 (CH), 126.6 (CH), 127.1 (CH), 127.8 (CH), 128.0 (CH), 128.2 (CH), 128.3 (CH), 128.5 (C), 132.8 (C), 133.6 (C), 134.2 (C), 134.5 (C), 135.8 (C), 135.9 (C), 157.5 (C); MS (EI) m/z (%): 315 (M+1, 24), 314 (M^+, 100), 252 (16), 239 (17), 218 (39), 130 (14), 68 (28); HRMS calculated for $C_{22}H_{18}O_2$ M^+ 314.1307, found 314.1352.

3.1.59. (6-Methoxy-1-phenylnaphthalen-2-yl)methanol 27c. Carbaldehyde **26c** (0.18 g, 0.686 mmol) in ethanol (5 mL) was converted into the alcohol **27c**, as a thick yellow oil (0.18 g, 100%) using sodium borohydride (0.03 g, 0.858 mmol) in the same manner as outlined above. IR ν_{max} (cm^{-1}) 3385 (s, broad, OH stretch), 1625, 1598, 1575 (s, C=C stretch); ^1H NMR δ/ppm 7.70 (1H, d, J=8.4 Hz, 4-H), 7.55 (1H, d, J=8.4 Hz, 3-H), 7.46–7.36 (4H, m, 4×ArH), 7.24–7.09 (4H, m, 4×ArH), 6.94 (1H, dd, J=9.2, 2.5 Hz, 7-H), 4.44 (2H, s, CH_2OH), 3.84 (3H, s, OCH_3); ^{13}C NMR δ/ppm 55.3 (OCH_3), 63.4 (CH_2OH), 105.8 (CH), 118.6 (CH), 126.6 (CH), 126.8 (CH), 127.4 (CH), 128.2 (CH), 128.3 (2×CH), 130.1 (2×CH), 130.9 (C), 133.4 (C), 134.2 (C), 138.1 (C), 138.2 (C), 157.5 (C); MS (EI) m/z (%): 264 (M^+, 100), 235 (26), 202 (24), 159 (12), 94 (32), 82 (85); HRMS calculated for $C_{18}H_{16}O_2$ M^+ 264.1150, found 264.1146.

3.1.60. [6-Methoxy-1-(*o*-tolyl)naphthalen-2-yl]methanol 27d. In the same way as described above, sodium borohydride (0.02 g, 0.678 mmol) was used to convert carbaldehyde **26d** (0.15 g, 0.543 mmol) in ethanol (5 mL) into the alcohol **27d**, produced as a light yellow oil (0.14 g, 93%). IR ν_{max} (cm^{-1}) 3405 (s, broad, OH stretch), 1625, 1598, 1576 (s, C=C stretch); ^1H NMR δ/ppm 7.78 (1H, d, J=8.4 Hz, 4-H), 7.64 (1H, d, J=8.4 Hz, 3-H), 7.36–7.24 (3H, m, 3×ArH), 7.18–7.12 (3H, m, 3×ArH), 7.00 (1H, dd, J=9.2, 2.6 Hz, 7-H), 4.45 (2H, s, CH_2OH), 3.91 (3H, s, OCH_3), 1.91 (3H, s, $ArCH_3$); ^{13}C NMR δ/ppm 19.7 ($ArCH_3$), 55.3 (OCH_3), 63.3 (CH_2OH), 105.9 (CH), 118.7 (CH), 125.8 (CH), 126.5 (CH), 126.7 (CH), 127.7 (CH), 127.8 (CH), 129.9 (CH), 130.0 (CH), 133.2 (C), 134.2 (C), 136.9 (C), 137.2 (C), 137.7 (C), 157.5 (C) (one quaternary carbon missing); MS (EI) m/z (%): 278 (M^+, 19), 260 (14), 129 (15), 108 (43), 84 (63), 82 (100), 46 (20); HRMS calculated for $C_{19}H_{18}O_2$ M^+ 278.1306, found 278.1297.

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Two new luffarin derivatives from the Adriatic Sea sponge *Fasciospongia cavernosa*

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Abstract—Together with the known luffarin V and 6*Z*-luffarin V, two new sesterterpenes (**1a** and **2**), related to luffarins have been isolated from the sponge *Fasciospongia cavernosa*, collected in the Northern Adriatic Sea. The structures of the new compounds were proposed on the basis of spectroscopic data. The absolute stereochemistry of compound **1a** was determined by application of Mosher's method.

1. Introduction

Within the class of terpenoids, the sesterterpenes form a rare group of isoprenoids, which occur in widely differing sources and have been isolated from terrestrial fungi,[1] plants[2] and insects[3] as well as from marine organisms,[4,5] mainly from sponges and nudibranchs. Marine organisms have provided a large number of sesterterpenoids, possessing novel carbon skeletons, which are different from those present in terrestrial species. Several sesterterpenoids isolated from marine organisms have shown biological activity.[6]

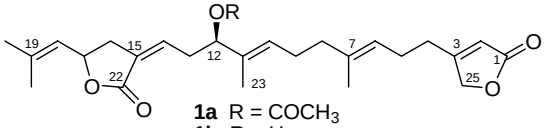
Marine sponges belonging to the family Thorectidae, which includes the genera *Cacospongia*, *Fasciospongia*, *Luffariella* and *Thorecta*, are known[4,5] to be a rich source of novel sesterterpenoids (see above). Some containing a γ-hydroxybutenolide moiety showed strong anti-inflammatory activity, for example, manoalide,[7] the first sesterterpene to be reported from a *Luffariella* sp., has been extensively investigated as a potent inhibitor of phospholipase A_2.[4,5] Subsequently many related metabolites from *Luffariella* sp. were reported.[4,5] Among the manoalide congeners, particularly interesting are cacospongionolides, which exhibit specific inhibition of human phospholipase A_2 and are more stable than manoalide.[6]

Our group has investigated the chemistry of a number of specimens of *Fasciospongia cavernosa* Schmidt (family Thorectidae) collected in the Mediterranean Sea, in order to provide sufficient cacospongionolides. We have reported the isolation of novel related metabolites,[6] including the 6*Z* isomer of luffarin V,[8] a metabolite isolated from the Australian sponge *Luffariella geometrica*.[9] We have isolated two new sesterterpenoids (**1a** and **2**) related to luffarins, from a sample of *F. cavernosa* collected in the Northern Adriatic Sea. The structure determination of these compounds are reported in this paper.

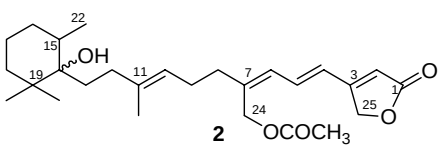
2. Results and discussion

The Et_2O-soluble fraction of the Me_2CO extract of *F. cavernosa* was chromatographed on Si gel, followed by reverse HPLC, to give compounds **1a** and **2**, together with two, their relatives luffarin V[9] and its 6*Z* isomer.[8]

The spectral data of luffarin V and (6*Z*)-luffarin V[10] were in excellent agreement with those reported in the literature. Furthermore, (6*Z*)-luffarin V was identified by comparison with an authentic sample.



1a R = $COCH_3$
1b R = H
1c R = (*R*)-MTPA
1d R = (*S*)-MTPA



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Keywords: Luffarins; *Fasciospongia cavernosa*; Sesterterpenoids.
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Table 1. NMR spectral data of **1a**

Position	^{13}C	^{1}H multiplicity (J in Hz)	HMBC ($J_{C-H}=10$ Hz)
1	174.0s	—	5.82 (H-2), 4.72 (H-25)
2	115.5d	5.82tt (1.7, 1.6)	4.72 (H-25), 2.44 (H-3)
3	170.2s	—	5.82 (H-2), 4.72 (H-25), 2.44 (H-4), 2.27 (H-5)
4	28.6t	2.44 br t (7.2)	5.82 (H-2), 2.27 (H-5)
5	25.6t	2.27dt (7.1, 7.2)	—
6	122.3d	5.07 br t (7.1)	2.44 (H-4), 2.27 (H-5), 2.00 (H-8), 1.59 (H-24)
7	136.8s	—	2.44 (H-4), 2.27 (H-5), 2.00 (H-8), 1.59 (H-24)
8	38.9t	2.00 br t (7.3)	5.07 (H-6), 2.08 (H-9), 1.59 (H-24)
9	25.8t	2.08 br dt (6.5, 7.3)	2.00 (H-8)
10	127.8d	5.40 br t (6.5)	5.19 (H-12), 2.08 (H-9), 1.60 (H-23)
11	132.9s	—	2.08 (H-9), 1.60 (H-23)
12	77.9d	5.19m[a]	6.05 (H-14), 5.40 (H-10), 1.60 (H-23)
13a	31.1t	3.08m[a]	6.05 (H-14)
13b		3.02m[a]	6.05 (H-14)
14	137.5d	6.05ddt (7.3, 2.5, 2.0)	5.19 (H-12), 3.08 (H-13a), 3.02 (H-13b)
15	126.9s	—	2.99 (H16a), 2.56 (H-16b)
16a	36.4t	2.99ddd (15.6, 7.0, 2.0)	5.20 (H-18)
16b		2.56ddd (15.6, 6.7, 2.5)	5.20 (H-18)
17	74.1d	5.11	2.56 (H-16b)
18	123.2d	5.20m[a]	5.11 (H-17), 1.74 (H-20), 1.71 (H-21)
19	139.8s	—	5.11 (H-17), 1.74 (H-20), 1.71 (H-21)
20	25.6q	1.74d (1.2)	5.20 (H-18), 1.71 (H-21)
21	18.3q	1.71d (1.2)	5.20 (H-18), 1.74 (H-20)
22	169.5s	—	6.05 (H-14), 2.99 (H-16a)
23	12.0q	1.60s	5.40 (H-10), 5.19 (H-12)
24	16.1q	1.59s	5.07 (H-6), 2.00 (H-8)
25	73.1d	4.72d (1.7)	5.82 (H-2), 2.44 (H-4)
26	170.2s	—	2.02 (H-27), 5.19 (H-12)
27	25.7q	2.02s	—

[a] Overlapped signals.

Compound **1a** had $[\alpha]_D$ −34.6 and a molecular formula $C_{27}H_{36}O_6$, as derived by HRMS. The UV absorption at 220 nm and IR bands at 1778, 1744, 1672, 1625 and 1240 cm^{-1}, suggested the presence of two γ-butenolide moieties and an acetate function in the molecule. The analysis of the NMR data (Table 1) established the presence of a β-substituted α,β-unsaturated γ-butenolide moiety [^1H NMR δ 5.82 (1H, tt, $J=1.7$, 1.6 Hz, H-2) and 4.72 (2H, d, $J=1.7$ Hz, H-25); ^{13}C NMR δ 174.0 (s, C-1), 170.2 (s, C-3), 115.5 (d, C-2), 73.1 (t, C-25)], two trisubstituted double bonds [δ 5.40 (1H, t, $J=6.5$ Hz, H-10), 5.07 (1H, t, $J=7.1$ Hz, H-6); 136.8 (s, C-7), 132.9 (s, C-11), 127.8 (d, C-10), 122.3 (d, C-6)] along with associated methyls [δ 1.60 (3H, s, H-23), 1.59 (3H, s, H-24); 16.1 (q, C-24), 12.0 (q, C-24)] indicating an *E* geometry, and a terminal trisubstituted double bond [δ 5.20 (1H, H-18); 139.8 (s, C-19), 123.2 (d, C-18)] along with two olefinic methyls [δ 1.74 (3H, d, $J=1.2$ Hz, H-20), 1.71 (3H, d, $J=1.2$ Hz, H-21); 25.6 (q, C-20), 18.3 (q, C-21)]. The COSY spectrum indicated that the oxymethine proton at δ 5.19 (H-12) was coupled to the non-equivalent methylene protons at δ 3.08 and 3.02 (H-13a, H-13b), which in turn were coupled with an olefinic proton at δ 6.05 (H-14). These data, together with the HMBC correlation of the oxymethine proton at δ 5.19 (H-12) with the carbonyl at δ 170.2 (C-26) allowed us to locate the second butenolide functionality and the acetate group in the C-12/C-18 portion of the molecule, defining the structure of compound **1a**. The location of the acetyl functionality at C-12 was also supported by chemical shift of C-23, which appeared as an upfield carbon shifted to δ 12.0 ppm. The geometry of Δ^{14} was assigned as *Z* on the basis of a comparison of the NMR data with those of an authentic sample of (6*Z*)-luffarin V[8] and related compounds.[9]

The absolute stereochemistry of compound **1a** was determined by application of modified Mosher's method,[11] to the deacetyl derivative **1b**, which was obtained by treatment of **1a** with MeOH saturated with Na_2CO_3. The alcohol **1b** was treated with *S*-(−)- and *R*-(+)-α-methoxy-α-(trifluromethyl)phenylacetyl chloride (MTPA-Cl) to yield the corresponding *R*- and *S*-MTPA esters (**1c** and **1d**, respectively). The proton chemical shifts of both diastereoisomers **1c** and **1d** were carefully assigned by analysis of their COSY spectra. From the MTPA determination rule,[11] the positive and negative $\Delta\delta$ ($\delta_{S\text{-MTPA ester}}-\delta_{R\text{-MTPA ester}}$) value observed for signals protons were located on the right and on the left side of the MTPA plane, respectively, showing clearly that the absolute configuration at C-9 is *R*.

Compound **2** had $[\alpha]_D$ −5.07 and a molecular formula $C_{27}H_{40}O_5$, as derived by HRMS. IR bands at 3300, 1778, 1744, 1672, 1240, 1233 and 1050 cm^{-1} indicated the presence of ester, γ-butenolide, and hydroxyl functions in the molecule. The UV absorption at 257 nm and ^1H NMR resonances at δ 6.86 (1H, dd, $J=15.6$, 11.3 Hz, H-5), 6.47 (1H, br d, $J=15.6$ Hz, H-4), 6.13 (1H, br d, $J=11.3$ Hz, H-6), 5.93 (1H, br s, H-2) and 5.01 (2H, br s, H-25) confirmed the presence of a diene conjugated with a β-substituted α,β-unsaturated γ-butenolide moiety. Furthermore, the ^1H NMR spectrum (Table 2) of **2** showed resonances due to one secondary, two tertiary and one olefinic methyl groups [δ 0.94 (3H, d, $J=7.0$ Hz), 0.95 (3H, s), 0.97 (3H, s) and 1.64 (3H, br s)], an oxymethylene [δ 4.76 (2H, s)], and an olefinic proton [δ 5.15 (br t, $J=6.9$ Hz)]. ^{13}C NMR resonances observed at δ 137.4 (s), 122.6 (d), 76.5 (s) and 61.4 (t) confirmed the presence of a trisubstituted double bond and of an oxymethylene, and

Table 2. NMR spectral data of **2**

Position	^{13}C	^{1}H multiplicity (J in Hz)	HMBC ($J_{C-H}=10$ Hz)
1	173.5s	—	5.93 (H-2), 5.01 (H-25)
2	115.3d	5.93 br s	6.47 (H-4), 5.01 (H-25)
3	161.7s	—	6.86 (H-5), 6.47 (H-4), 5.93 (H-2), 5.01 (H-25)
4	122.6d	6.47 br d (15.6)	6.13 (H-6), 5.93 (H-2), 5.01 (H-25)
5	131.9d	6.86dd (11.3, 15.6)	6.13 (H-6)
6	128.5d	6.13 br d (11.3)	6.86 (H-25), 6.47 (H-4), 4.76 (H-24), 2.27 (H-8)
7	143.5s	—	6.86 (H-25), 4.76 (H-24), 2.27 (H-8), 2.19 (H-9)
8	35.8t	2.27t (7.3)	6.13 (H-6), 4.76 (H-24), 2.19 (H-9)
9	26.4t	2.19dd (6.9, 7.3)	5.15 (H-10), 2.27 (H-8)
10	122.6d	5.15 br t (6.9)	2.19 (H-9), 2.07 (H-12), 1.64 (H-23)
11	137.4s	—	2.19 (H-9), 2.07 (H-12), 1.64 (H-23)
12	34.7t	2.07m[a]	5.15 (H-10), 1.64 (H-23), 1.60 (H-13)
13	28.8t	1.60m[a]	2.07 (H-12)
14	76.5s	—	1.60 (H-13), 0.95 (H-20), 0.94 (H-22)
15	37.5d	1.87m[a]	1.60 (H-13, H-16), 1.46 (H-17), 1.17 (H-16)
16	30.9t	1.60m,[a] 1.17m	1.46 (H-17), 0.94 (H-22)
17	20.3t	1.46m	1.36 (H_1-18)
18	37.5t	1.87m,[a] 1.36m	1.46 (H-17), 0.97 (H-21), 0.95 (H-20)
19	39.2s	—	1.60 (H-13), 1.46 (H-17), 0.97 (H-21), 0.95 (H-20)
20	25.0q	0.95s	0.97 (H-21)
21	23.2q	0.97s	0.95 (H-20)
22	16.1q	0.94d (7.0)	—
23	16.1q	1.64 br s	5.15 (H-10), 2.07 (H-12)
24	61.4t	4.76s	6.13 (H-6), 2.27 (H-8)
25	70.4t	5.01 br s	6.47 (H-4), 5.93 (H-2)
26	170.5s	—	4.76 (H-24), 2.07 (H-12)
27	20.9q	2.09s	—

[a] Overlapped signals.

showed the presence of a tertiary alcohol. An HMBC correlation observed between the H-6 proton (δ 6.13) and the carbon triplet at δ 61.4 located the oxymethylene on C-24. Furthermore, HMBC correlation between H-24 and the carbonyl of the acetate group at δ 170.5 located the acetoxy group at C-24. The COSY spectrum indicated that the H-6 proton (δ 6.13) had a long-range coupling to the methylene protons at δ 2.27 (t, $J=7.3$ Hz, H-8). This was further coupled to the methylene double doublet observed at δ 2.19 (dd, $J=7.3$, 6.9 Hz, H-9), which in turn was coupled with the olefinic proton at δ 5.15 (H-10). This latter olefinic proton had in turn a long-range coupling to the olefinic methyl at δ 1.64 (H-23) and with methylene at δ 2.07 (H-12). This was in turn coupled with the methylene protons at δ 1.60 (H-13). The remaining COSY data allowed for the definition of the spin system delineated by H-16/H-17/H-18/H-19/H-20. Taking into account the molecular formula and the data discussed thus far, the molecule of **2** must possess a carbo-monocyclic skeleton. Further interpretation of the COSY, HMQC and HMBC data allowed us to assign all the chemical shifts in the ^{1}H and ^{13}C NMR spectra and to define the presence of a 1-hydroxy-2,6,6-trimethylcyclohexane moiety connected to C-13 [δ 1.60 (m); 28.8 (t)].

The (4*E*,6*Z*,10*E*)-stereochemistry was determined from $J_{4,5}=15.6$ Hz, by the presence of a NOE between the H-5 and the oxymethylene protons at δ 4.76 (H-24), and by the upfield ^{13}C NMR chemical shift for the olefinic methyl (16.1 ppm). It was not possible to ascertain the absolute configuration of C-14 and C-15 from the very small amount of compound isolated.

The carbon skeleton of compound **2** resembles those of luffarin-P[9] and manoalide diol.[12]

The isolation of several related constituents from individual specimens of *F. cavernosa* confirms the peculiarity of the sponges belonging to the family Thorectidae. Similar variation of related metabolites were observed for the sponges *L. geometrica*,[9] *L. variabilis*,[13] and *Thorectandra excavatus*.[14]

3. Experimental

3.1. General experimental procedures

UV spectra were obtained on a Varian DMS 90 spectrophotometer. IR spectra were recorded on a Bio-Rad FTS-7 FT-IR spectrometer. Optical rotations were measured on a Jasco DIP 370 polarimeter, using a 10-cm microcell. Mass spectra were recorded on an AEI MS-50 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, on a Bruker Avance-400 spectrometer, using an inverse probe fitted with a gradient along the *Z*-axis, in $CDCl_3$, using the solvent signal as an internal standard. The 2D NMR spectra were obtained using Bruker's microprograms. Si gel chromatography was performed using pre-coated Merck F_{254} plates and Merck Kieselgel 60 powder.

3.2. Animal material

The sponge *F. cavernosa* (order Dictyoceratida; family Thorectidae) was collected by dredging (−25 m) in May 2002 at Rovinj (Croatia). It was frozen at −20° until extracted and identified by Prof. R. Pronzato of Dip.Te.Ris. dell'Università di Genova, Italy. A voucher specimen is maintained in the Pozzuoli institute collection (voucher No. S6R/02).

3.3. Extraction and isolation

The frozen sponge (102.3 g dry wt after extraction) was extracted with acetone and, after elimination of the solvent under reduced pressure, the aqueous residue was extracted with diethyl ether. The ethereal extract was evaporated under reduced pressure to obtain brown oil (4.2 g), which was applied on a column of Si gel. The column was eluted with a solvent gradient system from petroleum ether (40–70°) to AcOEt.

Fractions eluted with petroleum ether–AcOEt (6/4) was purified by preparative HPLC (Kromasil C18; CH_3CN/H_2O, 94:6; flow 3 ml/min) yielding luffarin V (2.1 mg), (6*Z*)-luffarin V (3.7 mg), compound **1a** (45.7 mg) and compound **2** (1.3 mg).

3.3.1. Luffarin V. $[\alpha]_D$ −29.8 (*c* 0.02, $CHCl_3$); UV, IR, MS, and ^1H, ^{13}C NMR data are in agreement with those reported in literature.[9]

3.3.2. (6*Z*)-Luffarin V. $[\alpha]_D$ −17.8 (*c* 0.03, $CHCl_3$); UV, IR, MS, and ^1H, ^{13}C NMR data are in agreement with those of authentic sample.

3.3.3. Compound 1a. Amorphous solid; $[\alpha]_D$ −34.6 (*c* 0.2, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 220 (3.64) nm; IR ($CHCl_3$) ν_{max} 1778, 1744, 1672, 1625, 1240, 1055 cm^{-1}; NMR data see Table 1; EIMS (70 eV) *m/z* (%) $[M]^+$ 456.2515 ($C_{27}H_{36}O_6$ requires 456.2512) (2), $[M-CH_3CO_2H]^+$ 396 (13), 378 (60), 249 (100), 213 (90), 166 (95), 121 (60).

3.3.4. Compound 2. Amorphous solid; $[\alpha]_D$ −5.1 (*c* 0.01, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 257 (3.76) nm; IR ($CHCl_3$) ν_{max} 3300, 1778, 1744, 1672, 1240, 1233, 1050 cm^{-1}; NMR data see Table 2; cross peaks were observed in a NOESY spectrum between the following signals (only cross peaks not sensitive to strong filtering are reported): δ 6.13–2.27 (H-6, H-8), 5.15–2.27 (H-10, H-8), 6.86–5.01 (H-5, H-25), 6.86–4.76 (H-5, H-24); EIMS (70 eV) *m/z* (%) $[M]^+$ 444.2678 ($C_{27}H_{40}O_5$ requires 444.2676) (5), $[M-H_2O]^+$ 426 (3), 382 (10), 341 (8), 279 (20), 267 (28), 195 (50), 167 (50), 149 (100), 123 (80), 121 (65).

3.4. Alkaline hydrolysis of compound 1a

Compound **1a** (10 mg) was dissolved in 3 ml of MeOH saturated with Na_2CO_3, and the solution was kept at room temperature for 18 h. After neutralization the reaction mixture was extracted with EtOAc. The EtOAc extract was purified on Si gel column using Et_2O as eluent to obtain **1b** (6 mg).

3.4.1. Compound 1b. Amorphous solid; UV (MeOH) λ_{max} (log ε) 222 (3.60) nm; IR ($CHCl_3$) ν_{max} 3350 (br), 1778, 1672, 1625, 1233 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.29 (1H, ddt, *J*=7.8, 2.4, 2.2 Hz, H-14), 5.85 (1H, tt, *J*=1.7, 1.6 Hz, H-2), 5.38 (1H, br t, *J*=6.7 Hz, H-10), 5.22 (1H, m, H-18), 5.18 (1H, ddd, *J*=7.1, 6.8, 1.7 Hz, H-17), 5.09 (1H, br t, *J*=6.9 Hz, H-6), 4.73 (2H, d, *J*=1.7 Hz, H-25), 4.10 (1H, br t, *J*=6.5 Hz, H-12), 3.06 (1H, dddd, *J*=15.9, 7.1, 2.4, 1.7 Hz, H-16a), 2.92 (2H, m, H-13), 2.61 (1H, dddd, *J*=15.9, 6.8, 2.4, 2.2 Hz, H-16b), 2.46 (2H, br t, *J*=7.2 Hz, H-4), 2.31 (2H, dt, *J*=7.2, 6.9 Hz, H-5), 2.12 (2H, m, H-9), 2.05 (2H, m, H-8), 1.77 (3H, d, *J*=1.2 Hz, H-20), 1.74 (3H, d, *J*=1.2 Hz, H-21), 1.77 (3H, d, *J*=1.2 Hz, H-20), 1.65 (3H, br s, H-23), 1.62 (3H, br s, H-24); ^{13}C NMR ($CDCl_3$): δ 174.1 (s, C-1), 170.3 (s, C-3), 169.7 (s, C-22), 139.8 (s, C-19), 139.2 (d, C-14), 136.9 (s, C-7), 135.7 (s, C-11), 126.8 (s, C-15), 125.1 (d, C-10), 123.3 (d, C-18), 122.4 (d, C-6), 115.6 (d, C-2), 76.6 (d, C-12), 74.4 (d, C-17), 73.2 (t, C-25), 39.1 (t, C-8), 36.5 (t, C-16), 33.7 (t, C-13), 28.6 (t, C-4), 25.9 (t, C-9), 25.6 (t, C-5), 25.5 (q, C-20), 18.4 (q, C-21), 15.9 (q, C-24), 12.3 (q, C-23); EIMS (70 eV) *m/z* (%) $[M]^+$ 414 (5), $[M-H_2O]^+$ 396 (15), 378 (55), 249 (100), 213 (85), 166 (95), 121 (55).

3.5. Preparation of *R*- and *S*-MTPA esters of compound 1b

S-(−)-MTPA chloride (Aldrich) (20 µl) was added to a solution of compound **1b** (2 mg) in dry pyridine (0.5 ml) and the resulting mixture was kept at room temperature for 2 h. After the removal of the solvent under reduced pressure the residue was subjected to preparative TLC on Si gel plate (petroleum ether/Et_2O; 4:1) to give *R*-MTPA ester **1c** (1.5 mg) of compound **1b**. The *S*-MTPA ester **1d** (1.3 mg) was obtained in the same manner, starting from *R*-(+)-MTPA chloride. Only chemical shifts of the C-12 region are reported because all other are remote from the MTPA group, so that their $\Delta\delta$ values are zero, and their chemical shifts were reported before.

3.5.1. (*R*)-MTPA esters 1c. ^1H NMR ($CDCl_3$): δ 6.06 (1H, ddt, *J*=7.8, 2.4, 2.2 Hz, H-14), 5.55 (1H, t, *J*=6.5 Hz, H-12), 5.39 (1H, br t, *J*=6.7 Hz, H-10), 3.28 (1H, m, H-13a), 3.21 (1H, m, H-13b), 2.98 (1H, dddd, *J*=15.9, 7.1, 2.4, 1.7 Hz, H-16a), 2.56 (1H, dddd, *J*=15.9, 6.8, 2.4, 2.2 Hz, H-16b), 2.09 (2H, m, H-9), 2.02 (2H, m, H-8), 1.60 (3H, br s, H-23).

3.5.2. (*S*)-MTPA esters 1d. ^1H NMR ($CDCl_3$): δ 5.89 (1H, ddt, *J*=7.8, 2.4, 2.2 Hz, H-14), 5.56 (1H, t, *J*=6.5 Hz, H-12), 5.46 (1H, br t, *J*=6.7 Hz, H-10), 3.09 (2H, m, H-13), 2.90 (1H, dddd, *J*=15.9, 7.1, 2.4, 1.7 Hz, H-16a), 2.55 (1H, dddd, *J*=15.9, 6.8, 2.4, 2.2 Hz, H-16b), 2.13 (2H, m, H-9), 2.05 (2H, m, H-8), 1.65 (3H, br s, H-23).

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Chemoselective ring closure of thiacalix[4]arene-1,3-bis(*N*-ω-hydroxyalkylamides) via the Mitsunobu reaction

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Abstract—Chemoselective intramolecular ring closure on the phenolic OH groups of *p-tert*-butylthiacalix[4]arene-1,3-bis(*N*-ω-hydroxyalkylamides) attained under Mitsunobu conditions affords inherently chiral macrocycles capped by carboxamide bridges. Oxazoline or oxazine cyclization products derived from self-condensation of the hydroxyalkylamide moieties were not isolated. In one case the detection of enantiomers was achieved by chiral HPLC.

1. Introduction

The great number of calixarene derivatives is partly ascribed to the regio- and conformation selective reactions developed in the last decades. Among them the partial O-alkylation and acylation of calix[4]arenes (CA) provide important synthetic tools for designing supramolecules of great variety.[1] Similar selective reactions, at least with the same efficiency, have rarely been found in the thiacalixarene chemistry.[2] The lack of regio- and stereoselectivity in the base mediated O-alkylation and acylation reactions of thiacalix[4]arenes (TCA) can be attributed to the substantially fewer differences between the OH acidities[3] and the larger cavity compared with the CA counterpart (the average bond length of the sulfide bridges is ca. 15% larger than that of the methylene bridges).[4,5] Seeking a general method to alleviate this drawback, we have found the Mitsunobu reaction working under neutral conditions provides an extremely useful alternative for O-alkylation. In this way the distal dialkylation and ring closure of TCA with a series of alcohols and glycols have been accomplished with high regioselectivity.[6–9] It is noteworthy that with tri-, tetra-and pentaethylene glycols 1,3-thiacalix[4]-monocrown-4, -5 and -6 derivatives were obtained[7,9] in yields of 40–50%, which cannot be achieved by the classical templated procedure.[10,11] Following our studies with the short chained diethylene glycol and its aza- and thia-analogues, quite different reaction pathways were observed. While thiodiethylene glycol (**a**) gave exclusively dimer **1a**, diethylene glycol (**b**) and *N*-phenyl-iminodiethanol (**c**) afforded the tethered 1,2-monocrowns **2b**,**c** in a competitive intramolecular reaction beside dimers **1b**,**c**[12] (Fig. 1).

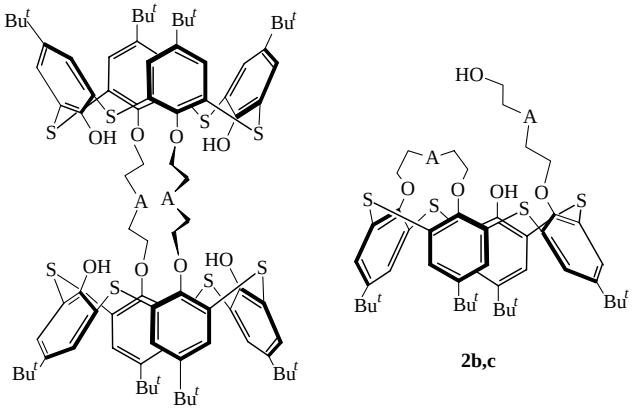

Figure 1. The reaction products of TCA and various diethylene glycols under Mitsunobu condition.

It was surprising that the outcome of the reaction was remarkably influenced by minor differences in the chain length of glycols (**a**>**b**>**c**).

Keywords: Thiacalix[4]arenes; Cyclizations; Hydroxyalkylamides; Mitsunobu reaction.
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To obtain further information on how the intra- versus intermolecular cyclization routes of TCA are influenced by the structural features of linkers, thiacalix[4]arene-1,3-bis(*N*-ω-hydroxyalkylamides) with various chain lengths were synthesized and their ability to cyclize under the Mitsunobu protocol was studied. In this model the carboxamide groups not only rigidify the chains, but they provide additional targets for the cyclization. Mitsunobu cyclodehydration of *N*-hydroxyalkylamides affording five,six-membered *O*,*N*-heterocycles by coupling with the oxygen or nitrogen atom of the carboxamide moiety, have been well-documented in the literature. Generally oxazolines and oxazines and even *N*-acylpyrrolidines and piperidines are formed depending on the chain lengths.[13] If this possibility is also taken into consideration, these compounds seemed to be good candidates to study whether the weakly acidic OHs in TCA, or the heteroatoms of the carboxamide groups, or both are attacked under Mitsunobu conditions.

Earlier in the calix[4]arene series we investigated the ring closure of 1,3-bis(ω-chloroalkylamides) **4a**–**c**, using a biphasic phase-transfer catalytic reaction under strongly basic (aq NaOH) conditions. We achieved successful cyclization in the case of **4b** affording the inherently chiral, doubly capped **5b** in high yield.[14] With the shorter-chain **4a** and the longer-chain **4c**, only hydrolysis by-products were formed, cyclic molecules including the alternative oxazoline or dihydro-oxazine derivatives **6** were not detected (Fig. 2). The Mitsunobu reaction of calixarene hydroxyamides **3** have not yet been investigated.

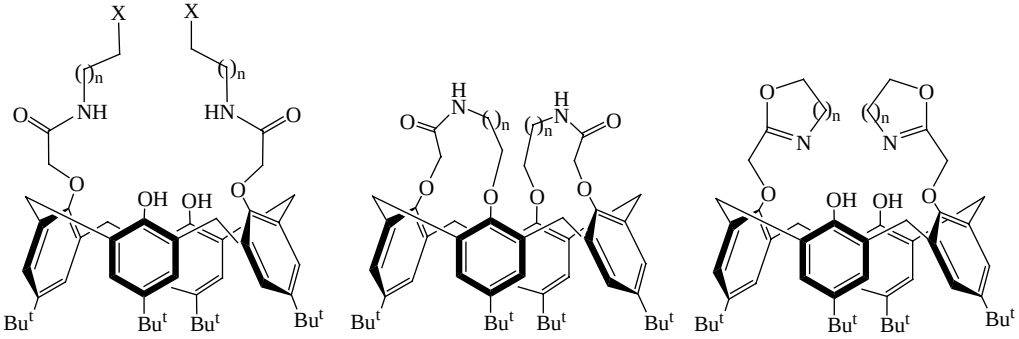
After these preliminary studies we were interested in how the outcome of reaction with the analogous thiacalixarene hydroxyamides would be affected by the larger intramolecular distances between the reacting sites (TCA > CA), and by using a mild and neutral cyclodehydration method.

2. Results and discussion

Starting materials **8**–**10** were prepared by the amination of the respective diesters **7a**–**c** with aminoalcohols as described for the calixarene series.[14] Diesters **7b**,**c** were first synthesized in our laboratory by the selective Mitsunobu alkylation of TCA with ethyl (*S*)-lactate (**7b**) and ethyl (*R*)-mandelate (**7c**), respectively.[6] The base-promoted alkylation of TCA with ethyl bromoacetate reported for the preparation of **7a**[15] was unsatisfactory in our hand (chromatographic separation was required), in turn the Mitsunobu coupling with glycolic acid ethyl ester cleanly afforded the desired **7a** at room temperature. The amination of **7a**,**b** went smoothly with all aminoalcohols, but mandelate **7c** only gave complete conversion with 2-aminoethanol (Scheme 1).

The Mitsunobu reaction was then performed with triphenylphosphine (TPP) and diethyl azodicarboxylate (DEAD) in toluene using a molar ratio of **8**–**10**/(TPP/DEAD) = 1:3 at ambient temperature. From compounds **8a**–**c**, **9a**,**b** and **10a** only doubly capped thiacalixarenes **11a**–**c**, **12a**,**b** and **13a** were obtained in acceptable yields, and heterocycles **14**, **15** were not detected (Scheme 1). With hydroxyamide **9c** the reaction did not go to completion even at elevated temperature: a series of spots was seen on the TLC sheet containing the starting **9c**, Ph_3PO, probably singly and doubly cyclized products and others, but we were unable to separate any product in pure form. The success of double cyclization on the phenolic OHs was found to primarily depend on the length of the hydroxyalkyl chain and is not affected by the temperature.

It was notable that the base-promoted cyclization of calix[4]arene chloroalkylamides **4** was much more sensitive to the chain length of the chloroalkyl moiety, because only the propyl derivative **4b** gave cyclic product, suggesting the necessity of the appropriate intramolecular distance between the adjacent phenolate and the electrophilic site.[14] As the diameter of the lower rim in TCA is larger than that of CA (vide supra), consequently the respective intramolecular distances should also be larger. The clean cyclization of **8a**, **9a** and **10a** possessing the same chain lengths as **4a**, therefore contradict this. When the respective calixarene counterparts **3a**–**c** were also subjected to analogous Mitsunobu cyclization at 80 °C, no positive reactions were found: neither doubly capped calixarenes **5** nor heterocycles **6** could be identified. The failure of the former reaction may be due to the weaker acidity of the remaining OHs in distally dialkylated calixarenes as compared to the TCA counterparts,[3] which prevents their further alkylation under Mitsunobu conditions.[8] Perhaps

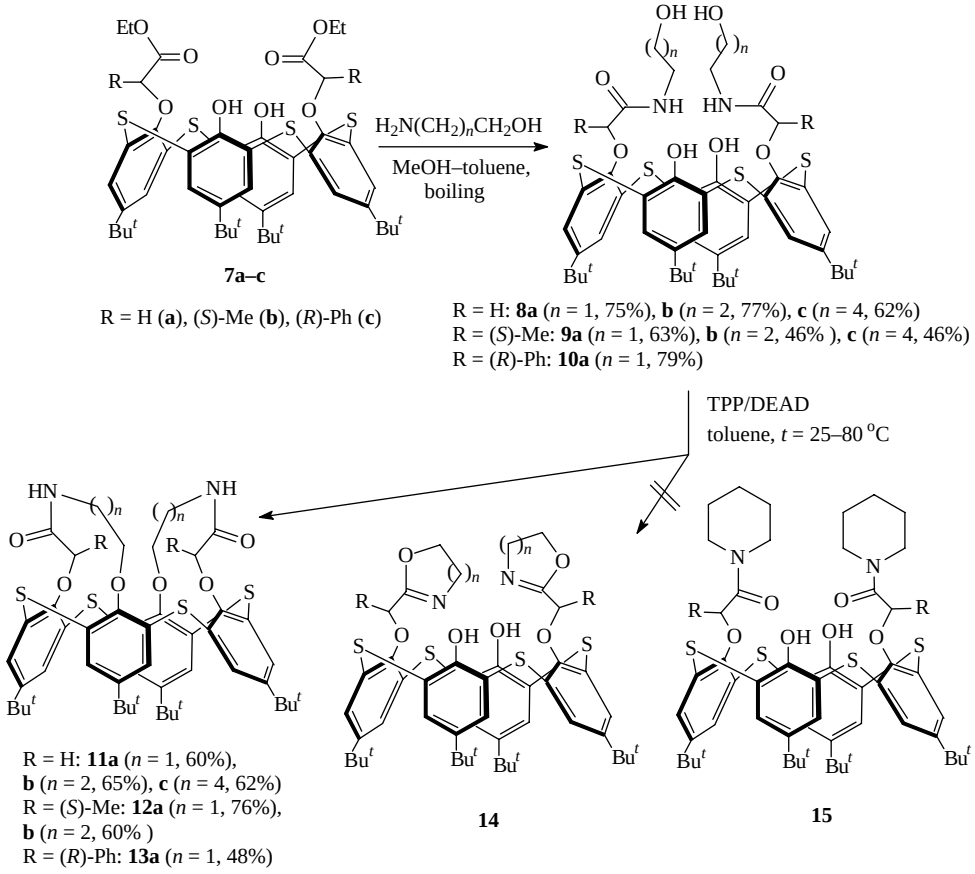


3 (X = OH)
4 (X = Cl)
n = 1(**a**), 2(**b**), 4(**c**)

5b (n = 2)

6a,b

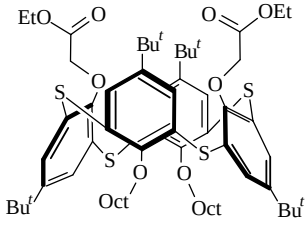
Figure 2. Survey of products obtained or expected in the base-promoted cyclization of **4**.



Scheme 1. Synthesis and Mitsunobu cyclization of *N*-hydroxylkylamides **8**–**10**.

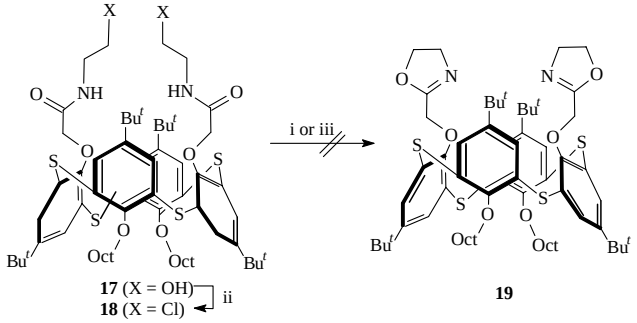
more reactive azodicarboxylate and phosphine coupling agents could help, but so far DIPAD/TPP has been tried without success.

It was rather surprising that the carboxamide groups remained intact, though various *N*-(hydroxyalkyl)amides were reported to undergo different self-cyclizations via the mild Mitsunobu reaction.[13] To check the reactivity of the carboxamide groups, the participation of the phenolic OHs in the cyclization had to be excluded by using an *O*-protected derivative. As the base-promoted O-alkylation of **8a** led to a mixture of 1,3-alt, cone and paco conformers, the highly lipophilic (and soluble) distal 1,3-dioctyloxy-TCA[6] was alkylated with ethyl bromoacetate/Cs_2CO_3 and 1,3-alt diester **16** was obtained.



16

This compound was then treated with 2-aminoethanol resulting in 1,3-alt bisamide **17**, which was subjected to Mitsunobu cyclization. However, we failed to isolate bisoxazoline **19**, only the starting material was recovered (Scheme 2).



Scheme 2. Attempts to cyclize *O*-protected bisamides **17**, **18**. Reagents and conditions: (i) **17**, TPP/DEAD, toluene, 80 °C; (ii) $SOCl_2$, $CHCl_3$, Δ; (iii) **18**, NaOEt, EtOH, Δ.

The bischloro derivative **18** also could not be cyclized to **19** under strongly basic conditions, analogously to the ring closure of *N*-(2-chloroethyl)phenoxyacetamide giving 2-phenoxymethyl-1,3-oxazoline.[16] In contrast, the basic treatment of 1,3-dihydroxy-bis(chloroethoxy)amide derived from **8a** gave selectively again the Mitsunobu product **11a**, thereby providing further evidence for the suppressed reactivity of the carboxamide groups in our models.[†]

[†] To eliminate the adverse effect of the bulky *tert*-butyl groups in the 1,3-alt **17** and **18**, for the referee's suggestion the respective de-*tert*-butylated derivatives were also prepared (as the $AlCl_3$-promoted dealkylation of **17** and **18** was expected to be uncertain due to the reactive endgroups, therefore the same route described for **16** was used) and subjected to Mitsunobu reaction and basic treatment, respectively. However, both trials failed, the expected bisoxazoline could not be achieved.

These experiments revealed that the chemoselectivity in the transformation of thiacalixarene 1,3-bisamides **8–10** to doubly capped **11–13** versus bis(*O*,*N*-heterocycles) **14**, **15** can be attributed to the resistance of the carboxamide groups to self-cyclization, the cause of which is not clear at this point (other approaches to prepare **19** are being tried). The reaction has another interesting aspect as compared with the results obtained with TCA and diethylene glycols, where only single ring closure was attained under the same conditions (see the tethered **2b**,**c** in Fig. 1). We assume the carboxamide NHs of bisamides **8–10** are hydrogen-bonded to the neighbouring phenolic OHs (δNH = 8.5–9.0t, 2H), which in turn, are hydrogen-bonded to the adjacent phenol ether oxygens (δOH = 7.5–8.0s, 2H) keeping the alkyl chains in the vicinity of the nucleophilic sites, thereby facilitating the double cyclization.

The ^{1}H and ^{13}C NMR spectra of doubly capped **11–13** are quite complex due to the asymmetric structure. For example **11c** displays one singlet (7.81) and two doublets (7.00, 6.94) for the aromatic protons and two doublets (5.97, 4.08) for the methylene protons in the ArOCH_2CONH moieties. The inherent chirality of these macrocycles was demonstrated by

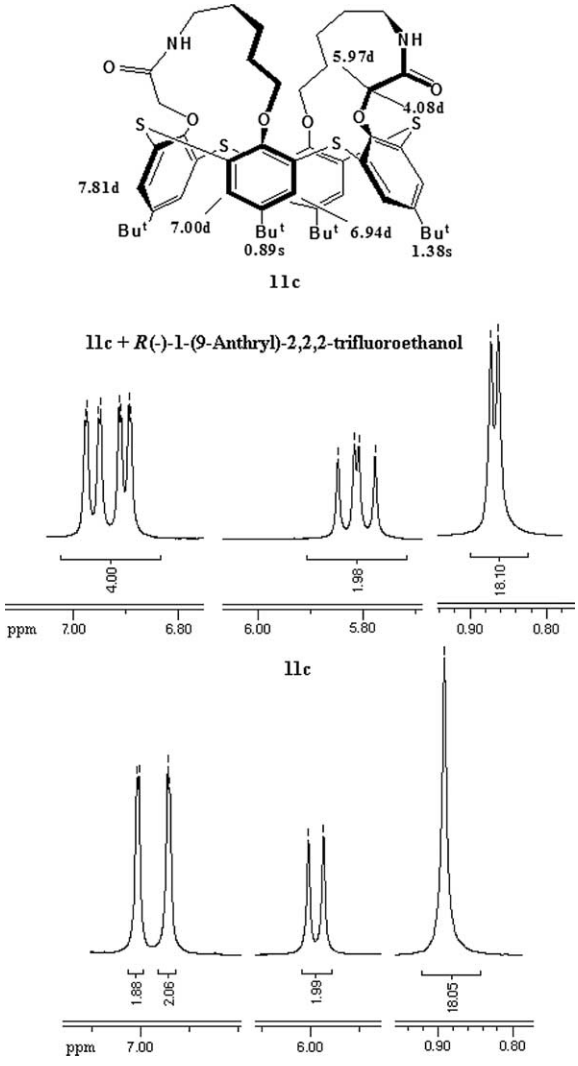


Figure 3. Partial ^{1}H NMR spectra of **11c** in $CDCl_3$ without (lower) and with (upper) Pirkle reagent.

taking the ^{1}H NMR spectrum of **11c** in the presence of Pirkle reagent and the labelled signals were doubled in a 1:1 ratio (Fig. 3).

The enantiomeric resolution of **11c** racemate was attempted by HPLC separation using chiral stationary phases. Earlier, Chiralpak AD column was successfully applied for the separation of **2c**,[12] but in this case it was unsuitable, instead Chiracel OD-H (cellulose tris-(3,5-dimethylphenylcarbamate)) column gave satisfactory resolution for the detection of enantiomers (Fig. 4). Unfortunately, the difference in retention times for the enantiomers (Δt = 2.3 min) did not make their separation feasible on a semi-preparative scale and CD spectra, therefore, were not recorded.

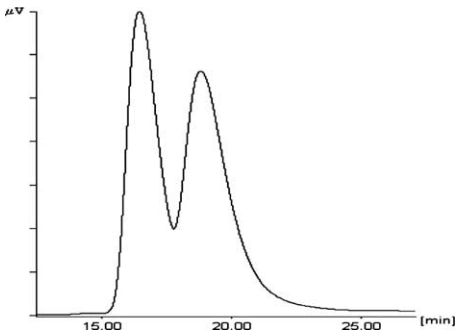


Figure 4. HPLC separation of **11c** on Chiracel OD-H (mobile phase *n*-hexane/2-propanol = 95:5 at 0.5 ml/min).

3. Conclusions

Chemoselective intramolecular ring closure on the phenolic OH groups of *p-tert*-butylthiacalix[4]arene 1,3-bis(*N*-ω-hydroxyalkylamides) was attained under Mitsunobu conditions affording inherently chiral doubly capped derivatives **11–13**. Oxazoline or oxazine cyclization products **14**, **15** derived from self-condensation of the hydroxyalkylamide moieties were not isolated. We pointed out that the chemoselectivity in the transformation of thiacalixarene 1,3-bisamides **8–10** to doubly capped **11–13** versus bis(*O*,*N*-heterocycles) **14**, **15** can be attributed to the markedly decreased reactivity of the carboxamide groups that could not cyclize even in the absence of the competing phenolic OHs.

The new macrocycles were obtained as racemic mixtures as demonstrated by ^{1}H NMR measurement of **11c** carried out in the presence of Pirkle reagent and by the detection of its enantiomers with HPLC using a chiral stationary phase.

4. Experimental

Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ at 500/125 MHz on a Bruker Avance DRX-500 spectrometer. FAB mass spectra were recorded (frequently in the presence of a mixture of alkali picrates) on a Finigan MAT 8430 instrument (matrix: *m*-NBA, gas: xenon, accelerating voltage: 9 kV). Precoated silica gel plates (Merck 60 F_{254}) were used for analytical TLC and Kieselgel 60 for column chromatography. All chemicals were reagent grade and used without further purification. *n*-Hexane and 2-propanol (HPLC grade) were purchased from Merck.

Compounds **7a–c**[6] and DEAD[17] were synthesized as described in the literature (CAUTION! DEAD may explode if exposed to shock, friction or heating).

The HPLC measurements were performed on a JASCO liquid chromatograph (pump 1580) with UV spectrophotometric detector (UV-1575) operating at 256 nm. The column (250×4.6 mm) was packed with Chiracel OD-H coated on 5 μm silicagel (Daicel, Tokyo).

4.1. General procedure for the synthesis of thiacalix[4]arene 1,3-bis(ω-hydroxyalkylamides) 8–10

Our early method used for the preparation of the respective calix[4]arene bisamides[14] was adapted. Thus, **7a–c** (1 mmol), aminoalcohol (10 mmol) in toluene–methanol solvent mixture (1/1, 20 ml) were refluxed overnight. The volatiles was then evaporated and the residue was triturated with MeOH to give white solids with sufficient purity.

4.1.1. Compound 8a. Yield: 75%, mp 253–254 °C; ^{1}H NMR δ 8.99 (t, 2H, J=5.5 Hz, N*H*), 7.71 (s, 4H, Ar*H*), 7.61 (s, 2H, O*H*), 7.31 (s, 4H, Ar*H*), 4.77 (s, 4H, ArOCH_2CO), 3.85 (m, 4H, HOCH_2), 3.64 (m, 4H, HNCH_2), 1.32 (s, 18H, Bu^t), 1.00 (s, 18H, Bu^t); ^{13}C NMR δ 169.4 (*C*O), 156.7, 156.2, 149.7, 144.2, 135.6, 135.2, 128.5, 121.3 (Ar), 75.5 (O*C*H$_2$), 62.0 (HO*C*H$_2$), 42.4 (HN*C*H$_2$), 34.6, 34.4 (*C*(CH$_3$)$_3$), 31.5, 31.0 (C(*C*H$_3$)$_3$); FAB-MS *m*/*z* (%): 923.5 [M+H]$^+$, 945.5 [M+Na]$^+$, 961.5 [M+K]$^+$. Anal. Calcd for $C_{48}H_{62}N_2O_8S_4$ (922.34): C 62.44, H 6.77, N 3.03, S 13.89, found: C 62.32, H 6.82, N 3.11, S 13.71%.

4.1.2. Compound 8b. Yield: 77%, mp 242–243 °C; ^{1}H NMR δ 8.96 (t, 2H, J=5.5 Hz, N*H*), 7.62 (s, 2H, O*H*), 7.71 (s, 4H, Ar*H*), 7.46 (s, 4H, Ar*H*), 4.77 (s, 4H, ArOCH_2CO), 3.74 (t, 4H, J=5.5 Hz, HOCH_2), 3.64 (q, 4H, J=6.0 Hz, HNCH_2), 1.86 (m, 4H, CH_2), 1.31 (s, 18H, Bu^t), 1.09 (s, 18H, Bu^t); ^{13}C NMR δ 169.1 (*C*O), 157.0, 156.4, 150.2, 144.3, 136.0, 135.9, 128.4, 120.9 (Ar), 75.8 (O*C*H$_2$), 59.3 (HO*C*H$_2$), 35.9 (HN*C*H$_2$), 34.7, 34.4 (*C*(CH$_3$)$_3$), 32.4 (*C*H$_2$), 31.5, 31.0 (C(*C*H$_3$)$_3$); FAB-MS *m*/*z* (%): 951.5 [M+H]$^+$, 973.8 [M+Na]$^+$, 989.5 [M+K]$^+$. Anal. Calcd for $C_{50}H_{66}N_2O_8S_4$ (950.37): C 63.13, H 6.99, N 2.94, S 13.48, found: C 63.28, H 7.02, N 2.81, S 13.27%.

4.1.3. Compound 8c. Yield: 62%, mp 200–202 °C; ^{1}H NMR δ 8.94 (t, 2H, J=5.5 Hz, N*H*), 7.69 (s, 4H, Ar*H*), 7.68 (s, 2H, O*H*), 7.51 (s, 4H, Ar*H*), 4.70 (s, 4H, ArOCH_2CO), 3.54 (t, 4H, J=6.0 Hz, HOCH_2), 3.45 (dt, 4H, J=5.5, 7.5 Hz, HNCH_2), 1.68 (m, 4H, CH_2), 1.58 (m, 4H, CH_2), 1.49 (m, 4H, CH_2), 1.29 (s, 18H, Bu^t), 1.10 (s, 18H, Bu^t); ^{13}C NMR δ 168.1 (*C*O), 157.2, 156.6, 150.3, 144.3, 136.5, 135.8, 128.3, 120.7 (Ar), 76.1 (O*C*H$_2$), 62.4 (HO*C*H$_2$), 39.6 (HN*C*H$_2$), 34.7, 34.4 (*C*(CH$_3$)$_3$), 32.5 (*C*H$_2$), 31.6, 31.1 (C(*C*H$_3$)$_3$), 29.0, 23.2 (*C*H$_2$); FAB-MS *m*/*z* (%): 1007.2 [M+H]$^+$, 1029.2 [M+Na]$^+$, 1045.4 [M+K]$^+$. Anal. Calcd for $C_{54}H_{74}N_2O_8S_4$ (1006.43): C 64.38, H 7.40, N 2.78, S 12.73, found: C 64.21, H 7.47, N 2.83, S 12.85%.

4.1.4. Compound 9a. Yield: 63%, mp 248–250 °C; ^{1}H NMR δ 8.75 (t, 2H, J=5.5 Hz, N*H*), 7.71 (s, 4H, Ar*H*), 7.64 (s, 2H, O*H*), 7.20 (d, 4H, J=2.5 Hz, Ar*H*), 7.16 (d, 4H, J=2.5 Hz, Ar*H*), 4.76 (q, 2H, J=7.0 Hz, ArO(CH$_3$)C*H*CO), 3.85 (m, 4H, HOCH_2), 3.67 (m, 2H, HNCH_2), 3.60 (m, 2H, HNCH_2), 1.60 (d, 6H, J=7.0 Hz, CH_3), 1.35 (s, 18H, Bu^t), 0.92 (s, 18H, Bu^t); ^{13}C NMR δ 172.2 (*C*O), 155.7, 154.7, 149.1, 143.9, 135.3, 135.1, 134.8, 133.6, 129.2, 128.5, 122.1, 121.5 (Ar), 83.9 (ArO*C*HCO), 62.4 (HO*C*H$_2$), 42.3 (HN*C*H$_2$), 34.4, 34.4 (*C*(CH$_3$)$_3$), 31.6, 30.9 (C(*C*H$_3$)$_3$), 17.7 (CH$_3$); FAB-MS *m*/*z* (%): 951.5 [M+H]$^+$, 974.5 [M+Na]$^+$, 989.5 [M+K]$^+$. Anal. Calcd for $C_{50}H_{66}N_2O_8S_4$ (950.37): C 63.13, H 6.99, N 2.94, S 13.48, found: C 62.85, H 7.05, N 2.83, S 13.20%.

4.1.5. Compound 9b. Yield: 46%, mp 240–244 °C; ^{1}H NMR δ 8.94 (t, 2H, J=5.5 Hz, N*H*), 7.69 (s, 4H, Ar*H*), 7.57 (s, 2H, O*H*), 7.32 (d, 2H, J=2.0 Hz, Ar*H*), 7.27 (d, 2H, J=2.0 Hz, Ar*H*), 4.83 (q, 2H, J=6.5 Hz, ArO(CH$_3$)C*H*CO), 3.71 (t, 4H, J=5.5 Hz, HOCH_2), 3.67 (dt, 2H, J=6.0, 7.0 Hz, HNCH_2), 3.48 (dt, 2H, J=6.0, 7.0 Hz, HNCH_2), 1.83 (m, 4H, CH_2), 1.60 (d, 6H, J=6.5 Hz, CH_3), 1.32 (s, 18H, Bu^t), 0.98 (s, 18H, Bu^t); ^{13}C NMR δ 172.4 (*C*O), 156.0, 154.8, 149.5, 144.1, 135.6, 135.6, 135.1, 134.4, 129.0, 128.7, 121.7, 121.1 (Ar), 83.6 (ArO*C*HCO), 59.4 (HO*C*H$_2$), 36.1 (HN*C*H$_2$), 34.5, 34.4 (*C*(CH$_3$)$_3$), 32.2 (*C*H$_2$), 31.6, 30.9 (C(*C*H$_3$)$_3$) 17.7 (CH$_3$); FAB-MS *m*/*z* (%): 979.6 [M+H]$^+$, 1001.5 [M+Na]$^+$, 1017.6 [M+K]$^+$. Anal. Calcd for $C_{52}H_{70}N_2O_8S_4$ (978.40): C 63.77, H 7.20, N 2.86, S 13.10, found: C 63.68, H 7.14, N 2.91, S 13.05%.

4.1.6. Compound 9c. Yield: 46%, mp 188–192 °C; ^{1}H NMR δ 8.81 (t, 2H, J=5.5 Hz, N*H*), 7.69 (s, 4H, Ar*H*), 7.64 (s, 2H, O*H*), 7.35 (d, 4H, J=12.5 Hz, Ar*H*), 4.93 (q, 2H, J=7.0 Hz, ArO(CH$_3$)C*H*CO), 3.51 (t, 4H, J=6 Hz, HOCH_2), 3.46 (dt, 2H, J=6.0, 7.5 Hz, HNCH_2), 3.38 (dt, 2H, J=6.0, 7.5 Hz, HNCH_2), 1.66 (m, 8H, CH_2), 1.54 (d, 6H, J=7.0 Hz, CH_3), 1.46 (m, 4H, CH$_2$), 1.32 (s, 18H, Bu^t), 0.99 (s, 18H, Bu^t); ^{13}C NMR δ 171.4 (*C*O), 156.2, 154.7, 149.5, 144.1, 135.9, 135.5, 134.9, 129.0, 128.9, 128.6, 121.7, 121.0 (Ar), 83.3 (ArO*C*HCO), 62.5 (HO*C*H$_2$), 39.8 (HN*C*H$_2$), 34.5, 34.4 (*C*(CH$_3$)$_3$), 32.4 (*C*H$_2$), 31.6, 31.1 (C(*C*H$_3$)$_3$) 29.0, 23.2 (*C*H$_2$), 17.5 (CH$_3$); FAB-MS *m*/*z* (%): 1035.3 [M+H]$^+$. Anal. Calcd for $C_{56}H_{78}N_2O_8S_4$ (1034.46): C 64.95, H 7.59, N 2.71, S 12.39, found: C 65.12, H 7.52, N 2.84, S 12.30%.

4.1.7. Compound 10a. Yield: 79%, mp 240–242 °C; ^{1}H NMR δ 8.99 (t, 2H, J=5.5 Hz, N*H*), 7.65 (d, 2H, J=2.5 Hz, Ar*H*), 7.63 (d, 2H, J=2.5 Hz, Ar*H*), 7.56 (s, 2H, O*H*), 7.31–7.41 (m, 10H, Ar*H*), 7.09 (d, 2H, J=2.5 Hz, Ar*H*), 6.90 (d, 2H, J=2.5 Hz, Ar*H*), 4.76 (s, 2H, ArOPhC*H*CO), 3.85–3.94 (m, 4H, HOCH_2), 3.71 (m, 4H, HNCH_2), 1.32 (s, 18H, Bu^t), 0.81 (s, 18H, Bu^t); ^{13}C NMR δ 170.4 (*C*O), 155.6, 154.5, 148.8, 143.8, 135.0, 134.9, 134.8, 134.4, 133.3, 130.0, 129.6, 128.8, 128.1, 122.7, 121.5 (Ar), 89.3 (ArO*C*HCO), 62.2 (HO*C*H$_2$), 42.4 (HN*C*H$_2$), 34.4, 34.3 (*C*(CH$_3$)$_3$), 31.6, 30.8 (C(*C*H$_3$)$_3$); FAB-MS *m*/*z* (%): 1075.6 [M+H]$^+$, 1098.6 [M+Na]$^+$, 1113.8 [M+K]$^+$. Anal. Calcd for $C_{60}H_{70}N_2O_8S_4$ (1074.40): C 67.01, H 6.56, N 2.60, S 11.93, found: C 67.16, H 6.49, N 2.46, S 11.80%.

4.2. General procedure for the synthesis of doubly capped thiacalix[4]arenes 11–13

To the mixture of **8–10** (1 mmol) and TPP (0.79 g, 3 mmol) in toluene (20 ml), 40% toluene solution of DEAD (1.30 ml,

3 mmol) was dropped under stirring at ambient temperature and allowed to react overnight. The suspension was then evaporated to dryness and the residue was triturated with MeOH to give **11–13** as white solids in substantially pure form. Compounds **11a**,**b** were sparingly soluble in $CDCl_3$ and DMSO-d_6, which prevented the measurement of suitable NMR spectra.

4.2.1. Compound 11a. Yield: 60%, mp>360 °C; IR (KBr) 3390, 3342 (NH), 2963, 2872 (CH_2), 1684 (amide CO), 1561, 1440, 1384, 1270, 1090, 1035 cm^{-1}; FAB-MS *m/z* (%): 887.8 $[M+H]^+$(91). Anal. Calcd for $C_{48}H_{58}N_2O_6S_4$ (886.32): C 64.98, H 6.59, N 3.16, S 14.46, found: C 65.10, H 6.52, N 3.32, S 14.27%.

4.2.2. Compound 11b. Yield: 65%, mp>360 °C; IR (KBr) 3392, 3340 (NH), 2961, 2870 (CH_2), 1684 (amide CO), 1560, 1439, 1384, 1271, 1094, 1030 cm^{-1}; FAB-MS *m/z* (%): 916.0 $[M+H]^+$(100). Anal. Calcd for $C_{50}H_{62}N_2O_6S_4$ (914.35): C 65.61, H 6.83, N 3.06, S 14.01, found: C 65.47, H 6.77, N 3.02, S 14.17%.

4.2.3. Compound 11c. Yield: 62%, mp 340–342 °C; IR (KBr): 3390, 3334 (NH), 2962, 2871 (CH_2), 1677 (amide CO), 1543, 1444, 1382, 1268, 1093, 1027 cm^{-1}; ^1H NMR δ 8.40 (t, 2H, $J=5.8$ Hz, N*H*), 7.79 (s, 4H, Ar*H*), 6.99 (d, 2H, $J=2.5$ Hz, Ar*H*), 6.93 (d, 2H, $J=2.4$ Hz, Ar*H*), 5.97 (d, 2H, $J=15.5$ Hz, ArOCH_2CO), 4.08 (d, 2H, $J=15.5$ Hz, ArOCH_2CO), 4.01 (dt, 2H, $J=8.7$, 3.4 Hz, NCH_2), 3.80 (tt, 2H, $J=3.0$, 3.0 Hz, NCH_2), 3.62 (tdd, 2H, $J=11.1$, 8.9, 2.2 Hz, OCH_2), 3.35 (tt, 2H, $J=9.0$, 3.0 Hz, OCH_2), 2.14 (m, 2H, CH_2), 2.13 (m, 2H, CH_2), 1.93 (m, 2H, CH_2), 1.91 (m, 2H, CH_2), 1.80 (m, 2H, CH_2), 1.61 (m, 2H, CH_2), 1.36 (s, 18H, Bu^t), 0.87 (s, 18H, Bu^t); ^{13}C NMR δ 169.0, 161.0, 156.8, 147.2, 147.1, 137.3, 137.1, 133.7, 131.9, 130.2, 129.1, 128.7, 128.5 (Ar), 74.9, 78.4 (OCH_2), 36.3 (HNCH_2), 34.4, 34.1 ($C(CH_3)_3$), 31.4, 30.9 (C(CH_3)$_3$), 26.3, 20.5 (CH_2); FAB-MS *m/z* (%): 971.3 $[M+H]^+$(62). Anal. Calcd for $C_{54}H_{70}N_2O_6S_4$ (970.41): C 66.77, H 7.26, N 2.88, S 13.20, found: C 66.91, H 7.32, N 2.96, S 13.04%.

4.2.4. Compound 12a. Yield: 76%, mp>360 °C; ^1H NMR δ 8.94 (dd, 2H, $J=10.8$, 1.7 Hz, N*H*), 7.84 (d, 2H, $J=2.4$ Hz, Ar*H*), 7.79 (d, 2H, $J=2.4$ Hz, Ar*H*), 7.21 (d, 2H, $J=2.4$ Hz, Ar*H*), 7.18 (d, 2H, $J=2.4$ Hz, Ar*H*), 4.59 (q, 2H, $J=6.7$ Hz, ArOC*H*CH$_3$), 4.28 (dd, 2H, $J=8.4$, 4.4 Hz, OCH_2), 4.14 (ddd, 2H, $J=13.7$, 11.0, 4.1 Hz, NHCH_2), 3.85 (ddd, 2H, $J=11.6$, 8.5, 4.3 Hz, OCH_2), 3.62 (dddd, 2H, $J=13.7$, 11.7, 4.4, 2.0 Hz, NHCH_2), 1.73 (d, 6H, $J=6.9$ Hz, CH_3), 1.33 (s, 18H, Bu^t), 0.89 (s, 18H, Bu^t); ^{13}C NMR δ 175.3 (*C*O), 160.5, 155.9, 148.4, 146.1, 137.7, 136.8, 134.3, 134.1, 133.0, 130.0, 129.1, 124.6 (Ar), 83.5 (O*C*H), 74.1 (O*C*H$_2$), 38.0 (NH*C*H$_2$), 34.5, 34.0 ($C(CH_3)_3$), 31.4, 30.0 (C(CH_3)$_3$), 19.6 (CH_3); FAB-MS *m/z* (%): 915.4 $[M+H]^+$. Anal. Calcd for $C_{50}H_{62}N_2O_6S_4$ (914.35): C 65.61, H 6.83, N 3.06, S 14.01, found: C 65.37, H 6.77, N 3.02, S 14.17%.

4.2.5. Compound 12b. Yield: 60%, mp>360 °C; ^1H NMR δ 8.95 (dd, 2H, $J=6.1$, 2.3 Hz, N*H*), 7.80 (d, 2H, $J=2.4$ Hz, Ar*H*), 7.79 (d, 2H, $J=2.4$ Hz, Ar*H*), 7.37 (d, 2H, $J=2.1$ Hz, Ar*H*), 7.31 (d, 2H, $J=2.1$ Hz, Ar*H*), 4.79 (dd, 2H, $J=9.6$, 7.0 Hz, OCH_2), 4.42 (q, 2H, $J=6.7$ Hz, ArOC*H*CH$_3$), 3.95 (ddd, 2H, $J=10.2$, 6.6, 3.7 Hz, NHCH_2), 3.92 (t, 2H, $J=8.8$ Hz, OCH_2), 3.40 (m, 2H, HNCH_2), 2.45 (m, 2H, CH_2), 2.08 (m, 2H, CH_2), 1.69 (d, 6H, $J=6.7$ Hz, CH_3), 1.31 (s, 18H, Bu^t), 0.96 (s, 18H, Bu^t); ^{13}C NMR δ 172.2 (*C*O), 161.1, 156.4, 147.8, 147.4, 137.7, 136.8, 134.7, 134.4, 131.0, 129.8, 129.6, 129.3 (Ar), 83.9 (O*C*H), 79.0 (O*C*H$_2$), 40.6 (NH*C*H$_2$), 34.4, 34.1 ($C(CH_3)_3$), 31.4, 30.9 (C(CH_3)$_3$), 28.0 (CH_2), 17.7 (CH_3); FAB-MS *m/z* (%): 943.4 $[M+H]^+$. Anal. Calcd for $C_{52}H_{66}N_2O_6S_4$ (942.38): C 66.21, H 7.05, N 2.97, S 13.60, found: C 66.08, H 6.92, N 3.12, S 13.77%.

4.2.6. Compound 13a. Yield: 48%, mp 320–324 °C; ^1H NMR δ 8.25 (dd, 2H, $J=10.9$, 1.8 Hz, N*H*), 7.89 (d, 4H, $J=7.6$ Hz, Ar*H*), 7.85 (s, 4H, Ar*H*), 7.42 (t, 4H, $J=7.6$ Hz, Ar*H*), 7.35 (t, 2H, $J=7.4$ Hz, Ar*H*), 7.23 (d, 2H, $J=2.4$ Hz, Ar*H*), 7.14 (d, 2H, $J=2.4$ Hz, Ar*H*), 5.54 (s, 2H, ArOPhC*H*CO), 4.36 (dd, 2H, $J=8.5$, 4.4 Hz, ArOCH_2), 4.17 (ddd, 2H, $J=14.0$, 11.1, 4.0 Hz, HNCH_2), 4.00 (ddd, 2H, $J=11.9$, 8.6, 4.1 Hz, ArOCH_2), 3.72 (dddd, 2H, $J=14.1$, 11.9, 4.0, 2.5 Hz, HNCH_2), 1.35 (s, 18H, Bu^t), 0.88 (s, 18H, Bu^t); ^{13}C NMR δ 172.9 (*C*O), 160.5, 155.9, 148.4, 146.2, 137.9, 137.0, 136.9, 134.2, 134.1, 133.0, 129.9, 128.8, 128.4, 128.3, 126.6, 124.1 (Ar), 87.8 (ArO*C*HCO), 74.3 (ArO*C*H$_2$), 38.2 (HN*C*H$_2$), 34.5, 34.0 ($C(CH_3)_3$), 31.4, 30.8 (C(CH_3)$_3$); FAB-MS *m/z* (%): 1039.5 $[M+H]^+$. Anal. Calcd for $C_{60}H_{66}N_2O_6S_4$ (1038.38): C 69.33, H 6.40, N 2.70, S 12.34, found: C 69.42, H 6.49, N 2.83, S 12.20%.

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The total synthesis of pamamycin-607. Part 2: Synthesis of the C6–C18 domain

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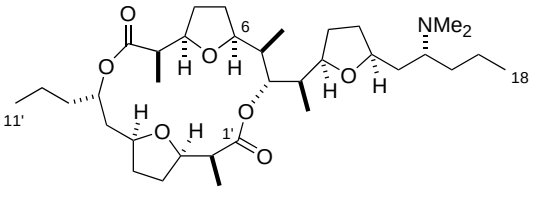
Abstract—Synthesis of the C6–C18 domain of pamamycin-607 was achieved in ten steps and 7% overall yield from commercially available D-norvaline. The key asymmetric transformations included a Paterson *anti* aldol addition, an *anti* selective reduction of the resultant β-hydroxy ketone and a cis selective Bartlett type ring closure.

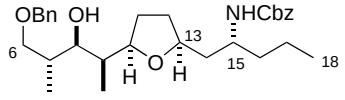
1. Introduction

Pamamycin-607 **1** (Scheme 1) is a member of a group of homologous naturally-occurring macrodiolides first isolated by Marumo from *Streptomyces alboniger* and *Streptomyces aurantiacus*.[1,2] Structurally, the interesting features include a 16-member macrodiolide and three *cis*-2,5-disubstituted tetrahydrofurans with adjacent methyl substituted stereogenic centres. Biologically, they show strong antibiotic activity against *Cochliobolus miyaneanus* and *Diaporthe citri*, but more importantly show potent activity against multiple antibiotic resistant strains of *Mycobacterium tuberculosis*.[3] Interestingly, this activity is due to their ability to inhibit adenine and uracil uptake.[4] Although structurally similar to the ionophore nonactin, pamamycin is incapable of transporting cations from aqueous to organic phases, but instead transports anions such as permanganate (MnO_4^-) and dichromate ($Cr_2O_7^{2-}$) from aqueous (pH ~ 5) to organic phases.[5–8] An interesting application of this was Grafe's demonstration of pamamycins capacity to transport drug molecules through the membranes of pathogenic bacteria.[9] In addition to antibiotic activity, the pamamycins also show autoregulatory activity by disrupting calcium ion accumulation and affecting aerial mycelium growth in *S. alboniger*.[8]

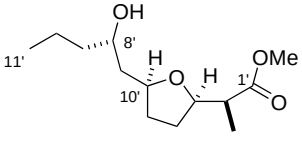
The aforementioned biological properties and complex stereochemistry make pamamycin-607 **1** an interesting



pamamycin-607 **1**



C6–C18 domain **3**



C1'–C11' domain **2**

Scheme 1. The C6–C18 (**3**) and C1′–C11′ **2** domains of pamamycin-607 (**1**).

Keywords: Tetrahydrofuran; Cyclisation; *anti* Aldol; Pamamycin; Stereoselective.
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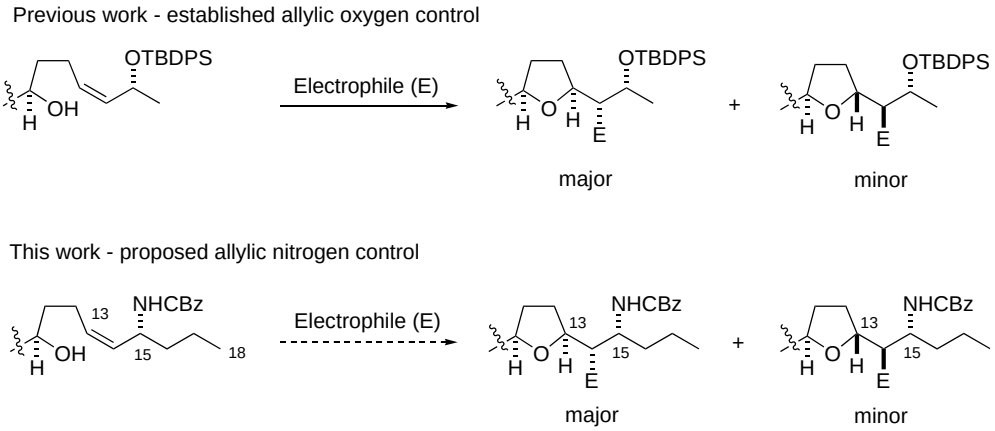


Scheme 2. Intramolecular electrophilic cyclisation of alkenes bearing a remote allylic heteroatom.

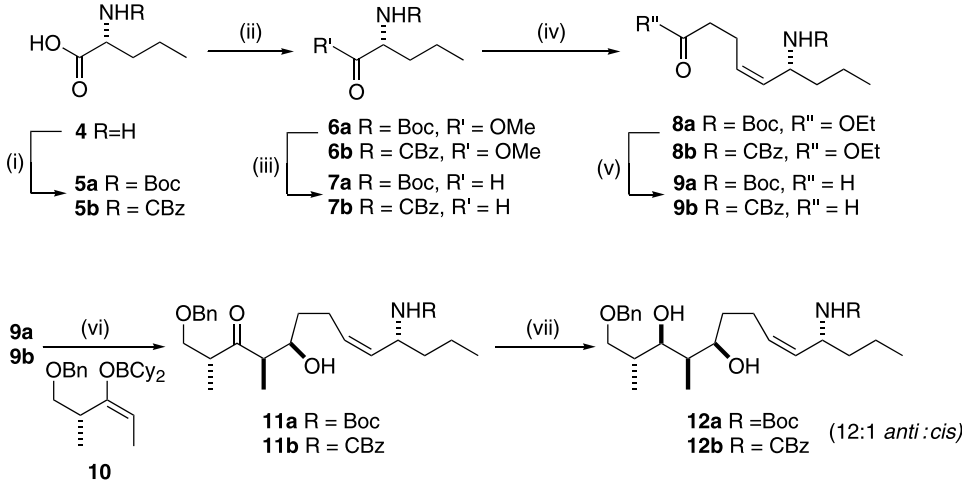
and challenging target for total synthesis, and indeed, so far four groups have reported total syntheses.[10–13] Towards that goal we previously reported a synthesis of the C1′–C11′ domain **2**.[14] Herein, we report our synthesis of the C6–C18 domain **3** of pamamycin-607 **1**.

Unlike other approaches, in our planned route to pamamycin-607 **1** the C15 allylic nitrogen was intended to be present throughout the synthesis, obviating the need for stereocontrolled introduction of nitrogen late in the synthesis. We envisaged applying an intramolecular electrophilic cyclisation reaction to form the key *cis* 2,5-disubstituted tetrahydrofuran moiety in a similar manner to that used to prepare the C1′–C11′ domain fragment **2** (Scheme 2).[14] It was anticipated that the C15 allylic nitrogen would influence the stereochemistry of the newly formed C13 centre, consistent with our previous work on related allylic oxygen systems.[15]

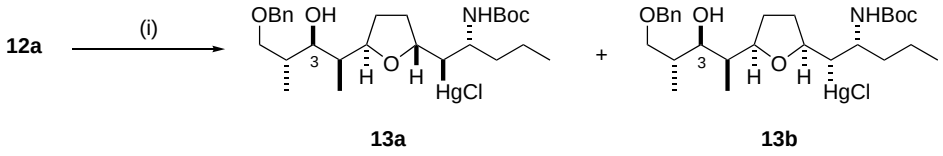
The diastereoselectivity of electrophilic cyclisations of alkenes bearing a remote protected allylic amine (Scheme 2) was not known at the beginning of this investigation and some preliminary results of our studies are included in this report.

2. Results and discussion

The synthesis began with the preparation of ring closure precursors **12a** and **12b** and was achieved in seven steps from commercially available D-norvaline **4** (Scheme 3). Treatment of D-norvaline **4** with benzylchloroformate/NaH gave CBz-D-norvaline **5b**, whilst the Boc analogue **5a** was obtained from a commercial supplier. Subsequent DIBAL-H reduction of the corresponding methyl esters **6a** and **6b** gave aldehydes **7a** and **7b** from which Wittig chain extension followed by DIBAL-H reduction afforded alkenals **9a** and **9b** in good yield and high *Z*:*E* selectivity (95:5, 96:4, respectively). Both aldehydes then underwent highly diastereoselective *anti* aldol addition with the (*E*)-enolate **10** of Paterson's chiral ketone **10a**[16] to afford diastereomerically pure aldols **11a** and **11b** after chromatography. The stereochemical assignment of **11a** and **11b** was consistent with literature precedent, and the $J_{2,3}$ coupling constants of 7.0, 7.1 Hz, respectively, are within the expected 7–9 Hz range for *anti* aldol adducts.[17] A final *anti*-selective reduction under Evans' conditions gave ring closure precursors **12a** and **12b** with excellent diastereoselectivity (both 12:1).[18,19]



Scheme 3. Synthesis of cyclisation precursors **12a** and **12b**. Reagents and conditions: (i) NaH, BnO_2CCl, DMF, 3 h, 100%; (ii) CH_2N_2, Et_2O, 0 °C, 1 h, **6a** 100%, **6b** 100%; (iii) DIBAL-H, toluene, −78 °C, 3 h; **7a** 78%, **7b** 97%; (iv) $BrPh_3P(CH_2)_3CO_2Et$, $NaN(TMS)_2$, THF, 0 °C, 1 h; **8a** 75%, **8b** 78%; (v) DIBAL-H, toluene, −78 °C, 3 h; **9a** 85%, **9b** 91%; (vi) **10**, ether, −78 °C, 2 h, −20 °C, o/n; **11a** 60%, **11b** 85%; (vii) $Me_4NBH(OAc)_3$, 1:1 AcOH/MeCN, −20 °C, 4 h, **12a** 68%, **12b** 78%.



Scheme 4. Cyclisation of diol **12a**. Reagents and conditions: (i) $Hg(OAc)_2$, MeCN, 0 °C, 3 h; 92%.

Investigation of electrophilic intramolecular cyclisations began with Boc diol **12a** (Scheme 4). Treatment with $Hg(OAc)_2$ at 0 °C in MeCN[15] gave a 10:1 mixture of *trans*-**13a** to *cis*-**13b**. Attempts to decrease or reverse this selectivity by decreasing reaction temperature were unsuccessful as reaction temperatures below 0 °C gave slow and impractical reaction rates. The use of the alternative electrophiles iodine and phenylselenium bromide was also unsuccessful and resulted in a complex mixture of inseparable products.

In order to establish if the C3 alcohol was playing any role in the observed trans selectivity, cyclisation of aldol adduct **11a** was carried out (Scheme 5). Treatment of **11a** with $Hg(OAc)_2$ in acetonitrile gave a 9:1 mixture of *trans* chloromercurial **14a** to *cis* chloromercurial **14b**.

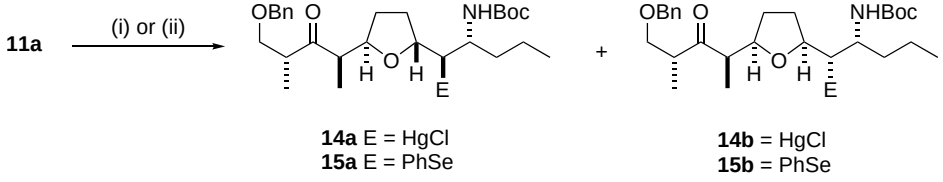
A similar result was obtained with PhSeBr where *trans*-tetrahydrofuran **15a** was favoured (5:1) over *cis*-tetrahydrofuran **15b** (Scheme 5). These results suggested that the C3 hydroxy was not an important factor in the observed trans selectivity.

Our previous work had shown the diastereoselectivity of this type of cyclisation was diminished for (*E*)-alkene substrates.[15] In an effort to reverse or suppress the trans-selectivity, (*E*)-alkene cyclisation precursor **19** was prepared by alkene isomerisation[20] of (*Z*)-ester **8a**. This was followed immediately by DIBAL reduction to give aldehyde **17**, which then underwent aldol addition to yield adduct **18**. A final *anti*-selective reduction afforded precursor **19** in good yield (Scheme 6).

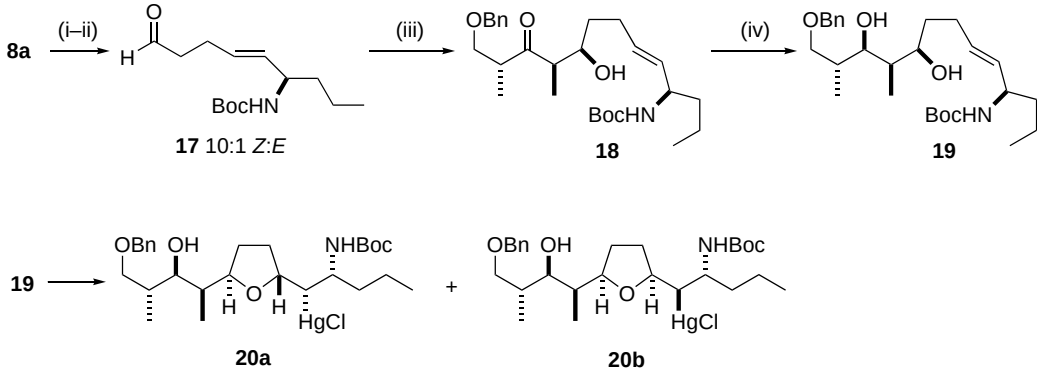
However, treatment of **19** with $Hg(OAc)_2$ in acetonitrile at 0 °C, again favoured the undesired *trans*-tetrahydrofuran **20a** over *cis*-**20b**, albeit with slightly improved (1:6) diastereoselectivity.

As forming the desired cis stereochemistry was proving difficult, we explored Bartlett's method for cis selective formation of 2,5-disubstituted tetrahydrofurans.[21] A similar approach was used by Kang, in their a total synthesis of pamamycin-607, which involved an iodine promoted cyclisation of a TES ether bearing a remote allylic oxygen substituent.[11] We first explored cyclisation of the TBS ether **23** derivative, which was easily prepared by treatment of diol **12b** with TBSOTf (Scheme 7).

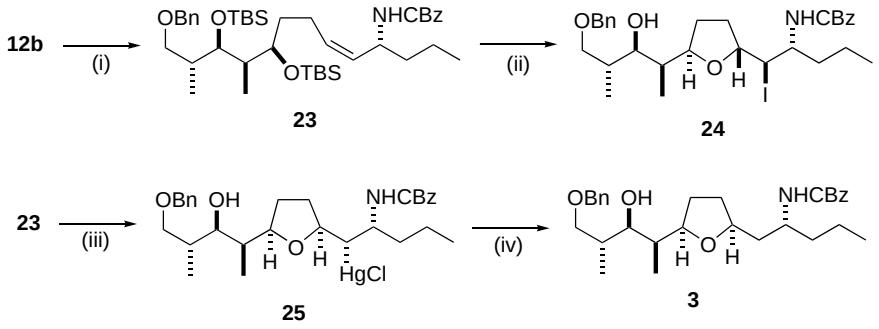
Subsequent iodocyclization of **23** proceeded in favour of *trans*-tetrahydrofuran **24**. This result may be due to cleavage of the TBS group being faster than the subsequent cyclization reaction. In an effort to reverse this result, the alternative electrophile $Hg(O_2CCF_3)_2$ was utilized with bis-TBS ether **23** in light of promising cis-selective oxymercurations of bis-TBS ethers reported by Walkup and co-workers.[22] Subsequent cyclisation of bis-TBS **23**



Scheme 5. Cyclisation of aldol adduct **11a**. Reagents and conditions: (i) $Hg(OAc)_2$, MeCN, 0 °C, 2 h; 73%; (ii) PhSeBr, DCM, −78 °C, 2 h, 52%.



Scheme 6. Synthesis and cyclisation of (*E*)-diol **19**. Reagents and conditions: (i) Ph_2S_2, benzene, hν, 2 days, (7:1 *E*/*Z*); (ii) DIBAL-H, toluene, −78 °C, 3 h, (10:1 *E*/*Z*); 51% over two steps; (iii) enolate **10**, ether, −78 °C, 2 h, −20 °C, o/n, 50%; (iv) $Me_4NBH(OAc)_3$, 1:1 AcOH/MeCN, −20 °C, 4 h, 92%; (v) $Hg(OAc)_2$, MeCN, 0 °C, 5 h, 60%.



Scheme 7. Synthesis and cyclisation of ether **23**. Reagents and conditions: (i) TBSOTf, 2,6-lutidine, THF, 0 °C, 4 h, 69%; (ii) I_2, $NaHCO_3$, MeCN, 0 °C, 3 h, 69%; (iii) $Hg(O_2CCF_3)_2$, DCM, −78 °C, 6 h, NaCl (satd), 51%; (iv) Bu_3SnH, AIBN, toluene, 60 °C, 3 h, 79%.

with $Hg(O_2CCF_3)_2$ in MeCN afforded *cis* tetrahydrofuran **25** in a 4:1 diastereoselectivity and moderate 48% yield. The *cis*-tetrahydrofuran stereochemistry was assigned by observation of an NOE between H2 and H5 of **25**. Removal of the chloromercurial group by treatment with tributylstannane and AIBN afforded the C6–C18 domain **3** in overall 7% yield from D-norvaline.

3. Conclusions

The combination of a Paterson aldol addition and *anti*-selective β-hydroxy ketone reduction has provided a very efficient and highly diastereoselective means for installing the four C7–C10 stereogenic centres of Pamamycin-607. A Bartlett type ring closure, using a $Hg(CO_2CF_3)_2$ electrophile reversed what appeared a highly trans-selective ring closure by providing a 4:1 cis selectivity. Further work is currently underway on the C1–C6 domain in our laboratories to complete our total synthesis of Pamamycin-607.

4. Experimental

4.1. General

Most chemicals were purchased from the Aldrich Chemical Company (Sydney, Australia) and were used as supplied. D-norvaline and Boc-D-norvaline were purchased from Novabiochem. Drying agents and inorganic salts were purchased from AJAX or BDH chemicals. Solvents were purified as follows. Anhydrous diethyl ether was distilled from sodium/benzophenone ketyl prior to use. Dichloromethane (DCM) was distilled from calcium hydride. Hexanes were distilled prior to use and refer to the fraction boiling between 40–60 °C. Silica gel used for chromatography was 40–63 μm (230–400 mesh) silica gel 60 (Merck No. 9385). Analytical thin-layer chromatography (TLC) was performed on Polygram Sil G/UV_{254} plastic sheets coated with silica gel containing UV_{254} fluorescent indicator and visualized under UV light and/or dipped in an ammonium molybdate/cerium sulphate solution. Proton NMR (^{1}H NMR) spectra were recorded at 300 MHz on a Varian Mercury spectrometer or Bruker AM 300 spectrometer and 400 MHz on a Bruker Avance DRX 400 spectrometer. Chemical shifts were recorded on the δ scale in parts per million (ppm). Unless otherwise stated, spectra were measured in deuterochloroform ($CDCl_3$) using the residual $CHCl_3$ (7.26 ppm) signal as an internal reference. Each resonance was reported according to the following convention: chemical shift (δ ppm) [multiplicity, coupling constant(s) (Hz), number of hydrogens. Multiplicities are designated as s=singlet, d=doublet, t=triplet, q=quartet, p=pentuplet and m=multiplet. Carbon NMR (^{13}C NMR) were recorded at 75 MHz on a Varian Mercury spectrometer or Bruker AM 300 spectrometer using deuterochloroform ($CDCl_3$) unless otherwise stated. The spectra were referenced using the solvent carbon signal ($CDCl_3$= 77.16 ppm). 2D NMR techniques such as homonuclear correlation spectroscopy (COSY), heteronuclear multiple quantum coherence (HMQC), heteronuclear multiple bond coherence (hmbc) and nuclear Overhauser effect spectroscopy (NOESY) were used to aid assignment of some NMR spectra. Mass spectrometry (ESI) was performed on a Micromass Platform QMS spectrometer. High-resolution mass spectra (HRMS) were recorded on a Bruker BioApex 47e FTMS using NaI for accurate mass calibration. M^+ refers to the molecular ion infrared spectra (IR) were recorded on a Perkin Elmer 1600 Series Fourier Transform spectrometer as neat solutions, chloroform ($CHCl_3$) solutions or as paraffin (Nujol) mulls of solids between NaCl plates. Melting points were recorded on a Kofler hot stage apparatus and are uncorrected.

4.1.1. (*R*)-2-Benzyloxycarbonylaminopentanoic acid (5b). To a solution of D-norvaline (5 g, 42.5 mmol) in THF (100 mL) at rt was added K_2CO_3 (29.4 g, 213 mmol) and benzylchloroformate (14.5 g, 12.1 mL, 85 mmol). The suspension was stirred o/n before being acidified to pH 1 with 2 M HCl. Ether (100 mL) was added and the organic phase separated from the aqueous phase, and the aqueous phase extracted with ether (3×20 mL). The combined organic extracts were then washed (satd $NaHCO_3$, brine), dried ($MgSO_4$) and the solvent removed under reduced pressure to yield the title compound **5b** as a colourless oil (10.7 g, 100%). $[\alpha]_D^{22}$ +19.5 (*c* 2.58, $CHCl_3$) lit.[23] (+14.1, *c* 1, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (3H, t, *J*= 7.2 Hz, CH_2CH_3), 1.37–1.44 (2H, m, CH_2), 1.65–1.85 (2H, m, CH_2), 4.41 (1H, m, CHN), 5.12 (2H, br s, CH_2Ph), 5.36 (1H, d, *J*=8.2 Hz, NH), 7.26–7.39 (5H, m, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 18.6, 34.5, 53.7, 67.3, 128.2, 128.3, 128.6, 136.2, 156.2, 177.5. IR (neat) υ_{max} 3329, 3036, 2962, 2875, 1716 (broad), 1587, 1532, 1456, 1416, 1345, 1229, 1106, 1028, 910, 777, 735, 698 cm^{-1}. MS *m*/*z* 274.1 ($M+Na^+$). HRMS *m*/*z* calcd for $C_{13}H_{17}NO_4Na^+$= 274.1055. Found *m*/*z* 274.1049. Anal. Calcd for

$C_{13}H_{17}NO_4$: C, 62.1; H, 6.8; N, 5.6. Found: C, 62.2; H, 6.9; N, 5.3.

4.1.2. Methyl (*R*)-2-*tert*-butoxycarbonylaminopentanoate (6a). Diazomethane (generated from 5 g Diazald®/satd KOH) gas was passed through a solution of NBoc protected norvaline (5 g, 21.6 mmol) in ether (50 mL) at 0 °C. The solution immediately turned yellow and was allowed to stir at 0 °C for 1 h. Nitrogen was passed continuously through the solution until it became colourless, indicating dissipation of excess diazomethane. The ether was then removed under reduced pressure to give the title compound **6a** as a colourless oil (5.32 g, 100%). $[\alpha]_D^{22}$ −2.7 (*c* 1.68, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (3H, t, J=7.4 Hz, CH_2CH_3), 1.26–1.38 (2H, m, CH_2), 1.41 (9H, s, $C(CH_3)_3$), 1.46–1.80 (2H, m, CH_2), 3.70 (3H, s, CH_3 methyl ester), 4.26 (1H, m, C*H*N), 5.20 (1H, d, J=7.8 Hz, N*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 19.0, 28.6, 35.2, 52.5, 53.5, 80.0, 155.5, 173.6. IR (neat) υ_{max} 3364, 2962, 2876, 1715, 1505, 1455, 1391, 1366, 1304, 1163, 1105, 1055, 1014, 919, 871, 780, 760 cm^{-1}. MS *m*/*z* 254.2 (M+Na$^+$). HRMS *m*/*z* calcd for $C_{11}H_{21}NO_4Na^+$=254.1368. Found: 254.1374. Anal. Calcd for $C_{11}H_{21}NO_4$: C, 57.2; H, 9.2; N, 6.1. Found: C, 57.3; H, 9.4; N, 6.2.

4.1.3. Methyl (*R*)-2-benzyloxycarbonylaminopentanoate (6b). Diazomethane (generated from 5 g Diazald®/satd KOH) gas was passed through a solution of NCBz protected norvaline **5b** (5 g, 18.9 mmol) in ether (50 mL) at 0 °C. The solution immediately turned yellow and was allowed to stir at 0 °C for 1 h. Nitrogen was then passed continuously through the solution until it became colourless, indicating dissipation of excess diazomethane. The ether was then removed under reduced pressure giving pure methyl ester **6b** as a colourless oil (5.28 g) in quantitative yield. $[\alpha]_D^{22}$ −2.8 (*c* 2.75, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (3H, t, J=7.3 Hz, CH_2CH_3), 1.31–1.41 (2H, m, CH_2), 1.51–2.15 (2H, m, CH_2), 3.63 (3H, s, OCH_3), 4.37 (1H, m, C*H*N), 5.11 (2H, s, CH_2Bn CBz), 5.30 (1H, d, J=7.2 Hz, N*H*), 7.27–7.36 (5H, m, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 18.6, 34.9, 52.3, 53.8, 67.1, 128.2, 128.6, 128.8, 136.4, 156.0, 173.2. IR (neat) υ_{max} 3342, 3065, 3033, 2880, 2874, 1725, 1714, 1538, 1455, 1380, 1304, 1216, 1170, 1105, 1061, 1027, 911, 778, 740, 698 cm^{-1}. MS *m*/*z* 288.1 (M+Na$^+$). HRMS *m*/*z* calcd for $C_{14}H_{19}NO_4Na^+$= 288.1212. Found: *m*/*z* 288.1216. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.4; H, 7.2; N, 5.3. Found: C, 63.5; H, 7.2; N, 5.5.

4.1.4. (*R*)-2-*tert*-Butoxycarbonylaminopentanal (7a). To a solution of ester **6a** (5.32 g, 18.9 mmol) in toluene (150 mL) cooled to −78 °C was slowly added DIBAL-H (1 M in toluene, 54 mL, 54 mmol). Care was taken to ensure the reaction temperature did not exceed −70 °C during addition. The solution stirred for 2 h at −78 °C and was carefully quenched by addition of acetone (10 mL) and satd NH_4Cl (10 mL) whilst again being careful to maintain the reaction temperature below −70 °C. The solution was then warmed to rt, filtered, and the solvent removed under reduced pressure. The resultant crude oil was purified by flash chromatography (10% EtOAc/hexanes) yielding the title compound **7a** as a colourless oil (3.41 g, 78%). $[\alpha]_D^{22}$ −56.9 (*c* 1.875, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (3H, t, J=7.2 Hz, CH_2CH_3), 1.32–1.60 (2H, m, CH_2), 1.43 (9H, s, $C(CH_3)_3$), 1.76–1.90 (2H, m, CH_2), 4.21 (1H, m, C*H*N), 5.06 (1H, br s, N*H*), 9.56 (1H, s, *H*C=O). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 18.9, 28.6, 31.6, 60.0, 80.2, 155.7, 200.1. IR (neat) υ_{max} 3350, 2964, 2875, 2815, 1720, 1698, 1518, 1458, 1392, 1387, 1252, 1169, 1063, 1017, 876, 782, 740 cm^{-1}. MS *m*/*z* 224.2 (M+Na$^+$). HRMS *m*/*z* calcd for $C_{10}H_{19}NO_3Na^+$=224.1263. Found: *m*/*z* 224.1253. Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.7; H, 9.5; N, 7.0%. Found: C, 59.8; H, 9.1; N, 7.2%.

4.1.5. (*R*)-2-Benzyloxycarbonylaminopentanal (7b). To a solution of ester **6b** (5.50 g, 19.7 mmol) in toluene (120 mL) cooled to −78 °C was slowly added DIBAL-H (1 M in toluene, 43.4 mL, 43.4 mmol). Care was taken to ensure reaction temperature did not exceed −70 °C during addition. The solution was stirred for 2 h at −78 °C and was carefully quenched by addition of acetone (10 mL) and satd NH_4Cl (10 mL) whilst again being careful to maintain a reaction temperature below −70 °C. The solution was then warmed to rt, filtered, and the solvent removed under reduced pressure. The resultant crude oil was purified by flash chromatography (10% EtOAc/hexanes) yielding the title compound **7b** as a colourless oil (4.49 g, 97%). $[\alpha]_D^{22}$ −40.7 (*c* 2.21, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (3H, t, J=6.9 Hz, CH_2CH_3), 1.32–1.91 (4H, m, 2×C8H_2), 4.28 (1H, apparent q, J=7.2 Hz, C*H*N), 5.01 (2H, s, CH_2Ph), 5.50 (1H, d, J=6.6 Hz, N*H*), 7.26–7.35 (5H, m, Ar*H*), 9.54 (1H, s, *H*C=O). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 18.8, 31.4, 60.4, 67.4, 128.3, 128.4, 128.7, 136.4, 156.3, 199.6. IR (neat) υ_{max} 3332, 3066, 3033, 2961, 2934, 2874, 1712 (broad), 1521, 1456, 1405, 1381, 1339, 1256, 1179, 1065, 1028, 912, 843, 755, 698, 666 cm^{-1}. MS *m*/*z* 257.9 (M+Na$^+$). HRMS *m*/*z* calcd for $C_{13}H_{17}NO_3Na^+$= 258.1106. Found: *m*/*z* 258.1112. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.4; H, 7.3; N, 6.0%. Found: C, 66.3; H, 7.3; N, 6.1%.

4.1.6. Ethyl (4*Z*)-(6*R*)-6-*tert*-butoxycarbonylaminonon-4-enoate (8a). To a stirred suspension of the triphenylphosphonium salt of ethyl 4-bromobutyrate (23.9 g, 52.2 mmol) in THF (150 mL) at 0 °C was added, dropwise, sodium bistrimethylsilylamide (1 M in THF, 52.2 mL, 52.2 mmol). Stirring continued at 0 °C for 1 h before aldehyde **7a** (3.00 g, 17.4 mmol) in THF (30 mL) was added dropwise over 10 min. The solution was then stirred at 0 °C for a further hour, after which time it was diluted with ether (100 mL) and poured into satd NH_4Cl (100 mL). The organic phase was separated from the aqueous phase and the aqueous phase extracted with ether (3×50 mL). The combined organic extracts were washed (brine), dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure. The resulting crude yellow oil was subjected to flash chromatography (20% EtOAc/hexanes) to yield the title compound **8a** as a colourless oil (3.91 g, 75%). $[\alpha]_D^{22}$ −19.2 (*c* 1.34, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, t, J=6.9 Hz, CH_2CH_3), 1.21 (3H, t, J=7.2 Hz, CH_2CH_3 ethyl ester), 1.26–1.53 (4H, m, 2×CH_2), 1.39 (9H, s, $C(CH_3)_3$), 2.28–2.46 (4H, m, 2×CH_2), 4.06 (2H, q, J=7.2 Hz, CH_2CH_3 ethyl ester), 4.28 (1H, m, C*H*N), 4.45 (1H, br s, N*H*), 5.18 (1H, apparent t, J=9.9 Hz, *H*C=C), 5.40 (m, 1H, C=C*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 14.6, 19.3, 23.1, 23.5, 28.7, 34.5, 38.5, 60.6, 79.3, 129.8,

132.2, 155.2, 173.1. IR (neat) υ_{max} 3376, 2977, 2933, 2874, 1733, 1714, 1514, 1456, 1391, 1367, 1300, 1246, 1174, 1114, 1078, 1050, 699, 868, 773, 741 cm^{-1}. MS *m/z* 322.3 ($M+Na^+$). HRMS *m/z* calcd for $C_{16}H_{29}NO_4Na^+$ = 322.1994. Found: *m/z* 322.1981. Anal. Calcd for $C_{16}H_{29}NO_4$: C, 64.2; H, 9.8; N, 4.7%. Found: C, 63.7; H, 9.7; N, 4.8%.

4.1.7. Ethyl (4*Z*)-(6*R*)-6-benzyloxycarbonylaminonon-4-enoate (8b). To a stirred suspension of the triphenylphosphonium salt of ethyl 4-bromobutyrate (20.5 g, 44.7 mmol) in THF (150 mL) at 0 °C was added, dropwise, sodium bistrimethylsilylamide (1 M in THF, 44.7 mL, 44.7 mmol). Stirring continued at 0 °C for 1 h and after which aldehyde **7b** (3.50 g, 14.9 mmol) in THF (30 mL) was added dropwise over 10 min. The solution was then stirred at 0 °C for another hour, after which time it was diluted with ether (100 mL) and poured into satd NH_4Cl (100 mL). The organic phase was separated from the aqueous phase and the aqueous phase extracted with ether (3×50 mL). The combined organic extracts were washed (brine), dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure. The resulting crude yellow oil was subjected to flash chromatography (20% EtOAc/hexanes) to yield the title compound **8b** as a colourless oil (3.80 g, 78%). $[\alpha]_D^{22}$ −33.0 (*c* 1.55, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (3H, t, *J*=7.1 Hz, CH_2CH_3), 1.24 (3H, t, *J*=7.0 Hz, CH_2CH_3 ethyl ester), 1.28–1.40 (2H, m, CH_2), 1.46–1.58 (2H, m, CH_2), 2.28–2.54 (4H, m, 2×CH_2), 4.11 (2H, q, *J*=7.2 Hz, CH_2CH_3 ethyl ester), 4.39 (1H, m, C*H*N), 4.75 (1H, br s, N*H*), 5.07 (2H, br s, CH_2Ph), 5.21 (1H, m, *H*C=C), 5.47 (1H, m, C=C*H*), 7.26–7.39 (5H, m, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 14.6, 19.3, 23.5, 34.5, 36.2, 48.7, 60.7, 66.8, 128.2, 128.4, 128.7, 130.2, 131.7, 136.7, 155.7, 173.1. IR (neat) υ_{max} 3320, 2923, 2853, 1737, 1681, 1539, 1465, 1424, 1374, 1354, 1307, 1266, 1246, 1199, 1175. 1110, 1082, 1050, 1023, 1002, 723, 696 cm^{-1}. MS *m/z* 356.3 ($M+Na^+$). HRMS *m/z* calcd for $C_{19}H_{27}NO_4Na^+$ = 356.1838. Found: 356.1845. Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.5; H, 8.2; N, 4.2%. Found: C, 68.8; H, 8.2; N, 4.1%.

4.1.8. (4*Z*)-(6*R*)-6-*tert*-Butoxycarbonylaminonon-4-enal (9a). DIBAL-H (1 M in toluene, 21 mL, 21 mmol) was added slowly to a cooled solution of the ester **8a** (2.50 g, 8.35 mmol) in toluene (100 mL) whilst ensuring the reaction temperature did not exceed −70 °C. The solution stirred for 2 h at −78 °C and was carefully quenched by addition of acetone (10 mL) and satd NH_4Cl (10 mL) whilst again being careful to maintain a reaction temperature below −70 °C. The solution then warmed to rt, which induced precipitation of aluminium salts, was filtered and the solvent removed under reduced pressure giving a crude oil, which was subjected to flash chromatography (10% EtOAc/hexanes) to yield the title compound **9a** as a colourless oil (1.81 g, 85%). $[\alpha]_D^{22}$ −16.2 (*c* 1.86, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 0.80 (3H, t, *J*=7.2 Hz, CH_2CH_3), 1.20–1.45 (4H, m, 2×CH_2), 1.34 (9H, s, $C(CH_3)_3$), 2.25–2.48 (4H, m, 2×CH_2), 4.23 (1H, m, C*H*N), 4.48 (1H, d, *J*=7.9 Hz, N*H*), 5.12 (1H, ddq, *J*=10.5, 7.9, 1.3 Hz, *H*C=C), 5.30 (1H, dt, *J*=10.5, 6.8 Hz, C=C*H*), 9.65 (1H, d, *J*=1.4 Hz, *H*C=O). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.8, 17.9, 19.5, 27.3, 37.0, 42.6, 46.6, 80.6, 128.1, 131.3, 154.1, 200.8. IR (neat) υ_{max} 3352, 2963, 2873, 1721, 1694, 1515, 1456, 1392, 1366, 1331, 1246, 1172, 1112, 1080, 1053, 1006, 900, 869, 772 cm^{-1}. MS *m/z* 278.2 ($M+Na^+$). HRMS *m/z* calcd for $C_{14}H_{25}NO_3Na^+$ = 278.1732. Found: *m/z* 278.1738. Anal. Calcd for $C_{14}H_{25}NO_3$: C, 65.9; H, 9.9; N, 5.5%. Found: C, 66.2; H, 10.1; N, 5.5%.

4.1.9. (4*Z*)-(6*R*)-6-Benzyloxycarbonylaminonon-4-enal (9b). DIBAL-H (1 M in toluene, 25 mL, 25 mmol) was added slowly to a cooled solution of the ester **8b** (3.80 g, 11.4 mmol) ensuring the reaction temperature did not exceed −70 °C. The solution stirred for 2 h at −78 °C and was then carefully quenched by addition of acetone (5 mL) and satd NH_4Cl (5 mL) whilst again being careful to maintain a reaction temperature below −70 °C. The solution was warmed to rt, which induced precipitation of aluminium salts, was filtered and the solvent removed under reduced pressure. The resultant crude oil, which was subjected to flash chromatography (10% EtOAc/hexanes) to yield the title compound **9b** as a colourless oil (3.01 g, 91%). $[\alpha]_D^{22}$ −25.6 (*c* 2.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, t, *J*=7.1 Hz, CH_2CH_3), 1.24–1.58 (4H, m, 2×CH_2), 2.32–2.60 (4H, m, 2×CH_2), 4.38 (1H, m, C*H*N), 4.65 (1H, m, N*H*), 5.06 (2H, br s, CH_2Ph), 5.21 (1H, apparent t, *J*=9.9 Hz, HC=C), 5.41 (1H, m, C=CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9, 18.0, 19.6, 36.9, 42.7, 47.4, 65.7, 127.2, 127.6, 127.9, 128.9, 130.9, 135.7, 154.7, 200.9. IR (neat) υ_{max} 3358, 1725, 1689 cm^{-1}. MS *m/z* 312.2 ($M+Na^+$). HRMS *m/z* calcd for $C_{17}H_{23}NO_3Na^+$ = 312.1276. Found: 312.1273. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.6; H, 8.0; N, 4.8%. Found: C, 70.3; H, 8.2; N, 4.7%.

4.1.10. (4*E*)-(6*R*)-6-*tert*-Butoxycarbonylaminonon-4-enal (17). To a solution of ester **8a** (0.50 g, 1.67 mmol) in C_6D_6 was added Ph_2S_2 (72 mg, 0.33 mmol). The solution was then irradiated with UV light for 3 days. Daily monitoring of the reaction by ^1H NMR revealed after 3 days the isomerisation reaction had reached an equilibrium ratio of 7:1 *E*/*Z* alkenes. The solvent was then removed under reduced pressure and the crude oil passed through a short plug of silica gel (20% EtOAc/hexanes). The crude product was immediately dissolved in toluene (50 mL) and cooled to −78 °C. DIBAL (1 M in toluene, 2.5 mL, 2.5 mmol) was slowly added ensuring the reaction temperature did not exceed −70 °C. The solution stirred for 2 h at −78 °C and was then carefully quenched by addition of acetone (2 mL) and satd NH_4Cl (2 mL) whilist again being careful to maintain a reaction temperature below −70 °C. The solution then warmed to rt, which induced precipitation of aluminium salts, was then filtered and the solvent removed under reduced pressure giving a crude oil, which was subjected to flash chromatography (15% EtOAc/hexanes) to yield the title compound **17** (10:1 *E*/*Z*) as a colourless oil (217 mg, 51%). $[\alpha]_D^{22}$ +6.3 (*c* 0.95, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (3H, t, *J*=7.2 Hz, CH_2CH_3), 1.17–1.42 (4H, m, 2×CH_2), 1.38 (9H, s, $C(CH_3)_3$), 2.28 (2H, dtd, *J*=6.4, 5.5, 1.1 Hz, CH_2), 2.46 (2H, dt, *J*=1.4, 5.5 Hz, CH_2), 3.96 (1H, m, C*H*N), 4.42 (1H, m, N*H*), 5.32 (1H, ddt, *J*=15.4, 6.2, 1.3 Hz, C=CH), 5.52 (1H, dtd, *J*=15.4, 6.3, 1.1 Hz, C=CH), 9.70 (1H, t, *J*=1.6 Hz, HC=O). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 19.0, 24.9, 37.7, 28.4, 43.2, 52.1, 79.2, 128.4, 132.5, 155.4, 201.8. IR (neat) υ_{max}

3351, 2960, 2932, 2874, 2723, 1715, 1698, 1520, 1456, 1391, 1366, 1248, 1173, 1079, 1053, 1009, 971, 871, 778 cm^{-1}. MS *m/z* 278.2 ($M+Na^+$). HRMS *m/z* calcd for $C_{14}H_{25}NO_3Na^+$ = 278.1732. Found: *m/z* 278.1728. Anal. Calcd for $C_{14}H_{25}NO_3$: C, 65.9; H, 9.9; N, 5.5%. Found: C, 65.8; H, 10.0; N, 5.6%.

4.1.11. (*R*)-1-Benzyloxy-2-methylpentan-3-one (10a). The known three-step procedure of Paterson and co-workers was followed and yielded the title compound **10a** as a colourless oil (8.78 g, 63% over three steps).[24] $[\alpha]_D^{22}$ −26.7 (*c* 8.0, $CHCl_3$) lit.[24] (−25.8, *c* 8.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.06 (3H, t, *J*=7.6 Hz, CH_2CH_3), 1.09 (3H, d, *J*=7.3 Hz, $CHCH_3$), 2.52 (2H, q, *J*=7.6 Hz, CH_2CH_3), 2.89 (1H, dqd, *J*=8.3, 7.3, 5.8 Hz, $CHCH_3$), 3.43 (1H, dd, *J*=9.4, 5.8 Hz, one of CH_2OBn), 3.62 (1H, dd, *J*=9.4, 8.3 Hz, one of CH_2OBn), 4.45 (1H, d, *J*=12.8 Hz, OCH_2Ph), 4.51 (1H, d, *J*=12.8 Hz, OCH_2Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.6, 13.7, 35.6, 46.4, 72.5, 73.2, 127.8, 128.0, 128.8, 138.6, 214.1.

4.1.12. Benzyl (1*R*,2*Z*,6*R*,7*R*,9*R*)-10-benzyloxy-6-hydroxy-7, 9-dimethyl-8-oxo-1-propyl-dec-2-enyl)-carbamate (11b). The general *anti* aldol procedure of Paterson was applied.[16] To a stirred solution of dicyclohexylboronchloride (11.1 mL, 11.1 mmol, 1 M solution in hexanes) was added ether (20 mL). The solution was cooled to 0 °C and ketone **10a** (1.43 g, 6.93 mmol) and Et_3N (1.74 mL, 12.3 mmol) were added. The solution continued stirring for 2 h at 0 °C and was then cooled to −78 °C (dry ice/acetone bath). To this was added, dropwise, a solution of aldehyde **9b** (3.00 g, 10.4 mmol) in ether (10 mL). The solution continued stirring at −78 °C for 4 h before being transferred to a freezer (−20 °C) o/n. After removal from the freezer, the solution was diluted with methanol (30 mL) and pH 7 phosphate buffer (30 mL), and cooled to 0 °C. Hydrogen peroxide (12.0 mL, 30% aqueous) was then added dropwise and stirring continued for 3 h at rt. The solution was then diluted with DCM (50 mL) and the aqueous and organic phases separated. The aqueous phase was extracted with DCM (3×30 mL) and the combined organic extracts were washed (brine), dried ($MgSO_4$) and the solvent removed under reduced pressure to give a crude oil, which after flash chromatography (25% EtOAc/hexanes) yielded the title compound **11b** as a colourless oil (2.91 g, 85%). $[\alpha]_D^{22}$ −27.9 (*c* 2.11, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (3H, t, *J*=7.1 Hz, CH_2CH_3), 1.03 (3H, d, *J*=7.0 Hz, $CHCH_3$), 1.08 (3H, d, *J*=7.1 Hz, $CHCH_3$), 1.20–1.41 (2H, m, CH_2), 1.50–1.61 (2H, m, CH_2), 1.69–1.93 (2H, m, CH_2), 2.11–2.28 (2H, m, CH_2), 2.30–2.48 (1H, m, one of CH_2), 2.73 (1H, apparent p, *J*=6.4 Hz, $CHCH_3$), 3.08 (1H, m, $CHCH_3$), 3.43 (1H, dd, *J*=5.0, 8.9 Hz, one of CH_2OBn), 3.60 (1H, m, CHOH), 3.68 (1H, dd, *J*=8.9, 8.7 Hz, one of CH_2OBn), 3.72 (1H, br s, OH), 4.41 (1H, m, CHN), 4.45 (1H, d, *J*=12.0 Hz, one of OCH_2Ph), 4.50 (1H, d, *J*=12.0 Hz, one of OCH_2Ph), 4.69 (1H, br s, NH), 5.08 (2H, s, CBz OCH_2Ph), 5.18 (1H, ddt, *J*=10.7, 7.9, 1.5 Hz, HC═C), 5.49 (dt, *J*=10.7, 7.9 Hz, 1H, C═CH), 7.23–7.38 (m, 10H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.3, 13.8, 14.0, 19.0, 24.2, 34.5, 35.6, 45.8, 48.5, 52.2, 66.7, 72.4, 73.1, 73.4, 127.7, 127.8, 128.2, 128.5, 128.6, 129.6, 130.7, 131.3, 158.1, 217.7. IR (neat) υ_{max} 3363, 3065, 3032, 2933, 2856, 1702, 1529, 1454, 1407, 1364, 1329, 1270, 1070, 1026, 970, 910, 844, 734, 698 cm^{-1}. MS *m/z* 518.3 ($M+Na^+$). HRMS *m/z* calcd for $C_{30}H_{41}NO_5Na^+$ = 518.2882. Found: *m/z* 518.2885. Anal. Calcd for $C_{30}H_{41}NO_5$: C, 72.7; H, 8.3; N, 2.8%. Found: C, 72.5; H, 8.4; N, 3.0%.

4.1.13. *tert*-Butyl (1*R*,2*Z*,6*R*,7*R*,9*R*)-(10-benzyloxy-6-hydroxy-7,9-dimethyl-8-oxo-1-propyl-dec-2-enyl)-carbamate (11a). The general procedure of Paterson was followed.[16] To a stirred solution of dicyclohexylboronchloride (11.6 mL, 11.6 mmol, 1 M solution in hexanes) was added ether (20 mL). The solution was cooled to 0 °C and ketone **10a** (1.49 g, 7.27 mmol) and Et_3N (1.81 mL, 12.8 mmol) were added. The solution continued stirring for 2 h at 0 °C and was then cooled to −78 °C (dry ice/acetone bath) after which a solution of aldehyde **9a** (2.32 g, 9.09 mmol) in ether (10 mL) was added dropwise. The solution continued stirring at −78 °C for 4 h before being transferred to a freezer (−20 °C) o/n. After removal from the freezer, the solution was diluted with methanol (30 mL) and pH 7 phosphate buffer (30 mL), and cooled to 0 °C. Hydrogen peroxide (10 mL, 30% aqueous) was then added dropwise and stirring continued for 3 h at rt. The solution was then diluted with DCM (50 mL) and the aqueous and organic phases separated. The aqueous phase was extracted with DCM (3×30 mL) and the combined organic extracts were washed (brine), dried ($MgSO_4$) and the solvent removed under reduced pressure to give a crude oil, which after flash chromatography (20% EtOAc/hexanes) yielded the title compound **11a** as a colourless oil (2.01 g, 60%). $[\alpha]_D^{22}$ −19.1 (*c* 2.65, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (3H, t, *J*=7.1 Hz, CH_2CH_3), 1.04 (3H, d, *J*=7.0 Hz, $CHCH_3$), 1.08 (3H, d, *J*=7.1 Hz, $CHCH_3$), 1.11–1.39 (2H, m, CH_2), 1.39 (9H, s, $C(CH_3)_3$), 1.68–1.79 (2H, m, CH_2), 1.73–1.95 (2H, m, CH_2), 2.10–2.23 (1H, m, one of CH_2), 2.35–2.49 (1H, m, one of CH_2), 2.75 (1H, dq, *J*=7.0, 7.1 Hz, $CHCH_3$), 3.06 (1H, ddq, *J*=5.2, 8.9, 7.0 Hz, $CHCH_3$), 3.43 (1H, dd, *J*=5.2, 8.9 Hz, one of CH_2OBn), 3.62 (1H, m, CHOH), 3.67 (1H, dd, *J*=8.9, 8.9 Hz, one of CH_2OBn), 3.72 (1H, m, OH), 4.33 (1H, m, CHN), 4.42 (1H, m, NH), 4.44 (1H, d, *J*=12.1 Hz, one of OCH_2Ph), 4.50 (1H, d, *J*=12.1 Hz, one of OCH_2Ph), 5.16 (1H, ddt, *J*=10.6, 9.3, 1.3 Hz, HC═C), 5.47 (1H, dt, *J*=10.6, 8.0 Hz, C═CH), 7.25–7.37 (5H, m, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.3, 12.6, 12.9, 18.7, 27.5, 29.1, 34.9, 37.9, 39.1, 40.4, 52.8, 72.5, 74.1, 75.7, 79.6, 125.5, 126.7, 126.8, 127.4, 127.8, 136.9, 154.5, 216.3. IR (neat) υ_{max} 3381, 2986, 2933, 2873, 1698, 1498, 1455, 1391, 1366, 1329, 1247, 1172, 1099, 1006, 755, 698, 666 cm^{-1}. MS *m/z* 484.4 ($M+Na^+$). HRMS *m/z* calcd for $C_{27}H_{43}NO_5Na^+$ = 484.3039. Found: *m/z* 484.3031. Anal. Calcd for $C_{27}H_{43}NO_5$: C, 70.3; H, 9.4; N, 3.0%. Found: C, 70.6; H, 9.2; N, 3.1%.

4.1.14. *tert*-Butyl (1*R*,2*E*,6*R*,7*R*,9*R*)-(10-benzyloxy-6-hydroxy-7,9-dimethyl-8-oxo-1-propyl-dec-2-enyl)-carbamate (18). The general procedure of Paterson was followed.[16] To a stirred solution of dicyclohexylboronchloride (1.25 mL, 1.25 mmol, 1 M solution in hexanes) was added ether (2 mL). The solution was cooled to 0 °C and ketone **10a** (161 mg, 0.78 mmol) and Et_3N (195 μl, 1.38 mmol) were added. The solution continued stirring for 2 h at 0 °C and was then cooled to −78 °C (dry ice/acetone bath) after which a solution of aldehyde **17** (250 mg, 0.98 mmol) in ether (1 mL) was added dropwise.

The solution continued stirring at −78 °C for 4 h before being transferred to a freezer (−20 °C) o/n. After removal from the freezer, the solution was diluted with methanol (3 mL) and pH 7 phosphate buffer (3 mL), and cooled to 0 °C. Hydrogen peroxide (1 mL, 30% aqueous) was then added dropwise and stirring continued for 3 h at rt. The solution was then diluted with DCM (5 mL) and the aqueous and organic phases separated. The aqueous phase was extracted with DCM (3×10 mL) and the combined organic extracts were washed (brine), dried ($MgSO_4$) and the solvent removed under reduced pressure to give a crude oil, which after flash chromatography (20% EtOAc/hexanes) yielded the title compound **18** as a colourless oil (180 mg, 50%). $[\alpha]_D^{21}$ +8.5 (*c* 1.76, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, t, *J*=7.1 Hz, CH_2CH_3), 1.02 (3H, d, *J*=7.0 Hz, $CHCH_3$), 1.10 (3H, d, *J*=7.1 Hz, $CHCH_3$), 1.18–1.38 (4H, m, 2×CH_2), 1.43 (9H, s, $C(CH_3)_3$), 1.48–1.64m (2H, m, CH_2), 2.00–2.25 (2H, m, CH_2), 2.69 (1H, dq, *J*=7.1, 7.1 Hz, $CHCH_3$), 3.05 (1H, ddq, *J*=4.9, 8.9, 7.0 Hz, $CHCH_3$), 3.40 (1H, dd, *J*=4.9, 8.9 Hz, one of CH_2OBn), 3.68 (1H, dd, *J*=8.9, 8.9 Hz, one of CH_2OBn), 3.68 (1H, br s, O*H*), 3.96 (1H, m, C*H*N), 4.40–4.46 (1H, m, N*H*), 4.43 (1H, d, *J*=12.0 Hz, CH_2Ph), 4.48 (1H, d, *J*=12.0 Hz, CH_2Ph), 5.31 (1H, dd, *J*=15.3, 6.4 Hz, *H*C=C), 5.54 (1H, dt, *J*=15.3, 6.7 Hz, C=C*H*), 7.20–7.36 (5H, m, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 14.1, 14.3, 19.4, 28.8, 29.0, 34.6, 38.2, 45.9, 52.4, 72.7, 73.2, 73.8, 79.5, 128.0, 128.1, 128.8, 130.7, 131.9, 137.2, 155.8, 218.2. IR (neat) υ_{max} 3444, 2978, 2935, 2875, 1706, 1498, 1456, 1391, 1367, 1244, 1168, 1076 cm^{-1}. MS *m*/*z* 484.3 ($M+Na^+$). HRMS *m*/*z* calcd for $C_{27}H_{43}NO_5Na^+$= 484.3039. Found: 484.3029. Anal. Calcd for $C_{27}H_{43}NO_5$: C, 70.3; H, 9.4; N, 3.0%. Found: C, 70.8; H, 9.3; N, 3.2%.

4.1.15. Benzyl (9*S*,8*S*,7*R*,6*R*,2*Z*,1*R*)-(10-benzyloxy-6,8-dihydroxy-7,9-dimethyl-1-propyl-dec-2-enyl)-carbamate (12b). The general procedure of Evans was followed.[18] To a solution of $Me_4NBH(OAc)_3$ (12.6 g, 28.3 mmol) in dry 1:1 acetonitrile/AcOH (10 mL) cooled to −15 °C was added a solution of aldol adduct **11b** (2.80 g, 5.65 mmol) in dry 1:1 acetonitrile/AcOH (10 mL). The solution was stirred for 4 h at −15 °C before being quenched by sodium potassium tartrate solution (0.5 M, 40 mL) and diluted with DCM (20 mL). The aqueous phase was separated from the organic phase and extracted with DCM (3×10 mL). The combined organics were then washed (satd $NaHCO_3$), dried ($Mg(SO_4)$) and the solvent removed under reduced pressure to give a crude oil, which upon purification by flash chromatography (40% EtOAc/hexanes) yielded the title compound **12b** as a colourless oil (2.21 g, 78%). $[\alpha]_D^{22}$ −59.9 (*c* 1.45, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76 (3H, d, *J*=7.0 Hz, $CHCH_3$), 0.89 (3H, t, *J*=7.5 Hz, CH_2CH_3), 0.99 (3H, d, *J*=7.1 Hz, $CHCH_3$), 1.21–1.45 (4H, m, 2×CH_2), 1.45–1.91 (4H, m, CH_2), 2.05–2.43 (2H, m, CH_2), 3.49–3.65 (4H, m, 2×C*H*OH and CH_2OBn), 3.85 (1H, d, *J*=12.1 Hz, O*H*), 4.31–4.40 (1H, m, C*H*N), 4.45 (1H, m, O*H*), 4.52 (2H, br s, CH_2Ph), 4.75 (1H, br s, N*H*), 5.08 (2H, s, CH_2Ph CBz), 5.19 (1H, dd, *J*=9.3, 6.4 Hz, *H*C=C), 5.52 (1H, m, C=C*H*), 7.23–7.38 (m, 10H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.9, 14.3, 14.7, 19.8, 27.4, 36.8, 36.3, 36.5, 37.9, 46.4, 65.9, 70.2, 71.9, 76.5, 77.1, 128.4, 128.5, 128.8, 130.8, 131.3, 137.7, 156.7. IR (neat) υ_{max} 3439, 2961, 2940, 2873, 1710, 1506, 1455, 1333, 1270, 1074, 1028, 975, 909, 733, 698, 648 cm^{-1}. MS *m*/*z* 520.4 ($M+Na^+$). HRMS *m*/*z* calcd for $C_{30}H_{43}NO_5Na^+$=520.3039. Found: 520.3033. Anal. Calcd for $C_{30}H_{43}NO_5$: C, 72.4; H, 8.7; N, 2.8%. Found: C, 72.5; H, 9.0; N, 2.7%.

4.1.16. *tert*-Butyl (9*S*,8*S*,7*R*,6*R*,2*E*,1*R*)-(10-benzyloxy-6,8-dihydroxy-7,9-dimethyl-1-propyl-dec-2-enyl)-carbamate (19). The general procedure of Evans was followed.[18] To a solution of $Me_4NBH(OAc)_3$ (0.5 g, 1.9 mmol) in dry 1:1 acetonitrile/AcOH (3.6 mL) cooled to −15 °C was added a solution of aldol adduct **18** (180 mg, 0.39 mmol) in dry 1:1 acetonitrile/AcOH (3.6 mL). The solution was stirred for 4 h at −15 °C before being quenched by sodium potassium tartrate solution (0.5 M, 5 mL) and diluted with DCM (5 mL). The aqueous phase was separated from the organic phase and extracted with DCM (3×5 mL). The combined organics were then washed (satd $NaHCO_3$), dried ($Mg(SO_4)$) and the solvent removed under reduced pressure to give a crude oil, which upon purification by flash chromatography (40% EtOAc/hexanes) yielded the title compound **19** as a colourless oil (166 mg, 92%). $[\alpha]_D^{21}$ +2.4 (*c* 1.66, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.72 (3H, d, *J*=6.9 Hz, $CHCH_3$), 0.88 (3H, t, *J*=7.4 Hz, CH_2CH_3), 0.98 (3H, d, *J*=7.0 Hz, $CHCH_3$), 1.18–1.40 (4H, m, 2×CH_2), 1.41 (9H, s, $C(CH_3)_3$), 1.53–1.78 (4H, m, 2×CH_2), 1.89–2.29 (2H, m, CH_2), 3.40–3.72 (5H, m, 2×C*H*OH, CH_2OBn and O*H*), 3.86 (1H, d, *J*=13.6 Hz, O*H*), 4.00 (1H, m, C*H*N), 4.37 (1H, br s, N*H*), 4.50 (2H, s, CH_2Ph), 5.34 (1H, dd, *J*=15.2, 5.1 Hz, *H*C=C), 5.56 (1H, dt, *J*=15.2, 6.5 Hz, C=C*H*), 7.18–7.34 (5H, m, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.5, 13.3, 14.2, 19.1, 28.5, 29.4, 35.5, 35.9, 36.5, 37.9, 52.3, 72.3, 72.7, 75.6, 76.5, 77.7, 127.5, 127.6, 128.3, 130.8, 131.3, 137.7, 156.7. IR (neat) υ_{max} 3450, 3349, 2931, 2873, 1694, 1504, 1455, 1392, 1366, 1333, 1248, 1172, 1098, 971, 870, 754, 698, 665 cm^{-1}. MS *m*/*z* 486.4 ($M+Na^+$). HRMS *m*/*z* calcd for $C_{27}H_{45}NO_5Na^+$486.3195. Found: 486.3194. Anal. Calcd for $C_{27}H_{45}NO_5$: C, 69.9; H, 9.8; N, 3.0%. Found: C, 70.3; H, 10.0; N, 3.2%.

4.1.17. *tert*-Butyl (9*S*,8*S*,7*R*,6*R*,2*Z*,1*R*)-(10-benzyloxy-6,8-dihydroxy-7,9-dimethyl-1-propyl-dec-2-enyl)-carbamate (12a). The general procedure of Evans was followed.[18] To a solution of $Me_4NBH(OAc)_3$ (1.34 g, 3.0 mmol) in dry 1:1 acetonitrile/AcOH (5 mL) cooled to −15 °C was added a solution of aldol adduct **11a** (0.5 g, 1.08 mmol) in dry 1:1 acetonitrile/AcOH (5 mL). The solution was stirred for 4 h at −15 °C before being quenched by sodium potassium tartrate solution (0.5 M, 10 mL) and diluted with DCM (10 mL). The aqueous phase was separated from the organic phase and extracted with DCM (3×5 mL). The combined organics were then washed (satd $NaHCO_3$), dried ($Mg(SO_4)$) and the solvent removed under reduced pressure to give a crude oil, which upon purification by flash chromatography (40% EtOAc/hexanes) yielded the title compound **12a** as a colourless oil (340 mg, 68%). $[\alpha]_D^{21}$ +1.3 (*c* 3.75, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (3H, d, *J*=6.6 Hz, $CHCH_3$), 0.90 (3H, t, *J*=7.3 Hz, CH_2CH_3), 0.96 (3H, d, *J*=6.9 Hz, $CHCH_3$), 1.22–1.38 (4H, m, 2×CH_2), 1.41 (9H, s, $C(CH_3)_3$), 1.44–1.56 (4H, m, 2×CH_2), 2.19–2.38 (1H, m, one of CH_2), 2.45–2.65 (1H, m, one of CH_2), 3.43–3.61 (2H, m, C*H*OH and one of CH_2OBn), 3.61–3.73 (1H, m, one of CH_2OBn), 3.86 (1H, d, *J*=9.6 Hz, O*H*), 4.14 (1H, s, O*H*),

4.35 (1H, m, C*H*N), 4.50 (1H, m, C*H*OH), 4.51 (1H, d, J= 13.2 Hz, one of CH_2Ph), 4.55 (1H, d, J=13.2 Hz, one of CH_2Ph), 4.62 (1H, br s, N*H*), 5.16 (1H, apparent t, J= 10.2 Hz, *H*C=C), 5.34 (1H, dt, J=10.2 Hz, 4.5 Hz, C=C*H*), 7.22–7.39 (5H, m, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.7, 13.8, 14.1, 19.1, 23.8, 28.6, 35.6, 36.7, 38.1, 38.9, 48.1, 73.1, 73.5, 74.3, 75.1, 80.0, 127.7, 127.8, 128.6, 130.9, 132.2, 138.7, 155.8. IR (neat) υ_{max} 3430, 2962, 2932, 2873, 1688, 1520, 1455, 1366, 1247, 1170, 1086, 736, 697 cm^{-1}. MS *m/z* 486.5 (M+Na$^+$). HRMS *m/z* calcd for $C_{27}H_{45}NO_5Na^+$= 486.3195. Found: 486.3187. Anal. Calcd for $C_{27}H_{45}NO_5$: C, 69.9; H, 9.8; N, 3.0%. Found: C, 70.1; H, 9.7; N, 2.8%.

4.1.18. *tert*-Butyl (3′*S*,2′*S*,1′*S*,5″*R*,2″*R*,1α*R*,1*R*)-((1-{[5″-(4′-benzyloxy-2′-hydroxy-1′,3′-dimethyl-butyl)-tetrahydro-furan-2″-yl]-chloromercurio-methyl}-butyl)-carbamate (13a). To a stirred solution of diol **12a** (50 mg, 0.11 mmol) in acetonitrile (3 mL) at 5 °C was added mercury (II) acetate (120 mg, 0.38 mmol). The hetereogeneous mixture was stirred for 5 h at 5 °C. Brine (3 mL) was then added and stirring continued for another 1 h. The organic and aqueous phases were then separated and the aqueous phase extracted with DCM (3×2 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure to give a 10:1 mixture of chloromercurials *trans*-**13a** and *cis*-**13b**, which after purification by flash chromatography (25% EtOAc/hexanes) afforded the title compound **13a** (72 mg, 92%) as a colourless oil. $[\alpha]_D^{21}$ +24.5 (*c* 1.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (3H, d, J=6.9 Hz, CHCH_3), 0.83 (3H, d, J=6.9 Hz, CHCH_3), 0.89 (3H, t, J=7.2 Hz, CH_2CH_3), 1.22–1.71 (7H, m, 2×CH_2, 2×C*H*CH_3 and one of CH_2), 1.34 (9H, s, C(CH_3)$_3$), 1.88–2.17 (3H, m, three of 2×CH_2), 2.99 (1H, apparent t, J=4.1 Hz, C*H*Hg), 3.39 (1H, br s, O*H*), 3.53 (1H, d, J=9.8 Hz, one of CH_2OBn), 3.59 (1H, d, J=9.8 Hz, one of CH_2OBn), 3.75 (1H, apparent dt, J=2.3, 9.2 Hz, C*H*OH), 3.87 (1H, m, C*H*N), 4.05 (1H, m, *H*COC), 4.25 (1H, dt, J=4.1, 5.0 Hz, *H*COC), 4.48 (1H, d, J=11.8 Hz, one of CH_2Ph), 4.55 (1H, d, J= 11.8 Hz, one of CH_2Ph), 4.89 (1H, d, J=8.4 Hz, N*H*), 7.22–7.34 (5H, m, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.8, 12.6, 12.8, 18.7, 27.5, 29.6, 34.2, 34.9, 37.9, 39.1, 52.8, 66.1, 72.4, 74.1, 74.9, 77.0, 78.7, 79.5, 126.6, 126.7, 127.3, 136.9, 154.5. IR (neat) υ_{max} 3440, 3011, 2967, 2932, 2872, 1698, 1501, 1455, 1392, 1367, 1247, 1216, 1167, 1076, 1028, 997, 758, 698, 667 cm^{-1}. MS *m/z* 722.3 (M+Na$^+$). HRMS *m/z* calcd for $C_{27}H_{44}ClHgNO_5Na^+$=722.2512. Found: 722.2500. Anal. Calcd for $C_{27}H_{44}ClHgNO_5$: C, 46.4; H, 6.4, N, 2.0%. Found: C, 46.4; H, 6.5; N, 1.9%.

4.1.19. *tert*-Butyl (3′*R*,2′*R*,1′*R*,5″*R*,1α*R*,1*R*)-(1-{[5″-(4′-benzyloxy-1′,3′-dimethyl-2′-oxo-butyl)-tetrahydro-furan-2″-yl]-chloromercurio-methyl}-butyl)-carbamate (14a). To a stirred solution of aldol adduct **11a** (100 mg, 0.22 mmol) in acetonitrile (2 mL) at 5 °C was added mercury (II) acetate (138 mg, 0.43 mmol). The hetereogeneous mixture was stirred for 2 h at 5 °C. Brine (3 mL) was then added and stirring continued for another 1 h. The organic and aqueous phases were then separated and the aqueous phase extracted with DCM (3×2 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure to give a 9:1 mixture of chloromercurials *trans*-**14a** and *cis*-**14a**, which after purification flash chromatography (25% EtOAc/hexanes) afforded the title compound **14a** (110 mg, 73%) as a semi-crystalline colourless oil. $[\alpha]_D^{21}$ +6.7 (*c* 3.02, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (3H, t, J= 7.2 Hz, CH_2CH_3), 0.97 (3H, d, J=6.9 Hz, CHCH_3), 1.09 (3H, d, J=7.0 Hz, CHCH_3), 1.21–61 (6H, m, 3×CH_2), 2.01–2.21 (2H, m, CH_2), 2.72–2.82 (1H, m, C*H*CH$_3$), 2.96–3.07 (2H, m, C*H*CH$_3$ and C*H*Hg), 3.47 (1H, dd, J=5.5, 9.0 Hz, one of CH_2OBn), 3.63 (1H, dd, J=7.7, 9.0 Hz, one of CH_2OBn), 3.84–3.89 (1H, m, C*H*N), 4.10–4.21 (1H, m, *H*COC), 4.29–4.35 (1H, m, *H*COC), 4.36 (1H, d, J= 12.0 Hz, one of CH_2Ph), 4.50 (1H, d, J=12.0 Hz, one of CH_2Ph), 4.79 (1H, apparent d, J=7.1 Hz, N*H*), 7.21–7.38 (m, 5H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.8, 13.6, 14.1, 19.9, 30.6, 35.4, 39.0, 47.1, 51.5, 54.1, 67.2, 72.7, 73.5, 79.0, 80.1, 81.0, 127.8, 127.9, 128.6, 138.4, 155.6, 215.1. IR (neat) υ_{max} 3362, 2927, 1709, 1678, 1521, 1455, 1367, 1295, 1251, 1169, 1114, 1050, 994, 911, 730, 695 cm^{-1}. MS *m/z* 720.2 (M+Na$^+$). HRMS *m/z* calcd for $C_{27}H_{42}ClHgNO_5Na^+$=720.2355. Found: 720.2341. Anal. Calcd for $C_{27}H_{42}ClHgNO_5$: C, 46.6; H, 6.1; N, 2.0%. Found: C, 46.3; H, 6.3; N, 2.2%.

4.1.20. *tert*-Butyl (3′*R*,1′*R*,5″*R*,2″*R*,1α*R*,1*R*)-(1-{[5″-(4′-benzyloxy-1′,3′-dimethyl-2′-oxo-butyl)-tetrahydro-furan-2″-yl]-phenylselanyl-methyl}-butyl)-carbamate (15a). To a stirred solution of PhSeBr (102 mg, 0.43 mmol) in DCM (2 mL) at −78 °C was added a solution of ketone **11a** (100 mg, 0.22 mmol) in DCM (2 mL). The homogeneous mixture stirred for 4 h at −78 °C before satd $NaHCO_3$ (4 mL) was added. The organic and aqueous phases were then separated and the aqueous phase extracted with DCM (3×3 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure to give a 5:1 mixture of selenylphenyls *trans*-**15a** and *cis*-**15b**, which after purification by flash chromatography (20% EtOAc/hexanes) afforded pure **15a** (70 mg, 52%) as pale yellow oil. $[\alpha]_D^{21}$ −23.8 (*c* 1.04, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, J=7.3 Hz, CH_2CH_3), 0.98 (3H, d, J=6.0 Hz, CHCH_3), 1.09 (3H, d, J=6.9 Hz, CHCH_3), 1.21–1.65 (4H, m, 2×CH_2), 2.00–2.14 (4H, m, 2×CH_2), 2.77–2.84 (1H, m, C*H*CH$_3$), 3.01–3.18 (1H, m, C*H*CH$_3$), 3.50 (1H, dd, J=5.7, 9.1 Hz), 3.52 (1H, m, C*H*Se), 3.64 (1H, dd, J=7.4, 9.1 Hz, one of CH_2OBn), 3.87 (1H, m, C*H*N), 4.18 (1H, apparent dd, J= 4.9, 9.4 Hz, *H*COC), 4.22–4.29 (1H, m, *H*COC), 4.46 (1H, d, J=12.0 Hz, one of CH_2Ph), 4.51 (1H, d, J=12.0 Hz, one of CH_2Ph), 5.00 (1H, d, J=9.3 Hz, N*H*), 7.17–7.38 (8H, m, Ar*H*), 7.52–7.58 (2H, m, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.6, 12.9, 13.9, 19.5, 28.4, 30.8, 31.7, 34.6, 46.6, 51.6, 55.0, 59.3, 72.6, 73.2, 78.9, 79.6, 82.7, 126.9, 127.5, 127.7, 128.3, 129.0, 130.1, 133.6, 138.2, 156.1, 215.4. IR (neat) υ_{max} 3378, 2966, 2945, 1706, 1687, 1518, 1455, 1365, 1247, 1171, 1076, 1023, 738, 696 cm^{-1}. MS. *m/z* 640.2 (M+Na$^+$). HRMS *m/z* calcd for $C_{33}H_{47}NO_5SeNa^+$=640.2517. Found: 640.2504. Anal. Calcd for $C_{33}H_{47}NO_5Se$: C, 64.3; H, 7.7, N, 2.3%. Found: C, 64.6; H, 7.8; N, 2.5%.

4.1.21. *tert*-Butyl (3′*S*,2′*S*,1′*S*,5″*R*,2″*R*,1α*S*,1*R*)-(1-{[5″-(4′-benzyloxy-2′-hydroxy-1′,3′-dimethyl-butyl)-tetrahydro-furan-2″-yl]-chloromercurio-methyl}-butyl)-carbamate (20a). To a stirred solution of (*E*)-diol **19** (166 mg, 0.36 mmol) in acetonitrile (4 mL) at 0 °C was

added mercury (II) acetate (215 mg, 0.72 mmol). The hetereogeneous mixture was stirred for 5 h at 5 °C before warming to rt and stirring o/n. Brine (4 mL) was then added and stirring continued for another 1 h. The organic and aqueous phases were then separated and the aqueous phase extracted with DCM (3×3 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure to give a 4:1 mixture of chloromercurials *trans*-**20a** and *cis*-**20b**, which after purification of the mixutre by flash chromatography (25% EtOAc/hexanes) gave pure **20a** (150 mg, 60%) as a colourless oil. $[\alpha]_D^{21}$ +15.1 (*c* 2.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79 (3H, d, J=5.5 Hz, CHCH_3), 0.81 (3H, d, J=6.8 Hz, CHCH_3), 0.88 (3H, t, J=7.3 Hz, CH_2CH_3), 1.11–1.65 (7H, m, 2×CH_2, 2×CHCH$_3$ and one of CH_2), 1.85–1.98 (1H, m, one of CH_2), 2.02–2.10 (1H, m, one of CH_2), 2.15–2.29 (1H, m, one of CH_2), 2.85 (1H, apparent t, J=4.5 Hz, CHHg), 3.41 (1H, br s, OH), 3.53 (1H, d, J=11.5 Hz, one of CH_2OBn), 3.72 (1H, dt, J=11.5, 2.3 Hz, one of CH_2OBn), 3.81–3.99 (1H, m, CHOH), 3.99–4.05 (1H, m, HCOC), 4.18–4.29 (1H, m, HCOC), 4.47 (1H, d, J=11.9 Hz, one of CH_2Ph), 4.52 (1H, d, J=11.9 Hz, one of CH_2Ph), 4.80 (1H, d, J=8.2 Hz, NH), 7.21–7.33 (5H, m, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.8, 12.6, 12.9, 18.5, 27.6, 29.8, 34.6, 35.1, 37.7, 39.0, 51.9, 64.2, 72.4, 73.9, 74.7, 77.7, 80.8, 79.8, 126.6, 126.8, 127.4, 137.0, 154.4. IR (neat) υ_{max} 3448, 3011, 2966, 2932, 2873, 1686, 1499, 1455, 1392, 1367, 1248, 1216, 1166, 1092, 1047, 1092, 1047, 951, 872, 759, 699, 668 cm^{-1}. MS *m*/*z* 722.2 (M+Na$^+$). HRMS *m*/*z* calcd for $C_{27}H_{44}ClHgNO_5Na^+$=722.2512. Found: 722.2508. Anal. Calcd for $C_{27}H_{44}ClHgNO_5$: C, 46.4; H, 6.4; N, 2.0%. Found: C, 46.3; H, 6.6; N, 2.1%.

4.1.22. Benzyl (9*S*,8*R*,7*R*,6*R*,2*Z*,1*R*) [10-benzyloxy-6,8-bis-(*tert*-butyl-dimethyl-silanyloxy)-7,9-dimethyl-1-propyl-dec-2-enyl]-carbamate (23). To a solution of diol **12b** (100 mg, 0.20 mmol) in THF (3 mL) was added 2,6-lutidine (155 µl, 1.34 mmol) and TBSOTf (230 µl, 1.0 mmol). The solution stirred for 4 h at rt before being quenched by satd NH_4Cl (5 mL). The solution was diluted with DCM (5 mL) and the organic and aqueous phases separated. The aqueous phase was extracted with DCM (3×3 mL) and the combined organic extracts were washed (brine), dried ($MgSO_4$) and the solvent removed under reduced pressure to give a crude oil, which after purification by flash chromatography (25% EtOAc/hexanes) yielded the title compound **23** (101 mg, 69%) as a colourless oil. $[\alpha]_D^{22}$ −4.2 (*c* 1.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (12H, s, 2×Si(CH_3)$_2$), 0.85–0.90 (24H, m, 2×SiC(CH_3)$_3$, CHCH_3 and CH_2CH_3), 0.96 (3H, d, J=6.9 Hz, CHCH_3), 1.24–1.60 (6H, m, 3×CH_2), 1.91–2.31 (3H, m, CH_2 and CHCH$_3$), 3.25 (1H, dd, J=8.1, 9.2 Hz, one of CH_2OBn), 3.53 (1H, dd, J=5.2, 9.2 Hz, CH_2OBn), 3.59–3.65 (2H, m, 2×CHOTBS), 4.36 (1H, m, CHN), 4.44 (1H, d, J=12.0 Hz, CH_2Ph), 4.49 (1H, d, J=12.0 Hz, CH_2Ph), 4.55 (1H, br s, NH), 5.05 (2H, br s, CH_2Ph CBz), 5.15 (1H, apparent dt, J=10.7, 1.6 Hz, HC=C), 5.43 (1H, dt, J=10.7, 7.0 Hz, C=CH), 7.25–7.33 (10H, m, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.2, −5.2, −4.7, −4.6, 9.6, 12.9, 13.7, 17.1, 17.4, 24.9, 25.1, 31.2, 37.2, 38.5, 40.5, 47.7, 65.5, 71.6, 72.1, 73.1, 73.9, 126.4, 126.5, 126.6, 126.9, 127.3, 127.5, 129.3, 131.4, 135.7, 137.8, 156.1. IR (neat) υ_{max} 3334, 2956, 2930, 2857, 1712, 1498, 1463, 1361, 1339, 1255, 1076, 1005, 835, 772, 734, 694 cm^{-1}. MS *m*/*z* 748.5 (M+Na$^+$). HRMS *m*/*z* calcd for $C_{42}H_{71}NO_5Si_2Na^+$= 748.4768. Found: 748.4765. Anal. Calcd for $C_{42}H_{71}NO_5Si_2$: C, 69.5; H, 9.9; N, 1.9%. Found: C, 69.4; H, 10.0; N, 1.8%.

4.1.23. Benzyl (3′*S*,2′*S*,1′*S*,5″*R*,2″*R*,1α*R*,1*R*)-(1-{[5″-(4′-benzyloxy-2′-hydroxy-1′,3′-dimethyl-butyl)-tetrahydro-furan-2″-yl]-iodo-methyl}-butyl)-carbamate (24). An adaptation of the general iodocyclisation procedure of Bartlett was followed.[21] To a solution of TBS ether **23** (48 mg, 0.07 mmol) in acetonitrile (2 mL) at −10 °C was added a solution of iodine (34 mg, 0.14 mmol) in acetonitrile (2 mL). The solution was stirred for 1 h at −10 °C before being quenched by pH 7 phosphate buffer (5 mL) and satd sodium sulphite solution (2 mL). The solution was then diluted with DCM (5 mL) and the organic and aqueous phases separated. The aqueous phase was extracted with DCM (3×3 mL) and the combined organic extracts were washed (brine), dried ($MgSO_4$) and the solvent removed under reduced pressure to give a 5:1 crude mixture of *cis*/*trans* tetrahydrofurans, which after purification by flash chromatography (25% EtOAc/hexanes) yielded the title compound **24** (101 mg, 69%) as a colourless oil. $[\alpha]_D^{22}$ −4.1 (*c* 0.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (1H, d, J=6.9 Hz, CHCH_3), 0.85 (1H, d, J=6.9 Hz, CHCH_3), 0.93 (3H, t, J=7.3 Hz, CH_2CH_3), 1.30–1.55 (4H, m, 2×CH_2), 1.61–1.72 (2H, m, CH_2), 1.78–2.18 (4H, m, 2×CHCH$_3$ and CH_2), 3.19 (1H, d, J=3.0 Hz, OH), 3.51 (1H, d, J=5.8 Hz, one of CH_2OBn), 3.57–3.71 (1H, m, one of CH_2OBn), 3.57–3.61 (1H, m, CHN), 3.61–3.69 (1H, m, HCOC), 3.72–3.78 (1H, dt, J=9.2, 3.0 Hz, CHOH), 4.10–4.17 (1H, m, HCOC), 4.39 (1H, apparent t, J=3.5 Hz, CHI), 4.42 (1H, d, J=11.8 Hz, one of CH_2Ph), 4.48 (1H, d, J=11.8 Hz, one of CH_2Ph), 5.10 (2H, s, CH_2Ph CBz), 5.48 (1H, d, J=9.0 Hz, NH), 7.24–7.36 (10H, m, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.1, 14.0, 14.1, 19.6, 30.6, 36.2, 36.6, 40.3, 48.6, 56.1, 66.8, 73.5, 75.4, 75.6, 78.5, 82.4, 127.7, 128.0, 128.1, 128.5, 128.6, 128.7, 136.3, 137.5, 155.8. IR (neat) υ_{max} 3450, 3155, 2965, 1794, 1717, 1508, 1466, 1382, 1217, 1095, 912, 731, 651 cm^{-1}. MS *m*/*z* 646.2 (M+Na$^+$). HRMS *m*/*z* calcd for $C_{30}H_{42}INO_5Na^+$= 646.2005. Found: 646.1990. Anal. Calcd for $C_{30}H_{42}INO_5$: C, 57.8; H, 6.8; N, 2.3%. Found: C, 57.5; H, 6.7; N, 2.1%.

4.1.24. Benzyl (3′*S*,2′*S*,1′*S*,5″*R*,2″*S*,1α*S*,1*R*)-(1-{[5″-(4′-benzyloxy-2′-hydroxy-1′,3′-dimethyl-butyl)-tetrahydro-furan-2″-yl]-chloromercurio-methyl}-butyl)-carbamate (25). An adaptation of the cyclisation procedure of Walkup was used.[22] To a solution of bis-TBS ether **23** (100 mg, 0.14 mmol) in acetonitrile (4 mL) at 0 °C was added $Hg(O_2CCF_3)_2$ (71 mg, 0.17 mmol). The solution was warmed to rt and stirred for a further 2 h before being quenched by addition of satd NH_4Cl (4 mL) and brine (4 mL). The solution was then stirred for another 1 h before being diluted with DCM (4 mL) and the organic and aqueous phases separated. The aqueous phase was extracted with DCM (3×3 mL) and the combined organic extracts were washed (brine), dried ($MgSO_4$) and the solvent removed under reduced pressure to give a 4:1 mixture of *cis*/*trans* chloromercurials, which after purification by flash chromatography (20% EtOAc/hexanes) yielded the title compound **25** (52 mg, 51%) as a colourless oil. $[\alpha]_D^{21}$ +11.9 (*c* 2.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79 (3H, d,

J=6.9 Hz, CHCH_3), 0.82 (3H, d, J=6.9 Hz, CHCH_3), 0.87 (3H, t, J=7.0 Hz, CH_2CH_3), 1.26–1.71 (6H, m, 3×CH_2), 1.85–2.21 (4H, m, 2×C*H*CH$_3$ and CH_2), 2.81 (1H, dd, J= 4.5, 6.1 Hz, C*H*Hg), 3.53–3.57 (2H, m, one of CH_2OBn and O*H*), 3.68 (1H, m, one of CH_2OBn), 3.79–3.86 (2H, m, C*H*OH and *H*COC), 3.92–4.01 (1H, m, C*H*N), 4.11–4.17 (1H, m, *H*COC), 4.20 (1H, d, J=11.7 Hz, CH_2Ph), 4.52 (1H, d, J=11.7 Hz, CH_2Ph), 4.97 (1H, d, J=9.6 Hz, N*H*), 7.22–7.32 (10H, m, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.1, 13.5, 14.0, 19.2, 31.1, 31.7, 34.2, 36.1, 40.2, 41.5, 54.2, 67.5, 73.1, 77.1, 75.5, 78.6, 80.6, 81.3, 127.8, 127.8, 127.9, 127.9, 128.2, 128.3, 128.6, 128.7, 136.1, 137.2, 156.2. IR (neat) υ_{max} 3374, 2969, 2933, 1708, 1509, 1455, 1366, 1249, 1169, 1098, 912, 734, 698 cm^{-1}. MS m/z 756.3 (M+Na$^+$). HRMS m/z calcd for $C_{30}H_{42}ClHgNO_5Na^+$=756.2355. Found: 756.2361. Anal. Calcd for $C_{30}H_{42}ClHgNO_5$: C, 49.2; H, 5.8; N, 1.9%. Found: C, 49.1; H, 5.9; N, 2.0%.

4.1.25. Benzyl (3′*S*,2′*S*,1′*S*,5″*R*,2″*S*,1*R*)-{1-[5″-(4′-benzyloxy-2′-hydroxy-1′,3′-dimethyl-butyl)-tetrahydro-furan-2″-ylmethyl]-butyl}-carbamate (3). To a solution of chloromercurial **25** (50 mg, 0.07 mmol) in toluene at rt (2 mL) was added Bu_3SnH (45 μl, 0.17 mmol) and AIBN (7 μmol). Precipitation of metallic mercury occurred almost immediately and stirring continued o/n after which CCl_4 (2 mL) was added and stirring continued for a further 2 h. The solution was then diluted with 25% DCM/hexanes (10 mL) and washed with 5% KF solution (3×5 mL). The organic phase was washed (brine), dried ($MgSO_4$) and the solvent removed under reduced pressure giving a crude grey oil, which after purification by flash chromatography (20% EtOAc/hexanes) yielded the title compound **3** as a colourless oil (27 mg, 79%). $[\alpha]_D^{21}$ −5.1 (c 1.12, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (3H, d, J=7.1 Hz, CHCH_3), 0.88 (3H, d, J=6.9 Hz, CHCH_3), 0.96 (3H, t, J=10.7 Hz, CH_2CH_3), 1.21–1.64 (6H, m, 3×CH_2), 1.88–2.21 (6H, m, 2×CH_2 and 2×C*H*CH$_3$), 3.40 (1H, br s, O*H*), 3.51 (1H, dd, J=6.6, 11.2 Hz, one of CH_2OBn), 3.62 (1H, dd, J=7.2, 11.2 Hz, one of CH_2OBn), 3.78–3.85 (2H, m, C*H*OH and *H*COC), 3.89 (1H, m, C*H*N), 4.15 (1H, m, *H*COC), 4.31 (1H, d, J=10.8 Hz, CH_2Ph), 4.58 (1H, d, J=10.8 Hz, CH_2Ph), 4.78 (1H, d, J=8.2 Hz, N*H*), 7.21–7.38 (10H, m, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.5, 12.3, 12.9, 18.4, 28.4, 30.7, 32.7, 36.4, 40.8, 49.2, 65.9, 72.8, 73.5, 75.6, 77.0, 78.3, 80.2, 80.7, 127.7, 127.8, 127.8, 127.9, 127.9, 128.1, 128.5, 128.9, 136.4, 136.8, 156.7. IR (neat) υ_{max} 3482, 2946, 2917, 2853, 1460, 1348, 1245, 1235, 1145, 1095, 1045, 791, 773 cm^{-1}. MS m/z 520.3 (M+Na$^+$). HRMS m/z calcd for $C_{30}H_{43}NO_5Na^+$=520.3039. Found: 520.3046. Anal. Calcd for $C_{30}H_{43}NO_5$: C, 72.4; H, 8.7; N, 2.8. Found: C, 72.7; H, 8.6; N, 2.8.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.01.005. NOESY spectra of **13a**, **14a**, **15a**, **20a**, **24** and **25** for assignment of *cis*/*trans* tetrahydrofuran stereochemistry. This information is available free of charge via the internet at http://pubs.acs.org.

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Solid-state tubular assemblies of thiolactones: synthesis and structural characterization

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Abstract—The synthesis of cyclic thiolactones, 2,5,8-trithiacyclododecane-1,9-dione (**4**), 2,5,8,14,17,20-hexathiacyclotetracosane-1,9,13,21-tetraone (**5**), 2,5,8-trithiacyclotetradecane-1,9-dione (**6**) and 2,5,8,16,19,22-hexathiacyclooctacosane-1,9,15,23-tetraone (**7**) was achieved by tin-template reaction of 2,2-dibutyl-2-stanna-1,3,6-trithiacyclooctane (**1**) with corresponding diacyl chlorides. The structures of 12-, 14-, 24- and 28-membered ring systems of **4**, **6**, **5**, and **7**, respectively, were investigated by X-ray structure analysis. These investigations revealed that, in the solid-state, thiolactones **4** and **7** form tubular assemblies. However, the crystal structure of **5** forms layered packing dominated by CH···O hydrogen bonds whereas **6** forms three-dimensional network via CH···O hydrogen bonds and van der Waals interactions.

1. Introduction

The chemistry of macrocycles has initiated the development of supramolecular chemistry, in which not only monomeric but also dimeric and oligomeric structures play a central role.[1] Tubular molecular structures have attracted the attention of chemists due to their occurrence in nature and their potential in materials science. Tailor-made tubular assemblies have an important impact on many areas of research, in particular, drug development, molecular electronics and materials science. Recent scientific literature reports inorganic and organic tubular assemblies such as graphite,[2] boron nitride nanotubes,[3] zeolites,[4] polymeric lipid-based tubules,[5] carbohydrate-based nanotubes,[6] cyclic chalcogen alkynes[7] or cyclic peptide nanotubes.[8]

As an extention of our interest in the synthesis and characterization of novel macrocyclic polythiaethers that contain one or more cage moieties within the crown ether framework[9] we have turned to the preparation of macrocyclic polythiolactones.[10a] Our in-depth studies on polythiolactones revealed that some of the molecules form tubular assemblies in the solid-state through weak C–H···O interactions. Thus, we report the synthesis and molecular and crystal structures of the 12-, 14-, 24- and 28-membered cyclic thiolactones determined by X-ray structure analysis.

2. Results and discussion

2.1. Synthesis

To prepare cyclic polythiolactones, we used the strategy via ring-opening condensation of stannapolythiane with diacyl chloride,[10] as shown in Scheme 1.

Stannathiane **1**, prepared from dibutyltin oxide and 2,2′-thiadiethanthiole,[10a] was reacted with glutaryl chloride **2** or pimeloyl chloride **3** to afford di- and tetra-polythiolactones **4**–**7** in good to moderate yields. Table 1 shows that in the reaction of **2** ($n=3$) the product yield is lower than that of **3** ($n=5$). Since all of the products **4**–**7** have large rings, it is likely that the difference in the obtained yields could be due to difference in the reactivity between **2** and **3**. It should be pointed out that efficient macrocyclization can be achieved by proper adjustment of experimental conditions.[11] The reaction conditions were adjusted to favour the formation of dimers.[12] However, the ratio of the products **4**:**5** and **6**:**7** depends on the ring size, Table 1. Thus, the 14-membered di-thiolactone **6** is formed as a major ring product in preference to the 28-membered tetra-thiolactone **7**. On the contrary, the 12-membered di-thiolactone **4** competes equally with the 24-membered tetra-thiolactone **5**, to give

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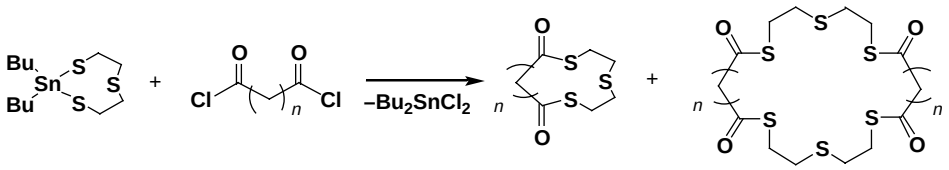

1 **2** $n=3$, **3** $n=5$ **4** $n=3$, **6** $n=5$ **5** $n=3$, **7** $n=5$

Scheme 1. Reagents and conditions: $CHCl_3$ reflux, 2,2′-bipyridyl, rt.

Table 1. Reaction of stannathiane **1** with diacyl chlorides **2** and **3**

Diacyl chloride	Products	Mp (°C)[a]	Ring size	Product ratio[b]	(k'_n)[c]	Yield (%)[d]
2	**4**	113–117	12	1:1	0.03	44
	5	108–109	24		0.28	
3	**6**	118–119	14	3:1	0.20	80
	7	98–100	28		0.70	

[a] Melting points are not corrected.
[b] Determined by HPLC.
[c] HPLC capacity factor of the eluted compound ($k'_n=t_n-t_0/t_0$).
[d] The yield of pure isolated products.

a mixture of products in a 1:1 ratio. The observed formation of thiolactones **4**–**7** from cyclic stannapolythiane **1** and diacyl chloride **2** and **3** is in accord with the results obtained for the formation of macrocyclic lactones, which is a kinetically controlled cyclization type of reaction.[13] Inspection of Table 1 also reveals that there are striking regularities in the melting points of thiolactones **4**–**7**. Dimers **5** and **7** exhibit lower melting points than monomers **4** and **6**. This is in accord with crystal packing densities of the compounds in the solid-state: dimers **5** and **7** have lower crystal packing density than the corresponding monomers **4** and **6**, (see Section 2, Table 4).

All new compounds were characterized by analysis of their respective IR, ^1H and ^{13}C NMR spectra, elemental microanalysis and/or HRMS (see Section 3).

2.2. Molecular structures and ring conformations

Crystal and molecular structures of 12-, 14-, 24-, and 28-membered polythiolactones were determined and their conformations are shown in Figures 1–4. Their conformations defined by characteristic S–C–C–S fragments are listed in Table 2. The influence of the ring size and steric strain on the conformation is analysed by extending data extracted from the Cambridge Structural Database.[14]

The 12-membered ring of compound **4** (Fig. 1) reveals an unusual 'heart-shape' conformation with the sulfur atoms positioned somewhere between *endo*- and *exo*-orientation. The conformation of the two S–C–C–S moieties is

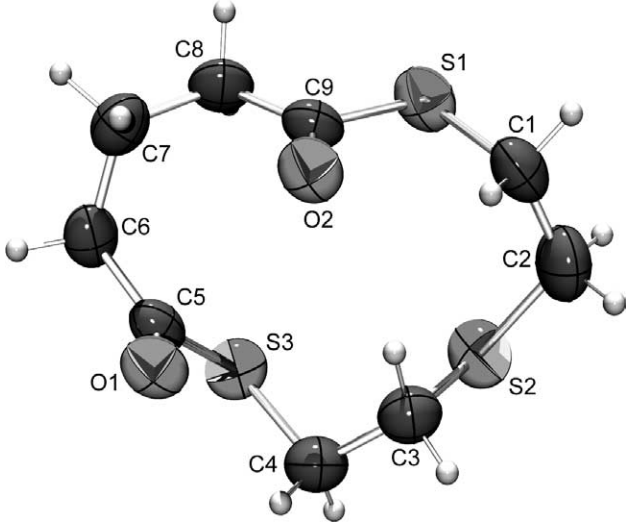

Figure 1. Molecular structures of **4**. Torsion angles defining the ring conformation are (clockwise from S1–C1 bond): $^{+}g\ ^{-}g\ a\ ^{-}g\ ^{-}g\ a\ ^{-}g\ ^{+}g\ ^{-}g\ a\ a$.

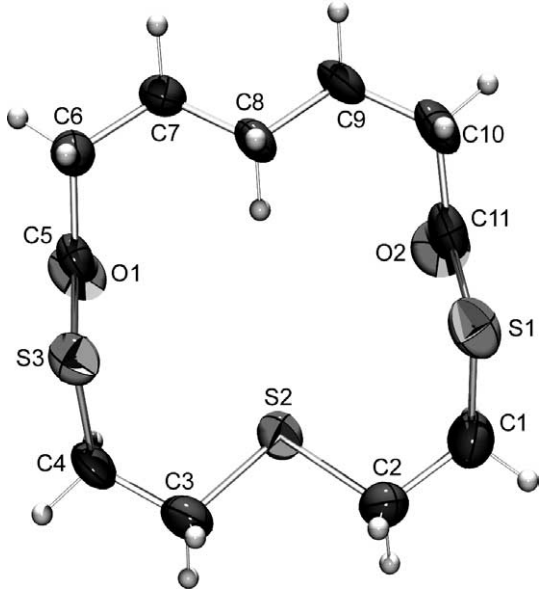

Figure 2. Molecular structure of **6**. The unit cell comprises two similar conformers, one of them is shown. Torsion angles defining the ring conformation are (clockwise from S1–C4 bond): $^{-}g\ ^{+}g\ a\ a\ ^{-}g\ ^{+}g\ a\ a\ ^{-}g\ a\ a\ ^{+}g\ ^{-}g\ a$.

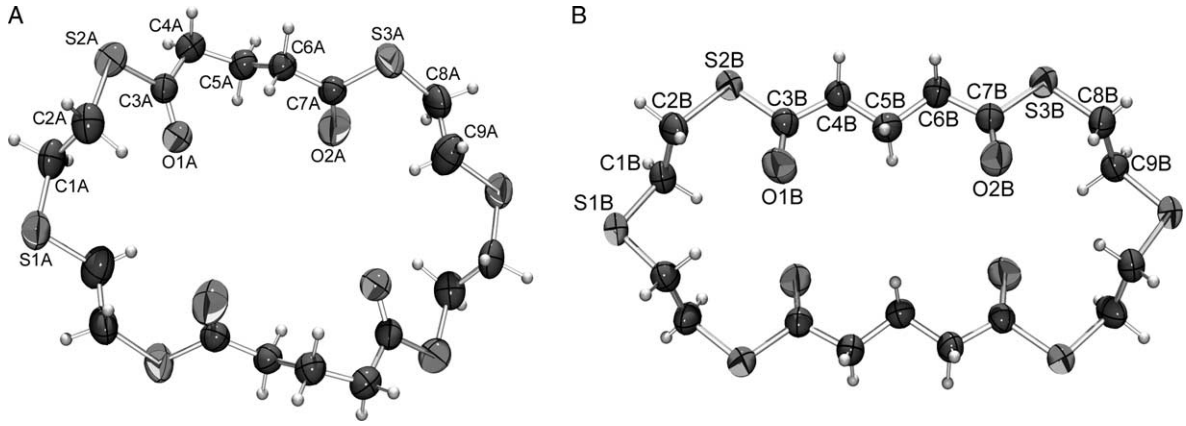

Figure 3. There are two conformers in the crystal of **5**: the molecules A and B. Both rings exhibit C_i molecular symmetry. Torsion angles defining conformations are: (for A clockwise from S1A–C1A bond) $^{-}g\ a\ ^{-}g\ a\ a\ ^{-}g\ a\ a\ a\ ^{-}g\ a\ a$ and (for B clockwise from S1B–C1B bond) $^{+}g\ a\ ^{+}g\ a\ a\ a\ a\ a\ a\ ^{-}g\ a\ ^{-}g$.

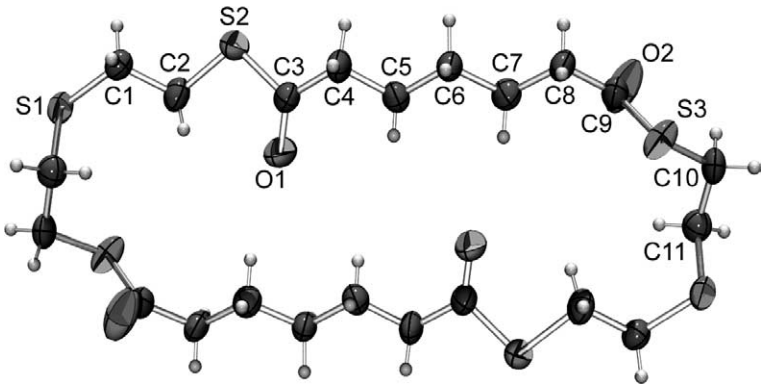

Figure 4. Tetra-thiolactone **7** in the solid-state is of the C_i molecular symmetry. The crystallographically independent unit is a half of the molecule. Torsion angles defining the ring conformation are (clockwise from S1–C1 bond): $^{-}g\ a\ a\ a\ a\ a\ a\ a\ a\ ^{+}g\ a\ ^{+}g\ ^{+}g\ a$.

$^{-}$*gauche* (Table 2, Fig. 5a). Compounds **5** and **6** comprise two crystallographically independent molecules in the unit cells (Table 2). Thus, the 14-membered ring of compound **6** occurs as two conformers of similar conformations (Figs. 2 and 5b): in both rings the conformations of S–C–C–S moieties are $^{+}$*gauche*, $^{-}$*gauche*. One sulfur atom adopts the *endo*-orientation whereas the other two have orientations somewhere between *endo* and *exo*. Both conformers of compound **5** (Fig. 3), in the solid-state, exhibit C_i molecular symmetry (Table 2); conformer A is in a crown-like conformation (Fig. 5c) whereas conformer B appears in a twisted conformation (Fig. 5d). In both rings, sulfur and oxygen atoms are *exo*-oriented. The 24-membered ring of compound **7** (Fig. 4) also reveals C_i molecular symmetry (Table 2). The conformation is illustrated in Figure 5e with four sulfur atoms *exo*-oriented whereas two of them exhibit geometry somewhere between *endo* and *exo*. The present data support *exo*-orientation of sulfur atoms to be sterically favored in large rings (24- and 28-membered ones).

To examine possible steric strain on the ring conformation we have focused on the ring systems involving the Csp^2 atoms that affect the flexibility of the S–C–C–S moieties.[15] In the present analysis, based on our data and data extracted from the Cambridge Structural Database,[14] special attention

Table 2. The conformations of S–C–C–S fragments in cyclic structures **4–7**

Compound	Molecular symmetry	No. of atoms in the ring	S–C–C–S torsion angle (°)[a]			
			1	2	3	4
4	C_1	12	−50.4(5)	−63.9(4)	—	—
6A[b]	C_1	14	73.6(5)	−68.1(5)	—	—
6B[b]	C_1	14	65.2(5)	−69.5(5)	—	—
5A[b]	C_i	24	−174.8(3)	168.3(3)	174.8(3)	−168.3(3)
5B[b]	C_i	24	−172.0(3)	175.9(3)	172.0(3)	−175.9(3)
7	C_i	28	−175.5(4)	69.3(3)	175.5(4)	−69.3(3)

[a] The numbering of torsion angles 1–4 is in agreement with the atom numbering given in Figures 1–4.
[b] Two crystallographically independent molecules.

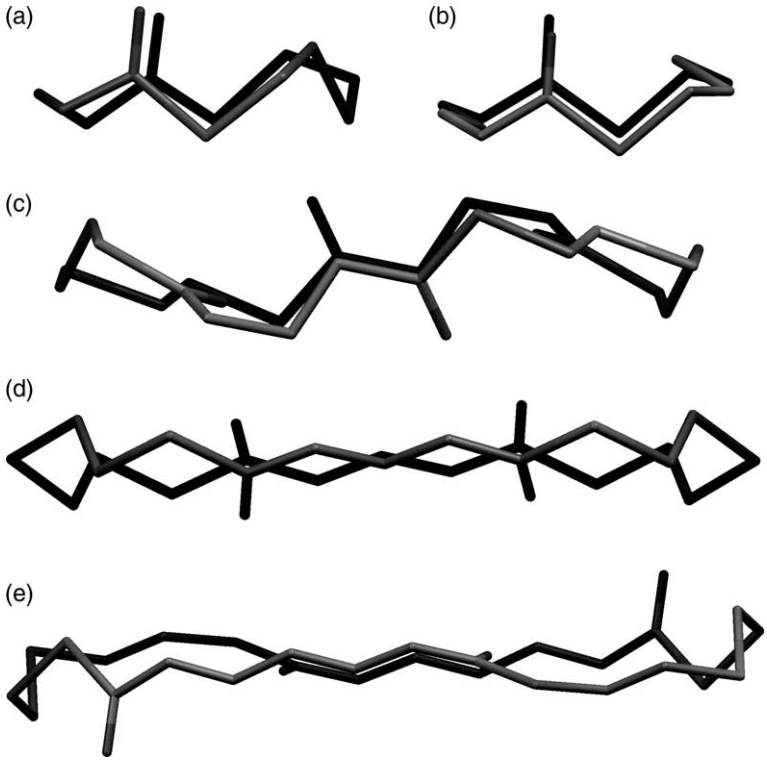

Figure 5. Side-views of the molecules **4**–**7** illustrating different ring conformations: (a) **4**, (b) **6**A, (c) **5**A (d) **5**B, (e) **7**. Conformations of **6**A and **6**B are similar; thus **6**A is shown, only.

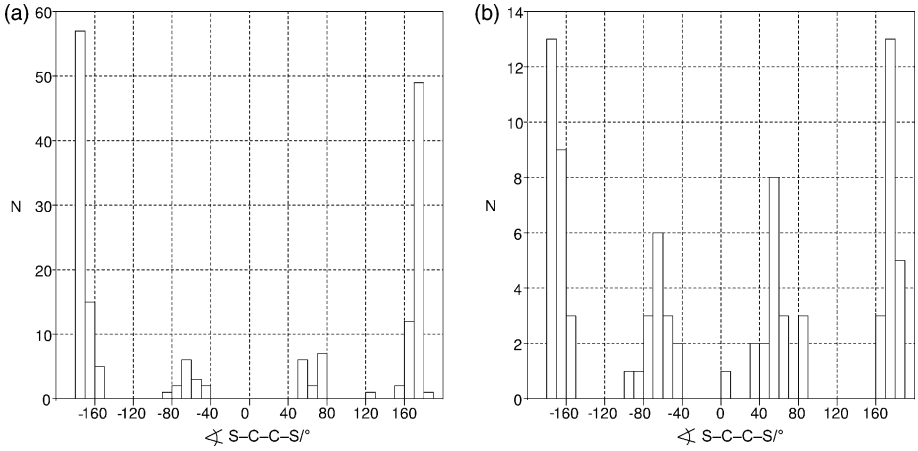

Figure 6. (a) Highly populated $\pm$*anti* conformation of torsion angles S–C–C–S for moieties CH_2–S–CH_2–CH_2–S–CH_2 of macrocyclic compounds found in the CSD; (b) distribution of torsion angles S–C–C–S for moieties Csp^2–S–CH_2–CH_2–S–Csp^2 of macrocyclic compounds found in the CSD show both *anti* and *gauche* conformations.

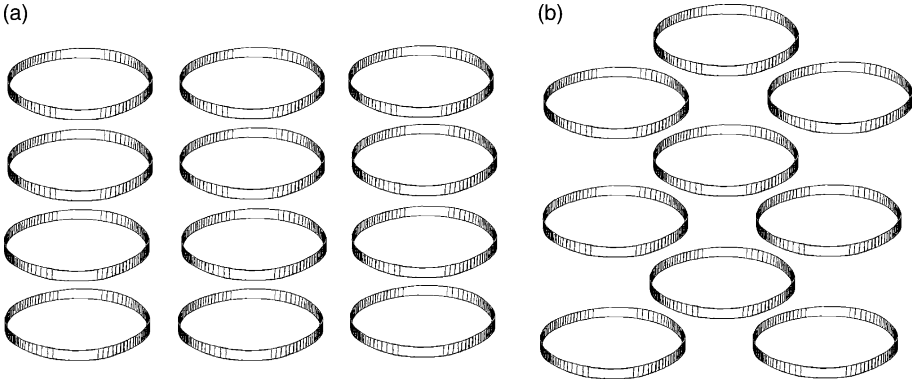

Figure 7. Two ways of stacking rings in tubular assemblies: (a) discrete tubes, (b) partially overlapping tubes.

Table 3. C–H···O interactions generating tubular assemblies in compounds **4** and **7**

Compound	Hydrogen bond	C–H (Å)	H···O (Å)	C···O (Å)	C–H···O (°)	Symmetry operation on acceptor
4	C1–H1B···O1	0.97(5)	2.53(5)	3.464(5)	162(3)	$1+x, y, z$
	C6–H6A···O1	0.92(4)	2.54(4)	3.293(4)	140(3)	$1+x, y, z$
	C8–H8A···O1	1.02(4)	2.71(4)	3.366(3)	132(3)	$1+x, y, z$
	C8–H8B···O2	0.92(4)	2.68(7)	3.335(4)	129(5)	$-x, 1-y, 1-z$
7	C8-H8B···O1	1.05(5)	2.69(5)	3.703(4)	162(4)	$-x, -\frac{1}{2}+y, \frac{1}{2}-z$
	C10–H10A···O2	0.96(6)	2.53(6)	3.225(5)	132(4)	$-x, \frac{1}{2}+y, \frac{1}{2}-z$

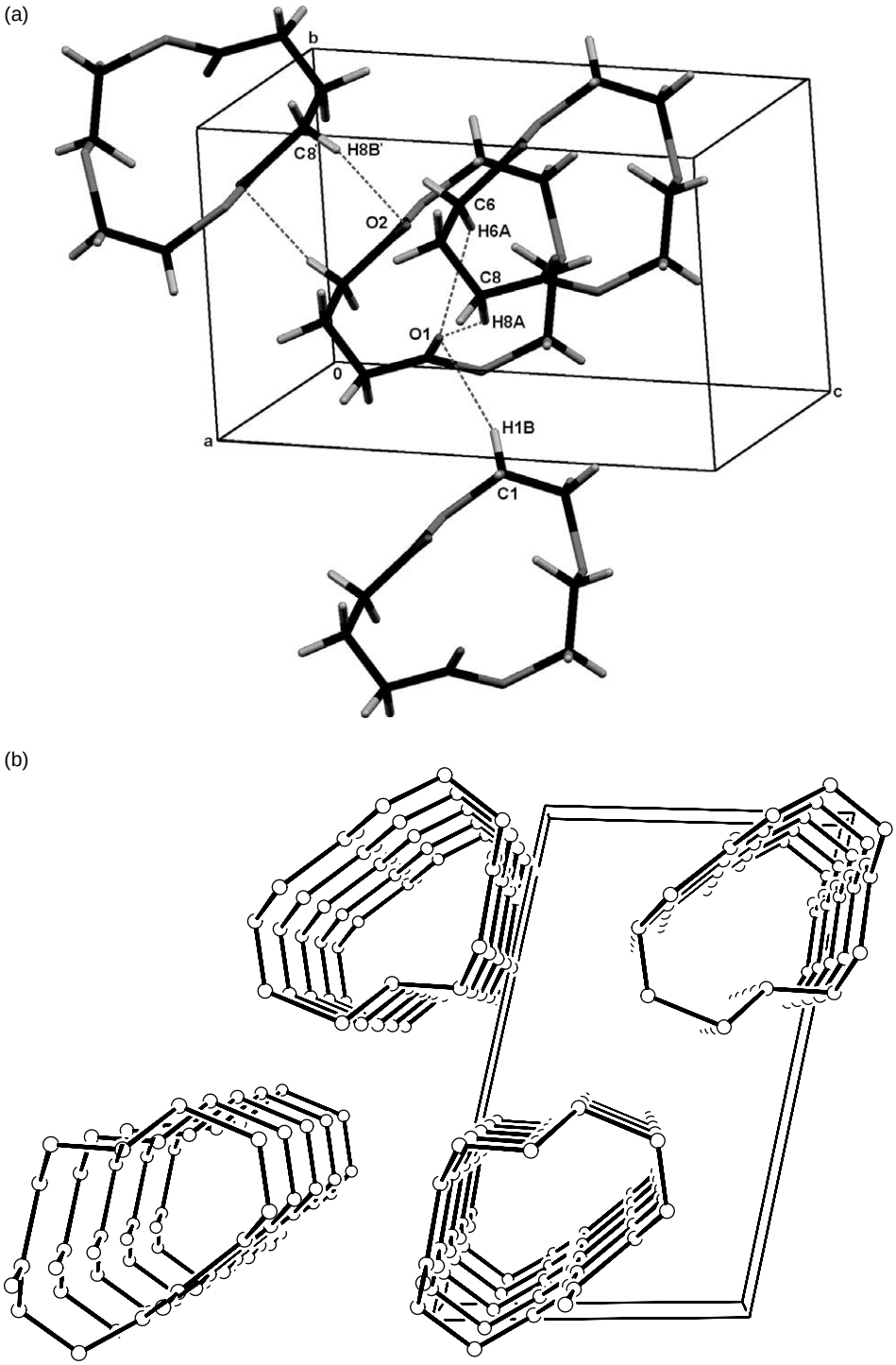

Figure 8. (a) The three-dimensional crystal packing of **4** with details of intratubular (C6–H6A···O1 and C8–H8A···O1) and intertubular (C1–H1B···O1 and C8–H8B···O2) hydrogen bonding. The atom O1 acts as a triple acceptor (Table 3). (b) The rings are stacked along [100] forming tubular assemblies.

is paid to the hybridization of the terminal carbon atoms of the Cα–S–CH_2–CH_2–S–Cα moiety. In the structures reported, one of the Cα(S) atoms is a methylene carbon and the other is a carbonyl carbon. The Cambridge Structural Database only reveals structures with both Cα(S) having the same hybridization: both Cα(S) are Csp^3 (methylene) or both Cα(S) are Csp^2 (carbonyl). As Csp^3 atoms do not impose steric strain, the moiety S–CH_2–CH_2–S predominantly has the *anti* conformation (Fig. 6a). The presence of the Csp^2 atoms imposes steric strain on the ring and hence the *gauche* conformation of the S–C–C–S moiety is more common (Fig. 6b) although the *anti* conformation does occur.

The analysis of about 900 structures (CSD)[14] including up to 11-membered rings reveals a preference for $^{\pm}$*gauche* conformation for the atom sequence S–C–C–S and *endo*-orientation of the sulfur atoms. However, the analysis for 12-membered and larger rings of macrocyclic polythianes (CSD, 137 entries) reveals that in most cases, sulfur atoms are *exo*-oriented as we have observed for the 24- and 28-membered rings of **5** and **7**, respectively. Rings with 12 or more atoms having no steric strain on the atom sequence S–CH_2–CH_2–S prefer the *anti* conformation. Compounds **4** and **6** having 12- and 14-membered rings, respectively, reveal *gauche* conformation for the sequence S–C–C–S due to the presence of Csp^2 (carbonyl) atoms.

2.3. Crystal structures and tubular assemblies

Hydrogen bonding is utilized extensively in the supramolecular chemistry due to its directionality and well defined donor and acceptor sites, which enable recognition and copying with high fidelity. These non-covalent interactions with appropriately crafted macrocycles can lead to tubular structures. Macrocyclic molecules can form topologically different tubular arrays.[7,8,16] A preference to form a tube-like stacking is found in oligopeptides[8b] and chalcogen alkynes.[7] The Cambridge Structural Database (137 entries selected of 12-membered rings and larger with at least one S–CH_2–CH_2–S moiety) was used to analyze assembly of such molecules. The analysis revealed that over 40% of the structures comprise tubular assemblies with the topology shown in Figure 7a whereas only a small portion generate partially overlapping tubes (Fig. 7b).

However, macrocyclic polythianes are less studied and there are no data about polythiolactones. Among the four structures presented in this work, polythiolactones **4**–**7**, two of them, **4** and **7**, reveal tubular structures in the solid-state with similar topology as shown in Figure 7a.

The crystal packing of reported macrocyclic polythianes is governed by weak C–H···O and van der Waals interactions that connect molecules into two-dimensional (**5** and **7**)

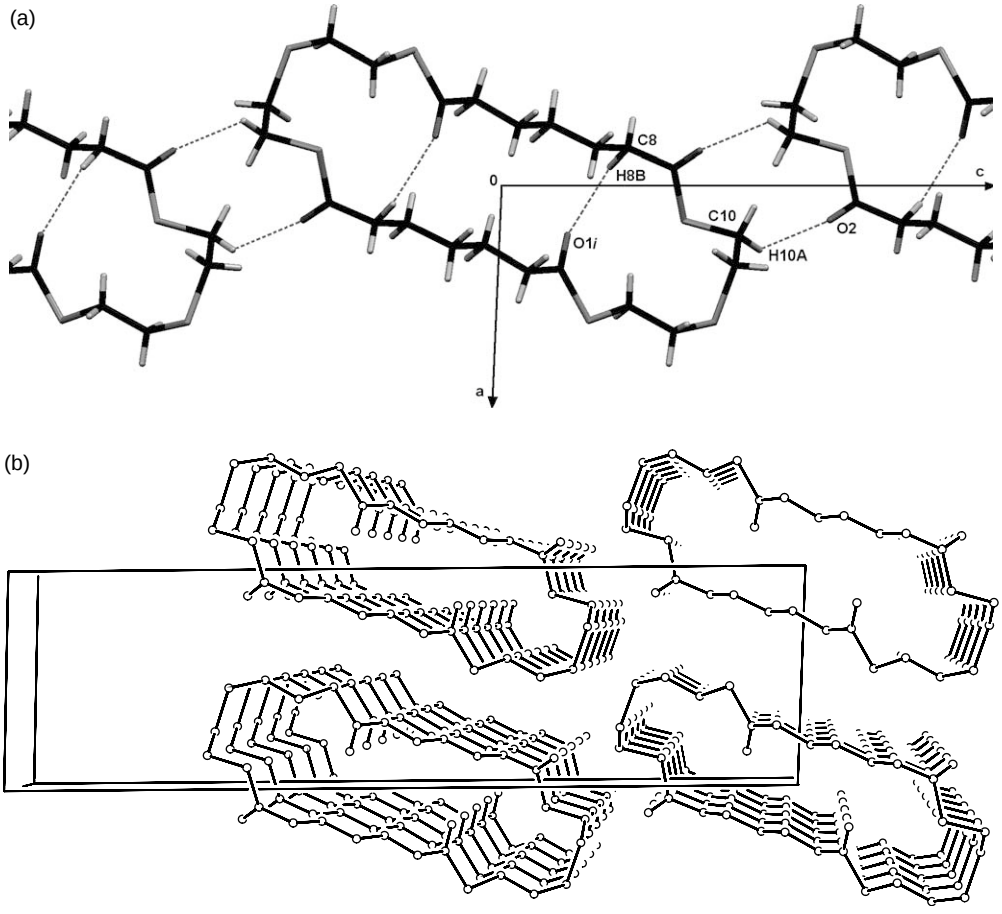

Figure 9. (a) The structure of **7** with intratubular [C8–H8B···O1^i ($i=-x$, $-\frac{1}{2}+y$, $\frac{1}{2}-z$)] and intertubular (C10–H10A···O2) hydrogen bonds. (b) Tubular assemblies are generated along [010] direction.

Table 4. Crystallographic parameters, data collection and structure refinement data for polythiolactones **4**, **5**, **6** and **7**

Compound	**4**	**5**	**6**	**7**
Empirical formula	$C_9H_{14}O_2S_3$	$C_{18}H_{28}O_4S_6$	$C_{11}H_{18}O_2S_3$	$C_{22}H_{36}O_4S_6$
Formula wt (g mol^{-1})	250.38	500.76	278.43	556.87
Crystal dimensions (mm)	0.15×0.15×0.10	0.8×0.3×0.18	0.4×0.4×0.05	0.25×0.20×0.10
Space group	*P*-1	$P2_1/a$	$P2_12_12_1$	$P2_1/c$
a (Å)	5.5049(5)	9.7259(3)	9.2304(5)	8.4793(4)
b (Å)	8.244(4)	9.7267(4)	9.3203(5)	5.3034(3)
c (Å)	13.479(7)	25.8877(9)	31.281(2)	30.716(1)
α (°)	77.64(4)	90	90	90
β (°)	84.39(4)	100.544(3)	90	92.446(4)
γ (°)	78.9(3)	90	90	90
Z	2	4	8	2
V (Å^3)	585.3(4)	2407.7(1)	2691.1(3)	1380.0(2)
D_{calc} (g cm^{-3})	1.421	1.381	1.374	1.340
μ (mm^{-1})	5.582	5.428	4.911	4.788
Θ range (°)	3.36–76.52	1.74–76.61	2.83–76.42	2.88–76.3
Range of *h*, *k*, *l*	$-6>h>6$; $0>k>10$; $-16>l>16$	$-12>h>0$; $-12>k>0$; $-32>l>32$	$-11>h>0$; $-11>k>0$; $-39>l>0$	$-10>h>10$; $-6>k>0$; $-38>l>0$
Reflections collected	2918	5674	3553	2952
Independent reflections	2443	5070	3229	2894
Observed reflections ($I\geq 3\sigma$)	1794	3031	3049	1434
R_{int}	0.1921	0.0782	0.1424	0.0351
$R(F)$	0.055	0.0624	0.0677	0.0620
$R_w(F^2)$	0.1674	0.1878	0.1799	0.1699
Goodness of fit	0.874	1.020	1.083	0.981
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.504; −0.401	0.457; −0.457	0.447; −0.665	0.389; −0.338

and three-dimensional networks (**4** and **6**). The reported C–H···O hydrogen bonds in Table 3 satisfied their function in crystal packing and the geometric parameters using liberal cut-off criteria as suggested by Desiraju and Steiner.[17] However, open-ended tubular molecular assemblies are generated in two structures: di-thiolactone **4**, of the 12-membered ring skeleton (Fig. 8) and tetra-thiolactone **7** of the 28-membered ring (Fig. 9). In both structures the placement of a pair of self-complementary hydrogen bonding functions, that is, C–H and O=C of neighbouring rings favours non-covalent interactions and ring stacking (Table 3).

In general, the governing principle for creating tubular assemblies can be attributed to complementary requirements producing the stacking of the ring. It should be pointed out that cyclic thiolactones **4** and **7**, which both form tubular structures, do not exhibit twisted conformations (Fig. 5a and e). The more chair-like conformations in **4** and **7** have carbonyl groups accessible for hydrogen bonding CH···O between the rings (Table 3). Thus, stacked rings can be connected into a tubular array of molecules. In both structures, **4** and **7** stacked rings are related by translation along the axis *a* (5.5049 Å) and *b* (5.3034 Å), respectively (Table 4).

In conclusion, the synthesis of cyclic di- and tetra-thiolactones **4**–**7** was achieved via ring-opening condensation of corresponding stannapolythiane **1** with diacyl chlorides **2** and **3**. The molecular structures of cyclic ring systems **4**, **6**, **5**, and **7**, were investigated by X-ray structure analysis. In the crystal structures of **5** and **6** there are crystallographically independent molecules. In **5** there are two different conformers where each of them generates a layer. In **6** two conformers are very similar and they are connected by C–H···O hydrogen bonds generating the three-dimensional pattern of hydrogen bonding. However, thiolactones **4** and **7** form tubular assemblies governed by CH···O hydrogen bonding between the stacked rings. To the best of our knowledge, these are the first columnar structures of polythiolactone systems reported.

3. Experimental

3.1. General remarks

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on 300 and 600 MHz spectrometers using TMS or $CDCl_3$ as the internal standard. HPLC-analyses were performed on an instrument equipped with a UV detector operated at $\lambda=$ 230 nm. An OmniSpher C18 (250×4.6 mm) chromatography column was employed by eluting with CH_3CN at a flow rate of 1 mL/min. Dibutyltin oxide and 2,2′-thiadiethanthiol were used as obtained from commercial sources. The diacyl chlorides **2** and **3** were prepared according to the standard procedure.[18] For the single crystals of polythiolactones **4**–**7**, all polythiolactones were recrystallized from a mixture of $CHCl_3$/MeOH in a 1:1 ratio.

3.2. General procedure for the synthesis of the di-thiolactones and tetra-thiolactones 4–7

A solution of stannathiane **1** (2.5 mmol) in dry $CHCl_3$ (40 mL) was heated to reflux, and a solution of corresponding diacyl chloride **2** or **3** (2.5 mmol) in dry $CHCl_3$ (10 mL) was added dropwise over 4 h with stirring. After the addition of reagents had been completed, the resulting mixture was refluxed during 1 h, cooled to ambient temperature and then was treated with 2,2′-bipyridyl (2.5 mmol). The resulting mixture was filtered through small pad of silica, and the filtrate was concentrated in vacuo. A gross mixture of products was separated on a Florisil column (60–100 mesh) by using a 0→20% of

EtOAc–CH_2Cl_2 gradient elution scheme to afford the corresponding products.

3.2.1. 2,5,8-Trithiacyclododecane-1,9-dione (4). White solid (20% yield); mp 113–117 °C. IR (KBr) 2937, 2912, 1694, 1426, 1395, 1079, 1016, 976, 824, 675 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.15–2.24 (m, 2H), 2.66–2.74 (m, 4H), 2.81–2.89 (m, 4H), 3.17–3.24 (m, 4H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 20.8, 28.5, 29.6, 43.5, 197.6. Anal. Calcd for $C_9H_{14}O_2S_3$: C, 43.17; H, 5.64. Found: C, 43.39; H, 5.93.

3.2.2. 2,5,8,14,17,20-Hexathiacyclotetracosane-1,9,13,21-tetraone (5). White solid (24% yield); mp 108–109 °C. IR (KBr) 2931, 2904, 1686, 1402, 1052, 989, 954, 753 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.98–2.11 (m, 4H), 2.66 (t, 8H, $J=7.3$ Hz), 2.78 (d, 4H, $J=8.9$ Hz), 2.81 (d, 4H, $J=7.8$ Hz), 3.11 (d, 4H, $J=7.8$ Hz), 3.13 (d, 4H, $J=8.9$ Hz). ^{13}C NMR (300 MHz, $CDCl_3$): δ 21.1, 29.2, 31.9, 42.5, 197.8. Anal. Calcd for $C_{18}H_{28}O_4S_6$: C, 43.17; H, 5.64. Found: C, 43.43; H, 5.84.

3.2.3. 2,5,8-Trithiacyclotetradecane-1,9-dione (6). White solid (60% yield); mp 118–119 °C. IR (KBr) 2910, 2856, 1685, 1431, 1260, 1100, 1036, 948 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 1.45–1.52 (m, 2H), 1.70–1.78 (m, 4H), 2.54–2.61 (m, 4H), 2.81–2.86 (m, 4H), 3.14–3.19 (m, 4H). ^{13}C NMR (600 MHz, $CDCl_3$): δ 25.5, 26.0, 28.6, 33.1, 43.0, 198.9. HRMS calcd for $C_{11}H_{18}O_2S_3$ $[M]^+$ 278.046347, found 278.043494. Anal. Calcd for $C_{11}H_{18}O_2S_3$: C, 47.45; H, 6.52. Found: C, 47.26; H, 6.43.

3.2.4. 2,5,8,16,19,22-Hexathiacyclooctacosane-1,9,15,23-tetraone (7). White solid (20% yield); mp 98–100 °C. IR (KBr) 2935, 2852, 1685, 1467, 1423, 1102, 1017, 969 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 1.34–1.44 (m, 4H), 1.65–1.73 (m, 8H), 2.55–2.61 (m, 8H), 2.74–2.80 (m, 8H), 3.07–3.14 (m, 8H). ^{13}C NMR (600 MHz, $CDCl_3$): δ 25.0, 27.8, 29.1, 32.0, 43.6, 198.5. HRMS calcd for $C_{22}H_{36}O_4S_6$ $[M+H]^+$ 557.101068, found 557.101752. Anal. Calcd for $C_{22}H_{36}O_4S_6$: C, 47.45; H, 6.52. Found: C, 47.14; H, 6.54.

3.3. X-ray diffraction analysis

Data collection was performed on an Enraf Nonius CAD4 diffractometer, using a graphite monochromated Cu Kα (1.54179 Å) radiation at room temperature [293(2) K]. Three standard reflections were measured every 120 min as an intensity control. Absorption correction based on eight ψ-scan reflexions was performed.[19] The WinGX standard procedure was applied for data reduction.[20] Each structure was solved with SHELXS97[21] and refined with SHELXL97.[22] The models were refined using the full matrix least squares refinement on F^2. Hydrogen atoms were refined as free entities. The atomic scattering factors were those included in SHELXL97.[22] Molecular geometry calculations were performed with PLATON,[23] and molecular graphics were prepared using ORTEP-3,[24] and CCDC-Mercury.[25] Crystallographic data can be obtained from the Cambridge Crystallographic Data Centre, deposit@ccdc.cam.ac.uk; CCDC-273292, CCDC-273293, CCDC-273294 and CCDC273407.

Acknowledgements

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11. (a) Chloroform used in the reaction should be freshly washed with water to remove traces of EtOH, and then dried over $MgSO_4$. (b) When CH_2Cl_2 was used as the reaction solvent the NMR spectra showed that the crude mixture of products

contained significant amounts of Bu_2SnCl_2, which makes purification of the products much more difficult. (c) It should be noted that in the reaction of stannathiane **1** with glutaryl chloride **2**, HPLC analysis of reaction mixture revealed the several cyclic oligomers. Column chromatography of the product mixture led to the isolation of the first two, monomer **4** and dimer **5**.

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Cinnamic acid amides and lignanamides from *Aptenia cordifolia*

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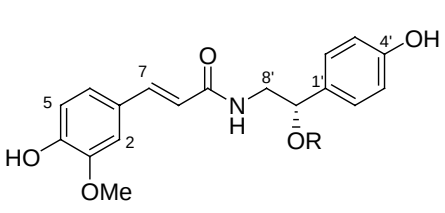
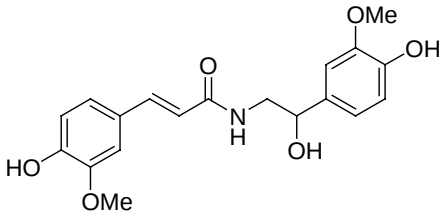
Dedicated to the memory of Professor Gaspare Barone (1943–2005)

Abstract—Examination of the hydroalcoholic extract of the leaves of *Aptenia cordifolia* has afforded three cinnamic acid amides and two lignanamides. Structures were established on the basis of spectroscopic data, including 2D-NMR analyses.

1. Introduction

As part of our ongoing research program on the identification of novel bioactive constituents from plants of the Mediterranean area, we have investigated *Aptenia cordifolia*. Previous chemical studies of the aerial part of *A. cordifolia* evidenced the presence of flavonoids.[1] A study of the leaves extract of *A. cordifolia* belonging to Aizoaceae family, led to the isolation and characterization of novel phytotoxic oxyneolignans.[2] Further examination of the hydroalcoholic extract of the leaves has afforded compounds with amide and lignanamide skeletons. Hydrocinnamic acid amides have been observed in several higher plant.[3] Some of this compounds were identified in the leaves of virus-infected tobacco and the authors[4] suggested that





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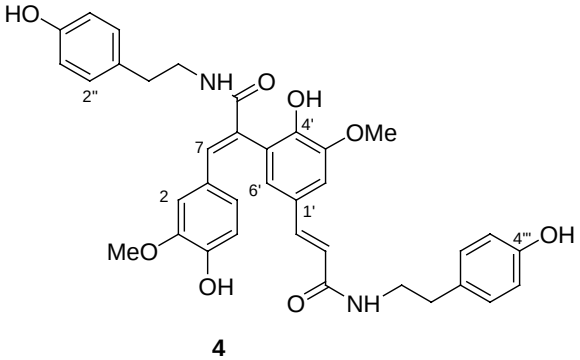

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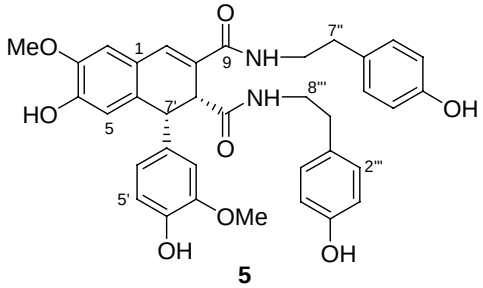

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Keywords: *Aptenia cordifolia*; Cinnamic acid amides; Lignanamides; Spectroscopic analysis.
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they have antiviral effect. Amides and lignanamides are common in *Cannabis sativa* and *Procelia macrocarpa*.[5]

2. Results and discussion

The hydroalcoholic infusion of fresh leaves of *A. cordifolia* was reduced in volume and precipitated with acetone. The acetone/water soluble part was fractionated by Amberlite XAD-2 column chromatography and fractions were purified by silica gel chromatography and HPLC, yielding five compounds **1**–**5**.

The molecular formula of compound **1** was deduced to be $C_{18}H_{19}NO_5$ as the HREIMS spectrum showed the $[M]^+$ ion at *m*/*z* 329.1267 (calcd for $[C_{18}H_{19}NO_5]^+$: 329.1263). The UV spectrum revealed bands at 222, 294, and 316 nm. Signals at δ 7.44 (1H, d, J=15.8 Hz, H-7), and 6.45 (1H, d, J=15.8 Hz, H-8), in the ^{1}H NMR spectrum, indicated the presence of a trans-substituted double bond. Signals at δ 7.12 (1H, d, J=1.9 Hz, H-2), 6.79 (1H, d, J=8.8 Hz, H-5), and 7.03 (1H, dd, J=8.8, 1.9 Hz, H-6) in the ^{1}H NMR spectrum suggested the presence of a 1,3,4-trisubstituted aromatic ring, as did signals at δ 111.7 (C-2), 116.1 (C-5), and 123.3 (C-6) in the ^{13}C NMR (DEPT) spectrum. In the HMBC spectrum, long-range correlations from the H-7 olefinic proton to the carbonyl carbon (δ 169.6, C-9) and the methine carbons C-2 and C-6 were observed, indicating the presence of a feruloyl group. Signals at δ 7.22 (2H, d, J=8.9 Hz, H-2′, H-6′), and 6.77 (2H, d, J=8.9 Hz, H-3′, H-5′) in the ^{1}H NMR spectrum, and signals at δ 128.4 (C-2′, C-6′), and 116.5 (C-3′, C5′), in the ^{13}C NMR (DEPT) spectrum, suggested the presence of a *p*-substituted aromatic ring. In the ^{1}H NMR spectrum, the signals at δ 4.72 (1H, dd, J=7.8, 4.9 Hz, H-7′), 3.53 (1H, dd, J=13.7, 4.9 Hz, H-8a′), 3.44 (1H, dd, J=13.7, 7.8 Hz, H-8b′), as well as signals at δ 73.5 (C-7′), and 48.1 (C-8′) in the ^{13}C NMR (DEPT) spectrum indicated the presence of a 2-amino ethanoyl chain. In the HMBC spectrum, long-range correlations from the H-8′ protons to the carbonyl carbon and the methine carbon (δ 73.5, C-7′) were observed, indicating the presence of a 2-hydroxy-2-(4-hydroxyphenyl) ethyl amine group (octopamine) linked to C-9 of the ferulic unit. The structure of compound **1** was *N*-[2-hydroxy-2-(4-hydroxyphenyl)ethyl] ferulamide. The optical rotation of **1** was found to be −3.0, establishing the *S* (−) absolute configuration at C-7′ chiral center.[6] The *R* (+) isomer was previously isolated from root bark of *Lycium chinense*[7] and it showed antifungal activity. This substance was synthesized in a combinatorial library of a small molecule that selectively induces apoptosis in cancer cells.[8]

Compound **2** was identified as *N*-feruloyl normetanephrine. It had molecular formula $C_{19}H_{21}NO_6$ as deduced from the molecular peak at *m*/*z* 359.1368 in the HREIMS spectrum. The UV spectrum revealed bands at 226, 298, and 320 nm. The ^{13}C NMR spectrum (Table 1) showed the presence of 17 signals. The DEPT experiment evidenced a methyl, a methylene, and nine methines. In the ^{1}H NMR spectra, signals corresponding to two 1,3,4-trisubstituted aromatic rings were present. The H-2, H-5 and H-6 of the ferulic moiety, in the ^{1}H NMR spectrum (Table 1), were at δ 7.13, 6.80, and 7.03, as a narrow doublet, a doublet, and a double doublet, respectively. The H-2′, H-5′, and H-6′ of the normetanephrine moiety were at δ 7.00, 6.77, and 6.83, respectively. Furthermore, the spectrum showed the H-7 and H-8 trans olefinic protons at δ 7.45 and 6.47, the H-8′ methylene as two double doublets at δ 3.54 and 3.44, and the H-7′ as a double doublet at δ 4.73. In a NOE experiment the protons of the methoxyl group at δ 3.88 had relation with the proton doublet at δ 7.13, and the protons of the methoxyls at δ 3.86 had relation with the protons at δ 7.00. Finally, the HMBC experiment evidenced the following

Table 1. ^{1}H and ^{13}C NMR data of compound **1**–**3** (CD_3OD, 500 MHz)[a]

No.	1		2		3	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1		128.4		128.7		128.8
2	7.12 (d, 1.9)	111.7	7.13 (d, 1.5)	112.0	7.15 (d, 2.5)	112.2
3		149.9		149.8		150.3
4		149.3		149.5		149.8
5	6.79 (d, 8.8)	116.1	6.80 (d, 8.5)	116.5	6.81 (d, 9.5)	117.0
6	7.03 (dd, 8.8, 1.9)	123.3	7.03 (dd, 8.5, 1.5)	123.8	7.05 (dd, 9.5, 2.5)	123.8
7	7.44 (d, 15.8)	142.3	7.45 (d, 16.0)	142.8	7.46 (d, 19.5)	142.7
8	6.45 (d, 15.8)	118.7	6.47 (d, 16.0)	119.1	6.49 (d, 19.5)	119.2
9		169.6		170.0		169.7
1′		134.5		128.7		132.7
2′	7.22 (d, 8.9)	128.4	7.00 (d, 1.5)	111.3	7.19 (d, 10.5)	129.6
3′	6.77 (d, 8.9)	116.5		147.6	6.82 (d, 10.5)	116.8
4′		158.1		150.5		158.8
5′	6.77 (d, 8.9)	116.5	6.77 (d, 8.6)	117.0	6.82 (d, 10.5)	116.8
6′	7.22 (d, 8.9)	128.4	6.83 (dd, 8.6, 1.5)	120.5	7.19 (d, 10.5)	129.6
7′	4.72 (dd, 7.8, 4.9)	73.5	4.73 (dd, 7.8, 4.9)	74.1	4.37 (dd, 8.2, 5.3)	81.5
8′	3.53 (dd, 13.7, 4.9), 3.44 (dd 13.7, 7.8)	48.1	3.54 (dd, 13.6, 4.8), 3.44 (dd, 13.6, 7.9)	48.8	3.51 (dd, 14.0, 5.3), 3.44 (dd 14.0, 8.2)	47.7
3-OMe	3.87 (s)	56.4	3.88 (s)	56.9	3.91 (s)	56.9
3′-OMe			3.86 (s)	56.9		
1″					3.28 (obscured)	72.1
2″					1.58 (ses, 7.6)	24.5
3″					0.92 (t, 7.6)	11.5

[a] J values are in parentheses and reported in Hz; chemical shifts are given in ppm; assignments were confirmed by COSY, HSQC, and HMBC experiments.

correlations: H-2′ with C-4′, H-5′ with C-1′ and C-3′, H-6′ with C-4′ and C-7′, H-8′ with C-9 and C-1′, H-2 with C-4, H-5 with C-1 and C-3, H-6 with C-4 and C-7, H-7 with C-9 and H-8 with C-1. This is the first report of *N*-feruloyl normetanephrine from plant extract. It was previously identified during the cloning and expression of a potato cDNA encoding hydroxycinnamoyl-CoA:tyramine *N*-(hydroxycinnamoyl) trasferase.[9]

The new compound **3** had the molecular formula $C_{21}H_{25}NO_5$ as deduced from the molecular peak at *m/z* 371.1730 in the HREIMS spectrum. The general features of its MS and NMR spectra closely resembled those of **1**, except that for the presence of 42 mass unit more than **1**, and three signals in the ^{1}H (δ 3.28, 1.58, and 0.92) and ^{13}C NMR (δ 72.1, 24.5, and 11.5) spectra attributed to an *n*-propyl group. The long-range correlations, in the HMBC spectrum, from the H-7′ protons to the C-8′ carbon and the methine carbon (δ 72.1, C-1″) were observed, indicating that the *n*-propyl group was linked at the alcoholic hydroxyl.

The new compound **4** showed the molecular ion peak at *m/z* 624 $[M]^+$ and significant fragments at *m/z* 488 $[M-136]^+$, 459 $[M-165]^+$ in the MALDI-MS spectrum. Its molecular formula was deduced to be, from the elemental analysis and NMR spectral data, $C_{36}H_{36}N_2O_8$. The UV spectrum revealed bands at 246, 315, and 336 nm. The ^{1}H and ^{13}C resonances of **4** were assigned by combination of COSY, DEPT, HMQC and HMBC experiments (Table 2). Two doublets at δ 7.40 and 6.38 (J=16.0 Hz), in the ^{1}H NMR spectrum, indicated the presence of a trans-substituted double bond. Furthermore, an olefinic proton singlet at δ 7.59 was evident. Signals at δ 6.52 (1H, d, J=2.0 Hz, H-2), 6.65 (1H, d, J=8.0 Hz, H-5), and 6.74 (1H, dd, J=8.0, 2.0 Hz, H-6), in the ^{1}H NMR spectrum, suggested the presence of a trisubstituted aromatic ring, as did correlations with the signals at δ 113.6 (C-2), 116.4 (C-5), and 116.8 (C-6) in the HSQC spectrum. The ^{1}H NMR spectrum showed two narrow doublets at δ 7.19 (1H, d, J=2.0 Hz, H-2′), 6.83 (1H, d, J=2.0 Hz, H-6′), of a 1,3,4,5-tetrasubstituted aromatic ring, correlated in the HSQC experiment at δ 112.2 and 125.1 carbon signals, respectively. Furthermore, eight *ortho*-coupled protons of two disubstituted aromatic rings were present as doublets at δ 7.04 (2H, d, J=8.0 Hz, H-2″, H-6″), 6.70 (2H, d, J=8.0 Hz, H-3″, H-5″), 6.91 (2H, d, J=8.0 Hz, H-2‴, H-6‴), and 6.62 (2H, d, J=8.0 Hz, H-3‴, H-5‴), correlated in the HSQC experiment to the carbon signals at δ 131.2 and 116.8. Signals at δ 3.47 (2H, t, J=6.8 Hz, H-8″), 2.75 (2H, t, J=6.8 Hz, H-7″), 3.43 (2H, t, J=6.8 Hz, H-8‴), 2.65 (2H, t, J=6.8 Hz, H-7‴), correlated in the HSQC experiment to the carbons at δ 43.0 (C-8″, C-8‴), 36.2 (C-7″), and 35.9 (C-7‴), indicated the presence of two 2-amino ethyl chains of a tyramine group. Long-range correlations between the H-7 olefinic proton and the carbonyl carbon (δ 170.4, C-9), the C-2 and C-6 methine carbons, and the C-1 and C-5′ quaternary carbons in the HMBC spectrum indicate the presence of a 8-linked feruloyl group. Long-range correlations from the H-7′ proton to the carbonyl carbon (δ 169.5), the C-2′, C-6′, C-8′ methine carbons, and the C-1′ quaternary carbon, in the HMBC spectrum indicating the presence of a 5-linked feruloyl group. These correlations were consistent with a 8-5′ neolignan structure. The correlations from the H-8″ protons to the C-9, and from the H-8‴ protons to the C-9′ indicate the presence of two tyramine groups linked to C-9, and C-9′ carbons. The analysis of the NOESY spectrum (Table 2) evidenced NOEs between the H-7 proton with H-2 and H-6, the H-2 proton with 3-OMe, the H-2′ with H-8′ and 3′-OMe, the H-7″ and H-8″ with H-2″ and H-6″, and the H-7‴ and H-8‴ with H-2‴ and H-6‴. These data confirmed the structure of compound **4** as depicted.

Table 2. NMR (CD_3OD, 500 MHz) data for compound **4**

No.	^{13}C (ppm)[a]	^{1}H δ (m, *J*/Hz)	NOESY	HMBC[b]
1	127.0			
2	113.6	65.2 (d, 2.0)	3-OMe	1, 3, 4, 7
3	150.6			
4	149.3			
5	116.4	6.65 (d, 8.0)		4
6	116.8	6.74 (dd, 8.0, 2.0)		2, 4, 7
7	139.1	7.59 (s)	2, 6	1, 2, 9, 5′
8	129.4			
9	170.4			
3-OMe	56.2	3.38 (s)	2	3
1′	128.8			
2′	112.2	7.19 (d, 2.0)	3′-OMe, 8′	3′, 6′, 7′
3′	149.9			
4′	148.7			
5′	129.7			1′, 4′
6′	125.1	6.83 (d, 2.0)	8′	1′, 2′, 4′, 7′
7′	141.9	7.40 (d, 16.0)		1′, 2′, 6′, 8′, 9′
8′	120.2	6.38 (d, 16.0)		1′, 9′
9′	169.5			
3′-OMe	57.2	3.96 (s)	2′	3′
1″	131.8			
2″	131.2	7.04 (d, 8.0)	7″, 8″	1″, 4″
3″	116.8	6.70 (d, 8.0)		1″, 2″, 4″, 6″
4″	157.3			
5″	116.8	6.70 (d, 8.0)		1″, 3″, 4″
6″	131.2	7.04 (d, 8.0)	7″, 8″	2″, 4″, 7″
7″	36.2	2.75 (t, 6.8)	2″, 6″	1″, 2″, 6″, 8″
8″	43.0	3.47 (t, 6.8)	2″, 6″	1″, 7″, 9
1‴	131.6			
2‴	131.2	6.91 (d, 8.0)	7‴, 8‴	1‴, 3‴, 4‴
3‴	116.8	6.62 (d, 8.0)		1‴, 2‴, 4‴
4‴	157.3			
5‴	116.8	6.62 (d, 8.0)		1‴, 3‴, 4‴
6‴	131.2	6.91 (d, 8.0)	7‴, 8‴	2‴, 4‴, 7‴
7‴	35.9	2.65 (t, 6.8)	2‴, 6‴	8‴
8‴	43.0	3.43 (t, 6.8)	2‴, 6‴	9′, 1‴, 7‴

[a] ^{13}C NMR assignments are supported by a DEPT experiment.
[b] HMBC correlations from H to C.

Compound **5** showed the molecular ion peak at *m/z* 624 $[M]^+$ and significant fragments at *m/z* 501 $[M-123]^+$, 488 $[M-136]^+$, 460 $[M-164]^+$ and 352 $[M-272]^+$ in the MALDI-MS spectrum. Its molecular formula was deduced to be, from the elemental analysis and NMR spectral data, $C_{36}H_{36}N_2O_8$. The ^{1}H and ^{13}C resonances of **5** were assigned by combination of COSY, DEPT, HMQC and HMBC experiments (Table 3). The ^{1}H NMR spectrum of **5** showed the presence of two tyramine moieties, six aromatic and/or olefinic protons, two methoxy signals and two methine protons signals, which were coupled with each other. The ^{1}H and ^{13}C NMR data of **5** were almost coincident with those reported by Sakakibara et al.[10] for the dihydronaphthalene lignan, cannabisin D. The authors indicated a trans configuration of the phenyl group at C-7′ and the

Table 3. NMR (CD_3OD, 500 MHz) data for compound **5**

No.	^{13}C (ppm)[a]	^{1}H δ (m, *J*/Hz)	NOESY	HMBC[b]
1	125.3			
2	113.7	6.88 (s)	7, 3-OMe	3, 4, 6, 7
3	148.7			
4	147.2			
5	117.7	6.52 (s)	7′	1, 3, 7′
6	133.0			
7	135.1	7.21 (s)	2	2, 8, 9, 8′
8	128.0			
9	170.0			
3-OMe	57.1	3.90 (s)	2	3
1′	136.4			
2′	113.0	6.69 (d, 1.0)	3′-OMe, 7′	4′, 6′, 7′
3′	150.1			
4′	146.0			
5′	116.2	6.66 (d, 8.0)		1′, 4′
6′	121.9	6.41 (dd, 8.0, 2.0)		2′, 4′, 7′
7′	48.1	4.36 (d, 3.9)	5, 2′	1, 5, 6, 8, 1′, 2′, 6′, 6′, 9′
8′	50.3	3.70 (d, 3.9)		6, 7, 8, 9, 8′, 9′
9′	175.0			
3′-OMe	56.8	3.75 (s)	2′	3′
1″	131.9			
2″	131.3	6.97 (d, 8.5)	7″	1″, 3″, 4″, 7″
3″	116.7	6.68 (d, 8.5)		1″, 4″, 5″
4″	157.4			
5″	116.7	6.68 (d, 8.5)		1″, 3″, 4″
6″	131.3	6.97 (d, 8.5)	7″	1″, 4″, 5″, 7″
7″	36.2	2.65 (t, 6.8)	2″, 6″	2″, 6″, 8″
8″	43.0	3.42 (t, 6.8)		9, 1″, 7″
1‴	131.6			
2‴	131.2	6.82 (d, 8.5)	7‴	1‴, 4‴, 7‴
3‴	116.7	6.65 (d, 8.5)		1‴, 4‴, 5‴
4‴	157.4			
5‴	116.7	6.65 (d, 8.5)		1‴, 3‴, 4‴
6‴	131.2	6.82 (d, 8.5)	7‴	1‴, 4‴, 7‴
7‴	35.9	2.50 (t, 6.8)	2‴, 6‴	2‴, 6‴, 8‴
8‴	42.9	3.23 (t, 6.8)		9′, 1‴

[a] ^{13}C NMR assignments are supported by a DEPT experiment.
[b] HMBC correlations from H to C.

amide carbonyl at C-8′ supported by the coupling constant between H-7′ and H-8′. Compound **5** showed, in the ^{1}H NMR spectrum, the relative protons as two doublets at 4.36 and 3.70 ($J=3.9$ Hz). The coupling constant between H-7′ and H-8′ indicates that the corresponding dihedral angle should be ca. 45°. The minimized structure obtained by MM2 calculation[11] was used to generate dihedral angles and an angle of 52° was measured, which is compatible with a cis configuration (Fig. 1).[12] Correspondingly, the NOESY spectrum of **5** showed NOE between H-7′ with H-5 and H-2′, so the quasi-equatorial orientation of bond C-7′–H-7′ was supposed, and quasi-axial orientation of C-8′–H-8′.

The compounds isolated from *A. cordifolia* were tested for their phytotoxicity on the seeds of *Lactuca sativa*.[13] This species was selected as representative of main dicotyledon commercial crops.[13] It has been used extensively as a test organism because of its fast germination and high sensitivity, and allows comparison of bioassay results for many different compounds.[14,15] Aqueous solution of compounds **1**–**5**, ranging between 10^{-4} and 10^{-7} M, were tested on germination, root length and shoot length of treated lettuce seeds (Fig. 2). Compounds **2** and **3** reduced the germination by 20% compared to the control at 10^{-4} M,

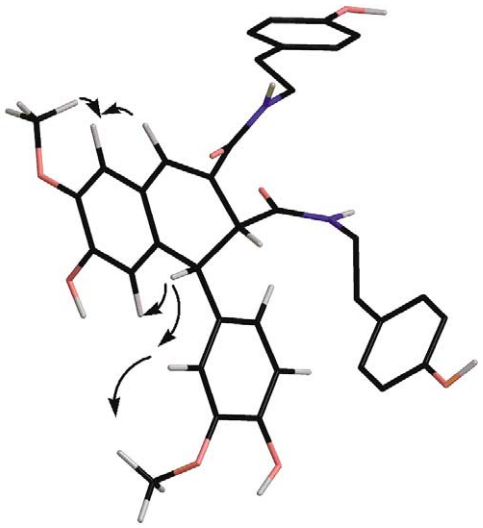

Figure 1. Selected NOEs of minimized structure of **5**.

and dose dependence effects were observed. Compounds **1** and **4** were inactive, and compound **5** reduced the germination by 11% at highest concentration tested. The root elongation of *L. sativa* was not affected by compounds tested, with exception of lignanamide **4** that showed 25% of inhibition at 10^{-4} M. Amongst compounds **1**–**5**, only amide **2** stimulated shoot elongation at all concentrations tested and no important effects were observed for compounds **1**, **3**, **4** and **5**.

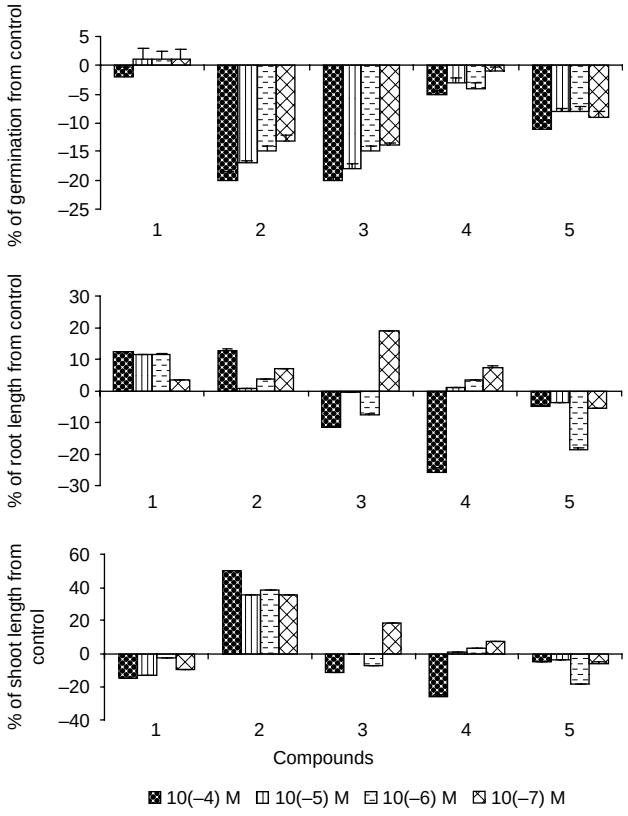

Figure 2. Effect of compounds **1**–**5** on *Lactuca sativa* L. Value presented as percentage differences from control.

The compounds **1**–**5** isolated from *A. cordifolia* could be considered as natural product hybrids.[16] This class of compounds usually exhibit a different biological activity to that of single components. Thus, they could represent a promising approach for the development of new lead structures for bioactive compounds for medicine and agriculture.[16]

3. Experimental

3.1. General experimental procedures

^{1}H and ^{13}C NMR spectra were run on a Varian INOVA 500 NMR spectrometer at 500 and 125 MHz, respectively, in CD_3OD. Matrix assisted laser desorption ionization (MALDI) mass spectra were recorded using a Voyager-DE MALDI-TOF mass spectrometer. MS spectra were obtained with a HP 6890 spectrometer equipped with a MS 5973 N detector. IR spectra were recorded in $CHCl_3$ on a Nicolet 5700 FT-IR spectrometer. UV–vis spectra were recorded in CH_3OH on a Perkin-Elmer Lambda 7 spectrophotometer. HPLC was performed on an Agilent 1100 by using an UV detector. Silica gel 60 (230–400 mesh, E. Merck) or Sephadex LH-20 (Pharmacia) was used for CC, and preparative TLC was performed on silica gel (UV-254 precoated) plates with 0.5 and 1.0 mm thickness (E. Merck). Preparative HPLC was performed using RP-18 (LiChrospher 10 μm, 250×10 mm i.d., Merck) column.

3.2. Plant material

Leaves of *A. cordifolia* were collected in Italy (Campania) during the summer (August) and identified by Professor Pollio of the Dipartimento di Biologia Vegetale of University Federico II of Napoli. A voucher specimen (HERBNAPY680) has been deposited in the herbarium at the University Federico II.

3.3. Extraction and isolation

Fresh leaves (12 kg) of the plants were powdered and extracted with H_2O–CH_3OH (9/1) at room temperature (25 °C) for 7 days. To an aqueous suspension (800 ml) of the crude extract (450 g), cold CH_3COCH_3 (1.0 l) was added, and the mixture was placed on a stir plate in a cold room (−18 °C) overnight. The CH_3COCH_3 addition produced heavy precipitation consisting mostly of proteinaceous material, which was removed by centrifugation. The CH_3COCH_3 was removed by evaporation and the clear aqueous extract, reduced to 150 ml, was chromatographed on Amberlite XAD-2, with H_2O, CH_3OH and, CH_3COCH_3 to give six fractions.

The fraction eluted with CH_3COCH_3 (50.0 g) was rechromatographed on silica gel column to give 11 fractions.

Fraction 3 (4.3 g), eluted with AcOEt, was rechromatographed on SiO_2 flash column eluting with CH_2Cl_2–CH_3COCH_3 gradient to afford fractions A–I. Fraction D (51 mg), eluted with CH_2Cl_2–CH_3COCH_3 (9/1), was purified by preparative TLC [$CHCl_3$–CH_3COCH_3 (9/1)] and, reversed-phase HPLC column [CH_3OH–CH_3CN–H_2O (3/1/6)], to give **2** (8 mg). Fraction E (28 mg) eluted with CH_2Cl_2–CH_3COCH_3 (7/3) was purified by reversed-phase HPLC column [CH_3OH–CH_3CH–H_2O (6/3/11)], to give **1** (11 mg), **5** (2 mg) and, **4** (3 mg), respectively.

Fraction 8 (16.0 g), eluted with CH_3OH, was rechromatographed on SiO_2 flash column eluting with CH_2Cl_2–CH_3OH gradient to afford fractions A–G. Fraction F (20 mg) eluted with CH_2Cl_2–CH_3OH (11/9) was purified by reversed-phase HPLC column [H_2O–CH_3OH (1/1)], to give **3** (5 mg).

3.3.1. (2*S*,*E*)-*N*-[2-Hydroxy-2-(4-hydroxyphenyl)ethyl] ferulamide (1). Colourless oil; HREIMS *m/z* 329.1267 $[M]^+$ (calcd for $C_{18}H_{19}NO_5$ 329.1263); $[\alpha]_D^{25}$ −3.0 (*c* 0.12, CH_3OH); ν_{max} (CH_2Cl_2) 3580, 3400, 2940, 1705, 1670, 1592, 1424, 1334, 1019 cm^{-1}; UV λ_{max} (CH_3OH) nm (log ε): 222 (3.9), 294 (2.5), 316 (2.4); MALDI-MS *m/z* (%): 329 (40), 192 (10), 177 (30), 137 (100); δ_H (500 MHz, CD_3OD) 7.44 (1H, d, J=15.8 Hz, H-7), 7.22 (2H, d, J=8.9 Hz, H-2′, H-6′), 7.12 (1H, d, J=1.9 Hz, H-2), 7.03 (1H, dd, J=8.8, 1.9 Hz, H-6), 6.79 (1H, d, J=8.8 Hz, H-5), 6.77 (2H, d, J=8.9 Hz, H-3′, H-5′), 6.45 (1H, d, J=15.8 Hz, H-8), 4.72 (1H, dd, J=7.8, 4.9 Hz, H-7′), 3.87 (3H, s, 3-OMe), 3.53 (1H, dd, J=13.7, 4.9 Hz, H-8′a), 3.44 (1H, dd, J=13.7, 7.8 Hz, H-8′b); δ_C (125 MHz, CD_3OD) 169.6, 158.1, 149.9, 149.3, 142.3, 134.5, 128.4, 123.3, 118.7, 116.5, 116.1, 111.7, 7.35, 56.4, 48.1.

3.3.2. (*E*)-*N*-[2-Hydroxy-2-(4-hydroxy-3-methoxyphenyl)-ethyl] ferulamide (2). Colourless oil; HREIMS *m/z* 359.1368 $[M]^+$ (calcd for $C_{19}H_{21}NO_6$ 359.1269); $[\alpha]_D^{25}$ 0.0 (*c* 0.10, CH_3OH); ν_{max} (CH_2Cl_2) cm^{-1} 3676, 3433, 3046, 2940, 1663, 1601, 1512, 1424, 1057; UV λ_{max} (CH_3OH) nm (log ε): 226 (2.9), 298 (1.2), 320 (1.1); MALDI-MS *m/z* (%): 359 (15), 192 (20), 182 (40), 167 (100); δ_H (500 MHz, CD_3OD) 7.45 (1H, d, J=16.0 Hz, H-7), 7.13 (1H, d, J=1.5 Hz, H-2), 7.03 (1H, dd, J=8.5, 1.5 Hz, H-6), 7.00 (1H, d, J=1.5 Hz, H-2′), 6.83 (1H, dd, J=8.6, 1.5 Hz, H-6′), 6.80 (1H, d, J=8.5 Hz, H-5), 6.77 (1H, d, J=8.6 Hz, H-5′), 6.47 (1H, d, J=16.0 Hz, H-8), 4.73 (1H, dd, J=7.8, 4.9 Hz, H-7′), 3.88 (3H, s, 3-OMe), 3.86 (3H, s, 3′-OMe), 3.54 (1H, dd, J=13.6, 4.8 Hz, H-8′a), 3.44 (1H, dd, J=13.6, 7.9 Hz, H-8′b); δ_C (125 MHz, CD_3OD) 170.0, 150.5, 149.8, 149.5, 147.6, 142.8, 128.7, 123.8, 120.5, 119.1, 117.0, 116.5, 112.0, 111.3, 74.1, 56.9, 48.8.

3.3.3. (*E*)-*N*-[2-(4-Hydroxyphenyl)-2-propoxyethyl] ferulamide (3). Colourless oil; HREIMS *m/z* 371.1730 $[M]^+$ (calcd for $C_{21}H_{25}NO_5$ 371.1733); $[\alpha]_D^{25}$ −2.0 (*c* 0.08, CH_3OH); ν_{max} ($CHCl_3$) 3625, 3522, 3400, 2943, 1705, 1673, 1594, 1512, 1425, 1334, 1019 cm^{-1}; UV λ_{max} (CH_3OH) nm (log ε): 280 (3.1); MALDI-MS *m/z* (%): 372 (18), 254 (30), 209 (100), 163 (40); δ_H (500 MHz, CD_3OD) 7.46 (1H, d, J=19.5 Hz, H-7), 7.19 (2H, d, J=10.5 Hz, H-2′, H-6′), 7.15 (1H, d, J=2.5 Hz, H-2), 7.05 (1H, dd, J=9.5, 2.5 Hz, H-6), 6.82 (2H, d, J=10.5 Hz, H-3′, H-5′), 6.81 (1H, d, J=9.5 Hz, H-5), 6.49 (1H, d, J=19.5 Hz, H-8), 4.37 (1H, dd, J=8.2, 5.3 Hz, H-7′), 3.91 (3H, s, 3-OMe), 3.51 (1H, dd, J=14.0, 5.3 Hz, H-8′a), 3.44 (1H, dd, J=14.0, 8.2 Hz, H-8′b), 3.28 (2H, m, H-1″), 1.58 (2H, ses, J=7.6 Hz, H-2″), 0.92 (3H, t, J=7.6 Hz, H-3″); δ_C (125 MHz, CD_3OD) 169.7, 158.8, 150.3, 149.8, 142.7, 132.7, 129.6,

128.8, 123.8, 119.2, 117.0, 116.8, 112.2, 81.5, 72.1, 56.9, 47.7, 24.5, 11.5.

3.3.4. (*E*,*E*)-*N*,*N*-Dityramin-4,4′-dihydroxy-3,5′-dimethoxy-β,3′-bicinnamamide (4). Amorphous powder; UV λ_{max} (CH_3OH) nm (log ε): 336 (0.9), 315 (2.6), 246 (3.2); ν_{max} ($CHCl_3$) 3684, 3595, 2927, 2857, 1740, 1598, 1509, 1455, 1057 cm^{-1}; MALDI-MS *m/z* (%): 624 (100), 488 (40), 459 (20), 136 (50). Anal. Calcd for $C_{36}H_{36}N_2O_8$: C, 69.22, H, 5.81, N, 4.48. Found: C, 68.96, H, 5.84, N, 4.35. δ_H (500 MHz, CD_3OD) 7.59 (1H, s, H-7), 7.40 (1H, d, J=16.0 Hz, H-7′), 7.19 (1H, d, J=2.0 Hz, H-2′), 7.04 (2H, d, J=8.0 Hz, H-2″, H-6″), 6.91 (2H, d, J=8.0 Hz, H-2‴, H-6‴), 6.83 (1H, d, J=2.0 Hz, H-6′), 6.74 (1H, dd, J=8.0, 2.0 Hz, H-6), 6.70 (2H, d, J=8.0 Hz, H-3″, H-5″), 6.65 (1H, d, J=8.0 Hz, H-5), 6.62 (2H, d, J=8.0 Hz, H-3‴, H-5‴), 6.52 (1H, d, J=2.0 Hz, H-2), 6.38 (1H, d, J=16.0 Hz, H-8′), 3.96 (3H, s, 3′-OMe), 3.47 (2H, t, J=6.8 Hz, H-8″), 3.43 (2H, t, J=6.8 Hz, H-8‴), 3.38 (3H, s, 3-OMe), 2.75 (2H, t, J=6.8 Hz, H-7″), 2.65 (2H, t, J=6.8 Hz, H-7‴); δ_C (125 MHz, CD_3OD) 170.4, 169.5, 157.3, 150.6, 149.9, 149.3, 148.7, 141.9, 139.1, 131.8, 131.6, 131.2, 129.7, 129.4, 128.8, 127.0, 125.1, 120.2, 116.8, 116.4, 113.6, 112.2, 57.2, 56.2, 43.0, 36.2, 35.9.

3.3.5. 7-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)-*N*^{2},*N*^{3}-bis(4-hydroxyphenethyl)-6-methoxy-1,2-dihydronaphthalene-2,3-dicarboxamide (5). Amorphous powder; $[\alpha]_D^{25}$ 0.0 (*c* 0.20, CH_3OH); ν_{max} ($CHCl_3$) 3684, 3595, 3414, 3043, 2981, 1660, 1605, 1513, 1431, 1308, 945 cm^{-1}; UV λ_{max} (CH_3OH) nm (log ε): 223 (3.9), 284 (1.2), 333 (1.1); MALDI-MS *m/z* (%): 624 (100), 501 (10), 488 (30), 460 (10), 352 (10). Anal. Calcd for $C_{36}H_{36}N_2O_8$: C, 69.22, H, 5.81, N, 4.48. Found: C, 68.86, H, 5.78, N, 4.40. δ_H (500 MHz, CD_3OD) 7.21 (1H, s, H-7), 6.97 (2H, d, J=8.5 Hz, H-2″, H-6″), 6.88 (1H, s, H-2), 6.82 (2H, d, J=8.5 Hz, H-2‴, H-6‴), 6.69 (1H, d, J=1.0 Hz, H-2′), 6.68 (2H, d, J=8.5 Hz, H-3″, H-5″), 6.66 (1H, d, J=8.0 Hz, H-5′), 6.65 (2H, d, J=8.5 Hz, H-3‴, H-5‴), 6.52 (1H, s, H-5), 6.41 (1H, dd, J=8.0, 2.0 Hz, H-6′), 4.36 (1H, d, J=3.9 Hz, H-7′), 3.90 (3H, s, 3-OMe), 3.75 (3H, s, 3′-OMe), 3.70 (1H, d, J=3.9 Hz, H-8′), 3.42 (2H, t, J=6.8 Hz, H-8″), 3.23 (2H, t, J=6.8 Hz, H-8‴), 2.65 (2H, t, J=6.8 Hz, H-7″), 2.50 (2H, t, J=6.8 Hz, H-7‴); δ_C (125 MHz, CD_3OD) 175.0, 170.0, 157.4, 150.1, 148.7, 147.2, 146.0, 136.4, 135.1, 133.0, 131.9, 131.6, 131.3, 131.2, 128.0, 125.3, 121.9, 117.7, 116.7, 116.2, 113.7, 113.0, 57.1, 56.8, 50.3, 48.1, 43.0, 42.9, 36.2, 35.9.

3.4. Bioassays

Seeds of *L. sativa* L. (cv. Cavolo di Napoli, collected during 2003, were obtained from Ingegnoli Spa (Milan, Italy)). All undersized or damaged seeds were discarded and the assay seeds were selected for uniformity. For the bioassays we used Petri dishes of 50 mm diameter with one sheet of Whatman No. 1 filter paper as support. In four replicate experiments, germination and growth were conducted in aqueous solutions at controlled pH. Test solutions (10^{-4} M) were prepared using MES (2-[*N*-morpholino]ethanesulfonic acid, 10 mm, pH 6) and the rest (10^{-5}–10^{-7} M) were obtained by dilution. Parallel controls were performed. After adding 25 seeds and 2.5 ml test solutions, Petri dishes were sealed with Parafilm® to ensure closed-system models. Seeds were placed in a growth chamber KBW Binder 240 at 25 °C in the dark. Germination percentage was determined daily for 5 days (no more germination occurred after this time). After growth, plants were frozen at −20 °C to avoid subsequent growth until the measurement process. Data are reported as percentage differences from control in the graphics and tables. Thus, zero represents the control, positive values represent stimulation of the parameter studied and negative values represent inhibition.

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Synthesis and conformational analysis of tetrahydroisoquinoline- and piperidine-fused 1,3,4,2-oxadiazaphosphinanes, new ring systems

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Dedicated to Professor Géza Stájer on his 70th birthday

Abstract—Through cyclization of tetrahydroisoquinoline and piperidine 1,2-hydrazino alcohols with phenylphosphonic dichloride and phenyl dichlorophosphate, *P*-epimeric diastereomers of 1,6,7,11b-tetrahydro-4*H*-1,3,4,2-oxadiazaphosphino[5,4-*a*]isoquinoline-3-oxides (**13** and **14**), 1,6,11,11a-tetrahydro-4*H*-1,3,4,2-oxadiazaphosphino[4,5-*b*]isoquinoline-3-oxides (**15** and **16**) and 1,6,7,8,9,9a-hexahydro-4*H*-pyrido[1,2-*d*][1,3,4,2]oxadiazaphosphinane-3-oxides (**17** and **18**), the first representatives of these ring systems, were prepared. NMR and X-ray diffraction studies revealed that, independently of the *P*-substituent and the relative configuration of the phosphorus atom, **13**, **14**, **17** and **18** could be characterized by trans-connected hetero rings and the chair conformation of the 1,3,4,2-oxadiazaphosphinane moiety, while the stereochemistry of the connection of the hetero rings in the 1,3,4,2-oxadiazaphosphinanes linearly fused to tetrahydroisoquinoline (**15** and **16**) was found to be dependent on the *P*-configuration relative to that of the carbon at the annelation.

1. Introduction

In consequence of their valuable pharmacological effects and wide-ranging potential for synthetic applications, considerable interest has been focused towards 1,3,2-O,N,P heterocycles.[1] The 1,3,2-oxazaphosphinane ring system is found in alkylating anticancer drugs (cyclophosphamide and ifosfamide), numerous derivatives of which have been prepared to determine their structure–activity relationships.[2] Compounds containing a 1,3,2-oxazaphosphinane moiety were recently reported to possess matrix metalloproteinase-inhibitory,[3] pesticidal[4] and antimicrobial[5] activities. Phosphorus-stabilized carbanions derived from chiral 1,3,2-oxazaphosphinane 2-oxides have been widely used in the diastereoselective formation of carbon–carbon bonds.[6]

In contrast with the thoroughly investigated 1,3,2-oxazaphosphinane-2-oxide derivatives, less attention has been paid to the preparation and transformations of the corresponding 1,3,4,2-oxadiazaphosphinane-2-oxides containing an additional nitrogen atom in the heterocyclic ring.[7–10] The first representatives of this ring system were prepared with the aim of identifying potential antitumour agents. However, despite the close structural analogy, cyclophosphamide-analogue 1,3,4,2-oxadiazaphosphinane-2-oxides, and the homologous 1,3,4,2-oxadiazaphosphepin-2-oxides, proved to exhibit negligible antileukaemic activity.[9,10] Furthermore, there has been only one stereochemical investigation of this ring system: 4-methyl-2-phenoxy-1,3,4,2-oxadiazaphosphinane-2-oxide proved to exist predominantly in the chair conformation, with the P═O group occupying an axial position.[8]

As a continuation of our previous stereochemical studies on 1,2,3,4-tetrahydroisoquinoline-condensed 1,3- and 1,2,3-heterocycles,[11] our present aim was to prepare 1,3,4,2-oxadiazaphosphinane-2-oxides attached angularly or linearly to the tetrahydroisoquinoline ring in order to investigate the effects of the substituents and the configurations of the substituted atoms on the predominant conformations of the nitrogen-bridged tricyclic system. To determine the effects of the attached aromatic ring on the stereochemistry of the ring junction, a further aim was to synthesise the parent piperidine-condensed derivatives. To the best of our knowledge, nitrogen-bridged 1,3,4,2-oxadiazaphosphinane-

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2-oxides with a condensed skeleton have not been reported previously in the literature.

2. Results and discussion

2.1. Syntheses

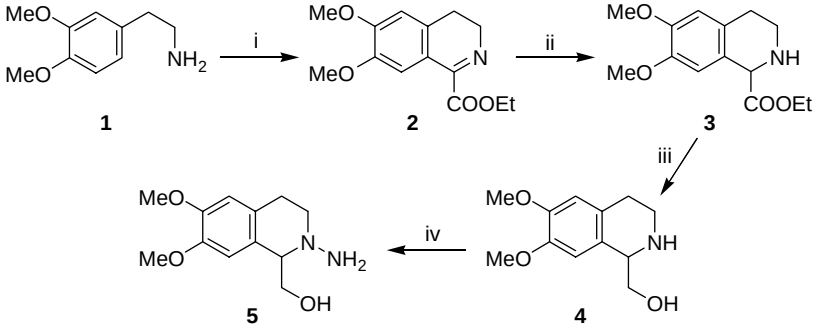
Most of the methods applied earlier to the synthesis of 1,3,4,2-oxadiazaphosphinanes were based on the ring closures of the corresponding hydrazino alcohols with the appropriate phosphorus-containing fragments.[7–9] This methodology was also applied for the preparation of our target compounds.

Regioisomeric tetrahydroisoquinoline hydrazino alcohols **5** and **8a**,**b**, starting materials for the phosphorus-containing model compounds, were prepared from the corresponding amino alcohol derivatives **4** and **7a**,**b** by using a two-step procedure (*N*-nitrosation and a subsequent $LiAlH_4$ reduction) usually applied for the preparation of *N*-substituted hydrazines or hydrazino alcohols from secondary amines or amino alcohols, respectively (Schemes 1 and 2).[12]

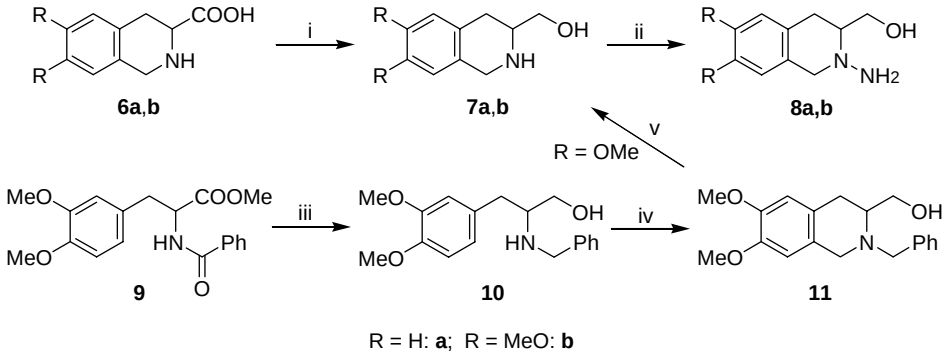
Due to its natural occurrence, many procedures have been developed for the preparation of the tetrahydroisoquinoline amino alcohol derivative calycotomine (**4**),[13] which was obtained by $LiAlH_4$ reduction of the corresponding amino ester **3**. Compound **3** was prepared using a three-step process starting from homoveratrylamine (**1**) (Scheme 1).[14]

The amino alcohols **7a**,**b** necessary for the linearly fused model compounds were prepared by $LiAlH_4$ reduction of the corresponding 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids (TIC: **6a** and 6,7-diMeO-TIC: **6b**) (Scheme 2).[15,16] The lengthy hydrolysis step of **9** towards 2-amino-3-(3,4-dimethoxyphenyl)propanoic acid,[15] an intermediate of **6b**, proved to be a tedious reaction on a 0.1 mol scale. Accordingly, an alternative procedure,[17] based on a change in the sequence of the transformation of the functional groups of **9**, was applied for the synthesis of larger quantities of **7b**. $LiAlH_4$ reduction of **9** resulted in *N*-benzyl amino alcohol **10**, which was converted to the corresponding tetrahydroisoquinoline derivative **11** by Pictet-Spengler cyclization with formaldehyde. Removal of the benzyl group of **11** by catalytic hydrogenation in the presence of Pd/C led to 6,7-dimethoxy-1,2,3,4-tetrahydro-3-isoquinolinylmethanol (**7b**) (Scheme 2).

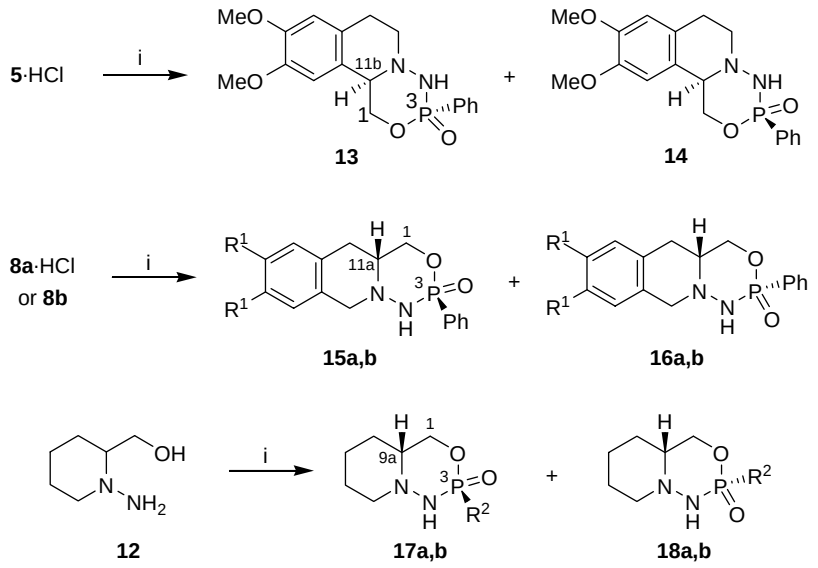
Hydrazino alcohols **5**, **8a**,**b** and **12**[18] were cyclized with phenylphosphonic dichloride, and phenyl dichlorophosphate at room temperature in THF in the presence of Et_3N, resulting in 1,6,7,11b-tetrahydro-4*H*-1,3,4,2-oxadiazaphosphino-[5,4-*a*]isoquinoline-3-oxides (**13** and **14**), 1,6,11,11a-tetrahydro-4*H*-1,3,4,2-oxadiazaphosphino[4,5-*b*]isoquinoline-3-oxides (**15** and **16**) and 1,6,7,8,9,9a-hexahydro-4*H*-pyrido[1, 2-*d*][1,3,4,2]oxadiazaphosphinane-3-oxides (**17** and **18**), which are the first representatives of these ring systems (Scheme 3). In most cases, two *P*-2 epimeric diastereomers, differing in the cis or trans position of the *P*-substituent and the hydrogen at the annelation (H-an), were formed and separated by column chromatography. A significant



Scheme 1. Reagents and conditions: (i) 1. $(COOOEt)_2$, 140 °C, 6 h, 2. $POCl_3$, PhMe, EtOH, Δ, 3.5 h, 49% (1+2); (ii) H_2, 5% Pt/C, EtOH, rt, 1 atm, 6 h, 82%; (iii) $LiAlH_4$, THF, Δ, 3 h, 66%; (iv) 1. $NaNO_2$, AcOH, H_2O, rt, 8 h, 2. $LiAlH_4$, THF, rt, 2 h, 52%.



Scheme 2. Reagents and conditions: (i) $LiAlH_4$, THF, Δ, 8 h, 51% (for R=MeO); (ii) 1. $NaNO_2$, AcOH, H_2O, rt, 8 h, 2. $LiAlH_4$, THF, rt, 2 h, 45% (**8a**), 67% (**8b**); (iii) $LiAlH_4$, THF, Δ, 5 h, 78%; (iv) CH_2O, HCl, H_2O, Δ, 6 h, 92%; (v) H_2, 10% Pd/C, MeOH, 30 bar, 40 °C, 30 h, ~100%.



Compound	R^1	R^2	Diastereomeric ratio in the crude product
13:**14**	–	–	48:52
15a:**16a**	H	–	50:50
15b:**16b**	OMe	–	~0:~100
17a:**18a**	–	Ph	21:79
17b:**18b**	–	OPh	50:50

Scheme 3. Reagents and conditions: (i) Cl_2POPh or $Cl_2PO(OPh)$, Et_3N, THF, rt, 48 h, 34–51%.

difference in the ratios of the *P*-2 epimers, was found for **17a** and **18a**, the trans isomer (**18a**) being the main product, while in the ring closure of **8b**, the minor oxadiazaphosphinane diastereomer (**15b**) could not be detected, even in the crude product (by ^{1}H NMR spectroscopy).

2.2. Structure

In keeping with the nitrogen-bridged saturated bi- or polycyclic heterocycles, the stereo-structures of the prepared 1,3,4,2-oxadiazaphosphinanes (**13**–**18**) can be described by a conformational equilibrium of cis[1]–trans–cis[2] type.[19] In the trans structure, the B/C hetero rings are trans-connected, with a trans-diaxial arrangement of H-an and the nitrogen lone pair. In the two other configurations, the hetero rings are cis-connected: for the cis-1 conformation, C-1 is in the inside, while for the cis-2 conformation, C-1 is in the outside position (Fig. 1). The phosphorus-containing 1,2,3-heterocycles are prone to participate in a conformational equilibrium involving chair, twisted chair and other distorted conformations.[1,20]

The stereochemistry of the model compounds was determined in two steps. First, the predominant conformation was assigned on the basis of the characteristic ^3J couplings and NOE interactions. Second, the relative configuration of the *P*-phenyl substituent was observed by using the NOEs from the *P*-phenyl group to the annelation protons (where applicable) and/or the significant differences in the chemical shifts for certain indicator nuclei.

The orientation of H-an (i.e., H-11b for **13** and **14**; H-11a for **15** and **16**; and H-9a for **17** and **18**) and the protons connected to the carbons adjacent to the annelation (H-1 and H-X; H-X: H-11 for **15** and **16**, and H-9 for **17** and **18**) or the protons connected to the carbons adjacent to the

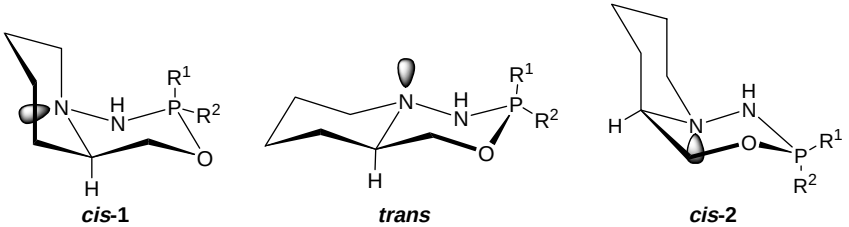


Figure 1. Possible ring connections of 1,6,7,8,9,9a-hexahydro-4*H*-pyrido[1,2-*d*]-[1,3,4,2]oxadiazaphosphinanes.

Table 1. Characteristic vicinal coupling constants in Hz[a]

Compound	H-1_{ax}-H-an	H-1_{eq}-H-an	H-X_{ax}-H-an	H-X_{eq}-H-an	H-1_{ax}-P	H-1_{eq}-P
13	9.3	4.3	—	—	5.3	17.1
14	10.6	2.8	—	—	1.3	18.6
15a	4.0	2.5	11.8	5.5	3.8	20.0
16a	9.8	4.0	10.6	4.8	7.3	18.4
16b	8.2	3.8	10.3	4.8	8.1	18.1
17a	9.8	3.3	10.1	2.8	3.5	18.9
18a	10.3	3.0	10.0	3.1	2.0	20.4
17b	10.6	3.5	10.1	3.0	1.6	19.9
18b	9.0	3.5	Overlap	Overlap	2.3	26.4

[a] For the meanings of H-an and H-X, see the text.

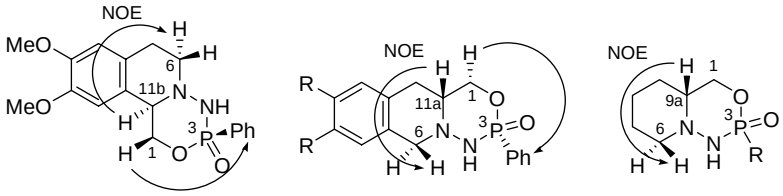


Figure 2. Detected NOEs.

nitrogen-bridge (H-6) were assigned by using the vicinal coupling constants (Table 1) and the detected NOESY cross-peaks (Fig. 2).

The data in Table 1 show that H-an for **16a**,**b**, **17a**,**b** and **18a** has two high vicinal couplings to the axial protons connected to the carbons adjacent to the annelation (H-X, i.e., H-11 for **15a**,**b** and **16a**,**b**; and H-9 for **17a**,**b** and **18a**,**b**), indicating that H-an is in an axial position and the hetero rings are trans-connected. The vicinal couplings of H-11b for **13** and **14** correspond to a trans diaxial position for H-11b and H-1_{ax}, which excludes the hetero ring connection of cis-2 type. The NOESY cross-peaks detected for H-11b and H-6_{ax} indicate the trans connection of the hetero rings for both compounds.

For **15a**, the ^3J (H-1_{ax}-H-11a) and ^3J (H-1_{eq}-H-11a) values were 4.0 and 2.5 Hz, respectively, which suggest that H-an is equatorial to the oxadiazaphosphinane ring. This is supported by a strong NOE from H-11a to both H-1 protons. The vicinal couplings between H-11a and H-11 show an axial orientation of H-11a with respect to the isoquinoline ring. These findings are in accord with two possible conformations: a cis-2-connected chair–chair and a trans-connected chair-boat. In order to establish the most stable conformer, ab initio calculations were performed at the HF/6-31* level. The calculations revealed that conformation cis-2 is 5.3 kcal/mol more stable, and we therefore believe that the hetero rings are predominantly cis-connected (cis-2 conformation; Fig. 3).

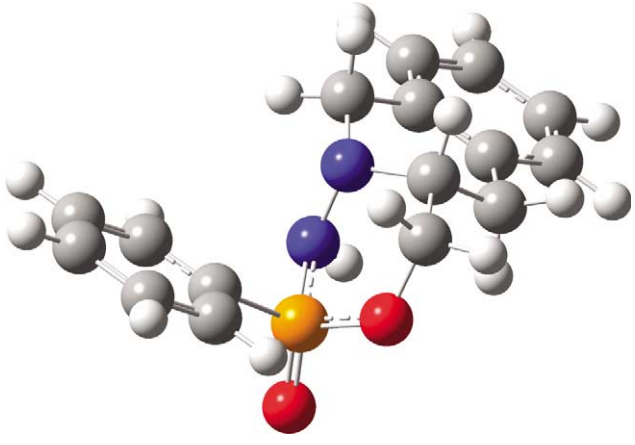


Figure 3. Ab initio geometry obtained for **15a**.

Concerning the orientation of the *P*-substituent, P-Ph-H-1_{ax} NOE interactions could readily be detected in **14** and **16a**,**b** (Fig. 2), which indicates the axial arrangement of the *P*-phenyl group and its position trans to H-an (H-11b or H-11a, respectively).

P-Ph-H-1_{ax} or P-OPh-H-1_{ax} NOE interactions could not be determined unambiguously for compounds **17a** and **18a**, and the *P*-configuration was therefore deduced from the chemical shifts calculated by using the GIAO method at the HF/6-31G* level and the geometrical constraints obtained by means of NMR. It is a trend that H-1_{ax} exhibits an upfield shift in compounds containing an axial *P*-phenyl group (i.e., trans to H-an), due to the ring current shielding. The comparison of the experimental and theoretical chemical shifts (Table 2) unambiguously corroborated the assignment. Unfortunately, the phenoxy derivatives

Table 2. Experimental and calculated characteristic chemical shifts in ppm ($\delta_{TMS}=0$)

Compound	H-1_{ax}		H-1_{eq}	
	Exp.	Calcd	Exp.	Calcd
13	4.72	4.09	4.58	3.91
14	4.05	3.29	4.72	3.87
15a	4.44	3.27	4.32	3.48
16a	3.99	3.04	4.51	3.53
16b	3.97	3.01	4.46	3.49
17a	4.42	3.97	4.13	3.45
18a	3.78	3.02	4.16	3.39
17b	4.23	3.69	4.17	3.18
18b	4.26	3.73	4.31	3.50

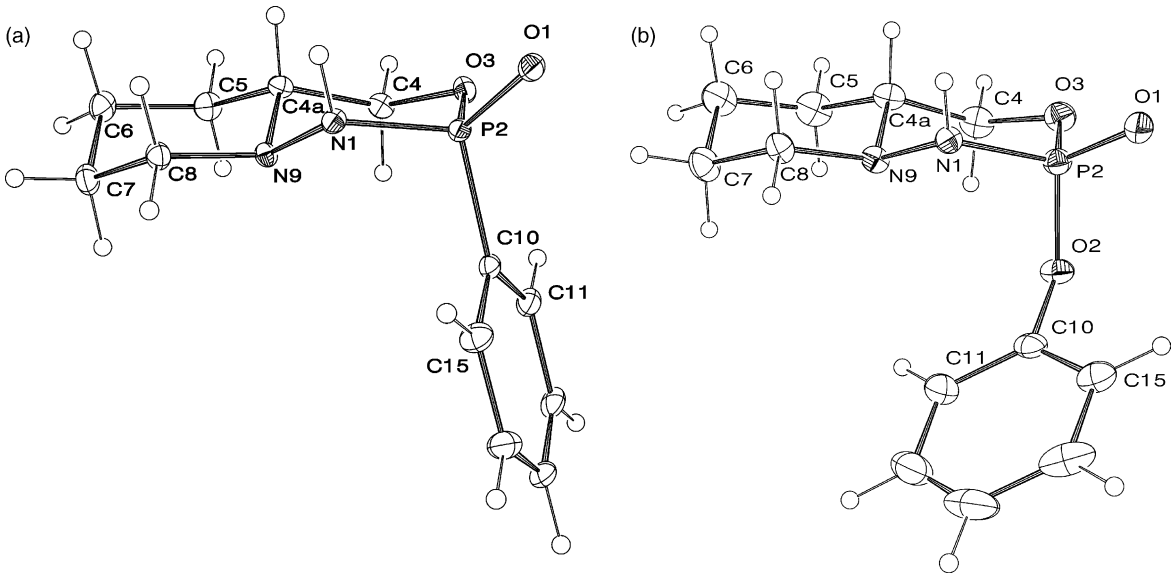


Figure 4. X-ray crystal structures of **18a** and **18b**. The thermal displacement ellipsoids are drawn at a probability level of 30%.

(**17b** and **18b**) did not allow utilization of the shielding effect because of the flexible aromatic substituent; the stereochemical assignment is therefore based purely on the X-ray data. The steric assignment of the *P*-2 epimers of **17** and **18**, based on the results of NMR experiments and theoretical calculations, was in accordance with the X-ray crystal structures of **18a** and **18b** (Fig. 4).

The stereochemical assignments for **13–18** are presented in Table 3.

Table 3. Stereochemical assignments for **13–18**

Compound	Steric position of H-an and the *P*-substituent	Stereochemistry of the junction of the hetero rings	Oxadiazaphosphinane ring conformation
13	cis	trans	chair
14	trans	trans	chair
15a	cis	cis	chair
16a	trans	trans	chair
16b	trans	trans	chair
17a	cis	trans	chair
18a	trans	trans	chair
17b	cis	trans	chair
18b	trans	trans	chair

The chair conformation found for 1,3,4,2-diazaphosphinanes angularly fused to tetrahydroisoquinoline (**13**, **14**) is substantially different from the steric structures of the analogous 1,3,2-oxazaphosphino[4,3-*a*]isoquinolines, which could be characterized by distorted conformations of the 1,3,2-oxazaphosphinane ring.[20]

3. Conclusions

The first representatives of the new ring systems, which are *P*-epimeric diastereomers of 1,6,7,11b-tetrahydro-4*H*-1,3,4,2-oxadiazaphosphino[5,4-*a*]isoquinoline-3-oxides (**13** and **14**), 1,6,11,11a-tetrahydro-4*H*-1,3,4,2-oxadiazaphosphino[4,5-*b*]isoquinoline-3-oxides (**15** and **16**) and 1,6,7,8,9,9a-hexahydro-4*H*-pyrido[1,2-*d*][1,3,4,2]oxadiazaphosphinane-3-oxides (**17** and **18**), have been prepared via cyclization of the corresponding tetrahydroisoquinoline or piperidine hydrazino alcohols. The NMR spectroscopic and X-ray diffraction data allowed the preferred conformation of **13–18** to be identified. This revealed that, independent of the *P*-substituent and the relative configuration of the phosphorus atom, **13**, **14**, **17** and **18** could be characterized by trans-connected hetero rings and the chair conformation of the 1,3,4,2-oxadiazaphosphinane moiety, while the stereochemistry of the connection of the hetero rings (trans or cis-2) was found to be dependent on the *P*-configuration relative to that of the carbon at the annelation site for 1,3,4,2-oxadiazaphosphinanes linearly fused to tetrahydroisoquinoline (**15** and **16**).

4. Experimental

4.1. General

The NMR spectra were recorded in $CDCl_3$ or in D_2O solutions at 300 K on a Bruker AVANCE DRX 400 spectrometer. Chemical shifts are given in δ (ppm) relative to TMS ($CDCl_3$) or to TSP (D_2O) as internal standards; multiplicities were recorded as s (singlet), br s (broad singlet), d (doublet), dd (double doublet), ddd (double double doublet), td (triple doublet), dtd (double triple doublet), dddd (double double double doublet), t (triplet), dt (double triplet), tt (triple triplet), q (quartet), dq (double quartet), tq (triple quartet) and m (multiplet). IR spectra were run in KBr discs on a Perkin-Elmer Paragon 1000 PC FT-IR spectrometer controlled by GRAMS Analyst for PE 1000 3.01A software. Melting points were recorded on a Kofler hot-plate microscope apparatus and are uncorrected. For column chromatography, silica gel 60 (0.063–0.200 mm) was used.

X-ray crystallographic study. Crystallographic data were collected at 173 K with a Nonius Kappa CCD area-detector diffractometer, with the use of graphite-monochromatized

Mo-K_α radiation (λ=0.71073 Å). The data collection was performed with ϕ and ω scans. The data were processed with DENZO-SMN ν 0.93.0.[21]

The structures were solved by direct methods with use of the SIR92 program,[22] and full-matrix, least-squares refinements on F^2 were performed with the SHELXL-97 program.[23] In both cases, all heavy atoms were refined anisotropically. The CH hydrogen atoms were included at fixed distances from their host atoms, with fixed displacement parameters. The NH hydrogen atoms were refined with isotropic displacement parameters. Figures were drawn with ORTEP-3 for Windows.[24] CCDC-284666 (**18a**) and CCDC-284667 (**18b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (Internet) +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk].

Compounds **6b**,[16] **7a**,[15] **9**[16] and **12**[18] were prepared according to known procedures.

4.1.1. Ethyl 6,7-dimethoxy-3,4-dihydroisoquinoline-1-carboxylate (2). A mixture of 2-(3,4-dimethoxyphenyl)-ethylamine (**1**) (54.4 g, 0.3 mol) and diethyl oxalate (131.5 g, 0.9 mol) was stirred at 140 °C for 6 h. The ethanol formed and the excess of diethyl oxalate were distilled off in vacuo, and the oily residue was treated with Et_2O, resulting in ethyl *N*-[2-(3,4-dimethoxyphenyl)ethyl]oxamate as a crystalline product. The crystals were filtered off, washed with Et_2O and used in the next step without further purification. Yield: 68.7 g (81%).

An analytical sample of the product was recrystallized from iPr$_2$O to give shining white plates. Mp: 68–70 °C (lit.[25] mp: 73–74 °C). [Found: C, 59.89; H, 6.75; N, 5.03. $C_{14}H_{19}NO_5$ requires C, 59.78; H, 6.81; N, 4.98%]; ν_{max} 1746, 1683, 1516, 1238, 1023 cm^{-1}; δ_H ($CDCl_3$) 1.38 (t, 3H, J=7.2 Hz, CH_2CH_3), 2.82 (t, 2H, J=6.8 Hz, ArCH_2), 3.58 (q, 2H, J=6.8 Hz, NCH_2), 3.87 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.33 (q, 2H, J=7.2 Hz, OCH_2), 6.70–6.76 (m, 2H, C_6H_3), 6.82 (d, 1H, J=8.1 Hz, C_6H_3), 7.14 (br s, 1H, N*H*).

To a stirred solution of ethyl *N*-[2-(3,4-dimethoxyphenyl) ethyl]oxamate (40.0 g, 0.142 mol) in abs toluene (350 mL) and abs EtOH (30 mL), $POCl_3$ (120.0 g, 0.783 mol) was added. The resulting mixture was stirred and refluxed for 3.5 h, and then evaporated under reduced pressure. The oily residue was carefully dissolved in warm 96% ethanol (100 mL) and the solution was added to a mixture of ice-cold water (500 mL) and EtOAc (250 mL). The resulting mixture was made alkaline with concd NH_4OH under vigorous stirring and external cooling on an ice-water bath. The organic layer was separated and the aqueous layer was extracted with EtOAc (2×250 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. The oily residue was treated with Et_2O to give **2** as a beige crystalline product, which was filtered off, washed with Et_2O and used in the next step without any further purification. Yield: 22.4 g (60%).

An analytical sample of **2** was recrystallized from iPr$_2$O to give pale-beige crystals. Mp: 76–78 °C (lit.[14b] mp: 81.5–83 °C). [Found: C, 63.95; H, 6.60; N, 5.30. $C_{14}H_{17}NO_4$ requires C, 63.87; H, 6.51; N, 5.32%]; ν_{max} 1719, 1518, 1277, 1198, 1135 cm^{-1}; δ_H ($CDCl_3$) 1.44 (t, 3H, J=7.1 Hz, CH_2CH_3), 2.67–2.74 (m, 2H, ArCH_2), 3.83–3.89 (m, 2H, NCH_2), 3.90 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.43 (q, 2H, J=7.1 Hz, OCH_2), 6.70 (s, 1H, C_6H_2), 7.39 (s, 1H, C_6H_2).

4.1.2. Ethyl 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (3). To a solution of dihydroisoquinoline **2** (22.0 g, 83.6 mmol) in EtOH (200 mL), 5% platinum on activated charcoal catalyst (1.00 g) was added and the mixture was stirred under hydrogen at atmospheric pressure and ambient temperature. When the hydrogen uptake had ceased (approx 6 h), the catalyst was filtered off and the filtrate was evaporated. The oily product was dissolved in EtOH (30 mL) and treated with 22% ethanolic HCl (20 mL) and Et_2O (100 mL) to yield crystalline **3**·HCl. The crystals were filtered off and washed with a 1:4 mixture of EtOH and Et_2O (100 mL). Yield: 20.7 g (82%). For the further transformations, the free base **3** was liberated from the above hydrochloride salt in the usual manner (Na_2CO_3 and EtOAc).

An analytical sample of **3**·HCl was recrystallized from EtOH–Et_2O to give yellowish-white crystals. Mp: 202–204 °C. [Found: C, 55.48; H, 6.37; N, 4.60. $C_{14}H_{20}ClNO_4$ requires C, 55.72; H, 6.68; N, 4.64%]; ν_{max} 1740, 1522, 1264, 1238, 1027 cm^{-1}; δ_H (D_2O) 1.34 (t, 3H, J=7.1 Hz, CH_2CH_3), 3.02–3.18 (m, 2H, ArCH_2), 3.59–3.72 (m, 2H, NCH_2), 3.88 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.38 (q, 2H, J=7.1 Hz, OCH_2), 5.40 (s, 1H, NC*H*), 6.95 (s, 1H, C_6H_2), 7.17 (s, 1H, C_6H_2).

4.1.3. (6,7-Dimethoxy-1,2,3,4-tetrahydro-1-isoquinolyl)-methanol (4). To a stirred and ice-cooled suspension of $LiAlH_4$ (3.10 g, 81.7 mmol) in dry THF (100 mL), a solution of compound **3** (12.0 g, 39.8 mmol) in dry THF (35 mL) was added dropwise. The mixture was stirred and refluxed for 3 h and then cooled, and the excess of $LiAlH_4$ was decomposed by the addition of a mixture of water (6.2 mL) and THF (50 mL). After stirring at room temperature for 1 h, the inorganic salts were filtered off and washed with hot EtOAc (3×120 mL). The combined organic filtrate and washings were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude amino alcohol **4** as a crystalline product, which was filtered off, washed with Et_2O and recrystallized from EtOAc. Yield: 5.87 g (66%). Mp: 138–139 °C (lit.[26] mp: 134–135 °C). ν_{max} 3316, 1517, 1259, 1225, 1060 cm^{-1}. The ^{1}H NMR spectrum of **4** was in accordance with the literature[27] data on the (*S*) enantiomer of **4**.

4.1.4. (6,7-Dimethoxy-1,2,3,4-tetrahydro-3-isoquinolyl)-methanol (7b). *Method A*. To a stirred and ice-cooled suspension of $LiAlH_4$ (5.85 g, 154 mmol) in dry THF (300 mL), compound **6b** (10.50 g, 38.4 mmol) was added in small portions. The mixture was stirred and refluxed for 8 h, which was followed by the usual work-up (see the previous procedure), resulting in the crude amino alcohol **7b** as a crystalline product. Recrystallization from EtOAc gave analytically pure **7b** as white needles. Yield: 4.4 g (51%). Mp: 146–147 °C. [Found: C, 64.73; H, 7.52; N, 6.33.

$C_{12}H_{17}NO_3$ requires C, 64.55; H, 7.67; N, 6.27%]; ν_{max} 3286, 1522, 1239, 1227, 1079 cm^{-1}; δ_H ($CDCl_3$) 2.50 (dd, 1H, J=10.5, 16.0 Hz, 4-CH_2), 2.61 (dd, 1H, J=4.4, 16.0 Hz, 4-CH_2), 3.00–3.08 (m, 1H, NCH), 3.52 (dd, 1H, J=8.0, 10.8 Hz, OCH_2), 3.77 (dd, 1H, J=3.7, 10.8 Hz, OCH_2), 3.83 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.98 (s, 2H, 1-CH_2), 6.53 (s, 1H, C_6H_2), 6.57 (s, 1H, C_6H_2).

Method B. A mixture of compound **11**·HCl (35.0 g, 0.1 mol), 10% Pd/C catalyst (2.0 g) and MeOH (500 mL) was hydrogenated in an autoclave at 40 °C and 30 bar for 30 h. The catalyst was removed by filtration, and the filtrate was evaporated to dryness to give **7b**·HCl as a crystalline product. The crystals were filtered off and washed with Et_2O. Yield: 25.8 g (~100%). For the further transformations, free base **7b** was liberated from the above hydrochloride salt in the usual manner (Na_2CO_3 and EtOAc).

An analytical sample of **7b**·HCl was recrystallized from 95% MeOH–Et_2O to give a white powder. Mp: 280–282 °C. [Found: C, 55.24; H, 6.81; N, 5.37. $C_{12}H_{18}ClNO_3$ requires C, 55.49; H, 6.99; N, 5.39%]; ν_{max} 3374, 2911, 2765, 1522, 1230, 1130 cm^{-1}; δ_H (D_2O) 2.92–3.07 (m, 2H, 4-CH_2), 3.60–3.68 (m, 1H, NCH), 3.78–3.90 (m, 7H, 2×OCH_3, OCH_2), 4.03 (dd, 1H, J=3.5, 12.5 Hz, OCH_2), 4.32–4.43 (m, 2H, 1-CH_2), 6.86 (s, 1H, C_6H_2), 6.89 (s, 1H, C_6H_2).

4.1.5. 2-Benzylamino-3-(3,4-dimethoxyphenyl)-1-propanol (10). To a stirred and ice-cooled suspension of $LiAlH_4$ (12.0 g, 316 mmol) in dry THF (400 mL), compound **9** (23.0 g, 67 mmol) was added in small portions. The mixture was stirred and refluxed for 5 h. The usual work-up (see above) resulted in crude amino alcohol **10** as a crystalline product. The crystals were filtered off, washed with Et_2O and used in the next step without further purification. Yield: 15.8 g (78%).

An analytical sample of the product was recrystallized from iPr$_2$O–EtOAc to give white needles. Mp: 115–115.5 °C (lit.[17] mp: 114–116 °C). [Found: C, 71.44; H, 7.49; N, 4.50. $C_{18}H_{23}NO_3$ requires C, 71.73; H, 7.69; N, 4.65%]; ν_{max} 3286, 2837, 1517, 1264, 1238, 1136 cm^{-1}; δ_H ($CDCl_3$) 2.70–2.77 (m, 2H, ArCH_2C), 2.88–2.96 (m, 1H, NCH), 3.36 (dd, 1H, J=4.9, 10.7 Hz, OCH_2), 3.66 (dd, 1H, J=3.9, 10.7 Hz, OCH_2), 3.72–3.82 (m, 2H, NCH_2), 3.83 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.63–6.67 (m, 1H, C_6H_3), 6.70 (dd, 2H, J=1.6, 8.0 Hz, C_6H_3), 6.77–6.82 (m, 5H, C_6H_5).

4.1.6. (2-Benzyl-6,7-dimethoxy-1,2,3,4-tetrahydro-3-isoquinolyl)methanol (11). A mixture of compound **10** (13.8 g, 45.8 mmol), water (500 mL), 36% formalin (55 mL) and concd HCl (28 mL) was stirred and refluxed for 6 h. The solution was left to cool to ambient temperature, then made alkaline (under ice-bath cooling) with 10% NaOH solution and extracted with $CHCl_3$ (4×150 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give crude **11** as a yellow oil. The oily product was dissolved in MeOH (50 mL) and converted to the crystalline hydrochloride of **11** by adding an excess of 22% ethanolic HCl (20 mL) and Et_2O (300 mL). The crystals were filtered off, washed with a 1:10 mixture of MeOH and Et_2O and used in the next step without further purification. Yield: 14.8 g (92%).

An analytical sample of **11**·HCl was recrystallized from MeOH–Et_2O to give white needles. Mp: 209–211 °C. [Found: C, 65.48; H, 7.03; N, 3.91. $C_{19}H_{24}ClNO_3$ requires C, 65.23; H, 6.91; N, 4.00%]; ν_{max} 3220, 1525, 1225, 1193, 1092 cm^{-1}; δ_H (D_2O) 3.04 (dd, 1H, J=6.9, 17.6 Hz, 4-CH_2), 3.21 (dd, 1H, J=2.8, 17.6 Hz, 4-CH_2), 3.84 (s, 3H, OCH_3) 3.85–3.99 (m, 5H, OCH_2, OCH_3, NCH), 4.02–4.11 (m, 1H, OCH_2), 4.16–4.49 (m, 4H, 2×NCH_2) 6.80 (s, 1H, C_6H_2), 6.98 (s, 1H, C_6H_2), 7.42–7.62 (m, 5H, C_6H_5).

4.2. General procedure for the preparation of the hydrazino alcohols 5, 8a and 8b

A solution of $NaNO_2$ (1.38 g, 20 mmol) in H_2O (10 mL) was added dropwise to a suspension of the corresponding amino alcohol (**4** or **7a** or **7b**, 10 mmol) in H_2O (50 mL) with vigorous stirring on an ice-cold bath, and AcOH (0.90 g, 15 mmol) was then added dropwise. The mixture was stirred at room temperature for 8 h and then extracted with EtOAc (4× 50 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the *N*-nitroso derivatives of **4**, **7a** and **7b** in nearly quantitative yields. According to TLC, the products were pure enough to be used in the next step without further purification.

The solution of the corresponding crude *N*-nitroso derivative of **4** or **7a** or **7b** in THF (15 mL) was added dropwise to a stirred and ice-cooled suspension of $LiAlH_4$ (0.76 g, 20 mmol) in THF (30 mL). The mixture was stirred at room temperature for 2 h, after which the usual work-up (see above) resulted in the crude hydrazino alcohols as oily (**5**, **8a**) or crystalline (**8b**) products. The crystalline **8b** was filtered off, washed with *n*-hexane and recrystallized from iPr$_2$O–EtOAc. The oily products (**5** and **8a**) were converted to the crystalline hydrochlorides by treatment of their solution in MeOH with an excess of 22% ethanolic HCl and Et_2O.

4.2.1. Compound 5·HCl. Yield: 1.95 g (71%). Mp: 210–215 °C (95% MeOH–Et_2O). [Found: C, 52.13; H, 6.85; N, 10.01. $C_{12}H_{19}ClN_2O_3$ requires C, 52.46; H, 6.97; N, 10.20%]; ν_{max} 3335, 3289, 1524, 1269, 1230 cm^{-1}; δ_H (D_2O) 3.13–3.19 (m, 2H, 4-CH_2), 3.56–3.62 (m, 1H, 3-CH_2), 3.82–3.89 (m, 1H, 3-CH_2), 3.90 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.99 (dd, 1H, J=8.0, 12.8 Hz, 1′-CH_2), 4.26 (dd, 1H, J=3.2, 12.8 Hz, 1′-CH_2), 4.57 (m, 1H, 1-CH), 6.94 (s, 1H, C_6H_2), 6.98 (s, 1H, C_6H_2).

4.2.2. Compound 8a·HCl. Yield: 1.42 g (66%). Mp: 195–197 °C. [Found: C, 55.63; H, 6.79; N, 12.98. $C_{10}H_{15}ClN_2O$ requires C, 55.94; H, 7.04; N, 13.05%]; ν_{max} 3341, 2980, 2752, 1449, 1086, 766 cm^{-1}; δ_H (D_2O) 3.04 (dd, 1H, J=10.5, 17.5 Hz, 4-CH_2), 3.13 (dd, 1H, J=5.2, 17.5 Hz, 4-CH_2), 3.68–3.76 (m, 1H, 3-CH), 3.79 (dd, 1H, J=6.8, 12.4 Hz, 1′-CH_2), 4.01 (dd, 1H, J=3.6, 12.4 Hz, 1′-CH_2), 4.46 (s, 2H, 1-CH_2), 7.24–7.37 (m, 4H, C_6H_4).

4.2.3. Compound 8b. Yield: 1.60 g (67%). Mp: 91–93 °C. [Found: C, 59.62; H, 7.70; N, 11.51. $C_{12}H_{18}N_2O_3$ requires C, 60.49; H, 7.61; N, 11.76%]; ν_{max} 1520, 1255, 1228, 1120, 1049 cm^{-1}; δ_H ($CDCl_3$) 2.59 (dd, 1H, J=4.2, 16.1 Hz, 4-CH_2), 2.67–2.88 (m, 2H, 4-CH_2, 3-CH), 3.73–3.88 (m, 9H, OCH_2, 2×OCH_3, 1-CH_2), 3.98 (d, 1H, J=14.5 Hz, 1-CH_2), 6.51 (1H, s, C_6H_2), 6.59 (1H, s, C_6H_2).

4.3. General procedure for the preparation of the 1,3,4,2-oxadiazaphosphino[5,4-*a*]isoquinolines (13, 14), 1,3,4,2-oxadiazaphosphino[4,5-*b*]isoquinolines (15a,b; 16b) and pyrido[1,2-*d*]1,3,4,2-oxadiazaphosphinanes (17a,b; 18a,b)

To a solution of the corresponding hydrazino alcohol (**8b** or **12**, 10 mmol) or hydrazino alcohol hydrochloride (**5**·HCl or **8a**·HCl, 10 mmol) and Et_3N (2.02 g, 20 mmol; in the case of **5**·HCl and **8a**·HCl: 3.04 g, 30 mmol) in anhydrous THF (100 mL) at room temperature, a solution of phenylphosphonic dichloride or phenyl dichlorophosphate (10 mmol) in anhydrous THF (20 mL) was added dropwise over a period of 30 min. The mixture was stirred at room temperature for 48 h and then filtered, and the filtrate was evaporated in vacuo to afford a yellow oil containing a mixture of the corresponding oxadiazaphosphinane diastereomers. The diastereomeric ratios were determined from the ^{1}H NMR spectra of the crude products. Purification of the crude products by column chromatography gave **14**, **15a**, **17b** and **18a** as the more mobile, and **13**, **16a**, **17a** and **18b** as the less mobile diastereomers. Compound **16b** was the only product in the ring closure.

Compounds **13**:**14**=48:52. Eluent: EtOAc.

Compound **13**. A white solid; yield: 0.44 g (12%). Mp: 173–176.5 °C (*i*Pr_2O–EtOAc). [Found: C, 59.95; H, 5.91; N, 7.82. $C_{18}H_{21}N_2O_4P$ requires C, 60.00; H, 5.87; N, 7.77%]; ν_{max} 3122, 1513, 1228, 1128, 797 cm^{-1}; δ_H ($CDCl_3$) 2.79 (dt, 1H, *J*=4.0, 15.4 Hz, H-9eq), 3.10 (dd, 1H, *J*=4.5, 8.8 Hz, H-9ax), 3.15 (td, 1H, *J*=4.0, 8.8 Hz, H-10ax), 3.6 (dd, 1H, *J*=4.5, 10.3 Hz, H-10eq), 3.88 (s, 3H, OC*H*$_3$), 3.89 (s, 3H, OC*H*$_3$), 4.25 (dd, 1H, *J*=4.3, 9.3 Hz, H-4a), 4.58 (ddd, 1H, *J*=4.3, 11.6, 17.1 Hz, H-4eq), 4.72 (ddd, 1H, *J*=5.3, 9.3, 11.6 Hz, H-4ax), 6.55 (s, 1H, H-5), 6.64 (s, 1H, H-8), 7.52 (dt, 2H, *J*=4.0, 7.5 Hz, *m*-Ar), 7.63 (dt, 1H, *J*=1.5, 7.3 Hz, *p*-Ar), 8.0 (ddd, 2H, *J*=1.5, 8.3, 13.0 Hz, *o*-Ar); δ_C ($CDCl_3$) 26.7 (C-9), 51.9 (C-10), 56.0 (C-6, C-7), 60.5 (C-4a), 67.6 (C-4), 108.5 (C-5), 112.1 (C-8), 123.2 (C-4b), 125.6 (C-8a), 128.1 (CP), 128.6 (*m*-Ar), 132.1 (*o*-Ar), 133.0 (*p*-Ar).

Compound **14**. A white foam; yield: 0.80 g (22%). [Found: C, 59.92; H, 5.89; N, 7.80. $C_{18}H_{21}N_2O_4P$ requires C, 60.00; H, 5.87; N, 7.77%]; ν_{max} 2933, 1522, 1235, 1129, 799 cm^{-1}; δ_H ($CDCl_3$) 2.67 (dt, 1H, *J*=3.0, 15.4 Hz, H-9eq), 2.93 (td, 1H, *J*=2.8, 10.3 Hz, H-10ax), 3.01 (ddd, 1H, *J*=5.0, 10.8, 15.9 Hz, H-9ax), 3.26–3.31 (m, 1H, H-10eq), 3.84 (s, 3H, OC*H*$_3$), 3.85 (s, 3H, OC*H*$_3$), 4.01 (d, 1H, *J*=11.0 Hz, H-4a), 4.05 (td, 1H, *J*=1.3, 10.6 Hz, H-4ax), 4.72 (ddd, 1H, *J*=2.8, 10.3, 18.6 Hz, H-4eq), 6.48 (s, 1H, H-5), 6.58 (s, 1H, H-8), 7.48 (dt, 2H, *J*=4.0, 7.5 Hz, *m*-Ar), 7.55 (dt, 1H, *J*=1.5, 7.3 Hz, *p*-Ar), 7.93 (ddd, 2H, *J*=1.5, 8.3, 13.6 Hz, *o*-Ar); δ_C ($CDCl_3$) 29.6 (C-9), 52.8 (C-10), 56.2 (C-6,C-7), 63.1 (C-4a), 73.4 (C-4), 108.0 (C-5), 111.7 (C-8), 122.8 (C-4b), 126.6 (C-8a), 130.1 (CP), 128.5 (*m*-Ar), 131.1 (*o*-Ar), 132.0 (*p*-Ar).

Compounds **15a**:**16a**=50:50. Eluent: EtOAc.

Compound **15a**. A white solid; yield: 0.81 g (27%). Mp: 145–148 °C [Found: C, 63.82; H, 5.55; N, 9.46. $C_{16}H_{17}N_2O_2P$ requires C, 64.00; H, 5.71; N, 9.33%]; ν_{max} 3118, 1390, 1241, 1130, 950 cm^{-1}; δ_H ($CDCl_3$) 2.73 (dd, 1H, *J*=5.5, 17.6 Hz, H-5eq), 3.19 (m, 1H, H-4a), 3.48 (dd, 1H, *J*=11.8, 17.6 Hz, H-5ax), 4.09 (d, 1H, *J*=16.1 Hz, H-10eq), 4.28 (dd, 1H, *J*=2.5, 6.5 Hz, H-10ax), 4.32 (ddd, 1H, *J*=2.5, 11.3, 17.9 Hz, H-4eq), 4.44 (ddd, 1H, *J*=3.3, 4.0, 11.3 Hz, H-4ax), 7.09 (dd, 1H, *J*=2.8, 6.3 Hz, H-9), 7.16–7.26 (m, 3H, H-6, H-7, H-8), 7.52 (dt, 2H, *J*=4.0, 7.3 Hz, *m*-Ar), 7.59 (dt, 1H, *J*=1.3, 7.5 Hz, *p*-Ar), 7.96 (ddd, 2H, *J*=1.3, 8.3, 13.6 Hz, *o*-Ar); δ_C ($CDCl_3$) 23.4 (C-5), 53.9 (C-4a), 58.2 (C-10), 70.8 (C-4), 127.2 (C-7, C-8), 127.4 (C-6), 129.0 (C-9), 130.5 (C-5a), 131.2 (C-9a), 127.3 (CP), 129.0 (*m*-Ar), 131.3 (*o*-Ar), 132.3 (*p*-Ar).

Compound **16a**. A white solid; yield: 0.42 g (14%). Mp: 209–211 °C. [Found: C, 64.15; H, 5.68; N, 9.21. $C_{16}H_{17}N_2O_2P$ requires C, 64.00; H, 5.71; N, 9.33%]; ν_{max} 3108, 1450, 1238, 1004, 817 cm^{-1}; δ_H ($CDCl_3$) 2.71 (dd, 1H, *J*=10.3, 16.1 Hz, H-5ax), 2.84 (dd, 1H, *J*=4.8, 16.2 Hz, H-5eq), 3.07 (tt, 1H, *J*=4.0, 10.8 Hz, H-4a), 3.78 (d, 1H, *J*=14.9 Hz, H-10ax), 3.99 (ddd, 1H, *J*=7.3, 9.8, 11.6 Hz, H-4ax), 4.36 (d, 1H, *J*=14.6 Hz, H-10eq), 4.51 (ddd, 1H, *J*=4.0, 11.6, 18.38 Hz, H-4eq), 7.09 (dd, 2H, *J*=3.3, 5.3 Hz, H-6, H-9), 7.19 (dd, 2H, *J*=3.5, 5.3 Hz, H-7, H-8), 7.48 (dt, 2H, *J*=4.0, 7.5 Hz, *m*-Ar), 7.55 (dt, 1H, *J*=1.3, 7.3 Hz, *p*-Ar), 7.98 (ddd, 2H, *J*=1.5, 8.3, 13.6 Hz, *o*-Ar); δ_C ($CDCl_3$) 31.1 (C-5), 58.6 (C-4a), 58.9 (C-10), 70.7 (C-4), 126.2 (C-6), 126.7 (C-7, C-8), 128.1 (C-9), 128.5 (*m*-Ar), 131.1 (C-9a), 131.4 (C-5a), 126.5 (CP), 131.5 (*o*-Ar), 132.4 (*p*-Ar).

Compound **16b**. Eluent: EtOAc/MeOH=9:1.

Compound **16b**. Transparent crystals; yield: 1.43 g (40%). Mp: 201–205 °C (*i*Pr_2O–EtOAc). [Found: C, 60.10; H, 5.74; N, 7.86. $C_{18}H_{21}N_2O_4P$ requires C, 60.00; H, 5.87; N, 7.77%]; ν_{max} 3092, 1519, 1236, 1028, 804 cm^{-1}; δ_H ($CDCl_3$) 2.61 (dd, 1H, *J*=10.3, 16.3 Hz, H-5ax), 2.74 (dd, 1H, *J*=4.8, 16.4 Hz, H-5eq), 3.06 (tt, 1H, *J*=4.0, 10.8 Hz, H-4a), 3.75 (d, 1H, *J*=14.1 Hz, H-10ax), 3.82 (s, 3H, OC*H*$_3$), 3.84 (s, 3H, OC*H*$_3$), 3.97 (td, 1H, *J*=8.1, 11.6 Hz, H-4ax), 4.23 (d, 1H, *J*=14.4 Hz, H-10eq), 4.46 (ddd, 1H, *J*=3.8, 11.6, 18.1 Hz, H-4eq), 6.53 (s, 2H, H-6, H-9), 7.47 (dt, 2H, *J*=4.0, 7.5 Hz, *m*-Ar), 7.55 (dt, 1H, *J*=1.3, 7.5 Hz, *p*-Ar), 7.96 (ddd, 2H, *J*=1.3, 8.3, 13.6 Hz, *o*-Ar); δ_C ($CDCl_3$) 30.6 (C-5), 55.9 (C-7, C-8), 58.4 (C-4a), 58.5 (C-10), 70.7 (C-4), 110.2 (C-6, C-9), 123.0 (C-5a), 124.2 (C-9a), 127.7 (CP), 128.6 (*m*-Ar), 132.0 (*p*-Ar), 132.1 (*o*-Ar).

Compounds **17a**:**18a**=21:79. Eluent: EtOAc/MeOH=9:1.

Compound **17a**. Transparent needles; yield: 0.50 g (20%). Mp: 178–181 °C (EtOAc). [Found: C, 57.11; H, 6.81; N, 11.13. $C_{12}H_{17}N_2O_2P$ requires C, 57.14; H, 6.79; N, 11.11%]; ν_{max} 3109, 2933, 1439, 1224, 801 cm^{-1}; δ_H ($CDCl_3$) 1.31 (tq, 1H, *J*=3.5, 12.3 Hz, H-6ax), 1.42 (dq, 1H, *J*=3.5, 12.8 Hz, H-5ax), 1.54–1.75 (m, 4H, H-5eq), 1.75–1.83 (m, 2H, H-6eq, H-7), 2.33 (dt, 1H, *J*=3.0, 11.3 Hz, H-8ax), 2.58 (tt, 1H, *J*=3.0, 13.4 Hz, H-4a), 3.29 (td, 1H, *J*=3.5, 10.8 Hz, H-8eq), 4.17 (ddd, 1H, *J*=3.3, 11.3, 18.9 Hz, H-4eq), 4.49 (ddd, 1H, *J*=3.5, 9.8, 11.3 Hz, H-4ax), 7.5 (dt, 2H, *J*=4.0, 7.8 Hz, *m*-Ar), 7.6 (dt, 1H, *J*=1.3, 7.5 Hz, *p*-Ar), 7.9 (ddd, 2H, *J*=1.3, 8.3, 12.8 Hz, *o*-Ar); δ_C ($CDCl_3$) 22.9 (C-6), 24.1 (C-7), 26.2 (C-5), 58.2 (C-8), 63.5 (C-4a), 70.2 (C-4), 126.7 (CP), 128.5 (*m*-Ar), 132.0 (*o*-Ar), 133.0 (*p*-Ar).

Compound **18a**. White crystals; yield: 0.54 g (21%). Mp: 146–148 °C (EtOAc). [Found: C, 57.20; H, 6.84; N, 11.09. $C_{12}H_{17}N_2O_2P$ requires C, 57.14; H, 6.79; N, 11.11%]; ν_{max} 3112, 2944, 1456, 1225, 810 cm^{-1}; δ_H ($CDCl_3$) 1.06 (dtd, 1H, J=3.8, 11.3, 13.4 Hz, H-5ax), 1.19–1.32 (m, 1H, H-6), 1.48–1.8 (m, 4H, H-5eq, H-6eq, H-7), 2.29 (ddd, 1H, J=2.3, 10.3, 12.6 Hz, H-8ax), 2.46 (tt, 1H, J=3.0, 10.8 Hz, H-4a), 3.26 (td, 1H, J=2.3, 11.0 Hz, H-8eq), 3.53 (d, 1H J=10.6 Hz, N*H*), 3.81 (ddd, 1H, J=2.0, 10.3, 11.3 Hz, H-4ax), 4.18 (ddd, 1H, J=3.0, 11.3, 20.4 Hz, H-4eq), 7.46 (dt, 2H, J=4.0, 7.3 Hz, *m*-Ar), 7.53 (dd, 1H, J=1.3, 7.3 Hz, *p*-Ar), 7.9 (ddd, 2H, J=1.3, 7.8, 12.8 Hz, *o*-Ar); δ_C ($CDCl_3$) 22.7 (C-6), 26.1 (C-7), 26.6 (C-5), 58.1 (C-8), 62.5 (C-4a), 73.13 (C-4), 128.3 (CP), 128.6 (*m*-Ar), 131.3 (*o*-Ar), 132.0 (*p*-Ar).

Compounds **17b**:**18b**=50:50. Eluent: EtOAc.

Compound **17b**. Transparent needles; yield: 0.54 g (20%). Mp: 153–154.5 °C (*i*Pr_2O–EtOAc). [Found: C, 53.80; H, 6.36; N, 10.41. $C_{12}H_{17}N_2O_3P$ requires C, 53.73; H, 6.39; N, 10.44%]; ν_{max} 3129, 2943, 1263, 1010, 942 cm^{-1}; δ_H ($CDCl_3$) 1.2 (dddd, 1H, J=3.8, 11.1, 13.6, 16.9 Hz, H-5ax), 1.31 (tq, 1H, J=4.0, 13.1 Hz, H-6ax), 1.56–1.81 (m, 4H, H-5eq, H-6eq, H-7), 2.26 (dt, 1H, J=2.8, 11.8 Hz, H-8ax), 2.45 (tt, 1H, J=3.0, 10.6 Hz, H-4a), 3.20 (dt, 1H, J=3.5, 10.8 Hz, H-8eq), 3.75 (d, 1H, J=9.8 Hz, N*H*), 4.17 (ddd, 1H, J=3.5, 11.0, 19.9 Hz, H-4eq), 4.21–4.27 (m, 1H, H-4ax) 7.19 (t, 1H, J=7.05 Hz, *p*-Ar), 7.29–7.38 (m, 4H, Ar); δ_C ($CDCl_3$) 22.6 (C-6), 25.0 (C-7), 25.8 (C-5), 57.6 (C-8), 62.1 (C-4a), 74.1 (C-4), 150.5 (CP), 120.8 (*m*-Ar), 124.9 (*p*-Ar), 129.7 (*o*-Ar).

Compound **18b**. A pale yellow solid; yield: 0.37 g (14%). Mp: 123–125 °C (*i*Pr_2O–EtOAc). [Found: C, 53.69; H, 6.41; N, 10.39. $C_{12}H_{17}N_2O_3P$ requires C, 53.73; H, 6.39; N, 10.44%]; ν_{max} 3129, 2940, 1251, 1209, 957 cm^{-1}; δ_H ($CDCl_3$) 1.26–1.44 (m, 2H, H-5ax, H-6ax), 1.44–1.84 (m, 4H, H-5eq, H-6eq, H-7), 2.64 (td, 1H, J=2.8, 12.3 Hz, H-8ax), 2.75 (m, 1H, H-4a), 3.23 (td, 1H, J=3.1, 11.8 Hz, H-8eq), 4.26 (dd, 1H, J=8.6, 11.6 Hz, H-4ax), 4.31 (ddd, 1H, J=3.5, 11.6, 26.4 Hz, H-4eq), 7.19 (t, 1H, J=7.3 Hz, *p*-Ar), 7.23–7.38 (*m*, 4H, Ar); δ_C ($CDCl_3$) 22.7 (C-7), 23.1 (C-6), 24.4 (C-5), 57.8 (C-8), 60.5 (C-4a), 72.9 (C-4), 150.5 (CP), 120.5 (*m*-Ar), 124.9 (*p*-Ar), 129.8 (*o*-Ar).

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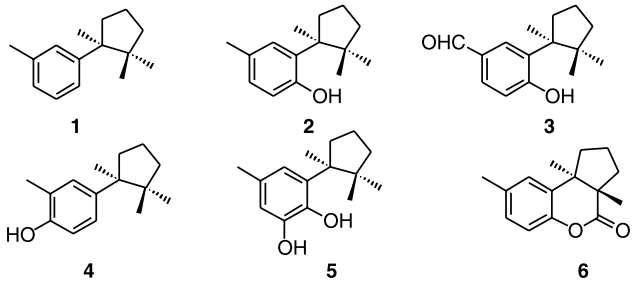
Abstract—A formal total synthesis of the sesquiterpene (±)-herbertenediol and its dimers mastigophorenes A–D has been accomplished, starting from vanillin via 2,3-dimethoxy-5-methylbenzaldehyde. A combination of Claisen rearrangement and ring-closing metathesis reactions were employed for the generation of the two vicinal quaternary carbons on a cyclopentane ring.

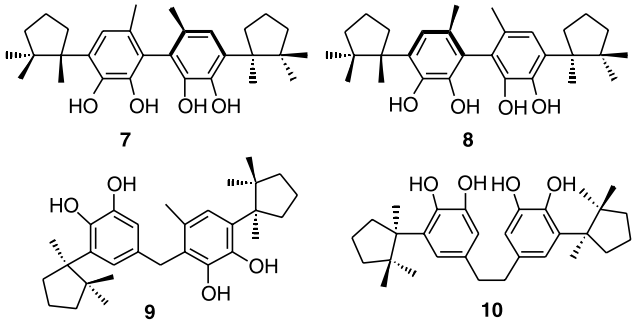
1. Introduction

Liverworts, belonging to the Hepaticae family, are endowed with a rich and wide variety of mono-, sesqui- and diterpenoids and/or lipophilic aromatic compounds. An important endogenous character of the Hepaticae family is that most of the sesquiterpenoids isolated from liverworts are enantiomeric to those isolated from the higher plants.[1] Several compounds obtained from liverworts show a wide spectrum of biological properties such as muscle relaxing activity, antimicrobial, antifungal, 5-lipoxygenase, cyclo-oxygenase, cytotoxic, insect antifeedant, neurotropic sprouting, piscicidal, cathepsin B and L, calmodulin inhibitory and anti-HIV activities. Liverworts from the genus *Herbertus* contain herbertane sesquiterpenoids, which are considered as chemical markers of the genus.[2] The herbertane group is a small group of aromatic sesquiterpenes, isomeric to cuparenes, containing a sterically crowded 1-aryl-1,2,2-trimethylcyclopentane carbon framework incorporating two vicinal quaternary carbon atoms on a cyclopentane ring. The first member of this class of sesquiterpenes, herbertene **1**, was isolated in 1981 by Matsuo and co-workers from the ethyl acetate extract of the liverwort *Herberta adunca* (Dicks) Gray.[3] In 1982, Matsuo and co-workers reported the isolation of three phenolic herbertanes, α-herbertenol **2**, α-formylherbertenol **3** and β-herbertenol **4** along with herbertene **1** and cuparene sesquiterpenes from the same liverwort.[4] Asakawa and co-workers in 1982 reported the isolation of herbertene **1** and the phenolic herbertenes, α-herbertenol **2** and β-herbertenol **4** from *H. aduncus*, *H. sakuraii* and *H. subdetatus*. Isolation of more herbertenoids, herbertenediol **5** and herbertenolide **6** was reported in 1983 by Matsuo and co-workers.[4]



1 **2** **3** **4** **5** **6**

In 1988 and 1991 Asakawa and co-workers reported the isolation of the dimeric herbertanes, mastigophorenes A–D **7**–**10**, dimers of herbertenediol **5**, from the liverwort *Mastigophora diclados* (Mastigophoraceae).[5] The mastigophorenes A–D **7**–**10** are presumably formed by one electron oxidative phenolic coupling of herbertenediol **5**. Subsequently, isolation of a few other phenolic herbertanes have been reported.[2,6]



7 **8** **9** **10**

The phenolic herbertanes[4–7] have been shown to possess interesting biological properties such as growth inhibiting

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activity and antilipid peroxidation activity. Mastigophorenes A–D **7–10** were found to exhibit intriguing neurotropic properties, that is, promote neuronal outgrowth and enhance choline acetyl transferase activity in the primary cultures of fetal rat cerebral hemisphere.

The presence of an interesting carbon framework, a sterically crowded 1-aryl-1,2,2-trimethylcyclopentane, the difficulty associated with the construction of vicinal quaternary carbon atoms on a cyclopentane ring, and the biological properties associated with the phenolic herbertanes and mastigophorenes made them challenging synthetic targets.[8,9] Recently, a large number of reports have appeared on the synthesis of these sesquiterpenes making them a topic of contemporary interest. Herein, we describe the formal synthesis of herbertenediol and mastigophorenes.[10]

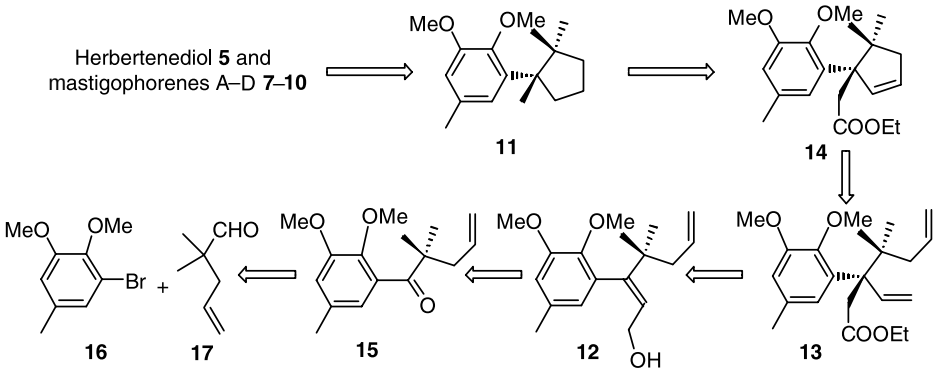
2. Results and discussion

Olefin metathesis[11] is an important reaction in which two olefins undergo bond reorganization leading to redistribution of the alkylidene moieties. With the advent of efficient catalysts, the metathesis reaction has emerged as a powerful tool, in particular the intramolecular version, that is, ring-closing metathesis (RCM), for the formation of C–C bonds in organic synthesis.[12] Recently,[10] we have developed a methodology for the total synthesis of α- and β-herbertenols starting from 2,2-dimethylpent-4-enaldehyde and appropriate aryl bromides employing a combination of orthoester Claisen rearrangement and RCM reactions. Extrapolation of this methodology has been investigated for the formal total synthesis of herbertenediol **5** and mastigophorenes A–D **7–10**. The retrosynthesis is depicted in Scheme 1. Since herbertenediol dimethyl ether **11** has already been transformed into herbertenediol **5** and mastigophorenes A–D **7–10**, it was chosen as the target molecule. It was envisioned that orthoester Claisen rearrangement[13] of the allyl alcohol **12** followed by RCM reaction of the diene **13** would generate cyclopenteneacetate **14**, containing the two vicinal quaternary carbon atoms, which is a higher homologue of herbertenediol **5** and could be transformed into **11** by one carbon degradation. It was thought that the cinnamyl alcohol **12** could be generated from the ketone **15** employing a Wittig reaction based methodology, and the ketone **15** could be obtained from the bromide **16** and the aldehyde **17**.

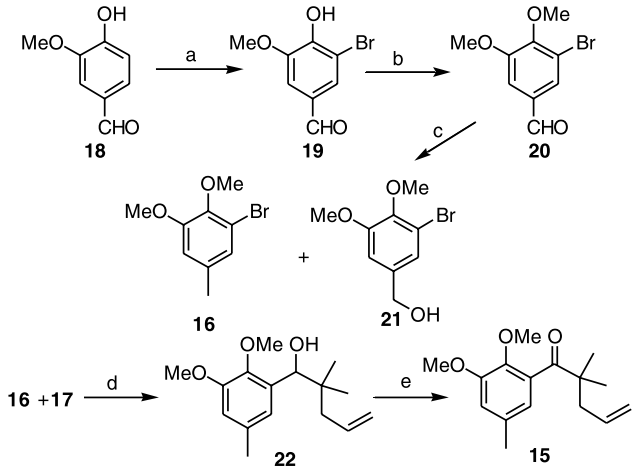
Attention was first focused on the synthesis of the aryl ketone **15** via the bromide **16**,[14] and vanillin **18** containing two oxygen atoms on vicinal carbons was chosen as the suitable starting material, as depicted in Scheme 2. Thus, bromination of vanillin **18** followed by methylation of bromovanillin **19** furnished bromoveratraldehyde **20**.[14] An ionic hydrogenation methodology[15] was explored for the reductive deoxygenation of the aldehyde group in **20**. Reaction of the aldehyde **20** with sodium cyanoborohydride in the presence of boron trifluoride etherate in refluxing THF for 10 h gave a 1:2 mixture of the bromoarene **16** and the benzyl alcohol **21** in 95% yield. Conventional Grignard and transmetallation reactions failed to couple the bromide **16** with the aldehyde **17**. Sonochemically accelerated Barbier reaction of the bromide **16** with the aldehyde **17** and lithium in THF generated the benzyl alcohol **22** in very low yield (16%), which on oxidation with PCC and silica gel in methylene chloride at rt furnished the ketone **15**.

Since the coupling of the bromide **16** with aldehyde **17** was inefficient, an alternative strategy was investigated for the synthesis of the ketone **15** via the aldehyde **23** (Scheme 3). Thus, Clemensen reduction of vanillin **18** with amalgamated zinc generated the phenol **24**, which on etherification with allyl bromide furnished the allyl aryl ether **25**. Claisen rearrangement of the allyl aryl ether **25**, followed by base catalyzed isomerisation of the double bond in the resultant *o*-allylphenol **26** generated the phenol[16] **27**. Etherification of the phenol **27** with sodium hydroxide and dimethyl sulfate, followed by ozonolysis of the double bond in the resultant styrene **28** furnished the aldehyde **23**.[17] Grignard reaction of the aldehyde **23** with isopropylmagnesium bromide in ether for 3 h furnished the benzyl alcohol **29** in 88% yield, which on oxidation with pyridinium chlorochromate (PCC) and silica gel in methylene chloride at rt for 2 h generated the ketone **30**. Reaction of the ketone **30** with sodium hydride and allyl bromide in refluxing THF for 10 h generated a mixture of the *C*-allylated ketone **15** and the allyl enol ether **31**, which on thermal rearrangement at 180 °C in a sealed tube for 30 min gave the ketone **15** in 91% yield. The structure of the ketone **15** was established from its spectral data, in particular the presence of a carbonyl absorption band at 1693 cm^{-1} in the IR spectrum, presence of a singlet at δ 1.10 in ^1H NMR and a two carbon signal at 24.3 ppm in the ^{13}C NMR for the two symmetric tertiary methyl groups in addition to other signals.

Initially for the conversion of the ketone **15** into the ciannamyl alcohol **12**, Wittig reaction followed by



Scheme 1.

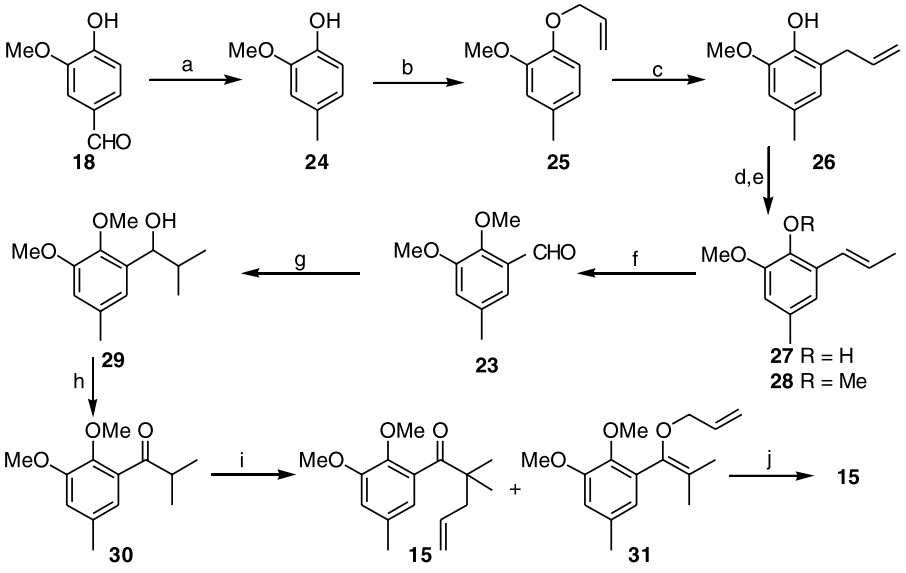


Scheme 2. (a) Br_2, CH_2Cl_2, 0 °C, 30 min, 98%; (b) K_2CO_3, MeI, acetone, reflux, 30 h, 57%; (c) $NaCNBH_3$, $BF_3 \cdot Et_2O$, THF, reflux, 10 h, 95% (**16**:**21** 1:2); (d) Li, THF, 1 h 16%; (e) PCC, silica gel, CH_2Cl_2, rt, 3 h, 90%.

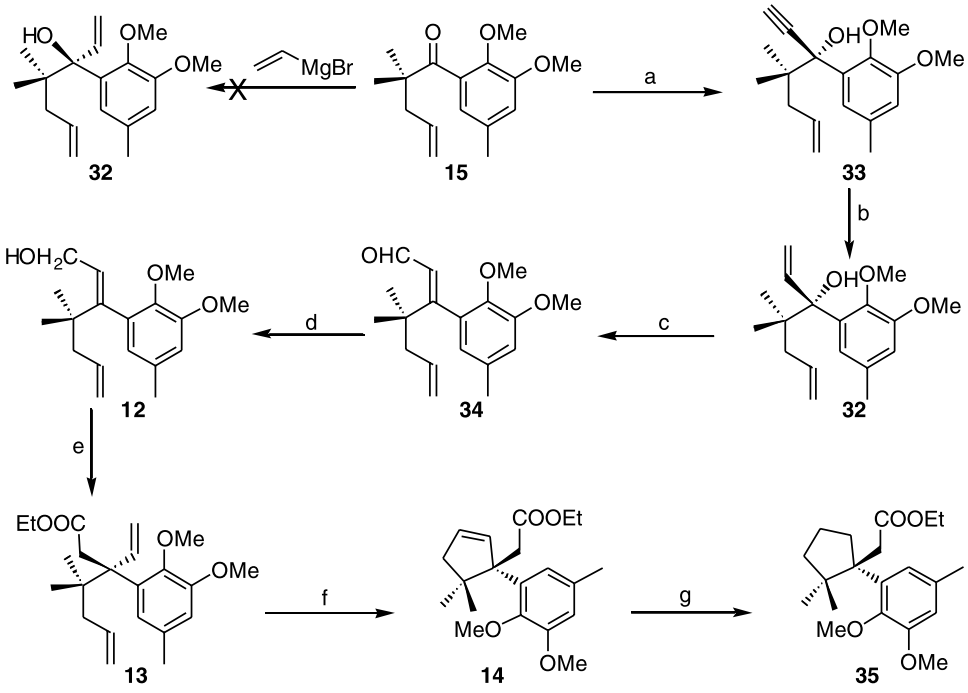
reduction was considered. As in the case of earlier examples,[10] the Wittig reaction and its Horner–Wadsworth–Emmons variant failed, presumably due to steric reasons. Subsequently, a 1,3-transposition methodology[18] was contemplated via addition of a vinyl group followed by rearrangement (Scheme 4). However, reaction of the aryl ketone **15** with vinylmagnesium bromide failed to generate the tertiary alcohol **32**, and resulted in the replacement of one of the aromatic methoxy groups with a vinyl group. Hence, an alternate methodology via the corresponding acetylene was chosen. Thus, reaction of the ketone **15** with lithiumacetylide ethylenediamine complex in dry THF for 2 h furnished the tertiary alcohol **33**, whose structure was established from the spectral data. Presence of an absorption band at 3447 cm^{-1} due to the hydroxy group in the IR spectrum; presence of a singlet at δ 2.55 in the ^1H NMR due to the acetylenic proton, and two quaternary carbons at 86.4 and 81.6, and a methine at 73.5 due to the propargylic alcohol part of the compound in addition to other signals confirmed the structure of the enynol **33**. Controlled hydrogenation of the acetylene group with Lindlar's catalyst in ethanol for 24 h at rt gave the tertiary alcohol **32** in 97% yield. Reaction of the alcohol **32** with PCC and silica gel in methylene chloride at rt for 30 h generated the aldehyde **34** in 85% yield, which on regioselective reduction with sodium borohydirde in methanol at 0 °C for 1.5 h furnished the alcohol **12** in 75% yield.

The orthoester Claisen rearrangement of the allyl alcohol **12** with triethyl orthoacetate and a catalytic amount of propionic acid in a sealed tube at 180 °C for 48 h furnished the γ,δ-unsaturated ester **13** in 28% yield. The steric crowding experienced in the transition state in generating a quaternary centre in-between the already existing quaternary centre and the tetrasubstituted aryl group is presumably the reason for the low yield in the Claisen rearrangement. Next, the key step in the sequence, RCM reaction of the diene ester **13** was investigated. RCM reaction of the diene **13** with 7 mol% Grubbs' first generation catalyst in methylene chloride furnished the cyclopenteneacetate **14** in 80% yield, whose structure was established from its spectral data. The absence of signals due to the terminal olefinic protons and carbons in the NMR spectra, and the presence of two doublets at δ 6.20 and 5.70 due to the cyclopentene olefinic protons and a high field shifted methyl singlet at 0.51 (typical for the methyl group cis to the aryl group in cuparene and herbertenoids) established the structure of the ester **14**. This was further confirmed by the presence of signals due to four methine and five quaternary sp^2 carbons, and six methyl, three methylene and two quaternary aliphatic carbons in the ^{13}C NMR spectrum of the ester **14**. Hydrogenation of the olefin in **14** with 10% palladium on activated charcoal as the catalyst in ethanol furnished the cyclopentaneacetate **35** in 99% yield.

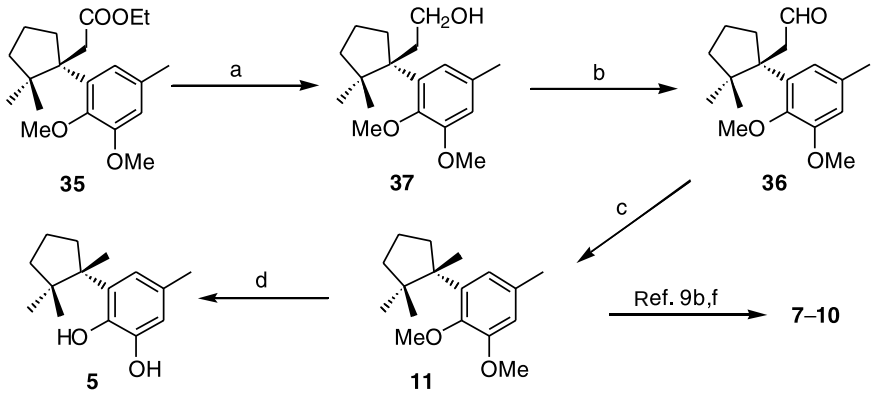
For the conversion of the ester **35** into herbertenol dimethyl ether **11**, degradation of one carbon was required. A three-step protocol via the aldehyde **36** was explored for the



Scheme 3. (a) Zn, concd HCl, EtOH, reflux, 3 h, 80%; (b) K_2CO_3, $CH_2{=}CHCH_2Br$, acetone, reflux, 6 h, 95%; (c) sealed tube, 180 °C, 24 h, 90%; (d) KOH, MeOH, reflux, 10 h, 95%; (e) Me_2SO_4, NaOH, reflux, 1 h, 96%; (f) O_3/O_2, CH_2Cl_2, MeOH, −70 °C; Me_2S, rt, 6 h, 80%; (g) *i*-PrMgBr, Et_2O, 0 °C→rt, 3 h, 88%; (h) PCC, silica gel, CH_2Cl_2, rt, 2 h, 96%; (i) NaH, THF, reflux; $CH_2{=}CHCH_2Br$, 10 h, 99%; (j) sealed tube, 180 °C, 0.5 h, 92%.



Scheme 4. (a) HC≡CLi·$(NH_2CH_2)_2$, THF, 15–20 °C, 2 h, 90%; (b) H_2, Pd–$CaCO_3$, EtOH, 24 h, 97%; (c) PCC, silica gel, CH_2Cl_2, rt, 30 h, 85%; (d) $NaBH_4$, MeOH, 0 °C→rt, 1.5 h, 75%; (e) $CH_3C(OEt)_3$, EtCOOH, 180 °C, 48 h, 28%; (f) $Cl_2(PCy_3)_2Ru$=CHPh, CH_2Cl_2, rt, 6 h, 80%; (g) H_2 (1 atm), 10% Pd–C, EtOH, 3 h, 99%.



Scheme 5. (a) LAH, Et_2O, 0 °C, 1 h, 98%; (b) PCC, silica gel, CH_2Cl_2, rt, 0.5 h, 89%; (c) $(Ph_3P)_3RhCl$ (20 mol%), C_6H_6, sealed tube, 120–130 °C, 20 h, 77%; (d) BBr_3, CH_2Cl_2, −40 °C→rt, 2 h, 98%.

degradation (Scheme 5). Reduction of the ester **35** with LAH in ether gave the alcohol **37** in 98% yield, which on oxidation with PCC and silica gel furnished the aldehyde **36**. Wilkinson catalyst mediated decarbonylation of the aldehyde **36** in benzene at 120–130 °C in a sealed tube for 20 h furnished herbertenediol dimethyl ether **11** in 77% yield, which exhibited spectral data identical to that of an authentic sample. Finally, demethylation of the ether **11** with boron tribromide in methlylene chloride furnished (±)-herbertenediol **5** in 98% yield. Since the dimethyl ether **11** has already been transformed into mastigophorenes A–D **7**–**10**, the present sequence constitutes a formal total synthesis of these terpenoids.

In conclusion, we have accomplished synthesis of the sesquiterpene (±)-herbertenediol **5** and its dimers mastigophorenes A–D **7**–**10** starting from vanillin **18** via 2,3-dimethoxy-5-methylbenzaldehyde **16**. A combination of Claisen rearrangement and ring-closing metathesis reactions have been employed for the generation of the two vicinal quaternary carbons on a cyclopentane ring. Even though the conversion of the alcohol **12** to **13** by the orthoester Claisen rearrangement is low yielding, it is reasonably compensated by the high efficiency of the other steps. An overall yield of 6% was obtained for the conversion of the aldehyde **23** into herbertenediol in 15 steps.

3. Experimental

3.1. General

IR spectra were recorded on a Jasco FTIR 410 spectrophotometer. ^1H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on JNM λ-300 spectrometer. The chemical shifts (δ ppm) and coupling constants (Hz) are reported in

the standard fashion with reference to either internal tetramethylsilane (for ^1H) or the central line (77.1 ppm) of $CDCl_3$ (for ^{13}C). NMR samples were prepared using a 1:1 mixture of $CDCl_3$ and CCl_4 as solvent. In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2 or CH_3) were determined by recording the DEPT-135 and are given in parentheses. Low-resolution mass spectra were recorded using a Shimadzu QP-5050A GCMS instrument using direct inlet (EI) mode. Relative intensities are given in parentheses. High-resolution mass spectra were recorded on a Micromass Q-TOF micro mass spectrometer using electron spray ionization mode. Ozonolysis experiments were carried out using Fischer 502 ozone generator. The oxygen flow was adjusted and calibrated to generate 1 mmol of ozone per 4 min. Acme's silica gel (100–200 mesh) was used for column chromatography (approximately 15–20 g per 1 g of the crude product). Dry THF was obtained by distillation over sodium-benzophenone ketyl. Dry ether was obtained by distillation over sodium and stored over sodium wire. Dry CH_2Cl_2 was prepared by distilling over calcium hydride. All the commercial reagents were used as such without further purification.

3.1.1. 3-Bromo-1,2-dimethoxy-5-methylbenzene (16). To a magnetically stirred solution of the aldehyde **20** (301 mg, 1.23 mmol) in dry THF (5 mL) were added $Na(CN)BH_3$ (387 mg, 6.16 mmol) and $BF_3{\cdot}Et_2O$ (1.09 mL, 8.63 mmol) and refluxed for 10 h. The reaction mixture was cooled to rt; aqueous $NaHCO_3$ solution (5 mL) was added to the reaction mixture and extracted with ether (3×3 mL). The combined organic layer was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue using ethyl acetate–hexane (1/20) as eluent furnished the ether **16** (87 mg, 31%) as an oil.[14] IR (neat): ν_{max}/cm^{-1} 1598, 1568; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.88 (1H, s), 6.57 (1H, s), 3.81 (3H, s), 3.76 (3H, s), 2.25 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 153.4 (C), 144.5 (C), 134.6 (C), 125.1 (CH), 117.4 (C), 112.6 (CH), 60.3 (CH_3), 55.9 (CH_3), 21.1 (CH_3). Further elution of the column using ethyl acetate–hexane (1/20) furnished the benzyl alcohol **21** (195 mg, 64%) as an oil.[19] IR (neat): ν_{max}/cm^{-1} 3384, 1599, 1570; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.94 (1H, s), 6.72 (1H, s), 4.45 (2H, s), 3.78 (3H, s), 3.74 (3H, s), 2.94 (1H, br s).

3.1.2. 1-(2,3-Dimethoxy-5-methylphenyl)-2,2-dimethylpent-4-en-1-ol (22). To a sonochemically irradiated suspension of lithium (48 mg, 6.92 mmol) in dry THF (1 mL) in a round bottom flask, placed in an ultrasonic cleaning bath, was added a mixture of the aldehyde **17** (77 mg, 0.69 mmol) and the bromoarene **16** (320 mg, 1.38 mmol) in THF (1 mL) at 15–20 °C over a period of 2 min, and sonochemically irradiated for 1 h. Then the reaction mixture was decanted from the excess lithium, quenched with saturated aqueous NH_4Cl solution (3 mL) and extracted with ether (3×3 mL). The ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1/20) as eluent furnished the benzyl alcohol **22** (30 mg, 16%) as an oil. IR (neat): ν_{max}/cm^{-1} 3470, 1638, 1589; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.70 (1H, s), 6.58 (1H, s), 6.00–5.78 (1H, m), 5.10–5.00 (2H, m), 4.72 (1H, s), 3.83 (3H, s), 3.78 (3H, s), 2.31 (3H, s), 2.23 (1H, br s), 2.14 (1H, dd, J=13.8, 7.5 Hz), 2.05 (1H, dd, J=13.8, 7.5 Hz), 0.88 (3H, s), 0.81 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 151.8 (C), 144.9 (C), 135.8 (CH), 134.6 (C), 132.3 (C), 121.3 (CH), 117.2 (CH_2), 112.2 (CH), 75.5 (CH), 60.4 (CH_3), 55.6 (CH_3), 43.6 (CH_2), 39.4 (C), 23.2 (CH_3), 22.5 (CH_3), 21.6 (CH_3); Mass: m/z 264 (M^+, 1%), 182 (13), 181 (100), 153 (55), 151 (25), 138 (17), 123 (13); HRMS: m/z Calcd for $C_{16}H_{24}O_3Na$ (M+Na): 287.1623. Found: 287.1606.

3.1.3. 1,2-Dimethoxy-5-methyl-3-(prop-1-enyl)benzene (28). To a cold (10 °C) magnetically stirred solution of the phenol **27** (700 mg, 3.93 mmol) in 10% aqueous NaOH solution (8 mL) was added dimethyl sulfate (0.37 mL, 3.93 mmol) drop-wise. The reaction mixture was refluxed for 1 h. It was then cooled and extracted with ether (3×3 mL). The ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent followed by purification over a silica gel column using ethyl acetate–hexane (1/10) as eluent furnished the methyl ether **28** (724 mg, 96%) as an oil.[16] IR (neat): ν_{max}/cm^{-1} 1579; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.76 (1H, s), 6.62 (1H, dq, J=16.2, 1.8 Hz), 6.50 (1H, s), 6.14 (1H, dq, J=16.8, 6.6 Hz), 3.81 (3H, s), 3.72 (3H, s), 2.27 (3H, s), 1.90 (3H, dd, J=6.6, 1.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 152.7 (C), 144.3 (C), 132.9 (C), 131.5 (C), 126.2 (CH), 125.7 (CH), 118.4 (CH), 111.8 (CH), 60.6 (CH_3), 55.7 (CH_3), 21.6 (CH_3), 19.0 (CH_3); Mass: ($C_{12}H_{16}O_2$) m/z 192 (M^+, 16%), 177 (7), 161 (4), 149 (8), 135 (2), 119 (4), 117 (5), 115 (3), 105 (4), 91 (9), 49 (100).

3.1.4. 2,3-Dimethoxy-5-methylbenzaldehyde (23). A mixture of dry ozone in oxygen was passed through a cold (−70 °C) solution of the ether **28** (640 mg, 3.34 mmol) and a catalytic amount of $NaHCO_3$ in 1:4 methanol/CH_2Cl_2 (10 mL) for 13 min. The reaction mixture was flushed off with oxygen to remove excess ozone, and dimethyl sulfide (1.6 mL) was added to the reaction mixture. It was then slowly warmed up to rt and magnetically stirred for 8 h. Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column using ethyl acetate–hexane (1/10) as eluent furnished the aldehyde **23** (477 mg, 80%) as an oil.[17] IR (neat): ν_{max}/cm^{-1} 2750, 1693, 1682, 1607, 1586; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 10.32 (1H, s), 7.14 (1H, s), 6.89 (1H, s), 3.89 (3H, s), 3.85 (3H, s), 2.30 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 189.6 (CH), 152.6 (C), 150.6 (C), 133.7 (C), 129.3 (C), 119.0 (CH), 118.9 (CH), 62.1 (CH_3), 55.8 (CH_3), 21.1 (CH_3).

3.1.5. 1-(2,3-Dimethoxy-5-methylphenyl)-2-methylpropan-1-ol (29). A solution of isopropylmagnesium bromide (5.5 mmol), prepared from Mg (152 mg, 6.33 mmol), isopropyl bromide (0.71 mL, 7.6 mmol) and a catalytic amount of iodine in 3 mL of dry ether, was added to a cold (0 °C), magnetically stirred solution of the aldehyde **23** (228 mg, 1.26 mmol) in dry ether (1 mL). The reaction mixture was slowly warmed up to rt and stirred for 3 h. It was then poured into saturated aqueous NH_4Cl solution (5 mL) and extracted with ether (3×3 mL). The ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1/20) as eluent furnished the secondary alcohol **29** (250 mg, 88%)

as an oil. IR (neat): ν_{max}/cm^{-1} 3449, 1590; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.64 (1H, s), 6.57 (1H, s), 4.43 (1H, br s), 3.83 (3H, s), 3.80 (3H, s), 2.29 (3H, s), 2.15 (1H, s), 2.00–1.80 (1H, m), 1.02 (3H, d, $J=6.6$ Hz), 0.79 (3H, d, $J=6.6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 152.1 (C), 144.4 (C), 136.8 (C), 133.1 (C), 120.1 (CH), 112.2 (CH), 75.9 (CH), 60.7 (CH_3), 55.6 (CH_3), 35.0 (CH), 21.6 (CH_3), 19.9 (CH_3), 18.7 (CH_3); Mass: *m/z* 224 (M^+, 11%), 181 (100), 166 (17), 153 (77), 151 (24), 138 (34), 123 (15), 91 (17); HRMS: *m/z* Calcd for $C_{13}H_{20}O_3Na$ (M+Na): 247.1310. Found: 247.1300.

3.1.6. 1-(2,3-Dimethoxy-5-methylphenyl)-2-methylpropan-1-one (30). To a magnetically stirred suspension of PCC (721 mg, 3.34 mmol) and silica gel (721 mg) in dry CH_2Cl_2 (1 mL) was added a solution of the *sec*-alcohol **29** (250 mg, 1.11 mmol) in CH_2Cl_2 (1 mL) and stirred vigorously for 2 h at rt. The reaction mixture was then filtered through a small silica gel column, and the column eluted with more CH_2Cl_2. Evaporation of the solvent furnished the ketone **30** (238 mg, 96%) as an oil. IR (neat): ν_{max}/cm^{-1} 1693, 1603, 1586; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.70 (1H, s), 6.67 (1H, s), 3.80 (3H, s), 3.74 (3H, s), 3.26 (1H, septet, $J=6.9$ Hz), 2.26 (3H, s), 1.08 (6H, d, $J=6.9$ Hz); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 207.4 (C), 152.4 (C), 145.0 (C), 134.4 (C), 133.5 (C), 120.6 (CH), 115.5 (CH), 61.4 (CH_3), 55.7 (CH_3), 40.1 (CH), 21.2 (CH_3), 18.6 (2C, CH_3); Mass: *m/z* 222 (M^+, 10%), 207 (4), 180 (12), 179 (100), 136 (17), 91 (15); HRMS: *m/z* Calcd for $C_{13}H_{18}O_3Na$ (M+Na): 245.1154. Found: 245.1146.

3.1.7. 1-(2,3-Dimethoxy-5-methylphenyl)-2,2-dimethylpent-4-en-1-one (15). To a magnetically stirred suspension of NaH (234 mg, 60% dispersion in oil, 5.85 mmol, washed with dry hexanes) in dry THF (1 mL) was added a solution of the ketone **30** (260 mg, 1.17 mmol) in dry THF (2 mL) and stirred for 40 min at rt. Allyl bromide (0.5 mL, 5.85 mmol) was added to the reaction mixture and stirred for 10 h at rt. It was then quenched with water (5 mL) and extracted with ether (3×4 mL). The combined ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1/20) as eluent furnished a mixture of *O*-allylated and *C*-allylated compounds (**31** and **15**), which was taken into a sealed tube (neat) and heated at 180 °C for 30 min. Purification of the reaction mixture over a silica gel column using ethyl acetate–hexane (1/20) as eluent furnished the ketone **15** (279 mg, 91%) as an oil. IR (neat): ν_{max}/cm^{-1} 1693, 1639, 1588; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.62 (1H, s), 6.31 (1H, s), 5.85–5.60 (1H, m), 5.10–4.90 (2H, m), 3.79 (3H, s), 3.66 (3H, s), 2.26 (3H, s), 2.35–2.25 (2H, m), 1.10 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 211.4 (C), 152.1 (C), 142.4 (C), 136.5 (C), 134.4 (CH), 133.4 (C), 117.8 (CH_2), 117.6 (CH), 113.3 (CH), 61.2 (CH_3), 55.4 (CH_3), 47.7 (C), 43.8 (CH_2), 24.3 (2C, CH_3), 21.3 (CH_3); Mass: *m/z* 262 (M^+, 3%), 180 (11), 179 (100), 136 (8), 91 (8); HRMS: *m/z* Calcd for $C_{16}H_{22}O_3Na$ (M+Na): 285.1467. Found: 285.1452.

3.1.8. 3-(2,3-Dimethoxy-5-methylphenyl)-4,4-dimethylhept-6-en-1-yn-3-ol (33). To a sonochemically irradiated suspension of lithiumacetylide ethylenediamine complex (1.23 g, 13.3 mmol) in dry THF (1 mL) in a round bottom flask, placed in an ultrasonic cleaning bath, was added a solution of the ketone **15** (700 mg, 2.67 mmol) in dry THF (2 mL) at 15–20 °C over a period of 3 min, and the reaction mixture was sonochemically irradiated for 2 h. It was then quenched with saturated aqueous NH_4Cl solution (5 mL) and extracted with ether (3×7 mL). The ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1/10) as eluent furnished the tertiary alcohol **33** (693 g, 90%) as an oil. IR (neat): ν_{max}/cm^{-1} 3447, 3301, 1637, 1585, 912; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.93 (1H, s), 6.61 (1H, s), 5.80–5.50 (1H, m), 4.97 (1H, d, $J=9.9$ Hz), 4.96 (1H, d, $J=17.1$ Hz), 3.86 (3H, s), 3.82 (3H, s), 2.55 (1H, s), 2.29 (3H, s), 2.29–2.10 (2H, m), 1.23 (1H, br s), 0.91 (3H, s), 0.90 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 152.0 (C), 145.2 (C), 135.8 (2C, C and CH), 131.7 (C), 123.6 (CH), 117.4 (CH_2), 112.9 (CH), 86.4 (C), 81.6 (C), 73.5 (CH), 61.3 (CH_3), 55.7 (CH_3), 44.1 (C), 41.2 (CH_2), 22.0 (CH_3), 21.6 (CH_3), 21.5 (CH_3); Mass: *m/z* 273 (M^+-Me, 2%), 205 (100), 191 (14), 190 (33), 179 (29), 121 (10); HRMS: *m/z* Calcd for $C_{18}H_{24}O_3Na$ (M+Na): 311.1623. Found: 311.1618.

3.1.9. 3-(2,3-Dimethoxy-5-methylphenyl)-4,4-dimethylhept-6-en-3-ol (32). To activated Lindlar's catalyst (200 mg) was added a solution of the enynol **33** (500 mg, 1.73 mmol) in ethanol (2 mL). The reaction mixture was stirred for 24 h at rt in an atmosphere of hydrogen, created by evacuative replacement of air (balloon), and then the catalyst was filtered off. Evaporation of the solvent furnished the dienol **32** (488 mg, 97%) as an oil. IR (neat): ν_{max}/cm^{-1} 3475, 1637, 1583, 914; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): 6.70 (1H, dd, $J=16.8$, 10.5 Hz), 6.67 (1H, s), 6.57 (1H, s), 5.76 (1H, ddt, $J=18.0$, 9.0, 7.5 Hz), 5.46 (1H, d, $J=16.8$ Hz), 5.17 (1H, d, $J=10.5$ Hz), 4.95 (1H, d, $J=9.0$ Hz), 4.94 (1H, d, $J=18.0$ Hz), 4.60 (1H, br s), 3.82 (6H, s), 2.32 (3H, s), 2.15–1.95 (2H, m), 0.84 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 152.4 (C), 145.2 (C), 141.6 (CH), 136.4 (CH), 135.9 (C), 131.6 (C), 122.9 (CH), 117.1 (CH_2), 113.9 (CH_2), 112.1 (CH), 82.2 (C), 61.1 (CH_3), 55.7 (CH_3), 42.8 (C), 41.4 (CH_2), 22.4 (CH_3), 22.0 (CH_3), 21.8 (CH_3); Mass: *m/z* 207 ($M^+-C_6H_{11}$, 73%), 175 (12); HRMS: *m/z* Calcd for $C_{18}H_{26}O_3Na$ (M+Na): 313.1780. Found: 313.1770.

3.1.10. 3-(2,3-Dimethoxy-5-methylphenyl)-4,4-dimethylhepta-2,6-dienal (34). To a magnetically stirred suspension of PCC (3.62 g, 16.8 mmol) and silica gel (3.62 g) in dry CH_2Cl_2 (10 mL) was added a solution of the tertiary alcohol **32** (488 mg, 1.68 mmol) in CH_2Cl_2 (2 mL) and stirred vigorously for 30 h at rt. The reaction mixture was then filtered through a small silica gel column, and the column eluted with more CH_2Cl_2. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1/20) as eluent furnished the enal **34** (412 mg, 85%) as an oil. IR (neat): ν_{max}/cm^{-1} 2748, 1676, 1638, 1583, 916; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 9.25 (1H, d, $J=8.1$ Hz), 6.68 (1H, s), 6.37 (1H, s), 6.15 (1H, d, $J=8.1$ Hz), 5.85–5.65 (1H, m), 5.07 (1H, d, $J=9.0$ Hz), 5.04 (1H, d, $J=16.2$ Hz), 3.87 (3H, s), 3.68 (3H, s), 2.32 (3H, s), 2.24 (2H, d, $J=6.9$ Hz), 1.13 (3H, s), 1.07 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 193.5 (CH), 171.0

(C), 152.3 (C), 144.0 (C), 134.5 (CH), 132.8 (C), 130.9 (C), 128.5 (CH), 121.9 (CH), 117.9 (CH_2), 112.9 (CH), 60.1 (CH_3), 55.4 (CH_3), 45.8 (CH_2), 40.7 (C), 26.9 (CH_3), 26.7 (CH_3), 21.3 (CH_3); Mass: *m/z* 288 (M^+, 10%), 259 (64), 257 (100), 216 (63), 189 (39), 173 (20); HRMS: *m/z* Calcd for $C_{18}H_{24}O_3Na$ (M+Na): 311.1623. Found: 311.1619.

3.1.11. 3-(2,3-Dimethoxy-5-methylphenyl)-4,4-dimethylhepta-2,6-dien-1-ol (12). To an ice cold, magnetically stirred solution of the aldehyde **34** (360 mg, 1.25 mmol) in dry methanol (3 mL) was added $NaBH_4$ (47.5 mg, 1.25 mmol) and stirred for 90 min at the same temperature. The solvent was removed under reduced pressure, diluted with water (5 mL) followed by quenched with 3 N aqueous HCl (5 mL) and extracted with CH_2Cl_2 (5×6 mL). The combined CH_2Cl_2 extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1/20–1/10) as eluent furnished the primary alcohol **12** (271 mg, 75%) as an oil. IR (neat): ν_{max}/cm^{-1} 3423, 1638, 1583, 911; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.56 (1H, s), 6.26 (1H, s), 5.95–5.60 (2H, m), 5.00–4.90 (2H, m), 3.79 (3H, s), 3.68 (3H, s), 3.80–3.40 (2H, m), 2.24 (3H, s), 2.24–2.00 (2H, m), 1.98 (1H, br s), 1.02 (3H, s), 0.96 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 152.2 (C), 147.8 (C), 143.9 (C), 135.9 (CH), 132.8 (C), 132.4 (C), 125.7 (CH), 122.8 (CH), 116.8 (CH_2), 112.1 (CH), 60.8 (CH_2), 60.2 (CH_3), 55.4 (CH_3), 46.1 (CH_2), 38.8 (C), 27.7 (CH_3), 27.3 (CH_3), 21.3 (CH_3); Mass: *m/z* 290 (M^+, 42%), 260 (44), 249 (39), 231 (69), 207 (85), 205 (75), 179 (87), 175 (98), 165 (80), 151 (65), 115 (50), 97 (80), 91 (80); HRMS: *m/z* Calcd for $C_{18}H_{26}O_3Na$ (M+Na): 313.1780. Found: 313.1787.

3.1.12. Ethyl 3-vinyl-3-(2,3-dimethoxy-5-methylphenyl)-4,4-dimethylhept-6-enoate (13). A solution of the allyl alcohol **12** (244 mg, 0.84 mmol), triethyl orthoacetate (1.53 mL, 8.41 mmol) and a catalytic amount of propionic acid was placed in a sealed tube and heated to 180 °C for 2 days in an oil bath. The reaction mixture was then cooled, diluted with ether (5 mL), washed with 3 N aqueous HCl (5 mL) followed by saturated $NaHCO_3$ solution (5 mL) and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1/40) as eluent furnished the diene ester **13** (85 mg, 28%) as an oil. IR (neat): ν_{max}/cm^{-1} 1746, 1637, 1582, 911; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.84 (1H, dd, *J*=18.0, 10.4 Hz), 6.61 (1H, s), 6.57 (1H, s), 5.85–5.55 (1H, m), 5.12 (1H, d, *J*=11.1 Hz), 5.04 (1H, d, *J*=17.4 Hz), 5.00–4.85 (2H, m), 3.97 (2H, q, *J*=6.9 Hz), 3.81 (3H, s), 3.68 (3H, s), 2.79 (1H, d, *J*=17.4 Hz), 2.26 (3H, s), 2.30–1.90 (3H, m), 1.14 (3H, t, *J*=6.9 Hz), 0.83 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 171.8 (C), 152.6 (C), 147.1 (C), 142.1 (2C, C and CH), 136.0 (CH), 130.3 (C), 123.8 (CH), 117.3 (CH_2), 114.0 (CH_2), 111.7 (CH), 60.2 (CH_3), 55.6 (CH_3), 59.5 (CH_2), 53.0 (C), 41.9 (CH_2), 41.4 (C), 37.4 (CH_2), 22.7 (2C, CH_3), 21.8 (CH_3), 14.3 (CH_3); Mass: *m/z* 360 (M^+, 1%), 278 (42), 231 (20), 203 (100), 189 (28), 173 (18); HRMS: *m/z* Calcd for $C_{22}H_{32}O_4Na$ (M+Na): 383.2198. Found: 383.2211.

3.1.13. Ethyl 2-[1-(2,3-dimethoxy-5-methylphenyl)-5,5-dimethylcyclopent-2-enyl]acetate (14). To a magnetically stirred solution of the diene ester **13** (130 mg, 0.36 mmol) in anhydrous CH_2Cl_2 (13 mL) was added a solution of Grubbs' catalyst (21 mg, 7 mol%) in anhydrous CH_2Cl_2 (10 mL) and the reaction mixture was stirred at rt for 6 h. Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column using ethyl acetate–hexane (1/30) as eluent furnished the cyclopentene ester **14** (67 mg, 80%) as an oil. IR (neat): ν_{max}/cm^{-1} 1738, 1584; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.59 (1H, s), 6.54 (1H, s), 6.20 (1H, d, *J*=6.0 Hz), 5.70 (1H, d, *J*=6.0 Hz), 3.92 (2H, q, *J*=7.2 Hz), 3.81 (3H, s), 3.80 (3H, s), 3.51 (1H, d, *J*=15.3 Hz), 2.39 (1H, d, *J*=15.3 Hz), 2.34 (1H, d, *J*=16.5 Hz), 2.26 (3H, s), 2.13 (1H, dd, *J*=16.5, 1.5 Hz), 1.25 (3H, s), 0.51 (3H, s), 1.06 (3H, t, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 172.2 (C), 152.4 (C), 146.1 (C), 139.6 (CH), 134.9 (C), 131.4 (C), 127.2 (CH), 122.1 (CH), 111.9 (CH), 60.0 (CH_3), 59.5 (CH_2), 58.8 (C), 55.6 (CH_3), 48.4 (CH_2), 45.7 (C), 41.1 (CH_2), 28.5 (CH_3), 24.4 (CH_3), 21.7 (CH_3), 14.2 (CH_3); Mass: *m/z* 332 (M^+, 62%), 258 (52), 245 (86), 243 (58), 215 (100), 189 (45), 185 (41), 175 (43), 149 (69), 115 (50), 91 (66); HRMS: *m/z* Calcd for $C_{20}H_{28}O_4Na$ (M+Na): 355.1885. Found: 355.1883.

3.1.14. Ethyl 2-[1-(2,3-dimethoxy-5-methylphenyl)-2,2-dimethylcyclopent-1-yl]acetate (35). To an activated 5% Pd–C (15 mg) was added a solution of the ester **14** (35 mg, 0.10 mmol) in ethanol (1 mL). The reaction mixture was stirred for 3 h at rt in an atmosphere of hydrogen, created by evacuative replacement of air (balloon), and then the catalyst was filtered off. Evaporation of the solvent furnished the cyclopentane ester **35** (35 mg, 99%) as an oil. IR (neat): ν_{max}/cm^{-1} 1737, 1582; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.59 (1H, s), 6.54 (1H, s), 3.87 (2H, q, *J*=6.9 Hz), 3.80 (3H, s), 3.77 (3H, s), 3.42 and 2.37 (2H, 2×d, *J*=15.3 Hz), 2.85–2.50 (1H, m), 2.26 (3H, s), 2.15–2.00 (1H, m), 1.85–1.65 (2H, m), 1.54 (1H, d, *J*=9.0 Hz), 1.51 (1H, d, *J*=6.9 Hz), 1.10 (3H, s), 1.01 (3H, t, *J*=6.9 Hz), 0.64 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 172.2 (C), 152.4 (C), 146.8 (C), 136.0 (C), 130.9 (C), 122.2 (CH), 112.0 (CH), 59.9 (CH_3), 59.2 (CH_2), 55.6 (CH_3), 53.8 (C), 46.1 (C), 41.1 (CH_2), 39.4 (CH_2), 36.3 (CH_2), 27.3 (CH_3), 25.7 (CH_3), 21.9 (CH_3), 20.8 (CH_2), 14.3 (CH_3); Mass: *m/z* 334 (M^+, 68%), 252 (100), 219 (41), 189 (61), 172 (53), 165 (35), 149 (70); HRMS: *m/z* Calcd for $C_{20}H_{30}O_4Na$ (M+Na): 357.2042. Found: 357.2056.

3.1.15. 2-[1-(2,3-Dimethoxy-5-methylphenyl)-2,2-dimethylcyclopent-1-yl]ethanol (37). To a cold (0 °C), magnetically stirred solution of the ester **35** (20 mg, 0.06 mmol) in 1 mL of dry ether was added $LiAlH_4$ (11.37 mg, 0.29 mmol) and stirred for 1 h. The reaction mixture was then diluted with ether (3 mL) and carefully quenched with two drops of water. The organic layer was separated and the aqueous phase was extracted with ether (3×2 mL). The combined organic phase was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1/10–1/5) as eluent furnished the primary alcohol **37** (17 mg, 98%). IR (neat): ν_{max}/cm^{-1} 3363, 1579; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.57 (1H, s), 6.54 (1H, s), 3.81 (3H, s), 3.78 (3H, s), 3.45 (1H, td, *J*=9.6, 5.7 Hz), 3.30 (1H, td, *J*=9.6, 5.4 Hz), 2.70–2.30 (2H, m), 2.26 (3H, s), 2.00–1.80 (1H, m), 1.80–1.40 (6H, m), 1.34 (3H, s), 0.66 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3+$

CCl_4): δ 152.6 (C), 146.9 (C), 136.7 (C), 131.5 (C), 122.1 (CH), 111.7 (CH), 61.6 (CH_2), 60.1 (CH_3), 55.6 (CH_3), 53.9 (C), 45.9 (C), 40.8 (CH_2), 37.3 (CH_2), 29.8 (CH_2), 27.1 (CH_3), 25.5 (CH_3), 21.7 (CH_3), 20.9 (CH_2); Mass: *m/z* 292 (M^+, 74%), 210 (100), 207 (30), 191 (45), 179 (66), 166 (61), 165 (50), 149 (62), 115 (33), 105 (31), 91 (57); HRMS: *m/z* Calcd for $C_{18}H_{28}O_3Na$ (M+Na): 315.1936. Found: 315.1925.

3.1.16. 2-[1-(2,3-Dimethoxy-5-methylphenyl)-2,2-dimethylcyclopent-1-yl]acetaldehyde (36). To a magnetically stirred suspension of PCC (62.7 mg, 0.29 mmol) and silica gel (62.7 mg) in dry CH_2Cl_2 (0.5 mL) was added a solution of the primary alcohol **37** (17 mg, 0.06 mmol) in CH_2Cl_2 (0.5 mL) and stirred vigorously for 30 min at rt. The reaction mixture was then filtered through a small silica gel column, and the column eluted with more CH_2Cl_2. Evaporation of the solvent furnished the aldehyde **36** (15 mg, 89%) as an oil, which was found to decompose slowly. IR (neat): ν_{max}/cm^{-1} 2729, 1719, 1579; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 9.43 (1H, t, $J=3.0$ Hz), 6.69 (1H, s), 6.66 (1H, s), 3.83 (3H, s), 3.79 (3H, s), 3.50 (1H, d, $J=16.2$ Hz), 2.83–2.62 (1H, m), 2.39 (1H, dd, $J=16.2$, 3.0 Hz), 2.29 (3H, s), 1.95–1.68 (5H, m), 1.11 (3H, s), 0.69 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 205.3 (CH), 152.7 (C), 146.4 (C), 135.1 (C), 132.0 (C), 121.9 (CH), 112.1 (CH), 60.1 (CH_3), 55.6 (CH_3), 52.7 (C), 48.4 (CH_2), 45.8 (C), 40.5 (CH_2), 36.6 (CH_2), 26.5 (CH_3), 25.3 (CH_3), 21.6 (CH_3), 20.5 (CH_2).

3.1.17. 1-(2,3-Dimethoxy-5-methylphenyl)-1,2,2-trimethylcyclopentane (11). Wilkinson catalyst (23 mg, 0.025 mmol) was added to a solution of the aldehyde **36** (15 mg, 0.05 mmol) in dry benzene (0.5 mL) and heated at 120–130 °C for 20 h in a sealed tube. Evaporation of the solvent under reduced pressure followed by purification on a silica gel column using ethyl acetate–hexane (1/30) as eluent furnished herbertenediol dimethyl ether **11** (9 mg, 77% based on consumed aldehyde **36**). IR (neat): ν_{max}/cm^{-1} 1580; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.75 (1H, s), 6.62 (1H, s), 3.85 (3H, s), 3.77 (3H, s), 2.70–2.50 (1H, m), 2.30 (3H, s), 1.85–1.30 (5H, m), 1.36 (3H, s), 1.12 (3H, s), 0.70 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 153.0 (C), 146.6 (C), 140.1 (C), 131.6 (C), 121.6 (CH), 111.0 (CH), 60.4 (CH_3), 55.6 (CH_3), 51.5 (C), 45.0 (C), 40.8 (CH_2), 38.9 (CH_2), 26.8 (CH_3), 25.2 (CH_3), 24.1 (CH_3), 21.7 (CH_3), 20.3 (CH_2); Mass: *m/z* 262 (M^+, 29%), 257 (25), 180 (52), 179 (20), 165 (13), 149 (9); HRMS: *m/z* Calcd for $C_{17}H_{26}O_2Na$ (M+Na): 285.1830. Found: 285.1831. Further elution of the column with ethyl acetate–hexane (1/30) as eluent furnished the unreacted aldehyde **36** (2 mg).

3.1.18. 1-(2,3-Dihydroxy-5-methylphenyl)-1,2,2-trimethylcyclopentane [(±)-herberenediol 5]. A solution of BBr_3 (1 M in CH_2Cl_2, 0.30 mL, 0.30 mmol) was added drop-wise to a magnetically stirred solution of the ether **11** (8 mg, 0.03 mmol) in CH_2Cl_2 (2 mL) at −40 °C. The reaction mixture slowly warmed up to rt and stirred for 2 h at rt. It was then quenched with saturated aqueous $NaHCO_3$ solution (1 mL) and extracted with CH_2Cl_2 (3×2 mL). The combined organic layer was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1/10) as eluent furnished herbertenediol **5** (7 mg, 98%). IR (neat): ν_{max}/cm^{-1} 3526, 1599; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.68 (1H, s), 6.56 (1H, s), 5.39 (1H, s), 5.23 (1H, br s), 2.70–2.59 (1H, m), 2.22 (3H, s), 1.82–1.43 (5H, m), 1.41 (3H, s), 1.18 (3H, s), 0.76 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 143.5 (C), 141.2 (C), 133.6 (C), 128.4 (C), 122.0 (CH), 113.6 (CH), 51.3 (C), 45.0 (C), 41.1 (CH_2), 39.4 (CH_2), 27.0 (CH_3), 25.6 (CH_3), 23.0 (CH_3), 21.3 (CH_3), 20.4 (CH_2); Mass: *m/z* 234 (M^+, 43%), 164 (40), 152 (85), 151 (100).

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Synthesis of cesium selective pyridyl azocalix[*n*]arenes

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Abstract—A series of pyridylazo calix[*n*]arenes ($n=4$, 6, 8) including the first examples of mixed hetroaryl azocalix(*n*)arenes have been synthesized by coupling calix[*n*]arenes with diazonium salts derived from amino pyridines. It has been observed that the coupling reaction of diazonium salt obtained from 3-aminopyridine with calix[*n*]arene gives tetrakis-, hexakis- and octakis (pyridylazo)calix[*n*]arenes ($n=4,6,8$) while those derived from 4-aminopyridine give partially substituted (4-pyridylazo)calix[*n*]arene analogs. There is no reaction of calix(*n*)arenes with diazonium salts derived from 2-aminopyridine under identical conditions of experiments. The conformational analysis of synthesized compounds have been ascertained by detailed spectral measurements and single crystal X-ray analysis of 5-(3′-pyridylazo)-25,26,27,28-tetrahydroxycalix[4]arene. A rational explanation for the observed partial and exhaustive coupling reaction in the synthesis of heteroaryl azocalix(*n*)arenes has been suggested. Preliminary evaluation of synthesized derivatives as molecular receptors for metal ions indicates that they have good potential to function as selective ionic filters for cesium ions.

1. Introduction

Calix[*n*]arenes ($n=4$–20, where *n* is the number of phenyl units, Fig. 1a) are phenolic [1*n*]-metacyclophanes that can be easily obtained by base or acid-catalyzed condensation of *p*-substituted phenols with formaldehyde or paraformaldehyde.[1] They are known to provide useful building blocks for hollow molecular scaffolds with easily functionalizable hydrophilic and hydrophobic lower and upper rims, respectively.[2–4] Introduction of azo groups into the calix[*n*]arene framework confer chromogenicity that can be employed for the development of molecular diagnostics and sensor materials for metal ions and organic molecules.[5–7] For example, typically substituted azocalix[*n*]arenes (Fig. 1b) have been studied by various researchers in the recent past for their use in ionic and molecular recognition.[8,9] However, despite such studies, predictive information on the usefulness of coupling reaction between calix[*n*]arenes and diazonium salts to provide regioselective azo substituted calix[*n*]arenes is very limited. For example, it has been reported that the reaction of calix[4]arene with substituted benzene diazonium flouroborate in the presence of pyridine provides tetrakis(phenylazo)calix[4]arene[10–11] in good yield but the same reaction with benzene diazonium salt derived from aniline gives a very poor yield of the related product.

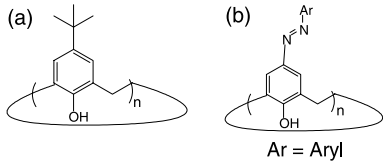

Figure 1. (a) *p-tert* Butyl calix[*n*]arene $n=4$–20, (b) *p*-substituted azo calix[*n*]arene $n=4,6,8$.

Since the base-catalyzed diazotization reaction involving diazo flouroborates usually led to the formation of tetrakis(arylazo)calix[4]arenes, Shinkai et al. ascribed this outcome to autocatalysis of the coupling reaction and suggested that deprotonation of a phenolic group by the basic solvent facilitates the reaction through hydrogen bond assistance.[12] Whether such an influence of hydrogen bonds is operative in all diazocoupling reactions is as yet a matter of speculation. During recent years, several reports have appeared in the literature[13–15] wherein the synthesis and characterization of partially substituted azo calixarenes have been utilized to elicit photoresponse to ionic or molecular recognition events. Differential observations and outcome of the coupling reaction of calix[*n*]arenes with diazonium salts derived from different aryl amine structures do not seem to have been explained. In the present work, we have attempted to understand the diazocoupling reaction of calix[*n*]arenes to rationally obtain chromogenic molecular filters that may be selective for metal ions and organic substrates. The choice of diazonium cations derived from aminopyridines[16,17] was

Keywords: Calix[*n*]arenes; Diazotization; Cesium; Hydrogen bond.
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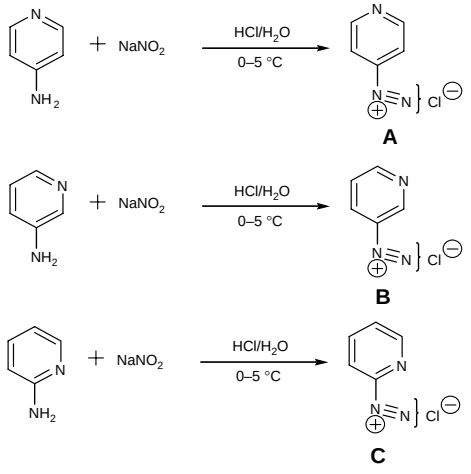
motivated by the expectation that the new azocalixarene derivatives might provide additional binding sites for the ionic and molecular guests and they may provide better visualization of the recognition process. We report herein, the results obtained on the reaction of calix[*n*]arenes with diazotized amino pyridines, a synthesis of mixed heteroaryl-azocalix[*n*]arenes and the preliminary evaluation of the synthesized derivatives for ionic recognition.

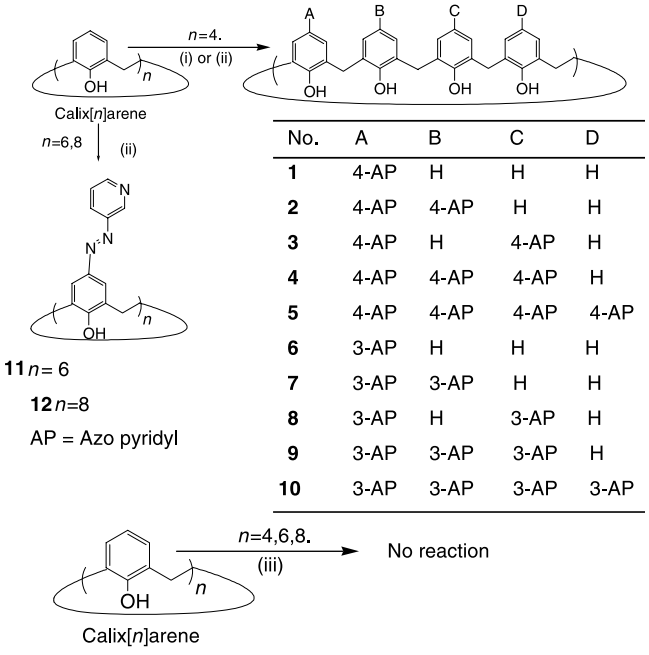
2. Results and discussion

2.1. Synthesis

The diazonium salts (**A**–**C**, Scheme 1) were prepared by treatment of corresponding amino pyridines with sodium nitrite and hydrochloric acid at low temperature (0–5 °C). (**A**), (**B**) and (**C**) were coupled with different calix[*n*]arenes as per the described experimental conditions and the products were isolated as given in Schemes 2 and 3.

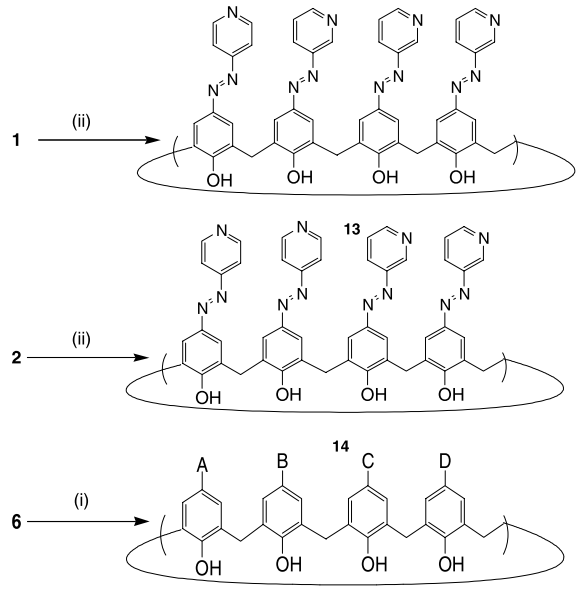


Scheme 1. Synthesis of various diazonium salts from respective amines and 2–3 equiv of $NaNO_2$ at 0–5 °C.

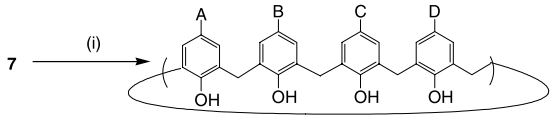


No.	A	B	C	D
1	4-AP	H	H	H
2	4-AP	4-AP	H	H
3	4-AP	H	4-AP	H
4	4-AP	4-AP	4-AP	H
5	4-AP	4-AP	4-AP	4-AP
6	3-AP	H	H	H
7	3-AP	3-AP	H	H
8	3-AP	H	3-AP	H
9	3-AP	3-AP	3-AP	H
10	3-AP	3-AP	3-AP	3-AP

Scheme 2. Synthesis of pyridyl azocalix[*n*]arenes (*n*=4, 6, 8).



No.	A	B	C	D
15	3-AP	4-AP	H	H
16	3-AP	H	4-AP	H
17	3-AP	4-AP	4-AP	H
18	3-AP	4-AP	H	4-AP
19	3-AP	4-AP	4-AP	4-AP



No.	A	B	C	D
20	3-AP	3-AP	4-AP	H
14	3-AP	3-AP	4-AP	4-AP

Scheme 3. Synthesis of mixed pyridyl azocalix[4]arenes at 0–5 °C. Reagents: (i) diazonium salt (A), DMF/MeOH, CH_3COONa; (ii) diazonium salt (B), DMF/MeOH, CH_3COONa; (iii) diazonium salt (C), DMF/MeOH, CH_3COONa.

2.2. Results

The coupling reaction of 8 equiv diazonium salt (**A**) and calix[4]arene for 4 h, provided a mixture of products (Table 1), which contained mono(4-pyridylazo)calix[4]-arene **1** as the major product (yield 30%) along with small amounts of bis(4-pyridylazo)calix[4]arenes **2** and **3** (yield 12 and 3%, respectively). A major portion of calix[4]arene was found to remain unchanged in this reaction and tris- and tetrakis(4-pyridylazo)calix[4]arene products could not be obtained at all. However, when four successive portions of 5 equiv of A were added in the coupling reaction after every 6 h and the reaction was continued for 30 h, the tris- and tetrakis (4-pyridylazo)calix[4]arenes **4** and **5** could be obtained in 12 and 4% yield (Table 1).

A similar coupling reaction of the diazonium salt (**A**) with calix[6]arene or calix[8]arene under identical experimental conditions, always resulted in a mixture of products, which was difficult to separate. Fully substituted

Table 1. Effect of reaction parameters on product distribution of coupling of calix[4]arene with diazonium salts (**A**), (**B**) and (**C**)

S. no.	Reactant (AP)[a]	Molar ratio[b]	Reaction time (h)	Product distribution (mmol %)					Proximal product:distal product ratio
				Mono-	Bis-(distal)	Bis-(proximal)	Tris-	Tetrakis-	
1	4-AP	1:1	1	3	—	—	—	—	—
2	4-AP	1:4	1	8	—	—	—	—	—
3	4-AP	1:4	4	16	—	4	—	—	—
4	4-AP	1:8	4	30	3	12	—	—	4
5	4-AP	1:16	4	35	6	20	—	—	3.3
6	4-AP	1:30[c]	24	25	7	22	12	4	3.1
7	3-AP	1:1	3	20	6	21	3	4	3.5
8	3-AP	1:2	3	30	10	35	5	15	3.5
9	3-AP	1:4.5	3	—	—	—	—	94	—
10	2-AP	1:16	24			No reaction			—

[a] Aminopyridine.
[b] Molar ratio of aminopyridine: calix[4]arene.
[c] Addition was effected in small portions.

(4-pyridylazo)calix[*n*]arenes (*n*=6, 8) were never obtained as major products in these reactions.

On the other hand the coupling reaction of a diazonium salt (**C**) and calix[*n*]arene (*n*=4,6,8) did not yield any diazo-coupled product even after 24 h of the reaction under identical conditions of experiments and respective starting materials could be recovered from the reaction broth (Scheme 2).

When the coupling reaction was attempted with a diazonium salt (**B**) with calix[4]arene, it exhibited significantly different results (Scheme 2). The use of 1 equiv of a diazonium salt gave a mixture of products (**6–10**). When the quantity of the diazonium salt was increased to 4.5 equiv, the tetra substituted compound **10** was obtained in 95% yield. Though the isolated yield of **10** was found to change with varying molar equivalents of the diazonium salt, the formation of the tetra substituted product was always observed in the reaction. Similarly, hexasubstituted compound **11** and octasubstituted compound **12** could be obtained in more than 90% yield through the coupling reaction of diazonium salt (**B**) with calix[6]arene and calix[8]arene, respectively (Scheme 2).

2.3. Characterization of products of the reaction

The IR spectra of synthesized pyridyl azocalixarenes (**1–20**) showed absorptions for OH as a broad band at a considerable higher frequency (3450–3200 cm^{-1}) than parent calix[4]-arenes[18] (~3120 cm^{-1}) indicating that hydrogen bonds are comparatively weaker in pyridyl azocalix[*n*]arenes. An asymmetric stretching vibration for the –N=N– group appeared in the 1600–1550 cm^{-1} range.[19]

The synthesized pyridyl azocalix[4]arenes (**1–20**) could be characterized by analysis of their ^1H and ^{13}C NMR spectra. The position of NMR signals for methylene carbons in the δ 29–34 range for synthesized compounds allowed us to conclude that these derivatives were present in their cone conformation. This conclusion is in accordance with results reported in the literature.[20] The chemical shift values and splitting pattern of synthesized bis(pyridylazo)calix[4]-arenes are listed in Table 2.

The identification of distal and proximal isomers of bis(pyridylazo)calix[4]arenes could be achieved by analysis of their ^1H and ^{13}C NMR spectra. For instance, four protons

Table 2. ^1H NMR spectral analysis of synthesized bis(pyridylazo)calix[4]arenes and ^{13}C NMR data for methylene carbons (δ, 300 MHz, 25 °C)

Compound no.	^1H NMR values and splitting patterns (δ, 300 MHz, 25 °C)			^{13}C NMR values for methylene carbons
	Pyridine core protons	Calixarene core protons	Methylene bridge protons	
2	8.75 (br s, 4H), 7.62 (d, *J*=5.1 Hz, 4H)	7.83 (s, 2H), 7.76 (s, 2H), 7.17 (d, *J*=8.1 Hz, 2H), 7.11 (d, *J*=7.2 Hz, 2H), 6.80 (t, *J*=7.5 Hz, 2H)	4.33 (br s, 4H), 3.73 (br s, 4H)	33.98, 32.72, 32.33
3	8.57 (br s, 4H), 7.56 (d, *J*=5.4 Hz, 4H)	7.70 (s, 4H), 6.99 (m, 4H,), 6.47 (m, 2H)	3.87 (br s, 4H)[a]	31.68
7	9.01 (s, 2H), 8.56 (br s, 2H), 7.99 (d, *J*=7.2 Hz, 2H), 7.37 (br s, 2H)	7.74 (s, 2H), 7.67 (s, 2H), 7.11 (d, *J*=7.2 Hz, 2H), 7.04 (d, *J*=7.2 Hz, 2H), 6.72 (t, *J*=7.2 Hz, 2H)	3.99 (br s, 6H)[a]	32.34, 31.38, 31.02
8	9.02 (s, 2H), 8.56 (br s, 2H), 7.96 (d, *J*=7.2 Hz, 2H), 7.35 (dd, *J*=4.2 Hz, 2H)	7.65 (s, 4H), 7.14 (d, *J*=7.5 Hz, 4H), 6.77 (t, *J*=7.5 Hz, 2H)	4.25 (br s, 4H), 3.65 (br s, 4H)	31.23
15	9.11 (s, 1H), 8.74 (d, *J*=3.6 Hz, 2H), 8.65–8.63 (m, 1H), 8.05 (d, *J*=8.1 Hz, 1H), 7.62 (d, *J*=6.3 Hz, 2H), 7.41 (dd, *J*=4.5, 4.5 Hz, 1H)	7.84–7.72 (m, 4H), 7.17 (dd, *J*=3.6 Hz, *J*=2.7 Hz, 2H), 7.10 (d, *J*=7.5 Hz, 2H), 6.79 (t, *J*=7.5 Hz, 2H)	4.33 (br s, 4H), 3.73 (br s, 4H)	31.82, 31.70, 31.58
16	9.02 (s, 1H), 8.68 (br s, 2H), 8.57 (br s, 1H), 7.99 (d, *J*=7.5 Hz, 1H), 7.58 (br s, 2H), 7.36 (dd, *J*=4.5, 4.5 Hz, 1H)	7.75–7.53 (m, 4H), 7.12 (d, *J*=7.8 Hz, 4H), 6.78 (t, *J*=7.8 Hz, 2H)	4.25 (br s, 4H), 3.65 (br s, 4H)	31.69

[a] The signals due to contaminant H_2O and solvents disturb this region.

of substituted calixarene core of **7** exhibited two singlets at δ 7.74 and 7.67 in its ^{1}H NMR spectrum while **8** gave a singlet at δ 7.65 for these protons. Methylene bridge carbons in **7** appeared as three peaks at δ 32.34, 31.38 and 31.03 in the ^{13}C NMR spectrum while only one resonance at δ 31.23 was observed for the methylene carbon in the NMR spectrum of **8**. These data indicate that **7** was proximal isomer while **8** was a distal isomer. Similarly, other proximal (**2**, **15**) and distal (**3**, **16**) isomers (Fig. 2) were characterized.

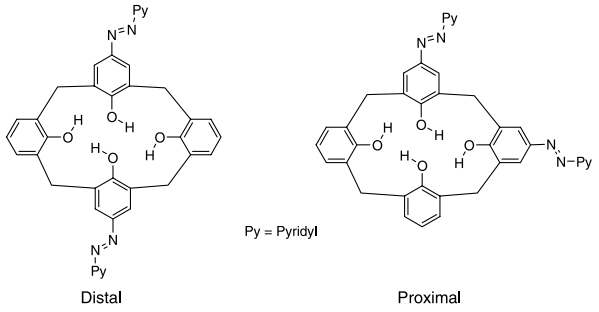


Figure 2. The distal and proximal isomers of bis(pyridylazo)calix[4]arene.

The appearance of only one resonance at δ 31.69 for the methylene carbon in the ^{13}C NMR spectrum of the tetrakis(3-pyridylazo)calix[4]arene **10** could also be attributed to its symmetric nature. This could be further confirmed by its DQF-COSY spectrum, which exhibited correlating cross peaks for only two types of methylene protons as given in Figure 3b. The detailed spectral analysis also led to the assignment of signals at δ 9.08, 8.71, 8.25 and 7.70 to the pyridine protons and the signals centered at δ 7.87 to the calixarene core protons in the ^{1}H NMR spectrum of **10**. Their correlations are represented in Figure 3a.

Mixed azo calix[4]arenes substituted by differently mixed azo calix[4]arenes substituted by differently positioned pyridyl groups could also be characterized by ^{1}H and ^{13}C NMR spectra. For example, signals at δ 8.96, 8.59, 8.04 and 7.50 for the 3-azopyridyl protons, signals at δ 8.67 and 7.61 for the 4-azopyridyl protons and a broad signal at δ 7.80 for the calix[4]arene core aromatic protons could be discovered in the ^{1}H NMR spectrum of **13**. ^{13}C NMR spectrum of **13** gave two signals at δ 31.73 and 31.89, which could be attributed to the methylene bridge carbons.

2.4. X-ray crystallographic analysis

Some of the synthesized azocalix[*n*]arenes were subjected to crystallization in different solvents to obtain single crystal X-ray diffraction for structural elucidation. For example, **6** could be crystallized from chloroform–diethyl ether (10/1) to provide crystals suitable for analysis by X-ray diffraction. An ORTEP diagram[21] and content of the unit cell for **6** are shown in Figure 4a and b. It appears that **6** crystallizes with chloroform embedded in the calixarene cavity with torsion angles ϕ and χ around Ar-CH_2-Ar bonds about C7, C14, C21 and C28 as −97.7(1), 86.4(1), −88.0(1), 92.2(1), −95.3(1), 84.6(1), −86.1(1) and 86.0(1), respectively. This is consistent with the cone conformation[22,23] found in parent *p-tert*-butylcalix[4]arene[24] and calix[4]arene.[25] All the four aromatic rings A(C1–C6), B(C8–C13), C(C15–C20) and D(C22–C27) seem to be almost planar with angles C6–C7–C8 = 112.86(85), C12–C14–C15 = 113.47(90), C19–C21–C22 = 113.51(93) and C26–C28–C2 = 114.36(96). The dihedral angle between the azo pyridyl group plane (C29–C33) is −10.5(17), which corroborate the alignment of heterocyclic ring with the cone conformation of calixarene skeleton. The corresponding hydroxyl substituents O1, O2, O3 and O4 are directed inwards the cavity of the calixarene architecture. The chloroform molecule shows prominent C–H–π interactions with an average H···π distance of 3.4 Å that holds the solvent molecule within the cavity. Hydroxyl groups corresponding to plane A and D do not seem to take part in intramolecular hydrogen bonding, while a significant intramolecular hydrogen bonding is observed amongst hydroxyl groups attached to plane B and C (O3–H3O–O4 = 1.877(8), O2–H2–O3 = 1.864(8) (Fig. 4c). There is prominent C–H–π interaction (with H–π distance 3.56 Å) that brings the substituted azo pyridyl group much closer to the plane A of adjacent ring with inversion center lying between the two calixarene molecules (Fig. 4c). Intermolecular C–H···N hydrogen bonds between N2 and H11 are observed at a distance of 2.75(2) Å. A prominent intermolecular C–H–π interaction exists between pyridyl hydrogen (C31–H31) and ring A (with H–π distance 3.37 Å) resulting in columnar packing (Fig. 4d) with two parallel up and down columns running along the axis *b*.

2.5. Discussion

The foregoing results reveal that exhaustively coupled (3-pyridylazo)calix[*n*]arenes are obtained in the case of

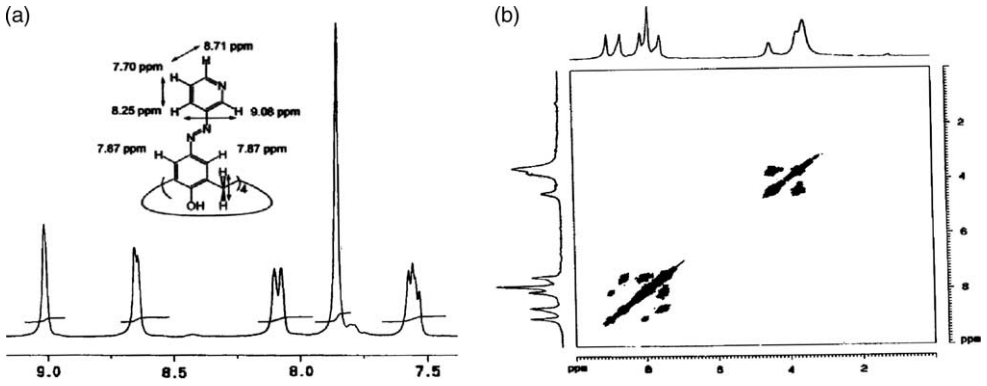


Figure 3. (a) Aromatic region of the ^{1}H NMR spectrum of **10** and DQF-COSY correlations given by arrows in the structure, (b) correlation of methylene and aromatic protons in DQF-COSY spectrum of **10** in d_6-DMSO at 25 °C and 300 MHz.

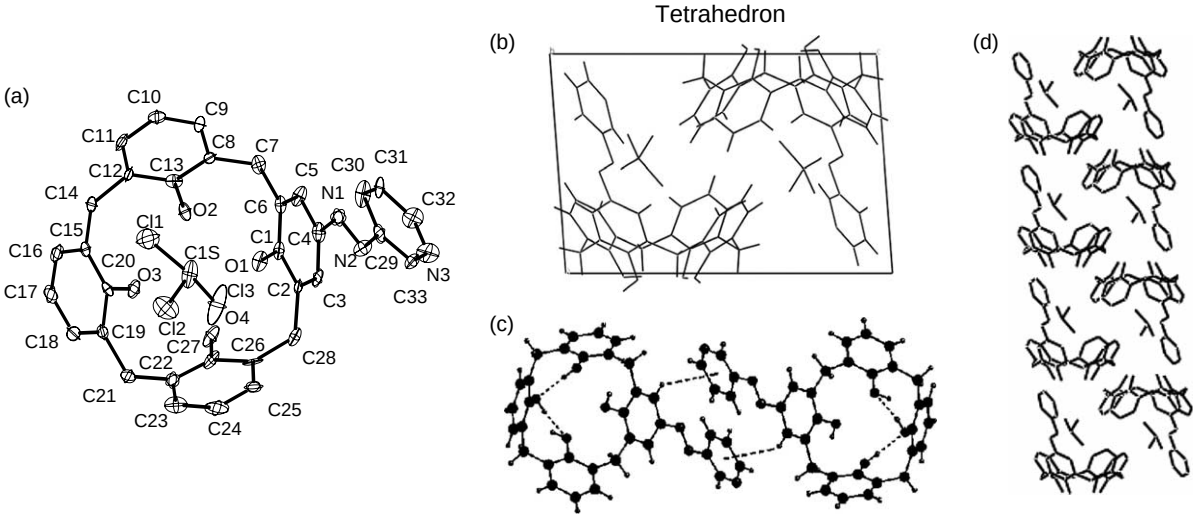


Figure 4. (a) ORTEP diagram showing labeling of atoms in **6** containing encapsulated chloroform. Hydrogens have been omitted for clarity, (b) contents of the unit cell, (c) intramolecular hydrogen bonds and CH–π interactions in **6**, (d) view of the molecular packing along the axis *b*.

diazotized 3-aminopyridine, while partially coupled (4-pyridylazo)calix[*n*]arenes are obtained in the case of 4-aminopyridines. These observations can be explained on the basis of differential electron attraction in (**A**) and (**B**) with appropriate position of ring nitrogen. Since the formation of tetrakis(phenylazo)calix[4]arenes have been earlier ascribed to hydrogen bond assistance,[12] one can reasonably believe that hydrogen bond assistance is inhibited in the coupling reaction of (**A**) and (**C**). Since calixarene skeleton and experimental conditions remain the same in all the reactions, it can *inter alia* be concluded that the earlier proposed autocatalysis of diazonium coupling due to hydrogen bond assistance is operative only in the case of coupling reaction of (**B**) and calixarene, but only partially in the case of coupling reactions of (**A**) with the same substrate. There does not seem to be any assistance in the case of diazo coupling reaction of (**C**) under identical reaction conditions and one needs to develop a different strategy for the desired (2-pyridylazo)calix[*n*]arenes.

Since diazonium salts in the present study were produced in situ, the results could also be ascribed to differential basic nature of aminopyridines, which might ionize calixarene hydroxyls to different extents [pK_a values at 20 °C = 5.98 (3-aminopyridine), 6.86 (2-aminopyridine), 9.17 (4-aminopyridine).[26] This conjecture, however, seems less likely to be true because diazonium salts from aminopyridines were obtained in situ when the solution was made acidic. This acidic solution was added to a calix[4]arene solution in DMF and methanol. The adopted reaction conditions were chosen in such a way that formation of self-coupled products from aminopyridines was avoided.

The above observations were further examined by carrying out the coupling reaction of calix[*n*]arenes with a mixture of diazonium salts to obtain mixed pyridyl azocalixarenes. For example, calix[4]arene on reaction with an equimolar mixture of (A) and (B) (5 equiv each) yielded **13** as the major product. Since 13 has more substituents derived from (**B**) than those from A, it indicates a better reactivity of (**B**) in comparison to that of (**A**) in the coupling reaction of calix[4]arenes with diazotized aminopyridines. Likewise when **1** was reacted with (**B**), it gave **13** (with three *para* positions substituted by 3-azopyridyl groups and one position substituted by 4-azopyridyl group), while when **2** was reacted with the same reaction mixture under identical conditions of experiments, it gave **14** as the only product, that is, completely substituted azocalix[4]arene derivative was formed. On the other hand, when partially substituted (3-pyridylazo)calix[4]arene was reacted with comparatively less reactive diazonium salt (**A**), it again resulted in a partially substituted (4-pyridylazo)calix-[*n*]arene. For example, when **6** was reacted with (**A**) it resulted in a mixture of compounds, which included **15** as the major product. Likewise, when reacted with (**A**), **7** gave **20** as the major product.

The above observations on the diazo coupling reaction of calix[*n*]arenes indicate that the earlier suggestion[12] to explain exhaustive coupling reaction in calix[*n*]arenes in terms of hydrogen bond assistance is not enough.

It was also observed that the diazo coupling reaction led to the formation of both the proximal and the distal isomers in the case of bis(pyridylazo) calix[4]arenes. Though the reason for the higher yield of the proximal isomers [**2**, **7**, **15**] as compared to that of the distal [**3**, **8**, **16**] isomers (about 3–4 times as much) can be ascribed to higher statistical probability of substitution due to deprotonation of one hydroxyl leading to further reaction to yield proximal compounds in the diazocoupling reaction. Since the ratio of proximal: distal compounds (as given in Table 1) has been found to be almost constant in all the reactions carried out; for example, reaction of calix[4]arene with (**A**) or (**B**) or that of **6** with (**A**), the initial reaction seems to be hydrogen bond assisted to lead to disubstituted derivatives. The reaction may then proceed further to form a tetra substituted compound only if it is favoured by electronic factors, for example, in the case of 3-aminopyridine.

It can therefore be concluded that the major product of the diazocoupling reaction of calix[*n*]arenes is decided by a subtle interplay of stereoelectronic factors and hydrogen bond assistance.

Table 3. Optical response of pyridyl azocalix[*n*]arenes (**1**, **2**, **4**, **6**, **7**, **9**, **10**, **11**, **12**, **13** and **14**) on addition of various metal ion salts

No.		**1**[a]	**2**[a]	**4**	**6**	**7**	**9**	**10**	**11**	**12**	**13**	**14**
λ_{max} (nm)		433	392	381	422	382	380	368	370	360	369	375
Salts		Metal-induced wavelength changes ($\Delta\lambda_{max}$ (nm))[b]										
Li^+		0	—	0	0	0	0	−6	+10	+3	+4	−1
Na^+		0	0	+8	0	0	0	−4	+6	+4	+3	+4
K^+		0	+3	+14	0	0	0	+2	+10	+11	+12	+21
Rb^+		—	—	+22	0	0	0	+11	+20	+10	+15	+33
Cs^+[c]	i	0	+35	+44	0	0	0	+40	+32	0	+28	+50
	ii	0	+108	+131	0	0	0	+122	+123	+16	+134	+118
Mg^{++}		0	0	0	0	0	0	0	0	−4	+3	0
Ca^{++}		0	0	0	0	0	0	0	0	+1	+3	0
Ba^{++}		0	0	+30	−46	−11	−8	−1	0	+3	+11	+30
Ti^{+++}		—	—	+31	—	−17	−13	—	—	—	—	+29
Cr^{+++}		−16	—	+30	−82	−27	−25	−12	−8	0	−9	+31
Co^{++}		+1	—	+30	−48	−13	−9	−1	0	+9	+12	+27
Ni^{++}		0	—	0	−8	+1	+2	0	+8	+7	+4	0
Cu^{++}		+16	—	+9	−11	−3	0	0	0	+1	+2	0
Hg^{++}		0	−3	+43	−51	−11	−4	+4	0	+1	+13	+23
Cd^{++}		0	+3	0	−63	0	0	0	0	—	+2	—
Ag^+		—	—	+28	−66	−30	−14	—	0	+10	+2	+28
Pb^{++}		—	—	+29	−46	−11	−10	−2	0	+7	+11	+6

Addition of a few drops of $CHCl_3$ were used for better solubility.
[a] Excess of metal salts were added in place of 100 equiv.
[b] (+) and (−) in wavelength changes denote red and blue shifts, respectively. Samples were prepared by mixing equal volumes of stock solutions of **1**, **2**, **4**, **6**, **7**, **9**, **10**, **11**, **12**, **13** and **14** and the metal salts.
[c] In addition to the red shift of the main band (i) a new peak (ii) also observed.

2.6. Preliminary investigation of synthesized pyridyl azocalix[*n*]arenes for ionic recognition

We were curious to determine if the azopyridyl unit in the compounds in this series could play a role in encapsulating metal ions to elicit changes in the absorption maxima in the UV/vis spectrum. All the synthesized compounds except **6**, **7** and **9** were found to exhibit a red shift of about 50 nm on addition of excess of cesium metal ion with the appearance of a new absorption band near 500 nm accompanied by a profound color change. Other ions did not interfere in such an interaction with cesium. Since till date, no azo calixarene without crown loop has been reported to be used as a selective filter for the radioactive wastes[27] containing cesium,[28,29] these compounds were examined as selective ionic filters for it. The changes in λ_{max} of the pyridyl azocalix[*n*]arenes (**1**, **2**, **4**, **6**, **7**, **9**, **10**, **11**, **12**, **13** and **14**) on addition of different ions, are given in Table 3. One representative example of changes in the UV/vis spectra of **14** on addition of alkali metal salts in methanol are depicted in Figure 5. Two isobestic points at 311 and 393 nm were

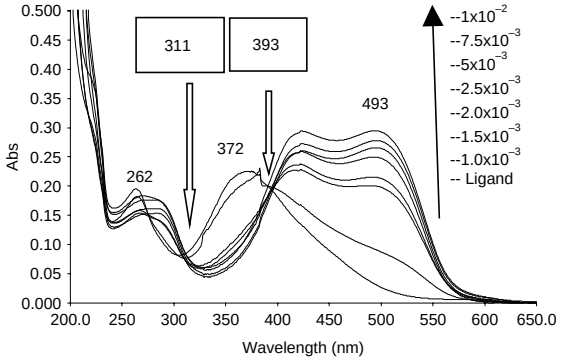


Figure 5. Change in the UV/vis spectrum of **14** when titrated by Cs_2CO_3 showing isobestic points at 311 and 393 nm.

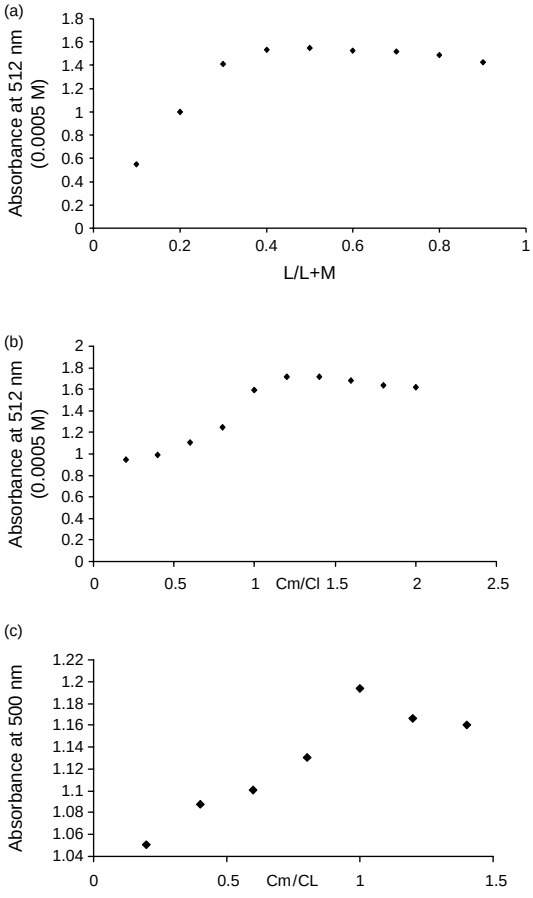


Figure 6. (a) Job's plot for complexation of **4** with Cs^+ ion revealing 1:1 stoichiometry, (b) mole ratio plot for complexation of **4** with Cs^+ ion confirming 1:1 stoichiometry and (c) mole ratio plot for complexation of **13** with Cs^+ ion revealing 1:1 stoichiometry.

identified in the case of **14** when it was titrated with Cs_2CO_3 solution in methanol.

Application of Job's continuous variation method[30] to probe a possible complexation ratio between **4**, **13** and Cs^+ ion revealed that the complex concentration approaches its maximum when the mole fraction of [L]/[L]+[Cs^+] was about 0.5 (Fig. 6a), where L represents the synthesized azocalixarenes examined in this study. The results obtained indicate the formation of a 1:1 complex in general. Similar results were obtained in the mole ratio experiments[30] (Fig. 6b and c). Further work to determine the specific nature of the interaction is in progress.

3. Experimental

All the reagents used in the study were purchased from Sigma–Aldrich or Merck and were chemically pure. The solvents used were distilled and used further without drying. Column chromatography was performed on silica gel (60–120 mesh) obtained from Merck. ^{1}H, ^{13}C NMR, DEPT-135 and DQF-COSY spectra were recorded on a 300 MHz Bruker DPX 300 instrument at room temperature using tetramethylsilane (TMS) at 0.00 as an internal standard. IR spectra were recorded on a Nicolet Protégé 460 spectrometer in KBr disks while X-ray data was recorded using a Bruker SMART CCD single crystal diffractometer. UV/vis spectra were obtained on a Perkin Elmer (Lambda-3B) recording spectrophotometer. The FAB mass spectra were recorded on a JEOL SX102/DA-6000 Mass spectrometer/Data System using Argon/Xenon (6 kV, 10 mA) as the FAB gas. Melting points were determined on an electrothermal toshniwal melting point apparatus and were uncorrected.

3.1. General procedure for the synthesis of pyridyl azocalix[*n*]arene

The pyridyl diazonium chloride solutions were prepared by the addition of an aqueous solution of sodium nitrite (1.5 equiv of amine) into solution of aminopyridine (2-, 3- or 4-substituted) in concd HCl (10–20 equiv) and distilled water (5–10 ml) at 0–5 °C. The diazotized solution was slowly added (in standardized molar ratio with respect to calix[*n*]arenes) into an ice-cold (0–5 °C) solution of calix[*n*]arenes (n=4, 6, 8) in DMF–methanol (8/5), sodium acetate (pH 7–9) with constant stirring to give yellow to dark red suspension. Reaction mixture was stirred for 2–24 h (variable for different compounds) at 0–5 °C and then for 30 min at room temperature. The suspension was poured into water, acidified with concd HCl to give a yellow to dark red precipitate, which was filtered to give a product or a mixture of products. The mixture was then separated by column chromatography (silica gel) to give substituted azocalix[*n*]arene derivatives.

p-tert-Butylcalix[4]arene, *p-tert*-butylcalix[6]arene, *p-tert*-butylcalix[8]arene, calix[4]arene, calix[6]arene and calix[8]arene were synthesized by the method described by Gutsche.[31,32]

3.1.1. 5-(4′-Pyridylazo)-25,26,27,28-tetrahydroxycalix[4]arene, 1. A solution of 4-aminopyridine (0.71 g, 7.5 mmol) in 2 N HCl (5 ml) was chilled in an ice bath and 1.04 g (15.1 mmol) of chilled $NaNO_2$ solution in H_2O (2 ml) was added to it to produce a diazonium salt solution. After 15 min stirring, this diazonium salt solution was added dropwise to calix[4]arene (0.20 g, 0.47 mmol) at 0–5 °C in a mixture of DMF (16 ml), MeOH (10 ml) and sodium acetate trihydrate (5 g, 36.7 mmol). The reaction mixture was stirred at the same temperature for 3 h. 2 N HCl was added to precipitate a deep red suspension, which was filtered off and washed with water. Further separation by column chromatography using chloroform–methanol (9.9/0.1) as the eluent afforded 0.087 g of **1** as dark red solid. Yield: 35%, mp>230 °C (decomp.), IR (KBr pellet, cm^{-1}): 3606, 3092, 1631, 1592, 1449. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.70 (d, J=5.7 Hz, 2H), 7.90 (d, J=6.3 Hz, 2H), 7.85 (s, 4H), 7.90 (d, J=6.3 Hz, 2H), 7.15–7.03 (m, 6H), 6.64–6.56 (m, 3H), 4.20 (br s, 8H); ^{13}C NMR (300 MHz, DMSO-d_6): 174.5, 160.5, 151.9, 151, 144.7, 143.1, 133.1, 130.7, 128.4, 128.2, 127.8, 127.3, 120.3, 119.9, 116, 32.1, 30.7. DEPT-135 NMR (300 MHz, DMSO-d_6): 144.6, 128.4, 128.2, 127.8, 127.3, 120.3, 119.9, 116.0 (CH), 32.1, 30.7 (CH_2). ES MS m/z: 530.0 (M^+). Anal. Calcd for $C_{33}H_{27}N_3O_4$: C, 74.84; H, 5.14; N, 7.93. Found: C, 74.74; H, 5.14; N, 7.94. UV (λ_{max}, MeOH): 280, 434 nm.

3.1.2. 5,11-Bis(4′-pyridylazo)-25,26,27,28-tetrahydroxycalix[4]arene, 2. By the procedure described for **1**, **2** was synthesized and purified by column chromatography using chloroform–methanol (9.8/0.2) as the eluent to afford 0.075 g of **2** as dark red solid. Yield: 20%, mp>230 °C (decomp.), IR (KBr pellet, cm^{-1}): 3422, 1634, 1593, 1457. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.19 (br s, 4H, D_2O exchangeable), 8.75 (br s, 4H), 7.83 (s, 2H), 7.76 (s, 2H), 7.62 (d, J=5.1 Hz, 4H), 7.17 (d, J=8.1 Hz, 2H), 7.11 (d, J=7.2 Hz, 2H), 6.80 (t, J=7.5 Hz, 2H), 4.33 (br s, 4H), 3.73 (br s, 4H); ^{13}C NMR (300 MHz, $CDCl_3$): 152.5, 151.1, 148.4, 147.3, 129.3, 129.2, 128.2, 127.2, 125.5, 124.7, 124.2, 122.6, 116, 31.7, 31.6, 29.6. DEPT-135 NMR (300 MHz, DMSO-d_6): 150.9, 129.2, 129.0, 125.3, 124.0, 122.4, 115.8 (CH), 31.7, 31.6, 29.6 (CH_2). ES MS m/z: 635.5 (M^++1). Anal. Calcd for $C_{38}H_{30}N_6O_4$: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.61; H, 4.77; N, 13.20. UV (λ_{max}, MeOH): 271, 392 nm.

3.1.3. 5,17-Bis(4′-pyridylazo)-25,26,27,28-tetrahydroxycalix[4]arene, 3. By the procedure described for **1**, **3** was synthesized and purified by column chromatography using chloroform–methanol (9.85/0.15) as the eluent to afford 0.018 g of **3** as dark red solid. Yield: 6%, mp>230 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.29 (br s, 4H, D_2O exchangeable), 8.67 (br s, 4H), 7.75 (s, 4H), 7.62 (d, J=5.4 Hz, 4H), 7.07 (t, J=7.5 Hz, 4H), 6.56 (t, J=7.5 Hz, 2H), 4.39 (d, J=12.6 Hz, 4H), 4.17 (d, J=12.9 Hz, 2H), 3.67 (d, J=13.2 Hz, 2H). ES MS m/z: 635.5 (M^++1). Anal. Calcd for $C_{38}H_{30}N_6O_4$: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.84; H, 4.78; N, 13.30. UV (λ_{max}, MeOH): 273, 390 nm.

3.1.4. 5,11,17-Tris(4′-pyridylazo)-25,26,27,28-tetrahydroxycalix[4]arene, 4. A solution of 4-aminopyridine (0.22 g, 2.35 mmol) in 2 N HCl (5 ml) was chilled in an ice bath and chilled $NaNO_2$ (0.32 g, 4.7 mmol) solution in H_2O (2 ml) was added to it to yield a solution of the diazonium

salt. After about 15 min stirring, this diazonium salt solution was added dropwise at 0–5 °C to calix[4]arene (0.20 g, 0.47 mmol) in DMF (16 ml), MeOH (10 ml) and sodium acetate trihydrate (5 g, 36.7 mmol) solution. The reaction mixture was stirred at the same temperature for 6 h. Three successive portions of same amount of 4-aminopyridyl diazonium salt solution were freshly prepared and added to debutylated calix[4]arene after every 6 h while maintaining the temperature at 0–5 °C. The reaction was continued for 6 h at 0–5 °C and 2 N HCl was added to precipitate a deep red suspension, which was filtered off and washed with water. Further purification by column chromatography using chloroform–methanol (9.6/0.4) as the eluent afforded 0.042 g of **3** as dark red solid. Yield: 12%, mp > 230 °C (decomp.), IR (KBr pellet, cm^{-1}): 3432, 1635, 1591, 1384. ^1H NMR (300 MHz, DMSO-d_6): δ 8.67 (br s, 6H), 7.83 (s, 2H), 7.78 (s, 2H), 7.76 (s, 2H), 7.61 (br s, 6H), 7.09 (d, J= 7.2 Hz, 2H), 6.59 (t, J=7.2 Hz, 1H), 4.40 (br s, 4H), 3.58 (br s, 4H). ES MS *m/z*: 740.1 (M^+). Anal. Calcd for $C_{43}H_{33}N_9O_4$: C, 69.81; H, 4.50; N, 17.04. Found: C, 69.70; H, 4.50; N, 16.98. UV (λ_{max}, MeOH): 262, 381 nm.

3.1.5. 5,11,17,23-Tetrakis(4′-pyridylazo)-25,26,27,28-tetrahydroxycalix[4]arene, 5. Reported by our group in Ref. 17. By the procedure described for **4**, **5** was synthesized and purified by column chromatography using chloroform–methanol (9.4/0.6) as the eluent to afford 0.016 g of **5** as dark red solid. Yield: 4%, mp > 230 °C (decomp.). ^1H NMR (300 MHz, DMSO-d_6): δ 8.66 (br s, 8H), 7.71 (s, 8H), 7.60 (br s, 8H), 4.38–372 (m, 8H). FAB MS *m/z*: 845 (M^+). Anal. Calcd for $C_{48}H_{36}N_{12}O_4$: C, 68.24; H, 4.29; N, 19.89. Found: C, 68.30; H, 4.26; N, 19.88. UV (λ_{max}, MeOH): 274, 392 nm.

3.1.6. 5-(3′-Pyridylazo)-25,26,27,28-tetrahydroxycalix[4]arene, 6. A solution of 3-aminopyridine (0.09 g, 0.95 mmol) in 2 N HCl (5 ml) was chilled in an ice bath and chilled $NaNO_2$ (0.13 g, 1.91 mmol) solution in H_2O (2 ml) was added to it to yield a solution of the diazonium salt. After about 15 min stirring, this diazonium salt solution was added dropwise at 0–5 °C to calix[4]arene (0.20 g, 0.47 mmol) in DMF (16 ml), MeOH (10 ml) and sodium acetate trihydrate (5 g, 36.7 mmol) solution. The reaction mixture was stirred for 3 h and 2 N HCl was added to precipitate an orange suspension, which was filtered off and washed with water. Further purification by column chromatography using chloroform–methanol (9.95/0.05) as the eluent afforded 0.050 g of **6** as a yellow solid. Yield: 30%, mp > 230 °C (decomp.), IR (KBr pellet, cm^{-1}): 3199, 1591, 1455. ^1H NMR (300 MHz, $CDCl_3$): δ 9.08 (s, 1H), 8.64 (d, J=4.5 Hz, 1H), 8.06 (d, J=7.8 Hz, 1H), 7.73 (s, 2H), 7.44 (dd, J=9.0, 4.8 Hz, 1H), 7.17–7.06 (m, 6H), 6.79–6.70 (m, 3H), 3.99 (br s, 4H), 2.94 (br s, 4H); ^{13}C NMR (300 MHz, $CDCl_3$): 152.3, 150.87, 148.3, 147, 146.6, 129, 128.9, 128.8, 128.1, 127.8, 127.3, 126.5, 124, 123.6, 122.2, 31.4, 31.3. FAB MS *m/z*: 530 (M^+). Anal. Calcd for $C_{33}H_{27}N_3O_4$: C, 74.84; H, 5.14; N, 7.93. Found: C, 74.98; H, 5.13; N, 7.90. UV (λ_{max}, MeOH): 277, 422 nm.

3.1.7. 5,11-Bis(3′-pyridylazo)-25,26,27,28-tetrahydroxycalix[4]arene, 7. By the procedure described for **6**, **7** was synthesized and purified by column chromatography using chloroform–methanol (9.85/0.15) as the eluent afforded 0.105 g of **7** as orange solid. Yield: 35%, mp > 230 °C (decomp.), IR (KBr pellet, cm^{-1}): 3394, 3219, 1688, 1584, 1457. ^1H NMR (300 MHz, DMSO-d_6): δ 9.01 (s, 2H,), 8.56 (br s, 2H), 7.99 (d, J=7.2 Hz, 2H), 7.74 (s, 2H), 7.67 (s, 2H), 7.37 (br s, 2H), 7.11 ((d, J=7.2 Hz, 2H), 7.04 (d, J= 7.2 Hz, 2H), 6.72 (t, J=7.2 Hz, 2H), 3.99 (br s, 8H); ^{13}C NMR (300 MHz, DMSO-d_6): 161.8, 151.3, 148.3, 147.5, 144, 142.9, 131.2, 130.8, 129.8, 129.4, 128.2, 125.4, 124.6, 124.1, 120.2, 32.3, 31.3, 31.0. FAB MS *m/z*: 635 (M^+). Anal. Calcd for $C_{38}H_{30}N_6O_4$: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.78; H, 4.71; N, 13.26. UV (λ_{max}, MeOH): 271, 382 nm.

3.1.8. 5,17-Bis(4′-pyridylazo)-25,26,27,28-tetrahydroxycalix[4]arene, 8. By the procedure described for **6**, **8** was synthesized and purified by column chromatography using chloroform–methanol (9.85/0.15) as the eluent afforded 0.030 g of **8** as orange solid. Yield: 10% mp > 230 °C (decomp.), IR (KBr pellet, cm^{-1}): 3457, 3428, 1615, 1454. ^1H NMR (300 MHz, $CDCl_3$): δ 10.1 (br s, 4H, D_2O exchangeable), 9.02 (s, 2H), 8.56 (br s, 2H), 7.96 (d, J= 7.2 Hz, 2H), 7.65 (s, 4H), 7.35 (dd, J=4.2 Hz, 2H), 7.14 (d, J=7.5 Hz, 4H), 6.77 (t, J=7.2 Hz, 2H), 4.25 (br s, 4H), 3.65 (br s, 4H); ^{13}C NMR (300 MHz, DMSO-d_6): 160.4, 151.3, 147.8, 147.5, 144.2, 142.1, 131.0, 129.6, 128.2, 124.6, 124.3, 119.2, 31.23. FAB MS *m/z*: 635 (M^+). Anal. Calcd for $C_{38}H_{30}N_6O_4$: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.77; H, 4.70; N, 13.24. UV (λ_{max}, MeOH): 266, 376 nm.

3.1.9. 5,11,17-Tris(4′-pyridylazo)-25,26,27,28-tetrahydroxycalix[4]arene, 9. By the procedure described for **6**, **9** was synthesized and purified by column chromatography using chloroform–methanol (9.4/0.6) as the eluent afforded 0.017 g of **9** as orange solid. Yield: 5%, mp > 230 °C (decomp.), IR (KBr pellet, cm^{-1}): 3435, 1594, 1472. ^1H NMR (300 MHz, DMSO-d_6): δ 12.7 (br s, 4H, D_2O exchangeable), 8.96 (s, 3H), 8.59 (br s, 3H), 8.05 (d, J= 8.1 Hz, 3H), 7.79 (s, 2H), 7.75 (s, 2H), 7.73 (s, 2H), 7.53 (dd, J=4.5, 6 Hz, 3H), 7.08 (d, J=7.5 Hz, 2H), 6.59 (t, J= 7.5 Hz, 2H), 4.45 (d, J=11.7 Hz, 2H), 4.33 (d, J=12 Hz, 2H), 3.63 (d, J=11.7 Hz, 2H), 3.46 (d, J=12.6 Hz, 2H); ^{13}C NMR (300 MHz, DMSO-d_6): 160.1, 150.4, 147.7, 145.5, 144.5, 131.6, 130.1, 128.1, 126.5, 124.3, 123.2, 120, 32.3, 31.44. ES MS *m/z*: 740.3 ($M^+ + 1$). Anal. Calcd for $C_{43}H_{33}N_9O_4$: C, 69.81; H, 4.50; N, 17.04. Found: C, 69.84; H, 4.52; N, 17.01. UV (λ_{max}, MeOH): 268, 380 nm.

3.1.10. 5,11,17,23-Tetrakis(3′-pyridylazo)-25,26,27,28-tetrahydroxycalix[4]arene, 10. A solution of 3-aminopyridine (0.22 g, 2.35 mmol) in 2 N HCl (5 ml) was chilled in an ice bath. A chilled $NaNO_2$ (0.32 g, 4.70 mmol) solution in H_2O (2 ml) was added to it to yield a solution of the diazonium salt of 3-aminopyridine. After about 15 min stirring, this diazonium salt solution was added dropwise at 0–5 °C to calix[4]arene (0.20 g, 0.47 mmol) in DMF (16 ml), MeOH (10 ml) and sodium acetate trihydrate (5 g, 36.7 mmol) solution. The reaction mixture was stirred for 3 h at 0–5 °C and 2 N HCl was added to precipitate an orange suspension, which was filtered off and washed with water, chloroform and methanol to afford 0.374 g of **10** as yellow solid. Yield: 94%, mp > 230 °C (decomp.), IR (KBr pellet, cm^{-1}): 3484, 1592, 1471. ^1H NMR (300 MHz,

DMSO-d_6): δ 13.05 (br s, 4H, D_2O exchangeable), 9.01 (s, 4H), 8.65 (d, $J=3.9$ Hz, 4H), 8.09 (d, $J=7.8$ Hz, 4H), 7.85 (s, 8H), 7.57 (dd, $J=4.8$, 6 Hz, 4H), 4.45 (br s, 4H), 3.71 (br s, 4H); ^{13}C NMR (300 MHz, DMSO-d_6): 160.3, 148.6, 148.1, 144.6, 143.8, 130.6, 128.6, 125, 124.2, 31.6; DEPT-135 NMR (300 MHz, DMSO-d_6): 149.5, 144.7, 129.4, 125.9, 125.0 (CH), 31.6 (CH_2). ES MS *m/z*: 845.6 ($M^+ + 1$). Anal. Calcd for $C_{48}H_{36}N_{12}O_4$: C, 68.24; H, 4.29; N, 19.89. Found: C, 68.24; H, 4.24; N, 19.87. UV (λ_{max}, MeOH): 262, 367 nm.

3.1.11. 5,11,17,23,29,35-Hexakis(3′-pyridylazo)-37,38,39,40,41,42-hexahydroxycalix[4]arene, 11. A solution of 3-aminopyridine (0.21 g, 2.23 mmol) in 2 N HCl (5 ml) was chilled in an ice bath and chilled $NaNO_2$ (0.31 g, 4.46 mmol) solution in H_2O (2 ml) was added to it to produce a diazonium salt solution. After stirring for 15 min, the diazonium salt solution was added dropwise at 0–5 °C to calix[6]arene (0.20 g, 0.31 mmol) in DMF (16 ml), MeOH (10 ml) and sodium acetate trihydrate (5 g, 36.7 mmol) solution and the reaction mixture was stirred for 3 h at 0–5 °C. 2 N HCl was added to precipitate an orange suspension, which was filtered off and washing with water and chloroform to provide 0.358 g of **11** as yellow solid. Yield: 90%, mp > 230 °C (decomp.), IR (KBr pellet, cm^{-1}): 3405, 1568, 1410. ^{1}H NMR (300 MHz, DMSO-d_6): δ 14.18 (br s, 6H, D_2O exchangeable), 9.0 (s, 6H), 8.6 (br s, 6H), 8.1 (d, $J=8.1$ Hz, 6H), 7.96 (s, 4H), 7.87 (s, 4H), 7.57 (br s, 6H), 7.37 (s, 4H), 4.28 (d, $J=11.7$ Hz, 4H), 3.96 (s, 4H), 3.77 (d, $J=11.7$ Hz, 4H); ^{13}C NMR (300 MHz, DMSO-d_6): 168, 160.2, 150.9, 149.9, 149.4, 148.6, 148.1, 145.8, 145.4, 145, 143, 142.4, 130.4, 129.6, 128.6, 127.4, 125, 124.4, 123.9, 119.7, 33.62, 32.63. FAB MS *m/z*: 1268 (M^+). Anal. Calcd for $C_{72}H_{54}N_{18}O_6$: C, 68.24; H, 4.29; N, 19.89. Found: C, 68.09; H, 4.26; N, 19.85. UV (λ_{max}, MeOH): 264, 379 nm.

3.1.12. 5,11,17,23,29,35,41,47-Octakis(3′-pyridylazo)-49,50,51,52,53,54,55,56-octahydroxycalix[4]arene, 12. A solution of 3-aminopyridine (0.20 g, 2.12 mmol) in 2 N HCl (5 ml) was chilled in an ice bath and chilled $NaNO_2$ (0.29 g, 4.25 mmol) solution in H_2O (2 ml) was added to it to give a solution of diazonium salt. After 15 min stirring, this diazonium salt solution was added dropwise at 0–5 °C to calix[8]arene (0.20 g, 0.23 mmol) in DMF (16 ml), MeOH (10 ml) and sodium acetate trihydrate (5 g, 36.7 mmol) solution and the reaction mixture was stirred for 3 h at 0–5 °C. 2 N HCl was added to precipitate an orange suspension, which was filtered off and washed with water and chloroform to afford 0.366 g of **12** as yellow solid. Yield: 92%, mp > 230 °C (decomp.), IR (KBr pellet, cm^{-1}): 3429, 1635, 1592, 1466. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.0 (s, 8H), 8.62 (br s, 8H), 8.09 (d, $J=6.3$ Hz, 8H), 7.78 (s, 16H), 7.52 (br s, 8H), 4.07 (br s, 16H); ^{13}C NMR (300 MHz, DMSO-d_6): 160.5, 150.5, 147.7, 145.6, 144.3, 129.3, 127.9, 126.6, 124.4, 32.2; DEPT-135 NMR (300 MHz, DMSO-d_6): 151.3, 147.6, 129.5, 127.5, 125.2 (CH), 32.2 (CH_2). FAB MS *m/z*: 1690 (M^+). Anal. Calcd for $C_{96}H_{72}N_{24}O_8$: C, 68.24; H, 4.29; N, 19.89. Found: C, 68.37; H, 4.31; N, 19.87. UV (λ_{max}, MeOH): 280, 352 nm.

3.1.13. 5,11,17-Tris(3′-pyridylazo)-23-(4′-pyridylazo)-25,26,27,28-tetrahydroxycalix[4]arene, 13. A solution of 3-aminopyridine (0.12 g, 1.32 mmol) in of 2 N HCl (5 ml) was chilled in an ice bath and chilled $NaNO_2$ (0.18 g, 2.64 mmol) solution in H_2O (2 ml) was added to it to produce a solution of the diazonium salt. After 15 min stirring, this diazonium salt solution was added dropwise at 0–5 °C to **1** (0.20 g, 0.38 mmol) in DMF (16 ml), MeOH (10 ml) and sodium acetate trihydrate (5 g, 36.7 mmol) solution. The reaction mixture was stirred for 3 h at 0–5 °C followed by addition of 2 N HCl was added to precipitate a deep red suspension, which was filtered off. It was washed with water to give 0.290 g of **13** as dark red solid. Yield: 91%, mp > 230 °C (decomp.), IR (KBr pellet, cm^{-1}): 3484, 1633, 1592, 1473. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.96 (s, 3H), 8.67 (br s, 2H), 8.59 (br s, 3H), 8.04 (d, 3H), 7.85 (s, 8H), 7.61 (br s, 2H), 7.50 (br s, 3H), 4.40 (br s, 4H); ^{13}C NMR (300 MHz, DMSO-d_6): 159.7, 151.1, 150.6, 147.7, 145.6, 144.7, 130.7, 126.6, 124.3, 123.9, 115.7, 31.8, 31.7; DEPT-135 NMR (300 MHz, DMSO-d_6): 151.1, 150.6, 146.6, 126.6, 124.6, 124.3, 124.0, 115.7 (CH), 31.8, 31.7 (CH_2). FAB MS *m/z*: 845 (M^+). Anal. Calcd for $C_{48}H_{36}N_{12}O_{44}$: C, 68.24; H, 4.29; N, 19.89. Found: C, 68.19; H, 4.29; N, 19.79. UV (λ_{max}, MeOH): 263, 368 nm.

3.1.14. 5,11-Bis(3′-pyridylazo)-17,23-bis(4′-pyridylazo)-25,26,27,28-tetrahydroxycalix[4]arene, 14. A solution of 3-aminopyridine (0.06 g, 0.63 mmol) in 2 N HCl (5 ml) was chilled in an ice bath and chilled $NaNO_2$ (0.09 g, 1.27 mmol) solution in H_2O (2 ml) was added to it to produce a diazonium salt solution. After stirring for 15 min, the diazonium salt solution was added dropwise at 0–5 °C to **2** (0.20 g, 0.31 mmol) in DMF (16 ml), MeOH (10 ml) and sodium acetate trihydrate (5 g, 36.7 mmol) solution. The reaction mixture was stirred for 3 h at 0–5 °C followed by addition of 2 N HCl was added to precipitate a red suspension, which was filtered off and washed with water to give 0.224 g of **14** as dark orange solid. Yield: 84%, mp > 230 °C (decomp.), IR (KBr pellet, cm^{-1}): 3383, 1597, 1457. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.02 (s, 2H), 8.74 (br s, 4H), 8.67 (br s, 2H), 8.10 (d, $J=7.2$ Hz, 2H), 7.90 (m, 8H), 7.67 (br s, 4H), 7.58 (dd, $J=4.2$ Hz, 2H), 4.45 (br s, 4H), 3.74 (br s, 4H); ^{13}C NMR (300 MHz, DMSO-d_6): 161.4, 159.3, 157.1, 151.1, 150.7, 147.8, 145.5, 144.8, 144.4, 139.4, 130.7, 126.7, 124.52, 124, 115.8, 108.7, 31.9, 31.7, 31.4; DEPT-135 NMR (300 MHz, DMSO-d_6): 146.0, 145.6, 140.4, 121.5, 119.5, 118.9, 110.7, 103.6 (CH), 31.9, 31.7, 31.4 (CH_2). FAB MS *m/z*: 845 (M^+). Anal. Calcd for $C_{48}H_{36}N_{12}O_4$: C, 68.24; H, 4.29; N, 19.89. Found: C, 68.08; H, 4.28; N, 19.86. UV (λ_{max}, MeOH): 262, 374 nm.

3.1.15. 5-(3′-Pyridylazo)-11-(4′-pyridylazo)-25,26,27,28-tetrahydroxycalix[4]arene, 15. A solution of 4-aminopyridine (0.21 g, 2.26 mmol) in 2 N HCl (5 ml) was chilled in an ice bath and chilled $NaNO_2$ (0.31 g, 4.53 mmol) solution in H_2O (2 ml) was added to it to produce a diazonium salt solution. After stirring for 15 min, the diazonium salt solution was added dropwise at 0–5 °C to **6** (0.20 g, 0.38 mmol) in DMF (16 ml), MeOH (10 ml) and sodium acetate trihydrate (5 g, 36.7 mmol) solution. The reaction mixture was stirred for 3 h at 0–5 °C. 2 N HCl was added to precipitate a deep red suspension, which was filtered off and washing with water afforded 0.072 g of **15** as dark red solid. Yield: 30%, mp > 230 °C (decomp.), IR (KBr pellet, cm^{-1}): 3383, 1630, 1598, 1457. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.10 (br s, 4H, D_2O exchangeable), 9.11 (s, 1H),

8.74 (d, J=3.6 Hz, 2H), 8.65–8.63 (m, 1H), 8.05 (d, J=8.1 Hz, 1H), 7.84–7.72 (m, 4H), 7.62 (d, J=6.3 Hz, 2H), 7.41 (dd, J=4.5, 4.5 Hz, 1H), 7.25–7.07 (m, 4H), 6.79 (t, J=7.5 Hz, 2H), 4.31 (br s, 4H), 3.72 (br s, 4H); ^{13}C NMR (300 MHz, $CDCl_3$): 152.3, 151.1, 151.0, 148.5, 147.9, 147.4, 146.9, 129.3, 129.2, 128.5, 128.2, 127.3, 126.78, 125.5, 125.1, 124.7, 124.3, 123.9, 123.8, 122.5, 116.0, 31.8, 31.7, 31.5. FAB MS m/z: 635 (M^+). Anal. Calcd for $C_{38}H_{30}N_6O_4$: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.76; H, 4.75; N, 13.20. UV (λ_{max}, MeOH): 264, 378 nm.

3.1.16. 5-(3′-Pyridylazo)-17-(4′-pyridylazo)-25,26,27,28-tetrahydroxycalix[4]arene, 16. By the procedure described for **15**, **16** was synthesized and purified by column chromatography using $CHCl_3$–methanol (9.8/0.2) as the eluent to afford 0.019 g of **16** as a dark red solid. Yield: 8%, mp>230 °C (decomp.), IR (KBr pellet, cm^{-1}): 3429, 1635, 1592, 1466. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.16 (br s, 4H, D_2O exchangeable), 9.02 (s, 1H), 8.68 (br s, 1H), 8.57 (br s, 2H), 7.99 (d, J=7.5 Hz, 1H), 7.75–7.64 (m, 4H), 7.58 (br s, 2H), 7.36 (dd, J=4.5, 4.5 Hz, 1H), 7.12 (d, J=7.5 Hz, 4H), 6.78 (t, J=7.5 Hz, 2H), 4.25 (br s, 4H), 3.48 (br s, 4H); ^{13}C NMR (300 MHz, $CDCl_3$): 152.3, 151.0, 148.5, 146.9, 129.3, 128.2, 127.3, 126.7, 125.5, 125.1, 124.7, 123.8, 122.5, 116.0, 31.6. FAB MS m/z: 635 (M^+). Anal. Calcd for $C_{38}H_{30}N_6O_4$: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.68; H, 4.75; N, 13.21. UV (λ_{max}, MeOH): 265, 379 nm.

3.1.17. 5-(3′-Pyridylazo)-11,17-bis(4′-pyridylazo)-25,26,27,28-hydroxycalix[4]arene, 17. By the procedure described for **15**, **17** was synthesized and purified by column chromatography using $CHCl_3$–methanol (9.5/0.5) as the eluent to afford 0.028 g of **17** as a dark red solid. Yield: 10%, mp>230 °C (decomp.), IR (KBr pellet, cm^{-1}): 3378, 1601, 1456. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.75 (s, 1H), 8.52–8.47 (m, 4H), 8.41 (br s, 1H), 7.84 (d, J=8.7 Hz, 1H), 7.69–7.42 (m, 10H), 7.33 (dd, J=4.5, 4.8 Hz, 1H), 6.90 (t, J=7.5 Hz, 2H), 6.40–6.35 (m, 1H), 4.05 (br s, 8H); ^{13}C NMR (300 MHz, DMSO-d_6): 158.7, 153.0, 152.6, 152.3, 152.0, 151.8, 149.5, 149.2, 148.3, 147.8, 131.6, 131.0, 130.1, 129.6, 129.3, 128.9, 128.3, 126.8, 125.9, 125.0, 124.5, 123.3, 120.2, 116.3, 115.9, 32.0, 31.7, 31.1, 29.0. ES MS m/z: 740.3 (M^+). Anal. Calcd for $C_{43}H_{33}N_9O_4$: C, 69.81; H, 4.50; N, 17.04. Found: C, 69.71; H, 4.52; N, 17.01. UV (λ_{max}, MeOH): 268, 380 nm.

3.1.18. 5-(3′-Pyridylazo)-11,23-bis(4′-pyridylazo)-25,26,27,28-hydroxycalix[4]arene, 18. By the procedure described for **15**, **18** was synthesized and purified by column chromatography using $CHCl_3$–methanol (9.5/0.5) as the eluent to afford 0.011 g of **18** as a dark red solid. Yield: 4%, mp>230 °C (decomp.), ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.03 (s, 1H), 8.66 (br s, 4H), 8.57 (br s, 1H), 7.96 (d, J=8.7 Hz, 1H), 7.76 (s, 4H), 7.69 (s, 2H), 7.53 (s, 4H), 7.31 (dd, J=4.5, 4.8 Hz, 1H), 7.18 (d, J=7.5 Hz, 2H), 6.75 (t, J=7.5 Hz, 1H), 4.28 (br s, 4H), 3.68 (br s, 4H); ^{13}C NMR (300 MHz, $CDCl_3$): 157.3, 152.2, 151.1, 147.0, 129.5, 126.7, 125.69, 125.1, 124.2, 123.8, 122.8, 116.0, 114.0, 31.7, 29.7. ES MS m/z: 740.3 (M^+). Anal. Calcd for $C_{43}H_{33}N_9O_4$: C, 69.81; H, 4.50; N, 17.04. Found: C, 69.86; H, 4.51; N, 17.04. UV (λ_{max}, MeOH): 268, 380 nm.

3.1.19. 5-(3′-Pyridylazo)-11,17,23-tris(4′-pyridylazo)-25,26,27,28-tetrahydroxycalix[4]arene, 19. A solution of 4-aminopyridine (0.32 g, 3.39 mmol) in 2 N HCl (5 ml) was chilled in an ice bath and chilled $NaNO_2$ (0.47 g, 6.79 mmol) solution in H_2O (2 ml) was added to it to yield a solution of diazonium salt. After stirring for 15 min, the diazonium salt solution was added dropwise at 0–5 °C to **6** (0.20 g, 0.38 mmol) in DMF (16 ml), MeOH (10 ml) and sodium acetate trihydrate (5 g, 36.7 mmol) solution. The reaction mixture was stirred for 3 h at 0–5 °C. 2 N HCl was then added to precipitate a deep red suspension, which was filtered off and washed with water. Further purification by column chromatography using $CHCl_3$–methanol (8.5/1.5) as the eluent afforded 0.080 g of **19** as a dark red solid. Yield: 20%, mp>230 °C (decomp.), IR (KBr pellet, cm^{-1}): 3394, 1631, 1592, 1386. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.83 (s, 1H), 8.54 (br s, 7H), 7.87 (d, J=4.5 Hz, 1H), 7.75–7.67 (m, 8H), 7.53 (br s, 6H), 7.33 (br s, 1H), 4.21 (br s, 4H), 3.74 (br s, 4H). ES MS m/z: 845.6 (M^++1). Anal. Calcd for $C_{48}H_{36}N_{12}O_4$: C, 68.24; H, 4.29; N, 19.89. Found: C, 68.13; H, 4.31; N, 19.91. UV (λ_{max}, MeOH): 262, 367 nm.

3.1.20. 5,11-Bis(3′-pyridylazo)-17-(4′-pyridylazo)-25,26,27,28-tetrahydroxycalix[4]arene, 20. A solution of 4-aminopyridine (0.12 g, 1.27 mmol) in 2 N HCl (5 ml) was chilled in an ice bath and chilled $NaNO_2$ (0.18 g, 2.55 mmol) solution in H_2O (2 ml) was added to it to produce a diazonium salt solution, which was added dropwise to **7** (0.20 g, 0.31 mmol) in DMF (16 ml), MeOH (10 ml) and sodium acetate trihydrate (5 g, 36.7 mmol) solution at 0–5 °C. The reaction mixture was stirred for 3 h at 0–5 °C. 2 N HCl was added to precipitate a deep red suspension, which was filtered off and washed with water. Further separation by column chromatography using $CHCl_3$–MeOH (9.4/0.6) as the eluent provided 0.093 g of **20** as a dark red solid. Yield: 58%, mp>230 °C (decomp.), IR (KBr pellet, cm^{-1}): 3448, 1633, 1592, 1457. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.66 (br s, 4H, D_2O exchangeable), 8.88 (s, 2H), 8.58 (br s, 2H), 8.51 (br s, 2H), 7.95 (br s, 2H), 7.69–7.42 (m, 10H), 6.90 (br s, 2H), 6.40–6.35 (br s, 1H), 4.33 (br s, 8H). ES MS m/z: 740.3 (M^+). Anal. Calcd for $C_{43}H_{33}N_9O_4$: C, 69.81; H, 4.50; N, 17.04. Found: C, 69.71; H, 4.52; N, 17.05. UV (λ_{max}, MeOH): 268, 380 nm.

3.2. UV/vis experiments

3.2.1. General procedures for UV/vis experiments. All the UV/vis experiments were carried out in methanol unless otherwise specified. Any shift in the UV/vis spectra of the pyridyl azocalixarenes were recorded on addition of metal salt (100 equiv) solutions.

3.2.2. Job's plot experiments. A stock solution of pyridyl azocalixarenes and Cs_2CO_3 were prepared in methanol. The Cs_2CO_3 and pyridyl azocalix[n]arene solutions with identical concentrations were mixed in different ratios in such a way that the total volume of the reactants in each mixture remains fixed at 5.0 ml but the mole ratio of the reactants varied systematically. After shaking for 5 min, the UV/vis absorbance at 500 nm was recorded. Assuming that only one complex was formed (ML_n) at equilibrium, the value of n could be calculated from the plot of χ_{max} [mole fraction of the ligand (χL) at maximum absorption] by

the following relationship —$n=\chi_{max}/[1-\chi_{max}]$ from the plot of absorbance versus χL, the value of χ_{max} was noted.

3.2.3. Mole ratio experiments. Solutions of pyridyl azocalixarenes in methanol and Cs_2CO_3 in methanol were prepared as stock solutions. The concentration of calixarene dye solution was held constant while that of the metal ion solution was varied. After shaking for 5 min, the UV/vis absorbance at 500 nm was recorded. A plot of absorbance versus mole ratio of the reactants was then prepared to calculate the mole ratio of calixarene and metal ion forming a potential complex.

3.3. X-ray structure determination of 6

Crystal data: $C_{37}H_{27}N_3O_4\cdot CHCl_3$, $M=648.94$, triclinic, $a=9.496(8)$ Å, $b=11.183(9)$ Å, $c=14.841(12)$ Å, $\alpha=76.317(14)^\circ$, $\beta=83.586(13)^\circ$, $\gamma=80.741(14)^\circ$, $V=1507(2)$ Å^3, $Z=2$, $D_c=1.430$ g cm^{-3}, $\mu=0.349$ mm^{-1} space group=P-1. Intensity data were collected up to $\theta=42^\circ$ by using 2θ scanning mode with graphite filtered Mo Kα radiation ($\lambda=0.71073$) on a $0.231\times0.098\times0.045$ mm^3 crystal at 298 K. A total of 7252 reflections were measured, 3234 were independent and of, which 1324 [$I>2$ (I)] were considered observed. The structure was solved by direct methods and refined by full matrix least-square techniques on F^2 using SHELXTL. All the nonhydrogen atoms were refined anisotropically. C–H hydrogen atoms were placed in geometrically calculated positions by using a riding model. SADABS was applied for absorption correction. Final R indices [$I>2\sigma$ (I)] $R1=0.2090$, $wR2=0.2160$, and R indices (all data) $R1=0.0897$, $wR2=0.1689$ was found for 3234 observed reflections, 0 restraints and 404 parameters. Torsion angles and H-bonding were calculated by using PARST. Crystal data have been deposited with the Cambridge Crystallographic Data Center, under reference CCDC 268185.

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Enantio-complementary deracemization of (±)-2-hydroxy-4-phenylbutanoic acid and (±)-3-phenyllactic acid using lipase-catalyzed kinetic resolution combined with biocatalytic racemization

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Abstract—Deracemization of (±)-3-phenyllactic acid (**1**) and (±)-2-hydroxy-4-phenylbutanoic acid (**2**) was accomplished by lipase-catalysed kinetic resolution coupled to biocatalytic racemization of the non-reacting substrate enantiomers using *Lactobacillus paracasei* DSM 20008. Cyclic repetition of this sequence led to a single enantiomeric product from the racemate. Access to both enantiomers was achieved by switching between lipase-catalysed acyl-transfer and ester hydrolysis reactions. Both products constitute important building blocks for virus protease- and ACE-inhibitors, respectively.

1. Introduction

3-Phenyllactate (**1**) and derivatives thereof are frequently used in nonracemic form as components of pharmaceuticals and natural antibiotic agents.[1] They represent an integral part of bioactive peptides, such as Aeruginosins[2] and Microcin,[3] which were shown to be potent protease inhibitors. The *p*-fluoro-analog of **1** is a key building block for the synthesis of AG7088 (Ruprintrivir), a potent rhinovirus inhibitor currently being tested in clinical trials to treat the common cold.[4] Several approaches to obtain **1** in nonracemic form have been reported.[5] The majority of them is based on racemate resolution[6] or the asymmetric transformation of a suitable non-chiral synthetic precursor.[4a,7]

(*R*)-2-Hydroxy-4-phenylbutanoic acid (**2**) is an important building block for the production of a large variety of angiotensin converting enzyme (ACE) inhibitors having in common the (*S*)-homophenylalanine moiety as the central pharmacophore unit.[8] These agents from the the 'pril-family', such as Enalapril, Lisinopril, Cilapril or Benazepril, efficiently expand the range of antihypertensives, like β-blockers, A_2-antagonists or Ca-channel blockers. Due to the fact that many of these drugs have lost patent protection (or soon will do so), the production costs of the required building blocks has become a major issue. For the synthesis of **2** in nonracemic form, numerous strategies based on (i) racemate resolution via crystallization[9] or (ii) kinetic resolution of a racemate[10] or (iii) the asymmetric transformation of a prochiral precursor[11] have been devised.

The majority of these routes have one or more weak points:[4,5,11m] high cost of reagents, such as chiral transition metal complexes, insufficient catalyst selectivity or activity, sensitivity of catalysts in asymmetric hydrogenation, or low stability of starting materials, such as α-keto acids.

The most dramatic limitation common for all strategies relying on kinetic resolution is the maximum theoretical yield of 50% for a single enantiomer. In order to overcome this fundamental drawback, two approaches—summarized under the term 'deracemization'[12]—were recently proposed: (i) dynamic kinetic resolution[13] and (ii) microbial stereo-inversion.[14]

Although both of these methods have the clear merit of a 100% theoretical yield of a single stereoisomeric product, its absolute configuration is determined by the enantiopreference of the biocatalyst employed. Since mirror-image enzymes *sensu stricto* do not exist,[15] production of both

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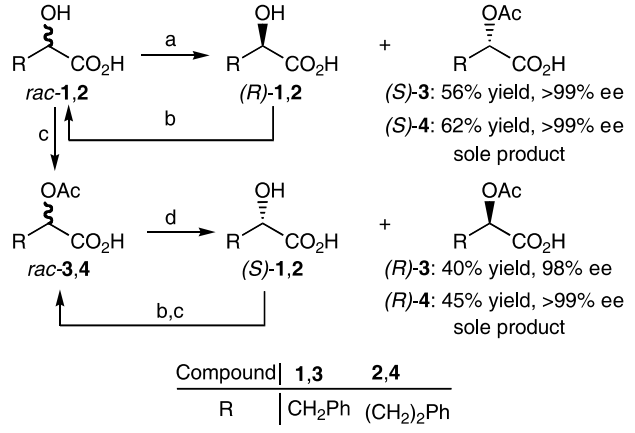
enantiomers through biocatalytic deracemization by simple choice of the 'matching enantiomer' of the chiral (bio)catalyst is virtually impossible.

In order to circumvent this limitation, we envisaged to apply lipase-catalyzed ester hydrolysis and ester formation via acyl transfer to our recently developed deracemization protocol[16] based on the enzymatic racemization of the non-reacting substrate enantiomer using a racemase.[17] Taking into consideration that ester hydrolysis and esterification represent reactions in opposite directions, products of opposite configuration are to be expected. The proof of principle for this concept was recently verified by us using a lipase–mandelate racemase two-enzyme process.[18] However, the restricted substrate tolerance of mandelate racemase (EC 5.1.2.2), which is unable to isomerize 3-phenyllactate (**1**) or 2-hydroxy-4-phenylbutanoate (**2**) imposed severe limitations[19] and forced us to employ a suitable β,γ-unsaturated synthetic precursor for 2-hydroxy-4-phenylbutanoate (i.e., 2-hydroxy-4-phenylbut-3-enoate) instead, which required additional synthetic steps and thus unfavorably enhanced the overall complexity of the process. Since this substrate-analog-trick could not be applied to 3-phenyllactate (**1**), the latter compound could not be deracemized by using the above mentioned mandelate racemase–lipase protocol. In search for a suitable biocatalyst for the racemization of a wide variety of saturated aliphatic 2-hydroxycarboxylic acids, we recently identified whole resting cells of *Lactobacillus* sp. as a promising alternative.[20]

In order to demonstrate the general applicability of this method, we envisaged to develop an enantio-complementary deracemization protocol as follows (Scheme 1).



Scheme 1. Reagents and conditions: (a) *Pseudomonas* sp. lipase (Amano PS-C-II), vinyl acetate, *i*-Pr_2O, 25 °C; (b) *Lactobacillus paracasei* DSM 20008, buffer pH 6.5, 42 °C; (c) Ac_2O, pyridine; (d) porcine pancreas lipase (EC 3.1.1.3, for **3**), *Candida antarctica* lipase B/Novozyme 435 (for **4**), buffer pH 7.5, acetone, 30 °C.

2. Results and discussion

2.1. (*S*)-Series (Scheme 1)

Kinetic resolution of (±)-**1** via *Pseudomonas* sp. lipase catalysed acyl-transfer using vinyl acetate as acyl donor proceeded with excellent enantioselectivities ($E>200$) to furnish a mixture of (*S*)-**3** and unreacted (*R*)-**1** in >99% ee at 50% conversion. Biocatalytic racemization of (*R*)-**1** was accomplished without separation from the *O*-acetylated product **3** using whole cells of *Lactobacillus paracasei* DSM 20008 in aqueous buffer. After the mixture of *rac*-**1** and (*S*)-**3** thus obtained was subjected to two subsequent cycles of lipase-catalysed kinetic resolution/biocatalytic racemization as described above, (*S*)-**3** was obtained in 56% overall yield from the racemate as the sole product. Finally, hydrolysis of the *O*-acetyl group gave (*S*)-3-phenyllactic acid (**1**) without loss of optical purity in 69% yield and >99% ee.

When this deracemization protocol was applied to 2-hydroxy-4-phenylbutanoic acid (*rac*-**2**), (*S*)-**2** was obtained in >99% ee in similar yield.

2.2. (*R*)-Series (Scheme 1)

It was expected, that lipase-catalysed hydrolysis of *rac*-*O*-acetate esters **3** and **4** would give access to the corresponding enantiomeric products, that is, (*S*)-**1**,**2** and nonreacted α-acetoxycarboxylic acids (*R*)-**3**,**4**. However, initial attempts were hampered by solubility problems of the rather polar substrates and insufficient enantioselectivities of various lipases. For instance, *Candida rugosa* lipase (Amano AY), various *Pseudomonas* sp. lipases (Amano PS-C-I, PS-D), and *Candida antarctica* lipase A displayed low enantioselectivity. After some experimentation, we identified two lipases, that is, porcine pancreas lipase (EC 3.1.1.3) for *rac*-**3** and *Candida antarctica* lipase B for *rac*-**4**, which showed excellent enantioselectivity. In addition, solubility problems were overcome by using acetone as co-solvent. Without separation of materials, the cyclic sequence of acetylation/hydrolysis/racemization was repeated two times to give (*R*)-**3** and (*R*)-**4** in 98% and >99% ee, respectively, as the sole products. Finally, deacylation of the latter compounds furnished α-hydroxycarboxylic acids (*R*)-**1** and (*R*)-**2** in 74–75% yield. Biocatalysts could be recovered by filtration and reused for the whole number of cycles until completion of the process.

The main limitation of this process lies in the neccessity to switch between aqueous-organic solvent systems, which furnishes a consecutive sequence of steps rather than a dynamic process. Attempts to conduct the biocatalytic racemization in situ in an organic solvent were unsuccessful so far. Although isolated overall yields were still below the theoretical 100%, this threshold should be approachable using improved recovery procedures for the polar hydroxycarboxylic acids from the aqueous medium (e.g., by ion exchange chromatography or continuous extraction). Detailed analysis showed that this process is virtually free of yield-limiting side reactions and that microbial degradation of *rac*-**1**,**2** during the racemization step by was negligible.[21] The possibility to determine the stereochemical configuration of the sole product by a simple switch between lipase-catalyzed acyl-transfer- and hydrolysis-mode demonstrates the flexibility of this process.

3. Conclusion

In summary, both enantiomers of 3-phenyllactic acid (**1**) and 2-hydroxy-4-phenylbutanoic acid (**2**) were obtained as single stereoisomers in >98% ee from the corresponding racemates via a stepwise deracemization protocol consisting of a lipase-kinetic resolution followed by biocatalytic racemization. Whereas (*S*)-enantiomers were accessed through lipase-catalysed acyl-transfer, the (*R*)-counterparts were obtained via ester hydrolysis.

4. Experimental

4.1. General

Determination of conversion and enantiomeric excess were determined via HPLC on a chiral stationary phase. HPLC analyses were carried out on a Jasco HPLC-system (pumps PU-980, multi-wave-length-detector MD-910, autosampler AS-950, degasser CMA/260) using a Chiralpak AD column (column A, Daicel, 0.46 cm×25 cm). Compounds were purified by flash chromatography on silica gel Merck 60 (230–400 mesh). Melting points were obtained on a Gallenkamp melting point apparatus MFB-595 in open capillary tubes, optical rotation values were measured on a Perkin-Elmer polarimeter 341 at 589 nm (Na-line) in a 1 dm cuvette and are given in units of 10^{-1} deg cm^2 g^{-1}.

4.1.1. (*S*)-*O*-Acetyl-3-phenyllactic acid (*S*)-3. Kinetic resolution step (a): to a solution of *rac*-**1** (0.5 g, 3 mmol) in diisopropyl ether (50 mL), vinyl acetate (5 mL) and *Pseudomonas* sp. lipase (Amano PS-C-II, 0.5 g) were added and the mixture was shaken for 48 h at 25 °C and 150 rpm. The enzyme was filtered, washed and dried for reuse, the filtrate was evaporated to dryness.

Racemization step (b): (*S*)-**3** and (*R*)-**1** obtained from step (a) were dissolved in bis-Tris-buffer (5 mL, 50 mmol, pH 6.5, 10^{-2} M $MgCl_2$) and the pH was adjusted to 6.5. Then, lyophilized whole cells of *Lactobacillus paracasei* DSM 20008[20b] [2 g, rehydrated in bis-Tris-buffer (12 mL, 50 mmol, pH 6.5, 10^{-2} M $MgCl_2$) for 30 min] were added and the mixture was shaken for 48–72 h at 42 °C and 120 rpm until racemization of (*R*)-**1** was complete. After centrifugation, the solution was acidified to pH 1–2 with HCl (3 M) and *rac*-**1** and (*S*)-**3** were extracted three times with ethyl acetate, dried with Na_2SO_4 and evaporated.

After cyclic repetition of step (a) twice and step (b) once, the residue obtained by extraction was purified by flash chromatography (to remove minor impurities emerging from the cells) using dichloromethane/methanol (gradient from 0–10% MeOH) to yield (*S*)-**3** as the sole product (0.35 g, 56%, oil); HPLC analysis showed a single peak at T_{Ret} 14.8 min using a Chiralpak AD column (Daicel, heptane/2-propanol/CF_3COOH 90:10:0.1; 0.5 mL/min, 18 °C); $[\alpha]_D^{20}$ −10.25 (*c* 1.79; acetone, >99% ee).

4.1.2. (*S*)-3-Phenyllactic acid (*S*)-1. Hydrolysis step: a mixture of (*S*)-**3** (0.2 g, 1 mmol), MeOH (8 mL) and K_2CO_3 (1 g) was stirred at 0 °C for 5 h. After acidification with HCl (3 M) to pH 1–2, the product was extracted three times with ethyl acetate, the organic layer was dried (Na_2SO_4), evaporated and the residue was purified by flash chromatography using dichloromethane/methanol (gradient from 0–10% MeOH) as eluent to yield (*S*)-**1** (0.11 g, 69%); mp 122–123 °C; lit.[22] mp: 120–121 °C; $[\alpha]_D^{20}$ −27.55 (*c* 1.0; acetone, >99% ee); lit.[23] $[\alpha]_D^{25}$ −27.80 (*c* 1.13; acetone); HPLC analysis using the method described above showed a single peak at T_{Ret} 24.53 min.

4.1.3. (*S*)-2-Acetoxy-4-phenylbutanoic acid (*S*)-4. In the same manner as described above, *rac*-**2** (0.5 g, 2.77 mmol) was converted to (*S*)-**4** (0.38 g) in a total yield of 62%; mp: 28–30 °C; $[\alpha]_D^{20}$ −6.61 (*c* 0.5; acetone, >99% ee); lit.[24] $[\alpha]_D^{25}$ −11.0 (*c* 0.92; EtOH); HPLC analysis showed a single peak at T_{Ret} 19.12 min using a Chiralpak AD column (Daicel, heptane/2-propanol/CF_3COOH 90:10:0.1; 0.4 mL/min, 18 °C).

4.1.4. (*S*)-2-Hydroxy-4-phenylbutanoic acid (*S*)-2. In the same manner as described above, (*S*)-**4** (0.22 g, 1 mmol) was converted to (*S*)-**2** (0.13 g; 73%); mp 115–117 °C; lit.[23] mp: 114 °C; $[\alpha]_D^{20}$ +8.1 (*c* 1.0; EtOH, >99% ee); lit.[23] $[\alpha]_D^{25}$ +7.5 (*c* 0.5; EtOH, 84% ee). HPLC analysis using the method described above showed a single peak at T_{Ret} 27.01 min.

4.1.5. (*R*)-*O*-Acetyl-3-phenyllactic acid (*R*)-3. Acylation step (c): a solution of *rac*-**1** (0.5 g, 3 mmol) in acetic anhydride (4 mL) and pyridine (0.25 mL) was kept at 0–5 °C. After 6 h the solution was poured into ice-water (50 mL), which was acidified with HCl (3 M) to pH 1–2 and extracted three times with ethyl acetate. The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4) and evaporated to yield *rac*-**3** (0.50 g, 80%).

Kinetic resolution step (d): to a solution of *rac*-**3** (0.5 g, 2.6 mmol) in acetone (21 mL) and phosphate buffer (35 mL, pH 7.5; 50 mmol), lipase from porcine pancreas (EC 3.1.1.3, 5 g, Sigma Type II, crude) was added and the mixture was shaken for 20 h at 30 °C and 150 rpm. After centrifugation, acetone was evaporated from the filtrate. The residue was acidified with HCl (3 M) to pH 1–2, extracted three times with ethyl acetate, dried (Na_2SO_4) and evaporated.

For the racemization step (b) see above.

After performing steps (c) and (d) twice and step (b) once, the residue obtained by extraction was purified by flash chromatography (to remove minor impurities emerging from the cells) using dichloromethane/methanol (gradient from 0–10% MeOH) to yield (*R*)-**3** as the sole product (0.25 g, 40%), oil; $[\alpha]_D^{20}$ +8.86 (*c* 1.39; acetone, 98% ee). HPLC analysis using the method described above showed a single peak at T_{Ret} 17.80 min.

4.1.6. (*R*)-3-Phenyllactic acid (*R*)-1. In the same manner as described for (*S*)-**1**, (*R*)-**3** (0.15 g, 0.7 mmol) was converted to (*R*)-**1** (0.09 g, 75%); mp 124–125 °C; lit.[22] mp: 120–121 °C; $[\alpha]_D^{20}$ +26.95 (*c* 1.0; acetone, 98% ee); lit.[22] $[\alpha]_D^{25}$ 29.8 (*c* 1.13; acetone). HPLC analysis using the method described above showed a single peak at T_{Ret} 20.38 min.

4.1.7. (*R*)-2-Acetoxy-4-phenylbutanoic acid (*R*)-4. In the same manner as described above, *rac*-**2** (0.5 g, 2.8 mmol) was converted to *rac*-**4** (0.84 g, 87%).

Kinetic resolution step (d): to a solution of *rac*-**4** (0.54 g, 2.4 mmol) in acetone (2.5 mL) and phosphate buffer (25 mL, pH 7.5, 50 mmol), lipase from *Candida antarctica* B (Novozyme 435, 0.5 g) was added and the mixture was shaken for 24 h at 30 °C and 150 rpm. The lipase was recovered by filtration and dried for reuse. The filtrate was evaporated from acetone, the residue was acidified with HCl (3 M) to pH 1–2, extracted three times with ethyl acetate, dried (Na_2SO_4) and evaporated.

For the racemization step (b) see above.

After repeating steps (c) and (d) twice and step (b) once, the residue obtained by extraction was purified by flash chromatography (to remove minor impurities emerging from the cells) using dichloromethane/methanol (gradient from 0–10% MeOH) to yield (*R*)-**4** as sole product (0.28 g, 45%); mp: 27–30 °C; $[\alpha]_D^{20}$ +5.21 (*c* 1.36; acetone, >99% ee). HPLC analysis using the method described above showed a single peak at T_{Ret} 24.4 min.

4.1.8. (*R*)-2-Hydroxy-4-phenylbutanoic acid (*R*)-2. In the same manner as described above, (*R*)-**4** (0.2 g; 0.9 mmol) was converted to (*R*)-**2** (0.12 g, 74%); mp 115–117 °C; lit.[23] mp: 114 °C; $[\alpha]_D^{20}$ −8.5 (*c* 1.0; EtOH, >99% ee); lit.[23] $[\alpha]_D^{25}$ −9.0 (*c* 0.1; EtOH). HPLC analysis using the method described above showed a single peak at T_{Ret} 24.8 min.

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A brief total synthesis of fumaramidine

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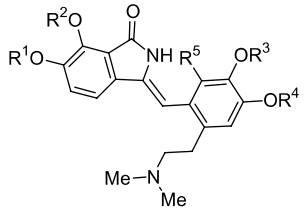
Abstract—The first total synthesis of the alkaloid fumaramidine is reported. The synthetic tactics involve the sequential construction of the isoindolinone template by a Parham cyclization process followed by benzylic lactam deprotonation, interception with the suitable carboxaldehyde and ultimate E1cb elimination. Final *N*-lactam deprotection completes the synthesis of the *Z* configured title compound.

1. Introduction

The creeper *Fumaria parviflora Lam* (*Fumariaceae*) is widespread in Pakistan where it is commonly known as Pit Papra and where its extracts are used in folk medicine as a blood purifier and as an anthelmintic, as well as in the treatment of skin diseases and diarrhea.[1] The crude alkaloidal extracts have initially indicated the presence of 17 isoquinoline bases[2] and additionally four enelactams, that is, fumaramidine **1**, fumaramine **2**, fumaridine **3** and narceine imide **4** (Fig. 1) were isolated from the strongly basic ethanolic extracts of dried plant material.[3]

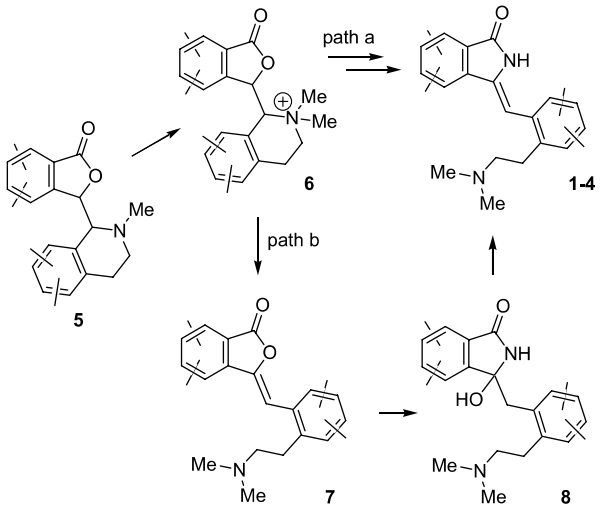


1	Fumaramidine	$R^1,R^2 = -CH_2-$; $R^3 = R^4 = Me$; $R^5 = H$
2	Fumaramine	$R^1,R^2 = R^3,R^4 = -CH_2-$; $R^5 = H$
3	Fumaridine	$R^1 = R^2 = Me$; $R^3,R^4 = -CH_2-$; $R^5 = H$
4	Narceine imide	$R^1 = R^2 = Me$; $R^3,R^4 = -CH_2-$; $R^5 = OMe$

Figure 1.

However, their presence in the natural source is not guaranteed and is still a subject for discussion. They can indeed be formed by a logical biogenetic sequence involving N-methylation of the phthalideisoquinolines **5** to their quaternary analogs **6** followed by unspecified rearrangements including Hoffmann elimination (Scheme 1, path a).[4]

But it has also been conjectured that the transformation of **6** to **1**–**4** might be performed with ammonium hydroxide usually used in the course of their isolation since it has been shown that enol lactones **7** react with ammonia to form hydroxylactams **8** liable to undergo facile dehydration to the enelactams **1**–**4** (Scheme 1, path b).[5] Until and unless the presence of hydroxyl and enelactams **8** and **1**–**4**, respectively is conclusively demonstrated in the plant extracts prior to strongly base treatments it can be concluded that these enelactams are artifacts and not true alkaloids. This problem



Scheme 1.

Keywords: Alkaloids; Parham procedure; Ene lactams; Isoindolinones.
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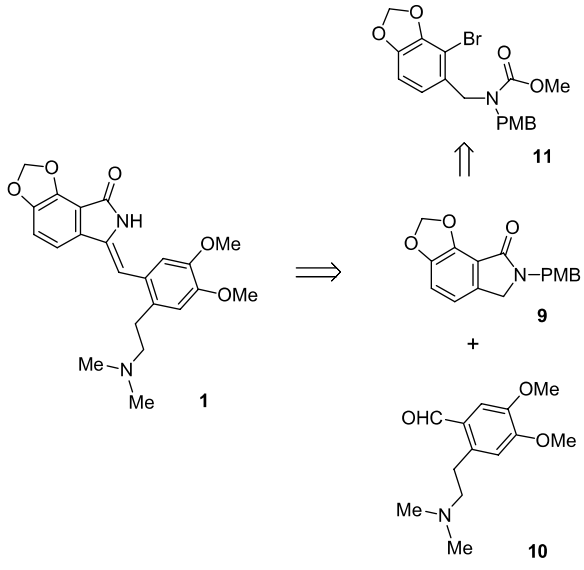
prompted us to launch a project related to the total synthesis of these highly conjugated models and we delineate in this paper a tactically new synthesis of the exemplary representative fumaramidine **1** that relies upon our long-standing experience in the field of *N*-acylenamine and isoindoline chemistry.[6,7]

2. Results and discussion

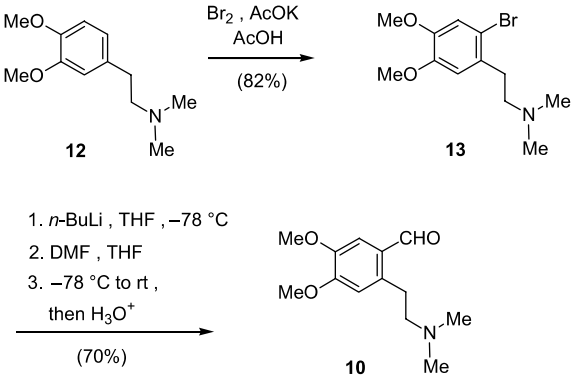
A swift skimming over the structural composition of this enelactam reveals that this alkaloid can be regarded as having a *Z* configured stilbenoid system fused with a lactam ring. But besides it turns out that a number of synthetic issues has also to be addressed such as (i) the connection of diverse and dense functionalities on the environmentally different aromatic units and in particular the assemblage of an unsymmetrically disubstituted isoindolinone and (ii) the presence of an unsubstituted nitrogen lactam, which may require a problematic deprotection step for such models with a high degree of conjugation.[8] As far as we are aware no total synthesis of **1** has appeared in print. For the elaboration of compound **1** we opted for the synthetic route depicted in the retrosynthetic Scheme 2.



Scheme 2.

We assumed that fumaramidine **1** would be conceivably assembled by sequential basic treatment of the protected isoindolinone **9**, quenching with the poly and differentially substituted benzaldehyde **10** followed by dehydration of the primary adduct and ultimate deprotection. We envisaged building up the parent isoindolinone **9** by reliance on the Parham cyclization process involving the tetrasubstituted aromatic carbamate **11**. Literature precedents gave support to the feasibility of this synthetic approach. Isoindolinones have been successfully metalated at the benzylic position of the heteroring system thus allowing the connection of a range of electrophiles.[9] E1cb elimination from *erythro* and *threo* isoindolinones equipped with an *O*-alkoxybenzyl appendage on the lactam ring has been shown to be particularly efficient owing to the highly conjugated character of the resulting enelactams.[10] And finally, application of the Parham cyclization process for the elaboration of five-membered lactams are scarce but a number of structurally related systems have been successfully prepared under the agency of this process.[11]

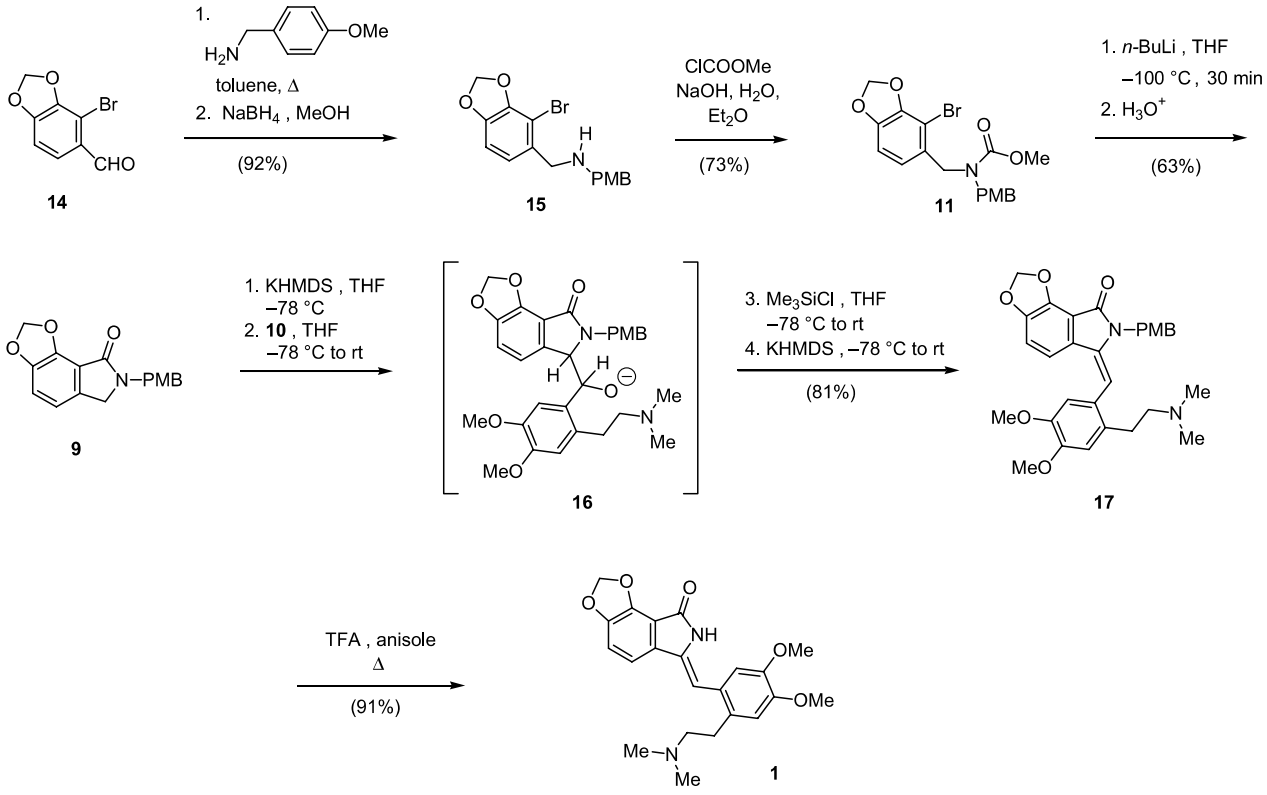
The first facet of the synthesis was then the elaboration of the polyfunctionalized aldehyde **10**. This compound was readily obtained by regioselective bromination of the dimethoxylated phenethylamine derivative **12** and the subsequent installation of the formyl functionality was achieved by bromine/lithium interconversion from **13** and subsequent trapping with DMF as the formylating agent (Scheme 3).



Scheme 3.

The elaboration of the second partner of the synthesis, that is, isoindolinone **9**, required the preliminary preparation of the bromoarylcarbamate **11**. This compound was readily obtained by the two-step sequence portrayed in Scheme 4. Reductive amination involving the easily available bromopiperonal **14** and *para*-methoxybenzylamine delivered the secondary amine **15** incorporating the nitrogen protecting group *para*-methoxybenzyl (PMB). Treatment of **15** with methyl chloroformate provided the carbamate **11** candidate for the planned Parham cyclization process. This annulation technique hinges upon aromatic lithiation and subsequent trapping with an internal electrophile. Carbamate **11** was then exposed to *n*-BuLi at −100 °C to ensure halogen/lithium interconversion and the intramolecular ring closure was instantaneous since the annulated compound **9** was solely obtained in an excellent yield upon immediate aqueous work up (scheme 4).

The final installation of the pendant arylmethylene unit on the isoindolinone framework required four phases, which could be fortunately performed as a single one-pot reaction. For this purpose compound **9** was smoothly deprotonated with KHMDS in THF at −78 °C and subsequently allowed to react with the appropriate aldehyde **10** (Scheme 4). To trigger off the E1cb elimination process the transient oxanion **16** was *O*-silylated in situ with TMSCl and subsequently treated in the sequel with KHMDS at −78 °C. Warming to 0 °C was followed by acidic aqueous work up and gratifyingly



Scheme 4.

conducting this reaction according to this procedure afforded straightforwardly and solely the protected arylmethylideneisoindolinone **17** with an excellent yield. Compound **17** was obtained exclusively with the undesired *E* geometry and configurational assignments were determined by NOE experiments. However, at this stage stereochemical considerations about the central double bond were not crucial for the ultimate formation of the *Z* configured target product. Indeed removal of the selected benzyl protection of the nitrogen lactam of **17** is usually achieved by treatment in boiling TFA in the presence of anisole as cation scavenger.[12] These conditions are appropriate to favor the formation of the thermodynamically more stable stereoisomer with the mandatory *Z* configuration and the target product **1** was obtained exclusively and in an excellent yield by this technique. The constitution and stereochemistry of this synthetic enelactam **1** agree with those reported for the alkaloid extracted from natural sources.[4]

3. Conclusion

In conclusion, a simple and efficient first total synthesis of the enelactam fumaramidine from *fumariceae* species has been disclosed. The advantages of this synthesis, which lie mainly in the small number of steps, their procedural simplicity and high efficiency provide a strong incentive for the elaboration of similar structurally modified alkaloids as well as their biogenetically related congeners.

4. Experimental

4.1. General

Tetrahydrofuran (THF) was pre-dried with anhydrous Na_2SO_4 and distilled over sodium benzophenone ketyl under Ar before use. DMF, CH_2Cl_2, NEt_3, and toluene were distilled from CaH_2. Dry glassware was obtained by oven drying and assembly under dry Ar. The glassware was equipped with rubber septa and reagent transfer was performed by syringe techniques. For flash chromatography, Merck silica gel 60 (40–63 μm; 230–400 mesh ASTM) was used. The melting points were obtained on a Reichert-Thermopan apparatus and are not corrected. NMR spectra: Bruker AM 300 (300 and 75 MHz, for ^1H, and ^{13}C), $CDCl_3$ as solvent, TMS as internal standard. Microanalyses were performed by the CNRS microanalysis center.

N,*N*-Dimethyl-3,4-dimethoxy-β-phenethylamine **12**[13] and 2-bromopiperonal **14**[14] were synthesized according to literature methods.

4.2. Synthesis of the benzaldehyde derivative 14

4.2.1. *N*,*N*-Dimethyl-3,4-dimethoxy-5-bromo-β-phenethylamine (13). Bromine (7.6 mmol, 0.4 mL) was added dropwise under stirring to a solution of *N*,*N*-dimethyl-3,4-dimethoxy-β-phenethylamine **12** (800 mg, 3.8 mmol) and potassium acetate (560 mg, 3.8 mmol). Stirring was maintained for 16 h at room temperature, the solution was concentrated under vacuum and the residue was dissolved in

CH_2Cl_2 (60 mL). The solution was washed successively with saturated aqueous Na_2CO_3 (20 mL), aqueous sodium thiosulfate (10%, 20 mL), and brine. The organic layer was dried (Na_2SO_4) and the solvent was evaporated under vacuum. The crude oily residue was purified by column chromatography using AcOEt–hexanes–NEt_3 (80/10/10) as eluent to deliver the amine **13** as a yellow oil. Yield 921 mg (82%); ^{1}H NMR (δ_H) 2.30 (s, 6H, 2×NCH_3), 2.44–2.49 (m, 2H, CH_2), 2.79–2.84 (m, 2H, CH_2), 3.81 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.72 (s, 1H aromatic H), 6.96 (s, 1H, aromatic H) ppm; ^{13}C NMR (δ_C) 34.1, 45.3, 56.0, 56.1, 59.7, 113.1, 114.1, 115.6, 131.5, 147.9, 148.4 ppm. Anal. Calcd for $C_{12}H_{18}BrNO_2$ (288.2): C, 50.01; H, 6.30; N 4.86%. Found: C, 50.25; H, 4.63; N 4.67%.

4.2.2. 2-(2-Dimethylaminoethyl)-4,5-dimethoxybenzaldehyde (10). A solution of *n*-BuLi (1.64 mL, 1.6 M in hexane, 2.6 mmol) was added dropwise by syringe at −78 °C under Ar to a solution of amine **13** (550 mg, 2.0 mmol) in dry THF (50 mL). The reaction mixture was stirred at −78 °C for 15 min and DMF (140 mg, 0.2 mL, 2.6 mmol) was added. The solution was stirred at −78 °C for 1 h, then at room temperature for an additional 1 h and treated with saturated aqueous NH_4Cl (5 mL). The mixture was diluted with water (10 mL), extracted with Et_2O (3×50 mL) and the combined organic extracts were dried ($MgSO_4$). Evaporation of solvents in vacuo left an oily residue, which was purified by flash column chromatography with AcOEt–hexanes–NEt_3 (80/10/10) as eluent to furnish **10** as a yellow solid. Yield 331 mg (70%); mp 54–55 °C (from hexane–toluene); ^{1}H NMR (δ_H) 2.25 (s, 6H, 2×NCH_3), 2.43–2.48 (m, 2H, CH_2), 3.03–3.08 (m, 2H, CH_2), 3.85 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.68 (s, 1H, aromatic H), 7.24 (s, 1H, aromatic H), 10.12 (s, 1H, CH═O) ppm; ^{13}C NMR (δ_C) 30.1, 45.3, 55.9, 56.0, 62.0, 111.1, 113.0, 126.8, 138.3, 147.6, 153.6, 189.5 (CHO) ppm. Anal. Calcd for $C_{13}H_{19}NO_3$ (237.3): C, 65.80; H, 8.07; N 5.90%. Found: C, 66.01; H, 8.03; N 6.05%.

4.3. Synthesis of the isoindolinone 9

4.3.1. *N*-(4-Bromobenzo[1,3]dioxol-5-ylmethyl)-*N*-(4-methoxybenzyl)amine (15). A solution of 2-bromopiperonal (4.85 g, 20 mmol) and 4-methoxybenzylamine (2.74 g, 20 mmol) in toluene (70 mL) was refluxed in the Dean–Stark apparatus for 3 h. Evaporation of the solvent under vacuum left quantitatively the [1-(4-bromobenzo-[1,3]dioxol-5-ylmethyl)methylidene]-(4-methoxybenzyl)-amine as a yellow oil, which was treated in the next step without further purification. (6.98 g); ^{1}H NMR (δ_H) 3.79 (s, 3H, CH_3), 4.75 (s, 2H, NCH_2), 6.07 (s, 2H, OCH_2O), 6.77 (d, J=8.3 Hz, 1H, aromatic H), 6.88 (d, J=8.3 Hz, 2H, aromatic H), 7.24 (d, J=8.3 Hz, 2H, aromatic H), 7.65 (d, J=8.3 Hz, 1H, aromatic H), 8.60 (s, 1H, CH═N) ppm; ^{13}C NMR (δ_C) 55.3, 64.5, 103.8, 104.0, 107.8, 113.9, 122.9, 128.4, 129.1, 131.3, 146.1, 149.4, 158.7, 159.1 (CH═N) ppm. Sodium borohydride (832 mg, 22 mmol) was added portionwise to a solution of the crude imine (6.98 g, 20 mmol) in MeOH (100 mL). The reaction mixture was then stirred at room temperature for 30 min and then concentrated under vacuum. The oily residue was dissolved in CH_2Cl_2 (100 mL). The solution was washed with water (2×30 mL), brine and dried (Na_2SO_4). After evaporation of the solvent, the crude oily residue was purified by column chromatography using AcOEt–NEt_3 (90/10) as eluent to deliver the amine **15** as a light yellow oil. Yield 6.45 mg (92%); ^{1}H NMR (δ_H) 1.71 (br s, 1H, NH), 3.70 (s, 2H, NCH_2), 3.78 (s, 5H, NCH_2+OCH_3), 6.02 (s, 2H, OCH_2O), 6.71 (d, J=7.8 Hz, 1H, aromatic H), 6.82–6.87 (m, 3H, aromatic H), 7.25 (d, J=8.3 Hz, 2H, aromatic H) ppm; ^{13}C NMR (δ_C) 52.1, 52.2, 55.3, 101.4, 102.7, 107.0, 113.7, 123.0, 129.4, 132.3, 132.6, 146.3, 146.7, 158.6 ppm. Anal. Calcd for $C_{16}H_{16}BrNO_3$ (350.2): C, 54.87; H, 4.61; N 4.00%. Found: C, 54.65; H, 4.92; N 4.11%.

4.3.2. Methyl *N*-(4-bromobenzo[1,3]dioxol-5-ylmethyl)-*N*-(4-methoxbenzyl)carbamate (11). Methyl chloroformate (1.04 g, 11 mmol) was added slowly under stirring to a cooled (0 °C) solution of amine **15** (3.51 g, 10 mmol) in Et_2O (50 mL) followed by a solution of NaOH (440 mg, 11 mmol) in water (5 mL). The mixture was stirred at 0 °C for 30 min and the ethereal layer was separated, washed with aqueous HCl (4 M; 3×30 mL), water (30 mL) and dried (Na_2SO_4). After evaporation of the solvent, the crude oily residue was purified by column chromatography using AcOEt–hexanes (40/60) as eluent to deliver the carbamate **11** as a colorless oil. Yield 2.98 g (73%); ^{1}H NMR (δ_H) 3.78 (s, 6H, 2×OCH_3), 4.37–4.46 (m, 4H, 2×NCH_2), 6.02 (s, 2H, OCH_2O), 6.62–6.73 (m, 3H, aromatic H), 6.83 (d, J=8.5 Hz, 2H, aromatic H), 7.13 (d, J=11.5 Hz, 2H, aromatic H) ppm; ^{13}C NMR (δ_C) 48.5, 49.2, 53.0, 55.3, 101.5, 107.3, 113.9, 120.8, 122.2, 128.8, 129.3, 129.5, 146.3, 146.9, 157.3, 159.0 ppm. Anal. Calcd for $C_{18}H_{18}BrNO_5$ (408.2): C, 52.96; H, 4.44; N 3.43%. Found: C, 53.09; H, 4.33; N 3.27%.

4.3.3. 7-(4-Methoxybenzyl)-6,7-dihydro[1,3]dioxolo[4,5-*e*]-isoindol-8-one (9). A solution of *n*-BuLi (3.6 mL, 1.6 M in hexane, 5.76 mmol) was added dropwise by syringe at −90 °C under Ar to a solution of carbamate **11** (1.96 g, 4.8 mmol) in dry THF (50 mL). The reaction mixture was stirred at −90 °C for 20 min then allowed to warm to −40 °C over a period of 30 min followed by addition of saturated aqueous NH_4Cl (5 mL). The mixture was diluted with water (20 mL), extracted with Et_2O (3×25 mL) and the combined organic layers were dried ($MgSO_4$). Evaporation of the solvent in vacuo left an oily residue, which was purified by flash column chromatography with AcOEt–hexanes (60/40) as eluent to furnish the isoindolinone **9** as a yellow oil. Yield 898 mg (63%); ^{1}H NMR (δ_H) 3.74 (s, 3H, OCH_3), 4.14 (s, 2H, NCH_2), 4.62 (s, 2H, NCH_2), 6.07 (s, 2H, OCH_2O), 6.72 (d, J=7.8 Hz, 1H, aromatic H), 6.80 (d, J=8.5 Hz, 2H, aromatic H), 6.86 (d, J=7.8 Hz, 1H, aromatic H) 7.19 (d, J=8.5 Hz, 2H, aromatic H) ppm; ^{13}C NMR (δ_C) 45.7, 49.4, 55.3, 102.6, 111.0, 114.1, 115.2, 129.0, 129.5, 130.2, 134.3, 143.4, 148.3, 159.1, 165.8 (CO) ppm. Anal. Calcd for $C_{17}H_{15}BrNO_4$ (297.3): C, 68.68; H, 5.09; N 4.71%. Found: C, 68.46; H, 5.39; N 4.82%.

4.4. Synthesis of fumaramidine (1)

4.4.1. 6-{1-[2-(2-Dimethylaminoethyl)-4,5-dimethoxyphenyl]meth-(*E*)-ylidene}-7-(4-methoxybenzyl)-6,7-dihydro[1,3]dioxolo[4,5-*e*]isoindo-8-one (17). A solution of KHMDS (2.2 mL, 0.5 M in toluene, 1.1 mmol) was

added dropwise at −78 °C under Ar to a stirred solution of isoindolinone **9** (297 mg, 1 mmol) in THF (50 mL). After stirring at −78 °C for 10 min a solution of benzaldehyde derivative **10** (260 mg, 1.1 mmol) in THF (10 mL) was added dropwise. The resulting solution was allowed to warm to room temperature over 15 min then recooled to −78 °C. Chlorotrimethylsilane (119 mg, 1.1 mmol) was added and the mixture was allowed to warm slowly to room temperature and recooled to −78 °C. KHMDS (2.2 mL, 0.5 M in toluene, 1.1 mmol) was then added and warming to room temperature over 30 min allowed the completion of E1cb elimination reaction. Saturated aqueous NH_4Cl (5 mL) was added and the mixture was diluted with water (20 mL), extracted with Et_2O (3×20 mL). After drying of the combined organic layers (Na_2SO_4), evaporation of solvent in vacuo left an oily residue, which was purified by flash column chromatography with AcOEt–NEt_3 (90/10) as eluent to furnish the arylmethyleneisoindolinone **17** as a yellow oil. Yield 418 mg (81%); ^{1}H NMR (δ_H) 1.90 (s, 6H, 2×NCH_3), 2.11 (t, J=7.5 Hz, 2H, CH_2), 2.41 (t, J=7.5 Hz, 2H, CH_2), 3.63 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.95 (s, 2H, NCH_2), 6.13 (s, 2H, OCH_2O), 6.36 (s, 1H, CH═), 6.69–6.74 (m, 3H, aromatic H), 6.82 (s, 1H, aromatic H), 7.14–7.21 (m, 3H, aromatic H), 7.25 (m, 1H, aromatic H) ppm; ^{13}C NMR (δ_C) 31.7 (CH_2Ar), 45.1 (2×NCH_3), 42.6 (CH_2, PMB), 55.0 (OCH_3, PMB), 55.8 (OCH_3), 55.9 (OCH_3), 60.3 (NCH_2), 100.6 (OCH_2O), 110.1 (CH═), 112.6 (CH), 113.3 (CH), 113.4 (CH), 114.1 (2×CH, PMB), 123.2 (CH), 125.7 (C), 127.3 (2×CH, PMB), 129.1 (C), 130.1 (C), 132.1 (C), 135.1 (C), 136.0 (C), 144.3 (C), 147.1 (C), 148.8 (C), 149.3 (C), 158.8 (C), 166.6 (CO) ppm. Anal. Calcd for $C_{30}H_{32}N_2O_6$ (516.6): C, 69.75; H, 6.24; N 5.42%. Found: C, 69.58; H, 6.11; N 5.17%.

4.4.2. Fumaramidine (1). A solution of the arylmethylene isoindolinone **17** (260 mg, 0.5 mmol) and anisole (540 mg, 5.0 mmol) in trifluoroacetic acid (10 mL) was refluxed under Ar for 24 h. The reaction mixture was concentrated under vacuum, the residue was dissolved in CH_2Cl_2 (20 mL) and NEt_3 (0.5 mL) was added with stirring. Water (3× 50 mL) was then added, and the organic layer was washed with brine, dried ($MgSO_4$) and concentrated to yield an oily residue. Purification by flash column chromatography using AcOEt–NEt_3 (95/5) as eluent and recrystallization from EtOH gave a yellow solid: mp 266–267 °C (dec). The spectral data of synthetic **1** (180 mg, 91%) matched those reported for the natural product.[3,4] ^{1}H NMR (δ_H) 2.24 (s, 6H, 2×NCH_3), 2.46 (t, J=7.9 Hz, 2H, CH_2), 2.77 (t, J= 7.9 Hz, 2H, CH_2), 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.14 (s, 2H, OCH_2O), 6.43 (s, 1H, CH═), 6.74 (s, 1H, aromatic H), 6.82 (s, 1H, aromatic H), 7.02 (d, J=8.0 Hz, aromatic H), 7.25 (d, J=8.0 Hz, aromatic H), 8.34 (br s, 1H, NH) ppm; ^{13}C NMR (δ_C) 31.8 (CH_2Ar), 45.5 (2×NCH_3), 55.9 (OCH_3), 56.2 (OCH_3), 60.7 (NCH_2), 103.0 (CH═), 103.1 (OCH_2O), 111.7 (CH), 112.0 (CH) 113.1 (CH), 113.2 (CH), 125.6 (C), 131.8 (C), 132.0 (C), 133.3 (C), 143.4 (C), 147.7 (C), 148.7 (C), 149.3 (C), 166.1 (CO) ppm.

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Palladium supported on hydrotalcite as a catalyst for the Suzuki cross-coupling reaction

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Abstract—The efficiency of various palladium salts as catalysts in the Suzuki cross-coupling reaction, and the influence of the base and temperature used on its conversion, were studied. The use of $PdCl_2$ supported on hydrotalcite as catalyst in the presence of potassium carbonate as base was found to provide the best results. Reaction temperatures above 90 °C ensured conversion levels on a par with those for many homogeneous catalysts.

1. Introduction

The palladium-catalysed Suzuki cross-coupling reaction has for some time been one of the most powerful tools for the formation of carbon–carbon bonds in organic synthesis.[1–3] In most cases, the reaction involves a homogeneous palladium catalyst and a ligand of variable nature such as a phosphine.[2,4–6] Recently, however, some cross-coupling processes have used palladium supported on various types of supports such as sepiolites,[7,8] silica,[9] zeolites and zeolitic materials,[10–12] layered double hydroxides,[13,14] carbon[15,16] and organic complexes bound to inorganic solids.[17–21] These heterogeneous catalysts are being increasingly used to circumvent some shortcomings of homogeneous catalysts such as the need to remove the catalyst after the reaction, its poor reusability and potential environmental pollution problems. Also, palladium ligands and precursors are expensive, which severely restricts their industrial use.

Hydrotalcite is a naturally occurring mineral of the layered double hydroxide family that constitutes a major class of anionic clay materials. Hydrotalcite is structurally related to brucite [$Mg(OH)_2$]: magnesium cations are at the centres of octahedra the vertices of which are occupied by hydroxyl groups to form stacks. In hydrotalcite, some Mg^{2+} ions are replaced by aluminium cations, which introduces a charge deficiency in the layers. In order to ensure electroneutrality in the overall structure, the positive charge is countered by carbonate ions present in a disorderly manner in the interlayer spacing, which also contains crystallization water (Fig. 1).[22] Hydrotalcite has been extensively used by our research group in organic processes such as the epoxidation of limonene,[23,24] the Meerwein–Ponndorf–Verley reduction[25–27] and the α-arylation of diethyl malonate.[28]

In this work, we prepared various catalysts consisting of Pd^{2+} supported on hydrotalcite by using various precursor salts and employed them in the Suzuki cross-coupling reaction in the presence of various inorganic bases (see Scheme 1). We studied the influence of the aryl halide and temperature used. All catalysts and the hydrotalcite

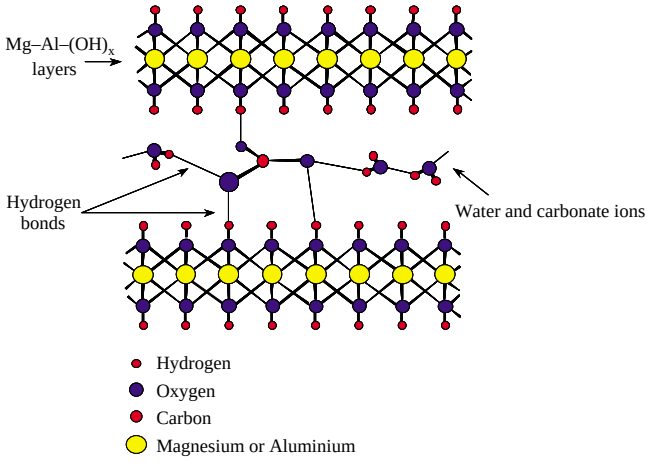

Figure 1. Structure of hydrotalcite.

Keywords: Suzuki cross-coupling; Hydrotalcite; Palladium; Boronic acid.
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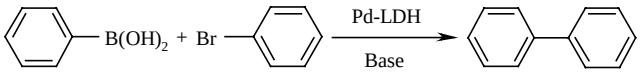

Scheme 1. Suzuki cross-coupling reaction studied.

precursor were characterized in terms of structure and surface properties by using various instrumental techniques.

2. Results and discussion

2.1. Characterization of catalysts

Based on the elemental analysis, the hydrotalcite and the palladium catalysts that were supported on it had an Mg/Al ratio of 2:1 and a Pd^{2+} content of 1%.

The XRD analysis of solid HT (Fig. 2) revealed a high crystallinity. As can be seen from the XRD pattern, the solid had a typical structure of stacked layers similar to those previously found by Reichle et al.[29] in hydrotalcites. Therefore, using the hydrotalcite as a support for our Pd catalysts caused no structural change in the mineral as the catalysts deposited on its outer surface only (XRD patterns for the catalysts not shown). Some anions from the palladium salt may have been exchanged with the carbonate ions in the interlayer spacing. Such an exchange would have altered the interlayer distance, which is defined by the lattice parameter c (viz. three times the distance between two adjacent layers). Based on the position of the strongest line, corresponding to the crystallographic indices (003), the lattice distance, d_{003}, was calculated and used to determine c ($c=3\cdot d_{003}$, Table 1). The c values thus obtained differed, which suggests that some carbonate ions were replaced by the anions of the palladium salt; however, the difference was so small that it had no practical consequences—particularly in catalytic terms.

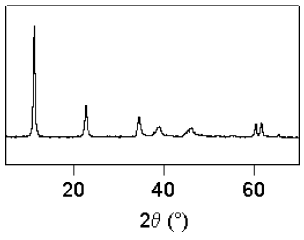

Figure 2. XRD patterns for HT.

Table 1. Specific surface area and lattice parameter c for the catalysts

Catalyst	c (A)[a]	S_{BET} (m^2/g)[b]
HT	23.1844	75.7
HT–$PdCl_2$	23.1075	86.5
HT–$Pd(AcO)_2$	23.2647	86.2
HT–$PdCl_4$	23.2227	87.3

[a] Lattice parameter.
[b] Specific surface area.

Table 1 also shows the specific surface area of the hydrotalcite and catalysts. As can be seen, it increased slightly upon deposition of the metal.

2.2. Suzuki reaction

The Suzuki cross-coupling reaction is known to require a base in order to abstract the proton during the reductive elimination of the organopalladium intermediate leading to the end-product.[1] The bases most frequently used in this process are carbonates or acetates of alkaline metals such as sodium or potassium, as well as some organic amines. The best choice in each case must be determined on an individual basis. To this end, we used our hydrotalcite-supported Pd catalysts in the Suzuki reaction between phenylboronic acid and bromobenzene in the presence of various inorganic bases. The sole reaction product obtained in all cases was biphenyl.

Table 2 shows the conversion results and Figure 3 the temporal variation of the conversion for the three studied catalysts in the presence of K_2CO_3 as the base. All reactions exhibited a linear relationship between the natural logarithm of the bromobenzene concentration and the reaction time, which suggests that the reaction is first-order in such a concentration:

$$\mathrm{Ln}\,(c_0/c) = kt$$

where c_0 and c are the bromobenzene concentrations at times zero and t, respectively, k the rate constant and t time.

Table 2. Conversion obtained in the Suzuki cross-coupling reaction[a]

Catalyst	Base	Conversion (%)[b]	k (h^{-1})[c]
HT–$PdCl_2$	K_2CO_3	47.2	0.312
	Rb_2CO_3	2.1	0.003
	CsF	2.2	0.003
	K_3PO_4	7.1	0.009
HT–$Pd(AcO)_2$	K_2CO_3	27.21	0.171
	Rb_2CO_3	1.3	0.004
	CsF	2.5	0.005
	K_3PO_4	10.64	0.047
HT–$PdCl_4$	K_2CO_3	25.6	0.137
	Rb_2CO_3	3.9	0.006
	CsF	1.0	0.003
	K_3PO_4	8.24	0.024
Blank-1[d]	K_2CO_3	0	—
Blank-2[e]	—	0	—

[a] Reactions conditions: 1.98 mmol PhBr; 3 mmol $PhB(OH)_2$; 3.96 mmol K_2CO_3; 0.24 g (0.04 mol%); 5 mL toluene, $T=55$ °C.
[b] Conversion to biphenyl (reaction time: 3 h).
[c] Rate constant.
[d] Blank without catalyst.
[e] Blank without base.

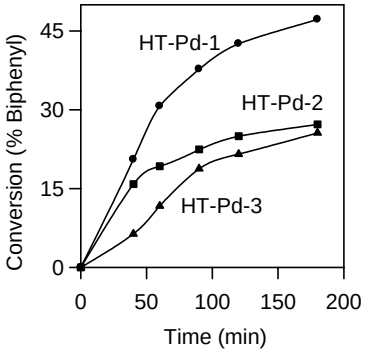

Figure 3. Temporal variation of the biphenyl conversion in the Suzuki cross-coupling reaction.

As can be seen from Table 2, K_2CO_3 was the base providing the best conversion and catalytic activity results, well ahead of K_3PO_4. The other bases studied exhibited very poor conversion. Also, catalyst $PdCl_2$, in the presence of K_2CO_3, was that providing the best results; it was therefore adopted for further testing, which included examining the influence of the reaction temperature and aryl halide, as well as catalyst leaching and reuse tests.

The influence of temperature on the conversion and rate of the Suzuki reaction between bromobenzene and phenylboronic acid using catalyst Pd–HT-1 in the presence of K_2CO_3 was examined at 55, 75, 90 and 110 °C. Table 3 shows the biphenyl conversion and rate constant obtained as described above. As expected, raising the temperature substantially increased the conversion, which exceeded 90% after only 3 h of reaction at 90 °C. These results are quite good; in fact, they are as good as or even better than those obtained with other heterogeneous catalysts and many homogeneous ones. The activation energy for the process as calculated from an Arrhenius plot was 47 kJ/mol.

Table 3. Conversion obtained in the Suzuki cross-coupling reaction at a variable temperature[a]

T (°C)	Conversion (%)[b]	k (h^{-1})[c]
55	47.2	0.312
75	72.4	1.795
90	90.6	2.873
110	95.3	4.168

[a] Reactions conditions: 1.98 mmol PhBr; 3 mmol $PhB(OH)^2$; 3.96 mmol K_2CO_3; 0.24 g HT–Pd-1 1 (0.04 mol%); 5 mL toluene.
[b] Conversion to biphenyl (reaction time: 3 h).
[c] Rate constant.

We then studied the influence of the phenyl halide on the coupling reaction, using the previous catalyst (HT–$PdCl_2$) and base (K_2CO_3). One of the major shortcomings of this process is its inefficiency with aryl chlorides or fluorides as substrates. This has aroused much interest in developing efficient catalysts (particularly aryl chlorides, which are more readily available and inexpensive than aryl bromides). Most catalysts for the Suzuki reaction are of the homogeneous type, and not all provide acceptable conversion.[4,30–33] We used both chlorobenzene and fluorobenzene and found the reaction to develop as summarized in Table 4. As can be seen, chlorobenzene provided good results: the conversion amounted to 28% after only 3 h of reaction at quite a low temperature (55 °C). Fluorobenzene gave poorer, but still promising, results; in fact, aryl fluorides started to be used in this process only 2 years ago[34,35] as the C–F bond is the strongest of all C–halogen bonds and its cleavage had been achieved in only a few cases and never with heterogeneous palladium catalysts.

Table 4. Influence of the phenyl halide used in the Suzuki cross-coupling reaction[a]

Phenylhalide	Conversion (%)[b]	k (h^{-1})[c]
Ph-F	14.9	0.090
Ph-Cl	28.1	0.191
Ph-Br	47.2	0.312

[a] Reactions conditions: 1.98 mmol PhX; 3 mmol $PhB(OH)^2$; 3.96 mmol K_2CO_3; 0.24 g HT–Pd-1 1 (0.04 mol%); 5 mL toluene, T=55 °C.
[b] Conversion to biphenyl (reaction time: 3 h).
[c] Rate constant.

The heterogeneous character of the Pd^{2+} catalyst was determined in a leaching test on the reaction between bromobenzene and phenylboronic acid at 55 °C using solid HT–$PdCl_2$ as the catalyst and K_2CO_3 as the base. After 30 min, the reaction was stopped—the biphenyl conversion at the time was 23.1%—to remove the catalyst and base by filtration. The remaining solution was supplied with K_2CO_3 and the reaction allowed to proceed at 55 °C for a further 24 h. The biphenyl conversion thus obtained was identical, so the catalytic action of Pd^{2+} was of the heterogeneous type. Also, we have made experiments without bromobenzene, and the conversion to biphenyl is negligible, so we rule out the homocoupling of the boronic acid.

Finally, we studied the reusability of the catalyst, again by using the reaction between bromobenzene and phenylboronic acid at 55 °C in the presence of HT–$PdCl_2$ as the catalyst and K_2CO_3 as the base. Figure 4 shows the results obtained after three catalytic cycles; as can be clearly seen, the catalyst lost some activity after each reuse. Therefore, reusing the catalyst entails its prior reactivation. This is also the case with other heterogeneous catalysts used in the Suzuki reaction.

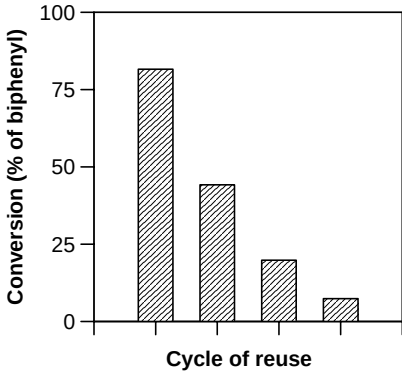

Figure 4. Influence of catalyst reuse on the biphenyl conversion in the Suzuki cross-coupling reaction.

3. Conclusions

The results obtained in this work show that the deposition of palladium salts on hydrotalcite is an effective method for preparing solids that are active catalysts in the Suzuki cross-coupling reaction—particularly those obtained by depositing $PdCl_2$. The biphenyl conversion in the reaction between bromobenzene and phenylboronic acid was found to depend on the particular base used, of which K_2CO_3 proved the best among those tested. These catalysts are also active in the reduction of chloro- and fluorobenzenes, where few catalysts—particularly of the heterogeneous type—are effective. The temperature is one other crucial variable here. The activation energy for the process was calculated to

be 47 kJ/mol. Finally, testing revealed the catalytic process to be completely heterogeneous in nature.

4. Experimental

The hydrotalcite used was prepared by mixing two solutions of $Mg(NO_3)_2 \cdot 6H_2O$ and $Al(NO_3)_3 \cdot 9H_2O$ in a 2:1 ratio, using a coprecipitation method described elsewhere.[36] In a typical synthetic run, a solution containing 0.3 mol of $Mg(NO_3)_2 \cdot 6H_2O$ and 0.15 mol of $Al(NO_3)_3 \cdot 9H_2O$ in 250 mL of de-ionized water was used. The solution was slowly dropped over 500 mL of an Na_2CO_3 solution at pH 10 at 60 °C under vigorous stirring. During precipitation, the pH was kept constant by adding appropriate volumes of 1 M NaOH. The suspension obtained was kept at 80 °C for 24 h, after which it was filtered and washed with 2 L of de-ionized water. Any residual nitrate ions in the hydrotalcite structure were removed by exchange with carbonate ions. For this purpose, 2.5 g of the LDH was dispersed in 125 mL of de-ionized water, the dispersion being supplied with 250 mg of Na_2CO_3 and refluxed for 2 h. Then, the solid was separated by centrifugation and the water discarded. The hydrotalcite obtained following exchange with carbonate ions was designated HT.

The hydrotalcite was used as a support for the palladium catalysts, which were obtained by impregnation, a method previously used by our group to prepare Pd catalysts supported on various materials such as silica and aluminium orthophosphate.[37,38] The catalysts used in this work were obtain as follows: the amounts of $PdCl_2$, $Pd(AcO)_2$ and Na_2PdCl_4 required to obtain a final Pd content of 1% in the catalyst were dissolved in *N*,*N*-dimethylformamide and supplied with 2 g of hydrotalcite in a flask. The mixture was kept at room temperature in a rotavapor for 24 h, after which the solvent was evaporated at a low pressure to obtain the three supported palladium catalysts, which were designated HT–$PdCl_2$, HT–$Pd(AcO)_2$ and HT–$PdCl_4$ according to whether they were obtained from the chloride, acetate or tetrachloropalladate, respectively, as precursor.

The catalysts and the hydrotalcite support were characterized by using various instrumental techniques including X-ray diffraction and nitrogen adsorption.

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Regioselective hydroxylation of phenols by simultaneous photochemical generation of phenol cation-radical and hydroxyl radical

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Abstract—Substituted phenols having pendant isoquinoline *N*-oxide were synthesized and their photochemical and luminiscent properties studied. Photolysis in an acid medium was found to yield the related photohydroxylation products, in a regioselective process, in addition to the isoquinoline deoxygenated precursor. Photoinduced electron transfer from the donor phenols to the protonated form of the first excited singlet state (S_1) of the pendant isoquinoline *N*-oxide acting as acceptor leads to a red-shifted emissive charge transfer (CT) state that is in fact a radical/cation-radical pair. Homolysis of the N–OH bond restores the aromatic isoquinoline nucleus and produces a hydroxyl radical that can couple to the required ring carbon in the phenol cation-radical to give the photohydroxylation products in a regioselective process controlled by the spin density of the phenol cation-radical. These photohydroxylation processes efficiently compete with the reported tendency to deprotonation in phenol cation-radicals. The photohydroxylation process by itself, and its regioselectivity, exclude a proton-coupled electron transfer mechanism or a consecutive electron transfer/deprotonation reaction. By contrast, the phenol cation-radical exists long enough to undergo the hydroxyl radical coupling reaction that leads to the photohydroxylation products.

1. Introduction

Hydroxyl radicals cause cell damage when generated in excess amounts or if the cellular antioxidant defense is impaired. Also, free iron levels are known to play a crucial role in initiating and catalyzing a variety of radical reactions in the presence of oxygen.[1,2] Aromatic hydroxylation is an important metabolic process, as shown by the reaction of heme-containing P450 flavin monooxygenases, pterin-dependent nonheme monooxygenases, nonheme mononuclear iron dioxygenases and diiron hydroxylases.[3] These enzymes are involved in a number of vital processes such as biosynthesis, degradation of xenobiotics, carcinogenesis and drug metabolism.[4] The rate and selectivity for substrate oxidation is determined jointly by steric effects[5] at the enzyme active site and by intrinsic electronic reactivity.[6] Depending on the particular substrate and the enzyme specificity, the choice of substrates and hydroxylation sites may be dictated by either orientation effects at the binding site or chemical reactivity at the different positions in the substrates. Although experimental evidence for the presence of superoxide in these enzyme mediated reactions exists,[7] the iron-oxene intermediate may act directly in a single oxygen insertion into the substrate following cleavage of the dioxygen bond.[8] The whole mechanism of oxygen insertion into substrates is an area of considerable debate.[9] Although hard experimental evidence is difficult to obtain, the formation of an active oxygen intermediate consisting of a single oxygen atom is a likely pathway for enabling direct oxygen insertion into most known substrates;[6] mechanistic schemes involving peroxy species can also be formulated in some instances, however.[10]

Highly reactive hydroxyl radicals can attack a variety of targets such as lipids, fats and proteins; also, they are involved in a number of major degenerative diseases including aging.[11] Thus, hydroxyl radicals attack the amino acid phenylalanine or salicylate to give, under physiological conditions, *ortho*-, *meta*- and *para*-tyrosines, or 2,3- and 2,5-dihydroxybenzoates, respectively.[12] These nonenzymatic reactions have no control over the position of the highly reactive hydroxyl radical attack on the aromatic ring, so a mixture of almost every possible hydroxylated isomer is usually obtained. These processes commonly involve a reaction between the free hydroxyl radical and

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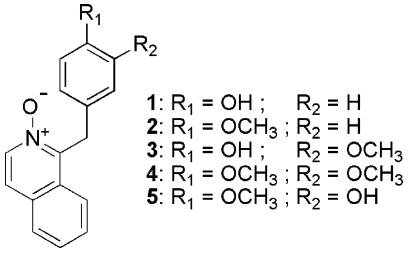
the intact aromatic ring. However, we recently showed that the reaction between free hydroxyl radicals and methoxy substituted aromatic cation-radicals exhibits these well-defined chemical structures for hydroxyl radical attack to form a new C–OH bond and is an efficient process that is regiochemically controlled by the spin density of the cation-radical.[13]

The ability to include hydroxyl groups rather than methoxy groups as substituents on the aromatic ring has enabled the obtainment of the corresponding phenol cation-radicals. Studying the photochemistry of the acceptor-spacer-donor (AsD) systems designed by the authors, where the acceptor is an isoquinoline *N*-oxide nucleus, the spacer a methylene bridge and the donor a variably substituted phenol, may allow one to describe the oxidation of phenols via PET to a pendant protonated isoquinoline *N*-oxide electron acceptor as a model for the oxidation of phenols, a prototype for these types of electron and proton transfer reactions, and a model for the hydroxylation of phenols. Unlike methoxy substituted donors, the oxidation of phenols should result in a pK_a shift of more than 12 units[14] and no longer rely on its phenolic protons. The electron transfer must thus be coupled to deprotonation and may occur either as a consecutive electron transfer/deprotonation reaction or as a single, concerted, reaction step. This paper reports our results for the PET from phenol donors of compounds **1**, **3** and **5** to bridged protonated isoquinoline *N*-oxide and compares them with those for the previously studied methoxylated derivatives **2** and **4**.

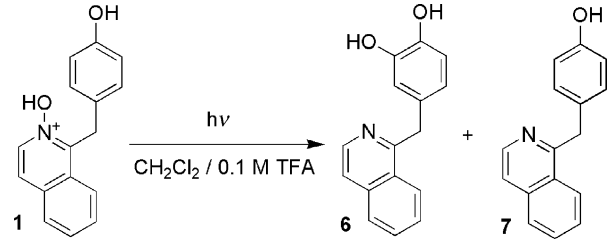


2. Results and discussion

2.1. Photochemical reactivity

Excitation of the protonated forms of the isoquinoline *N*-oxides to the corresponding first excited singlet state S_1 showed electron transfers from donors to produce a charge transfer (CT) state and the resulting radical/cation-radical pair to evolve to hydroxylation of the donor moiety.[13] In parallel, *isc* to the corresponding triplet state T_1 led to the corresponding deoxygenated material. Thus, photolysis of compound **1** (Scheme 1), having a hydroxy substituent in the donor moiety, in CH_2Cl_2/0.1 M TFA led to the corresponding hydroxylated compound **6** (an *ortho*-diphenol) in 21% yield in addition to 50% of the corresponding deoxygenated compound **7**. No other photohydroxylated material was detected.

In order to expand our knowledge of the radical scavenging mechanism in our photochemical process, we studied the



Scheme 1.

influence of various substituents and of the position of the hydroxyl group in some related phenol donors in the AsD system. To this end, we synthesized and photolyzed compound **3**, having a methoxy group *ortho* to the phenol in the donor moiety. Photolysis under identical experimental conditions gave a mixture of the hydroxylated compounds **8** and **9** (48% total hydroxylation yield: 35% of **8** and 13% of **9**; **8/9**=2.7/1) plus the related deoxygenated compound **10** (28%) (Scheme 2).

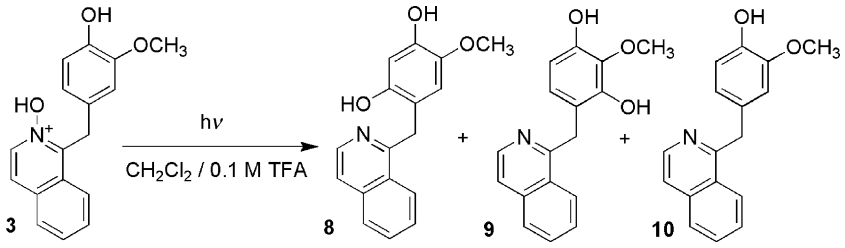
Irradiation of the isomeric compound **5** gave a similar result to that for compound **3**. The exchange of methoxyl and hydroxyl substituents altered neither the balanced yield nor the regioselectivity of the photochemical reaction. Photolysis of **5** yielded a mixture of the hydroxylated compounds **11** and **12** (45% total hydroxylation yield: 30% of **11** and 15% of **12**; **11/12**=3/1) plus the related deoxygenated compound **13** (32%) (Scheme 3). Therefore, the photolysis of the isomeric compounds **3** and **5** provided comparable yields of hydroxylated (**11** and **12**) and deoxygenated (**13**) material, and resulted in similar regioselectivity in the hydroxylation process.

2.2. Influence of the photoreaction conditions

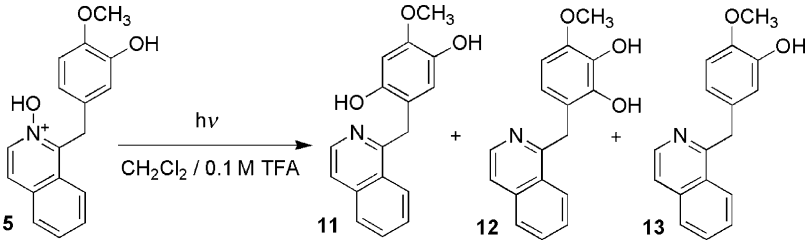
In order to gain additional knowledge about the photoreaction mechanism and the influence of the conditions on the outcome, we photolysed compound **1** using the same TFA concentration as previously (0.1 M), but water as solvent. The outcome of the photoreaction was identical, and only compound **6** and **7** were detected, in the same relative proportion. The only change worth noting was a relative decrease in the reaction rate resulting from the need for longer irradiation timers in order to obtain similar conversion levels. Similarly, the photoloysis of compound **3** in water exhibited no change in the deoxygenated/hydroxylated ratio—only a similar decrease in reaction rate was observed now—, nor in the **8/9** photohydroxylated regioisomer ratio. This compound was also photolysed in 0.1 M trifluoromethanesulfonic acid in water (i.e., in a more acidic medium by ca. 13 pK_a units), the reaction profile and yields remaining unaltered.

2.3. Fluorescence

From the data in Table 1 it follows that all the compounds discussed here exhibit a dual fluorescence emission that is related to the LE emission on excitation at a short wavelength (λ_{exc} 330 nm), and a CT emission on excitation at a long wavelength (λ_{exc}=360 nm). The LE emission is a common emission band because all studied compounds possess the same acceptor (viz. the isoquinoline *N*-oxide).



Scheme 2.



Scheme 3.

Table 1. Fluorescence spectroscopy data: dichloromethane 0.1 M TFA

Compound	λ_{fl} (ϕ)[a]	
	λ_{exc} 330 (nm)[b]	λ_{exc} 366 (nm)[c]
1	386 (1.0×10^{-3})	480 (4.3×10^{-2})
2[d]	380 (2.0×10^{-3})	479 (2.0×10^{-2})
3	382 (4.0×10^{-4})	497 (2.0×10^{-2})
4[d]	382 (4.0×10^{-3})	500 (5.4×10^{-2})

[a] Emission maximum (nm).
[b] Emission corresponding to the protonated locally excited (LE) state.
[c] Emission corresponding to the charge transfer (CT) state.
[d] Data from Ref. 13.

The CT emission appears at the same wavelength for the monosubstituted compounds **1** and **2**; this suggests that the CT state of these monosubstituted donor compounds is in the same energy situation and possess similar fluorescence quantum yields. This is a result of the electron-transfer process producing an equivalent CT state for phenol and methoxy substituted donor compounds.

This situation is also observed in the disubstituted compounds **3**, **4** and **5**. The dimethoxy substituted compound **4**, and the monomethoxy–monohydroxy substituted homologs **3** and **5**, exhibit the CT state emission at the same energy level (emissions around 500 nm), red shifted with respect to the monosubstituted **1** and **2** by effect of their ability to act as donors. However, the only variable that alters the CT state wavelength emission is the number of oxa substituents on the donor ring—not the quality as methoxyl or hydroxyl groups—; therefore, the CT states of the related phenol cation-radicals are homologous to the methoxy derivatives and the photohydroxylation reaction occurs as a result.

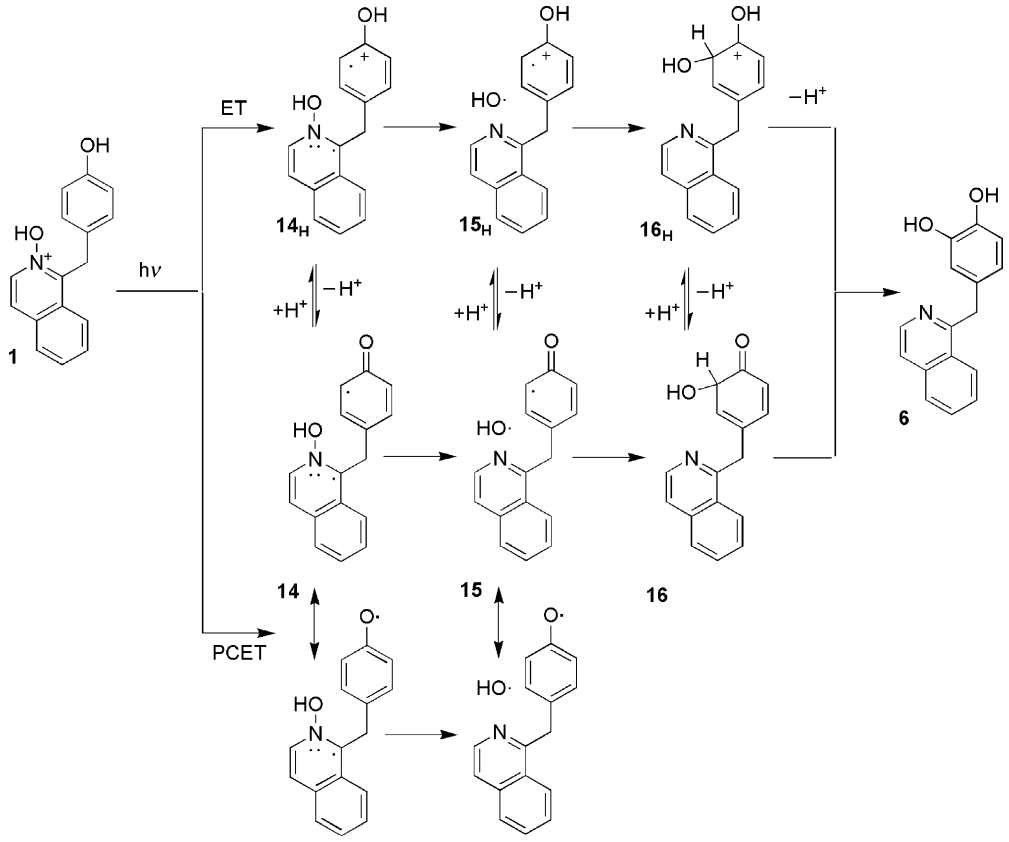
2.4. Mechanistic considerations

The outcome of the photolysis of the studied compounds reveals that the coupling of the hydroxyl radical to the phenol cation-radical is a regioselective process. The preferred positions for the coupling of the hydroxyl radical over the phenol cation-radical are consistent with the reported positions in the aromatic moiety. As shown in Scheme 4, the mechanism for the photochemical hydroxylation of aryls by excitation of the protonated isoquinoline *N*-oxide can be interpreted as a stepwise process in which the photoinduced electron transfer produces a hydroxyl radical that subsequently couples with the cation-radical of the aryl to form a new C–OH bond. As a result, the spin density of the transient phenol cation-radical will dictate the final hydroxylation position in the overall photoreaction.

We can thus assume a mechanism similar to that reported for the photohydroxylation in the related compound **2** (Scheme 4; ET) to operate for the hydroxy substituted compound **1** as well. In this way, electron transfer from the phenol moiety to the first excited singlet state S_1 of the acceptor, the protonated form of the isoquinoline *N*-oxide **1**, will produce a CT state $\mathbf{14_H}$ that will in fact be a radical/cation-radical pair. Homolytic N–OH bond cleavage results in rearomatization of the isoquinoline nucleus to give the cation-radical $\mathbf{15_H}$ and release the hydroxyl radical. The cation $\mathbf{16_H}$ loses a proton to rearomatize the donor moiety and give the hydroxylated diphenol **6**.

Based on the proposed mechanism (Scheme 4; ET), the driving force that determines the regioselective hydroxylation site is related with the spin density in the transient phenol cation-radical (see Section 4). The spin density in $\mathbf{14_H}$ is highest in the *ortho* position to the phenol group and lowest in the *meta* position. Therefore, the experimental regiocontrol exhibited by the photochemical reaction of **1** is consistent with this assumption.

Although only a few experiments have been conducted to determine the pK_a values[15] or lifetimes of phenolic cation-radicals,[16] nonpolar solvents have provided a convenient way of producing cation-radicals from a variety of solutes via ET.[17] However, the phenol cation-radical is subsequently deprotonated in a process that is subject to a

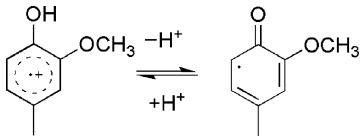


Scheme 4.

very low energy barrier[18] and yields the phenoxyl radical as a result of the markedly increased acidity order of the phenol cation-radical relative to neutral phenols. Therefore, one must consider the possibility of the transient intermediates $\mathbf{14_H}$–$\mathbf{16_H}$ donor cationic species being deprotonated to the corresponding donor radicals **14**–**16** in a proton coupled electron transfer mechanism (Scheme 4, PCET). However, the keto form of these intermediates concentrates the spin density at the same position in the donor ring as the corresponding protonated forms $\mathbf{14_H}$–$\mathbf{16_H}$ and the regioselectivity for hydroxyl coupling remains unchanged as a result. Although an equilibrium between the protonated or keto form of the deprotonated intermediates in the reaction medium is possible, both species induce the same regiocontrol over the hydroxylation process as they result in the same location for the highest spin densities in the donor ring. Therefore, bond formation in the hydroxylation process can occur over the protonated or deprotonated form of the phenol donor cation-radical.

2.4.1. Does the deprotonation of the phenol cation-radical precede the radical coupling reaction? If the deprotonation of the phenol cation-radical were the main reaction pathway for these transient intermediates, then the resulting radicals, (e.g., **14** or **15** in Scheme 4) would be better defined as phenoxy radicals than as carbon centered radicals. Oxygen centered radicals (e.g., $ArO^{\cdot}$) do not react with hydroxyl radical to form a peroxy derivative as this process is endoergonic,[19] so only the carbon centered radicals can give the observed hydroxylation products. Therefore, deprotonation of the corresponding phenol cation-radicals leading to phenoxyl radicals[18] need not be the main pathway for our compounds, even though this phenomenon has been extensively studied and postulated as the main pathway for phenol cation-radical intermediates. The possibility of the proton coupled electron-transfer mechanism reported for phenols[20] directly yielding the phenoxyl radical and hence inhibiting the hydroxylation process as an alternative to this stepwise mechanism can therefore be discarded.

From the photoreaction of **3** one may conclude that the presence of the methoxy group on the aromatic donor ring strongly influences the outcome of the hydroxylation process. The hydroxylation position in the donor ring changes from that nearest to the phenol group to the two possible *meta* sites (**8** and **9**) and the ratio of hydroxylation to deoxygenation products increases as a result. This is consistent with our hypothesized PET pathway from the donor to the S_1 state of the acceptor, which is favored by an increased electron donor ability. The regiochemistry of the hydroxylation reaction is now consistent with that previously reported for the parent compound **4** having two methoxy groups instead of the monomethoxy–monohydroxyl derivative **3**. Because the hydroxyl-radical coupling can occur over the donor phenol cation-radical before the proton is lost, the calculated spin densities are consistent with the preferred orientation of hydroxylation also observed in the parent compound **4**. However, if the deprotonation of the donor phenol cation-radical occurs before the hydroxyl-radical coupling, the unpaired electron in the resulting keto-radical (Scheme 5) will be in a ring



Scheme 5.

position inconsistent with the photohydroxylation products obtained (**8** and **9**). Therefore, the phenol cation-radical must be the intermediate responsible for the formation of **8** and **9**, and hence for the corresponding deprotonated species not forming.

Two different configurations can be formulated for the disubstituted cation-radicals resulting from **3** and **5** (Scheme 6). The cation-radial formed in the electron-transfer process of **3** (a, Scheme 6) can be described as the two limiting cations-radicals **a1** and **a2**. While all resonant forms resulting from cation-radical **a1** can only undergo hydroxylation by hydroxyl-radical/carbon-centered radical coupling on the ring *meta*-position (with respect to the methylene bridge; empty arrow), the corresponding cation-radical **a2** localizes the radical density at appropriate positions (black arrows), which is quite consistent with the regioselectivity observed in the photohydroxylation process.

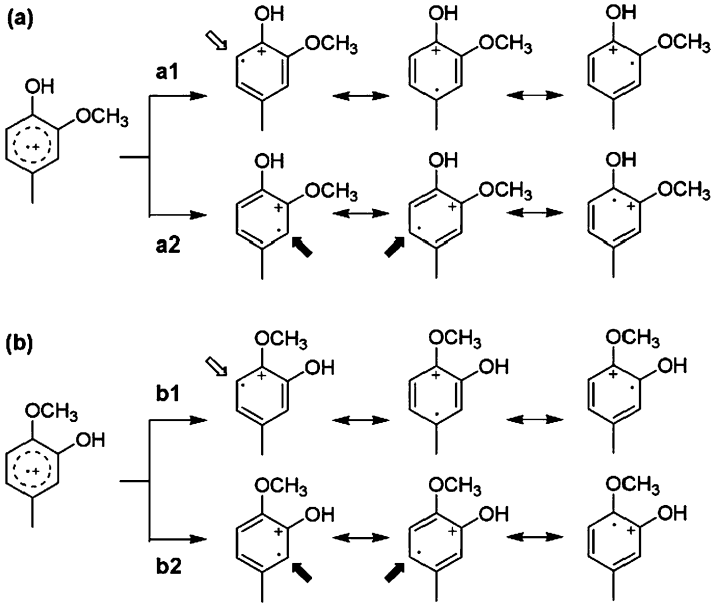
Thus, the preferred charge density is located over the methoxyl-substituted carbon instead of the hydroxyl-substituted one, which hinders deprotonation and favors photohydroxylation.

However, in the isomeric cation-radical formed from compound **5** (b, Scheme 6), the cation-radical **b2**, which locates the positive charge over the hydroxyl substituted carbon, is the resonant form that correlates well with the observed photohydroxylation positions. Because the hydroxylation products obtained in the photolysis of **5** have the phenol group in *ortho* with respect to the methylene bridge, the positive charge must be localized in the same relative position as in **a2**, which allows high spin densities to be concentrated at appropriate carbon atoms in the aromatic ring.

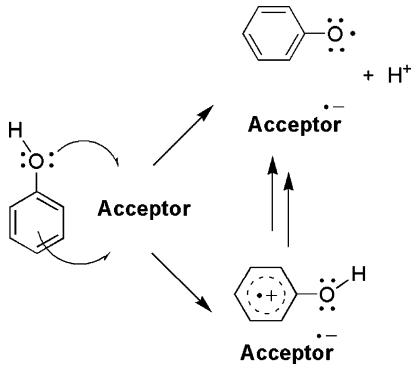
The charge and unpaired electron densities distributions for various substituted phenols and the corresponding methoxyl derivatives have been widely discussed in relation to SN2Ar* and radical processes in the literature.[21] The directing influence of the electron-donor susbstituents can be rationalized in terms of the calculated values for cation-radicals. The B3LYP/6-31g(d,p) electronic spin densities for 4-methyl phenol, 2-methoxy-4-methyl phenol and 2-methoxy-3-methyl phenol cations-radicals as model molecules were calculated and the resulting values found to be consistent with their experimental counterparts (i.e., with the encounter hydroxylation positions).[22]

2.4.2. π-Electron versus oxygen centred electron transfer mechanisms. Intermolecular electron-transfer reactions from phenols to selected acceptors have been studied and direct, synchronous formation of phenoxyl radicals and phenol cation-radicals in nearly the same relative amounts observed in all cases (Scheme 7).[16b,23] This was ascribed to two competing electron-transfer channels depending on the geometry of encounter between the parent acceptor and the phenol molecule. The electron transfer was found to occur via two different pathways synchronously generating the phenol cation-radical ($ArOH^{+\cdot}$) and phenoxyl radicals ($ArO^{\cdot}$). The proportion of the fast formation of the two transients by electron-transfer can be expected to be about 50% for each reaction channel. This means that both pathways have the same probability.

Thus, intermolecular electron-transfer from the aromatic ring to the acceptor occurs, the positive charge being stabilized within the aromatic system with the assistance of substituents of the ring. The other type of attack involves an interaction between the phenolic oxygen atom and the acceptor,



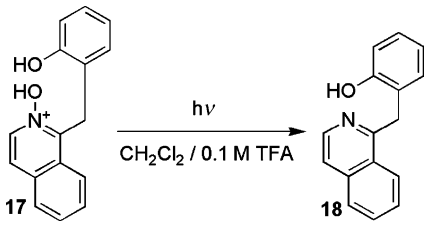
Scheme 6.



Scheme 7.

immediately followed by deprotonation, the products being phenoxyl radicals. Obviously, this intermolecular reaction can take place via two different channels involving encounters between the parent ions and the aromatic ring, as well as the hydroxyl group in the solute molecule. Hence, such different encounter situations lead to the synchronous formation of the phenol cation-radical and phenoxyl radicals. Two different types of products can therefore be obtained depending on the particular intermolecular encounter geometry.[16b,24]

When the phenols and the acceptor moieties are covalently bridged, as was the case in our intramolecular situation, the encounter geometries for the electron-transfer are restricted by the short methylene chain. In this situation, restricted geometries can govern the reaction pathways. In compounds **1**, **3** and **5**, the hydroxyl groups in the aromatic donors are faraway oriented with respect to the protonated isoquinoline *N*-oxide acceptor, so, based on the previous argument, intramolecular electron-transfer from the aromatic ring to the acceptor, leading to the phenol cation-radical, will occur instead of direct electron transfer from the phenolic oxygen atom, which will follow immediate deprotonation with the production of phenoxyl radicals. In this way, a carbon centered radical capable of reacting with the hydroxyl radical that can give the photohydroxylation products is obtained. Rapid generation of the cation-radicals and their delayed deprotonation into radicals can occur in all cases studied in nonpolar solvents. Studies have shown that, even though the cation-radicals are deprotonated, they are stable enough to be characterized in dry solvents at room temperature. This mechanism is supported by the photochemical reaction of the isomeric compound **17**, for which no photohydroxylation product was detected; the sole product obtained was the corresponding deoxygenated compound **18**, in 85% yield (Scheme 8). Here, the encounter geometry can determine the characteristics of the electron transfer product.[24]



Scheme 8.

Hence, the proximity of the hydroxyl group of the phenol in **17** to the acceptor can be assumed to result in a preferred electron transfer from the phenolic oxygen atom directly leading to the phenoxyl radical—which cannot couple with the hydroxyl radical—, the photohydroxylation process being inhibited as a result. Based on these results, we can assume the presence of two structures strongly differing in their tendency to rapid dissociation after ionization: whereas the oxygen-localized cation-radical dissociates immediately to a phenoxyl-radical, the delocalized planar cation-radical is a metastable species on a timescale of a few 100 ns.[23b] Subsequently, it can be deprotonated more slowly—albeit before it can undergo hydroxyl radical coupling to give the photohydroxylation products.

This reflects in the fact that, the charge and spin densities in the direct electron transfer from the aromatic ring to the protonated isoquinoline *N*-oxide acceptor to give the corresponding donor cation-radical are strongly influenced by the position of the oxa-substituents; however, they have no decisive influence on the quality of homologous substituents such as hydroxyl/methoxyl groups. On the other hand, the resulting cation-radical possesses a long enough lifetime to allow the radical to couple and produce the hydroxylated material prior to deprotonation.

3. Conclusions

The photolysis of a protonated isoquinoline *N*-oxide covalently bonded to a substituted phenol gives the corresponding hydroxylated diphenol derivatives with absolute regiocontrol over the hydroxylation position of the starting phenols. Our proposed electron transfer-initiated photohydroxylation mechanism is also feasible for these phenol derivatives if one excludes the commonly accepted PCET and sequential electron transfer/deprotonation reactions. The ET from the donor phenol ring to the protonated isoquinoline *N*-oxide involves the simultaneous formation of a hydroxyl radical and the phenol cation-radical, which undergo hydroxyl coupling before deprotonation to give the photohydroxylated material. Because the hydroxyl radical and the phenol cation-radical are simultaneously produced, the radical coupling reaction takes complete regiocontrol over the ring hydroxylation process. The photohydroxylation process produced by isoquinoline *N*-oxide photochemistry is effective enough to compete with the deprotonation process put forward for phenol cation-radicals.

4. Experimental

Material and equipment. All reagents were used as received. The solvents for absorption and fluorescence measurements were spectrophotometric grade and used without further purification. HRMS are reported as *m*/*z*. ^{1}H and ^{13}C NMR spectra (200 and 50 MHz, respectively) were recorded from $CDCl_3$ solutions, using the solvent residual proton signal as standard. TLC analyses were performed on silica gel 60 F 256 plates and column chromatography was carried out on silica gel 60 (70–230 mesh). Melting points were obtained in open capillaries and are given uncorrected.

Spectroscopic studies. Samples for recording UV/vis and fluorescence emission spectra were prepared in spectroscopic grade solvents and adjusted to a linear grade response. Fluorescence quantum yields were determined by comparison with quinine sulfate and corrected for the refractive index of the solvent.

4.1. Synthesis of 1-(4-hydroxybenzyl)isoquinoline *N*-oxide (1)

4.1.1. 4-Tosyloxy-benzaldehyde (19).[25] A mixture of 50 mL of dichloromethane and 20 mL of a 30% aqueous solution of NaOH was vigorously stirred, and 1.59 g (13 mmol) of 4-hydroxybenzaldehyde and 200 mg of TEBA added under nitrogen atmosphere. A solution of tosyl chloride containing 4.34 g (21 mmol) in 50 mL of dichloromethane was then added dropwise and the reaction mixture stirred for 6 h. The organic phase was washed with water (2×50 mL), dried and concentrated. The crude product was pure enough for use without further purification in the next step. White solid; mp=72–73 °C (hexane); yield 82%; ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3H,), 7.15 (d, 2H, J=9.1 Hz), 7.30 (d, 2H, J=8.5 Hz), 7.70 (d, 2H, J=8.5 Hz), 7.81 (d, 2H, J=8.6 Hz), 9.95 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.4, 122.7, 128.1, 129.8, 131.0, 131.7, 134.6, 145.7, 153.5, 190.4; MS *m*/*z* (%) 276 (4) $[M]^+$, 155 (25), 91 (100), 65 (72). Anal. Calcd for $C_{14}H_{12}O_4S$: C, 60.86; H, 4.38. Found: C, 60.88; H, 4.40.

4.1.2. 4-Tosyloxy-benzylalcohol (20).[26] A solution of 4-tosyloxy-benzaldehyde containing 3.04 g (11 mmol) in MeOH (50 mL) was supplied with 0.416 g (11 mmol) of $NaBH_4$ at 0 °C in four portions. After stirring for 5 h, water was added to the reaction mixture and the resulting product extracted with CH_2Cl_2, dried over $MgSO_4$ and evaporated to obtain the protected benzyl alcohol. Oil; yield 78%; ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H), 4.61 (s, 2H), 6.93 (d, 2H, J=8.5 Hz), 7.22–7.67 (m 4H), 7.67 (d, 2H, J=8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 21.0, 63.5, 121.6, 127.3, 127.7, 129.1, 139.2, 144.7, 148.1; MS *m*/*z* (%) 278 (6) $[M]^+$, 155 (24), 107 (11), 106, (100), 91 (100), 65 (64). Anal. Calcd for $C_{14}H_{14}O_4S$: C, 60.42; H, 5.07. Found: C, 60.40; H, 5.10.

4.1.3. 4-Tosyloxy-benzylchloride (21).[26] A round-bottom flask containing 1.67 g (6 mmol) of 4-tosyloxy-benzyl-alcohol was cooled in a water–ice mixture and supplied with $SOCl_2$ (0.5 mL; 7 mmol) via a dropping funnel. The reaction mixture was heated in a water bath for 6 h. Excess $SOCl_2$ was then removed in vacuo and the residue dissolved in CH_2Cl_2 (200 mL), washed with water (3×50 mL), dried and concentrated. White solid; mp=80–82 °C (hexane); yield 88%; ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3H), 4.51 (s, 2H), 6.95 (d, 2H, J=8.5 Hz), 7.27–7.31 (m, 4H), 7.67 (d, 2H, J=8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 21.5, 45.0, 122.5, 128.3, 129.7, 132.1, 136.3, 145.4, 149.3; MS *m*/*z* (%) 298 (2) $[M^+ + 2]$, 296 (4) $[M]^+$, 155 (33), 106, (50), 91 (100), 65 (46). Anal. Calcd for $C_{14}H_{13}ClO_3S$: C, 56.66; H, 4.42. Found: C, 56.67; H, 4.45.

4.1.4. 4-Hydroxybenzyl isoquinoline (7).[27] In a 100 mL two-necked flask were placed 1 g (3.3 mmol) of 4-tosyloxy-benzylchloride, isoquinoline Reissert (0.73 g; 2.8 mmol) and TEBA (200 mg) in 20 mL of benzene under an argon atmosphere. The resulting mixture was vigorously stirred and a solution of 50% aqueous NaOH (10 mL) was added. After stirring at room temperature for 24 h, the organic layer was collected, washed with water, dried and concentrated to obtain a residue that was subsequently hydrolyzed.

The crude residue was dissolved in a mixture of 5 mL of methanol and 10 mL of 20% aqueous NaOH, the resulting solution being refluxed for 3 h. Once cool, the solution was extracted with CH_2Cl_2 (3×100 mL). The organic extracts were dried with $MgSO_4$, the solvent being removed in vacuo. The product was purified by column chromatography. Yellow solid; yield 72%; ^{1}H NMR ($CDCl_3$) δ 4.57 (s, 2H,), 6.63 (d, 2H, J=8.5 Hz), 7.03 (d, 2H, J=8.5 Hz), 7.49–7.57 (m, 2H), 7.64 (t, 1H, J=6.7 Hz), 7.80 (d, 1H, J=8.5 Hz), 8.16 (d, 1H, J=7.9 Hz), 8.45 (d, 1H, J=5.5 Hz); ^{13}C NMR ($CDCl_3$) δ 40.4, 115.2, 120.1, 125.9, 126.9, 127.1, 127.3, 129.2, 129.8, 130.1, 136.5, 140.5, 155.0, 160.4; MS *m*/*z* (%) 236 (4) $[M]^+$, 235 (33), 234 (100), 233 (19), 204 (15), 75 (36). Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.76; H, 5.85; N, 5.97.

4.1.5. 1-(4-Hydroxybenzyl)isoquinoline *N*-oxide (1). To a solution of 4-hydroxybenzyl isoquinoline (0.8 g; 3.4 mmol) in 25 mL of chloroform, MCPBa (0.828 g; 4.8 mmol) was added and the resulting solution stirred at room temperature for 24 h. The solution was washed with saturated aqueous $NaHCO_3$ and water, dried and concentrated, the resulting solid being recrystalized from AcOEt. Brown solid; mp=203–204 °C (AcOEt); yield 83%; ^{1}H NMR ($CDCl_3$) δ 4.69 (s, 2H), 6.57 (d, 2H, J=8.5 Hz), 7.05 (d, 2H, J=8.5 Hz), 7.54–7.68 (m, 3H), 7.78 (d, 1H, J=8.5 Hz), 8.03 (d, 1H, J=7.9 Hz), 8.21 (d, 1H, J=7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 30.5, 115.1, 122.9, 124.4, 126.9, 127.2, 128.2, 129.2, 129.4, 129.9, 135.4, 148.3, 155.3; MS *m*/*z* (%) 251 (34) $[M]^+$, 234 (100), 204 (43). Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.21; H, 5.28; N, 5.80.

4.2. Synthesis of 1-(3-methoxy-4-hydroxybenzyl)isoquinoline *N*-oxide (3)

4.2.1. 3-Methoxy-4-tosyloxy-benzaldehyde (22).[28] Prepared by using the above-described procedure for **19**. White solid; mp=116–117 °C (hexane); yield 85%; ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3H), 3.63 (s, 3H), 7.25–7.44 (m, 5H), 7.75 (d, 2H, J=7.9 Hz), 9.91 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.6, 55.7, 111.1, 124.1, 128.4, 129.4, 132.9, 135.7, 142.9, 145.4, 152.5, 190.7; MS *m*/*z* (%) 306 (2) $[M]^+$, 155 (34), 91 (100), 65 (69). Anal. Calcd for $C_{15}H_{14}O_5S$: C, 58.81; H, 4.61. Found: C, 58.83; H, 4.64.

4.2.2. 3-Methoxy-4-tosysloxy-benzylalcohol (23).[28] Prepared by using the above-described procedure for **20**. White solid; mp=90–91 °C (AcOEt); yield 90%; ^{1}H NMR ($CDCl_3$) δ 1.97 (t, 1H, J=4.9 Hz), 2.43 (s, 3H), 3.51 (s, 3H), 4.62 (s, 2H), 6.80–6.87 (m, 2H), 7.08 (d, 1H, J=8.5 Hz), 7.28 (d, 2H, J=7.9 Hz), 7.73 (d, 2H, J=7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 21.5, 55.4, 64.4, 111.0, 118.5, 123.7, 128.5, 129.3, 133.1, 137.4, 141.2, 145.0, 151.7; MS *m*/*z* (%) 308 (3) $[M]^+$, 155 (17), 91 (100), 65 (47). Anal. Calcd for $C_{15}H_{16}O_5S$: C, 58.43; H, 5.23. Found: C, 58.46; H, 5.24.

4.2.3. 3-Methoxy-4-tosysloxy-benzylchloride (24). Prepared by using the above-described procedure for **21**. White solid; mp=110–112 °C (AcOEt); yield 86%; ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3H), 3.57 (s, 3H), 4.50 (s, 2H), 6.85–6.89 (m, 2H), 7.08 (d, 1H, J=9.1 Hz), 7.28 (d, 2H, J=7.9 Hz), 7.74 (d, 2H, J=7.9 Hz); ^{13}C NMR ($CDCl_3$) δ 21.5, 45.5, 55.5, 112.8, 120.5, 123.9, 128.4, 129.3, 133.0, 137.4, 138.1, 145.1, 151.8; MS m/z (%) 326 (6) $[M]^+$, 91 (100), 65 (66). Anal. Calcd for $C_{15}H_{15}O_4ClS$: C, 55.13; H, 4.63. Found: C, 55.14; H, 4.65.

4.2.4. 1-(3-Methoxy-4-hydroxybenzyl)isoquinoline (10). Prepared by using the above-described procedure for **7**. White solid; mp=139–140 °C (AcOEt); yield 73%; ^{1}H NMR ($CDCl_3$) δ 3.70 (s, 3H), 4.57 (s, 2H), 6.77–6.79 (m, 3H), 7.48–7.59 (m, 3H), 7.79 (d, 1H, J=8.5 Hz), 8.16 (d, 1H, J=8.5 Hz), 8.47 (d, 1H, J=6.1 Hz); ^{13}C NMR ($CDCl_3$) δ 41.6, 55.7, 111.3, 114.4, 119.8, 121.3, 125.8, 127.1, 127.3, 129.2, 129.9, 131.2, 136.6, 141.8, 144.2, 146.7, 160.4; MS m/z (%). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.98; H, 5.73; N, 5.29.

4.2.5. 1-(3-Methoxy-4-hydroxybenzyl)isoquinoline *N*-oxide (3). An amount of 0.8 g (3.0 mmol) of 1-(3-methoxy-4-hydroxybenzyl)isoquinoline was reacted as for the preparation of **1**. White solid; mp=204–205 °C (AcOEt); yield 73%; ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H), 4.55 (s, 2H), 5.60 (s, 1H), 6.74 (s, 2H), 7.04 (s, 1H), 7.50–7.64 (m, 3H), 7.76 (d, 1H, J=7.9 Hz), 8.02 (d, 1H, J=7.9 Hz), 8.20 (d, 1H, J=6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 31.2, 55.8, 111.9, 114.6, 120.5, 121.0, 122.5, 124.1, 127.3, 128.7, 129.2, 129.3, 136.6, 144.7, 147.0, 147.5; MS m/z (%) 281 (13) $[M]^+$, 280 (20), 264 (100). Anal. Calcd for $C_{17}H_{15}NO_3$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.99; H, 5.73; N, 5.30.

4.2.6. 1-(3-Hydroxy-4-methoxybenzyl)isoquinoline *N*-oxide (5). An amount of 0.75 g (2.8 mmol) of 1-(3-hydroxy-4-methoxybenzyl)isoquinoline[13] was reacted as for the preparation of **1**. Brown solid; mp=195–196 °C (AcOEt); yield 73%; ^{1}H NMR ($CDCl_3$): δ 3.79 (s, 3H, $-OCH_3$), 4.71 (s, 2H, $-CH_2-$), 5.65 (s, 1H, OH), 6.71 (d, 1H, J=7.9 Hz, $H_{5'}$), 6.80–6.86 (m, 2H, $H_{2'}$, $H_{6'}$), 7.50–7.65 (m, 3H, H_4, H_6, H_7), 7.76 (d, 1H, J=8.2 Hz), 7.99 (d, 1H, J=8.5 Hz, H_8), 8.22 (d, 1H, J=7.3 Hz, H_3); ^{13}C NMR ($CDCl_3$): δ 30.6, 55.4, 111.4, 115.0, 119.4, 120.3, 122.9, 124.2, 124.4, 127.2, 128.3, 129.1, 129.4, 129.8, 135.4, 146.0, 148.1; MS (EI, relative %) 281 (30) $[M]^+$, 280 (60), 264 (100). Anal. Calcd for $C_{17}H_{15}NO_2$ (281.31): C, 76.96; H, 5.70; N, 5.28. Found: C, 76.99; H, 5.72; N, 5.29.

4.2.7. 1-(2-Hydroxybenzyl)isoquinoline *N*-oxide (17).[29]

4.3. General procedure for irradiation of samples

A 10^{-3} M solution of the corresponding *N*-oxide in CH_2Cl_2 and 0.1 M TFA was bubbled with argon and irradiated through Pyrex at room temperature under an Ar atmosphere, using a medium-pressure mercury lamp (150 W) for 10 min. The solutions were then washed with aqueous $NaHCO_3$ and H_2O, and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the resulting material separated by column chromatography. When necessary, mixtures of regioisomeric phenols were further separated by preparative TLC.

4.3.1. 1-(3,4-Dihydroxybenzyl)isoquinoline (6). See Ref. 30.

4.3.2. 1-(2,4-Dihydroxy-5-methoxybenzyl)isoquinoline (8). Oil; yield 35%; ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H), 4.48 (s, 2H), 6.60 (s, 1H), 6.77 (s, 1H), 7.55 (d, 1H, J=6.1 Hz), 7.64–7.76 (m, 2H), 7.83 (d, 1H, J=7.9 Hz), 8.34 (d, 1H, J=6.1 Hz), 8.40 (d, 1H, J=7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 31.2, 55.8, 111.9, 114.6, 120.9, 122.8, 124.3, 127.4, 128.3, 128.6, 128.8, 129.5, 129.6, 136.1, 144.5, 146.9, 147.9; MS m/z (%) 281 (100) $[M]^+$, 168 (72), 167 (79); HRMS (FAB) m/z calcd for $C_{17}H_{15}NO_3$ $(M)^+$281.1052, found 281.1060.

4.3.3. 1-(2,4-Dihydroxy-3-methoxybenzyl)isoquinoline (9). Oil; yield 13%; ^{1}H NMR ($CDCl_3$) δ 3.98 (s, 3H), 4.51 (s, 2H), 6.41 (d, 1H, J=8.5 Hz), 6.91 (d, 1H, J=8.5 Hz), 7.56 (d, 1H, J=5.5 Hz), 7.68–7.76 (m, 2H), 7.83 (d, 1H, J=6.7 Hz), 8.34 (d, 1H, J=6.1 Hz), 8.40 (d, 1H, J=8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 36.2, 57.4, 111.4, 122.7, 123.6, 125.2, 125.8, 126.8, 128.6, 129.0, 131.6, 136.5, 136.6, 140.9, 145.9, 148.1, 158.3; MS m/z (%) 281 (100) $[M]^+$, 168 (72), 167 (79); HRMS (FAB) m/z calcd for $C_{17}H_{15}NO_3$ $(M)^+$281.1052; found 281.1056.

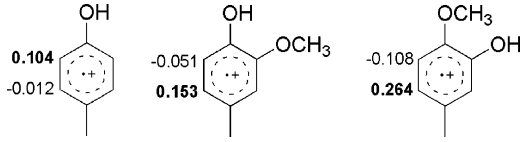
4.3.4. 1-(2,5-Dihydroxy-4-methoxybenzyl)isoquinoline (11). Oil; yield 30%; ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H), 4.48 (s, 2H), 6.59 (s, 1H), 6.77 (s, 1H), 7.55 (d, 1H, J=6.5 Hz), 7.20–7.60 (m, 2H), 7.82 (d, 1H, J=6.7 Hz), 8.34 (d, 1H, J=6.1 Hz), 8.40 (d, 1H, J=9.1 Hz); ^{13}C NMR ($CDCl_3$) δ 36.1, 56.2, 101.4, 122.8, 122.9, 125.9, 126.5, 126.9, 128.6, 131.6, 140.9, 144.2, 147.6, 153.6, 156.7; MS m/z (%) 281 (100) $[M]^+$, 280 (72), 167 (79); HRMS (FAB) m/z calcd for $C_{17}H_{15}NO_3$ $(M)^+$281.1052; found 281.1059.

4.3.5. 1-(2,3-Dihydroxy-4-methoxybenzyl)isoquinoline (12). Oil; yield 15%; ^{1}H NMR ($CDCl_3$) δ 3.77 (s, 3H), 4.53 (s, 2H), 6.36 (d, 1H, J=8.5 Hz), 6.91 (d, 1H, J=8.5 Hz), 7.53 (d, 1H, J=5.7 Hz), 7.62–7.69 (m, 2H), 7.79 (d, 1H, J=7.3 Hz), 8.33–8.40 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 36.1, 56.3, 108.2, 122.8, 125.8, 126.5, 126.9, 127.2, 128.5, 131.6, 136.6, 138.5, 141.0, 144.0, 148.1, 157.5; MS m/z (%) 281 (100) $[M]^+$, 168 (72), 167 (79); HRMS (FAB) m/z calcd for $C_{17}H_{15}NO_3$ $(M)^+$: 281.1052; found 281.1057.

4.4. Theoretical calculations

In order to ensure reliable results, density functional theory (DFT) calculations were carried out by using the software Gaussian 98[22a] on an SGI Origin 2000 supercomputer. We used Becke's three-parameter exchange functional in combination with the LYP correlation functional (B3LYP).[22b] The hybrid functional (HF/DFT) B3LYP was previously shown to provide electronic spin densities similar to those obtained from high-level CAS computations with the same basis sets.[22c] We used the 6-31g(d,p) basis set,[22d] which is a split-valence set and includes a series of *d*-polarization functions on heavy atoms and *p*-polarization

functions for the hydrogens. This set provides a compromise between accuracy and applicability to large molecules.



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Corrigendum

Corrigendum to "A new tripodal anion receptor with selective binding for $H_2PO_4^-$ and F^- ions" [Tetrahedron 62 (2006) 765]

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On page 767, the claim 'To our knowledge, compound **1** is the first pyrrole-based acyclic tripodal anions receptor' is imprecise. Before this paper, a pyrrole-based tripodal anions receptor has been reported by Schmuck and co-worker.[1] The authors apologize for this oversight.

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