Synthesis of (*S*)-(−)-*N*-acetylcolchinol using intramolecular biaryl oxidative coupling

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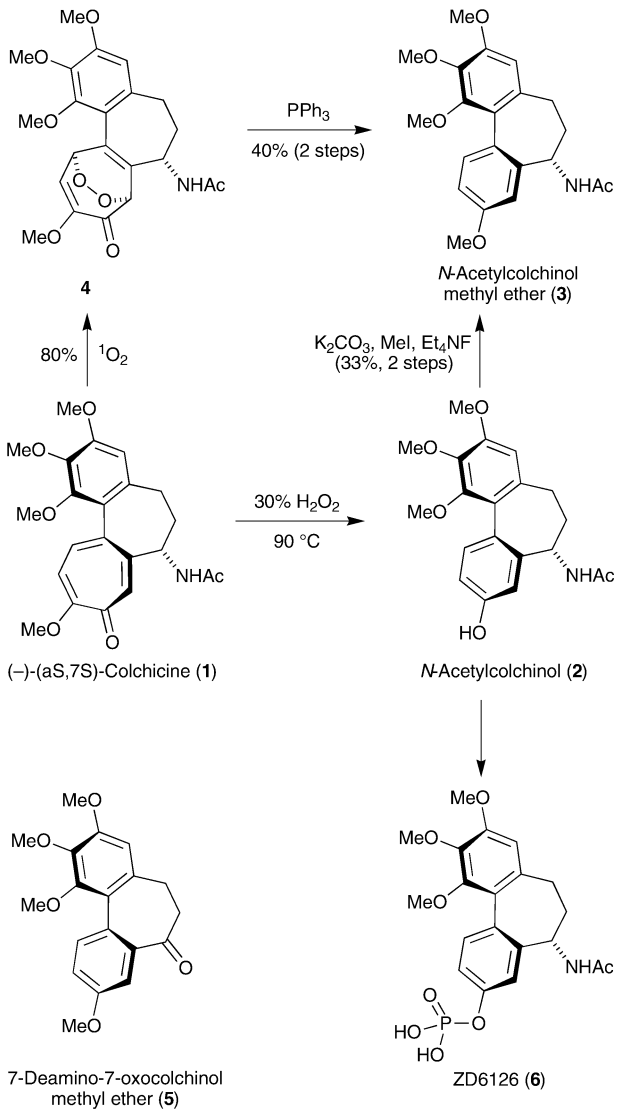
An asymmetric synthesis of the tubulin polymerisation inhibitor (*S*)-(−)-*N*-acetylcolchinol is reported based on an intramolecular biaryl oxidative coupling of a 1,3-diarylpropyl acetamide intermediate using phenyliodonium bis(trifluoroacetate) as the final step. Three syntheses of the penultimate 1,3-diarylpropyl acetamide intermediate (*S*)-(−)-*N*-[1-[3-(*tert*-butyldimethylsilyloxy)phenyl)]-3-(3,4,5-trimethoxyphenyl)propyl] acetamide are described which differ in the means by which the stereogenic centre was introduced.

Introduction

The first indication that colchicine (**1**) affects malignant tumour growth was described by Dominici in 1932[1] and shortly thereafter the likely mode of action, mitotic poisoning, was reported by Lits[2] and Dustin.[3] Widespread interest in the subject was aroused by Amoroso's observations in 1935 of tumour regression in mice and dogs caused by injections of colchicine.[4] However, the hope that colchicine might find a place in cancer chemotherapy was thwarted by its high toxicity (LD_{50} = 1.6 mg kg^{-1} in rats). A significant development in cancer chemotherapy was the discovery that allocolchinoids with a benzene ring in place of the tropolone ring also arrest mitosis by inhibiting tubulin polymerisation.[5] Examples include *N*-acetylcolchinol methyl ether (**3**), which binds to tubulin more strongly than colchicine itself,[6–8] and 7-deamino-7-oxocolchinol methyl ether (**5**).[9] ZD6126 (**6**) is under development by AstraZeneca as a water-soluble phosphate pro-drug which is converted *in vivo* to *N*-acetylcolchinol (**2**).[10,11] In animal models, ZD6126 selectively induced tumour vascular damage and tumour necrosis at well tolerated doses and it is currently undergoing clinical trials.[12]

The allocolchinoids are typically obtained by transformation of colchicine (**1**) (Scheme 1). Thus, *N*-acetylcolchinol (**2**) is obtained by treatment of colchicine (**1**) with 30% hydrogen peroxide and *O*-methylation affords the methyl ether **3** in 33% overall yield.[9,13,14] Recently **3** has been obtained by photooxygenation of colchicine (**1**) to give the peroxide **4** which then rearranges on treatment with triphenylphosphine to give **3** in 40% overall yield.[15] Given their structural simplicity and early promise as chemotherapeutic agents, it is surprising that so little effort has been invested in the synthesis of allocolchinoids.[16] In their pioneering syntheses of *N*-acetylcolchinol methyl ether (**3**), Cook[17] and Rapoport[18] first installed the biaryl as the phenanthrene derivatives **8** and **9** after which oxidative scission of ring B preceded its reconstitution as a 7-membered ring in the closing stages (Scheme 2). The synthesis of (±)-*N*-acetylcolchinol (**2**) by Sawyer and Macdonald[19] featured a non-phenolic oxidative coupling of the 1,3-diarylpropyl acetamide derivative **10** to construct the biaryl and 7-membered ring simultaneously.[20] A similar strategy was employed by LeBlanc



Scheme 1

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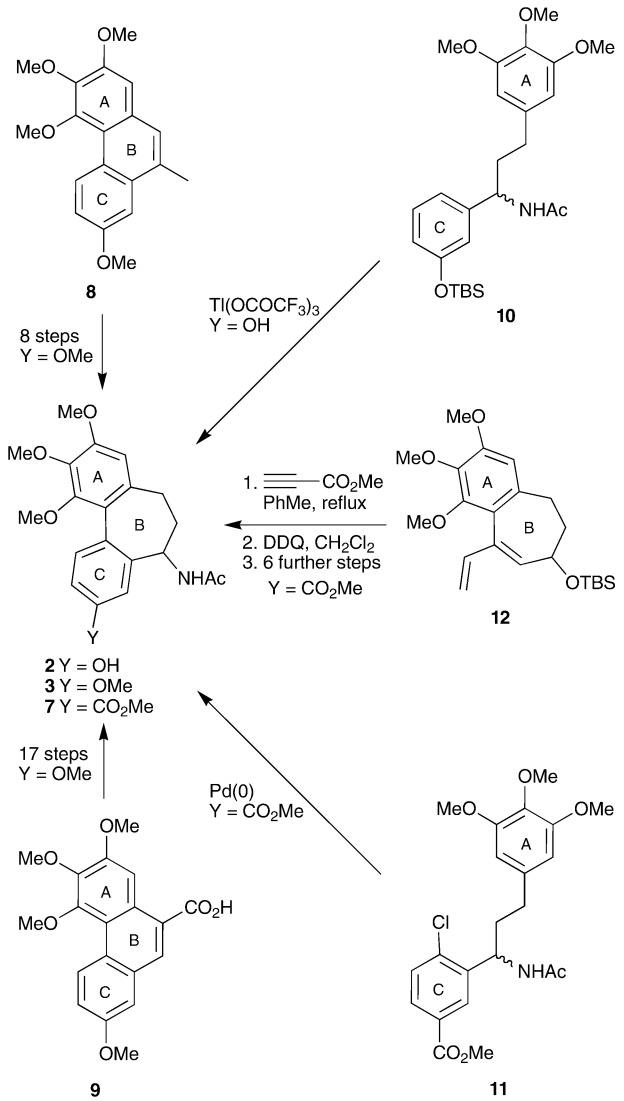
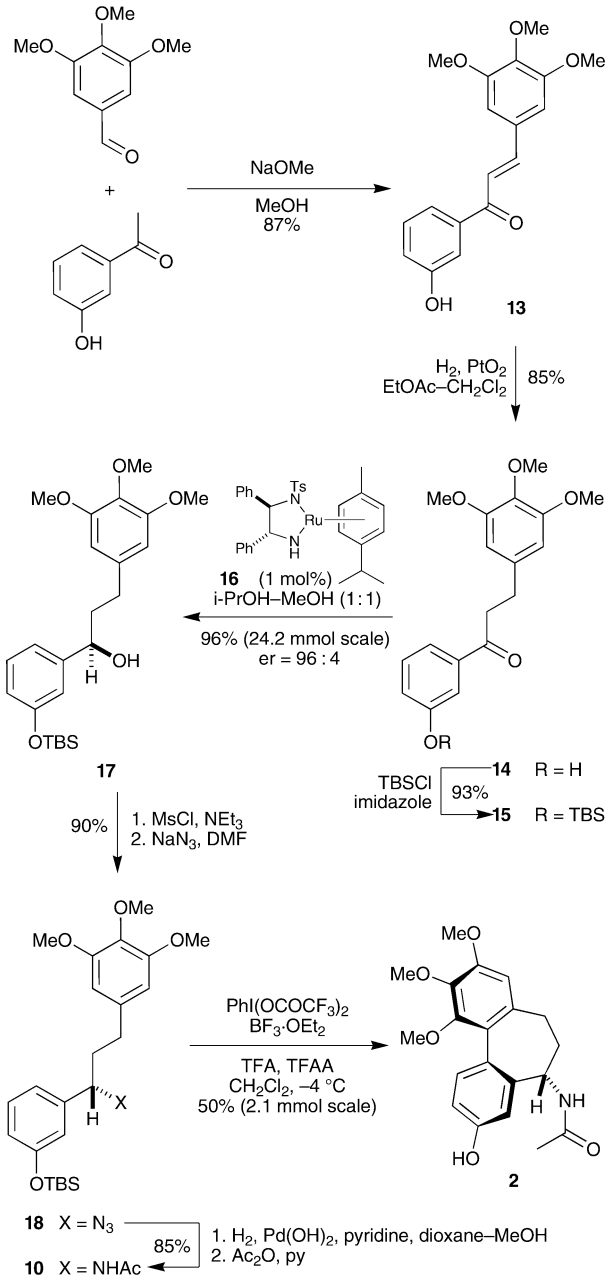


Scheme 2



Scheme 3

and Fagnou[21] in their recent synthesis of (−)-allocolchicine (**7**) in which the biaryl was fashioned from the 1,3-diarylpropane **11** by a Pd(0)-catalysed direct arylation. In all the previous syntheses, the aromatic rings were extant in the starting materials whereas the Wulff synthesis of (−)-allocolchicine[22] departs from convention by constructing the aromatic ring C by a Diels–Alder reaction of diene **12**. We now report three short asymmetric syntheses of (−)-*N*-acetylcolchinol (**2**), the active component of ZD6126, based on a variant of the Sawyer–Macdonald oxidative biaryl coupling. The three syntheses converge on the common 1,3-diarylpropyl acetamide intermediate **10** and differ primarily in the chemistry used to construct the single stereogenic centre.

Results and discussion

Route 1: Asymmetric reduction installs the stereogenic centre

A crossed aldol condensation of cheap, commercially available 3-hydroxyacetophenone with 3,4,5-trimethoxybenzaldehyde (Scheme 3) gave the crystalline chalcone **13**[23] in 87% yield on a 0.5 mol scale thereby installing all the carbon atoms of the target in the first step. Reduction of the alkene to the 1,3-diarylpropanone **14** was complicated by over-reduction of the carbonyl to an alcohol and thence hydrogenolysis to give a 1,3-diarylpropane. Even use of the Lindlar catalyst in methanol for 9 h as described by Holt and co-workers[23] gave the 1,3-diarylpropane as the major product. By using Adams' catalyst (PtO_2) in a mixture of ethyl acetate and dichloromethane, fast and selective reduction ensued to give the desired crystalline ketone **14** in 85% yield. After protection of the phenolic hydroxyl in **14** as its *tert*-butyldimethylsilyl ether **15**, the ketone was reduced enantioselectively to the (*R*)-alcohol **17** by three methods. With lithium borohydride in the presence of a stoichiometric amount of the chiral Lewis acid (+)-TarB-NO_2,[24] the reduction occurred in THF at room temperature to give **17** in 99% yield and er = 94 : 6 on a small scale.[25] Similar efficiency

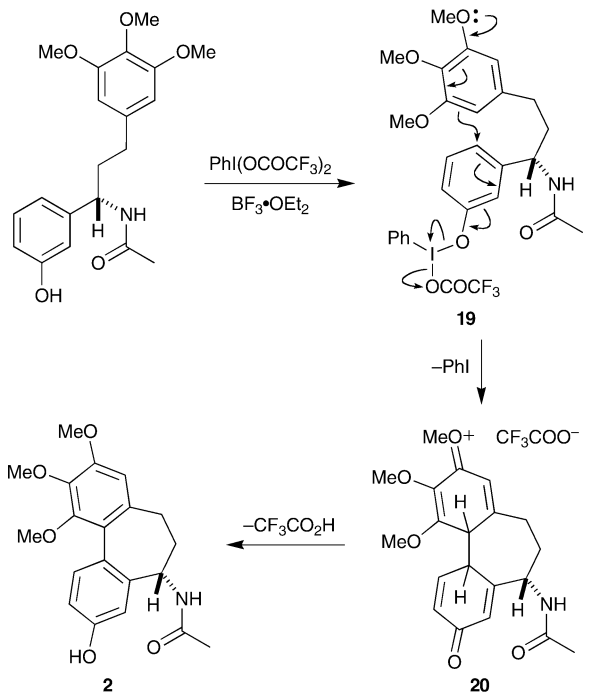
(99% yield, er = 94 : 6) was obtained by the second method, the Corey–Bakshi–Shibata reduction[26,27] using 10 mol% of an (*S*)-oxazaborolidine catayst. However, Noyori asymmetric transfer hydrogenation[28–30] using 1 mol% Ru[(1*R*,2*R*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethanediamine]-(η^6-*p*-cymene) (**16**) was superior in terms of cost and scalability, giving **17** in 96% yield (er = 96 : 4) on a 24 mmol scale.

The next phase of the synthesis required nucleophilic substitution of the hydroxyl group in **17** with a nitrogen nucleophile. A Mitsunobu-type reaction using diisopropyl azodicarboxylate and diphenylphosphoryl azide[31] gave an 85% yield of the inverted azide **18** but a tedious chromatographic separation from the diisopropyl hydrazinedicarboxylate by-product was required. Tanaka and co-workers[32] reported a variation of the Mitsunobu azidation using 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one to activate the triphenylphosphine instead of diisopropyl azodicarboxylate and $Zn(N_3)_2 \cdot 2Pyr$ as the azide source.[33] The reaction worked on a small scale to give the desired azide **18** in 84% yield but once again chromatography was required to separate the copious 2,4,6-tribromophenol by-product. A very simple and atom efficient two-step procedure was the method of choice. Alcohol **17** was converted to its mesylate ester whence nucleophilic substitution with sodium azide in DMF at room temperature gave the azide **18** in 90% overall yield for the two steps. Reduction of the azide to the corresponding amine was best achieved by hydrogenation using $Pd(OH)_2$ as catalyst, pyridine and a mixture of dioxane and methanol as solvent. Both catalyst and solvent choice were critical to success. With other solvent and Pd(0) catalyst combinations, a significant side reaction was hydrogenolysis of the amino function to give a useless 1,3-diarylpropane. Reduction of the azide to the amine was also accomplished in 89% yield using excess zinc and ammonium chloride in methanol. After acetylation of the amine under the usual conditions, the crystalline 1,3-diarylpropyl acetamide **10** was obtained in 85% overall yield from **18**. Recrystallisation from ethyl acetate–hexane afforded product that was at least 99.6% enantiomerically pure according to chiral HPLC.

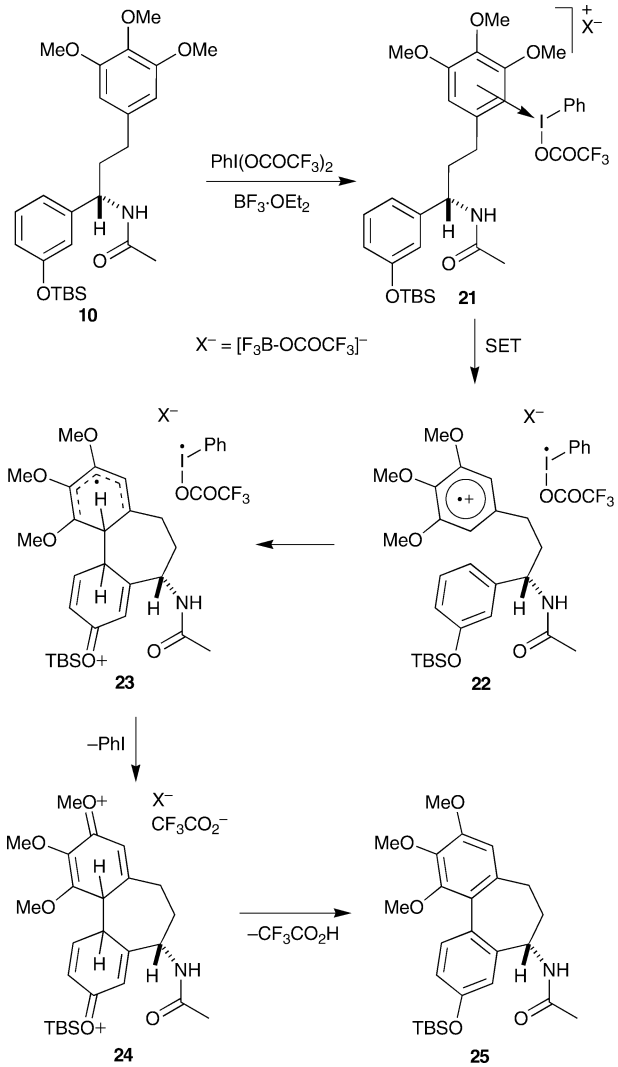
The final and key step of the sequence was the oxidative cyclisation of 1,3-diarylpropyl acetamide **10**. In their pioneering work, Sawyer and Macdonald[19] performed the reaction by addition of thallium(III) trifluoroacetate (TTFA, 1.1 equiv.) to a dilute solution of 1,3-diarylpropyl acetamide **10** and boron trifluoride etherate (35 equiv.) in a 20:1 mixture of trifluoroacetic acid (TFA) and trifluoroacetic anhydride (TFAA) at 0 °C. In our hands these conditions delivered *N*-acetylcolchinol (**2**) in 31% yield in contrast to the 71% yield reported. The conditions reported by Taylor and McKillop[34–36] gave better results. Thus, a dichloromethane solution of **10** was added to a 4 mM solution of TTFA (1.1 equiv.) in TFA–TFAA (20 : 1) at −4 °C followed by addition of the boron trifluoride etherate (35 equiv.) to give **2** in 47% yield. However, the requirement for large amounts of boron trifluoride etherate under high dilution conditions using an expensive and toxic Tl(III) reagent militated for cheaper and safer alternatives.

Kita and co-workers have published extensively[37] on the use of Lewis acid-activated hypervalent iodine(III) reagents for the oxidative nucleophilic substitution of phenol ether derivatives,[38] the oxidative aryl–aryl coupling of phenols to spirodienones and phenol ethers to biaryls.[39] Especially pertinent to the present study was the report of efficient oxidative cyclisation of 1,3-diarylpropane derivatives to dibenzocycloheptene derivatives using phenyliodonium bis(trifluoroacetate) (PIFA) in the presence of only 1–2 equiv of boron trifluoride etherate in dichloromethane at −40 °C.[40] Unfortunately application of these conditions to 1,3-diarylpropyl acetamide **10** gave *N*-acetylcolchinol in only 12% yield. Eventually we found that the use of PIFA (1.2 equiv.) and boron trifluoride etherate (2.4 equiv.) in a mixture of TFA, TFAA and dichloromethane at −4 °C gave the cleanest reactions consistently returning *N*-acetylcolchinol in 50% yield after aqueous workup. The remainder of the mass consisted of highly polar chromatographically immobile materials and several minor components which were not identified. Use of TBSOTf[41] (2.2 equiv.) in a mixture of TFA, TFAA and dichloromethane at −4 °C also gave *N*-acetylcolchinol in *ca.* 50% yield but there were several minor by-products that were difficult to separate by crystallisation or chromatgraphy. Two of these minor products were identified (see experimental). Polyoxometallate activation of the PIFA failed.[39]

As part of our optimisation studies we examined the cyclisation of relatives of 1,3-diarylpropyl acetamide **10** in which the TBS group was replaced by TIPS, Ac and MOM. With MOM none of the desired product was obtained whereas TIPS and Ac gave slightly inferior yields (47%). TBS was optimal in terms of stability, yields and cleanliness of reaction. Surprisingly, the unprotected phenol cyclised in up to 25% yield using PIFA–$BF_3 \cdot OEt_2$ suggesting that the reaction could take place, at least in part, by a phenolic oxidative pathway (Scheme 4). However, when the cyclisation of 1,3-diarylpropyl acetamide **10** was followed by LCMS, we found no evidence for removal of the TBS during the cyclisation and therefore its eventual loss must occur on aqueous workup. Consequently, the mechanism of the cyclisation is likely to follow the non-phenolic pathway (Scheme 5) in which the first step entails the formation of a charge transfer complex **21** involving the



Scheme 4

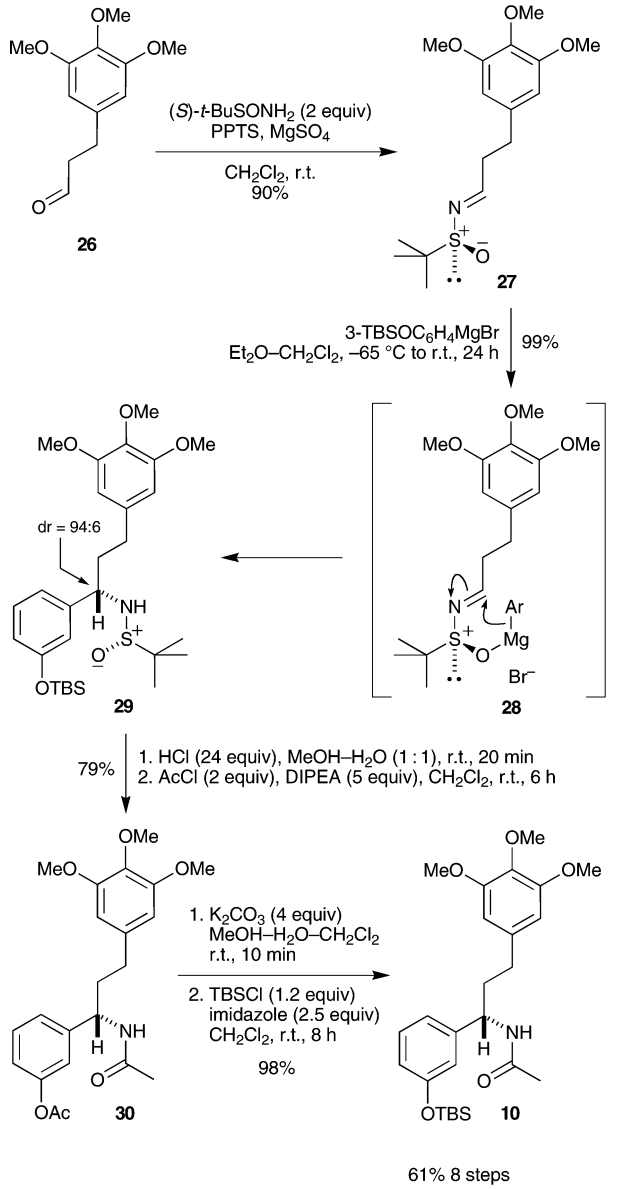


Scheme 5

more electron-rich trimethoxy-substituted arene followed by single electron transfer to the radical cation **22**. Kita and co-workers[38] have provided conclusive ESR evidence for the formation of radical cations in the PIFA oxidation of phenol ethers.

Route 2: Nucleophilic addition to a homochiral *N*-sulfinyl imine installs the stereogenic centre

In the route to 1,3-diarylpropyl acetamide **10** described above, the creation of the 3-carbon bridge between the two arene rings, the installation of the stereogenic centre and the transformation of a secondary alcohol to an amino function were three separate operations. In the second route (Scheme 6) we achieved the construction of the 3-carbon bridge and the installation of the secondary amino function in a single operation[42] by the addition of an arylmagnesium bromide to a homochiral *N*-*tert*-butylsulfinyl imine as described extensively by Ellman and co-workers.[43] The requisite sulfinyl imine **27** was generated by condensation of (*S*)-(−)-*tert*-butylsulfinamide[44] with 3-(3,4,5-trimethoxyphenyl)propanal[44] which is prepared in two steps from commercial 3-(3,4,5-trimethoxyphenyl)propanoic acid. Addition of an ethereal solution of 3-(*tert*-butyldimethylsilyloxy)phenylmagnesium bromide to a solution of sulfinyl imine **27** in dichloromethane at −65 °C occurred in 99% yield to give an easily separable mixture of diastereoisomeric adducts (dr = 94 : 6) in which the desired (S_S,*S*)-diastereoisomer **29** predominated.[45] The stereochemistry of the addition was established by X-ray crystallography (see the Experimental section) and corresponds to internal delivery of the arene in intermediate **28** according to the chelation-controlled model of Ellman and co-workers.[46]



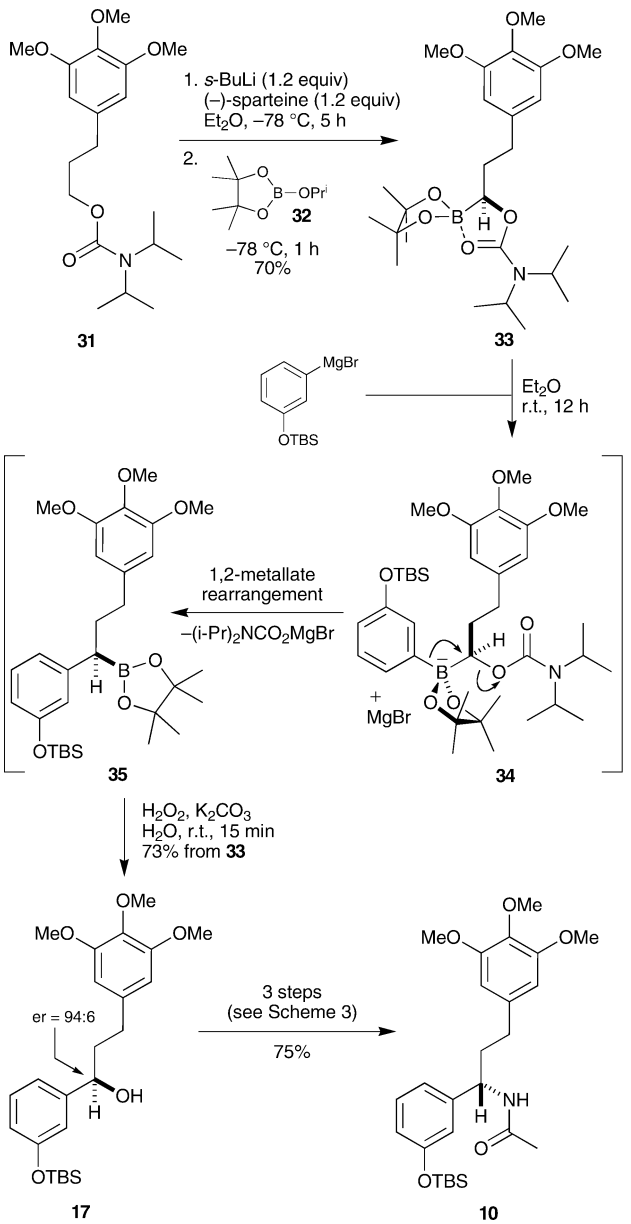
Scheme 6

Acidolysis of the *tert*-butylsulfinyl group with excess HCl was accompanied by removal of the TBS protecting group. The resultant aminophenol was acetylated to give acetamide **30** in 79% overall yield from **29**. Restoration of the TBS protector was then accomplished in two standard steps to give 1,3-diarylpropyl acetamide **10** in 98% yield.

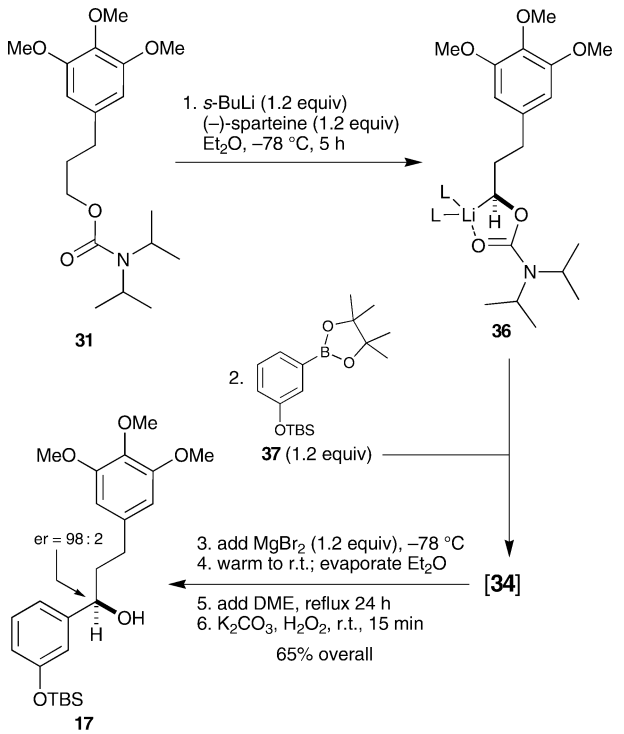
Route 3: An asymmetric metallation and 1,2-metallate rearrangement installs the stereogenic centre

The third route to the 1,3-diarylpropane **10** (Scheme 7) exploits a stereospecific 1,2-metallate rearrangement of an α-(carbamoyloxy)alkylboronate according to a protocol described by Hoppe and co-workers.[47] The sequence began with the enantioselective metallation of the *N*,*N*-diisopropylcarbamate **31** with the *s*-BuLi-(−)-sparteine complex. The resultant (*S*)-organolithium reagent reacted with clean retention of configuration with borate ester **32** to give the stable and storable α-(carbamoyloxy)alkylboronate **33** in 70% yield. The remarkable stability of **33** can be explained by the intramolecular coordination of the carbamate carbonyl oxygen to the boron atom as revealed by an X-ray crystal structure of racemic **33** (see the Experimental section). α-(Carbamoyloxy)alkylboronate **33** reacted with 3-(*tert*-butyldimethylsilyloxy)phenylmagnesium bromide in Et_2O to give an intermediate boronate complex **34** which underwent a Matteson-type[48,49] 1,2-metallate rearrangement with inversion of configuration to the boronate **35**.[50] Workup with hydrogen peroxide under mildly basic conditions then effected oxidation of **35** to give the alcohol **17** (er = 94 : 6) in 73% overall yield from **33**. Alcohol **17** was converted to the desired 1,3-diarylpropyl acetamide **10** in 3 steps as described in Scheme 3.

A one-pot variation of the chemistry depicted in Scheme 7 also inverts the roles of the two fragments (Scheme 8). Thus, the intermediate organolithium **36** added to the boronic acid derivative **37** to give the same boronate complex **34**. Addition of magnesium bromide and replacement of ether by 1,2-dimethoxyethane[51] effected the 1,2-metallate rearrangement after 12 h at reflux. The resultant boronate **35** was finally oxidised by addition of hydrogen peroxide (1.4 equiv.) and potassium carbonate to give the alcohol **17** in 65% overall yield (er = 98 : 2).



Scheme 7



Scheme 8

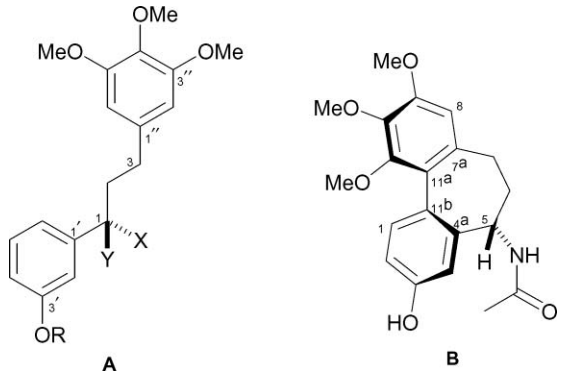
Conclusion

In conclusion, we have described a synthesis of (−)-*N*-acetylcolchinol based on the oxidative cyclisation of 1,3-diarylpropyl acetamide intermediate **10** mediated by phenyliodonium bis(trifluoroacetate) and boron trifluoride etherate (50% yield). The key cyclisation reaction, based on the work of Kita and co-workers,[37] is a safer and cheaper variant of the reaction previously used by Sawyer and Macdonald[19] to prepare racemic *N*-acetylcolchinol. Three syntheses of the penultimate 1,3-diarylpropyl acetamide intermediate **10** are described that differ in the method by which the stereogenic centre was installed. In the first synthesis (Scheme 3, 7 steps, 51% overall), the stereogenic centre was introduced by a Noyori asymmetric transfer hydrogenation of 1,3-diarylpropan-1-one **15** (96%, er = 97 : 3).

In the second synthesis (Scheme 6, 8 steps, 61% overall from 3-(3,4,5-trimethoxyphenyl)propanoic acid), 3-TBSOC$_6$H$_4$MgBr added with high diastereoselectivity (dr = 94 : 6) to the (S_S)-N-*tert*-butylsulfinyl imine **27** in 99% yield. The third synthesis (Scheme 7, 8 steps, 33% overall from 3-(3,4,5-trimethoxyphenyl)propanoic acid) exploited a stereospecific 1,2-metallate rearrangment of the *α*-(carbamoyloxy)alkylboronate **34** to construct the stereogenic centre in **17** (73% yield, er = 94 : 6). In the first synthesis, the construction of the propane bridge, installation of the stereogenic centre and the amination reaction were three separate transformations. All three transformations were conflated into a single step in the second synthesis, whereas the third synthesis required two transformations (1,2-metallate rearrangement and amination). Although the *N*-sulfinyl imine route was the most efficient in terms of yield, the first synthesis was the most scalable and four of the six intermediates (**10**, **13**, **14**, **15**) were easily purified by crystallisation.

Experimental

Reactions requiring anhydrous conditions were conducted in flame-dried apparatus under a static atmosphere of nitrogen. Organic extracts were evaporated at 5–20 mm Hg using a rotary evaporator. Samples were freed of remaining traces of solvents under high vacuum (0.1 mmHg). Where appropriate, solvents and reagents were dried by standard methods, *i.e.* distillation from the usual drying agents prior to use: diethyl ether and tetrahydrofuran were distilled from sodium–benzophenone; acetonitrile, pentane, dichloromethane, *N*,*N*-dimethylformamide, toluene were distilled from calcium hydride; diisopropylethylamine, pyridine and triethylamine were distilled from potassium hydroxide; methanol was distilled from magnesium methoxide. Boron trifluoride etherate was distilled from calcium hydride just before use. Alkyllithium and Grignard reagents were titrated against salicylaldehyde phenylhydrazone.[52] All reactions were magnetically stirred and were monitored by thin layer chromatography using Macherey–Nagel Alugram SiO_2 G/UV_{254} pre-coated aluminium foil sheets, layer thickness 0.25 mm. Compounds were visualised by UV irradiation (254 and 366 nm) and 20% (*w*/*v*) phosphomolybdic acid in ethanol. Column chromatography was performed on Fisher Scientific Matrex Silica 60 (35–70 μm). The chiral HPLC columns were purchased from Daicel Chemical Industries Ltd. Optical rotations were recorded on an Optical Activity AA-1000 polarimeter (units in 10^{-1} deg cm^2 g^{-1}). Melting points were measured on a Griffin electrothermal apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer as thin films supported on sodium chloride plates or on a Diffuse Reflectance sampling cell. Absorptions are reported as values in cm^{-1} followed by the relative intensity: s = strong, m = medium, w = weak. ^{1}H and ^{13}C NMR spectra were recorded on Brüker DPX300 or DRX500 Fourier Transform spectrometers using an internal deuterium lock. All spectra were obtained in $CDCl_3$ or CD_3OD solution in 5 mm diameter tubes, and the chemical shift in ppm is quoted relative to the residual signals of chloroform (δ_H 7.26, δ_C 77.4) or methanol (δ_H 3.34, δ_C 49.9) as the internal standard unless otherwise specified. ^{11}B NMR spectra were recorded on a Bruker ARX 250 spectrometer using $BF_3{\cdot}OEt_2$ as an external standard. Multiplicities in the ^{1}H NMR spectra are described as: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad and app = apparent. Coupling constants (*J*) are reported in Hz. Numbers of attached protons in the ^{13}C NMR spectra were revealed by the DEPT spectral editing technique, with secondary pulses at 90 and 135°. Signal assignments were based on COSY, HMQC and HMBC correlations. For ease of identification, all NMR assignments are based on the atom positions shown in structure **A** except for *N*-acetylcolchinol which is based on structure **B**:



Mass spectrometry (MS) was carried out on a VG autospec mass spectrometer, operating at 70 eV, using electron impact ionisation (EI). Electron spray ionisation (ES) was performed on either a Micromass LCT TOF spectrometer or a Waters-Micromass ZMD spectrometer. High resolution mass spectrometry (HRMS) was obtained by peak matching using perfluorokerosene or reserpine as a standard. Ion mass/charge (*m*/*z*) ratios are reported as values in atomic mass units followed, in parenthesis, by the peak intensity relative to the base peak (100%). Mass spectra were recorded on samples judged to be ≥95% pure by ^{1}H and ^{13}C NMR spectroscopy unless otherwise stated. High performance liquid chromatography (HPLC) was performed on a Dionex Autosampler Model ASI-100 with the columns and solvents specified.

(*E*)-1-(3-Hydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (13)

The title compound was prepared by a modification of a literature procedure.[53] To a 5 L flask containing a stirred solution of freshly prepared NaOMe in MeOH (2.0 M, 1.0 L) at 0 °C was added dropwise a solution of 3,4,5-trimethoxybenzaldehyde (100 g, 0.51 mol) and 3-hydroxyacetophenone (69.4 g, 0.51 mol) in dry MeOH (1.0 L) over 1 h. The resulting solution was allowed to stir at ambient temperature for 4 d. The solvent was then removed *in vacuo* and the residue cautiously dissolved in water (1.5 L). The basic aqueous layer (pH 12) was washed with Et_2O (3 × 400 mL), and acidified by addition of conc. HCl until pH 1. The aqueous layer was then extracted with EtOAc (3 × 500 mL), and the combined AcOEt extracts concentrated under reduced pressure. The residual yellow solid was recrystallised from ethanol–water to afford the chalcone **13** (140 g, 0.45 mol, 87%) as a yellow solid: mp 177–178.5 °C, lit.[53] mp 173–174 °C. ^{1}H and ^{13}C NMR spectroscopic data agree with those described by Holt and co-workers.[23]

1-(3-Hydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)propan-1-one (14)

The title compound was prepared by a modification of a literature procedure.[53] A 500 mL round-bottomed flask was charged with chalcone **13** (15.7 g, 50 mmol), platinum(IV) oxide (227 mg,

1.0 mmol) and EtOAc–CH_2Cl_2 (3 : 1, 300 mL). The reaction mixture was degassed 5 times with hydrogen, and stirred under 1 atm of H_2 for 4 h until complete dissolution of the suspension. The reaction mixture was then filtered (celite). The filtrate was concentrated under reduced pressure leaving a white solid that was recrystallised from acetone–hexane to give the title compound (13.5 g, 43 mmol, 85%) as colourless plates: mp 140.5–141.5 °C (lit.[53] mp 140–140.5 °C). ^{1}H and ^{13}C NMR spectroscopic data agree with those described by Holt and co-workers.[23]

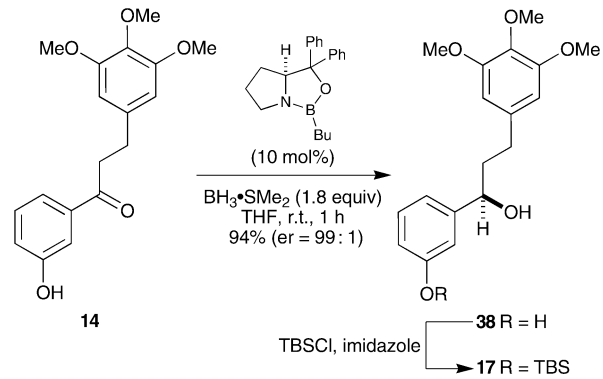
1-[3-(*tert*-Butyldimethylsilyloxy)phenyl]-3-(3,4,5-trimethoxyphenyl)propan-1-one (15)

To a solution of ketone **14** (13.0 g, 41 mmol) and *tert*-butyldimethylsilyl chloride (7.4 g, 49 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added imidazole (7.0 g, 102 mmol) in one portion. The cooling bath was removed and the reaction mixture stirred for 12 h at r.t. Water (200 mL) was added and the aqueous layer extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with 10% aqueous HCl (250 mL), water (250 mL), brine (250 mL) and then dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The solid residue was recrystallised from EtOAc–hexane, affording the title compound (16.5 g, 38 mmol, 93%) as colourless needles: mp 75–76.5 °C. IR (diamond compression system): ν = 2997 m, 2940 s, 1685 s, 1588 s, 1506 s, 1454 s, 1434 s, 1359 s, 1279 s, 1263 m, 1241 s, 1181 m, 1163 m, 1147 m, 1124 s, 1009 s, 976 m, 915 s, 897 s, 835 s, 817 s, 776 s cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.55 (1H, ddd, *J* 7.7, 1.5, 1.1, C6′H), 7.42 (1H, app t, *J* 2.1, C2′H), 7.31 (1H, t, *J* 7.9, C5′H), 7.04 (1H, ddd, *J* 8.1, 2.6, and 1.0, C4′H), 6.46 (2H, s, C2″H and C6″H), 3.84 (6H, s, C3″OCH_3, and C5″OCH_3), 3.82 (3H, s, C4″OCH_3), 3.26 (2H, t, *J* 7.7, C2H_2), 3.01 (2H, t, *J* 7.7, C3H_2), 1.00 (9H, s, C(CH_3)$_3$), 0.22 (6H, s, Si(CH_3)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 199.4 (C=O), 156.4 (C3′), 153.6 (C3″ and C5″), 138.8 (C1′), 137.5 (C4″), 136.7 (C1′), 130.0 (C5′H), 125.3 (C4′H), 121.6 (C6′H), 119.7 (C2′H), 105.7 (C2″H and C6″H), 61.3 (C4O″O*C*H$_3$), 56.5 (C3″O*C*H$_3$ and C5″O*C*H$_3$), 41.1 (C2H_2), 31.1 (C3H_2), 26.0 (C(*C*H$_3$)$_3$), 18.6 (Si*C*), −4.0 (Si(CH_3)$_2$). LRMS (ES): *m*/*z* (%) = 431 (M + H)$^+$ (80), 432 (55), 385 (45), 181 (100). HRMS (ES): *m*/*z* calcd for $C_{24}H_{35}O_5Si$ (M + H)$^+$: 431.2254. Found 431.2265. Anal. calcd for $C_{24}H_{34}O_5Si$: C, 66.94; H, 7.96%. Found: C, 66.75; H, 8.20%.

(*R*)-(+)-1-[3-(*tert*-Butyldimethylsilyloxy)phenyl]-3-(3,4,5-trimethoxyphenyl)propan-1-ol (17) *via* asymmetric hydrogenation

To a suspension of the protected ketone **15** (10.4 g, 24.2 mmol) in *i*PrOH–MeOH (1 : 1) (70 mL, HPLC grade), under argon was added Ru[(1*R*,2*R*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethanediamine]-(η^6-*p*-cymene) (**16**)[28] (145 mg, 0.242 mmol, 1 mol%) in one portion. The solution turns brown after dissolution of the starting material. The reaction mixture was stirred at r.t. for 3 d before removal of the solvent under reduced pressure. The residue was purified by column chromatography (SiO_2, 4 : 1 EtOAc–petrol) to give the title compound (10.0 g, 23.0 mmol, 96%) as a colourless oil. HPLC (Chiralpak AS–RH, particle size 5 µm, 4.6 × 150 mm, MeCN–H_2O) indicated the er = 96 : 4 [t_R 27.1 min (minor); 28.5 min (major)]. $[\alpha]_D$ (24 °C) +14.8 (*c* = 1, $CHCl_3$). IR (neat): ν = 3467 s, 2997 m, 2948 s, 2932 s, 2858 s, 1590 s, 1508 s, 1483 s, 1463 s, 1421 s, 1390 m, 1361 m, 1337 m, 1240 s, 1183 m, 1128 s, 1064 m, 1004 m, 969 m, 839 s, 781 s, 733 m cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.19 (1H, t, *J* 7.9, C5′H), 6.93 (1H, d, *J* 7.7, C6′H), 6.86 (1H, s, C2′H), 6.75 (1H, dd, *J* 8.0 and 2.0, C4′H), 6.39 (2H, s, C2″H and C6″H), 4.63 (1H, app t, *J* 7 and 6, C1H), 3.81 (6H, s, C3″OCH_3 and C5″OCH_3), 3.80 (3H, s, C4″OCH_3), 2.70–2.61 (1H, m, C3H_AH$_B$), 2.62–2.53 (1H, m, C3H$_A$$H_B$), 2,29 (1H, bs, OH), 2.12–2.04 (1H, m, C2H_AH$_B$), 2.03–1.92 (1H, m, C2H$_A$$H_B$), 0.99 (9H, s, C(C$H_3$)$_3$), 0.20 (6H, s, Si(C$H_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 156.2 (C3′), 153.5 (C3″ and C5″), 146.7 (C1′), 138.1 (C1″), 136.4 (C4″), 129.8 (C5′H), 119.6 (C6′H), 119.3 (C4′H), 118.1 (C2′H), 105.7 (C2″H and C6″H), 74.0 (C1H), 61.2 (C4″O*C*H$_3$), 56.4 (C3″O*C*H$_3$, and C5″O*C*H$_3$), 40.9 (C2H_2), 32.8 (C3H_2), 26.1 (C(*C*H$_3$)$_3$), 18.6 (Si*C*), −4.3 (Si(CH_3)$_2$). LRMS (ES): *m*/*z* (%) = 455 (M + Na)$^+$ (40), 176 (45), 207 (85), 181 (100). HRMS (ES): *m*/*z* calcd for $C_{24}H_{36}O_5SiNa$ (M + Na)$^+$ 455.2230; found: 455.2219.

An alternative synthesis of **17** is summarised in Scheme 9. Reduction of the ketone **14** using the Corey–Bakshi–Shibata procedure[26] gave the diol **36** in 94% yield (er = 99 : 1). Diol **36** could be obtained enantiopure by recrystallisation. Selective protection of the phenolic hydroxyl then gave **17**.



Scheme 9

(*R*)-(+)-3-[1-Hydroxy-3-(3,4,5-trimethoxyphenyl)propyl]phenol (36)

A 5 mL flame-dried round-bottomed flask was charged with (*S*)-tetrahydro-1-butyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*]-[1,3,2]oxazaborole[54,55] (446 µL of a 0.2 M solution in toluene, 89.2 µmol) under nitrogen. A stoichiometric amount of BH_3·Me_2S (138 µL of a 0.65 M solution in THF) was added. Then separate solutions of ketone **14** (0.282 g, 0.89 mmol, azeotropically dried with benzene) in dry THF (1.6 mL) and BH_3·Me_2S (1.0 M, 1.6 mL) were then added simultaneously to the solution of the oxazaborolidine catalyst over 1 h. After the addition was complete, the reaction mixture was stirred for an additional 20 min, before the cautious addition of MeOH (3 mL), followed by 10% HCl aq. solution (2 mL). The reaction was first extracted with CH_2Cl_2 (5 mL) and then with EtOAc (4 × 5 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. HPLC analysis on the crude mixture (Chiralpak AS–RH, HPLC, particle size 5 µm, 4.6 × 150 mm, 5% 2-propanol in hexanes, 1 mL min^{-1}, λ = 210 nm) showed an er = 99 : 1; t_R: 119.9 min for the minor isomer;

130.1 min for the major isomer. An analytical sample was prepared by filtration through a pad of silica gel (6 : 1, hexanes–EtOAc → EtOAc), followed by recrystallisation from acetone–hexanes afforded the title compound (0.268 g, 0.84 mmol, 94%) as white plates: mp 123–125 °C (acetone–hexanes). $[\alpha]_D$ (26 °C) +13.8 (c = 1, acetone). IR (neat): ν = 3510 m, 3462 s, 3252 s, 2994 m, 2950 s, 2934 s, 2829 m, 1591 s, 1508 m, 1458 s, 1420 m, 1327 m, 1240 s, 1121 s, 1060 m, 1002 m, 880 m, 826 m, 779 m, 705 m cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.18 (1H, m app t, J 7.7, C5′H), 6.87–6.84 (2H, m, C4′H, C2′H), 6.75 (1H, d, J 7.7, C6′H), 6.38 (2H, s, C2″H and C6″H), 6.26 (1H, bs, ArOH), 4.63 (1H, m, C1H), 3.81 (6H, s, C3″OCH_3 and C5″OCH_3), 3.80 (3H, s, C4″OCH_3), 2.70–2.64 (1H, m, C3H_AH$_B$), 2.61–2.55 (1H, m, C3H$_A$$H_B$), 2.47 (1H, bs, OH), 2.09–2.06 (1H, m, C2H_AH$_B$), 2.02–1.93 (1H, m, C2H$_A$$H_B$). ^{13}C NMR (75 MHz, CD_3OD): δ_C = 158.8 (C1′), 154.6 (C3″ and C5″), 148.2 (C3′), 140.2 (C1″), 137.3 (C4″), 130.6 (C5′H), 118.6 (C4′H), 115.4 (C2′H), 114.2 (C6′H), 106.9 (C2″H and C6″H), 74.6 (C1H), 61.4 (C4″OCH_3), 56.8 (C3″OCH_3 and C5″OCH_3), 42.3 (C2H$_2$), 33.8 (C3H$_2$). LRMS (ES$^+$): m/z = 341 (M + Na)$^+$ (100%), 181 (95), 207 (80), 342 (30). HRMS (ES+): m/z calcd for $C_{18}H_{22}O_5Na$: 341.1365; found: 341.1380. Anal. calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 67.7; H, 6.9%.

Selective protection of the phenol 36 to give 17

To a solution of phenol **36** (0.076 g, 0.24 mmol) in CH_2Cl_2 (5 mL), imidazole (0.041 g, 0.60 mmol) and TBSCl (0.036 g, 0.024 mmol) were added. The solution was stirred at r.t. for 12 h, then poured into water (10 mL) and extracted with Et_2O (2 × 10 mL). The combined extracts were dried (Na_2SO_4), concentrated and the crude product purified by column chromatography (SiO_2, hexanes–Et_2O) to give the TBS ether **17** (0.066 g, 0.153 mmol, 63%) as a colourless oil and recovered phenol **36** (0.014 g, 0.044 mmol, 18%). The yield based on recovered starting material was 81%. Chiral HPLC of **36** revealed an er = 96 : 4. The ^{1}H and ^{13}C NMR were identical to those reported above.

(*S*)-(−)-1-Azido-[3-(*tert*-butyldimethylsilyloxy)phenyl]-3-(3,4,5-trimethoxyphenyl)propane (18). A solution of the alcohol **17** (9.1 g, 21.1 mmol) in CH_2Cl_2 (40 mL) was cooled to 0 °C in an ice/salt bath. Triethylamine (4.4 mL, 31.6 mmol) was added followed by methanesulfonyl chloride (2.0 mL, 25.3 mmol). After stirring for 30 min with ice/salt bath cooling, the reaction was quenched with ice cold water (40 mL). The organic layer was separated and washed successively with cold aqueous HCl (10%, 2 × 15 mL), saturated aqueous $NaHCO_3$ (2 × 15 mL) and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the unstable mesylate (10.5 g, 98%) as a pale yellow oil which was used directly in the next step. A sample gave ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.31 (1H, t, J 7.9, C5′H), 7.02 (1H, d, J 7.7, C6′H), 6.91 (2H, m, C2′H and C4′H), 6.45 (2H, s, C2″H and C6″H), 5.50 (1H, dd, J 8.5 and 5.1, C1H), 3.89 (6H, s, C3″OCH_3 and C5″OCH_3), 3.87 (3H, s, C4″OCH_3), 2.80–2.68 (2H, m, C3H$_2$), 2.67 (3H, s, OMs), 2.45 (1H, m, C2H_AH$_B$), 2.18 (1H, m, C2H$_A$$H_B$), 1.03 (9H, s, C(CH$_3$)$_3$), 0.25 (6H, s, Si(CH$_3$)$_2$).

To a solution of the crude mesylate (10.5 g) in anhydrous DMF (70 mL) was added NaN_3 (4.1 g, 63.2 mmol) in one portion. After stirring at r.t. for 18 h, the solvent was evaporated under reduced pressure (oil pump) and the residue partitioned between EtOAc (60 mL) and water (40 mL). The organic layer was separated and washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was then purified by column chromatography (SiO_2, 4 : 1 hexanes–Et_2O) to give the title compound (8.7 g, 19.0 mmol, 90%) as a colourless oil: $[\alpha]_D$ (25 °C) −58.1 (c = 1, $CHCl_3$). IR ($CHCl_3$): ν = 2955 s, 2931 s, 2858 m, 2096 s, 1589 s, 1508 m, 1484 m, 1462 m, 1421 m, 1278 s, 1239 s, 1152 m, 1129 s, 1003 m, 965 m, 839 s, 782 s cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.25 (1H, t, J 7.7, C5′H), 6.90 (1H, d, J 7.7, C6′H), 6.81 (2H, m, C2′H and C4′H), 6.37 (2H, s, C2″H and C6″H), 4.36 (1H, dd, J 7.7 and 6.4, C1H), 3.85 (6H, s, C3″OCH_3 and C5″OCH_3), 3.83 (3H, s, C4″OCH_3), 2.71–2.52 (2H, m, C3H$_2$), 2.17–1.95 (2H, m, C2H$_2$), 1.00 (9H, s, C(CH$_3$)$_3$), 0.21 (6H, s, Si(CH$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 156.5 (C3′), 153.6 (C3″ and C5″), 141.3 (C1′), 137.1 (C4″), 136.6 (C1″), 130.2 (C5′H), 120.4 (C6′H), 119.1 (C2′H and C4′H), 105.6 (C2″H and C6″H), 65.6 (C1H), 61.3 (C4″O*C*H$_3$), 56.5 (C3″O*C*H$_3$ and C5″O*C*H$_3$), 38.1 (C2H$_2$), 33.2 (C3H$_2$), 26.1 (C(*C*H$_3$)$_3$), 18.6 (Si*C*), −4.0 (Si(CH$_3$)$_2$). LRMS (ES): m/z (%) = 480 (M + Na)$^+$ (50), 481 (10), 415 (65), 207 (100). HRMS (ES): m/z calcd for $C_{24}H_{35}N_3O_4SiNa$ (M + Na)$^+$: 480.2295; found: 480.2294.

(*S*)-(−)-*N*-[1-[3-(*tert*-Butyldimethylsilyloxy)phenyl)]-3-(3,4,5-trimethoxyphenyl)propyl] acetamide (10). To a solution of the azide **18** (9.0 g, 19.7 mmol) in MeOH (40 mL) and dioxane (40 mL), pyridine (1.6 mL, 19.7 mmol) was added followed by $Pd(OH)_2$ (0.14 g, 5 mol%). The resulting suspension was flushed with H_2 and stirred for 51 h at r.t. under 1 atm of H_2 (balloon). The suspension was filtered through celite and concentrated under reduced pressure to afford the crude amine as a dark brown oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.15 (1H, t, J 7.7, C5′H), 7.02 (1H, d, J 7.7, C6′H), 6.83 (1H, s, C2′H), 6.77 (1H, dd, J 8.0 and 2.0, C4′H), 6.33 (2H, s, C2″H and C6″H), 3.96 (1H, m, C1H), 3.82 (6H, s, C3″OCH_3 and C5″OCH_3), 3.80 (3H, s, C4″OCH_3), 2.37–2.30 (1H, m, C3H_AH$_B$), 2.28–2.21 (1H, m, C3H$_A$$H_B$), 2.16–2.08 (1H, m, C2$H_AH_B$), 2.02–1.93 (1H, m, C2H$_A$$H_B$), 0.96 (9H, s, C(CH$_3$)$_3$), 0.18 (6H, s, Si(CH$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 156.1 (C3′), 153.1 (C3″ and C5″), 147.9 (C1′), 137.8 (C1″), 136.0 (C4″), 129.5 (C5′H), 120.6 (C6′H), 119.5 (C2′H), 118.1 (C4′H), 105.2 (C2″H and C6″H), 60.9 (C4″O*C*H$_3$), 56.0 (C3″O*C*H$_3$ and C5″O*C*H$_3$), 55.7 (C1H), 41.0 (C2H$_2$), 33.2 (C3H$_2$), 25.7 (Si(CH$_3$)$_3$), 18.2 (Si*C*), −4.3 (Si(CH$_3$)$_2$).

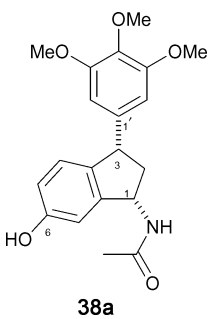
Reduction of the azide **18** to the corresponding amine was also accomplished by the following procedure. A 250 mL flask equipped with a nitrogen outlet, was charged with azide **18** (3.0 g, 6.55 mmol), zinc dust (17.0 g, 262 mmol), ammonium chloride (14.0 g, 262 mmol) and methanol (130 mL). The mixture was vigorously stirred at r.t. for 24 h. The mixture was filtered and the residual solid was washed thoroughly with methanol. The combined filtrate and washes were concentrated under reduced pressure. The residue was treated with aq. NaOH (1 M, 100 mL), and extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude amine (2.51 g, 5.81 mmol, 89%) as a yellow oil.

To a solution of the crude amine in CH_2Cl_2 (40 mL) and pyridine (40 mL) was added a few crystals of DMAP. The mixture was cooled to 0 °C and Ac_2O (6.0 g, 59.1 mmol, 3 equiv.)) was

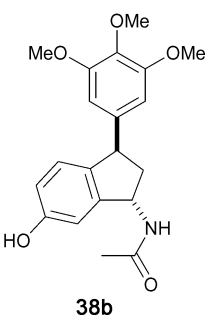
added dropwise. The reaction mixture was then stirred at r.t. for 48 h. EtOAc (100 mL) was added and the solution was washed with saturated copper(II) sulfate solution (3 × 50 mL), saturated $NaHCO_3$ solution (3 × 50 mL), water (2 × 50 mL) and brine. The organic layer was dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a pale yellow solid. Recrystallisation from EtOAc–hexane afforded the title compound (6.4 g, 13.5 mmol, 69%) as colourless plates, mp 106–108 °C. The er (99.8 : 0.2) was determined by HPLC (Chiralgel OD–RH, particle size 5 μm, 4.6 × 150 mm, MeCN–H_2O) t_R 22.9 min (minor); 24.2 min (major). $[\alpha]_D$ (25 °C) −42 (c = 1, $CHCl_3$). The mother liquor was concentrated under reduced pressure and recrystallisation of the residue afforded a second crop of the title compound (1.5 g, 3.2 mmol, 16%). The er of the second crop was 97.5 : 2.5. IR ($CHCl_3$): ν = 3282 m, 3006 s, 2932 s, 2858 s, 1651 s, 1590 s, 1544 m, 1508 s, 1485 m, 1463 s, 1422 m, 1278 s, 1240 s, 1151 m, 1129 s, 1003 m, 840 m, 781 m, 756 s cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H = 7.21 (1H, t, J 7.7, C5′H), 6.89 (1H, d, J 7.7, C6′H), 6.77 (2H, m, C2′H and C4′H), 6.36 (2H, s, C2″H and C6″H), 5.73 (1H, d, J 7.9, NH), 4.97 (1H, dd, J 15.6 and 7.4, C1H), 3.83 (6H, s, C3″OCH_3 and C5″OCH_3), 3.81 (3H, s, C4″OCH_3), 2.61–2.46 (2H, m, C3H_2), 2.21–2.13 (1H, m, C2H_AH$_B$), 2.09–2.01 (1H, m, C2H$_A$$H_B$), 1.97 (3H, s, O=C–C$H_3$), 0.98 (9H, s, C(C$H_3$)$_3$), 0.20 (6H, s, Si(C$H_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 169.6 (C=O), 156.1 (C3′), 153.5 (C3″ and C5″), 143.7 (C1′), 137.6 (C4″), 136.4 (C1″), 130.1 (C5′H), 120.0 (C6′H), 119.5 (C2′H), 119.0 (C4′H), 105.5 (C2″H and C6″H), 61.3 (C4″OCH_3), 56.4 (C3″OCH_3 and C5″OCH_3), 53.6 (C1H), 37.9 (C2H_2), 33.6 (C3H_2), 26.1 (C(CH_3)$_3$), 23.7 (O=C–CH_3), 18.3 (SiC), −4.0 (Si(CH_3)$_2$). LRMS (ES): m/z (%) = 474 (M + H)$^+$ (90), 475 (40), 496 (M + Na)$^+$ (40), 415 (100). HRMS (ES): m/z calcd for $C_{26}H_{40}NO_5Si$: 474.2676; found: 474.2668. Anal. calcd for $C_{26}H_{39}NO_5Si$: C, 65.93; H, 8.30; N, 2.96%. Found: C, 66.75; H, 8.45; N, 2.95%.

(*S*)-(−)-*N*-(3-Hydroxy-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-5-yl)-acetamide [(−)-*N*-acetylcolchinol] (2). A 50 mL flame-dried two-neck flask equipped with a stirring bar, nitrogen inlet and an immersion thermometer was charged with phenyliodonium bis(trifluoroacetate) (1.1 g, 2.5 mmol) and CH_2Cl_2 (45 mL). TFA (20 mL) and TFAA (5 mL) were added and the mixture was cooled to −4 °C (ice/salt bath). To the colourless solution was added a solution of the acetamide **10** (1.0 g, 2.1 mmol) in CH_2Cl_2 (5 mL) followed immediately by $BF_3{\cdot}OEt_2$ (0.64 mL, 5.0 mmol). The reaction mixture turned yellow on addition of the acetamide and then from yellow to green and to dark brown on addition of $BF_3{\cdot}OEt_2$. The reaction mixture was removed from the ice/salt bath and allowed to warm to r.t. After 4 h at r.t., saturated $NaHCO_3$ solution was added portionwise to the resulting dark brown solution at 0 °C. The organic layer was separated and the aqueous layer extracted several times with CH_2Cl_2. The extracts were combined, washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The brown residue was purified by column chromatography (SiO_2, EtOAc) to afford the title compound (0.375 g, 1.05 mmol, 50%) as an off-white fluffy solid. Recrystallisation from MeOH–H_2O afforded white prisms: mp 209–212 °C; lit.[14] mp: 213–215 °C. The ^1H NMR spectra recorded in $CDCl_3$ revealed three components presumed to be atropisomers/rotamers. ^1H NMR (500 MHz, $CDCl_3$): Isomer 1 (*ca.* 45%) δ_H = 7.52 (1H, bs, OH), 7.35 (1H, d, J 8.2, C1H), 6.80 (1H, d, J 2.8, C4H), 6.77 (1H, dd, J 2.5, 10.7, C2H), 6.57 (1H, s, C8H), 5.96 (1H, d, J 7.7, NH), 4.78 (1H, m, C5H), 3.94 (3H, s, C9OCH_3), 3.90 (3H, s, C10OCH_3), 3.53 (3H, s, C11OCH_3), 2.44–2.33 (4H, m, C6H, C7H), 2.01 (3H, s, (O=C–CH_3). Isomer 2 (*ca.* 40%): δ_H = 8.4 (1H, bs, OH), 7.37 (1H, d, J 8.4, C1H), 6.83 (1H, dd, J 2.6, 8.3, C2H), 6.81 (1H, d, J 2.8, C4H), 6.66 (1H, s, C8H), 5.40 (1H, d, J 8.8, NH), 5.05 (1H, m, C5H), 3.93 (3H, s, C10OCH_3), 3.93 (3H, s, C9OCH_3), 3.61 (3H, s, C11OCH_3), 2.57–2.50 (2H, m, C7H_2), 2.18–2.12 (1H, m, C6H_AH$_B$), 1.82–1.79 (1H, m, C6H$_A$$H_B$), 1.64 (3H, s, O=C–C$H_3$). Isomer 3 (*ca.* 15%): 8.65 (1H, bs, OH), 6.60 (1H, s, C8H), 6.18 (1H, d, J 2.8, NH), 4.26 (1H, m, C5H), 3.92 (3H, s, C9OCH_3), 3.57 (3H, s, C11OCH_3), 1.73 (3H, s, O=C–CH_3). The ^1H and ^{13}C NMR spectra recorded in CD_3OD revealed a single isomer. ^1H NMR (500 MHz, CD_3OD): δ_H = 7.26 (1H, d, J 8.1, C1H), 6.81 (1H, d, J 2.6, C4H), 6.75 (1H, dd, J 8.3 and 2.6, C2H), 6.73 (1H, s, C8H), 4.64 (1H, dd, J 12.2 and 6.4, C5H), 3.90 (3H, s, C9OCH_3), 3.88 (3H, s, C10OCH_3), 3.51 (3H, s, C11OCH_3), 2.53–2.51 (1H, m, C6H_AH$_B$), 2.29–2.27 (2H, m, C7H_2), 2.03 (3H, s, O=C–CH_3), 1.99–1.93 (1H, m, C6H$_A$$H_B$). ^{13}C NMR (125 MHz, CD_3OD): δ_C = 172.7 (C=O), 158.2 (C3), 154.0 (C9), 152.4 (C11), 142.7, 142.6 (C10, C4a), 136.9 (C7a), 132.4 (C1H), 127.0 (C11b), 126.8 (C11a), 114.4 (C2H), 111.1 (C4H), 109.3 (C8H), 61.9 (C10OCH_3), 61.6 (C11OCH_3), 56.9 (C9OCH_3), 50.8 (C5H), 40.1 (C6H_2), 31.8 (C7H_2), 22.9 (O=C–CH_3). LRMS (ES): m/z (%) = 380 (M + Na)$^+$ (70), 358 (M + H)$^+$ (65), 300 (30), 299 (100). HRMS (ES): m/z calcd for $C_{20}H_{23}NO_5Na$ (M + Na)$^+$: 380.1474; found: 380.1465. The ^1H and ^{13}C NMR spectra of synthetic **2** recorded at 500 and 125 MHz, respectively, were identical to those recorded on an authentic sample of (−)-*N*-acetylcolchinol derived from degradation of colchicine.[14] For a discussion of the conformational analysis of colchinoids by NMR spectroscopy see the review by Boyé and Brossi.[56]

When the forgoing experiment was repeated on the same scale using TBSOTf to activate the PIFA instead of $BF_3{\cdot}OEt_2$, *N*-acetylcolchinol was obtained in similar yield but it was contaminated by a coloured impurity along with several minor products that were difficult to separate by chromatography. Two of these minor products (*ca.* 5% each estimated by NMR spectroscopic analysis of the crude reaction mixture) were identified as the indane derivatves **38a** and **38b**. Indane **38a** was slightly less polar than *N*-acetylcolchinol and could be separated by column chromatography. The more polar product **38b** co-eluted with *N*-acetylcolchinol and was separated by HPLC.



38a



38b

***N*-[(1*S*,3*S*)-6-Hydroxy-3-(3,4,5-trimethoxyphenyl)]-2,3-dihydro-1*H*-inden-1-yl)acetamide (38a).** Pale yellow solid, mp 111–112 °C (MeOH–H_2O). $[\alpha]_D$ (22 °C) −80 (c = 0.5, MeOH). IR

(diamond compression system): $\nu = 3334$ br s, 2939 s, 2840, 2480 m, 1629 s, 1589 s, 1415 s, 1344 s, 1230s, 1122 s, 994 s cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD): $\delta_H = 6.73$ (1H, d, J 8.4, C4H), 6.72 (1H, dd, J 1.9, 0.7, C7H), 6.68 (1H, ddd, J 8.2, 2.4, 0.8, C5H), 6.56 (2H, s, C2′H and C6′H), 5.37 (1H, dd, J 9.1, 7.8, C1H), 4.14 (1H, dd, J 10.3, 7.3, C3H), 3.80 (6H, s, C3′OCH_3 and C5′OCH_3), 3.78 (3H, s C4′OCH_3), 2.90 (1H, td, J 12.4, 7.3, C2H_AH$_B$), 2.07 (3H, s, CH_3C=O), 1.85 (1H, dt, J 12.3, 10.1, C2H$_A$$H_B$). ^{13}C NMR (75 MHz, CD_3OD): $\delta_C = 174.1$ (C=O), 159.0 (C), 155.4 (C3′ and C5′), 147.2 (C), 143.2 (C), 138.7 (C), 138.5 (C), 127.5 (CH), 117.1 (CH), 111.8 (CH), 107.3 (C2′H and C6′H), 62.0 (C4′OCH_3), 57.4 (C3′OCH_3 and C5′OCH_3), 55.2 (C1H), 50.2 (C3H), 46.7 ($C2H_2$), 23.6 (CH_3C=O). HRMS (ES): m/z calcd for $C_{20}H_{24}NO_5$ $(M + H)^+$: 358.1649. Found: 358.1655.

The stereochemistry of **38a** was assigned on the basis of NOE enhancements observed by irradiating first C1H (2.3% enhancement of C3H) and then C3H (3.3% enhancement of C1H). No NOE enhancement was observed in the case of the same NMR experiment carried out with **38b**.

***N*-[(1*S*,3*R*)-6-Hydroxy-3-(3,4,5-trimethoxyphenyl)]-2,3-dihydro-1*H*-inden-1-yl)acetamide (38b).** Pale yellow solid, mp 106–107 °C (H_2O). $[\alpha]_D$ (22 °C) −59 ($c = 0.3$, MeOH). IR (diamond compression system): $\nu = 3307$ br s, 2939 s, 2829 s, 2480 m, 1629 m, 1587 s, 1539 m, 1500 s, 1451 s, 1418 s, 1330 m, 1231 m, 1122 s, 995 m cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD): $\delta_H = 6.89$ (1H, d, J 8.2, C4H), 6.81 (1H, d, J 2.3, C7H), 6.73 (1H, ddd, J 8.2, 2.4, 0.5, C5H), 6.42 (2H, s, C2′H and C6′H), 5.45 (1H, t, J 6.3, C1H), 4.44 (1H, t, J 6.9, C3H), 3.78 (6H, s, C3′OCH_3 and C5′OCH_3), 3.76 (3H, s, C4′OCH_3), 2.41 (2H, dd, J 6.8, 6.5, $C2H_2$), 2.01 (3H, s, CH_3C=O). HRMS (ES): m/z calcd for $C_{20}H_{24}NO_5$ $(M + H)^+$: 358.1649. Found: 358.1650.

3-(3,4,5-Trimethoxyphenyl)propanal (26). To a solution of 3-(3,4,5-trimethoxyphenyl)propionic acid (7.2 g, 30 mmol) in dry THF (35 mL) was added dropwise at 0 °C BH_3·THF (33 mL of 1 M solution in THF, 33 mmol). The reaction mixture was stirred at r.t. for 21 h before the cautious addition of water–THF (1 : 1, 40 mL) at 0 °C. Potassium hydroxide pellets (5 g, 90 mmol) were added and the solvent removed *in vacuo.* The aqueous layer was then extracted with Et_2O (4 × 30 mL), the ethereal extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo.* The residue was purified by Kugelrohr distillation (bp 142 °C, 0.05 mm Hg; lit.[57] bp 136–139 °C, 0.3 mm Hg) to give the corresponding alcohol (6.72 g, 29.7 mmol, 98%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta_H = 6.39$ (2H, s, C2″H, C6″H), 3.81 (6H, s, C3″OCH_3 and C5″OCH_3), 3.79 (3H, s, C4″OCH_3), 3.66–3.63 (2H, m, $C1H_2$), 2.63–2.60 (2H, m, $C3H_2$), 2.13 (1H, bs, OH), 1.88–1.82 (2H, m, $C2H_2$). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta_C = 153.2$ (C3″ and C5″), 138.0 (C1″), 136.0 (C4″), 105.3 (C2″H and C6″H), 62.1 ($C1H_2$), 61.0 (C4″OCH_3), 56.1 (C3″OCH_3 and C5″OCH_3), 34.4 ($C2H_2$), 32.7 ($C3H_2$). This procedure is more convenient than the reduction with lithium aluminium hydride (88%) reported by Rapoport and Campion.[57]

To a solution of 3-(3,4,5-trimethoxyphenyl)propan-1-ol (4.52 g, 20.0 mmol) in CH_2Cl_2 (160 mL) at 0 °C was added freshly prepared Dess–Martin periodinane[58] (10.17 g, 24.0 mmol) in one portion. The reaction mixture was stirred at r.t. for 3 h before the addition of sat. $Na_2S_2O_3$ aq. solution (100 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were then washed with sat. $NaHCO_3$ aq. solution (4 × 100 mL), brine (2 × 100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo.* The residue was purified by column chromatography on silica gel (1 : 1, hexanes–Et_2O) followed by Kugelrohr distillation (bp 160 °C, 0.05 mm Hg; lit.[59] bp 173–176 °C, 666.6 Pa) to give the title compound (4.03 g, 18.0 mmol, 90%) as a yellow oil which was used immediately in the following step. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta_H = 9.75$ (1H, m, C1H), 6.36 (2H, s, C2″H, C6″H), 3.79 (6H, s, C3″OCH_3 and C5″OCH_3), 3.76 (3H, s, C4″OCH_3), 2.86–2.82 (2H, m, $C3H_2$), 2.74–2.70 (2H, m, $C2H_2$). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta_C = 201.7$ (C1H), 153.4, 153.2 (C3″, C4″, C5″), 136.4 (C1″), 105.3 (C2″H and C6″H), 60.9 (C4″OCH_3), 56.2 (C3″OCH_3 and C5″OCH_3), 45.5 ($C2H_2$), 28.6 ($C3H_2$). This procedure was more efficient and reproducible on a larger scale than the procedure of Müller and co-workers using pyridinium chlorochromate.[59] Oxidation with TEMPO (10 mol%) was slow and gave a 63% yield of the aldehyde at best.

(S_S,E)-(+)-2-Methyl-*N*-[3-(3,4,5-trimethoxyphenyl)propylidene]propane-2-sulfinamide (27). To a solution of (S_S)-2-methyl-2-propanesulfinamide[44] (500 mg, 4.12 mmol) in dry CH_2Cl_2 (7 mL) was added pyridinium *p*-toluenesulfonate (50 mg, 0.2 mmol) and anhydrous $MgSO_4$ (2.4 g, 0.2 mol), followed by aldehyde **26** (1.79 g, 8.0 mmol). The mixture was stirred at r.t. for 24 h. $MgSO_4$ was filtered through a pad of celite and thoroughly washed with CH_2Cl_2. The combined filtrate and washes were concentrated and the residue chromatographed on silica gel (1 : 1, hexanes–Et_2O, 0.5% v/v Et_3N) to afford the title compound (1.26 g, 3.7 mmol, 90%) as a yellow oil: $[\alpha]_D$ (22 °C) +137.8 ($c = 1.93$, $CHCl_3$). IR (neat): $\nu = 2958$ s, 2838 s, 1723 m, 1622 s, 1590 s, 1508 s, 1456 s, 1422 s, 1362 m, 1342 m, 1332 m, 1239 s, 1184 m, 1152 m, 1128 s, 1086 s, 1011 s, 823 m cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta_H = 8.09$ (1H, t, J 4.3, C1H), 6.39 (2H, s, C2″H and C6″H), 3.81 (6H, s, C3″OCH_3), C5″OCH_3), 3.78 (3H, s, C4″OCH_3), 2.92–2.87 (2H, m, $C3H_2$), 2.85–2.80 (2H, m, $C2H_2$), 1.10 (9H, s, $C(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta_C = 168.3$ (C1H), 153.1 (C3″, C5″), 136.2 (C1″), 135.9 (C4″), 105.1 (C2″H and C6″H), 60.7 ($C(CH_3)_3$), 56.4 (C4″OCH_3), 55.9 (C3″OCH_3 and C5″OCH_3), 37.4 ($C3H_2$), 31.7 ($C2H_2$), 22.1 C(CH_3)$_3$). LRMS (ES+): $m/z = 350$ $(M + Na)^+$ (40%), 382 (15), 206 (100). Anal. calcd for $C_{16}H_{25}NO_4S$: C 58.69, H 7.70, N 4.28, S 9.79; found: C 58.85, H 7.75, N 4.35, S 9.8.

(S_S)-*N*-[(*S*)-1-[3-(*tert*-Butyldimethylsilyloxy)phenyl]-3-(3,4,5-trimethoxyphenyl)propyl]-2-methylpropane-2-sulfinamide (29). To a solution of (S_S)-(+)-**27** (327 mg, 1.0 mmol) in dry CH_2Cl_2 (6 mL) was added the Grignard reagent prepared from (3-bromophenoxy)-*tert*-butyldimethylsilane[60] (1.3 mL of a 1.64 M solution in Et_2O, 2 mmol) at −65 °C, over 5 min. The reaction was allowed to warm to r.t. over 24 h and then quenched by addition of sat. NH_4Cl aq. solution (2 mL). The layers were separated, the aqueous layer was extracted with Et_2O (4 × 2 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified by column chromatography on silica gel (1 : 4, hexanes–Et_2O → Et_2O) to afford the title compound (531 mg, 0.99 mmol, 99%) as a viscous yellow oil (94 : 6 mixture of diastereoisomers determined by integration of the signals of the aromatic protons at 6.19 and 6.38 ppm in the ^{1}H NMR spectrum of the crude mixture). IR ($CHCl_3$): $\nu = 2957$ s, 2932 s, 2902 m, 2860 m, 1590 s, 1508 s, 1484 s,

1463 s, 1421 m, 1277 s, 1252 s, 1239 s, 1150 m, 1129 s, 1059 m, 1004 m, 909 s, 839 s, 782 m cm^{-1}. LRMS (ES+): m/z = 536 $(M + H)^+$ (80%), 537 (50), 430 (70), 415 (100). HRMS (ES+): m/z calcd for $C_{28}H_{46}NO_5{}^{28}Si^{32}S$: 536.2866; found: 536.2845. Major diastereoisomer (S_S,S)-**29**: R_f 0.3 (Et_2O). $[a]_D$ (21 °C) +33.4 (c = 1.38, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ_H = 7.10 (1H, m app t, J 7.7, C5′H), 6.81 (1H, d, J 7.7, C6′H), 6.80–6.65 (2H, m, C2′H, C4′H), 6.19 (2H, s, C2″H and C6″H), 4.23 (1H, m, C1H), 3.73 (6H, s, C3″OCH_3 and C5″OCH_3), 3.69 (3H, s, C4″OCH_3), 3.36 (1H, bd, J 3.1, NH), 2.46–2.25 (3H, m, C2$H_A$$H_B$, $C3H_2$), 2.05–1.85 (1H, m, C2$H_A$$H_B$), 1.29 (9H, s, $SC(CH_3)_3$), 1.10 (9H, s, $C(CH_3)_3$), 0.86 (6H, s, $Si(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 155.4 (C3′), 152.6 (C3″ and C5″), 143.1 (C1′), 136.7 (C1″), 135.5 (C4″), 129.3 (C5′H), 119.9 (C6′H), 119.2 (C4′H), 118.4 (C2′H), 104.6 (C2″H and C6″H), 60.2 (C4″OCH_3), 57.5 (C1H), 55.5 (C3″OCH_3 and C5″OCH_3), 55.1 ($SC(CH_3)_3$), 37.6 ($C2H_2$), 31.8 ($C3H_2$), 25.2 ($C(CH_3)_3$), 22.1 ($SiC(CH_3)_3$), 17.7 (Si*C*), −4.9 ($Si(CH_3)_2$). Minor diastereoisomer (S_S,*R*)-**29**: R_f 0.17 (Et_2O). $[a]_D$ (20 °C) +48 (c = 0.6, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ_H = 7.24 (1H, app t, J 6.7, C5′H), 6.93 (1H, d, J 7.7, C6′H), 6.82 (2H, d, J 6.7, C2′H and C4′H), 6.38 (2H, s, C2″H and C6″H), 4.39 (1H, m, C1H), 3.87 (6H, s, C3″OCH_3 and C5″OCH_3), 3.84 (3H, s, C4″OCH_3), 3.42 (1H, bd, J 3.1, NH), 2.57–2.50 (2H, m, $C3H_2$), 2.30–2.15 (2H, m, $C2H_2$), 1.17 (9H, s, $SC(CH_3)_3$), 1.01 (9H, s, $SiC(CH_3)_3$), 0.22 (6H, s, $Si(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 155.9 (C3′), 153.2 (C3″ and C5″), 143.3 (C1′), 136.9 (C1″), 129.5 (C5′H), 120.8 (C6′H), 119.4 (C4′H), 119.2 (C2′H), 105.2 (C2″H and C6″H), 60.8 (C4″O*C*H_3), 59.0 (C1H), 56.1 (C3″O*C*H_3 and C5″O*C*H_3), 55.5 ($SC(CH_3)_3$), 40.2 ($C2H_2$), 32.8 ($C3H_2$), 25.6 ($SC(CH_3)_3$), 22.6 ($SiC(CH_3)_3$), 18.2 (Si*C*), −4.4 ($Si(CH_3)_2$). The C4″ signal could not be located.

The reaction described above was also performed using (R_S)-(−)-**27** and a single crystal X-ray analysis† established the absolute configuration of the sulfinamide product (R_S,*R*)-**29** (Fig. 1). $C_{22}H_{31}NO_5S$, CH_2Cl_2, orthorhombic, space group $P2_12_12_1$, a = 9.7734(11)Å, b = 13.3223(16) Å, c = 20.380(2) Å, V = 2653.5(5) Å^3, Z = 4, ρ_{calc} = 1.268 mg m^{-3}, μ = 0.355 mm^{-1}, crystal size: 0.18 × 0.12 × 0.04 mm, data collection range: 2.31 ≤ θ ≤ 23.09°, 100306 measured reflections, final $R(wR)$ values: 0.0545, (0.1448) for 5205 independent data and 297 parameters [$I > 2\sigma(I)$], largest residual peak and hole: 0.802, −0.629 e Å^{-3}. The structure solved in spacegroup $P2_12_12_1$ and the asymmetric unit contains one molecule of the title compound and one molecule of dichloromethane. Hydrogen atoms, H(31) and H(8), attached to N(31) and O(8) respectively, were found from the Fourier difference map and H(31) was found to be positioned pyramidally. Both the position and thermal parameters of H(31) and H(8) were allowed to freely refine resulting in a N–H distance of N(31)–H(31), 0.82 Å and an O–H distance of O(8)–H(8), 0.79 Å. All other hydrogen atoms were positioned geometrically with the following carbon–hydrogen distances: methyl, 0.98 Å; methylene, 0.99 Å; methine, 1.00 Å; aromatic C–H, 0.95 Å. All carbon Uiso(H) values were constrained to be 1.2 times Ueq of the parent atom. The absolute configuration was established since the molecule contained a chiral reference of known absolute configuration and

† CCDC reference numbers 601950–601951. For crystallographic data in CIF format see DOI: 10.1039/b603857c

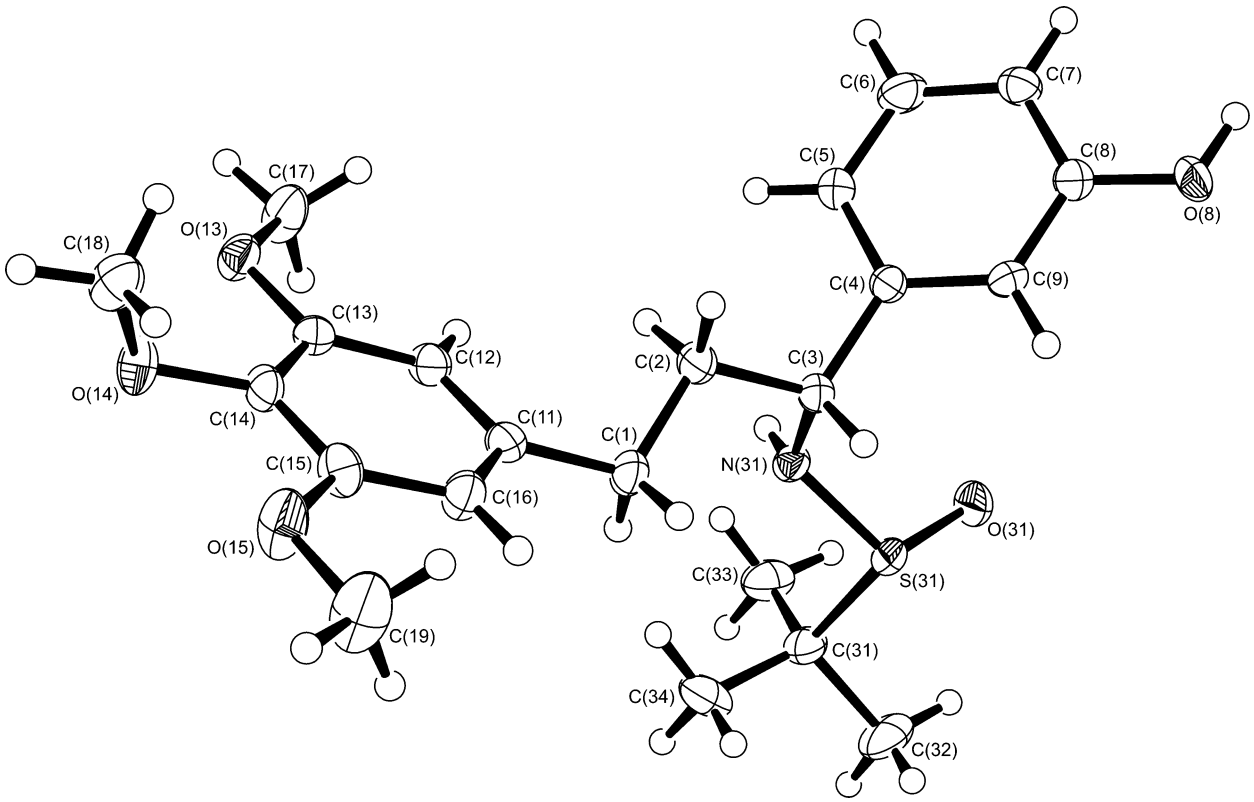


Fig. 1 X-Ray structure of sulfinamide (R_S,*R*)-**29**. The ellipsoid probabilities are 50%.

this was confirmed by anomalous dispersion effects since the Flack parameter refined to 0.04(10).

Acetic acid (*S*)-(−)-3-[1-acetylamino-3-(3,4,5-trimethoxyphenyl)propyl]phenyl ester (30). To a solution of (S_S,S)-**29** (0.54 g, 1.0 mmol) in methanol (4 mL) was added 6 M HCl (4 mL, 24 mmol). The reaction mixture was stirred at r.t. for 20 min and then concentrated to dryness before addition of Et_2O. The precipitate was filtered off, washed thoroughly with Et_2O and dried under reduced pressure. The crude amine hydrochloride was then dissolved in dry CH_2Cl_2 (10 mL) and cooled at 0 °C, before the drop-wise addition of DIPEA (0.45 mL, 0.65 g, 5 mmol) followed by acetyl chloride (140 μL, 157 mg, 2 mmol). The reaction mixture was then stirred at r.t. for 6 h, before addition of sat. NH_4Cl aq. solution (10 mL) and extraction of the aqueous layer with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with 10% HCl aq. solution (30 mL), brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified by column chromatography on silica gel (EtOAc) to afford the title compound (317 mg, 0.79 mmol, 79% over two steps) as a viscous yellow oil. $[\alpha]_D$ (25 °C) −41 (c = 1, $CHCl_3$). IR ($CHCl_3$): ν = 3019 s, 1765 m, 1670 m, 1591 m, 1507 m, 1422 m, 1215 s, 1130 m, 928 m, 757 s cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.39 (1H, m app t, J 7.7, C5′H), 7.23 (1H, d, J 7.7, C2′H), 7.11–7.05 (2H, m, C4′H, C6′H), 6.44 (2H, s, C2″H and C6″H), 5.95 (1H, d, J 8.5, NH), 5.11 (1H, dd, J 7.7, 15.3, C1H), 3.90 (6H, s, C3″OCH$_3$ and C5″OCH$_3$), 3.88 (3H, s, C4″OCH$_3$), 2.71–2.57 (2H, m, C3H$_2$), 2.35 (3H, s, O=C(N)*C*H$_3$), 2.27–2.09 (2H, m, C2H$_2$), 2.02 (3H, s, O=C–CH$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 169.1 and 169.0 (C=O), 152.9 (C1′), 150.7 (C3″ and C5″), 143.4 (C3′), 136.6 (C1″), 135.9 (C4″), 129.4 (C5′H), 123.9 (C4′H), 120.4 (C2′H), 119.6 (C6′H), 105.0 (C2″H and C6″H), 60.5 (C4″OCH$_3$), 55.8 (C3″OCH$_3$ and C5″OCH$_3$), 52.4 (C1H), 36.9 (C2H$_2$), 32.6 (C3H$_2$), 23.1 (O=C(N)*C*H$_3$), 20.8 (O=C–*C*H$_3$). LRMS (ES+): m/z = 402 (M + H)$^+$ (100%), 343 (85), 181 (58), 424 (M + Na)$^+$ (55%). HRMS (ES+): m/z calcd for $C_{22}H_{28}NO_6$: 402.1917; found: 402.1905.

Conversion of phenol acetate 30 to phenol silyl ether 10. Phenol acetate **30** (0.21 g, 0.52 mmol) was dissolved in a mixture of CH_2Cl_2 (3 mL) and MeOH (6 mL). Water (0.5 mL) was added followed by potassium carbonate (0.29 g, 2.08 mmol). The mixture was allowed to stir at ambient temperature for 10 min whereupon the solvent was evaporated and the residue partitioned between CH_2Cl_2 and water. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo.* The residue was dissolved in CH_2Cl_2 (4 mL) and *tert*-butyldimethylsilyl chloride (0.094 g, 0.62 mmol) was added followed by imidazole (0.088 g, 1.3 mmol). After 8 h at r.t., the mixture was diluted with Et_2O (20 mL) and then extracted with HCl (0.1 M, 15 mL), sat. aq. $NaHCO_3$ (10 mL) and water (10 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo.* The residue was filtered through a plug of silica gel (hexanes–Et_2O, 1 : 1) to give the title silyl ether **10** (0.51 mmol 98%) as a colourless oil. The ^{1}H and ^{13}C NMR spectroscopic data were identical to those described above.

Di(isopropyl)carbamic acid 3-(3,4,5-trimethoxyphenyl)propyl ester (31). The procedure of Hoppe and co-workers[61] was employed. To a solution of 3-(3,4,5-trimethoxyphenyl)propanol[57] (6.08 g, 26.9 mmol) in pyridine (74 mL) was added (*i*-Pr)$_2$NCOCl (4.8 g, 29.5 mmol) followed by DMAP (73 mg). The solution was stirred under N_2 at 90–100 °C for 12 h. The reaction mixture was then cooled to r.t., diluted with Et_2O (200 mL), washed consecutively with 5% HCl (3 × 200 mL), water, sat. aq. $NaHCO_3$ and then dried (Na_2SO_4) and concentrated *in vacuo.* The yellow residue was purified by column chromatography (SiO_2, hexanes–Et_2O) to give carbamate **31** (8.14 g, 23.0 mmol, 86%) as a pale yellow oil. IR (film): ν = 2967 s, 2838 m, 1689 s, 1590 s, 1509 s, 1463 s, 1369 s, 1310 s, 1239 s, 1189 s, 1130 s, 1058 s, 1012 s, 773 s cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 6.41 (2H, s, C2″H and C6″H), 4.13 (2H, t, J 6.8, C1H$_2$), 3.93 (2H, br, 2 × (CH$_3$)$_2$C*H*), 3.85 (6H, s, C3″OCH$_3$ and C5″OCH$_3$), 3.82 (3H, s, C4″OCH$_3$), 2.66 (2H, dd, J 7.3, 8.1, C3H$_2$), 1.98 (2H, dq, J 6.4, 8.1, C2H$_2$), 1.23 (12H, d, J 6.8, 4 × CH$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 155.9 (C=O), 153.3 (C3″ and C5″), 137.4 (C4″), 136.2 (C1″), 105.3 (C2″H and C6″H), 64.1 (C1H$_2$), 61.0 (C4″O*C*H$_3$), 56.2 (C3″O*C*H$_3$ and C5″O*C*H$_3$), 45.9 (2 × (CH$_3$)$_2$*C*H, broad), 33.0 (C3H$_2$), 31.0 (C2H$_2$), 21.2 (4 × CH$_3$, broad). HRMS (ES): m/z calcd for $C_{19}H_{32}NO_5$ (M + H)+: 354.2280. Found: 354.2290.

Diisopropylcarbamic acid (*S*)-1-(4,4,5,5-tetramethyl[1,3,2]-dioxaborolan-2-yl)-3-(3,4,5-trimethoxyphenyl)propyl ester ((*S*)-(+)-33). The compound was prepared by a 1-step simplification of Hoppe's 2-step general procedure[47] by using 2-isopropoxy-4,4,5,5-tetramethyl[1,3,2]dioxaborolane **32** instead of tri-*iso*-propyl borate. To a solution of carbamate **31** (0.707 g, 2.0 mmol) and (−)-sparteine (0.56 g, 2.4 mmol) in anhydrous Et_2O (10 mL), at −78 °C, *s*-BuLi (1.8 mL, 1.35 M, 2.4 mmol) was added dropwise. The solution was stirred at −78 °C for 5 h and then 10 mL of Et_2O was added followed by freshly distilled 2-isopropoxy-4,4,5,5-tetramethyl[1,3,2]dioxaborolane (**32**, 0.56 g, 3.0 mmol, dropwise). The stirring was continued for 1 h at −78 °C whereupon water (5 mL) was added. The mixture was allowed to warm to r.t. and extracted with Et_2O (2 × 10 mL), dried (Na_2SO_4), filtered and concentrated to give a pale yellow oil (1.45 g). The crude product was purified by column chromatography (SiO_2, CH_2Cl_2–Et_2O) to give (*S*)-(+)-**33** (0.67 g, 1.39 mmol, 70%) as a colourless oil: $[\alpha]_D$ (26 °C) +44.4 (c = 1, $CHCl_3$). IR (film): ν = 3450 w, 2970 s, 2838 m, 1631 s, 1589 s, 1457 s, 1420 s, 1371 s, 1337 s, 1313 s, 1237 s, 1127 s, 1010 s, 1011 s, 970 s, 899 s cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 6.43 (2H, s, C2″H and C6″H), 4.07 (1H, septet, J 6.8, (CH$_3$)$_2$C*H*), 3.84 (6H, s, C3″OCH$_3$ and C5″OCH$_3$), 3.82 (3H, s, C4″OCH$_3$), 3.86–3.81 (1H, m, C1H), 3.78 (1H, septet, J 6.8, (CH$_3$)$_2$C*H*), 2.79 (1H, ddd, J 14.1, 9.8, 5.3, C3*H*$_A$H$_B$), 2.67 (1H, ddd, J 14.1, 9.2, 6.6, C3H$_A$*H*$_B$), 2.09–1.99 (1H, m, C2*H*$_A$H$_B$), 1.96–1.87 (1H, m, C2H$_A$*H*$_B$), 1.26 (6H, d, J 6.8, (C*H*$_3$)$_2$CH), 1.22 (6H, d, J 6.4, (C*H*$_3$)$_2$CH), 1.19 (12H, s, (CH$_3$)$_2$CC(CH$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 162.7 (C=O), 153.0 (C3″ and C5″), 138.3 (C4″), 135.8 (C1″), 105.3 (C2″H and C6″H), 79.7 (Me$_2$*C*CMe$_2$), 79.3 (br, C1H), 60.8 (C4″OCH$_3$), 55.9 (C3″OCH$_3$ and C5″OCH$_3$), 48.4 ((CH$_3$)$_2$*C*H), 46.6 ((CH$_3$)$_2$*C*H), 34.7 (C3H$_2$), 33.3 (C2H$_2$), 25.3 and 24.9 ((*C*H$_3$)$_2$CC(*C*H$_3$)$_2$), 20.5 ((*C*H$_3$)$_2$CH), 20.3 ((*C*H$_3$)$_A$(CH$_3$)$_B$CH), 20.2 ((CH$_3$)$_A$(*C*H$_3$)$_B$CH). HRMS (ES): m/z calcd for $C_{25}H_{43}BNO_7$ (M + H)+: 480.3133. Found: 480.3123.

Racemic **33** was also prepared by the general procedure of Hoppe and co-workers.[62] To a solution of carbamate **31** (3.54 g, 10.0 mmol) and TMEDA (1.39 g, 12.0 mmol) in anhydrous Et_2O (20 mL) at −78 °C, *s*-BuLi (10.3 mL, 1.16 M,

12.0 mmol) was added dropwise. The solution was stirred at −78 °C for 1 h and then freshly distilled 2-isopropoxy-4,4,5,5-tetramethyl[1,3,2]dioxaborolane (**32**, 1.86 g, 10.0 mmol) was added dropwise. At this point the mixture became viscous and the stirring stopped whereupon Et_2O (80 mL) was added to restore stirring. Stirring was continued for 1 h at −78 °C whereupon water (20 mL) was added. The mixture was allowed to warm to r.t. and extracted with Et_2O (2 × 50 mL), dried (Na_2SO_4), filtered and concentrated to give a pale yellow oil (4.65 g). The crude product was purified by column chromatography (SiO_2, hexanes–Et_2O) to give a white sticky solid which was transferred to a sinter funnel and washed several times with hexane to give *rac*-**33** (2.69 g, 5.6 mmol, 56%) as a white solid.

A sample of *rac*-**33** recrystallised from Et_2O–hexane (mp 99–100 °C) was analysed by X-ray crystallography† (Fig. 2). $C_{25}H_{44}BNO_8$, orthorhombic, space group $Pca2_1$, $a = 13.3627(3)$ Å, $b = 15.6068(3)$ Å, $c = 27.3395(7)$ Å, $V = 5701.6(2)$ Å^3, $Z = 8$, $\rho_{calc} = 1.159$ mg m^{-3}, $\mu = 0.084$ mm^{-1}, crystal size: 0.19 × 0.09 × 0.03 mm, data collection range: $3.0 \leq \theta \leq 26.0°$, 29479 measured reflections, final $R(wR)$ values: 0.0437, (0.1028) for 5715 independent data and 669 parameters [$I > 2\sigma(I)$], largest residual peak and hole: 0.158, −0.191 e Å^{-3}. The structure solved in space group *Pca*21 with two molecules of *rac*-**33** and two molecules of water in the asymmetric unit. Both molecules have the same numbering scheme and are distinguished with the suffixes A and B. All hydrogen atoms attached to carbon were placed in calculated positions and refined using a riding model. C–H distances: methyl, 0.98 Å; methylene, 0.99 Å; methine, 1.00 Å; aromatic C–H, 0.95 Å. All carbon Uiso(H) values were constrained to be 1.2 times Ueq of the parent atom. Hydrogens in the water molecules were located in the Fourier difference map. Those attached to O1S were refined freely whereas those attached to O2S were constrained to have bond lengths of 1.00 Å. In the absence of significant anomalous scattering effects, the absolute configuration could not be confirmed from the diffraction data and Friedel pairs were merged. The depicted model has been arbitrarily chosen.

The C=O–B coordination revealed in Fig. 2 is reflected in the ^{11}B NMR spectrum of **33** (80 MHz, $CDCl_3$): $\delta = 12$ ppm. Tricoordinate boron atoms with one C and two O ligands typically resonate at $\delta = 32$ relative to $BF_3{\cdot}OEt_2$ whereas the signals are shifted upfield by $\delta = 5$–15 for tetracoordinate compounds.[63]

(*R*) - 1 - (3 - (*tert* - Butyldimethylsilyloxy)phenyl) - 3 - (3,4,5 - trimethoxyphenyl)propan-1-ol (17) *via* 1,2-metallate rearrangement.

Method A. The procedure generally follows Hoppe's methodology[47] but the use of milder base (K_2CO_3 instead of NaOH) was crucial to avoid the substantial deprotection of TBS ether in the oxidation step. To a solution of 1-bromo-3-(*tert*-butyldimethylsilyloxy)benzene[60] (0.57 g, 2.0 mmol) in Et_2O (10 mL) was added Mg (0.096 g, 4.0 mmol) followed by 1 drop of 1,2-dibromoethane. The mixture was refluxed for 4 h, then cooled to r.t. and a solution of boronate (+)-**33** (0.48 g, 1.0 mmol) in Et_2O (10 mL) transferred by cannula (1 mL of Et_2O was used for washing). The solution was stirred at r.t. for 12 h, then treated with an aq. solution of K_2CO_3 (2.4 mL, 0.5 M, 1.2 mmol) and H_2O_2 (0.18 g, 0.16 mL, 30%, 1.4 mmol). The mixture was stirred for 15 min at r.t. then poured into brine (10 mL) and extracted with Et_2O (3 × 20 mL). The combined extracts were washed with aq. sat. $Na_2S_2O_3$, dried (Na_2SO_4) and concentrated to give a yellow oil (0.66 g). The crude product was purified by column chromatography (SiO_2, CH_2Cl_2–Et_2O) to give **17** (0.32 g, 0.73 mmol, 73%) as a colourless oil, er = 94 : 6 (chiral HPLC). The ^{1}H and ^{13}C NMR spectra recorded at 500 and 75 MHz, respectively, were identical with the sample prepared above.

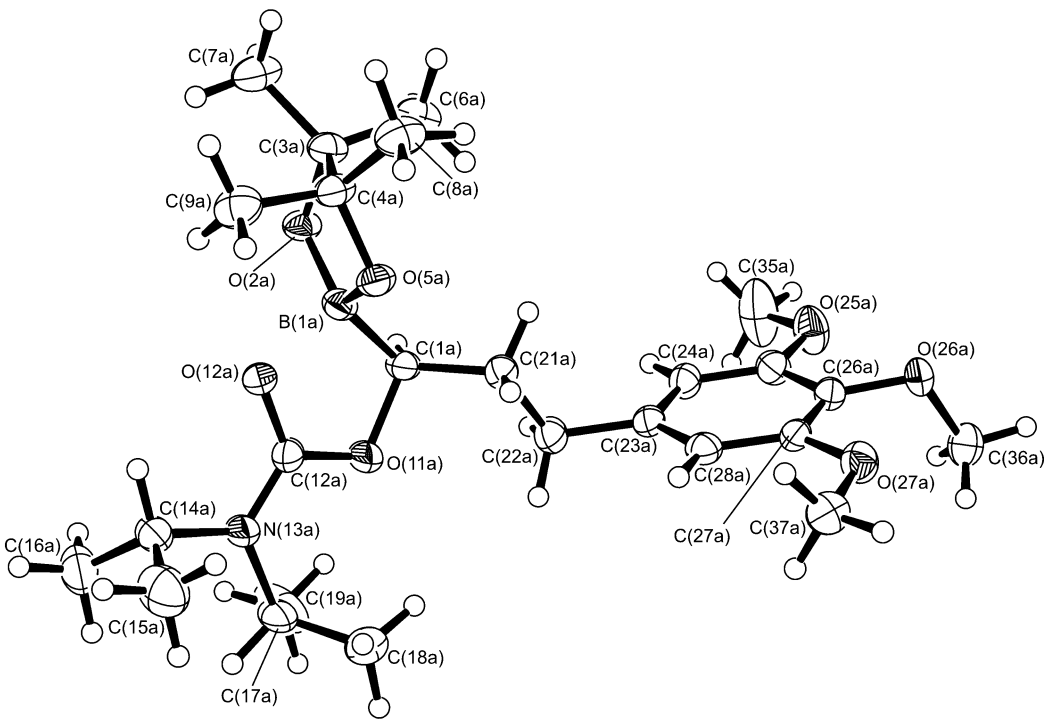


Fig. 2 X-Ray structure of *rac*-**33** The ellipsoid probabilities are 50%.

Method B. To a solution of carbamate **31** (0.35 g, 1.0 mmol) and (−)-sparteine (0.28 g, 1.2 mmol) in Et_2O (10 mL), at −78 °C, was added dropwise *s*-BuLi (1.3 M, 0.92 mL, 1.2 mmol). The solution was stirred at −78 °C for 5 h and then a solution of arylboronate **37** (0.37 g, 1.1 mmol) in diethyl ether (5 mL) was added dropwise followed by $MgBr_2$ (prepared from 1,2-dibromoethane (0.226 g, 1.2 mmol), Mg (0.048 g, 2 mmol) in Et_2O (10 mL) by stirring at rt for 4 h). The mixture was allowed to warm gradually to r.t. for 12 h while nitrogen was passed through it to remove the solvent. To the solid residue DME (10 mL, freshly distilled from CaH_2) was added and the mixture refluxed for 12 h. The mixture was cooled to r.t. and then treated with an aq. solution of K_2CO_3 (2.4 mL, 0.5 M, 1.2 mmol) and H_2O_2 (30%, 0.18 g, 0.16 mL, 1.4 mmol). The mixture was stirred for 15 min at r.t. then poured into water (10 mL) and extracted with Et_2O (3 × 10 mL). The combined extracts were washed with aq. sat. $Na_2S_2O_3$, dried (Na_2SO_4) and concentrated to give a yellow oil (0.68 g). The crude product was purified twice by column chromatography (SiO_2, first CH_2Cl_2–Et_2O and then hexanes–Et_2O) to give **17** as a colourless oil (0.28 g, 0.65 mmol, 65%). The product had some impurities (*ca* 10%) that were impossible to remove by column chromatography. The er of the product, determined by chiral HPLC, was 98 : 2.

4,4,5,5-Tetramethyl-2-(3-*tert*-butyldimethylsilyloxyphenyl)-1,3-dioxaborolane (37). To a solution of 4,4,5,5-tetramethyl-2-(3-hydroxyphenyl)-1,3-dioxaborolane (0.99 g, 4.5 mmol) in DMF (10 mL) was added imidazole (0.77 g, 11.4 mmol) followed by TBSCl (0.82 g, 5.42 mmol). The solution was stirred at r.t. for 12 h, then poured into water (100 mL) and extracted with Et_2O (2 × 20 mL). The combined extracts were dried (Na_2SO_4), concentrated *in vacuo* and the residue purified by column chromatography (SiO_2, hexanes–Et_2O) to give silyl ether **37** (1.25 g, 3.75 mmol, 83%) as a colourless oil that solidified after storing a few days in a refrigerator: mp 37–38 °C. IR (film): ν = 3047 s, 2950 s, 2931 s, 2859 s, 1574 s, 1487 m, 1422 s, 1356 s, 1314 s, 1235 s, 1145 s, 969 s, 838 s cm^{-1}. ^{1}H NMR (500 MHz, CDCl3): δ_H = 7.40 (1H, d, *J* 7.2, CH), 7.24 (1H, t, *J* 7.7, C5H), 7.27 (1H, s, C2H), 6.93 (1H, dd, *J* 1.6, 8.0), 1.35 (12H, s, 4 × CH_3), 1.00 (9H, s, $C(CH_3)_3$), 0.21 (6H, s, $(CH_3)_2Si$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 155.3 (C3), 130.7 (br, C1), 129.0 (CH), 127.9 (CH), 126.3 (CH), 123.0 (CH), 83.9 (2 × $C(CH_3)_2$), 25.9 ($C(CH_3)_3$), 25.0 (4 × CH_3CO), 18.3($C(CH_3)_3$), −4.2 ($Si(CH_3)_2$). ^{11}B NMR (80 MHz, CDCl3): δ = 30.8 ppm. HRMS (ES): *m/z* calcd for $C_{18}H_{31}BO_3Si$ $(M + H)^+$: 335.2208 Found: 335.2224. Anal. calcd for $C_{18}H_{31}BO_3Si$: C, 64.66; H, 9.35%. Found: C, 64.4; H, 9.5%.

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